

*THE WHO  
ESSENTIAL  
MEDICINES LIST  
ANTIBIOTIC BOOK*

Improving antibiotic AWaRe-ness

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**DRAFT**

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# 1 INTRODUCTION

2 There is a clear need for simple resources to improve the quality of antibiotic prescribing globally.  
3 The Handbook was designed as a tool to make the WHO model Essential Medicines Lists for  
4 adults and children (EML and EMLc) of antibiotics more helpful to prescribers and to update the  
5 previous WHO 2001 *WHO Model Prescribing Information (1)*.

## 6 Aim and Scope

7 The aim of the Handbook is to provide short, clinical guidance on the management of common  
8 infections, including recommendations for empiric antibiotic treatment at the first clinical  
9 presentation and when a “No antibiotic” approach is appropriate. Guidance is given on the choice  
10 of antibiotics that should be used to treat the most likely bacterial pathogens causing each  
11 infection in adults and children, the dosage and treatment duration.

12 The Handbook is intended for all health care workers who prescribe and dispense antibiotics in  
13 high-, middle- and low-income settings in both the primary health care and the facility/hospital  
14 setting. It aims to complement WHO’s Policy Guidance on Integrated Stewardship Activities and  
15 the Toolkit for health care facilities in low- and middle-income countries (LMIC) (2). The  
16 Handbook is not intended to replace existing local and national antibiotic prescribing guidelines  
17 and clinical judgment, but to provide simple guidance where currently none is available.

## 18 Methodology

19 The antibiotic treatment recommendations outlined in this Handbook are based on reviews of  
20 the evidence undertaken for the 2017, 2019 and 2021 updates of the EML and EMLc. The  
21 EML/EMLc provide a list of safe and effective antibiotics that should be available and affordable  
22 for patients globally. The EML Handbook provides guidance on how to best use these antibiotics  
23 based on the principles of the AWaRe framework.

### *Box 1 – Principles of the AWaRe framework*

- 1) Maximizing clinical effectiveness
- 2) Minimizing toxicity
- 3) Minimising unnecessary costs to patients and healthcare systems
- 4) Reducing the emergence and spread of antibiotic resistance (i.e. prioritizing antibiotics that are less likely to lead to antibiotic resistance in an individual patient and the community)
- 5) Parsimony (i.e. avoiding the inclusion of many similar antibiotics)
- 6) Simplification (i.e. favouring a smaller number of antibiotics that can be used to treat different infections)
- 7) Alignment with existing WHO guidelines

24 The detailed reviews on the optimal choice of antibiotics to be used for each specific clinical  
25 infection were based on a standardised analysis by experts in evidence-based medicines from  
26 McMaster University (Hamilton, Canada) of systematic reviews, meta-analyses and clinical  
27 practice guidelines.

28 Details regarding the evidence underlying the recommendations and the methodology can be  
29 found here:

- 30 • <https://apps.who.int/iris/handle/10665/259481>
- 31 • <https://apps.who.int/iris/handle/10665/330668>

32 The choice of antibiotics to use for each specific infection are formal recommendations based on  
33 the evaluation made by the EML Expert Committee on the evidence presented for the EML  
34 updates or derived from existing WHO guidelines where available. The Handbook also provides  
35 guidance on diagnosis, symptomatic treatment and treatment duration based on non-systematic  
36 reviews of the literature and expert opinion.

*Box 2 – General considerations about the use of the Handbook*

As with any general guidance document, the individual circumstances of the patients need to be considered. Comorbidities (e.g. immunosuppression which changes the pathogens that need to be considered, or renal or hepatic insufficiency which may require dose adaption of antibiotics), concomitant medications (risk of interactions), pregnancy and breastfeeding status (some antibiotics may be contraindicated), allergies (see separate chapter) and national regulations all may require an adaption of the guidance and it is the responsibility of each prescriber to make sure that all these considerations are taken into account when prescribing an antimicrobial.

Patients should be informed about the most common side-effects of the antibiotic, how it should be stored and taken, how long to take it for and what to do if symptoms worsen or fail to improve and how leftover antibiotics should be properly disposed of.

## 37 Structure

38 There are separate chapters for 36 infections, divided for ease of use into “Primary health care”  
39 and “Hospital facility” sections fully acknowledging that there is overlap between these groups.

40 Each chapter on a clinical infection includes:

- 41 • **Background information.** The pathophysiology, epidemiology, global burden, most  
42 common pathogens and how to make the clinical diagnosis, including assessing disease  
43 severity.
- 44 • **Diagnostic tools.** As the availability of diagnostic tools varies considerably in different  
45 settings, the empiric antibiotic recommendations are based on clinical signs and  
46 symptoms. Relevant diagnostic tests (including imaging and laboratory tests) are  
47 suggested based on the WHO’s Essential *in-vitro* Diagnostics List (EDL) (4). The list of tests

- 48 provided for each infection is not based on a formal assessment of their predictive value,  
 49 but as a general guide of tests that could be clinically helpful, where available.
- 50 • **Treatment.** Guidance is given where appropriate for “No Antibiotic Care” including  
 51 symptomatic management for low-risk patients with minor infections that do not need  
 52 antibiotic treatment. First- and second-choice antibiotic options are then given where  
 53 relevant based on the EML/c and AWaRe system as well as other WHO guidance  
 54 documents.
  - 55 • Guidance on which infections may most benefit from **targeted clinical microbiology**  
 56 **surveillance** to help inform both local and national empiric antibiotic guidance.

57 Each chapter is complemented by an infographic containing a short summary of the most  
 58 important information (e.g. clinical presentation, diagnostic tests, treatment) separately for  
 59 children and adults that can be rapidly and easily consulted when needed (see example below  
 60 of a children infographic).

**Community-Acquired Pneumonia**  
Page 1 of 2

**Definition**  
An acute illness affecting the lungs usually presenting with cough, and rapid and difficult breathing with a new or worsening pulmonary infiltrate on a chest radiograph

**Investigating for TB**  
• Consider in endemic settings especially in high risk patients  
• Specific investigations for TB should be performed as indicated

**Diagnosis**  
**Clinical Presentation**  
• Clinical features may include: new onset (<2 weeks) or worsening cough with sputum production, dyspnea, tachypnea, reduced oxygen saturation, crackles on lung auscultation, chest pain/discomfort without alternative explanation, fever >38.0°C (may be absent)  
• Pneumonia is diagnosed on: fast breathing for age and/or chest indrawing  
• Check for hypoxia with saturimeter if available  
• Children with coryza and a cough usually do not have pneumonia and should not receive an antibiotic, only home care advice

**Laboratory Tests**  
No test clearly differentiates viral or bacterial CAP  
Consider: full blood count and C-reactive protein  
Note: Tests depend on availability

**Microbiological Tests**  
Severe cases (to guide antimicrobial treatment): blood cultures

**Chest Radiograph**  
• Not essential in non-severe cases  
• Look for lobar consolidation or pleural effusion  
• Cannot be used to accurately predict pathogen

**Most Likely Pathogens**  
**Typical Bacteria:**  
• Streptococcus pneumoniae  
• Haemophilus influenzae  
• Moraxella catarrhalis  
• Staphylococcus aureus  
• Enterobacteriaceae  
Most common bacterial cause of CAP beyond the 1st week of life is S. pneumoniae  
**Atypical Pathogens:**  
• Mycoplasma pneumoniae  
• M. pneumoniae and Chlamydia spp. more frequent in children >5 years (compared to younger children)  
**Respiratory Viruses:**  
• Influenza  
• Respiratory syncytial virus (RSV)  
• Metapneumovirus  
• Coronavirus (including SARS-CoV-2)  
• Parainfluenza virus  
• Adenovirus  
• Rhinovirus

**Severity Assessment and Considerations**  
Children with pneumonia should be treated with oral amoxicillin at home with home care advice  
Pneumonia is diagnosed by:  
• Fast breathing (respiratory rate >50 breaths/min in children aged 2-11 months; respiratory rate >40 breaths/min in children aged 1-5 years)  
OR  
• Chest indrawing  
Children with severe pneumonia should be admitted to hospital and treated with intravenous antibiotics (or a child with pneumonia who cannot tolerate oral antibiotics)  
Severe pneumonia is diagnosed on:  
• A cough or difficulty in breathing plus one of:  
• Oxygen saturation below 90%  
• Central cyanosis  
• Severe respiratory distress (grunting or severe chest indrawing)  
OR  
• Signs of pneumonia with a general danger sign:  
• Inability to drink or breast feed  
• Persistent vomiting  
• Convulsions  
• Lethargy or unconsciousness  
• Severe respiratory distress

**Community-Acquired Pneumonia**  
Page 2 of 2

**Treatment**  
**Treatment Duration**  
Treat for 5 days  
If severe disease, consider longer treatment and look for complications such as empyema, if patient not clinically stable at day 5.

**Mild to Moderate Cases**  
**First Choice**  
Amoxicillin ORAL  
4-10kg 250mg q12h  
10-14kg 500mg q12h  
14-20kg 750mg q12h  
20-30kg 1000mg q12h  
**Second Choice**  
Amoxicillin-clavulanic acid ORAL  
3-6kg 250mg amx/dose q12h  
6-10kg 375mg amx/dose q12h  
10-16kg 500mg amx/dose q12h  
16-21kg 875mg amx/dose q12h  
21-30kg 1000mg amx/dose q12h

**Severe Cases**  
Please see Severity Assessment and Considerations for diagnosis of severe cases  
**First Choice**  
Gentamicin IV/IM  
All children except neonates: 7.5 mg/kg/dose q24h  
Neonates: 5 mg/kg/dose q24h  
COMBINED WITH  
Ampicillin 50 mg/kg/dose IV/IM  
• <1wk of life: q12h  
• >1wk of life: q8h  
OR  
Amoxicillin 50 mg/kg/dose IV/IM  
• <1wk of life: q12h  
• >1wk of life: q8h  
OR  
Benzylpenicillin 50 000 IU/kg q8h IV/IM  
PCP = IF HIV AND <1 YR OLD, ADD  
Sulfamethoxazole-trimethoprim 8 mg/kg TMP+40 mg/kg SMX q12h IV or ORAL for 3wks  
**Second Choice if NO Clinical Response to First Choice**  
Cefotaxime 50 mg/kg/dose q8h IV/IM  
OR  
Ceftriaxone 50-100 mg/kg/dose q24h IV/IM

61 Further guidance is given on how the Handbook could be used to improve the use of antibiotics  
 62 based on general antibiotic stewardship principles.  
 63

64 The Handbook also includes chapters on the **Reserve antibiotics** listed in the 2021 EML/c, the  
 65 principles behind their selection and how these last-resort medicines should be used to preserve  
 66 their effectiveness.

67 The Handbook is available both in a print and an electronic format. Simple, downloadable  
 68 infographics with the key information for end-users are also provided for each infection.

## 69 Improving the use of antibiotics with the Handbook

### 70 Background

71 About 90% of all antibiotics are taken by patients in the primary health care setting. It is estimated  
72 that around half of all antibiotic use is inappropriate in some way, such as the use of an antibiotic  
73 when none is indicated, the choice of an antibiotic with unnecessarily broad spectrum (e.g.  
74 Watch instead of Access, see below), the dose, the duration of treatment, and the delivery or  
75 formulation of the antibiotic (3).

### 76 AWaRE

77 This Handbook gives guidance on first- and second-choice antibiotics for common infections in  
78 line with the recommendation in the EML/c (4, 5). WHO has classified antibiotics into four groups,  
79 Access, Watch, Reserve (AWaRe) and a fourth “Not Recommended” group. As well as the  
80 antibiotics on the EML/c, over 200 other antibiotics have now been classified into  
81 Access/Watch/Reserve groups to help inform local and national policy development and  
82 implementation (<https://aware.essentialmeds.org/list>).

83 **Access** antibiotics have a narrow spectrum of activity, lower cost, a good safety profile and  
84 generally low resistance potential. They are recommended as empiric first- or second-choice  
85 treatment options for common infections.

86 **Watch** antibiotics are broader-spectrum antibiotics, generally with higher costs and are  
87 recommended only as first-choice options for patients with more severe clinical presentations or  
88 for infections where the causative pathogens are more likely to be resistant to Access antibiotics  
89 (e.g. upper urinary tract infections).

90 **Reserve** antibiotics are last-choice antibiotics used to treat multidrug-resistant infections (see  
91 chapter on Reserve antibiotics).

92 The AWaRe system is also represented as a traffic-light approach: Access = Green,  
93 Watch = Yellow and Reserve = Red (3). Simple graphics using the traffic light approach can be  
94 used to show the proportions of Access and Watch antibiotics used in settings such as a  
95 community clinic or pharmacy or as part of central monitoring of antibiotic consumption.

96 Countries, regions and districts are encouraged to use the Handbook as a basis for developing  
97 their own quality indicators and targets for safely reducing total levels of inappropriate antibiotic  
98 prescribing to improve patient safety and care, while reducing resistant infections and costs for  
99 patients and health systems.

#### Box 3 – WHO target for the use of Access antibiotics

To promote responsible use of antibiotics and slow the spread of antibiotic resistance, the WHO Global Programme of Work includes a target that at least **“60% of total antibiotic prescribing at the country level should be Access antibiotics by 2023”** (6, 7)

100

*Box 4 – Improving the use of antibiotics with the Handbook*

1. No Antibiotic Care - safely reducing antibiotic use
2. Improving Access use and reducing inappropriate oral Watch antibiotics
3. Reducing the use of Not Recommended antibiotics
4. Improving AWaRe-ness!
5. Appropriate antibiotic dosing and duration

101 **1. No Antibiotic Care - safely reducing antibiotic use**

102 **Key messages**

1. Most otherwise healthy patients with mild common infections can be treated **without antibiotics** as these infections are frequently self-limiting
2. The risks of taking antibiotics when they are not needed should always be considered (e.g. side effects, allergic reactions, *C. difficile* infection, selection of resistant bacteria)

103 **Management of low risk (mild) infections in primary health care**

104 Most infections encountered in primary health care are not caused by bacteria (e.g. most  
 105 respiratory tract infections have a viral cause) and therefore the patient will not benefit from  
 106 antibiotic treatment (Table 1). Even when the cause of the infection is bacterial, many infections  
 107 are frequently self-limiting, with a low risk of severe complications and the benefit of antibiotics  
 108 is limited (shortening of the duration of symptoms by usually only around 1 or 2 days). Most  
 109 otherwise healthy patients with mild infections may safely receive symptomatic treatment alone  
 110 (e.g. anti-inflammatory medicines, pain killers or complementary medicines). Whenever  
 111 appropriate, guidance on diagnosing mild infections that can be treated with *No Antibiotic Care*  
 112 is given in the Handbook.

113 *Table 1 Common infections in primary health care that can be safely treated with No Antibiotic*  
 114 *Care (i.e. symptomatic management only) for mild cases – see individual chapters for more*  
 115 *details.*

Infection (in alphabetical order)	Can it be safely treated without antibiotics?	Comment
Acute diarrhoea	Yes, in the great majority of cases (unless there is significant bloody diarrhoea)	Most cases do not require antibiotic treatment because the infection is of viral origin and the illness is usually self-limiting regardless of the causative pathogen. The cornerstone of treatment is rehydration.

Bronchitis	Yes	Nearly all cases have a viral origin and there is no evidence that antibiotics are needed.
COPD exacerbations	Yes, in most mild cases	Most exacerbations of COPD are not triggered by bacterial infections; only certain cases will benefit from antibiotic treatment.
Dental infections	Yes, in most mild cases	Dental treatment rather than prescribing antibiotics is generally more appropriate in the management of dental infections.
Otitis media	Yes, in most mild cases	Most non-severe cases of acute otitis media can be managed symptomatically and do not require antibiotic treatment.
Pharyngitis	Yes, in most mild cases	Most cases do not require antibiotics because the infection is viral.
Sinusitis	Yes, in most mild cases	Most cases do not require antibiotics as the infection is viral.
Skin and soft tissue infections (mild)	Only for certain conditions and in certain patients	<ul style="list-style-type: none"> <li>• In cases of wounds at low risk of becoming infected, antibiotic treatment is not needed.</li> <li>• In cases of animal bites, only wounds in high-risk anatomical locations and patients with severe immunosuppression benefit from antibiotic treatment.</li> </ul>
Urinary tract infection (lower)	Only in a few patients with no risk factors for complicated infections	In young women who are not pregnant, with mild symptoms and who may wish to avoid or delay antibiotic treatment, symptomatic treatment alone can be considered.

116 COPD: chronic obstructive pulmonary disease

## 117 Are antibiotics needed?

118 In 2006, the WHO proposed that the percentage of patients attending a primary health care  
 119 facility receiving an antibiotic should be less than 30% (9), but on average around half of patients  
 120 presenting with any infection in primary care still receive an antibiotic, contributing to the  
 121 emergence and spread of antimicrobial resistance (AMR) (10). It is therefore important that both  
 122 healthcare professionals and patients consider the risks of taking antibiotics when they are not  
 123 needed. These include the immediate risk of side-effects of the medicine, most commonly  
 124 diarrhoea or allergic reactions (such as a rash; see chapter on allergy to antibiotics) and rarely  
 125 more serious side effects. Bacteria in patients prescribed an antibiotic for a respiratory or urine  
 126 infection (as examples of infections for which antibiotics are often prescribed) commonly develop  
 127 antibiotic resistance to the prescribed (and other) antibiotics. They are also more likely to acquire  
 128 resistant bacteria from other sources (other people, animals, food) and to transmit resistant  
 129 bacteria to other people (8). Patients with infections caused by antibiotic-resistant bacteria are  
 130 more likely to have a delayed clinical recovery(9). Furthermore, antibiotic treatment alters the  
 131 patient’s microbiota (i.e. all microorganisms that live in or on the human body), with potential  
 132 long-term consequences (and increasing the risk of infection by *Clostridioides difficile* (a  
 133 bacterium that can cause severe diarrhoea).

## 134 Think **D8** – before prescribing!

*Box 5 – Points to always consider when prescribing*

**Diagnose** – what is the clinical diagnosis, is there evidence of a significant bacterial infection?

**Decide** – are antibiotics really needed? Do I need to take any cultures or other tests?

**Drug (medicine)** – which antibiotic to prescribe - is it Access or Watch or Reserve? Are there any allergies, interactions, or other contraindications?  
**Dose** – what dose, how many times a day, are any dose adjustments needed e.g. because of renal impairment?  
**Delivery** – what formulation to use, is this a quality product? If intravenous treatment, when is Step Down to oral possible?  
**Duration** –for how long – what is the Stop Date?  
**Discuss** – inform the patient of the diagnosis, likely duration of symptoms, any likely medicine toxicity and what to do if not recovering.  
**Document** – write down all the decisions and management plan.

## 135 2. Improving Access use and reducing inappropriate oral 136 Watch antibiotics

### 137 Key messages

1. The great majority of common infections in primary health care can be treated without any antibiotics or with Access antibiotics
2. Reducing the inappropriate use of Watch antibiotics is key to control antibiotic resistance

138 The 68<sup>th</sup> World Health Assembly in May 2015 endorsed a global action plan to tackle antimicrobial  
139 resistance(10).

#### *Box 6 – The 5 objectives of the global action plan*

- 1) Improve awareness and understanding of antimicrobial resistance
- 2) Strengthen surveillance and research
- 3) Reduce the incidence of infection
- 4) **Optimize the use of antimicrobial medicines**
- 5) Ensure sustainable investment in countering antimicrobial resistance

140 The Handbook therefore aims to address one of the objectives of the WHO global action plan  
141 “Optimize the use of antimicrobial medicines” with a focus on antibacterial medicines or  
142 antibiotics (antimicrobials also include antifungal, antiviral and antiprotozoal medicines). The  
143 Handbook provides guidance on when not to prescribe antibiotics and – if indicated - which  
144 antibiotics to prescribe for the most common infections. The Handbook focusses on the optimal  
145 use of Access antibiotics as they remain the first choice options for the majority of infections.

146 The Handbook recommends that 9 of the 10 (90%) most common infections seen in primary  
147 health care can be treated safely with either no antibiotics or Access antibiotics (Table 2). Only  
148 one infection, acute bloody diarrhoea (dysentery), requires the empiric treatment with  
149 antibiotics in the Watch category (e.g. ciprofloxacin or azithromycin).

150 Oral Watch antibiotics use globally is increasing. They are now very commonly taken by patients  
151 in primary health care for minor infections (fever/cough/diarrhoea) in both high-income

152 countries (HIC) and low- and middle-income countries (LMIC). Reducing the inappropriate use of  
 153 both oral and intravenous Watch antibiotics is a critical strategy for the global control of antibiotic  
 154 resistance, while ensuring vulnerable populations have continued or, where appropriate,  
 155 improved “**access to Access**” antibiotics.

156 *Table 2 Common infections seen in primary health care settings and the antibiotic options*  
 157 *recommended in the Handbook*

<b>Infection</b>	<b>ACCESS (A)/WATCH (W)</b>	<b>First-choice antibiotic option (when an antibiotic is indicated<sup>a</sup>)</b>
Bronchitis	No antibiotic	No antibiotic
Community-acquired pneumonia (mild cases)	A	Amoxicillin or Phenoxymethylpenicillin
Chronic obstructive pulmonary disease exacerbations	A	Amoxicillin  (for most mild cases the first choice is symptomatic treatment and antibiotics are not necessary)
Dental infections	A	Amoxicillin or Phenoxymethylpenicillin  (for most cases the first choice is a dental procedure and antibiotics are not necessary)
Infectious diarrhoea <sup>b</sup>	No antibiotic or W	Most mild non-bloody diarrhoea is caused by viral infections and antibiotics are not necessary  For acute severe bloody diarrhoea/dysentery - Ciprofloxacin or Azithromycin or Cefixime or Sulfamethoxazole+trimethoprim
Otitis media	A	Amoxicillin  (for most mild cases the first choice is symptomatic treatment and antibiotics are not necessary)
Pharyngitis	A	Phenoxymethylpenicillin or Amoxicillin  (for most mild cases the first choice is symptomatic treatment and antibiotics are not necessary)
Sinusitis	A	Amoxicillin or Amoxicillin+clavulanic acid  (for most mild cases the first choice is symptomatic treatment and antibiotics are not necessary)

Skin and soft tissue infection (mild cases)	A	Amoxicillin+clavulanic acid or Cefalexin or Cloxacillin
Urinary tract infection, lower	A	Nitrofurantoin or Sulfamethoxazole+trimethoprim or Trimethoprim or Amoxicillin+clavulanic acid

158 <sup>a</sup>The decision to treat is based on assessment of the patient and on a minimum set of criteria to start antibiotics  
 159 described in the chapters for each infection.

160 <sup>b</sup>Only oral antibiotic options are reported here.

161 ACCESS antibiotics are indicated in green, WATCH antibiotics are indicated in yellow.

### 162 3. Reducing the use of Not Recommended antibiotics

#### 163 Key messages

1. The wide use of fixed-dose combinations that are not compatible with the EML and not approved by the major regulatory agencies is of concern and their used should be reduced as these combinations may result in increased toxicity and selection of resistance.
2. The EML has now developed a list of fixed-dose combinations whose use is strongly discouraged (<https://apps.who.int/iris/handle/10665/327957>)

164 In some countries there is a substantial use of fixed-dose combinations of antibiotics, which  
 165 contain two or more agents in a single formulation and recent data suggest they represent up to  
 166 20% of global antibiotic prescribing, especially in middle-income countries(11). Some fixed-dose  
 167 combinations of antibiotics are well established (e.g. sulfamethoxazole+trimethoprim) but other  
 168 combinations often consisting of two or more broad-spectrum antibiotics, combined with  
 169 antifungal and probiotic agents are of concern because they may contribute to the emergence  
 170 and spread of AMR.

### 171 4. Improving AWaRe-ness!

#### 172 Key messages

1. All prescribers have a responsibility to improving the use of antibiotics
2. Patients also have responsibilities and efforts should be made to ensure they know basic principles of appropriate antibiotic use (e.g. taking antibiotics as prescribed, not using leftover antibiotics for a later illness) and symptomatic care

173 All prescribers, dispensers and users of antibiotics, including both private and public providers,  
 174 have a clear responsibility to ensure the best use of the medicines they give or take. Table 3  
 175 outlines some of the responsibilities of these various stakeholders. The aim is to provide a  
 176 general framework of responsibility with broad examples that could lead into a programme of  
 177 interventions.

178 *Table 3 Responsibilities of different stakeholders for improving the use of antibiotics*

Group	Responsibility	Examples of practical actions
Health care policy-makers and relevant programme managers	<ul style="list-style-type: none"> <li>• The unnecessary use of antibiotics should be discouraged</li> <li>• Focus on promoting the use of Access antibiotics where appropriate</li> <li>• Ensure local access to and availability of antibiotics in the national EML at the appropriate cost, quality and in the correct formulation<sup>a</sup></li> <li>• Make sure that the national EML is regularly updated and whenever adequate aligned with the model lists</li> <li>• Undertake regular surveillance of antibiotic use at all levels, including by AWaRe group (e.g. Access/Watch ratio)</li> </ul>	<ul style="list-style-type: none"> <li>• Review national and local guidance documents and compare them with the Handbook</li> <li>• Disseminate new guidance to all levels of the health care services</li> <li>• Review provision of Access antibiotics, cost, quality<sup>b</sup>, sustainability and barriers to use</li> <li>• Develop a monitoring programme for antibiotic use across all levels of health care provision, including the ratio of Access and Watch antibiotics</li> <li>• Regularly review national EML and align to model list where synergies exist</li> <li>• Disseminate data back to providers on antibiotic use appropriately and regularly</li> </ul>
Physicians	<ul style="list-style-type: none"> <li>• Be AWaRe of the Handbook and focus clinical care on D8!</li> <li>• Diagnosis – which infection</li> <li>• Decisions – are antibiotics needed</li> <li>• Drug (medicine) – which antibiotic</li> <li>• Dose – at what dose</li> <li>• Duration – for how long</li> <li>• Delivery – what formulation</li> <li>• Document – in the notes</li> <li>• Discussion – with patient</li> <li>• Know which infections could be managed with antibiotics in your setting</li> <li>• Know which signs and symptoms would require hospital referral</li> </ul>	<ul style="list-style-type: none"> <li>• Review national and local guidance documents and compare them with the Handbook</li> <li>• “Adapt or adopt” EML guidance</li> <li>• Assist with developing and implementing educational programmes</li> <li>• Develop local tools for monitoring local patterns of antibiotic use and disseminate data appropriately and regularly</li> <li>• Act as local champions of the Handbook</li> </ul>
Pharmacists	<ul style="list-style-type: none"> <li>• Be AWaRe of the Handbook</li> <li>• Do not provide antibiotics without a prescription</li> <li>• Discourage self-medication with antibiotics</li> <li>• Monitor relative use of Access and Watch antibiotics</li> </ul>	<ul style="list-style-type: none"> <li>• Review, adapt or adopt the Handbook in line with local guidance document</li> <li>• Ensure in-pharmacy availability of the commonest infection chapters of the Handbook and summaries of Access and Watch lists</li> <li>• Monitor local patterns of antibiotic use as Access/Watch ratios and disseminate data appropriately and regularly</li> </ul>
Professional societies	<ul style="list-style-type: none"> <li>• Be aware of AWaRe and of the Handbook</li> <li>• Contribute to awareness campaigns</li> <li>• Educate health care workers about AWaRe</li> </ul>	<ul style="list-style-type: none"> <li>• Disseminate new guidance to all levels of the health care services</li> </ul>

Nurses	<ul style="list-style-type: none"> <li>• Be AWaRe of Handbook and advise or prescribe accordingly</li> </ul>	<ul style="list-style-type: none"> <li>• Review, adapt or adopt the Handbook in line with local guidance documents</li> <li>• Review local availability of antibiotics</li> <li>• Review practices and procedures that are non-compliant with the Handbook</li> <li>• Monitor patterns of antibiotic use</li> </ul>
Community health workers	<ul style="list-style-type: none"> <li>• Know which infections could be managed with antibiotics or with symptomatic treatment alone in your setting</li> <li>• Know which signs and symptoms would require medical referral</li> <li>• Be AWaRe of the Handbook</li> </ul>	
Patients	<ul style="list-style-type: none"> <li>• Be aware of AWaRe</li> <li>• Avoid using leftover antibiotics</li> <li>• Avoid asking for antibiotics over the counter in pharmacies and asking physicians to prescribe them</li> <li>• Avoid stockpiling leftover antibiotics</li> <li>• Contribute to awareness campaigns (e.g. with family members, the community)</li> </ul>	<ul style="list-style-type: none"> <li>• Act as champions for the better use of antibiotics</li> <li>• Promote antibiotic-related educational activities for patients</li> </ul>

179 EML: WHO model lists of essential medicines (2).

180 <sup>a</sup>This includes discouraging the excessive use of fixed-dose combinations of antibiotics.

181 <sup>b</sup>This includes preventing and detecting the production and use of substandard and falsified medicinal antibiotics.

## 182 Substandard and falsified medicinal antibiotics

183 As antibiotics are the most common medicines used globally, the production and use of  
 184 substandard and falsified medicinal antibiotics is a major problem. WHO estimates that up to one  
 185 in 10 medical products in LMIC settings are substandard or falsified with antibiotics amongst the  
 186 most commonly reported(12). These products are typically found in informal market settings,  
 187 which are a major source of antibiotics for patients globally, but also in less well-regulated  
 188 pharmacies. All those involved in giving antibiotics to patients should take all reasonable steps to  
 189 ensure that quality medicinal products are provided, which are registered and licensed by the  
 190 relevant national medicines regulatory authorities. Guidance on how to identify a possible  
 191 problem of substandard and falsified medicinal antibiotics is provided in the WHO publication:  
 192 *Substandard and falsified medical products (12)*.

## 193 Community health care workers

194 Community health care workers include informal health care providers (i.e. providers with no or  
 195 limited formal training) that in rural areas in LMIC settings are often the first medical contact for  
 196 many people within the rural population. Antibiotics are commonly prescribed by these informal  
 197 providers, including the inappropriate use of broad-spectrum antibiotics or frequent use of  
 198 antibiotics to treat upper respiratory tract infections that are often of viral origin (13).  
 199 Improved antibiotic use could be helped by enhanced education of this sector focussing on the  
 200 optimal use of Access antibiotics. Educational activities and training on how to manage common  
 201 infections using the Handbook could be considered (e.g. to decrease use of oral Watch antibiotics  
 202 and limit the use of antibiotics to severe infections).

## 203 5. Appropriate antibiotic dosing and duration

### 204 Key messages

1. Prescribers should always consult local and national dosing guidelines, where available.
2. The dosing guidance provided is for the most common clinical infections in patients with normal kidney and liver function but the need for dose adjustments should always be considered.
3. The guidance on duration of treatment is generally the shortest suggested duration for specific infections. More severe infections or patients with underlying conditions or immunosuppression may require longer courses of treatment than suggested in the Handbook.

#### *Box 1 Other relevant WHO documents (please check regularly for updates)*

- [https://www.who.int/selection\\_medicines/committees/expert/22/applications/ABWG\\_paediatric\\_dosing\\_AB.pdf](https://www.who.int/selection_medicines/committees/expert/22/applications/ABWG_paediatric_dosing_AB.pdf)

205 For each infection discussed in this Handbook, guidance is given for both children and adults on  
206 the dose of antibiotic to be given, how often the dose should be taken, the route of  
207 administration of the antibiotic and the duration of antibiotic treatment.

208 The guidance is based on: (i) existing WHO guidelines, (ii) a review of recent literature, (iii) a  
209 review of recent guidelines from different WHO regions (iv) expert opinion (the EML Antibiotic  
210 Working Group). A list of the guidelines used for the preparation of this Handbook can be  
211 accessed online as Supplement.

212 Users of this Handbook should be aware of the limited evidence underlying many antibiotic  
213 prescribing strategies and particularly the very poor evidence for dosing guidance for older  
214 antibiotics (when approval processes were less stringent and methods to determine PK/PD target  
215 attainment less developed), which may explain some of the variation in international  
216 recommendations. The Handbook therefore does not provide formal recommendations for  
217 dosage, frequency of use, route of administration and duration, but rather it provides general  
218 guidance on what would be considered appropriate dosing strategies and duration in most  
219 clinical cases.

### 220 Dosing

221 Wherever appropriate the same dose is given for each antibiotic for all infections to help local  
222 procurement and prescribing. In the Hospital Facility section, guidance is also given on when to  
223 consider **Step Down** from intravenous to oral antibiotics, encouraging the early discharge of  
224 patients from hospital when clinically appropriate.

225 Guidance on dose adjustments for abnormal kidney and liver function is not covered, and the  
226 summary of product characteristics should be consulted. Also detailed information on antibiotic  
227 administration, for example the use of continuous or prolonged infusion times of beta-lactams  
228 in multidrug-resistant infections is not covered as this is beyond the scope of this Handbook (14,  
229 15).

230 Even though this is not covered in this Handbook, higher doses or more frequent administration  
231 may be required in selected situations such as:

- 232 • Patients with very severe infections (including sepsis / septic shock)
- 233 • Patients with significant underlying disease (e.g. severe immunosuppression)
- 234 • Patients with increased weight

## 235 Dosing in Children

236 For children, weight-based dosing was generally used for oral treatments based on WHO ranges.  
237 For children above 30 kg of weight, adult dosing should be considered. The 2019 EML report on  
238 consensus guidance on paediatric dosing regimens was used as a reference but adapted by  
239 infection and severity of disease(16).

## 240 Treatment duration

241 For treatment **duration**, where there was an acceptable range for the duration of therapy, the  
242 lowest number of days supported by the review of guidelines and expert opinion is used.  
243 Strong evidence-based guidance on the most appropriate duration of treatment for many  
244 infections is limited. Therefore, duration is often individualized based on clinical response, on the  
245 success of surgical source control and, if available, changes in laboratory markers of infection.  
246 When an alternative diagnosis is established which does not require antibiotics, antibiotic  
247 treatment should be stopped. Shorter treatment where clinically appropriate is generally  
248 associated with less toxicity, a lower risk of selection and transmission of antibiotic resistance,  
249 with equivalent clinical outcomes.

## 250 Allergy to antibiotics

### 251 Key messages

1. True severe allergy to antibiotics is rare and allergies are often over-reported
2. Beta-lactam antibiotics (penicillins, cephalosporins) of the Access group are among the most effective and safe medicines for many infections, and they should only be avoided when there is a high suspicion of true allergy
3. Cephalosporins and carbapenems can be safely used in most cases of non-severe penicillin allergy
4. All patients who are labelled as allergic should be carefully evaluated and their antibiotic allergy risk level should be determined
5. Routine skin testing before prescribing a beta-lactam antibiotic (e.g. penicillin, amoxicillin) is not needed

252 The Handbook does not include alternative antibiotic options in cases of allergy to first-choice  
 253 antibiotics. The reason for this is that a true allergy to antibiotics (“true” meaning an allergic  
 254 reaction clinically confirmed or confirmed with an appropriate diagnostic test with a high degree  
 255 of probability) is rare and the Handbook focuses on the empiric treatment options for most  
 256 patients. Beta-lactam antibiotics of the Access group are among the most effective and safe  
 257 medicines for many infections. Avoiding the use of this class unless clearly justified because of  
 258 severe allergy, exposes the patient to the risk of receiving suboptimal treatment for their  
 259 infection, unless clearly justified because of severe allergy.

260 This chapter describes general principles of the mechanisms of allergies to antibiotics and the  
 261 implications for treatment. From the perspective of antibiotic stewardship, it is important to  
 262 avoid over-diagnosing antibiotic allergies. Such over-diagnosis often occurs with antibiotics in the  
 263 Access category, for example with penicillins and can lead to the subsequent prescription of  
 264 antibiotics in the Watch category, for example macrolides that may be less effective and less safe.  
 265 The detailed management of allergic reactions is beyond the scope of this chapter.

## 266 Definitions

- 267 • An **allergy** is a reaction of the immune system to a “foreign” substance.
- 268 • An **adverse reaction** is a response to a medicine which is harmful and unintended, and  
 269 which occurs at the doses normally used (17). Most adverse reactions can be classified as  
 270 type A or type B reactions (Table 1) depending on whether or not their effects are related  
 271 to the primary mechanism of action of the medicine (type A, i.e. if they are predictable  
 272 based on the mechanism of action or not) and also whether the immune system is  
 273 involved (type B, hypersensitivity reactions)(18).
- 274 • A **hypersensitivity reaction** is any adverse reaction that is immunologically mediated.  
 275 Hypersensitivity reactions are type B reactions and can be classified based on the timing  
 276 of onset of symptoms after taking the antibiotic as well as on the underlying mechanism,  
 277 i.e. immediate reactions (potentially IgE-mediated) or delayed reactions (potentially T  
 278 cell-mediated). Immediate reactions usually occur within 4 hours of taking the antibiotic  
 279 and delayed reactions usually after more than 24 hours.

280 *Table 1 Characteristics of adverse reactions to medicines*

Type A (or on-target) adverse reaction <sup>a</sup> : characteristics	Type B (or off-target) adverse reaction <sup>a</sup> : characteristics
<ul style="list-style-type: none"> <li>• Pharmacologically predictable</li> <li>• Dose / level dependent</li> <li>• Non-immune mediated</li> <li>• Less influenced by genetic factors</li> </ul> <p>Example: side-effects such as antibiotic-associated diarrhoea, acute tubular necrosis due to aminoglycosides</p>	<ul style="list-style-type: none"> <li>• Pharmacologically unpredictable</li> <li>• Non-dose dependent</li> <li>• Often immunologically mediated hypersensitivity reactions<sup>b</sup> (IgE or T-cell mediated)</li> </ul> <p>Examples: skin reactions, angioedema or anaphylaxis (immune-mediated)</p>

281 <sup>a</sup>On-target (or augmented) means the effects are related to the primary mechanism of action of the medicine. Off-  
 282 target means the effects are not related to the primary mechanism of action of the medicine.

283 <sup>b</sup>These reactions are immunologically mediated. They can be immediate (< 4 hours), intermediate (4–24 hours) or  
284 delayed (> 24 hours) reactions based on when symptoms appear after the administration of the antibiotic.

## 285 Epidemiology

286 Allergies to medicines are frequently self-reported, especially for antibiotics (19) with 5–15% of  
287 patients in high-income countries reporting a penicillin allergy (18). However, in most cases  
288 (> 95%), these patients do not have a true immunologically-mediated allergy and it is very likely  
289 that they can tolerate the antibiotic if re-exposed (20).

290 Severe allergies to antibiotics (e.g. anaphylactic shock) are rare; nonetheless, antibiotics are the  
291 most common cause of life-threatening immunologically-mediated reactions (18). Allergy to  
292 antibiotics is often over-diagnosed and patients are frequently labelled in health records as  
293 allergic to certain antibiotics (particularly to beta-lactams and sulfonamides) based on an  
294 unverified, vague, unknown or old (e.g. > 10 years) history of allergy reported by the patient,  
295 most often rashes. In most cases, these patients are unlikely to have a true allergy to the  
296 antibiotic and they will be able to safely tolerate it. Alternative explanations may exist for what  
297 the patients experienced previously: for example, (i) the antibiotic may have interacted with a  
298 concomitant infection (e.g. antibiotic–infection interactions can occur in case of viral infections,  
299 e.g. the rash observed in patients with infectious mononucleosis caused by EBV exposed to  
300 amoxicillin), or (ii) there may have been an “intolerance” / type A adverse reaction of the  
301 antibiotic manifested as, for example, nausea, vomiting, diarrhoea or headache; or (iii) a viral  
302 rash may have been confused with an allergic reaction. In addition, it is important to bear in mind  
303 that even true allergies are not always long-lasting and may decrease or disappear over time  
304 (> 10 years) (20).

305 This over-diagnosis of allergy has important consequences because incorrectly labelling a patient  
306 as allergic to an antibiotic often results in the unnecessary use of alternative antibiotics. These  
307 alternatives may be less effective for the infection being treated and may expose the patient to  
308 other (sometimes more toxic) side-effects.  
309 Unfortunately, most patients with a history of allergy to antibiotics are not evaluated to confirm  
310 the existence (or persistence) of the allergy.

## 311 Cross-reactivity

312 Antibiotic cross-reactivity refers to the development of an allergic reaction to different  
313 substances that have a closely related structure, for example, cross-reactivity can occur between  
314 penicillin and other beta-lactams (Table 2) (21), which may be due to an immunological reaction  
315 to the beta-lactam ring shared by these antibiotics.

316 *Table 2 Cross-reactivity to antibiotics(20)*

Penicillins with other beta-lactams	% of cross-reactivity <sup>a</sup>	Safety of use
Penicillins and cephalosporins(22)	< 2	Cephalosporins can be safely used in most cases of penicillin allergy and vice versa <sup>b</sup>
Penicillins and carbapenems	< 1	Carbapenems can be safely used in most cases of penicillin allergy and vice versa <sup>b</sup>
Penicillins and monobactams	0	Monobactams can be safely used in case of penicillin, cephalosporins (except ceftazidime) or carbapenem allergy <sup>c</sup>

317 <sup>a</sup>Percentage of patients allergic to penicillins that can develop an allergic reaction if exposed to a different beta-  
 318 lactam (cephalosporins, carbapenems or monobactams).

319 <sup>b</sup>In cases of previous life-threatening reactions caused by the exposure to penicillins or other beta-lactams, any use  
 320 of beta-lactams should be avoided, or an allergy specialist should be consulted.

321 <sup>c</sup>Monobactams can be safely used in cases of beta-lactam allergies except when there is an allergy to ceftazidime,  
 322 a third-generation cephalosporin, because of similarities in the side chains of aztreonam and ceftazidime.

## 323 Clinical presentation

324 Signs and symptoms of antibiotic allergy can vary in severity, ranging from mild reactions that  
 325 can be safely managed in an outpatient setting with or without need for symptomatic treatment  
 326 (e.g. antihistamines) to severe reactions that require hospitalization and even admission to  
 327 intensive care. Immediate and delayed reactions can be severe or non-severe.

328 Gastrointestinal symptoms and headache are not usually due to an allergic reaction but rather to  
 329 an intolerance of the antibiotic that can vary in intensity from person to person or to  
 330 *Clostridioides difficile* infection in case of diarrhoea.

331 Most cases of allergic reactions to antibiotics are not severe and often present as mild skin  
 332 reactions (most commonly mild rash, hives and itching) with no systemic symptoms.

333 Severe reactions are rare but can become life-threatening. They can be immediate or delayed  
 334 after administration of the antibiotic.

335 • Immediate severe reactions should be suspected if there is airway involvement,  
 336 bronchospasm, wheezing, angioedema (swelling of the tissue under the skin with or  
 337 without hives) or anaphylaxis. Usually, these reactions develop less than 4 hours after  
 338 taking the antibiotic.

339 • Delayed severe reactions should be suspected in patients who have taken an antibiotic  
 340 and present with severe skin symptoms (e.g. a painful blistering rash) and fever, joint pain  
 341 or signs of organ involvement (e.g. hepatitis). Thrombocytopenia (low platelet count),  
 342 haemolytic anaemia (destruction of red blood cells) and signs and symptoms of hepatitis  
 343 or nephritis in severe cases are suggestive of organ involvement. Usually, these reactions  
 344 develop more than 24 hours after taking the antibiotic.

## 345 Allergy evaluation

346 All patients who are labelled as allergic should be carefully evaluated, if possible, by an allergy  
 347 specialist, and their antibiotic allergy risk level should be determined. When evaluating a patient,

348 a full history of their allergy should be taken from the patient with details of past reactions,  
 349 including timing relative to antibiotic administration (immediate, intermediate, delayed or  
 350 unknown) and treatment received (if any). Patients can be classified in three risk categories for  
 351 allergy to antibiotics: low, moderate, and high risk; see Table 3 for examples. Detailed  
 352 documentation of all elements of the allergy is crucial. The patient should be educated about  
 353 what types of antibiotics to avoid (if any) and should be provided, if possible, with written  
 354 information such as an “allergy” passport.

355 *Table 3 Antibiotic allergy risk levels based on the patient’s allergy history*

Allergy risk category	Examples
Low risk	<ul style="list-style-type: none"> <li>• Patients with a history of isolated symptoms consistent with intolerance of an antibiotic, such as nausea, vomiting, diarrhoea or headache</li> <li>• Patients with a history of mild skin reactions</li> <li>• Patients with a history of unknown reactions a long time ago without features of immediate IgE-mediated reactions</li> <li>• Patients with a family history of antibiotic allergy</li> </ul>
Moderate risk	<ul style="list-style-type: none"> <li>• Patients with a history of urticaria or other pruritic (itchy) rashes</li> <li>• Patients with a history of reactions that look like IgE-mediated reactions but with no history of anaphylaxis</li> </ul>
High risk	<ul style="list-style-type: none"> <li>• Patients with a history of severe or life-threatening reaction (immediate or delayed) to an antibiotic (e.g. anaphylaxis)</li> <li>• Patients with a positive skin test</li> <li>• Patients with recurrent reactions or reactions to multiple antibiotics</li> </ul>

356 Source: Shenoy ES, et al (5).

357 Testing techniques for patients at low and moderate risk of antibiotic allergy include skin tests  
 358 (this applies only to IgE-mediated reactions) and direct challenge tests. In direct challenge tests,  
 359 a single therapeutic dose of the antibiotic is given orally to the patient under medical supervision  
 360 and with an anaphylaxis kit readily available in case of an anaphylactic reaction. The patient  
 361 should be kept under observation (usually at least 1-2 hours) to check for objective signs of an  
 362 allergic reaction. A detailed description of different types of tests available is beyond the scope  
 363 of this chapter. Routine skin testing before prescribing a beta-lactam antibiotic (e.g. penicillin,  
 364 amoxicillin) is not needed in children or adults and should not be recommended in guidelines as  
 365 this is an unnecessary barrier to the use of Access antibiotics.

366 In settings where allergy testing, specialist advice or treatment for anaphylaxis are not available,  
 367 then pragmatic decisions should be based on a detailed history of any reported possible penicillin  
 368 allergy. A rapid risk assessment needs to be done, including the medical importance of the  
 369 infection the patient is presenting with (i.e. benefit-risk assessment in that patient and also  
 370 whether an antibiotic is really needed) and the availability of alternative antibiotics with similar  
 371 effectiveness. Please see the relevant infection chapters and symptomatic non-antibiotic  
 372 treatment of minor infections within chapters.

373 Patients with a definite history of immediate collapse, breathing difficulties or severe facial  
374 swelling within a few minutes to 1–2 hours of taking a penicillin class of antibiotic are likely to  
375 have had a true anaphylactic reaction. If any alternative antibiotics are available, they should be  
376 preferred. Patients who have only had gastrointestinal symptoms or a rash appearing a few days  
377 after receiving an antibiotic of the penicillin group and who have shown no signs of becoming  
378 seriously unwell are generally less likely to develop severe anaphylaxis if they receive such  
379 antibiotics again in the future. Therefore, if one of these antibiotics is the most appropriate and  
380 available treatment option, these patients can be given it and advised to stop it if they develop a  
381 new skin rash, especially if the onset is rapid, the rash is raised and itchy and/or accompanying  
382 symptoms are present (e.g. shortness of breath).

DRAFT

# PRIMARY HEALTH CARE

DRAFT

# Bronchitis

## Key messages

1. **Antibiotics are not needed** for most cases
2. Acute bronchitis usually presents as a persistent cough, with or without mild fever
3. Virtually all cases are viral and self-limiting; patients should be informed that cough can last several weeks
4. Yellow/green colour of the sputum does not indicate bacterial infection and need for antibiotics
5. Clinical presentation can differentiate bronchitis from pneumonia

### Box 1 Other relevant WHO documents (please check regularly for updates)

- WHO 2013 pocket book of hospital care for children <https://apps.who.int/iris/handle/10665/81170> (23)
- COVID-19 pandemic: <https://www.who.int/emergencies/diseases/novel-coronavirus-2019>
- COVID-19 clinical management: living guidance, 25 January 2021. Geneva: World Health Organization <https://apps.who.int/iris/handle/10665/33882>
- Therapeutics and COVID-19: living guideline, 24 September 2021. <https://apps.who.int/iris/handle/10665/345356>
- Pneumococcal conjugate vaccines in infants and children under 5 years of age: WHO position paper – February 2019. Weekly Epidemiological Record, 94 (08), 85 - 103. Geneva: World Health Organization <https://apps.who.int/iris/handle/10665/310970>
- Haemophilus influenzae type b (Hib) Vaccination Position Paper – July 2013: Introduction. Weekly Epidemiological Record, 88 (39), 413 - 426. Geneva: World Health Organization <https://apps.who.int/iris/handle/10665/243126>
- Vaccines against influenza WHO position paper – November 2012. Weekly Epidemiological Record, 87 (47), 461 - 476. Geneva: World Health Organization <https://apps.who.int/iris/handle/10665/241993>

## Definition

Acute bronchitis is a self-limiting inflammation of the trachea and bronchi characterized by persistent cough, with or without fever usually caused by a viral infection(24).

## Pathophysiology

Acute bronchitis is caused by the tissue damage of the bronchial wall and inflammatory response triggered by the proliferation of microorganisms in the affected bronchi.

## Epidemiology

Acute bronchitis is a very common condition that can affect people of all ages, mostly during the seasons when respiratory viruses are common. Smoking and exposure to air pollution are risk

13 factors. Acute bronchitis is one of the most common reasons for consultations in the primary  
 14 health care setting and it is associated with frequent unnecessary use of antibiotics both in  
 15 children and adults(25-27).

## 16 Microbiology epidemiology

17 A causative pathogen is not identified in most cases of acute bronchitis. Most cases of acute  
 18 bronchitis are of viral origin (Table 1).

19 *Table 1 Pathogens most frequently associated with acute bronchitis (in descending order of*  
 20 *frequency)*

<b>Respiratory viruses</b>
Rhinovirus
Influenza virus (A and B)
Parainfluenza virus
Coronavirus (including SARS-CoV-2)
Respiratory syncytial virus (RSV)
Metapneumovirus
Adenovirus

21 Note: nearly all cases of acute bronchitis have a viral origin. Only in a very small proportion of cases, are “atypical”  
 22 pathogens (*Mycoplasma pneumoniae*, *Chlamydia pneumoniae*) involved. “Atypical” bacteria are intracellular and  
 23 are colourless with Gram staining. They also have intrinsic resistance to beta-lactams either because they lack a  
 24 cell wall (*Mycoplasma*) and / or are intracellular pathogens (*Chlamydia*).

## 25 Clinical presentation

26 Well-established clinical features of acute bronchitis include acute onset (less than 2 weeks) of  
 27 cough lasting > 5 days with or without sputum production (of note yellow/green sputum does  
 28 not indicate a bacterial infection). Bronchitis is generally a mild condition with no tachycardia (i.e.  
 29 no increased heart rate) or tachypnoea (i.e. no increased respiratory rate) and in most cases of  
 30 acute bronchitis there is no fever. Cough usually persists for 10-20 days (around one to three  
 31 weeks) but it can last longer.

32 Because the predominant symptoms are cough with or without fever, these symptoms can  
 33 overlap with the clinical picture of pneumonia. As a result, patients can be incorrectly diagnosed  
 34 as having pneumonia in the initial assessment and are often therefore inappropriately treated  
 35 with antibiotics. This misdiagnosis can be avoided with careful patient assessment to clearly  
 36 differentiate the two infections.

37 Patients with pneumonia are usually:

- 38 • clinically unwell and with systemic signs of infection (e.g. fever, increased heart rate,  
39 increased respiratory rate, focal chest signs)
- 40 • short of breath
- 41 • have cough with sputum production

42 Please refer to the chapter on community-acquired pneumonia for the typical clinical  
43 presentation of patients with pneumonia.

44 In patients with pre-existing chronic obstructive pulmonary diseases (COPD), please refer to the  
45 chapter on this condition.

## 46 Laboratory tests

### 47 I. Patient microbiology tests

48 No microbiology test is usually required.

49 During the influenza season or in case of outbreaks, a nasopharyngeal swab to test for influenza  
50 could be considered. Local policies should be followed as to whether during the COVID-19  
51 pandemic a nasopharyngeal swab or other sample (e.g. pharyngeal swab or saliva) for SARS-CoV-  
52 2 (nucleic acid amplification test or rapid antigen test) should be obtained. See the WHO  
53 Guidelines for the management of patients with suspected SARS-CoV-2 infection(28).

### 54 II. Other tests

55 In the great majority of cases of bronchitis, laboratory tests are not needed.

56 In uncertain cases some experts advocate the use of biomarkers of infection (C-reactive protein,  
57 procalcitonin) to differentiate viral bronchitis from bacterial pneumonia but these add costs and  
58 can also result in inappropriate prescribing due to the limited sensitivity and specificity of these  
59 tests.

### 60 III. Using microbiology surveillance data

61 As antibiotics are not recommended no routine microbiology surveillance is required.

62 Surveillance of circulating respiratory viruses can be useful to predict and follow epidemics and  
63 outbreaks (e.g. SARS-CoV-2, influenza virus, respiratory syncytial virus).

## 64 Imaging

65 Imaging is usually not needed.

## 66 “No antibiotic care”

67 Patients or parents should be informed about the natural course of acute bronchitis. It should be  
 68 explained that the cough can persist for several weeks, often at night, that the great majority of  
 69 cases are self-limiting (and of viral origin) and there is no benefit from a course of antibiotic  
 70 treatment. For symptomatic care for cold or mild influenza symptoms refer to Table 2. There is  
 71 no clear evidence to support the usefulness of bronchodilators (in case of wheezing), or mucolytic  
 72 or antitussive agents, but their use could be considered based on local practices and patient  
 73 preferences.

74 *Table 2 Medicines to consider for symptomatic treatment of acute bronchitis*

Molecule	Formulation	Dose and frequency
Ibuprofen <sup>a</sup>	Oral liquid: 200 mg/5 mL Tablet: 200 mg; 400 mg; 600 mg	<b>Adults:</b> 200–400 mg given every 6 to 8 hours (maximum dose of 2.4 g a day) <b>Children:</b> <ul style="list-style-type: none"> <li>• Pain control / Antipyretic treatment: 5–10 mg/kg given every 6 to 8 hours</li> </ul> 6–<10 kg: 50 mg given every 8 hours 10–<15 kg: 100 mg given every 8 hours 15–<20 kg: 150 mg given every 8 hours 20–<30 kg: 200 mg given every 8 hours ≥30 kg: Use adult dose
Paracetamol (acetaminophen) <sup>b</sup>	Oral liquid: 120 mg/5 mL; 125 mg/5 mL Suppository: 100 mg Tablet: 100 mg to 500 mg	<b>Adults:</b> 500 mg–1 g given every 4 to 6 hours (maximum dose of 4 g a day) <sup>c</sup> <b>Children:</b> <ul style="list-style-type: none"> <li>• Pain control/ Antipyretic treatment: 10–15 mg/kg given every 6 hours</li> </ul> 3–<6 Kg: 60 mg given every 6 hours 6–<10 kg: 100 mg given every 6 hours 10–<15 kg: 150 mg given every 6 hours 15–<20 kg: 200 mg given every 6 hours 20–<30 kg: 300 mg given every 6 hours ≥30 kg: Use adult dose

75 <sup>a</sup>Not for children < 3 months.76 <sup>b</sup>Not recommended for use as an anti-inflammatory as it has not been proven to have such an effect.77 <sup>c</sup>In patients with hepatic impairment or cirrhosis, maximum daily dose should be 2 g.

## 78 Antibiotic treatment

79 Antibiotic treatment is **not recommended** for acute bronchitis and should be avoided. There is  
 80 no evidence of a meaningful clinical benefit of antibiotics and their use is not supported by the  
 81 available clinical evidence(29).

# 1 Acute otitis media

## 2 Key messages

1. **Antibiotics are not needed** for most cases
2. Symptomatic treatment alone (pain and fever control with close follow up) is appropriate in mild cases especially in children > 2 years
3. Antibiotic treatment could be considered in selected cases (severe symptoms, immunosuppression, bilateral otitis in children < 2 years)
4. Amoxicillin has good activity against *Streptococcus pneumoniae* (the most common bacterial pathogen)
5. Higher doses of amoxicillin are effective against most resistant strains

3

### *Box 1 Other relevant WHO documents (please check regularly for updates)*

- WHO 2013 pocket book of hospital care for children <https://apps.who.int/iris/handle/10665/81170> (23)
- Pneumococcal conjugate vaccines in infants and children under 5 years of age: WHO position paper – February 2019. Weekly Epidemiological Record, 94 (08), 85 - 103. Geneva: World Health Organization <https://apps.who.int/iris/handle/10665/310970>
- Haemophilus influenzae type b (Hib) Vaccination Position Paper – July 2013: Introduction. Weekly Epidemiological Record, 88 (39), 413 - 426. Geneva: World Health Organization <https://apps.who.int/iris/handle/10665/242126>
- Vaccines against influenza WHO position paper – November 2012. Weekly Epidemiological Record, 87 (47), 461 - 476. Geneva: World Health Organization <https://apps.who.int/iris/handle/10665/241993>

## 4 Definition

5 Acute otitis media is an infection of the middle ear that occurs mostly in infants and children  
6 under 5 years of age, typically as a complication of a viral upper respiratory tract infection.

## 7 Pathophysiology

8 Pathogens that infect the middle ear come from the nasopharynx through the Eustachian tube  
9 usually following a viral infection of the upper respiratory tract. Inflammation and oedema cause  
10 narrowing of the tube and accumulation of mucosal secretions which favours growth of  
11 pathogens in the middle ear. This sequence of events triggers the typical signs and symptoms of  
12 otitis media.

## 13 Epidemiology

14 Acute otitis media is very common in young children under 5 years of age with most experiencing  
 15 at least one episode before the age of 3 years. Acute otitis media can complicate upper  
 16 respiratory tract infections in up to a third of cases, especially in the first year of life(30). The  
 17 estimated global incidence of acute otitis media in 2017 was 317 million cases, for all ages and  
 18 both sexes combined(31). Children are more at risk of acute otitis media because their Eustachian  
 19 tubes are narrower than those of an adult, which results in impaired drainage of fluids away from  
 20 the middle ear. The incidence declines with age and adults are rarely affected. In countries where  
 21 vaccination programmes against pneumococcal infection have been implemented, the incidence  
 22 of acute otitis media among children has declined substantially(32, 33). In LMIC, acute otitis  
 23 media is still an important cause of hearing loss in children due to its progression into chronic  
 24 suppurative otitis media when untreated(34).

## 25 Microbiology epidemiology

26 Several bacterial and/or viral respiratory pathogens are associated with acute otitis media  
 27 (Table 1)(35). Most cases of otitis media are triggered by infections with respiratory viruses  
 28 (respiratory syncytial virus, rhinovirus and coronavirus), which can be complicated by  
 29 superinfection with bacteria.

30 *Table 1 Pathogens most frequently associated with acute otitis media (in descending order of*  
 31 *frequency)*

Respiratory viruses (most cases)	Bacteria (rarely)
Respiratory syncytial virus (RSV)	<i>Streptococcus pneumoniae</i>
Rhinovirus	<i>Haemophilus influenzae</i>
Coronavirus (including SARS-CoV-2)	<i>Moraxella catarrhalis</i>
Influenza virus (A and B)	<i>Streptococcus pyogenes</i> (group A <i>Streptococcus</i> )

## 32 Otitis media caused by possible antibiotic-resistant pathogens

33 Amoxicillin has good activity against most isolates of *Streptococcus pneumoniae*. Local patterns  
 34 of susceptibility and individual risk factors should be considered when evaluating the possibility  
 35 of an infection caused by isolates likely to be resistant to amoxicillin. Resistance is more likely in  
 36 the case of recent exposure to amoxicillin (less than 3 months) or recurrent episodes (more than  
 37 four episodes a year) of acute otitis media. Higher doses of amoxicillin are still active against most  
 38 resistant strains and remains the treatment of choice.

## 39 Clinical presentation

40 Typical signs and symptoms of acute otitis media include recent onset of ear pain (unilateral or  
 41 bilateral), fever ( $\geq 38.0^{\circ}$ ) and at times, ear discharge.

## 42 Laboratory tests

### 43 I. Patient microbiology tests

44 In uncomplicated cases, microbiological tests are usually not needed and cultures of pus from  
45 perforated ear drums should not be used to guide treatment.

### 46 II. Other tests

47 When acute otitis media is suspected clinically, blood tests are usually not needed (except in  
48 situations where complications such as mastoiditis are suspected).

### 49 III. Using microbiology surveillance data

50 There is no role for routine surveillance for resistant pathogens.

## 51 Otoscopy

52 Otoscopy is required for a definitive diagnosis of acute otitis media. However, otoscopy or health  
53 care personnel with otoscopy skills may not be available in all settings.

54 In settings where otoscopy is available, classic findings include bulging, inflamed/congested  
55 tympanic membrane that may be opaque and show decreased mobility.

56 Source: <https://bestpractice.bmj.com/topics/en-us/39>



## 58 Imaging

59 In uncomplicated cases, no imaging study is needed. If available, imaging (e.g. computer  
60 tomography scan) may be indicated only in situations where complications such as mastoiditis  
61 are suspected.

## 62 “No antibiotic care”

63 Most non-severe cases of acute otitis media can be managed symptomatically and do not require  
64 antibiotic treatment, especially in children older than 2 years of age.

65 Non-severe cases usually have mild symptoms, often pain in one ear, and mild fever (< 39.0 °C  
66 which improves with antipyretics). A watchful waiting approach with symptomatic management

67 (i.e. analgesics and antipyretics) is appropriate (Table 2). Watchful waiting involves careful  
 68 monitoring of the child by caregivers, with instructions to seek care in case of worsening of fever,  
 69 pain or persistence of the symptoms.

70 The great majority of cases usually resolve spontaneously over a few days with no need for  
 71 antibiotic treatment and the risk of complications (e.g. acute mastoiditis) is very low.  
 72 Reassessment could be considered if symptoms do not improve over 3 days.

73 *Table 2 Medicines to consider for pain control of acute otitis media*

Molecule	Formulation	Dose and frequency
Paracetamol (acetaminophen) <sup>a</sup>	Oral liquid: 120 mg/5 mL; 125 mg/5 mL Suppository: 100 mg Tablet: 100 mg to 500 mg	<b>Adults:</b> 500 mg–1 g given every 4 to 6 hours (maximum dose of 4 g a day) <sup>b</sup>  <b>Children:</b> <ul style="list-style-type: none"> <li>• Pain control/ Antipyretic treatment: 10–15 mg/kg given every 6 hours</li> </ul> 3–<6 kg: 60 mg given every 6 hours 6–<10 kg: 100 mg given every 6 hours 10–<15 kg: 150 mg given every 6 hours 15–<20 kg: 200 mg given every 6 hours 20–<30 kg: 300 mg given every 6 hours ≥30 kg: Use adult dose
Ibuprofen <sup>c</sup>	Oral liquid: 200 mg/5 mL Tablet: 200 mg; 400 mg; 600 mg	<b>Adults:</b> 200–400 mg given every 6 to 8 hours (maximum dose of 2.4 g a day)  <b>Children:</b> <ul style="list-style-type: none"> <li>• Pain control / Antipyretic treatment: 5–10 mg/kg given every 6 to 8 hours</li> </ul> 6–<10 kg: 50 mg given every 8 hours 10–<15 kg: 100 mg given every 8 hours 15–<20 kg: 150 mg given every 8 hours 20–<30 kg: 200 mg given every 8 hours ≥30 kg: Use adult dose

74 <sup>a</sup>Not recommended for use as an anti-inflammatory as it has not been proven to have such an effect.

75 <sup>b</sup>In patients with hepatic impairment or cirrhosis, maximum daily dose should be 2 g.

76 <sup>c</sup>Not for children < 3 months.

## 77 Antibiotic treatment

78 Antibiotic treatment should be considered in specific cases (see Table 3 for choice of  
 79 antibiotics):

- 80 • In cases with severe symptoms (e.g. systemically very unwell, severe ear pain, fever
- 81     ≥ 39.0 °C)
- 82 • In immunosuppressed children (because of the higher risk of complications)
- 83 • In cases with bilateral acute otitis media in children under 2 years

84 There is no clear consensus on offering antibiotic treatment in non-severe cases of recurrent  
 85 acute otitis media (i.e. three or more episodes in the previous 6 months or four or more episodes  
 86 in the previous year), in non-severe cases presenting with otorrhoea and in non-severe cases in  
 87 neonates.

88 *Table 3 Empiric antibiotic treatment for acute bacterial otitis media*

89 **Antibiotic treatment is not required in the great majority of cases**  
 90 **(see the "Antibiotic treatment" section above for when antibiotics may be indicated)**

	Adults	Children	Total treatment duration(36-38)
<b>First choice</b>	<b>Amoxicillin</b> (oral): 500 mg given every 8 hours	<b>Amoxicillin</b> (oral) 40-50 mg/kg/dose given every 12 hours  Oral weight bands: 3-<6 kg: 125 mg given every 12 hours 6 - <10 kg: 250 mg given every 12 hours 10 - <15 kg: 500 mg given every 12 hours 15-<20 kg: 750mg given every 12 hours 20-<30 kg: 1000 mg given every 12 hours ≥ 30 kg : Use adult dose	5 days
<b>Second choice</b>	<b>Amoxicillin+clavulanic acid</b> (oral): 500 mg + 125 mg given every 8 hours	<b>Amoxicillin+clavulanic acid<sup>a</sup></b> (oral) 40-50 mg/kg/dose of amoxicillin component, given every 12 hours OR 30 mg/kg/dose given every 8 hours  Oral weight bands: 3-<6 kg: 250 mg of amoxicillin/dose given every 12 hours 6-<10 kg: 375 mg of amoxicillin/dose given every 12 hours 10-<15 kg: 500 mg of amoxicillin/dose given every 12 hours 15-<20 kg: 750 mg of amoxicillin/dose given every 12 hours 20-<30 kg: 1000 mg of amoxicillin/dose given every 12 hours ≥ 30 kg: Use adult dose	5 days

91 Notes: All dosages are for normal renal and hepatic function.

92 <sup>a</sup>Oral liquid must be refrigerated after reconstitution.

93 **ACCESS** antibiotics are indicated in green, **WATCH** antibiotics in yellow and **RESERVE** antibiotics in red.

## 94 Prevention

95 Prevention of otitis media is like prevention of upper respiratory tract infections. All strategies  
 96 (e.g. hand hygiene) that help prevent upper respiratory tract infections can be useful in  
 97 preventing otitis media including vaccination against *Streptococcus pneumoniae* and

98 *Haemophilus influenzae* type b for all children(39, 40). For countries considering vaccination  
99 programmes for influenza, vaccination of high-risk groups could also be considered (e.g. young  
100 children)(41).

DRAFT

# Pharyngitis

## Key messages

1. **Antibiotics are not needed** for most cases since most cases are self-limiting and of viral origin
2. Pharyngitis (sore throat) is a very common condition and one of the main causes of antibiotic overuse in primary health care
3. Antibiotic treatment only reduces sore throat pain for around one day
4. Cases caused by *Streptococcus pyogenes* (group A *Streptococcus*) can very rarely be complicated by complications such as rheumatic fever, rheumatic heart disease, and acute glomerulonephritis
5. The only clear indication for antibiotic treatment of pharyngitis is to reduce the probability of developing rheumatic fever in endemic settings

### Box 1 Other relevant WHO documents (please check regularly for updates)

- WHO 2013 pocket book of hospital care for children <https://apps.who.int/iris/handle/10665/81170> (23)
- Guideline for prevention and management of rheumatic fever and rheumatic heart disease - Call for consultation. <https://www.who.int/news-room/articles-detail/guideline-for-prevention-and-management-of-rheumatic-fever-and-rheumatic-heart-disease>
- Rheumatic fever and rheumatic heart disease: report of a WHO expert consultation, Geneva, 20 October - 1 November 2001. <https://apps.who.int/iris/handle/10665/42898>
- Diphtheria vaccine: WHO position paper – August 2017. Weekly Epidemiological Record , 92 (31), 417 - 435. <https://apps.who.int/iris/handle/10665/258683>

## Definition

Pharyngitis is commonly defined as an inflammation of the pharynx characterized by sore throat and painful swallowing.

## Pathophysiology

Viruses and bacteria responsible for pharyngitis gain access to the mucosal cells of the pharynx through different mechanisms and start replicating in these cells. Damage is caused to the cells where pathogens are replicating. Transmission occurs in most cases by hand contact with nasal discharge and respiratory secretions.

## 12 Epidemiology

13 Sore throat is one of the most common conditions in patients presenting to primary health care  
14 and remains a very frequent cause of inappropriate antibiotic prescribing. Up to 60% of patients  
15 with sore throat are given antibiotics in many high-income outpatient settings (42, 43).

16 Incidence and prevalence data on sore throat are unavailable for most LMIC settings. Most cases  
17 are self-limiting and of viral origin. Cases of sore throat caused by bacteria (mostly *Streptococcus*  
18 *pyogenes*) are rare and were responsible for about 10% of cases among patients of all ages with  
19 sore throat in a meta-analysis (3), but severe complications can occur (44). These are either due  
20 to invasion of the organism in the pharynx (e.g. suppurative complications such as quinsy) or to  
21 an abnormal immunological response (e.g. acute rheumatic fever) (45, 46). Suppurative  
22 complications occur in a very small number of cases, are difficult to predict and most can be  
23 readily treated (47, 48). For this reason, the prevention of suppurative complications should not  
24 be considered an indication for antibiotic treatment in sore throat.

25 Rheumatic fever is also a rare complication due to an autoimmune inflammatory reaction to  
26 untreated streptococcal pharyngitis; usually less than 3% of untreated cases of pharyngitis  
27 caused by *S. pyogenes* trigger rheumatic fever in settings where this condition is endemic (49,  
28 50). The incidence of rheumatic fever peaks between 5 and 15 years of age and is rare in people  
29 older than 30 years.

30 When rheumatic fever develops, it usually presents (70–75% of cases) as an acute febrile illness  
31 with joint manifestations (e.g. pain or tenderness) and carditis. Less frequently, it can present as  
32 a predominately neurological and/or behavioural disorder. Symptoms usually develop 2–3 weeks  
33 after the initial symptoms of pharyngitis are evident. Ultimately, rheumatic fever can result in  
34 damage to the heart valves (rheumatic heart disease). About 60% of people with rheumatic fever  
35 will develop rheumatic heart disease and the risk is two times higher for females than males.

36 Despite the lack of data from many countries, 30 million people worldwide are thought to be  
37 affected by rheumatic heart disease, with an estimated 320 000 deaths in 2015 (51).

38 Cases of rheumatic fever are concentrated in the WHO African, South-East Asian and Western  
39 Pacific regions; these regions account for about 84% of cases. With 27% of all cases of rheumatic  
40 fever in 2015 India has the highest burden worldwide (50).

## 41 Microbiology epidemiology

42 Most (> 80%) cases of pharyngitis are caused by a viral infection (respiratory viruses have been  
43 identified in 25–45% of cases; less frequently, the Epstein–Barr virus or other viruses of the  
44 herpesvirus family or SARS-CoV-2 are the cause). A minority of cases of pharyngitis are caused by  
45 bacteria, mainly *Streptococcus pyogenes* (group A *Streptococcus*). Other streptococci (group C  
46 and G) have also been implicated as causes of pharyngitis. Other infectious causes that need to  
47 be considered are acute HIV-infection and other sexually transmitted infections (syphilis,  
48 gonorrhoea), acute toxoplasmosis and diphtheria. Rarely, the cause of pharyngitis is non-  
49 infectious (e.g. exposure to pollution, allergens and smoking).

50 *Table 1 Pathogens most frequently associated with pharyngitis (in descending order of*  
 51 *frequency)*

Respiratory viruses (most cases)	Bacteria (rarely)
Respiratory syncytial virus (RSV)	<i>Streptococcus pyogenes</i> (group A <i>Streptococcus</i> )
Rhinovirus	Group C <i>Streptococcus</i>
Coronavirus (including SARS-CoV-2)	Group G <i>Streptococcus</i>
Influenza virus (A and B)	<i>Treponema pallidum</i>
<b>Other viruses (rarely)</b>	<i>Neisseria gonorrhoeae</i>
Epstein–Barr virus	
HIV	

53 **Pharyngitis caused by antibiotic-resistant pathogens**

54 *S. pyogenes* is still universally very susceptible to penicillin (resistance to penicillin has never been  
 55 reported, including no evidence of increasing minimal inhibitory concentrations). However,  
 56 resistance to macrolides is common in some settings.

57 **Clinical presentation**

58 Pharyngitis is characterized by sore throat and painful swallowing. Typical accompanying signs  
 59 and symptoms can vary depending on the etiology. If the cause is viral, symptoms match those  
 60 of a viral upper respiratory tract infection, and cough, headache and myalgia are likely to be  
 61 present. If the cause is bacterial, a more severe presentation is usually seen, with fever  
 62 (> 38.0 °C), tender cervical lymph nodes and pharyngeal exudates. Several clinical scoring  
 63 systems have been developed to identify patients with higher likelihood of pharyngitis being  
 64 caused by *Streptococcus pyogenes* (see below).

65 **Scoring symptoms of pharyngitis**

66 The specific cause of pharyngitis may be difficult to recognize based on symptoms alone. Scoring  
 67 systems can help differentiate a viral infection from one of bacterial origin. The rationale is to  
 68 help health care workers standardize the therapeutic approach and decide whether antibiotic  
 69 treatment could be given based on the most likely etiology. However, scoring systems have a low  
 70 specificity (i.e. high risk of incorrectly identifying patients with viral pharyngitis incorrectly as  
 71 having a *S. pyogenes* infection) and can lead to unnecessary antibiotic treatment. Moreover,  
 72 most have only been validated in high-income settings.

73 One of the most widely used systems in the adult population is the Centor clinical scoring system  
 74 However, even with a high score ≥ 4, the probability of an infection caused by *S. pyogenes* is only  
 75 50% (Table 1)(52).

76 In LMIC, other scores could be considered that have been specifically validated in these  
 77 settings(53).

78 *Table 1 Centor score for the clinical assessment of pharyngitis*

Relevant signs and symptoms	Points
Fever > 38 °C	1
No cough	1
Tender anterior lymphadenitis	1
Tonsillar exudates	1
<b>Total score</b>	<b>Likelihood of <i>S. pyogenes</i> infection (%)</b>
0	1–2.5
1	5–10
2	11–17
3	28–35
≥ 4	51–53
<b>Centor score 0 – 1 – 2</b>	<ul style="list-style-type: none"> <li>• <i>S. pyogenes</i> pharyngitis unlikely</li> <li>• Give symptomatic treatment only</li> </ul>
<b>Centor score 3 – 4 – 5</b>	<ul style="list-style-type: none"> <li>• Score suggestive of <i>S. pyogenes</i> pharyngitis</li> <li>• In countries with a low prevalence of rheumatic fever, antibiotic treatment can be withheld even in cases of likely <i>S. pyogenes</i> pharyngitis</li> <li>• In countries with medium to high prevalence of rheumatic fever (RF), antibiotic treatment is recommended as it reduces the likelihood of developing RF by around two thirds.</li> </ul>

79 **Laboratory tests**80 **I. Patient microbiology tests**

81 The choice of whether microbiological tests are helpful and which to consider is based on the  
 82 likelihood of *S. pyogenes* infection. In many settings no tests are routinely available. The  
 83 rationale for identifying cases caused by *S. pyogenes* is that those are the cases that may  
 84 benefit the most from antibiotic treatment in certain settings (mostly to prevent rheumatic  
 85 fever). In general, most guidelines prefer rapid antigen tests to cultures because they give  
 86 results more quickly. Table 2 summarizes the laboratory tests that could be considered to  
 87 diagnose pharyngitis.

88 *Table 2 Microbiology tests that could be considered if available for the diagnosis of pharyngitis as*  
 89 *indicated in the WHO SGL (54)*

Diagnostic test	Purpose of the test	Settings where the test should be available
Throat culture	First step in detection and identification of bacterial species for selection of appropriate antibiotic regimens	Health care facilities with clinical laboratories
Group A <i>Streptococcus</i> antigen <sup>a</sup>	To aid in the diagnosis of Group A streptococcal pharyngitis	Community settings and health facilities without laboratories <sup>a</sup>

(RDT)		
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90 RDT: rapid diagnostic test.

91 <sup>a</sup>Community and health settings without laboratories are settings such as health posts and centres, doctors’ offices,  
 92 outreach clinics, ambulatory care. These tests are also assumed to be available at health care facilities with  
 93 laboratories.

94 <sup>a</sup>Possible specimens include: throat swab.

- 95 • In the case of a low likelihood of *S. pyogenes* as the causative pathogen (this  
 96 corresponds to a Centor score of 0 to 2; see Table 1 for Centor scoring): rapid antigen  
 97 test or throat culture are usually not needed.
- 98 • In the case of a higher likelihood of *S. pyogenes* as the causative pathogen (i.e. Centor  
 99 score 3–4): rapid antigen test or throat culture could be considered, especially in  
 100 countries where rheumatic fever and rheumatic heart disease are important problems.  
 101 (Note: WHO recommends the use of a rapid antigen test as part of the strategy for  
 102 primary prevention of rheumatic fever through the effective treatment of streptococcal  
 103 pharyngitis(50)).

104 In children and adolescents with a Centor score of 3 or 4, a negative rapid antigen test could be  
 105 confirmed with a throat culture if available.

106 **II. Other tests**

107 When pharyngitis is suspected, blood tests are not usually needed unless a complication is  
 108 thought to be present.

109 **III. Using microbiology surveillance data**

110 As amoxicillin or penicillin are the recommended first line treatment and *S. pyogenes* is still  
 111 universally very susceptible to these antibiotics, there is no role for routine surveillance to  
 112 inform empiric guidance.

113 **Imaging**

114 When pharyngitis is thought to be the cause of clinical symptoms, imaging is usually not  
 115 required unless a complication is suspected.

116 **“No antibiotic care”**

117 Most cases of pharyngitis are of viral origin and do not benefit from antibiotics. In most cases,  
 118 including those of bacterial origin, symptoms resolve within a week. Symptomatic treatment with  
 119 oral analgesics and/or antipyretics, such as paracetamol and/or ibuprofen (Table 3) may be  
 120 helpful.

121 *Table 3 Medicines to consider for pain control of pharyngitis*

Molecule	Formulation	Dose and frequency
Paracetamol (acetaminophen) <sup>a</sup>	Oral liquid: 120 mg/5 mL; 125 mg/5 mL Suppository: 100 mg Tablet: 100 mg to 500 mg	<b>Adults:</b> 500 mg–1 g given every 4 to 6 hours (maximum dose of 4 g a day) <sup>b</sup>  <b>Children:</b> <ul style="list-style-type: none"> <li>• Pain control / Antipyretic treatment: 10–15 mg/kg given every 6 hours</li> </ul> 3–<6 Kg: 60 mg given every 6 hours 6–<10 kg: 100 mg given every 6 hours 10–<15 kg: 150 mg given every 6 hours 15–<20 kg: 200 mg given every 6 hours 20–<30 kg: 300 mg given every 6 hours ≥30 kg: Use adult dose
Ibuprofen <sup>c</sup>	Oral liquid: 200 mg/5 mL Tablet: 200 mg; 400 mg; 600 mg	<b>Adults:</b> 200–400 mg given every 6 to 8 hours (maximum dose of 2.4 g a day)  <b>Children:</b> <ul style="list-style-type: none"> <li>• Pain control / Antipyretic treatment: 5–10 mg/kg given every 6 to 8 hours</li> </ul> 6–<10 kg: 50 mg given every 8 hours 10–<15 kg: 100 mg given every 8 hours 15–<20 kg: 150 mg given every 8 hours 20–<30 kg: 200 mg given every 8 hours ≥30 kg: Use adult dose

122 <sup>a</sup>Not recommended for use as an anti-inflammatory as it has not been proven to have such an effect.123 <sup>b</sup>In patients with hepatic impairment or cirrhosis, maximum daily dose should be 2 g.124 <sup>c</sup>Not for children < 3 months.125 

## Antibiotic treatment

126 Most cases of pharyngitis are of viral origin and do not benefit from antibiotics.

127 When bacterial pharyngitis is suspected or proven, the decision to give antibiotic treatment is  
 128 usually based on the likelihood of *S. pyogenes* infection and on the local prevalence or patient  
 129 history of rheumatic fever. Options to consider are reported in Table 4. Second choice options  
 130 reported in Table 4 should only be considered in patients allergic to first-choice options. In the  
 131 case of clarithromycin, the prevalence of macrolide resistance in the setting where the patient  
 132 acquired the infection should be considered since macrolide resistance among *S. pyogenes* is high  
 133 in certain countries.

134 In general, patients will fall into one of the following two categories.

- 135 • Patients treated in settings with a low prevalence of rheumatic fever. **Antibiotic**  
 136 **treatment is not needed in most cases.** Antibiotics could be considered in some patients  
 137 who have a high likelihood of pharyngitis caused by *S. pyogenes* (i.e. Centor score 3–4).  
 138 However even with a Centor score of 3 or 4, antibiotic treatment is not necessary in most

- 139 cases. Antibiotic treatment reduces sore throat pain only by around one day (which can  
 140 alternatively be managed by regular analgesia).
- 141 • Antibiotic treatment could be discussed with patients or their caregivers on a case-by-  
 142 case basis, weighing the benefits (e.g. reduced transmission and slight reduction in  
 143 duration of symptoms) and risks (e.g. side-effects of antibiotics, effect on the intestinal  
 144 microbiota)(55). Relief of symptoms or prevention of suppurative complications is not  
 145 considered an indication for antibiotic treatment. The rationale is that most suppurative  
 146 complications are not severe and can be readily recognized and treated.
  - 147 • Patients treated in settings with a medium to high prevalence of rheumatic fever and  
 148 rheumatic heart disease or patients with a history of rheumatic fever or rheumatic heart  
 149 disease. Antibiotic treatment is usually given if the likelihood of *S. pyogenes* pharyngitis is  
 150 high (i.e. Centor score 3–4). The rationale is to prevent rheumatic fever or its recurrence.  
 151 However, after 21 years of age, the risk of rheumatic fever is usually lower.

152 *Table 4 Empiric antibiotic treatment in patients with a high likelihood of S. pyogenes pharyngitis*

153 **The only clear indication for antibiotic treatment is to reduce the probability of developing**  
 154 **rheumatic fever (RF) in endemic settings (however, after 21 years of age the risk of RF is**  
 155 **lower.**

	Adults	Children	Total treatment duration(56, 57)
<b>First choice</b>	Phenoxymethylpenicillin (oral): 500 mg (800,000 IU <sup>a</sup> ) given every 6 hours OR Amoxicillin (oral): 500 mg given every 8 hours	Phenoxymethylpenicillin (oral): 15 mg/kg/dose (24,000 IU/kg/dose <sup>a</sup> ) given every 6 hours OR Amoxicillin (oral) 40-50 mg/kg/dose given every 12 hours Oral weight bands: 3-<6 kg: 125 mg given every 12 hours 6 - <10 kg: 250 mg given every 12 hours 10 - <15 kg: 500 mg given every 12 hours 15-<20 kg: 750mg given every 12 hours 20-<30 kg: 1000 mg given every 12 hours ≥ 30 kg: Use adult dose	5 <sup>b</sup> or 10 <sup>c</sup> days depending on the local prevalence or previous history of rheumatic fever
<b>Second choice</b>	Clarithromycin <sup>d</sup> (oral): 500 mg given every 12 hours OR Cefalexin (oral): 500 mg given every 8 hours	Clarithromycin <sup>d</sup> (oral): 7.5 mg/kg/dose given every 12 hours OR Cefalexin (oral): 25 mg/kg/dose given every 12 hours  Oral weight bands: 3- <6 Kg: 125 mg given every 12 hours 6-<10 kg: 250 mg given every 12 hours 10-<15 kg: 375 mg given every 12 hours 15-<20 kg 500 mg given every 12 hours	5 days

		20-<30 kg: 625 mg given every 12 hours ≥ 30 kg: Use adult dose	
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156 IU: International units.

157 Notes: All dosages are for normal renal and hepatic function.

158 <sup>a</sup>Units of the potassium salt.

159 <sup>b</sup>In settings with a low prevalence of rheumatic fever or in patients with no history of rheumatic fever or rheumatic heart disease.

161 <sup>c</sup>In settings with a high prevalence of rheumatic fever or in patients with a history of rheumatic fever or rheumatic heart disease and who are aged between 3 and 21 years.

163 <sup>d</sup>In settings with a high prevalence of macrolide resistance among *S. pyogenes*, clarithromycin should not be recommended for the empiric treatment of *S. pyogenes* pharyngitis.

165 ACCESS antibiotics are highlighted in green, WATCH antibiotics in yellow and RESERVE antibiotics in red.

## 166 Prevention

### 167 *S. pyogenes* pharyngitis, rheumatic fever and rheumatic heart disease

168 Currently, there is no licensed vaccine to prevent pharyngitis caused by *S. pyogenes*. Hand  
169 hygiene is the best method to limit transmission to others. In countries where rheumatic fever is  
170 endemic, primary prevention of rheumatic fever relies on effective treatment of *S. pyogenes*  
171 pharyngitis.

172 In patients with a previous episode of rheumatic fever, long-term antibiotic prophylaxis (with  
173 benzathine benzylpenicillin every 3–4 weeks) is recommended in order to prevent subsequent  
174 episodes of *S. pyogenes* pharyngitis which would carry a higher risk of a new episode of rheumatic  
175 fever and ultimately rheumatic heart disease(50). The duration of prophylaxis should be decided  
176 on a case-by-case basis.

177 Of note, WHO is currently developing guidelines for the prevention and management of  
178 rheumatic fever and rheumatic heart disease  
179 (<https://www.who.int/news-room/articles-detail/guideline-for-prevention-and-management-of-rheumatic-fever-and-rheumatic-heart-disease>).

### 181 Other causes of bacterial pharyngitis: diphtheria

182 WHO recommends that all children worldwide be immunized against diphtheria and that people  
183 of any age who are unvaccinated or not fully vaccinated against diphtheria receive the doses  
184 necessary to complete their vaccination(58).

# 1 Sinusitis - acute

## 2 Key messages

1. **Antibiotics are not needed** in the great majority of cases
2. Most cases of sinusitis occur as a complication of a viral upper respiratory tract infection and are self-limited
3. Symptoms can last for a long time (up to 4 weeks)
4. Yellow / green colour nasal discharge alone is not a sign of bacterial infection and not an indication for antibiotic treatment
5. If antibiotic treatment is required, amoxicillin has good activity against *Streptococcus pneumoniae* (the most common bacterial cause of acute bacterial sinusitis)

3

### Box 1 Other relevant WHO documents (please check regularly for updates)

- Pneumococcal conjugate vaccines in infants and children under 5 years of age: WHO position paper – February 2019. Weekly Epidemiological Record, 94 (08), 85 - 103. <https://apps.who.int/iris/handle/10665/330970>
- Haemophilus influenzae type b (Hib) Vaccination Position Paper – July 2013: Introduction. Weekly Epidemiological Record, 88 (39), 413 - 426. <https://apps.who.int/iris/handle/10665/242126>
- Vaccines against influenza WHO position paper – November 2012. Weekly Epidemiological Record, 87 (47), 461 - 476. [(<https://apps.who.int/iris/handle/10665/241993>)]

## 4 Definition

5 Acute sinusitis is a symptomatic inflammation of the paranasal sinuses and nasal cavity. Most  
6 cases occur as a complication of a viral upper respiratory tract infection (e.g. a common cold  
7 caused by respiratory viruses such as rhinovirus) and symptoms can last up to 4 weeks. Acute  
8 sinusitis can also be associated with asthma, allergic rhinitis, smoking or exposure to smoke. This  
9 guidance applies mainly to maxillary sinusitis as this is the most common clinical condition.

## 10 Pathophysiology

11 Nasal congestion, usually triggered by an infection of the upper respiratory tract, can lead to  
12 obstruction of the sinus ostia with consequent hypoxia of the sinuses (mostly the maxillary and  
13 the anterior ethmoid sinuses are involved) and mucus retention. The inflammatory response that  
14 develops produces the signs and symptoms of acute sinusitis.

15 **Epidemiology**

16 Upper respiratory tract infections are a common reason for consultations in an outpatient  
 17 setting, both for children and adults. According to the 2017 Global Burden of Disease study, upper  
 18 respiratory tract infections are one of the top three causes of new disease globally for all ages  
 19 and both sexes combined – an estimated 17.1 billion cases are recorded a year(31). Acute  
 20 sinusitis accounts for 0.5% of all upper respiratory tract infections and is much more common in  
 21 adults than in children whose sinuses are not fully developed.

22 Most available data are from high-income settings and show that antibiotics are frequently  
 23 prescribed in cases of acute viral sinusitis(3, 27).

24 **Microbiology epidemiology**

25 Acute sinusitis is usually caused by respiratory viruses (Table 1); only a small percentage (usually  
 26 less than 2%) of cases are complicated by bacterial infection (Table 1).

27 *Table 1 Pathogens most frequently associated with acute sinusitis (in descending order of*  
 28 *frequency)*

Respiratory viruses (most cases) <sup>a</sup>	Bacteria (rarely)
Influenza virus (A and B)	<i>Streptococcus pneumoniae</i>
Respiratory syncytial virus	<i>Haemophilus influenzae</i>
Parainfluenza virus	Very rarely:
Rhinovirus	<i>Moraxella catarrhalis</i>
Coronavirus (including SARS-CoV-2)	<i>Streptococcus pyogenes</i> (group A <i>Streptococcus</i> )
	<i>Staphylococcus aureus</i>

29 <sup>a</sup>Note: about 98% of cases are caused by respiratory viruses.

30 **Sinusitis caused by antibiotic-resistant pathogens**

31 Amoxicillin has good clinical activity against the great majority of isolates of *Streptococcus*  
 32 *pneumoniae*. However, since the introduction of anti-pneumococcal vaccines, there is concern  
 33 about increasing incidence of acute sinusitis caused by *Haemophilus influenzae* and *Moraxella*  
 34 *catarrhalis* and an increased incidence of beta-lactamase production among these strains that  
 35 may result in amoxicillin resistance.

36 Local patterns of susceptibility and individual risk factors should be considered when evaluating  
 37 the possibility of facing an infection caused by isolates likely to be resistant to amoxicillin.

## 38 Clinical presentation

39 The diagnosis of sinusitis is made based on clinical criteria and the time pattern; it is important  
40 to consider that symptoms of acute bacterial sinusitis and acute viral sinusitis overlap  
41 considerably. Symptoms usually last 10–14 days and are self-limiting.

42 The main symptoms of acute sinusitis are purulent nasal drainage, nasal obstruction or  
43 congestion, unilateral dental or facial pain, facial fullness or pressure. Cough may also be present.

44 The location of pain in sinusitis depends on which sinuses are affected. For example, pain can be  
45 localized on the forehead (frontal sinuses), over cheekbones/teeth/upper jaw (maxillary sinuses)  
46 or behind the nose (ethmoid and sphenoid sinuses).

47 Acute bacterial sinusitis should be suspected in two situations:

- 48 • signs and symptoms persist without improvement for more than 10 days
- 49 • symptoms become significantly worse after an initial mild phase.

50 Yellow / green colour of nasal discharge alone is not a sign of bacterial infection and is not an  
51 indication for antibiotic treatment.

## 52 Laboratory tests

### 53 I. Patient microbiology tests

54 When sinusitis is suspected clinically, nasal cultures or nucleic acid tests for respiratory viruses  
55 are not usually needed.

### 56 II. Other tests

57 When sinusitis is suspected clinically, blood tests are usually not needed.

### 58 III. Using microbiology surveillance data

59 As the great majority of cases have no positive bacterial cultures, there is no role for routine  
60 surveillance to inform empiric guidance.

## 61 Imaging

62 When sinusitis is suspected clinically, imaging is not usually needed unless a complication or an  
63 alternative diagnosis is suspected.

## 64 “No antibiotic care”

65 The goal of treatment is to improve symptoms. Antibiotics have only minimal effect on the  
66 duration of symptoms in most cases and current evidence suggests that even without antibiotic  
67 treatment, most cases in healthy patients resolve within 1–2 weeks(59).

68 Most guidelines recommend using disease severity (i.e. duration and intensity of symptoms) to  
69 direct treatment.

70 In case of mild to moderate presentation (less than 10 days duration and improving symptoms),  
71 a watchful waiting approach with symptom relief and no antibiotic treatment is usually adequate.  
72 Symptoms should be managed with antipyretic and analgesic medications (Table 2). Nasal  
73 irrigation with a saline solution and topical intranasal glucocorticoids or decongestants may also  
74 be used to relieve symptoms, even though their effectiveness in relieving symptom is still  
75 uncertain(60).

76 The rationale of a watchful waiting approach is that in uncomplicated cases in adults, antibiotics  
77 (compared to no treatment) can shorten the duration of symptoms and improve the course of  
78 infection (e.g. resolution of purulent nasal discharge) only in a small percentage of patients.  
79 However, these potential benefits must be balanced against the risk of adverse events from  
80 antibiotics (e.g. gastrointestinal side-effects, allergic reaction, rash) and of increasing bacterial  
81 resistance(59).

82 *Table 2 Medicines to consider for symptomatic treatment of acute sinusitis*

Molecule	Formulation	Dose and frequency
Paracetamol (acetaminophen) <sup>a</sup>	Oral liquid: 120 mg/5 mL; 125 mg/5 mL Suppository: 100 mg Tablet: 100 mg to 500 mg	<b>Adults:</b> 500 mg–1 g every 4–6 hours (maximum dose of 4 g a day) <sup>b</sup> <b>Children:</b> <ul style="list-style-type: none"> <li>• Pain control/Antipyretic treatment: 10–15 mg/kg every 6 hours</li> </ul> 3-<6 Kg: 60 mg given every 6 hours 6-<10 kg: 100 mg given every 6 hours 10-<15 kg: 150 mg given every 6 hours 15-<20 kg: 200 mg given every 6 hours 20-<30 kg: 300 mg given every 6 hours ≥30 kg: Use adult dose
Ibuprofen <sup>c</sup>	Oral liquid: 200 mg/5 mL Tablet: 200 mg; 400 mg; 600 mg	<b>Adults:</b> 200–400 mg every 6–8 hours (maximum dose of 2.4 g a day) <b>Children:</b> <ul style="list-style-type: none"> <li>• Pain control / Antipyretic treatment: 5–10 mg/kg every 6–8 hours</li> </ul> 6-<10 kg: 50 mg given every 8 hours 10-<15 kg: 100 mg given every 8 hours 15-<20 kg: 150 mg given every 8 hours 20-<30 kg: 200 mg given every 8 hours ≥30 kg: Use adult dose

83 <sup>a</sup>Not recommended for use as an anti-inflammatory as it has not been proven to have such an effect.

84 <sup>b</sup>In patients with hepatic impairment or cirrhosis, maximum daily dose should be 2 g.

85 <sup>c</sup>Not for children < 3 months.

## 86 Antibiotic treatment

87 Antibiotic treatment is not required in the great majority of cases.

88 Antibiotic treatment could be considered in certain cases: severe onset of symptoms, patients  
 89 with underlying comorbid diseases or in those at increased risk of complications (see antibiotic  
 90 options in Table 3). Severe onset is defined as fever  $\geq 39.0^{\circ}\text{C}$  and purulent nasal discharge or  
 91 facial pain for at least 3–4 consecutive days(61). The decision to treat with antibiotics in patients  
 92 with chronic comorbid diseases should always be made on a case-by-case basis. Relevant  
 93 comorbid conditions to consider include, for example, chronic malignancies and  
 94 immunodeficiency.

95 Antibiotic treatment could also be considered in cases with “red flag” signs and symptoms  
 96 suggestive of a complicated infection, such as systemic toxicity, persistent fever  $\geq 39.0^{\circ}\text{C}$ ,  
 97 periorbital redness and swelling, severe headache and altered mental status.

98 *Table 3 Empiric antibiotic treatment for bacterial sinusitis*

99 **Antibiotic treatment is not required in the great majority of cases**  
 100 **(see the "Antibiotic treatment" section above for when antibiotics may be indicated)**

Adults	Children	Total treatment duration(62)
<p><b>Amoxicillin</b> (oral): 1 g given every 8 hours</p> <p>OR</p> <p><b>Amoxicillin+clavulanic acid</b> (oral): 500 mg + 125 mg given every 8 hours</p>	<p><b>Amoxicillin</b> (oral) 40-50 mg/kg/dose given every 12 hours</p> <p>Oral weight bands:                      3-&lt;6 kg: 125 mg given every 12 hours                      6-&lt;10 kg: 250 mg given every 12 hours                      10-&lt;15 kg: 500 mg given every 12 hours                      15-&lt;20 kg: 750mg given every 12 hours                      20-&lt;30 kg: 1000 mg given every 12 hours  <math>\geq 30</math> kg: Use adult dose</p> <p>OR</p> <p><b>Amoxicillin+clavulanic acid<sup>a</sup></b> (oral):                      40-50 mg/kg/dose of amoxicillin component, given every 12 hours                      OR 30 mg/kg/dose given every 8 hours</p> <p>Oral weight bands:                      3-&lt;6 kg: 250 mg of amoxicillin/dose given every 12 hours                      6-&lt;10 kg: 375 mg of amoxicillin/dose given every 12 hours                      10-&lt;15 kg: 500 mg of amoxicillin/dose given every 12 hours                      15-&lt;20 kg: 750 mg of amoxicillin/dose given every 12 hours                      20-&lt;30 kg: 1000 mg of amoxicillin/dose given every 12 hours  <math>\geq 30</math> kg: Use adult dose</p>	<p>5 days</p>

101 Notes: All dosages are for normal renal and hepatic function.

102 <sup>a</sup>Oral liquid must be refrigerated after reconstitution.

103 ACCESS antibiotics are indicated in green, WATCH antibiotics in yellow and RESERVE antibiotics in red.

## 104 Prevention

105 Prevention of sinusitis is based on the prevention of upper respiratory tract infections. All  
106 strategies (e.g. hand hygiene, influenza and pneumococcal vaccines) that help prevent upper  
107 respiratory tract infections could be useful in preventing sinusitis including vaccination against  
108 *Streptococcus pneumoniae* and *Haemophilus influenzae* type b for all children worldwide(39, 40).  
109 For countries considering vaccination programmes for influenza, vaccination of high-risk groups  
110 could be considered (e.g. children aged 6 months to 5 years)(41).

DRAFT

# 1 Dental infections

2 **Antibiotic prophylaxis prior to dental procedures is not addressed in this chapter.**

3 **Key messages**

1. **Antibiotics are not needed** usually for mild dental pain or infection, which can be treated with symptomatic care (or a dental procedure to remove the source of the inflammation or infection).
2. Antibiotics should not be used before a dental procedure to “calm an infection”, to “decrease inflammation”, to cure toothache or to prevent surgical site infections.
3. For people with a spreading severe dental infection, effective antibiotics are vital; sepsis and the spread of infection toward vital structures may occur rapidly. These conditions can be life-threatening.
4. Prevention of dental caries is key to maintain good dental health and includes reducing sugar consumption, regular toothbrushing and interdental cleaning and stopping tobacco smoking.

4

*Box 1 Other relevant WHO documents (please check regularly for updates)*

- Guideline: sugars intake for adults and children. <https://apps.who.int/iris/handle/10665/149782>
- Oral health. <https://www.who.int/news-room/fact-sheets/detail/oral-health>
- Ending childhood dental caries: WHO implementation manual <https://apps.who.int/iris/handle/10665/230643>

5

## 6 Definitions (presented in alphabetical order)

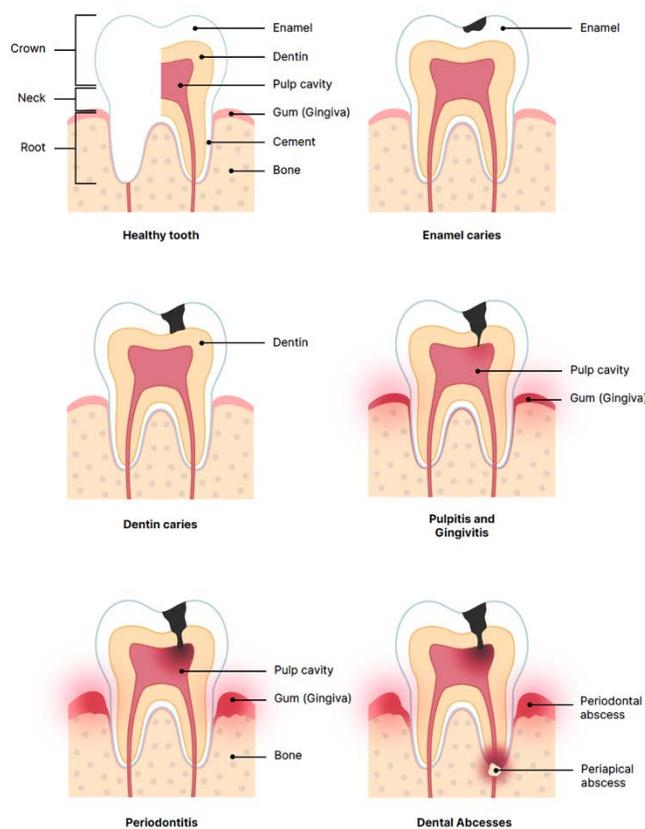


Figure 1. Dental infections

**Alveolar bone:** part of the jawbones which surrounds and supports the teeth.

**Apical periodontitis:** pain on chewing, percussion, or palpation of the tooth but without swelling caused by inflammation within the alveolar bone located around the apex of a tooth. This occurs as a consequence of caries and pulpitis and can progress to a dental abscess.

**Dental abscess:** localized collection of pus caused by a bacterial infection in the tooth, gingivae (gums) or alveolar bone supporting the tooth.

Abscesses can be categorized as:

1) apical abscess, when the infection at the apex of the dental root originates from within the dental pulp. This is the most common form of dental abscess and usually results from untreated dental caries.

2) periodontal abscess, when the infection originates from around the tooth

32 leading to the destruction of the gingival tissue or of the alveolar bone. This type of dental abscess  
 33 usually results from serious gum diseases.

34 3) abscess with spreading infection, when there are signs of systemic involvement,  
 35 including fever, malaise, cellulitis, sepsis, or spread through the fascial spaces to vital structures.

36 **Dental caries:** localized destruction of dental hard tissue (enamel or dentine) by acid-producing  
 37 plaque bacteria in the presence of dietary sugar. This process can be reversible in early lesions.  
 38 Caries can sometimes lead to the formation of cavities (i.e. small holes in the tooth).

39 **Dental pulp:** the inner part of the tooth that contains blood vessels and nerves.

40 **Dry socket (alveolar osteitis):** a recognised inflammatory complication of tooth extraction which  
 41 develops a few days after extraction and is extremely painful.

42 **Gingivae (gums):** soft tissue covering the alveolar bone.

43 **Noma (cancrum oris / gangrenous stomatitis):** an acute necrotizing disease that destroys the  
44 soft tissues and bones of the mouth and face as it progresses from necrotizing ulcerative  
45 gingivitis.

46 **Pericoronitis:** inflammation of the gingiva (gum) surrounding a partially erupted tooth, often a  
47 lower wisdom tooth.

48 **Periodontal disease:** a group of inflammatory diseases affecting the tissues that surround and  
49 support the teeth.

50 This includes:

- 51 1. **Gingivitis** when the gingivae (gums) are affected.
- 52 2. **Necrotizing ulcerative gingivitis**, a severe gum infection characterized by necrosis and  
53 ulcerations caused by a bacterial infection and often accompanied by severe pain and a  
54 strongly unpleasant smell.

55 **Periodontitis** when the alveolar bone supporting the teeth is affected. This condition  
56 results in loss of periodontal attachment (i.e. the abnormal formation of a space between  
57 the gum and the tooth) and can ultimately result in the destruction of the tissue that  
58 surrounds and supports the tooth (i.e. periodontium).

59 **Plaque:** biofilm of microbes, mainly bacteria, which sticks to the teeth and contributes to oral  
60 diseases such as caries and periodontal disease.

61 **Pulpitis:** inflammation of the dental pulp causing pain. This condition often occurs as a result of  
62 the progression of dental caries and can lead to apical periodontitis which can then evolve into a  
63 dental abscess.

## 64 Pathophysiology

65 Dental infections originate from dental plaque. Dental plaque is a microbe rich biofilm which  
66 sticks to surfaces within the mouth, including teeth, dentures and orthodontic appliances. In the  
67 presence of free sugars, especially sucrose from the diet, plaque bacteria can create an  
68 environment that favours tooth decay (dental caries). Acid produced by plaque bacteria in the  
69 presence of sugar causes this destruction, which is reversible only when confined to the outer  
70 enamel layer. Unless it is removed, the progression of caries is hard to stop once it enters the  
71 deeper parts of the tooth.

72 If dental caries progresses to reach the pulp, inflammatory pain (pulpitis) occurs which can  
73 eventually lead to pulpal necrosis and the tooth becoming non-vital. When this does occur, a  
74 tooth may initially be pain free or become tender to touch (apical periodontitis). Left to progress  
75 further, a localized accumulation of pus (periapical abscess) may form or an infection of the  
76 tooth, gums or alveolar bone supporting the tooth may spread to adjacent vital structures in the  
77 head and neck (e.g. cellulitis) or through the bloodstream (e.g. sepsis).

78 Accumulation of dental plaque around the gingival margin of teeth (at the gumline) and in  
79 periodontal pockets (below the gumline) can stimulate an inflammatory response. In some

80 people this can lead to immune-mediated destruction of the periodontal structures (e.g. gums or  
81 alveolar bone) which support the teeth. Progressive destruction of these periodontal tissues may  
82 lead to teeth becoming mobile and eventually to tooth loss.

83 Some protective mechanisms to reduce plaque accumulation include saliva and the cleansing  
84 action of the tongue. Regular removal of plaque through oral hygiene practices, such as  
85 toothbrushing and interdental cleaning, is essential to prevent and manage dental caries and  
86 periodontal disease.

## 87 Epidemiology

88 Despite being largely preventable, oral disease (including dental caries and periodontal disease)  
89 is common and an important public health problem(63).

90 Untreated dental caries impact almost half of the world's population (42% in 2015) making it the  
91 most prevalent of the oral conditions reported in the Global Burden of Disease Study(63).

92 The prevalence of untreated caries in permanent teeth was highest in young people aged 15–19  
93 years. Periodontal disease is less common than dental caries, with an overall yearly prevalence  
94 of around 7%. As periodontal disease may progress through life, it is highest in older people aged  
95 55–59 years(63)

96 Common risk factors for dental infections include diets high in free sugars and poor oral hygiene  
97 leading to dental caries. Poor oral hygiene, smoking or chewing tobacco, stress, malnutrition and  
98 being immunocompromised are risk factors for periodontal diseases, including acute necrotizing  
99 ulcerative gingivitis. Poor oral hygiene and severe malnutrition are also risk factors for noma, a  
100 necrotizing disease most commonly seen in children living in low-income countries and with a  
101 90% fatality rate if left untreated.

## 102 Microbiology epidemiology

103 The normal oral microbiota is richly diverse, including both aerobic and anaerobic bacteria,  
104 together with fungi (especially *Candida* spp.). Most dental infections are caused by conditions in  
105 the oral environment which favour the growth of pathogens. For example, an abundance of free  
106 sugars (such as sucrose) favours cariogenic bacteria (such as *Streptococcus mutans*) resulting in  
107 tooth decay. Reduced saliva flow makes patients with a dry mouth at increased risk of dental  
108 caries as there is less natural protection from the saliva. Furthermore, a recent course of  
109 antibiotics is a common cause for oral candidiasis (thrush). Whilst the precise composition of an  
110 individual's oral microbiota will differ between parts of the mouth and will change over time and  
111 between individuals, Table 1 shows a typical mix of the bacteria that are part of the oral  
112 microbiota in health and disease. The oral microbiota and associated disease can be significantly  
113 different depending on the precise location. For example, enamel caries is more often associated  
114 with *Streptococcus mutans* whereas *Actinomyces* spp. predominate in root caries.

115 *Table 1 Normal resident oral microbiota and pathogens most frequently associated with dental*  
 116 *infections (in descending order of frequency)*

"Normal" resident oral microbiota <sup>a</sup>	Bacteria associated with caries <sup>b</sup>	Bacteria associated with periodontal disease
<i>Streptococcus</i> spp. <i>Actinomyces</i> spp. <i>Prevotella</i> spp. <i>Veillonella</i> spp.	<i>Streptococcus</i> spp. (e.g. <i>Streptococcus mutans</i> ) <i>Lactobacillus</i> spp. <i>Actinomyces</i> spp.	Anaerobes (most cases): <i>Prevotella</i> spp. <i>Capnocytophaga</i> spp. <i>Aggregatibacter</i> spp. <i>Porphyromonas</i> spp.

117 <sup>a</sup>A richly diverse group of pathogens, including both aerobic bacteria and anaerobes.

118 <sup>b</sup>Mostly acidogenic bacteria

## 119 Clinical presentation (presented in alphabetical order)

120 Typical signs and symptoms of selected oral conditions are described below. Dental pain is often  
 121 due to inflammation rather than infection and careful diagnosis is required to ensure optimal  
 122 treatment is provided and antibiotic use minimised.

123 The severity of signs and symptoms may range from mild diseases (most cases) that can be safely  
 124 managed in an outpatient setting to severe infections of dental origin (including sepsis) that  
 125 require hospitalization and intravenous treatment. Please also refer to the chapter on sepsis if  
 126 suspected.

## 127 Dental abscess



128 An apical abscess (the most common type of dental abscess) is often, but not always, painful  
 129 and characterized by persistent localized pain that can radiate to the ear, jaw and neck.

131 Tooth tenderness (stimulated by chewing or food trapping) is common as well as swelling of the  
 132 soft tissues adjacent to the affected tooth.

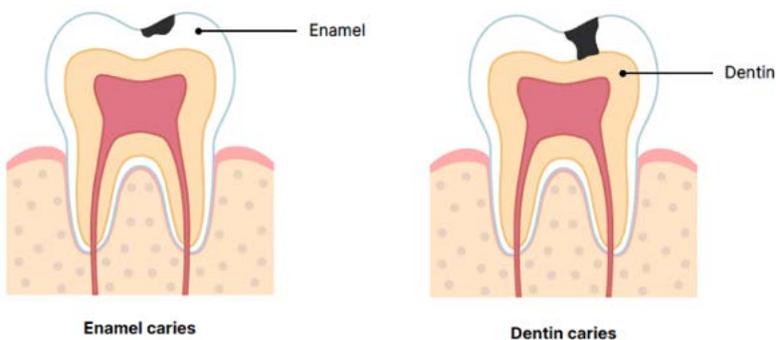
133 If this is left untreated, there is a high risk of spread to vital structures of the head and neck or  
 134 systemic spread of the infection that can then lead to sepsis. Signs that the infection has spread  
 135 include cellulitis around the eye or throat (causing difficulties swallowing or breathing e.g.  
 136 Ludwig's angina), fever (> 38.0 °C), malaise, tachycardia (increased heart rate) and  
 137 lymphadenopathy. This must be treated as a medical emergency.

138 A periodontal abscess (less common) is usually a localised accumulation of pus in the periodontal  
139 tissues (gums and alveolar bone supporting the tooth) which can be readily drained by  
140 professional cleaning of the periodontal pocket or by extraction of the tooth.

### 141 Dental caries progression to pulp disease

142 Dental caries (tooth decay) usually presents as cavities (holes in the tooth), although they are  
143 often hidden in the space between the teeth. Diagnosis relates to response of the tooth to  
144 cold/hot stimulus and radiographic imaging. Cavities and devitalised teeth may appear dark in  
145 colour compared to other teeth.

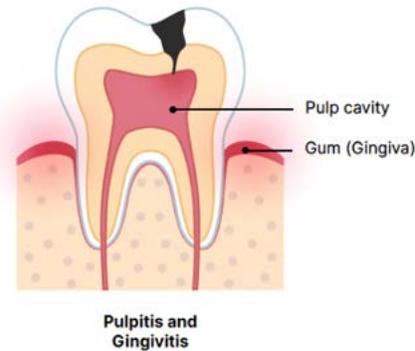
146 Caries develops slowly and can be pain free in the initial phase. However, if left untreated, the  
147 lesion can extend to the dental pulp causing pulpitis initially, then pulpal necrosis and ultimately  
148 dental abscess. Severe disease or necrosis of the dental pulp as a consequence of dental caries  
149 can be associated with systemic infections.



150  
151 Reversible pulpitis is characterized by acute pain or discomfort initially caused by drinking hot or  
152 cold beverages. It is possible to treat the problem at this stage with a simple restoration.

153 If caries progresses, irreversible pulpitis develops causing constant severe pain which  
154 characteristically keeps the patient awake at night. This pain may stop suddenly when  
155 progression of the disease leads to necrosis of the dental pulp.

156 If left untreated, apical periodontitis often develops, characterised by dull throbbing in the  
157 surrounding area (mouth and jaw) and soreness while biting. The pain may be eased by cold and  
158 made worse by hot (e.g. beverages). Progression of the condition may lead to an apical abscess,  
159 and this is the commonest cause of dental abscess.



160

### 161 Dry socket/Alveolar osteitis

162 Dry socket (alveolar osteitis) is a recognised inflammatory complication of tooth extraction.  
163 Severe pain develops a few days after the dental procedure, associated with slow healing of the  
164 socket and may be accompanied by an unpleasant taste. Appropriate pain control is necessary  
165 as pain may last for many days. Antibiotics are not appropriate for the prophylaxis or treatment  
166 of dry socket.

### 167 Noma

168 Noma is a necrotizing disease that destroys the mouth and face. It begins as necrotizing ulcerative  
169 gingivitis that progresses rapidly, destroying the soft tissues and bones of the mouth and further  
170 progressing to perforate the hard tissues and skin of the face. It mostly affects young children  
171 between the ages of 2 and 6 years suffering from severe malnutrition, living in extreme poverty  
172 and with weakened immune systems. Its prevalence is highest in sub-Saharan Africa. Noma is  
173 fatal for 90% of the children affected. If detected early, its progression can be rapidly halted,  
174 either through basic hygiene rules or with antibiotics. Early detection helps to prevent suffering,  
175 disability and death.

### 176 Pericoronitis

177 Pericoronitis is inflammation (and sometimes infection) of the gum around a partially erupted  
178 tooth, often a lower wisdom tooth. It usually occurs in late adolescence and early adult life and  
179 can be treated by professional cleaning, saline (hot salty water) mouthwash and, if necessary, by  
180 draining the infection. Antibiotics are not normally required, although if infection is present, it  
181 should be carefully monitored as it can spread rapidly causing difficulty opening the mouth,  
182 swallowing or breathing. Cellulitis of the neck (e.g. Ludwig's angina) is a medical emergency.

183 Periodontal disease



Periodontitis

184  
185 Periodontal disease is the term used to describe a range of conditions affecting the tissues that  
186 surround and support the teeth, including gingivitis and periodontitis. As these are generally  
187 immune-mediated diseases, it is usually inappropriate to use antibiotics for their treatment.

- 188 • **Gingivitis** is characterized by redness and swelling of the gums due to the build-up of food  
189 debris and microbial biofilm. It is usually painless, but bleeding when toothbrushing is  
190 common. Halitosis may be present. In its early stages, gingivitis is reversible with good  
191 oral hygiene. Severe forms of gingivitis are known but are rare.
- 192 • One of the most severe form is **necrotizing ulcerative gingivitis** which is characterized by  
193 severe pain and inflamed ulcerated gums that bleed easily, necrosis of the interdental  
194 papillae, foul breath and a bad taste in the mouth. It may also be accompanied by  
195 systemic symptoms, such as fever >38°C, malaise and lymphadenopathy.
- 196 • **Periodontitis** is an inflammatory disease characterized by the progressive destruction of  
197 the alveolar bone which supports the teeth. It is often a hidden disease as it is generally  
198 painless and progresses below the gums. Halitosis may be present. In case of periapical  
199 periodontitis, soreness while biting can occur due to a devitalised (dead) tooth.

200 The disease process of periodontitis occurs over time (usually years) and people often  
201 only become aware of it when their teeth start to move or fall out; a more aggressive  
202 destruction of the bone may sometimes be seen. Oral health professionals use special  
203 probes when carrying out periodontal screening to enable early diagnosis and treatment  
204 of periodontitis. Addressing risk factors, including effective cleaning of the periodontal  
205 tissues (under the gums), smoking cessation and good diabetic control are essential.  
206 Antibiotics are only appropriate for the treatment of aggressively destructive conditions;  
207 antibiotics are not appropriate for chronic periodontitis.

208 Laboratory tests

209 I. Patient microbiology tests

210 Routine microbiology tests are not required in most cases of dental infection but can be  
211 considered in severe cases requiring hospitalization, when culture and sensitivity testing can help  
212 in the selection of an appropriate antibiotic for example if cellulitis (e.g. Ludwig’s angina) is

213 spreading to vital structures or if sepsis is suspected. Please also refer to the chapter on sepsis if  
214 suspected.

## 215 II. Other tests

216 Most dental infections are bacterial, except for oral thrush (a fungal infection usually caused by  
217 *Candida* spp.) and cold sores (a viral infection) which are easily recognisable clinically.

218 Acute dental conditions are routinely diagnosed using point-of-care tests and investigations (see  
219 'Point-of-care tests and investigations' below).

220 Routine laboratory tests are not required in most cases of dental infections but may be  
221 considered in severe cases requiring hospitalization.

## 222 III. Using microbiology surveillance data

223 Routine microbiology surveillance of oral microbiota does not generally take place, so it is  
224 unavailable to inform clinical guidance.

## 225 Point-of-care tests and investigations

226 Establishing the source of the dental pain/infection is an important element of accurate  
227 diagnosis, which is essential to make appropriate treatment decisions. Sensitivity of the tooth to  
228 a cold stimulus indicates a vital pulp; depending on the intensity and duration of the stimulated  
229 pain this may indicate pulpitis. No response to cold indicates a non-vital pulp, which should be  
230 treated before the condition progresses to an infection. Tenderness to percussion (tapping the  
231 tooth) indicates that the pain originates in the supporting bone and may be due to pulpal necrosis  
232 or to an abscess.

## 233 Imaging

234 If a dental infection is suspected, imaging using dental radiographs (X-rays) should be undertaken  
235 wherever possible as part of the diagnosis. Radiographs are important for differentiating  
236 between the various causes of dental pain, including how far caries (decay) has progressed and  
237 where tenderness to percussion is associated with a radiolucency (i.e. black area on radiographic  
238 image) in the alveolar bone suggesting an abscess.

## 239 Treatment

240 Dental bacterial infections are rarely self-limiting and may rapidly become life threatening. Most  
241 dental infection and pain is amenable to treatment by removal of the cause and drainage of the  
242 infection using a dental procedure, such as extraction of the tooth. Removal of the cause of the  
243 infection using a dental procedure is usually the quickest and safest way of resolving the problem.  
244 This is essential to avoid the risk of rapidly spreading potentially life-threatening infection.  
245 Antibiotics are normally only required for the treatment of spreading infections.

## 246 “No antibiotic care”

247 Most dental infections are characterized by some level of dental pain and, whilst adequate pain  
248 control should always be offered, the prescription of medications alone is not usually appropriate  
249 (Table 2).

250 Caries, pulpal disease and dental abscesses are best treated with a dental procedure to remove  
251 the source of the problem; using painkillers alone is suboptimal as the condition can progress to  
252 a life-threatening spreading infection.

253 Dry socket (alveolar osteitis) is an extremely painful and common occurrence following dental  
254 extraction. This requires optimum pain management.

255 Ibuprofen and paracetamol are first choice painkillers for dental pain (Table 2). In the case of  
256 severe pain, ibuprofen and paracetamol may work better when taken in combination.

257 Caution should be exercised as the incidence of paracetamol (acetaminophen) overdose in  
258 relation to dental pain is relatively high. Opioid painkillers should be avoided as they offer no  
259 benefit for this sort of pain and are associated with the risk of substance misuse.

260 *Table 2 Medicines to control acute dental pain*

Molecule	Formulation	Dose and frequency
Ibuprofen <sup>a</sup>	Oral liquid: 200 mg/5 mL Tablet: 200 mg; 400 mg; 600 mg	<b>Adults:</b> 200–400 mg given every 6 to 8 hours (maximum dose of 2.4 g a day)  <b>Children:</b> <ul style="list-style-type: none"> <li>• Pain control / Antipyretic treatment: 5–10 mg/kg given every 6 to 8 hours</li> </ul> 6–<10 kg: 50 mg given every 8 hours 10–<15 kg: 100 mg given every 8 hours 15–<20 kg: 150 mg given every 8 hours 20–<30 kg: 200 mg given every 8 hours ≥30 kg: Use adult dose
Paracetamol (acetaminophen) <sup>b</sup>	Oral liquid: 120 mg/5 mL; 125 mg/5 mL Suppository: 100 mg Tablet: 100 mg to 500 mg	<b>Adults:</b> 500 mg–1 g given every 4 to 6 hours (maximum dose of 4 g a day) <sup>c</sup>  <b>Children:</b> <ul style="list-style-type: none"> <li>• Pain control/Antipyretic treatment: 10–15 mg/kg given every 6 hours</li> </ul> 3–<6 Kg: 60 mg given every 6 hours 6–<10 kg: 100 mg given every 6 hours 10–<15 kg: 150 mg given every 6 hours 15–<20 kg: 200 mg given every 6 hours 20–<30 kg: 300 mg given every 6 hours ≥30 kg: Use adult dose

261 <sup>a</sup>Not for children < 3 months, or for people with hypersensitivity to aspirin or any other NSAID (nonsteroidal anti-  
262 inflammatory drug), or for people with a history of gastro-intestinal bleeding or ulceration.

263 <sup>b</sup>Not recommended for use as an anti-inflammatory as it has not been proven to have such an effect. Warning:  
264 overdose is relatively common among people with severe dental pain.

265 <sup>c</sup>In patients with hepatic impairment or cirrhosis, maximum daily dose should be 2 g.

## 266 Oral antiseptics

267 Regular use of mouthwashes with an antiseptic product (e.g. chlorhexidine) is not required for  
 268 the control of dental infections. Such products could be considered in case of acute exacerbations  
 269 of periodontal disease. Of note, no formulation of oral antiseptics is currently included in the  
 270 EML/c and rinsing with saline (salty water) is usually adequate as well as being cheaper and more  
 271 readily available. Caution should be exercised with the use of chlorhexidine mouthwash in  
 272 patients following extractions or treatment of alveolar osteitis (dry socket following dental  
 273 extraction) as it has been associated with anaphylaxis.

## 274 Dental procedures

275 Dental procedures are usually the quickest and safest solutions for dental pain and infection.

276 Commonly performed dental procedures are briefly described in Table 3. Detailed information  
 277 on these procedures is beyond the scope of this chapter.

278 *Table 3 Commonly performed procedures for certain dental diseases*

Dental disease	Procedure
Abscess	1. Apical abscess Source control through: <ul style="list-style-type: none"> <li>• Tooth extraction;</li> <li>• Pulp extirpation (drainage of pus and removal of necrotic pulp tissue by drilling through the tooth into the pulp) followed by root canal treatment;</li> </ul> or <ul style="list-style-type: none"> <li>• Soft tissue incision and drainage followed by tooth extraction or root canal treatment.</li> </ul> 2. Periodontal abscess Source control through: <ul style="list-style-type: none"> <li>• Tooth extraction;</li> </ul> or <ul style="list-style-type: none"> <li>• Drainage of any pus collection by professional cleaning of the periodontal tissues.</li> </ul>
Apical periodontitis/ pulpal necrosis	Source control through: <ul style="list-style-type: none"> <li>• Tooth extraction;</li> </ul> or <ul style="list-style-type: none"> <li>• Pulp extirpation (drainage of pus and removal of necrotic pulp tissue by drilling through the tooth into the pulp) followed by root canal treatment</li> </ul>
Dental caries (decay) / reversible pulpitis	Removal of caries and restorative filling. Where access to dental care is not readily available or for people who are unable to accept a dental procedure (for example due to dental phobia), silver diamine fluoride may be appropriate to arrest progression of the caries.
Dry socket (alveolar osteitis)	Reassurance that this is a common yet painful outcome. Irrigation of the socket with saline.
Pericoronitis	Source control through: <ul style="list-style-type: none"> <li>• Tooth extraction;</li> </ul>

	or <ul style="list-style-type: none"> <li>• Drainage of any pus collection by irrigation under the operculum (flap of gum over the erupting tooth) with saline.</li> </ul>
Pulpitis (when irreversible)	Source control through: <ul style="list-style-type: none"> <li>• Tooth extraction;</li> </ul> or <ul style="list-style-type: none"> <li>• Pulp extirpation (removal of the inflamed pulp and treatment of the root canal)</li> </ul>
Necrotizing ulcerative gingivitis <sup>a</sup>	<ul style="list-style-type: none"> <li>• Regular tooth brushing with a fluoride-containing toothpaste and use of an interdental brush or dental floss to remove plaque</li> <li>• Professional cleaning around the teeth and periodontal tissues to remove the mineralized material known as scale, tartar or calculus</li> <li>• Smoking cessation advice</li> </ul>

279 <sup>a</sup>Acute necrotising ulcerative gingivitis can often be resolved by procedures alone – antibiotics are often not  
280 required.

## 281 Antibiotic treatment

282 Up to 10% of antibiotic prescribing in the outpatient setting can be for oral infections, of which  
283 up to 80% have been shown to be unnecessary or inappropriate(64). Efforts should be made to  
284 restrict the use of antibiotics only to situations when their use is strictly necessary(64, 65).

285 Antibiotic treatment is required only for few dental conditions.

286 Antibiotics are not appropriate for inflammatory conditions (including periodontitis, irreversible  
287 pulpitis and for dry socket treatment) because they do not prevent the development of severe  
288 complications and cannot replace local surgical or non-surgical treatment.

289 Antibiotics should not be used before a dental procedure to “calm an infection”, to “decrease  
290 inflammation”, to cure toothache (pain relief is best achieved by a dental procedure not a dental  
291 prescription) or to prevent surgical site infections.

292 Antibiotic treatment is essential in patients with severe, spreading dental infections. Severe cases  
293 include those with systemic signs of infection (e.g. facial swelling, inability to open the mouth,  
294 severe pain, fever > 38.0 °C, tachycardia). Even when necessary, antibiotics should only be used  
295 to complement surgical source control (e.g. drainage of the abscess or tooth extraction).  
296 Antibiotic use could also be considered in severely immunocompromised patients (including  
297 patients with uncontrolled diabetes) because they have a higher risk of complications. When  
298 antibiotic treatment is considered necessary, empiric use of amoxicillin or  
299 phenoxymethylpenicillin as indicated in Table 4 is considered appropriate. Using two antibiotics  
300 (e.g. amoxicillin and metronidazole) as adjunctive treatment is not necessary in the vast majority  
301 of cases.

302 The Handbook does not include alternative antibiotic options in cases of allergy to first-choice  
303 antibiotics which in the case of dental infections, where only penicillin options are recommended  
304 by this Handbook, may be considered problematic by some prescribers. However, even though  
305 allergies to antibiotics (particularly to beta-lactams) are frequently self-reported or indicated in  
306 health records, in most cases (> 95%), these patients do not have a true immunologically-

307 mediated allergy and it is very likely that they can safely tolerate the medicine if re-exposed to  
 308 it. Please refer to the chapter on allergies to antibiotics for more information about this aspect.

309 *Table 4 Empiric antibiotic treatment for selected cases of severe dental infections*

310 **Antibiotic treatment is not required for most dental conditions**  
 311 **(dental procedures - e.g. drainage of an abscess, tooth extraction - are the main treatment.**

Adults	Children	Total treatment duration
<p><b>Amoxicillin<sup>a</sup></b> (oral): 500 mg given every 8 hours                      OR  <b>Phenoxymethylpenicillin<sup>a</sup></b> (oral): 500 mg (800.000 IU<sup>b</sup>) given every 6 hours</p>	<p><b>Amoxicillin</b> (oral)<sup>a</sup>                      40-50 mg/kg/dose given every 12 hours</p> <p>Oral weight bands:                      3-&lt;6 kg: 125 mg given every 12 hours                      6-&lt;10 kg: 250 mg given every 12 hours                      10-&lt;15 kg: 500 mg given every 12 hours                      15-&lt;20 kg: 750mg given every 12 hours                      20-&lt;30 kg: 1000 mg given every 12 hours                      ≥ 30 kg: Use adult dose</p> <p>OR  <b>Phenoxymethylpenicillin</b> (oral)<sup>a</sup>:                      15 mg/kg/dose (24.000 IU/kg/dose<sup>b</sup>) given every 6 hours                      ≥ 30 kg: Use adult dose</p>	<p>3 days, if adequate source control is achieved;                      otherwise 5 days<sup>c</sup></p> <p>Patients should be reassessed before the end of treatment to check the resolution of the infection.</p>

312 IU: International units.

313 Notes: All dosages are for normal renal and hepatic function.

314 <sup>a</sup>For the treatment of infections of the dental soft tissues (e.g. pericoronitis or necrotizing ulcerative gingivitis),  
 315 metronidazole is usually used.

316 <sup>b</sup>Units of the potassium salt.

317 <sup>c</sup>If source control is not achieved or in cases where operative dental treatment is not available (often due to  
 318 unavailability of dentists in many low resource settings).

319 **ACCESS** antibiotics are indicated in green, **WATCH** antibiotics in yellow and **RESERVE** antibiotics in red.

## 320 Prevention

321 Dental caries does not occur without sugar; minimizing dietary free sugars is key to avoiding  
 322 dental pain and infections caused by dental caries. Further information on dietary sugar can be  
 323 found in the WHO guidance document on sugar intake for adults and children(66)

324 As the progression of dental caries and periodontal disease may continue slowly from childhood  
 325 to adulthood, the negative health effects of oral disease are cumulative. Even a small reduction  
 326 in the risk factors early in life confers significant benefit in later life.

327 Stopping tobacco use, whether smoked or smokeless, should also be promoted for the  
 328 prevention of periodontal disease and oral cancer.

329 Preventing the accumulation of dental plaque is important for preventing dental diseases such  
 330 as dental caries or periodontal disease.

331 Where people are unable to perform adequate oral hygiene themselves, regular professional  
332 dental cleaning may be necessary to maintain oral health.

333 Fluoride plays an important role in improving oral health by strengthening the tooth enamel  
334 and making it more resistant to dental caries. Further information on fluoride and oral health  
335 can be found on the WHO website (67). For prevention of dental caries in children, refer to the  
336 WHO guidance document(68).

DRAFT

# 1 Localized acute bacterial 2 lymphadenitis

3 This chapter does not include severe or generalized infections or infections caused by viral, fungal or  
4 parasitic pathogens

## 5 Key messages

1. **Antibiotics are not needed** for the great majority of cases of enlarged lymph nodes as they are caused by viral infections.
2. A watchful waiting approach is reasonable when the patient is not severely ill and bacterial lymphadenitis or a malignancy is not suspected, because the condition is usually self-limiting.
3. HIV infection and tuberculosis should always be considered in the differential diagnosis
4. If a bacterial lymphadenitis is suspected, empiric antibiotic treatment should cover *Staphylococcus aureus* and *Streptococcus pyogenes* with Access group antibiotics such as amoxicillin+clavulanic acid

## 6 Definition

7 Lymphadenitis is the inflammation and enlargement (> 1–2 cm) of one or several lymph nodes.  
8 It can be classified as “localized” (most cases) where only one lymph node region is affected or  
9 “generalized” based on how many lymph node regions are affected. Lymphadenitis can also be  
10 classified based on the lymph node region affected (e.g. cervical or axillary) and on the depth of  
11 the lymph node affected, either superficial or deep lymph nodes. Lymphadenitis has several  
12 infectious and non-infectious causes, including skin infections, cancer or lymphoproliferative  
13 disorders. The term lymphadenitis (i.e. enlargement of a lymph node with inflammatory signs)  
14 and lymphadenopathy (i.e. disease of a lymph node in which they are abnormal in size and/or  
15 consistency) are often used interchangeably, although in lymphadenitis the inflammatory  
16 component (redness, warmth, pain) is more pronounced. Infection in the lymph nodes can be  
17 caused by bacteria, viruses, fungi or parasites. This chapter focuses on localized acute bacterial  
18 lymphadenitis, although most enlarged lymph nodes are caused by viral infections.

## 19 Pathophysiology

20 Lymph nodes are an important part of the immune system which act as filters of lymph fluid.  
21 Lymphadenitis from an infectious cause is due to the immune system’s response to localized or  
22 generalized inflammation and to the pathogen spreading to one or more lymph node regions.  
23

## 24 Epidemiology

25 Lymphadenitis is a common condition worldwide and can occur at all ages (e.g. cervical  
26 lymphadenitis occurs very frequently in healthy children). Lymphadenitis is usually associated  
27 with benign conditions (e.g. most infectious causes); however, it can also be a sign of malignancy  
28 (e.g. lymphoma).

29 Since lymphadenitis has many different causes, the epidemiology of the disease will reflect the  
30 specific aetiology. For example, in Africa, tuberculous lymphadenitis (the most frequent cause of  
31 extrapulmonary tuberculosis) is still an important cause of persistent lymphadenitis and chronic  
32 lymphadenopathy may be a sign of HIV infection(69).

## 33 Microbiology epidemiology

34 Pathogens that can cause lymphadenitis are listed in Table 1.

35 *Table 1 Pathogens most frequently associated with acute lymphadenitis (in descending order of*  
36 *frequency)*

Viruses	Bacteria
<p><b>Most cases:</b></p> <p>Epstein–Barr virus Cytomegalovirus Respiratory viruses</p> <p><b>More rarely:</b> HIV</p>	<p><b>Most cases:</b></p> <p><i>Staphylococcus aureus</i> (including MRSA strains) <i>Streptococcus pyogenes</i> (group A <i>Streptococcus</i>)</p> <p><b>More rarely<sup>a</sup>:</b> Anaerobes <i>Bartonella henselae</i> (mostly following cat bites or scratches) <i>Chlamydia trachomatis</i> (serovars L<sub>1</sub>, L<sub>2</sub> and L<sub>3</sub> which cause lymphogranuloma venereum) <i>Corynebacterium diphtheriae</i> <i>Francisella tularensis</i> <i>Haemophilus ducreyi</i> <i>Neisseria gonorrhoeae</i> <i>Rickettsia</i> spp.</p>

37 MRSA: methicillin-resistant *Staphylococcus aureus*.

38 <sup>a</sup>Pathogens associated with chronic lymphadenitis such as mycobacteria are not included.

39 <sup>b</sup>This is not a full list but aims to show the variety of bacteria associated with localized lymphadenitis. The bacteria  
40 are listed in alphabetical order. Sexually transmitted diseases and zoonoses need to be considered in the differential  
41 diagnosis.

## 42 Clinical presentation

43 Lymphadenitis is a noticeable enlargement (> 1–2 cm) of a lymph node. Acute onset, unilateral  
44 involvement, fluctuance and fluid that drains from the lymph node to the skin suggest a bacterial  
45 cause. Tenderness and inflammation are frequently associated with infectious causes. Fever  
46 (> 38.0 °C) and other signs and symptoms of systemic disease may be present, accompanied by

47 cellulitis. Viral respiratory infections, infectious mononucleosis (caused by Epstein–Barr virus or  
48 cytomegalovirus), (acute) HIV infection and mycobacterial infections (mostly tuberculosis) always  
49 need to be considered when diagnosing the cause of acute lymphadenitis based on clinical history  
50 and findings. As the first step, it is important to identify the cause of the enlargement. Location  
51 of the enlarged lymph node and accompanying signs and symptoms of infection (e.g. skin lesion,  
52 pharyngitis, signs and symptoms of a sexually transmitted disease) can help establishing the  
53 diagnosis. History and physical examination usually help in the diagnosis and guide the  
54 investigation and treatment.

## 55 Laboratory tests

### 56 I. Patient microbiology tests

57 Routine microbiology testing is usually not needed because in most cases with an infectious  
58 cause, identifying the etiologic agent will not change the initial management. However, HIV  
59 infection and tuberculosis should be considered in the differential diagnosis and adequate  
60 testing should be done when these diseases are suspected.

### 61 II. Other tests

62 Routine laboratory testing is usually not needed. However, it may be considered in certain cases  
63 (e.g. persistent lymph node enlargement for more than 4 weeks or presence of warning signs  
64 such as important weight loss).

### 65 III. Using microbiology surveillance data

66 Routine surveillance is not helpful to inform empiric guidance.

## 67 Biopsy

68 An excisional biopsy of the lymph node could be considered if a malignancy is suspected. An  
69 alternative technique that can be used is fine needle aspiration (another type of biopsy technique  
70 where a very thin needle is inserted into the mass under examination for sampling of cells/tissue).

## 71 Imaging

72 Routine imaging is usually not needed to begin with. An ultrasound can be considered to confirm  
73 lymph node involvement, to measure the size of the enlargement and to detect the presence of  
74 an abscess. However, ultrasound cannot reliably rule out malignancies; in suspected cases an  
75 excisional biopsy should be performed.

## 76 Antibiotic treatment

77 In certain cases, a watchful waiting approach, without antibiotics is indicated when follow-up is  
78 feasible and the patient is not severely ill or a malignancy is not suspected. This approach is

79 reasonable because the condition is frequently self-limiting – for example, mild cervical  
 80 lymphadenitis is usually caused by a viral infection of the upper respiratory tract, especially in  
 81 children.

82 If symptoms are consistent with a bacterial infection (e.g. fever, and painful, tender and inflamed  
 83 lymph node), empiric treatment against *Staphylococcus aureus* and *Streptococcus pyogenes* is  
 84 indicated. Antibiotic options are given in Table 1.

85 *Table 1 Empiric antibiotic treatment for bacterial lymphadenitis<sup>a</sup>*

Adults	Children	Total treatment duration
<p><b>Amoxicillin+clavulanic acid</b> (oral): 500 mg + 125 mg given every 8 hours                      OR  <b>Cefalexin</b> (oral): 500 mg given every 8 hours                      OR  <b>Cloxacillin<sup>b</sup></b> or <b>flucloxacillin</b> (oral): 500 mg given every 8 hours</p>	<p><b>Amoxicillin+clavulanic acid</b> (IV/oral): 40–50 mg/kg per dose of amoxicillin component, every 12 hours                      OR 30 mg/kg/dose given every 8 hours</p> <p>Oral weight bands<sup>b</sup>:</p> <p>3-&lt;6 kg: 250 mg of amoxicillin/dose given every 12 hours                      6-&lt;10 kg: 375 mg of amoxicillin/dose given every 12 hours                      10-&lt;15 kg: 500 mg of amoxicillin/dose given every 12 hours                      15-&lt;20 kg: 750 mg of amoxicillin/dose given every 12 hours                      20-&lt;30 kg: 1000 mg of amoxicillin/dose given every 12 hours                      ≥ 30 kg: Use adult dose</p> <p>OR</p> <p><b>Cefalexin</b> (oral): 25 mg/kg/dose given every 12 hours</p> <p>Oral weight bands:</p> <p>3-&lt;6 Kg: 125 mg given every 12 hours                      6-&lt;10 kg: 250 mg given every 12 hours                      10-&lt;15 kg: 375 mg given every 12 hours                      15-&lt;20 kg: 500 mg given every 12 hours                      20-&lt;30 kg: 625 mg given every 12 hours                      ≥ 30 kg: Use adult dose</p> <p>OR</p> <p><b>Cloxacillin<sup>c</sup></b> or <b>flucloxacillin</b> (IV/oral):</p> <ul style="list-style-type: none"> <li>• Neonates: 25-50 mg/kg/dose given every 12 hours</li> <li>• Children: 25 mg/kg/dose given every 6 hours</li> </ul> <p>Oral weight bands:</p> <p>3-&lt;6 kg: 125 mg given every 6 hours                      6-&lt;10 kg: 250 mg given every 6 hours                      10-&lt;15 kg: 250 mg given every 6 hours                      15-&lt;20 kg: 500 mg given every 6 hours                      20-&lt;30 kg: 750 mg given every 6 hours</p>	<p>5 days</p>

	≥ 30 kg: Use adult dose	
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- 86 Notes: All dosages are for normal renal and hepatic function.  
87 <sup>a</sup>Patient history is key in order to adapt treatment if necessary (e.g. lymphadenitis in the context of cat scratch  
88 fever caused by *Bartonella henselae* would require a different antibiotic treatment).  
89 <sup>b</sup>Oral liquid must be refrigerated after reconstitution as clavulanic acid is rapidly metabolized in high ambient  
90 temperatures.  
91 <sup>c</sup>Cloxacillin (or dicloxacillin or flucloxacillin) has a narrower spectrum of antibacterial activity compared to  
92 amoxicillin+clavulanic acid and cefalexin while maintaining good efficacy in cases of mild skin infections. Therefore,  
93 from an antibiotic stewardship perspective, it would be the preferred option whenever possible. Cloxacillin,  
94 dicloxacillin and flucloxacillin are preferred for oral administration because of better bioavailability (i.e. the extent  
95 at which the medicine enters systemic circulation, thereby accessing the site of action).  
96 ACCESS antibiotics are indicated in green, WATCH antibiotics in yellow and RESERVE antibiotics in red.

DRAFT

# 1 Bacterial eye infections

2 (excluding trachoma – see separate chapter)

## 3 Key messages

- **Conjunctivitis** is mostly self-limiting and of viral origin. Allergies and toxic irritants should be included in the differential diagnosis. Topical antibiotics can be considered if a bacterial infection is suspected. STI should be included in the differential diagnosis in sexually active people and in newborns of infected mothers.
- **Keratitis** is mostly caused by bacteria and viruses (high-income countries) while fungi predominate in low- and middle-income countries. Risk factors include eye trauma and prolonged contact lens use (in this case *Acanthamoeba*, a parasite, or *Pseudomonas aeruginosa* should be considered as potential causes of the infection). Topical antibiotics are indicated as infectious keratitis is a potentially blinding condition.
- **Endophthalmitis** mostly occurs after a penetrating eye trauma (including eye surgery) or dissemination to the eye of a distant infection (e.g. endocarditis) and can be caused by bacteria or fungi. Treatment ideally requires both intravitreal and intravenous antibiotics as it is a potentially blinding condition.
- **Periorbital cellulitis** is usually a mild condition more common in children and can be treated with oral antibiotics active against Gram-positive pathogens from the skin (e.g. *Staphylococcus aureus*). It is very important to distinguish periorbital from orbital cellulitis (deeper more severe infection) because the management is different.

4

*Box 1 Other relevant WHO documents (please check regularly for updates)*

- WHO 2013 pocket book of hospital care for children [https://apps.who.int/iris/handle/10665/81170\(23\)](https://apps.who.int/iris/handle/10665/81170(23)).

## 5 Definition

6 Pathogens can infect most ocular structures and present with many combinations of signs and  
7 symptoms. It is important to determine which anatomical part is infected (Figure 1) because the  
8 most probable causative pathogens may differ, with implications for treatment. In addition, eye  
9 infections can be acquired in different ways (e.g. exogenous or endogenous, see the  
10 pathophysiology section for more information on transmission) and this also has implications for  
11 treatment and helps determine the most likely causative pathogens.

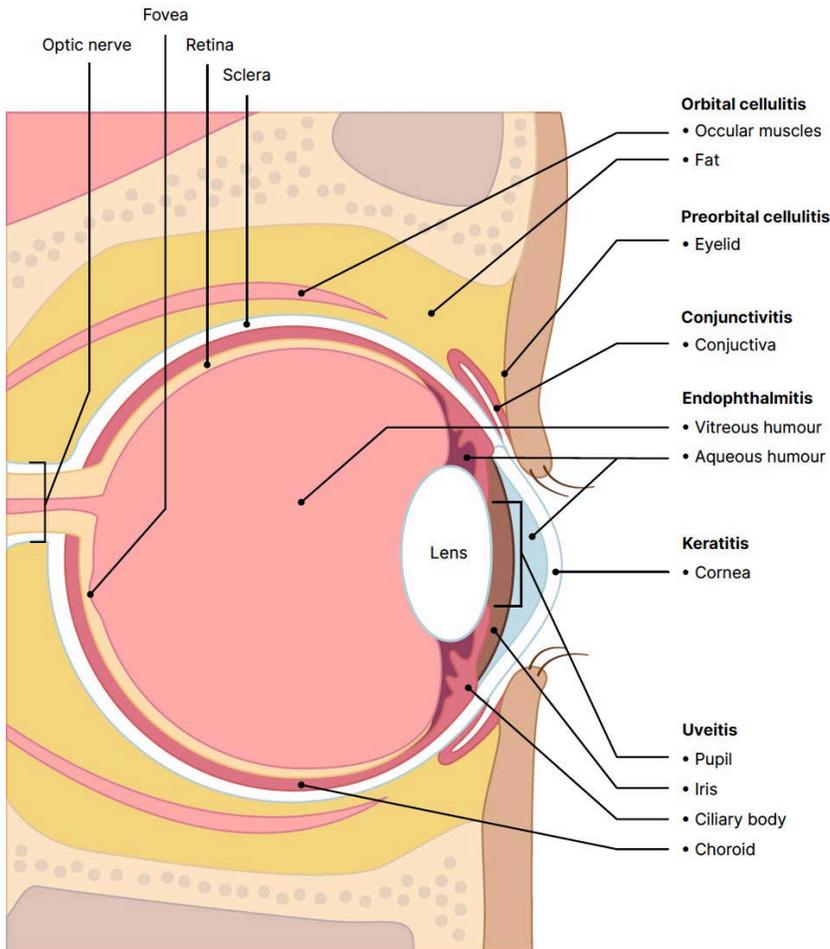
12 It should be noted that many conditions presented in this chapter could also be of non-infectious  
13 origin (e.g. systemic inflammatory diseases affecting other parts of the body or in case of

14 conjunctivitis allergies or toxic irritants), but non-infectious eye conditions are beyond the scope  
15 of this chapter.

16 **This chapter focuses on eye infections of bacterial origin presented in alphabetical order.**

17 Infections not addressed in the Handbook (because they are rare) include: canaliculitis (infection  
18 of the lacrimal canaliculi) and dacryocystitis (infection of the lacrimal sac).

19 *Figure 1 Eye anatomy and locations of common eye infections*



20

## 21 Pathophysiology

22 Eye infections can result either from external contamination through direct inoculation of the  
23 pathogen into the eye/s (exogenous transmission) or from dissemination of the pathogen  
24 through the bloodstream from a distant site of infection (endogenous transmission). Exogenous  
25 transmission can occur by contact with infected secretions (mostly by rubbing the eye/s with  
26 contaminated hands) or as a result of a penetrating eye injury; this includes eye surgery where  
27 bacteria from the flora could be “introduced”. The use of contact lenses and eye contact with  
28 water (e.g. during swimming) are also risk factors for exogenous transmission. In addition, certain

29 sexually transmitted infections (e.g. gonococcal and chlamydial infections) can be transmitted  
30 from infected mothers to their child during vaginal delivery. Endogenous transmission occurs  
31 when pathogens are spread through the bloodstream from other sites of infection (e.g. in case  
32 of endocarditis, urinary tract infections, abdominal abscesses, meningitis, indwelling catheters),  
33 mainly in high-risk patients (e.g. immunocompromised patients, people who inject drugs).  
34

DRAFT

# 35 Blepharitis

## 36 Definition

### TYPE OF EYE INFECTIONS

### ANATOMICAL LOCATION

<b>Blepharitis/Hordeolum</b>	<p>Infection of the eyelid margin. It can be anterior (less common than posterior blepharitis and characterized by inflammation at the base of the eyelashes) or posterior (more common type, it is characterized by inflammation of the inner portion of the eyelid at the level of the meibomian glands)</p> <p>Hordeolum is a common acute bacterial infection of one or more eyelid glands</p>
------------------------------	--

## 37 Epidemiology

38 Blepharitis is a chronic condition and most cases are not due to infections but to a dysfunction of  
 39 oil glands in the eyelids. In posterior blepharitis (the most common form), chronic infections may  
 40 also play a role. The bacteria that comprise the flora in posterior blepharitis are the same as those  
 41 found on the skin but present in greater numbers(70).

## 42 Microbiology epidemiology

43 *Table 1 Pathogens most frequently associated with blepharitis (in descending order of frequency)*

TYPE OF EYE INFECTION	MOST COMMON CAUSATIVE PATHOGENS
<b>Blepharitis (usually not of infectious origin)</b>	Bacteria: mostly <i>Staphylococcus aureus</i> and coagulase-negative Staphylococci Mites: <i>Demodex folliculorum</i> <sup>a</sup> , <i>Demodex brevis</i> <sup>b</sup>

44 <sup>a</sup>*Demodex folliculorum* has been identified in 30% of patients with chronic anterior blepharitis but is also found with  
 45 approximately the same prevalence in asymptomatic persons. However, it is clearly a contributing factor in some  
 46 patients as evidenced by the improvement seen in response to eradicated therapy.

47 <sup>b</sup>*Demodex brevis*, has been associated with posterior blepharitis.

## 48 Clinical presentation

49 Patients with blepharitis typically present with inflamed eyelids that are red, swollen and itchy  
 50 with crusts at the base of the eyelid and on the eyelashes mostly in the morning. Usually both  
 51 eyes are affected, and most cases are chronic.

52 Blepharitis is more common in adults than in children, but children can have dramatic episodes  
 53 of anterior and/or posterior blepharitis, often characterized by more conjunctival and corneal  
 54 findings(71, 72).

55 Blepharitis related to *Demodex* infestation characteristically presents with cylindrical dandruff or  
56 “sleeves” on the eyelashes(73). Patients with hordeolum usually present with a tender swelling  
57 of the eyelid/s with a lash at its apex.

## 58 Laboratory tests

### 59 I. Patient microbiology tests

60 Microbiology tests are usually not needed.

### 61 II. Other tests

62 Laboratory tests (other than microbiology) are usually not helpful.

### 63 III. Using microbiology surveillance data

64 Routine surveillance is not helpful to inform empiric guidance.

## 65 Imaging

66 Imaging is usually not needed.

## 67 Antibiotic treatment

68 Antibiotic treatment is usually not needed. Good eyelid hygiene is the most important treatment  
69 and cases usually resolve without further measures. Warm compresses 5 to 10 minutes twice to  
70 four times per day, lid massage and washing and use of preservative-free artificial tears four to  
71 eight times per day can also help.

72 Patients with severe or refractory symptoms may require additional therapies but this is beyond  
73 the scope of this chapter.

# 74 Conjunctivitis

## 75 Definition

### TYPE OF EYE INFECTIONS

### ANATOMICAL LOCATION

<b>Conjunctivitis</b>	Infection of the conjunctiva (i.e. the mucosa that covers the inside part of the eyelids and the outer surface of the eye - the sclera)
-----------------------	---

## 76 Epidemiology

77 Conjunctivitis is the most frequent eye infection, and most cases are of viral origin both in  
 78 children and in adults. Bacterial cases, although less common, can occur especially in children  
 79 (74). Non-infectious causes (mostly allergies but sometimes also toxic irritants) should always be  
 80 considered in the differential diagnosis(74). Most cases of conjunctivitis are exogenous, and  
 81 infection is mostly acquired by touching the eye with contaminated hands.

## 82 Microbiology epidemiology

83 *Table 2 Pathogens most frequently associated with conjunctivitis in descending order of*  
 84 *frequency)*

### TYPE OF EYE INFECTION

### MOST COMMON CAUSATIVE PATHOGENS

<b>Conjunctivitis(74)</b>	<p><b>Viruses:</b> most infectious cases are of viral origin, mostly adenovirus, rarely herpes simplex virus</p> <p><b>Bacteria(75):</b></p> <ul style="list-style-type: none"> <li>• In children: <i>Staphylococcus aureus</i>, <i>Streptococcus pneumoniae</i>, <i>Haemophilus influenzae</i>, <i>Moraxella catarrhalis</i>.</li> <li>• In adults: <i>Staphylococcus aureus</i></li> </ul> <p><b>Consider</b> <i>Chlamydia trachomatis</i> (serovars D-K) and <i>Neisseria gonorrhoeae</i> in the context of sexually transmitted infections or in neonates after vaginal delivery from infected mothers  <i>Chlamydia trachomatis</i> (serovars A-C) can cause trachoma. Trachoma is covered in a separate chapter</p>
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## 85 Clinical presentation

86 Patients with conjunctivitis (including cases of viral origin) usually present with a red, watery and  
 87 itchy eye. They often describe a feeling of “sand in the eye” with no pain (if there is pain, this  
 88 usually indicates corneal involvement) and have normal vision. In cases of bacterial infection, a  
 89 thick purulent discharge from the eye is usually present. Patients may refer to all discharge as

90 “pus”, however, in bacterial conjunctivitis the complaint of discharge predominates, while in viral  
91 and allergic conjunctivitis patients report a burning and gritty feeling or itching. In most cases,  
92 conjunctivitis is a mild self-limiting condition.

93 A severe form of conjunctivitis is hyperacute bacterial conjunctivitis which is mostly caused by  
94 *Neisseria gonorrhoeae*. It is characterized by severe purulent discharge and decreased vision.  
95 Usually, eyelid swelling, pain on palpation and preauricular adenopathy are present(74).

## 96 Laboratory tests

### 97 I. Patient microbiology tests

98 Usually no test is required unless *Neisseria gonorrhoeae* or *Chlamydia trachomatis* are  
99 suspected.

### 100 II. Other tests

101 Laboratory tests (other than microbiology) are usually not helpful.

### 102 III. Using surveillance microbiology data

103 Routine surveillance is not helpful to inform empiric guidance.

## 104 Imaging

105 Imaging is usually not needed.

## 106 Antibiotic treatment

107 Most cases of infectious conjunctivitis are self-limiting, of viral origin and resolve without  
108 treatment in 7-10 days. In patients with typical presentation of bacterial conjunctivitis (i.e. red  
109 eye with purulent discharge and normal vision) antibiotic treatment could be considered to  
110 shorten the duration of symptoms (76) based on the patient’s preferences. In these cases,  
111 antibiotic treatment is usually topical (eye drops or eye ointment) and prescribed empirically  
112 (Table 3) based on local availability. Systemic antibiotic treatment is only required in cases of  
113 systemic infections (e.g. conjunctivitis in the context of a sexually transmitted infection, Table 4).  
114 Steroid eye drops (alone or in combination with antibiotic drops) are not usually needed for the  
115 treatment of conjunctivitis; in fact, steroids might even make the condition worse if this is caused  
116 by herpes virus infection or the cornea is affected.

117 Urgent referral of the patient to an ophthalmologist, if available, should be considered when  
118 hyperacute bacterial conjunctivitis (mostly caused by *Neisseria gonorrhoeae*) is suspected  
119 because of the risk for rapid progression to corneal perforation.

120 *Table 3 Empiric antibiotic treatment for bacterial conjunctivitis*

Type of eye infection	Antibiotic treatment	Total treatment duration
Bacterial conjunctivitis (children and adults)	<b>Gentamicin</b> (eye drops): 0.3%, 1 drop in the affected eye given every 6 hours OR <b>Ofloxacin</b> (eye drops): 0.3% 1 drop in the affected eye given every 6 hours OR <b>Tetracycline</b> (eye ointment): 1% 1 cm in the affected eye given every 6 hours	5 days
Gonococcal conjunctivitis (adults, adolescents)	<b>Ceftriaxone</b> (IM) <sup>a</sup> : 250 mg AND <b>Azithromycin</b> (oral): 1 g	Single dose
Gonococcal ophthalmia neonatorum (i.e. gonococcal conjunctivitis of the newborn)	<b>Ceftriaxone</b> (IM) <sup>b</sup> : 50mg/kg	Single dose
Chlamydial ophthalmia neonatorum (i.e. chlamydial conjunctivitis of the newborn) <sup>c</sup>	<b>Azithromycin</b> (oral): 20 mg/kg given once a day  Topical therapy alone is not effective.	3 days
Ocular prophylaxis (topical treatment for the prevention of both gonococcal and chlamydial ophthalmia neonatorum) <sup>d</sup>	<b>Erythromycin</b> 0.5% eye ointment OR <b>Tetracycline</b> 1% eye ointment	Antibiotic needs to be applied to both eyes soon after birth (single dose)

121 Notes: All dosages are for normal renal and hepatic function.

122 IM: intramuscular; IV: intravenous.

123 <sup>a</sup>Concurrent treatment with azithromycin for chlamydial infection is usually recommended.

124 <sup>b</sup>Ceftriaxone should not be administered in neonates receiving calcium-containing intravenous fluids and it should  
125 be avoided in infants with hyperbilirubinaemia. Cefotaxime can be used as an alternative. Alternatives to  
126 ceftriaxone indicated in the WHO 2016 guidelines but not included the EML for this indication are kanamycin (IM)  
127 25mg/kg or spectinomycin (IM) 25mg/kg (77).

128 <sup>c</sup>An alternative indicated in the WHO 2016 guidelines but not included the EML for this indication is erythromycin  
129 (oral) 50 mg/kg per day divided in 4 doses for 14 days(77).

130 <sup>d</sup>Alternatives indicated in the WHO 2016 guidelines but not included the EML for this indication: povidone–iodine  
131 (water-based solution. Do not use alcohol-based solutions): 2.5%; silver nitrate (solution): 1%; chloramphenicol (eye  
132 ointment): 1% (77).

133 **ACCESS** antibiotics are indicated in green, **WATCH** antibiotics in yellow and **RESERVE** antibiotics in red.

# 1 Endophthalmitis

## 2 Definition

### TYPE OF EYE INFECTIONS

### ANATOMICAL LOCATION

**Endophthalmitis**

Infection of the inner part of the eye globe (in particular the intraocular fluids: vitreous and aqueous humor and the retina)

## 3 Epidemiology

4 Endophthalmitis mostly has an exogenous cause, and occurs as a result of penetrating eye  
 5 trauma, after eye surgery or as a complication of keratitis. Endogenous cases of endophthalmitis  
 6 are rare but can occur because of bacteremia or fungemia from distant sites of infection (most  
 7 often endocarditis and liver abscess depending on the setting(78, 79)). Injection of drugs is a  
 8 common risk factor in patients with endogenous infections. Endophthalmitis refers to bacterial  
 9 or fungal infection within the eye, including involvement of the vitreous and/or aqueous humors.  
 10 Endophthalmitis is not caused by viruses or parasites, infections due to these organisms are  
 11 included in the term "uveitis"(80).

## 12 Microbiology epidemiology

13 *Table 4 Pathogens most frequently associated with endophthalmitis (in descending order of*  
 14 *frequency)*

### TYPE OF EYE INFECTION

### MOST COMMON CAUSATIVE PATHOGENS

**Endophthalmitis**

**Bacteria:**

**Most cases:**

Coagulase-negative Staphylococci

**Less frequently:**

*Staphylococcus aureus*(81)

*Streptococcus* spp.<sup>a</sup>

*Klebsiella* spp. (more frequent in Asia)

*Bacillus cereus* (mostly in case of penetrating trauma)

**Fungi<sup>b</sup>:**

mostly *Candida albicans*, *Fusarium* spp., *Aspergillus* spp.

15 <sup>a</sup>*Streptococcus viridans* is more frequently encountered in case of post-intravitreal injection endophthalmitis  
 16 compared to post-cataract endophthalmitis(82).

17 <sup>b</sup>In temperate climates, fungal endophthalmitis is usually endogenous and caused by *Candida spp.* In tropical regions,  
18 fungal endophthalmitis is often due to molds and is usually exogenous in origin.

## 19 Clinical presentation

20 Endophthalmitis is usually an acute condition and patients present with a painful red eye, blurred  
21 vision and trouble looking at bright light (i.e. photophobia). Most cases are exogenous and  
22 typically occur after eye surgery (usually within days or a few weeks) or trauma. In rare cases,  
23 endophthalmitis can result from the hematogenous spread of pathogens from distant sites of  
24 infection (e.g. endocarditis, liver abscess). In these cases, signs and symptoms of bacteremia can  
25 be present although in most cases ocular symptoms occur first.

## 26 Laboratory tests

### 27 I. Patient microbiology tests

28 A positive culture of aqueous or vitreous humour in the presence of compatible signs and  
29 symptoms could confirm the diagnosis.

30 *Table 5 Microbiology tests to consider when endophthalmitis is suspected as indicated in the*  
31 *WHO EDL (54)*

Diagnostic test	Purpose of the test	Settings where the test should be available
Microscopy (Gram stain) and culture of aqueous or vitreous humour aspirate	Microbial morphology and detection and identification of bacterial and fungal species for selection of appropriate antimicrobial regimens	Healthcare facilities with clinical laboratories
Blood cultures	To detect bacterial and fungal bloodstream infections in patients with suspected endogenous endophthalmitis	Healthcare facilities with clinical laboratories

### 32 II. Other tests

33 Laboratory tests (other than microbiology) are usually not needed.

### 34 III. Using microbiology surveillance data

35 Routine surveillance is not helpful to inform empiric guidance.

## 36 Imaging

37 Imaging is usually not needed.

## 38 Antibiotic treatment

39 This condition should be treated by an ophthalmologist where available. Urgent referral of the  
40 patient to an ophthalmologist, if available, should be considered when endophthalmitis is  
41 suspected because this condition could potentially threaten the patient’s sight.

42 With bacterial endophthalmitis treatment, there are two common approaches:

- 43 • “tap and inject”: first a sample of vitreous humour is collected for culture (through  
44 vitreous aspiration) and then antibiotics are injected into the vitreous
- 45 • vitrectomy is performed (i.e. eye surgery to remove some or all the inflamed vitreous  
46 from the eye as a form of source control) and during the procedure, the antibiotic is  
47 injected into the vitreous

48 Systemic antibiotics (in combination with intravitreal antibiotics) should also be considered given  
49 the severity of this condition, especially when referral to an ophthalmologist is not readily  
50 available (Table 6). In cases of endogenous infections, systemic antibiotics should always be  
51 given. However, evidence of their efficacy (e.g. on visual acuity) is still controversial. The ability  
52 to rapidly reach adequate concentrations of antibiotics in the eye varies by antibiotic. (83)

53 There is limited evidence of benefit for the additive treatment with intravitreal steroid therapy  
54 compared to antibiotics alone (84).

55 *Table 6 Empiric antibiotic treatment for bacterial endophthalmitis*

Type of eye infection	Antibiotic treatment	Total treatment duration
Bacterial endophthalmitis	<p><b>Intravitreal injection:</b>  <b>Vancomycin</b> 1 mg + <b>ceftazidime</b> 2.25 mg</p> <p><b>ADD Systemic treatment</b> (in case of endogenous infection)</p> <p><b>Adults:</b>  <b>Ceftriaxone</b> (IV): 2g given once a day  <b>AND Vancomycin</b> (IV): 15-20mg/kg given every 12 hours</p> <p><b>Neonates and children:</b>  <b>Ceftriaxone</b> (IV): 80 mg/kg/dose given once a day  <b>AND Vancomycin</b> (IV):</p> <ul style="list-style-type: none"> <li>• Neonates: 15 mg/kg/ dose, given every 12 hours</li> <li>• Children: 15 mg/kg/dose, given every 8 hours</li> </ul> <p>Systemic antibiotics alone are not effective in treating bacterial exogenous endophthalmitis. Whether systemic antibiotics provide any</p>	<p>Intravitreal antibiotics: single dose (if no clinical improvement after 48 hours, the intravitreal injection can be repeated)</p> <p>For endogenous endophthalmitis, the duration of systemic antibiotics should be determined by the need to treat the underlying source of bacteremia (e.g. six weeks in many cases of endocarditis).</p>

	benefit in these cases as adjunctive therapy to intravitreal antibiotics is still debatable.	
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56 Notes: All dosages are for normal renal and hepatic function.

57 **ACCESS** antibiotics are indicated in green, **WATCH** antibiotics in yellow and **RESERVE** antibiotics in red.

DRAFT

# 1 Keratitis

## 2 Definition

TYPE OF EYE INFECTIONS	ANATOMICAL LOCATION
Keratitis	Infection of the cornea (i.e. the transparent covering of the eye)

## 3 Epidemiology

4 Keratitis is common, the estimated number of cases is more than 2 million cases per year(85).  
 5 The highest – epidemic – burden is in South, South East and East Asia(85), especially in rural  
 6 settings among male workers in high-risk professions (eye trauma being the predominant risk  
 7 factor)(86). In high-income countries, the number of cases of keratitis has increased over time  
 8 probably because of the increased use of contact lenses – use of lenses is currently the most  
 9 common risk factor in this setting. The disease is rare in children, but it is also harder to  
 10 diagnose, mostly because it is more difficult to obtain a clinical history and to collect a sample  
 11 for microbiology tests.

## 12 Microbiology epidemiology

13 *Table 7 Pathogens most frequently associated with keratitis (in descending order of frequency)*

TYPE OF EYE INFECTION	MOST COMMON CAUSATIVE PATHOGENS
Keratitis(85, 86) <sup>a</sup>	<p><b>Fungi:</b> mostly <i>Fusarium</i> spp., <i>Aspergillus</i> spp.</p> <p><b>Bacteria:</b> <i>Pseudomonas</i> spp (contact lenses), <i>Staphylococcus epidermidis</i>, <i>Staphylococcus aureus</i>, <i>Streptococcus pneumoniae</i></p> <p><b>Viruses:</b> mostly herpes simplex virus (usually type 1), varicella zoster virus</p> <p><b>Parasites:</b> <i>Acanthamoeba</i> (contact lenses)</p>

14 <sup>a</sup>Bacteria and viruses are the most common causes of keratitis in high-income countries while fungi predominate in  
 15 low- and middle-income countries. Global variations in etiology largely reflect patient-based risk factors such as  
 16 population demographic, occupation, contact lens use, concomitant ocular and systemic illness, as well as  
 17 environmental factors such as geographical location, climate, and virulence of causative organisms. For example,  
 18 *Pseudomonas* spp. and *Acanthamoeba* spp. are often associated with the use of contact lenses and fungal keratitis  
 19 must be considered after any traumatic corneal injury, notably from vegetable matter. In the pediatric population,  
 20 it seems there is a higher incidence of atypical infections (e.g. due to *Acanthamoeba*)(85).

## 21 Clinical presentation

22 Patients with keratitis generally present with a painful eye, decreased vision, more tears and  
 23 corneal oedema. They often describe a feeling of “having something in the eye” and have  
 24 difficulty keeping the affected eye open. A discharge from the eye may be seen depending on the  
 25 causative pathogen. Most infectious cases are of bacterial origin, although in low-and middle-  
 26 income countries fungal infections are common (e.g. as a result of trauma from plants or sand or  
 27 mud in rural settings)(85). Reactivation of herpes simplex virus could also cause keratitis  
 28 (especially in patients with HIV infection or in patients with other forms of immunosuppression).  
 29 Ophthalmologic examination with a slit lamp is usually needed to visualize the cornea and  
 30 confirm the diagnosis (focal white infiltrates in the corneal stroma with an epithelial defect and  
 31 underlying tissue loss are the critical sign of keratitis).

## 32 Laboratory tests

### 33 I. Patient microbiology tests

34 A positive culture in the presence of compatible signs and symptoms could confirm the  
 35 diagnosis.

36 *Table 8 Microbiology tests to consider when keratitis is suspected as indicated in the WHO EDL*  
 37 *(54)*

Diagnostic test	Purpose of the test	Settings where the test should be available
Microscopy (Gram stain) and culture of corneal scrapings or corneal biopsy material	Microbial morphology and detection and identification of bacterial and fungal species for selection of appropriate antimicrobial regimens	Healthcare facilities with clinical laboratories

38 Note: nucleic acid amplification testing (i.e. polymerase chain reaction) for viral etiology (e.g. herpes simplex virus)  
 39 could be considered based on clinical presentation and individual risk factors.

### 40 II. Other tests

41 Laboratory tests (other than microbiology) are usually not helpful.

### 42 III. Using microbiology surveillance data

43 Routine surveillance is not helpful to inform empiric guidance.

## 44 Imaging

45 Imaging is usually not needed. Specialist eye examination may be considered.

## 46 Antibiotic treatment

47 Patients should stop wearing contact lenses. Topical antibiotic treatment is indicated even  
48 though consensus on the most effective treatment is lacking (87) (Table 9). Cycloplegic eye drops  
49 (cyclopentolate 1% or atropine 1%) can be used for comfort, to reduce photophobia from ciliary  
50 spasm and to reduce the formation of pupillary adhesions to the lens.

51 Oral antibiotics can be considered in selected cases (e.g. scleral extension or impending  
52 perforation) or in case of gonococcal infection. With viral keratitis, topical and oral antiviral  
53 treatment is usually indicated (but management of viral infections is beyond the scope of this  
54 chapter).

55 **Note:** infectious keratitis as a potentially blinding condition is an ocular emergency for which  
56 the prospect of visual restoration is often poor.

57 *Table 9 Empiric antibiotic treatment for bacterial keratitis*

Type of eye infection	Antibiotic treatment	Total treatment duration
Bacterial keratitis (children and adults)	<b>Ofloxacin</b> <sup>a</sup> (eye drops): 0.3%, 1 drop given every hour in the affected eye for 48 hours then given every 4 hours until healed	2 weeks but duration is often personalized to the individual based on clinical improvement

58 <sup>a</sup>A fluoroquinolone is usually given to patients who wear contact lenses because *Pseudomonas aeruginosa* is often  
59 the causative pathogen.

60 For most patients, hourly treatment is indicated for the first 24 to 48 hours. Drops are preferred because ointments  
61 have poor corneal penetration. However, ointments may be used at bedtime to allow the patient to sleep through  
62 the night, but only after a positive response has been demonstrated to the initial intensive eyedrop treatment.

63 **ACCESS** antibiotics are indicated in green, **WATCH** antibiotics in yellow and **RESERVE** antibiotics in red.

# 1 Orbital cellulitis

## 2 Definition

TYPE OF EYE INFECTIONS	ANATOMICAL LOCATION
Orbital cellulitis	Infection affecting eye tissues behind the orbital septum within the bony orbit (i.e. fat and ocular muscles within the orbit) Treatment of this condition is not addressed in the Handbook.

## 3 Epidemiology

4 Orbital cellulitis is more common in young children and in most cases it is a complication of  
5 bacterial sinusitis.

## 6 Microbiology epidemiology

7 *Table 10 Pathogens most frequently associated with orbital cellulitis (in descending order of*  
8 *frequency)*

TYPE OF EYE INFECTION	MOST COMMON CAUSATIVE PATHOGENS
Orbital cellulitis	<p><b>Bacteria:</b></p> <ul style="list-style-type: none"> <li>• In adults: <i>Staphylococcus aureus</i>, <i>Streptococcus</i> spp., <i>Bacteroides</i> spp.</li> <li>• In children: <i>Haemophilus influenzae</i> (rare in vaccinated children(88)).</li> <li>• Following eye trauma: <i>Pseudomonas aeruginosa</i> and <i>Escherichia coli</i></li> <li>• Following a dental abscess: polymicrobial infection (including anaerobes)</li> </ul> <p><b>Fungi<sup>a</sup>:</b></p> <ul style="list-style-type: none"> <li>• Mostly in immunocompromised patients (e.g. diabetes, chemotherapy, HIV infection): zygomycetes (e.g. <i>Mucor</i>) and <i>Aspergillus</i> spp.</li> </ul>

9 <sup>a</sup>Fungal infections are rare but they should be considered in immunocompromised patients including patients with  
10 poorly controlled diabetes.

## 11 Clinical presentation

12 Patients with orbital cellulitis typically have unilateral local signs of inflammation around the  
13 affected eye. The eyelids are usually swollen, red, warm and tender. Sometimes fever is present  
14 (> 38.0°C). These findings are also present in cases of periorbital cellulitis (see below); however,  
15 in addition to these symptoms, patients with orbital cellulitis present with restricted extraocular  
16 motility with pain on attempted eye movement, conjunctival chemosis (i.e. swelling) and  
17 injection as critical sign. Usually this condition is accompanied by protrusion of the eye (i.e.  
18 proptosis), and loss of vision may be present(89). Signs of optic neuropathy (e.g. afferent

19 pupillary defect, dyschromatopsia) may be present in severe cases. In neglected cases orbital  
20 cellulitis may lead to cavernous sinus thrombosis, brain abscess or even death.

## 21 Laboratory tests

### 22 I. Patient microbiology tests

23 Blood cultures and cultures of samples collected can be considered.

24 *Table 13 Microbiology tests to consider when orbital cellulitis is suspected as indicated in the*  
25 *WHO EDL (54)*

Diagnostic test	Purpose of the test	Settings where the test should be available
Microscopy (Gram stain) and culture of abscess material <sup>a</sup>	Microbial morphology and detection and identification of bacterial and fungal species for selection of appropriate antimicrobial regimens	Healthcare facilities with clinical laboratories
Blood cultures	To detect bacterial and fungal bloodstream infections in patients with suspected endogenous endophthalmitis	Healthcare facilities with clinical laboratories

26 <sup>a</sup>Possible specimens (depending on the type of infection) include: conjunctival swabs, corneal scrapings or corneal  
27 biopsy, aqueous or vitreous humour aspirate.

### 28 II. Other tests

29 Laboratory tests (other than microbiology) are usually not helpful.

### 30 III. Using microbiology surveillance data

31 Routine surveillance is not helpful to inform empiric guidance.

## 32 Imaging

33 A computed tomography (CT) scan of the orbits and sinuses (axial, coronal, and parasagittal  
34 views, with contrast if possible) could be considered. The reason for doing a CT scan is to assess  
35 the presence or absence of orbital involvement when the diagnosis is uncertain and the presence  
36 of possible complications (e.g. subperiosteal or orbital abscess or cavernous sinus thrombosis,  
37 intracranial extension).

## 38 Antibiotic treatment

39 (General statements presented but treatment not addressed in the Handbook)

40 Patients with orbital cellulitis should be admitted to the hospital and an infectious disease  
41 physician and an otorhinolaryngology specialist should be consulted. Most patients with  
42 uncomplicated orbital cellulitis can be treated with antibiotics alone(90, 91).

43 Surgery for source control (e.g. drainage of purulent collections) may be needed in severe and  
44 complicated cases (e.g. in case of abscess) in combination with systemic antibiotic treatment (92,  
45 93). Surgery is almost always indicated in patients with intracranial extension of the infection.

DRAFT

# 1 Periorbital (or preseptal) cellulitis

## 2 Definition

TYPE OF EYE INFECTIONS	ANATOMICAL LOCATION
<b>Periorbital (or preseptal) cellulitis</b>	Infection of subcutaneous eyelid tissues anterior to the orbital septum (in this case the globe and the tissues within the bony orbit are not involved)

## 3 Epidemiology

4 This is usually a mild condition that most commonly affects children. Most cases are exogenous  
 5 and result from adjacent infection (hordeolum, dacryocystitis, infection of the periorbital sinuses)  
 6 or follow animal and insect bites or trauma of the eyelid. Periorbital (or preseptal) cellulitis is  
 7 much more common than orbital cellulitis(94).

8 *Table 12 Pathogens most frequently associated with periorbital cellulitis (in descending order of*  
 9 *frequency)*

TYPE OF EYE INFECTION	MOST COMMON CAUSATIVE PATHOGENS
<b>Periorbital (or preseptal) cellulitis</b>	<p><b>Bacteria:</b>  <i>Staphylococcus aureus</i> (including MRSA)  <i>Streptococcus pneumoniae</i>  <i>Haemophilus influenzae</i> (rare in vaccinated children(88))  <i>Moraxella catarrhalis</i>                      Anaerobes (suspect if there is a history of animal or human bite or if necrosis is present)</p> <p><b>Viruses:</b>                      A viral cause should be suspected if the infection is associated with a vesicular skin rash (e.g. herpes simplex virus or varicella-zoster virus).</p>

## 10 Clinical presentation

11 It is very important to distinguish preseptal from orbital cellulitis. Patients with preseptal cellulitis  
 12 typically present with unilateral local signs of inflammation around the affected eye but do not  
 13 have restricted or painful eye movements (as occurs in case of orbital cellulitis). The eyelid/s is  
 14 generally swollen, red, warm and tender and sometimes fever is present (> 38.0°C). In severe  
 15 cases, conjunctival chemosis (i.e. swelling) may also occur. Vision is normal (while in case of  
 16 orbital cellulitis loss of vision may be present)(89). In preseptal cellulitis serious complications are  
 17 rare(95).

## 18 Laboratory tests

### 19 I. Patient microbiology tests

20 Usually no test is required. Cultures are difficult to obtain, and blood cultures when performed  
21 are usually negative.

### 22 II. Other tests

23 Laboratory tests (other than microbiology) are usually not helpful.

### 24 III. Using surveillance microbiology data

25 Routine surveillance is not helpful to inform empiric guidance.

## 26 Imaging

27 A computed tomography (CT) scan of the orbits and sinuses (axial, coronal, and parasagittal  
28 views, with contrast if possible) could be considered. The reason for doing a CT scan is to assess  
29 the presence or absence of orbital involvement when the diagnosis is uncertain and the presence  
30 of possible complications is suspected (e.g. subperiosteal or orbital abscess or cavernous sinus  
31 thrombosis, intracranial extension).

## 32 Antibiotic treatment

33 Systemic antibiotic treatment is indicated and is usually given empirically based on the most likely  
34 causative pathogens because cultures are difficult to obtain, and blood cultures when performed  
35 are usually negative (Table 14). Empiric treatment of MRSA may be considered in certain cases  
36 based on individual risk factors (e.g. known MRSA colonization) and on the local prevalence of  
37 community-acquired MRSA. In these cases, the literature suggests using clindamycin or  
38 sulfamethoxazole+trimethoprim; however, no formal recommendation can be made in the  
39 Handbook as these options are not currently listed in the EML/c.

40 Most cases of periorbital cellulitis can be managed with oral antibiotic treatment; however, in  
41 severely ill patients or very young children, intravenous treatment may be considered(93).

42 Adults and children older than one year of age with mild preseptal cellulitis and no signs of  
43 systemic toxicity can generally be treated as outpatients with oral antibiotics provided that close  
44 follow-up can be ensured.

45 Children younger than one year of age, patients who cannot cooperate fully for an examination,  
46 who are severely ill or in case of no noticeable improvement or worsening after 24 to 48 hours  
47 of oral antibiotics should generally be admitted to the hospital and managed according to the  
48 recommendations for orbital cellulitis.

49 *Table 14 Empiric antibiotic treatment for periorbital (or preseptal) cellulitis<sup>a</sup>*

Adults	Children	Total treatment duration
<p><b>Amoxicillin+clavulanic acid</b> (IV): 1gr+ 200 mg given every 8 hours                      Oral: 500 mg+125 mg given every 8 hours</p> <p>OR</p> <p><b>Cefalexin</b> (oral): 500 mg given every 8 hours</p> <p>OR</p> <p><b>Cloxacillin</b> or <b>flucloxacillin</b> (IV): 2 gr given every 6 hours                      Oral: 500 mg given every 8 hours</p>	<p><b>Amoxicillin+clavulanic acid</b> (IV/oral) 40-50 mg/kg/dose of amoxicillin component given every 12 hours                      OR 30 mg/kg/dose given every 8 hours</p> <p>Oral weight bands<sup>b</sup>:</p> <p>3-&lt;6 kg: 250 mg of amoxicillin/dose given every 12 hours                      6-&lt;10 kg: 375 mg of amoxicillin/dose given every 12 hours                      10-&lt;15 kg: 500 mg of amoxicillin/dose given every 12 hours                      15-&lt;20 kg: 750 mg of amoxicillin/dose given every 12 hours                      20-&lt;30 kg: 1000 mg of amoxicillin/dose given every 12 hours                      ≥ 30 kg: Use adult dose</p> <p>OR</p> <p><b>Cefalexin</b> (oral): 25 mg/kg/dose given every 12 hours</p> <p>Oral weight bands:</p> <p>3- &lt;6 Kg: 125 mg given every 12 hours                      6-&lt;10 kg: 250 mg given every 12 hours                      10-&lt;15 kg: 375 mg given every 12 hours                      15-&lt;20 kg 500 mg given every 12 hours                      20-&lt;30 kg: 625 mg given every 12 hours                      ≥ 30 kg: Use adult dose</p> <p>OR</p> <p><b>Cloxacillin</b> or <b>flucloxacillin</b> (IV/oral):</p> <ul style="list-style-type: none"> <li>• Neonates: 25-50 mg/kg/dose, given every 12 hours</li> <li>• Children: 25 mg/kg/dose, given every 6 hours</li> </ul> <p>Oral weight bands:</p> <p>3-&lt;6 kg: 125 mg given every 6 hours                      6-&lt;10 kg: 250 mg given every 6 hours                      10-&lt;15 kg: 250 mg given every 6 hours                      15-&lt;20 kg: 500 mg given every 6 hours                      20-&lt;30 kg: 750 mg given every 6 hours                      ≥ 30 kg: Use adult dose</p>	<p>10-14 days                      (depending on the severity)</p>

50 Notes: All dosages are for normal renal and hepatic function.  
 51 IV: intravenous.

- 52 <sup>a</sup>It should be noted that these specific recommendations are not included in the EML/c(4, 5). The options  
53 presented are based on what is recommended for mild skin and soft tissues infections.  
54 <sup>b</sup>Oral liquid must be refrigerated after reconstitution as clavulanic acid is rapidly metabolized in high ambient  
55 temperatures.  
56 **ACCESS** antibiotics are indicated in green, **WATCH** antibiotics in yellow and **RESERVE** antibiotics in red.

DRAFT

# 1 Infectious uveitis

## 2 Definition

TYPE OF EYE INFECTIONS	ANATOMICAL LOCATION
<b>Uveitis</b>	<p>Infection of the uvea, which is composed of:</p> <ul style="list-style-type: none"> <li>• Iris (colored ring-shaped part of the eye behind the cornea)</li> <li>• Ciliary body (this part extends around the iris, has a muscular component and produces the aqueous humor that keeps the eye in a pressurized state)</li> <li>• Choroid (this is a vascular layer)</li> </ul> <p>The iris and ciliary body are part of the anterior segment of the eye while the choroid is part of the posterior segment of the uvea</p>

## 3 Epidemiology

4 Infectious uveitis can be caused by a large number of pathogens and most cases are associated  
 5 with systemic infections, but it may also occur as an isolated condition. Therefore, the  
 6 epidemiology depends on the underlying infection. In general, certain factors can increase the  
 7 risk of specific infections (e.g. cytomegalovirus is mostly associated with uveitis in  
 8 immunocompromised patients).

## 9 Microbiology epidemiology

10 *Table 15 Pathogens most frequently associated with uveitis (in alphabetical order)*

TYPE OF EYE INFECTION	MOST COMMON CAUSATIVE PATHOGENS
<b>Uveitis (usually in the context of infectious or autoimmune or inflammatory systemic conditions)<sup>a</sup></b>	<b>Bacteria:</b> <ul style="list-style-type: none"> <li>• <i>Bartonella henselae</i> (with cat-scratch disease)</li> <li>• <i>Mycobacterium tuberculosis</i><sup>b</sup></li> <li>• <i>Treponema pallidum</i> (with neurosyphilis)</li> </ul> <b>Parasites:</b> <i>Toxoplasma gondii</i> <b>Viruses:</b> cytomegalovirus, herpes simplex virus

11 <sup>a</sup>Consider individual risk factors and presentation to identify the most likely causative pathogen.

12 <sup>b</sup>Ocular tuberculosis usually results from haematogenous dissemination of the infection from pulmonary or extra-  
 13 pulmonary sites.

## 14 Clinical presentation

15 The symptoms of uveitis are nonspecific and depend upon the portion of the uveal tract that is  
 16 involved. Findings also differ depending upon the location of the involvement, and visual loss  
 17 may occur with anterior, intermediate, or posterior involvement. Anterior uveitis is about four  
 18 times more common than posterior uveitis(96) Patients with uveitis usually have a painful red  
 19 eye and decreased vision. Infectious forms of uveitis are mostly of viral origin (e.g. herpes simplex  
 20 virus, cytomegalovirus) or they may occur as a reactivation of toxoplasmosis.

21 When uveitis is suspected, patients should be seen by an ophthalmologist, if available, because  
 22 the list of potential conditions associated with uveitis is large and, in some cases, uveitis is a  
 23 potentially sight-threatening condition.

## 24 Laboratory tests

### 25 I. Patient microbiology tests

26 The need for microbiology tests should be guided by the type of eye infection suspected.

27 *Table 16 Microbiology tests to consider when uveitis is suspected as indicated in the WHO EDL*  
 28 *(54)*

Diagnostic test	Purpose of the test	Settings where the test should be available
Microscopy (Gram stain) and culture <sup>a</sup>	Microbial morphology and detection and identification of bacterial species for selection of appropriate antibiotic regimens	Healthcare facilities with clinical laboratories

29 <sup>a</sup>Possible specimens (depending on the type of infection) include: conjunctival swabs, corneal scrapings or corneal  
 30 biopsy, aqueous or vitreous humour aspirate.

31 Note: nucleic acid amplification testing (i.e. polymerase chain reaction) for viral etiology (e.g. herpes simplex virus)  
 32 could be considered based on clinical presentation and individual risk factors.

### 33 II. Other tests

34 Laboratory tests (other than microbiology) are usually not helpful.

### 35 III. Using microbiology surveillance data

36 Routine surveillance is not helpful to inform empiric guidance.

## 37 Imaging

38 Specialist eye examination may be considered depending on the type of infection.

39 **Antibiotic treatment**

40 (General statements presented but treatment not addressed in the Handbook)

41 Treatment for uveitis depends on the etiology (including non-infectious causes), location and  
42 clinical severity. Because of the large variety of conditions associated with uveitis, a review of  
43 treatment options is beyond the scope of this chapter.

DRAFT

# 1 Trachoma

## 2 Key messages

1. Trachoma is an eye disease caused by specific serovars (A through C) of the bacterium *Chlamydia trachomatis*
2. Repeated infections over the years can lead to permanent corneal damage and blindness
3. Treatment depends on the stage of the disease (it may require eye surgery to prevent blindness if corneal damage has already occurred)
4. Mass antibiotic administration programmes in endemic areas aim to reduce the reservoir of *Chlamydia trachomatis*

### 3 Box 1 Other relevant WHO documents (please check regularly for updates)

- Trachoma. <https://www.who.int/news-room/fact-sheets/detail/trachoma>
- World Health Assembly, 51. (1998). Global elimination of blinding trachoma. <https://apps.who.int/iris/handle/10665/29886>
- The simplified trachoma grading system, amended. Bull World Health Organ. 2020;98(10):698-705. 10.2471/blt.19.248708
- Trachoma control: a guide for programme managers <https://apps.who.int/iris/handle/10665/43405>

## 4 Definition

5 Trachoma is an eye disease caused by specific serovars (A through C) of the bacterium *Chlamydia*  
6 *trachomatis* (other serovars cause urogenital diseases, see chapter “Sexually transmitted  
7 infections – Chlamydia urogenital infections”). Trichiasis is the advanced clinical consequence of  
8 trachoma characterized by the eyelashes turning inwards which leads over time to permanent  
9 corneal damage. It is a sight-threatening condition that requires surgical treatment.

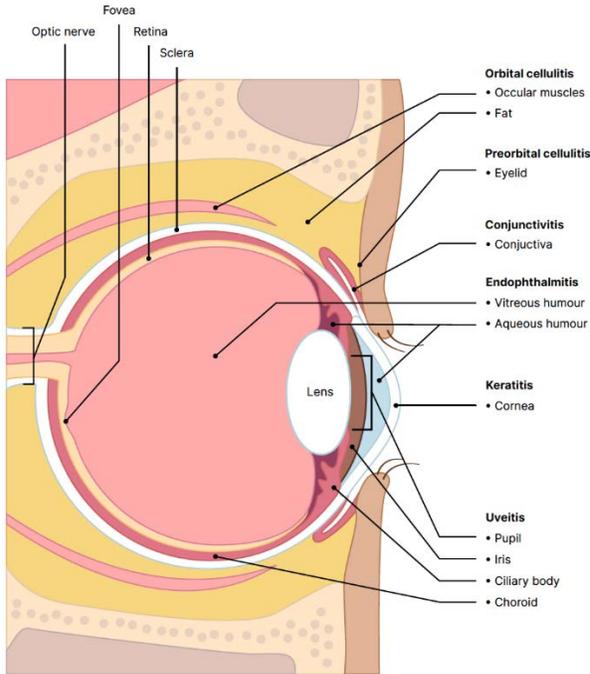
## 10 Microbiology epidemiology

11 Trachoma is caused by *Chlamydia trachomatis*, a Gram-negative obligate intracellular bacterium.  
12 There are several strains of *Chlamydia trachomatis*, some associated with trachoma and some  
13 associated with sexually transmitted urogenital diseases. Strains associated with trachoma are  
14 serovars A, B, Ba and C.

## 15 Pathophysiology

16 *Chlamydia trachomatis* infection spreads via the hands through direct contact with contaminated  
17 people or objects. Flies can also spread the infection by transporting contaminated eye and/or  
18 nose secretions from infected to non-infected people. Chronic inflammation of the conjunctiva  
19 caused by repeated infections over the years can cause inversion of the eyelashes that can lead

20 to permanent corneal damage through formation of scars on the cornea (the transparent front  
 21 part of the eye – see Figure). This can eventually lead to vision impairment and blindness(97).



22

## 23 Epidemiology

24 Trachoma is the leading cause of infectious blindness in the world and responsible for about 1%  
 25 of cases of blindness. According to the most recent WHO estimates, more than 137 million people  
 26 worldwide live with trachoma(98). The infection is a public health problem in over 40 countries,  
 27 most of which are in Africa(98).

28 Risk factors of trachoma include living in overcrowded conditions and poor sanitation and most  
 29 transmission occurs within families. Active disease (i.e. conjunctivitis) is more common in young  
 30 children living in endemic areas. Children younger than 10 years old, and those with intense  
 31 inflammatory trachoma, probably represent the major source of ocular *Chlamydia trachomatis*  
 32 infection in endemic communities(99). Corneal scars are mostly seen in adults because repeated  
 33 infections over time need to occur before permanent corneal damage is established. Individuals  
 34 with corneal scars are at increased risk of blindness.

35 In 1993, WHO adopted the SAFE strategy for the elimination of trachoma:

- 36 • Surgery to treat advanced diseases;
- 37 • Antibiotics to clear infection;
- 38 • Facial cleanliness; and
- 39 • Environmental improvement to reduce transmission.

40 In 1996, WHO established the alliance for the global elimination of trachoma, whose goal was  
 41 to eliminate trachoma as a public health problem by 2020. In addition, in 1998, the World

42 Health Assembly adopted a resolution on trachoma to urge WHO Member States to implement  
43 measures to target the elimination of trachoma (100). As of July 2020, 13 out of 30 countries  
44 that are implementing the SAFE strategy have achieved the WHO elimination targets. As part of  
45 the elimination strategy, data reported to WHO for 2019 indicate that about 92 000 people had  
46 corrective surgery for trichiasis and 95 million people received antibiotic treatment (i.e. 57% of  
47 people needing antibiotics for trachoma received them)(98).

*Box 2 WHO definitions*

WHO defines trachoma as a public health problem when:

- the prevalence of follicular trachoma in children aged 1–9 years is  $\geq 10\%$  (see the section on clinical presentation for the classification of trachoma), or
- the prevalence of trachomatous trichiasis in people aged  $\geq 15$  years is at least 1%.

WHO criteria for elimination of trachoma as a public health problem are(101):

- the prevalence of follicular trachoma in children aged 1–9 years is  $< 5\%$  or
- the prevalence of trachomatous trichiasis in people aged  $\geq 15$  years is  $< 0.2\%$
- there is evidence that the health system can identify and manage cases of trachomatous trichiasis.

## 48 Clinical presentation

49 Trachoma diagnosis is based on clinical signs. Trachoma presents as an active disease (i.e.  
50 conjunctivitis) with symptoms such as redness of the eye, eye discomfort, mucopurulent  
51 discharge and light sensitivity.

52 The other presentation is the advanced disease where there is conjunctival scarring, signs of  
53 chronic conjunctival inflammation and eyelashes turned inwards.

54 The WHO trachoma grading system is used in field assessments to evaluate the extent of disease  
55 during examination(102).

56 The grading system includes:

- 57 • Trachomatous inflammation, follicular – five or more follicles of  $> 0.5$  mm on a  
58 specific area of the upper tarsal conjunctiva
- 59 • Trachomatous inflammation, intense – papillary hypertrophy and inflammatory  
60 thickening of the upper tarsal conjunctiva obscuring more than half the deep tarsal  
61 vessels
- 62 • Trachomatous conjunctival scarring – grossly visible scars on the tarsal conjunctiva
- 63 • Trachomatous trichiasis – at least one ingrown eyelash touching the globe of the eye  
64 or evidence of epilation (eyelash removal)
- 65 • Corneal opacity – corneal opacity blurring part of the pupil margin.

## 66 Laboratory tests

### 67 I. Patient microbiology tests

68 The diagnosis of trachoma is mostly clinical and microbiology tests are not routinely done.  
69 However, such tests may be considered (Table 1) to decide whether to stop or continue  
70 antibiotic treatment at the population level, for example, on a selected subgroup of people(97).

71 *Table 1 Microbiology tests to consider if trachoma is suspected as indicated in the WHO EDL (54)*

Diagnostic test	Purpose of the test	Setting where the test should be available
Qualitative test for <i>Chlamydia trachomatis</i> (i.e. nucleic acid amplification test) <sup>a</sup>	To diagnose chlamydial infection	Health care facilities with clinical laboratories
Microscopy (Gram stain) and culture <sup>a</sup>	Initial step to detect and identify bacterial species for selection of appropriate antibiotic regimens	Health care facilities with clinical laboratories

72 <sup>a</sup>Possible specimens: conjunctival swabs.

### 73 II. Other tests

74 When trachoma is suspected based on clinical signs and epidemiology of the community,  
75 laboratory tests are not usually needed.

### 76 III. Using microbiology surveillance data

77 Routine surveillance is not helpful to inform empiric guidance.

## 78 Imaging

79 When trachoma is suspected, imaging is not usually needed.

## 80 Treatment

81 The appropriate treatment of trachoma depends on the stage of disease.

82 If trichiasis has already developed, surgery is needed to prevent blindness by stopping the  
83 eyelashes continuing to erode the cornea(103, 104).

84 Antibiotic treatment is generally given to treat *Chlamydia trachomatis* infection in association  
85 with reinforced education on personal and community hygiene measures. Usually, antibiotic  
86 treatment is given once a year for at least three years as part of a mass antibiotic administration  
87 programme in endemic areas to reduce the reservoir of *Chlamydia trachomatis* (Table 2)(103).

88 *Table 2 Empiric antibiotic treatment for trachoma*

Adults and children	Total treatment duration
Azithromycin (oral): 20 mg/kg (maximum 1 g)	Single dose (azithromycin)

<p>OR  <b>Azithromycin</b> (eye drops)<sup>a</sup> 1.5%, 1 drop administered to both eyes every 12 hours                  OR  <b>Tetracycline</b> (eye ointment): 1% 1 cm administered to both eyes every 12 hours                  (topical treatment is used in areas where oral azithromycin is not readily available)</p>	<p>3 days (topical treatment with azithromycin)                  6 weeks (topical treatment with tetracycline)</p>
---	--

89 Notes: Antibiotic treatment is mostly given once a year for at least three years as part of mass drug administration  
 90 programmes in endemic areas.

91 <sup>a</sup>Azithromycin eye drops may be as effective as oral azithromycin(105).

92 **ACCESS** antibiotics are indicated in green, **WATCH** antibiotics in yellow and **RESERVE** antibiotics in red.

### 93 Prevention

94 For prevention of trachoma, please refer to the epidemiology section where the WHO SAFE  
 95 strategy is described.

DRAFT

# 1 Community-acquired 2 pneumonia – Mild

## 3 Key messages

1. Rapidly decide if the patient has mild CAP which can be managed in primary care with oral antibiotic treatment or severe CAP (higher short-term mortality risk and need for hospital admission). Scores can be helpful to make this distinction
2. Clinically relevant high-level beta-lactam resistance in *Streptococcus pneumoniae* (the main bacterial cause of CAP) is rare in most countries and oral Access group penicillins (amoxicillin, phenoxymethylpenicillin) remain first choice for mild and moderate cases
3. Laboratory tests are usually not needed in mild cases
4. Treatment duration can be limited to 5 days in most cases (3 days in children in areas of low HIV prevalence)

4

### *Box 1 Other relevant WHO documents (please check regularly for updates)*

- WHO 2013 pocket book of hospital care for children [https://apps.who.int/iris/handle/10665/81170\(23\)](https://apps.who.int/iris/handle/10665/81170(23))
- Revised WHO classification and treatment of pneumonia in children at health facilities: evidence summaries. <https://apps.who.int/iris/handle/10665/137319>
- Pneumococcal conjugate vaccines in infants and children under 5 years of age: WHO position paper – February 2019. Weekly Epidemiological Record, 94 (08), 85 - 103. <https://apps.who.int/iris/handle/10665/310970>
- Haemophilus influenzae type b (Hib) Vaccination Position Paper – July 2013: Introduction. Weekly Epidemiological Record, 88 (39), 413 - 426. <https://apps.who.int/iris/handle/10665/242126>
- Vaccines against influenza WHO position paper – November 2012. Weekly Epidemiological Record, 87 (47), 461 - 476. [(<https://apps.who.int/iris/handle/10665/241993>)]
- Guidelines for treatment of drug-susceptible tuberculosis and patient care, 2017 update. <https://apps.who.int/iris/handle/10665/255052>

## 5 Definition

6 Community-acquired pneumonia (CAP) is an acute illness affecting the lungs caused by  
7 pathogens (most often bacteria and viruses). It usually presents with cough, sputum production  
8 (in adults), rapid and difficult breathing with new or worsening pulmonary infiltrate(s) on chest  
9 imaging.

## 10 Pathophysiology

11 CAP occurs when microbial pathogens (usually inhaled in the upper airways) reach the lower  
 12 respiratory tract and proliferate in the alveoli. Less frequently, these pathogens can also reach  
 13 the alveoli via the blood or by direct spread (e.g. from an infection of the pleural or intra-  
 14 abdominal space). Once in the alveoli, host immune defences are activated to eliminate the  
 15 pathogens. Only when these defences fail, pneumonia manifests itself because of the tissue  
 16 damage and inflammatory response triggered by the proliferation of microorganisms in the  
 17 affected lung(s).

## 18 Epidemiology

19 CAP is common worldwide and is a leading cause of morbidity and mortality, with an especially  
 20 high burden in low-income countries (106). According to the Global Burden of Disease study, in  
 21 2017 there were an estimated 471 million new cases of lower respiratory tract infections  
 22 (including CAP but also a majority of cases of viral bronchitis – therefore caution is needed in  
 23 interpreting this number) globally among all ages and sexes combined (31). The incidence of CAP  
 24 varies with age and a country's income level. The most common causative pathogen worldwide  
 25 is *Streptococcus pneumoniae* and viruses (see below); viral–bacterial coinfections may occur.

26 In low-income countries, lower respiratory tract infections (including CAP) were the leading cause  
 27 of death in 2016 with a crude yearly attributable mortality of about 75 per 100 000 population  
 28 (107). In general, the incidence of CAP is highest in children under 5 years in these countries. In  
 29 2015, an estimated 0.9 million children under 5 years died of pneumonia and of these, about 0.5  
 30 million occurred in sub-Saharan Africa (108). Undernutrition, HIV infection, exposure to smoke  
 31 and air pollution are common risk factors for severe CAP in children under 5. As a result of better  
 32 access to medical care, better nutrition and greater vaccination coverage, global mortality rates  
 33 in children have declined by more than 30% since 2000. In high-income countries, CAP mainly  
 34 affects adults 65 years and older and, in general, the incidence of CAP and risk of death increase  
 35 with age (109).

## 36 Microbiology epidemiology

37 In **neonates** (up to 2 months), pneumonia is mainly caused by *Streptococcus pneumoniae*, group  
 38 B *Streptococcus*, Enterobacteriales or *Staphylococcus aureus*.

39 In **children aged 2 months to 5 years**, pneumonia is more likely to be of viral origin (e.g.  
 40 respiratory syncytial virus, influenza and parainfluenza virus). The most important bacterial  
 41 pathogen in children under 5 years is *Streptococcus pneumoniae*. In older children *S. pneumoniae*  
 42 is still common but “atypical bacteria” such as *Mycoplasma pneumoniae* and *Chlamydia*  
 43 *pneumoniae* may occur (“atypical bacteria” have intrinsic resistance to beta-lactam antibiotics  
 44 and cannot be visualized by Gram staining). *Haemophilus influenzae*, *Moraxella catarrhalis* and  
 45 *Staphylococcus aureus* also cause CAP in some children (Table 1).

46 In adults, viruses are common causes of CAP (Table 1), either by directly causing pneumonia or  
 47 by favouring superinfection with bacteria. Among bacteria, the most common causative agents  
 48 are *Streptococcus pneumoniae*, followed by “atypical bacteria” (see definition in the paragraph  
 49 above) such as *Mycoplasma pneumoniae*, *Chlamydia pneumoniae* and *Legionella pneumophila*.  
 50 *Haemophilus influenzae*, *Moraxella catarrhalis* and *Staphylococcus aureus* are also quite  
 51 common (Table 1).

52 However, determining the cause of bacterial pneumonia is difficult in all age groups and no  
 53 causative pathogen is identified in most cases, even if extensive microbiological tests are  
 54 performed (which is usually not the case for mild cases). Furthermore, there may be important  
 55 geographic differences in the cause of pneumonia; for example, *Burkholderia pseudomallei* is a  
 56 cause of CAP in South-East Asia, while *Coxiella burnetii* is more common in regions with exposure  
 57 to livestock.

58 *Table 1 Pathogens most frequently associated with community-acquired pneumonia (in*  
 59 *descending order of frequency)*

“Typical” bacteria	“Atypical” pathogens <sup>a</sup>	Respiratory viruses	Other pathogens to consider in specific settings
<i>Streptococcus pneumoniae</i> <sup>b</sup>  <i>Haemophilus influenzae</i>  <i>Moraxella catarrhalis</i>  <i>Staphylococcus aureus</i>  Enterobacterales (e.g. <i>Escherichia coli</i> , <i>Klebsiella pneumoniae</i> )	<i>Mycoplasma pneumoniae</i> <sup>c</sup>  <i>Chlamydia pneumoniae</i> <sup>c</sup> and <i>Chlamydia psittaci</i> <sup>c</sup>  <i>Legionella</i> spp.  <i>Coxiella burnetii</i>	Influenza virus (A and B)  Respiratory syncytial virus (RSV) <sup>d</sup>  Metapneumovirus  Parainfluenza virus  Coronavirus (including SARS-CoV-2)  Adenovirus  Rhinovirus	<i>Burkholderia pseudomallei</i> (South-East Asia, Australia)  <i>Mycobacterium tuberculosis</i>  <i>Pneumocystis jirovecii</i> (in people with HIV or other types of cellular immunosuppression)

60 <sup>a</sup>“Atypical” bacteria remain colourless with Gram staining. They also have intrinsic resistance to beta-lactams.

61 <sup>b</sup>The most common bacterial cause of CAP in all age groups (beyond the first week of life) is *Streptococcus pneumoniae*.

62 <sup>c</sup>*Mycoplasma pneumoniae* and *Chlamydia* spp. are more frequent in children > 5 years (compared with younger children) and in young adults.

63 <sup>d</sup>Up to 50% of cases of pneumonia in children < 5 years are caused by a virus (most commonly respiratory syncytial virus)

## 67 Community-acquired pneumonia caused by antibiotic-resistant 68 pathogens

69 Antimicrobial resistance is a potential problem with all pathogens associated with CAP. Clinically  
 70 relevant high-level beta-lactam resistance in *Streptococcus pneumoniae* is though still rare

71 globally. Resistance to macrolides in *Streptococcus pneumoniae* and *Mycoplasma pneumoniae*  
 72 is highly prevalent in some settings (110, 111).

**CAP caused by low level and intermediate level pneumococcal penicillin resistance can be successfully treated with higher oral doses of the Access antibiotics amoxicillin or penicillin in children and adults.**

73 There is no evidence of improved clinical outcomes in patients with pneumococcal pneumonia in  
 74 the primary health care setting treated with oral cephalosporins, amoxicillin + clavulanic acid or  
 75 macrolides compared to amoxicillin and penicillin, and these antibiotics are associated with  
 76 higher rates of toxicity.

## 77 Clinical presentation

78 Nearly all respiratory diseases can mimic the symptoms of CAP. Based on clinical features alone  
 79 it is often impossible to distinguish bacterial from viral pneumonia or from other non-infectious  
 80 causes (local epidemiology and laboratory tests may help).

81 Well-established clinical features of CAP include a combination of: new onset (less than 2 weeks)  
 82 of symptoms, worsening cough with or without sputum production, dyspnoea (difficulty in  
 83 breathing), tachypnoea (abnormal respiratory rates to diagnose rapid breathing vary with age),  
 84 reduced oxygen saturation, crepitations on lung auscultation, or chest pain or discomfort without  
 85 an alternative explanation. Fever  $\geq 38.0\text{ }^{\circ}\text{C}$  for 3–4 days is usually present but may be absent,  
 86 especially in the elderly. Extrapulmonary features such as confusion or disorientation may be the  
 87 main symptoms in elderly people, immunosuppressed patients and malnourished children. The  
 88 severity of signs and symptoms may range from a mild disease that can be safely managed in an  
 89 outpatient setting with oral antibiotic treatment to severe pneumonia with respiratory distress,  
 90 sepsis requiring intensive care and intravenous antibiotic treatment with a high associated  
 91 mortality.

92 **In children** the WHO defines fast breathing pneumonia as a child with a high respiratory rate for  
 93 their age (>50 breaths/minute in children 2-11 months of age; >40 breaths/minute in children  
 94 aged 1-5 years). They may or may not have chest indrawing.

## 95 Laboratory tests

### 96 I. Patient microbiology tests

97 In mild cases that can be managed in the outpatient setting, microbiology tests are usually not  
 98 needed.

### 99 II. Other tests

100 In mild cases, laboratory tests are usually not needed. If available, point-of-care testing for C-  
 101 reactive protein (CRP) could be considered in adult patients if there is diagnostic uncertainty.

102 In general, CRP has good negative predictive value, and a negative test can be used to help rule  
 103 out bacterial pneumonia (unless the pre-test probability is high or the clinical presentation is  
 104 severe).

### 105 III. Using microbiology surveillance data

106 The great majority of episodes of CAP in the primary care setting are caused by pneumococcal  
 107 isolates that clinically respond to oral penicillins. Therefore, routine clinical microbiology  
 108 surveillance of CAP does not help to inform local empiric guidance.

## 109 Imaging

110 When mild CAP is suspected clinically, a chest radiograph is usually not necessary.

## 111 Scores to determine disease severity and guide treatment 112 decisions

113 The WHO recommends that children that meet the criteria of severe pneumonia should be  
 114 admitted to hospital (see the Hospital facility section for the management of severe cases).

115 As a general rule for children, hospitalization is indicated in cases of severe illness (e.g. cough  
 116 and severe respiratory distress, marked tachypnoea and tachycardia) and/or if the child is unable  
 117 to take oral therapy.

118 In children, **Severe Pneumonia** is characterized by cough or difficulty breathing plus any of the  
 119 following: i). oxygen saturation < 90%; ii). central cyanosis; iii). severe respiratory distress (e.g.  
 120 grunting, severe chest indrawing) **OR** signs of **Pneumonia (fast breathing with or without chest**  
 121 **indrawing – see above) PLUS a general danger sign** - inability to breastfeed, drink, convulsions,  
 122 lethargy or unconsciousness; and severe respiratory distress (23, 112).

123 **In adults**, several scores exist that measure severity and help predict 30-day mortality. These  
 124 scores, in addition to clinical judgment, can be used to determine the need for hospitalization in  
 125 immunocompetent adults diagnosed with CAP. In view of its simplicity, one of the more  
 126 frequently used scores is the CURB-65(113), or its modification, CRB-65, which does not require  
 127 laboratory values for its calculation (Table 4). However, it should be noted that these scores have  
 128 not been extensively validated in low-income settings and for this reason there is no clear  
 129 consensus about their use in these settings (114). As well as severity scores, other factors, such  
 130 as severe comorbid illnesses (e.g. HIV infection) or inability to maintain oral therapy, should  
 131 always be taken into account in determining the need for hospital admission.

132 *Table 4 CURB-65 criteria and scoring, and treatment decisions*

Criterion	Points
Presence of confusion (new onset)	1
Urea > 19 mg/dL (or > 7 mmol/L) <sup>a</sup>	1
Respiratory rate > 30 breaths/min	1

Systolic blood pressure < 90 mmHg (<12 kPa) or diastolic blood pressure ≤ 60 mmHg (<8 kPa)	1
Age ≥ 65 years	1
<b>CURB-65 score / CRB-65 score</b>	<b>Where to treat</b>
0–1	<b>Candidate for outpatient treatment</b> Low 30-day mortality risk (< 1.5%)
2	<b>Consider inpatient treatment</b> 30-day mortality risk ≈ 10% Consider adding clarithromycin (see Table 6) If tests are available, consider testing for atypical pathogens (e.g. <i>Legionella</i> spp., <i>Mycoplasma</i> spp.)
≥ 3	<b>Inpatient treatment (consider admission to intensive care)</b> High 30-day mortality risk (≈ 20%) Consider adding clarithromycin (see Table 6) Consider testing for atypical pathogens (e.g. <i>Legionella</i> spp., <i>Mycoplasma</i> spp.)

133 Score not validated in low-and middle-income countries (LMICs).

134 <sup>a</sup>Urea is not required for the calculation of the CRB-65 score, a modification of the CURB-65 score that does not  
135 require the execution of laboratory tests.

## 136 Ruling out tuberculosis

137 Tuberculosis (TB) is a cause of subacute lower respiratory tract infection and should be  
138 considered in settings endemic for TB, especially in high-risk patients (e.g. children or adults with  
139 HIV), with a slow onset of symptoms and persistent cough, or those that do not respond to the  
140 initial antibiotic treatment. In such cases, specific investigations for TB should be done. A rapid  
141 molecular test (GeneXpert<sup>®</sup> MTB/RIF assay) performed on a single sputum specimen is currently  
142 the preferred first-line diagnostic test for pulmonary TB and to detect rifampicin resistance in  
143 both children and adults. When this rapid test is not available, microscopy examination of sputum  
144 smears could be considered for the detection of acid-fast bacilli (115). For TB management and  
145 treatment, refer to the WHO *Guidelines for treatment of drug-susceptible tuberculosis and*  
146 *patient care* (116).

## 147 Symptomatic care

148 Patients and/or their caregivers in the primary health care setting should be informed about the  
149 natural course of CAP, including the possibility of a viral etiology that would not benefit from  
150 antibiotic treatment and that cough and other symptoms often take 2-3 weeks to fully recover  
151 back to normal. Patients should also receive clear advice on seeking medical care with any  
152 worsening of symptoms and recommended symptomatic treatment (e.g., antipyretics) (Table 5).

153 *Table 5 Medicines to consider for symptomatic treatment of community-acquired pneumonia*

Molecule	Formulation	Dose and frequency
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<p>Paracetamol (acetaminophen)<sup>a</sup></p>	<p>Oral liquid: 120 mg/5 mL; 125 mg/5 mL Suppository: 100 mg Tablet: 100 mg to 500 mg</p>	<p><b>Adults:</b> 500 mg–1 g given every 4 to 6 hours (maximum dose of 4 g a day)<sup>b</sup></p> <p><b>Children:</b></p> <ul style="list-style-type: none"> <li>• Pain control/ Antipyretic treatment: 10–15 mg/kg given every 6 hours</li> </ul> <p>3-&lt;6 Kg: 60 mg given every 6 hours 6-&lt;10 kg: 100 mg given every 6 hours 10-&lt;15 kg: 150 mg given every 6 hours 15-&lt;20 kg 200 mg given every 6 hours 20-&lt;30 kg: 300 mg given every 6 hours ≥30 kg: Use adult dose</p>
<p>Ibuprofen<sup>c</sup></p>	<p>Oral liquid: 200 mg/5 mL Tablet: 200 mg; 400 mg; 600 mg</p>	<p><b>Adults:</b> 200–400 mg given every 6 to 8 hours (maximum dose of 2.4 g a day)</p> <p><b>Children:</b></p> <ul style="list-style-type: none"> <li>• Pain control / Antipyretic treatment: 5–10 mg/kg given every 6 to 8 hours</li> </ul> <p>6-&lt;10 kg: 50 mg given every 8 hours 10-&lt;15 kg: 100 mg given every 8 hours 15-&lt;20 kg 150 mg given every 8 hours 20-&lt;30 kg: 200 mg given every 8 hours ≥30 kg: Use adult dose</p>

154 <sup>a</sup>Not recommended for use as an anti-inflammatory as it has not been proven to have such an effect.

155 <sup>b</sup>In patients with hepatic impairment or cirrhosis, maximum daily dose should be 2 g.

156 <sup>c</sup>Not for children < 3 months.

## 157 Antibiotic treatment

158 The primary goal of empiric antibiotic treatment in CAP is to provide effective and timely  
159 treatment for *Streptococcus pneumoniae* infection because this is the predominant bacterial  
160 pathogen and untreated pneumococcal pneumonia is associated with high mortality (see Table 6  
161 for adults and 7 for children for treatment recommendations). Amoxicillin or  
162 phenoxymethylpenicillin (sometimes also called penicillin V) are the recommended first choice  
163 options for mild-to-moderate CAP.

164 Empiric treatment should be guided by the age of the patient, severity of symptoms, presence of  
165 comorbidities and previous antibiotic treatment. Clinical improvement should be evident within  
166 48–72 hours of starting antibiotic therapy. If there is no response to treatment, a complication  
167 (such as empyema) should be considered. Duration of treatment should be guided by measures  
168 of clinical improvement (e.g. resolution of fever); usually 5 days of treatment are adequate for  
169 adults and 3-5 days in children.

170 *Table 6 Empiric antibiotic treatment for mild cases of community-acquired pneumonia in adults*

	Adults	Total treatment duration(117, 118)
First choice	Amoxicillin (oral): 1 g given every 8 hours	

	OR <b>Phenoxymethylpenicillin</b> (oral): 500 mg (800.000 IU <sup>a</sup> ) given every 6 hours	5 days
<b>Second choice</b>	<b>Amoxicillin+clavulanic acid</b> (oral): 875 mg + 125 mg given every 8 hours OR <b>Doxycycline</b> (oral): 100 mg given every 12 hours	5 days

171 IU: International units.

172 Notes: All dosages are for normal renal and hepatic function.

173 <sup>a</sup>Units of the potassium salt.

174 **ACCESS** antibiotics are indicated in green, **WATCH** antibiotics in yellow and **RESERVE** antibiotics in red.

175 *Table 7 Empiric antibiotic treatment for mild cases of community-acquired pneumonia in children*  
 176 *(from the WHO document “Revised WHO classification and treatment of childhood pneumonia at*  
 177 *health facilities”)(112)*

	Children	Total treatment duration
<b>Pneumonia (fast breathing and/or chest indrawing)</b>  <b>(treat at home with oral antibiotic)</b>	<b>Amoxicillin</b> (oral): 40-50 mg/kg/dose given every 12 hours  Oral weight bands: 3-<6 kg: 125 mg given every 12 hours 6 - <10 kg: 250 mg given every 12 hours 10 - <15 kg: 500 mg given every 12 hours 15-<20 kg: 750 mg given every 12 hours 20-<30 kg: 1000 mg given every 12 hours ≥ 30 kg: Use adult dose  Children with fast-breathing pneumonia who fail on first-line treatment with amoxicillin should have the option of referral to a facility where there is appropriate second-line treatment.	3 days for children in areas of low HIV prevalence and no chest indrawing  5 days if the child has chest indrawing or lives in region of higher HIV prevalence

178 Notes: All dosages are for normal renal and hepatic function.

179 **ACCESS** antibiotics are indicated in green, **WATCH** antibiotics in yellow and **RESERVE** antibiotics in red.

## 180 Prevention

181 Vaccination can prevent many cases of CAP. Available vaccines are active against pneumococcal  
 182 infection, *Haemophilus influenzae* type b disease and influenza and several vaccines against  
 183 SARS-CoV-2 are available. Vaccines are never 100% effective and because they are serogroup-  
 184 specific, they do not protect against all strains of bacteria or viruses. Duration of protection is  
 185 also variable. As a result, even vaccinated people can develop CAP. *Haemophilus influenzae* type  
 186 b conjugate vaccines and pneumococcal conjugate vaccines should be included in all routine  
 187 infant immunization programmes as they have been very successful in reducing invasive disease  
 188 and in many countries, rates of pneumococcal resistance. Countries should consider the inclusion  
 189 of yearly seasonal influenza vaccination for high-risk populations (pregnant women, elderly

190 people, patients with chronic medical conditions and health care workers) in their vaccination  
191 plan.

DRAFT

# Exacerbation of Chronic Obstructive Pulmonary Disease

## Key messages

1. **Antibiotics are not needed** for most mild cases.
2. Avoid routine sputum culture in mild cases as patients may be colonized by multiple bacteria, making results difficult to interpret.
3. Supplementary oxygen and short-acting inhaled beta-2-agonists are the mainstay of treatment. Steroids are also recommended in many guidelines (improve lung function and shorten time to recovery)
4. Consider antibiotics only in severe cases requiring hospital admission. Most exacerbations are not due to acute bacterial infection.

### Box 1 Other relevant WHO documents (please check regularly for updates)

- Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: 2021 report. Global Initiative for Chronic Obstructive Lung Disease; 2021 [https://goldcopd.org/wp-content/uploads/2020/11/GOLD-REPORT-2021-v1.1-25Nov20\\_WMV.pdf](https://goldcopd.org/wp-content/uploads/2020/11/GOLD-REPORT-2021-v1.1-25Nov20_WMV.pdf)
- Chronic obstructive pulmonary disease (COPD). [https://www.who.int/news-room/fact-sheets/detail/chronic-obstructive-pulmonary-disease-\(copd\)](https://www.who.int/news-room/fact-sheets/detail/chronic-obstructive-pulmonary-disease-(copd))
- Global surveillance, prevention and control of chronic respiratory diseases: a comprehensive approach. <https://apps.who.int/iris/handle/10665/43776>
- Pneumococcal conjugate vaccines in infants and children under 5 years of age: WHO position paper – February 2019. Weekly Epidemiological Record, 94 (08), 85 - 103. <https://apps.who.int/iris/handle/10665/310970>
- Vaccines against influenza WHO position paper – November 2012. Weekly Epidemiological Record, 87 (47), 461 - 476. <https://apps.who.int/iris/handle/10665/241993>

## Definition

An exacerbation of chronic obstructive pulmonary disease (COPD) is an acute event characterized by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication in patients with underlying COPD(119).

## 9 Pathophysiology

10 Exacerbations of COPD are a worsening of the existing underlying chronic inflammation of the  
11 respiratory tract and are caused in most cases by irritants (e.g. pollution, smoking, dusts and  
12 chemicals) or respiratory tract infections. Exacerbations can accelerate a decline in lung function  
13 (i.e. disease progression). The frequency of exacerbations of COPD is variable among individuals  
14 with COPD but they occur more often in case of severe COPD(120).

## 15 Epidemiology

16 According to the global burden of diseases study, in 2017, there were 299 million prevalent cases  
17 of COPD and 3.19 million deaths caused by COPD(31, 121). In 2014, more than 90% of deaths  
18 occurred in low to middle income countries(122).

19 COPD includes emphysema and chronic bronchitis. The most prevalent risk factor is exposure to  
20 tobacco smoke and indoor household air pollution (123). The incidence of exacerbations  
21 increases with age, especially in smokers, and mortality is higher in severe episodes.

## 22 Microbiology epidemiology

23 Exacerbations of COPD are triggered by viral infections in most cases when a pathogen is  
24 identified (Table 1). However, in most cases of exacerbation of COPD, no pathogen is  
25 identified(124, 125).

26 *Table 1 Pathogens most frequently associated with exacerbations of COPD (in descending order*  
27 *of frequency)*

Respiratory viruses (most cases)	Bacteria (less frequently)
Influenza virus (A and B)	<i>Haemophilus influenzae</i>
Respiratory syncytial virus	<i>Moraxella catarrhalis</i>
Parainfluenza virus	<i>Streptococcus pneumoniae</i>
Rhinovirus	Gram-negative bacteria, including <i>Pseudomonas aeruginosa</i> (including multidrug-resistant strains such as those producing ESBL and carbapenemases)
Coronavirus (including SARS-CoV-2)	

## 28 Clinical presentation

29 An exacerbation of COPD should be suspected in cases of recent and sustained worsening of  
30 dyspnoea and cough with increased sputum production compared with the baseline of patients  
31 with COPD (i.e. chronic bronchitis, emphysema and asthma). Symptoms can overlap with those  
32 of pneumonia; however, tachycardia, tachypnoea at rest and crepitations that persist (i.e. that  
33 do not clear) after coughing suggest pneumonia.

34 The decision to hospitalize a person with exacerbation of COPD should be guided by the severity  
35 of symptoms, assessment of comorbidities and availability of home support.

## 36 Laboratory tests

### 37 I. Patient microbiology tests

38 When an exacerbation of COPD is suspected clinically, sputum Gram stain and culture are not  
39 recommended routinely. In people with COPD, the respiratory tract may for example be  
40 colonized with *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and  
41 *Pseudomonas aeruginosa* and a positive culture may indicate colonization rather than acute  
42 infection.

### 43 II. Other tests

44 When exacerbations of COPD are suspected clinically, certain laboratory tests could be  
45 considered, in particular tests that can help identify patients with bacterial infections and that  
46 can help assess the severity of the exacerbation. The rationale is that these patients would  
47 benefit the most from antibiotic treatment. For example, C-reactive protein(126, 127),  
48 procalcitonin and complete blood count and blood gas analysis may be useful. However, there is  
49 no clear consensus across guidelines about which tests should be performed routinely in the  
50 hospital setting and such tests may not be available in many settings.

### 51 III. Using microbiology surveillance data

52 Routine surveillance of clinical isolates from patients presenting with exacerbations of COPD is  
53 not helpful to inform local or national prescribing guidance.

## 54 Imaging

55 A chest radiograph could be considered in patients requiring hospitalization in order to exclude  
56 other diagnoses (e.g. pneumonia, pulmonary oedema) or in outpatients if pneumonia is  
57 suspected and chest radiography is available.

## 58 “No antibiotic care”

59 The core treatment of an exacerbation episode consists of supplementary oxygen and short-  
60 acting inhaled beta<sub>2</sub>-agonists (with or without anticholinergics). Most guidelines currently  
61 recommend using systemic steroids because they help improve lung function and shorten time  
62 to recovery.

63 **A detailed discussion of non-antibiotic management of COPD is beyond the scope of this**  
64 **chapter. Additional information can be found at the WHO website(128).**

## 65 Antibiotic treatment

66 Most exacerbations of COPD are not triggered by bacterial infections, therefore only certain  
67 cases will benefit from antibiotic treatment.

68 **Antibiotics are not needed** for most cases. Their use could be considered in **severe exacerbations**  
69 **of COPD**. Most guidelines suggest antibiotic treatment for patients hospitalized because of an  
70 acute exacerbation of COPD, especially if an increased volume and purulence of sputum is  
71 present, because these cases are more likely to be caused by a bacterial infection. Severe  
72 exacerbations benefit more from antibiotic treatment (see Table 2 for antibiotic options). Current  
73 evidence suggests that the benefit in terms of reduced short-term mortality and reduced  
74 treatment failure is limited to hospitalized patients in intensive care units(129). Previous  
75 colonization of the respiratory tract (e.g. with *Pseudomonas aeruginosa*) needs to be taken into  
76 account when choosing empiric treatment; patients with frequent episodes of COPD  
77 exacerbations may have received multiple courses of antibiotic treatment during the year and  
78 have a higher risk of infections caused by multidrug-resistant pathogens.

79 *Table 2 Empiric antibiotic treatment for exacerbation of chronic obstructive pulmonary disease*

80 **Antibiotic treatment is not required in the great majority of cases**  
81 **(see the "Antibiotic treatment" section above for when antibiotics may be indicated)**

	First choice	Second choice	Total treatment duration
Mild to moderate cases	Amoxicillin (oral): 500 mg given every 8 hours	Cefalexin (oral): 500 mg given every 12 hours OR Doxycycline (oral): 100 mg given every 12 hours	5 days
Severe cases	Amoxicillin+clavulanic acid (oral) 500 mg + 125 mg given every 8 hours	-	5 days

82 Notes: All dosages are for normal renal and hepatic function.

83 ACCESS antibiotics are indicated in green, WATCH antibiotics in yellow and RESERVE antibiotics in red.

## 84 Prevention

85 Appropriate measures to prevent further exacerbations include smoking cessation, reduced  
86 indoor air pollution, use of long-acting inhaled beta<sub>2</sub>-agonists (with or without anticholinergics)  
87 and vaccination (against influenza and *Streptococcus pneumoniae* infection)(39, 41). Currently,  
88 there is no clear consensus on the prophylactic use of antibiotics (e.g. macrolides) in patients  
89 with severe COPD and frequent episodes of exacerbation (130). For specific preventive measures  
90 for chronic respiratory diseases, refer to the WHO publication on global surveillance, prevention  
91 and control of chronic respiratory diseases (131).

# 1 Infectious diarrhoea /

## 2 gastroenteritis

3 (this chapter does not include enteric fever and *Clostridioides difficile* infection; please refer to  
4 the respective chapters when these infections are suspected)

### 5 Key messages

1. **Antibiotics are not needed** in the great majority of cases of watery diarrhoea with or without a fever.
2. Most cases of infectious diarrhoea are self-limiting and are caused by viruses.
3. Antibiotics should only be used in patients with severe bloody diarrhoea (dysentery) or in immunosuppressed patients.
4. When an antibiotic is needed, ciprofloxacin (Watch) is first choice, but azithromycin is preferred in areas of high prevalence of ciprofloxacin resistance among specific bacteria causing infectious diarrhoea (e.g. *Salmonella* spp., *Shigella* spp.).
5. Cholera should be treated with antibiotics only in the context of outbreaks to prevent transmission but the most important intervention is rehydration.

### 6 *Box 1 Other relevant WHO documents (please check regularly for updates)*

- WHO 2013 pocket book of hospital care for children [https://apps.who.int/iris/handle/10665/81170\(23\)](https://apps.who.int/iris/handle/10665/81170(23))
- The treatment of diarrhoea: a manual for physicians and other senior health workers, 4th rev. <https://apps.who.int/iris/handle/10665/43209>
- Diarrhoeal disease [internet]. [(<https://www.who.int/news-room/fact-sheets/detail/diarrhoeal-disease>)]
- Cholera vaccines: WHO position paper – August 2017. Weekly Epidemiological Record, 92 (34), 477 - 498. <https://apps.who.int/iris/handle/10665/258764>
- Rotavirus vaccines: WHO position paper – July 2021. Weekly Epidemiological Record, 96 (28), 301 - 219. [(<https://apps.who.int/iris/handle/10665/342905>)]

### 7 Definition

8 Acute diarrhoeal disease (also known as gastroenteritis) is a disease characterized by acute onset  
9 (usually defined as duration < 14 days) of diarrhoea. Diarrhoea is defined as the passage of  
10 unusually loose or watery stools occurring at least 3 times a day (or more frequent than is normal  
11 for the individual). Consistency (how liquid/runny) rather than frequency (how often) is the most

12 important factor to consider and frequent passing of formed stool is not diarrhoea. In breastfed  
 13 babies, frequent loose “pale” stools are not considered diarrhoea(132). Most cases of acute  
 14 diarrhoea have an infectious origin, but non-infectious causes are also possible (e.g. adverse  
 15 effects of medicines, including antibiotics and cytotoxic chemotherapy; endocrine diseases,  
 16 inflammatory bowel diseases, irritable bowel syndrome). Acute diarrhoea can be further  
 17 subclassified as watery diarrhoea or bloody diarrhoea (i.e. presence of visible blood in the stool).

## 18 Pathophysiology

19 Acute diarrhoeal diseases can be acquired through ingestion of food or water contaminated with  
 20 viral or bacterial pathogens (rarely protozoal or fungal pathogens) or through direct contact with  
 21 someone carrying the pathogen. Establishment of an enteric infection depends on the capacity  
 22 of the pathogen to invade the mucosa and overcome the host defences. It is dependent on  
 23 several factors, including the inoculum, the virulence of the organism and the status of host  
 24 defences. Production of enterotoxins (i.e. bacterial proteins that act on the host’s intestinal cells)  
 25 is a frequently encountered mechanism of disease.

## 26 Epidemiology

27 In 2017, 6.2 billion episodes of diarrhoeal disease are estimated to have occurred worldwide,  
 28 including 500 000 incident cases of non-typhoidal *Salmonella* disease(31).  
 29 Children under 5 years of age are often affected. About 1.7 billion cases of acute diarrhoeal  
 30 disease occur each year in this age group where it is an important cause of death (about 450 000  
 31 deaths in 2016). Acute malnutrition, living in or travelling to areas with limited access to safe  
 32 drinking-water and adequate sanitation are the leading risk factors for acute diarrhoeal  
 33 diseases(133, 134).

## 34 Microbiology epidemiology

35 Most cases of community-acquired acute watery diarrhoeal disease have a viral origin.  
 36 However, bacteria and parasites can also be causes(135). For returning travellers It is important  
 37 to consider travel-associated diarrhoea. Table 1 and 2 give the pathogens most frequently  
 38 associated with acute diarrhoeal disease (in children and adults respectively), and Table 3 those  
 39 associated with chronic or persistent diarrhoea.

40 *Table 1 Pathogens most frequently associated with acute infectious diarrhoea in children (in*  
 41 *descending order of frequency)*

	<b>Viruses (most cases)</b>	<b>Bacteria</b>	<b>Parasites</b>
Low-income settings	Rotavirus  Measles virus <sup>a</sup>	<i>Escherichia coli</i> <i>Shigella</i> spp.	<i>Cryptosporidium</i> spp.
High-income settings	Norovirus Rotavirus Adenovirus	<i>Salmonella</i> spp. <i>Campylobacter</i> spp.	

	Measles virus <sup>a</sup>		
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42 <sup>a</sup>Diarrhoea is the most common complication in measles.

43 *Table 2 Pathogens most frequently associated with acute infectious diarrhoea in adults (in*  
 44 *descending order of frequency)*

	Viruses (most cases)	Bacteria
Low-income settings	Norovirus	<i>Campylobacter</i> spp. <i>Salmonella</i> spp. <i>Shigella</i> spp. <i>Escherichia coli</i>
High-income settings	Norovirus	<i>Salmonella</i> spp. <i>Campylobacter</i> spp. <i>Escherichia coli</i> <i>Shigella</i> spp. <i>Listeria monocytogenes</i>

45 *Table 3 Pathogens most frequently associated with persistent (14–29 days) or chronic (>30 days)*  
 46 *infectious diarrhoea in HIV patients<sup>a</sup>(in descending order of frequency)*

Viruses	Parasites	Fungi (rarely) <sup>a</sup>
<i>Cytomegalovirus</i>	<i>Cryptosporidium</i> spp. <i>Microsporidium</i> spp. <i>Cystoisospora belli</i>	<i>Histoplasma capsulatum</i> <i>Coccidioides</i> spp. <i>Penicillium</i> spp.

47 <sup>a</sup> It should be noted that in these cases, patients often receive unnecessary antibiotic treatment.

48 <sup>b</sup>Rarely in the context of disseminated infections in patients with low CD4 count.

## 49 Clinical presentation

50 In acute diarrhoea, the main symptom is new onset (< 14 days) of three or more unformed stools  
 51 a day, with or without fever. Nausea, vomiting, bloating, abdominal pain and cramping may also  
 52 be present. In most cases, the disease is self-limiting. Since some causative pathogens can be  
 53 endemic in certain settings and absent in others, it is always important to consider where the  
 54 patient became infected (including history of recent travel) and recent consumption of  
 55 potentially unsafe food (e.g. raw meat or unpasteurized milk products). Recent antibiotic use  
 56 (last three months), cytotoxic chemotherapy or the presence of immunosuppression (e.g. HIV  
 57 infection) also need to be investigated.

58 Five common clinical presentations can help identify cases that require specific treatment and  
 59 management(132).

- 60 1. Patients with **watery diarrhoea**: in these patients, the most likely cause is viral (mostly  
 61 rotavirus and norovirus). A mild fever and vomiting may also occur. The main risk is severe  
 62 dehydration and management is symptomatic (e.g. fluid replacement).
- 63 2. Patients with **bloody diarrhoea** (dysentery or invasive diarrhoea with damage to the  
 64 intestinal mucosa): in these patients, the most likely cause are bacteria, mostly *Shigella*  
 65 spp., *Campylobacter* spp., *Salmonella* spp. or enterotoxigenic *Escherichia coli* (ETEC).

66 These cases may benefit from antibiotic treatment. In addition to dehydration these  
 67 infections can be complicated by sepsis and malnutrition. *Schistosoma* (only *Schistosoma*  
 68 *mansoni* and *Schistosoma japonicum*, the intestinal species) and *Entamoeba histolytica*  
 69 can rarely also cause bloody diarrhoea weeks or months after the infection (often these  
 70 infections are responsible for chronic rather than acute bloody diarrhoea).

71 3. Patients with **persistent diarrhoea** (symptoms lasting > 14 days): in these patients, a  
 72 parasite is often implicated (e.g. *Giardia intestinalis*, *Entamoeba histolytica*) and the main  
 73 risks are malnutrition and dehydration.

74 4. **Diarrhoea with severe malnutrition**: in these patients, malnutrition is both a cause and  
 75 consequence of diarrhoea.

76 5. **Diarrhoea with recent antibiotic exposure** (*Clostridioides difficile*). This condition is  
 77 mostly hospital-acquired; please refer to the Handbook chapter on *Clostridioides difficile*  
 78 infection if this is suspected.

79 Patients may present with varying degree of dehydration and this should be promptly assessed,  
 80 especially in children and elderly people. In children, the degree of dehydration can be rated on  
 81 a scale of three as indicated below (Table 4)(133).

82 *Table 4 Classification of dehydration*

Severe dehydration (at least two signs from the list on the right must be present)	<ul style="list-style-type: none"> <li>• Lethargy and/or unconsciousness</li> <li>• Sunken eyes</li> <li>• Inability to drink</li> <li>• Skin pinch goes back very slowly (<math>\geq 2</math> seconds)</li> </ul>
Some dehydration (at least two signs from the list on the right must be present)	<ul style="list-style-type: none"> <li>• Restlessness, irritability</li> <li>• Sunken eyes</li> <li>• Drinks eagerly, is thirsty</li> </ul>
No dehydration	Too few signs to classify as some or severe dehydration

83 WHO classification taken from the Pocket book of Hospital care for children (2013).

## 84 Laboratory tests

### 85 I. Patient microbiology tests

86 Routine stool testing is not needed since most cases are self-limiting and knowing the causative  
 87 agent would not alter management. Testing may be done for infection control purposes (i.e. high  
 88 risk of spreading the disease in specific settings).

89 However, in certain cases and based on local availability, a stool test (e.g. stool microscopy, stool  
 90 culture, antigen testing, nucleic acid amplification tests) could be considered (see Table 5), but  
 91 only when identifying the causative pathogen may benefit the patient (e.g. because specific  
 92 treatment can be provided or a multidrug-resistant pathogen may be detected).

93 Selected cases that could benefit from stool testing include:

- 94 • Patients with bloody diarrhoea
- 95 • Patients with suspected cholera in the context of outbreaks
- 96 • Immunocompromised patients with acute diarrhoea (e.g. to exclude parasitic infections
- 97 often associated with chronic diarrhoea)
- 98 • History of diarrhoea following antibiotic use (suspicion of *Clostridioides difficile*
- 99 infection). Please refer to the Handbook chapter on *Clostridioides difficile* infection if
- 100 this infection is suspected.

101 *Table 5 Microbiology tests to consider in certain cases of diarrhoeal disease as indicated in the*  
 102 *WHO EDL (54)*

Diagnostic test	Purpose of the test	Setting where the test should be available
Stool culture	To detect and identify bacterial species for selection of appropriate antibiotic regimens	Health care facilities with clinical laboratories
Stool microscopy	To detect and identify parasites and their ova (i.e eggs) or cysts	Health care facilities with clinical laboratories
<i>Vibrio cholerae</i> antigen <sup>a</sup> (RDT)	To detect or exclude a cholera outbreak (not for use in case management)	Community settings and health facilities without laboratories

103 RDT: rapid diagnostic test.

104 <sup>a</sup>Possible specimens include: stool and rectal swab.

## 105 II. Other tests

106 Routine laboratory tests are usually not needed. However, for severe cases, electrolytes should  
 107 be checked if available.

## 108 III. Using microbiology surveillance data

109 Targeted clinical microbiological surveys of cases of acute bloody diarrhoea in the primary care  
 110 setting in children and adults, specifically focussing on quinolone and macrolide resistance rates  
 111 in *Shigella* and *Salmonella* spp. may be helpful to inform local empiric antibiotic guidance.

## 112 Imaging

113 Routine imaging is not needed for acute diarrhoeal disease.

## 114 “No antibiotic care”

115 Rehydration is the main treatment for acute diarrhoeal disease (oral or intravenous). In children,  
 116 treating any diarrhoea with an oral rehydration solution (ORS) is recommended. An oral  
 117 rehydration solution is composed of clean water, sugar and salt (“make-at-home” ORS is  
 118 composed of 1L water, 6 tablespoons of sugar, 1/2 tablespoon of salt, more information available  
 119 in the EML/c - <https://list.essentialmeds.org/recommendations/1112>). In addition, zinc tablets

120 (10–20 mg/day) for 10–14 days are usually recommended to shorten the duration and severity  
121 of symptoms (3).

122 In adults, an oral rehydration solution is not usually needed, and fluid losses can be compensated  
123 by drinking adequate fluids and fruit juices. However, in severely dehydrated adult patients, an  
124 oral rehydration solution can be given. Antidiarrhoeal and antiemetic medicines are not routinely  
125 needed because they do not prevent dehydration and do not improve nutritional status(132).

## 126 Antibiotic treatment

127 **Antibiotics are not needed** in most cases of acute diarrhoeal disease because they are of viral  
128 origin and the illness is usually self-limiting regardless of the causative pathogen. Rehydration is  
129 the main treatment for acute diarrhoeal disease(132). Even in cases with severe dehydration,  
130 antibiotic treatment is not routinely needed.

131 However, in patients with significant bloody diarrhoea and in severely immunosuppressed  
132 patients, antibiotics may be given (see Table 6 for empiric options based on the risk of  
133 fluoroquinolone resistance). If symptoms do not resolve after 24–48 hours of antibiotic  
134 treatment, adding a treatment course of metronidazole for possible *Entamoeba histolytica* and  
135 *Giardia intestinalis* infection could be considered.

136 In addition, antibiotic treatment could be considered in the context of cholera outbreaks to  
137 reduce transmission. Severe dehydration is not in itself a reason for giving antibiotic treatment  
138 in case of cholera (Table 7).

139 Bloody diarrhoea could be caused by certain strains of *E. coli* (Shiga toxin-producing *E. coli* also  
140 known as Enterohemorrhagic *E. coli*). In these cases (mostly in children) the use of antibiotics is  
141 controversial because there is a theoretical concern that it could worsen symptoms of haemolytic  
142 uremic syndrome (characterized by haemolytic anemia, renal injury and low platelets).

143 *Table 6 Empiric antibiotic treatment for selected cases of infectious acute diarrhoea*

144 **It is important to note that only certain cases of diarrhoeal disease benefit from antibiotic**  
145 **treatment.**

	Adults	Children	Total treatment duration
<b>First Choice</b>	Ciprofloxacin <sup>a</sup> (oral): 500 mg given every 12 hours	Ciprofloxacin <sup>a</sup> (oral): 10-20 mg/kg/dose given every 12 hours  Oral weight bands: 3-<6 kg: 50 mg given every 12 hours 6-<10 kg: 100 mg given every 12 hours 10-<15 kg: 150 mg given every 12 hours 15-<20 kg: 200 mg given every 12 hours 20-<30 kg: 300 mg given every 12 hours ≥ 30 kg: Use adult dose	3 days
<b>Second Choice</b>	<b>Oral options</b> Azithromycin <sup>b</sup> (oral): 500 mg given once a day (on day 1)	<b>Oral options</b> Azithromycin <sup>b</sup> (oral): 10 mg/kg/dose given once a day OR	Azithromycin: 4 days

	<p>followed by 250 mg given once a day for 3 days OR <b>Cefixime<sup>c</sup></b> (oral): 400 mg given once a day OR <b>Sulfamethoxazole+trimethoprim<sup>c,d</sup></b> (oral): 800 mg + 160 mg given every 12 hours</p> <p><b>Parenteral option</b> <b>Ceftriaxone<sup>c</sup></b> (IV/IM): 1 g given once a day</p>	<p><b>Cefixime<sup>f</sup></b> (oral): 10 mg/kg/dose given once a day  OR <b>Sulfamethoxazole+trimethoprim<sup>c,d</sup></b> (oral): 20 mg/kg + 4 mg/kg given every 12 hours</p> <p>Oral weight bands (mg of the sulfamethoxazole/trimethoprim component): 3-&lt;6 kg: 100 mg/20 mg given every 12 hours 6-&lt;10 kg: 200 mg/40 mg given every 12 hours 10-&lt;15 kg: 400 mg/80 mg given every 12 hours 15-&lt;20 kg: 400 mg/80 mg given every 12 hours 20-&lt;30 kg: 400 mg/80 mg given every 12 hours ≥ 30 kg: Use adult dose</p> <p><b>Parenteral option</b> <b>Ceftriaxone<sup>c</sup></b> (IV/IM): 80 mg/kg/dose given once a day</p>	<p>Cefixime: 3 days (adults), 5 days (children)</p> <p>Sulfamethoxazole +trimethoprim: 5 days</p> <p>Ceftriaxone: 3 days</p>
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- 146 Notes: All dosages are for normal renal and hepatic function.
- 147 <sup>a</sup>If symptoms do not resolve within 24–48 hours of treatment, consider *Entamoeba histolytica* or *Giardia intestinalis*
- 148 as possible causes and provide appropriate treatment.
- 149 <sup>b</sup>Azithromycin is preferred in case of high prevalence of ciprofloxacin resistance among bacteria frequently
- 150 associated with acute infectious diarrhoea (e.g. *Salmonella* spp., *Shigella* spp.).
- 151 <sup>c</sup>Cefixime, ceftriaxone and sulfamethoxazole+ trimethoprim are not active against *Campylobacter* spp.
- 152 <sup>d</sup>Ideally, sulfamethoxazole+trimethoprim should only be used if local data suggest susceptibility or if the isolated
- 153 strain is susceptible. As per WHO 2005 guidelines, this antibiotic should not be used empirically when shigellosis is
- 154 suspected (132).
- 155 **ACCESS** antibiotics are indicated in green, **WATCH** antibiotics in yellow and **RESERVE** antibiotics in red.

156 *Table 7 Empiric antibiotic treatment for cholera*

157 **Antibiotic treatment for cholera should only be considered in the context of an outbreak and**

158 **not based on the degree of dehydration. The rationale of giving an antibiotic during outbreaks**

159 **is to reduce transmission but the cornerstone of treatment remains rehydration.**

Adults	Children
<p><b>First choice</b> <b>Azithromycin<sup>a</sup></b> (oral): 1 g, single dose OR</p>	<p><b>First choice</b> <b>Azithromycin<sup>a</sup></b> (oral): 20 mg/kg, single dose</p>

<p><b>Doxycycline</b> (oral): 300 mg, single dose (or 100 mg given every 12 hours for 3 days if single dose is not tolerated)</p>	
<p><b>Second choice</b></p> <p><b>Ciprofloxacin</b> (oral): 1 g, single dose</p>	<p><b>Second choice</b></p> <p><b>Ciprofloxacin</b> (oral): 10-20 mg/kg, single dose OR <b>Doxycycline</b> (oral):</p> <ul style="list-style-type: none"> <li>• &lt;45 Kg (&lt;12 years): 2 to 4 mg/kg, single dose</li> <li>• &gt;45 Kg (&gt;12 years): 300 mg, single dose</li> </ul>

160 Notes: All dosages are for normal renal and hepatic function.  
 161 <sup>a</sup>Azithromycin is preferred because of the decreasing susceptibility of cholera to tetracyclines and  
 162 fluoroquinolones. Because of the long half-life of azithromycin, it should only be recommended for outbreak  
 163 situations, where single-dose treatment is especially useful.  
 164 **ACCESS** antibiotics are indicated in green, **WATCH** antibiotics in yellow and **RESERVE** antibiotics in red.

## 165 Prevention

166 Key measures to prevent acute diarrhoeal diseases include access to safe drinking-water, use of  
 167 improved sanitation, hand washing with soap, exclusive breastfeeding for the first 6 months of  
 168 life, good personal and food hygiene, health education about how infections spread and  
 169 vaccination against rotavirus, particularly in countries with a high rate of death associated with  
 170 rotavirus(133). Vaccination against cholera should also be considered, especially in endemic  
 171 areas, in humanitarian crises (high-risk of cholera) and during outbreaks. Vaccination against  
 172 cholera should always be accompanied with other prevention and control strategies. Vaccination  
 173 against measles could also substantially reduce the incidence and severity of diarrhoeal diseases  
 174 and therefore every infant should be immunized against measles at the recommended age. For  
 175 updated information on vaccination, refer to the most recent WHO position paper on  
 176 vaccination(136, 137).

# 1 Enteric fever

## 2 Key messages

1. Most cases of enteric fever are caused by *Salmonella* Typhi (70–80% of cases).
2. Access to safe water and appropriate hygiene among food handlers is key to prevent the infection (vaccination should also be offered in endemic areas and during outbreaks)
3. Symptoms are often difficult to distinguish from other febrile illnesses
4. Blood cultures should be taken in all cases requiring hospitalization
5. Choice of empiric antibiotic treatment depends on the risk of fluoroquinolone resistance of *Salmonella* Typhi

### 3 Box 1 Other relevant WHO documents (please check regularly for updates)

- WHO 2013 pocket book of hospital care for children [https://apps.who.int/iris/handle/10665/81170\(23\)](https://apps.who.int/iris/handle/10665/81170(23))
- Typhoid vaccines: WHO position paper – March 2018 – Weekly Epidemiological Record, 93 (13), 153 - 172. <https://apps.who.int/iris/handle/10665/272273>

## 4 Definition

5 Enteric fever is a severe systemic illness characterized by fever and abdominal pain caused by  
6 the bacterium *Salmonella enterica*, serotypes Typhi or Paratyphi.

## 7 Microbiology epidemiology

8 Enteric fever is caused by *Salmonella enterica* serotypes Typhi or Paratyphi A, B or C, a Gram-  
9 negative bacterium. *Salmonella* spp. (non-typhi) is not a cause of enteric fever but a cause of  
10 infectious gastroenteritis (see chapter).

## 11 Pathophysiology

12 Enteric fever is acquired through ingestion of food or water contaminated with *Salmonella* Typhi  
13 or Paratyphi or through direct contact with someone carrying the pathogen. Humans are the only  
14 source of these bacteria. Once the pathogen is ingested, it invades the intestinal mucosa  
15 primarily through the distal ileum. Once there, host immune defences are activated to eliminate  
16 the pathogen. However, these white cells can also act as carriers of the infection through the  
17 lymphatic system to the liver, spleen, bone marrow and lymph nodes, and ultimately to the  
18 bloodstream. Natural infection does not provide complete protection so recurrent illness is  
19 possible(138).

## 20 Epidemiology

21 Most cases of enteric fever are caused by *Salmonella* Typhi (70–80% of cases). Even though the  
22 absolute number of new cases of enteric fever has declined by 45% and the number of deaths by  
23 41% since the 1990s, the disease is still endemic, mostly in sub-Saharan Africa and in South  
24 Asia(139). Based on available data, India, Pakistan and Bangladesh are the countries with the  
25 highest incidence of enteric fever (> 500 cases per 100 000 population in 2017)(139). In 2017,  
26 about 14.3 million cases of enteric fever occurred worldwide(139). In endemic countries, children  
27 are affected the most with almost 60% of cases occurring in children under 15 years of age. Based  
28 on the data available, when appropriately treated with antibiotics, the case fatality rate for  
29 enteric fever is about 1%(139). Complications (e.g. intestinal perforation) in hospitalized cases  
30 are estimated to occur in 20–30% of cases, with a higher risk in people presenting for care after  
31 having had symptoms for more than 10 days(140).

## 32 Clinical presentation

33 Symptoms of enteric fever are often non-specific, making it difficult to distinguish enteric fever  
34 from other febrile illnesses. As a result, misdiagnosis of cases can occur. In patients with enteric  
35 fever, protracted fever ( $\geq 38.0$  °C for more than 3 days) is the main symptom. Headache is often  
36 present as well as loss of appetite and nausea. Gastrointestinal symptoms may not be present,  
37 and diarrhoea is seen more frequently in children and in people with HIV. The clinical  
38 presentation can vary from mild illness with a low-grade fever and malaise to severe disease  
39 presenting with septic shock and peritonitis because of intestinal bleeding and perforation.  
40 Encephalopathy can also occur in severe cases. Of note, clinical features are also not useful to  
41 distinguish infections caused by *Salmonella enterica* serotype Typhi from those caused by  
42 *Salmonella enterica* serotype Paratyphi.

## 43 Laboratory tests

### 44 Patient microbiology tests

45 In patients with suspected enteric fever, the diagnosis is largely dependent on the clinical  
46 presentation and detection of the pathogen in blood cultures, even though the sensitivity is low,  
47 especially when antibiotic treatment has already been started (Table 1). **A blood culture should  
48 be taken in all possible cases with fever requiring hospitalization, ideally before starting  
49 antibiotic treatment.** Bone marrow cultures is the most sensitive diagnostic method, but these  
50 cultures are very rarely done because they are more difficult to perform and invasive. Stool  
51 cultures are usually negative in the early phases of the infection and therefore they are of limited  
52 diagnostic use. Widal serology is still widely used in LMIC; however, it is not a reliable method to  
53 diagnose acute illness because a positive result may represent a previous infection and in  
54 returning travellers, vaccination prior to travel affects the results. Ideally the Widal serology  
55 requires two samples taken 10 days apart to demonstrate a 4-fold rise of anti- *S. typhi* antibodies  
56 and this is not practical in many low-resource settings.

57 *Table 1 Microbiology tests to consider when enteric fever is suspected as indicated in the WHO*  
 58 *EDL (54)*

Diagnostic test	Purpose of the test	Setting where the test should be available
Blood cultures <sup>a</sup>	To detect bacterial and fungal bloodstream infections (sepsis)	Health care facilities with clinical laboratories
Bone marrow culture <sup>b</sup>	Initial step in detection and identification of bacterial and fungal species for selection of appropriate antibiotic regimens	Health care facilities with clinical laboratories
Stool culture <sup>c</sup>	Initial step in detection and identification of bacterial and fungal species for selection of appropriate antibiotic regimens	Health care facilities with clinical laboratories

59 <sup>a</sup>Often the mainstay of diagnosis; Without antibiotic treatment blood cultures are often positive (5-7 out of 10  
 60 patients) however, sensitivity is low, if antibiotics have already been started.

61 <sup>b</sup>The gold standard for diagnosis but it is often not feasible to do.

62 <sup>c</sup>Low sensitivity and not useful in the early phase (1<sup>st</sup> week) of disease when the test is often negative.

## 63 II. Other tests

64 Routine laboratory testing is not always needed but could be considered in severe cases (i.e.  
 65 routine haematology and biochemistry).

## 66 III. Using microbiology surveillance data

67 Targeted clinical microbiological surveys of enteric fever related blood stream infection focussing  
 68 on *Salmonella enterica* serotype Typhi and Paratyphi resistance rates may help inform local and  
 69 national empiric antibiotic guidance.

## 70 Imaging

71 Routine imaging is not needed.

## 72 Antibiotic treatment

73 In cases of enteric fever, antibiotic treatment should be started promptly because delays are  
 74 associated with higher risk of complications and severe disease. In general, antibiotic treatment  
 75 is given to shorten the duration of symptoms and to reduce the risk of complications, such as  
 76 intestinal perforation and chronic carriage (chronic carriers are asymptomatic persons who  
 77 continue to harbor the pathogen for months or even years after their initial infection and can  
 78 transmit the infection). Fever usually decreases slowly, after around 3–5 days of effective  
 79 treatment. Mild cases can be treated as outpatients with oral treatment, while severe cases  
 80 should be treated as inpatients with systemic intravenous treatment.

81 The choice of oral antibiotic if possible, should be based on the sensitivity of the isolated  
 82 pathogen. When choosing empiric treatment, the local prevalence of fluoroquinolone resistance  
 83 should be considered because of the increasing number of resistant isolates, mostly in Asia(141).  
 84 In these settings, a third-generation cephalosporin or azithromycin are appropriate options  
 85 because resistance to these antibiotics is still low in most settings (< 5% for ceftriaxone and only  
 86 sporadic cases with resistance to azithromycin). Of note, antibiotics that were widely used in the  
 87 1980s and 1990s but fell in disuse because of resistance or toxicity concerns (e.g. ampicillin,  
 88 chloramphenicol and sulfamethoxazole+trimethoprim) are again effective in some settings  
 89 (mostly in Asia). However, the empiric use of these “old” first options for treatment is  
 90 discouraged because it could prompt a rebound of multidrug-resistant organisms.

91 **Step-down** to oral treatment is based on improvement of symptoms and signs of infection and  
 92 the ability to take oral antibiotics allowing discharge of the patient home when clinically  
 93 appropriate.

## 94 Combination treatment

95 Currently, a single-antibiotic regimen is recommended (Table 2). However, the combination of a  
 96 third-generation cephalosporin (ceftriaxone) and azithromycin has been reported to reduce the  
 97 duration of symptoms. This approach is suggested in some guidelines for severe cases(142, 143).

98 *Table 2 Empiric antibiotic treatment for enteric fever*

Risk of fluoroquinolone resistance <sup>a</sup>	Adults	Children	Total treatment duration
Low	<b>Ciprofloxacin</b> (oral): 500 mg given every 12 hours	<b>Ciprofloxacin</b> (oral): 10-20 mg/kg/dose given every 12 hours  Oral weight bands: 3-<6 kg: 50 mg given every 12 hours 6-<10 kg: 100 mg given every 12 hours 10-<15 kg: 150 mg given every 12 hours 15-<20 kg 200 mg given every 12 hours 20-<30 kg: 300 mg given every 12 hours ≥ 30 kg: Use adult dose	Mild cases: 7 days  Severe cases: 10 days if the patient is clinically improving and without a fever for 48 hours
High	<b>Mild cases</b> <b>Azithromycin</b> (oral): 1 g given once a day (on day one) followed by 500 mg given once a day  <b>Severe cases</b>	<b>Mild cases</b> <b>Azithromycin</b> (oral): 20 mg/kg/dose given every 12 hours  <b>Severe cases</b>	

	Ceftriaxone <sup>b</sup> (IV): 2 g given once a day	Ceftriaxone <sup>b</sup> (IV): 80 mg/kg/ dose given once a day	
--	---	--	--

99 Notes: All dosages are for normal renal and hepatic function.

100 <sup>a</sup>It should be noted that there is no clearly defined prevalence of resistance in a certain setting that defines low  
101 versus high risk of fluoroquinolone resistance.

102 <sup>b</sup>In settings where ceftriaxone-resistance is increasing, azithromycin should be prioritized. In general, when  
103 ceftriaxone is used, changing to oral treatment could be considered when there is symptomatic improvement. If  
104 available, the choice of oral options to use could be guided by susceptibility testing results, including the possibility  
105 of using certain first-choice options that were used in the past.

106 ACCESS antibiotics are indicated in green, WATCH antibiotics in yellow and RESERVE antibiotics in red.

## 107 Prevention

108 Access to safe water and adequate sanitation, health education, appropriate hygiene among food  
109 handlers, and typhoid vaccination are all effective strategies for prevention and control of  
110 typhoid fever(144). For updated information on vaccines to prevent enteric fever, please refer  
111 to the most recent WHO position paper on vaccination(144). Vaccination should be prioritized in  
112 countries with the highest burden of enteric fever (especially where antibiotic resistance is high)  
113 and in response to confirmed outbreaks. A recent systematic review evaluated the effects of  
114 different types vaccines for preventing enteric fever and found that the two commonly used  
115 vaccines (Ty21a and Vi polysaccharide) overall prevent around half of typhoid cases during the  
116 first three years after vaccination(145).

# Skin and soft tissue infections - Mild bacterial impetigo, erysipelas and cellulitis

This chapter does not cover severe skin infections or skin infections caused by viral, fungal or parasitic pathogens, or management of diabetic foot infections. Please refer to the specific chapters about other skin and soft tissue infections – traumatic wounds (including bite wounds), burn wounds, necrotizing fasciitis, pyomyositis - if these infections are suspected.

## Key messages

1. Topical treatment can be used for mild impetigo.
2. Diagnostic tests are usually not needed in mild cases (avoid swabs of intact skin).
3. The most likely causative pathogens are *Staphylococcus aureus* and *Streptococcus* spp.
4. Oral antibiotics of the Access group are adequate for most cases.
5. There is no need to empirically treat for MRSA in most cases.

### Box 1 Other relevant WHO documents (please check regularly for updates)

- WHO 2013 pocket book of hospital care for children <https://apps.who.int/iris/handle/10665/81170> (23).

## Definition

The terminology used to define skin and soft tissue infections (SSTIs) has changed over the years. In general, the terms “bacterial skin and soft tissue infections” and “bacterial skin and skin structures infections” are often used interchangeably.

While there is no universally accepted classification of skin infections, there are numerous ways to classify SSTIs based on certain characteristics of the infection such as anatomic location (folliculitis, fasciitis, myositis), body location (e.g. extremities, face), timing (acute, chronic, recurrent), presence of tissue necrosis (necrotizing or not necrotizing), macroscopic presence of pus (purulent or non-purulent) or involvement of deep subcutaneous tissue and / or severity of disease (complicated or uncomplicated). Further classifications are based on the origin of the infection (bites, burns; see corresponding chapters) or host characteristics (immunosuppression, diabetes etc.).

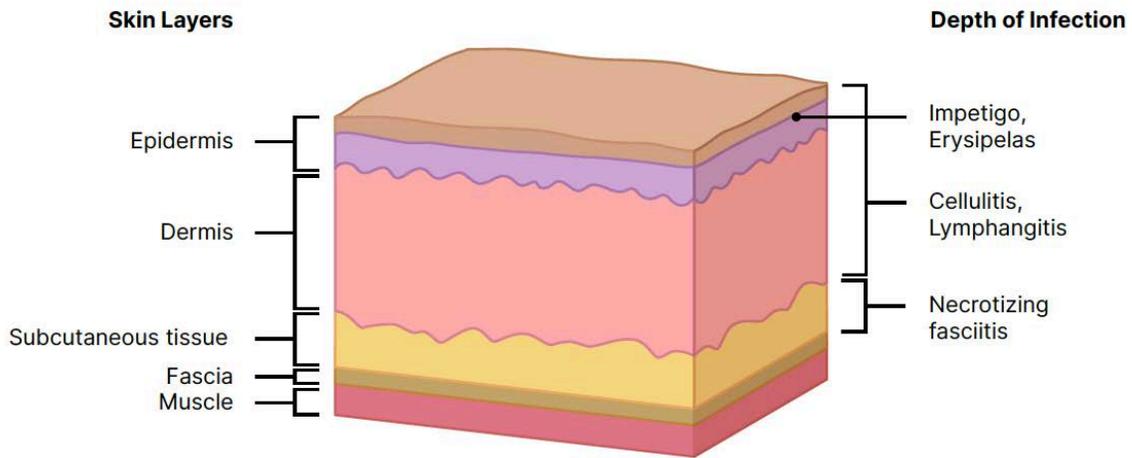
A more recent definition by the United States Food and Drug Administration uses the term “acute bacterial skin and skin structure infections – ABSSSI ” to include a subset of conditions such as

24 cellulitis and erysipelas, wound infections and major cutaneous abscesses provided the area of  
 25 the skin surface affected is at least 75 cm<sup>2</sup>. This definition was introduced “to assist sponsors  
 26 developing drugs for the treatment of skin infections” and has limited clinical applicability outside  
 27 trials (146).

28 This chapter focuses on the mild superficial forms of skin infections that do not affect deeper  
 29 tissue layers: impetigo, erysipelas and cellulitis. For the more severe forms of SSTI, please refer  
 30 to the corresponding chapters: necrotizing fasciitis; pyomyositis; burn wounds; and severe  
 31 infections with sepsis. The following syndromes are not covered in the current version of this  
 32 Handbook: acne; diabetic foot infections; and surgical site infections.

### 33 Pathophysiology

34 Damage of the skin can lead to infections of the deeper layers beneath the epidermis. When such  
 35 damage occurs, both endogenous (i.e. pathogens that naturally reside in the body) and  
 36 exogenous (i.e. pathogens that enter the body from the environment) pathogens can penetrate  
 37 the epidermis and spread to deeper structures through the lymphatic system. Depending on the  
 38 depth of the infection, different clinical diseases can occur: impetigo and erysipelas (infections  
 39 of the upper layer of the skin) and cellulitis (infection of the deep dermis and subcutaneous  
 40 tissue) (Figure).



41

### 42 Epidemiology

43 Bacterial skin infections occur worldwide and can affect all age groups; erysipelas is more  
 44 frequent in children and elderly patients. In 2013, skin diseases (not limited to bacterial  
 45 infections) were the fourth leading cause of non-fatal diseases(147). Cellulitis, the most common  
 46 skin infection, accounted for 0.04% (4 in 10,000) of the overall burden of all diseases combined  
 47 in 2013. It was the only skin condition that showed a significant decrease (–13.2%) between 2005  
 48 and 2013 in disability-adjusted life years (DALYs), a proxy for morbidity and mortality; this

49 decrease was attributed to reduced mortality(147). In 2017, the Global Burden of Disease study  
 50 reported 43 million new cases of cellulitis worldwide(31). Diabetes, peripheral arterial disease,  
 51 HIV infection and other causes of immunosuppression are risk factors for severe skin infections.

## 52 Microbiology epidemiology

53 The most common pathogens causing skin infections are listed in Table 1.

54 *Table 1 Pathogens most frequently associated with skin infections (in descending order of*  
 55 *frequency)*

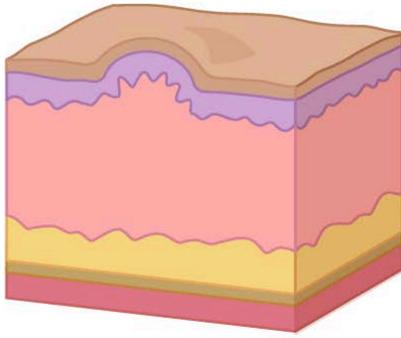
	<b>Bacteria</b>
Most cases	<i>Streptococcus pyogenes</i> (group A <i>Streptococcus</i> ) - especially in case of erysipelas  <i>Staphylococcus aureus</i> (including MRSA strains)
More rarely  (e.g. immunosuppressed and / or diabetic patients, traumatic skin lesions)	Enterobacterales (including multidrug-resistant strains such as those producing ESBL and carbapenemases)  <i>Pseudomonas aeruginosa</i> (including multidrug-resistant strains such as those producing ESBL and carbapenemases)  Anaerobes
Cases with specific environmental exposures	<i>Aeromonas hydrophila</i> (exposure to fresh water)  <i>Erysipelothrix rhusiopathiae</i> (contact with animals colonized with the organism, mostly pigs and fish)  <i>Vibrio vulnificus</i> (exposure to seawater)

56 ESBL: extended-spectrum beta-lactamases; MRSA: methicillin-resistant *Staphylococcus aureus*.

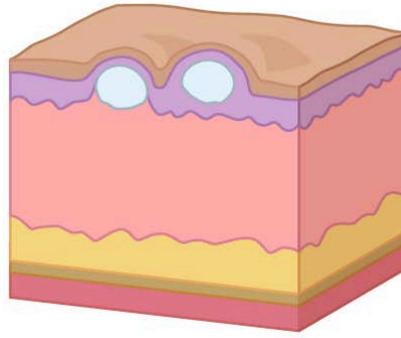
## 57 Clinical presentation (only mild cases are covered)

58 *Table 2 Glossary for skin lesions*

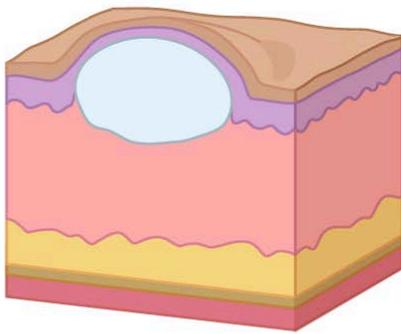
<b>Type of skin lesion</b>	<b>Definition</b>
Bulla	Large fluid-filled blister
Papule	Small, elevated lesions that can be palpated
Pustule	Small blister or pimple
Vesicle	Small fluid-filled blister



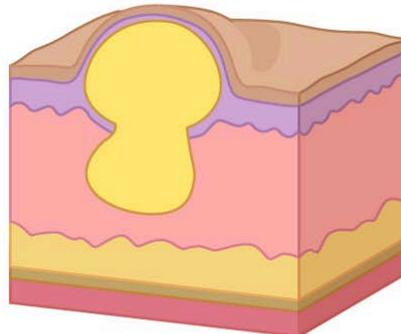
**Papule**



**Vesicle**



**Bulla**



**Pustule**

59

OK!

## 60 Impetigo

61 Impetigo is characterized by acute onset of superficial skin lesions usually without associated  
62 systemic symptoms. In most cases, impetigo presents with papules that progress to vesicles and  
63 pustules (see Table 2 for definitions) which break to finally form crusts (non-bullous form). In a  
64 minority of cases (mostly in young children) vesicles develop to form larger bullae (bullous  
65 form).



66  
67 Source: <https://en.wikipedia.org/wiki/Impetigo>

## 68 Erysipelas

69 Erysipelas is characterized by acute onset of a red skin lesion with well-defined indurated  
70 margins, usually on the face or legs. Bullae (Table 2) may be present or develop in the first few  
71 days. The lesion is usually painful. Fever (> 38.0 °C) and other signs of systemic infection (e.g.  
72 tachycardia, leukocytosis) may be present.



73  
74 Source: <https://en.wikipedia.org/wiki/Erysipelas>

## 75 Cellulitis

76 While erysipelas affects only the superficial skin layers and has clearly demarcated borders,  
77 cellulitis also affects subcutaneous tissues. Cellulitis is characterized by an acute onset of a skin  
78 lesion presenting with a combination of redness, swelling and induration, warm to touch and  
79 pain (or tenderness) of the affected area. The condition can occur anywhere on the body, but  
80 predominantly affects the skin of the lower part of the legs and feet or the face. Fever (> 38.0 °C)  
81 and other signs of systemic infection (e.g. tachycardia, leukocytosis) may be present. Skin redness  
82 alone may not indicate an infection, for example, redness is often present in patients with chronic  
83 venous stasis (bilateral versus unilateral involvement may indicate a non-infectious aetiology,  
84 although bilateral cellulitis can occasionally occur). The severity of the infection should always be

85 carefully assessed, especially to exclude the possibility of involvement of the muscular fascia  
86 (fasciitis).

## 87 Laboratory tests

### 88 I. Patient microbiology tests

89 Most mild cases of impetigo, erysipelas and cellulitis do not require routine microbiology tests.  
90 Surface swabs of intact, unbroken skin should not be taken in cases of erysipelas or cellulitis to  
91 avoid detecting pathogens that colonize the skin leading to unnecessary antibiotic treatment.

92 Tissue swab cultures can be considered in certain cases (Table 3). For example, cultures could be  
93 done for lesions that are clearly purulent (therefore most likely due to *Staphylococcus aureus*) to  
94 diagnose or exclude the presence of methicillin-resistant *Staphylococcus aureus* (MRSA).  
95 However, in many settings doing tissue swab cultures is not standard practice outside of the  
96 operating theatre. When swabs are performed, the lesion should always be cleaned and debrided  
97 before sample collection to identify the pathogens causing the infection and not colonizing  
98 organisms. For a correct interpretation of cultures it is very important that the origin of the  
99 culture (exact location, superficial swab or intraoperatively obtained culture) is adequately  
100 documented.

101 Cultures can be considered for chronic lesions such as diabetic foot infections (not covered in this  
102 chapter) to exclude the presence of multidrug-resistant organisms (e.g. those producing  
103 extended-spectrum beta-lactamases).

104 *Table 3 Microbiology tests to consider for the diagnosis of skin infections in certain cases as*  
105 *indicated in the WHO EDL (54)*

Diagnostic test	Purpose of the test	Settings where the test should be available
Tissue swab culture	Initial step to detect and identify bacterial and fungal species for selection of appropriate antibiotic regimens	Health care facilities with clinical laboratories

### 106 II. Other tests

107 Routine laboratory tests are not required in mild cases (148).

### 108 III. Using microbiology surveillance data

109 Routine surveillance is not helpful in informing empiric guidance.

## 110 Imaging

111 Routine imaging of mild cases of impetigo, erysipelas and cellulitis is not necessary. However,  
112 initial imaging (e.g. ultrasound, X-ray) may be considered if an abscess or subdermal involvement

113 are suspected. In these cases, management often requires a surgical approach (e.g. incision and  
114 drainage in case of abscess).

## 115 Topical treatment

### 116 (only for localized non-bullous impetigo)

117 For localized non-bullous impetigo, topical treatment could be considered as an alternative to  
118 oral antibiotics. This treatment can be as effective as oral antibiotic treatment and has the  
119 advantage that the risk of adverse events is minimal because of less systemic absorption(149).  
120 Of the different topical treatments available, mupirocin ointment (2%) could be considered for a  
121 short course of treatment (5 days). However, widespread use of mupirocin can rapidly increase  
122 resistance to mupirocin in *Staphylococcus aureus* and limit its usefulness for targeted preventive  
123 purposes in carriers of *Staphylococcus aureus* (mupirocin is active against both methicillin-  
124 susceptible *Staphylococcus aureus* and MRSA). Alternative treatments are available but they are  
125 not included in the EML/EMLc (4, 5). These alternatives are fusidic acid and hydrogen peroxide  
126 cream (1%). Topical corticosteroids should not be used routinely in these cases.

## 127 Antibiotic treatment

### 128 (widespread impetigo, erysipelas and cellulitis)

129 In most cases of mild infections, oral antibiotic treatment is adequate (Table 4). Empiric antibiotic  
130 options need to have good activity against the most likely pathogens (*Streptococcus* spp and  
131 *Staphylococcus aureus*). Empiric treatment against community-acquired MRSA may be  
132 considered in certain cases (e.g. clearly purulent lesions) based on individual risk factors (e.g.  
133 known MRSA colonization) and on the local prevalence of community-acquired MRSA. In these  
134 cases, the literature suggests using clindamycin or sulfamethoxazole+trimethoprim; these  
135 options are however not currently listed in the EML/c for this indication.

136 *Table 4 Empiric antibiotic treatments for mild skin infections*

Adults	Children	Total treatment duration
<p>Amoxicillin+clavulanic acid<sup>a</sup>(oral): 500 mg + 125 mg given every 8 hours</p> <p>OR</p> <p>Cefalexin(oral): 500 mg given every 8 hours</p> <p>OR</p> <p>Cloxacillin<sup>a</sup> or flucloxacillin (oral): 500 mg given every 8 hours</p>	<p>Amoxicillin+clavulanic acid<sup>b</sup> (oral): 40-50 mg/kg/dose of amoxicillin component, given every 12 hours OR 30 mg/kg/dose given every 8 hours</p> <p>Oral weight bands: 3-&lt;6 kg: 250 mg of amoxicillin/dose given every 12 hours 6-&lt;10 kg: 375 mg of amoxicillin/dose given every 12 hours 10-&lt;15 kg: 500 mg of amoxicillin/dose given every 12 hours 15-&lt;20 kg: 750 mg of amoxicillin/dose given every 12 hours</p>	5 days <sup>d</sup>

	<p>20-&lt;30 kg: 1000 mg of amoxicillin/dose given every 12 hours                  ≥ 30 kg: Use adult dose</p> <p>OR</p> <p><b>Cefalexin</b>(oral): 25 mg/kg/dose given every 12 hours</p> <p>Oral weight bands:                  3- &lt;6 kg: 125 mg given every 12 hours                  6-&lt;10 kg: 250 mg given every 12 hours                  10-&lt;15 kg: 375 mg given every 12 hours                  15-&lt;20 kg: 500 mg given every 12 hours                  20-&lt;30 kg: 625 mg given every 12 hours                  ≥ 30 kg: Use adult dose</p> <p>OR</p> <p><b>Cloxacillin</b><sup>a,c</sup> or <b>flucloxacillin</b> (oral):</p> <ul style="list-style-type: none"> <li>• Neonates: 25-50 mg/kg/dose given every 12 hours</li> <li>• Children: 25 mg/kg/dose given every 6 hours</li> </ul> <p>Oral weight bands:                  3-&lt;6 kg: 125 mg given every 6 hours                  6-&lt;10 kg: 250 mg given every 6 hours                  10-&lt;15 kg: 250 mg given every 6 hours                  15-&lt;20 kg: 500 mg given every 6 hours                  20-&lt;30 kg: 750 mg given every 6 hours                  ≥ 30 kg: Use adult dose</p>	
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137 Notes: All dosages are for normal renal and hepatic function.

138 <sup>a</sup>Cloxacillin (or dicloxacillin or flucloxacillin) has a narrower spectrum of antibacterial activity compared to  
 139 amoxicillin+clavulanic acid and cefalexin while maintaining good efficacy in cases of mild skin infections. Therefore,  
 140 from an antibiotic stewardship perspective, it would be the preferred option whenever possible. Cloxacillin,  
 141 dicloxacillin and flucloxacillin are preferred for oral administration because of better bioavailability (i.e. the extent  
 142 at which the medicine enters systemic circulation, thereby accessing the site of action).

143 <sup>b</sup>Oral liquid must be refrigerated after reconstitution as clavulanic acid is rapidly metabolized in high ambient  
 144 temperatures.

145 <sup>c</sup>The WHO *Packet book of hospital care for children*(23) suggests amoxicillin plus cloxacillin. However, cloxacillin  
 146 can be safely used as a single antibiotic option because it has good activity against both methicillin-susceptible  
 147 *Staphylococcus aureus* and *Streptococcus pyogenes* (often referred to as group A *Streptococcus*). Amoxicillin alone  
 148 is not suitable because it has variable activity against methicillin-susceptible *Staphylococcus aureus*.

149 <sup>d</sup>The optimal duration of antibiotic treatment is not known(150); duration is often individualized based on clinical  
 150 response.

151 **ACCESS** antibiotics are indicated in green, **WATCH** antibiotics in yellow and **RESERVE** antibiotics in red.

# 1 Burn wound-related infections

## 2 Key messages

1. Burn wounds predispose to infections (damage of the skin's protective barrier, immunosuppression in severe cases) and should be monitored for signs of cellulitis (redness, pain and swelling around the wound).
2. Avoid the routine use of antibiotics to prevent infections if there are no signs of systemic infection and in otherwise healthy patients.
3. Mild infections should be treated with antibiotics with good activity against the most likely pathogens (Gram-positive bacteria from the skin microbiota)
4. Multidrug-resistant organisms are a major concern in patients with severe burn wounds often because of prolonged hospitalization and frequent antibiotic exposure.
5. Sepsis and septic shock are a frequent complication of severe burns.

3

### *Box 1 Other relevant WHO documents (please check regularly for updates)*

- WHO 2013 pocket book of hospital care for children <https://apps.who.int/iris/handle/10665/81170> (23)
- Burns (Fact sheet)(151)

## 4 Definition

5 A burn wound is an injury to the skin or other organic tissue primarily caused by heat or due to  
6 radiation, radioactivity, electricity, friction or contact with chemicals. Burns can be classified  
7 based on the cause and depth of the burn.

## 8 Pathophysiology

9 Burns predispose to infection because they allow entry of pathogens from the patient's own skin  
10 microbiota and the environment into the wound. Burns can also cause immunosuppression that  
11 allows rapid bacterial colonization and proliferation. Sepsis and septic shock are a frequent  
12 complication of severe burns.

## 13 Epidemiology

14 Burn wounds are an important public health problem in low- and middle-income countries where  
15 they are among the leading causes of disability-adjusted life years (DALYs) lost. An estimated  
16 180,000 deaths every year are caused by burns and most occur in LMIC (151). Infections

17 (including but not limited to the skin) are the most frequent complications encountered in  
 18 patients with burn injuries and are the leading cause of death in patients with severe wounds.  
 19 Skin infections (e.g. cellulitis) are in general the first infections to occur, usually in the first week  
 20 of the injury.

## 21 Microbiology epidemiology

22 Table 1 gives the pathogens that often infect burn wounds. In most cases, infection is caused by  
 23 several pathogens. Multidrug-resistant organisms are a major concern in burn patients often  
 24 because of prolonged hospitalization and frequent antibiotic exposure (152).

25 *Table 1 Pathogens most frequently associated with infected burn wounds (in descending order of*  
 26 *frequency)*

	Bacteria	Fungi
Soon after the injury	<i>Streptococcus</i> spp. <i>Staphylococcus aureus</i> (including MRSA strains) <i>Staphylococcus</i> spp. other than <i>S. aureus</i> Enterobacterales (including multidrug-resistant strains such as those producing ESBL and carbapenemases)	-
Additionally, during hospitalization	<i>Pseudomonas aeruginosa</i> <i>Acinetobacter baumannii</i> (including multidrug-resistant strains such as those producing ESBL and carbapenemases)	<i>Candida</i> spp.

27 ESBL: extended-spectrum beta-lactamases; MRSA: methicillin-resistant *Staphylococcus aureus*.

## 28 Clinical presentation

29 Diagnosis of a burn wound infection requires clinical examination. For this reason, burn wounds  
 30 should be monitored for signs of infection, such as increased pain and redness or swelling of the  
 31 area surrounding the wound. Redness alone may represent inflammation and does not  
 32 necessarily indicate infection. Signs of invasive infection (e.g. change in the colour of the wound,  
 33 signs of sepsis) should also be carefully monitored. Please also refer to the chapter on sepsis if  
 34 suspected. Patients with burn injuries may also develop other complications dependent on their  
 35 supportive care such as pneumonia, urinary tract infections or catheter-related infections.

## 36 Laboratory tests

### 37 I. Patient microbiology tests

38 In mild cases of infection of a burn wound where there are no signs of systemic infection, routine  
39 testing (including wound cultures) is not required. These tests are not needed because identifying  
40 the causative pathogen in mild cases will not benefit the patient as it will not change  
41 management. In severe cases, blood cultures can be considered. Please also refer to the chapter  
42 on sepsis if suspected.

### 43 II. Other tests

44 Routine testing in mild cases with no signs of systemic infection is not required. In addition,  
45 because of the inflammatory response associated with the burn itself, results of laboratory tests  
46 (e.g. biomarkers of infection) may be of limited help.

47 In severe cases, certain laboratory tests can be considered to make an initial assessment of the  
48 patient and to help guide the duration of antibiotic treatment. Please also refer to the chapter  
49 on sepsis if suspected.

### 50 III. Using microbiology surveillance data

51 Targeted clinical surveys of blood stream infection isolates at a local unit level may be helpful to  
52 inform empiric guidance. Empiric guidance should not usually be informed by routine surface  
53 culture skin swabs.

## 54 Imaging

55 Routine imaging is not required unless a complication is suspected.

## 56 Management

57 Irrigation and debridement of necrotic tissue to prevent infection of the burn wound is  
58 suggested. Appropriate daily cleaning and dressing of the wound are the cornerstone of  
59 treatment.

60 Infection control procedures should be meticulously observed to prevent transmission of  
61 multidrug-resistant organisms.

## 62 Topical treatment

63 Local antiseptics could be considered based on local protocols.

## 64 Preventive antibiotic use

65 Routine use of antibiotics to prevent infection in burn wounds should be avoided if there are no  
 66 signs of systemic infection or in otherwise healthy patients. Use of antibiotics as a preventive  
 67 treatment is controversial because there is no clear evidence that it can prevent infection(153,  
 68 154). In addition, such use can lead to colonization with resistant microorganisms, so caution is  
 69 needed.

## 70 Antibiotic treatment

71 Empiric treatment of mild infections should include antibiotics with good activity against the  
 72 most likely pathogens (*Staphylococcus aureus* and *Streptococcus* spp.). Antibiotic options are  
 73 shown in Table 2. Empiric treatment against community-acquired methicillin-resistant  
 74 *Staphylococcus aureus* (MRSA) may be considered and should be based on local prevalence of  
 75 invasive isolates and individual patient risk factors (e.g. known MRSA colonization).

76 It is important to note that because hospital-acquired multidrug-resistant organisms are  
 77 frequently found in burn units the results of microbiology cultures should where possible guide  
 78 antibiotic treatment. Empiric use of RESERVE group antibiotics should, however, generally be  
 79 avoided. Please also refer to the chapter on sepsis if suspected.

80 *Table 2 Empiric antibiotic treatment for mild burn wound infections*

81 **It is important to note that only infected wounds should be treated with antibiotics.**

Adults	Children	Total treatment duration
<p><b>Amoxicillin+clavulanic acid</b> (oral): 500 mg + 125 mg given every 8 hours</p> <p><b>OR</b></p> <p><b>Cefalexin</b> (oral): 500 mg given every 8 hours</p> <p><b>OR</b></p> <p><b>Cloxacillin<sup>a</sup> or flucloxacillin</b> (oral): 500 mg given every 8 hours</p>	<p><b>Amoxicillin+clavulanic acid<sup>b</sup></b> (oral): 40-50 mg/kg/dose of amoxicillin component given every 12 hours                      OR 30 mg/kg/dose given every 8 hours</p> <p>Oral weight bands:</p> <p>3-&lt;6 kg: 250 mg of amoxicillin/dose given every 12 hours                      6-&lt;10 kg: 375 mg of amoxicillin/dose given every 12 hours                      10-&lt;15 kg: 500 mg of amoxicillin/dose given every 12 hours                      15-&lt;20 kg: 750 mg of amoxicillin/dose given every 12 hours                      20-&lt;30 kg: 1000 mg of amoxicillin/dose given every 12 hours                      ≥ 30 kg: Use adult dose</p> <p><b>OR</b></p>	<p>5 days</p>

	<p><b>Cefalexin</b> (oral): 25 mg/kg/dose given every 12 hours</p> <p>Oral weight bands:          3- &lt;6 Kg: 125 mg given every 12 hours          6-&lt;10 kg: 250 mg given every 12 hours          10-&lt;15 kg: 375 mg given every 12 hours          15-&lt;20 kg: 500 mg given every 12 hours          20-&lt;30 kg: 625 mg given every 12 hours          ≥ 30 kg: Use adult dose</p> <p><b>OR</b></p> <p><b>Cloxacillin</b><sup>a,c</sup> or <b>flucloxacillin</b> (oral):</p> <ul style="list-style-type: none"> <li>• Neonates: 25-50 mg/kg/dose given every 12 hours</li> <li>• Children: 25 mg/kg/dose given every 6 hours</li> </ul> <p>Oral weight bands:          3-&lt;6 kg: 125 mg given every 6 hours          6-&lt;10 kg: 250 mg given every 6 hours          10-&lt;15 kg: 250 mg given every 6 hours          15-&lt;20 kg: 500 mg given every 6 hours          20-&lt;30 kg: 750 mg given every 6 hours          ≥ 30 kg: Use adult dose</p>	
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82 Notes: All dosages are for normal renal and hepatic function.

83 <sup>a</sup>Cloxacillin (or dicloxacillin or flucloxacillin) has a narrower spectrum of antibacterial activity compared to  
 84 amoxicillin+clavulanic acid and cefalexin while maintaining good efficacy in cases of mild skin infections. Therefore,  
 85 from an antibiotic stewardship perspective, it would be the preferred option whenever possible. Cloxacillin,  
 86 dicloxacillin and flucloxacillin are preferred for oral administration because of better bioavailability (i.e. the extent  
 87 at which the medicine enters systemic circulation, thereby accessing the site of action).

88 <sup>b</sup>Oral liquid must be refrigerated after reconstitution as clavulanic acid is rapidly metabolized in high ambient  
 89 temperatures.

90 <sup>c</sup>The WHO *Pocket book of hospital care for children* suggests amoxicillin plus cloxacillin; however, cloxacillin can be  
 91 safely used as a single antibiotic option since it has good activity against both methicillin-susceptible *Staphylococcus*  
 92 *aureus* and *Streptococcus pyogenes*. Amoxicillin alone is not suitable because it has variable activity against  
 93 methicillin-susceptible *Staphylococcus aureus*.

94 **ACCESS** antibiotics are indicated in green, **WATCH** antibiotics in yellow and **RESERVE** antibiotics in red.

# 1 Wound and bite-related 2 infections

3 This chapter does not include severe infections, surgical wounds and management of bites from  
4 poisonous animals or arthropods (insects, ticks, mites).

5 Please refer to the specific chapters about other skin and soft tissue infections – burn wounds, impetigo /  
6 erysipelas / cellulitis, necrotizing fasciitis, pyomyositis - if these infections are suspected.

## 7 Key messages

1. In general, uninfected wounds **do not require antibiotic treatment** except in very selected cases.
2. Skin wounds predispose to infection (e.g. cellulitis) but not every wound becomes infected (in fact only a minority of wounds become infected in immunocompetent people).
3. Adequate cleaning and debridement of the skin wound are the cornerstone of initial treatment.
4. Need for post-exposure prophylaxis for certain infectious diseases (e.g. tetanus, rabies) should always be evaluated on a case-by-case basis.
5. The presence of signs of invasive infection should always be carefully evaluated.

8

### *Box 1 Other relevant WHO documents (please check regularly for updates)*

- For prevention and management of wound infections, please refer to the 2013 WHO guidance publication(155). <https://www.who.int/publications/i/item/prevention-and-management-of-wound-infection>
- WHO 2013 pocket book of hospital care for children <https://apps.who.int/iris/handle/10665/81170> (23)
- For snakebite envenoming, please refer to the WHO website, this includes the 2019 WHO global strategy for prevention and control of snakebite envenoming(156).
- For road traffic injuries, please refer to the WHO report on road safety(157)
- Tetanus vaccines: WHO position paper – February 2017. Weekly Epidemiological Record, 92 (6), 53 - 76. <https://apps.who.int/iris/handle/10665/254583>
- Rabies vaccines: WHO position paper – April 2018 . Weekly Epidemiological Record, 93 (16), 201 - 219. <https://apps.who.int/iris/handle/10665/272372>

- Hepatitis B vaccines: WHO position paper – July 2017. Weekly Epidemiological Record, 92 (27), 369 - 392. [(<https://apps.who.int/iris/handle/10665/255873>)]
- Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Second edition. <https://apps.who.int/iris/handle/10665/208825>

9 **Definition**

10 Skin wounds include any traumatic injury characterized by damage to and exposure of deeper  
 11 skin tissue. Examples of skin wounds include those caused by human or animal bites or burns,  
 12 traffic road injuries, gun shots and stab wounds. The severity of the clinical findings can vary from  
 13 mild wounds with no systemic involvement to severe infections including tetanus (infection by  
 14 *Clostridium tetani*) and gas gangrene (infection by gas producing bacteria such as *Clostridium*  
 15 *perfringens*).

16 **Pathophysiology**

17 Skin wounds predispose to infection because they facilitate entry of pathogens from the patient’s  
 18 own skin microbiota and the environment into the wound. With bites, pathogens from the oral  
 19 cavity of the biting animal can also penetrate the skin.

20 **Epidemiology**

21 **Traumatic wounds**

22 Road traffic injuries occur worldwide but the majority of deaths (>90%) occur in low and middle-  
 23 income countries (157, 158). Overall each year about 1.3 million people die as a result of road  
 24 traffic accidents with many more suffering from non-fatal injuries (between 20 and 50 million  
 25 people)(157, 158). In young people (under 30 years of age), this is the leading cause of death.

26 In 2016, the Global Burden of Disease study reported about 251,000 deaths from firearm injuries  
 27 globally (outside of war settings), the majority caused by homicides (64%), followed by suicides  
 28 (27%) and unintentional firearm deaths (9%)(159). Overall, the global age-standardized rate of  
 29 firearm deaths decreased by about 0.9% per year between 1990 and 2016 with differences  
 30 between countries (159). Most firearm injury deaths occur among people aged 20 to 24  
 31 years(159).

32 **Bite wounds**

33 Human and animal bites occur worldwide; most cases are caused by animals (dogs in > 90% of  
 34 cases)(160). Less frequently, bites are caused by other mammals such as cats, rodents (e.g. rats,

35 mice) and bats. In certain countries (e.g. in Africa and in South-East Asia), snake and monkey bites  
 36 are also frequently reported. Children are more likely to have animal bites(161). The risk of  
 37 developing a bacterial infection from a dog bite is unclear and depends on many different factors  
 38 related to the patient (*i.e.* the person bitten), the characteristics of the bite (depth, location) and  
 39 the initial management of the bite. However, available data suggest that in 10–20% of cases of  
 40 dog bites, the wound will become infected(161, 162). In comparison, wounds caused by cat bites  
 41 have a higher risk of becoming infected (up to 50%) because of the deeper penetration of their  
 42 teeth(161, 162).

43 Animal bites are a significant risk factor for transmission of rabies, especially in settings where  
 44 prophylaxis with rabies vaccine in domestic and wild animals is not routinely given. The Global  
 45 Burden of Disease study estimated 13.400 new cases of rabies worldwide in 2017(31). Deaths  
 46 from rabies and dog bites are a problem mostly in low- and middle-income countries where post-  
 47 exposure treatment and appropriate access to health care may be lacking(160).

48 Small rodents are vectors of numerous pathogens and are a reservoir for many zoonotic diseases.  
 49 Rodents (mostly rats) are also responsible for an appreciable proportion of bites to humans(163).  
 50 Rat bites primarily affect people (mostly children < 5 years) living in poorer conditions in rat-  
 51 infested environments, including in high-income countries. Most bites occur on the face and  
 52 hands and usually occur at night while sleeping. Although rare, rat bites can cause severe  
 53 infections, such as rat-bite fever (caused by *Streptobacillus moniliformis* or *Spirillum minus*).  
 54 Tetanus infection can also be caused by bites and it should be considered in patients who have  
 55 not been immunized against the infection. In 2019, almost 15.000 cases of tetanus were reported  
 56 globally(164).

57 **Microbiology epidemiology**

58 **Traumatic wounds**

59 In most cases, infections from traumatic wounds are polymicrobial with a mix of human skin  
 60 microbiota and environmental organisms (Table 1).

61 *Table 1 Pathogens most frequently associated with traumatic skin wounds in descending order of*  
 62 *frequency (except bites, presented in another table)*

	<b>Bacteria</b>
Most cases <sup>a</sup>	<i>Streptococcus spp.</i> <i>Staphylococcus aureus</i> (including MRSA strains)
More rarely	Anaerobes Enterobacterales <i>Enterococcus spp.</i> <i>Clostridium tetani</i> (soil contaminant)

63 MRSA: methicillin-resistant *Staphylococcus aureus*.

64 <sup>a</sup>Mostly Gram-positive pathogens from the skin microbiota.

65 **Bite wounds**

66 In infections from bites, causative pathogens may also be from the animal/human oral microbiota  
 67 with differences among species (Table 2) (8,9).

68 *Table 2 Pathogens most frequently associated with bites*

Species causing the bite	Pathogens
Human <sup>a</sup>	<p><b>Commonly isolated pathogens</b></p> <p>Anaerobes from the oral microbiota such as <i>Prevotella</i> and <i>Fusobacterium</i> spp.  <i>Streptococcus</i> spp.  <i>Staphylococcus aureus</i></p> <p><b>Other non-bacterial pathogens that can be transmitted through human bites</b></p> <p>Hepatitis B virus  Hepatitis C virus  HIV</p>
Cat <sup>a</sup>	<p><b>Commonly isolated pathogens</b></p> <p>Anaerobes such as <i>Bacteroides</i> spp., <i>Cutibacterium</i> spp., <i>Fusobacterium</i> spp.,  <i>Peptostreptococcus</i> spp. and <i>Prevotella</i> spp.</p> <p><i>Pasteurella multocida</i>  <i>Staphylococcus aureus</i></p> <p><b>Other bacterial pathogens that can be transmitted through cat bites</b></p> <p><i>Bartonella henselae</i> (agent of cat-scratch disease)  <i>Francisella tularensis</i> (agent of tularemia)</p> <p><b>Other non-bacterial pathogens that can be transmitted through cat bites</b></p> <p>Rabies virus</p> <p><b>Soil contaminants</b></p> <p><i>Clostridium tetani</i></p>

<p>Dog<sup>a</sup></p>	<p><b>Commonly isolated pathogens</b></p> <p>Anaerobes such as <i>Bacteroides</i> spp., <i>Cutibacterium</i> spp., <i>Fusobacterium</i> spp., <i>Peptostreptococcus</i> spp. and <i>Prevotella</i> spp.</p> <p><i>Capnocytophaga canimorsus</i></p> <p><i>Pasteurella multocida</i></p> <p><i>Staphylococcus aureus</i></p> <p><b>Other pathogens that can be transmitted through dog bites</b></p> <p><i>Francisella tularensis</i> (agent of tularemia)</p> <p><i>Leptospira</i> spp.</p> <p>Rabies virus</p> <p><b>Soil contaminants</b></p> <p><i>Clostridium tetani</i></p>
<p>Monkey<sup>a</sup></p>	<p>Anaerobes such as <i>Bacteroides</i> spp., <i>Cutibacterium</i> spp., <i>Fusobacterium</i> spp., <i>Peptostreptococcus</i> spp. and <i>Prevotella</i> spp.</p> <p><i>Streptococcus</i> spp.</p> <p><i>Staphylococcus aureus</i></p> <p><b>Other non-bacterial pathogens that can be transmitted through monkey bites</b></p> <p>Hepatitis B virus (macaques)</p> <p>Herpes B virus</p> <p>Monkeypox virus</p> <p>Rabies virus</p> <p><b>Soil contaminants</b></p> <p><i>Clostridium tetani</i></p>

<p>Rodent<sup>a</sup> (e.g. mice, rats)</p>	<p><i>Pasteurella multocida</i></p> <p><b>Other bacterial pathogens that can be transmitted through rodent bites</b></p> <p><i>Francisella tularensis</i> (agent of tularemia)</p> <p><i>Leptospira</i> spp.</p> <p><i>Spirillum minor</i> (agent of rat-bite fever in Asia)</p> <p><i>Streptobacillus moniliformis</i> (agent of rat-bite fever in North America)</p> <p><b>Other non-bacterial pathogens that can be transmitted through rodent bites</b></p> <p>Rabies virus</p> <p>Monkeypox virus</p> <p><b>Soil contaminants</b></p> <p><i>Clostridium tetani</i></p>
<p>Reptile (e.g. crocodiles, lizards, snakes, turtles)</p>	<p>Anaerobes such as <i>Prevotella</i> and <i>Fusobacterium</i> spp.</p> <p>Enterobacterales</p> <p><i>Pseudomonas aeruginosa</i></p> <p><i>Salmonella</i> spp.</p> <p><b>Soil contaminants</b></p> <p><i>Clostridium tetani</i></p>

69 <sup>a</sup> Mammals.

70 **Clinical presentation**  
 71 **(only mild cases are covered)**

72 Wounds range in severity from minor superficial abrasions to deep wounds with involvement and  
 73 destruction of the deep tissues. An infection may or may not be present at the time of clinical  
 74 evaluation. Usually signs and symptoms of infection appear > 12 hours after the injury. Superficial  
 75 infections may manifest with signs and symptoms of cellulitis characterized by redness, swelling,  
 76 warmth, lymphangitis and pain of the area surrounding the wound. Fever (> 38.0 °C) may be  
 77 present. Patients should also be carefully monitored for signs of invasive infection (e.g. change  
 78 in colour of the wound due to necrosis and signs of sepsis).

## 79 Laboratory tests

### 80 I. Patient microbiology tests

81 In mild cases with no signs of systemic infection, routine testing (including wound cultures) is not  
82 required. These tests are not needed because identifying the causative pathogen in mild cases is  
83 rare even when microbiologic tests are performed, most infections are polymicrobial and  
84 microbiologic results will not affect management of the condition in most cases.

### 85 II. Other tests

86 Routine testing in mild cases with no signs of systemic infection is not required.

### 87 III. Using microbiology surveillance data

88 Routine surveillance is not helpful in informing empiric guidance.

## 89 Imaging

90 Routine imaging is not required. Imaging may be considered in certain cases based on the size  
91 and depth of the wound, particularly if a complication such as development of an abscess or  
92 necrotizing infection is suspected.

## 93 “No antibiotic care”

### 94 Initial management of wounds

95 It is important to provide rapid and appropriate treatment of a wound after an injury has  
96 occurred to minimize the risk of infection. For prevention and management of wound infections,  
97 please refer to the 2013 WHO guidance publication(155)

98 Adequate cleaning and debridement are the cornerstone of initial treatment. It is important to  
99 thoroughly wash and flush the wound for about 15 minutes with soap or detergent and a lot of  
100 clean water, followed by debridement and immobilization of the wound.

## 101 Post-exposure prophylaxis

### 102 Traumatic wounds

103 After any wound, the risk of tetanus needs to be promptly evaluated to provide adequate post-  
104 exposure prophylaxis by vaccination +/- passive immunization using tetanus immunoglobulin  
105 when needed according to local / international recommendations.

- 106 • For tetanus post-exposure prophylaxis, please refer to the most recent WHO position  
107 paper (2017)(165).

## 108 Bite wounds

109 With animal bites, in addition to the risk of tetanus, the risk of rabies needs also to be rapidly  
110 evaluated based on the exposure category to provide adequate post-exposure prophylaxis when  
111 needed (Table 3).

- 112 • For rabies post-exposure prophylaxis, please refer to the most recent WHO position paper  
113 (2018)(166).

114 With human bites, the risk of hepatitis B and C virus and HIV transmission needs also to be  
115 evaluated and post-exposure prophylaxis offered when applicable(167, 168).

116 *Table 3 Risk of rabies exposure according to the type of contact with the animal suspected of*  
117 *having rabies(166)*

Category <sup>a</sup>	Type of contact	Risk of exposure
Category I	Touching or feeding animals, animal licks on intact skin	No exposure
Category II	Nibbling of uncovered skin, minor scratches or abrasions without bleeding	Exposure
Category III	Single or multiple transdermal bites or scratches, contamination of mucous membrane or broken skin with saliva from animal licks, exposures due to direct contact with bats	Severe exposure

118 <sup>a</sup>The category of exposure determines the indicated post-exposure prophylaxis procedure.

## 119 Preventive antibiotic use

120 Routine use of antibiotics to prevent infection of the wound is not required in most cases (unless  
121 there are systemic signs of infection in which case antibiotics would be used as treatment and  
122 not as prophylaxis) and should be discouraged.

123 Preventive antibiotic use may be considered in very few specific cases where the potential risk of  
124 infection is judged to outweigh the risk of “overusing” antibiotics.

125 This includes:

- 126 • Wounds in high-risk clinical areas (e.g. face, hands, areas near a joint)

127 There is though no clear evidence that use of antibiotic can prevent the infection after wounds  
128 (including bite wounds). In addition, such use exposes the patient to the negative effects of  
129 antibiotic use (alteration of the intestinal microbiota; selection of resistant microorganisms).

## 130 Antibiotic treatment

131 If signs and symptoms of infection are present, empiric treatment should include antibiotics with  
 132 good activity against the most likely pathogens (*Staphylococcus aureus* and *Streptococcus* spp.  
 133 and anaerobic organisms). With animal bites, the type of animal should also be considered (Table  
 134 2), but in general, empiric treatment against both aerobic and anaerobic bacteria is required,  
 135 since most infections are caused by multiple pathogens (polymicrobial infections). Empiric  
 136 treatment against community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) is  
 137 usually not required. If cellulitis around the wound develops, refer to the chapter on bacterial  
 138 impetigo, erysipelas and cellulitis. Antibiotic options for empiric treatment are indicated in Table  
 139 4.

140 *Table 4 Empiric antibiotic treatment for mild infections from traumatic wounds and bites*

141 **It is important to note that only infected wounds should be treated with antibiotics.**

Adults	Children	Total treatment duration
<p><b>Amoxicillin+clavulanic acid<sup>a</sup></b> (oral): 500 mg + 125 mg given every 8 hours</p> <p>OR</p> <p><b>Cefalexin</b> (oral): 500 mg given every 8 hours</p> <p>OR</p> <p><b>Cloxacillin<sup>b</sup></b> or <b>flucloxacillin</b> (oral): 500 mg given every 8 hours</p>	<p><b>Amoxicillin+clavulanic acid<sup>a,c</sup></b> (oral): 40-50 mg/kg/dose of amoxicillin component, given every 12 hours OR 30 mg/kg/dose given every 8 hours</p> <p>Oral weight bands: 3-&lt;6 kg: 250 mg of amoxicillin/dose given every 12 hours 6-&lt;10 kg: 375 mg of amoxicillin/dose given every 12 hours 10-&lt;15 kg: 500 mg of amoxicillin/dose given every 12 hours 15-&lt;20 kg: 750 mg of amoxicillin/dose given every 12 hours 20-&lt;30 kg: 1000 mg of amoxicillin/dose given every 12 hours ≥ 30 kg: Use adult dose</p> <p>OR</p> <p><b>Cefalexin</b> (oral): 25 mg/kg/dose given every 12 hours</p> <p>Oral weight bands: 3- &lt;6 kg: 125 mg given every 12 hours 6-&lt;10 kg: 250 mg given every 12 hours 10-&lt;15 kg: 375 mg given every 12 hours 15-&lt;20 kg 500 mg given every 12 hours 20-&lt;30 kg: 625 mg given every 12 hours ≥ 30 kg: Use adult dose</p>	<p>3 days (preventive treatment of wounds at high risk of infection)</p> <p>5 days (treatment of infected wounds)</p>

	<p>OR</p> <p><b>Cloxacillin<sup>b</sup></b> or <b>flucloxacillin</b> (oral):</p> <ul style="list-style-type: none"> <li>• Neonates: 25-50 mg/kg/dose given every 12 hours</li> <li>• Children: 25 mg/kg/dose given every 6 hours</li> </ul> <p>Oral weight bands:</p> <p>3-&lt;6 kg: 125 mg given every 6 hours          6-&lt;10 kg: 250 mg given every 6 hours          10-&lt;15 kg: 250 mg given every 6 hours          15-&lt;20 kg: 500 mg given every 6 hours          20-&lt;30 kg: 750 mg given every 6 hours          ≥ 30 kg: Use adult dose</p>	
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- 142 Notes: All dosages are for normal renal and hepatic function.
- 143 <sup>a</sup>Amoxicillin+clavulanic acid is the preferred choice for bite wounds because it gives a better coverage of anaerobes.
- 144 <sup>b</sup>Cloxacillin does not provide good activity against anaerobic bacteria (therefore it is not the preferred option for the
- 145 treatment of infected bite wounds). Cloxacillin (or dicloxacillin or flucloxacillin) has a narrower spectrum of
- 146 antibacterial activity compared to amoxicillin+clavulanic acid and cefalexin while maintaining good efficacy in cases
- 147 of mild skin infections. Therefore, from an antibiotic stewardship perspective, it would be the preferred option
- 148 whenever possible (except for bite wounds). Cloxacillin, dicloxacillin and flucloxacillin are preferred for oral
- 149 administration because of better bioavailability (i.e. the extent at which the medicine enters systemic circulation,
- 150 thereby accessing the site of action).
- 151 <sup>c</sup>Oral liquid must be refrigerated after reconstitution as clavulanic acid is rapidly metabolized in high ambient
- 152 temperatures.
- 153 **ACCESS** antibiotics are indicated in green, **WATCH** antibiotics in yellow and **RESERVE** antibiotics in red.

DRAFT

# Sexually Transmitted Infections – Chlamydia urogenital infection

## Key messages

1. *Chlamydia trachomatis* urogenital infection is a common sexually transmitted infection (STI) globally especially among young sexually active people
2. Symptoms overlap with gonococcal infection and co-infection is frequent therefore patients should be tested for both pathogens simultaneously, when available and evaluated for other STIs (HIV, syphilis, trichomoniasis)
3. Asymptomatic people should also be treated because they can transmit the infection to others
4. Preventive services should be offered (e.g. condoms, brief sexuality education, HIV pre-exposure prophylaxis to people at high risk for HIV infection) and sexual partners should be informed and treated
6. Reporting of this infection to health authorities is encouraged according to local regulations

### Box 1 Other relevant WHO documents (please check regularly for updates)

- Sexually transmitted infections (STIs). Factsheets. [https://www.who.int/news-room/factsheets/detail/sexually-transmitted-infections-\(stis\)](https://www.who.int/news-room/factsheets/detail/sexually-transmitted-infections-(stis))
- WHO guidelines for the treatment of *Chlamydia trachomatis*, 2016 <https://www.who.int/publications/i/item/978-92-4-154971-4>
- WHO guideline for the laboratory diagnosis of sexually transmitted infections including HIV, 2013 (<https://apps.who.int/iris/handle/10665/85343>)
- Global progress report on HIV, viral hepatitis and sexually transmitted infections, 2021 <https://www.who.int/publications/i/item/9789240027077>

*In general this chapter applies to adults and young people aged over 12 years. In children specialist advice should be sought where possible. Consideration should be given that an STI in a child may be due to child sexual abuse.*

## 9 Definition

10 Chlamydial urogenital infection is a sexually transmitted infection caused by certain biovars of  
11 the bacterium *Chlamydia trachomatis*.

## 12 Microbiology epidemiology

13 Chlamydial urogenital infection is caused by *Chlamydia trachomatis*, an intracellular Gram-  
14 negative bacterium. There are several strains of *Chlamydia trachomatis* and not all are associated  
15 with sexually transmitted infections (see the chapter on trachoma). Chlamydial urogenital  
16 infections associated with sexually transmitted infection are mostly genital tract biovars  
17 (serovars D to K) and, more rarely, lymphogranuloma venereum biovar (serovars L1, L2, L3).  
18 Lymphogranuloma venereum is an ulcerative disease extending to regional lymph nodes (often  
19 the inguinal and anorectal area) and is more common in men (see below). It is endemic in many  
20 tropical and sub-tropical regions, in other settings infection is most commonly seen among men  
21 who have sex with men.

## 22 Pathophysiology

23 *Chlamydia trachomatis* infects the mucosa of the urogenital tract during sexual contact and  
24 produces a local inflammatory response that causes vaginal, urethral or anal discharge. Invasive  
25 infections caused by more invasive serovars of *Chlamydia trachomatis* can also spread to regional  
26 lymph nodes.

## 27 Epidemiology

28 Chlamydial urogenital infection is one of the most common sexually transmitted infections  
29 worldwide, including in low-income settings where it is probably underreported(169, 170). Young  
30 sexually active adults are at particularly high risk. Undiagnosed and untreated, chlamydial  
31 urogenital infections can lead to complications such as pelvic inflammatory disease (infection of  
32 the upper female reproductive tract), ectopic pregnancy and infertility in women(171, 172).  
33 Maternal infection can cause serious health problems to the child such as preterm birth, low birth  
34 weight or conjunctivitis. The 2021 WHO Global progress report on HIV, viral hepatitis and sexually  
35 transmitted infections reported an estimated 128 million new chlamydial infections in 2020  
36 among adults aged 15 to 49 years of age(173).

## 37 Clinical presentation

38 Signs and symptoms of chlamydial infection mostly overlap with those of gonococcal infection.

39 In most cases the infection is asymptomatic, and it is therefore impossible to determine how long  
40 a person has been infected. Even in the absence of symptoms, infected individuals can transmit  
41 the infection.

42 When symptoms occur (usually 1-2 weeks after being infected), particularly in men, the most  
 43 common clinical presentation is acute urethritis characterized by profuse usually clear urethral  
 44 discharge and dysuria. Most women with chlamydial cervical infection are asymptomatic. The  
 45 ones who may be symptomatic have vaginal discharge, dyspareunia (painful intercourse) and  
 46 dysuria. Several women may have lower abdominal pain or pelvic tenderness because of  
 47 ascending infection, causing pelvic inflammatory disease.

48 In both sexes (but in males more than females), symptoms of acute proctitis with pain, pruritus,  
 49 discharge and bleeding of the rectum may occur. Pharyngitis (mostly manifesting as a mild sore  
 50 throat) and conjunctivitis are other conditions that usually coexist with genital infection.

51 **Lymphogranuloma venereum** is characterized by inguinal or femoral lymphadenopathy (usually  
 52 unilateral) with or without an associated primary lesion. The classic lesion is a transient,  
 53 ulcerative lesion or a papule usually located on the genitalia or rectum. In many cases the lesion  
 54 may remain unnoticed (e.g. it may be completely asymptomatic in women when located on the  
 55 cervix or the infection can sometimes present with symptoms of acute urethritis in men). Rectal  
 56 exposure can cause proctitis with pain, pruritus, discharge and bleeding of the rectum.

## 57 Laboratory tests

### 58 I. Patient microbiology tests

59 Molecular testing has greatly improved the detection of *Chlamydia trachomatis* (and *Neisseria*  
 60 *gonorrhoeae*) among both symptomatic and asymptomatic men and women and has become the  
 61 recommended reference standard technology to diagnose and screen populations for *C.*  
 62 *trachomatis* and *N. gonorrhoeae* (Table 1 also indicates the types of specimens that can be used  
 63 for this purpose).

64 For more comprehensive information on the diagnosis of chlamydial infection, please refer to  
 65 the most recent WHO guideline for the laboratory diagnosis of sexually transmitted  
 66 infections – most recent version at publication of this Handbook was issued in 2013 (174).

67 **Please check the WHO website regularly for possible updates.** Patients with chlamydial  
 68 urogenital infection should be offered testing for HIV and other sexually transmitted infections  
 69 (e.g. hepatitis B, hepatitis C, gonococcal infection and syphilis). Test of cure (i.e. testing after the  
 70 end of treatment) could be considered in pregnant women 3-4 weeks after the end of treatment.

71 Tests to consider when chlamydial infection is suspected are listed in Table 1. Additional tests for  
 72 other sexually transmitted infections that could be considered when chlamydial urogenital  
 73 infection is confirmed or suspected are shown in Table 2. Surveillance including etiologic studies  
 74 of STI syndromes will be important to inform local and national guidance.

75 If symptoms persist at review, partner notification and treatment history should be checked.  
 76 People with recurrent or persistent infection, should be referred to a centre with laboratory  
 77 capacity to diagnose *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Mycoplasma genitalium*  
 78 and *Trichomonas vaginalis* and to test for antibiotic-resistant *N. gonorrhoeae* and *M. genitalium*.

79 *Table 1 Microbiology tests to consider when chlamydial infection is suspected as indicated in the*  
 80 *WHO EDL (54)*

Diagnostic test	Purpose of the test	Settings where the test should be available
Qualitative test for <i>Chlamydia trachomatis</i> and <i>Neisseria gonorrhoeae</i> infections (i.e. nucleic acid amplification test) <sup>a,b</sup>  <b>This is the recommended reference standard</b>	To diagnose chlamydial and/or gonorrhoeal urogenital disease and extragenital infection	Healthcare facilities with clinical laboratories
Microscopy (Gram stain) <sup>c</sup>  Gram stain of vaginal and urethral discharge will usually show the presence of leukocytes (>10 leukocytes/high power field for urethral discharge and >20 leukocytes/high power field for vaginal discharge) but this finding is not specific for chlamydial infections. If carried out by an experienced person, a Gram stain negative for intracellular diplococci ( <i>Neisseria gonorrhoeae</i> is an intracellular diplococcus) with the presence of >5 leukocytes/high power field in the context of urethral discharge in a man, can be presumed to suggest non-gonococcal urethritis.	To assess microbial morphology, and presence or absence of white blood cells	Healthcare facilities with clinical laboratories
Culture <sup>c,d</sup>  Rarely performed	Initial step to detect and identify bacterial species for selection of appropriate antibiotic regimens	Healthcare facilities with clinical laboratories

81 <sup>a</sup>Usually chlamydial and gonococcal infections are tested at the same time since their clinical presentations are very  
 82 similar.

83 <sup>b</sup>Possible specimens are: 1) among women, a vulvovaginal specimen, which may be self-collected. An endocervical  
 84 swab can also be an alternative but requires a speculum. First-catch urine is another option, but the sensitivity and  
 85 specificity tend to be lower in women 2) Among men, first catch urine or urethral swabs are appropriate. Anorectal  
 86 and pharyngeal samples are also adequate. For anorectal samples among men who have sex with men, *Chlamydia*  
 87 genovar testing for lymphogranuloma venereum should be done to guide the appropriate treatment regimen for  
 88 lymphogranuloma venereum

89 <sup>c</sup>Possible specimens are: urethral swabs, endocervical swabs, vaginal swabs, rectal swabs, oropharyngeal swabs,  
 90 conjunctival swabs. Note: urine samples are not good specimens for microscopy and culture.

91 <sup>d</sup>Consider culture if symptoms persist despite adequate treatment (note: urine samples are not good specimens for  
 92 culture). Processing *C. trachomatis* for culture requires highly experienced laboratories and technicians and is  
 93 complex, laborious and time-consuming to be of economic value. It is rarely performed in middle- or high-income  
 94 countries nowadays except for special purposes.

95 *Table 2 Additional tests for other sexually transmitted infections to consider in patients with*  
 96 *confirmed or suspected chlamydial urogenital infection as indicated in the WHO EDL (54)*

Infection	Diagnostic test	Purpose of the test	Settings where the test should be available
Gonorrhoea	<i>Neisseria gonorrhoeae</i> nucleic acid amplification test	To diagnose gonorrhoeal urogenital disease and extragenital infection	Health care facilities with clinical laboratories
HIV	Anti-HIV-1 and -HIV-2 antibody (RDT)	Self-testing to screen for HIV	Community settings and health facilities without laboratories <sup>a</sup>
HIV	Anti-HIV-1 and -HIV-2 antibody (RDT and immunoassay)	To screen for HIV infection	Community settings and health facilities without laboratories <sup>a</sup> (RDT)  Healthcare facilities with clinical laboratories (immunoassay)
HIV	Combined anti-HIV-1/HIV-2 antibody and p24 antigen (RDT and immunoassay)	To screen for HIV infection	Community settings and health facilities without laboratories <sup>a</sup> (RDT)  Healthcare facilities with clinical laboratories (immunoassay)
Hepatitis B	Hepatitis B virus surface antigen (RDT, immunoassay)	To screen for acute and chronic hepatitis B virus infection in people aged > 12 months	Community settings and health facilities without laboratories <sup>a</sup> (RDT)  Healthcare facilities with clinical laboratories (immunoassay)
Hepatitis B	IgM-specific antibodies to hepatitis B core antigen (immunoassay)	To aid in the diagnosis of acute HBV infection in the context of outbreak investigation	Healthcare facilities with clinical laboratories
Hepatitis C	Anti-hepatitis C antibody (RDT, immunoassay)	To screen for hepatitis C virus infection in people aged > 18 months	Community settings and health facilities without laboratories <sup>a</sup> (RDT)  Healthcare facilities with clinical laboratories (immunoassay)
Syphilis	Antibodies to <i>Treponema pallidum</i> <sup>b</sup> (RDT)	To diagnose or help to diagnose <i>Treponema pallidum</i>	Community settings and health facilities without laboratories <sup>a</sup>
Syphilis and HIV (combined test)	Combined antibodies to <i>Treponema pallidum</i> and to HIV-1 and HIV-2 (RDT)	To diagnose or help to diagnose HIV and/or <i>Treponema pallidum</i>	Community settings and health facilities without laboratories <sup>a</sup>

Trichomoniasis	Microscopy	To assess microbial morphology, and presence or absence of white blood cells	Healthcare facilities with clinical laboratories
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97 RDT: rapid diagnostic test.

98 <sup>a</sup>Community and health settings without laboratories are facilities such as health posts and centres, doctors' offices, outreach clinics and ambulatory care. These tests are assumed to be available at health care facilities with laboratories.

100  
101 <sup>b</sup>Usually a non-treponemal test (e.g. rapid plasma reagin, Venereal Disease Research Laboratory test) is used for  
102 screening (please refer to the chapter on syphilis for more details on testing).

## 103 II. Other tests

104 When chlamydial urogenital infection is suspected, laboratory tests other than microbiology are  
105 not usually needed.

## 106 III. Using microbiology surveillance data

107 Routine surveillance is not helpful to inform empiric guidance.

## 108 Imaging

109 When chlamydial urogenital infection is suspected, imaging is not usually needed.

## 110 Antibiotic treatment

111 Antibiotic treatment is always indicated when the infection is diagnosed. Table 3 gives  
112 recommendations taken from the most recent WHO guidelines on the treatment of chlamydial  
113 infections – most recent version at publication of this Handbook was issued in 2016 (175). Please  
114 check the WHO website regularly for possible updates. Recommendations in the EML overlap  
115 with the 2016 WHO guidelines (azithromycin or doxycycline are the recommended treatment  
116 options) but fewer treatment alternatives are included in the EML(4).

117 *Table 3 Empiric antibiotic treatment for chlamydial urogenital infections as indicated in the most*  
118 *recent WHO guidelines(175)*

119 *Please check the WHO website regularly for possible updates*

Type of chlamydial infection	Treatment	Total treatment duration
Uncomplicated urogenital infection <sup>a</sup>	Doxycycline <sup>b</sup> (oral): 100 mg given every 12 hours OR Azithromycin (oral): 1 g	7 days (doxycycline)  Single dose (azithromycin)
Anorectal infection	Doxycycline <sup>b</sup> (oral): 100 mg given every 12 hours	7 days
Infection in pregnant women <sup>c</sup>	Azithromycin (oral): 1 g	Single dose

Lymphogranuloma venereum <sup>d</sup>	<b>First choice</b> <b>Doxycycline</b> (oral): 100 mg given every 12 hours  <b>Second choice</b> <b>Azithromycin</b> (oral): 1 g given once a day	21 days
Ophthalmia neonatorum <sup>e</sup>  (i.e. chlamydial conjunctivitis)	<b>Azithromycin</b> (oral): 20 mg/kg given once a day	3 days
Ocular prophylaxis <sup>f</sup>  (topical treatment for the prevention of both gonococcal and chlamydial ophthalmia neonatorum)	<b>Erythromycin</b> (eye ointment): 0.5%	Antibiotic needs to be applied to both eyes soon after birth (single dose)

120 Notes: All dosages are for normal renal and hepatic function.

121 <sup>a</sup>Alternatives indicated in the WHO 2016 guidelines but not included in the EML for this indication: tetracycline (oral):  
122 500 mg every 6 hours; erythromycin (oral): 500 mg every 6 hours; ofloxacin (oral): 200–400 mg every 12 hours. The  
123 recommended duration of treatment is 7 days for all three options.

124 <sup>b</sup>According to recent data doxycycline is more effective than azithromycin and could be given priority if adherence  
125 to treatment is not of concern (176–178).

126 <sup>c</sup>Alternatives indicated in the WHO 2016 guidelines but not included in the EML for this indication: amoxicillin (oral):  
127 500 mg every 8 hours; erythromycin (oral): 500 mg every 12 hours. The recommended duration of treatment is 7  
128 days for both options.

129 <sup>d</sup>Alternatives indicated in the WHO 2016 guidelines but not included in the EML for this indication: erythromycin  
130 (oral): 500 mg every 6 hours for 21 days. This option should be considered only when doxycycline or azithromycin  
131 are not available.

132 <sup>e</sup>Alternatives indicated in the WHO 2016 guidelines but not included in the EML for this indication: erythromycin  
133 (oral): 50 mg/kg per day divided in 4 doses for 14 days.

134 <sup>f</sup>Alternatives indicated in the WHO 2016 guidelines but not included in the EML for this indication: tetracycline  
135 hydrochloride (eye ointment): 1%; povidone–iodine (water-based solution. Do not use alcohol-based solutions):  
136 2.5%; silver nitrate (solution): 1%; chloramphenicol (eye ointment): 1%.

137 **ACCESS** antibiotics are indicated in green, **WATCH** antibiotics in yellow and **RESERVE** antibiotics in red.

138 If symptoms persist at review:

- 139 • check partner notification and treatment history; and  
140 • for people with recurrent or persistent urethral discharge, refer to a centre with laboratory  
141 capacity to diagnose *N. gonorrhoeae*, *C. trachomatis*, *M. genitalium* and *T. vaginalis* and test  
142 for antimicrobial-resistant *N. gonorrhoeae* and *M. genitalium*.

## 143 Prevention

144 Important elements of prevention include counselling and behavioural approaches including  
145 comprehensive sexuality education, pre- and post-test counselling, safe sex and risk reduction  
146 counselling and promoting consistent use of condoms. Interventions targeting high-risk groups  
147 (e.g. men who have sex with men, transgender people, sex workers, people who inject drugs)

148 may be considered. Also consider offering pre-exposure prophylaxis for HIV to people at high risk  
149 for HIV infection. Sexual partners should always be informed of the infection and treated  
150 (179). Reporting of this infection to health authorities according to local regulations should also  
151 be done.

DRAFT

# Sexually Transmitted Infections

## - Gonococcal infection

### Key messages

1. *Neisseria gonorrhoeae* is a common curable STI and resistance to antibiotics (including extensively resistant strains) is an increasing public health problem
2. Symptoms overlap with urogenital *Chlamydia trachomatis* infection and co-infection is frequent therefore patients should be tested for both pathogens simultaneously, when available and evaluated for other STIs (HIV, syphilis, trichomoniasis)
3. Asymptomatic people should also be treated because they can transmit the infection to others
4. Preventive services should be offered (e.g. condoms, brief sexuality education, HIV pre-exposure prophylaxis to people at high risk for HIV infection) and sexual partners should be informed and treated
5. Reporting of this infection to health authorities is encouraged according to local regulations

#### Box 1 Other relevant WHO documents (please check regularly for updates)

- Sexually transmitted infections (STIs). Factsheets. [https://www.who.int/news-room/factsheets/detail/sexually-transmitted-infections-\(stis\)](https://www.who.int/news-room/factsheets/detail/sexually-transmitted-infections-(stis))
- Global action plan to control the spread and impact of antimicrobial resistance in *Neisseria gonorrhoeae*. <https://apps.who.int/iris/handle/10665/44863>
- **WHO guidelines for the treatment of *Neisseria gonorrhoeae*, 2016**  
<https://www.who.int/reproductivehealth/publications/rtis/gonorrhoea-treatment-guidelines/en/>
- **WHO guideline for the laboratory diagnosis of sexually transmitted infections including HIV, 2013** (<https://apps.who.int/iris/handle/10665/85343>)
- Global progress report on HIV, viral hepatitis and sexually transmitted infections, 2021  
<https://www.who.int/publications/i/item/9789240027077>
- Global Antimicrobial Resistance and Use Surveillance System (GLASS) Report: 2021  
<https://www.who.int/publications/i/item/9789240027336>

6 *In general this chapter applies to adults and young people aged over 12 years. In children*  
7 *specialist advice should be sought where possible. Consideration should be given that an STI in a*  
8 *child may be due to child sexual abuse.*

## 9 Definition

10 Gonococcal infection is a sexually transmitted infection caused by the bacterium *Neisseria*  
11 *gonorrhoeae*.

## 12 Microbiology epidemiology

13 *Neisseria gonorrhoeae*, the organism causing gonorrhoea, is a Gram-negative bacterium.

14 The bacterium easily develops resistance to antibiotics which has led to infections that are  
15 difficult to treat. As a result, resistance to antibiotics used for treatment (including third-  
16 generation cephalosporins) is a serious problem worldwide. Therefore, in 2012, WHO launched  
17 a global action plan to control the spread and impact of resistance in *Neisseria gonorrhoeae*  
18 (180).

19 Data on *Neisseria gonorrhoeae* resistance are collected through the WHO Global Antimicrobial  
20 Resistance Surveillance System (GLASS) and the WHO Global Gonococcal Antimicrobial  
21 Surveillance Programme (GASP network) and are regularly published (181, 182) (183, 184).

## 22 Pathophysiology

23 *Neisseria gonorrhoeae* usually enters the mucosa (mostly of the genital tract) during sexual  
24 contact. Because of its many virulence factors, this bacterium can adapt to the local environment,  
25 evade immune response mechanisms and proliferate causing local inflammatory response and  
26 disease and, more rarely, systemic infection (i.e. gonococcal bacteraemia). If left untreated, or if  
27 it is inappropriately treated, complications may occur. In particular in women, pelvic  
28 inflammatory disease (i.e. an infection of the upper female reproductive tract) with inflammation  
29 of the uterine tubes (i.e. salpingitis), endometrium (i.e. endometritis) or abscess formation in the  
30 ovary/ovaries and tubes can occur. In men, complications include epididymitis and periurethritis  
31 with abscess formation. These complications can lead to infertility.

32 Disseminated gonococcal infection can occur as a result of bacteremia secondary to mucosal  
33 infection (mostly of the genital tract) and can lead to arthritis, skin manifestations and other  
34 complications.

35 Infants of mothers with gonococcal infection can be infected at delivery, resulting in neonatal  
36 conjunctivitis manifesting as purulent ocular discharge and swollen eyelids. Untreated  
37 conjunctivitis may lead to scarring and blindness.

## 38 Epidemiology

39 Gonococcal infection is one of the most common sexually transmitted infections worldwide.

40 The 2021 WHO Global progress report on HIV, viral hepatitis and sexually transmitted infections  
41 reported an estimated 82 million new gonococcal infections in 2020 among adults aged 15 to 49  
42 years of age (173).

43 The highest incidence of gonococcal infection is in the Africa and Western Pacific regions; this  
44 includes China and Australia among others (185). Gonococcal infection increases the risk of HIV  
45 infection by 2 to 3 folds.

46 Risk factors for gonococcal infection include HIV infection, young age, having multiple sexual  
47 partners or a new sexual partner, having partners with STIs, having had previous gonococcal  
48 infection and / or other STIs and several socioeconomic factors (e.g. low socioeconomic or  
49 educational level, substance abuse). Infection does not induce protective immunity therefore  
50 reinfection is possible. Resistance of *Neisseria gonorrhoeae* to antibiotics used to treat the  
51 infection is a concern (see the microbiology epidemiology section for more information about  
52 resistance) (183).

## 53 Clinical presentation

54 Signs and symptoms of gonococcal infection vary in men and women and overlap with those of  
55 chlamydial infection. Some people with gonococcal infection may be asymptomatic even though  
56 they can still transmit the infection. When symptoms occur (usually a few days after being  
57 infected), the most common clinical presentation in men is acute urethritis characterized by  
58 profuse mucopurulent urethral discharge and dysuria; testicular discomfort can also be present.  
59 In women mucopurulent vaginal discharge and dysuria are the most common symptoms. Several  
60 women may have lower abdominal pain because of ascending infection causing pelvic  
61 inflammatory disease. Gonorrhoea causes cervical infection that presents with cervical  
62 discharge, cervical ectopy and friability and easy bleeding on contact.

63 In both sexes (but in males more than females), symptoms of acute proctitis with pain, pruritus,  
64 discharge and bleeding of the rectum may occur. Pharyngitis (mostly manifesting as a mild sore  
65 throat) and conjunctivitis are other conditions that usually coexist with genital infection.

66 Rarely, the infection can disseminate (i.e. gonococcal bacteraemia) and this can typically lead to  
67 localized infection in one or more joints (i.e. gonococcal arthritis). Please refer to the Handbook  
68 chapter on septic arthritis for more information on this topic.

69 In pregnant women, the infection can be transmitted to the child during vaginal delivery. In  
70 newborns, gonococcal infection can present with acute ocular infection (i.e. conjunctivitis) or  
71 pharyngitis which manifest a few days after birth. Disseminated infection with septic arthritis  
72 (usually with multiple joints involved) can also occur in newborns.

## 73 Laboratory tests

74

### 75 I. Patient microbiology tests

76 Molecular testing has greatly improved the detection of *Neisseria gonorrhoeae* (and *Chlamydia*  
77 *trachomatis*) among both symptomatic and asymptomatic men and women and has become the  
78 recommended gold standard technology to diagnose and screen populations for *N. gonorrhoeae*  
79 and *C. trachomatis* (Table 2 also indicates the types of specimens that can be used for this  
80 purpose).

81 Culture of *N. gonorrhoeae* is still the standard method for performing antibiotic susceptibility  
82 testing. However, this organism is not easy to grow in the laboratory, requiring special training  
83 and a special culture medium. For this reason, culture of *N. gonorrhoeae* is not routinely  
84 performed as part of managing people with gonococcal infection in resource-limited settings.

85 *N. gonorrhoeae* can also be identified by light microscopy of Gram-stained samples and a  
86 presumptive diagnosis can be made if intracellular Gram-negative diplococci are observed in  
87 polymorphonuclear leukocytes, best seen when there is a urethral discharge. Gram-stained  
88 smears from the cervix are also considered positive for the presumptive diagnosis of gonorrhoea  
89 in women if intracellular Gram-negative diplococci are observed in polymorphonuclear  
90 leukocytes. Gram stain of urethral samples among women has low yield and may not be cost-  
91 effective.

92 For more comprehensive information on the diagnosis of gonococcal infection, please refer to  
93 the most recent WHO guideline for the laboratory diagnosis of sexually transmitted  
94 infections – most recent version at publication of this Handbook was issued in 2013(174). Please  
95 check the WHO website regularly for possible updates. Patients with gonococcal infection are  
96 also usually evaluated also for other sexually transmitted infections (e.g. chlamydial infection,  
97 hepatitis B, hepatitis C, HIV and syphilis).

98 Tests to consider when gonococcal infection is suspected are listed in Table 1. Additional tests  
99 for other sexually transmitted infections that could be considered when gonococcal infection is  
100 confirmed or suspected are shown in Table 2.

101 *Table 1 Microbiology tests to consider when gonococcal infection is suspected as indicated in the*  
102 *WHO CDI (54)*

Diagnostic test	Purpose of the test	Settings where the test should be available
Qualitative test for <i>Neisseria gonorrhoeae</i> and <i>Chlamydia trachomatis</i> infections (i.e. nucleic acid amplification test) <sup>a,b</sup>  <b>This is the recommended reference standard</b>	To diagnose gonorrhoeal and/or chlamydial urogenital disease and extragenital infection	Healthcare facilities with clinical laboratories
Microscopy (Gram stain) <sup>c</sup>	To assess microbial morphology, and presence or absence of white blood cells	Healthcare facilities with clinical laboratories
Culture <sup>d</sup> Consider if symptoms persist despite adequate treatment and for surveillance purposes.	Initial step to detect and identify bacterial species for selection of appropriate antibiotic regimens	Healthcare facilities with clinical laboratories

Blood cultures  Consider if disseminated infection is suspected.	To detect bacterial bloodstream infections (sepsis)	Healthcare facilities with clinical laboratories
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103 <sup>a</sup>Usually gonococcal and chlamydial infections are tested at the same time since their clinical presentations are  
104 very similar.

105 <sup>b</sup>Possible specimens are: 1) among women, a vulvovaginal specimen, which may be self-collected. An endocervical  
106 swab can also be an alternative but requires a speculum. First-catch urine is another option, but the sensitivity and  
107 specificity tend to be lower in women 2) Among men, first catch urine or urethral swabs are appropriate. Anorectal  
108 and pharyngeal samples are also adequate. Nucleic acid amplification tests also perform well for pharyngeal and  
109 anorectal samples.

110 <sup>c</sup>Possible specimens are: urethral swabs, endocervical swabs and conjunctival swabs. Note: urine samples are not  
111 good specimens for microscopy.

112 <sup>d</sup>Possible specimens are: urethral swabs, endocervical swabs, vaginal swabs, rectal swabs, oropharyngeal swabs  
113 and conjunctival swabs. Note: urine samples are not good specimens for culture. Culture is the standard method  
114 for performing antibiotic susceptibility testing.

115 *Table 2 Additional tests for other sexually transmitted infections to consider in patients with*  
116 *confirmed or suspected gonococcal infection as indicated in the WHO EDL (54)*

Infection	Diagnostic test	Purpose of the test	Settings where the test should be available
Chlamydial urogenital infection	<i>Chlamydia trachomatis</i> nucleic acid amplification test	To diagnose chlamydial urogenital disease and extragenital infection	Healthcare facilities with clinical laboratories
HIV	Anti-HIV-1 and -HIV-2 antibody (RDT)	Self-testing to screen for HIV	Community settings and health facilities without laboratories <sup>a</sup>
HIV	Anti-HIV-1 and -HIV-2 antibody (RDT and immunoassay)	To screen for HIV infection	Community settings and health facilities without laboratories <sup>a</sup> (RDT)  Healthcare facilities with clinical laboratories (immunoassay)
HIV	Combined anti-HIV-1/HIV-2 antibody and p24 antigen (RDT and immunoassay)	To screen for HIV infection	Community settings and health facilities without laboratories <sup>a</sup> (RDT)  Healthcare facilities with clinical laboratories (immunoassay)
Hepatitis B	Hepatitis B virus surface antigen (RDT, immunoassay)	To screen for acute and chronic hepatitis B virus infection in people aged > 12 months	Community settings and health facilities without laboratories <sup>a</sup> (RDT)  Healthcare facilities with clinical laboratories (immunoassay)
Hepatitis B	IgM-specific antibodies to	To aid in the diagnosis of acute HBV infection in the	Healthcare facilities with clinical laboratories

	hepatitis B core antigen (immunoassay)	context of outbreak investigation	
Hepatitis C	Anti-hepatitis C antibody (RDT, immunoassay)	To screen for hepatitis C virus infection in people aged > 18 months	Community settings and health facilities without laboratories <sup>a</sup> (RDT)  Healthcare facilities with clinical laboratories (immunoassay)
Syphilis	Antibodies to <i>Treponema pallidum</i> <sup>b</sup> (RDT)	To diagnose or help to diagnose <i>Treponema pallidum</i>	Community settings and health facilities without laboratories <sup>a</sup>
Syphilis and HIV (combined test)	Combined antibodies to <i>Treponema pallidum</i> and to HIV-1 and HIV-2 (RDT)	To diagnose or help to diagnose HIV and/or <i>Treponema pallidum</i>	Community settings and health facilities without laboratories <sup>a</sup>
Trichomoniasis	Microscopy	To assess microbial morphology, and presence or absence of white blood cells	Healthcare facilities with clinical laboratories

117 RDT: rapid diagnostic test.

118 <sup>a</sup>Community and health settings without laboratories are defined as community and health facilities such as health  
119 posts and centres, doctors' offices, outreach clinics and ambulatory care. These tests are also assumed to be  
120 available at healthcare facilities with laboratories.

121 <sup>b</sup>Usually a non-treponemal test (e.g. rapid plasma reagin, Venereal Disease Research Laboratory test) is used for  
122 screening (please refer to the chapter on syphilis for more details on testing).

## 123 II. Other tests

124 When gonococcal infection is suspected, laboratory tests other than microbiology are not usually  
125 needed. However, microscopy of vaginal or urethral secretions will usually show the presence of  
126 leukocytes (> 10 leukocytes/field).

## 127 III. Using microbiology surveillance data

128 Monitoring antibiotic resistance in *Neisseria gonorrhoeae* is recommended to inform local,  
129 national and global guidance.

## 130 Imaging

131 When gonococcal infection is suspected, imaging is not usually needed.

## 132 Antibiotic treatment

133 The recommendations on antibiotic treatment reported here are based on the most recent WHO  
134 guidelines for the treatment of gonorrhoea– most recent version at publication of this Handbook  
135 was issued in 2016(77). Because of increasing antibiotic resistance to azithromycin in *N.*  
136 *gonorrhoeae* and *M. genitalium* and reduced susceptibility of *N. gonorrhoeae* to cephalosporins,

137 WHO is in the process of revising current treatment recommendations and dosages. **Please check**  
 138 **the WHO website regularly for possible updates.**

139 All people (including pregnant women) diagnosed with gonorrhoea should receive adequate  
 140 antibiotic treatment (see Table 3).

141 When choosing treatment, local resistance data should determine the choice of the most  
 142 appropriate therapy and if data are not available, dual therapy (i.e. two antibiotics) should be  
 143 given. If symptoms do not resolve within about 5 days of adequate antibiotic treatment, a  
 144 resistant infection should be suspected, or an alternative diagnosis sought.

145 *Table 3 Antibiotic treatment for gonococcal infection as indicated in the most recent WHO*  
 146 *guidelines for the treatment of gonorrhoea (77)*

147 *Please check the WHO website regularly for possible updates.*

Type of gonococcal infection	Treatment	Total treatment duration
Genital and anorectal infections ( <b>dual therapy</b> <sup>a</sup> )	<b>First choice</b> Ceftriaxone (IM): 250 mg AND Azithromycin (oral): 1 g  <b>Second choice</b> Cefixime (oral): 400 mg AND Azithromycin (oral): 1 g	Single dose
Genital and anorectal infections ( <b>single therapy</b> ); if local resistance data confirm susceptibility to the antibiotic <sup>b</sup>	Ceftriaxone (IM): 250 mg  <b>Second choice</b> Spectinomycin (IM): 2 g OR Gentamicin <sup>c</sup> (IM): 240 mg	Single dose
Oropharyngeal infections <sup>d</sup> ( <b>dual therapy</b> <sup>a</sup> )	<b>First choice</b> Ceftriaxone (IM): 250 mg AND Azithromycin (oral): 1 g  <b>Second choice</b> Cefixime (oral): 400 mg AND Azithromycin (oral): 1 g	Single dose
Oropharyngeal infections <sup>d</sup> ( <b>single therapy</b> ); if local resistance data confirm susceptibility to the antibiotic	Ceftriaxone (IM): 250 mg	Single dose
Gonococcal ophthalmia neonatorum <sup>e</sup> (i.e. gonococcal conjunctivitis)	Ceftriaxone (IM): 50mg/kg OR Spectinomycin (IM): 25mg/kg	Single dose
Ocular prophylaxis <sup>f</sup>  (topical treatment for the prevention of both chlamydial and gonococcal ophthalmia neonatorum)	Erythromycin (eye ointment): 0.5%	Antibiotic needs to be applied to both eyes soon after birth (single dose)
Retreatment after treatment failure	Ceftriaxone (IM): 500 mg AND Azithromycin (oral): 2 g OR Cefixime (oral): 800 mg AND Azithromycin (oral): 2 g	Single dose

Consider treatment failure if symptoms persist after 5 days of adequate treatment	OR Gentamicin (IM): 240 mg AND Azithromycin (oral): 2 g OR Spectinomycin <sup>d</sup> (IM): 2 g AND Azithromycin(oral): 2 g	
---	--	--

148 Notes: All dosages are for normal renal and hepatic function.

149 IM: intramuscular.

150 <sup>a</sup>Dual therapy should be given if no reliable local data on resistance are available.

151 <sup>b</sup>Alternatives indicated in the WHO 2016 guidelines but not included in the EML for genital and anorectal infections:  
152 single therapy with cefixime (oral) 400 mg single dose.

153 <sup>c</sup>The EML lists gentamicin (single dose) for this indication, however, this option is not recommended in the WHO  
154 2016 guidelines (except for retreatment after treatment failure) (77). Unless new information supporting the use of  
155 gentamicin in gonococcal infections is provided, the 2023 Expert Committee might consider gentamicin for deletion  
156 for this indication.

157 <sup>d</sup>Do not use spectinomycin to treat cases of oropharyngeal infection.

158 <sup>e</sup>Alternative indicated in the WHO 2016 guidelines but not included in the EML for gonococcal ophthalmia  
159 neonatorum: kanamycin (IM): 25mg/kg.

160 <sup>f</sup>Alternatives indicated in the WHO 2016 guidelines but not included in the EML for the prevention of both chlamydial  
161 and gonococcal ophthalmia neonatorum: tetracycline hydrochloride (eye ointment): 1%; povidone-iodine (water-  
162 based solution. Do not use alcohol-based solutions): 2.5%; silver nitrate (solution): 1%; chloramphenicol (eye  
163 ointment): 1%.

164 Legend: ACCESS antibiotics are indicated in green, WATCH antibiotics in yellow and RESERVE antibiotics in red

## 165 Prevention

166 No effective vaccine against *Neisseria gonorrhoeae* is available. Prevention is therefore one of  
167 the key elements included in the WHO 2012 global action plan to control the spread and impact  
168 of antimicrobial resistance in *Neisseria gonorrhoeae* (180).

169 Important elements of prevention include counselling and behavioural approaches including  
170 comprehensive sexuality education, pre- and post-test counselling, safe sex and risk reduction  
171 counselling and promoting consistent use of condoms. Interventions targeting high-risk groups  
172 (e.g. men who have sex with men, transgender people, sex workers, people who inject drugs)  
173 and offering HIV pre-exposure prophylaxis to people at high risk for HIV infection may be  
174 considered. Sexual partners should always be informed of the infection and treated. Reporting  
175 of this infection to health authorities according to local regulations should also be done.

# Sexually Transmitted Infections

## - Syphilis

### Key messages

1. Syphilis has several stages of infection with different clinical presentations and remains common worldwide
2. All pregnant women should be screened for syphilis and treated if infected to prevent congenital syphilis in the child
3. Asymptomatic people should also be treated because they can transmit the infection to others and all people with syphilis should also be evaluated for other STIs
4. Preventive services should be offered (e.g. condoms, brief sexuality education, HIV pre-exposure prophylaxis to people at high risk for HIV infection) and sexual partners should be informed and treated
5. Reporting of this infection to health authorities is encouraged according to local regulations

#### Box 1 Other relevant WHO documents (please check regularly for updates)

- Sexually transmitted infections (STIs). Factsheets. [https://www.who.int/news-room/factsheets/detail/sexually-transmitted-infections-\(stis\)](https://www.who.int/news-room/factsheets/detail/sexually-transmitted-infections-(stis))
- Global progress report on HIV, viral hepatitis and sexually transmitted infections, 2021: accountability for the global health sector strategies 2016–2021: actions for impact. <https://apps.who.int/iris/handle/10665/341413>
- WHO 2016 guidelines for the treatment of *Treponema pallidum* (<https://apps.who.int/iris/handle/10665/249572>)
- WHO guideline for the laboratory diagnosis of sexually transmitted infections including HIV, 2013 (<https://apps.who.int/iris/handle/10665/85343>)
- WHO guideline on syphilis screening and treatment for pregnant women. (<https://apps.who.int/iris/handle/10665/259003>)

*In general this chapter applies to adults and young people aged over 12 years. In children specialist advice should be sought where possible. Consideration should be given that an STI in a child may be due to child sexual abuse.*

### Definition

Syphilis is a sexually transmitted infection caused by the bacterium *Treponema pallidum* subspecies *pallidum*. Syphilis is one of other treponematoses (i.e. diseases caused by spirochaetes of the species *Treponema pallidum*). Other *Treponema pallidum* subspecies causing

12 human diseases include subspecies *pertenue* (the causative pathogen of yaws(186)), subspecies  
 13 *endemicum* (the causative pathogen of endemic syphilis or bejel) and subspecies *carateum* (the  
 14 causative pathogen of pinta)(187). This chapter will only address disease caused by *Treponema*  
 15 *pallidum* subspecies *pallidum* (syphilis). Information about other treponematoses is available on  
 16 the WHO website(186).

17 Syphilis can be classified as “early” or “late” based on the time since becoming infected (usually  
 18 infections of  $\leq 2$  years duration are defined “early” and infections of  $> 2$  years are defined “late”)  
 19 and “primary”, “secondary” or “tertiary” based on the clinical presentation. There is usually a  
 20 long latent phase with no clinical manifestations between secondary and tertiary infection – the  
 21 tertiary phase only develops in untreated or inadequately treated infections. Overlap between  
 22 definitions exists with early infection including primary and secondary syphilis and late infection  
 23 including the latent phase and tertiary syphilis.

24 The latent phase can also be divided into two phases – “early latent” and the “late latent”.

25 Early latent is usually defined as  $< 2$  years after infection while late latent is defined as  $> 2$  years.  
 26 However, this distinction is difficult to apply because it is often impossible to establish the time  
 27 of the initial infection.

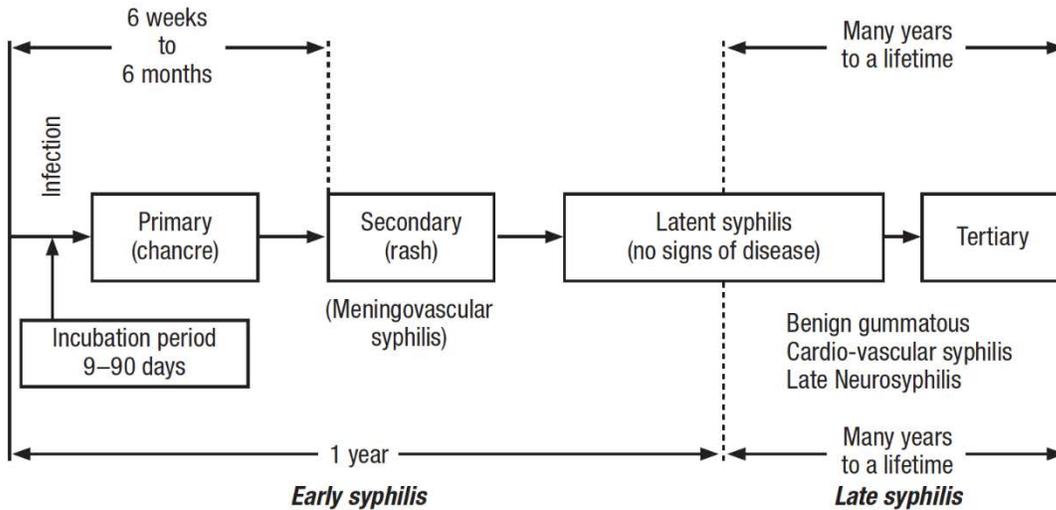


Figure 10.1  
 Schematic representation of the course of untreated syphilis

28 Source: WHO 2013 guidelines: Laboratory diagnosis of sexually transmitted infections, including HIV.  
 29

## 30 Microbiology epidemiology

31 Syphilis is caused by *Treponema pallidum* subspecies *pallidum* a bacterium of the phylum  
 32 Spirochaetes (other members of this phylum include e.g. *Leptospira* and *Borrelia*).

33 *Treponema pallidum* is characterized by slow growth, difficulty in culturing *in vitro*, and its  
 34 thinness (0.2  $\mu\text{m}$  compared to about 0.5  $\mu\text{m}$  for a bacterium like *Escherichia coli*) which makes it  
 35 difficult to see with conventional microscopy.

36 Resistance to penicillin has not yet been reported and therefore it remains the antibiotic of choice  
37 for the treatment of syphilis. Resistance to azithromycin has been reported in some settings(188).

## 38 Pathophysiology

39 Syphilis is usually acquired through sexual contact with infectious lesions on the mucosa or skin  
40 or, much more rarely, through the bloodstream. The infection can also be transmitted from the  
41 mother to her fetus because *Treponema pallidum* subspecies *pallidum* can cross the placenta and  
42 cause fetal death and congenital infection.

43 With sexual transmission, once *Treponema pallidum* subspecies *pallidum* enters the  
44 subcutaneous tissue, infection develops within 2-6 weeks (usually about 3 weeks) with formation  
45 of an ulcerative lesion that occurs at the site of inoculation. Usually, the immune system is able  
46 to control the early infection and, even if left untreated, the primary ulcerative lesion (i.e.  
47 chancre) resolves. However, dissemination of *Treponema pallidum* through the bloodstream can  
48 occur at the time of primary infection and this can result over time in secondary or tertiary  
49 syphilis in the absence of adequate treatment. In particular, tertiary syphilis has a long incubation  
50 period (up to years or decades after the initial infection) and develops in about a third of patients  
51 with untreated syphilis. In 2017, 370 000 prevalent cases of tertiary syphilis were reported  
52 worldwide but this number is probably an underestimation of the true burden of the disease(31).

53 Congenital syphilis can occur as a result of vertical transmission of the pathogen from an infected  
54 mother to the fetus. The risk of transmission depends on a combination of factors including  
55 maternal titers of non-treponemal tests (see Table 1 for an explanation about tests), timing and  
56 adequacy of maternal treatment, and stage of maternal infection. The estimated number of total  
57 cases of congenital syphilis worldwide in 2016 was 661 000 (or 473 per 100 000 live births)(189).

## 58 Epidemiology

59 Syphilis is a common curable sexually transmitted infection, and its incidence is increasing  
60 globally. WHO estimates 7 million new cases in 2020 (173). Although other bacterial sexually  
61 transmitted infections occur more frequently (for example, in 2020 more than 82 million new  
62 cases of gonorrhoea and about 128 million new cases of chlamydial infection were reported)(173),  
63 syphilis has an important public health impact because of the potential serious consequences if  
64 left untreated, including maternal transmission to the fetus resulting in congenital syphilis and  
65 fetal death and complications such as neurosyphilis and cardiovascular syphilis.

66 Moreover, as for other sexually transmitted infections, syphilis affects quality of life and increases  
67 the risk of transmitting or acquiring other sexually transmitted infections including HIV; This HIV  
68 risk is of particular concern because sexually transmitted infections characterized by the  
69 presence of ulcerative lesions have the highest risk of HIV transmission (190).

70 The risk factors for syphilis include having multiple sexual partners or a new sexual partner,  
71 having partners with STIs, having had a previous STI, and several socioeconomic factors (e.g. low  
72 socioeconomic or educational level, substance abuse, young age)(191, 192). Lack of access to  
73 adequate prenatal care is an important risk factor for congenital syphilis.

## 74 Clinical presentation

75 Signs and symptoms vary depending on the stage of the disease (early or late).

76 Early syphilis has the following signs and symptoms.

- 77
- 78 • Primary infection (localized disease): characterized by the presence of a localized non-  
79 painful ulcerative lesion (i.e. chancre) with indurated margins, usually associated with  
80 local lymphadenopathy. The lesion is usually located on the genitalia, mouth or rectum  
81 but other locations are possible depending on the site of inoculation. The lesion is often  
82 asymptomatic and can remain unnoticed particularly among women. If left untreated,  
83 the lesion usually resolves within a few weeks without leaving a scar.
  - 84 • Secondary infection (disseminated disease): characterized by skin and mucosal  
85 manifestations. Generally, a maculopapular non-irritant rash appears which is usually  
86 diffuse and extends bilaterally over the trunk and the extremities. A characteristic feature  
87 is the involvement of the palms of the hands and soles of the feet. The mucous  
88 membranes of the mouth and perineum can also show lesions (mostly flat lesions) that  
89 are highly infectious. Systemic manifestations (e.g. fever > 38.0°C, generalized  
90 lymphadenopathy and malaise) are usually present. Neurologic manifestations (e.g.  
meningitis), hepatitis and ocular involvement can also occur in this phase.

91 Late syphilis has the following signs and symptoms.

- 92
- 93 • Tertiary syphilis (disseminated disease): this can occur as the result of an untreated early  
94 syphilis after a period of latency (with no clinical manifestations) that may last years  
95 – usually tertiary syphilis develops more rapidly in patients with HIV. In this phase  
96 different organ systems can be affected particularly: the cardiovascular system (typically  
97 with signs and symptoms of aortitis), the skin, soft tissues and bones (typically with  
98 granulomatous or nodular lesions also known as gummas) and the central nervous  
99 system (typically with symptoms of progressive dementia, psychiatric syndrome and  
100 tabes dorsalis characterized by problems with coordination of movements, pain radiating  
from the spine and impaired response of the pupils to light).

101 Congenital syphilis: infection during pregnancy can lead to spontaneous abortion or premature  
102 birth. Most babies with congenital syphilis are asymptomatic at birth but when symptoms are  
103 present, they usually develop days or weeks after birth. These symptoms often include anaemia,  
104 thrombocytopenia, rash (maculopapular, desquamative rash particularly over the palms, soles,  
105 mouth and anus), generalized lymphadenopathy, hepatomegaly and jaundice, nasal discharge  
106 (that may turn bloody), painful osteitis (mostly in long bones) and teeth abnormalities. The  
107 cerebrospinal fluid is abnormal, indicating neurological disease, in up to half of all babies. Of note,  
108 neurological consequences can be expressed later in life and this should always be considered in  
109 case of congenital syphilis.

## 110 Laboratory tests

111 For more comprehensive information on diagnosis of syphilis, please refer to the most recent  
112 WHO guideline for the laboratory diagnosis of sexually transmitted infections – the most recent  
113 version at publication of this Handbook was issued in 2013 (174). Please check the WHO website  
114 regularly for possible updates.

### 115 I. Patient microbiology tests

116 In patients with suspected syphilis, microbiology tests can support the diagnosis (Table 1). Certain  
117 microbiology tests are also used to screen asymptomatic pregnant women. For screening during  
118 pregnancy please refer to the most recent WHO guideline on syphilis screening and treatment  
119 for pregnant women – the most recent version at publication of this Handbook was issued in  
120 2017 (193).

#### 121 Direct detection methods

122 These methods can be used to detect the pathogen in specimens obtained from skin or tissues  
123 lesions (Table 1). This includes dark-field microscopy (where *Treponema pallidum*  
124 from lesions of primary syphilis can be observed. Of note a negative dark-field result does not  
125 exclude syphilis) and nucleic acid amplification tests (to detect *T. pallidum*-specific DNA  
126 sequences). Direct detection is considered the “gold standard” but it is much less frequently  
127 used today because it is more time consuming than serological tests.

#### 128 Serological tests

129 Two types of serological tests can be done, treponemal and nontreponemal tests (Table 1).

- 130 • Treponemal tests detect antibodies to treponemal antigens and usually remain positive  
131 after infection even after successful treatment. These tests include: fluorescent  
132 treponemal antibody absorption (FTA-ABS) test, *Treponema pallidum* particle  
133 agglutination (TPPA) assay and *Treponema pallidum* haemagglutination (TPHA) assay.  
134 Treponemal rapid diagnostic tests for syphilis are available and prequalified by WHO.
- 135 • Non-treponemal tests detect antibodies that react to lipids (e.g. cardiolipin released  
136 during cellular damage that occurs in response to *Treponema Pallidum*). These are  
137 qualitative and quantitative tests that can also be used to monitor response to treatment  
138 because their titers tend to decline after adequate treatment and may become negative  
139 (i.e. nonreactive) over time. These tests include: rapid plasma reagin (RPR) test, Venereal  
140 Disease Research Laboratory (VDRL) test).

141 Initially, a two-step approach is used to test for syphilis (both types of tests – treponemal and  
142 non-treponemal- need to be positive to confirm the diagnosis). In order to increase access and  
143 ensure same-day treatment, WHO recommends the use of a rapid treponemal test followed (if  
144 positive) by a non-treponemal test.

145 However, starting with a non-treponemal test and confirm positive results with a treponemal  
146 test is also appropriate.

147 All serological tests for syphilis (non-treponemal and treponemal tests) are negative in the early  
148 phase of primary syphilis, taking 1–4 weeks after the chancre appears to become reactive. Both  
149 treponemal and non-treponemal tests are reactive in secondary or tertiary syphilis (Table 2).

150 Non-treponemal tests can rarely give false positive results (e.g. during pregnancy or during an  
151 acute febrile illness). Tables 2, 3 and 4 can be used to help with the interpretation of results of  
152 serological tests.

153 Additional tests for other sexually transmitted infections that could be considered when syphilis  
154 is confirmed or suspected are shown in Table 5.

155 *Table 1 Microbiology tests to consider when syphilis is suspected as indicated in the WHO EDL*  
156 *(54)*

Diagnostic test	Purpose of the test	Settings where the test should be available
Microscopy of specimens obtained from skin and tissues lesions <sup>a</sup>	To assess microbial morphology	Healthcare facilities with clinical laboratories
Antibodies to <i>Treponema Pallidum</i> (RDT)	To diagnose or help to diagnose <i>Treponema pallidum</i>	Community settings and health facilities without laboratories <sup>b</sup>
Combined antibodies to <i>Treponema pallidum</i> and to HIV-1 and HIV-2 (RDT)	To diagnose or help to diagnose HIV and/or <i>Treponema pallidum</i>	Community settings and health facilities without laboratories <sup>b</sup>
Non-treponemal test: rapid plasma reagin (RPR)	To screen for syphilis and monitor effectiveness of treatment	Healthcare facilities with clinical laboratories
Non-treponemal test: venereal disease research laboratory (VDRL) <sup>c</sup>	To screen for syphilis and monitor effectiveness of treatment and also to screen for, diagnose and confirm neurosyphilis <sup>c</sup>	Healthcare facilities with clinical laboratories
Treponemal test: <i>Treponema pallidum</i> haemagglutination (TPHA) <sup>d</sup>	To confirm syphilis and diagnose early and late syphilis	Healthcare facilities with clinical laboratories
Treponemal test: <i>Treponema pallidum</i> particle agglutination (TPPA) <sup>d</sup>	To confirm syphilis and diagnose early and late syphilis	Healthcare facilities with clinical laboratories

157 RDT: rapid diagnostic test.

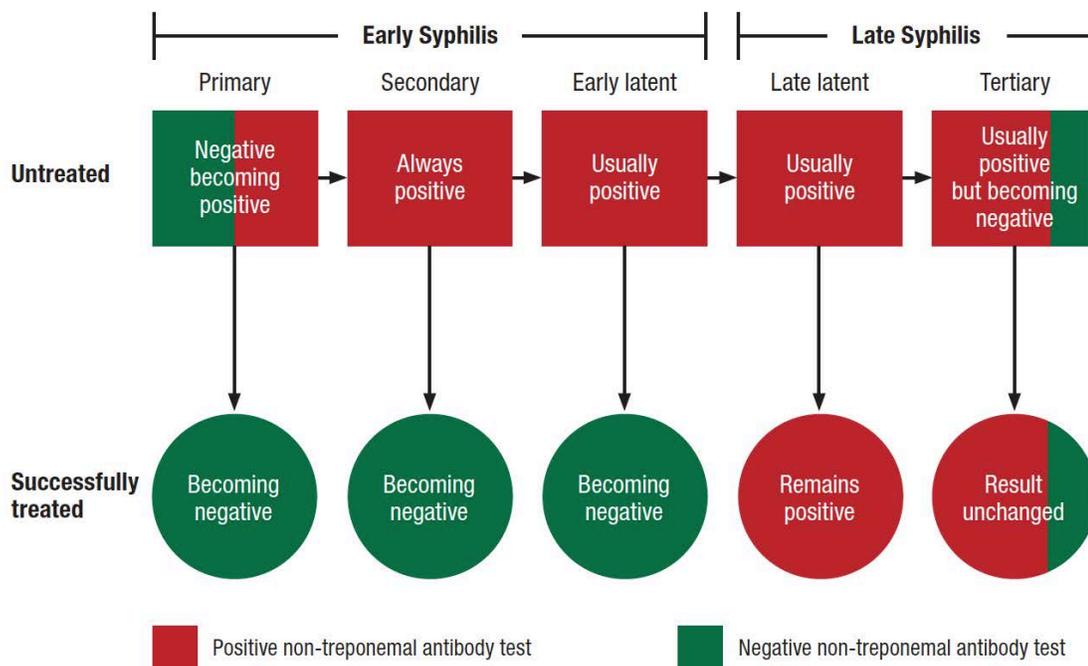
158 <sup>a</sup>Nucleic acid amplification tests (e.g. PCR) of specimens obtained from skin and tissues lesions could also be  
159 considered if available.

160 <sup>b</sup>Community and health settings without laboratories are defined as community and health facilities such as health  
161 posts and centres, doctors' offices, outreach clinics and ambulatory care. These tests are also assumed to be  
162 available at healthcare facilities with laboratories.

163 <sup>c</sup>If neurosyphilis is suspected (this can occur at any stage of infection including in the first few months) the VDRL test  
164 can also be performed on the cerebrospinal fluid in the presence of a positive syphilis serology. The test has a high  
165 specificity (i.e. few false positive results) but a low sensitivity (i.e. many false negative results). Examination of the  
166 cerebrospinal fluid is recommended in case of clinical evidence of neurological involvement and is also highly  
167 desirable in all patients with syphilis of more than two years duration or of uncertain duration in order to evaluate  
168 the possible presence of asymptomatic neurosyphilis(194).

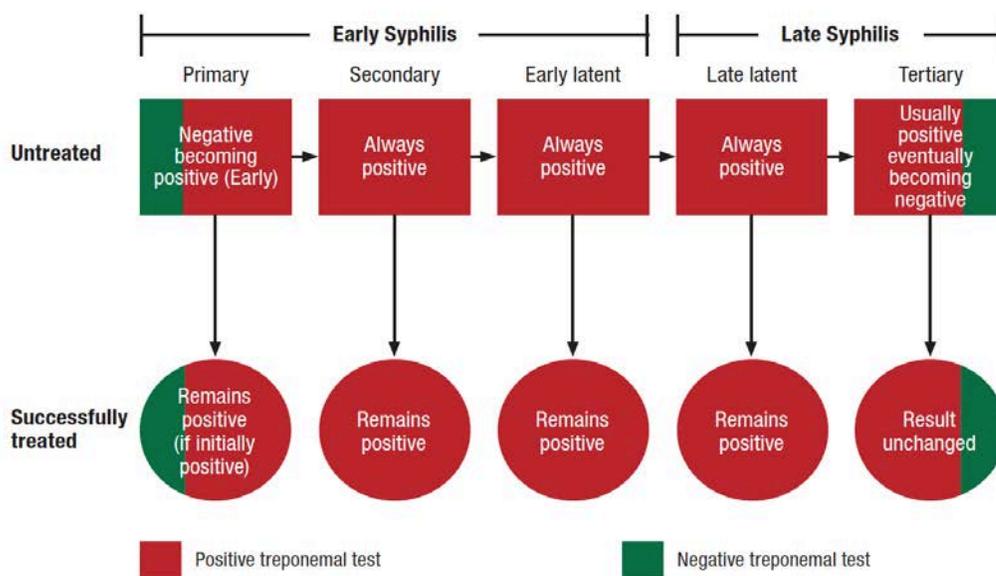
169 <sup>d</sup>Treponemal tests usually remain positive after the infection has been cleared.

170 *Table 2 Reactivity of non-treponemal serological tests by stage of syphilis and effect of treatment*



171 Source: Unemo (WHO STI laboratory manual available at <https://apps.who.int/iris/handle/10665/85343>).  
 172

173 *Table 3 Reactivity of treponemal serological tests by stage of syphilis and effect of treatment*



174 Source: Unemo (WHO STI laboratory manual available at <https://apps.who.int/iris/handle/10665/85343>).  
 175

176 *Table 4 Possible interpretation of combinations of non-treponemal and treponemal test results*

Non-treponemal test (RPR or VDRL)	Treponemal test (FTA-ABS, TPPA, TPHA, RDT)	Interpretation
Positive	Positive	This supports the diagnosis of syphilis (the stage of disease and need for treatment should be determined on a case-by-case basis)  Note: these cases should be notified to the local authority according to national guidance for disease notification
Negative	Positive	Usually this can occur as a result of a successfully treated previous infection (because treponemal tests tend to remain positive) otherwise it could be a very early (or late) phase of the infection
Positive	Negative	Usually this can be considered a false positive result (e.g. during pregnancy)
Negative	Negative	Usually the diagnosis of syphilis can be excluded

177 FTA-ABS: fluorescent treponemal antibody absorption; RDT: rapid diagnostic test; RPR: rapid plasma reagin; TPHA:  
178 *Treponema pallidum* haemagglutination; TPPA: *Treponema pallidum* particle agglutination; VDRL: Venereal Disease  
179 Research Laboratory.

180 *Table 5 Additional tests for other sexually transmitted infections to consider in patients with*  
181 *confirmed or suspected syphilis as indicated in the WHO EDL (54)*

Infection	Diagnostic test	Purpose of the test	Settings where the test should be available
Chlamydial urogenital infection and gonococcal infection	Qualitative test for <i>Chlamydia trachomatis</i> and <i>Neisseria gonorrhoeae</i> infections (i.e. nucleic acid amplification test)	To diagnose chlamydial and/or gonorrhoeal urogenital disease and extragenital infection	Healthcare facilities with clinical laboratories
HIV	Anti-HIV-1 and -HIV-2 antibody (RDT)	Self-testing to screen for HIV	Community settings and health facilities without laboratories <sup>a</sup>
HIV	Anti-HIV-1 and -HIV-2 antibody (RDT and immunoassay)	To screen for HIV infection	Community settings and health facilities without laboratories <sup>a</sup> (RDT)  Healthcare facilities with clinical laboratories (immunoassay)
HIV	Combined anti-HIV-1/HIV-2 antibody and p24 antigen (RDT and immunoassay)	To screen for HIV infection	Community settings and health facilities without laboratories <sup>a</sup> (RDT)

			Healthcare facilities with clinical laboratories (immunoassay)
Hepatitis B	Hepatitis B virus surface antigen (RDT, immunoassay)	To screen for acute and chronic hepatitis B virus infection in people aged > 12 months	Community settings and health facilities without laboratories <sup>a</sup> (RDT) Healthcare facilities with clinical laboratories (immunoassay)
Hepatitis B	IgM-specific antibodies to hepatitis B core antigen (immunoassay)	To aid in the diagnosis of acute HBV infection in the context of outbreak investigation	Healthcare facilities with clinical laboratories
Hepatitis C	Anti-hepatitis C antibody (RDT, immunoassay)	To screen for hepatitis C virus infection in people aged > 18 months	Community settings and health facilities without laboratories <sup>a</sup> (RDT) Healthcare facilities with clinical laboratories (immunoassay)
Trichomoniasis	Microscopy	To assess microbial morphology, and presence or absence of white blood cells	Healthcare facilities with clinical laboratories

182 RDT: rapid diagnostic test.

183 <sup>a</sup>Community and health settings without laboratories are defined as community and health facilities such as health  
184 posts and centres, doctors' offices, outreach clinics and ambulatory care. These tests are also assumed to be  
185 available at healthcare facilities with laboratories.

## 186 II. Other tests

187 When primary syphilis is suspected, blood tests other than serology are not usually needed.  
188 However, in case of secondary or tertiary syphilis, laboratory tests may be required. If signs and  
189 symptoms of neurological disease (i.e. neurosyphilis) are present, a lumbar puncture to test the  
190 cerebrospinal fluid is indicated if available (Table 6).

191 *Table 6 Laboratory tests (other than microbiology) to consider when late syphilis is suspected as*  
192 *indicated in the WHO EDL (54)*

Diagnostic test	Purpose of the test	Settings where the test should be available
Basic CSF Profile (CSF leukocyte count <sup>a</sup> , CSF differential leukocyte count and CSF protein <sup>b</sup> and glucose)	To aid in the diagnosis of neurosyphilis	Health care facilities with clinical laboratories

193 CSF: cerebrospinal fluid.

194 <sup>a</sup>CSF leukocyte count: usually > 5 white blood cell /  $\mu\text{l}$  (> 0.01X10<sup>9</sup>/L), higher cut-off > 20 cell /  $\mu\text{l}$  in HIV positive  
195 patients (> 0.02X10<sup>9</sup>/L) even though this is not a specific finding of neurosyphilis.

196 <sup>b</sup>CSF protein levels: protein concentration is usually increased (> 45 mg/dL or > 0.45 g/L) but not a specific finding of  
197 neurosyphilis.

198 <sup>c</sup>CSF glucose levels: glucose concentrations are usually decreased but not a specific finding of neurosyphilis.

### 199 III. Using microbiology surveillance data

200 Routine surveillance is not helpful to inform empiric guidance.

## 201 Imaging

202 When syphilis is suspected, imaging is not usually needed unless a complication of late syphilis  
203 is suspected.

## 204 Antibiotic treatment

205 All patients (including pregnant women) diagnosed with syphilis should receive a full course of  
206 antibiotic treatment (Table 6). Serological response to treatment can be assessed by repeating a  
207 non-treponemal quantitative test (ideally the same type of non-treponemal test used at the time  
208 of diagnosis) to detect a reduction in titre. A four-fold reduction (or higher) in titres should be  
209 seen to confirm an adequate response to treatment for early syphilis (usually with repeated  
210 assessments at 3, 6 and 12 months after the end of treatment).

211 In case of early syphilis (primary or secondary), the partners of infected people should also be  
212 treated if they have had sexual relations with the infected person in the 90 days before the  
213 person was diagnosed with syphilis. If more than 90 days have elapsed, serological testing is  
214 usually suggested and treatment is given accordingly.

215 The antibiotic treatment recommendations reported here (Table 6) are aligned with the most  
216 recent WHO guidelines for the treatment of syphilis – most recent version at publication of this  
217 handbook was issued in 2016 (195).

218 *Table 6 Antibiotic treatment for syphilis by stage of the disease as indicated in the most recent*  
219 *WHO guidelines for the treatment of syphilis(195).*

220 *Please check the WHO website regularly for possible updates*

Type of infection	Treatment	Total treatment duration
<p><b>Early syphilis</b> (adults and adolescents)</p> <p>Early syphilis includes primary, secondary and early latent syphilis of no more than 2 years duration</p>	<p><b>First choice</b> Benzathine benzylpenicillin<sup>a</sup> (IM): 2.4 million IU (1.8 g)</p> <p><b>Second choice</b> Procaine benzylpenicillin (IM): 1.2 million IU (1.2 g) given once a day</p>	<p>Benzathine benzylpenicillin: single dose</p> <p>Procaine benzylpenicillin: 10-14 days</p>
<p><b>Late syphilis or unknown stage</b> (adults and adolescents)</p> <p>This includes infection of more than 2 years duration without evidence of</p>	<p><b>First choice</b> Benzathine benzylpenicillin<sup>b</sup> (IM): 2.4 million IU (1.8 g)</p> <p><b>Second choice</b></p>	<p>Benzathine benzylpenicillin: one dose per week for 3 consecutive weeks (e.g. on days 1, 8 and 15)</p>

<p>treponemal infection (i.e. asymptomatic infection)</p>	<p><b>Procaine benzylpenicillin</b> (IM): 1.2 million IU (1.2 g) given once a day</p>	<p>The interval between doses should not exceed 14 days</p> <p>Procaine benzylpenicillin: 20 days</p>
<p><b>Congenital syphilis</b>                  Infants with confirmed disease or infants who are clinically normal but whose mother had untreated or inadequately treated syphilis<sup>c</sup></p> <p>Inadequate treatment refers to treatment &lt; 30 days prior to delivery and/or treatment with a non-penicillin regimen</p>	<p><b>Benzylpenicillin</b> (IV):                  50 000-75 000 IU /kg/dose (30-45 mg/kg/dose) given every 12 hours</p> <p>OR</p> <p><b>Procaine benzylpenicillin</b> (IM):                  50 000 IU/kg (50 mg/kg) per day</p> <p>If intravenous access is available, aqueous benzylpenicillin should be preferred over procaine benzylpenicillin.</p>	<p>10-15 days</p>
<p><b>Neurosyphilis<sup>d</sup></b></p>	<p><b>Benzylpenicillin<sup>e</sup></b> (IV): 2–4 million IU (1.2 - 2.4 g) given every 4 hours</p> <p>OR</p> <p><b>Procaine benzylpenicillin<sup>f</sup></b> (IM): 1.2 million IU (1.2 g) given once a day AND Probenecid (oral): 500 mg given every 6 hours</p>	<p>14 days</p>
<p><b>Syphilis in pregnancy</b></p>	<p><b>Early syphilis:</b>  <b>Benzathine benzylpenicillin</b> (IM): 2.4 million IU (1.8 g)</p> <p>Alternative options (not in the EML) in case of allergy to penicillin (or stock-outs): Ceftriaxone 1 gr for 10-14 days. Azithromycin (2 gr single dose) or erythromycin (500 mg every 6 hours for 14 days) can also be used however neither of them cross the placental barrier completely, therefore only the mother is treated, not the fetus.</p> <p><b>Late syphilis or unknown stage:</b>  <b>Benzathine benzylpenicillin</b> (IM): 2.4 million IU (1.8 g)</p> <p>Alternative option (not in the EML) in case of allergy to penicillin (or stock-outs): Erythromycin 500 mg every 6 hours for 30 days (but this does not treat the fetus since erythromycin does not cross the</p>	<p><b>Early syphilis:</b> single dose</p> <p><b>Late syphilis or unknown stage:</b>                  One dose per week for 3 consecutive weeks (e.g. on days 1, 8 and 15).                  The interval between doses should not exceed 14 days</p>

	placental barrier completely, therefore only the mother is treated).	
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221 Notes: All dosages are for normal renal and hepatic function.

222 IM: intramuscular; IV: intravenous; IU: international units.

223 <sup>a</sup>Alternative options in case of allergy to penicillin (or stock-outs) are indicated in the WHO 2016 guidelines but not  
224 included in the EML for this indication. These are: doxycycline (oral) 100 mg every 12 hours (except in pregnant  
225 women) for 14 days or ceftriaxone 1 gr (IM) for 10-14 days(195); in special circumstances (i.e. when susceptibility is  
226 likely, based on local epidemiology) azithromycin 2 gr (oral) as a single dose can be given. If penicillin cannot be used,  
227 doxycycline is the preferred choice (except in pregnant women) because of its lower cost and oral  
228 administration(195).

229 <sup>b</sup>An alternative option, in case of allergy to penicillin (or stock-outs), is indicated in the WHO 2016 guidelines but this  
230 option is not included in the EML for this indication. This option is: doxycycline (oral) 100 mg every 12 hours (except  
231 in pregnant women) for 30 days(195).

232 <sup>c</sup>If the mother was adequately treated and the infant is clinically normal, close monitoring of the infant is suggested  
233 or if treatment is provided, the WHO 2016 guidelines indicate benzathine benzylpenicillin 50 000 IU/kg (37.5 mg)  
234 per day single dose IM as an option.

235 <sup>d</sup>From the 2003 WHO guidelines on management of sexually transmitted infections (194).

236 <sup>e</sup>Alternative options are indicated in the WHO 2003 guidelines for non-pregnant patients allergic to penicillin but  
237 they are not included in the EML. These options are: doxycycline (oral): 200 mg every 12 hours; tetracycline (oral):  
238 500 mg every 6 hours. Treatment duration is 30 days in both cases.

239 <sup>f</sup>Some authorities recommend adding benzathine benzylpenicillin, 2.4 million IU (1.8 g) by intramuscular injection,  
240 in three consecutive doses once weekly, after completing this regimen, but there are no data to support this  
241 approach. Benzathine benzylpenicillin, 2.4 million IU (1.8 g) by intramuscular injection does not give adequate  
242 therapeutic levels in the cerebrospinal fluid(195).

243 Legend: **ACCESS** antibiotics are indicated in green, **WATCH** antibiotics in yellow and **RESERVE** antibiotics in red

## 244 Prevention

245 Sexual transmission typically occurs only during primary, secondary and early latent infection.  
246 Mother-to-child transmission, however, has been documented to occur up to several years after  
247 the initial infection(195).

248 Prevention of infection is a key strategy; no effective vaccine against *Treponema pallidum* is yet  
249 available therefore other preventive measures can be used.

250 The main elements of prevention include: comprehensive sexuality education, pre- and post-test  
251 counselling, safe sex and risk reduction counselling and promoting consistent use of condoms.  
252 Interventions targeting groups who have a higher risk of infection (e.g. men who have sex with  
253 men, transgender people, sex workers, people who inject drugs, indigenous communities,  
254 persons in prisons) should be considered. Offering HIV pre-exposure prophylaxis to people at  
255 high risk for HIV infection may be considered.

256 Access of pregnant women to early and adequate prenatal care, including screening at first visit  
257 and immediate treatment initiation if needed are key to prevent congenital syphilis.

258 Sexual partners should always be informed of the infection and treated (179); Reporting of this  
259 infection to health authorities according to local regulations should also be done.

# Sexually Transmitted Infection - Trichomoniasis

## Key messages

1. Trichomoniasis is the most common curable sexually transmitted infection (STI) and in women it can manifest as a vaginal discharge (men are usually asymptomatic)
2. Asymptomatic people should also be treated because they can transmit the infection to others and all people with trichomoniasis should also be evaluated for other STIs
3. Preventive services should be offered (e.g. condoms, brief sexuality education, HIV pre-exposure prophylaxis to people at high risk for HIV infection) and sexual partners should be informed and treated
4. Reporting of this infection to health authorities is encouraged according to local regulations

### Box 1 Other relevant WHO documents (please check regularly for updates)

- Sexually transmitted infections (STIs). Factsheets. [https://www.who.int/news-room/factsheets/detail/sexually-transmitted-infections-\(stis\)](https://www.who.int/news-room/factsheets/detail/sexually-transmitted-infections-(stis))
- Global progress report on HIV, viral hepatitis and sexually transmitted infections, 2021: accountability for the global health sector strategies 2016–2021: actions for impact. <https://apps.who.int/iris/handle/10665/341412>
- WHO guideline for the laboratory diagnosis of sexually transmitted infections including HIV, 2013 (<https://apps.who.int/iris/handle/10665/85343>)
- Guidelines for the management of symptomatic sexually transmitted infections (<https://apps.who.int/iris/handle/10665/342523>)(196)

*In general this chapter applies to adults and young people aged over 12 years. In children specialist advice should be sought where possible. Consideration should be given that an STI in a child may be due to child sexual abuse.*

## Definition

Trichomoniasis is a sexually transmitted infection caused by the protozoan *Trichomonas vaginalis*.

## 11 Microbiology epidemiology

12 Trichomoniasis is caused by *Trichomonas vaginalis*, an anaerobe flagellated protozoan.



13  
14 Source: [https://de.wikipedia.org/wiki/Trichomonas\\_vaginalis](https://de.wikipedia.org/wiki/Trichomonas_vaginalis)

## 15 Pathophysiology

16 *Trichomonas vaginalis* infects the mucosa of the urogenital tract during sexual contact and  
17 produces a local inflammatory response that causes vaginal or urethral discharge.

## 18 Epidemiology

19 Trichomoniasis is the most prevalent sexually transmitted infection worldwide with an estimated  
20 156 million new cases in 2020 as reported by WHO(173).

21 The infection most commonly affects women older than 40 years of age. As for other sexually  
22 transmitted infections, the risk of acquiring or transmitting HIV is higher in cases of  
23 trichomoniasis and the infection is associated with adverse outcomes in pregnancy (e.g. preterm  
24 delivery, premature rupture of membranes, low birth weight)(197). If left untreated,  
25 trichomoniasis can persist for months or years and in pregnant women, it can be transmitted to  
26 the baby during delivery. Common risk factors for infection include multiple sex partners, a  
27 history of having other sexually transmitted infections (e.g. HIV) and substance abuse.

## 28 Clinical presentation

29 Most cases of trichomoniasis are asymptomatic, especially in men, or have mild symptoms. In  
30 women, symptoms include acute onset of vaginal inflammation and discharge (usually  
31 characterized by a bad smell and with a frothy appearance), dysuria and pelvic pain. In men,  
32 symptomatic infection usually presents with urethral discharge, dysuria and testicular discomfort  
33 or pain. Epididymitis and prostatitis can also occur in a minority of cases.

## 34 Laboratory tests

35 For more comprehensive information on the diagnosis of trichomoniasis, please refer to the  
36 most recent WHO guideline on the laboratory diagnosis of sexually transmitted infections – the  
37 most recent version at publication of this Handbook was issued in 2013 (174). Please check the  
38 WHO website regularly for possible updates.

### 39 I. Patient microbiology tests

40 All people with trichomoniasis are also usually evaluated for other sexually transmitted infections  
41 (e.g. chlamydial infection, gonococcal infection, hepatitis B and hepatitis C, HIV and syphilis).

42 Tests to consider when trichomoniasis is suspected are indicated in Table 1.

43 Molecular assays such as nucleic acid amplification tests have the highest sensitivity of all  
44 diagnostic methods to detect *T. vaginalis* but they are not currently widely available as rapid  
45 point-of-care tests. However, if available, they should be used. Vaginal swabs are the samples of  
46 choice, but endocervical samples and urine can be used for some assays.

47 Historically, trichomoniasis has been diagnosed by performing wet mount microscopy. Although  
48 this is not the gold standard technique, a wet mount is frequently used because it is quick,  
49 inexpensive and easy to perform. However, to have a good chance of successfully identifying the  
50 motile trichomonads, the slide should be read within 10 minutes of collection since trichomonads  
51 quickly lose their motility. Non-motile cells cannot be diagnosed as trichomonads (due to possible  
52 misidentification, e.g. a non-motile trichomonad is difficult to differentiate from the nucleus of  
53 a vaginal epithelial cell).

54 Culture of *T. vaginalis*, which has a higher sensitivity than the wet mount microscopic  
55 examination, was the cornerstone for detecting *T. vaginalis* before the advent of point-of-care  
56 antigen tests and nucleic acid amplification tests. Although a culture medium is commercially  
57 available, cultures of samples from women with trichomoniasis are usually positive in the first  
58 three days of inoculation, but they have to be incubated for up to seven days to rule out infection.  
59 Routine culture methods detecting *T. vaginalis* are no longer widely performed.

60 Additional tests for other sexually transmitted infections that could be considered when  
61 trichomoniasis is confirmed or suspected are shown in Table 2.

62 *Table 1 Microbiology tests to consider when trichomoniasis is suspected as indicated in the WHO*  
63 *EDL (54)*

Diagnostic test	Purpose of the test	Settings where the test should be available
Microscopy <sup>a,b</sup>	To assess microbial morphology and presence or absence of white blood cells	Healthcare facilities with clinical laboratories
Culture <sup>b</sup>	Initial step to detect and identify bacterial species for selection of appropriate antibiotic regimens	Healthcare facilities with clinical laboratories

64 <sup>a</sup>If available, nucleic acid amplification tests for *Trichomonas vaginalis* could be considered, especially if the  
 65 microscopy examination is negative. Nucleic acid tests for trichomoniasis are not listed in the third version of the  
 66 EDL.

67 <sup>b</sup>Possible specimens are: urethral swabs endocervical swabs, vaginal swabs.

68 *Table 2 Additional tests for other sexually transmitted infections to consider in patients with*  
 69 *confirmed or suspected trichomoniasis as indicated in the WHO EDL (54)*

Infection	Diagnostic test	Purpose of the test	Settings where the test should be available
Chlamydial urogenital infection and gonococcal infection	Qualitative test for <i>Chlamydia trachomatis</i> and <i>Neisseria gonorrhoeae</i> infections (i.e. nucleic acid amplification test)	To diagnose chlamydial and/or gonorrhoeal urogenital disease and extragenital infection	Healthcare facilities with clinical laboratories
HIV	Anti-HIV-1 and -HIV-2 antibody (RDT)	Self-testing to screen for HIV	Community settings and health facilities without laboratories <sup>a</sup>
HIV	Anti-HIV-1 and -HIV-2 antibody (RDT and immunoassay)	To screen for HIV infection	Community settings and health facilities without laboratories <sup>a</sup> (RDT)  Healthcare facilities with clinical laboratories (immunoassay)
HIV	Combined anti-HIV-1/HIV-2 antibody and p24 antigen (RDT and immunoassay)	To screen for HIV infection	Community settings and health facilities without laboratories <sup>a</sup> (RDT)  Healthcare facilities with clinical laboratories (immunoassay)
Hepatitis B	Hepatitis B virus surface antigen (RDT, immunoassay)	To screen for acute and chronic hepatitis B virus infection in people > 12 months	Community settings and health facilities without laboratories <sup>a</sup> (RDT)  Healthcare facilities with clinical laboratories (immunoassay)
Hepatitis B	IgM-specific antibodies to hepatitis B core antigen (immunoassay)	To aid in the diagnosis of acute HBV infection in the context of outbreak investigation	Healthcare facilities with clinical laboratories
Hepatitis C	Anti-hepatitis C antibody (RDT, immunoassay)	To screen for hepatitis C virus infection in people > 18 months	Community settings and health facilities without laboratories <sup>a</sup> (RDT)  Healthcare facilities with clinical laboratories (immunoassay)

Syphilis	Antibodies to <i>Treponema pallidum</i> <sup>b</sup> (RDT)	To diagnose or help to diagnose <i>Treponema pallidum</i>	Community settings and health facilities without laboratories <sup>a</sup>
Syphilis and HIV combined test	Combined antibodies to <i>Treponema pallidum</i> and HIV-1/HIV-2 (RDT)	To diagnose or help to diagnose HIV and/or <i>Treponema pallidum</i>	Community settings and health facilities without laboratories <sup>a</sup>

70 RDT: rapid diagnostic test.

71 <sup>a</sup>Community and health settings without laboratories are facilities such as health posts and centres, doctors' offices, outreach clinics, ambulatory care and home-based and self-testing. These tests are also assumed to be available at healthcare facilities with laboratories.

72  
73  
74 <sup>b</sup>Usually a non-treponemal test (e.g. rapid plasma reagin, Venereal Disease Research Laboratory test) is used for screening (please refer to the chapter on syphilis for more details on testing).

## 76 II. Other tests

77 When trichomoniasis is suspected, laboratory tests (other than microbiology) are not usually  
78 needed.

## 79 III. Using microbiology surveillance data

80 Routine surveillance is not helpful to inform empiric guidance.

## 81 Imaging

82 When trichomoniasis is suspected, imaging is not usually needed.

## 83 Antibiotic treatment

84 Antibiotic treatment is always indicated when trichomoniasis is diagnosed (Table 3), including in  
85 asymptomatic patients to stop transmission. Sexual partners should also be tested and treated if  
86 infected.

87 *Table 3 Antibiotic treatment for trichomoniasis as indicated in the most recent WHO guidelines  
88 for the management of symptomatic sexually transmitted infections(196)*

89 *Please check the WHO website regularly for possible updates*

Treatment	Total treatment duration
Metronidazole (oral) 2 g	Single dose
OR	
Metronidazole (oral) 400 or 500 mg given every 12 hours <sup>a</sup>	7 days

90 Notes: All dosages are for normal renal and hepatic function.

91 <sup>a</sup>If compliance is not a problem, consider giving 500 mg (oral) every 12 hours for 7 days. Evidence supports better  
92 cure rates with a 7-day course of treatment compared with a single dose(198).

93 Legend: ACCESS antibiotics are indicated in green, WATCH antibiotics in yellow and RESERVE antibiotics in red

94

## 95 Prevention

96 No effective vaccine against *Trichomonas vaginalis* is available. Prevention of infection is  
97 therefore a key strategy. Important elements of prevention include counselling and behavioural  
98 approaches including comprehensive sexuality education, pre- and post-test counselling, safe sex  
99 and risk reduction counselling and promoting consistent use of condoms. Interventions targeting  
100 high-risk groups (e.g. men who have sex with men, transgender people, sex workers, people who  
101 inject drugs) may be considered. Offering HIV pre-exposure prophylaxis to people at high risk for  
102 HIV infection may be considered.

103 Sexual partners should always be informed of the infection and treated (179). Reporting of this  
104 infection to health authorities according to local regulations should also be done.

DRAFT

# 1 Urinary Tract Infection - Lower

2 Focus on community-acquired acute cystitis

## 3 Key messages

1. Infections are more common in women and increase with age and frequency of sexual activity
2. Most cases are caused by *Escherichia coli*
3. Urine culture should be considered in children and in people at higher risk of complicated infections (e.g. men, pregnant women) or in the case of recurrent infections
4. Oral nitrofurantoin for 5 days is the main recommended treatment for lower UTI
5. A positive urine culture in asymptomatic patients is not an indication for antibiotic treatment in the great majority of cases

4

*Box 1 Other relevant WHO documents (please check regularly for updates)*

- WHO 2013 pocket book of hospital care for children <https://apps.who.int/iris/handle/10665/81170> (23)

## 5 Definition

6 Lower urinary tract infections (UTI) are acute infections in which only the lower part of the urinary  
7 tract is affected (e.g. the bladder - cystitis). These infections are often classified as either  
8 complicated or uncomplicated based on the presence of risk factors that make them more  
9 difficult to treat.

10 Complications can occur with lower UTIs because of certain patient-related risk factors. While  
11 there is no universally accepted definition of what constitutes a complicated UTI, lower UTIs in  
12 individuals with certain conditions of the urinary tract (e.g. anatomical anomalies and kidney  
13 stones) are generally complicated. Infections in pregnant women are also usually included in this  
14 category. Examples of factors that may increase the risk of a complicated lower UTI are shown in  
15 Box 1 but should not be considered a complete list.

*Box 1 Factors that may increase the risk of a complicated lower urinary tract infection*

Obstruction at any site of the urinary tract  
Foreign body (e.g. urinary catheters and stents)  
Incomplete voiding  
Vesicoureteral reflux  
Recent history of instrumentation  
Male sex  
Pregnancy  
Diabetes  
Immunosuppression

**Notes:** The list gives some examples but is not aimed to be complete. No widely accepted definition of a complicated urinary tract infection currently exists. Some experts suggest that the list above is too long and may result in diagnosing too many patients with a “complicated” infection. The presence of one or more of these risk factors does not mean that the infection is complicated and in need of a different treatment approach.

Source: Guidelines on urological infections of the European Association of Urology

## 16 Pathophysiology

17 Lower UTIs occur when pathogens (usually ascending the urethra from the perineal area) reach  
 18 the bladder and overcome the host defences, which leads to parenchymal damage and an  
 19 inflammatory response. Microorganisms in the urine do not inevitably lead to infection. Infection  
 20 will depend on the interaction between the organism (for example, because of virulence factors  
 21 of the pathogen), the patient (who may have more infections because of underlying diseases)  
 22 and the environment (for example, the presence of a urinary catheter).

## 23 Epidemiology

24 Lower UTIs are very common worldwide and can affect people of any age. According to the Global  
 25 Burden of Disease study, in 2017 there were an estimated 274 million new cases of UTIs (lower  
 26 and upper) globally, combining all ages and both sexes(31).

27 The incidence of UTIs is highest in women and increases with age (e.g. UTIs increase after  
 28 menopause) and frequency of sexual activity. These infections are particularly common in  
 29 women because of the anatomy of their lower urinary tract; women have a shorter urethra than  
 30 men and so microorganisms colonizing the skin of the perineal area can more easily reach the  
 31 bladder. However, after 65 years of age, rates of lower UTIs in men and women tend to be more  
 32 similar(199). It is estimated that more than 50% of women experience at least one episode of  
 33 lower UTI in their lifetime. After a first episode, the risk of recurrence in young women has been  
 34 estimated to be about 70% within a year(200). Risk factors for UTIs include anatomical and  
 35 functional abnormalities of the urinary tract (e.g. conditions that predispose to incomplete  
 36 emptying of the bladder, renal insufficiency and urinary incontinence). Defective host immune  
 37 factors (e.g. poorly controlled diabetes or neutropenia) and instrumentation of the urinary tract  
 38 (e.g. urinary catheters and stents) are also predisposing factors.

## 39 Microbiology epidemiology

40 Lower UTIs are usually caused by bacteria that are part of the human intestinal microbiota, most  
 41 frequently *Escherichia coli*. In clinical practice a causative pathogen is usually only identified in  
 42 more severe cases when urinary cultures are obtained. Pathogens that most frequently cause  
 43 UTIs are shown in Table 1. Data on causative organisms from LMIC are limited; however, if a  
 44 difference exists in the proportion of less common pathogens, it is unlikely to affect  
 45 management. In Africa and the Middle East *Schistosoma haematobium* can present with  
 46 haematuria and signs of a UTI, particularly in children.

47 *Table 1 Pathogens most frequently associated with urinary tract infections (in descending order*  
 48 *of frequency)*

- |   |
|---|
| <ul style="list-style-type: none"> <li>• Enterobacterales (including multidrug-resistant strains such as those producing ESBL's)           <ul style="list-style-type: none"> <li>○ <i>Escherichia coli</i> (responsible for &gt; 80% of cases)</li> <li>○ <i>Klebsiella pneumoniae</i></li> <li>○ <i>Proteus mirabilis</i></li> </ul> </li> <li>• Coagulase-negative Staphylococci           <ul style="list-style-type: none"> <li>○ <i>Staphylococcus saprophyticus</i> (in young women)</li> </ul> </li> <li>• <i>Streptococcus agalactiae</i> (group B <i>Streptococcus</i>)</li> <li>• <i>Enterococcus</i> spp.</li> <li>• <i>Pseudomonas aeruginosa</i><sup>a</sup> (including multidrug-resistant strains such as those producing ESBL)</li> <li>• <i>Acinetobacter baumannii</i><sup>a</sup> (including multidrug-resistant strains such as those producing ESBL)</li> </ul> |
|---|

49 ESBL: extended-spectrum beta-lactamases.

50 <sup>a</sup>Especially in patients with recent antibiotic exposure.

## 51 Clinical presentation

52 Classical symptoms of lower UTIs include a combination of acute (< 1 week) dysuria, increased  
 53 urinary urgency and frequency, lower abdominal pain or discomfort, and sometimes gross  
 54 haematuria (i.e. blood can be seen in the urine). In women, vaginal discharge or irritation should  
 55 be excluded before concluding a diagnosis of lower UTI. In elderly patients with pre-existing  
 56 urinary symptoms (e.g. urinary incontinence), the evaluation may be more difficult. However, the  
 57 most reliable symptoms in these cases are still acute urinary changes compared with the  
 58 baseline. Atypical symptoms, such as falls and altered mental status, are unreliable. In addition,  
 59 cloudy and smelly urine alone are not reliable signs of a UTI.

60 In children, symptoms can include vomiting, low grade fever, increased urgency, frequency,  
 61 dysuria, new incontinence, smelly urine or lower abdominal pain and discomfort.

## 62 Laboratory tests

### 63 I. Patient microbiology tests

64 In symptomatic patients at a higher risk of complications and in children, a urine culture may be  
 65 performed (Table 2). The rationale is to confirm the diagnosis and to adjust empiric treatment  
 66 based on susceptibility results.

67 In children a clean catch specimen is difficult to obtain but is preferred to a urine specimen  
 68 obtained with a bag. Positive urine cultures in patients without symptoms (asymptomatic  
 69 bacteriuria) are frequent and not indicative of bacterial cystitis. Except for very selected cases  
 70 (e.g. pregnant women, before invasive urologic interventions) asymptomatic bacteriuria should  
 71 not be treated with antibiotics.

72 *Table 2 Microbiology tests to consider for diagnosis of lower urinary tract infections as indicated*  
 73 *in the WHO EDL (54)*

Diagnostic test	Purpose of the test	Setting where the test should be available
Urine culture <sup>a</sup>	Initial step to detect and identify bacterial and fungal species for selection of appropriate antibiotic regimens	Health care facilities with clinical laboratories

74 <sup>a</sup>A positive urine culture in an asymptomatic patient indicates bacterial colonization and does not require treatment  
 75 except in pregnant women or in patients undergoing urological procedures in which bleeding is anticipated. Bacterial  
 76 colonization of the urine is a common finding especially in women, in the elderly (both sexes) and in individuals with  
 77 underlying urological abnormalities. Of note, the absence of urine leucocytes has a good negative predictive value  
 78 but the positive predictive value of leukocyturia is poor.

## 79 II. Other tests

80 A urinalysis (dipstick or microscopy) may be done to detect the presence of bacteriuria and pyuria  
 81 (Table 3), while blood tests are not generally used to confirm infection (tests results would be  
 82 normal in case of lower UTI). In a symptomatic patient, leukocyturia (> 10 leukocytes/ $\mu$ L, 10 M/l),  
 83 the presence of leukocyte esterase and/or positive nitrites are indirect signs of infection. Of note,  
 84 leukocyturia or presence of leukocyte esterase without symptoms is not an indication for  
 85 antibiotic treatment.

86 *Table 3 Laboratory tests to consider for diagnosis of lower urinary tract infections as indicated in*  
 87 *the WHO EDL (54)*

Diagnostic test	Purpose of the test	Setting where the test should be available
Urinalysis test strips	To detect urinary tract infections	Community settings and health facilities without laboratories <sup>a</sup>

88 <sup>a</sup>Community and health settings without laboratories are settings such as health posts and centres, doctors'  
 89 offices, outreach clinics and ambulatory care. These tests are also assumed to be available at health care facilities  
 90 with laboratories.

## 91 III. Using microbiology surveillance data

92 Empiric guidance given by the Handbook would ideally be guided by recent local clinically  
 93 relevant microbiology surveillance data. This would include clinical microbiology surveys of urine  
 94 culture data from patients with lower urinary tract infection in the primary care/community  
 95 setting (not hospital out-patient clinic data which likely over estimate the prevalence of  
 96 resistance). These surveys would ideally include information on the current and previous recent  
 97 antibiotic treatment, clinical disease severity, patient risk factors and clinical outcomes. The focus  
 98 would be on significant urine bacterial isolates resistant to EML/c recommended antibiotics such  
 99 as nitrofurantoin.

## 100 Imaging

101 Initial imaging (e.g. ultrasound) of the urinary tract is not needed to diagnose a lower UTI. Imaging  
102 to investigate possible underlying abnormalities of the urinary tract could be considered, mostly  
103 in children and male patients.

## 104 Antibiotic treatment

105 Antibiotic treatment is usually given empirically if there are compatible signs and symptoms of a  
106 UTI AND a positive test (urinalysis or urine culture). If diagnostic tests cannot be performed,  
107 treatment may be given based on clinical presentation alone. If a urine culture is performed,  
108 empiric treatment should be reassessed once the results of susceptibility testing are available.

109 Clinical improvement should be within 48–72 hours of starting treatment. In general, antibiotics  
110 shorten the duration of symptoms by about 2 days (201). Efforts to reduce patient self-  
111 medication with antibiotics should be made as it is still very common in some settings (202).

112 Local patterns of antimicrobial resistance (mostly to *E. coli*) should be considered when available  
113 but interpreted with caution. In most cases, the summary prevalence of resistance reported by  
114 hospital microbiology laboratories will probably not be representative of first infections in the  
115 primary healthcare setting and may overestimate “true” prevalence of resistance for lower UTIs  
116 because of selection bias.

117 Most urine cultures are done on patients who have relapsed after their first empiric treatment  
118 and are being re-treated or have underlying reason for a higher risk of resistant infections. Most  
119 lower UTIs in patients who are not at risk of complications are still caused by pathogens that are  
120 susceptible to commonly used antibiotics. However, patterns of resistance based on good quality  
121 local data when available and on individual risk factors (e.g. previous urine culture results and  
122 recent antibiotic exposure) should be considered (203-205). In particular, *E. coli* may have varying  
123 levels of resistance to first-choice antibiotics (206) and resistance is associated with higher rates  
124 of clinical failure (9).

125 Nitrofurantoin for 5 days is the main antibiotic recommended for acute cystitis. However, the  
126 paediatric formulation (syrup) may not be widely available and is currently expensive, even in  
127 high-income settings. Nitrofurantoin still has activity against most isolates producing extended-  
128 spectrum beta-lactamases (ESBL) (207).

129 Different empiric antibiotic options for treating lower UTIs are indicated in Table 4;

130 Treatment duration is influenced by the antibiotic used, the age and sex of the patient, and for  
131 women by the presence of pregnancy.

132 *Table 4 Empiric antibiotic treatment for lower urinary tract infections*

Adults	Children	Total treatment duration <sup>d</sup>

<p><b>Nitrofurantoin</b> (oral):</p> <ul style="list-style-type: none"> <li>•100 mg given every 12 hours (modified-release formulation)</li> <li>•50 mg given every 6 hours (immediate-release formulation)</li> </ul>	<p><b>Nitrofurantoin</b> (oral) 2-4 mg/kg/dose given every 12 hours</p>	<p>5 days</p>
<p><b>Sulfamethoxazole+trimethoprim<sup>a</sup></b> (oral): 800 mg + 160 mg given every 12 hours</p>	<p><b>Sulfamethoxazole+trimethoprim<sup>a</sup></b>(oral) 4 mg/kg (of trimethoprim component), every 12 hours Oral weight bands: (mg of sulfamethoxazole/trimethoprim component) 3-&lt;6 kg: 100mg/20 mg given every 12 hours 6-&lt;10 kg: 200mg/40 mg given every 12 hours 10-&lt;15 kg: 400mg/80 mg given every 12 hours 15-&lt;20 kg: 400mg/80 mg given every 12 hours 20-&lt;30 kg: 400mg/80 mg given every 12 hours ≥ 30 kg: Use adult dose</p>	<p>3 days</p>
<p><b>Trimethoprim<sup>a</sup></b> (oral): 200 mg given every 12 hours</p>	<p><b>Trimethoprim<sup>a</sup></b> (oral) 4 mg/kg, every 12 hours  Oral weight bands: 3-&lt;6 kg: 20 mg given every 12 hours 6-&lt;10 kg: 40 mg given every 12 hours 10-&lt;15 kg: 80 mg given every 12 hours 15-&lt;20 kg: 80 mg given every 12 hours 20-&lt;30 kg: 80 mg given every 12 hours ≥ 30 kg: Use adult dose</p>	<p>3 days</p>
<p><b>Amoxicillin+clavulanic acid<sup>b</sup></b>(oral): 500 mg + 125 mg given every 8 hours</p>	<p><b>Amoxicillin+clavulanic acid<sup>b,c</sup></b>(oral) 40-50 mg/kg/dose of amoxicillin component, given every 12 hours OR 30 mg/kg/dose given every 8 hours  Oral weight bands: 3-&lt;6 kg: 250 mg of amoxicillin/dose given every 12 hours 6-&lt;10 kg: 375 mg of amoxicillin/dose given every 12 hours 10-&lt;15 kg: 500 mg of amoxicillin/dose given every 12 hours 15-&lt;20 kg: 750 mg of amoxicillin/dose given every 12 hours 20-&lt;30 kg: 1000 mg of amoxicillin/dose given every 12 hours ≥ 30 kg: Use adult dose</p>	<p>3–5 days</p>

133 Notes: All dosages are for normal renal and hepatic function.

134 <sup>a</sup>Resistance to sulfamethoxazole+trimethoprim is high in many settings (208, 209). It is ineffective against isolates  
135 producing extended-spectrum beta-lactamases (ESBL). Not recommended in the first trimester of pregnancy.

136 <sup>b</sup>Amoxicillin+clavulanic acid: *Escherichia coli* resistance rates to amoxicillin+clavulanic acid are lower than to  
137 amoxicillin alone. This combination still has activity against some ESBL-producing isolates and it can be considered  
138 an acceptable option, particularly in young children.

139 <sup>c</sup>Oral liquid must be refrigerated after reconstitution as clavulanic acid is rapidly metabolized in high ambient  
140 temperatures.

141 <sup>d</sup>In general shorter treatments are indicated for children or non-pregnant women (3-5 days depending on the  
 142 antibiotic) while longer treatments are indicated for pregnant women (usually 5 days) or men (usually 7 days).  
 143 **ACCESS** antibiotics are highlighted in green, **WATCH** antibiotics in yellow and **RESERVE** antibiotics in red.

## 144 “No antibiotic care”

145 Analgesic treatment should be complementary to antibiotic treatment to relieve pain associated  
 146 with lower UTIs (Table 5). In young women who are not pregnant, clinically well, with a mild  
 147 infection and who may wish to avoid or delay antibiotic treatment, symptomatic treatment alone  
 148 (with a back-up antibiotic prescription) could be considered.

149 *Table 5 Medicines to consider for pain control of lower UTIs*

Molecule	Formulation	Dose and frequency
Paracetamol (acetaminophen) <sup>a</sup>	Oral liquid: 120 mg/5 mL; 125 mg/5 mL Suppository: 100 mg Tablet: 100 mg to 500 mg	<b>Adults:</b> 500 mg–1 g every 4–6 hours (maximum dose of 4 g a day) <sup>b</sup> <b>Children:</b> <ul style="list-style-type: none"> <li>• Pain control/ Antipyretic treatment: 10–15 mg/kg every 6 hours</li> <li>6–&lt;10 kg: 100 mg given every 6 hours</li> <li>10–&lt;15 kg: 150 mg given every 6 hours</li> <li>15–&lt;20 kg: 200 mg given every 6 hours</li> <li>20–&lt;30 kg: 300 mg given every 6 hours</li> <li>≥30 kg: Use adult dose</li> </ul>
Ibuprofen <sup>c</sup>	Oral liquid: 200 mg/5 mL Tablet: 200 mg; 400 mg; 600 mg	<b>Adults:</b> 200–400 mg every 6–8 hours (maximum dose of 2.4 g a day) <b>Children:</b> <ul style="list-style-type: none"> <li>• Pain control (mild pain): 5–10 mg/kg every 6–8 hours</li> <li>• Antipyretic treatment 10 mg/kg every 6–8 hours</li> <li>6–&lt;10 kg: 50 mg given every 8 hours</li> <li>10–&lt;15 kg: 100 mg given every 8 hours</li> <li>15–&lt;20 kg: 150 mg given every 8 hours</li> <li>20–&lt;30 kg: 200 mg given every 8 hours</li> <li>≥30 kg: Use adult dose</li> </ul>

150 <sup>a</sup>Not recommended for use as an anti-inflammatory as it has not been proven to have such an effect.

151 <sup>b</sup>In patients with hepatic impairment or cirrhosis, maximum daily dose should be 2 g.

152 <sup>c</sup>Not for children < 3 months.

# HOSPITAL FACILITY

DRAFT

# 1 Sepsis in adults

## 2 (including septic shock)

### 3 Key messages

1. Sepsis is an acute life-threatening condition characterized by organ dysfunction due to a dysregulated host response to infection. Its most severe form – associated with high mortality – is septic shock
2. Usually signs and symptoms are nonspecific, the presence of any danger signs of severe illness should always be assessed to guide clinical management
3. Antibiotic treatment should be started as soon as possible when sepsis is suspected. However, not every patient with an infection has sepsis and the term “sepsis” should therefore be used carefully
4. Diagnostic tests and imaging should not delay treatment and should be guided by the suspected site of primary infection
5. Antibiotic treatment should be regularly re-evaluated including the possibility to simplify or stop antibiotics

### 4

#### *Box 1 Other relevant WHO documents (please check regularly for updates)*

- <https://www.who.int/news-room/fact-sheets/detail/sepsis>
- <https://www.who.int/news/item/08-09-2020-who-calls-for-global-action-on-sepsis---cause-of-1-in-5-deaths-worldwide>
- Global report on the epidemiology and burden of sepsis: current evidence, identifying gaps and future directions <https://apps.who.int/iris/handle/10665/334216>
- Resolution of the World health Assembly: Improving the prevention, diagnosis and clinical management of sepsis. Resolution WHA70.7. In: Seventieth World Health Assembly, Geneva, 22-31 May 2017 ([http://apps.who.int/gb/ebwha/pdf\\_files/WHA70/A70\\_R7-en.pdf](http://apps.who.int/gb/ebwha/pdf_files/WHA70/A70_R7-en.pdf))
- Pneumococcal conjugate vaccines in infants and children under 5 years of age: WHO position paper – February 2019. Weekly Epidemiological Record, 94 (08), 85 - 103. <https://apps.who.int/iris/handle/10665/310970>
- Typhoid vaccines: WHO position paper – March 2018 – Weekly Epidemiological Record , 93 (13), 153 - 172.; [153-72]. <https://apps.who.int/iris/handle/10665/272273>
- Meningococcal A conjugate vaccine: updated guidance, February 2015. Weekly Epidemiological Record, 90 (08), 57 - 62. <https://apps.who.int/iris/handle/10665/242320>

## 5 Definition

6 In some patients with infection, a dysregulated host immune response to the infection  
 7 contributes to the severity of the disease and organ dysfunction. These patients are at increased  
 8 risk of death and severe sequelae and should be identified and treated rapidly. The definition of  
 9 sepsis has remained a challenge because sepsis is not a single entity (the pathogens and primary  
 10 sites of infection causing sepsis, for example, vary widely) but a continuum of many different  
 11 clinical presentations.

12 Because of the serious clinical consequences of sepsis (see section on epidemiology), many  
 13 attempts have been made to provide clinicians with simple and easy-to-use criteria for identifying  
 14 patients with sepsis.

Sepsis in adults was last defined in 2016 by the Third International Consensus Definitions for Sepsis and Septic Shock (known as SEPSIS-3)(210). According to this definition, sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection.

15 Compared with previous definitions (SEPSIS-1 in 1991 and SEPSIS 2 in 2001), SEPSIS-3 removed  
 16 the criteria for “systemic inflammatory response syndrome (SIRS)” from the definition because  
 17 the criteria lacked specificity (SIRS referred to an exaggerated inflammatory response of the body  
 18 to a noxious cause characterized by a combination of symptoms such as fever or hypothermia,  
 19 increased heart and / or respiratory rate and increased white blood cell count). SEPSIS-3 also  
 20 dropped the term severe sepsis because the concept of non-severe sepsis was not helpful (all  
 21 sepsis being a severe disease) and could be misleading reducing the attention in providing rapid  
 22 and effective treatment. Instead, SEPSIS-3 differentiates only between sepsis and septic shock.  
 23 Septic shock is defined as a type of sepsis in which underlying circulatory and cellular and/or  
 24 metabolic abnormalities are severe enough to substantially increase mortality(211). Patients  
 25 with septic shock have persistent hypotension that requires vasopressor medication to maintain  
 26 a mean arterial pressure of 65 mmHg or more and a level of serum lactate more than 2 mmol/L  
 27 (> 18 mg/dL) in the absence of hypovolaemia(211).

### Box 2 Bacteraemia

It should be noted that the detection of bacteria in blood cultures (i.e. bacteraemia) is not part of the definition of sepsis. While many patients with sepsis have bacteraemia, this is not a universal finding and most patients with bacteraemia do not meet sepsis criteria. The term septicaemia should be avoided. The terms bacteraemia and bloodstream infection (which can also be caused by other pathogens such as *Candida* spp.) are often used interchangeably.

The Global Antimicrobial Resistance Surveillance System (GLASS) uses the following definition of suspected bloodstream infection (212):

Presence of two or more of the following clinical signs in an adult patient:

- Hyperthermia (> 38.0 °C) or hypothermia (< 36.0 °C)
- Respiratory rate ≥ 20 breaths/minute
- Heart rate > 90 beats/minute.

A confirmed bloodstream infection requires the isolation of a clinically relevant pathogen from a blood sample of a patient (all ages) seeking health care at a health care facility.

28 The criteria to identify sepsis according to SEPSIS-3 are difficult to apply in LMIC because severity  
 29 is based on criteria and tests that may not be routinely available in these settings; for example,  
 30 the use of inotropes, and determination of arterial oxygen partial pressure, bilirubin levels,  
 31 creatinine concentrations and platelet counts. Furthermore, the SOFA score (see definition  
 32 below) has been validated mostly in high-income settings and its performance in LMIC, where  
 33 causes of sepsis rarely encountered in most high-income settings (e.g. dengue and malaria) are  
 34 frequent and HIV infection is more prevalent, is unclear.

35 To implement the SEPSIS-3 definition, clinical and laboratory signs are graded to give an overall  
 36 score (called the Sequential Organ Failure Assessment (SOFA) score), and an acute change of two  
 37 or more points in the baseline score is proposed to identify organ dysfunction due to infection  
 38 and predict the short-term mortality risk (210).

39 The SOFA score (range 0–24) includes six parameters – two clinical and four laboratory ones.  
 40 Each parameter can have a value from 0 to 4 (Table 1). The baseline SOFA score can be assumed  
 41 to be zero in patients with no known pre-existing organ dysfunction.

42 *Table 1 Sequential Organ Failure Assessment (SOFA) score*

Parameter	Score				
	0	1	2	3	4
PaO <sub>2</sub> mmHg (kPa)/FiO <sub>2</sub> (%)	≥ 400 (53.3)	< 400 (53.3)	< 300 (40)	< 200 (26.7)	< 100 (13.3)
MAP mmHg (kPa) and catecholamine doses needed (µg/kg/min for ≥ 1 h)	MAP ≥ 70 (9.3)	MAP < 70 (9.3)	Dopamine < 5 Or dobutamine any dose	Dopamine 5–15 Or epinephrine (adrenaline)/ norepinephrine ≤ 0.1	Dopamine > 15 Or epinephrine/ norepinephrine > 0.1
Platelets (x 10 <sup>3</sup> /µL, x 10 <sup>9</sup> /L)	≥ 150	< 150	< 100	< 50	< 20
Bilirubin mg/dL (mmol/L)	< 1.2 (20)	1.2–1.9 (20–32)	2–5.9 (33–101)	6.0–11.9 (102–204)	> 12.0 (204)
Glasgow coma scale <sup>a</sup>	15	13–14	10–12	6–9	< 6
Creatinine mg/dL (µmol/L)	< 1.2 (110)	1.2–1.9 (110–170)	2.0–3.4 (171–299)	3.5–4.9 (300–440)	> 5.0 (440)
Urine output (mL/day)				< 500	< 200

43 FiO<sub>2</sub>: fractional inspired oxygen; PaO<sub>2</sub>: arterial oxygen partial pressure; MAP: mean arterial pressure.

44 <sup>a</sup>The Glasgow coma scale is a clinical scale used to measure a person's level of consciousness based on the  
 45 assessment of three parameters: eye opening response (max 4 points assigned), best verbal response (max 5 points  
 46 assigned) and best motor response (max 6 points assigned). The total score can range from 3 (completely  
 47 unresponsive) to 15 (responsive). Scores below 8 usually indicate a comatose state. To calculate the Glasgow coma  
 48 scale, several online calculators exist.

49 A simplified quick version of the SOFA score called qSOFA (Table 2) exists that only includes three  
 50 clinical criteria (mental status, blood pressure and respiratory rate) and an increase by two points  
 51 can be used at the bedside for early identification of sepsis even in low-resource settings (213).  
 52 A retrospective analysis of cohort studies conducted in 17 hospitals in 10 LMIC in sub-Saharan  
 53 Africa, Asia and the Americas found that a high qSOFA score identified patients with infections

54 who were at an increased risk of death (beyond the risk they had based on their baseline risk  
55 factors), with some variability among cohorts (214).

56 *Table 2 qSOFA (quick Sequential Organ Failure Assessment) scoring*

Parameter	Value
Respiratory rate	≥ 22 breaths/min
Altered mental status	Glasgow coma scale < 15 <sup>a</sup>
Systolic blood pressure	≤ 100 mmHg (≤ 13.3 kPa)

57 <sup>a</sup>The Glasgow come scale is a clinical scale used to measure a person's level of consciousness based on the  
58 assessment of three parameters: eye opening response (max 4 points assigned), best verbal response (max 5 points  
59 assigned) and best motor response (max 6 points assigned). The total score can range from 3 (completely  
60 unresponsive) to 15 (responsive). Scores below 8 usually indicate a comatose state. To calculate the Glasgow coma  
61 scale, several online calculators exist.

## 62 Pathophysiology

63 Sepsis is a serious and complex clinical condition caused by the complicated interplay between  
64 an infectious agent and a dysregulated systemic immunological response by the patient,  
65 potentially resulting in multiple organ dysfunction and possibly death. Risk factors for sepsis  
66 mostly overlap with those that predispose patients to infection (e.g. very old and very young,  
67 immunosuppression due to HIV, cancer or medications, cirrhosis, alcohol abuse, poorly  
68 controlled diabetes, indwelling catheters and malnutrition). Genetic factors are also implicated  
69 in the likelihood of developing sepsis in patients with an infection(215).

## 70 Epidemiology

71 Sepsis is an important global health problem that can be difficult to diagnose and manage,  
72 especially in low-income settings(216, 217). According to the Global Burden of Disease study,  
73 about 49 million new cases of sepsis occurred worldwide in 2017, a decrease of almost 19%  
74 compared with 1990(218). The most common underlying cause of sepsis is still diarrhoeal disease  
75 (9 million attributable cases in 2017). The number of sepsis-related deaths decreased worldwide  
76 (a 29% decrease compared with 1990) but deaths were still high (11 million in 2017) with the  
77 highest burden in sub-Saharan Africa. The most common underlying cause of sepsis-related  
78 death was lower respiratory tract infections (1.8 million attributable deaths in 2017). Children  
79 were more affected by sepsis than adults; in 2017, 20 million new cases of sepsis were in children  
80 < 5 years of age (see the chapter on sepsis in children and neonates). However, a second peak in  
81 incidence in older adults was reported. About one in four cases of sepsis is estimated to be  
82 hospital-acquired with high mortality rates(219).

83 Sepsis can also develop during pregnancy or in the first weeks after delivery. This form of sepsis  
84 is called maternal sepsis. In 2017, about 12 million new cases of maternal sepsis were  
85 reported(218). In the period 2003–2009, sepsis was the third leading cause of maternal death  
86 worldwide (10.7% of all maternal deaths or about 260 000 deaths) after haemorrhage and

87 hypertensive disorders(220). Based on results of the global maternal sepsis study from more than  
 88 700 facilities in 52 countries, 70 pregnant women per 1000 live births in the study cohort were  
 89 hospitalized with an infection, mostly of bacterial origin (77% of those where a pathogen was  
 90 identified)(221). Infections with severe maternal outcomes (e.g. death) were frequent, 11 per  
 91 1000 live births; however, large variations existed across countries – 15 per 1000 live births in  
 92 low- and middle-income countries and 0.6 per 1000 in high-income countries(221). Infections  
 93 originated most often from the genital (endometritis and chorioamnionitis) or urinary tract  
 94 followed by skin, respiratory and abortion-related infections(221).

95 Infections with antibiotic-resistant bacteria are an increasingly important cause of sepsis  
 96 worldwide with important implications for the management, especially in settings with limited  
 97 resources. Antibiotic resistance can affect patient outcomes, increasing short-term mortality,  
 98 mostly because in these cases effective antibiotic treatment active against the resistant pathogen  
 99 may not be available or given late. In a 2015 European study, 170 disability-adjusted life years  
 100 (DALYs, a proxy for morbidity and mortality) per 100 000 population were due to infections  
 101 caused by antibiotic-resistant bacteria, of which about 70% were caused by bloodstream  
 102 infections(222).

103 In 2017, the World Health Assembly adopted a resolution on sepsis to urge WHO Member States  
 104 to implement measures to reduce the burden of sepsis by increasing efforts to improve sepsis  
 105 prevention, diagnosis and treatment, including through increased research, training of health  
 106 care professionals and public awareness campaigns(223).

## 107 Microbiology epidemiology

108 Sepsis can originate from any type of infection (bacterial, viral, fungal and protozoal) in any organ  
 109 system. Infections can be community-acquired (CAI) or hospital acquired (HAI) (or health care-  
 110 associated). The bacterial pathogens associated with sepsis will vary widely depending on the  
 111 primary site of infection, geography and place of acquisition (community/hospital see table 3).

112 The mortality from sepsis is higher with infections caused by multi-drug resistant bacteria, which  
 113 are commonly identified in HAIs.

114 *Table 3 Pathogens most frequently identified in blood cultures in patients with sepsis (also refer*  
 115 *to Box 2 about bacteremia)*

	<b>Bacteria</b>	<b>Viruses</b>	<b>Parasites</b>
<b>Community setting</b>	<i>Escherichia coli</i> , <i>Klebsiella pneumoniae</i> and other Enterobacterales (including multidrug-resistant strains such as those producing ESBL and carbapenemases)  <i>Staphylococcus aureus</i> (including MRSA)	Respiratory viruses such as Influenza virus and SARS-coV-2  <b>In endemic settings or after travel to endemic settings:</b> Viruses causing viral haemorrhagic fevers (e.g. dengue, yellow fever, Ebola virus disease, Lassa fever, Marburg virus disease)	<b>In endemic settings or after travel to endemic settings:</b> <i>Plasmodium</i> spp. (pathogen causing malaria)

	<p><i>Streptococcus pneumoniae</i> (including penicillin non-susceptible strains) <i>Salmonella</i> spp. (including <i>Salmonella</i> Typhi and Paratyphi) <i>Streptococcus pyogenes</i> (group A <i>Streptococcus</i>)</p> <p><i>Neisseria meningitidis</i> (including strains resistant to third-generation cephalosporins)</p> <p><i>Burkholderia pseudomallei</i> (pathogen causing melioidosis)</p>		
<b>Hospital setting</b>	<p><i>Acinetobacter baumannii</i> and <i>Pseudomonas aeruginosa</i> (including multidrug-resistant strains such as those producing ESBL and carbapenemases)</p> <p><i>Escherichia coli</i>, <i>Klebsiella pneumoniae</i> and other Enterobacterales (including multidrug-resistant strains such as those producing ESBL and carbapenemases)</p> <p><i>Staphylococcus aureus</i> (including MRSA)</p>		
<b>Maternal sepsis</b> <b>(additional pathogens to consider)<sup>a</sup></b>	<p><i>Listeria monocytogenes</i></p> <p><i>Streptococcus agalactiae</i> (group B <i>Streptococcus</i>)</p>		

116 ESBL: extended-spectrum beta-lactamases; MRSA: methicillin-resistant *Staphylococcus aureus*.

117 <sup>a</sup>In cases of maternal sepsis, however, urinary tract infections are the main source of infection (see epidemiology section).

119 Note: Most data on the pathogens associated with sepsis come from high-income settings.

## 120 Clinical presentation

Presenting symptoms and signs and the clinical course of sepsis are highly variable and depend on the underlying pathogen, the main organ affected and the host response. Early recognition and treatment of sepsis is essential and can affect mortality. Therefore, signs of severe infection and organ dysfunction should be identified promptly.

121 Patients with sepsis usually present with non-specific signs and symptoms. The most frequent  
 122 symptoms include fever (> 38.0 °C) or hypothermia (< 36.0 °C), some degree of respiratory  
 123 distress (e.g. increased respiratory rate), tachycardia, acute altered mental status (e.g.  
 124 disorientation and agitation) and hypotension. Oliguria (i.e. reduced urine output) may also be  
 125 present.

126 Sepsis may be more difficult to diagnose in countries where vector-transmitted diseases (e.g.  
 127 malaria and dengue) are endemic; therefore, sepsis should always be considered if there are any  
 128 signs and symptoms of sepsis in these settings.

129 As outlined above, bacteraemia (i.e. the detection of bacteria in blood cultures) may be present  
 130 depending on the type of pathogen, the primary site of infection and whether antibiotic  
 131 treatment was administered before obtaining blood cultures. However, bacteraemia is not  
 132 always found in patients with sepsis and on the other hand most patients with bacteraemia do  
 133 not have sepsis.

Accurate identification of patients with sepsis is difficult and no single gold standard test exists. Therefore, adoption and use of internationally accepted case definitions (e.g. the SEPSIS-3 definition) is critical to avoid overdiagnosis and overtreatment; not every patient with an infection has sepsis, in fact, only a very small proportion of patients with infection have sepsis. The term “sepsis” should therefore be used carefully.

134 **Sepsis of unknown origin:** treatment is based on the most probable clinical situation. Patients  
 135 should be carefully examined to localize a source of infection, including pressure ulcers, deep-  
 136 seated abscesses and indwelling vascular and urinary catheters. In n patients with central lines,  
 137 the possibility of a central line-associated bloodstream infection should be considered with a  
 138 positive blood culture and no other apparent source of infection. Bloodstream infections can also  
 139 be associated with peripheral vascular lines.

## 140 Laboratory tests

### 141 I. Patient microbiology tests

Diagnostic tests should be guided by the suspected primary site of infection. Tests (and management, see below) will be different for suspected pneumonia, intra-abdominal infection, urinary tract infection, meningitis or sepsis of unknown origin. Please also refer to specific chapters of the Handbook based on the suspected underlying infection.

142 Microbiology tests help establish a definitive diagnosis of sepsis and identify the causative  
 143 pathogen and underlying infection. Isolating a pathogen from a normally sterile body site (e.g.  
 144 blood, cerebrospinal fluid) that is compatible with the clinical signs and symptoms usually  
 145 confirms diagnosis. However, the causative pathogen is not identified in a substantial proportion  
 146 of cases especially in patients pre-treated with antibiotics.

147 Tests to consider when sepsis of bacterial origin is suspected include those listed in Table 4.  
 148 Ideally, these tests should be done before starting antibiotic treatment.

149 *Table 4 Microbiology tests to consider when sepsis of bacterial origin is suspected depending on*  
 150 *the most likely source of infection as indicated in the WHO EDL (54)*

<b>Suspected underlying infection</b>	<b>Diagnostic test</b>	<b>Purpose of the test</b>	<b>Settings where the test should be available</b>
All cases where sepsis is suspected	Blood cultures	To detect bacterial bloodstream infections (sepsis)	Health care facilities with clinical laboratories
Lower respiratory tract infection	Sputum microscopy (Gram stain)	To assess microbial morphology and adequacy of the specimen for culture by identifying white blood cells and squamous epithelial cells	Health care facilities with clinical laboratories
Lower respiratory tract infection	Sputum culture	Initial step to detect and identify bacterial and fungal species for selection of appropriate antibiotic regimens	Health care facilities with clinical laboratories
Meningitis	Cerebrospinal fluid Gram stain and bacterial culture	Initial step to detect and identify bacterial and fungal species for selection of appropriate antibiotic regimens	Health care facilities with clinical laboratories
Meningitis	Cerebrospinal fluid microscopy	To assess microbial morphology, number of white blood cells and red blood cells	Health care facilities with clinical laboratories
Diarrhoeal disease, enteric fever <sup>a</sup>	Stool culture	Initial step to detect and identify bacterial species for selection of appropriate antibiotic regimens	Health care facilities with clinical laboratories
Abscess (e.g. in the context of intra-abdominal infections, skin and soft-tissue infections, dental infections)	Culture of abscess and/or fluid collections that can be drained	Initial step to detect and identify bacterial and fungal species for selection of appropriate antibiotic regimens	Health care facilities with clinical laboratories
Urinary tract infection	Urine culture	Initial step to detect and identify bacterial and fungal species for selection of appropriate antibiotic regimens	Health care facilities with clinical laboratories

151 <sup>a</sup>If enteric fever is suspected, note that stool cultures have a low sensitivity and are not useful in the early phase  
 152 (first week) of the disease when the test is often negative.

## 153 II. Other tests

154 Laboratory tests can be used to complement the clinical examination and history. Tables 5 and  
 155 6 indicate the tests that could be considered to make an initial assessment of the patient and to  
 156 help guide the duration of antibiotic treatment. Additional laboratory tests may be considered  
 157 based on local availability.

158 *Table 5 Laboratory tests (other than microbiology) to consider when sepsis is suspected to identify*  
 159 *a bacterial infection as indicated in the WHO EDL (54)*

Diagnostic test	Purpose of the test	Settings where the test should be available
White blood count	To help in the diagnosis of infections	Health care facilities with clinical laboratories but also in primary care settings
C-reactive protein <sup>a</sup>	To detect inflammation as an indicator of various conditions (e.g. sepsis)	Health care facilities with clinical laboratories
Procalcitonin <sup>a</sup>	To guide antibiotic therapy or discontinuation in sepsis	Only in tertiary health care facilities

160 <sup>a</sup>Biomarkers (C-reactive protein and procalcitonin) may help determine whether an infection is caused by bacteria  
 161 and regular serial measurement of these biomarkers can also help decide when antibiotic therapy can be  
 162 stopped(224) (225, 226). It is important to note that the probability of sepsis based on the patient's initial clinical  
 163 assessment before testing (pre-test probability) needs to be considered. If the pre-test probability is high,  
 164 inflammatory markers in the normal range do not rule out sepsis.

165 *Table 6 Laboratory tests (other than microbiology) to consider when sepsis is suspected to identify*  
 166 *organ dysfunction as indicated in the WHO EDL (54)*

Diagnostic test	Purpose of the test	Settings where the test should be available
Bilirubin	To detect or monitor liver disease, bile duct disorders and red cell destruction <b>Required for SOFA score calculation</b>	Community settings and health facilities without laboratories <sup>b</sup>
Blood pH and gases	To assess lung function and metabolic or kidney disorders, and monitor oxygen therapy <b>Required for SOFA score calculation (for PaO<sub>2</sub>/FIO<sub>2</sub>)</b>	Health care facilities with clinical laboratories
Blood urea nitrogen	To assess kidney function <b>Required for CURB-65 score calculation (if pneumonia is suspected<sup>a</sup>)</b>	Health care facilities with clinical laboratories
Complete blood count	To detect a wide range of disorders, including infections	Health care facilities with clinical laboratories
Creatinine	To monitor kidney function for management of severe infections (i.e. sepsis) and to adjust antimicrobial regimen <b>Required for SOFA score calculation</b>	Health care facilities with clinical laboratories
Electrolytes	To monitor fluid, electrolyte and acid–base balance	Health care facilities with clinical laboratories
Glucose	To diagnose intermediate hyperglycaemia and hypoglycaemia	Community settings and health facilities without laboratories <sup>b</sup>
Haemoglobin	To diagnose and monitor anaemia Clinical marker for some severe infections (e.g. malaria and viral haemorrhagic fevers)	Community settings and health facilities without laboratories <sup>b</sup>

Platelet count	To diagnose thrombocytopenia or thrombocytosis Marker to manage severe infections associated with sepsis (e.g. viral haemorrhagic fever and meningococcaemia) <b>Required for SOFA score calculation</b>	Health care facilities with clinical laboratories
White blood cell count	To aid in the diagnosis of infections	Health care facilities with clinical laboratories
Whole blood lactate	To assess metabolic acidosis, sepsis and dehydration	Community settings and health facilities without laboratories <sup>b</sup>

167 SOFA: sequential organ failure assessment; PaO<sub>2</sub> = arterial oxygen partial pressure; FIO<sub>2</sub> = fractional inspired  
168 oxygen.

169 <sup>a</sup>See the chapter on community-acquired pneumonia for more information.

170 <sup>b</sup>Community and health settings without laboratories are facilities such as health posts and centres, doctors'  
171 offices, outreach clinics, ambulatory care and home-based and self-testing. These tests are assumed to be available  
172 at health care facilities with laboratories.

173 Note: The tests are listed in alphabetical order.

### 174 III. Using microbiology surveillance data

175 Empiric guidance given by the Handbook could be reviewed and adapted based on local clinically  
176 relevant microbiology surveillance data. For example, clinically relevant isolates for this infection  
177 would be blood culture data of significant isolates from patients with confirmed sepsis.

## 178 Imaging

Imaging studies should be guided by the suspected primary site of infection. Please also refer to specific chapters of the Handbook based on the suspected underlying infection.

179 When sepsis is suspected and respiratory distress is present, a chest X-ray (or lung ultrasound) is  
180 indicated to confirm a lower respiratory tract infection. If an abdominal source of infection is  
181 suspected, in settings where it is available, a computed tomography scan of the abdomen could  
182 be considered (e.g. to confirm an intra-abdominal infection). A low-dose computed tomography  
183 scan is an acceptable option, including in pregnant women(227). However, because abdominal  
184 ultrasound is more widely available, it can be a very helpful alternative depending on the exact  
185 site of infection. If sepsis caused by an infection of the urinary tract is suspected, initial imaging  
186 (e.g. ultrasound) of the urinary tract or during follow-up could be considered if an outflow  
187 obstruction (e.g. because of urolithiasis) or an abscess are suspected.  
188

## 189 Treatment

190 Treatment of sepsis includes treatment of the underlying infection and life-saving interventions  
191 such as fluid resuscitation and vital organ support which are beyond the scope of this  
192 Handbook. For more specific guidance on treating sepsis, please refer to the 2016 international  
193 guidelines for management of sepsis and septic shock(228). Please also consult a 2016 review  
194 on the pathophysiology and clinical management of sepsis(229).

195 **Antibiotic treatment**  
 196 **(if bacterial sepsis is suspected)**

Intravenous (IV) antibiotic treatment should be started as soon as possible when sepsis of bacterial origin is suspected. Taking laboratory and microbiology tests or waiting for the results should not delay administration of the first dose of antibiotic treatment.

197 When selecting empiric antibiotic treatment, several factors should be considered, such as the  
 198 most likely site of primary infection, the infecting pathogens, and the local pattern of  
 199 antimicrobial resistance. Comorbidities of the patient including malnutrition and  
 200 immunosuppression (e.g. due to HIV or neutropenia) and other factors, such as known  
 201 colonization and/or previous infection with multidrug-resistant organisms, are also important  
 202 factors to consider. Many variables must be considered to provide the best treatment to patients  
 203 with sepsis.

204 Table 7 outlines suggested empiric treatment regimens for common primary sites of infection. In  
 205 many infections (e.g. necrotizing fasciitis and intra-abdominal infections), source control (e.g.  
 206 drainage of an abscess, surgical debridement) is essential.

207 If the pathogen causing the infection is identified and once its antibiotic susceptibilities are  
 208 known, antibiotics should be reviewed and modified accordingly. However, even if enough  
 209 suitable samples have been obtained and tested, a pathogen is identified only in a minority of  
 210 patients with sepsis(230). When no pathogen is identified, antibiotic treatment should be guided  
 211 by available laboratory results and clinical response. If an alternative cause of a non-bacterial  
 212 cause of sepsis has been identified, the possibility to stop treatment should be evaluated.

213 Treatment duration is often decided on an individual basis according to clinical response and (if  
 214 available) changes in laboratory markers of infection.

215 **Simplify** empiric treatment to a more narrow-spectrum antibiotic based on culture results or  
 216 based on rapid clinical improvement when no microbiology test results are available. In general,  
 217 the intravenous (IV) route is preferred, for the initial phase of treatment.

218 **Step-down** to oral treatment is based on improvement of symptoms and signs of infection and  
 219 the ability to take oral antibiotics allowing discharge of the patient home when clinically  
 220 appropriate.

221 In patients with suspected sepsis of bacterial origin, a risk assessment based on clinical factors  
 222 needs to be done followed by appropriate tests and investigations to choose the best empiric  
 223 antibiotic treatment. Patient-level and setting-level risk factors for infections caused by resistant  
 224 bacteria need to be carefully considered.

- 225 • **Low-risk patients:** patients with no clinical risk factors for adverse outcomes. These  
 226 patients have a low risk of infections caused by multidrug-resistant bacteria.

- 227 • **High-risk patients:** patients with major pre-existing comorbidities or immunosuppressed  
228 and/or previous colonization or infection with a resistant pathogen. These patients have  
229 a higher risk of infections caused by multidrug-resistant bacteria.

230 *Table 7 Empiric antibiotic treatment for community-acquired sepsis of bacterial origin in adults*

Most probable source of infection	Empiric antibiotic treatment	Total treatment duration
Clinical sepsis of unknown origin <sup>a</sup>	<p>Ceftriaxone<sup>b</sup> (IV): 2 g given once a day OR Cefotaxime<sup>b</sup> (IV): 2 g given every 8 hours</p> <p>AND</p> <p>Gentamicin<sup>c</sup> (IV): 5 mg/kg given once a day OR Amikacin<sup>c</sup>: 15 mg/kg given once a day</p>	7 days (but duration depends on the patient's underlying disease, the causative pathogen (if any identified later on) and clinical progression)
Enteric fever	Ceftriaxone <sup>d</sup> (IV): 2 g given once a day	10 days
Intra-abdominal infection	<p><b>First choice</b> Ceftriaxone (IV): 2 g given once a day AND Metronidazole (IV): 500 mg given every 8 hours</p> <p>OR Cefotaxime (IV): 2 g given every 8 hours AND Metronidazole (IV): 500 mg given every 8 hours</p> <p>OR Piperacillin+tazobactam<sup>e</sup> (IV): 4 g + 500 mg given every 6 hours</p> <p><b>Second choice</b> Meropenem<sup>f</sup> (IV): 2 g given every 8 hours</p>	<p>Generally 7 days. Duration depends on type of infection, whether adequate surgical source control was achieved and on clinical recovery.</p> <p>Please refer to specific chapters of the Handbook based on the suspected underlying infection</p>
Meningitis	<p><b>First choice</b> Ceftriaxone (IV): 2 g given every 12 hours OR Cefotaxime (IV): 2 g given every 6 hours</p> <p><b>Second choice</b> Ampicillin (IV): 2 g given every 4 hours OR Amoxicillin (IV): 2 g given every 4 hours OR Chloramphenicol<sup>h</sup> (IV): 1 g given every 6 hours OR Benzylpenicillin (IV): 4 million international units (2.4 g) given every 4 hours</p>	10 days <sup>g</sup>
Lower respiratory tract infection	<p>Ceftriaxone (IV): 2 g given once a day OR Cefotaxime (IV): 2 g given every 8 hours</p> <p>AND Clarithromycin (IV): 500 mg given every 12 hours</p>	5 days

Skin and soft tissues infection	Ceftriaxone <sup>i</sup> (IV): 2 g given once a day AND Metronidazole <sup>j</sup> (IV): 500 mg given every 8 hours (In case of necrotizing fasciitis, use this treatment option only if <i>Streptococcus pyogenes</i> infection has been excluded first)  OR  Piperacillin+tazobactam <sup>k</sup> (IV): 4 g + 500 mg given every 6 hours AND Clindamycin <sup>l</sup> (IV): 900 mg given every 8 hours  <b>If MRSA is suspected, ADD</b> Vancomycin <sup>m</sup> (IV): 15–20 mg/kg given every 12 hours	Generally 7 days. Duration depends on type of infection, whether adequate surgical source control was achieved and clinical recovery.  Please refer to specific chapters of the Handbook based on the suspected underlying infection
Urinary tract infection	Ceftriaxone <sup>n</sup> (IV): 1 g given once a day OR Cefotaxime (IV): 1 g given every 8 hours AND Amikacin <sup>o</sup> (IV): 15 mg/kg given once a day	7 days

231 Notes: All dosages are for normal renal and hepatic function. Dose adjustments may be required in patients with  
 232 septic shock.

233 IV: intravenous.

234 <sup>a</sup>If the source of the infection is determined please follow infection-specific guidance.

235 <sup>b</sup>Ceftriaxone or cefotaxime are alternative options. The choice can be made based on local availabilities.

236 <sup>c</sup>Gentamicin and amikacin are alternative options. The choice can be made based on local availabilities. In addition,  
 237 amikacin is still effective against isolates producing extended-spectrum beta-lactamases (ESBL) and is considered an  
 238 appropriate carbapenem-sparing option in settings where ESBL-producing isolates are very prevalent.

239 <sup>d</sup>Some countries may have problems of increasing ceftriaxone resistance.

240 <sup>e</sup>In patients considered at risk of infections with ESBL-producing Enterobacterales, piperacillin+tazobactam does not  
 241 provide adequate activity against many ESBL-producing isolates. In these cases, meropenem can be considered.

242 <sup>f</sup>Meropenem should be considered only in settings with a high prevalence of ESBL-producing Enterobacterales.

243 <sup>g</sup>Duration differs in the context of epidemics as indicated by WHO(231) and also depending on the pathogen  
 244 identified.

245 <sup>h</sup>Use chloramphenicol only when no other choice is available.

246 <sup>i</sup>Ceftriaxone and metronidazole is the preferred option if the suspected source of infection is polymicrobial (type 1)  
 247 necrotizing fasciitis but it is also an adequate option in case of severe cellulitis.

248 <sup>j</sup>Piperacillin+tazobactam (or penicillin) and clindamycin is the preferred option if the suspected source of infection is  
 249 necrotizing fasciitis caused by *Streptococcus pyogenes* but it is also an adequate option in case of severe cellulitis.

250 <sup>m</sup>Alternative antibiotics to consider based on local resistance data are piperacillin+tazobactam and carbapenems.

251 <sup>n</sup>Amikacin is still effective against ESBL-producing isolates and is considered an appropriate carbapenem-sparing  
 252 option in settings where ESBL-producing isolates are prevalent.

253 ACCESS antibiotics are indicated in green, WATCH antibiotics in yellow and RESERVE antibiotics in red.

## 254 Prevention

255 Any infection can progress to sepsis; therefore, preventing sepsis requires either preventing the  
 256 infection or preventing the progression of the infection to sepsis.

257 Factors that contribute to preventing infections in the community include: vaccinations (Table 8),  
 258 adequate nutrition and healthy living environments (including access to safe water and  
 259 sanitation). It is beyond the scope of this chapter to address in detail these topics.

260 *Table 8 Vaccinations to consider for prevention of certain infections*

Vaccination <sup>a</sup>	Population where the vaccine should be considered
Meningococcal vaccination(232)	<p>Countries with high (&gt; 10 cases per 100 000 population/year) or intermediate (2–10 cases per 100 000 population/year) incidence of meningococcal disease or with frequent epidemics: all individuals aged 1–29 years (including pregnant women) should be vaccinated with the meningococcal A conjugate vaccine.</p> <p>Countries with low incidence of meningococcal disease (&lt; 2 cases per 100 000 population/year): vaccination only for defined high-risk groups such as children and young adults or individuals with immunodeficiency. The choice of the recommended vaccine depends on the local prevalence of the meningococcal serogroups.</p>
Pneumococcal vaccination(39)	<p>All children should be vaccinated with pneumococcal conjugate vaccines. In adults, the vaccine is recommended in many countries for elderly people (&gt; 65 years) and for high-risk groups (e.g. patients with chronic pulmonary disease, splenectomised).</p>
<i>Salmonella</i> Typhi vaccination(144)	<p>Individuals living in countries with a high burden of enteric fever or antimicrobial-resistant <i>Salmonella</i> Typhi should be vaccinated with typhoid conjugate vaccines. Vaccination should also be offered during outbreaks.</p>

261 <sup>a</sup> References are to WHO position papers that support the evidence for vaccination.

# 1 Sepsis in neonates (< 28 days) 2 and children (28 days–12 years)

## 3 Key messages

### **Both neonates and older children:**

1. Sepsis is an acute life-threatening condition characterized by organ dysfunction due to a dysregulated host response to infection
2. Antibiotic treatment should be started as soon as possible when sepsis is suspected
3. Diagnostic tests and imaging should not delay treatment which should be guided by the suspected site of primary infection

### **Neonates (<28 days):**

1. Sepsis in neonates can be classified based on setting of acquisition of the infection (community/hospital) or time of onset after birth (early/late), which are used to try and predict the most likely causative pathogens and guide empiric antibiotic treatment
2. Multiple clinical signs and symptoms are used to determine whether an infant has neonatal sepsis, as well as perinatal risk factors (e.g. prematurity/gestational age)
3. Neonates are much more likely to have a primary bloodstream infection with no underlying source of infection identified

### **Older children:**

1. Common causative pathogens vary globally and combined with the setting of acquisition of the infection, this can be used to predict the most likely causative pathogens and choose empiric antibiotic treatment
2. Usually signs and symptoms are nonspecific, the presence of danger signs of illness should always be assessed to guide clinical management

4

### *Box 1 Other relevant WHO documents (please check regularly for updates)*

- <https://www.who.int/news-room/fact-sheets/detail/sepsis>
- Global report on the epidemiology and burden of sepsis: current evidence, identifying gaps and future directions <https://apps.who.int/iris/handle/10665/334216>
- Haemophilus influenzae type b (Hib) Vaccination Position Paper — July 2013: Introduction. Weekly Epidemiological Record, 88 (39), 413 - 426. Geneva: World Health Organization; <https://apps.who.int/iris/handle/10665/242126>
- Meningococcal A conjugate vaccine: updated guidance, February 2015. Weekly Epidemiological Record, 90 (08), 57 - 62. <https://apps.who.int/iris/handle/10665/242320>

- Pneumococcal conjugate vaccines in infants and children under 5 years of age: WHO position paper – February 2019. Weekly Epidemiological Record, 94 (08), 85 - 103.  
<https://apps.who.int/iris/handle/10665/310970>
- Typhoid vaccines: WHO position paper – March 2018 – Weekly Epidemiological Record, 93 (13), 153 - 172.; [153-72].<https://apps.who.int/iris/handle/10665/272273>

## 5 Definition

6 Because of differences in the microbiology, sepsis in children is often classified into neonatal  
7 sepsis (newborns < 28 days) and pediatric sepsis (28 days–12 years).

## 8 Neonatal sepsis

9 There is no universally accepted definition of neonatal sepsis and definitions vary among  
10 studies(233). However, the term is used to describe a serious systemic condition of infectious  
11 origin (most commonly bacterial) associated with a combination of clinical and laboratory signs  
12 that occurs in the first month of life.

13 Neonates are much more likely to have a primary bloodstream infection with no underlying  
14 source of infection identified. Furthermore, because of differences in the host (neonates have  
15 reduced immune responses) and the way the pathogen can be acquired (e.g. exposure to  
16 maternal pathogens at birth or in utero), the sepsis definitions currently used for adults and older  
17 children are not specifically designed for use in young infants(234, 235).

18 Neonatal sepsis has historically been categorized based on either the timing of clinical disease  
19 onset (Early Onset Sepsis [EOS] or Late Onset Sepsis [LOS]) or based on where the infection was  
20 likely acquired (Community Acquired Infection [CAI] –or Hospital Acquired Infection [HAI]) (Box  
21 1). The aim of these categorizations is to predict the most likely causative pathogens and guide  
22 empiric treatment. However, these categorizations have become less helpful as more infants  
23 worldwide are born in health care facilities and are exposed to multidrug-resistant pathogens in  
24 the early neonatal period either acquired from their mother or through nosocomial acquisition  
25 in the health facility or hospital.

### *Box 1 Commonly used classifications of neonatal sepsis*

#### *By timing of onset*

- early onset<sup>a</sup> (occurring  $\leq$  3 days after birth, often acquired vertically from the mother or in the peripartum period)
- late onset (occurring > 3 days after birth, often hospital acquired)

#### *By setting of acquisition*

- community setting
- hospital setting

26 <sup>a</sup>A range of different post-natal ages have been used to define EOS, including less than 3, 5 or 7 days of life.

27 In settings with limited access to any laboratory tests, an alternative clinical definition used by  
28 the WHO is “possible Serious Bacterial Infection” (pSBI) (236, 237). This definition is based on the  
29 presence of multiple clinical signs. If at least one of the signs is present, the neonate or young

30 infant requires prompt treatment with antibiotics. Relevant signs to consider include difficulty  
 31 feeding, history of convulsions, movement only when stimulated, respiratory rate > 60  
 32 breaths/minute, severe chest retractions and temperature > 38 °C or < 35.5 °C.

*Box 2 Definition of Possible Serious Bacterial Infection (PSBI)*

PSBI is a clinical syndrome used in the Integrated Management of Childhood Illness package. A young infant is classified as having PSBI when any one or more of the following signs is present:

- Not able to feed since birth or stopped feeding well (confirmed by observation)
- No movement or movement only on stimulation
- convulsions
- fast breathing (60 breaths per minute or more) in infants less than 7 days of age
- severe chest in-drawing
- fever (38 °C or greater)
- low body temperature (less than 35.5 °C).

33 Clinical signs and symptoms are important predictors of neonatal sepsis, as well as perinatal risk  
 34 factors (e.g. prematurity/gestational age). Several scores exist that measure severity of sepsis  
 35 and help predict short-term mortality, but these are virtually all derived in the high-income  
 36 setting. Scores are used to promptly identify neonates who would benefit the most from optimal  
 37 antibiotic treatment and supportive care.

38 Because of its simplicity, one of the most frequently used scores is the Score for Neonatal Acute  
 39 Physiology–II (SNAP-II score) (238). This score was developed in 2001 to predict outcomes  
 40 (usually short-term mortality) in cases of possible neonatal sepsis. It should be noted, however,  
 41 that this score has not been extensively validated in LMIC and therefore there is no clear  
 42 consensus on its use. Some evidence exists from LMIC settings that SNAP-II scores differ  
 43 significantly in neonates with sepsis who survive or die in the short-term irrespective of  
 44 gestational age (239). The SNAPPE-II score is an extension of the SNAP-II score which includes  
 45 additional perinatal parameters (238).

## 46 Sepsis in children beyond neonatal age

47 The WHO Integrated Management of Childhood Illnesses (WHO-IMCI) defines sepsis as “a  
 48 diagnosis of exclusion, characterized by the presence of acute fever (> 39.0 °C) and severe illness  
 49 when no other cause is found” (indicating that it is possibly caused by an infection)(23). The  
 50 definition outlined above (in the section about neonatal sepsis) of possible Serious Bacterial  
 51 Infection can also be used beyond neonatal age to children under 5 years.

52 Other paediatric sepsis definitions in use include:

- 53 • International Pediatric Sepsis Consensus Conference, 2005(240). Suspected or proven  
 54 infection caused by any pathogen or clinical syndrome associated with a high probability  
 55 of infection AND systemic inflammatory response syndrome. Systemic inflammatory  
 56 response syndrome is defined as abnormal temperature or white blood cell count AND  
 57 one of the following age-adjusted signs: tachycardia or bradycardia, tachypnoea and/or  
 58 mechanical ventilation(241).

- 59 • Paediatric adaptation of the Sepsis-3 adult sepsis definition, including the paediatric  
60 version of the Sequential Organ Failure Assessment (pSOFA) score (Table 3) (242).

61 *Table 3 Paediatric Sequential Organ Failure Assessment (pSOFA) score*

Parameter	Score				
	0	1	2	3	4
PaO <sub>2</sub> mmHg (kPa)/FiO <sub>2</sub> (%)	≥ 400 (53.3)	< 400 (53.3)	< 300 (40)	< 200 (26.7) with respiratory support	< 100 (13.3) with respiratory support
MAP mmHg (kPa) by age group (in months) and catecholamine doses needed (µg/kg/min for ≥ 1 h)					
< 1	≥ 46 (6.1)	< 46 (6.1)	Dopamine < 5 OR Dobutamine any dose	Dopamine 5.1–15 OR Epinephrine (adrenaline)/ norepinephrine ≤ 0.1	Dopamine > 15 OR epinephrine/ norepinephrine > 0.1
1–11	≥ 55 (7.3)	< 55 (7.3)	As above	As above	As above
12–23 (1–2 years)	≥ 60 (8)	< 60 (8)	As above	As above	As above
24–59 (2–5 years)	≥ 62 (8.2)	< 62 (8.2)	As above	As above	As above
60–143 (6–11 years)	≥ 65 (8.6)	< 65 (8.6)	As above	As above	As above
144–216 (12–18 years)	≥ 67 (8.9)	< 67 (8.9)	As above	As above	As above
Platelets (x 10 <sup>3</sup> /µL, x 10 <sup>9</sup> /L)	≥ 150	< 150	< 100	< 50	< 20
Bilirubin mg/dL (mmol/L)	< 1.2 (20)	1.2–1.9 (20–32)	2–5.9 (33–101)	6.0–11.9 (102–204)	> 12.0 (204)
Glasgow coma scale	15	13–14	10–12	6–9	< 6
Creatinine mg/dL (µmol/L) by age group (months)					
< 1	< 0.8 (71)	0.8–0.9 (71–80)	1.0–1.1 (88–97)	1.2–1.5 (110–133)	≥ 1.6 (141)
1–11	< 0.3 (26)	0.3–0.4 (26–35)	0.5–0.7 (44–62)	0.8–1.1 (71–97)	≥ 1.2 (110)
12–23 (1–2 years)	< 0.4 (35)	0.4–0.5 (35–44)	0.6–1.0 (53–88)	1.1–1.4 (97–124)	≥ 1.5 (133)
24–59 (2–5 years)	< 0.6 (53)	0.6–0.8 (53–71)	0.9–1.5 (79–133)	1.6–2.2 (141–195)	≥ 2.3 (203)
60–143 (6–11 years)	< 0.7 (62)	0.7–1.0 (62–88)	1.1–1.7 (97–150)	1.8–2.5 (159–221)	≥ 2.6 (230)

144–216 (12–18 years)	< 1.0 (88)	1.0–1.6 (88-141)	1.7–2.8 (150-247)	2.9–4.1 (256-362)	≥ 4.2 (371)
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62 FIO<sub>2</sub>: fractional inspired oxygen; PaO<sub>2</sub>: arterial oxygen partial pressure; MAP: mean arterial pressure.

### Box 3 Bacteraemia

It should be noted that bacteraemia (i.e. the detection of bacteria in blood cultures) is not part of the definition of sepsis. While many patients with sepsis have bacteraemia, this is not a universal finding and most patients with bacteraemia do not meet sepsis criteria. The term septicaemia should be avoided.

The terms bacteraemia and bloodstream infection are often used interchangeably. However, bloodstream infections can also be caused by pathogens other than bacteria (e.g. fungi) and are associated with clinical signs and symptoms of inflammatory response. The Global Antimicrobial Resistance Surveillance System (GLASS) uses the following definition of suspected and confirmed bloodstream infection in children and neonates(212).

#### GLASS criteria for suspected bloodstream infection in children older than 28 days

All children (> 28 days–< 18 years) with two or more of the following clinical signs:

- Hyperthermia (> 38.0 °C) or hypothermia (< 36.0 °C);
- Respiratory rate > 2 standard deviations above the normal for age (Table 4), or receiving mechanical ventilation for an acute pulmonary process;
- Heart rate > 2 standard deviations above normal for age (Table 4), or for children < 1 year, mean heart rate < 10th centile for age.

#### Age-specific criteria for suspected bloodstream infection

Age group	Heart rate (beats/min)	Respiratory rate (breaths/min)
1 month–1 year	> 180 or < 90	> 34
2–5 years	> 140	> 22
6–12 years	> 130	> 18
13-18 years	> 110	> 14

#### GLASS criteria for suspected bloodstream infection in neonates (younger than 29 days)

All neonates with two or more of the following clinical signs:

- Temperature ≥ 37.5 °C or < 35.3 °C
- Respiratory rate > 60 breaths/minute or severe chest in-drawing or grunting or cyanosis
- Change in level of activity
- History of feeding difficulty
- History of convulsions.

#### GLASS criteria for confirmed bloodstream infection

- Isolation of a clinically relevant pathogen from a blood sample of a patient (all ages) seeking health care at a health care facility.

## 63 Pathophysiology

64 Sepsis is an acute life-threatening condition characterized by organ dysfunction/s due to a  
65 dysregulated host response to infection and to the direct effect of the pathogen(243).

66 A combination of factors contributes to the clinical manifestation and severity of sepsis. Severity  
67 of sepsis depends on a combination of the amount and virulence of the pathogen and the  
68 immune status of the host (e.g. immunological immaturity or dysfunction in preterm neonates,  
69 severe malnutrition, HIV infection). In addition, the timing of exposure to the pathogen plays an

70 important role in neonates. In this age group, early onset sepsis is usually associated with in utero  
 71 infections (e.g. chorioamnionitis) or infections caused by pathogens that colonize the maternal  
 72 genital tract and that can be acquired during delivery. Late onset sepsis is more commonly  
 73 associated with postnatal acquisition of community- or health care-associated pathogens.

74 Sepsis in neonates has a nonspecific clinical presentation and many neonates with suspected  
 75 sepsis who receive antibiotics do not have sepsis and do not have any significant infection. This  
 76 should be considered when sepsis is suspected to avoid overdiagnosis and overtreatment.

77 Beyond the neonatal age, sepsis in children can also be a primary bacterial bloodstream infection  
 78 (e.g. meningococcal or pneumococcal sepsis), most commonly community-acquired. Sepsis in  
 79 children may also be the result of an underlying infection in a particular site (pyelonephritis, intra-  
 80 abdominal infection or meningitis) or a health care-acquired infection.

## 81 Epidemiology

82 In 2015, about 6 million children under 5 years of age were estimated to have died, mostly in  
 83 sub-Saharan Africa and southern Asia(108). Neonates account for about half of the deaths in this  
 84 age group. Overall about 2.7 million neonates died in 2015 and of these, about 400 000 were  
 85 estimated to be the result of sepsis or meningitis (and 517 000 children under age 5 years died  
 86 from sepsis or meningitis). Sepsis is the third leading cause of death in neonates after prematurity  
 87 and birth asphyxia, both of which are associated with maternal infections such as  
 88 chorioamnionitis(108). Premature birth (< 37 weeks of gestation) and low birth weight are the  
 89 main risk factors for neonatal sepsis and are associated with higher mortality. In early onset  
 90 sepsis, additional risk factors are intra-amniotic infections (i.e. chorioamnionitis), prolonged  
 91 rupture of the membranes (e.g. > 18 hours) and maternal rectovaginal colonization with specific  
 92 pathogens (such as Group B Streptococci - GBS). Neonates with underlying disease such as  
 93 congenital malformations, or those undergoing invasive procedures, or those with central or  
 94 peripheral catheters, surgical procedures or those with prolonged hospital stays are also at  
 95 increased risk of sepsis.

## 96 Microbiology epidemiology

97 Sepsis can be caused by a variety of pathogens including fungi and viruses, although it is most  
 98 commonly caused by bacteria(243). Differences in causative pathogens may be present based on  
 99 the age of the child, presence or absence of underlying comorbidities and type of comorbidity  
 100 and geographical location (e.g. children in high-income versus low- and middle-income settings)  
 101 (Table 4 and Table 5). Pathogens most frequently associated with sepsis in neonates and children  
 102 beyond the neonatal age are shown in Tables 5 and 6.

103 *Table 4 Pathogens most frequently identified in blood cultures in neonates 28 days or younger*  
 104 *with sepsis (also refer to Box 3 about bacteremia)*

Setting	Infection acquired in the community	Infection acquired in hospital
Low- and middle-income	<b>Most common:</b> <i>Escherichia coli</i>	<i>Klebsiella</i> spp. <i>Escherichia coli</i>

	<p>(including multidrug-resistant strains such as those producing ESBL)</p> <p><i>Staphylococcus aureus</i> (including MRSA)</p> <p><i>Klebsiella</i> spp.</p> <p><i>Acinetobacter</i> spp. (including multidrug-resistant strains such as those producing ESBL and carbapenemases)</p> <p><i>Streptococcus agalactiae</i> (group B <i>Streptococcus</i>)</p> <p><i>Streptococcus pyogenes</i> (group A <i>Streptococcus</i>)</p> <p><i>Streptococcus pneumoniae</i></p> <p>non-typhoidal <i>Salmonella</i></p> <p><b>More rarely:</b></p> <p><i>Staphylococcus</i> spp. (other than <i>Staphylococcus aureus</i>)</p> <p><i>Listeria monocytogenes</i></p> <p><i>Haemophilus influenzae</i></p> <p>Gram-negative bacteria other than <i>Escherichia coli</i> and <i>Enterococcus</i> spp.</p>	<p><i>Acinetobacter</i> spp. (including multidrug-resistant strains such as those producing ESBL and carbapenemases)</p> <p><i>Staphylococcus aureus</i> (including MRSA)</p> <p>Gram-negative bacteria other than <i>E. coli</i> and <i>Klebsiella</i> spp. and <i>Acinetobacter</i> spp.</p> <p><i>Enterococcus</i> spp.</p>
High-income	<p><b>Most common:</b></p> <p><i>Escherichia coli</i> (including multidrug-resistant strains such as those producing ESBL)</p> <p><i>Staphylococcus aureus</i> (including MRSA)</p> <p><i>Streptococcus agalactiae</i> (group B <i>Streptococcus</i>)</p> <p><b>More rarely:</b></p> <p><i>Staphylococcus</i> spp. (other than <i>Staphylococcus aureus</i>)</p> <p><i>Listeria monocytogenes</i></p> <p><i>Haemophilus influenzae</i></p>	<p><i>Escherichia coli</i></p> <p><i>Klebsiella</i> spp. (including multidrug-resistant strains such as those producing ESBL and carbapenemases)</p> <p><i>Staphylococcus aureus</i> (including MRSA)</p> <p>Gram-negative bacteria other than <i>E. coli</i> and <i>Klebsiella</i> spp.</p> <p><i>Enterococcus</i> spp.</p>

105 Notes: As indicated in the definition section, the distinction between neonatal sepsis acquired in the community-  
 106 and in the hospital is usually used in low- and middle-income settings, but neonatal sepsis can also be classified as  
 107 early or late onset based on the time of onset of sepsis (counting days after delivery). The purpose of both  
 108 classifications is to help identify the most likely causative pathogens, however, overlap may exist in some settings  
 109 (e.g. *Acinetobacter* spp. is associated with early onset sepsis in some settings).  
 110 Hospital-acquired infections have a higher risk of being caused by multidrug-resistant organisms.  
 111 Only bacteria are listed in the table. Other pathogens to consider are viruses (mostly herpes simplex virus and  
 112 enteroviruses) and fungi (mostly *Candida* spp.).

113 *Table 5 Pathogens most frequently identified in blood cultures in children older than 28 days with*  
 114 *sepsis (also refer to Box 3 about bacteremia)*

Setting	Infection acquired in the community	Infection acquired in hospital
Low- and middle-income	Gram-negative bacteria (mostly <i>Escherichia coli</i> , <i>Klebsiella</i> spp.) (including multidrug-resistant strains such as those producing ESBL and carbapenemases)	<i>Klebsiella</i> spp., <i>Escherichia coli</i>

	<p><i>Streptococcus pneumoniae</i>  <i>Salmonella</i> spp.  <i>Streptococcus pyogenes</i> (group A <i>Streptococcus</i>)  <i>Staphylococcus aureus</i>  <i>Neisseria meningitidis</i>  <i>Haemophilus influenzae</i> type b</p>	<p>(including multidrug-resistant strains such as those producing ESBL and carbapenemases)  <i>Staphylococcus aureus</i> (including MRSA)</p> <p>Gram-negative bacteria other than <i>E. coli</i> and <i>Klebsiella</i> spp. (including multidrug-resistant strains such as those producing ESBL and carbapenemases)</p> <p><i>Enterococcus</i> spp.</p>
High-income	<p><i>Streptococcus pneumoniae</i>  <i>Streptococcus pyogenes</i> (group A <i>Streptococcus</i>)  <i>Staphylococcus aureus</i>  <i>Neisseria meningitidis</i>                      Gram-negative bacteria (mostly <i>Escherichia coli</i>, <i>Klebsiella</i> spp.)                      (including multidrug-resistant strains such as those producing ESBL and carbapenemases)</p>	<p><i>Klebsiella</i> spp.  <i>Escherichia coli</i>                      (including multidrug-resistant strains such as those producing ESBL and carbapenemases)</p> <p><i>Staphylococcus aureus</i> (including MRSA)</p> <p>Gram-negative bacteria other than <i>E. coli</i> and <i>Klebsiella</i> spp. (including multidrug-resistant strains such as those producing ESBL and carbapenemases)</p> <p><i>Enterococcus</i> spp.</p>

115 Notes: The child’s underlying medical conditions (i.e. comorbidities), such as HIV or malnutrition, should always be  
 116 assessed and taken into account, as immunosuppressed children are more likely to present with opportunistic  
 117 infections.  
 118 Only bacteria are listed in the table. Other pathogens to consider are viruses (mostly herpes simplex virus and  
 119 enteroviruses) and fungi (mostly *Candida* spp.).

## 120 Clinical presentation

121 The clinical presentation can vary according to the age of the child but usually signs and  
 122 symptoms are non-specific. In general, to identify the underlying clinical infection, knowledge of  
 123 local patterns of infections is helpful. Dengue and malaria related sepsis should also be  
 124 considered in endemic settings(244).

125 Neonates with sepsis commonly present with a combination of hypo- or hyperthermia  
 126 (temperature > 38.0 °C or < 35.5 °C), severe chest indrawing, tachycardia, poor feeding, reduced  
 127 spontaneous movements, hypotension and vomiting. More rarely irritability, diarrhoea,  
 128 abdominal distention and/or seizures may be present. Fast breathing alone is not a strongly  
 129 predictive sign of sepsis.

130 In children beyond neonatal age, the most frequent signs and symptoms include fever (> 38.0 °C),  
 131 respiratory symptoms, tachycardia, acute altered mental status, hypotension and vomiting.

132 The presence of any danger signs of illness (Box 2) requires prompt referral for further evaluation.

*Box 2 Danger signs of illness in children*

*WHO recommendations in newborn health, 2017 (236)*

- stopped feeding well
- history of convulsions
- fast breathing
- severe chest indrawing
- no spontaneous movement
- temperature > 37.5 °C or < 35.5 °C
- any jaundice in first 24 hours of life or yellow palms and soles at any age

*WHO pocket book of hospital care for children, 2013(23)*

- not feeding well
- convulsions
- drowsy or unconscious
- movement only when stimulated or no movement at all
- fast breathing (60 breaths/minute)
- grunting
- severe chest indrawing
- raised temperature, > 38 °C
- hypothermia, < 35.5 °C
- central cyanosis

133 **Laboratory tests**

134 **I. Patient microbiology tests**

135 Microbiology tests help establish a definitive diagnosis of sepsis and identify the causative  
 136 pathogen and underlying infection. Isolating a pathogen from a normally sterile body site (e.g.  
 137 blood, cerebrospinal fluid) that is compatible with the clinical signs and symptoms usually  
 138 confirms diagnosis. A septic screen in young infants would normally include culture of blood,  
 139 urine and cerebrospinal fluid, and a chest X-ray may be considered.

140 Diagnostic tests should be guided by the suspected primary site of infection and will be different  
 141 for pneumonia, meningitis or sepsis of unknown origin. Please also refer to specific chapters of  
 142 the handbook based on the suspected underlying infection.

143 Tests to consider when sepsis of bacterial origin is suspected are indicated in Table 6. Ideally,  
 144 these tests should be done before starting antibiotic treatment, but should not significantly delay  
 145 in treatment in a very unwell child.

146 *Table 6 Microbiology tests to consider when sepsis is suspected depending on the most likely*  
 147 *source of infection as indicated in the WHO EDL (54)*

Suspected underlying infection <sup>a</sup>	Diagnostic test	Purpose of the test	Settings where the test should be available
---	-----------------	---------------------	---

All cases where sepsis is suspected	Blood culture	To detect bacterial bloodstream infections (sepsis)	Health care facilities with clinical laboratories
Urinary tract infection	Urine culture	Initial step to detect and identify bacterial and fungal species for selection of appropriate antibiotic regimens	Health care facilities with clinical laboratories
Meningitis	Cerebrospinal fluid Gram stain and bacterial culture <sup>b</sup>	Initial step to detect and identify bacterial and fungal species for selection of appropriate antibiotic regimens	Health care facilities with clinical laboratories
Diarrhoeal disease, enteric fever <sup>c</sup>	Stool culture	Initial step to detect and identify bacterial species for selection of appropriate antibiotic regimens	Health care facilities with clinical laboratories
Abscess (e.g. in the context of intra-abdominal infections, skin and soft-tissue infections, dental infections)	Culture of abscess and/or fluid collections that can be drained	Initial step to detect and identify bacterial and fungal species for selection of appropriate antibiotic regimens	Healthcare facilities with clinical laboratories

148 <sup>a</sup>Additional tests may be considered in endemic settings or after travel to endemic settings (e.g. malaria, viruses  
 149 causing viral haemorrhagic fevers).

150 <sup>b</sup>Even though cerebrospinal fluid culture is rarely done, it is a very important test to perform.

151 <sup>c</sup>If enteric fever is suspected, note that stool cultures have a low sensitivity and are not useful in the early phase  
 152 (first week) of disease when the test is often negative.

## 153 II. Other tests

154 Laboratory tests can be used to complement the clinical examination and history to determine  
 155 the likelihood of an underlying bacterial infection (Table 7) and the presence and severity of  
 156 acute organ dysfunction (Table 8). Both tables include tests that can be considered based on  
 157 local laboratory availability and local protocols.

158 *Table 7. Laboratory tests (other than microbiology) to consider when sepsis is suspected to identify  
 159 a bacterial infection as indicated in the WHO EDL (54)*

Diagnostic test	Purpose of the test	Settings where the test should be available
White blood count	To help in the diagnosis of infections	Health care facilities with clinical laboratories and also in primary care settings
C-reactive protein	To detect inflammation as an indicator of various conditions (e.g. sepsis)	Health care facilities with clinical laboratories
Procalcitonin <sup>a</sup>	To guide antibiotic therapy or discontinuation in sepsis	Only in tertiary and higher health care facilities

160 <sup>a</sup>Procalcitonin is not widely available and has only moderate accuracy for the diagnosis of sepsis in neonates with  
 161 suspected sepsis at the cut-off of 2.0–2.5 ng/mL; different cut-offs in neonates with early versus late onset sepsis  
 162 may be necessary(245). Procalcitonin may possibly have a higher sensitivity and specificity than C-reactive protein,  
 163 (246) (246). A combination of both tests may improve the accuracy of diagnosis of neonatal sepsis(247).  
 164 *Table 8 Laboratory tests (other than microbiology) to consider when sepsis is suspected to identify*  
 165 *organ dysfunction as indicated in the WHO EDL (54)*

Diagnostic test	Purpose of the test	Settings where the test should be available
Bilirubin	To detect or monitor liver disease, bile duct disorders and red cell destruction	Health care facilities with clinical laboratories
Blood pH and gases	To assess lung function, metabolic or kidney disorders and monitor oxygen therapy	Health care facilities with clinical laboratories
Blood urea nitrogen	To assess kidney function	Health care facilities with clinical laboratories
Creatinine	To monitor kidney function for management of severe infections (i.e. sepsis,) and to adjust antimicrobial regimen	Health care facilities with clinical laboratories
Electrolytes	To monitor fluid, electrolyte and acid–base balance	Health care facilities with clinical laboratories
Glucose	To diagnose intermediate hyperglycaemia and hypoglycaemia	Health care facilities with clinical laboratories and also in primary care settings
Platelet count	To diagnose thrombocytopenia or thrombocytosis. Marker to manage severe infections associated with sepsis (e.g. viral haemorrhagic fever, meningococcaemia)	Health care facilities with clinical laboratories
Whole blood lactate	To assess metabolic acidosis	Health care facilities with clinical laboratories

### 166 III. Using surveillance microbiology data

167 Targeted clinical microbiology surveys of neonates and children with confirmed sepsis, including  
 168 clinical presentation and infection focus, underlying disease, blood stream isolate and resistance  
 169 phenotype, antibiotic treatment and clinical outcome, may be helpful at a local and national level  
 170 to inform empiric guidance.

### 171 Imaging

172 If available, imaging studies should be guided by the suspected primary site of infection as for  
 173 microbiological sampling. Please also refer to specific chapters of the handbook based on the  
 174 suspected underlying infection. When sepsis is suspected and respiratory distress is present, a  
 175 chest X-ray is indicated to confirm a lower respiratory tract infection that may not always be  
 176 clinically obvious.

177 If an abdominal source of infection is suspected, an abdominal ultrasound could be considered.  
 178 As an alternative and if available, a computed tomography scan of the abdomen could also be  
 179 considered; however, limiting exposure to radiation should always be considered, especially in  
 180 young children. If sepsis caused by an infection of the urinary tract is suspected, initial imaging  
 181 (e.g. ultrasound) of the urinary tract or during follow-up could be considered if an outflow  
 182 obstruction or collection are suspected.

## 183 Antibiotic treatment

184 Antibiotic treatment should be started as soon as possible when sepsis is suspected. Performance  
 185 and results of laboratory and microbiology tests should not delay the first dose of antibiotic  
 186 treatment.

187 Even though the presence of perinatal risk factors (prematurity, prolonged rupture of  
 188 membranes) often leads to early empiric antibiotic use in babies, there is good evidence that  
 189 these risk factors alone do not reliably predict neonatal sepsis. Therefore, antibiotic treatment  
 190 should generally be started in newborn infants based on a combination of clinical and laboratory  
 191 signs. In neonates with significant risk factors for infection (e.g. membranes ruptured > 18 hours  
 192 before delivery, mother had fever > 38.0 °C before delivery or during labour, or amniotic fluid  
 193 was foul smelling or purulent), prophylactic antibiotics (ampicillin and gentamicin) should be  
 194 given for only 2 days. The neonate should be reassessed after 2 days and treatment be continued  
 195 only if there are signs of sepsis or a positive blood culture(236).

196 Empiric treatment (see Table 9) should always cover the most probable causative pathogens:

- 197 • In neonates: Gram-negative bacteria, *Staphylococcus aureus*, *Group B Streptococcus*.
- 198 • In children beyond the neonatal age: Gram-negative bacteria, *Streptococcus pneumoniae*,  
 199 *Staphylococcus aureus* and *Neisseria meningitidis*.

200 **Simplify** empiric treatment to a more narrow-spectrum antibiotic based on culture results if a  
 201 pathogen is isolated. When no organism is identified, antibiotic treatment should be guided by  
 202 available laboratory results and clinical response. In low-risk neonates in the primary health care  
 203 setting simplification of empiric antibiotic regimens is being implemented, including two doses  
 204 of parenteral gentamicin combined with oral amoxicillin.

205 In malaria-endemic areas, it is often difficult to rule out sepsis in a child with shock or severe  
 206 illness and decreased alertness, particularly where parasitaemia is common. In all such cases,  
 207 empiric parenteral broad-spectrum antibiotics should be started immediately, together with  
 208 antimalarial treatment (248).

209 *Table 9 Empiric antibiotic treatment for community-acquired sepsis of bacterial origin in*  
 210 *neonates and children*

	Referral to hospital possible	Referral to hospital not possible(237)	Total treatment duration

<p><b>First choice<sup>a</sup></b></p>	<p><b>Ampicillin</b> (IV): 50 mg/kg/dose</p> <ul style="list-style-type: none"> <li>Given every 12 hours (1st week of life)</li> <li>Given every 8 hours (&gt;1st week of life)</li> </ul> <p>AND</p> <p><b>Gentamicin</b> (IV)</p> <ul style="list-style-type: none"> <li>Neonates: 5 mg/kg/dose given once a day</li> <li>Children: 7.5 mg/kg/dose given once a day</li> </ul> <p>OR</p> <p><b>Benzylpenicillin</b> (IV): 50.000 IU/kg/dose (30 mg/kg/dose) given every 8 hours</p> <p>AND</p> <p><b>Gentamicin</b> (IV):</p> <ul style="list-style-type: none"> <li>Neonates: 5 mg/kg/dose given once a day</li> <li>Children: 7.5 mg/kg/dose given once a day</li> </ul>	<p><b>Amoxicillin</b> (oral): 50 mg/kg/dose given every 12 hours</p> <p>AND</p> <p><b>Gentamicin</b> (IM):</p> <ul style="list-style-type: none"> <li>Neonates: 5 mg/kg/dose given once a day</li> <li>Children: 7.5 mg/kg/dose given once a day</li> </ul>	<p>7 days (14 days in case of meningitis)</p>
<p><b>Second choice<sup>b</sup></b></p>	<p><b>Ceftriaxone<sup>c</sup></b> (IV): 80 mg/kg/dose given once a day</p> <p>OR</p> <p><b>Cefotaxime</b> (IV): 50 mg/kg/dose given every 8 hours</p> <p>OR</p> <p><b>Cloxacillin<sup>d</sup></b> or flucloxacillin (IV):</p> <ul style="list-style-type: none"> <li>Neonates: 25–50 mg/kg/dose given every 12 hours</li> <li>Children: 25 mg/kg/dose given every 6 hours</li> </ul> <p>AND</p> <p><b>Amikacin<sup>e</sup></b> (IV): 15 mg/kg/dose given once a day</p>	<p>No specific option is indicated in the EML/c as second choice option when referral to hospital is not possible.</p>	<p>7 days</p>

211 **For the treatment of neonatal sepsis, an update of WHO guidelines is ongoing as to the date of publication of**  
 212 **this Handbook, please regularly check the WHO website for news on this topic.**

213 Notes: All dosages are for normal renal and hepatic function.

214 IM: intramuscular; IV: intravenous; MSSA: methicillin-susceptible *Staphylococcus aureus*; MRSA: methicillin-resistant *Staphylococcus aureus*.

215 <sup>a</sup>To cover for *Listeria monocytogenes* and Gram-negative bacteria.

216 <sup>b</sup>In settings with high resistance, particularly for suspected health care-associated infections, a broad-spectrum antibiotic with activity against Gram-negative bacteria should also be considered (e.g. piperacillin+tazobactam).

217 <sup>c</sup>Ceftriaxone should not be used in neonates with hyperbilirubinaemia and should not be administered with calcium.

218 Age restriction: use only in neonates of > 41 weeks corrected gestational age.

219 <sup>d</sup>Cloxacillin is a useful second-choice option when an infection caused by *Staphylococcus aureus* is suspected; the  
 220 presence of extensive skin pustules, abscess or omphalitis (i.e. infection of the umbilicus and/or surrounding tissues)  
 221 may suggest a staphylococcal infection. Of note, in community setting with high prevalence of MRSA, vancomycin  
 222 should be considered instead of cloxacillin.  
 223  
 224

225 <sup>e</sup>Amikacin can be used when gentamicin is not available. Amikacin would mostly be used as a treatment for  
 226 infections caused by Gram-negative bacteria and when antibiotic-resistant bacteria are suspected.  
 227 **ACCESS** antibiotics are indicated in green, **WATCH** antibiotics in yellow and **RESERVE** antibiotics in red.

## 228 Prevention

229 Sepsis rates can be reduced by preventing infection and by preventing the progression of  
 230 infection to sepsis. Infections can be prevented in the community with good hygiene, safe water  
 231 and sanitation, safe food preparation, good nutrition and vaccinations (Table 10). In hospitals,  
 232 adequate infection prevention and control practices are key to prevent infections – to prevent  
 233 neonatal sepsis, infection prevention and control practices in neonatal units and labour rooms  
 234 are essential. The main ways to prevent the progression of infections to sepsis include prompt  
 235 and adequate medical care including appropriate antibiotic treatment of the underlying  
 236 infection.

237 *Table 10 Vaccinations to consider to prevent certain infections*

Vaccination <sup>a</sup>	Population where the vaccine should be considered
<i>Haemophilus influenzae</i> type b vaccination (40)	All children should be vaccinated with <i>Haemophilus influenzae</i> type b conjugate vaccines.
Meningococcal vaccination(40, 232)	Countries with high (> 10 cases per 100 000 population/year) or intermediate (2–10 cases per 100 000 population/year) incidence of meningococcal disease or with frequent epidemics: all individuals aged 1–29 years (including pregnant women) should be vaccinated with the meningococcal A conjugate vaccine. Countries with low incidence of meningococcal disease (< 2 cases per 100 000 population /year): vaccination only for defined high-risk groups such as children and young adults or individuals with immunodeficiency. The choice of the recommended vaccine depends on the local prevalence of the meningococcal serogroups.
Pneumococcal vaccination(39)	All children should be vaccinated with pneumococcal conjugate vaccines.
<i>Salmonella</i> Typhi vaccination (144)	Individuals living in countries with a high burden of enteric fever or a high burden of antimicrobial resistant <i>Salmonella</i> Typhi should be vaccinated with typhoid conjugate vaccines; vaccination should also be offered during outbreaks.

238 <sup>a</sup>References are to WHO position papers that support the evidence for vaccination.

# 1 Bacterial meningitis

## 2 Key messages

1. Bacterial meningitis is a severe potentially life-threatening infection
2. Given the severity of this condition meningitis is always considered of bacterial origin until proven otherwise
3. The first dose of antibiotic should never be delayed (ideally given within 1 hour of presentation to care) and lumbar puncture and / or imaging should not delay starting treatment
4. The types of causative pathogens varies depending on the age and immune status of the patient

3

*Box 1 Other relevant WHO documents (please check regularly for updates)*

Defeating meningitis by 2030: a global road map. <https://apps.who.int/iris/handle/10665/342010>

Health topics - Meningitis. Geneva: World Health Organization; <https://www.who.int/health-topics/meningitis>

Meningococcal vaccines: WHO position paper, November 2011. Weekly Epidemiological Record, 86 (47), 521 - 539. <https://apps.who.int/iris/handle/10665/241846>

Meningococcal A conjugate vaccine: updated guidance, February 2015. Weekly Epidemiological Record, 90 (08), 57 - 62. <https://apps.who.int/iris/handle/10665/242320>

Pneumococcal conjugate vaccines in infants and children under 5 years of age: WHO position paper –February 2019. Weekly Epidemiological Record, 94 (08), 85 - 103. <https://apps.who.int/iris/handle/10665/310970>

Haemophilus influenzae type b (Hib) Vaccination Position Paper — July 2013: Introduction. Weekly Epidemiological Record, 88 (39), 413 - 426. Geneva: World Health Organization; <https://apps.who.int/iris/handle/10665/242125>

Summary of WHO position papers – recommended routine immunizations for children. [https://www.who.int/immunization/policy/Immunization\\_routine\\_table2.pdf](https://www.who.int/immunization/policy/Immunization_routine_table2.pdf)

## 4 Definition

- 5 Meningitis is an acute inflammation of the meninges, the membranes lining the brain and spinal
- 6 cord. It can be infectious or non-infectious in origin (e.g. associated with autoimmune disease)
- 7 and can be associated with high morbidity and mortality, even if treated promptly.

## 8 Pathophysiology

9 The pathogens that cause meningitis can colonize the upper respiratory tract and from there  
10 invade the bloodstream and get access to the central nervous system through the ventricular  
11 choroid plexus or can access the meninges by local spread. Because the central nervous system  
12 lacks effective immune defences, organisms can multiply rapidly, cause direct tissue injury to the  
13 meninges and produce an inflammatory response that contributes to neurological symptoms.

## 14 Epidemiology

15 Meningitis is found worldwide and can affect individuals of all ages, although some differences  
16 exist across geographic regions. Mortality is highest in children under 5 years of age. Outbreaks  
17 of meningococcal meningitis mostly occurring during cooler and drier seasons are a serious  
18 threat, especially in the so-called meningitis belt, an area in the peri-Saharan African region  
19 stretching from Senegal in the West to Ethiopia in the East. Although deaths from meningitis have  
20 overall decreased by about 20% between 1990 and 2016 (from an estimated 403 000 to about  
21 318 000 a year), the burden of bacterial meningitis is still high, especially in LMIC despite an  
22 increase in immunization programmes(249). According to data from the Global Burden of Disease  
23 study, in 2017, there were around 5 million new cases of meningitis (considering all ages and  
24 both sexes combined)(31). Almost half of the cases were of viral origin (2.4 million cases). In the  
25 same year, the number of new cases of acute pneumococcal (about 440 000) and meningococcal  
26 (about 400 000) meningitis were similar, while *Haemophilus influenzae* accounted for an  
27 estimated 262 000 new cases(31).

28 Tuberculous meningitis is more common in settings with a high prevalence of tuberculosis (TB)  
29 especially among patients living with HIV. In settings where TB is endemic, children and young  
30 adults are more at risk of TB meningitis (dissemination of primary infection from the lungs to the  
31 central nervous system) while in setting with a low prevalence of TB, adults are most at risk  
32 (reactivation of a latent TB infection)(250).

33 The incidence and mortality of meningitis are higher in countries with limited resources. In 2016,  
34 > 90% of new cases of meningitis and > 80% of deaths (about 270 000 deaths) occurred in  
35 countries with a low to middle socioeconomic index (as defined by the Global Burden of Disease  
36 study group)(249). In 2016, the highest mortality was reported for central and western sub-  
37 Saharan African regions (about 110 000 deaths). Nevertheless, of the 10 countries with the  
38 highest absolute number of meningitis deaths in 2016, four were located outside of the  
39 meningitis belt (Afghanistan, China, India and Pakistan). About 7% of new meningitis cases and  
40 4% of deaths in 2016 occurred in countries with a high or middle-to-high socioeconomic index  
41 (249).

## 42 Microbiology epidemiology

43 Viral meningitis (usually benign and mainly caused by enteroviruses and arboviruses) and non-  
44 infectious causes (e.g. autoimmune or neoplastic diseases or as a side-effect of certain medicines)  
45 can mimic the signs and symptoms of bacterial meningitis. Therefore, it is important to consider

46 these causes in the differential diagnosis. The most frequently implicated bacteria (beyond  
 47 neonatal age) are *Streptococcus pneumoniae*, *Neisseria meningitidis* and *Haemophilus influenzae*  
 48 (serotype b and non-typeable strains). The most likely causative bacteria may differ across age  
 49 groups (e.g. meningitis due to *Haemophilus influenzae* mainly affects children) and in patients  
 50 with immune system deficiencies (e.g. increased risk of *Listeria monocytogenes*, increased risk of  
 51 meningitis caused by encapsulated bacteria such as *N. meningitidis* and *S. pneumoniae* in  
 52 patients with asplenia or hyposplenia ) as shown in Table 1.

53 Tuberculous meningitis should also be considered in the differential diagnosis in patients living  
 54 in or coming from areas where tuberculosis (TB) is endemic especially if the onset of disease is  
 55 not acute.

56 In patients with severe immunosuppression (e.g. with advanced HIV disease), cryptococcal  
 57 meningitis and cerebral toxoplasmosis should also be considered, although the clinical  
 58 presentation of these two infections is usually less acute than bacterial meningitis. In patients  
 59 living in or visiting areas where malaria is endemic, cerebral malaria should also be included in  
 60 the differential diagnosis. Although most cases of meningitis are community-acquired, the  
 61 infection can also be health care-associated (e.g. after neurosurgical interventions and after  
 62 lumbar puncture). In that case, the most likely pathogens are *Staphylococcus aureus* or aerobic  
 63 Gram-negative bacilli, including multidrug-resistant strains. For prevention of health care-  
 64 associated meningitis refer to the WHO global guidance on prevention of surgical site  
 65 infections(251).

66 *Table 1 Pathogens most frequently associated with bacterial meningitis (in descending order of*  
 67 *frequency)*

Neonates (0–2 months)	Children and adolescents	Non-immunocompromised adults	Immunocompromised adults or adults > 50 years	Other
<i>Streptococcus agalactiae</i> (group B <i>Streptococcus</i> )	<i>Streptococcus pneumoniae</i>	<i>Streptococcus pneumoniae</i>	<i>Streptococcus pneumoniae</i>	<i>Streptococcus suis</i> <sup>c</sup>
<i>Escherichia coli</i>	<i>Neisseria meningitidis</i>	<i>Neisseria meningitidis</i>	<i>Neisseria meningitidis</i>	Viral infections (especially Enteroviruses, Herpesviridae and Arboviruses)
<i>Listeria monocytogenes</i>	<i>Haemophilus influenzae</i> type b and non-typeable strains		In addition to the above also consider:	<i>Mycobacterium tuberculosis</i> (mostly in endemic settings and/or in HIV positive patients)
<i>Streptococcus pneumoniae</i>	<i>Mycobacterium tuberculosis</i> <sup>a</sup>		<i>Listeria monocytogenes</i> <sup>b</sup>	<i>Cryptococcal meningitis</i> and cerebral toxoplasmosis in severely
			<i>Mycobacterium tuberculosis</i>	

				<p>immunosuppressed patients (HIV)</p> <p>Cerebral malaria (in patients living or travelling to endemic settings)</p> <p><i>Staphylococcus aureus</i> or Gram-negative bacteria<sup>d</sup>, including multidrug-resistant strains after neurosurgical interventions</p>
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68 <sup>a</sup>Mostly in settings where tuberculosis is endemic and/or in patients positive for HIV.

69 <sup>b</sup>Pregnant women also have an increased risk of *Listeria monocytogenes* infection.

70 <sup>c</sup>Consider if exposure to pigs.

71 <sup>d</sup>Gram-negative bacterial meningitis can also occur as a consequence of *Strongyloides* hyperinfection syndrome which is a rare but fatal condition that can occur in immunosuppressed people infected with *Strongyloides stercoralis*.

## 74 Meningitis caused by antibiotic-resistant pathogens

75 Data on the proportion of penicillin- and third-generation cephalosporin-resistant *Streptococcus*  
 76 *pneumoniae* isolates causing meningitis are scarce in most countries with a high incidence of  
 77 bacterial meningitis, however, whenever available, they should guide empiric antibiotic  
 78 treatment. Currently, because of the potential risk of penicillin-resistance in *Streptococcus*  
 79 *pneumoniae* isolates and because meningitis is a very serious and potentially fatal disease, a  
 80 third-generation cephalosporin is recommended for empiric treatment. Isolates with  
 81 intermediate or complete resistance to ceftriaxone have rarely been described (mainly in  
 82 patients with prolonged or multiple exposures to beta-lactam antibiotics in the previous three  
 83 months) and some experts suggest adding intravenous vancomycin or rifampicin empirically to  
 84 provide effective treatment for these isolates. Meningitis caused by multidrug-resistant Gram-  
 85 negative bacteria is also reported.

## 86 Clinical presentation

87 In adults, meningitis should be suspected in the case of acute onset (< 48 hours) of

- 88 • fever (> 38.0 °C) **AND/OR**
- 89 • headache and/or change in mental status and/or confusion **AND/OR**
- 90 • neck stiffness.

### Box 1 Clinical considerations

- All three of the classic signs and symptoms (fever, confusion and/or headache and neck stiffness) are present in only around half of patients with bacterial meningitis.

- However, 95% of adult patients usually have at least two of these symptoms and the absence of all three symptoms significantly reduces the probability of meningitis(252).

91 A haemorrhagic rash may also be present, especially in cases of meningitis caused by *Neisseria*  
92 *meningitidis* (although such a rash is not specific for meningococcal infection). Notably with *S.*  
93 *pneumoniae* foci of infection outside the CNS, such as otitis media, sinusitis, pneumonia and  
94 endocarditis, are also often observed.

95 Because bacterial meningitis is a serious illness and clinical and epidemiological features alone  
96 cannot always reliably differentiate bacterial and viral origin, all severe cases should be treated  
97 as if they were bacterial until this has been excluded or a viral cause has been clearly identified.

98 For the diagnosis of meningitis in children and neonates, refer to the latest edition of the WHO  
99 Pocketbook of hospital care for children(23). In neonates, the clinical presentation is less typical  
100 and symptoms are usually non-specific. Neonates often present with a combination of fever,  
101 poor feeding, lethargy, drowsiness, vomiting, irritability, seizures or a full fontanelle. Neck  
102 stiffness is very uncommon.

## 103 Laboratory tests

### 104 I. Patient microbiology tests

105 Whenever possible, certain microbiology tests should be considered (Table 2); ideally samples  
106 should be obtained before antibiotic treatment is started. The rationale for these tests is to  
107 establish the diagnosis and identify the pathogen as this affects treatment.

108 *Table 2 Microbiology tests to consider for the diagnosis of meningitis as indicated in the the WHO*  
109 *EDL (54)*

Diagnostic test	Purpose of the test	Settings where the test should be available
Blood cultures <sup>a</sup>	To detect bacterial and fungal bloodstream infections (sepsis)	Health care facilities with clinical laboratories
CSF microscopy (Gram stain)	To assess microbial morphology, number of white blood cells and red blood cells	Health care facilities with clinical laboratories
CSF culture	Initial step to detect and identify bacterial and fungal species for selection of appropriate antibiotic regimens	Health care facilities with clinical laboratories
Cryptococcal antigen test (CSF, blood)	To screen and diagnose cryptococcal meningitis in people living with advanced HIV disease	Health care facilities with clinical laboratories and also in primary care settings
<i>M. tuberculosis</i> DNA (CSF)	To diagnose active TB and simultaneously or sequentially detect rifampicin resistance	Health care facilities with clinical laboratories

110 CSF: cerebrospinal fluid.

111 <sup>a</sup>If blood is taken before starting antibiotic treatment, blood cultures are often positive in cases of bacterial  
112 meningitis (up to 75% of cases)(252, 253).

## 113 II. Other tests

114 In the presence of compatible signs and symptoms, a definitive diagnosis of bacterial meningitis  
 115 requires examination of cerebrospinal fluid. Therefore, whenever possible and if no  
 116 contraindications are present (such as increased bleeding risk, risk of herniation or a skin  
 117 infection at the site of the puncture), a lumbar puncture should be done before starting antibiotic  
 118 treatment. However, doing a lumbar puncture should never delay giving antibiotic treatment  
 119 when bacterial meningitis is suspected (if available at least blood cultures should be taken before  
 120 starting treatment). In settings where computer tomography is available, certain patients may  
 121 benefit from a scan of the head before the lumbar puncture because of the risk of cerebral  
 122 herniation after removing cerebrospinal fluid at the lumbar level if elevated intracranial pressure  
 123 is suspected. Computer tomography scanning should never delay the start of antibiotic  
 124 treatment. If available, imaging is indicated in patients with focal neurological signs, decreased  
 125 level of consciousness or coma or a history of central nervous system disease or recent onset of  
 126 seizures (< 1 week) or severe immunosuppression (e.g. advanced HIV disease).

127 Laboratory tests to consider when meningitis is suspected are given in Table 3. In the specific  
 128 context of epidemics, also consult the WHO meningitis epidemics guidelines(231).

129 In bacterial meningitis, the characteristics of cerebrospinal fluid vary widely (and may be normal  
 130 or only slightly altered in neonates); however, certain findings suggest a probable bacterial cause.  
 131 In particular, the following characteristics of the cerebrospinal fluid suggest bacterial meningitis:

- 132 • high opening pressure during lumbar puncture (reference range, 80-200 mm H<sub>2</sub>O or 8-20  
 133 cm H<sub>2</sub>O)
- 134 • turbid appearance of CSF
- 135 • elevated CSF white cell count (often several hundreds to several thousands WBC/mm<sup>3</sup> or  
 136 >0.1 to >1 X 10<sup>9</sup>/L)
- 137 • elevated CSF percentage of neutrophils (> 80%)
- 138 • elevated CSF protein (> 45 mg/dL or > 0.45 g/L)
- 139 • low CSF glucose (< 40 mg/dL or < 2.2 mmol/L)
- 140 • low cerebrospinal fluid / plasma glucose ratio (≤ 0.4)

141 *Table 3 Laboratory tests that could be considered for the diagnosis of meningitis as indicated in*  
 142 *the WHO EDL (54)*

Diagnostic test	Purpose of the test	Settings where the test should be available
Basic CSF Profile (CSF leukocyte count, CSF differential leukocyte count and CSF protein and glucose)	To aid in the diagnosis of bacterial, mycobacterial, fungal and viral meningitis	Health care facilities with clinical laboratories
Complete blood count	To detect a wide range of disorders, including infections	Health care facilities with clinical laboratories
Blood glucose	To diagnose hyperglycaemia/hypoglycaemia	Health care facilities with clinical laboratories but also in primary care settings

C-reactive protein	To detect inflammation as an indicator of various conditions, e.g. sepsis	Health care facilities with clinical laboratories
Procalcitonin	To guide antibiotic therapy or discontinuation in sepsis	Only in tertiary health care facilities
Whole blood lactate	To assess metabolic acidosis, sepsis and dehydration	Community settings and health facilities without laboratories

143 CSF: cerebrospinal fluid.

### 144 III. Using surveillance microbiology data

145 Targeted periodic clinical surveillance including risk factors, resistance of key pathogens and  
146 outcomes may be helpful to inform empiric guidance at a national level.

### 147 Tuberculosis meningitis

148 TB meningitis should always be considered in the differential diagnosis in high-risk patients and  
149 in settings where TB is endemic. TB meningitis can have an acute presentation and, similar to  
150 bacterial meningitis, its diagnosis cannot be made or excluded only on the basis of clinical  
151 presentation. Since TB meningitis is a serious disease, prompt diagnosis and treatment are  
152 essential(116).

### 153 Use of corticosteroids

154 The rationale for the use dexamethasone in cases of meningitis is to reduce the inflammatory  
155 response and the risk of neurological sequelae (e.g. hearing loss) and death. The use of adjunctive  
156 steroids is suggested only in high-income settings, where it has a proven benefit. Current  
157 evidence failed to show any significant benefit both in terms of mortality and sequelae in patients  
158 in low-income countries(254-256). In high-income countries, dexamethasone can be given before  
159 or at the time of the first antibiotic dose if bacterial meningitis is suspected and continued if  
160 *Streptococcus pneumoniae* is confirmed. The recommended dose is 0.15 mg/kg of  
161 dexamethasone every 6 hours. Steroids are not recommended in neonatal meningitis.

### 162 Antibiotic treatment

163 Antibiotic treatment should be started as soon as possible when bacterial meningitis is suspected  
164 (Table 4). The first dose of antibiotic treatment should not be delayed until the results of the  
165 lumbar puncture are available. The choice of empiric antibiotic treatment should take into  
166 account the age of the patient, presence of immunosuppression and local prevalence of  
167 *Streptococcus pneumoniae* isolates resistant to third-generation cephalosporins. The patient risk  
168 of *Listeria* meningitis should also be taken into account (e.g. pregnant women, patients who are  
169 immunosuppressed or > 50 years of age) because ceftriaxone (and cefotaxime) do not cover this  
170 pathogen and ampicillin should be used in these cases.

171 As a general rule, empiric treatment in children other than neonates (< 2 months) and in adults  
172 should always cover all three of the main causative pathogens (*Haemophilus influenzae*, *Neisseria*  
173 *meningitidis* and *Streptococcus pneumoniae*).

174 If a pathogen is isolated and its susceptibilities are known, antibiotics should be reviewed and  
 175 modified accordingly. When no pathogen is identified, the duration of antibiotic treatment  
 176 should be guided by available laboratory results and clinical response.

177 **Step-down** to oral treatment is less commonly used in meningitis management, where the  
 178 treatment is mainly parenteral where possible to maximise csf penetration.

179 *Table 4 Empiric antibiotic treatment for bacterial meningitis*

	Adults	Children (not neonates)	Neonates (< 2 months)	Total treatment duration
<b>First choice</b>	<p><b>Ceftriaxone</b> (IV): 2 g given every 12 hours</p> <p>OR</p> <p><b>Cefotaxime</b> (IV): 2 g given every 6 hours</p>	<p><b>Ceftriaxone</b> (IV): 100 mg/kg given once a day</p> <p>OR</p> <p><b>Cefotaxime</b> (IV): 50mg/kg/dose given every 8 hours</p>	<p><b>Ampicillin</b> (IV): 50 mg/kg/dose given every 12 hours (1<sup>st</sup> week of life) 50 mg/kg/dose given every 8 hours (&gt;1<sup>st</sup> week of life)</p> <p><b>AND</b></p> <p><b>Gentamicin</b> (IV): 5 mg/kg given once a day (1<sup>st</sup> week of life), 7.5 mg/kg given once a day (&gt; 1<sup>st</sup> week of life)</p> <p>OR</p> <p><b>Ceftriaxone</b> (IV): 100 mg/kg given once a day</p> <p>OR</p> <p><b>Cefotaxime</b> (IV): 50mg/kg/dose given every 12 hours (1<sup>st</sup> week of life) and given every 6 hours (&gt; 1<sup>st</sup> week of life)</p> <p><b>AND</b></p> <p><b>Gentamicin</b> (IV): 5 mg/kg given once a day (1<sup>st</sup> week of life), 7.5 mg/kg given once a day (&gt; 1<sup>st</sup> week of life)</p>	<p><b>Unconfirmed pathogen:</b> 10 days (adults and children) 3 weeks (neonates)</p> <p><b>Confirmed pneumococcal meningitis:</b> 10–14 days</p> <p><b>Confirmed meningococcal meningitis:</b> 5–7 days</p> <p>In epidemics, specific WHO recommendations on duration apply(231)</p> <p><b>Confirmed Listeria meningitis:</b> 21 days</p>
<b>Second choice</b>	<p><b>Ampicillin/ amoxicillin</b> (IV): 2 g given every 4 hours</p> <p>OR</p> <p><b>Chloramphenicol</b><sup>b</sup> (IV): 1 g given every 6 hours</p> <p>OR</p> <p><b>Benzylpenicillin</b></p>	<p><b>Ampicillin</b> (IV): 50 mg/kg/dose given every 8 hours</p> <p>OR</p> <p><b>Amoxicillin</b> (IV): 40-50 mg/kg/dose given every 12 hours</p> <p>OR</p> <p><b>Chloramphenicol</b><sup>a</sup> (IV): 25 mg/kg/dose given every 6 hours</p>	<p><b>Meropenem</b> (IV): 40 mg/kg/dose given every 8 hours</p>	<p>Same as above</p>

	(IV): 4 million IU (2.4 g) given every 4 hours	OR <b>Benzylpenicillin</b> (IV): 100 000 IU/kg/dose (60 mg/kg/dose) given every 6 hours		
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180 Notes: All dosages are for normal renal and hepatic function.

181 IM: intramuscular; IV: intravenous; IU: international units.

182 <sup>a</sup>Chloramphenicol should only be used when no other option is available because of toxicity (the most serious  
183 adverse event is bone marrow depression).

184 **ACCESS** antibiotics are indicated in green, **WATCH** antibiotics in yellow and **RESERVE** antibiotics in red.

## 185 Prevention

### 186 Vaccination and post-exposure prophylaxis

187 Primary prevention of bacterial meningitis relies on vaccination and antibiotic prophylaxis for  
188 close contacts of cases. Vaccination is a successful intervention to prevent bacterial meningitis.  
189 Available vaccines are active against meningococcal, pneumococcal and *Haemophilus influenzae*  
190 type b disease. Vaccines are never 100% effective and they do not protect against all strains of a  
191 bacterial pathogen. Duration of protection is also variable. As a result, even vaccinated people  
192 can develop bacterial meningitis. WHO recommendations for routine immunizations and the  
193 WHO roadmap towards defeating meningitis by 2030 are available online (257, 258).

### 194 Meningococcal vaccination(232, 259)

195 Appropriate large-scale meningococcal vaccination programmes in countries with a high (> 10  
196 cases per 100 000 population/year) or intermediate (2–10 cases per 100 000 population/year)  
197 incidence of meningococcal disease or with frequent epidemics should be in place. In countries  
198 of the meningitis belt, all individuals aged 1–29 years (including pregnant women) should be  
199 vaccinated with the meningococcal A conjugate vaccine.

200 In countries with a low incidence of meningococcal disease (< 2 cases per 100 000  
201 population/year), vaccination is recommended only for defined high-risk groups such as children  
202 and young adults or individuals with immunodeficiency. The choice of the recommended vaccine  
203 depends on the local prevalence of the different meningococcal serogroups.

### 204 Pneumococcal vaccination(39)

205 The inclusion of pneumococcal conjugate vaccines in childhood immunization programmes  
206 worldwide is recommended.

### 207 *Haemophilus influenzae* type b vaccination(40)

208 The inclusion of *Haemophilus influenzae* type b conjugate vaccines in childhood immunization  
209 programmes worldwide is recommended.

210 **Post-exposure antibiotic prophylaxis in case of meningococcal meningitis**

211 Post-exposure antibiotic prophylaxis should be considered in the following situations(260):

- 212     • outside of the African meningitis belt for all close contacts within the household  
213     • in the African meningitis belt for close contacts in non-epidemic situations.

214 Ciprofloxacin (usually 500 mg oral, single dose) is the antibiotic of choice, and ceftriaxone can be  
215 used in alternative (usually 250 mg IM single dose in adults and 125 mg IM single dose in children)  
216 (260).

DRAFT

# 1 Community-acquired 2 pneumonia – Severe

## 3 Key messages

1. Rapidly decide if the patient has severe CAP (higher short-term mortality risk and need for hospital / ICU admission) or mild CAP which can be managed in primary care with oral antibiotic treatment. Scores can be helpful to make this distinction
2. Laboratory tests can help assess disease severity and identify a bacterial versus a viral infection
3. Consider adding empiric antibiotic treatment with a macrolide to cover for atypical pathogens (*Chlamydia* or *Mycoplasma pneumoniae*)
4. Treatment duration can be limited to 5 days in most cases

4

### *Box 1 Other relevant WHO documents (please check regularly for updates)*

- WHO 2013 pocket book of hospital care for children [https://apps.who.int/iris/handle/10665/81170\(23\)](https://apps.who.int/iris/handle/10665/81170(23))
- Revised WHO classification and treatment of pneumonia in children at health facilities: evidence summaries. <https://apps.who.int/iris/handle/10665/137319>
- Pneumococcal conjugate vaccines in infants and children under 5 years of age: WHO position paper – February 2019. Weekly Epidemiological Record, 94 (08), 85 - 103. <https://apps.who.int/iris/handle/10665/310970>
- Haemophilus influenzae type b (Hib) Vaccination Position Paper – July 2013: Introduction. Weekly Epidemiological Record, 88 (39), 413 - 426. <https://apps.who.int/iris/handle/10665/242126>
- Vaccines against influenza WHO position paper – November 2012. Weekly Epidemiological Record, 87 (47), 461 - 476. [(<https://apps.who.int/iris/handle/10665/241993>)]
- Guidelines for treatment of drug-susceptible tuberculosis and patient care, 2017 update. <https://apps.who.int/iris/handle/10665/255052>

## 5 Definition

6 Community-acquired pneumonia (CAP) is an acute illness affecting the lungs caused by  
7 pathogens (most often bacteria and viruses). It usually presents with cough, sputum production  
8 (in adults), rapid and difficult breathing with new or worsening pulmonary infiltrate(s) on chest  
9 imaging.

## 10 Pathophysiology

11 CAP occurs when microbial pathogens (usually inhaled in the upper airways) reach the lower  
12 respiratory tract and proliferate in the alveoli. Less frequently, these pathogens can also reach  
13 the alveoli via the blood or by direct spread (e.g. from an infection of the pleural or intra-  
14 abdominal space). Once in the alveoli, host immune defences are activated to eliminate the  
15 pathogens. Only when these defences fail, pneumonia manifests itself because of the tissue  
16 damage and inflammatory response triggered by the proliferation of microorganisms in the  
17 affected lung(s).

## 18 Epidemiology

19 CAP is common worldwide and is a leading cause of morbidity and mortality, with an especially  
20 high burden in low-income countries (106). According to the Global Burden of Disease study, in  
21 2017 there were an estimated 471 million new cases of lower respiratory tract infections  
22 (including CAP but also a majority of cases of viral bronchitis – therefore caution is needed in  
23 interpreting this number) globally among all ages and sexes combined (31). The incidence of CAP  
24 varies with age and a country's income level. The most common causative pathogen worldwide  
25 is *Streptococcus pneumoniae* and viruses (see below); viral–bacterial coinfections may occur.

26 In low-income countries, lower respiratory tract infections (including CAP) were the leading cause  
27 of death in 2016 with a crude yearly attributable mortality of about 75 per 100 000 population  
28 (107). In general, the incidence of CAP is highest in children under 5 years in these countries. In  
29 2015, an estimated 0.9 million children under 5 years died of pneumonia and of these, about 0.5  
30 million occurred in sub-Saharan Africa (108). Undernutrition, HIV infection, exposure to smoke  
31 and air pollution are common risk factors for severe CAP in children under 5. As a result of better  
32 access to medical care, better nutrition and greater vaccination coverage, global mortality rates  
33 in children have declined by more than 30% since 2000. In high-income countries, CAP mainly  
34 affects adults 65 years and older and, in general, the incidence of CAP and risk of death increase  
35 with age (109).

## 36 Microbiology epidemiology

37 In **neonates** (up to 2 months), pneumonia is mainly caused by *Streptococcus pneumoniae*, group  
38 B *Streptococcus*, Enterobacteriales or *Staphylococcus aureus*.

39 In **children aged 2 months to 5 years**, pneumonia is more likely to be of viral origin (e.g.  
40 respiratory syncytial virus, influenza and parainfluenza virus). The most important bacterial  
41 pathogen in children under 5 years is *Streptococcus pneumoniae*. In older children *S. pneumoniae*  
42 is still common but “atypical bacteria” such as *Mycoplasma pneumoniae* and *Chlamydia*  
43 *pneumoniae* may occur (“atypical bacteria” have intrinsic resistance to beta-lactam antibiotics  
44 and cannot be visualized by Gram staining). *Haemophilus influenzae*, *Moraxella catarrhalis* and  
45 *Staphylococcus aureus* also cause CAP in some children (Table 1).

46 In adults, viruses are common causes of CAP (Table 1), either by directly causing pneumonia or  
 47 by favouring superinfection with bacteria. Among bacteria, the most common causative agents  
 48 are *Streptococcus pneumoniae*, followed by “atypical bacteria” (see definition in the paragraph  
 49 above) such as *Mycoplasma pneumoniae*, *Chlamydia pneumoniae* and *Legionella pneumophila*.  
 50 *Haemophilus influenzae*, *Moraxella catarrhalis* and *Staphylococcus aureus* are also quite  
 51 common (Table 1).

52 However, determining the cause of bacterial pneumonia is difficult in all age groups and no  
 53 causative pathogen is identified in most cases, even if extensive microbiological tests are  
 54 performed. Furthermore, there may be important geographic differences in the cause of  
 55 pneumonia; for example, *Burkholderia pseudomallei* is a cause of CAP in South-East Asia, while  
 56 *Coxiella burnetii* is more common in regions with exposure to livestock.

- **Identifying a pathogen on a specimen in the upper respiratory tract does not mean it is the cause of the pneumonia.**
- **Nasopharyngeal carriage of bacterial pathogens is very common.**

57 The type of sample (upper respiratory versus lower respiratory origin, blood cultures), the test  
 58 characteristics (sensitivity, specificity, predictive values), the local epidemiology, clinical  
 59 presentation and if available other laboratory test results always need to be considered when  
 60 deciding whether a positive result for a pathogen likely identifies the causative pathogen.

61 *Table 1 Pathogens most frequently associated with community-acquired pneumonia (in*  
 62 *descending order of frequency)*

“Typical” bacteria	“Atypical” pathogens <sup>a</sup>	Respiratory viruses	Other pathogens to consider in specific settings
<i>Streptococcus pneumoniae</i> <sup>b</sup> <i>Haemophilus influenzae</i> <i>Moraxella catarrhalis</i> <i>Staphylococcus aureus</i>  Enterobacteriales (e.g. <i>Escherichia coli</i> , <i>Klebsiella pneumoniae</i> )	<i>Mycoplasma pneumoniae</i> <sup>c</sup> <i>Chlamydia pneumoniae</i> <sup>c</sup> and <i>Chlamydia psittaci</i> <sup>c</sup> <i>Legionella</i> spp. <i>Coxiella burnetii</i>	Influenza virus (A and B) Respiratory syncytial virus (RSV) <sup>d</sup> Metapneumovirus Parainfluenza virus Coronavirus (including SARS-CoV-2) Adenovirus Rhinovirus	<i>Burkholderia pseudomallei</i> (South-East Asia, Australia) <i>Mycobacterium tuberculosis</i> <i>Pneumocystis jirovecii</i> (in people with HIV or other types of cellular immunosuppression)

63 <sup>a</sup>“Atypical” bacteria remain colourless with Gram staining. They also have intrinsic resistance to beta-lactams.

64 <sup>b</sup>The most common bacterial cause of CAP in all age groups (beyond the first week of life) is *Streptococcus pneumoniae*.

65 <sup>c</sup>*Mycoplasma pneumoniae* and *Chlamydia* spp. are more frequent in children > 5 years (compared with younger children) and in young adults.

68 <sup>d</sup>Up to 50% of cases of pneumonia in children < 5 years are caused by a virus (most commonly respiratory syncytial  
69 virus)

## 70 Community-acquired pneumonia caused by antibiotic-resistant 71 pathogens

72 Antimicrobial resistance is a potential problem with all pathogens associated with CAP. Clinically  
73 relevant high-level beta-lactam resistance in *Streptococcus pneumoniae* is though still rare  
74 globally. Resistance to macrolides in *Streptococcus pneumoniae* and *Mycoplasma pneumoniae*  
75 is highly prevalent in some settings (110, 111). It is important to note that also in the hospital  
76 setting parenteral penicillin/amoxicillin/ampicillin Access antibiotics achieve sufficient antibiotic  
77 exposure to treat the great majority of *Streptococcus pneumoniae* isolates.

**CAP caused by low level and intermediate level pneumococcal penicillin resistance can be successfully treated with higher doses of the Access antibiotics penicillin/amoxicillin/ampicillin in children and adults.**

## 78 Clinical presentation

79 Nearly all respiratory diseases can mimic the symptoms of CAP. Based on clinical features alone  
80 it is often impossible to distinguish bacterial from viral pneumonia or from other non-infectious  
81 causes (local epidemiology and laboratory tests may help).

82 Well-established clinical features of CAP include a combination of: new onset (less than 2 weeks)  
83 of symptoms, worsening cough with or without sputum production, dyspnoea (difficulty in  
84 breathing), tachypnoea (abnormal respiratory rates to diagnose rapid breathing vary with age),  
85 reduced oxygen saturation, crepitations on lung auscultation, or chest pain or discomfort without  
86 an alternative explanation. Fever  $\geq 38.0$  °C for 3–4 days is usually present but may be absent,  
87 especially in the elderly. Extrapulmonary features such as confusion or disorientation may be the  
88 main symptoms in elderly people, immunosuppressed patients and malnourished children.  
89 Severe pneumonia with respiratory distress, sepsis requiring intensive care and intravenous  
90 antibiotic treatment has a high associated mortality.

91 **In children** the WHO defines fast breathing pneumonia as a child with a high respiratory rate for  
92 their age (>50 breaths/minute in children 2-11 months of age; >40 breaths/minute in children  
93 aged 1-5 years). They may or may not have chest indrawing.

## 94 Laboratory tests

### 95 I. Patient microbiology tests

96 In severe cases the following tests could be considered to guide antimicrobial treatment  
97 (Table 2):

- 98 • blood cultures (ideally before starting antibiotic treatment)
- 99 • sputum microscopy and culture (ideally before starting antibiotic treatment)

- 100 • urinary antigens for *Legionella pneumophila* and *Streptococcus pneumoniae*.

101 Additionally, in selected cases, the following tests could also be considered (Table 2):

- 102 • rapid molecular test for *Mycobacterium tuberculosis* in sputum
- 103 • nucleic acid amplification test for influenza virus in a nasopharyngeal sample to help
- 104 decide on antiviral treatment and for infection prevention and control purposes (e.g. to
- 105 prevent transmission to other patients)
- 106 • nucleic acid amplification test or antigen test for SARS-CoV-2 depending on the current
- 107 epidemiology
- 108 • HIV testing in LMIC settings and in case of recurrent and severe pneumonia

109 Routine use of nasopharyngeal swab for nucleic acid tests for respiratory viruses other than

110 influenza or SARS-CoV-2 is usually not needed.

111 *Table 2 Microbiology tests to consider if community-acquired pneumonia is suspected as*

112 *indicated in the WHO EDL (54)*

Diagnostic test	Purpose of test	Setting where the test should be available	Comment
Blood cultures	To detect bacterial bloodstream infection	Health care facilities with clinical laboratories	Not routinely needed but suggested in severe cases <sup>a</sup>  Some guidelines suggest blood culture also in cases of recent antibiotic exposure (< 3 months) or if MRSA or <i>Pseudomonas aeruginosa</i> infection is suspected
Sputum microscopy (Gram stain)	To assess microbial morphology and adequacy of the specimen for culture by identifying white blood cells and squamous epithelial cells	Health care facilities with clinical laboratories	Not routinely needed but suggested in severe cases <sup>a</sup>  Some guidelines suggest sputum microscopy also in cases of recent antibiotic exposure (< 3 months) or if MRSA or <i>Pseudomonas aeruginosa</i> infection is suspected
Sputum culture	Initial step to detect and identify bacterial and fungal species for selection of appropriate antibiotic regimens	Health care facilities with clinical laboratories	Not routinely needed but suggested in severe cases <sup>a</sup>  Some guidelines suggest sputum culture also in cases of recent antibiotic exposure (< 3 months) or if suspicion of MRSA or <i>Pseudomonas aeruginosa</i> infection is suspected

Sputum rapid molecular test for <i>Mycobacterium tuberculosis</i>	To diagnose active tuberculosis and detect rifampicin resistance	Health care facilities with clinical laboratories	If <i>Mycobacterium tuberculosis</i> infection is suspected
Urinary antigens for <i>Legionella pneumophila</i> and <i>Streptococcus pneumoniae</i>	To diagnose legionellosis and pneumococcal pneumonia	– <sup>b</sup>	Not routinely needed but suggested in severe cases <sup>a</sup> . It is often difficult or impossible to obtain high-quality sputum e.g. from the elderly and children  Some guidelines also recommend urinary antigens in case of an outbreak of legionellosis or recent travel
Nasopharyngeal swab for nucleic acid amplification test for influenza viruses	To diagnose seasonal influenza infection	Health care facilities with clinical laboratories but also in primary care settings	Not routinely needed but suggested during the influenza season
SARS-CoV-2 Antigen  Upper respiratory specimens (e.g. nasopharyngeal or nasal swab)	To diagnose COVID-19	Community settings and health facilities without laboratories <sup>d</sup>	Not routinely needed but suggested depending on the epidemiologic situation
SARS-CoV-2 nucleic acid amplification test  Upper respiratory specimens (e.g. nasopharyngeal and oropharyngeal) and lower respiratory specimens (e.g. BAL)	To diagnose COVID-19	Health care facilities with clinical laboratories	Not routinely needed but suggested depending on the epidemiologic situation
Nasopharyngeal swab for nucleic acid amplification test for respiratory viruses other than influenza viruses or SARS-CoV-2 (e.g. respiratory syncytial virus)	To diagnose respiratory viruses other than influenza or SARS-CoV-2	– <sup>b</sup>	Not routinely needed but suggested in severe cases <sup>a</sup>
Anti-HIV-1 and -HIV-2 antibody (RDT) or Combined anti-HIV-1/HIV-2 antibody and p24 antigen (RDT)	To diagnose HIV infection	Community settings and health facilities without laboratories <sup>d</sup>	Please consult the WHO consolidated guidelines on HIV testing services (261).

113 BAL: bronchoalveolar lavage; MRSA: methicillin-resistant *Staphylococcus aureus*; NAT: nucleic acid test; RDT: rapid  
114 diagnostic test.

115 <sup>a</sup>Severe cases are those with CURB-65  $\geq$  2 (adults); for children, refer to the section: Scores to determine disease  
116 severity and guide treatment decisions.

117 <sup>b</sup>This test is not in the WHO EDL (54).

118 <sup>d</sup>Community and health settings without laboratories are defined as community and health facilities such as health  
119 posts and centres, doctors' offices, outreach clinics and ambulatory care. These tests are also assumed to be  
120 available at healthcare facilities with laboratories.

## 121 II. Other tests

122 In severe cases, several tests could be considered based on local availability (Table 3) to  
123 determine disease severity, help differentiate bacterial and viral aetiologies and determine  
124 treatment duration (and IV to oral switch) during follow up.

125 *Table 3 Laboratory tests to consider if community-acquired pneumonia is suspected as indicated*  
126 *in the WHO EDL (54)*

Diagnostic test	Purpose of test	Setting where the test should be available
Blood urea nitrogen (BUN)	To assess kidney function <sup>a</sup>	Health care facilities with clinical laboratories
White blood cell count	To help in the diagnosis of infection	Health care facilities with clinical laboratories
Blood pH and gases	To assess lung function and metabolic or kidney disorders, and monitor oxygen therapy To measure blood pH, O <sub>2</sub> and CO <sub>2</sub> , serum bicarbonate, and anion gap	Health care facilities with clinical laboratories
C-reactive protein	To detect inflammation as an indicator of various conditions	Health care facilities with clinical laboratories
Procalcitonin	To guide antibiotic therapy or discontinuation in sepsis and lower respiratory tract infection	Only in tertiary care facilities

127 <sup>a</sup>Required for the CURB-65 score calculation.

## 128 III. Using microbiology surveillance data

129 In the great majority of episodes of CAP in the hospital setting, parenteral antibiotics produce an  
130 exposure sufficient to treat most resistant isolates.

131 Routine clinical microbiology samples for CAP are biased towards more severe forms of CAP  
132 where more invasive sampling is performed (such as bronchoalveolar lavage) and microbiology  
133 results are therefore not representative for the general population with CAP.

134 Therefore, routine clinical microbiology surveillance of CAP in the hospital setting does not help  
135 to inform local empiric guidance.

## 136 Imaging

137 When severe CAP is suspected clinically a chest radiograph is needed because other conditions  
 138 have similar clinical features and antibiotics may be avoided if the chest radiograph does not  
 139 suggest bacterial pneumonia. Furthermore, chest radiographs can be difficult to interpret,  
 140 especially those of elderly people, and many other conditions (such as heart failure) can mimic  
 141 infectious infiltrates. In addition, the absence of a visible infiltrate does not always rule out  
 142 pneumonia, e.g. in dehydrated patients. As with any test, the pre-test probability of pneumonia  
 143 based on clinical picture and laboratory tests if available and the likelihood of alternative  
 144 diagnoses need to be considered when interpreting chest radiographs. It should also be noted  
 145 that the radiographic pattern cannot be used to accurately predict the microbial cause and does  
 146 not reliably distinguish typical from atypical or viral pathogens.

## 147 Scores to determine disease severity and guide treatment 148 decisions

149 The WHO recommends that children that meet the criteria of severe pneumonia should be  
 150 admitted to hospital. As a general rule for children, hospitalization is indicated in cases of severe  
 151 illness (e.g. cough and severe respiratory distress, marked tachypnoea and tachycardia) and/or if  
 152 the child is unable to take oral therapy.

153 **In children, Severe Pneumonia** is characterized by cough or difficulty breathing plus any of the  
 154 following: i). oxygen saturation < 90%; ii). central cyanosis; iii). severe respiratory distress (e.g.  
 155 grunting, severe chest indrawing) **OR** signs of **Pneumonia (fast breathing with or without chest**  
 156 **indrawing – see above) PLUS a general danger sign** - inability to breastfeed, drink, convulsions,  
 157 lethargy or unconsciousness; and severe respiratory distress (23, 112).

158 **In adults**, several scores exist that measure severity and help predict 30-day mortality. These  
 159 scores, in addition to clinical judgment, can be used to determine the need for hospitalization in  
 160 immunocompetent adults diagnosed with CAP. In view of its simplicity, one of the more  
 161 frequently used scores is the CURB-65(113), or its modification, CRB-65, which does not require  
 162 laboratory values for its calculation (Table 4). However, it should be noted that these scores have  
 163 not been extensively validated in LMIC settings and for this reason there is no clear consensus  
 164 about their use in these settings (114). As well as severity scores, other factors, such as severe  
 165 comorbid illnesses (e.g. HIV infection) or inability to maintain oral therapy, should always be  
 166 taken into account in determining the need for hospital admission.

167 *Table 4 CURB-65 criteria and scoring, and treatment decisions*

Criterion	Points
Presence of confusion (new onset)	1
Urea > 19 mg/dL (or > 7 mmol/L) <sup>a</sup>	1
Respiratory rate > 30 breaths/min	1
Systolic blood pressure < 90 mmHg (<12 kPa) or diastolic blood pressure ≤ 60 mmHg (<8 kPa)	1

Age ≥ 65 years	1
<b>CURB-65 score / CRB-65 score</b>	<b>Where to treat</b>
0–1	<b>Candidate for outpatient treatment</b> Low 30-day mortality risk (< 1.5%)
2	<b>Consider inpatient treatment</b> 30-day mortality risk ≈ 10%  Consider adding clarithromycin (see Table 6)  If tests are available, consider testing for atypical pathogens (e.g. <i>Legionella</i> spp., <i>Mycoplasma</i> spp.)
≥ 3	<b>Inpatient treatment (consider admission to intensive care)</b> High 30-day mortality risk (≈ 20%)  Consider adding clarithromycin (see Table 6)  Consider testing for atypical pathogens (e.g. <i>Legionella</i> spp., <i>Mycoplasma</i> spp.)

168 Score not validated in low-and middle-income countries (LMICs).

169 <sup>a</sup>Urea is not required for the calculation of the CRB-65 score, a modification of the CURB-65 score that does not  
170 require the execution of laboratory tests.

## 171 Ruling out tuberculosis

172 Tuberculosis (TB) is a cause of subacute lower respiratory tract infection and should be  
173 considered in settings endemic for TB, especially in high-risk patients (e.g. children or adults with  
174 HIV), with a slow onset of symptoms and persistent cough, or those that do not respond to the  
175 initial antibiotic treatment. In such cases, specific investigations for TB should be done. A rapid  
176 molecular test (GeneXpert® MTB/RIF assay) performed on a single sputum specimen is currently  
177 the preferred first-line diagnostic test for pulmonary TB and to detect rifampicin resistance in  
178 both children and adults. When this rapid test is not available, microscopy examination of sputum  
179 smears could be considered for the detection of acid-fast bacilli (115). For TB management and  
180 treatment, refer to the WHO *Guidelines for treatment of drug-susceptible tuberculosis and*  
181 *patient care* (116).

## 182 Symptomatic care

183 Patients with severe CAP should receive appropriate oxygen therapy. Routine treatment with  
184 corticosteroids is usually not needed unless otherwise indicated. (262-265).

## 185 Antibiotic treatment

186 The primary goal of empiric antibiotic treatment in CAP is to provide effective and timely  
187 treatment for *Streptococcus pneumoniae* infection because this is the predominant bacterial  
188 pathogen and untreated pneumococcal pneumonia is associated with high mortality (see Table 6  
189 for adults and 7 for children for treatment recommendations). Amoxicillin or

190 phenoxymethylpenicillin (sometimes also called penicillin V) are the recommended first choice  
 191 options for mild-to-moderate CAP.

192 Empiric treatment should be guided by the age of the patient, severity of symptoms, presence of  
 193 comorbidities and previous antibiotic treatment. In certain cases (e.g. immunosuppressed  
 194 patients), the epidemiology of antibiotic resistance for common pathogens causing CAP in the  
 195 setting in which the patient is being treated could be considered.

196 Clinical improvement should be evident within 48–72 hours of starting antibiotic therapy. If there  
 197 is no response to treatment, a complication (such as empyema) should be considered. Duration  
 198 of treatment should be guided by measures of clinical improvement (e.g. resolution of fever);  
 199 usually 5 days of treatment are adequate for adults and 3–5 days in children.

200 **Simplify** empiric treatment to a more narrow-spectrum antibiotic based on culture results or  
 201 based on rapid clinical improvement when no microbiology test results are available.

202 **Step-down** to oral treatment is based on improvement of symptoms and signs of infection and  
 203 the ability to take oral antibiotics allowing discharge of the patient home when clinically  
 204 appropriate.

205 *Table 6 Empiric antibiotic treatment for severe cases of community-acquired pneumonia in adults*

	Adults	Total treatment duration(117, 118)
<b>First choice</b>	<p><b>Ceftriaxone</b> (IV/IM): 2 g given once a day (IV), 1 g given once a day (IM)<sup>a</sup></p> <p>OR</p> <p><b>Cefotaxime</b> (IV/IM): 2 g given every 8 hours</p> <p><b>if CURB-65 ≥ 2 CONSIDER ADDING</b></p> <p><b>Clarithromycin</b><sup>b</sup> (oral or IV): 500 mg given every 12 hours</p>	<p>5 days</p> <p>(consider longer treatment and / or investigate for complications if the patient is not clinically stable at day 5)</p>
<b>Second choice</b>	<p><b>Amoxicillin+clavulanic acid</b> (IV): 1 g + 200 mg given every 8 hours (a higher dose could be considered: 1 g + 200 mg given every 6 hours)</p> <p><b>if CURB-65 ≥ 2 CONSIDER ADDING</b></p> <p><b>Clarithromycin</b><sup>b</sup> (oral or IV): 500 mg given every 12 hours</p>	<p>5 days</p>

206 Notes: All dosages are for normal renal and hepatic function.

207 IM: intramuscular; IV: intravenous; IU: international units.

208 <sup>a</sup>The reason for giving a lower dose when the ceftriaxone is given IM (rather than IV) is that a larger volume would  
 209 be painful to give as intramuscular injection.

210 <sup>b</sup>The rationale of adding clarithromycin to beta-lactam is to cover for possible atypical bacteria. Azithromycin could  
 211 be used as an alternative when clarithromycin is not available but there are increasing concerns about its potential  
 212 for the emergence and spread of antibiotic resistance because of its long half-life. Erythromycin could also be  
 213 considered but it is associated with higher toxicity (diarrhoea is frequently associated with its use). Macrolides have  
 214 good bioavailability and there is no need to use the intravenous route if the patient has a function gastrointestinal  
 215 tract.

216 **ACCESS** antibiotics are indicated in green, **WATCH** antibiotics in yellow and **RESERVE** antibiotics in red.

217 *Table 7 Empiric antibiotic treatment for severe cases of community-acquired pneumonia in*  
 218 *children (from the WHO document “Revised WHO classification and treatment of childhood*  
 219 *pneumonia at health facilities”)(112)*

	Children	Total treatment duration
<p><b>Severe pneumonia</b>   <b>(pneumonia with any danger sign<sup>a</sup>, which requires referral to facility/hospital, admission and injectable therapy)</b></p>	<p><b>Ampicillin</b> (IV/IM):                      50 mg/kg/dose given every 12 hours (1st week of life)                      50 mg/kg/dose given every 8 hours (&gt;1st week of life)  <b>AND</b>  <b>Gentamicin</b> (IV/IM):</p> <ul style="list-style-type: none"> <li>• Neonates: 5 mg/kg/ dose given once a day</li> <li>• Children: 7.5 mg/kg/ dose given once a day</li> </ul> <p><b>Ampicillin can be replaced by</b>  <b>Amoxicillin</b> (IV/IM):                      50 mg/kg/dose given every 12 hours (1st week of life)                      50 mg/kg/dose given every 8 hours (&gt;1st week of life)  <b>OR</b>  <b>Benzylpenicillin</b> (IV): 50.000 IU/kg (30 mg/kg) given every 8 hours</p> <p><b>If no clinical response to ampicillin AND gentamicin after 48-72 hours change to second line:</b></p> <p><b>Cefotaxime</b> (IV/IM): 50mg/kg/ dose given every 8 hours  <b>OR</b>  <b>Ceftriaxone</b> (IV/IM): 80 mg/kg/ dose given once a day</p> <p><b>Note:</b></p> <ul style="list-style-type: none"> <li>• if HIV-positive and greater than 1 month of age (<i>Pneumocystis jirovecii</i> pneumonia is a risk), add empiric sulfamethoxazole+trimethoprim: 8 mg/kg trimethoprim and 40 mg/kg sulfamethoxazole, given every 8 hours for 3 weeks</li> <li>• Severe pneumonia, particularly in school age children, may rarely be caused by <i>Mycoplasma pneumoniae</i>, which is unresponsive to beta-lactams and would be usually treated with macrolides, for example clarithromycin.</li> </ul>	<p>5 days                       (consider longer treatment if the patient is not clinically stable at day 5)</p>

220 Notes: All dosages are for normal renal and hepatic function.

221 IM: intramuscular; IV: intravenous; IU: international units.

222 <sup>a</sup>Not able to drink, persistent vomiting, convulsions, lethargic or unconscious, stridor in a calm child or severe  
 223 malnutrition.

224 **ACCESS** antibiotics are indicated in green, **WATCH** antibiotics in yellow and **RESERVE** antibiotics in red.

## 225 Prevention

226 Vaccination can prevent many cases of CAP. Available vaccines are active against pneumococcal  
227 infection, *Haemophilus influenzae* type b disease and influenza and several vaccines against  
228 SARS-CoV-2 are available. Vaccines are never 100% effective and because they are serogroup-  
229 specific, they do not protect against all strains of bacteria or viruses. Duration of protection is  
230 also variable. As a result, even vaccinated people can develop CAP. *Haemophilus influenzae* type  
231 b conjugate vaccines and pneumococcal conjugate vaccines should be included in all routine  
232 infant immunization programmes as they have been very successful in reducing invasive disease  
233 and in many countries, rates of pneumococcal resistance. Countries should consider the inclusion  
234 of yearly seasonal influenza vaccination for high-risk populations (pregnant women, elderly  
235 people, patients with chronic medical conditions and health care workers) in their vaccination  
236 plan.

DRAFT

# 1 Hospital-acquired pneumonia

## 2 Key messages

1. Antibiotic-resistant pathogens are more frequent in hospital-acquired pneumonia (HAP) than in community-acquired pneumonia (CAP). The frequency of multidrug-resistant pathogens as cause of HAP varies by setting (e.g. among different regions, or within a hospital) and this has implications for empiric guidance
2. HAP in ventilated patient (called ventilator-associated pneumonia -VAP-) is a special subset of HAP with higher frequency of multidrug-resistant pathogens and is not addressed specifically in this chapter
3. Risk factors for multidrug-resistant pathogens (e.g. longer hospital stay, previous colonization and antibiotic use) need to be considered when choosing empiric treatment
4. In people with HAP (and VAP), the respiratory tract is often colonized with bacteria and a positive culture may not indicate an acute infection
5. Potential overtreatment of hospital-acquired pneumonia with broad-spectrum antibiotics of the Watch and Reserve groups should be avoided when possible, particularly in non-ventilated patients

3

*Box 1 Other relevant WHO documents (please check regularly for updates)*

- WHO 2013 pocket book of hospital care for children [https://apps.who.int/iris/handle/10665/81170\(23\)](https://apps.who.int/iris/handle/10665/81170(23))

## 4 Definition

5 Hospital-acquired pneumonia (HAP) is an acute illness affecting the lungs caused by pathogens  
6 present in the hospital setting and presenting 48 hours or more after admission. If pneumonia  
7 develops while the patient is on a ventilator, HAP is also called ventilator-associated pneumonia  
8 (VAP). Of note, the cut-off of 48 hours after admission is arbitrary and chosen for convenience  
9 and surveillance purposes. Depending on the situation (particularly in non-ventilated patients),  
10 even pneumonias occurring several days to weeks after hospitalisation can be caused by  
11 pathogens similar to community-acquired pneumonia while nosocomial pathogens can be  
12 acquired and cause infection in patients hospitalized for less than 48 hours.

## 13 Pathophysiology

14 Colonization of the oropharynx by bacteria from the hospital environment, aspiration of  
15 secretions into the lower respiratory tract and compromised host defense mechanisms are all

16 implicated in the pathogenesis of HAP. Pathogens can also reach the lung alveoli through the  
 17 blood or by direct spread (e.g. from an infection of the pleural or intra-abdominal space).  
 18 Secretions may become contaminated with bacteria (including with multidrug-resistant strains)  
 19 during patient care despite infection prevention and control efforts. Inhalation of pathogens  
 20 (mostly viruses) is another mechanism of infection to consider especially during epidemic  
 21 seasons or during pandemics such as COVID-19.

22 The presence of an endotracheal tube represents a major risk factor for pneumonia (ventilator-  
 23 associated pneumonia) because the mechanisms that usually prevent the microaspiration of  
 24 secretions into the lower respiratory tract are bypassed and also because biofilms (where  
 25 bacteria can survive and multiply) can form on the internal and external surfaces of the tracheal  
 26 cannula.

## 27 Epidemiology

28 Hospital-acquired infections are frequent across the world (around a quarter of all hospital  
 29 antibiotic prescriptions were for healthcare-associated infections (HAI) in a 2015 global point  
 30 prevalence survey in hospitals in more than 50 countries(266)) and HAP is an important HAI. The  
 31 incidence of HAP can vary between hospitals, depending on the patient population being  
 32 evaluated and the case definition used. However, the incidence is overall higher in mechanically  
 33 ventilated patients treated in intensive care units than in non-ventilated patients not requiring  
 34 intensive care(267).

35 Risk factors for HAP in non-ventilated patients include (i) patient-related factors such as  
 36 swallowing dysfunction and severe underlying medical conditions (e.g. immunosuppression,  
 37 chronic lung disease); and (ii) treatment-related factors such as mechanical ventilation (for VAP)  
 38 and feeding through a nasogastric tube because their presence can lead to aspiration of  
 39 oropharyngeal secretions into the lower respiratory tract. These conditions are particularly  
 40 common in elderly and frail patients(268). HAP is associated with higher in-hospital mortality  
 41 than community-acquired pneumonia, and VAP is the form of HAP with the highest mortality  
 42 (268, 269).

## 43 Microbiology epidemiology

44 HAP may be caused by the same pathogens found in community-acquired pneumonia or by  
 45 multidrug-resistant pathogens (Table 1). In general antibiotic resistance is more prevalent in  
 46 hospital-acquired strains but the frequency of multidrug-resistant pathogens varies between  
 47 hospitals and different patient populations. Usually, the risk of infection with multidrug-resistant  
 48 pathogens is increased in patients with HAP because they have often been exposed to different  
 49 regimens of antibiotics before developing HAP. The risk increases with prolonged hospitalization  
 50 (higher risk of transmission, more antibiotic use) especially if in a critical care setting and in  
 51 intubated patients. It is important to note that most data on the microbiological etiology of HAP  
 52 comes from ventilated patients in an intensive care setting because samples from the lower  
 53 respiratory tract can be relatively easily obtained. In contrast, in non-ventilated patients  
 54 bronchoalveolar lavage is associated with a risk of respiratory deterioration and non-invasive

55 sampling techniques are often not sufficient to obtain an accurate microbiological diagnosis of  
 56 etiologic agents in pneumonia.

57 *Table 1 Pathogens most frequently associated with hospital-acquired pneumonia (in descending*  
 58 *order of frequency*

Bacteria	Viruses	Fungi
<i>Streptococcus pneumoniae</i>	Influenza virus (A and B)	Mostly <i>Aspergillus</i> spp. in severely immunosuppressed patients or ventilated patients with influenza
<i>Haemophilus influenzae</i>	Other respiratory viruses (including SARS-CoV-2)	
<i>Staphylococcus aureus</i> (including MRSA)		
Gram-negative bacteria including		
<i>Pseudomonas aeruginosa</i> and <i>Acinetobacter baumannii</i>		
(including multidrug-resistant strains such as those producing ESBL and carbapenemases)		
Anaerobes (mostly associated with aspiration of a large amount of secretions)		
<i>Legionella pneumophila</i>		

59 ESBL: extended spectrum beta-lactamase; MRSA: methicillin-resistant *Staphylococcus aureus*; SARS-CoV-2: severe  
 60 acute respiratory syndrome coronavirus 2.

## 61 Clinical presentation

62 The clinical manifestations are the same as in all other forms of pneumonia: new or worsening  
 63 cough with or without sputum production, dyspnoea (difficulty in breathing), tachypnoea (cut-  
 64 off points for rapid breathing vary with age), reduced oxygen saturation, crepitations on lung  
 65 auscultation, or chest pain or discomfort without an alternative explanation. Fever  $\geq 38.0$  °C is  
 66 usually present but may be absent, especially in elderly people.

67 In ventilated patients, pneumonia is usually suspected in those with increased secretions,  
 68 reduced oxygen saturation and a new lung infiltrate on a chest-radiograph.

69 HAP and VAP may progress to sepsis and septic shock. Please refer to the sepsis chapter if this is  
 70 suspected.

71 It is important to note that accurate diagnosis of HAP is difficult in the absence of a good  
 72 reference standard. Pulmonary infiltrates on chest X-ray may be caused by a variety of non-  
 73 infectious conditions and the clinical presentation may be very non-specific. There is considerable

74 interobserver variability among specialists in the diagnosis of HAP. It is important to consider the  
 75 possibility of over diagnosis of HAP and think about stopping antibiotic treatment if HAP is ruled  
 76 out or an alternative diagnosis can be made.

## 77 Laboratory tests

### 78 I. Patient microbiology tests

79 The following tests could be considered to guide antimicrobial treatment (Table 2):

- 80 • blood cultures (ideally before starting antibiotic treatment)
- 81 • microscopy and culture of respiratory samples (ideally before starting antibiotic  
 82 treatment)
  - 83 ○ Respiratory sampling can be done using invasive or non-invasive methods  
 84 depending on the patient's condition (e.g. if the patient is mechanically ventilated  
 85 or not) and local availability. Invasive methods include bronchoalveolar lavage  
 86 (BAL) and blind bronchial sampling (usually called mini-BAL). Non-invasive  
 87 methods include spontaneous expectoration of sputum, sputum induction,  
 88 nasotracheal suctioning or endotracheal aspiration.
- 89 • urinary antigens for *Legionella pneumophila* and *Streptococcus pneumoniae*.

90 Additionally, in selected cases, the following tests could be useful (Table 2):

- 91 • nucleic acid amplification test for influenza virus in a nasopharyngeal sample to help  
 92 decide on antiviral treatment and for infection prevention and control purposes (e.g. to  
 93 prevent transmission to other patients).
- 94 • nucleic acid amplification test or antigen test for SARS-CoV-2 depending on the current  
 95 epidemiology.

96 However, most patients will not have culture data to guide antibiotic treatment. In addition, in  
 97 people with HAP, the respiratory tract is often colonized with bacteria and a positive culture may  
 98 indicate colonization rather than an acute infection especially if the sample was obtained by non-  
 99 invasive methods.

100 *Table 2 Microbiology tests to consider if hospital-acquired pneumonia is suspected as indicated*  
 101 *in the WHO EDL (2011)*

Diagnostic test	Purpose of test	Setting where the test should be available
Blood cultures	To detect bacterial bloodstream infection	Health care facilities with clinical laboratories
Respiratory sample microscopy <sup>a</sup> (Gram stain)	To assess microbial morphology and adequacy of the specimen for culture by identifying white blood cells and squamous epithelial cells	Health care facilities with clinical laboratories

Respiratory sample culture <sup>a</sup>	Initial step to detect and identify bacterial and fungal species for selection of appropriate antibiotic regimens	Health care facilities with clinical laboratories
Urinary antigens for <i>Legionella pneumophila</i> and <i>Streptococcus pneumoniae</i>	To diagnose legionellosis and pneumococcal pneumonia	– <sup>b</sup>
Nasopharyngeal swab for nucleic acid amplification test for influenza	To diagnose seasonal influenza infection	Health care facilities with clinical laboratories but also in primary care settings
Nasopharyngeal swab for nucleic acid amplification test or antigen test for SARS-CoV-2	To diagnose COVID-19	Healthcare facilities with clinical laboratories (nucleic acid testing) and primary care settings (antigen test)
Nasopharyngeal swab for nucleic acid amplification test for respiratory viruses other than influenza or SARS-CoV-2 (e.g. respiratory syncytial virus)	To diagnose respiratory viruses other than influenza or SARS-CoV-2	– <sup>b</sup>

102 MRSA: methicillin-resistant *Staphylococcus aureus*; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.  
 103 <sup>a</sup>Respiratory sampling can be done using invasive or non-invasive methods depending on the patient’s condition (e.g.  
 104 if the patient is mechanically ventilated or not) and local availability. Invasive methods include bronchoalveolar  
 105 lavage (BAL) and blind bronchial sampling (usually called mini-BAL) while non-invasive methods include spontaneous  
 106 expectoration, sputum induction, nasotracheal suctioning or endotracheal aspiration.  
 107 <sup>b</sup>This test is not in the current WHO EDL (54).

## 108 II. Other tests

109 A number of tests could be considered based on local availability to determine disease severity,  
 110 help differentiate bacterial and viral causes and determine treatment duration (and the move  
 111 from intravenous to oral treatment) during follow up (Table 3). Please also refer to the chapter  
 112 on sepsis if suspected.

113 *Table 3 Laboratory tests to consider if hospital-acquired pneumonia is suspected as indicated in*  
 114 *the WHO EDL (54)*

Diagnostic test	Purpose of test	Setting where the test should be available
White blood cell count	To help in the diagnosis of infection	Health care facilities with clinical laboratories
Blood pH and gases	To assess lung function and metabolic or kidney disorders, and monitor oxygen therapy  To measure blood pH, O <sub>2</sub> and CO <sub>2</sub> , serum bicarbonate, and anion gap	Health care facilities with clinical laboratories
C-reactive protein	To detect inflammation as an indicator of various conditions, e.g. sepsis	Health care facilities with clinical laboratories
Procalcitonin	To guide antibiotic therapy or discontinuation in sepsis and	Only in tertiary care facilities

	lower respiratory tract infection	
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115 **III. Using microbiology surveillance data**

116 Routine microbiology surveillance of isolates associated with HAP and their antibiotic  
117 susceptibilities could help informing local empiric guidance. Therefore, empiric guidance given  
118 by the Handbook could be reviewed and adapted based on local clinically relevant microbiology  
119 surveillance data.

120 However, clinically relevant isolates for this infection would be local hospital blood culture and  
121 bronchoalveolar lavage (BAL) fluid cultures data from patients in intensive care diagnosed with  
122 HAP/VAP. Caution should be taken with surveillance of routine respiratory sampling culture data  
123 from patients with HAP/VAP due to the high rates of colonisation seen in many settings.

124 **Imaging**

125 When HAP (or VAP) is suspected clinically, a chest radiograph should be obtained. HAP (or VAP)  
126 presents with clinical signs and symptoms along with a new or worsening pulmonary infiltrate on  
127 a chest radiograph and leukocytosis.

128 A chest radiograph is needed because other conditions have similar clinical features and  
129 antibiotics may be avoided if the chest radiograph does not suggest bacterial pneumonia. Chest  
130 radiographs can be difficult to interpret and to correlate with the clinical presentation (especially  
131 in elderly people where the clinical presentation is usually non-specific), and many other  
132 conditions (such as heart failure) can mimic infectious infiltrates. Therefore, caution is warranted  
133 to avoid over diagnosis and overtreatment with antibiotics. It should also be noted that the  
134 radiographic pattern cannot be used to accurately predict the microbial etiology.

135 **Antibiotic treatment**

136 Empiric treatment should be guided by the severity of symptoms (scoring systems to evaluate  
137 disease severity exist but they are beyond the scope of this chapter) and by risk factors for  
138 multidrug-resistant infections. In particular, individualized assessment should be done based on  
139 risk factors such as previous antibiotic treatment (e.g. in the 90 days preceding the infection),  
140 prolonged hospital stay, particularly in the intensive care unit (>5 days), previous colonization  
141 with multidrug-resistant pathogens and a high local prevalence of multidrug-resistant pathogens  
142 (among potential causative pathogens of HAP such as *Staphylococcus aureus*, Gram-negative  
143 bacteria including *Pseudomonas aeruginosa*).

144 Antibiotic options to consider for empiric treatment in patients with HAP (non-VAP) are given in  
145 Table 4. Treatment should always be tailored to culture results once these become available.

146 Empiric treatment in patients with VAP should be chosen considering the time from ICU  
147 admission/intubation to symptom onset. In ventilated patients (like in non-ventilated patients  
148 that develop HAP), infections that develop early (e.g. a few days after admission) are unlikely to  
149 be caused by multidrug-resistant pathogens or *Pseudomonas aeruginosa* and could safely be

150 treated with amoxicillin+clavulanic acid. On the other end, an antibiotic with a larger spectrum  
 151 of activity (and active against *Pseudomonas aeruginosa*) is preferable in case of a longer time  
 152 interval between admission to hospital and onset of symptoms.

153 There are some areas of uncertainty about empiric treatment for HAP.

- 154 • Adding vancomycin to the first-choice antibiotic options as an empiric treatment when  
 155 methicillin-resistant *Staphylococcus aureus* (MRSA) infection is suspected (e.g. in settings  
 156 with a high prevalence of *Staphylococcus aureus* isolates that are methicillin resistant and  
 157 in patients known to be colonized by MRSA).
- 158 • The need for double coverage against *Pseudomonas* to improve coverage in severely ill  
 159 patients with VAP (e.g. septic shock, or in need of ventilatory support) because of the risk  
 160 of infection caused by *Pseudomonas aeruginosa* isolates resistant to an antibiotic used  
 161 for monotherapy. The need for double coverage could therefore be considered in  
 162 severely ill patients with VAP on a case-by-case basis based on local antibiotic resistance  
 163 data and the personal history of the patient (e.g. known respiratory colonization with  
 164 multidrug-resistant *Pseudomonas aeruginosa*, particularly in patients with underlying  
 165 chronic lung disease).

166 **Simplify** empiric treatment to a more narrow-spectrum antibiotic based on culture results or  
 167 based on rapid clinical improvement when no microbiology test results are available.

168 **Step-down** to oral treatment is based on improvement of symptoms and signs of infection and  
 169 the ability to take oral antibiotics allowing discharge of the patient home when clinically  
 170 appropriate.

171 *Table 4 Empiric antibiotic treatment for hospital-acquired pneumonia (not for ventilator-*  
 172 *associated pneumonia)*

Adults	Children	Total treatment duration
<p><b>Amoxicillin+clavulanic acid<sup>a</sup></b> (IV): 1 g + 200 mg given every 8 hours</p> <p><b>OR</b></p> <p><b>Ceftriaxone<sup>b</sup></b> (IV/IM): 2 g given once a day (IV), 1g given once a day (IM)</p> <p><b>OR</b></p> <p><b>Cefotaxime</b> (IV/IM): 2 g given every 8 hours</p> <p><b>OR</b></p> <p><b>Piperacillin+tazobactam<sup>c</sup></b> (IV): 4 g + 500 mg given every 6 hours</p>	<p><b>Amoxicillin+clavulanic acid<sup>d</sup></b> (IV/oral) 40-50 mg/kg/dose of amoxicillin component, given every 12 hours OR 30 mg/kg/dose given every 8 hours</p> <p>Oral weight bands: 3-&lt;6 kg: 250 mg of amoxicillin/dose given every 12 hours 6-&lt;10 kg: 375 mg of amoxicillin/dose given every 12 hours 10-&lt;15 kg: 500 mg of amoxicillin/dose given every 12 hours 15-&lt;20 kg: 750 mg of amoxicillin/dose given every 12 hours 20-&lt;30 kg: 1000 mg of amoxicillin/dose given every 12 hours ≥ 30 Kg: Use adult dose</p> <p>OR</p>	<p>7 days</p> <p>Reassess the diagnosis and consider longer treatment if the patient is not clinically stable at day 7</p>

	<p><b>Ceftriaxone</b> (IV/IM): 80 mg/kg/dose given once a day</p> <p>OR</p> <p><b>Cefotaxime</b> (IV/IM): 50mg/kg/dose given every 8 hours</p> <p>OR</p> <p><b>Piperacillin+tazobactam<sup>c</sup></b> (IV): 100 mg/k/dose of piperacillin component, given every 8 hours</p>	
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173 Notes: All dosages are for normal renal and hepatic function.  
 174 IM: intramuscular; IV: intravenous.  
 175 <sup>a</sup>Amoxicillin+clavulanic acid can be used in certain circumstances with low-risk of multidrug-resistant infections (e.g.  
 176 short hospitalization before symptom onset and if no prior antibiotic exposure).  
 177 <sup>b</sup>The reason for giving a lower dose when the ceftriaxone is given IM (rather than IV) is that a larger volume would  
 178 be painful to give as intramuscular injection.  
 179 <sup>c</sup>Piperacillin+tazobactam offers anti- *Pseudomonas* coverage (which the other options do not). Risk of *Pseudomonas*  
 180 *aeruginosa* is higher in patients with recent antibiotic exposure and especially in patients with known previous  
 181 respiratory colonization by *P. aeruginosa* and underlying lung diseases.  
 182 <sup>d</sup>Oral liquid must be refrigerated after reconstitution as clavulanic acid is rapidly metabolized in high ambient  
 183 temperatures.  
 184 **ACCESS** antibiotics are indicated in green, **WATCH** antibiotics in yellow and **RESERVE** antibiotics in red.

185 **Prevention**

186 A detailed discussion of the prevention of HAP and VAP is beyond the scope of this chapter;  
 187 however, general key principles are presented. Some measures such as vaccination against  
 188 pathogens that can commonly cause pneumonia overlap with those presented in the chapter on  
 189 community-acquired pneumonia. Specific measures that apply to the hospital setting include:  
 190 maintaining mobility, good oral and dental care, maintaining adequate nutritional support in  
 191 hospital, elevating the head of the bed to reduce the chances of aspirating respiratory secretions  
 192 into the lower lungs, avoiding intubation or reducing its duration as much as possible and good  
 193 hand hygiene (this applies to patients and staff or family caregivers that come into contact with  
 194 patients during the hospital stay). In addition, in the intensive care unit, locally adapted bundles  
 195 of interventions to prevent VAP are usually in place and include, for example, maintaining  
 196 adequate endotracheal tube cuff pressure, minimizing sedation and assessing regularly if the  
 197 endotracheal tube can be removed in order to extubate patients as soon as it is safe to do so.

198 Selective oral decontamination (SOD) and/or selective decontamination of the digestive tract  
 199 (SDD) can also be considered based on local ICU protocols. These preventive measures have been  
 200 extensively studied to prevent hospital-acquired infections and their rationale is to reduce the  
 201 bacterial burden of the upper (with SOD) and lower (with SDD) digestive tract through the  
 202 administration of non-absorbable antibiotics (topical antibiotics applied to the oropharynx for  
 203 SOD and non-absorbable antibiotics administered through nasogastric tube for SDD). Evidence  
 204 exists that these practices can help reducing the incidence of VAP but there is a significant  
 205 concern about the risk of selecting resistant bacteria.

# 1 Intra-abdominal infections -

## 2 Acute cholecystitis and

### 3 cholangitis

#### 4 Key messages

##### **Cholecystitis**

1. If cholecystectomy is performed, antibiotics should be stopped once the gallbladder is removed and there is good clinical recovery unless the patient had a severe presentation
2. Antibiotics should be chosen based on the severity of symptoms (mild or severe) with broader-spectrum agents for severe cases and should also be active against anaerobes as these pathogens are often involved in intra-abdominal infections

##### **Cholangitis**

1. Biliary drainage is the basis of treatment for obstructive cholangitis
2. Antibiotics should be chosen based on the severity of symptoms (mild or severe) with broader-spectrum agents for severe cases and given until drainage procedures are done and continued for a total of 5 days once control of the source of infection has been achieved

5 *Box 1 Other relevant WHO documents (please check regularly for updates)*

- WHO 2013 pocket book of hospital care for children [https://apps.who.int/iris/handle/10665/81170\(23\)](https://apps.who.int/iris/handle/10665/81170(23))

#### 6 Definition

7 Acute cholecystitis is an acute inflammation of the gallbladder and acute cholangitis is an acute  
8 inflammation in the bile duct system. Both conditions are classified as uncomplicated when there  
9 is no involvement of the peritoneal cavity and the inflammation is confined to the organ involved  
10 (i.e., no perforation, no abscess, no diffuse peritonitis). The conditions are classified as  
11 complicated when the inflammation extends to the peritoneal cavity with subsequent peritonitis  
12 or when an abscess is present.

## 13 Pathophysiology

14 In acute cholecystitis, a gallstone obstructing the cystic duct for prolonged periods of time and  
15 causing inflammation of the gallbladder is the most frequent cause (> 90%). Acalculous  
16 cholecystitis, where there is no evidence of gallstones or cystic duct obstruction, is uncommon,  
17 especially in adults. Rarely, certain parasites (e.g. the worm *Ascaris lumbricoides*) can also cause  
18 gallbladder perforation.

19 In acute cholangitis, the most common cause is choledocholithiasis (i.e. gallstones in the bile  
20 duct). Infection occurs when bacteria travel up the biliary tract from the intestine or via the portal  
21 venous system. Another cause may be obstruction by tumours (e.g. pancreatic cancer) or  
22 parasites (e.g. the liver fluke *Fasciola hepatica*)(270). In addition, congenital biliary strictures or  
23 strictures following inflammation or infection can cause acute cholangitis.

24 In both cholecystitis and cholangitis, if bacterial contamination or chemical irritation (usually due  
25 to leakage of sterile fluids that are irritants to the peritoneum; for example, bile or blood) of the  
26 peritoneal cavity occur, peritonitis develops. Abdominal abscesses (i.e. the presence of a  
27 collection of infected fluid in the peritoneal cavity) can also form as a result of a complicated  
28 infection.

## 29 Epidemiology

30 Acute cholecystitis is a common surgical emergency worldwide. The incidence of acute  
31 cholecystitis is declining where cholecystectomy (surgical removal of the gallbladder) has become  
32 a common procedure in cases of recurrent attacks of biliary colic (i.e. intermittent pain in the  
33 upper abdomen, usually on the right side). Acute cholecystitis mostly affects adults; children are  
34 rarely affected. The disease is more prevalent in men and elderly people. Obesity and diabetes  
35 are also well-known risk factors(271, 272). Short-term 30-day mortality is about 5% in severe  
36 cases and 1% in mild cases(273).

37 Acute cholangitis is a condition associated with high mortality if left untreated. It is a rare disease  
38 in children. Choledocholithiasis and malignant obstruction by tumours are the most common  
39 causes of cholangitis and their risk factors overlap (274).

## 40 Microbiology epidemiology

41 The most common pathogens involved in acute cholecystitis or cholangitis are Gram-negative  
42 bacilli and anaerobic bacteria from the intestinal microbiota (Table 1). Infections are often caused  
43 by more than one pathogen and may include fungal pathogens, especially in patients that have  
44 recently received antibiotic treatment. Certain parasites need to be considered in the differential  
45 diagnosis of abdominal pain in endemic settings.

46 *Table 1 Pathogens most frequently associated with acute cholecystitis and cholangitis (in*  
47 *descending order of frequency)*

Bacteria	Fungi	Parasites
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<p>Enterobacterales (mostly <i>Escherichia coli</i>) and other Gram-negative bacteria such as <i>Pseudomonas aeruginosa</i> and <i>Acinetobacter baumannii</i> (including multidrug-resistant strains such as those producing ESBL and carbapenemases)</p> <p><i>Streptococcus</i> spp. (e.g. of the <i>Streptococcus anginosus</i> group - old name: <i>Streptococcus milleri</i>)</p> <p><i>Enterococcus</i> spp.</p> <p>Anaerobes (mostly <i>Bacteroides</i> spp.)</p>	<p>Mostly <i>Candida albicans</i></p>	<p><i>Ascaris lumbricoides</i> <i>Fasciola hepatica</i></p>
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48 ESBL: extended-spectrum beta-lactamases.

## 49 Clinical presentation

50 Acute cholecystitis should be considered as a possible diagnosis in all cases of acute abdominal  
51 pain, especially if the pain is predominantly located in the right upper quadrant.

52 Acute cholangitis should be considered a possible diagnosis in all cases presenting with  
53 abdominal pain, fever and jaundice (i.e. yellow color of the skin and sclera due to increased levels  
54 of bilirubin).

55 Fever (> 38.0 °C), chills, nausea and vomiting may be present, mostly in complicated infections.  
56 Severe pain, diffuse rebound tenderness on sudden release of pressure on the abdomen and  
57 abdominal muscular defence are usually present in case of peritonitis. Hypotension and signs of  
58 organ hypoperfusion (e.g. reduced urine output) may be present in cases of organ failure and are  
59 a medical and /or surgical emergency. Please also refer to the chapter on sepsis if suspected.

## 60 Laboratory tests

### 61 1. Patient microbiology tests

62 In mild cases, routine microbiology tests are not usually needed and basing antibiotic treatment  
63 on pathogens cultured from the abdominal cavity at the time of operation is not  
64 recommended. Blood cultures and other microbiology tests could be considered in severely ill  
65 patients in order to adjust empiric antibiotic treatment once the results of susceptibility tests  
66 are available (see Table 2).

67 *Table 2 Microbiology tests to consider in severe cases of acute cholecystitis or cholangitis as*  
68 *indicated in the WHO EDL (54)*

Diagnostic test	Purpose of the test	Setting where the test should be available
Blood cultures	To detect bacterial bloodstream infections (sepsis)	Health care facilities with clinical laboratories

Microscopy and culture of fluid material or bile when these can be drained	Initial step to detect and identify bacterial and fungal species for selection of appropriate antibiotic regimens	Health care facilities with clinical laboratories
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## 69 II. Other tests

70 Laboratory tests can be used to complement the clinical examination and medical history. Based  
71 on availability, Table 3 indicates tests that could be considered in the patient's initial assessment  
72 and to help guide the duration of antibiotic treatment.

73 *Table 3 Laboratory tests (other than microbiology) that may help assess the severity of disease*  
74 *and identify a bacterial infection as indicated in the WHO EML (54)*

Diagnostic test	Purpose of the test	Setting where the test should be available
White blood cell count	To help in the diagnosis of infections	Health care facilities with clinical laboratories
Aspartate aminotransferase	To assess liver function	Health care facilities with clinical laboratories
Bilirubin	To detect or monitor liver disease, bile duct disorders and red cell destruction	Health care facilities with clinical laboratories
Alkaline phosphatase	To aid in diagnosis of hepatobiliary diseases	Health care facilities with clinical laboratories
C-reactive protein	To detect inflammation as an indicator of various conditions, e.g. sepsis	Health care facilities with clinical laboratories
Procalcitonin	To guide antibiotic therapy or discontinuation in sepsis	Only in tertiary care facilities

## 75 III. Using microbiology surveillance data

76 Routine surveillance of pathogens cultured from the abdominal cavity is not recommended.

77 Empiric guidance given by the Handbook could be reviewed and adapted based on local clinically  
78 relevant microbiology surveillance data. For example, clinically relevant isolates for this infection  
79 would be blood culture data from patients on surgical wards with intra-abdominal infections.

## 80 Imaging

81 Imaging is helpful to confirm cholecystitis and cholangitis. An abdominal ultrasound should  
82 always be considered when these conditions are suspected. Where available, a computed  
83 tomography (CT) scan of the abdomen may also be considered, especially if complications are  
84 suspected or the diagnosis is uncertain.

## 85 Treatment of acute cholecystitis

86 Patients with suspected or confirmed acute cholecystitis should be promptly referred for surgical  
 87 consultation. Eliminating the source of infection and the ongoing contamination of the peritoneal  
 88 cavity (e.g. in case of perforation) is the most important surgical intervention. Cholecystectomy  
 89 (i.e. removal of the gallbladder) is the only definitive treatment and an antibiotic should be given  
 90 until the gallbladder is removed(275). After surgery, in uncomplicated cases, antibiotic treatment  
 91 can be stopped provided the source of infection was adequately controlled and there is good  
 92 clinical recovery. In severe cases (i.e. critically ill patients), 5 days of antibiotic treatment are  
 93 usually adequate, provided there is good clinical recovery and the source of infection was  
 94 adequately controlled and eliminated with surgery(276).

## 95 Treatment of acute cholangitis

96 Biliary drainage is the main surgical intervention for acute cholangitis and antibiotic treatment  
 97 should be given in all cases irrespective of severity. Antibiotic treatment should be given until  
 98 drainage procedures are done and continued for a total of 5 days once control of the source of  
 99 infection has been achieved(276). Shorter courses of antibiotics (e.g. 3 days) have been evaluated  
 100 in observational studies (and in a systematic review) and were not associated with a higher  
 101 occurrence of complications; however, this practice remains controversial because the evidence  
 102 is not strong(277, 278).

## 103 Antibiotic treatment

104 Empiric antibiotic treatment should be chosen based on the severity of symptoms (mild or  
 105 severe), considering local prevalence of resistance, particularly isolates producing extended-  
 106 spectrum beta-lactamases since the prevalence can vary greatly in different settings(279) (Table  
 107 4). Individual risk factors for resistant pathogens (e.g. recent antibiotic treatment, colonization  
 108 with resistant pathogens) should also be considered.

109 **Simplify** empiric treatment to a more narrow-spectrum antibiotic based on culture results or  
 110 based on rapid clinical improvement when no microbiology test results are available.

111 **Step-down** to oral treatment is based on improvement of symptoms and signs of infection and  
 112 the ability to take oral antibiotics allowing discharge of the patient home when clinically  
 113 appropriate.

114 If signs and symptoms persist, abdominal imaging is suggested, or an alternative extra-abdominal  
 115 source of infection should be considered.

116 *Table 4 Empiric antibiotic treatment for acute cholecystitis or cholangitis*

117 **Mild cases** are defined as patients who are not critically ill with no signs of sepsis or septic shock.

118 **Severe cases** are defined as patients who are critically ill with signs of sepsis or septic shock

Severity	Adults	Children	Total treatment duration
Mild cases	<p><b>First choice</b>  <b>Amoxicillin+clavulanic acid</b> (oral): 875 + 125 mg given every 8 hours</p> <p><b>OR</b>  <b>Ceftriaxone</b> (IV): 2 g given once a day  <b>AND Metronidazole</b> (IV/oral): 500 mg given every 8 hours</p> <p><b>OR</b>  <b>Cefotaxime</b> (IV): 2 g given every 8 hours  <b>AND Metronidazole</b> (IV/oral): 500 mg given every 8 hours</p> <p><b>Second choice</b>  <b>Ciprofloxacin</b> (oral): 500 mg given every 12 hours <b>AND</b> <b>Metronidazole</b> (IV/oral): 500 mg given every 8 hours</p> <p><i>(Ciprofloxacin has excellent oral bioavailability and the IV route should be reserved for patients with impaired gastrointestinal function)</i></p>	<p><b>First choice</b>  <b>Amoxicillin+clavulanic acid</b> (IV/oral): 40-50 mg/kg/dose of amoxicillin component given every 12 hours  OR 30 mg/kg/dose given every 8 hours</p> <p>Oral weight bands<sup>b</sup>:  3-&lt;6 kg: 250 mg of amoxicillin/dose given every 12 hours  6-&lt;10 kg: 375 mg of amoxicillin/dose given every 12 hours  10-&lt;15 kg: 500 mg of amoxicillin/dose given every 12 hours  15-&lt;20 kg: 750 mg of amoxicillin/dose given every 12 hours  20-&lt;30 kg: 1000 mg of amoxicillin/dose given every 12 hours  ≥ 30 Kg: Use adult dose</p> <p><b>OR</b>  <b>Ceftriaxone</b> (IV): 80 mg/kg/ dose given once a day <b>AND</b> <b>Metronidazole</b>(IV/oral):</p> <ul style="list-style-type: none"> <li>• Neonates: 7.5 mg/kg/dose given every 12 hours (for IV starting with a loading dose of 15 mg/kg)</li> <li>• Children: 7.5 mg/kg/dose given every 8 hours</li> </ul> <p>Oral weight bands:  3-&lt;6 kg: 30 mg given every 8 hours  6-&lt;10 kg: 50 mg given every 8 hours  10-&lt;15 kg: 100 mg given every 8 hours  15-&lt;20 kg: 150 mg given every 8 hours  20-&lt;30 kg: 200 mg given every 8 hours  ≥ 30 Kg: Use adult dose</p> <p><b>OR</b>  <b>Cefotaxime</b> (IV): 50mg/kg/dose given every 8 hours <b>AND</b> <b>Metronidazole</b> (IV/oral):</p> <ul style="list-style-type: none"> <li>• Neonates: 7.5 mg/kg/dose given every 12 hours (for IV starting with a loading dose of 15 mg/kg)</li> </ul>	<p>Uncomplicated cases treated with cholecystectomy: stop after surgery if adequate control of the source of infection has been achieved and symptoms have resolved.</p>

		<ul style="list-style-type: none"> <li>• Children: 7.5 mg/kg/dose given every 8 hours</li> </ul> <p>Oral weight bands:          3-&lt;6 kg: 30 mg given every 8 hours          6-&lt;10 kg: 50 mg given every 8 hours          10-&lt;15 kg: 100 mg given every 8 hours          15-&lt;20 kg: 150 mg given every 8 hours          20-&lt;30 kg: 200 mg given every 8 hours          ≥ 30 Kg: Use adult dose</p> <p><b>OR</b>  <b>Ampicillin</b> (IV):</p> <ul style="list-style-type: none"> <li>• First week of life: 50 mg/kg/dose given every 12 hours</li> <li>• Beyond first week of life: 50 mg/kg/dose given every 8 hours</li> </ul> <p><b>AND</b>  <b>Gentamicin</b> (IV):</p> <ul style="list-style-type: none"> <li>• Neonates: 5 mg/kg given once daily</li> <li>• Children: 7.5 mg/kg given once daily</li> </ul> <p><b>AND</b>  <b>Metronidazole</b></p> <p>Oral/IV:</p> <ul style="list-style-type: none"> <li>• Neonates: 7.5 mg/kg/dose given every 12 hours (for IV starting with a loading dose of 15 mg/kg)</li> <li>• Children: 7.5 mg/kg/dose given every 8 hours</li> </ul> <p>Oral weight bands:          3-&lt;6 kg: 30 mg given every 8 hours          6-&lt;10 kg: 50 mg given every 8 hours          10-&lt;15 kg: 100 mg given every 8 hours          15-&lt;20 kg: 150 mg given every 8 hours          20-&lt;30 kg: 200 mg given every 8 hours          ≥ 30 Kg: Use adult dose</p> <p><b>Second choice</b>  <b>Ciprofloxacin</b> (IV/oral): 10-20 mg/kg/dose, given every 12 hours</p> <p>Oral weight bands:          3-&lt;6 kg: 50 mg given every 12 hours</p>	
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		<p>6-&lt;10 kg: 100 mg given every 12 hours          10-&lt;15 kg: 150 mg given every 12 hours          15-&lt;20 kg 200 mg given every 12 hours          20-&lt;30 kg: 300 mg given every 12 hours          ≥ 30 Kg: Use adult dose</p> <p><i>(Ciprofloxacin has excellent oral bioavailability and the IV route should be reserved for patients with impaired gastrointestinal function)</i></p> <p><b>AND Metronidazole (IV/oral):</b></p> <ul style="list-style-type: none"> <li>• Neonates: 7.5 mg/kg/dose given every 12 hours (for IV starting with a loading dose of 15 mg/kg)</li> <li>• Children: 7.5 mg/kg/dose given every 8 hours</li> </ul> <p>Oral weight bands:          3-&lt;6 kg: 30 mg given every 8 hours          6-&lt;10 kg: 50 mg given every 8 hours          10-&lt;15 kg: 100 mg given every 8 hours          15-&lt;20 kg: 150 mg given every 8 hours          20-&lt;30 kg: 200 mg given every 8 hours          ≥ 30 Kg: Use adult dose</p>	
<p>Severe cases</p>	<p><b>First choice</b>  <b>Piperacillin+tazobactam (IV):</b>          4 g + 500 mg given every 6 hours</p> <p><b>OR</b>  <b>Ceftriaxone (IV):</b> 2 g given once a day <b>AND Metronidazole (IV/oral):</b> 500 mg given every 8 hours</p> <p><b>OR</b>  <b>Cefotaxime (IV):</b> 2 g given every 8 hours <b>AND Metronidazole (IV/oral):</b> 500 mg given every 8 hours</p> <p><b>Second choice</b></p>	<p><b>First choice</b>  <b>Ampicillin (IV):</b></p> <ul style="list-style-type: none"> <li>• First week of life: 50 mg/kg/dose given every 12 hours</li> <li>• Beyond first week of life: 50 mg/kg/dose given every 8 hours</li> </ul> <p><b>AND</b>  <b>Gentamicin (IV):</b></p> <ul style="list-style-type: none"> <li>• Neonates: 5 mg/kg given once daily</li> <li>• Children: 7.5 mg/kg given once daily</li> </ul> <p><b>AND</b>  <b>Metronidazole</b>          Oral/IV:  <ul style="list-style-type: none"> <li>• Neonates: 7.5 mg/kg/dose given every 12 hours (for IV starting with a loading dose of 15 mg/kg)</li> </ul> </p>	<p><b>Acute cholecystitis:</b> 5 days in total if adequate control of the source of infection has been achieved with surgery and symptoms have resolved.</p> <p><b>Acute cholangitis:</b> continue antibiotic treatment for a total of 5 days once control of the source of infection has been achieved with biliary drainage and symptoms have resolved.</p>

	<p><b>Meropenem</b><sup>a</sup> (IV): 2 g given every 8 hours</p>	<ul style="list-style-type: none"> <li>• Children: 7.5 mg/kg/dose given every 8 hours</li> </ul> <p>Oral weight bands:</p> <p>3-&lt;6 kg: 30 mg given every 8 hours          6-&lt;10 kg: 50 mg given every 8 hours          10-&lt;15 kg: 100 mg given every 8 hours          15-&lt;20 kg: 150 mg given every 8 hours          20-&lt;30 kg: 200 mg given every 8 hours          ≥ 30 Kg: Use adult dose</p> <p><b>OR</b></p> <p><b>Piperacillin+tazobactam</b> (IV): 100 mg/kg/dose of piperacillin component given every 8 hours</p> <p><b>Second choice</b></p> <p><b>Meropenem</b><sup>b</sup>(IV): 20 mg/kg/dose given every 8 hours</p>	
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119 Notes: All dosages are for normal renal and hepatic function.  
 120 <sup>a</sup>Meropenem should not be considered for routine use for all severe cases but only in complicated cases (i.e. abscess  
 121 and/or peritonitis) in settings with a high prevalence of extended-spectrum beta-lactamase (ESBL)-producing  
 122 *Enterobacterales* or in patients with known prior colonization, treated with multiple antibiotic courses or at risk of  
 123 infections with pathogens resistant to the first-choice option. Empiric use of a “Reserve” antibiotic could be  
 124 considered exceptionally in very selected cases of seriously ill patients failing to respond to carbapenems or that  
 125 have previously been treated for infections caused by carbapenem-resistant pathogens or that are known to be  
 126 colonized with multidrug-resistant Gram-negative bacteria known to be susceptible to the selected “Reserve”  
 127 antibiotic. Please refer to the corresponding chapter for the definition and list of “Reserve” antibiotics included in  
 128 the EML/c.

129 <sup>b</sup>Oral liquid must be refrigerated after reconstitution as clavulanic acid is rapidly metabolized in high ambient  
 130 temperatures.

131 **ACCESS** antibiotics are indicated in green, **WATCH** antibiotics n yellow and **RESERVE** antibiotics in red.

# 1 Intra-abdominal infections -

## 2 Liver abscess - pyogenic

### 3 Key messages

1. In clinically stable patients, targeted antibiotic treatment based on the results of microbiology tests (cultures of abscess material, blood cultures) is always preferable
2. Early source control (i.e. drainage of the abscess) is usually required when feasible in addition to antibiotic treatment, especially for large abscesses (>5 cm in diameter)
3. The intravenous route is preferred for initial treatment
4. Consider the possibility of an amoebic abscess and hydatid disease in the differential diagnosis because these diagnoses require different management

### 4 Definition

5 A pyogenic liver abscess is defined as a collection of pus within the liver.

### 6 Pathogenesis

7 A pyogenic liver abscess develops when a biliary infection spreads directly to the liver or when a  
8 complicated intra-abdominal infection spreads to the liver via the portal circulation. In cases of  
9 systemic infection, the infection may also spread to the liver via the bloodstream.

### 10 Epidemiology

11 Pyogenic liver abscess is the most common type of visceral abscess(280). It is frequently  
12 associated with male sex and diabetes. Pyogenic liver abscess is more common in South-East  
13 Asia(281) probably due to the different epidemiology of certain causative pathogens (e.g.  
14 *Klebsiella pneumoniae*). Underlying hepatobiliary or pancreatic diseases (e.g. malignancy,  
15 cirrhosis, recent abdominal or biliary surgery) are common risk factors. Abscess rupture is a rare  
16 but severe complication associated with a high mortality if not treated immediately.

### 17 Microbiology epidemiology

18 Most cases of liver abscess are caused by enteric Gram-negative bacteria and anaerobes and  
19 most cases involve more than one pathogen (Table 1)(282). A hypervirulent strain of *Klebsiella*  
20 *pneumoniae* is an increasingly common cause of liver abscess in Asia(283, 284). *Burkholderia*

21 *pseudomallei* (a Gram-negative bacterium found in soil and water and transmitted by inhalation  
 22 or ingestion or inoculation) is also a cause of liver abscess in endemic countries (mostly in South-  
 23 East Asia and in Australia).

24 Parasites, notably *Entamoeba histolytica* (acquired by ingestion of contaminated food or water),  
 25 are another frequent cause of liver abscess in endemic settings (Indian subcontinent, Africa, and  
 26 Central and South America)(285, 286).

27 *Table 1 Pathogens most frequently associated with liver abscess (in descending order of*  
 28 *frequency)*

Bacteria	Fungi	Parasites
Enterobacterales (mostly <i>Escherichia coli</i> , <i>Klebsiella pneumoniae</i> <sup>a</sup> , <i>Enterobacter</i> spp.) including multidrug-resistant strains such as those producing ESBL and carbapenemases  <i>Staphylococcus</i> spp.  <i>Streptococcus</i> spp. (e.g. of the <i>Streptococcus</i> <i>anginosus</i> group - old name: <i>Streptococcus</i> <i>milleri</i> )  <i>Enterococcus</i> spp.  Anaerobes (mostly <i>Bacteroides</i> spp.)  In endemic settings consider: <i>Burkholderia pseudomallei</i> <sup>b</sup>	<i>Candida</i> spp. <sup>c</sup>	<i>Entamoeba histolytica</i> <sup>d</sup>

29 ESBL: extended-spectrum beta-lactamases.

30 <sup>a</sup>In Asia, *Klebsiella pneumoniae* is currently the main cause of liver abscess.

31 <sup>b</sup>*Burkholderia pseudomallei* is an important cause of liver abscess in South-East Asia and northern Australia.

32 <sup>c</sup>Often in combination with bacteria.

33 <sup>d</sup>This pathogen is not a cause of pyogenic abscess but needs to be considered in the differential diagnosis, especially  
 34 in patients who live or have travelled to settings where *Entamoeba histolytica* is endemic.

## 35 Clinical presentation

36 Pyogenic liver abscess should be considered as in all cases of fever (> 38.0 °C) and abdominal pain  
 37 (mostly localized in the right upper abdominal quadrant). Vomiting, nausea, anorexia, malaise  
 38 and jaundice are other common symptoms.

## 39 Laboratory tests

### 40 I. Patient microbiology tests

41 Whenever possible, a microbiology sample should be obtained (see Table 2) to guide antibiotic  
 42 treatment. Ideally, the sample should be obtained before antibiotic treatment is started. The

43 reason for doing microbiology tests is to determine the type of pathogen causing infection and  
44 its resistance profile in order to provide adequate treatment(287).

45 *Table 2 Microbiology tests to consider when a liver abscess is suspected (including testing for*  
46 *Entamoeba histolytica) as indicated in the WHO EDL (54)*

Diagnostic test	Purpose of test	Setting where the test should be available
Blood cultures	To detect bacterial bloodstream infections (sepsis)	Health care facilities with clinical laboratories
Microscopy and culture of abscess or pus aspirate	Initial step to detect and identify bacterial and fungal species for selection of appropriate antibiotic regimens	Health care facilities with clinical laboratories
Microscopy of stool sample for <i>Entamoeba histolytica</i>	To diagnose <i>Entamoeba histolytica</i> <sup>a</sup>	Health care facilities with clinical laboratories
Antigen or nucleic acid amplification test (i.e. polymerase chain reaction <sup>b</sup> ) of abscess aspirate material for <i>Entamoeba histolytica</i>	To diagnose <i>Entamoeba histolytica</i> <sup>a</sup>	— <sup>d</sup>
Serology for <i>Entamoeba histolytica</i> <sup>c</sup>	To diagnose <i>Entamoeba histolytica</i> <sup>a</sup>	— <sup>d</sup>

47 <sup>a</sup>*Entamoeba histolytica* is not a cause of pyogenic abscess but a cause of liver abscess that needs to be considered  
48 in the differential diagnosis in endemic settings. However, patients with amoebic liver abscess usually have no bowel  
49 symptoms; therefore, stool testing (microscopy or antigen) has a low sensitivity and is of limited usefulness for  
50 diagnosis.

51 <sup>b</sup>Antigen or nucleic acid amplification testing of abscess aspirate material for *Entamoeba histolytica* could be  
52 considered where available. Diagnosis is often difficult in low- and middle-income countries due to limited laboratory  
53 resources and the fact that most patients present after a failed course of antibiotic treatment for pyogenic abscess  
54 (therefore the yield of any microbiology tests is lower) (7,9).

55 <sup>c</sup>Serology is a useful test in the diagnosis of invasive amoebiasis and is positive in more than 90% of patients with  
56 the disease. A positive serology combined with a compatible clinical presentation suggests active disease. However,  
57 in endemic settings, a positive result is more difficult to interpret since serology can remain positive for months and  
58 even years after resolution of the infection. Therefore, past and current infections become difficult to distinguish.  
59 With negative results, if the clinical suspicion of invasive amoebiasis is still strong, serology could be repeated after  
60 1 week.

61 <sup>d</sup>This test is not in the WHO EDL (54).

## 62 II. Other tests

63 Laboratory tests can be used to complement the clinical examination and medical history even  
64 though they are not specific for the diagnosis. Table 3 indicates tests that could be considered in  
65 the patient's initial assessment. Please also refer to the chapter on sepsis if suspected.

66 *Table 3 Laboratory tests (other than microbiology) to consider if pyogenic liver abscess is*  
67 *suspected as indicated in the WHO EDL (54)*

Diagnostic test	Purpose of the test	Setting where the test should be available
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White blood count	To help in the diagnosis of infections	Health care facilities with clinical laboratories
Aspartate aminotransferase	To assess liver function	Health care facilities with clinical laboratories
Alanine aminotransferase	To assess liver function	Health care facilities with clinical laboratories
Bilirubin	To detect or monitor liver disease	Community settings and health facilities without laboratories <sup>a</sup>
Direct and indirect bilirubin	To detect or monitor liver disease, bile duct disorders and haemolytic anaemia, and to differentiate between these causes of jaundice	Health care facilities with clinical laboratories
Alkaline phosphatase	To aid in the diagnosis of hepatobiliary diseases	Health care facilities with clinical laboratories

68 <sup>a</sup>Community and health settings without laboratories are settings such as health posts and centres, doctors'  
69 offices, outreach clinics and ambulatory care. These tests are also assumed to be available at health care facilities  
70 with laboratories.

### 71 III. Using microbiology surveillance data

72 There is no role for routine surveillance to inform empiric guidance.

## 73 Imaging

74 Imaging is very helpful in the diagnosis of pyogenic liver abscess. An abdominal ultrasound should  
75 always be considered when this condition is suspected. In settings where it is available, a  
76 computed tomography (CT) scan of the abdomen may also be considered, especially if  
77 complications are suspected or the diagnosis is uncertain.

## 78 Treatment

79 Early control of the source of infection through drainage of the abscess is usually required when  
80 feasible in addition to antibiotic treatment, especially for large (> 5 cm) abscesses. Drainage is  
81 recommended because larger abscesses have a higher risk of rupture.

82 Drainage techniques include:

- 83 • Percutaneous drainage (image-guided procedure that is usually performed by an  
84 interventionist radiologist where available): a drain – usually a pigtail catheter – is  
85 inserted through the skin into the abscess and left in place until the collection is drained.
- 86 • Surgical drainage: this is done either as a conventional open procedure (i.e. laparotomy)  
87 or by laparoscopy.

88 In both cases, the drainage procedure is also important for diagnostic purposes to identify the  
89 type of pathogen causing the abscess and its resistance profile. Abscess material should therefore  
90 be obtained for culture when the drain is posed or the abscess is surgically removed.

## 91 Antibiotic treatment

92 In patients who are clinically stable, targeted treatment based on the results of microbiology  
 93 tests is always preferred. In particular, infections caused by Enterobacterales producing  
 94 extended-spectrum beta-lactamases (ESBL) or carbapenemases need to be considered in  
 95 patients with history of hospitalisation or previously colonised or infected with these resistant  
 96 pathogens as their prevalence varies greatly in different settings.

97 In more severe cases, empiric treatment is given, taking into account the most probable type of  
 98 causative pathogen (including the possibility of *Entamoeba histolytica* infection) and local  
 99 prevalence of resistance (especially for ESBL- and carbapenemase-producing isolates). Individual  
 100 risk factors for resistant pathogens (e.g. recent antibiotic treatment, colonization or previous  
 101 infections with resistant isolates) should also be considered.

102 The total duration of treatment is usually long (weeks) and depends on whether control of the  
 103 source of infection is achieved and on the causative pathogen. Therefore, early control of the  
 104 source of infection and identification of the causative pathogen are encouraged. In most cases,  
 105 at least 4 weeks of antibiotic treatment are needed with follow-up imaging to monitor response  
 106 and define treatment duration.

107 Longer duration of treatment is required in cases of liver abscess caused by *Burkholderia*  
 108 *pseudomallei* (usually 2 weeks of IV treatment followed by > 3 months of oral treatment with  
 109 sulfamethoxazole+trimethoprim to eradicate the infection and prevent relapse or recurrence).  
 110 In cases of amoebic liver abscess, a 10-day course of treatment (with oral metronidazole) is  
 111 usually adequate.

112 **Simplify** empiric treatment to a more narrow-spectrum antibiotic based on culture results or  
 113 based on rapid clinical improvement when no microbiology test results are available. In general,  
 114 the intravenous (IV) route is preferred for the initial phase of treatment.

115 **Step-down** to oral treatment is based on improvement of symptoms and signs of infection and  
 116 the ability to take oral antibiotics allowing discharge of the patient home when clinically  
 117 appropriate.

118 Oral step-down therapy can be considered quickly for mild cases after adequate drainage and  
 119 confirmed microbiology and susceptibility.

120 If signs and symptoms persist, abdominal imaging is suggested, or an alternative extra-abdominal  
 121 source of infection should be considered.

122 *Table 4 Empiric antibiotic treatment for pyogenic or amoebic liver abscess*

123 **In clinically stable patients, targeted treatment based on the results of microbiology tests is**  
 124 **preferred.**

125 **Mild cases** are defined as patients who are not critically ill with no signs of sepsis or septic shock  
 126 **Severe cases** are defined as patients who are critically ill with signs of sepsis or septic shock

Severity	Adults	Children	Total treatment duration
Mild cases	<p><b>First choice</b></p> <p><b>Amoxicillin+clavulanic acid:</b> (IV): 1g + 200 mg given every 8 hours Oral: 875 + 125 mg given every 8 hours</p> <p><b>OR</b></p> <p><b>Ceftriaxone</b> (IV): 2 g given once a day <b>AND</b> <b>Metronidazole</b> (IV/oral): 500 mg given every 8 hours</p> <p><b>OR</b></p> <p><b>Cefotaxime</b> (IV): 2 g given every 8 hours <b>AND</b> <b>Metronidazole</b> (IV/oral): 500 mg given every 8 hours</p> <p><b>Second choice</b></p> <p><b>Ciprofloxacin</b> (oral): 500 mg given every 12 hours <i>(Ciprofloxacin has excellent oral bioavailability and the IV route should be reserved for patients with impaired gastrointestinal function)</i></p> <p><b>AND</b> <b>Metronidazole</b>: 500 mg (IV/oral) given every 8 hours</p>	<p><b>First choice</b></p> <p><b>Amoxicillin+clavulanic acid</b> (IV/oral)<sup>b</sup>: 40-50 mg/kg per dose of amoxicillin component, every 12 hours OR 30 mg/kg/dose given every 8 hours</p> <p>Oral weight bands: 3-&lt;6 kg: 250 mg of amoxicillin/dose given every 12 hours 6-&lt;10 kg: 375 mg of amoxicillin/dose given every 12 hours 10-&lt;15 kg: 500 mg of amoxicillin/dose given every 12 hours 15-&lt;20 kg: 750 mg of amoxicillin/dose given every 12 hours 20-&lt;30 kg: 1000 mg of amoxicillin/dose given every 12 hours ≥ 30 Kg: Use adult dose</p> <p><b>OR</b></p> <p><b>Ceftriaxone</b> (IV): 80 mg/kg/dose given once a day <b>AND</b> <b>Metronidazole</b> (IV/oral):</p> <ul style="list-style-type: none"> <li>• Neonates: 7.5 mg/kg/dose given every 12 hours (for IV starting with a loading dose of 15 mg/kg)</li> <li>• Children: 7.5 mg/kg/dose given every 8 hours</li> </ul> <p>Oral weight bands: 3-&lt;6 kg: 30 mg given every 8 hours 6-&lt;10 kg: 50 mg given every 8 hours 10-&lt;15 kg: 100 mg given every 8 hours 15-&lt;20 kg: 150 mg given every 8 hours 20-&lt;30 kg: 200 mg given every 8 hours ≥ 30 Kg: Use adult dose</p> <p><b>OR</b></p> <p><b>Cefotaxime</b> (IV): 50mg/kg/dose given every 8 hours <b>AND</b> <b>Metronidazole</b> (IV/oral):</p> <ul style="list-style-type: none"> <li>• Neonates: 7.5 mg/kg/dose given every 12 hours (for IV starting with a loading dose of 15 mg/kg)</li> </ul>	<p>At least 4 weeks if adequate control of the source of infection is achieved (follow-up imaging is usually performed to guide treatment duration).</p>

		<ul style="list-style-type: none"> <li>• Children: 7.5 mg/kg/dose given every 8 hours</li> </ul> <p>Oral weight bands:  3-&lt;6 kg: 30 mg given every 8 hours  6-&lt;10 kg: 50 mg given every 8 hours  10-&lt;15 kg: 100 mg given every 8 hours  15-&lt;20 kg: 150 mg given every 8 hours  20-&lt;30 kg: 200 mg given every 8 hours  ≥ 30 Kg: Use adult dose</p> <p><b>OR</b></p> <p><b>Ampicillin</b> (IV):</p> <ul style="list-style-type: none"> <li>• First week of life: 50 mg/kg/dose given every 12 hours</li> <li>• Beyond first week of life: 50 mg/kg/dose given every 8 hours</li> </ul> <p><b>AND</b></p> <p><b>Gentamicin</b> (IV):</p> <ul style="list-style-type: none"> <li>• Neonates: 5 mg/kg given once daily</li> <li>• Children: 7.5 mg/kg given once daily</li> </ul> <p><b>AND</b></p> <p><b>Metronidazole</b></p> <p>Oral/IV:</p> <ul style="list-style-type: none"> <li>• Neonates: 7.5 mg/kg/dose given every 12 hours (for IV starting with a loading dose of 15 mg/kg)</li> <li>• Children: 7.5 mg/kg/dose given every 8 hours</li> </ul> <p>Oral weight bands:  3-&lt;6 kg: 30 mg given every 8 hours  6-&lt;10 kg: 50 mg given every 8 hours  10-&lt;15 kg: 100 mg given every 8 hours  15-&lt;20 kg: 150 mg given every 8 hours  20-&lt;30 kg: 200 mg given every 8 hours  ≥ 30 Kg: Use adult dose</p> <p><b>Second choice</b></p> <p><b>Ciprofloxacin</b> (oral): 10-20 mg/kg/dose, given every 12 hours</p> <p>Oral weight bands:  3-&lt;6 kg: 50 mg given every 12 hours  6-&lt;10 kg: 100 mg given every 12 hours  10-&lt;15 kg: 150 mg given every 12 hours  15-&lt;20 kg: 200 mg given every 12 hours  20-&lt;30 kg: 300 mg given every 12 hours</p>	
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		<p>≥ 30 Kg: Use adult dose (<i>Ciprofloxacin has excellent oral bioavailability and the IV route should be reserved for patients with impaired gastrointestinal function</i>)</p> <p><b>AND Metronidazole</b> (IV/oral):</p> <ul style="list-style-type: none"> <li>• Neonates: 7.5 mg/kg per dose given every 12 hours (for IV starting with a loading dose of 15 mg/kg)</li> <li>• Children: 7.5 mg/kg per dose given every 8 hours</li> </ul> <p>Oral weight bands:          3-&lt;6 kg: 30 mg given every 8 hours          6-&lt;10 kg: 50 mg given every 8 hours          10-&lt;15 kg: 100 mg given every 8 hours          15-&lt;20 kg: 150 mg given every 8 hours          20-&lt;30 kg: 200 mg given every 8 hours          ≥ 30 Kg: Use adult dose</p>	
<p>Severe cases</p>	<p><b>First choice</b></p> <p><b>Piperacillin+tazobactam</b> (IV): 4 g + 500 mg given every 6 hours</p> <p><b>OR</b></p> <p><b>Ceftriaxone</b> (IV): 2 g given once a day <b>AND</b> <b>Metronidazole</b> (IV/oral): 500 mg given every 8 hours</p> <p><b>OR</b></p> <p><b>Cefotaxime</b> (IV): 2 g given every 8 hours <b>AND</b> <b>Metronidazole</b> (IV/oral): 500 mg given every 8 hours</p> <p><b>Second choice</b></p> <p><b>Meropenem<sup>a</sup></b> (IV): 2 g given every 8 hours</p>	<p><b>First choice</b></p> <p><b>Piperacillin+tazobactam</b> (IV): 100 mg/kg/dose of piperacillin component given every 8 hours</p> <p><b>OR</b></p> <p><b>Ampicillin</b> (IV):</p> <ul style="list-style-type: none"> <li>• First week of life: 50 mg/kg/dose given every 12 hours</li> <li>• Beyond first week of life: 50 mg/kg/dose given every 8 hours</li> </ul> <p><b>AND</b></p> <p><b>Gentamicin</b> (IV):</p> <ul style="list-style-type: none"> <li>• Neonates: 5 mg/kg given once daily</li> <li>• Children: 7.5 mg/kg given once daily</li> </ul> <p><b>AND</b></p> <p><b>Metronidazole</b></p> <p>Oral/IV:</p> <ul style="list-style-type: none"> <li>• Neonates: 7.5 mg/kg/dose given every 12 hours (for IV starting with a loading dose of 15 mg/kg)</li> <li>• Children: 7.5 mg/kg/dose given every 8 hours</li> </ul> <p>Oral weight bands:          3-&lt;6 kg: 30 mg given every 8 hours          6-&lt;10 kg: 50 mg given every 8 hours          10-&lt;15 kg: 100 mg given every 8 hours          15-&lt;20 kg: 150 mg given every 8 hours</p>	<p>At least 4 weeks if adequate control of the source of infection is achieved (follow-up imaging is usually performed to guide treatment duration).</p>

		20-<30 kg: 200 mg given every 8 hours ≥ 30 kg: Use adult dose  <b>Second choice</b> <b>Meropenem<sup>a</sup></b> (IV): 20 mg/kg/dose given every 8 hours	
Amoebic liver abscess	<b>Metronidazole</b> (oral <sup>c</sup> ): 750 mg given every 8 hours, followed by paromomycin (oral): 25–35 mg/kg divided in 3 doses (to eradicate colonic colonization)	<b>Metronidazole</b> (oral <sup>c</sup> ): 10-15 mg/kg/dose given every 8 hours	10 days of metronidazole Followed by 7 days of paromomycin

- 127 Notes: All dosages are for normal renal and hepatic function.
- 128 The EML/c currently does not have specific recommendations for antibiotic treatment of pyogenic or amoebic liver
- 129 abscess; therefore the options presented in the table are extrapolated from the recommended treatment for
- 130 complicated intra-abdominal infections.
- 131 <sup>a</sup>Meropenem should not be considered for routine use in all severe cases but only in complicated cases in settings
- 132 with a high prevalence of extended-spectrum beta-lactamase (ESBL)-producing Enterobacterales or in patients with
- 133 known prior colonization, treated with multiple antibiotic courses or at risk of infections with pathogens resistant to
- 134 the first choice option. Empiric use of a “Reserve” antibiotic could be considered exceptionally in very selected cases
- 135 of seriously ill patients failing to respond to carbapenems or that have previously been treated for infections caused
- 136 by carbapenem-resistant pathogens or that are known to be colonized with multidrug-resistant Gram-negative
- 137 bacteria known to be susceptible to the selected “Reserve” antibiotic. Please refer to the corresponding chapter for
- 138 the definition and list of “Reserve” antibiotics included in the EML/c.
- 139 When *Burkholderia pseudomallei* is suspected empiric use of meropenem or imipenem could be considered,
- 140 although the preferred option is ceftazidime.
- 141 <sup>b</sup>Oral liquid must be refrigerated after reconstitution as clavulanic acid is rapidly metabolized in high ambient
- 142 temperatures.
- 143 <sup>c</sup>If the patient is unable to tolerate oral treatment or in severe infections, intravenous metronidazole should be given
- 144 (dose in adults: 500 mg every 8 hours).
- 145 Legend: **ACCESS** antibiotics are indicated in green, **WATCH** antibiotics in yellow and **RESERVE** antibiotics in red.

# Intra-abdominal infections - Acute appendicitis

## Key messages

1. Appendectomy remains the main approach to treatment in children
2. In adults, treatment with antibiotics alone (without surgery) can be considered if follow up is possible (about 1 in 3 patients treated with antibiotics alone will experience a recurrence within 2 years)
3. Antibiotics should be chosen based on the severity of symptoms (mild or severe) with broader-spectrum agents for severe cases
4. Treatment should also be active against anaerobes as these pathogens are often involved in intra-abdominal infections
5. Antibiotics should be stopped once the source of infection has been controlled (e.g. after appendectomy) if there is good clinical recovery

### Box 1 Other relevant WHO documents (please check regularly for updates)

- WHO 2013 pocket book of hospital care for children [https://apps.who.int/iris/handle/10665/81170\(23\)](https://apps.who.int/iris/handle/10665/81170(23))

## Definition

Appendicitis is an acute inflammation of the appendix sometimes followed by ischaemia and perforation. It is usually classified as uncomplicated (or simple) when there is no involvement of the peritoneal cavity and no abscess. When the appendix is perforated with subsequent peritonitis or when an abscess is present, appendicitis is defined as complicated. Most cases of appendicitis are uncomplicated (70%).

## Pathophysiology

The exact mechanism leading to appendicitis is poorly understood. Conditions associated with a higher risk of weakening and disrupting the normal anatomical barrier of the appendix or that can cause its luminal obstruction could be involved. In children, lymphoid hyperplasia can contribute to the risk of developing appendicitis. Rarely, parasitic infections (mostly *Enterobius vermicularis* [pinworm]) can contribute to the development of acute appendicitis(288). Perforation is usually the result of gangrene and a necrotic process and can lead to localized abscess formation or to peritonitis when the leak is not contained by structures surrounding the appendix.

## 20 Epidemiology

21 Acute appendicitis is a common surgical emergency worldwide, especially in children and young  
 22 adults. The yearly incidence of appendicitis has been declining in western European and North  
 23 American countries since the 1990s and has stabilized in the past 20 years to about 100–150  
 24 cases per 100 000 person-years. However, increasing trends are reported in Asia, South America  
 25 and the Middle East with the incidence of appendicitis higher than in many western European  
 26 and North American countries(289). In 2017, there were an estimated 19 million new cases  
 27 worldwide(31). The lifetime risk of appendicitis reported in the literature varies across countries,  
 28 ranging from about 2% in Africa to 16% in South Korea (290). Mortality attributable to  
 29 appendicitis has declined and with prompt diagnosis and management, mortality is now < 1% in  
 30 uncomplicated cases in most settings(291). Complicated cases or cases in the elderly are  
 31 associated with a higher mortality.

## 32 Microbiology epidemiology

33 The most common pathogens involved in appendicitis are Gram-negative bacilli and anaerobes  
 34 from the intestinal microbiota (Table 1). Infections are often caused by more than one pathogen  
 35 and may include fungal pathogens, especially in patients that have recently received antibiotic  
 36 treatment. Certain parasites need to be considered in the differential diagnosis of abdominal pain  
 37 in endemic settings.

38 *Table 1 Pathogens most frequently associated with complicated acute appendicitis (in*  
 39 *descending order of frequency)*

Bacteria	Fungi	Parasites
Enterobacterales (mostly <i>Escherichia coli</i> ) and other Gram-negative bacteria such as <i>Pseudomonas aeruginosa</i> and <i>Acinetobacter baumannii</i> (including multidrug-resistant strains such as those producing ESBL and carbapenemases)  <i>Streptococcus</i> spp. (e.g. of the <i>Streptococcus anginosus</i> group - old name: <i>Streptococcus milleri</i> )  <i>Enterococcus</i> spp.  Anaerobes (mostly <i>Bacteroides</i> spp.)	Mostly <i>Candida albicans</i>	Mostly <i>Enterobius vermicularis</i> [pinworm]) can contribute by causing obstruction of the appendix

40 ESBL: extended spectrum beta-lactamases.

## 41 Clinical presentation

42 Acute appendicitis should be considered as a possible diagnosis in all cases of acute abdominal  
 43 pain, especially if the pain is in the right lower quadrant or is moving from the periumbilical area

44 to the right lower quadrant. Nausea and vomiting are usually present. Fever (> 38.0 °C) and rigors  
 45 can be present.

46 Severe pain, diffuse rebound tenderness on sudden release of pressure on the abdomen and  
 47 abdominal muscular tensing are usually present in cases of peritonitis. Hypotension and signs of  
 48 organ hypoperfusion (e.g. reduced urine output) may be present in cases of organ failure and are  
 49 a medical and /or surgical emergency. Please also refer to the chapter on sepsis if suspected.

50 **Laboratory tests**

51 **I. Patient microbiology tests**

52 Routine microbiology tests are not usually needed and basing antibiotic treatment on pathogens  
 53 cultured from the abdominal cavity at the time of operation is not recommended but certain  
 54 microbiology tests could be considered in severely ill patients to adjust empiric antibiotic  
 55 treatment once the results of antibiotic susceptibility tests are available (see Table 2).  
 56 In more severe cases blood cultures should be taken and samples from the abdominal cavity may  
 57 be useful in certain situations such as severely immunocompromised patients or patients known  
 58 to be colonized with multidrug-resistant organisms or in patients presenting with septic shock.

59 *Table 2 Microbiology tests to consider in severe cases of appendicitis as indicated in the WHO EDL*  
 60 *(54)*

Diagnostic test	Purpose of the test	Setting where the test should be available
Blood cultures	To detect bacterial bloodstream infections (sepsis)	Health care facilities with clinical laboratories
Microscopy and culture of abscess fluid material when this can be drained	Not routinely recommended, but may be used in specific cases to identify bacterial and fungal species for selection of appropriate antibiotic regimens	Health care facilities with clinical laboratories

61 **II. Other tests**

62 Laboratory tests can be used to complement the clinical examination and medical history. Based  
 63 on availability, Tables 3 and 4 indicate tests that could be considered in the patient’s initial  
 64 assessment and to help guide the duration of antibiotic treatment.

65 *Table 3 Laboratory tests (other than microbiology) that may help identify an alternative cause of*  
 66 *abdominal pain that could mimic appendicitis as indicated in the WHO EDL (54)*

Diagnostic test	Purpose of the test	Setting where the test should be available
Pregnancy test	In the context of suspected appendicitis the purpose of the test is to exclude an ectopic pregnancy	Community settings and health facilities without laboratories <sup>a</sup>
Urinalysis test (dipstick)	To exclude a urinary tract infection	Community settings and health facilities without laboratories <sup>a</sup>

67 <sup>a</sup>Community and health settings without laboratories are settings such as health posts and centres, doctors’  
 68 offices, outreach clinics and ambulatory care. These tests are also assumed to be available at health care facilities  
 69 with laboratories.

70 *Table 4 Laboratory tests (other than microbiology) that may help assess the severity of disease*  
 71 *and identify a bacterial infection as indicated in the WHO EDL (54)*

Diagnostic test	Purpose of the test	Setting where the test should be available
White blood cell count	To help in the diagnosis of infections	Health care facilities with clinical laboratories
C-reactive protein	To detect inflammation as an indicator of various conditions, e.g. sepsis	Health care facilities with clinical laboratories
Procalcitonin	To guide antibiotic therapy or discontinuation in sepsis	Only in tertiary care facilities

72 **III. Using microbiology surveillance data**

73 Routine surveillance of pathogens cultured from the abdominal cavity is not recommended.

74 Empiric guidance given by the Handbook could be reviewed and adapted based on local clinically  
 75 relevant microbiology surveillance data. For example, clinically relevant isolates for this infection  
 76 would be blood culture data from patients on surgical wards with intra-abdominal infections.

77 **Imaging**

78 Imaging is helpful to confirm acute appendicitis. An abdominal ultrasound should always be  
 79 considered when this condition is suspected. Where available a computed tomography (CT) scan  
 80 of the abdomen may also be considered, especially if complications are suspected or the  
 81 diagnosis is uncertain.

82 **Treatment**

83 Surgery to eliminate/control the source of infection (e.g. abscess, perforated appendix) and  
 84 reduce contamination of the peritoneal cavity (e.g. in cases of perforation) are the foundation of  
 85 treatment. Patients with suspected or confirmed appendicitis should be promptly referred for  
 86 surgical consultation and antibiotic treatment should be started quickly.

87 **Uncomplicated cases treated with antibiotics alone**

88 Treating appendicitis with antibiotics alone is controversial – and not recommended by WHO for  
 89 children – mostly because of the higher risk of recurrences within a year(292-294). However, this  
 90 approach can be considered in adults in certain cases if close monitoring is possible, given that 1  
 91 in 3 patients treated this way will experience a recurrence within 2 years (295). Patient  
 92 preference should be one element considered when deciding the approach (avoidance of surgery  
 93 versus higher risk of recurrence with antibiotics).

94 When antibiotic treatment alone is offered, the suggested duration of treatment is 7 days  
 95 provided there is a good clinical response with resolution of symptoms. Patients should be re-  
 96 evaluated to assess the need for surgical intervention if they do not improve on antibiotics alone.

97 As stated above, in children with acute appendicitis, WHO discourages this approach in the WHO  
 98 *Pocket book of hospital care for children*: “appendectomy should be done as soon as possible to  
 99 prevent perforation, peritonitis and abscess formation. It is better to operate and be wrong about  
 100 the diagnosis than to delay and have peritonitis occur” (23).

## 101 Antibiotic treatment

102 In general, empiric antibiotic treatment should be chosen based on the severity of symptoms  
 103 (mild or severe), considering local prevalence of resistance, particularly isolates producing  
 104 extended-spectrum beta-lactamases, since prevalence can vary greatly among different settings  
 105 (Table 5). Individual risk factors for resistant pathogens (e.g. recent antibiotic treatment,  
 106 colonization with resistant pathogens) could also be considered.

107 **Simplify** empiric treatment to a more narrow-spectrum antibiotic based on culture results or  
 108 based on rapid clinical improvement when no microbiology test results are available. It should  
 109 be noted that anaerobes are difficult to culture and anaerobic coverage should usually be  
 110 continued even if no anaerobes are detected in microbiologic samples.

111 **Step-down** to oral treatment is based on improvement of symptoms and signs of infection and  
 112 the ability to take oral antibiotics allowing discharge of the patient home when clinically  
 113 appropriate.

114 If signs and symptoms persist, abdominal imaging is suggested, or an alternative extra-abdominal  
 115 source of infection should be considered.

116 *Table 5 Empiric antibiotic treatment for acute appendicitis*

117 **Mild cases** are defined as patients who are not critically ill with no signs of sepsis or septic shock.  
 118 **Severe cases** are defined as patients who are critically ill with signs of sepsis or septic shock.

Severity	Adults	Neonates and Children	Total treatment duration
Mild cases	<b>First choice</b> <b>Amoxicillin+clavulanic acid</b> <sup>a</sup> (oral): 875 + 125 mg given every 8 hours  <b>OR</b> <b>Ceftriaxone</b> (IV): 2 g given once a day <b>AND</b> <b>Metronidazole</b> (IV/oral): 500 mg given every 8 hours  <b>OR</b>	<b>First choice</b> <b>Amoxicillin+clavulanic acid</b> <sup>a,b</sup> (IV/oral): 40-50 mg/kg/dose of amoxicillin component given every 12 hours OR 30 mg/kg/dose given every 8 hours  Oral weight bands: 3-<6 kg: 250 mg of amoxicillin/dose given every 12 hours	<b>Uncomplicated cases treated with appendectomy:</b> stop antibiotics after surgery if adequate control of the source of infection has been achieved and symptoms have resolved.  <b>Complicated cases treated with appendectomy:</b> 5 days if adequate control of the source of infection has been achieved and symptoms have resolved.

	<p><b>Cefotaxime</b> (IV): 2 g given every 8 hours  <b>AND Metronidazole</b> (IV/oral): 500 mg given every 8 hours</p> <p><b>Second choice</b>  <b>Ciprofloxacin</b> (oral): 500 mg given every 12 hours  <b>AND Metronidazole</b> (IV/oral): 500 mg given every 8 hours</p> <p><i>(Ciprofloxacin has excellent oral bioavailability and the IV route should be reserved for patients with impaired gastrointestinal function)</i></p>	<p>6-&lt;10 kg: 375 mg of amoxicillin/dose given every 12 hours          10-&lt;15 kg: 500 mg of amoxicillin/dose given every 12 hours          15-&lt;20 kg: 750 mg of amoxicillin/dose given every 12 hours          20-&lt;30 kg: 1000 mg of amoxicillin/dose given every 12 hours          ≥ 30 Kg: Use adult dose</p> <p><b>OR</b></p> <p><b>Ceftriaxone</b> (IV): 80 mg/kg/dose given once a day  <b>AND Metronidazole</b>(IV/oral):</p> <ul style="list-style-type: none"> <li>• Neonates: 7.5 mg/kg/dose given every 12 hours (for IV starting with a loading dose of 15 mg/kg)</li> <li>• Children: 7.5 mg/kg/dose given every 8 hours</li> </ul> <p>Oral weight bands:          3-&lt;6 kg: 30 mg given every 8 hours          6-&lt;10 kg: 50 mg given every 8 hours          10-&lt;15 kg: 100 mg given every 8 hours          15-&lt;20 kg: 150 mg given every 8 hours          20-&lt;30 kg: 200 mg given every 8 hours          ≥ 30 Kg: Use adult dose</p> <p><b>OR</b></p> <p><b>Cefotaxime</b> (IV): 50 mg/kg/dose given every 8 hours <b>AND</b></p> <p><b>Metronidazole</b>(IV/oral):</p> <ul style="list-style-type: none"> <li>• Neonates: 7.5 mg/kg/dose given every 12 hours (for IV starting with a loading dose of 15 mg/kg)</li> </ul>	<p><b>Uncomplicated cases treated with antibiotics alone:</b> 7 days with close clinical monitoring and re-evaluation for surgery if symptoms do not resolve.</p>
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		<ul style="list-style-type: none"> <li>Children: 7.5 mg/kg/dose given every 8 hours</li> </ul> <p>Oral weight bands:          3-&lt;6 kg: 30 mg given every 8 hours          6-&lt;10 kg: 50 mg given every 8 hours          10-&lt;15 kg: 100 mg given every 8 hours          15-&lt;20 kg: 150 mg given every 8 hours          20-&lt;30 kg: 200 mg given every 8 hours          ≥ 30 Kg: Use adult dose</p> <p><b>OR</b></p> <p><b>Ampicillin</b></p> <ul style="list-style-type: none"> <li>First week of life: 50 mg/kg/dose given every 12 hours</li> <li>Beyond first week of life: 50 mg/kg/dose given every 8 hours</li> </ul> <p><b>AND</b></p> <p><b>Gentamicin:</b></p> <ul style="list-style-type: none"> <li>Neonates: 5 mg/kg given once daily</li> <li>Children: 7.5 mg/kg given once daily</li> </ul> <p><b>AND</b></p> <p><b>Metronidazole</b></p> <p>Oral/IV:</p> <ul style="list-style-type: none"> <li>Neonates: 7.5 mg/kg/dose given every 12 hours (for IV starting with a loading dose of 15 mg/kg)</li> <li>Children: 7.5 mg/kg/dose given every 8 hours</li> </ul> <p><b>Second choice</b></p> <p><b>Ciprofloxacin</b> (IV/oral): 10-20 mg/kg/dose given every 12 hours</p> <p>Oral weight bands:          3-&lt;6 kg: 50 mg given every 12 hours          6-&lt;10 kg: 100 mg given every 12 hours          10-&lt;15 kg: 150 mg given every 12 hours</p>	
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		<p>15-&lt;20 kg 200 mg given every 12 hours                  20-&lt;30 kg: 300 mg given every 12 hours                  ≥ 30 Kg: Use adult dose</p> <p><i>(Ciprofloxacin has excellent oral bioavailability and the IV route should be reserved for patients with impaired gastrointestinal function)</i></p> <p><b>AND</b>  <b>Metronidazole</b> (IV/oral):</p> <ul style="list-style-type: none"> <li>• Neonates: 7.5 mg/kg/ dose given every 12 hours (for IV starting with a loading dose of 15 mg/kg)</li> <li>• Children: 7.5 mg/kg/dose given every 8 hours</li> </ul> <p>Oral weight bands:                  3-&lt;6 kg: -                  6-&lt;10 kg: 50 mg given every 8 hours                  10-&lt;15 kg: 100 mg given every 8 hours                  15-&lt;20 kg: 150 mg given every 8 hours                  20-&lt;30 kg: 200 mg given every 8 hours                  ≥ 30 Kg: Use adult dose</p>	
<p>Severe cases</p>	<p><b>First choice</b>  <b>Piperacillin+tazobactam</b> (IV):                  4 g + 500 mg given every 6 hours</p> <p><b>OR</b></p> <p><b>Ceftriaxone</b> (IV): 2 g once a day <b>AND</b>  <b>Metronidazole</b> (IV/oral):                  500 mg given every 8 hours</p> <p><b>OR</b></p> <p><b>Cefotaxime</b> (IV): 2 g given every 8 hours <b>AND</b>  <b>Metronidazole</b> (IV/oral):                  500 mg given every 8 hours</p>	<p><b>First choice</b>  <b>Ampicillin</b></p> <ul style="list-style-type: none"> <li>• First week of life: 50 mg/kg/dose given every 12 hours</li> <li>• Beyond first week of life: 50 mg/kg/dose given every 8 hours</li> </ul> <p><b>AND</b>  <b>Gentamicin</b>:</p> <ul style="list-style-type: none"> <li>• Neonates: 5 mg/kg given once daily</li> <li>• Children: 7.5 mg/kg given once daily</li> </ul> <p><b>AND</b>  <b>Metronidazole</b></p> <p>Oral/IV:</p> <ul style="list-style-type: none"> <li>• Neonates: 7.5 mg/kg/dose given every 12 hours (for IV</li> </ul>	

	<p><b>Second choice</b>  <b>Meropenem</b><sup>c</sup> (IV): 2 g given every 8 hours</p>	<p>starting with a loading dose of 15 mg/kg)                  • Children: 7.5 mg/kg/dose given every 8 hours</p> <p><b>OR</b></p> <p><b>Piperacillin+tazobactam</b> (IV): 100 mg/kg/dose of piperacillin component given every 8 hours</p> <p><b>Second choice</b>  <b>Meropenem</b><sup>c</sup> (IV): 20 mg/kg/dose given every 8 hours</p>	
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- 119 Notes: All dosages are for normal renal and hepatic function.  
 120 <sup>a</sup>Prevalence of resistance to amoxicillin-clavulanic acid among *Escherichia coli* isolates is high in some settings and  
 121 this option should be considered taking local microbiology data into consideration where available.  
 122 <sup>b</sup>Oral liquid must be refrigerated after reconstitution as clavulanic acid is rapidly metabolized in high ambient  
 123 temperatures.  
 124 <sup>c</sup>Meropenem should not be considered for routine use for all severe cases but only in complicated cases (i.e. abscess  
 125 and/or peritonitis) in settings with a high prevalence of extended-spectrum beta-lactamase (ESBL)-producing  
 126 Enterobacterales or in patients with known prior colonization, treated with multiple antibiotic courses or at risk of  
 127 infections with pathogens resistant to the first-choice option.  
 128 Empiric use of a “Reserve” antibiotic could be considered exceptionally in very selected cases of seriously ill patients  
 129 with peritonitis failing to respond to carbapenems or that have previously been treated for infections caused by  
 130 carbapenem-resistant pathogens or that are known to be colonized with multidrug-resistant Gram-negative bacteria  
 131 known to be susceptible to the selected “Reserve” antibiotic. Please refer to the corresponding chapter for the  
 132 definition and list of “Reserve” antibiotics included in the EML/c.  
 133 **ACCESS** antibiotics are indicated in green, **WATCH** antibiotics in yellow and **RESERVE** antibiotics in red.

134 **Uncomplicated cases treated with appendectomy**

135 In patients with uncomplicated appendicitis, antibiotic treatment can be stopped once surgery is  
 136 performed provided adequate control of the source of infection was achieved and symptoms  
 137 have resolved. The rationale for stopping antibiotics is that in these cases the source of infection  
 138 is considered to have been eliminated with surgery.

139 **Complicated cases treated with appendectomy**

140 In patients with complicated appendicitis, **5 days** of total antibiotic treatment are usually  
 141 adequate, provided there is good clinical recovery, and the source of infection was eliminated  
 142 with surgery(296-298).

# 1 Intra-abdominal infections - 2 Acute diverticulitis

## 3 Key messages

1. Uncomplicated cases (without peritonitis nor abscess) in an immunocompetent patient are usually self-limiting and do not require antibiotic treatment
2. Complicated cases and cases in immunocompromised patients need treatment based on severity of symptoms (mild or severe) with broader-spectrum agents for severe cases
3. Treatment should also be active against anaerobes as these pathogens are often involved in intra-abdominal infections
4. In complicated cases treatment with 4 days of antibiotics is sufficient once primary source control is achieved surgically

## 4 Definition

5 Acute diverticulitis is the acute inflammation of diverticula (sac-like protrusions of the wall of the  
6 colon) that can cause severe abdominal pain. Acute diverticulitis is usually classified as  
7 uncomplicated when there is no involvement of the peritoneal cavity and the inflammation is  
8 localized to the diverticula (e.g. no perforation, no abscess, no diffuse peritonitis). When the  
9 inflammation extends to the peritoneal cavity or when an abscess is present, the condition is  
10 considered complicated.

## 11 Pathophysiology

12 In cases of acute diverticulitis, the first step in the pathogenesis is the formation of diverticula  
13 (i.e. diverticulosis). Diverticula are sac-like protrusions of the colonic wall. The mechanism leading  
14 to diverticulitis of the colon is the erosion of the wall of the diverticula by increased intraluminal  
15 pressure. If bacterial contamination and chemical irritation (usually due to leakage of sterile fluids  
16 that are irritants to the peritoneum; for example, bile or blood) of the peritoneal cavity occur,  
17 peritonitis develops. Intraabdominal abscesses (i.e. the presence of a collection of infected fluid  
18 in the peritoneal cavity) can also form as a result of a complicated diverticulitis.

## 19 Epidemiology

20 Acute diverticulitis is common in high-income countries and mostly affects adults older than 50  
21 years; its incidence increases with age. The condition is less frequent in many low- and middle-  
22 income countries, probably because of differences in the fibre content of diets. The overall risk  
23 of developing acute diverticulitis in patients with diverticulosis is low (299, 300) and most cases

24 (> 80%) are uncomplicated. Nonetheless, acute diverticulitis is still a common cause of colonic  
25 resection(301).

## 26 Microbiology epidemiology

27 The most common pathogens involved in acute diverticulitis are Gram-negative bacilli and  
28 anaerobic bacteria from the intestinal microbiota (Table 1). Infections are often caused by more  
29 than one pathogen and may include fungal pathogens, especially in patients pre-treated with  
30 antibiotics. Certain parasites need to be considered in the differential diagnosis of abdominal  
31 pain in endemic settings.

32 *Table 1 Pathogens most frequently associated with acute diverticulitis (in descending order of*  
33 *frequency)*

Bacteria	Fungi	Parasites
Enterobacteriales (mostly <i>Escherichia coli</i> ) and other Gram-negative bacteria such as <i>Pseudomonas aeruginosa</i> and <i>Acinetobacter baumannii</i> (including multidrug-resistant strains such as those producing ESBL and carbapenemases)	Mostly <i>Candida albicans</i>	<i>Enterobius vermicularis</i> [pinworm])
<i>Streptococcus</i> spp. (e.g. of the <i>Streptococcus anginosus</i> group - old name: <i>Streptococcus milleri</i> )		
<i>Enterococcus</i> spp.		
Anaerobes (mostly <i>Bacteroides</i> spp.)		

34 ESBL: extended-spectrum beta-lactamases

## 35 Clinical presentation

36 Acute diverticulitis should be considered as possible diagnosis in all cases of acute pain in the left  
37 lower abdominal quadrant. It should be noted that while left lower diverticulitis is more prevalent  
38 in European countries and North America, right lower diverticulitis is more common in Asia.

39 Fever (>38.0 °C), chills, nausea and vomiting may be present, mostly in complicated diverticulitis.  
40 Severe pain, diffuse rebound tenderness on sudden release of pressure on the abdomen and  
41 abdominal muscular defence are usually present in cases of peritonitis. Hypotension and signs of  
42 organ hypoperfusion (e.g. reduced urine output) can be present in cases of organ failure and are  
43 a medical and /or surgical emergency. Please also refer to the chapter on sepsis if suspected.

## 44 Laboratory tests

### 45 I. Patient microbiology tests

46 In mild cases, routine microbiology tests are not usually needed and basing antibiotic treatment  
47 on pathogens cultured from the abdominal cavity at the time of operation is not recommended.  
48 Certain microbiology tests (see Table 2) could be considered in severely ill patients to adjust  
49 empiric antibiotic treatment once the results of antibiotic susceptibility tests are available.

50 *Table 2 Microbiology tests to consider in severe cases as indicated in the EDL (54)*

Diagnostic test	Purpose of the test	Setting where the test should be available
Blood cultures	To detect bacterial bloodstream infections (sepsis)	Health care facilities with clinical laboratories
Microscopy and culture of abscess fluid material when this can be drained	First step to detect and identify bacterial and fungal species for selection of appropriate antibiotic regimens	Health care facilities with clinical laboratories

### 51 II. Other tests

52 Laboratory tests can be used to complement the clinical examination and medical history. Based  
53 on availability, Table 3 indicates several tests that could be considered in the patient's initial  
54 assessment and to help guide the duration of antibiotic treatment.

55 *Table 3 Laboratory tests (other than microbiology) that may help assess the severity of disease  
56 and the identification of a bacterial infection as indicated in the WHO EDL (54)*

Diagnostic test	Purpose of the test	Setting where the test should be available
White blood cell count	To help in the diagnosis of infections	Health care facilities with clinical laboratories
C-reactive protein	To detect inflammation as an indicator of various conditions (e.g. sepsis) <sup>a</sup>	Health care facilities with clinical laboratories
Procalcitonin	To guide antibiotic therapy or discontinuation in sepsis	Only in tertiary care facilities

57 <sup>a</sup>A cut-off value of 150–170 mg/L for C-reactive protein is sometimes used to discriminate between  
58 mild/uncomplicated cases and severe/complicated cases(302, 303).

### 59 III. Using microbiology surveillance data

60 Routine surveillance of pathogens cultured from the abdominal cavity is not recommended.  
61 Empiric guidance given by the Handbook could be reviewed and adapted based on local clinically  
62 relevant microbiology surveillance data. For example, clinically relevant isolates for this infection  
63 would be blood culture data from patients on surgical wards with intra-abdominal infections.

## 64 Imaging

65 Imaging is helpful to confirm acute diverticulitis. In settings where computed tomography (CT)  
66 scanning is available, a CT scan of the abdomen is the best imaging method to confirm acute  
67 diverticulitis and grade its severity. However, because ultrasound is more widely available,  
68 abdominal ultrasound can also be considered a valid alternative.

## 69 Treatment

70 Patients with suspected or confirmed complicated acute diverticulitis or with recurrent attacks  
71 should be promptly referred for surgical consultation.

### 72 Uncomplicated cases

73 In immunocompetent patients with uncomplicated diverticulitis (i.e. localized diverticular  
74 inflammation) and no signs of systemic inflammation, antibiotic treatment is usually not needed  
75 and in these patients uncomplicated diverticulitis can be considered a self-limiting condition  
76 where antibiotics do not offer a benefit in terms of clinical resolution and recurrence(304, 305).

## 77 Antibiotic treatment

78 In patients with complicated acute diverticulitis or in uncomplicated cases requiring antibiotic  
79 treatment (e.g. cases that did not resolve spontaneously after 2-3 days without antibiotic  
80 treatment) or cases in severely immunosuppressed patients, empiric antibiotic treatment should  
81 be chosen based on the severity of symptoms (mild or severe), taking into account local  
82 prevalence of resistance, particularly isolates of Enterobacterales producing extended-spectrum  
83 beta-lactamases, since the prevalence can vary greatly among settings (Table 4). Individual risk  
84 factors for resistant pathogens (e.g. recent antibiotic treatment, colonization with resistant  
85 pathogens) should also be considered. In settings where resistance to carbapenems is highly  
86 prevalent, alternative antibiotic options including Reserve antibiotics – see chapter – could be  
87 considered in severely ill patients who are deteriorating. **In complicated cases** (i.e. presence of  
88 perforation or abscess), empiric antibiotic treatment should be started as soon as the diagnosis  
89 is suspected and could be stopped 4 days after control of the source of infection is achieved  
90 provided there is good clinical recovery.

91 Patients with small abscesses (< 5 cm) or pericolic gas are usually treated with systemic antibiotic  
92 treatment alone provided close clinical follow up is possible and there is a good clinical response  
93 and symptoms have resolved (306).

94 In patients with large abscesses (e.g. percutaneous drainage of abscesses > 5 cm) and patients  
95 with peritonitis, control of the source of infection (e.g. colonic resection), in addition to systemic  
96 antibiotic treatment, is needed.

97 **Simplify** empiric treatment to a more narrow-spectrum antibiotic based on culture results or  
98 based on rapid clinical improvement when no microbiology test results are available.

99 **Step-down** to oral treatment is based on improvement of symptoms and signs of infection and  
 100 the ability to take oral antibiotics allowing discharge of the patient home when clinically  
 101 appropriate.

102 If signs and symptoms persist, abdominal imaging is suggested, or an alternative extra-abdominal  
 103 source of infection should be considered.

104 *Table 4 Empiric antibiotic treatment in case of acute diverticulitis*

105 **Mild cases** are defined as patients who are not critically ill with no signs of sepsis or septic shock.

106 **Severe cases** are defined as patients who are critically ill with signs of sepsis or septic shock.

Severity	Adults	Total treatment duration
Mild cases (these can be uncomplicated cases that did not resolve spontaneously after 2-3 days without antibiotics or complicated cases with mild symptoms)	<p><b>First choice</b>                      Amoxicillin+clavulanic acid (oral): 875 + 125 mg given every 8 hours</p> <p><b>OR</b>                      Ceftriaxone (IV): 2 g given once a day <b>AND</b> Metronidazole (IV/oral): 500 mg given every 8 hours</p> <p><b>OR</b>                      Cefotaxime (IV): 2 g given every 8 hours <b>AND</b> Metronidazole (IV/oral): 500 mg given every 8 hours</p> <p><b>Second choice</b>                      Ciprofloxacin (oral): 500 mg given every 12 hours <b>AND</b> Metronidazole (IV/oral): 500 mg given every 8 hours</p> <p><i>(Ciprofloxacin has excellent oral bioavailability and the IV route should be reserved for patients with impaired gastrointestinal function)</i></p>	Continue for 4 days after control of the source of infection is achieved provided that there is good clinical recovery.
Severe cases	<p><b>First choice</b>                      Piperacillin+tazobactam (IV): 4 g + 500 mg given every 6 hours</p> <p><b>OR</b>                      Ceftriaxone (IV): 2 g given once a day <b>AND</b> Metronidazole (IV): 500 mg every 8 hours</p> <p><b>OR</b>                      Cefotaxime (IV): 2 g given every 8 hours <b>AND</b> Metronidazole (IV/oral): 500 mg every 8 hours</p> <p><b>Second choice</b>                      Meropenem<sup>a</sup>(IV): 2 g given every 8 hours</p>	

107 Notes: All dosages are for normal renal and hepatic function.

108 <sup>a</sup>Meropenem should not be considered for routine use for all severe cases but only in complicated cases (i.e. abscess  
109 and/or peritonitis) in settings with a high prevalence of extended-spectrum beta-lactamase (ESBL)-producing  
110 Enterobacterales or in patients with known prior colonization, treated with multiple antibiotic courses or at risk of  
111 infections with pathogens resistant to the first choice option. Empiric use of a “Reserve” antibiotic could be  
112 considered exceptionally in very selected cases of seriously ill patients failing to respond to carbapenems or that  
113 have previously been treated for infections caused by carbapenem-resistant pathogens or that are known to be  
114 colonized with multidrug-resistant Gram-negative bacteria known to be susceptible to the selected “Reserve”  
115 antibiotic. Please refer to the corresponding chapter for the definition and list of “Reserve” antibiotics included in  
116 the EML.  
117 **ACCESS** antibiotics are indicated in green, **WATCH** antibiotics in yellow and **RESERVE** antibiotics in red.

DRAFT

# 1 Intra-abdominal infections- 2 *Clostridioides difficile* infection

## 3 Key messages

1. Most cases of *Clostridioides difficile* infection (CDI) occur in patients with current or recent antibiotic use. Good antibiotic prescribing practices (avoidance of antibiotics when not needed, preference for Access antibiotics whenever possible) are key for the control of CDI
2. If *Clostridioides difficile* infection (CDI) is confirmed or suspected all antibiotics that are not necessary should be stopped
3. Use oral antibiotics to treat the *C. difficile* infection wherever possible
4. Adopt infection control measures to prevent transmission
5. *C. difficile* diarrhoea may resolve slowly over days, but a clinical deterioration of a patient on appropriate antibiotics should lead to escalation of treatment and a surgical referral

4

### Box 1 Other relevant WHO documents (please check regularly for updates)

- Infection prevention and control [https://www.who.int/health-topics/infection-prevention-and-control#tab=tab\\_1](https://www.who.int/health-topics/infection-prevention-and-control#tab=tab_1)

## 5 Definition

6 *Clostridioides difficile* (formerly *Clostridium difficile*) infection is an infection of the colon caused  
7 by the bacterium *C. difficile*. The infection occurs mostly in patients with current or recent  
8 antibiotic use. For surveillance purposes *C. difficile* infection is usually classified as either health  
9 care-associated or community-associated based on where the infection was acquired, which is  
10 determined from the timing of onset of symptoms in relation to last contact with any health care  
11 setting.

## 12 Microbiology epidemiology

13 *C. difficile* is a Gram-positive anaerobic spore-forming bacterium that is widely present in the  
14 environment, especially in hospitals and long-term care facilities where spores can persist in the  
15 environment for months. Toxigenic and non-toxigenic strains exist but *C. difficile* infection is only

16 associated with toxigenic strains. Of these strains, BI/NAP1/027 is particularly virulent and in  
17 recent years has caused outbreaks, especially in North America.

## 18 Pathophysiology

19 *C. difficile* infection is acquired through the ingestion of toxigenic spores of the Gram-positive  
20 bacterium *C. difficile*. Spores are present in stools of symptomatic patients and asymptomatic  
21 carriers. Once ingested, the spores can colonize the colonic mucosa, germinate into vegetative  
22 bacteria, multiply and produce toxins (toxin A and/or B, binary toxin). In most cases, patients  
23 remain asymptomatic. However, if disruption of the normal colonic mucosa and intestinal  
24 microbiota occurs (e.g. after exposure to antibiotics or cytotoxic chemotherapy) and if there is  
25 no adequate antibody response to *C. difficile* toxins, clinical disease can occur. This disease ranges  
26 in severity, from mild diarrhoea to life-threatening pseudomembranous colitis and toxic  
27 megacolon. Not all strains of *C. difficile* produce toxins. Recurrent infections are a frequent  
28 problem, especially in elderly and immunocompromised patients, and the risk of relapse  
29 increases with each episode.

## 30 Epidemiology

31 *C. difficile* infection is the most frequent cause of health care-associated infectious diarrhoea and  
32 is associated with prolonged hospital stay and increased costs (307, 308).

33 Common risk factors for *C. difficile* infection (CDI) include age  $\geq 65$  years, recent use of antibiotics  
34 and previous hospital admission (309). Almost all antibiotics can increase the risk of infection but  
35 clindamycin, cephalosporins and fluoroquinolones have been most consistently associated with  
36 increased risk of CDI (the risk may vary across time and settings based on the resistance /  
37 susceptibility of *C. difficile* to certain antibiotics). Cytotoxic chemotherapy can also increase the  
38 risk of infection because inflammation of the intestinal mucosa (i.e. mucositis) is often present.  
39 Patients regularly exposed to health care settings (e.g. patients on dialysis) are also at increased  
40 risk.

41 In young children (especially under 2 years of age), clinical disease is rare, probably because  
42 cellular receptors to *C. difficile* toxins develop later in life; therefore, young children are often  
43 asymptomatic carriers.

## 44 Clinical presentation

45 The most common symptom of *C. difficile* infection is diarrhoea, usually defined as the presence  
46 of at least three unformed or liquid stools in 24 hours (with no other plausible cause), or more  
47 than what is normal for that individual. Abdominal pain, cramping and fever may also be present.  
48 Signs of severe disease include marked leukocytosis (e.g. white blood cell count  $> 15 \times 10^9/L$  or  
49  $15\ 000/\mu L$ ), severe abdominal pain, high fever and organ dysfunction (e.g. elevated serum  
50 creatinine, decreased serum albumin).

51 Rarely, *C. difficile* infection can present with signs and symptoms of toxic megacolon. Patients  
52 with this presentation often do not have diarrhoea but have signs of acute surgical abdomen

53 and/or sepsis and may need to be admitted to the intensive care unit. The absence of diarrhoea  
54 does therefore not exclude CDI. Severe cases may require a colectomy for source control.

## 55 Laboratory tests

### 56 I. Patient microbiology tests

57 Where available, a stool test in a symptomatic patient to detect toxigenic *C. difficile* (or toxin  
58 production) could be considered if the patient has no other reasons for diarrhoea (e.g. recent use  
59 of laxatives). The rationale is that, if infection is detected, an effective treatment can be provided,  
60 other antibiotics should be stopped if possible and infection control measures can be put in place  
61 (or reinforced) to limit transmission. Testing is not usually recommended in infants because of  
62 the high prevalence of colonization (i.e. “colonization” here refers to the presence of *C. difficile*  
63 in the stool without causing disease).

64 Even though the current version of the WHO EDL (54) does not include specific tests for *C. difficile*  
65 detection, Table 2 suggests tests that could be considered based on local availability.

66 Currently, no single test is completely reliable in diagnosing *C. difficile* infection and the best  
67 diagnostic approach to use is controversial (310). For both approaches it is important to limit  
68 testing to patients with a sufficiently high pre-test probability of CDI (diarrhoea, risk factors such  
69 as current or recent antibiotic use). The two following approaches are commonly used and could  
70 be considered based on local available tests and laboratory protocols.

- 71 • Starting with a highly sensitive test (nucleic acid amplification test or glutamate  
72 dehydrogenase test depending on local availability) that can detect the presence of  
73 *C. difficile*. Then confirm positive results with a test that can detect toxin production such  
74 as the toxin A/B enzyme immunoassay. It should be noted that if the toxin production test  
75 is negative, the patient could be colonized with *C. difficile* and therefore an alternative  
76 reason for diarrhoea should be sought.
- 77 • Starting with two tests at the same time (glutamate dehydrogenase test and toxin A/B  
78 enzyme immunoassay). If both tests are positive, *C. difficile* infection can be reliably  
79 confirmed; if both are negative, *C. difficile* infection can be excluded. If the results conflict,  
80 then symptomatic patients should be treated if the pre-test probability of *C. difficile*  
81 infection is sufficiently high (e.g., recent antibiotic exposure, absence of alternative  
82 causes of diarrhoea).

83 Repeat testing during the same episode and test of cure are not needed and should be avoided.

84 *Table 2 Microbiology tests to consider if C. difficile infection is suspected (no test for C. difficile is*  
85 *listed in the third version of the EDL, 2021)*

Type of test	Purpose of the test	Comment
<ul style="list-style-type: none"> <li>• Culture</li> <li>• Nucleic acid amplification test (NAAT)</li> </ul>	To detect toxigenic <i>C. difficile</i> strains	Usually NAAT (culture would be the gold standard but it is complex to perform and has a long turnaround time). With NAAT <sup>a</sup> , the main disadvantage is the high

		sensitivity of the test that could lead to over-diagnosis and overtreatment.
<ul style="list-style-type: none"> <li>GDH (glutamate dehydrogenase) antigen test</li> </ul>	To detect <i>C. difficile</i> toxigenic and non-toxigenic strains	The main disadvantage is that this test cannot predict the ability of the strain to produce toxins. However, a negative test will generally exclude <i>C. difficile</i> infection.
<ul style="list-style-type: none"> <li>Cytotoxicity assay</li> <li>Toxin A/B enzyme immunoassay (EIA)</li> </ul>	To detect <i>C. difficile</i> toxins	Usually EIA (cytotoxicity assay would be the gold standard but it is hard to do and has a long turnaround time). With EIA, the main disadvantage is the low sensitivity (i.e. high risk of false negative results).

86 <sup>a</sup>NAAT detect the presence of the gene for the toxin not its expression.

## 87 II. Other tests

88 Routine (non-microbiologic) laboratory testing is not always needed. However, for severe cases,  
89 certain tests could be considered (see Table 1) to assess disease severity.

90 *Table 1 Laboratory tests to consider if C. difficile infection is suspected as indicated in the WHO*  
91 *EDL (54)*

Diagnostic test	Purpose of the test	Setting where the test should be available
White blood cell count	To help in the diagnosis of infections	Health care facilities with clinical laboratories
Creatinine	To monitor kidney function for management of severe infections (i.e. sepsis) and adjustment of the antimicrobial regimen	Health care facilities with clinical laboratories
Electrolytes	To monitor fluid, electrolytes and acid–base balance	Health care facilities with clinical laboratories

## 92 III. Using pooled microbiology data

93 Resistance to metronidazole, vancomycin and multiple other antibiotics has been reported.

## 94 Imaging

95 Imaging is usually not needed unless a complication is suspected. In these cases, a computed  
96 tomography scan of the abdomen could be considered.

## 97 “No antibiotic care”

98 Rehydration (oral or intravenous) should always be recommended in patients with diarrhoea.  
99 Anti-diarrhoea medicines are not routinely required because they do not prevent dehydration  
100 and do not improve nutritional status(132).

## 101 Antibiotic treatment

102 **It is important to discontinue any other antibiotics except those treating the *C. difficile* infection as**  
 103 **soon as possible.**

104 Symptomatic patients diagnosed with *C. difficile* infection should promptly receive adequate  
 105 antibiotic treatment as indicated in Table 3. Whenever possible, it is also important to stop any  
 106 other antibiotic that could have favoured *C. difficile* infection by disrupting the microbiota in the  
 107 colon. If it is necessary to continue the antibiotic treatment (e.g. because of a clearly documented  
 108 or high suspicion of a concomitant infection) it is advisable to select antibiotics with lower risk of  
 109 selecting *C. difficile* infection (avoid ceftriaxone, fluoroquinolones, clindamycin).

110 Oral treatment with metronidazole is appropriate for a first episode of mild to moderate severity.  
 111 This antibiotic also is suggested because of concerns that oral vancomycin could favour selection  
 112 of vancomycin-resistant enterococci (VRE) in the intestinal microbiota and that the oral  
 113 formulation may be unavailable or too expensive to consider in some low-resource settings(311,  
 114 312). However, in severe cases of infection, the current evidence supports the use of oral  
 115 vancomycin rather than metronidazole, in part because of its benefit in reducing recurrent  
 116 episodes (311-313). Treatment of recurrent episodes (usually defined as *C. difficile* infection  
 117 within 8 weeks of a previous episode) with antibiotics or faecal microbiota transplantation is  
 118 beyond the scope of this chapter.

119 *Table 3 Antibiotic treatment for a first episode of C. difficile infection*

120 **It is important to discontinue any other antibiotics except those treating the *C. difficile* infection as**  
 121 **soon as possible.**

Adults	Neonates and children	Total treatment duration
<p><b>First choice</b>                      Metronidazole (oral): 500 mg given every 8 hours</p> <p><b>Second choice</b>                      Vancomycin (oral)<sup>a</sup>: 125 mg given every 6 hours</p>	<p><b>First choice</b>                      Metronidazole (oral):</p> <ul style="list-style-type: none"> <li>• Neonates: 7.5 mg/kg/dose given every 12 hours</li> <li>• Children: 7.5 mg/kg/dose given every 8 hours</li> </ul> <p>Oral weight bands:                      3-&lt;6 kg: 30 mg given every 8 hours                      6-&lt;10 kg: 50 mg given every 8 hours                      10-&lt;15 kg: 100 mg given every 8 hours                      15-&lt;20 kg: 150 mg given every 8 hours                      20-&lt;30 kg: 200 mg given every 8 hours                      ≥ 30 Kg: Use adult dose</p> <p><b>Second choice</b>                      Vancomycin (oral):</p> <ul style="list-style-type: none"> <li>• Neonates: 5-10 mg/kg/dose given every 6 hours</li> </ul>	<p>10 days</p>

	<ul style="list-style-type: none"><li>Children: 5-10 mg/kg/dose given every 6 hours</li></ul>	
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122 Notes: All dosages are for normal renal and hepatic function.

123 <sup>a</sup>Oral vancomycin is preferable to metronidazole in severe cases. If needed, the dose could be increased to 500 mg  
124 given every 6 hours. In severe fulminant cases, intravenous metronidazole could be added to treatment with oral  
125 vancomycin.

126 ACCESS antibiotics are indicated in green, WATCH antibiotics in yellow and RESERVE antibiotics in red

DRAFT

# Urinary Tract Infection - Upper

## Key messages

1. Most cases are caused by *Escherichia coli*
2. A urine culture should be obtained before starting antibiotic treatment
3. Mild cases can be treated with oral antibiotics in the outpatient setting
4. Empiric treatment varies depending on the severity of clinical presentation and underlying risk factors
5. The local prevalence of resistance among *E. coli* urinary isolates needs to be considered if data are available

### Box 1 Other relevant WHO documents (please check regularly for updates)

- WHO 2013 pocket book of hospital care for children <https://apps.who.int/iris/handle/10665/81170> (23)

## Definition

Upper urinary tract infection (UTIs) are acute infections in which pathogens (mostly bacteria from the intestinal microbiota colonizing the skin in the perineal area) reach the kidney/s by ascending through the urethra, bladder and the ureter/s. In addition, pathogens can gain access to the kidney/s through the bloodstream. An infection of the kidney/s is commonly referred to as pyelonephritis. Infections can be community acquired or hospital acquired. The focus of this chapter is on community acquired pyelonephritis in immunocompetent patients without a urinary catheter.

Complications can occur with upper UTIs because of patient-related risk factors that make the infection more difficult to treat. While there is no universally accepted definition of what constitutes a complicated UTI, upper UTIs in individuals with pre-existing conditions of the urinary tract (e.g. anatomical anomalies and kidney stones) are generally considered complicated. Upper UTIs in pregnant women are also usually considered complicated. Examples of factors that may increase the risk of a complicated upper UTI are shown in Box 1

### Box 1 Factors that may increase the risk of a complicated upper urinary tract infection

Obstruction at any site of the urinary tract  
Foreign body (e.g. urinary catheters and stents)  
Incomplete voiding  
Vesicoureteral reflux  
Recent history of instrumentation  
Male sex  
Pregnancy  
Diabetes  
Immunosuppression  
Health care-associated urinary tract infection

**Notes:** The list gives some examples but is not aimed to be complete. No widely accepted definition of a complicated urinary tract infection currently exists. Some experts argue that the list above is too long and may result in diagnosing too many patients with a “complicated” infection. The presence of one or more of these risk factors does not mean that the infection is complicated and in need of a different treatment approach.

Source: Guidelines on urological infections of the European Association of Urology(314).

## 18 Pathophysiology

19 Upper UTIs occur when pathogens reach the upper urinary tract and overcome the host  
20 defences, which leads to tissue damage and an inflammatory response. Pathogens in the urine  
21 do not inevitably lead to infection. Infection will depend on the interaction between the  
22 pathogen (for example the presence of specific virulence factors in the pathogen), the host (who  
23 may be more or less likely to have infections because of, for example, underlying diseases) and  
24 the local conditions within the urinary tract (for example, because of abnormalities of the urinary  
25 tract or the presence of foreign material such as a urinary catheter). Furthermore, it is important  
26 to note that urine can also become contaminated during sampling so that the presence of  
27 bacteria in a urine sample does not necessarily mean bacteria are present in the urinary tract.

## 28 Epidemiology

29 UTIs are very common worldwide and can affect people at any age. In 2017, there were an  
30 estimated 274 million new cases of UTIs globally (upper and lower), combining all ages and both  
31 sexes(31).

32 The incidence of UTIs is highest in women and increases with age (e.g. UTIs increase after  
33 menopause) and frequency of sexual activity. These infections are particularly common in  
34 women because of the anatomy of their lower urinary tract; women have a shorter urethra than  
35 men and so microorganisms colonizing the skin of the perineal area can more easily reach the  
36 bladder. Risk factors for UTIs include anatomical and functional abnormalities of the urinary tract  
37 (e.g. conditions that predispose to incomplete emptying of the bladder, renal insufficiency and  
38 urinary incontinence). Defective host immune factors (e.g. poorly controlled diabetes or  
39 neutropenia) and instrumentation of the urinary tract (e.g. urinary catheters and stents) are also  
40 predisposing factors.

## 41 Microbiology epidemiology

42 Most UTIs are caused by enteric Gram-negative bacteria, most frequently *Escherichia coli*, which  
43 is responsible for about 80% of cases in children and adults. Other causative pathogens are shown  
44 in Table 1. Data on causative pathogens from low- and middle-income countries are limited.

45 *Table 1 Pathogens commonly causing upper urinary tract infections (in descending order of*  
 46 *frequency)*

Most cases	Enterobacterales (including multidrug-resistant strains such as those producing ESBL and carbapenemases) <ul style="list-style-type: none"> <li>• <i>Escherichia coli</i> (&gt; 80% of cases)</li> <li>• <i>Klebsiella pneumoniae</i></li> <li>• <i>Proteus mirabilis</i></li> <li>• Other Enterobacterales</li> </ul>
More rarely	<i>Enterococcus</i> spp.  <i>Streptococcus agalactiae</i> (group B <i>Streptococcus</i> )  <i>Staphylococcus aureus</i> (rare in uncomplicated UTIs, often in patients with urinary catheters)
Additionally in patients with recent antibiotic exposure, hospitalization, or instrumentation of the urinary tract (e.g. insertion of a catheter)	<i>Pseudomonas aeruginosa</i> <i>Acinetobacter baumannii</i>  (including multidrug-resistant strains such as those producing ESBL and carbapenemases)

47 ESBL: extended-spectrum beta-lactamases.

## 48 Clinical presentation

49 Classical symptoms of pyelonephritis include flank pain, costovertebral angle tenderness, nausea  
 50 and vomiting, fever (> 38.0 °C) and signs of systemic illness. Symptoms of cystitis (dysuria,  
 51 suprapubic tenderness, increased urgency and frequency) may or may not be present.

52 Severity of signs and symptoms may range from mild disease (e.g. no nausea or vomiting, low-  
 53 grade fever) that can be safely managed in an outpatient setting with oral antibiotic treatment  
 54 to severe cases that require hospitalization and intravenous treatment to septic shock requiring  
 55 admission to intensive care.

56 In younger children symptoms are often non-specific, including high fever, irritability, vomiting  
 57 and diarrhoea. In older children (e.g. over 2 years of age) abdominal pain, urgency, frequency  
 58 and dysuria are more common.

## 59 Laboratory tests

### 60 I. Patient microbiology tests

61 A urine culture should be done where possible, ideally before starting antibiotic treatment. The  
 62 rationale is to confirm the diagnosis and to adjust empiric treatment based on susceptibility  
 63 results.

- 64 • Urine culture is considered positive when bacteria are above a certain cut-off (cut-off of
- 65 concentration of bacteria in the urine (e.g.  $\geq 10^5$  microorganisms/mL of urine) in
- 66 symptomatic patients.
- 67 • Minimum cut-offs to diagnose an infection can vary by laboratory.
- 68 • Lower cut-offs are often used to diagnose infections in females compared with males or
- 69 in patients with urinary catheters.

- **The presence of bacteria in the urine alone is not a sign of infection or an indication for antibiotic treatment.**
- **Cut-offs of concentration of bacteria in the urine alone cannot distinguish infection from colonization. The pre-test probability of urinary tract infections always needs to be considered when interpreting urine culture results.**
- **Patients with positive urine cultures without symptoms suggestive of a UTI usually do not require treatment (there may be some exception such as pregnant women or patients who have an invasive urological procedure scheduled).**

70 For patients requiring hospitalization, a blood culture should be done where possible before  
 71 starting antibiotic treatment to guide treatment.

72 Table 2 summarizes the microbiology tests that can be done to diagnose upper urinary tract  
 73 infections.

74 *Table 2 Microbiology tests for upper urinary tract infections as indicated in the WHO EDL (54)*

Diagnostic test	Purpose of the test	Settings where the test should be available
Urine culture	Initial step to detect and identify bacterial and fungal species for selection of appropriate antimicrobial regimens	Health care facilities with clinical laboratories
Blood cultures	To detect bacterial bloodstream infections (sepsis)	Health care facilities with clinical laboratories

75 **II. Other tests**

76 A urinalysis (dipstick or microscopy) may be done to detect the presence of bacteriuria and/or  
 77 indirect signs of infection (leukocyturia and nitrites). In a symptomatic patient, leukocyturia (> 10  
 78 leukocytes/ $\mu\text{L}$ ,  $0.01 \times 10^9/\text{L}$ ), the presence of leukocyte esterase and/or positive nitrites are  
 79 indirect signs of infection.

80 In patients with a severe clinical presentation and when sepsis of urinary origin is suspected, a  
 81 white blood cell count may be done to support the diagnosis of bacterial infection as well as  
 82 testing for biomarkers of infection (e.g. C-reactive protein). Table 3 summarizes the laboratory  
 83 tests that can be done to assist with the diagnosis of upper urinary tract infections.

84 *Table 3 Laboratory tests to consider for the diagnosis of upper urinary tract infections as indicated*  
 85 *in the WHO EDL (54)*

Diagnostic test	Purpose of the test	Settings where the test should be available
Urinalysis test strips	To detect urinary tract infections	Community settings and health facilities without laboratories <sup>a</sup>
Urine microscopy	Presence or absence of: white blood cells, red blood cells; presence of casts and crystals in urine	Health care facilities with clinical laboratories
White blood cell count <sup>b</sup>	To aid in the diagnosis of infections	Health care facilities with clinical laboratories
C-reactive protein <sup>b</sup>	To detect inflammation as an indicator of various conditions, e.g. sepsis	Health care facilities with clinical laboratories
Procalcitonin <sup>b</sup>	To guide antibiotic therapy or discontinuation in sepsis	Only in tertiary care facilities

86 <sup>a</sup>Community and health settings without laboratories are settings such as health posts and centres, doctors' offices,  
 87 outreach clinics and ambulatory care. These tests are also assumed to be available at health care facilities with  
 88 laboratories.

89 <sup>b</sup>Only in severe cases when sepsis of urinary origin is suspected.

### 90 III. Using microbiology surveillance data

91 Empiric guidance given by the Handbook could be reviewed and adapted based on local clinically  
 92 relevant microbiology surveillance data. For example, clinically relevant isolates for this infection  
 93 would be blood and urine culture data from patients being treated in the hospital with  
 94 community acquired upper urinary tract infections. Data on severity of clinical presentation,  
 95 underlying patient risk factors, previous and current antibiotic treatment, current microbiology  
 96 and clinical outcome would help to inform the development of local guidance.

### 97 Imaging

98 Initial imaging (e.g. ultrasound) of the urinary tract could be done in severely ill patients or during  
 99 follow-up if an outflow obstruction or a fluid collection (i.e. abscess) is suspected. Routine  
 100 imaging of all cases of upper UTI is not necessary.

101 *Table 4 Medicines to consider for pain control of upper urinary tract infections*

Molecule	Formulation	Dose and frequency
Paracetamol (acetaminophen) <sup>a</sup>	Oral liquid: 120 mg/5 mL; 125 mg/5 mL Suppository: 100 mg Tablet: 100 mg to 500 mg	<b>Adults:</b> 500 mg–1 g every 4–6 hours (maximum dose of 4 g a day) <sup>b</sup>  <b>Children:</b> <ul style="list-style-type: none"> <li>• Pain control/Antipyretic treatment: 10–15 mg/kg every 4–6 hours</li> </ul> 3–<6 Kg: 60 mg given every 6 hours

		6-<10 kg: 100 mg given every 6 hours 10-<15 kg: 150 mg given every 6 hours 15-<20 kg: 200 mg given every 6 hours 20-<30 kg: 300 mg given every 6 hours ≥ 30 Kg: Use adult dose
Ibuprofen <sup>c</sup>	Oral liquid: 200 mg/5 mL Tablet: 200 mg; 400 mg; 600 mg	<b>Adults:</b> 200–400 mg every 6–8 hours (maximum dose of 2.4 g a day)  <b>Children:</b> • Pain control / Antipyretic treatment: 5–10 mg/kg every 6–8 hours  6-<10 kg: 50 mg given every 8 hours 10-<15 kg: 100 mg given every 8 hours 15-<20 kg: 150 mg given every 8 hours 20-<30 kg: 200 mg given every 8 hours ≥ 30 Kg: Use adult dose

102 <sup>a</sup>Not recommended for use as an anti-inflammatory as it has not been proven to have such an effect.

103 <sup>b</sup>In patients with hepatic impairment or cirrhosis, maximum daily dose should be 2 g.

104 <sup>c</sup>Not for children < 3 months.

## 105 Antibiotic treatment

106 The primary goal of empiric antibiotic treatment is to provide effective and timely treatment for  
107 the main bacterial pathogens in upper UTI, most commonly *E. coli*. The choice of empiric  
108 treatment should be based on the severity of symptoms (mild/moderate or severe). Many upper  
109 UTIs can be managed with oral antibiotics in the outpatient setting (315).

### 110 Mild/moderate cases (adults and children)

111 Mild/moderate cases of upper UTI are defined as patients who are not critically ill and there are  
112 no clinical signs of systemic sepsis or septic shock. In these cases, a 7-day treatment course with  
113 oral ciprofloxacin should be considered if there is no nausea and vomiting, for adults (Table 5).  
114 For young children it is clinically more difficult to make a clear distinction between upper and  
115 lower UTIs, with fever and general systemic signs of infection seen in both groups. If systemic  
116 intravenous treatment is required, a third-generation cephalosporin (ceftriaxone or cefotaxime)  
117 is an option. Clinical improvement should be evident within 48–72 hours of starting treatment. If  
118 no improvement is seen in that time, a complication (such as an abscess) should be considered  
119 and investigated by imaging and the susceptibility of bacteria isolated in the urine culture should  
120 be reviewed.

121 **Step-down** to oral treatment is based on improvement of symptoms and signs of infection and  
122 the ability to take oral antibiotics allowing discharge of the patient home when clinically  
123 appropriate.

## 124 Severe cases (adults and children)

125 Severe cases of upper UTIs are defined as patients who are critically ill, with sepsis and/or septic  
 126 shock. Please also refer to the chapter on sepsis if suspected. These cases should be treated  
 127 rapidly with systemic antibiotics. A third-generation cephalosporin (ceftriaxone or cefotaxime) or  
 128 gentamicin or amikacin (Table 5) for 7 days, for both children and adults is recommended (316,  
 129 317). Clinical improvement is usually evident within 48–72 hours of starting treatment when a  
 130 switch to oral antibiotics should be considered.

131 **Simplify** empiric treatment to a more narrow-spectrum antibiotic based on culture results or  
 132 based on rapid clinical improvement when no microbiology test results are available.

133 **Step-down** to oral treatment is based on improvement of symptoms and signs of infection and  
 134 the ability to take oral antibiotics allowing discharge of the patient home when clinically  
 135 appropriate.

## 136 Settings with high rates of resistant isolates

137 Enterobacterales can develop resistance to antibiotics through different mechanisms (e.g.  
 138 production of extended-spectrum beta-lactamases (ESBL), AmpC beta-lactamases and  
 139 carbapenemases). Resistance to beta-lactam antibiotics, e.g. in ESBL producing strains, is often  
 140 associated with resistance to other classes of antibiotics, such as fluoroquinolones. Although  
 141 resistance is higher in hospital-acquired strains, it is also present in community-acquired  
 142 infections. Specific thresholds for when not to use particular antibiotics are given in some  
 143 guidelines; however, these lack a strong evidence base with no clear rationale for the suggested  
 144 cut-offs. Therefore, local knowledge of the prevalence of resistance to antibiotic classes used to  
 145 treat UTIs should be considered, as well as individual risk factors (e.g. previous infection or  
 146 colonization with a resistant pathogen) and severity of clinical presentation.

147 In hospital settings where resistance to first-choice antibiotics (see Table 5) is highly prevalent  
 148 and in severely ill patients who are clinically acutely deteriorating, piperacillin + tazobactam or a  
 149 carbapenem could be considered, even though the EML/c does not explicitly recommend these  
 150 options. Empiric use of a “Reserve” antibiotic could be considered exceptionally in very selected  
 151 cases of seriously ill patients failing to respond to carbapenems or that have previously been  
 152 treated for infections caused by carbapenem-resistant pathogens or that are known to be  
 153 colonized with multidrug-resistant Gram-negative bacteria known to be susceptible to the  
 154 selected “Reserve” antibiotic. Please refer to the corresponding chapter for the definition and  
 155 list of “Reserve” antibiotics included in the EML/c.

156 *Table 5 Empiric antibiotic treatment for upper urinary tract infections*

Upper UTI	Adults	Children	Total treatment duration
Mild to moderate cases	Ciprofloxacin <sup>a</sup> (oral): 500 mg given every 12 hours  (Ciprofloxacin has excellent oral bioavailability and the IV	Amoxicillin+clavulanic acid <sup>c</sup> (IV/oral) 40-50 mg/kg/dose of amoxicillin component, given every 12 hours OR 30 mg/kg/dose given every 8 hours	7 days

	<p><i>route should be reserved for patients with impaired gastrointestinal function)</i></p>	<p>Oral weight bands:                      3-&lt;6 kg: 250 mg given every 12 hours                      6-&lt;10 kg: 375 mg given every 12 hours                      10-&lt;15 kg: 500 mg given every 12 hours                      15-&lt;20 kg: 750 mg given every 12 hours                      20-&lt;30 kg: 1000 mg given every 12 hours                      ≥ 30 Kg: Use adult dose</p> <p>OR</p> <p><b>Ciprofloxacin</b>(IV/oral):                      10-20 mg/kg/dose given every 12 hours</p> <p>Oral weight bands:                      3-&lt;6 kg: 50 mg given every 12 hours                      6-&lt;10 kg: 100 mg given every 12 hours                      10-&lt;15 kg: 150 mg given every 12 hours                      15-&lt;20 kg 200 mg given every 12 hours                      20-&lt;30 kg: 300 mg given every 12 hours                      ≥ 30 Kg: Use adult dose</p> <p><i>(Ciprofloxacin has excellent oral bioavailability and the IV route should be reserved for patients with impaired gastrointestinal function)</i></p>	
<p>Severe cases</p>	<p><b>Ceftriaxone</b><sup>d</sup> (IV/IM): 1 g given every 24 hours</p> <p>OR</p> <p><b>Cefotaxime</b><sup>d</sup> (IV/IM): 1 g given every 8 hours</p> <p>AND/OR</p> <p><b>Gentamicin</b><sup>e</sup>(IV): 5 mg/kg given once a day</p> <p>AND/OR</p> <p><b>Amikacin</b><sup>e</sup> (IV): 15 mg/kg given once a day</p>	<p><b>Ceftriaxone</b><sup>d</sup>(IV/IM)                      80 mg/kg/dose given once a day</p> <p>OR</p> <p><b>Cefotaxime</b><sup>d</sup> (IV/IM): 50mg/kg/dose given every 8 hours</p> <p>AND/OR</p> <p><b>Gentamicin</b><sup>e</sup> (IV)</p> <ul style="list-style-type: none"> <li>• Neonates: 5 mg/kg/dose given once a day</li> <li>• Children: 7.5 mg/kg/dose given once a day</li> </ul> <p>AND/OR</p> <p><b>Amikacin</b><sup>e</sup>(IV): 15 mg/kg/dose given once a day</p>	<p>7 days</p>

157 Notes: All dosages are for normal renal and hepatic function.

158 ESBL: extended-spectrum beta-lactamases; IM: intramuscular; IV: intravenous.

159 <sup>a</sup>Resistance to quinolones is increasing including in low-and middle-income countries and in children (318-320).

160 <sup>b</sup>Resistance to sulfamethoxazole+trimethoprim is high in many settings (213, 214). It is ineffective against isolates  
161 producing extended-spectrum beta-lactamases (ESBL).

162 <sup>c</sup>Amoxicillin+clavulanic acid: *Escherichia coli* resistance rates to amoxicillin+clavulanic acid are lower than to  
163 amoxicillin alone. This combination still has activity against some ESBL-producing isolates and it can be considered  
164 an acceptable option, particularly in young children.

165 <sup>d</sup>Resistance to third-generation cephalosporins is increasing including in LMIC and in children (318-320). In very sick  
166 patients, gentamicin (or amikacin) can be given in combination with ceftriaxone (or cefotaxime).

167 <sup>e</sup>Amikacin and gentamicin are still effective against isolates producing ESBL and are considered appropriate  
168 carbapenem-sparing options in settings where ESBL-producing isolates are very prevalent. Use of aminoglycosides  
169 can be associated with nephrotoxicity and/or ototoxicity (especially when used for more than 7 days).

170 ACCESS antibiotics are highlighted in green, WATCH antibiotics in yellow and RESERVE antibiotics in red.

DRAFT

# 1 Acute bacterial osteomyelitis

## 2 Key messages

1. Osteomyelitis can occur alone or in combination with septic arthritis
  2. In clinically stable adult patients, targeted treatment based on the results of microbiology tests is always preferable (large number of potential causes, risk of resistant pathogens, long treatment)
  3. In children there is less variability in causative pathogens (mostly *Staphylococcus* spp. and *Streptococcus* spp.) and empiric treatment is common practice
  3. In general, the intravenous route is preferred for initial treatment but rapid oral step down is increasingly used
  4. Duration of treatment in children is usually shorter than in adults
1. Dead bone, which is usually present in chronic infections, needs to be removed surgically for antibiotic treatment to be successful

3

*Box 1 Other relevant WHO documents (please check regularly for updates)*

- WHO 2013 pocket book of hospital care for children <https://apps.who.int/iris/handle/10665/81170> (23)

## 4 Definition

5 Osteomyelitis is an infection of the bone characterized by inflammation and bone destruction.  
6 Infection can be classified according to how the pathogen spreads in the body (via the  
7 bloodstream or by local spread from nearby tissue) or the duration of symptoms (acute or  
8 chronic). Acute infections develop and evolve over days or weeks while chronic infections evolve  
9 over months or years. Chronic infections are also characterized by the presence of dead bone  
10 fragments (sequestrum).

11 Both classifications have implications for the management of osteomyelitis. For example, the  
12 pathogens infecting bone by local spread are more variable than those infecting bone via the  
13 bloodstream. In addition, dead bone, which is usually present in chronic infections, needs to be  
14 removed surgically for antibiotic treatment to be successful.

## 15 Pathophysiology

16 Bacteria can reach the bone from a source of infection by spreading through the bloodstream or  
17 by local spread or by direct inoculation (e.g. following trauma, bone surgery, prosthetic joint  
18 implantation, pressure or decubitus ulcers or diabetic foot infections). The infection can affect a

19 single portion of the bone or can extend to the surrounding soft tissue. Infections can rapidly lead  
20 to destruction of the affected bone.

21 The pathophysiology of osteomyelitis differs between children and adults; osteomyelitis caused  
22 by spread through the bloodstream is much more common in children (mostly < 5 years of age)  
23 where it usually affects long bones (mostly the tibia and femur) because the bones are more  
24 heavily vascularized in children. In adults, spread of the infection via the bloodstream is less  
25 common; nonetheless, it can occur (e.g. as a metastatic infection of infective endocarditis) and  
26 in most cases if osteomyelitis is caused, it concerns the vertebra and intervertebral disc (vertebral  
27 osteomyelitis). However, in the adult population dissemination by local spread (e.g. after trauma)  
28 is far more common.

## 29 Epidemiology

30 Risk factors for osteomyelitis are those associated with bacteraemia (e.g. presence of indwelling  
31 vascular catheters, injection drug use, haemodialysis) and those making the bone vulnerable to  
32 infection (e.g. bone surgery, open bone fracture, presence of foreign material such as prosthetic  
33 joint implants, sickle-cell disease, diabetes, impaired bone vascularization).

34 Acute osteomyelitis in children is more frequent in low-and middle-income countries and more  
35 common in boys than in girls. If left untreated or managed late, acute osteomyelitis can leave  
36 children with long-term disability.

37 The global burden of osteomyelitis is still high, mostly in low-and middle-income countries where  
38 the disease disproportionately affects the young and where delays in diagnosis and adequate  
39 management can lead to acute forms evolving into chronic osteomyelitis, which is very difficult  
40 to treat(321).

41 Most cases globally develop after a post-traumatic event (e.g. infections in open fractures  
42 following road traffic incidents). In addition, in high-income settings, diabetes (which can lead to  
43 foot osteomyelitis; not specifically addressed in this chapter) and spinal interventions (which can  
44 lead to vertebral osteomyelitis) contribute to the burden of disease.

## 45 Microbiology epidemiology

46 The most frequent pathogens associated with acute osteomyelitis in children and adults are  
47 shown in Tables 1 and 2, respectively.

48 *Table 1 Most frequent pathogens associated with acute osteomyelitis in children (in descending*  
49 *order of frequency)*

Pathogen	Most common way of spreading	Patients most at risk
<i>Staphylococcus aureus</i> (including MRSA)	Bloodborne or local spread	Mostly no risk factor identified – consider penetrating injuries or recent surgical procedures or patients with bite wounds.

<i>Streptococcus</i> spp. (mostly <i>S. pyogenes</i> -often called group A <i>Streptococcus</i> - and less commonly <i>S. pneumoniae</i> ). <i>Streptococcus agalactiae</i> is a potential pathogen for neonates.	Bloodborne	Mostly no risk factor identified.
<i>Kingella kingae</i> (a species of anaerobic Gram-negative bacilli)	Bloodborne	Young children with generally mild disease.
<i>Haemophilus influenzae</i> type b	Bloodborne	Young children not vaccinated against <i>H. influenzae</i> type b.
<i>Salmonella</i> spp.	Bloodborne	Children with sickle-cell disease.
Enterobacteriales	Bloodborne	Neonates and immunosuppressed children
<i>Pseudomonas aeruginosa</i>	Bloodborne or local spread	Immunosuppressed patients and immunocompetent children following wound puncture.

50 MRSA: methicillin-resistant *Staphylococcus aureus*.

51 *Table 2 Most frequent pathogens associated with acute osteomyelitis in adults (in descending*  
 52 *order of frequency)*

<b>Pathogen</b>	<b>Most common way of spreading</b>	<b>Patients most at risk</b>
<i>Staphylococcus aureus</i> (including MRSA)	Bloodborne or local spread	Mostly no risk factor identified – consider penetrating injuries, recent surgical procedures, patients with bite wounds or injection drug use.
<i>Staphylococcus</i> spp. other than <i>S. aureus</i>	Bloodborne or local spread	Patients with recent prosthetic joint implants or arthroscopy or patients with bite wounds.
<i>Streptococcus</i> spp.	Bloodborne or local spread	Splenic dysfunction
<b>Less frequent pathogens (in alphabetical order)</b>		
Anaerobes	Local spread	Patients with bite wounds or recent abdominal surgery. Diabetic foot infection.
<i>Bartonella</i> spp.	Bloodborne	Patients with cat bite wounds
<i>Brucella</i> spp.	Bloodborne	Patients with occupational or domestic exposure to infected animals (e.g. farmers, sheep herder, veterinarians) or ingestion of contaminated food (mostly dairy products).
<i>Candida</i> spp.	Bloodborne or local spread	Immunosuppressed patients, patients with invasive devices, patients who inject drugs (hematogenous spread) or patients with deep wounds (dissemination by local spread)
<i>Cryptococcus</i> spp.	Bloodborne	Immunosuppressed patients.
Enterobacteriales	Bloodborne or local spread	Patients with decubitus (pressure) ulcers, diabetic foot infections and burn wounds (especially if the wound

		is close to the perineum). Recent abdominal surgery.
<i>Histoplasma</i> spp.	Bloodborne	Immunosuppressed patients.
<i>Mycobacterium tuberculosis</i>	Bloodborne or local spread (e.g. from adjacent paravertebral lymph nodes)	Immunosuppressed patients (because of the risk of reactivation of tuberculosis)
<i>Pseudomonas aeruginosa</i>	Bloodborne or local spread	Immunosuppressed patients and following wound puncture (including injection drug use).

53 MRSA: methicillin-resistant *Staphylococcus aureus*.

## 54 Clinical presentation

Osteomyelitis can occur alone or in combination with septic arthritis

55 Acute osteomyelitis is characterized by gradual onset of localized pain and/or tenderness with a  
 56 combination of redness, swelling, pain and warmth of the affected area. Fever (> 38.0 °C) and  
 57 other signs of systemic infection (e.g. tachycardia, leukocytosis) may be present. In the context  
 58 of osteomyelitis involving the vertebral spine, hip and pelvis, pain is usually the main symptom.  
 59 In children where acute osteomyelitis often involves the femur and tibia, difficulty and/or  
 60 inability to walk or reluctance to move the limb may be a presenting symptom.

These infections can sometimes present as chronic illness; the patient appears less ill, with fewer marked local signs, and perhaps without a fever. Consider tuberculous osteomyelitis (mostly vertebral also known as Pott’s disease) when the illness is chronic, discharging sinuses are present (i.e. when a passage (sinus) forms from the infected bone to the surface of the skin and pus drains through) or the patient has other signs of tuberculosis.

## 61 Laboratory tests

### 62 I Patient microbiology tests

63 Determining the causative pathogen of osteomyelitis is important to target antibiotic treatment  
 64 because the number of potential causative pathogens is large and antibiotic resistant  
 65 pathogens (e.g. MRSA) are not infrequent; this makes it difficult to define appropriate empiric  
 66 treatment. Duration of treatment may be long (increasing the risk of side-effects of the  
 67 antibiotic therapy). Whenever possible, a microbiology sample should therefore be obtained to  
 68 guide antibiotic treatment (Table 3).

69 *Table 3 Microbiology tests to consider when osteomyelitis is suspected as indicated in the WHO*  
 70 *EDL (54)*

Diagnostic test	Purpose of the test purpose	Settings where the test should be available
Blood culture	To detect bacterial bloodstream infections (sepsis)	Health care facilities with clinical laboratories

Bone biopsy for microscopy and culture <sup>a</sup>	Initial step in detection and identification of bacterial and fungal species for selection of appropriate antibiotic regimens	Health care facilities with clinical laboratories
Microscopy and culture of deep samples of tissue and/or bone collected during debridement (i.e. when the surgeon removes as much of the diseased bone as possible) <sup>a</sup>	Initial step in detection and identification of bacterial and fungal species for selection of appropriate antibiotic regimens	Health care facilities with clinical laboratories

71 <sup>a</sup>Samples should be tested for special pathogens (e.g. mycobacteria, fungi, *Brucella* spp.) if compatible  
72 clinical/epidemiological features are evident.

## 73 II. Other tests

74 Laboratory tests can be used to complement the clinical examination and history. Table 4 gives  
75 several tests that could be considered in the initial patient assessment to differentiate between  
76 bacterial and reactive viral infections and to help guide the timing of changing to oral treatment  
77 and total duration of antibiotic treatment.

78 *Table 4 Laboratory tests (other than microbiology) to identify a bacterial infection, as indicated*  
79 *in the WHO EDL (54)*

Diagnostic test	Purpose of the test	Settings where the test should be available
White blood count	To help in the diagnosis of infections	Health care facilities with clinical laboratories
C-reactive protein	To detect inflammation as an indicator of various conditions	Health care facilities with clinical laboratories
Erythrocyte sedimentation rate	Erythrocyte sedimentation rate (ESR) could be used to complement C-reactive protein especially during follow up when clinical improvements may be slower to detect than laboratory improvements	Community settings and health facilities without laboratories <sup>a</sup>
Procalcitonin	To guide antibiotic therapy or discontinuation in sepsis	Only in tertiary care facilities

80 <sup>a</sup>Community health settings without laboratories are settings such as health posts and centres, doctors' offices,  
81 outreach clinics and ambulatory care. These tests are also assumed to be available at health care facilities with  
82 laboratories.

83 Additional tests that could be considered mostly to help exclude other bone diseases in adults  
84 (e.g. metastatic or metabolic bone disease) include calcium, phosphate and alkaline  
85 phosphatase. The rationale is that these tests are usually normal in case of osteomyelitis by they  
86 are usually abnormal in other bone diseases.

## 87 III. Using microbiology surveillance data

88 Routine clinical microbiology surveillance is generally not helpful in informing empiric guidance.

## 89 Imaging

90 Initial imaging with an X-ray is important when bone infections are suspected. However, a normal  
 91 X-ray on admission does not rule out acute osteomyelitis but it can help exclude alternative  
 92 diagnoses (e.g. a fracture or a malignant condition). In an X-ray, changes such as soft tissue  
 93 swelling, periosteal thickening and/or elevation and lytic lesions are often found later than  
 94 clinical disease. An X-ray could also help identify a sequester (dead bone) that needs to be  
 95 removed surgically. Where available, a computer tomography (CT) scan or magnetic resonance  
 96 imaging (MRI) could also be considered in certain patients (e.g. diagnostic uncertainty with X-  
 97 ray). MRI has a high degree of sensitivity and specificity to detect bone changes (especially in the  
 98 early phase). Nuclear imaging (e.g. bone scan or bone scintigraphy) could also be considered as  
 99 an alternative where available.

## 100 Surgical treatment

101 In adults, no surgical intervention is required in most cases of acute osteomyelitis that are  
 102 diagnosed and managed early in the course of illness. These cases can be treated with an  
 103 antibiotic alone with good bone penetration. However, in certain cases of acute osteomyelitis  
 104 (and always in case of chronic infections), surgical debridement of the bone may be required to  
 105 reduce the risk of complications because of impaired local vascularization (e.g. avascular necrosis  
 106 of the bone, permanent bone damage) and to remove “dead” bone and clean the surrounding  
 107 soft tissue.

108 In children, acute osteomyelitis is usually treated with medical management alone (i.e. no  
 109 surgery).

For prosthetic joint infections, treatment usually requires the surgical removal of the device. This can be done in one stage (the new prosthesis is immediately inserted) or two stages (the infected prosthesis is removed, the area is debrided, antibiotic treatment is given for several weeks and finally the new prosthesis is inserted). The choice of one stage or two stages depends on the location of the prosthesis (e.g. hip, knee), characteristics of the patient (e.g. advanced age, comorbidities) and local practices. A detailed discussion of prosthetic-joint infections is beyond the scope of this Handbook.

## 110 Antibiotic treatment

In adults with osteomyelitis, targeted antibiotic treatment based on microbiology is always preferred. In children, it is unusual to identify the pathogen and empiric treatment is usually given.

111 In adults empiric treatment is sometimes required (e.g. in severely ill patients requiring  
 112 immediate treatment or when it is not possible to obtain a clinical sample for microbiological  
 113 examination). In these cases, the choice of the antibiotic needs to be based on the pathogens  
 114 most commonly identified in this type of infections (see Table 5). In addition, empiric treatment

115 against community-acquired MRSA could be considered in some cases based on individual risk  
116 factors (e.g. MRSA colonization) and on the local prevalence of community-acquired MRSA.

117 Duration of treatment is usually long (weeks) but it differs in acute or chronic infections. Duration  
118 is also influenced by the presence, absence or removal of foreign bodies (including dead bone),  
119 the type of causative organism and its resistance profile and the use of antibiotics with an optimal  
120 antibiotic spectrum (i.e. based on microbiology results) and good bone penetration.

121 Total treatment duration of about 3 weeks is usually adequate in patients with uncomplicated  
122 disease and good clinical recovery, while complicated disease may require 6 weeks of treatment.

123 Uncomplicated infections are those with symptoms for < 14 days, no underlying disease, no  
124 penetrating trauma and no need for extensive surgical intervention.

125 Imaging studies are usually not useful to determine the duration of treatment.

126 **Simplify** empiric treatment to a more narrow-spectrum antibiotic based on culture results or  
127 rapid clinical improvement if culture results unavailable. Historically, the intravenous route has  
128 always been preferred, at least in the initial phase of treatment.

129 **Step down** to oral antibiotics at home is increasingly being used early in the treatment course  
130 (e.g. in the first week) when the disease is uncomplicated (322). Step down to oral treatment is  
131 based on improvement of symptoms and signs of infection, improved clinical function and the  
132 ability to take oral antibiotics with good bone penetration, especially in adults (e.g. clindamycin).

133 *Table 5 Empiric antibiotic treatment for osteomyelitis*

	Adults	Children and neonates	Total treatment duration
<b>First choice</b>	Cloxacillin <sup>a</sup> or flucloxacillin (IV): 2 g given every 6 hours	Cloxacillin <sup>a</sup> or flucloxacillin (IV/oral): <ul style="list-style-type: none"> <li>• Neonates: 25-50 mg/kg/dose given every 12 hours</li> <li>• Children: 25 mg/kg/dose given every 6 hours</li> </ul> Oral weight bands: 3-<6 kg: 125 mg given every 6 hours 6-<10 kg: 250 mg given every 6 hours 10-<15 kg: 250 mg given every 6 hours 15-<20 kg: 500 mg given every 6 hours 20-<30 kg: 750 mg given every 6 hours ≥ 30 Kg: Use adult dose	3 weeks <sup>e</sup> (in children with uncomplicated infections)  4-6 weeks <sup>f</sup> (in adults)
<b>Second choice</b>	Amoxicillin+clavulanic acid (IV): 1g + 200 mg given every 8 hours <b>OR</b> Cefazolin (IV): 2 g given every 8 hours <b>OR</b> Ceftriaxone <sup>b</sup> (IV): 2 g given once a day <b>OR</b>	Amoxicillin+clavulanic acid (IV/oral): 40-50 mg/kg/dose of amoxicillin component given every 12 hours <b>OR</b> 30 mg/kg/dose given every 8 hours  Oral weight bands <sup>d</sup> : 3-<6 kg: 250 mg of amoxicillin/dose given every 12 hours	Same as above

	<p><b>Cefotaxime<sup>b</sup></b> (IV) 2 g given every 8 hours  <b>OR</b>  <b>Clindamycin<sup>c</sup></b> (IV/oral): 600 mg given every 8 hours</p>	<p>6-&lt;10 kg: 375 mg of amoxicillin/dose given every 12 hours          10-&lt;15 kg: 500 mg of amoxicillin/dose given every 12 hours          15-&lt;20 kg: 750 mg of amoxicillin/dose given every 12 hours          20-&lt;30 kg: 1000 mg of amoxicillin/dose given every 12 hours          ≥ 30 Kg: Use adult dose</p> <p><b>OR</b>  <b>Cefazolin</b> (IV): 25 mg/kg/dose given every 12 hours  <b>OR</b>  <b>Ceftriaxone<sup>b</sup></b>(IV): 80 mg/kg/dose given once a day  <b>OR</b>  <b>Cefotaxime<sup>b</sup></b>(IV): 50mg/kg/dose given every 8 hours  <b>OR</b>  <b>Clindamycin<sup>c</sup></b>(IV/oral):</p> <ul style="list-style-type: none"> <li>• Neonates: 5 mg/kg/dose given every 8 hours</li> <li>• Children: 10 mg/kg/dose given every 8 hours</li> </ul>	
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134 IV: intravenous.

135 Notes: All dosages are for normal renal and hepatic function.

136 As mentioned in the text, empiric treatment should be avoided whenever possible in adults because there are many  
 137 potential causative pathogens and high levels of resistance (e.g. methicillin-resistant *Staphylococcus aureus*) making  
 138 it difficult to specify appropriate empiric treatment. In children there is usually less variability in the most likely  
 139 causative pathogens (in children the disease is mostly caused by spread of *Staphylococcus* spp. and *Streptococcus*  
 140 spp. through the bloodstream) and therefore empiric treatment is common practice.

141 In neonates, empirical antibiotic therapy should also cover Enterobacterales because infections caused by Gram-  
 142 negative bacteria can occur in neonates (but *Staphylococcus aureus* remains the most common pathogen).  
 143 Therefore, in neonates, empiric use of cefotaxime (or ceftriaxone) is appropriate (ceftriaxone should be avoided in  
 144 infants with hyperbilirubinemia). In older children, bone infections caused by Enterobacterales are very rare.

145 <sup>a</sup>If cloxacillin is unavailable, any other IV anti-staphylococcal penicillin could be used (e.g. dicloxacillin, flucloxacillin,  
 146 nafcillin, oxacillin).

147 <sup>b</sup>Ceftriaxone or cefotaxime is preferred if *Salmonella* spp. or Enterobacterales infection is suspected. In neonates,  
 148 cefotaxime is recommended in these cases.

149 <sup>c</sup>Clindamycin is still an acceptable option when community-acquired methicillin-resistant *Staphylococcus aureus*  
 150 (MRSA) is suspected or detected if antimicrobial susceptibility tests show that MRSA is sensitive to clindamycin or in  
 151 settings where MRSA maintains high levels of susceptibility to clindamycin. Clindamycin can also be used when  
 152 changing from the IV to the oral route, and in patients allergic to penicillin. In case of MRSA isolates resistant to  
 153 clindamycin and in settings where the prevalence of community-acquired MRSA is high, the use of vancomycin could  
 154 be considered when *Staphylococcus aureus* is suspected. Oral options to consider to complete the course of  
 155 treatment in case of MRSA or MSSA infections could be sulfamethoxazole+trimethoprim and doxycycline.

156 <sup>d</sup>Oral liquid must be refrigerated after reconstitution as clavulanic acid is rapidly metabolized in high ambient  
 157 temperatures.

158 <sup>e</sup>Three weeks of treatment (usually starting with 3–5 days IV treatment and then changing to oral treatment) are  
159 now commonly used in children with acute bloodborne osteomyelitis based on response to fever, ability to move  
160 the limb and reduction in levels of C-reactive protein (if available).  
161 <sup>f</sup>Longer treatments may be required if implants or foreign material are present or in case of inadequate control at  
162 the source of infection (e.g. where there is an abscess that has not been adequately drained).  
163 **ACCESS** antibiotics are highlighted in green, **WATCH** antibiotics in yellow and **RESERVE** antibiotics in red.

DRAFT

# 1 Septic arthritis

## 2 Key messages

1. Septic arthritis can occur alone or in combination with osteomyelitis
2. Ideally microbiology tests (e.g. synovial fluid culture) results should be obtained before starting antibiotics
3. Targeted treatment is preferable whenever possible in adults (because of the large number of potential causative pathogens) while in children empiric treatment is usually given
4. In general, the intravenous route is preferred for initial antibiotic treatment, but rapid oral step down is increasingly used.
5. Surgical lavage or needle aspiration as a form of source control is important in adults

3

*Box 1 Other relevant WHO documents (please check regularly for updates)*

- WHO 2013 pocket book of hospital care for children <https://apps.who.int/iris/handle/10665/81170> (23)

## 4 Definition

5 Septic arthritis is an infection of one or several joints usually of bacterial origin. Infections can be  
6 classified based on the causative pathogen (gonococcal or non-gonococcal), on the type of  
7 affected joint (large or small joint) and on the concomitant presence or absence of osteomyelitis.

## 8 Pathophysiology

9 In case of septic arthritis, bacteria can reach the joint through dissemination through the  
10 bloodstream, by local spread or by direct inoculation from a contiguous infected bone or soft  
11 tissue (e.g. local spread following trauma or bites, bone surgery, prosthetic joint implantation,  
12 pressure and decubitus ulcers, diabetic foot infections)(323). Dissemination through the  
13 bloodstream is more common both in children and adults. Once bacteria gain access into the  
14 joint space, they can adhere to the articular cartilage, produce an inflammatory response and  
15 promote cartilage destruction within hours. If left untreated, septic arthritis can rapidly lead to  
16 destruction of the cartilage. It therefore needs to be rapidly diagnosed and treated.

## 17 Epidemiology

18 Septic arthritis is associated with substantial morbidity (e.g. adverse joint outcomes) and a low  
 19 mortality(323, 324). People at risk of septic arthritis are people with a higher risk of bacteremia  
 20 (e.g. those with indwelling vascular catheters, injection drug users, patients on hemodialysis) and  
 21 those with a higher likelihood of the joint becoming infected (e.g. patients with rheumatoid  
 22 arthritis, diabetes, sickle-cell disease and prosthetic joints and other foreign material). Post-  
 23 surgical infections are common in adults. Community-acquired infections are quite rare in adults  
 24 while they are common in children.

25 In children, septic arthritis is more frequent in low-and middle-income countries and in boys  
 26 more than girls; if left untreated or managed late, septic arthritis can leave children with long-  
 27 term disability.

28 Gonococcal arthritis, characterized by dissemination of the infection through the bloodstream,  
 29 is a rare complication of gonorrhoea that mostly affects women.

## 30 Microbiology epidemiology

31 A large variety of pathogens can cause septic arthritis with some differences between children  
 32 and adults (Table 1 and Table 2).

33 *Table 1 Pathogens most frequently associated with acute septic arthritis in children (in descending*  
 34 *order of frequency)*

Pathogen	Most common mechanism of dissemination	Patients most at risk
<i>Staphylococcus aureus</i> (including MRSA)	Bloodborne or by local spread	Usually, no risk factors are identified but consider after penetrating injuries or recent surgical procedures, and in patients with bite wounds
<i>S. pyogenes</i> (group A <i>Streptococcus</i> ) and less commonly <i>S. pneumoniae</i>  <i>Streptococcus agalactiae</i> (group B <i>Streptococcus</i> ) is a potential pathogen for neonates	Bloodborne	Mostly no risk factors are identified but consider penetrating injuries or recent surgical procedures
<i>Kingella kingae</i> (a species of anaerobic Gram-negative bacilli)	Bloodborne	Young children, usually with milder clinical disease
<i>Haemophilus influenzae</i> type b	Bloodborne	Young children not vaccinated against <i>Haemophilus influenzae</i> type b
Non-typhoidal <i>Salmonella</i> spp.	Bloodborne	Children with sickle-cell disease
Enterobacterales	Bloodborne	Neonates and immunosuppressed children

35 MRSA: methicillin-resistant *Staphylococcus aureus*.

36 *Table 2 Pathogens most frequently associated with acute septic arthritis in adults*

Pathogen	Main dissemination mechanism	Patients most at risk
<i>Staphylococcus aureus</i> (including MRSA)	Bloodborne or by local spread	Patients with penetrating injuries or who underwent surgical procedures. Patients with bite wounds or intravenous drug injection
<i>Staphylococcus</i> spp. other than <i>Staphylococcus aureus</i>	Bloodborne or by local spread	Patients that underwent implantation of prosthetic joint implants or arthroscopy. Patients with bite wounds
<i>Streptococcus</i> spp.	Bloodborne or by local spread	Splenic dysfunction
<b>Less frequent (in alphabetical order)</b>		
Anaerobes	By local spread	Patients with bite wounds
<i>Bartonella</i> spp.	Bloodborne	Patients with cat bite wounds
<i>Brucella</i> spp.	Bloodborne	Patients with occupational or domestic exposure to infected animals (e.g. farmers, shepherds, veterinarians) or who have ingested contaminated food (mostly dairy products). Endemic in the Middle East and Mediterranean regions
<i>Candida</i> spp.	Bloodborne or by local spread	Immunosuppressed patients, patients with invasive devices, patients who inject drugs (hematogenous spread) or patients with deep wounds (dissemination by local spread)
<i>Cryptococcus</i> spp	Bloodborne	Immunosuppressed patients
Enterobacterales	Bloodborne or by local spread	Patients with decubitus or pressure ulcers, diabetic foot infections, burn wounds (especially if the wound is close to the perineum) and those having undergone recent abdominal surgery
<i>Histoplasma</i> spp	Bloodborne	Immunosuppressed patients
<i>Neisseria gonorrhoeae</i>	Bloodborne	Mostly women with disseminated gonococcal infection
<i>Mycobacterium tuberculosis</i>	Bloodborne	Immunosuppressed patients because of the risk of reactivation of tuberculosis
<i>Pseudomonas aeruginosa</i>	Bloodborne or by local spread	Immunosuppressed patients and people who inject drugs

37 MRSA: methicillin-resistant *Staphylococcus aureus*.38 **Clinical presentation**

Septic arthritis can occur alone or in combination with osteomyelitis.
--

39 Septic arthritis is characterized by acute onset (usually a few days, but up to 2 weeks) of joint  
40 pain (moderate to severe) and reduced range of motion with redness, swelling and warmth of  
41 the joint. The condition may be less evident when “deep” joints such as the hip, shoulder or  
42 sacroiliac joint are affected. In most cases, one single joint is affected (often the knee).  
43 Involvement of more than one joint (polyarticular infection) is more common with underlying  
44 rheumatoid arthritis. Other signs of systemic infection (e.g. fever >38.0°C, tachycardia, increased  
45 biomarkers of inflammation) are usually present.

46 In certain situations (e.g. septic arthritis of multiple joints), it is important to exclude an extra-  
47 articular source of infection (e.g. endocarditis).

48 In young children permanent destruction of the joint cartilage and long-term disability can occur  
49 rapidly, therefore rapid diagnosis and prompt empiric antibiotic treatment are essential.

50 In case of gonococcal arthritis, typical signs and symptoms of septic arthritis (mostly affecting  
51 one or a few joints and usually the knees and ankles) are usually accompanied by skin  
52 manifestations (e.g. rash, small papules on the trunk and distal extremities). Often patients with  
53 gonococcal arthritis have no signs or symptoms of cervicitis or urethritis.

## 54 Laboratory tests

### 55 I. Patient microbiology data

56 Determining the causative pathogen of septic arthritis is important for targeting antibiotic  
57 treatment because the number of potential causative pathogens is large (making it difficult to  
58 select empiric treatment) and treatment duration may be long (increasing the risk of side effects  
59 from the antibiotic therapy).

60 Whenever possible a microbiology sample should therefore be obtained to guide antibiotic  
61 treatment (Table 3). Ideally microbiology tests results should be obtained before starting  
62 antibiotic treatment, however because cartilage destruction can occur within hours, tests should  
63 never delay the start of antibiotic treatment.

64 *Table 3 Microbiology tests to consider when septic arthritis is suspected, as indicated in the WHO*  
65 *EDL (54)*

Diagnostic test	Purpose of the test	Settings where the test should be available
Synovial fluid for microscopy and culture <sup>a</sup>	Initial step to detect and identify bacterial and fungal species for selection of appropriate antibiotic regimens	Healthcare facilities with clinical laboratories
Blood cultures	To detect bacterial bloodstream infections (sepsis)	Healthcare facilities with clinical laboratories
Microscopy and culture of deep samples collected at debridement in case of prosthetic joint implant	Initial step to detect and identify bacterial and fungal species for selection of appropriate antibiotic regimens	Healthcare facilities with clinical laboratories

66 <sup>a</sup>Examination for particular pathogens (e.g. mycobacteria, fungi, *Brucella* spp.) should be done if  
 67 clinical/epidemiological features are compatible. In cases of gonococcal arthritis, the culture of the synovial fluid is  
 68 usually negative.

## 69 II. Other tests

70 Laboratory tests can be used to complement the clinical examination and history and may help  
 71 decide between bacterial septic arthritis and a viral reactive arthritis. Tables 4 and Table 5 list  
 72 tests that could be considered in the initial assessment of the patient to help make a diagnosis  
 73 and guide the duration of antibiotic treatment.

74 *Table 4 Laboratory tests (other than microbiology) to consider to identify a bacterial joint*  
 75 *infection, as indicated in the WHO EDL (54)*

Diagnostic test	Purpose of the test	Settings where the test should be available
White blood count	To help in the diagnosis of infections	Healthcare facilities with clinical laboratories but also in primary care settings
C-reactive protein	To detect inflammation as an indicator of various conditions	Healthcare facilities with clinical laboratories
Procalcitonin	To guide antibiotic therapy or discontinuation in sepsis	Only in tertiary care facilities
Erythrocyte sedimentation rate	To detect inflammation as an indicator of various conditions when C-reactive protein is not available	Community settings and health facilities without laboratories <sup>a</sup>

76 <sup>a</sup>Community and health settings without laboratories are settings such as health posts and centres, doctors'  
 77 offices, outreach clinics and ambulatory care. These tests are also assumed to be available at health care facilities  
 78 with laboratories.

79 *Table 5 Synovial fluid examination*

Diagnostic test	Purpose of the test	Settings where the test should be available
Synovial fluid: white cell count and crystals <sup>a</sup>	To detect the presence or absence of white blood cells and crystals	Healthcare facilities with clinical laboratories

80 <sup>a</sup>With septic arthritis, it is helpful to know the number of white blood cells in the synovial fluid and microscopy should  
 81 also be done to investigate alternative diagnoses such as gout or chondrocalcinosis. Compared to non-infectious  
 82 arthritis, acute bacterial infections are characterized by a much higher white cell count in the synovial fluid (usually  
 83 > 20 000 cells/μL [20 G/L]) with > 90% being neutrophils.

## 84 III. Using microbiology surveillance data

85 Due to the wide number of pathogens identified, there is no role for routine surveillance cultures  
 86 to inform empiric guidance.

## 87 Imaging

88 Initial imaging with an ultrasound is useful when joint infections are suspected to detect joint  
89 effusion and synovial swelling due to the presence of increased intra-articular fluid.

90 Magnetic resonance imaging (MRI) could also be considered, if available, in certain patients  
91 particularly when concomitant osteomyelitis is suspected, because MRI is more sensitive and  
92 specific in detecting bone changes.

## 93 Treatment

94 Prompt surgical drainage of any purulent material (aspiration) and washing of the joint (lavage)  
95 is a key part of the management of septic arthritis since antibiotics alone are usually not sufficient  
96 to control the source of the infection (at least in adults). Aspiration and lavage can reduce the  
97 risk of complications (e.g. permanent cartilage destruction, joint deformity and instability,  
98 degenerative arthritis). Immobilization of the joint is not necessary except for pain control.

For prosthetic-joint infections, treatment can be in one or two stages depending on the location of the prosthesis (e.g. hip, knee), characteristics of the patient (e.g. older age, comorbidities) and on local practices. In the one-stage procedure, the old device is surgically removed and the new prosthesis is immediately inserted. In the two-stage procedure, the infected prosthesis is removed, the area is debrided, and antibiotic treatment is given for several weeks. Then, in the second stage, the new prosthesis is inserted.

A detailed discussion of prosthetic-joint infections is beyond the scope of this chapter.

## 99 Antibiotic treatment

In adults, targeted antibiotic treatment based on microbiology results is always preferred (unless the patient is severely ill or it is impossible to obtain a clinical sample for microbiological examination) because there are many potential causative pathogens, which makes it difficult to select an appropriate empiric treatment.

In young children, the treatment is often empiric.

100 When patients require empiric treatment (mostly young children or severely ill patients or when  
101 it is impossible to obtain a clinical sample for microbiological examination), the choice should be  
102 based on the most probable pathogens in this type of infection (mostly *Staphylococcus aureus*  
103 and *Streptococcus* spp.; see Table 6). In addition, empiric treatment against community-acquired  
104 methicillin-resistant *Staphylococcus aureus* (CA-MRSA) or *Neisseria gonorrhoeae* may be  
105 considered in certain cases based on individual risk factors (e.g. known MRSA colonization) and  
106 compatible clinical and epidemiological features.

107 The duration of treatment is long (several weeks, except for gonococcal arthritis that requires  
108 shorter treatment) and is influenced by: the duration of symptoms (acute or chronic), the  
109 presence, absence or removal of foreign bodies (including devitalized bone if concomitant  
110 osteomyelitis is present), the type of causative pathogen and its resistance profile and the

111 concomitant presence of osteomyelitis (and therefore the availability of antibiotics with good  
112 bone penetration).

113 The total treatment duration is generally 3 weeks in children and 4-6 weeks in adults. In case of  
114 gonococcal arthritis, a shorter treatment duration (10-14 days) is adequate.

115 **Simplify** empiric treatment to a more narrow-spectrum antibiotic based on culture results or  
116 rapid clinical improvement if culture results unavailable. Historically, the intravenous route has  
117 always been preferred at least in the first week of treatment. However, recent evidence suggests  
118 that a change to oral antibiotics in the first week of treatment can be used for patients with  
119 uncomplicated disease.

120 **Step down** to oral treatment is based on improvement of symptoms and signs of infection,  
121 improvement in joint function and the ability to take oral antibiotics allowing discharge of the  
122 patient home when clinically appropriate.

123 *Table 6 Empiric antibiotic treatment for septic arthritis*

	Adults	Children	Total treatment duration
<b>First choice</b>	Cloxacillin or flucloxacillin <sup>a</sup> (IV): 2g given every 6 hours	Cloxacillin <sup>a</sup> or flucloxacillin (IV/oral): <ul style="list-style-type: none"> <li>• Neonates: 25-50 mg/kg/dose given every 12 hours</li> <li>• Children: 25 mg/kg/dose given every 6 hours</li> </ul> Oral weight bands: 3-<6 kg: 125 mg given every 6 hours 6-<10 kg: 250 mg given every 6 hours 10-<15 kg: 250 mg given every 6 hours 15-<20 kg: 500 mg given every 6 hours 20-<30 kg: 750 mg given every 6 hours ≥ 30 Kg: Use adult dose	Children: 3 weeks  Adults: 4-6 weeks <sup>d</sup>
<b>Second choice</b>	Amoxicillin+clavulanic acid (IV): 1g + 200 mg given every 8 hours  OR Cefazolin (IV): 2 g given every 8 hours  OR Ceftriaxone <sup>b</sup> (IV): 2g given once a day  OR Cefotaxime <sup>b</sup> (IV): 2 g given every 8 hours  OR	Amoxicillin+clavulanic acid (IV/oral): 40-50 mg/kg/dose of amoxicillin component, given every 12 hours OR 30 mg/kg/dose given every 8 hours  Oral weight bands <sup>d</sup> : 3-<6 kg: 250 mg of amoxicillin/dose given every 12 hours 6-<10 kg: 375 mg of amoxicillin/dose given every 12 hours 10-<15 kg: 500 mg of amoxicillin/dose given every 12 hours 15-<20 kg: 750 mg of amoxicillin/dose given every 12 hours 20-<30 kg: 1000 mg of amoxicillin/dose given every 12 hours	Children: 3 weeks  Adults: 4-6 weeks <sup>e</sup>

	<p>Clindamycin<sup>c</sup> (IV/oral): 600 mg given every 8 hours</p>	<p>≥ 30 Kg: Use adult dose</p> <p>OR</p> <p>Cefazolin(IV): 25 mg/kg/dose given every 12 hours</p> <p>OR</p> <p>Ceftriaxone<sup>b</sup> (IV): 80 mg/kg/dose given once a day</p> <p>OR</p> <p>Cefotaxime<sup>b</sup> (IV): 50mg/kg/dose given every 8 hours</p> <p>OR</p> <p>Clindamycin<sup>c</sup> (IV/oral):</p> <ul style="list-style-type: none"> <li>• Neonates: 5 mg/kg/dose given every 8 hours</li> <li>• Children: 10 mg/kg/dose given every 8 hours</li> </ul>	
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124 IV: intravenous.

125 Notes: All dosages are for normal renal and hepatic function.

126 As mentioned in the text, targeted treatment is preferable whenever possible in adults (because of the large number  
127 of potential causative pathogens) while in children empiric treatment is often given.

128 In neonates, empirical antibiotic therapy should also cover Enterobacterales because infections caused by Gram-  
129 negative bacteria can occur (but *Staphylococcus aureus* remains the most common pathogen). Therefore, in  
130 neonates, empiric use of cefotaxime (or ceftriaxone) is appropriate (ceftriaxone should be avoided in infants with  
131 hyperbilirubinemia). In older children, joint infections caused by Enterobacterales are very rare.

132 <sup>a</sup>If cloxacillin is unavailable, any other IV antistaphylococcal penicillin could be used (e.g. dicloxacillin, flucloxacillin,  
133 nafcillin, oxacillin).

134 <sup>b</sup>Ceftriaxone or cefotaxime is preferred in cases of suspected *Salmonella* spp. infection or Enterobacterales infection  
135 or gonococcal arthritis. In neonates, cefotaxime is recommended in these cases.

136 <sup>c</sup>Clindamycin is still an acceptable option when community-acquired methicillin-resistant *Staphylococcus aureus*  
137 (MRSA) is suspected if antimicrobial susceptibility tests show that MRSA is sensitive to clindamycin or in settings  
138 where MRSA maintains high levels of susceptibility to clindamycin (i.e. suspicion should be based on local prevalence  
139 of community-acquired MRSA). Clindamycin can also be used when changing from the IV to oral route, and in  
140 patients allergic to penicillin. For severe disease potentially caused by MRSA, vancomycin can be considered in  
141 settings with local high prevalence of community-acquired MRSA, even though this is not a recommendation  
142 included in the current EML/c (4, 5). In case of MRSA and based on susceptibility results, alternative oral options that  
143 could be considered to complete the course of treatment include sulfamethoxazole+trimethoprim and doxycycline.

144 <sup>d</sup>Oral liquid must be refrigerated after reconstitution as clavulanic acid is rapidly metabolized in high ambient  
145 temperatures.

146 <sup>e</sup>Shorter duration (10-14 days) in cases of gonococcal arthritis.

147 ACCESS antibiotics are highlighted in green, WATCH antibiotics in yellow and RESERVE antibiotics in red.

# 1 Skin and soft tissue infections -

## 2 Necrotizing fasciitis

### 3 Key messages

1. Life-threatening rapidly progressing infection of the deep soft tissue with pain out of proportion to skin findings
2. Surgery is both diagnostic and therapeutic (surgical exploration and debridement of necrotic tissue) and delays in surgery are associated with higher mortality
3. Antibiotic treatment is important but needs to be accompanied by source control (surgery)
4. Children are rarely affected (cases occur mostly in immunosuppressed children or as a complication of chickenpox)

### 4 Definition

5 Necrotizing fasciitis is a life-threatening necrotizing infection of the deep soft tissues that  
6 specifically affects the muscular fascia (the fascia is the connective tissue surrounding the  
7 muscle). The disease is caused mostly by bacteria and is characterized by acute and fulminant  
8 (severe and sudden onset) necrosis with tissue destruction and signs of systemic toxicity.  
9 Necrotizing fasciitis can be classified based on the causative pathogen; type 1 or polymicrobial  
10 necrotizing fasciitis (caused by multiple pathogens) or type 2 or monomicrobial necrotizing  
11 fasciitis (caused by a single pathogen); the presence or absence of gas in tissues (polymicrobial  
12 infections are more often associated with the presence of gas); the site of the infection (e.g. leg,  
13 head and neck, perineum); or the risk of a poor outcome (high versus low or moderate risk).  
14 Necrotizing fasciitis affecting the perineum is also called Fournier gangrene.

### 15 Pathophysiology

16 In necrotizing fasciitis, bacteria can reach the muscular fascia by local spread through a skin lesion  
17 or a break in the skin barrier (e.g. wounds, bites, injection of drugs, surgery) or through a breach  
18 in the mucosal barrier (usually in the intestine, e.g. the source could be a diverticulum or a  
19 malignancy, or in the oropharynx). Infections can thus be both exogenous (i.e. pathogens that  
20 enter the body from the environment) and endogenous (i.e. pathogens that naturally reside in  
21 the body). However, often a clear place of entry is not identified. Bacteria can also reach the  
22 muscular fascia via the bloodstream, although this is less common.

23 Necrotizing fasciitis is characterized by tissue damage with necrosis and inflammatory fluid  
 24 accumulation along the fascia and between muscle groups. The muscle is usually not affected;  
 25 however, sometimes muscular abscesses can form. Legs and arms are the most commonly  
 26 affected sites.

## 27 Epidemiology

28 Necrotizing fasciitis is a rare but life-threatening disease. Polymicrobial forms occur most  
 29 frequently in older adults and/or individuals with underlying comorbidities (mostly  
 30 diabetes(325), peripheral vascular disease, immunosuppression) or traumatic or surgical  
 31 wounds. Intravenous drug injection is also a risk factor. Monomicrobial forms can occur at any  
 32 age, including in otherwise healthy individuals, and they are the most common form in  
 33 children(326). Toxic shock syndrome is a rare life-threatening complication of necrotizing fasciitis  
 34 due to toxin production by *Streptococcus pyogenes* (often referred to as group A *Streptococcus*)  
 35 or *Staphylococcus aureus* and can also be the cause of septic shock when these pathogens are  
 36 involved.

## 37 Microbiology epidemiology

38 The most common pathogens causing mono- and polymicrobial necrotizing fasciitis are listed in  
 39 Table 1.

40 *Table 1 Pathogens most frequently associated with necrotizing fasciitis (in descending order of*  
 41 *frequency)*

Monomicrobial (single pathogen)/Type 2	Polymicrobial (multiple pathogens)/Type 1
<p><b>Most cases:</b>  <i>Streptococcus pyogenes</i> (group A <i>Streptococcus</i>)  <i>Streptococcus agalactiae</i>  <i>Streptococcus dysgalactiae</i> (mostly in elderly people and patients with chronic illness)</p> <p><b>Less frequently</b>  <i>Staphylococcus aureus</i> (MSSA and MRSA strains)</p> <p><b>Pathogens to consider in cases with specific environmental exposure</b>  <i>Aeromonas hydrophila</i> (exposure to fresh water)  <i>Vibrio vulnificus</i> (exposure to seawater)</p>	<p>Combination of anaerobes:</p> <ul style="list-style-type: none"> <li>• <i>Bacteroides</i> spp.</li> <li>• <i>Clostridium perfringens</i></li> <li>• <i>Peptostreptococcus</i> spp. or oral anaerobic organisms when the head and/or neck are affected)</li> </ul> <p>and</p> <ul style="list-style-type: none"> <li>• Enterobacterales</li> <li>• <i>Pseudomonas</i> spp.</li> <li>• <i>Streptococcus</i> spp.</li> <li>• <i>Staphylococcus aureus</i> (including MRSA strains)</li> </ul>

42 MSSA: methicillin-susceptible *Staphylococcus aureus*; MRSA: methicillin-resistant *Staphylococcus aureus*.

## 43 Clinical presentation

44 Clinical progression to severe disease is rapid. Therefore, the patient should always be carefully  
 45 monitored for signs of sepsis or septic shock. Please also refer to the chapter on sepsis if  
 46 suspected.

## 47 Adults

48 Necrotizing fasciitis is usually characterized by acute onset of pain out of proportion to physical  
49 findings in the affected area and rapid onset of systemic signs – for example, fever > 38.0 °C,  
50 tachycardia, and increased biomarker levels (leukocytosis, C-reactive protein and  
51 procalcitonin)(327).

52 Signs and symptoms of skin and soft tissue infections (i.e. redness, skin discolouration, swelling,  
53 induration (hardening of soft tissue) and warmth of the affected area) are usually present when  
54 pathogen entry is through the skin. However, at least initially, the overlying skin often appears  
55 only minimally affected, and skin changes – typically bullae and necrosis – only become apparent  
56 as the infection progresses.

57 In cases of necrotizing fasciitis of the perineum (Fournier gangrene), severe pain is accompanied  
58 by signs of necrosis in the perineal area (often the scrotum in men). Rapid progression of the  
59 infection to the abdominal wall and gluteal muscles is possible.

60 While in patients with cellulitis, skin abnormalities are the usual symptoms, in patients with  
61 necrotizing fasciitis, severe pain (often disproportionate to skin changes) is the characteristic  
62 symptom, at least in the initial phase. A definitive diagnosis requires the direct visualization of  
63 necrotic tissue in the muscular fascia through surgical exploration.

## 64 Children

65 Necrotizing fasciitis is very rare in children but may occur as a complication of varicella  
66 (chickenpox) or can be associated with a compromised immune system. Most characteristics  
67 described for adults also apply to children, but certain specific features exist(328). For example,  
68 in neonates and infants, the torso is often affected, while in older children the arms and legs and  
69 the face are affected.

## 70 Laboratory tests

### 71 1. Patient microbiology tests

72 Whenever possible, a microbiology sample of the affected tissue should be obtained to guide  
73 antibiotic treatment (e.g. samples can be collected at the time of surgical exploration). This will  
74 allow the causative pathogen(s) to be determined so that adequate antibiotic treatment can be  
75 given (e.g. single versus multiple causative pathogens). Blood cultures should also be obtained,  
76 ideally before antibiotic treatment is started (Table 2).

77 *Table 2 Microbiology tests to consider in a patient with suspected necrotizing fasciitis as indicated*  
78 *in the WHO EDL (54)*

Diagnostic test	Purpose of the test	Setting where the test should be available
Blood cultures	To detect bacterial and fungal bloodstream infections (sepsis)	Health care facilities with clinical laboratories

Microscopy and culture of deep samples of tissue collected at debridement <sup>a</sup>	Initial step in detection and identification of bacterial and fungal species for selection of appropriate antibiotic regimens	Health care facilities with clinical laboratories
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79 <sup>a</sup>Intraoperative tissue samples should also be sent for histopathology examination.

## 80 II. Other tests

81 Laboratory tests can be used to complement clinical examination and history. Tables 3 and 4 give  
82 several tests that could be considered in the initial assessment of the patient suspected of having  
83 necrotizing fasciitis and to help guide the length of antibiotic treatment. Please also refer to the  
84 chapter on sepsis if suspected.

85 *Table 3 Laboratory tests (other than microbiology) to consider to identify a bacterial infection as*  
86 *indicated in the WHO EDL (54)*

Diagnostic test	Purpose of the test	Setting where the test should be available
White blood count	To help in the diagnosis of infections	Health care facilities with clinical laboratories but also in primary care settings
C-reactive protein	To detect inflammation as an indicator of various conditions, e.g. sepsis	Health care facilities with clinical laboratories
Procalcitonin	To guide antibiotic therapy or discontinuation in sepsis	Only in tertiary health care facilities

87 *Table 4 Laboratory tests (other than microbiology) to consider in a patient with suspected*  
88 *necrotizing fasciitis as indicated in the WHO EDL (54)*

Diagnostic test	Purpose of the test	Setting where the test should be available
Complete blood count	To detect a wide range of disorders, including infections	Health care facilities with clinical laboratories
Creatinine	To monitor kidney function for management of severe infections (i.e. sepsis,) and adjustment of the antimicrobial regimen	Health care facilities with clinical laboratories
Electrolytes	To monitor fluid, electrolyte and acid–base balance	Health care facilities with clinical laboratories
Glucose	To diagnose intermediate hyperglycaemia and hypoglycaemia	Community settings and health facilities without laboratories
Haemoglobin	To diagnose and monitor anaemia Clinical marker for certain severe infections	Community settings and health facilities without laboratories

89 <sup>a</sup>If sepsis is suspected, additional tests may be needed (please refer to the chapter on sepsis).

## 90 III. Using microbiology surveillance data

91 There is no role for routine surveillance to inform empiric guidance.

## 92 Imaging

93 Imaging should not delay surgical exploration (or surgical inspection) since surgery is still the  
94 most reliable tool to diagnose and treat necrotizing fasciitis.

95 If available, ultrasound imaging may help in the diagnosis of necrotizing fasciitis and to evaluate  
96 the extent to which the tissue is affected and the presence or absence of gas and fluid along the  
97 muscular fascia. A computed tomography scan of the affected area could also be considered.

## 98 Management

99 Prompt surgical removal of the necrotic tissue through drainage and debridement is the  
100 cornerstone of treatment of necrotizing fasciitis. Delays in this step are usually associated with  
101 higher mortality(329). Antibiotic treatment is a complementary measure to adequate surgical  
102 source control of the infection.

103 Intravenous immunoglobulin is occasionally used when shock is a complication in necrotizing  
104 fasciitis and therefore toxic shock syndrome (mostly due to *S. pyogenes* or *S. aureus*) is suspected;  
105 however, the effect of the use of high cost intravenous immunoglobulin on mortality is  
106 unclear(330).

## 107 Antibiotic treatment

108 Because of the seriousness of necrotizing fasciitis and the speed at which it can progress, empiric  
109 antibiotic treatment should be given immediately when necrotizing fasciitis is suspected, the  
110 antibiotics should cover both Gram-positive bacteria (including methicillin-resistant  
111 *Staphylococcus aureus*) and anaerobic pathogens (Table 5).

112 In patients at higher risk of a Gram-negative bacterial infection (e.g. patients with severe  
113 immunosuppression), additional empiric medicines should be considered that have activity  
114 against these pathogens.

115 **Simplify** empiric treatment to a more narrow-spectrum antibiotic based on culture results or  
116 rapid clinical improvement if culture results unavailable.

117 **Step-down** to oral treatment is based on improvement of symptoms and signs of infection and  
118 the ability to take oral antibiotics allowing discharge of the patient home when clinically  
119 appropriate.

120 *Table 5 Empiric antibiotic treatment for suspected or confirmed necrotizing fasciitis*

Adults	Children	Total treatment duration
Piperacillin+tazobactam (IV): 4 g + 500 mg given every 6 hours AND clindamycin <sup>a</sup> (IV): 900 mg given every 8 hours	Piperacillin+tazobactam (IV): 100 mg/kg/dose of piperacillin component given every 8 hours AND clindamycin <sup>a</sup> (IV):	2–3 weeks <sup>b</sup>

<p>OR (only if <i>Streptococcus pyogenes</i> necrotizing fasciitis has been excluded):  <b>Ceftriaxone</b> (IV): 2 g given once a day                  AND <b>metronidazole</b> (IV): 500 mg given every 8 hours</p> <p>ADD  <b>Vancomycin</b> (IV) if MRSA is suspected:                  15-20 mg/kg given every 12 hours</p>	<ul style="list-style-type: none"> <li>• Neonates: 5 mg/kg/dose given every 8 hours</li> <li>• Children: 10 mg/kg/dose given every 8 hours</li> </ul> <p>OR (only if <i>Streptococcus pyogenes</i> necrotizing fasciitis has been excluded):  <b>Ceftriaxone</b> (IV): 80 mg/kg given once a day                  AND <b>metronidazole</b> (IV/oral):</p> <ul style="list-style-type: none"> <li>• Neonates: 7.5 mg/kg/dose given every 12 hours</li> <li>• Children: 7.5 mg/kg/dose given every 8 hours</li> </ul> <p>Oral weight bands:                  3-&lt;6 kg: 30 mg given every 8 hours                  6-&lt;10 kg: 50 mg given every 8 hours                  10-&lt;15 kg: 100 mg given every 8 hours                  15-&lt;20 kg: 150 mg given every 8 hours                  20-&lt;30 kg: 200 mg given every 8 hours                  ≥ 30 Kg: Use adult dose</p> <p>ADD  <b>Vancomycin</b> (IV) if MRSA is suspected:</p> <ul style="list-style-type: none"> <li>• Neonates: 15 mg/kg/dose given every 12 hours</li> <li>• Children: 15 mg/kg/dose given every 8 hours</li> </ul>	
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- 121 Notes: All dosages are for normal renal and hepatic function.  
 122 IV: intravenous, MRSA: methicillin-resistant *Staphylococcus aureus*.  
 123 <sup>a</sup>Clindamycin has the ability to suppress the expression of virulence factors in *Staphylococcus aureus* (i.e. it has an  
 124 anti-toxin effect).  
 125 <sup>b</sup>Knowledge on the most appropriate duration of treatment is limited. Therefore, duration is often individualized  
 126 based on clinical response, on the success of surgical source control and, if available, changes in laboratory  
 127 markers of infection. Usually total treatment duration is about 2–3 weeks.  
 128 **ACCESS** antibiotics are highlighted in green, **WATCH** antibiotics in yellow and **RESERVE** antibiotics in red.

# 1 Skin and soft tissue infections -

## 2 Pyomyositis

### 3 Key messages

1. Most cases occur in tropical countries in young children and adults
2. Most cases (> 90%) of pyomyositis are caused by *Staphylococcus aureus* and *Streptococcus* spp and Access group antibiotics are the mainstay of treatment
3. If an abscess is present, source control and antibiotic treatment have a complementary role in controlling the infection
4. Immunosuppression is a risk factor

4 *Box 1 Other relevant WHO documents (please check regularly for updates)*

- WHO 2013 pocket book of hospital care for children <https://apps.who.int/iris/handle/10665/81170> (23)

### 5 Definition

6 Pyomyositis is an infection of a skeletal muscle caused by bacteria usually accompanied by  
7 abscess formation.

### 8 Pathophysiology

9 In pyomyositis, bacteria reach the muscle from another source of infection spread by the  
10 bloodstream. Once bacteria reach the muscle, an inflammatory reaction develops with initial  
11 swelling of the muscle and progressive abscess formation and increasing oedema. The process  
12 may take days to few weeks for the signs of systemic infection to appear and the presence of a  
13 pus collection large enough to be drained to become clinically evident.

### 14 Epidemiology

15 Most cases of pyomyositis occur in tropical countries often in young children (< 5 years of age)  
16 or in adults (aged 20–45 years), and males are more affected than females. History of trauma or  
17 muscle strain are usually present. HIV, malnutrition and malignancies may be risk factors in the  
18 tropics, even though most patients are otherwise healthy. In non-tropical countries, the disease  
19 is more common in adults with underlying severe medical conditions (e.g. immunosuppressed  
20 patients)(331).

## 21 Clinical presentation

22 Pyomyositis is characterized by acute onset (usually days to a few weeks) of localized muscle pain  
 23 with cramping usually in the lower limbs or in the gluteal muscles (although any muscle can be  
 24 affected) with a fever > 38.0 °C. Swelling and induration (hardening of soft tissue) of the affected  
 25 area are also usually present when the disease becomes clinically evident. Other signs of systemic  
 26 infection (e.g. tachycardia, increased biomarker levels such as leukocytosis, C-reactive protein  
 27 and procalcitonin) are usually present. Abscess can form within days to weeks. Complications of  
 28 bacteraemia (e.g. septic emboli, septic arthritis and endocarditis) can occur. The patient should  
 29 always be monitored for signs of severe clinical progression (e.g. signs of sepsis or septic shock).  
 30 Please also refer to the chapter on sepsis if suspected.

## 31 Microbiology epidemiology

32 Most cases (> 90%) of pyomyositis are caused by *Staphylococcus aureus* including methicillin-  
 33 resistant *Staphylococcus aureus* (MRSA) strains or by *Streptococcus* spp. (mostly *Streptococcus*  
 34 *pyogenes* often referred to as group A *Streptococcus*) (Table 1). *Escherichia coli* can sometimes  
 35 be implicated, especially in patients with cancer. Mycobacteria (*Mycobacterium tuberculosis* and  
 36 certain non-tuberculous mycobacteria) can also be responsible for this infection.

37 *Table 1 Pathogens most frequently associated with pyomyositis (in descending order of*  
 38 *frequency)*

39 <b>Most cases</b>	<i>Staphylococcus aureus</i> (including MRSA) <i>Streptococcus pyogenes</i> (group A <i>Streptococcus</i> )
<b>More rarely</b>	<i>Escherichia coli</i> (mostly in patients with cancer) <i>Mycobacterium tuberculosis</i> and certain non-tuberculous mycobacteria

39 MRSA: methicillin-resistant *Staphylococcus aureus*.

## 40 Laboratory tests

### 41 I. Patient microbiology tests

42 Microbiology tests (cultures of blood and abscess material) can be done to determine the  
 43 causative pathogen and its resistance profile, ideally before starting antibiotic treatment (Table  
 44 2). In patients with severe disease, microbiology tests should however not delay antibiotic  
 45 treatment.

46 *Table 2 Microbiology tests to consider in a patient with suspected pyomyositis as indicated in the*  
 47 *WHO EDL (54)*

48 <b>Diagnostic test</b>	<b>Purpose of the test</b>	<b>Settings where the test should be available</b>
Blood cultures	To detect bacterial and fungal bloodstream infections (sepsis)	Health care facilities with clinical laboratories

Microscopy and culture of deep samples collected at aspiration / drainage of abscess	Initial step to detect and identify bacterial and fungal species for selection of appropriate antibiotic regimens	Health care facilities with clinical laboratories
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## 48 II. Other tests

49 Laboratory tests can be used to complement the clinical examination and history. Table 3  
50 indicates tests that could be considered in the initial assessment of the patient and to help guide  
51 the duration of antibiotic treatment.

52 *Table 3 Laboratory tests (other than microbiology) to consider to identify a bacterial infection as*  
53 *indicated in the WHO EDL (54)*

Diagnostic test	Purpose of the test	Settings where the test should be available
White blood count	To aid in the diagnosis of infections	Health care facilities with clinical laboratories but also in primary care settings
C-reactive protein	To detect inflammation as an indicator of various conditions, e.g. sepsis	Health care facilities with clinical laboratories
Procalcitonin	To guide antibiotic therapy or discontinuation in sepsis	Only in tertiary and higher health care facilities

## 54 III. Using microbiology surveillance data

55 There is no role for routine surveillance to inform empiric guidance.

## 56 Imaging

57 Initial imaging with an X-ray is important when pyomyositis is suspected to locate the site and  
58 extent of the infection, any bony involvement or to exclude an alternative diagnosis. However,  
59 If available, magnetic resonance imaging or a computed tomography scan could also be  
60 considered because they have greater sensitivity (compared to conventional X-ray) in identifying  
61 muscle swelling (i.e. inflammation) and the presence of infected tissue.

62 Ultrasound is helpful, if available, to detect the presence of an abscess (and to guide its drainage).

## 63 Management

64 Prompt drainage of the abscess (if present) is important for adequate control of the source of  
65 infection and is complementary to antibiotic treatment. If extensive muscle necrosis is present  
66 or if it is not possible to drain the collection of pus percutaneously, surgery may be necessary.

## 67 Antibiotic treatment

68 Targeted antibiotics based on microbiology tests are preferred in the treatment of pyomyositis.  
 69 However, when patients require immediate treatment (e.g. are severely ill) or when it is  
 70 impossible to obtain a clinical sample for microbiological examination, the choice of antibiotic  
 71 should be based on the pathogens most commonly seen in this type of infection (*Staphylococcus*  
 72 *aureus* and *Streptococcus* spp.) In addition, empiric treatment against community-acquired  
 73 methicillin-resistant *Staphylococcus aureus* (CA-MRSA) may be considered in some cases based  
 74 on individual risk factors (e.g. known MRSA colonization) and on the local prevalence of CA-  
 75 MRSA. In these cases, some international guidance documents suggest using vancomycin(332).

76 Intravenous antibiotics may be needed at least in the first phase of treatment.

77 Treatment duration is long (usually 2–3 weeks) and is influenced by the clinical and radiological  
 78 response and by the adequacy of drainage of the abscess, if present. Shorter duration of  
 79 treatment (2 weeks) could be considered in otherwise healthy patients and when adequate  
 80 source control is achieved (i.e. the abscess is well drained). Longer duration (3 weeks) could be  
 81 considered if source control is inadequate or in patients with underlying diseases.

82 **Simplify** empiric treatment to a more narrow-spectrum antibiotic based on culture results or  
 83 rapid clinical improvement if culture results unavailable.

84 **Step-down** to oral treatment is based on improvement of symptoms and signs of infection and  
 85 the ability to take oral antibiotics allowing discharge of the patient home when clinically  
 86 appropriate.

87 *Table 3 Empiric antibiotic treatment for pyomyositis*

Adults	Children	Total treatment duration
Amoxicillin+clavulanic acid <sup>b</sup> (IV): 1g + 200 mg given every 8 hours OR Cefalexin <sup>b</sup> (oral): 500 mg given every 8 hours OR Cloxacillin <sup>b</sup> or flucloxacillin (IV): 2 g given every 6 hours	Amoxicillin+clavulanic acid <sup>b,c</sup> (IV/oral): 40-50 mg/kg/dose of amoxicillin component given every 12 hours OR 30 mg/kg/dose given every 8 hours  Oral weight bands : 3-<6 kg: 250 mg of amoxicillin/dose given every 12 hours 6-<10 kg: 375 mg of amoxicillin/dose given every 12 hours 10-<15 kg: 500 mg of amoxicillin/dose given every 12 hours 15-<20 kg: 750 mg of amoxicillin/dose given every 12 hours 20-<30 kg: 1000 mg of amoxicillin/dose given every 12 hours ≥ 30 Kg: Use adult dose  OR	2–3 weeks

	<p><b>Cefalexin<sup>p</sup></b> (oral) 25 mg/kg per dose every 12 hours</p> <p>Oral weight bands:          3- &lt;6 Kg: 125 mg given every 12 hours          6-&lt;10 kg: 250 mg given every 12 hours          10-&lt;15 kg: 375 mg given every 12 hours          15-&lt;20 kg 500 mg given every 12 hours          20-&lt;30 kg: 625 mg given every 12 hours          ≥ 30 Kg: Use adult dose</p> <p>OR</p> <p><b>Cloxacillin<sup>b</sup></b> or <b>flucloxacillin</b> (IV/oral):</p> <ul style="list-style-type: none"> <li>• Neonates: 25-50 mg/kg/dose given every 12 hours</li> <li>• Children: 25 mg/kg/dose given every 6 hours</li> </ul> <p>Oral weight bands:          3-&lt;6 kg: 125 mg given every 6 hours          6-&lt;10 kg: 250 mg given every 6 hours          10-&lt;15 kg: 250 mg given every 6 hours          15-&lt;20 kg: 500 mg given every 6 hours          20-&lt;30 kg: 750 mg given every 6 hours          ≥ 30 Kg: Use adult dose</p>	
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- 88 Notes: All dosages are for normal renal and hepatic function.  
 89 IV: intravenous.  
 90 <sup>a</sup> It should be noted that these specific recommendation are not included in the EML and were extrapolated from  
 91 EML recommendations for skin and soft tissue infections(4).  
 92 <sup>b</sup>Vancomycin is not listed as first choice because in most settings methicillin-resistant *Staphylococcus aureus* is not  
 93 a frequent cause of community-acquired infections.  
 94 <sup>c</sup>Oral liquid must be refrigerated after reconstitution as clavulanic acid is rapidly metabolized in high ambient  
 95 temperatures.  
 96 **ACCESS** antibiotics are indicated in green, **WATCH** antibiotics in yellow and **RESERVE** antibiotics in red.

# 1 Febrile neutropenia

2 This chapter focuses on empiric treatment of suspected or confirmed bacterial infections in  
3 patients with neutropenia (including neutropenic sepsis) but it does not cover antiviral or  
4 antifungal treatment or antibiotic prophylaxis for patients with afebrile neutropenia, which are  
5 beyond the scope of this chapter.

## 6 Key messages

1. Neutropenia is the most common complication of cancer treatment with cytotoxic chemotherapy
2. Patients can be at low or high risk of serious infections based on the duration of neutropenia
3. Febrile neutropenia often presents as unexplained fever with no site of infection or pathogen identified
4. Diagnostic tests depend on the most likely site of primary infection
5. Empiric antibiotic treatment should be started in febrile patients with  $< 500$  neutrophils/ $\mu\text{L}$  ( $< 0.5 \times 10^9$  cells/L) with treatment duration adapted based on the clinical response irrespective of the neutrophil count

## 7 Definition

8 Febrile neutropenia is a severe condition that can be caused by common Gram-positive and  
9 Gram-negative bacteria, fungi and other opportunistic pathogens. Febrile neutropenia occurs  
10 mostly in patients with neoplastic diseases who are receiving cytotoxic myelosuppressive  
11 chemotherapy.

12 Two elements need to be considered in defining febrile neutropenia: fever and neutropenia.

13 For fever, there are no universally accepted temperature cut-offs and slightly different cut-offs  
14 are used in different centers. Generally, a pragmatic definition of fever is  $> 38.0^\circ\text{C}$ . A more precise  
15 definition is used by the Infectious Diseases Society of America in their 2010 *Clinical Practice*  
16 *Guideline for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer*(333) which is:

- 17 • A single oral temperature measurement of  $\geq 38.3^\circ\text{C}$  or
- 18 • A temperature of  $\geq 38.0^\circ\text{C}$  sustained over 1 hour.

19 There is less variation in definition of neutropenia, which is defined as a temporary reduction of  
20 the absolute neutrophil count; an absolute neutrophil count of  $< 1000$  cells (sometimes  $<$   
21  $1500$ )/ $\mu\text{L}$  ( $< 1.0 \times 10^9$  cells/L) is considered indicative of neutropenia. Neutropenia can be  
22 classified as severe when the absolute neutrophil count is  $< 500$  cells/ $\mu\text{L}$  ( $< 0.5 \times 10^9$  cells/L) (also  
23 called agranulocytosis) and profound when absolute neutrophil count is  $< 100$  cells/ $\mu\text{L}$  ( $< 0.1 \times$   
24  $10^9$  cells/L).

25 Febrile neutropenia can be characterized according to identification of the causative pathogen  
26 and source of infection as:

- 27 1) microbiologically proven infection (i.e. the causative pathogen is identified)
- 28 2) clinical source of infection diagnosed but no pathogen identified (e.g. pharyngitis)
- 29 3) unexplained fever (no pathogen identified and no clear source of infection)
- 30 4) non-infectious fever (e.g. medicine-induced)

31 Unexplained fever with no focus or positive culture is the most common scenario observed in  
32 clinical practice.

## 33 Pathophysiology

34 Neutropenia (i.e. decreased number of circulating neutrophils) can develop as the result of a  
35 reduced production of neutrophils by the bone marrow, or increased peripheral destruction or  
36 sequestration at localized inflammatory sites. Once neutrophils decrease below a certain  
37 threshold, the risk of developing infections increases. Severity and duration of neutropenia are  
38 independent risk factors for serious infection (i.e. the risk is higher with longer and more  
39 profound neutropenia).

40 It is beyond the scope of this chapter to describe how cytotoxic chemotherapies and cancer affect  
41 the immune system and predispose to infection. As well as a reduced absolute neutrophil count,  
42 patients with cancer and on cytotoxic chemotherapy often also have dysfunctional lymphocytes  
43 or immunoglobulin deficiencies, impaired natural barriers to infection (e.g. mucositis) and  
44 malnutrition that additionally weaken their ability to control infections. Furthermore, the  
45 presence of invasive devices (e.g. intravascular catheters) is an additional risk factor for infection  
46 to consider.

## 47 Epidemiology

48 Neutropenia is the most common complication of cytotoxic cancer treatment that can lead to  
49 treatment delays and reductions in the chemotherapy dose (334). The risk of developing febrile  
50 neutropenia depends on: the type of underlying tumor (e.g. very high in patients with acute  
51 leukemia and lower in patients with solid tumors); the type and dose of chemotherapy used; and  
52 individual risk factors (e.g. older age, advanced stage of disease, comorbidities, other  
53 concomitant myelotoxic medications)(335). The risk of developing severe infection depends on  
54 the duration and severity of neutropenia; therefore, initial risk assessment is an important step  
55 to identify patients at low or high risk of developing serious complications (e.g. complications  
56 requiring hospitalization or prolonging hospitalization). As well as the physician's assessment,  
57 several scoring systems exist (e.g. Multinational Association of Supportive Care in Cancer  
58 (MASCC) score) to help predict this risk (336). These systems usually include a combination of  
59 factors such as general clinical status of the patient, presence of comorbidities, age and whether  
60 the patient is hospitalized or not. However, no system can distinguish patients at low or high risk  
61 of infection with complete accuracy(337).

62 Low-risk patients are those expected to have a shorter duration of severe neutropenia ( $\leq 7$  days)  
 63 and have no comorbidities (other than cancer) or renal or hepatic dysfunction. High-risk patients  
 64 are expected to remain neutropenic for longer periods ( $> 7$  days) or are those with ongoing  
 65 comorbidities (other than cancer) and renal or hepatic dysfunction.

66 Neutropenia is also common in children receiving myelosuppressive treatment especially for  
 67 acute lymphoblastic leukemia or lymphoma (the most common forms of cancer in  
 68 childhood(338)) and for acute myeloid leukaemia, or after haemopoietic stem cell  
 69 transplantation or treatment for certain aggressive solid tumors (e.g. neuroblastoma)(339, 340).

## 70 Microbiology epidemiology

71 A fever of infectious origin in a patient with neutropenia is most likely caused by bacteria that  
 72 colonize the patient's own skin and bowel, including multi drug-resistant organisms such as  
 73 extended-spectrum beta-lactamase (ESBL)-producing or carbapenemase-producing Gram-  
 74 negative bacteria (Table 1). These patients often receive broad-spectrum antibiotics while in  
 75 hospital and are therefore at increased risk of antibiotic-resistant infections. Furthermore,  
 76 certain pathogens (e.g. fungi) become more frequent with longer duration of neutropenia.

77 *Table 1 Pathogens most frequently associated with febrile neutropenia (in descending order of*  
 78 *frequency)*

Bacteria	Viruses	Fungi
<i>Staphylococcus epidermidis</i> <i>Staphylococcus aureus</i> (including MRSA) <i>Streptococcus</i> spp. Other Gram-positive bacteria (e.g. <i>Enterococcus</i> spp. including VRE) Enterobacterales (including multidrug-resistant strains such as those producing ESBL and carbapenemases) <i>Pseudomonas aeruginosa</i> Anaerobes	Cytomegalovirus Human herpesvirus 6  (consider viruses in high-risk patients mostly because of reactivation of latent infections)	<i>Candida</i> spp.  <i>Aspergillus</i> spp. (in case of prolonged neutropenia)

79 MRSA: methicillin-resistant *Staphylococcus aureus*; ESBL: extended-spectrum beta-lactamases; VRE: vancomycin-  
 80 resistant Enterococci.

81 Notes: the risk of multidrug-resistant pathogens should always be carefully considered in patients with neutropenia  
 82 because often infections in these patients are health care-associated.

83 Most data come from tertiary care centers located in high-income settings.

## 84 Clinical presentation

85 Apart from fever, other accompanying signs and symptoms of febrile neutropenia vary greatly  
 86 depending on the underlying infection (e.g. pneumonia, urinary tract infection, skin infection,  
 87 meningitis, colitis). Bacteraemia (i.e. the detection of bacteria in blood cultures) may be present.

88 Because patients with neutropenia fail to produce effective inflammatory responses, they can  
89 sometimes present with few clinical findings and no fever despite infection.

90 A detailed clinical examination should always be done to help identify the site of infection. Skin  
91 changes (e.g. rash, ulcers, signs of vascular infection), changes in the oral mucosa and pharynx  
92 (e.g. ulcers inside the mouth, dental disease, thrush), abnormalities in the perineal and perirectal  
93 area, symptoms and signs of typhlitis (inflammation of the cecum) and colitis with abdominal  
94 pain, diarrhoea and sometimes rectal bleeding often due to mucositis should therefore always  
95 be carefully investigated.

96 Clinical progression to severe disease or death can be very rapid (over a few hours); therefore,  
97 the presence of any signs of sepsis or septic shock should always be carefully monitored. Please  
98 also refer to the chapter on sepsis if suspected.

## 99 Laboratory tests

### 100 I. Patient microbiology tests

101 Whenever possible a microbiology sample (e.g. blood cultures) should be obtained – ideally  
102 before antibiotic treatment is started – because results of the test can help establish the  
103 diagnosis and treatment can be adapted accordingly.

104 Tests to consider depend on the most likely primary site of infection and should therefore be  
105 adapted based on the clinical presentation (see Table 2). Some tests should always be performed  
106 (indicated as routine tests in Table 1) while others could be considered in certain cases, including  
107 for surveillance purposes and based on local availability. Additional tests not presented in the  
108 table but that could be considered, especially in high-risk patients, include tests to diagnose  
109 invasive fungal infections (e.g. *Aspergillus* galactomannan antigen screening) and those for other  
110 viral infections (e.g. nucleic acid amplification test for cytomegalovirus).

111 *Table 2 Microbiology tests to consider when febrile neutropenia is suspected depending on the*  
112 *most likely source of infection as indicated in the WHO EDL (54)*

Test priority	Diagnostic test	Purpose of the test	Settings where the test should be available
Routine	Blood cultures	To detect bacterial and fungal bloodstream infections (sepsis)	Healthcare facilities with clinical laboratories
Routine	Urine culture	Initial step to detect and identify bacterial and fungal species for selection of appropriate antibiotic regimens	Healthcare facilities with clinical laboratories

Consider in certain cases	Sputum microscopy (Gram stain)	To assess microbial morphology and adequacy of the specimen for culture by identifying white blood cells and squamous epithelial cells	Healthcare facilities with clinical laboratories
Consider in certain cases	Sputum culture	Initial step to detect and identify bacterial and fungal species for selection of appropriate antibiotic regimens	Healthcare facilities with clinical laboratories
Consider in certain cases (including for infection control purposes)	Nasopharyngeal swab for nucleic acid amplification test for influenza <sup>a</sup>	To diagnose seasonal influenza infection	Healthcare facilities with clinical laboratories but also in primary care settings
Consider in certain cases (including for infection control purposes)	Nasopharyngeal swab for nucleic acid amplification test or antigen test for SARS-CoV-2	To diagnose COVID-19	Healthcare facilities with clinical laboratories (NAT) and primary care settings (antigen test)
Consider in certain cases	Aspergillus antigen test	To diagnose Invasive aspergillosis in Immunocompromised patients	Healthcare facilities with clinical laboratories
Consider in certain cases	Cerebrospinal fluid microscopy	To assess microbial morphology, number of white blood cells and red blood cells	Healthcare facilities with clinical laboratories
Consider in certain cases	Cerebrospinal fluid Gram stain and bacterial culture	Initial step to detect and identify bacterial and fungal species for selection of appropriate antibiotic regimens	Healthcare facilities with clinical laboratories
Consider in certain cases	Stool culture	Initial step to detect and identify bacterial species for selection of appropriate antibiotic regimens	Health care facilities with clinical laboratories
Consider in certain cases	<i>Clostridioides difficile</i> testing (usually nucleic acid amplification test)	To diagnose <i>C. difficile</i> infection	— <sup>b</sup>

113 CSF: cerebrospinal fluid; NAAT: nucleic acid amplification test.

114 <sup>a</sup> Testing for respiratory viruses other than influenza (e.g. respiratory syncytial virus)) could be considered based on  
 115 availability and local epidemiology.

116 <sup>b</sup>This test is not in the EDL (54).

## 117 II. Other tests

118 Laboratory tests to consider if febrile neutropenia is suspected depend on the most likely source  
 119 of infection and are shown in Table 2.

120 *Table 2 Laboratory tests to consider when febrile neutropenia is suspected as indicated in the*  
 121 *WHO EDL (54)*

Diagnostic test	Purpose of the test purpose	Settings where the test should be available
Complete blood count	To detect a wide range of disorders (severity of neutropenia, anemia, thrombocytopenia), including infections	Healthcare facilities with clinical laboratories
C-reactive protein <sup>a</sup>	To detect inflammation as an indicator of various conditions (e.g. sepsis)	Healthcare facilities with clinical laboratories
Procalcitonin <sup>a</sup>	To guide antibiotic therapy or discontinuation in sepsis	Only in tertiary care facilities
Bilirubin	To detect or monitor liver disease	Community settings and health facilities without laboratories <sup>b</sup>
Creatinine	To monitor kidney function for management of severe infections (i.e. sepsis) and to adjust antimicrobial regimens	Healthcare facilities with clinical laboratories
Electrolytes	To monitor fluid, electrolyte and acid-base balance	Healthcare facilities with clinical laboratories
Blood pH and gases	To assess lung function, metabolic or kidney disorders and monitor oxygen therapy	Healthcare facilities with clinical laboratories
Whole blood lactate	To assess metabolic acidosis, sepsis and dehydration	Community settings and health facilities without laboratories <sup>b</sup>

122 <sup>a</sup>Measurement of biomarkers on admission (C-reactive protein and procalcitonin) might help identify high-risk  
 123 patients and predict severe outcomes (e.g. sepsis)(341-343)

124 <sup>b</sup>Community and health settings without laboratories are facilities such as health posts and centres, doctors' offices,  
125 outreach clinics, ambulatory care and home-based and self-testing. These tests are assumed to be available at health  
126 care facilities with laboratories.

### 127 III. Using microbiology surveillance data

128 Empiric guidance given by the Handbook could be reviewed and adapted based on local clinically  
129 relevant microbiology surveillance data. This would include blood culture data from local  
130 haemato-oncology patients, ideally risk stratified by underlying diagnosis.<sup>1</sup>

## 131 Imaging

132 Imaging based on clinical presentation should be considered in the patient's initial assessment to  
133 identify the source of infection. If there is no clinical improvement and the fever does not resolve  
134 with treatment in a few days, additional imaging could be considered (e.g. computed tomography  
135 scan of the lungs and sinuses, and other tests based on clinical suspicion) to expand diagnostic  
136 work-up or to exclude a complicated infection such as invasive fungal disease.

## 137 Treatment

138 This chapter focuses on antibiotic treatment of suspected or confirmed bacterial infections but  
139 it does not cover antiviral or antifungal treatment. It also does not cover prophylaxis with  
140 granulocyte colony-stimulating factors (i.e. growth factors that stimulate the bone marrow to  
141 produce more neutrophils) such as filgrastim listed on the EML since 2015 for the treatment of  
142 acquired neutropenia.

143 The use of granulocyte colony-stimulating factors for therapeutic purposes (i.e. in febrile  
144 patients) is controversial and guidelines vary in their recommendations. Evidence shows that  
145 their use in combination with antibiotics does not reduce mortality (compared with antibiotics  
146 alone), however granulocyte colony-stimulating factors could be considered in certain patients  
147 because their use is associated with shorter hospital stay and duration of antibiotic use (reduced  
148 by 1-2 days) most likely due to the faster neutrophil recovery(344).

149 It is important that source control is achieved as early as possible, this includes drainage of any  
150 abscesses and removal or change of invasive devices such as central venous catheters, where  
151 appropriate.

## 152 Antibiotic treatment

153 Patients with neutropenia who develop fever should promptly receive antibiotic treatment even  
154 when a clear site of infection is not identified(345).

155 Low-risk patients can be managed in an outpatient setting if adequate monitoring and follow-up  
156 is available and if they are able to tolerate oral treatment(346). High-risk patients (or patients  
157 where close follow-up is not feasible) require hospitalization and initial intravenous treatment to  
158 start with.

159 The choice of empiric treatment should always consider a combination of factors, including the  
 160 most likely site of primary infection and the infecting pathogens (including risk of viral and  
 161 invasive fungal infections) and the local pattern of antimicrobial resistance. Other factors, such  
 162 as known colonization or previous infection with multidrug-resistant organisms and recent  
 163 antibiotic exposure (including antibiotic prophylaxis) are also important factors to consider.  
 164 Recommended empiric antibiotic options are given in Table 3.

165 **Simplify** empiric treatment to a more narrow-spectrum antibiotic based on culture results or  
 166 rapid clinical improvement if culture results unavailable.

167  
 168 **Step down** to oral antibiotics is suggested when the patient has made a good clinical response,  
 169 the fever has settled and the patient can tolerate oral antibiotics.

170 *Table 3 Initial empiric antibiotic treatment for febrile neutropenia (absolute neutrophil*  
 171 *count: < 500 cells/ µL; < 0.5 × 10<sup>9</sup> cells/L) based on the patient’s initial risk assessment*

172 **This table refers to empiric treatment not to treatment escalation in case of persistent fever**  
 173 **which is beyond the scope of the chapter.**

Patient risk	Adults	Children	Total treatment duration
Low risk (expected duration of neutropenia < 7 days, no major comorbidities, no organ dysfunction, possible outpatient treatment)	<p><b>Amoxicillin+clavulanic acid</b> (oral): 500 mg+125mg given every 8 hours</p> <p><b>CONSIDER ADDING Ciprofloxacin</b> (oral): 500 mg given every 12 hours</p>	<p><b>Amoxicillin+clavulanic acid</b> (oral)                      40-50 mg/kg/dose of amoxicillin component given every 12 hours                      OR 30 mg/kg/dose given every 8 hours</p> <p>Oral weight bands<sup>d</sup>:                      3-&lt;6 kg: 250 mg of amoxicillin/dose given every 12 hours                      6-&lt;10 kg: 375 mg of amoxicillin/dose given every 12 hours                      10-&lt;15 kg: 500 mg of amoxicillin/dose given every 12 hours                      15-&lt;20 kg: 750 mg of amoxicillin/dose given every 12 hours                      20-&lt;30 kg: 1000 mg of amoxicillin/dose given every 12 hours                      ≥ 30 Kg: Use adult dose</p> <p><b>CONSIDER ADDING Ciprofloxacin</b> (oral) 10-20 mg/kg/dose given every 12 hours</p> <p>Oral weight bands:</p>	7 days

		<p>3-&lt;6 kg: 50 mg given every 12 hours                  6-&lt;10 kg: 100 mg given every 12 hours                  10-&lt;15 kg: 150 mg given every 12 hours                  15-&lt;20 kg: 200 mg given every 12 hours                  20-&lt;30 kg: 300 mg given every 12 hours                  ≥ 30 Kg: Use adult dose</p>	
<p>High risk (expected duration of neutropenia &gt; 7 days, major comorbidities, organ dysfunction)</p>	<p><b>First choice</b>  <b>Piperacillin+tazobactam</b>(IV):                  4g + 500 mg given every 6 hours</p> <p><b>Second choice</b>  <b>Meropenem</b><sup>a</sup> (IV): 1g given every 8 hours</p> <p><b>CONSIDER ADDING:</b>  <b>Amikacin</b><sup>b</sup>(IV): 15 mg/kg given once a day</p> <p><b>AND/OR</b>  <b>CONSIDER ADDING:</b>  <b>Vancomycin</b><sup>c</sup>(IV): 15-20 mg/kg given every 12 hours</p>	<p><b>First choice</b>  <b>Piperacillin+tazobactam</b> (IV):                  100 mg/kg/dose of piperacillin component given every 8 hours</p> <p><b>Second choice</b>  <b>Meropenem</b><sup>a</sup> (IV):                  20 mg/kg/dose given every 8 hours</p> <p><b>CONSIDER ADDING:</b>  <b>Amikacin</b><sup>b</sup>(IV): 15 mg/kg/dose given once a day</p> <p><b>AND/OR</b>  <b>CONSIDER ADDING:</b>  <b>Vancomycin</b><sup>c</sup>(IV):</p> <ul style="list-style-type: none"> <li>• Neonates: 15 mg/kg/dose given every 12 hours</li> <li>• Children: 15 mg/kg/dose given every 8 hours</li> </ul>	<p>Until clinical signs of infection have resolved, including absence of fever for at least 48 hours.</p> <p>If a pathogen is identified, the duration of therapy will be based on the particular pathogen and site of infection. If the patient still has neutropenia, he/she should be closely monitored for 24-48 hours and if fever returns, antibiotics should be restarted.</p>

174 Notes: All dosages are for normal renal and hepatic function.

175 IV: intravenous.

176 <sup>a</sup>Empiric meropenem should only be considered in settings with high prevalence of extended-spectrum beta-lactamases (ESBL)-producing *Enterobacterales* or in patients with known prior colonization or infection with resistant pathogens.

179 <sup>b</sup>Consider adding amikacin in combination with piperacillin+tazobactam or meropenem when infections with resistant Gram-negative bacteria are suspected based on local epidemiology and clinical presentation (e.g. severely ill patients including those who become clinically unstable after initial empiric monotherapy, and patients with known prior colonization or infection with extended-spectrum beta-lactamase (ESBL)-producing *Enterobacterales*). The need to continue combination treatment should be reassessed over time (e.g. after 48-72 hours) based on microbiology test results and clinical response.

185 <sup>c</sup>Consider adding vancomycin in combination with piperacillin–tazobactam or meropenem when methicillin-  
186 resistant *Staphylococcus aureus* (MRSA) is suspected (e.g. patients with MRSA colonization) or where a line infection  
187 is strongly suspected (because of the risk of multidrug-resistant coagulase-negative *Staphylococcus* infection). The  
188 need to continue combination treatment should be reassessed over time (e.g. after 48-72 hours) based on  
189 microbiology test results and clinical response.

190 <sup>d</sup>Oral liquid must be refrigerated after reconstitution as clavulanic acid is rapidly metabolized in high ambient  
191 temperatures

192 **ACCESS** antibiotics are highlighted in green, **WATCH** antibiotics in yellow and **RESERVE** antibiotics in red.

193 Antibiotic treatment for patients with febrile neutropenia may require adjustments in dose and  
194 frequency of administration because pharmacokinetic and pharmacodynamic parameters could  
195 be altered in these patients and renal and hepatic toxicity related to chemotherapy is  
196 common(347).

197 If the causative pathogen is identified, once susceptibilities are known, antibiotics should be  
198 reviewed and modified accordingly. However, even if adequate microbiological sampling is  
199 performed, a pathogen is often not identified.

200 If fever persists (e.g. patient still has a temperature 48-72 hours after the start of antibiotic  
201 treatment) and there is no clinical improvement, further diagnostic tests (e.g. imaging) could be  
202 performed to identify the source of infection (if this is still unclear) or to assess whether a local  
203 complication has developed (e.g. a fluid collection). In addition, a resistant pathogen or an  
204 invasive fungal disease should be considered as they could be responsible for the prolonged  
205 fever.

206 Duration of treatment will mostly depend on the clinical response (e.g. resolution of fever and  
207 clinical recovery) and (if identified) on the infectious site and the causative pathogen.

208 Continuation of antibiotic treatment until neutrophil recovery (absolute neutrophil count > 500  
209 cells /  $\mu\text{L}$ ; >  $0.5 \times 10^9$  cells/L) is controversial with guidelines varying in their recommendations.  
210 Evidence suggests that discontinuation of antibiotics based on a clinical assessment (e.g. if the  
211 clinical recovery is good and no source is identified or if an infection has been adequately treated  
212 and irrespective of the neutrophil count), can safely reduce exposure to antibiotics (348, 349).

# 1 Surgical prophylaxis

## 2 Key messages

1. Surgical site infections (SSI) represent an important complication of surgical procedures and appropriate antibiotic prophylaxis can reduce the risk of SSI for certain procedures
2. Access group antibiotics are recommended as first choice options in most cases
3. Depending on the type of surgery antibiotic prophylaxis may need to be adapted in people colonized with multidrug-resistant organisms
4. The indication and choice of antibiotic prophylaxis depends on the type of surgical procedure (not all surgical procedures require prophylaxis)
5. Prophylaxis should not be continued after surgery to prevent infection (one antibiotic dose covers the entire duration of potential contamination during surgery in most cases)

3

*Box 1 Other relevant WHO documents (please check regularly for updates)*

- World Health Organization. (2018). Global guidelines for the prevention of surgical site infection, 2nd ed.. World Health Organization. <https://apps.who.int/iris/handle/10665/277399>. License: CC BY-NC-SA 3.0 IGO

## 4 Definition of terms used in this chapter

5 Definitions are taken from the 2018 WHO publication: *Global guidelines for the prevention of*  
6 *surgical site infections* (251).

7 **Antibiotic prophylaxis:** prevention of infectious complications by administering an effective  
8 antimicrobial agent before exposure to contamination during surgery.

9 **Surgical procedure:** an operation where at least one incision (including laparoscopic incisions) is  
10 made through the skin or mucous membrane, or a reoperation through an incision that was left  
11 open after a previous operative procedure and takes place in the operating room.

12 **Surgical site infection:** “an infection that occurs after surgery in the part of the body where the  
13 surgery took place. Surgical site infections can sometimes be superficial infections involving the  
14 skin only. Other surgical site infections are more serious and can involve tissues under the skin,  
15 organs or implanted material”.

16 Surgical site infection is also defined as an infection that occurs up to 30 days after an operation  
17 and affects:

- 18 (i) the skin and subcutaneous tissue of the surgical incision (superficial incisional); and/or
- 19 (ii) (ii) the deep soft tissue (for example, fascia or muscle) of the incision (deep incisional)
- 20 and/or

21 (iii) (iii) any part of the anatomy (for example, organs and spaces) other than the incision  
 22 that was opened or manipulated during an operation (organ/space).

23 **Surgical wound:** a wound created when an incision is made with a scalpel or other sharp cutting  
 24 device and then closed in the operating room by suture, staple, adhesive tape, or glue and  
 25 bringing the skin edges together.

26 **Categories of surgical wound:**

- 27 • *Clean:* an uninfected surgical wound in which no inflammation is found, and which is not  
 28 in the respiratory, alimentary, genital or urinary tracts. In addition, clean wounds are  
 29 usually closed and, if necessary, drained with closed drainage. Surgical incisional wounds  
 30 that are done after non-penetrating (blunt) trauma should be included in this category if  
 31 they meet the criteria.
- 32 • *Clean-contaminated:* a surgical wound in the respiratory, alimentary, genital or urinary  
 33 tracts which was made under controlled conditions and without unusual contamination.  
 34 Operations involving the biliary tract, appendix, vagina and oropharynx are included in  
 35 this category, provided no evidence of infection or major (i.e. significant) break in sterile  
 36 technique is found.
- 37 • *Contaminated:* open, fresh, accidental wounds. Also included in this category are:  
 38 operations with major break in sterile technique (e.g. open cardiac massage) or  
 39 substantial spillage (of gastrointestinal contents) from the gastrointestinal tract; and  
 40 incisions in which acute, non-purulent inflammation is found, including necrotic tissue,  
 41 without evidence of purulent drainage (e.g. dry gangrene).
- 42 • *Dirty or infected:* old traumatic wounds with retained dead tissue and those that involve  
 43 existing clinical infection or perforated viscera. Such wounds suggest that the organisms  
 44 causing postoperative infection were present at the site of the surgery before the  
 45 operation.

46 **Epidemiology**

47 The percentage of surgical site infections varies depending on the type of surgical procedure. For  
 48 example, in 2017 in 13 European countries reporting data on > 600 000 surgical procedures, the  
 49 overall percentage of infections per 100 operations ranged from 0.5% after knee prosthesis  
 50 surgery to 10.1% after colon surgery(350). For most types of surgery more than 80% of patients  
 51 received antibiotic prophylaxis. The only exception was cholecystectomy for which a lower  
 52 percentage of patients received antibiotic prophylaxis – 44.1% in case of laparoscopic and 65.9%  
 53 in case of open cholecystectomy(350).

54 Another study included data collected in 2016 from more than 12 000 patients from 66 countries  
 55 with different human development indices (HDI); 10.2% of patients were from countries with a  
 56 low HDI. Overall, 12.3% of patients undergoing gastrointestinal surgery developed a surgical site  
 57 infection within 30 days. However, statistically significant differences in the incidence of surgical  
 58 site infections were found based on the HDI. In particular, the incidence of surgical site infections  
 59 was 9.4% in countries with a high HDI, 14.0% in countries with a medium HDI and 23.2% in those

60 with a low HDI. Patients in countries with a low HDI were 1.6 times more likely to develop an  
 61 infection than countries with a higher HDI(351). Variation in infection rates was also found after  
 62 caesarean sections with rates of infections ranging from 3% to 11% in high-income countries  
 63 compared to 3% to 24% in low- and middle-income countries(352).

64 Surgical site infections and surgical prophylaxis to prevent them are a frequent cause of antibiotic  
 65 use in hospitals. The 2015 Global Point Prevalence Survey on antibiotic use (reporting data from  
 66 303 hospitals in 53 countries) reported that on the day of the survey, 1.6% of admitted patients  
 67 were receiving antibiotics for a postoperative surgical site infection(266). Of note, 34.4% of adult  
 68 inpatients were receiving at least one antibiotic on the day of the survey. Of all total antibiotic  
 69 prescriptions, 17.8% were for surgical prophylaxis. The most frequently prescribed antibiotic was  
 70 cefazolin (prescribed in 27.5% of patients receiving surgical prophylaxis). Prolonged surgical  
 71 prophylaxis (> 1 day) was common in all regions, ranging from 40.6% in Oceania to 86.3% in  
 72 eastern Europe(266).

## 73 Microbiology epidemiology

74 The pathogens causing surgical site infections vary based on the type of surgical procedure  
 75 (Table 1).

76 *Table 1 Pathogens most frequently associated with surgical site infections by anatomical site of*  
 77 *the procedure*

Type of procedure	Pathogens most frequently associated with surgical site infections
Cardiac procedures	<i>S. aureus</i> and coagulase-negative staphylococci
Cardiac device insertion procedures (e.g. pacemaker implantation)	<i>S. aureus</i> and coagulase-negative staphylococci
Non-cardiac thoracic procedures (e.g. pulmonary resection)	<i>S. aureus</i> and coagulase-negative staphylococci <i>Haemophilus influenzae</i> <i>Enterobacter cloacae</i> <i>Klebsiella pneumoniae</i> <i>Acinetobacter</i> spp. <i>Pseudomonas aeruginosa</i> <i>Moraxella catarrhalis</i>
Gastroduodenal procedures	<i>S. aureus</i> and coagulase-negative staphylococci <i>Enterococcus</i> spp. Enterobacterales Anaerobes ( <i>Bacteroides</i> spp.)
Biliary tract procedures	Enterobacterales Anaerobes <i>Enterococcus</i> spp. <i>Streptococcus</i> spp. <i>S. aureus</i> and coagulase-negative staphylococci
Appendectomy	<i>Escherichia coli</i> Anaerobes ( <i>Bacteroides fragilis</i> )
Small intestine procedures	Enterobacterales Anaerobes <i>Enterococcus</i> spp. <i>Streptococcus</i> spp.

	<i>S. aureus</i> and coagulase-negative staphylococci
Hernia repair procedures	<i>Enterococcus</i> spp. <i>Streptococcus</i> spp. <i>S. aureus</i> and coagulase-negative staphylococci
Colorectal procedures	<i>Escherichia coli</i> Anaerobes ( <i>Bacteroides fragilis</i> )
Head and neck procedures	<i>Streptococcus</i> spp. <i>S. aureus</i> and coagulase-negative staphylococci Enterobacterales Anaerobes (from the oral microbiota)
Neurosurgical procedures	<i>S. aureus</i> and coagulase-negative staphylococci Gram-negative bacteria
Gynaecological procedures	<i>Streptococcus agalactiae</i> (group B streptococcus) <i>Staphylococcus aureus</i> <i>Enterococcus</i> spp. Anaerobes
Ophthalmic procedures	<i>S. aureus</i> and coagulase-negative staphylococci
Orthopaedic procedures	<i>S. aureus</i> and coagulase-negative staphylococci
Urological procedures	Enterobacterales (mostly <i>Escherichia coli</i> ) <i>Enterococcus</i> spp.
Vascular procedures	<i>S. aureus</i> and coagulase-negative staphylococci

78 Note: This list is based on data from high-income settings and aims to give a general overview (353). The  
79 distribution of the pathogens most frequently associated with surgical site infections may vary in other settings.

## 80 Antibiotic prophylaxis

81 The choice of the antibiotic should be based on the type of surgical procedure because not all  
82 procedures are associated with the same risk of developing infection.

83 In general, antibiotic prophylaxis before surgery where the most likely pathogens causing  
84 infection are Gram-positive bacteria should consist of intravenous first- or second-generation  
85 cephalosporins (cefazolin or, as an alternative second choice, cefuroxime). These surgeries  
86 include clean procedures such as cardiac and vascular surgery but also procedures that involve  
87 the placement of a prosthesis or implant.

88 If additional pathogens (e.g. anaerobes) could cause infection (e.g. in abdominal procedures),  
89 antibiotic prophylaxis should be adapted accordingly. In these cases, cefazolin in combination  
90 with metronidazole would be an appropriate option.

91 In patients known to be colonized with methicillin-resistant *Staphylococcus aureus* (MRSA) and  
92 who will have a skin incision, vancomycin prophylaxis (in addition to the routine recommended  
93 antibiotic prophylaxis) may be justified. This is recommended because vancomycin alone is less  
94 effective than cefazolin (the antibiotic recommended as prophylaxis in most surgical procedures)  
95 against methicillin-sensitive *Staphylococcus aureus* (and because vancomycin has no activity  
96 against Gram-negative bacteria). It should be noted that in patients colonized with MRSA,  
97 procedure-specific preventive measures other than antibiotic prophylaxis (e.g. nasal

98 decolonization with mupirocin ointment, skin antiseptic) may be beneficial but such measures  
 99 are not specifically addressed in this chapter. Please refer to the WHO guidelines for the  
 100 prevention of surgical site infections(251) for information on such preventive measures.

101 In the context of patients known to be colonized with multidrug-resistant Gram-negative bacteria  
 102 (e.g. bacteria producing extended-spectrum beta-lactamases or carbapenemases), the WHO  
 103 guidelines acknowledged a lack of high-quality evidence to make recommendations on the need  
 104 to include other antibiotics for prophylaxis to cover these pathogens(251). However, certain  
 105 factors, such as the closeness of the likely reservoir of these bacteria to the operative site or  
 106 characteristics of the patient could help to make decision on a case-by-case basis.

107 *Table 2 Antibiotic prophylaxis before surgical procedures*

Type of procedure	First choice	Second choice
Clean procedure <sup>a</sup>	<b>Cefazolin (IV):</b> <ul style="list-style-type: none"> <li>Children: 50 mg/kg - single dose</li> <li>Adults: 2 g<sup>b</sup> - single dose</li> </ul>	<b>Cefuroxime (IV):</b> <ul style="list-style-type: none"> <li>Children: 50 mg/kg - single dose</li> <li>Adults: 1.5 g – single dose</li> </ul>
Clean contaminated procedure <sup>c</sup> (except bowel surgery and urological procedures)	<b>Cefazolin (IV):</b> <ul style="list-style-type: none"> <li>Children: 50 mg/kg - single dose</li> <li>Adults: 2 g<sup>b</sup> - single dose</li> </ul>	<b>Cefuroxime (IV):</b> <ul style="list-style-type: none"> <li>Children: 50 mg/kg - single dose</li> <li>Adults: 1.5 g – single dose</li> </ul>
Contaminated procedure <sup>d</sup>	<b>Cefazolin (IV):</b> <ul style="list-style-type: none"> <li>Children: 50 mg/kg - single dose</li> <li>Adults: 2 g<sup>b</sup> - single dose</li> </ul> <p>AND</p> <b>Metronidazole (IV):</b> <ul style="list-style-type: none"> <li>Children: 7.5 mg/kg - single dose</li> <li>Adults: 500 mg - single dose</li> </ul>	<b>Amoxicillin+clavulanic acid (IV):</b> <ul style="list-style-type: none"> <li>Children: 40-50 mg/kg of amoxicillin component – single dose</li> <li>Adults: 2 g + 200 mg – single dose</li> </ul> <p>OR</p> <b>Gentamicin<sup>f</sup> (IV):</b> <ul style="list-style-type: none"> <li>Neonates: 5 mg/kg – single dose</li> <li>Children: 7.5 mg/kg – single dose</li> <li>Adults: 5 mg/kg – single dose</li> </ul> <p>AND</p> <b>Metronidazole (IV):</b> <ul style="list-style-type: none"> <li>Children: 7.5 mg/kg - single dose</li> <li>Adults: 500 mg - single dose</li> </ul>
Bowel surgery <sup>e</sup>	<b>Cefazolin (IV):</b> <ul style="list-style-type: none"> <li>Children: 50 mg/kg - single dose</li> <li>Adults: 2 g<sup>b</sup> - single dose</li> </ul> <p>AND</p> <b>Metronidazole (IV):</b> <ul style="list-style-type: none"> <li>Children: 7.5 mg/kg - single dose</li> <li>Adults: 500 mg - single dose</li> </ul>	<b>Amoxicillin+clavulanic acid (IV):</b> <ul style="list-style-type: none"> <li>Children: 40-50 mg/kg of amoxicillin component – single dose</li> <li>Adults: 2 g + 200 mg – single dose</li> </ul>
Urologic procedures	<b>Cefazolin (IV):</b>	<b>Gentamicin (IV):</b>

	<ul style="list-style-type: none"> <li>• Children: 50 mg/kg - single dose</li> <li>• Adults: 2 g<sup>b</sup> - single dose</li> </ul>	<ul style="list-style-type: none"> <li>• Neonates: 5 mg/kg – single dose</li> <li>• Children: 7.5 mg/kg – single dose</li> <li>• Adults: 5 mg/kg – single dose</li> </ul>
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108 Notes: All dosages are for normal renal and hepatic function.

109 IV: intravenous.

110 <sup>a</sup>Surgical procedures where the respiratory, alimentary, genital or urinary tracts are not entered.

111 <sup>b</sup>Higher doses of cefazolin (e.g. 3g) may be required in obese patients (> 120 kg).

112 <sup>c</sup>Surgical procedures where the respiratory, alimentary, genital or urinary tracts are entered under controlled conditions and without unusual contamination. Operations involving the biliary tract, appendix, vagina and oropharynx are included in this category.

115 <sup>d</sup>Operations with major (i.e. significant) interruptions in sterile technique (e.g. open cardiac massage) or substantial spillage from the gastrointestinal tract.

117 <sup>e</sup>Bowel surgery includes appendectomy, small intestine and colorectal surgical procedures.

118 <sup>f</sup>Gentamicin should be given in combination with metronidazole and not as a stand-alone option in contaminated surgical procedures because, if given alone, it provides insufficient coverage of anaerobic bacteria. Amikacin could be used instead of gentamicin based on local availability.

121 **ACCESS** antibiotics are indicated in green, **WATCH** antibiotics in yellow and **RESERVE** antibiotics in red.

## 122 Timing of antibiotic prophylaxis before surgery

123 According to the previously cited WHO guidelines, the antibiotic should be given 120 minutes or  
124 less before incision (251).

## 125 Duration of antibiotic prophylaxis

126 Antibiotic prophylaxis should not be continued after surgery for the purpose of preventing  
127 surgical site infections including in the presence of a surgical wound drain(251). This is because  
128 one dose of the prophylactic antibiotic should cover the entire period of potential contamination  
129 (i.e. from time of the incision until final closure of the wound) in most cases and continuing  
130 prophylaxis does not offer additional benefit in reducing the incidence of surgical site infections  
131 compared with discontinuing it (354). At the same time, limiting the duration to one single dose  
132 reduces the risk of selecting resistant bacteria in the patient's own microbiota and the risk of  
133 developing *Clostridioides difficile* infections.

134 Only in certain cases may a further dose of antibiotic be required, such as for prolonged surgical  
135 procedures (exceeding about 2 times the half-life of the antibiotic) or when there is major blood  
136 loss. If redosing is necessary, the half-life of the antibiotic should be considered (e.g. giving a  
137 second dose of cefazolin four hours after the initial preoperative dose in long surgeries) (Table  
138 3).

139 *Table 3 Half-life of the antibiotics recommended for surgical prophylaxis in the WHO EML(355)*

Antibiotic	Half-life (hours)
Amoxicillin–clavulanic acid	1–2
Cefazolin	1–2
Cefuroxime	1–2
Gentamicin	2–3
Metronidazole	6–8

140

# RESERVE ANTIBIOTICS

DRAFT

# 1 Overview

## 2 Key messages

1. Reserve antibiotics are antibiotics that retain activity against some of the multidrug-resistant bacteria listed in the WHO priority pathogen list
2. Countries should consider developing formal methods to monitor and control the use of Reserve antibiotics.
3. The list of Reserve antibiotics is updated every 2 years by the EML considering the availability of new antibiotics, new efficacy / effectiveness and safety data, updates of the WHO PPL or changing epidemiology
4. The list of Reserve antibiotics on the EML is closely aligned with the WHO list of critically important antimicrobials and WHO analysis of the clinical antibacterial pipeline

## 3

*Box 1 Other relevant WHO documents (please check regularly for updates)*

- <https://aware.essentialmeds.org/groups>

4 The Reserve group of antibiotics includes antibiotics that still have significant levels of activity  
5 against some of the multidrug-resistant bacteria listed in the WHO priority pathogen list including  
6 bacteria which are resistant to most or all of the EML antibiotics in the Access and Watch groups  
7 (Table 1).

8 In addition, all Reserve antibiotics are categorized as either “high priority” or “highest priority”  
9 in the WHO list of critically important antimicrobials (356). This list is intended for public health  
10 and animal health authorities who should ensure that critically important antibiotics for humans  
11 are also used sensibly in veterinary medicine. Use of any Reserve antibiotics in animals should be  
12 avoided wherever possible.

13 Reserve antibiotics can either be older off-patent antibiotics that have been reintroduced into  
14 clinical practice (e.g., polymyxin B, colistin, fosfomycin) or new antibiotics that have been recently  
15 licensed for the treatment of multidrug-resistant bacteria. It is important to note that not all  
16 antibiotics that have activity against strains of multidrug-resistant bacteria have been included in  
17 the EML (355). Between 2017 and 2021, the list of Reserve antibiotics was updated, and some  
18 antibiotics were removed and others added to this group. Only antibiotics listed on the  
19 EML/EMLc are considered essential for all health systems.

20 The EML needs to be continually updated as more evidence on the antibiotics in the list and new  
21 antibiotics become available. The list of Reserve antibiotics in the 2021 EML is closely aligned  
22 with the WHO analysis of the clinical antibacterial pipeline(357) which assesses how antibacterial  
23 drugs in the development pipeline address the WHO priority pathogens list. Ideally an antibiotic  
24 under development will progress through the pipeline and, after licensing, would be considered  
25 for listing in the EML as a Reserve antibiotic.

26 The overarching principle for listing an antibiotic as a Reserve antibiotic in the EML is evidence of  
 27 its utility to effectively treat an important clinical infection for which the currently available  
 28 treatment options are very limited, with a clear global unmet public health need. Other important  
 29 considerations are strong evidence that the antibiotic has: better efficacy, safety and durability  
 30 (low likelihood of selection of resistance on treatment) than comparable drugs; low impact on  
 31 the microbiome; and simplicity of administration. There is therefore likely to be a range of  
 32 Reserve antibiotics that cover different serious clinical infections. These antibiotics would  
 33 include, for example, systemic antibiotics targeted at particular multidrug-resistant phenotypes  
 34 (e.g. carbapenem-resistant organisms) or targeted at important pathogens (e.g. *Pseudomonas*  
 35 spp. or *Acinetobacter* spp.). Equally, there is an important unmet clinical need for active oral  
 36 drugs that can be used as targeted treatment of multidrug-resistant pathogens (e.g. *Klebsiella*  
 37 spp.). This focus on public health emphasizes the importance for Reserve antibiotics to have  
 38 phenotypic and genotypic activity that is globally relevant. For example, Reserve antibiotics that  
 39 are active against carbapenem-resistant pathogens should ideally also have activity against the  
 40 most common genetic types identified in low- and middle-income countries (eg metallo-  
 41 proteinases).

Glossary:

- Phenotypic resistance: Determined by methods such as disk diffusion, broth microdilution, and agar dilution and considered the “reference standard”. Susceptibility / resistance is determined based on the ability of defined concentrations of antibiotics to inhibit growth. It can generally not determine the cause of the resistance (e.g. beta-lactamase versus efflux pumps), an information that may be relevant for choosing the correct antibiotic
- Genotypic resistance: Detects resistance genes which may be important information for choosing the correct antibiotic and also for epidemiologic / surveillance reasons. Genes may however not always be expressed, and different gene products may interact so that there is an imperfect correlation between genotypic and phenotypic resistance. Ideally both methods are used in combination for multidrug-resistant organisms

42 Reserve antibiotics are considered “last-resort antibiotics” which are still effective for the  
 43 treatment of specific patient populations. There is a complex balance between using Reserve  
 44 antibiotics effectively in sick patients where needed and their overuse leading to a rapid decline  
 45 in their effectiveness. The great majority of Reserve antibiotics are intravenous and used in the  
 46 hospital facility setting. There is wider use of Reserve antibiotics in HIC’s than LMIC’s, raising clear  
 47 concerns about equity of access to Reserve antibiotics which are generally more expensive than  
 48 Access or Watch antibiotics.

49 Therefore, these antibiotics should be available for clinical care when needed but used only in  
 50 certain situations where their use is likely to have clear clinical benefits. Reserve antibiotics are  
 51 ideally used for targeted treatment once the multidrug-resistant bacteria are confirmed (eg  
 52 following laboratory identification of the pathogen from a blood culture and susceptibility testing  
 53 demonstrating wide multidrug resistance but sensitivity to a Reserve antibiotic). However, high

54 quality rapid culture and sensitivity data are often not available in many settings. The Handbook  
 55 focuses on empiric treatment when diagnostic test results, including microbiological cultures, are  
 56 not available. Reserve antibiotics could be considered for empiric therapy in very selected cases  
 57 where a multidrug-resistant pathogen as the cause of the infection can be strongly suspected  
 58 based on the clinical infection, local microbiology, previous treatment or known colonization with  
 59 a multidrug-resistant pathogen.

60 Reserve antibiotics are not listed as first- or second-choice options for any of the infections  
 61 included in this Handbook. However, to help with the appropriate use of Reserve antibiotics, a  
 62 comment about their potential role for empiric therapy has been added to specific chapters  
 63 where they are most likely to be used (e.g. severe hospital-acquired infections or severe  
 64 infections in heavily antibiotic experienced patients). The risks and benefits of treatment need to  
 65 be carefully considered in high-risk patient populations with multidrug-resistant infections with  
 66 high associated mortality. Some antibiotics on the Reserve list have substantial toxicity but may  
 67 still be used for treatment if there are no / few other treatment options and the risk of death /  
 68 permanent sequelae due to the infection are high. Focussing the optimal use of Reserve  
 69 antibiotics is complex and difficult at both a patient and country level, but control of the use of  
 70 Reserve antibiotics is critical to maintaining their future effectiveness. For example, Colistin in  
 71 South Africa is only authorised for use following specific criteria and approval from the Medicines  
 72 Control Council, as in section 21 of the Medicines and Related Substances Control Act.

- Preserving the effectiveness of these Reserve antibiotics (i.e. preventing the development of resistance to these antibiotics in the future) is key to maintaining their durability in clinical use.
- Therefore, all efforts should be made to ensure careful use of Reserve antibiotics within local and national stewardship strategies which should include routine local and/or national monitoring and reporting of their use.
- Countries should consider developing central and local monitoring of the use of Reserve antibiotics.
- Countries should consider developing formal guidance and control of the use of Reserve antibiotics at a national and local level, including through medicines regulation.

73 Prescribers need to recognise the very limited data available on the clinical efficacy of most  
 74 Reserve antibiotics in treating multidrug-resistant infections. Regulatory approval is usually  
 75 obtained through non-inferiority trials (usually in complicated UTI trials) containing few high-risk  
 76 patients with multidrug-resistant infections. Therefore, the effectiveness of these new molecules  
 77 on multidrug-resistant isolates is often based on *in vitro* data or case reports and retrospective  
 78 observational studies with high inherent risk of bias. Furthermore, recruitment of patients with  
 79 carbapenem-resistant pathogens into pathogen-focused or limited-population trials has been  
 80 difficult, which has led to estimates of clinical efficacy based on small studies. Strategic  
 81 comparative public health focused (rather than regulatory) trials for multidrug-resistant  
 82 infections that directly compare multiple agents in high-risk populations for clinical efficacy,  
 83 toxicity, resistance and health economic outcomes are urgently needed to inform the urgent  
 84 unmet public health priorities in this critical area.

85 *Table 1 Reserve antibiotic expected activity against third-generation cephalosporin and*  
 86 *carbapenem-resistant bacteria based on the type of beta-lactamase produced*

Type of beta-lactamase	ESBL <sup>a</sup>	KPC Carbapenemase	NDM, VIM, IMP Carbapenemase	AmpC	OXA-48 Carbapenemase	Expected activity against non-fermenters <sup>b</sup>
Ambler Class <sup>c</sup>	A Serine-beta-lactamases	A Serine-beta-lactamase	B Metallo-beta-lactamases	C Cephalosporinase	D Oxacillinase	-
Ceftazidime-avibactam	+	+	-	+	+	? <i>Acinetobacter baumannii</i> + <i>Pseudomonas aeruginosa</i>
Cefiderocol	+	+	+	+	+	+ (NOTE: higher mortality has been reported with carbapenem-resistant <i>Acinetobacter baumannii</i> infections)
Fosfomycin (IV)	+	+	+	+	+	?
Meropenem-vaborbactam	+	+	-	+	-	-
Plazomicin	+	+	-	+	+	-
Polymyxin B and colistin	+	+	+	+	+	+

87 **Expected activity:** + active; ? possibly active; - not or insufficiently active.

88 <sup>a</sup>ESBL (extended-spectrum beta-lactamases) are a group of different beta-lactamases.

89 <sup>b</sup>Non-fermenters refer to bacteria that cannot catabolize glucose and thus are unable to ferment. The most relevant  
 90 in this context are *Acinetobacter baumannii* and *Pseudomonas aeruginosa*. Please when using this table always  
 91 consider that even when activity of a certain Reserve antibiotic is reported against carbapenem-resistant non-  
 92 fermenters this ultimately depends on the type of carbapenemase produced and the resistance mechanism.

93 <sup>c</sup>The Ambler classification of beta-lactamases is the most widely used classification. According to this classification  
 94 beta-lactamases are divided into four classes (A, B, C and D) based upon similarities in their amino acid sequence.

# Cefiderocol

<https://list.essentialmeds.org/medicines/611>

## Key messages

1. The primary use of cefiderocol is for the treatment of infections caused by metallo-beta-lactamases (MBL)-producing carbapenem-resistant Enterobacterales
2. Very limited evidence for use in children
3. Caution needed with *Acinetobacter baumannii* infections because of higher mortality than best available alternative therapy described in a clinical trial

Cefiderocol is the first clinically available siderophore cephalosporin. Siderophore-antibiotic conjugates the ability of siderophores to bind extracellular free iron and use iron transporters to cross bacterial cell membranes (in the case of cefiderocol the outer membrane of aerobic Gram-negative bacteria), resulting in active accumulation of the antibiotic at the site of action. In addition, cefiderocol can also enter the bacterial cell by passively diffusing through porin channels similar to other beta-lactams.

Cefiderocol has been licensed for the treatment of complicated urinary tract infections, hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia in patients 18 years of age or older. Its indications include severe infections caused by certain strains of carbapenem-resistant Enterobacterales, *Pseudomonas aeruginosa* and *Acinetobacter baumannii* depending on the type of carbapenemase produced and the resistance mechanism in patients with limited treatment options.

The primary use of cefiderocol is for the treatment of infections caused by metallo-beta-lactamases (MBL)-producing carbapenem-resistant Enterobacterales for which alternative treatment options are very limited (as of the date of publication of this Handbook).

Particular caution is needed in patients with *Acinetobacter baumannii* infections because of concerning data from a randomized clinical trial that reported higher mortality with cefiderocol in this patient population (358, 359).

## Administration

Cefiderocol is currently only available as intravenous formulation (1 g/vial) and it should be infused over 3 hours.

## Mechanism of action

Cefiderocol acts by inhibiting bacterial enzymes responsible for cell-wall synthesis, primarily penicillin-binding proteins. This leads to cell lysis and death.

## 28 Spectrum of activity

29 Cefiderocol is only active against aerobic Gram-negative bacteria. Specifically, it is active against  
30 many carbapenem-resistant Enterobacterales, *Pseudomonas aeruginosa* and *Acinetobacter*  
31 *baumannii* clinical isolates. Cefiderocol has no, or only limited, activity against Gram-positive or  
32 anaerobes.

33 In vitro, cefiderocol inhibits the activity of extended-spectrum beta-lactamases (ESBL) and of  
34 certain types of carbapenemase, in particular *Klebsiella pneumoniae* carbapenemases (KPC),  
35 OXA-48 beta-lactamases and metallo-beta-lactamases (MBL) such as New Delhi metallo-beta-  
36 lactamases (NDM), Verona integron-encoded (VIM), or Imipenem-Resistant *Pseudomonas* (IMP)  
37 metallo-beta-lactamases.

38 Of note, cefiderocol is one of the few Reserve antibiotics with reported activity against metallo-  
39 beta-lactamases. The other such antibiotics are colistin/polymyxin B, fosfomycin and aztreonam  
40 combined with avibactam (in the form of ceftazidime+avibactam).

41 *Table 1 Cefiderocol expected activity against third-generation cephalosporin and carbapenem-*  
42 *resistant bacteria based on the type of beta-lactamase produced*

Type of beta-lactamase	ESBL <sup>a</sup>	KPC <sup>b</sup> Carbapenemase	NDM, VIM, IMP <sup>b</sup> Carbapenemase	AmpC	OXA-48 <sup>b</sup> Carbapenemase	Expected activity against non-fermenters <sup>c</sup>
Ambler class <sup>d</sup>	A Serine-beta-lactamases	A Serine-beta-lactamase	B Metallo-beta-lactamases	C Cephalosporinase	D Oxacillinase	-
Cefiderocol	+	+	+	+	+	+

(NOTE: higher mortality has been reported with carbapenem-resistant *Acinetobacter baumannii* infections)

43 **Expected activity:** + active; ? possibly active; - not or insufficiently active.

44 <sup>a</sup>ESBL (extended-spectrum beta-lactamases) are a group of different beta-lactamases.

45 <sup>b</sup>Carbapenemases.

46 <sup>c</sup>Non-fermenters refer to bacteria that cannot catabolize glucose and thus are unable to ferment. The most relevant  
47 in this context are *Acinetobacter baumannii* and *Pseudomonas aeruginosa*. Please when using this table always  
48 consider that even when activity of a certain Reserve antibiotic is reported against carbapenem-resistant non-  
49 fermenters this ultimately depends on the type of carbapenemase produced and the resistance mechanism.

50 <sup>d</sup>The Ambler classification of beta-lactamases is the most widely used classification. According to this classification  
51 beta-lactamases are divided into four classes (A, B, C and D) based upon similarities in their amino acid sequence.

## 52 Clinical efficacy

53 As of the date of publication of this Handbook, three randomized clinical trials have assessed the  
54 efficacy and safety of cefiderocol in adults. The results of these trials provide evidence that  
55 cefiderocol is not inferior to carbapenems for the treatment of infections caused by Gram-  
56 negative bacteria (not specifically multidrug-resistant) particularly for complicated urinary tract  
57 infections (358, 360), hospital-acquired pneumonia including ventilator-associated pneumonia  
58 (358, 361) and bloodstream infections or sepsis(358).

59 One study that enrolled 150 patients with confirmed carbapenem-resistant Gram-negative  
60 infection and compared cefiderocol to the best available therapy reported higher mortality in the  
61 cefiderocol group, which appeared to be driven by a worse outcome in the subgroup of patients  
62 with *Acinetobacter baumannii* infections(358). Mortality at day 28 was 24.8% (25/101) in the  
63 cefiderocol group versus 18.4% (9/49) in the best available therapy group (difference 6.4%, 95%  
64 confidence interval: -8.6% to 19.2%). The statistically significant difference persisted at day 49  
65 – 34/101 [33.7%] in the cefiderocol group versus 10/49 [20.4%] in the best available therapy  
66 group; difference 13.3%, 95% CI: -2.5% to 26.9%.

67 A possible explanation given by the authors for this difference was that, despite randomization,  
68 a higher mortality risk was present at the time of randomization in the cefiderocol group (e.g.  
69 more patients were in the intensive care unit or had experienced shock in the month preceding  
70 randomization). The increase in mortality remains, however, a major concern in this patient  
71 population and requires further investigation in clinical trials.

72 Although very small numbers of patients with metallo-beta-lactamase-producing  
73 Enterobacterales were included in these trials, outcomes in this group of patients was favourable.

74 As of the date of publication of this Handbook, cefiderocol is being assessed in phase 2 trials (i.e.  
75 trials that assess safety and effectiveness in small groups of patients) in children and good  
76 evidence about its efficacy and safety in the pediatric setting is lacking.

## 77 Toxicity

78 Cefiderocol has a good safety profile similar to other beta-lactams and is well tolerated. In clinical  
79 trials, side-effects were described in proportions similar to those experienced by patients in  
80 control groups. Gastrointestinal issues (e.g. diarrhoea) are those more commonly reported side-  
81 effects.

## 82 Dose

83 Cefiderocol requires dose adjustments in cases of renal impairment. Renal function should be  
84 closely monitored and doses adjusted accordingly. Dose adjustments are not covered in the  
85 Handbook. Please also refer to the chapter on dosing for more information.

86 *Table 2 Cefiderocol suggested doses*

Dose in adults	Dose in children	Dose in neonates
2 g given every 8 hours	There is no data for children or neonates	There is no data for children or neonates

87 Notes: All dosages are for normal renal and hepatic function.

88 

## Indication for the use of cefiderocol as a Reserve antibiotic

89 

### I. Targeted treatment

90 Cefiderocol could be considered in the following situations.

- 91 • As a last-resort option for the targeted treatment of severe invasive infections (e.g. positive blood culture) caused by laboratory-confirmed carbapenem-resistant Enterobacterales, particularly caused by metallo-beta-lactamases and *Pseudomonas aeruginosa*. The use of cefiderocol should be limited to situations where no other adequate therapeutic options are available. Given the increased mortality observed in the trial mentioned above (CREDIBLE-CR study), cefiderocol should be used with caution in patients with *Acinetobacter baumannii* infection.

92 To preserve its effectiveness (i.e. to prevent the development of resistance), cefiderocol should not be used to treat infections caused by isolates only producing extended-spectrum beta-lactamases when there are other options available.

101 

### II. Empiric treatment

- 102 • For empiric use exceptionally in very selected cases of seriously ill patients with invasive infections (e.g. patients with sepsis / septic shock) including:
  - 103 ○ Patients who have not responded to carbapenems if: (i) other causes of treatment failure have been excluded first, and (ii) there is a strong suspicion that the infection is caused by carbapenem-resistant bacteria, especially in settings with a high prevalence of metallo-beta-lactamase-producing Enterobacterales. However, if a patient is not improving, antibiotic failure is not the only possible cause to consider. Alternative reasons include for example: alternative diagnosis, development of complications (e.g. an abscess), inadequate control of the source of infection, suboptimal dose of the antibiotic or impossibility of the antibiotic to reach an adequate concentration at the site of infection. These possible causes of the lack of improvement in a patient are always important to consider before changing or adding new antibiotics.
  - 104 ○ Patients who have previously been treated for infections caused by carbapenem-resistant bacteria that are susceptible only to cefiderocol.
  - 105 ○ Patients who are known to be colonized with carbapenem-resistant bacteria found to be susceptible only to cefiderocol.

119 To help prescribers identify clinical scenarios where empiric use of Reserve antibiotics could  
120 exceptionally be considered, suggestions are given in the relevant chapters of the Handbook for  
121 certain infections (only for infections where empiric use could potentially be adequate on a case-  
122 by-case basis).

## 123 New resistance to cefiderocol in Enterobacterales, 124 Pseudomonas and Acinetobacter

125 Most Gram-negative bacteria are susceptible to cefiderocol. However, as of the date of  
126 publication of this Handbook, few data are available about resistance. Most evidence comes from  
127 two laboratory surveillance studies that tested the *in vitro* activity of cefiderocol in more than 30  
128 000 Gram-negative aerobic isolates (years 2014-2017) and showed that cefiderocol was effective  
129 at low minimum inhibitory concentrations for more than 99% of isolates(362, 363). An increase  
130 in minimum inhibitory concentrations to cefiderocol has emerged on treatment in a small  
131 proportion of patients in trials.

132 Data on resistance to cefiderocol are currently not reported by the Global Antimicrobial  
133 Resistance Surveillance System (GLASS).

### 134 Duration

135 Treatment duration varies according to indication and should be as short as possible, usually  
136 between 7-14 days.

DRAFT

# Ceftazidime+avibactam

<https://list.essentialmeds.org/medicines/395>

## Key messages

1. Activity against many carbapenem-resistant Enterobacterales and *Pseudomonas aeruginosa* (but not strains producing metallo-beta-lactamases (MBL))
2. When used to treat complicated intra-abdominal infections it should be given with metronidazole due to its unpredictable activity against anaerobes

Ceftazidime+avibactam is a combination of a third-generation cephalosporin (ceftazidime) in clinical use since the 1980s and a novel non- beta-lactam beta-lactamase inhibitor (avibactam). Its current indications in the EML/EMLc (355, 364) include infections caused by certain strains of carbapenem-resistant Enterobacterales and *Pseudomonas aeruginosa* depending on the type of carbapenemase produced and the resistance mechanism. Its activity against *Acinetobacter baumannii* is limited.

## Administration

Ceftazidime+avibactam is currently only available as intravenous/intramuscular formulation (powder for injection: 2 g + 0.5 g in vial) and it should be infused over 2 hours.

## Mechanism of action

Ceftazidime acts by inhibiting bacterial enzymes responsible for cell-wall synthesis, primarily penicillin binding protein 3. Avibactam targets the site of certain serine beta-lactamases and inactivates them, thus protecting ceftazidime from degradation.

## Spectrum of activity

Ceftazidime+avibactam is mainly active against aerobic Gram-negative bacteria. Specifically, it is active against ceftazidime-resistant and many carbapenem-resistant Enterobacterales and *Pseudomonas aeruginosa* clinical isolates, but its activity against *Acinetobacter* spp. is limited. Avibactam inhibits the activity of extended-spectrum beta-lactamases, AMPc beta-lactamases, *Klebsiella pneumoniae* carbapenemases and OXA-48 beta-lactamases (Table 1), and so preserves the activity of ceftazidime against many multidrug-resistant Gram-negative bacteria. However, avibactam does not inhibit the activity of metallo-beta-lactamases such as New Delhi metallo-beta-lactamase (NDM), Verona integron-encoded (VIM), or Imipenem Resistant *Pseudomonas* (IMP) metallo-beta-lactamases and therefore ceftazidime is inactive against strains expressing these beta-lactamases.

28 Ceftazidime+avibactam also has some antistreptococcal activity, very limited anti-staphylococcal  
 29 activity and no anti-enterococcal activity. Its activity against anaerobes varies: *Clostridium* spp.  
 30 are resistant and *Bacteroides* spp. show unpredictable susceptibility.

31 *Table 1 Ceftazidime+avibactam expected activity against third-generation cephalosporin and*  
 32 *carbapenem-resistant bacteria based on the type of beta-lactamase produced*

Type of beta-lactamase	ESBL <sup>a</sup>	KPC <sup>b</sup> Carbapenemase	NDM, VIM, IMP <sup>b</sup> Carbapenemase	AmpC	OXA-48 <sup>b</sup> Carbapenemase	Expected activity against non-fermenters <sup>c</sup>
Ambler class <sup>d</sup>	A Serine-beta-lactamases	A Serine-beta-lactamase	B Metallo-beta-lactamases	C Cephalosporinase	D Oxacillinase	-
Ceftazidime-avibactam	+	+	-	+	+	? <i>Acinetobacter baumannii</i> + <i>Pseudomonas aeruginosa</i>

33 **Expected activity:** + active; ? possibly active; - not or insufficiently active.

34 <sup>a</sup>ESBL (extended-spectrum beta-lactamases) are a group of different beta-lactamases.

35 <sup>b</sup>Carbapenemases.

36 <sup>c</sup>Non-fermenters refer to bacteria that cannot catabolize glucose and thus are unable to ferment. The most relevant  
 37 in this context are *Acinetobacter baumannii* and *Pseudomonas aeruginosa*. Please when using this table always  
 38 consider that even when activity of a certain Reserve antibiotic is reported against carbapenem-resistant non-  
 39 fermenters this ultimately depends on the type of carbapenemase produced and the resistance mechanism.

40 <sup>d</sup>The Ambler classification of beta-lactamases is the most widely used classification. According to this classification  
 41 beta-lactamases are divided into four classes (A, B, C and D) based upon similarities in their amino acid sequence.

## 42 Clinical efficacy

43 Several clinical trials have assessed the efficacy and safety of ceftazidime+avibactam in adults  
 44 and provide evidence that it is not inferior to carbapenems for the treatment of infections caused  
 45 by Gram-negative bacteria particularly for: complicated urinary tract infections (365, 366);  
 46 complicated intra-abdominal infections in combination with metronidazole (366-368); and  
 47 hospital-acquired pneumonia (369). Of note, in the majority of trials the infection being caused  
 48 by multidrug-resistant organisms was not an inclusion criterion. In children, as of the date of  
 49 publication of this Handbook, ceftazidime+avibactam has been assessed in phase 2 trials (i.e.  
 50 trials that assess safety and effectiveness in small groups of patients) for both the treatment of  
 51 complicated urinary tract infections, compared with cefepime (370) and in combination with  
 52 metronidazole for the treatment of complicated intra-abdominal infections, compared with  
 53 meropenem(371).

54 In both studies, ceftazidime+avibactam was well tolerated with a safety profile similar to that of  
 55 ceftazidime alone and appeared effective in children with complicated urinary or intra-abdominal  
 56 infections caused by Gram-negative pathogens.

## 57 Toxicity

58 Ceftazidime+avibactam is well tolerated and has side effects similar to those previously reported  
59 for ceftazidime alone. The most frequent side-effects are diarrhoea, nausea and vomiting.

## 60 Dose

61 Ceftazidime+avibactam requires dose adjustments in cases of renal impairment. Renal function  
62 should be closely monitored, and doses adjusted accordingly.

63 Please also refer to the chapter on dosing for more information.

64 *Table 2 Ceftazidime+avibactam suggested doses*

Dose in adults	Dose in children	Dose in neonates
2.5 g (2 g ceftazidime + 500 mg avibactam) given every 8 hours	62.5 mg/kg (max 2.5 g) given every 8 hours	62.5 mg/kg given every 8 hours

65 Notes: All dosages are for normal renal and hepatic function.

## 66 Indication for the use of ceftazidime+avibactam as a 67 Reserve antibiotic

### 68 I. Targeted treatment

69 Ceftazidime+avibactam could be considered:

- 70 • As a last-resort option for the targeted treatment of severe invasive infections (e.g.,  
71 septic shock with positive blood culture) caused by laboratory-confirmed carbapenem-  
72 resistant Enterobacterales or *Pseudomonas aeruginosa* (not *Acinetobacter baumannii*)  
73 including infections caused by strains producing certain carbapenemases that have  
74 tested susceptible to this antibiotic;
  - 75 ○ Ceftazidime+avibactam is not indicated for infections caused by strains producing  
76 metallo-beta-lactamases (sometimes ceftazidime+avibactam is combined with  
77 aztreonam for these strains but the evidence remains limited).
  - 78 ○ If ceftazidime+avibactam is used to treat intra-abdominal infections, it should be  
79 used as part of a combination treatment because it lacks activity against  
80 anaerobic organisms – therefore it is usually used in combination with  
81 metronidazole.
  - 82 ○ To preserve its effectiveness (i.e. to prevent the development of resistance),  
83 ceftazidime+avibactam should not be used to treat infections caused by isolates  
84 only producing extended-spectrum beta-lactamases or by ceftazidime-resistant  
85 bacteria when there are other options available.

86 **II. Empiric treatment**

87 Ceftazidime+avibactam could be considered for empiric use exceptionally in very selected cases  
 88 of seriously ill patients with invasive infections (e.g., patients with sepsis / septic shock without  
 89 microbiologic documentations) suspected to be caused by a multidrug-resistant pathogen (e.g.  
 90 severe hospital-acquired infections or infections in heavily antibiotic experienced patients  
 91 including carbapenems) such as in the following situations:

- 92 • Patients who have not responded to carbapenems if other causes of treatment failure  
 93 have been excluded first and there is a strong suspicion that the infection is caused by  
 94 carbapenem-resistant bacteria. Since ceftazidime+avibactam is not active against  
 95 metallo-beta-lactamases conveying carbapenem resistance, it is important to know the  
 96 most prevalent genotypic variants that are circulating for aerobic Gram-negative bacteria  
 97 in the setting where the patient acquired the infection. However, if a patient is not  
 98 improving, antibiotic failure is not the only possible cause to consider. Alternative  
 99 reasons include for example: alternative diagnosis, development of complications (e.g.  
 100 an abscess), inadequate source control, sub-optimal dose of the antibiotic or  
 101 impossibility of the antibiotic to reach an adequate concentration at the site of infection.  
 102 This is always important to consider before changing or adding new antibiotics.
- 103 • Patients who have previously been treated for infections caused by carbapenem-  
 104 resistant bacteria.
- 105 • Patients who are known to be colonized with carbapenem-resistant bacteria found to be  
 106 susceptible to ceftazidime+avibactam.

107 To help prescribers identify clinical scenarios where empiric use of Reserve antibiotics could  
 108 exceptionally be considered, suggestions are given in the relevant chapters of the Handbook for  
 109 selected infections (only for infections where empiric use could potentially be adequate on a  
 110 case-by-case basis).

111 **New resistance to ceftazidime+avibactam in**  
 112 **Enterobacterales and *Pseudomonas aeruginosa***

113 Most *Klebsiella pneumoniae* carbapenemase-producing Enterobacterales and *Pseudomonas*  
 114 *aeruginosa* are still susceptible to ceftazidime+avibactam; the proportion of isolates resistant to  
 115 ceftazidime+avibactam is low (higher for *Pseudomonas aeruginosa*) with variability across  
 116 geographical regions (372, 373). Data on resistance to ceftazidime+avibactam are currently not  
 117 reported by the Global Antimicrobial Resistance Surveillance System (GLASS). Resistance is often  
 118 associated with previous exposure to ceftazidime+avibactam(374).

119 **Duration**

120 Treatment duration varies according to indication and should be as short as possible, usually  
121 between 7-14 days.

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# Fosfomycin (intravenous)

<https://list.essentialmeds.org/medicines/343>

Only the formulation for intravenous use is addressed in this chapter.

## Key messages

1. Activity against MRSA, VRE and many carbapenem-resistant Enterobacterales
2. Usually used as part of combination treatments because of concerns about the emergence of resistance
3. Very limited evidence for use in children
4. Optimal dose not clearly defined

Fosfomycin is an antibiotic belonging to the class of phosphonic antibiotics discovered at the end of the 1960s. Its current indications in the EML/EMLc (355, 364) include infections caused by carbapenem-resistant Enterobacterales. For *Acinetobacter baumannii* and *Pseudomonas aeruginosa* the activity of fosfomycin is variable.

## Administration

Fosfomycin is available as intravenous (IV) formulation (powder for injection: 2 g; 4 g (as sodium) in vial). Fosfomycin has to be administered by slow infusion. Intramuscular use is discouraged by the European Medicine Agency because of insufficient data to confirm benefits to patients (375). Oral formulations (fosfomycin trometamol and fosfomycin calcium) mostly used for the treatment of lower urinary tract infections are not currently included in the EML/EMLc (355, 364) and therefore they are not covered in this chapter.

## Mechanism of action

Fosfomycin acts by inhibiting bacterial enzymes responsible for cell-wall synthesis, primarily pyruvyl transferase (an enzyme necessary for the synthesis of peptidoglycan).

## Spectrum of activity

Fosfomycin is active against several Gram-positive and Gram-negative bacteria but not as a single agent against *Streptococcus* spp., or *Acinetobacter* spp. or anaerobic bacteria. Specifically, it is usually active against *Enterococcus* spp. (including vancomycin-resistant strains), *Staphylococcus aureus* (including methicillin-resistant strains) and *Staphylococcus epidermidis*. It is also active against Gram-negative Enterobacterales (including extended-spectrum beta-lactamases producing strains), however, activity against carbapenem-resistant or carbapenemases-

26 producing strains is variable (Table 1). Fosfomycin's activity against *Pseudomonas aeruginosa* is  
27 variable.

28 *Table 1 Fosfomycin expected activity against third-generation cephalosporin and carbapenem-*  
29 *resistant bacteria based on the type of beta-lactamase produced*

Type of beta-lactamase	ESBL <sup>a</sup>	KPC <sup>b</sup> Carbapenemase	NDM, VIM, IMP <sup>b</sup> Carbapenemase	AmpC	OXA-48 <sup>b</sup> Carbapenemase	Expected activity against non-fermenters <sup>c</sup>
Ambler class <sup>d</sup>	A Serine-beta-lactamases	A Serine-beta-lactamase	B Metallo-beta-lactamases	C Cephalosporinase	D Oxacillinase	-
Fosfomycin (IV)	+	+	+	+	+	?

30 **Expected activity:** + active; ? possibly active; - not or insufficiently active.

31 <sup>a</sup>ESBL (extended-spectrum beta-lactamases) are a group of different beta-lactamases.

32 <sup>b</sup>Carbapenemases.

33 <sup>c</sup>Non-fermenters refer to bacteria that cannot catabolize glucose and thus are unable to ferment. The most relevant  
34 in this context are *Acinetobacter baumannii* and *Pseudomonas aeruginosa*. Please when using this table always  
35 consider that even when activity of a certain Reserve antibiotic is reported against carbapenem-resistant non-  
36 fermenters this ultimately depends on the type of carbapenemase produced and the resistance mechanism.

37 <sup>d</sup>The Ambler classification of beta-lactamases is the most widely used classification. According to this classification  
38 beta-lactamases are divided into four classes (A, B, C and D) based upon similarities in their amino acid sequence.

## 39 Clinical efficacy

40 Fosfomycin (IV) could be considered for the treatment of certain severe infections when other  
41 antibiotics cannot be used or are not effective. It is usually used as part of combination  
42 treatments, mostly because of concerns about the emergence of resistance when used alone.  
43 The benefits of combination treatment compared with monotherapy in terms of better clinical  
44 efficacy are unclear as there is limited clinical evidence(376, 377).

45 Few clinical trials have assessed the efficacy and safety of fosfomycin (IV) in adults. Fosfomycin  
46 has been assessed for the treatment of complicated urinary tract infections and the results  
47 showed that fosfomycin was not inferior to piperacillin+tazobactam(378). Another non-  
48 inferiority trial which compared fosfomycin with meropenem and ceftriaxone has recently been  
49 completed and results are expected(379). Fosfomycin has also been evaluated for the treatment  
50 of methicillin-resistant *Staphylococcus aureus* (MRSA) bacteraemia and endocarditis in  
51 combination with daptomycin and this combination was more effective than daptomycin alone  
52 (380).

53 Other evidence in support of the use of fosfomycin for difficult-to-treat *Staphylococcus aureus*  
54 infections (including MRSA) exists but it is anecdotal and inconclusive. This evidence is mostly  
55 from observational and *in-vitro* studies, including results from a clinical trial comparing  
56 fosfomycin (in combination with imipenem) to vancomycin alone for the treatment of

57 complicated MRSA bacteraemia and endocarditis but this study failed to reach an adequate  
58 sample size(381).

59 In children, the evidence is even more limited. One pharmacokinetic and safety trial has recently  
60 been completed of fosfomycin as an empiric treatment in neonatal sepsis (382).

61 The use of fosfomycin for other indications (e.g. bone and joint infections, healthcare-associated  
62 pneumonia, meningitis and abdominal infections) relies on evidence from case reports or other  
63 observational and *in vitro* studies which is therefore less robust.

## 64 Toxicity

65 Fosfomycin is well tolerated. However, use of the IV formulation can be associated with sodium  
66 overload related to the sodium salt formulation (this could be of concern in patients with heart  
67 failure) and hypokalaemia (therefore potassium levels should be regularly monitored).

## 68 Dose

69 The optimal IV dose needs still to be clearly defined. Usually doses vary with the severity of the  
70 disease and the patient's renal function. Dose adjustments are necessary in cases of renal  
71 impairment.

72 Please also refer to the chapter on dosing for more information.

73 *Table 2 Fosfomycin (IV) suggested doses*

Dose in adults	Dose in children	Dose in neonates
6 g given every 8 hours  (however total daily dose may vary depending on the indication and range between 12 and 24 g per day divided every 8 to 12 hours)	200-400 mg/kg/day divided every 6 to 8 hours	200mg/kg/day divided every 8 hours

74 Notes: All dosages are for normal renal and hepatic function.

## 75 Indication for the use of intravenous fosfomycin as a 76 Reserve antibiotic

### 77 I. Targeted treatment

78 Fosfomycin (usually as part of combination therapy to reduce the risk of the development of  
79 resistance) could be considered:

- 80 • As a last-resort option for the targeted treatment of severe infections caused by  
81 laboratory-confirmed carbapenem-resistant Enterobacterales or *Pseudomonas*  
82 *aeruginosa* (including strains producing carbapenemases) that have been shown to be  
83 susceptible to this antibiotic.

- 84 ○ Caution is needed with infections caused by *Pseudomonas aeruginosa* because
- 85 the activity of fosfomycin against this pathogen is variable.
- 86 ● Fosfomycin could also be considered as a last-resort option for difficult-to-treat
- 87 infections cause by *Staphylococcus aureus* (including MRSA) and *Enterococcus* spp.
- 88 (including vancomycin-resistant strains). However, the current version of the EML/EMLc
- 89 does not include this use.

## 90 II. Empiric treatment

- 91 ● Usually as part of combination therapy, fosfomycin could be considered for empiric use
- 92 in selected cases of seriously ill patients with invasive infections (e.g. patients with sepsis
- 93 / septic shock) suspected to be caused by a multidrug-resistant pathogen (e.g. severe
- 94 hospital-acquired infections or infections in heavily antibiotic experienced patients
- 95 including carbapenems) such as in the following situations:
- 96 ○ Patients who have not responded to carbapenems if other causes of treatment
- 97 failure have been excluded first and there is a strong suspicion that the infection
- 98 is caused by a carbapenem-resistant Enterobacterales (fosfomycin does not
- 99 reliably treat *Acinetobacter* spp. and its activity against *Pseudomonas aeruginosa*
- 100 is variable). However, if a patient is not improving, antibiotic failure is not the only
- 101 possible cause to consider. Alternative reasons include for example: alternative
- 102 diagnosis, , development of complications (e.g. an abscess), inadequate source
- 103 control, sub-optimal dose of the antibiotic or impossibility of the antibiotic to
- 104 reach an adequate concentration at the site of infection. This is always important
- 105 to consider before changing or adding new antibiotics.
- 106 ○ Patients who have previously been treated for infections caused by carbapenem-
- 107 resistant Enterobacterales. In certain settings *Klebsiella pneumoniae* may be
- 108 resistant to fosfomycin; therefore, local knowledge of susceptibility profiles for
- 109 aerobic Gram-negative bacteria is crucial(383). Fosfomycin does not reliably treat
- 110 *Acinetobacter* spp. and its activity against *Pseudomonas aeruginosa* is variable.
- 111 ○ Patients who are known to be colonized with carbapenem-resistant pathogens
- 112 found to be susceptible to fosfomycin.

113 To help prescribers identify clinical scenarios where empiric use of Reserve antibiotics could

114 exceptionally be considered, suggestions are given in the relevant chapters of the Handbook for

115 selected infections (only for infections where empiric use could potentially be adequate on a

116 case-by-case basis).

## 117 New resistance to fosfomycin in Enterobacterales

118 Cross-resistance is uncommon because of the unique structure and mechanism of action of

119 fosfomycin. Both chromosomal-mediated and plasmid-mediated (i.e. transmissible) resistance

120 can occur. Resistance can rapidly develop *in vitro*, but in clinical practice resistance is still  
121 uncommon, although it is increasing(384).

122 Data on resistance to fosfomycin are currently not reported by the Global Antimicrobial  
123 Resistance Surveillance System (GLASS).

## 124 Duration

125 Treatment duration varies according to indication and should be as short as possible, usually  
126 between 7-14 days.

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## 2 Linezolid

3 <https://list.essentialmeds.org/medicines/345>

### 4 Key messages

1. Activity against most strains of VRE and MRSA
2. Good oral bioavailability
3. Prolonged use (>4 weeks) associated with increased incidence of toxicity (myelosuppression, neuropathy) and should be avoided if possible

5 Linezolid is a synthetic antibiotic of the oxazolidinone class which has been in clinical use since  
6 the early 2000s for the treatment of infections caused by Gram-positive bacteria resistant to  
7 other antibiotics. Its current indications in the EML/EMLc (355, 364) include infections caused by  
8 methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Staphylococcus aureus*  
9 (VRSA) and vancomycin-resistant *Enterococcus* spp. (VRE) and multi-drug resistant  
10 *Mycobacterium tuberculosis*.

### 11 Administration

12 Linezolid is currently available as an intravenous (IV) formulation (injection for IV administration:  
13 2 mg/ mL in 300 mL bag) and as an oral formulation (tablet: 400 mg; 600 mg). A neonatal or  
14 pediatric formulation is also available (powder for oral liquid: 100 mg/5 mL).

15 Generic versions of linezolid are available.

### 16 Mechanism of action

17 Linezolid acts by binding to the 50S unit of the bacterial ribosome, inhibiting the synthesis of  
18 bacterial proteins.

### 19 Spectrum of activity

20 Linezolid is mainly active against aerobic Gram-positive bacteria. In particular it is active against  
21 most clinical isolates of vancomycin-resistant *Enterococcus*, MRSA and penicillin non-susceptible  
22 pneumococci. In addition, linezolid has some bactericidal activity against *Mycobacterium*  
23 *tuberculosis* including extensively drug-resistant strains and certain non-tuberculous  
24 mycobacteria.

25 Linezolid is not indicated for the treatment of Gram-negative infections. Even though linezolid  
26 has some *in vitro* activity against certain Gram-negative and anaerobic bacteria, clinical data are  
27 limited, and its use is not recommended for the treatment of these pathogens.

## 28 Clinical efficacy

29 Several clinical trials have assessed the efficacy and safety of linezolid compared to vancomycin  
 30 for the treatment of MRSA infections in general (385) and for skin and soft tissue infections in  
 31 particular (including those caused by MRSA) (386). Linezolid was associated with better short-  
 32 term survival compared to daptomycin for the treatment of bloodstream infections caused by  
 33 vancomycin-resistant *Enterococcus* spp. (387-389). However, linezolid's overall superiority to  
 34 daptomycin is less clear because a large cohort study showed greater treatment failure and short-  
 35 term mortality with linezolid than daptomycin (390). As to health care-associated pneumonia,  
 36 the results of a systematic review and meta-analysis did not show a clear benefit of linezolid for  
 37 clinical cure or microbiological eradication when compared to vancomycin or teicoplanin, and  
 38 linezolid was associated with more side-effects (391).

39 Linezolid can also be used as part of a longer regimen (longer than the standard TB treatment  
 40 duration) for the treatment of patients with multidrug- and rifampicin-resistant tuberculosis  
 41 (MDR/RR-TB) as indicated in WHO guidelines available at  
 42 <https://apps.who.int/iris/handle/10665/311389>.

## 43 Toxicity

44 Linezolid is generally well tolerated; however, it can cause myelosuppression (mostly  
 45 thrombocytopenia but also anaemia or leukopenia), which is usually reversible when linezolid is  
 46 stopped. Therefore, a complete blood cell count should be done weekly, especially in high-risk  
 47 patients (e.g., those with pre-existing myelosuppression, concomitant use of medicines that  
 48 cause bone marrow suppression). As with any other medicine, interactions with other medicines  
 49 should be checked before prescribing linezolid, this topic is, however, not addressed in the  
 50 handbook. Severe optic neuropathy can occur rarely, particularly if linezolid is used for over 28  
 51 days. Patients should be advised to report all new visual symptoms. Peripheral neuropathy is also  
 52 rarely associated with the (prolonged) use of linezolid. The risk of side-effects increases with  
 53 prolonged use (usually > 4 weeks), which should be avoided unless there are no alternatives.

## 54 Dose

55 Linezolid does not require dose adjustments in case of renal impairment.

56 Please also refer to the chapter on dosing for more information.

57 *Table 1 Linezolid suggested doses*

Dose in adults	Dose in children	Dose in neonates
400 to 600 mg given every 12 hours	10mg/kg given every 8 hours	10mg/kg given every 12 hours (1 <sup>st</sup> week of life) or every 8 hours (>1 <sup>st</sup> week of life)

58 Notes: All dosages are for normal renal and hepatic function.

## 59 Indication for the use of Linezolid as a Reserve antibiotic

60 Linezolid can be considered when:

- 61 • Oral treatment for MRSA is necessary and other less expensive oral alternatives to  
62 linezolid are not indicated or likely to be ineffective due to resistance or toxicity concerns.
  - 63 ○ Oral treatment may be necessary when maintaining access to parenteral  
64 treatment is difficult or for switching from IV to oral treatment when the patient  
65 could be discharged from hospital before the planned treatment course is  
66 completed.
  - 67 ○ In case of documented hypersensitivity to vancomycin.
- 68 • In case of severe renal impairment.
- 69 • In case of infections caused by vancomycin-resistant (or –intermediate) *Enterococcus* spp.  
70 or *Staphylococcus aureus*.
- 71 • In very selected cases of seriously ill patients with invasive infections that are known to  
72 be colonized with vancomycin-resistant *Enterococcus* spp. or *Staphylococcus aureus*.
- 73 • Linezolid can also be considered as a second-line option for the treatment of  
74 mycobacterial infections, including extensively drug-resistant *Mycobacterium*  
75 *tuberculosis* and is specifically mentioned in WHO guidelines (392).

76 When using linezolid, the risk of side-effects (mostly thrombocytopenia), especially with  
77 prolonged use, should always be taken into account. Because of this and because of the risk of  
78 emergence of resistance, linezolid use as Reserve antibiotic should be limited to well-defined  
79 patient populations and be as short as possible.

## 80 New resistance to linezolid in Gram-positive bacteria

81 Resistance to linezolid in usually susceptible Gram-positive bacteria most commonly arises  
82 through mutations in the bacterial 23S ribosomal RNA but it can also be transmitted through  
83 plasmids. Resistance can develop in the absence of prior treatment with linezolid and also after  
84 short periods of exposure to the antibiotic and should be carefully monitored.

85 Resistant isolates of enterococci, staphylococci and streptococci have been reported worldwide  
86 but their proportion remains low and in general, most Gram-positive bacteria are still susceptible  
87 to linezolid (393). Selection for resistance could be favoured by suboptimal dosing of the  
88 antibiotic especially in severely ill patients where volumes of distribution may be higher leading  
89 to low plasma levels (394).

90 Data on resistance to linezolid are currently not reported by the Global Antimicrobial Resistance  
91 Surveillance System (GLASS).

92 **Duration**

93 Treatment duration varies according to indication and should be as short as possible. Prolonged  
94 treatment (> 4 weeks) should be avoided whenever possible because of increased risk of toxicity  
95 (see above).

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# 1 Meropenem+vaborbactam

2 <https://list.essentialmeds.org/medicines/396>

## 3 Key messages

1. Activity against many carbapenem-resistant Enterobacterales especially those producing KPC carbapenemases (but not strains producing metallo-beta-lactamases (MBL and OXA-48))
2. Currently not licenced for children

4 Meropenem+vaborbactam is a combination of a carbapenem (meropenem) and a new non-  
5 beta-lactam beta-lactamase inhibitor (vaborbactam). Its current indications in the EML/EMLC  
6 (355, 364) include infections caused by certain strains of carbapenem-resistant Enterobacterales,  
7 *Acinetobacter baumannii* and *Pseudomonas aeruginosa* (but its activity varies) depending on the  
8 type of carbapenemase produced and the resistance mechanism.

9 The addition of vaborbactam has no additional advantage over meropenem alone for most  
10 strains of *Acinetobacter baumannii* and *Pseudomonas aeruginosa*.

## 11 Administration

12 Meropenem+vaborbactam is currently only available as intravenous formulation (powder for  
13 injection: 1 g + 1 g in vial) and it should be infused over 3 hours.

## 14 Mechanism of action

15 Meropenem+vaborbactam acts by inhibiting bacterial enzymes responsible for the cell wall  
16 synthesis, primarily penicillin-binding proteins. Vaborbactam targets the site of certain serine  
17 beta-lactamases (Ambler class B) and inactivates them, thus protecting meropenem from  
18 degradation.

## 19 Spectrum of activity

20 Meropenem+vaborbactam has a broad-spectrum of action including Gram-positive aerobic  
21 bacteria, Gram-negative aerobic bacteria and anaerobic bacteria. In particular, vaborbactam  
22 inhibits the activity of extended-spectrum beta-lactamases, AmpC beta-lactamases, *Klebsiella*  
23 *pneumoniae* carbapenemases, and thus preserves the activity of meropenem against many  
24 multidrug-resistant Gram-negative bacteria. However, vaborbactam does not inhibit the activity  
25 of metallo-beta-lactamases and OXA-48 beta-lactamases and therefore meropenem is not active  
26 against strains expressing these beta-lactamases.

27 *Table 1 Meropenem+vaborbactam expected activity against third-generation cephalosporin and*  
 28 *carbapenem-resistant bacteria based on the type of beta-lactamase produced*

Type of beta-lactamase	ESBL <sup>a</sup>	KPC <sup>b</sup> Carbapenemase	NDM, VIM, IMP <sup>b</sup> Carbapenemase	AmpC	OXA-48 <sup>b</sup> Carbapenemase	Expected activity against non-fermenters <sup>c</sup>
Ambler class <sup>d</sup>	A Serine-beta-lactamases	A Serine-beta-lactamase	B Metallo-beta-lactamases	C Cephalosporinase	D Oxacillinase	-
Meropenem-vaborbactam	+	+	-	+	-	-

29 **Expected activity:** + active; ? possibly active; - not or insufficiently active.

30 <sup>a</sup>ESBL (extended-spectrum beta-lactamases) are a group of different beta-lactamases.

31 <sup>b</sup>Carbapenemases.

32 <sup>c</sup>Non-fermenters refer to bacteria that cannot catabolize glucose and thus are unable to ferment. The most relevant in this context are *Acinetobacter baumannii* and *Pseudomonas aeruginosa*. Please when using this table always consider that even when activity of a certain Reserve antibiotic is reported against carbapenem-resistant non-fermenters this ultimately depends on the type of carbapenemase produced and the resistance mechanism.

36 <sup>d</sup>The Ambler classification of beta-lactamases is the most widely used classification. According to this classification beta-lactamases are divided into four classes (A, B, C and D) based upon similarities in their amino acid sequence.

## 38 Clinical efficacy

39 The TANGO I trial demonstrated that the efficacy and safety of meropenem+vaborbactam in  
 40 adults was non-inferior to piperacillin-tazobactam for the treatment of complicated urinary tract  
 41 infections (395). The TANGO II trial (77 patients) demonstrated improved clinical cure and  
 42 decreased short-term mortality and nephrotoxicity than the best-available therapy for the  
 43 treatment of infections caused by proven or suspected carbapenem-resistant Enterobacterales  
 44 (396).

## 45 Toxicity

46 Meropenem+vaborbactam is well tolerated and has side-effects similar to those previously  
 47 reported for meropenem alone. However, meropenem+vaborbactam is less damaging to the  
 48 kidneys than other antibiotics used to treat infections caused by carbapenem-resistant  
 49 Enterobacterales.

## 50 Dose

51 Dose adjustments are required in cases of renal impairment. In children, the optimal dose is  
 52 unknown because of limited paediatric-specific pharmacokinetics and pharmacodynamic  
 53 data(397). Please also refer to the chapter on dosing for more information.

54 *Table 2 Meropenem+vaborbactam suggested doses*

Dose in adults	Dose in children	Dose in neonates
4 g (2 g + 2 g vaborbactam) given every 8 hours	Currently not licenced for children	Currently not licenced for neonates

55 Notes: All dosages are for normal renal and hepatic function.

56 

## Indication for the use of meropenem+vaborbactam as a

  
57 

## Reserve antibiotic

58 

### I. Targeted treatment

59 Meropenem+vaborbactam could be considered:

- 60 • As a last-resort option for the targeted treatment of severe infections caused by laboratory-  
61 confirmed *Klebsiella pneumoniae* carbapenemase-producing Enterobacterales (not indicated  
62 in cases of metallo-beta-lactamases and OXA-48 production).
- 63 • In the treatment of infections caused by bacteria resistant to ceftazidime+avibactam
  - 64 ○ Based on the results of available trials, meropenem+vaborbactam could be  
65 considered in cases of severe complicated urinary tract and intra-abdominal  
66 infections and for hospital-acquired pneumonia when other antibiotics cannot be  
67 used or are not effective.

68 

### II. Empiric treatment

- 69 • Meropenem+vaborbactam could be considered for empiric use exceptionally in very selected  
70 cases of seriously ill patients with invasive infections (e.g. patients with sepsis / septic shock)  
71 suspected to be caused by a multidrug-resistant pathogen (e.g. severe hospital-acquired  
72 infections or infections in heavily antibiotic experienced patients including carbapenems)  
73 such as in the following situations:
  - 74 ○ Patients who have not responded to carbapenems if other causes of treatment failure  
75 have been excluded first and there is a strong suspicion that the infection is caused  
76 by a carbapenem-resistant pathogen. However, if a patient is not improving, antibiotic  
77 failure is not the only possible cause to consider. Alternative reasons include for  
78 example: alternative diagnosis, development of complications (e.g. an abscess),  
79 inadequate source control, sub-optimal dose of the antibiotic or impossibility of the  
80 antibiotic to reach an adequate concentration at the site of infection. This is always  
81 important to consider before changing or adding new antibiotics.
  - 82 ○ Patients who have previously been treated for infections caused by carbapenem-  
83 resistant pathogens.
  - 84 ○ Patients who are known to be colonized with carbapenem-resistant pathogens found  
85 to be susceptible to meropenem+vaborbactam.

86 To help prescribers identify these specific situations where empiric use of  
87 meropenem+vaborbactam could exceptionally be considered, suggestions are given in the  
88 relevant chapters of the Handbook for selected infections (only for infections where empiric  
89 use could be considered on a case-by-case basis).

## 90 New resistance to meropenem+vaborbactam in 91 Enterobacterales

92 Most *Klebsiella pneumoniae* carbapenemase-producing Enterobacterales are still susceptible to  
93 meropenem+vaborbactam with very few reports of resistant strains(398).

94 Data on resistance to meropenem+vaborbactam are currently not reported by the Global  
95 Antimicrobial Resistance Surveillance System (GLASS).

## 96 Duration

97 Treatment duration varies according to indication and should be as short as possible, usually  
98 between 7-14 days.

DRAFT

# 1 Plazomicin

2 <https://list.essentialmeds.org/medicines/397>

## 3 Key messages

1. Activity against many carbapenem-resistant Enterobacterales such as those producing KPC and OXA-48 carbapenemases (but not strains producing metallo-beta-lactamases (MBL))
2. Side effects similar to other aminoglycosides (usually kidney and inner ear)
3. Currently not licenced for children

4 Plazomicin is a new semisynthetic aminoglycoside derived from sisomicin, an older  
5 aminoglycoside(399). Its current indications in the EML/EMLc (355, 364) include infections  
6 caused by carbapenem-resistant Enterobacterales.

## 7 Administration

8 Plazomicin is currently only available as intravenous or intramuscular formulations (Injection:  
9 500 mg/10 mL).

## 10 Mechanism of action

11 Plazomicin acts by binding to the 30S unit of the bacterial ribosome thus inhibiting the start of  
12 the synthesis of bacterial proteins.

## 13 Spectrum of activity

14 Plazomicin is mainly active against Gram-negative aerobic bacteria including extended-spectrum  
15 beta-lactamase-producing Enterobacterales, carbapenem-resistant (including carbapenemase-  
16 producing) Enterobacterales (Table 1) and bacteria producing aminoglycoside-modifying  
17 enzymes (AME).

18 *Table 1 Plazomicin expected activity against third-generation cephalosporin and carbapenem-*  
19 *resistant bacteria based on the type of beta-lactamase produced*

Type of beta-lactamase	ESBL <sup>a</sup>	KPC <sup>b</sup> Carbapenemase	NDM, VIM, IMP <sup>b</sup> Carbapenemase	AmpC	OXA-48 <sup>b</sup> Carbapenemase	Expected activity against non-fermenters <sup>c</sup>
Ambler class <sup>d</sup>	A	A	B	C Cephalosporinase	D Oxacillinase	-

	Serine-beta-lactamases	Serine-beta-lactamase	Metallo-beta-lactamases <sup>e</sup>			
<b>Plazomicin</b>	<b>+</b>	<b>+</b>	<b>?</b>	<b>+</b>	<b>+</b>	<b>?</b>

20 **Expected activity:** + active; ? possibly active; - not or insufficiently active.

21 <sup>a</sup>ESBL (extended-spectrum beta-lactamases) are a group of different beta-lactamases.

22 <sup>b</sup>Carbapenemases.

23 <sup>c</sup>Non-fermenters refer to bacteria that cannot catabolize glucose and thus are unable to ferment. The most relevant  
24 in this context are *Acinetobacter baumannii* and *Pseudomonas aeruginosa*. Please when using this table always  
25 consider that even when activity of a certain Reserve antibiotic is reported against carbapenem-resistant non-  
26 fermenters this ultimately depends on the type of carbapenemase produced and the resistance mechanism. For  
27 plazomicin some *in vitro* studies have shown activity against *Pseudomonas aeruginosa* similar to amikacin(400).

28 <sup>d</sup>The Ambler classification of beta-lactamases is the most widely used classification. According to this classification  
29 beta-lactamases are divided into four classes (A , B, C and D) based upon similarities in their amino acid sequence.

30 <sup>e</sup>Susceptibility to plazomicin among strains producing metallo-beta-lactamases can be >50%.

## 31 Clinical efficacy

32 Plazomicin can be considered as salvage therapy for otherwise untreatable carbapenem-  
33 resistant Gram-negative infections.

34 Efficacy has been demonstrated only for the treatment of complicated urinary tract infections in  
35 adults which showed non-inferiority to meropenem(401).

36 Very limited evidence exists for the treatment of other types of infections and for its use in  
37 children. Plazomicin has also been compared with colistin as part of combination therapy for the  
38 treatment of severe infections caused by carbapenem-resistant Enterobacterales (e.g.  
39 bacteraemia and health care-associated pneumonia)(402). The results of the study indicated that  
40 plazomicin reduced short-term mortality and disease-related complications, but the trial was  
41 stopped early because of major difficulties with enrolling patients. The study therefore provides  
42 only descriptive statistics and findings and as such its results are inconclusive.

## 43 Toxicity

44 Plazomicin can cause damage to the kidneys and ears as with other aminoglycosides. The risk of  
45 nephrotoxicity is higher in older patients (>65 years) and in patients with pre-existing renal  
46 impairment; therefore, creatinine levels should be monitored regularly.

## 47 Dose

48 Weight-based once-daily dosing is used. No paediatric dosing is currently available.

49 Please also refer to the chapter on dosing for more information.

50 *Table 2 Plazomicin suggested doses*

Dose in adults	Dose in children	Dose in neonates
----------------	------------------	------------------

15 mg/kg given every 24 hours	Currently not licenced for children	Currently not licenced for neonates
-------------------------------	-------------------------------------	-------------------------------------

51 Notes: All dosages are for normal renal and hepatic function.

## 52 Indication for the use of plazomicin as a Reserve antibiotic

### 53 I. Targeted treatment

54 Plazomicin could be considered:

- 55 • As a last-resort option for the targeted treatment of severe infections (mostly urinary
- 56 tract infections) caused by laboratory-confirmed carbapenem-resistant Enterobacterales
- 57 including infections caused by strains producing carbapenemases that have been shown
- 58 to be susceptible to this antibiotic.
  - 59 ○ An important advantage of plazomicin is that it only needs to be given once a
  - 60 day, while other Reserve antibiotics that have a comparable spectrum of activity
  - 61 require multiple daily doses.
  - 62 ○ To preserve its effectiveness (i.e. to prevent the development of resistance), it
  - 63 should not be used to treat Enterobacterales isolates that only produce extended-
  - 64 spectrum beta-lactamases when other choices are available.
- 65 • For infections caused by Gram-negative bacteria resistant to other aminoglycosides (e.g.
- 66 gentamicin or amikacin).

### 67 II. Empiric treatment

- 68 • For empiric use exceptionally in very selected cases of seriously ill patients with invasive
- 69 infections (e.g. patients with sepsis / septic shock caused by infections of the urinary tract
- 70 if used as monotherapy while in other situations plazomicin like other aminoglycosides
- 71 would most likely be used in combination with other antibiotics) suspected to be caused
- 72 by a multidrug-resistant pathogen (e.g. severe hospital-acquired infections or infections
- 73 in heavily antibiotic experienced patients including carbapenems) such as in the following
- 74 situations:
  - 75 ○ Patients who have not responded to carbapenems if other causes of treatment
  - 76 failure have been excluded first and there is a strong suspicion that the infection
  - 77 is caused by carbapenem-resistant bacteria. However, if a patient is not
  - 78 improving, antibiotic failure is not the only possible cause to consider. Alternative
  - 79 reasons include for example: alternative diagnosis, development of complications
  - 80 (e.g. abscess), inadequate source control, sub-optimal dosing of the antibiotic or
  - 81 impossibility of the antibiotic to reach an adequate concentration at the site of
  - 82 infection. This is always important to consider before changing or adding new
  - 83 antibiotics.
  - 84 ○ Patients who have previously been treated for infections caused by carbapenem-
  - 85 resistant bacteria.

- 86                   ○ Patients who are known to be colonized with carbapenem-resistant bacteria  
87                   found to be susceptible to plazomicin.

88 To help prescribers identify clinical scenarios where empiric use of Reserve antibiotics could  
89 exceptionally be considered, suggestions are given in the relevant chapters of the Handbook for  
90 selected infections (only for infections where empiric use could potentially be adequate on a  
91 case-by-case basis).

## 92 New resistance to plazomicin in Enterobacterales

93 The main mechanisms of resistance overlap with some of those for other aminoglycosides. In  
94 particular ribosomal modifications of the target site within the ribosome can prevent plazomicin  
95 from binding to its target, and alterations to uptake and efflux pumps can decrease the antibiotic  
96 concentration at the site of action. However, unlike other aminoglycosides, plazomicin maintains  
97 activity against most aminoglycoside-modifying enzymes – enzymes that can reduce the affinity  
98 of the antibiotic for its ribosomal target through a mechanism that is different from ribosomal  
99 modifications. Plasmid-mediated resistance (i.e. transmissible resistance) has also been  
100 described.

101 Data on resistance to plazomicin are currently not reported by the Global Antimicrobial  
102 Resistance Surveillance System (GLASS).

## 103 Duration

104 Treatment duration varies according to indication and should be as short as possible.

DRAFT

# Polymyxin B and colistin (polymyxin E)

<https://list.essentialmeds.org/medicines/561>

## Key messages

- Polymyxin B and colistin have the same spectrum of activity that includes many strains of multidrug-resistant Gram-negative bacteria including *Pseudomonas aeruginosa* and *Acinetobacter baumannii*
- Usually used as part of combination treatments however, the only currently available randomized clinical trial did not show superiority over monotherapy
- Great care must be taken to avoid dosing errors since doses can be given in different units on labels and an initial loading dose is always necessary
- Main side effect is kidney damage (colistin>polymyxin B)

Polymyxin B and colistin are polypeptides belonging to the polymyxin class of antibiotics. These antibiotics became available for clinical use in the 1960s but were replaced by other classes because of their unfavourable safety profile, notably nephrotoxicity. They have, however, been “rediscovered” in recent years because they retain activity against many strains of multidrug-resistant Gram-negative bacteria including carbapenemase-producing strains. Polymyxin B and colistin have very similar chemical structures, however polymyxin B is administered directly as the active antibiotic while colistin is administered as inactive prodrug (sodium salt of colistin methane sulfonate also known as colistimethate). Since colistimethate is produced by chemical modification of colistin molecules through addition of methanesulfonate moieties, there are many different partially methanesulfonated derivatives in a given product resulting in batch-to-batch (and brand-to-brand) variation of the exact composition. Furthermore there is important patient to patient variation in the metabolism of colistimethate, making the pharmacokinetics of colistin difficult to predict (403).<sup>1</sup>

Their current indications for polymyxins B and colistin in the EML/EMLc (355, 364) include infections caused by carbapenem-resistant Enterobacterales, *Acinetobacter baumannii* and *Pseudomonas aeruginosa*.

## Administration

Polymyxin B and colistin are available as intravenous formulation (polymyxin B: powder for injection: 500.000 IU in vial; and colistin: powder for injection: 1 million IU in vial). There are important geographical differences in the availability of these antibiotics with polymyxin B, for

25 example not being available in many countries. The oral non-absorbable formulation of colistin  
 26 (colistin sulfate) is not currently included in the EML/EMLc (355, 364) and therefore is not  
 27 covered in this chapter.

## 28 Mechanism of action

29 Polymyxin B and colistin act by disrupting the bacterial cell membrane through interaction with  
 30 lipopolysaccharide (LPS) present in the membranes of Gram-negative bacteria thus leading to cell  
 31 lysis however the exact mechanism is unknown.

## 32 Spectrum of activity

33 Polymyxin B and colistin have the same antibacterial spectrum and both are active only against  
 34 aerobic Gram-negative bacteria with no activity against anaerobes, Gram-positive bacteria and  
 35 Gram-negative cocci (e.g. *Neisseria* spp.). Polymyxins are active against many clinical isolates of  
 36 carbapenem-resistant Enterobacterales, *Acinetobacter* spp. and *Pseudomonas aeruginosa*  
 37 clinical isolates (including many of the isolates producing carbapenemases –Table 1).

38 *Table 1 Polymyxins expected activity against third-generation cephalosporin and carbapenem-*  
 39 *resistant bacteria based on the type of beta-lactamase produced*

Type of beta-lactamase	ESBL <sup>a</sup>	KPC <sup>b</sup> Carbapenemase	NDM, VIM, IMP <sup>b</sup> Carbapenemase	AmpC	OXA-48 <sup>b</sup> Carbapenemase	Expected activity against non-fermenters <sup>c</sup>
Ambler class <sup>d</sup>	A Serine-beta-lactamases	A Serine-beta-lactamase	B Metallo-beta-lactamases	C Cephalosporinase	D Oxacillinase	-
Polymyxin B and colistin	+	+	+	+	+	+

40 **Expected activity:** + active; ? possibly active; - not or insufficiently active.

41 <sup>a</sup>ESBL (extended-spectrum beta-lactamases) are a group of different beta-lactamases.

42 <sup>b</sup>Carbapenemases.

43 <sup>c</sup>Non-fermenters refer to bacteria that cannot catabolize glucose and thus are unable to ferment. The most relevant  
 44 in this context are *Acinetobacter baumannii* and *Pseudomonas aeruginosa*. Please when using this table always  
 45 consider that even when activity of a certain Reserve antibiotic is reported against carbapenem-resistant non-  
 46 fermenters this ultimately depends on the type of carbapenemase produced and the resistance mechanism.

47 <sup>d</sup>The Ambler classification of beta-lactamases is the most widely used classification. According to this classification  
 48 beta-lactamases are divided into four classes (A, B, C and D) based upon similarities in their amino acid sequence.

## 49 Clinical efficacy

50 Polymyxin B and colistin can be considered as salvage therapy for otherwise untreatable  
 51 infections caused by carbapenem-resistant Gram-negative bacteria.

52 For severe infections, they are usually given as part of combination therapy often with high-doses  
 53 of carbapenems (but only if the minimum inhibitory concentration of carbapenems is  $\leq$  8-16  
 54 mg/L) or in combination with other antibiotics depending on the type of infection and *in vitro*  
 55 susceptibility (404).

56 However, the only currently available randomized clinical trial did not show that combination  
 57 therapy was superior to colistin monotherapy for short-term clinical success – at least for  
 58 infections caused by extensively drug-resistant *Acinetobacter* spp.; it is unclear whether this also  
 59 applies to carbapenemase-producing Enterobacterales (405). Evidence from observational  
 60 studies is available but should be interpreted with caution due to the inherent methodological  
 61 limitations (406, 407).

62 Polymyxin B and colistin were approved for use decades ago and were therefore not subjected  
 63 to the same development process that would be required for the approval of a new antibiotic  
 64 today. This point should be kept in mind when interpreting data about their efficacy and safety  
 65 (e.g. current products of polymyxins may be less nephrotoxic than those initially used(408)).  
 66 There are recently licensed Reserve group beta-lactam / beta-lactamase inhibitor combinations  
 67 (ceftazidime/avibactam, meropenem/vaborbactam) or siderophore-antibiotics (cefiderocol),  
 68 available that some experts consider preferable over polymyxins because of their better safety  
 69 profile and potentially better efficacy, although the evidence for this is weak and access and  
 70 affordability of these new antibiotics is a major issue in many LMIC settings.

## 71 Toxicity

72 The use of polymyxin B and colistin can cause kidney damage (colistin being more likely to cause  
 73 damage than polymyxin B) and, more rarely, neurotoxicity (e.g. paresthesia). The side effects are  
 74 reversible in most cases and are associated with the cumulative dose and duration of therapy  
 75 and use of concomitant medicines with similar toxicities.

## 76 Dose

77 Great care must be taken to avoid dosing errors with polymyxin B and colistin. Errors can arise  
 78 because doses can be given in different units on labels (409-411).

79 Polymyxin B doses can be given in international units (IU) or milligrams but the colistin dose can  
 80 be given as:

- 81 • IU of colistimethate
- 82 • mg of colistimethate
- 83 • mg of colistin base activity.

84 For example, a dose of 1 million IU of colistin corresponds to 80 mg of colistimethate and to 34  
 85 mg of colistin base activity.

86 When using polymyxins, it is crucial to start therapy with a loading dose followed by maintenance  
 87 dose after 12-24 hours. The reason is to achieve more rapidly plasma concentrations that may

88 be effective. In addition, for colistin (but not for polymyxin B), dose adjustments are necessary in  
 89 cases of renal impairment (412).

90 Few data are available for dosing in children. Current evidence suggests that doses approved by  
 91 regulatory agencies may be suboptimal for many children due to interpatient variability (412).

92 Please also refer to the chapter on dosing for more information.

93 *Table 2 Polymyxin B suggested doses*

	Dose in adults	Dose in children	Dose in neonates
<b>Loading dose</b>	2.5 mg/kg (25.000 IU/kg)	2.5 mg/kg (25.000 IU/kg)	2.5mg/kg (25.000 IU/kg)
<b>Maintenance dose</b> (start 12 hours after the loading dose)	1.5 mg/kg (15.000 IU/kg) given every 12 hours  Higher doses up to 25.000-30.000 units/kg (2.5-3 mg/kg) can be used but the maximal daily dose should not exceed 200 mg (2.000.000 IU)	1.5 mg/kg (15.000 IU/kg) given every 12 hours  <b>In children &lt; 2 years of age:</b> 1.5-4.5 mg (15.000 - 45.000 IU)/kg/day divided every 12 hours	1.5-4.5 mg (15.000-45.000 IU)/kg/day divided every 12 hours

94 Notes: All dosages are for normal renal and hepatic function.

95 *Table 3 Colistin suggested doses*

96 **Doses expressed in mg of colistin base activity (CBA) and in International Units (IU) of**  
 97 **colistimethate<sup>a</sup>**

	Dose in adults	Dose in children	Dose in neonates
<b>Loading dose</b>	300 mg of CBA / 9 Million IU of colistimethate		
<b>Maintenance dose</b> (start 12 hours after the loading dose)	150 mg given every 12 hours/ 4.5 Million IU given every 12 hours  Maximal daily dose should not exceed 300 mg of CBA or 9 (to 12) million IU	2.5-5 mg (75 000 – 150 000 IU)/kg/day divided in 2 to 4 doses	2.5-5 mg (75 000 – 150 000 IU)/kg/day divided in 2 to 4 doses

98 Notes: All dosages are for normal renal and hepatic function.

99 <sup>a</sup>34 mg of colistin base activity correspond to 1 million IU of colistimethate and to 80 mg of colistimethate.

## 100 Indication for the use of polymyxins as a Reserve antibiotic

### 101 I. Targeted treatment

102 Polymyxin B or colistin could be considered, usually as part of a combination therapy:

- 103 • As a last-resort option for the targeted treatment of severe infections caused by  
104 laboratory-confirmed carbapenem-resistant Gram-negative bacteria including infections  
105 caused by carbapenemase-producing strains that have been found to be susceptible to  
106 these antibiotics
  - 107 ○ If available, polymyxin B is usually preferred to colistin because it has better  
108 pharmacokinetic characteristics and less potential to cause kidney damage.
  - 109 ○ The only situation where the use of colistin is preferred is for the treatment of  
110 urinary tract infections because colistin reaches higher concentrations in urine  
111 compared to polymyxin B (the prodrug colistimethate is excreted primarily by the  
112 kidneys while polymyxin B is mainly eliminated through nonrenal pathways  
113 however the fraction of colistimethate being converted to colistin in the urine  
114 remains unclear(413)).

### 115 II. Empiric treatment

- 116 • For empiric use exceptionally in selected cases of seriously ill patients with invasive  
117 infections (e.g., patients with sepsis / septic shock) suspected to be caused by a multidrug-  
118 resistant pathogen (e.g., severe hospital-acquired infections or infections in heavily  
119 antibiotic experienced patients including carbapenems) such as in the following  
120 situations:
  - 121 • Patients who have not responded to carbapenems if other causes of treatment  
122 failure have been excluded first and there is a strong suspicion that the infection  
123 is caused by a carbapenem-resistant pathogen. However, if a patient is not  
124 improving, antibiotic failure is not the only possible cause to consider. Alternative  
125 reasons include for example: alternative diagnosis, development of complications  
126 (e.g. an abscess), inadequate source control, sub-optimal dose of the antibiotic  
127 or impossibility of the antibiotic to reach an adequate concentration at the site of  
128 infection. This is always important to consider before changing or adding new  
129 antibiotics.
  - 130 • Patients who have previously been treated for infections caused by carbapenem-  
131 resistant pathogens susceptible to polymyxins.
  - 132 • Patients who are known to be colonized with carbapenem-resistant pathogens  
133 found to be susceptible to polymyxins.

134 To help prescribers identify clinical scenarios where empiric use of Reserve antibiotics could  
135 exceptionally be considered, suggestions are given in the relevant chapters of the Handbook for

136 selected infections (only for infections where empiric use could potentially be adequate on a  
137 case-by-case basis).

## 138 New resistance to polymyxins in Enterobacterales, 139 Pseudomonas and Acinetobacter

140 Some technical challenges exist to identify resistance to polymyxin B and colistin (e.g. polymyxins  
141 diffuse poorly in diffusion-based assays such as disk-diffusion tests and broth microdilution,  
142 which is the recommended method, is impractical and rarely used in most laboratories)(414).  
143 Resistance can be related to chromosomal mutations that lead to changes in the bacterial  
144 membrane that impair the ability of polymyxin B and colistin to bind to their target. Plasmid-  
145 mediated resistance (i.e. transmissible resistance) due to mobilized colistin resistance (*mcr*)  
146 genes is also being increasingly described (415, 416).  
147 Unfortunately, data on resistance to colistin and polymyxin B are currently not reported by the  
148 Global Antimicrobial Resistance Surveillance System (GLASS).

### 149 Duration

150 Treatment duration varies according to indication and should be as short as possible, usually  
151 between 7-14 days.

DRAFT

## 1 FORMULARY

## 2 ADULTS

3 All dosages are for normal renal and hepatic function.

Antibiotic (alphabetic order)	Dose	Indication for the use of the antibiotic in the Handbook
Amikacin	IV: 15 mg/kg/dose given once daily	Febrile neutropenia (high risk) Sepsis (unknown origin) Upper UTI (severe)
Amoxicillin	Oral: <b>Lower dose:</b> 500 mg given every 8 hours <b>Higher dose:</b> 1 gram given every 8 hours	<b>Lower dose:</b> Pharyngitis Acute otitis media COPD exacerbations (mild) Dental infections  <b>Higher dose:</b> Acute sinusitis CAP (mild)
Amoxicillin+clavulanic acid	Oral: <b>Lower dose:</b> 500mg + 125 mg given every 8 hours <b>Higher dose:</b> 875mg + 125 mg given every 8 hours  IV: <b>Lower dose:</b> 1 gram of amoxicillin + 200 mg of clavulanic acid given every 8 hours <b>Higher dose:</b> 2 grams of amoxicillin + 200 mg of clavulanic acid (single dose for prophylaxis)	<b>Lower dose (oral):</b> Acute otitis media Acute sinusitis COPD exacerbations (severe) UTI (lower) SSTI (mild) Febrile neutropenia (low risk)  <b>Higher dose (oral):</b> CAP (mild) IAI (mild)  <b>Lower dose (IV)</b> Bone and joint infections CAP (severe)) HAP Periorbital cellulitis Pyomyositis  <b>Higher dose (IV)</b> Surgical prophylaxis
Ampicillin/Amoxicillin	IV: 2 grams given every 4 hours	Meningitis

<p><b>Azithromycin</b></p>	<p>Oral:  <b>Lower dose:</b> 500 mg given once daily  <b>Higher dose:</b> 1 gram (single dose)</p>	<p><b>Lower dose</b>  Enteric fever (mild)  Infectious acute diarrhoea</p> <p><b>Single dose</b>  Chlamydia infection  Cholera  Gonococcal infection  Trachoma</p>
<p><b>Benzylpenicillin</b>  (Only for IV use)</p> <p><i>Synonyms are aqueous benzylpenicillin, benzylpenicillin potassium, benzylpenicillin sodium, crystalline penicillin, penicillin G potassium, and penicillin G sodium</i></p>	<p>IV: 4 million international units (2.4 g) given every 4 hours</p>	<p>Meningitis  Neurosyphilis</p>
<p><b>Benzathine benzylpenicillin</b>  (Only for IM use)</p>	<p>IM: 2.4 million international units (1.8 g)</p> <p>(the number of doses depends on the stage of the infection)</p>	<p>Syphilis</p>
<p><b>Procaine benzylpenicillin</b>  (Only for IM use)</p>	<p>IM: 1.2 million international units (1.2 g) given once daily</p>	<p>Syphilis  Neurosyphilis</p>
<p><b>Cefalexin</b></p>	<p>Oral: 500 mg given every 8 hours</p>	<p>COPD exacerbations (mild)  Periorbital cellulitis  Pharyngitis  Pyomyositis  SSTI (mild)</p>
<p><b>Cefazolin</b></p>	<p>IV: 2 grams given every 8 hours or single dose</p>	<p>Bone and joint infections  Surgical prophylaxis (single dose)</p>
<p><b>Cefiderocol</b></p>	<p>IV: 2 grams given every 8 hours</p>	
<p><b>Cefixime</b></p>	<p>Oral: 400 mg given once daily</p>	<p>Infectious acute diarrhoea  Gonococcal infection (single dose)</p>
<p><b>Cefotaxime</b></p>	<p>IV:  <b>Lower dose:</b> 1 g given every 8 hours  <b>Higher dose:</b> 2 g given every 8 hours  <b>Highest dose:</b> 2g given every 6 hours</p>	<p><b>Lower dose (3 g/day):</b>  Upper UTI (severe)</p> <p><b>Higher dose (6 g/day):</b>  Bone and joint infections  CAP (severe)  HAP  IAI (mild and severe)  Bone and joint infections  Sepsis (unknown origin)</p> <p><b>Highest dose (8 g/day)</b>  Meningitis</p>
<p><b>Ceftazidime+avibactam</b></p>	<p>IV: 2 grams ceftazidime + 500 mg avibactam given every 8 hours</p>	

<p><b>Ceftriaxone</b></p>	<p>IV / IM:  <b>Single dose:</b> 250 mg  <b>Lower dose:</b> 1 gram given once daily  <b>Higher dose:</b> 2 grams given once daily  <b>Highest dose:</b> 2 grams given every 12 hours</p>	<p><b>Single dose:</b>  Gonococcal infection</p> <p><b>Lower dose (1 g/day):</b>  Infectious acute diarrhoea (severe)  Upper UTI (severe)</p> <p><b>High dose (2g/day):</b>  Bone and joint infections  CAP (severe)  Endophthalmitis  Enteric fever (severe)  HAP  IAI (mild and severe)  Necrotizing fasciitis  Sepsis (unknown origin)</p> <p><b>Highest dose (4 g/day):</b>  Meningitis</p>
<p><b>Cefuroxime</b></p>	<p>IV: 1.5 grams (single dose)</p>	<p>Surgical prophylaxis</p>
<p><b>Ciprofloxacin</b></p>	<p>Oral:  500 mg given every 12 hours  1 gram (single dose)</p>	<p>Upper UTI (mild)  Infectious acute diarrhoea  IAI (mild)  Enteric fever  Febrile neutropenia (low risk)  Cholera (single dose)</p>
<p><b>Chloramphenicol</b></p>	<p>IV: 1 gram given every 6 hours</p>	<p>Meningitis</p>
<p><b>Clarithromycin</b></p>	<p>Oral: 500 mg given every 12 hours</p> <p>IV:  400 mg given every 12 hours</p> <p><i>Clarithromycin has excellent oral bioavailability and the intravenous route should be reserved for patients with impaired gastrointestinal function.</i></p>	<p>Pharyngitis  CAP (severe)</p>
<p><b>Clindamycin</b></p>	<p>IV/oral:  <b>Lower dose:</b> 600 mg given every 8 hours  <b>Higher dose:</b> 900 mg given every 8 hours</p>	<p><b>Lower dose:</b>  Bone and joint infections</p> <p><b>Higher dose:</b>  Necrotizing fasciitis</p>
<p><b>Cloxacillin or Flucloxacillin</b></p>	<p>Oral/IV:  <b>Lower dose:</b> 500 mg given every 8 hours</p> <p><b>Higher dose:</b> 2 grams given every 6 hours</p>	<p><b>Lower dose:</b>  SSTI (mild)</p> <p><b>Higher dose:</b>  Bone and joint infections  Periorbital cellulitis  Pyomyositis</p>
<p><b>Doxycycline</b></p>	<p>Oral:</p>	<p>CAP (mild)</p>

	100 mg given every 12 hours 300 mg (single dose)	COPD exacerbations (mild) Chlamydia infection Cholera (single dose)
<b>Gentamicin</b>	IV: 5 mg /kg given once daily	Sepsis (unknown origin) Surgical prophylaxis Upper UTI (severe)
<b>Fosfomycin (IV)</b>	IV: 6 grams given every 8 hours  (range 12-24 grams per day depending on the indication)	<b>Empiric use should be exceptional</b> (e.g. seriously ill patients with risk factors for carbapenem-resistant infections or failing to respond to carbapenems when other causes of treatment failure have been excluded)
<b>Linezolid</b>	IV/Oral: 400 to 600 mg given every 12 hours	
<b>Meropenem</b>	IV: <b>Lower dose:</b> 1 gram given every 8 hours <b>Higher dose:</b> 2 grams given every 8 hours	<b>Lower dose:</b> Febrile neutropenia (high risk)  <b>Higher dose:</b> IAI (severe) Febrile neutropenia (high-risk)
<b>Meropenem+vaborbactam</b>	IV: 2 grams of meropenem + 2 grams of vaborbactam given every 8 hours	<b>Empiric use should be exceptional</b> (e.g. seriously ill patients with risk factors for carbapenem-resistant infections or failing to respond to carbapenems when other causes of treatment failure have been excluded)
<b>Metronidazole</b>	Oral/IV: <b>Single dose:</b> 500 mg, 2 grams  <b>Lowest dose:</b> 500 mg given every 12 hours <b>Lower dose:</b> 500 mg given every 8 hours <b>Higher dose:</b> 750 mg given every 8 hours	<b>Single dose:</b> Surgical prophylaxis (500 mg) Trichomoniasis (2 gr)  <b>Lowest dose:</b> Trichomoniasis  <b>Lower dose:</b> <i>C. difficile</i> infection IAI (mild and severe) Necrotizing fasciitis  <b>Higher dose:</b> Amoebic abscess
<b>Nitrofurantoin</b>	Oral: 100 mg given every 12 hours (modified release) 50 mg given every 6 hours (immediate release)	UTI (lower)
<b>Phenoxymethylpenicillin</b>	Oral: 500 mg (800,000 international units*) given every 6 hours  *Units of the potassium salt	Pharyngitis CAP (mild) Dental infections

Piperacillin+tazobactam	IV: 4 grams + 500 mg q6h	HAP IAI (severe) Necrotizing fasciitis Febrile neutropenia (high-risk)
Plazomicin	15 mg/kg/dose give once daily	<b>Empiric use should be exceptional</b> (e.g. seriously ill patients with risk factors for carbapenem-resistant infections or failing to respond to carbapenems when other causes of treatment failure have been excluded)
Polymixin B	IV: <b>Loading dose:</b> 2.5 mg/kg (25.000 international units/kg)  <b>Maintenance dose:</b> 1.5 mg/kg (15.000 international units/kg) given every 12 hours  Higher doses up to 25.000-30.000 units/kg (2.5-3 mg/kg) can be used but the maximal daily dose should not exceed 200 mg (2.000.000 international units)	<b>Empiric use should be exceptional</b> (e.g. seriously ill patients with risk factors for carbapenem-resistant infections or failing to respond to carbapenems when other causes of treatment failure have been excluded)
Polymyxin E (colistin)	<b>Loading dose:</b> 300 mg of colistin base activity / 9 million international units (IU) of colistimethate  <b>Maintenance dose:</b> 150 mg / 4.5 million IU given every 12 hours  Maximal daily dose should not exceed 300 mg of CBA or 9 (to 12) million IU	<b>Empiric use should be exceptional</b> (e.g. seriously ill patients with risk factors for carbapenem-resistant infections or failing to respond to carbapenems when other causes of treatment failure have been excluded)
Sulfamethoxazole+trimethoprim	Oral: 800 mg of sulfamethoxazole+ 160 mg of trimethoprim given every 12 hours	UTI (lower) Infectious acute diarrhoea
Trimethoprim	Oral: 200 mg given every 12 hours	UTI (lower)
Vancomycin	IV: 15-20 mg/kg given every 12 hours  Oral: 125 mg q6h or 500 mg given every 6 hours	IV: Endophthalmitis Febrile neutropenia (high risk) Necrotizing fasciitis (if MRSA suspected)  Oral: <i>C. difficile</i> infection (higher dose for severe cases)

4 ACCESS antibiotics are indicated in green, WATCH antibiotics in yellow and RESERVE antibiotics in red.

# 1 CHILDREN

2 All dosages are for normal renal and hepatic function.

Antibiotic (alphabetic order)	Dose	Indication for the use of the antibiotic in the Handbook
Amikacin	IV: 15 mg/kg/dose given once daily	Febrile neutropenia (high risk) Sepsis (unknown origin) Upper UTI (severe)
Amoxicillin	<p>Oral: 40-50 mg/kg/dose given every 12 hours</p> <p><b>Weight bands:</b>            3-&lt;6 kg: 125 mg given every 12 hours            6-&lt;10 kg: 250 mg given every 12 hours            10-&lt;15 kg: 500 mg given every 12 hours            15-&lt;20 kg: 750 mg given every 12 hours            20-&lt;30 kg: 1000 mg given every 12 hours            ≥ 30 kg: Use adult dose</p> <p>IV:            • First week of life: 50 mg/kg/dose given every 12 hours            • Beyond first week of life: 50 mg/kg/dose given every 8 hours</p>	Pharyngitis Acute otitis media Dental infections Acute sinusitis CAP (mild) Sepsis (referral to hospital not possible)
Amoxicillin+clavulanic acid	<p>Oral/IV:            40-50 mg/kg/dose (amoxicillin component) given every 12 hours            OR            30 mg/kg/dose given every 8 hours</p> <p><b>Weight bands:</b>            3-6 kg: 250 mg of amoxicillin/dose given every 12 hours            6-10 kg: 375 mg of amoxicillin/dose given every 12 hours            10-15 kg: 500 mg of amoxicillin/dose given every 12 hours            15-20 kg: 750 mg of amoxicillin/dose given every 12 hours            20-&lt;30 kg: 1000 mg of amoxicillin/dose given every 12 hours            ≥ 30 kg: Use adult dose</p> <p><i>Oral liquid must be refrigerated after reconstitution.</i></p>	Acute otitis media Acute sinusitis UTI (lower) SSTI (mild) Febrile neutropenia (low risk) IAI (mild) Bone and joint infections HAP Periorbital cellulitis Pyomyositis Surgical prophylaxis

<p><b>Ampicillin/Amoxicillin</b></p>	<p>IV:  <ul style="list-style-type: none"> <li>• First week of life: 50 mg/kg/dose given every 12 hours</li> <li>• Beyond first week of life: 50 mg/kg/dose given every 8 hours</li> </ul> </p>	<p>Meningitis                      Sepsis                      IAI mild and severe                      CAP</p>
<p><b>Azithromycin</b></p>	<p>Oral:  <b>Lower dose:</b>                      10 mg/kg/dose given once daily  <b>Higher dose:</b>                      20 mg/kg/dose given every 12 hours</p>	<p><b>Lower dose:</b>                      Infectious acute diarrhoea  <b>Higher dose:</b>                      Enteric fever (mild)                      Cholera (single dose)                      Trachoma (single dose)</p>
<p><b>Benzylpenicillin</b>                      (Only for IV use)</p> <p><i>Synonyms are aqueous benzylpenicillin, benzylpenicillin potassium, benzylpenicillin sodium, crystalline penicillin, penicillin G potassium, and penicillin G sodium</i></p>	<p>IV:  <b>Lower dose:</b>                      50 000-75 000 IU/kg/dose (30-45 mg/kg/dose) given every 12 hours  <b>Higher dose:</b>  <b>Severe CAP / Sepsis</b>                      50.000 IU/kg/dose (30 mg/kg/dose) given every 8 hours  <b>Meningitis</b>                      100 000 IU/kg/dose (60 mg/kg/dose) given every 6 hours</p>	<p><b>Lower dose:</b>                      Congenital syphilis  <b>Higher dose:</b>                      Severe CAP                      Sepsis                      Meningitis</p>
<p><b>Procaine benzylpenicillin</b>                      (Only for IM use)</p>	<p>IM: 50 000 IU (50 mg) / kg per day</p>	<p>Congenital syphilis</p>
<p><b>Cefalexin</b></p>	<p>Oral: 25 mg/kg/dose given every 12 hours</p> <p><b>Weight bands:</b>                      3-&lt;6 kg: 125 mg given every 12 hours                      6-&lt;10 kg: 250 mg given every 12 hours                      10-&lt;15 kg: 375 mg given every 12 hours                      15-&lt;20 kg: 500 mg given every 12 hours                      20-&lt;30 kg: 625 mg given every 12 hours                      ≥ 30 kg: Use adult dose</p>	<p>Periorbital cellulitis                      Pharyngitis                      Pyomyositis                      SSTI (mild)</p>
<p><b>Cefazolin</b></p>	<p>IV:                      25 mg/kg/dose given every 12 hours                      50 mg/kg (single dose for surgical prophylaxis)</p>	<p>Bone and joint infections                      Surgical prophylaxis</p>
<p><b>Cefiderocol</b></p>	<p>There is no data for children or neonates</p>	
<p><b>Cefixime</b></p>	<p>Oral: 10 mg/kg/dose given once daily</p>	<p>Infectious acute diarrhoea</p>
<p><b>Cefotaxime</b></p>	<p>IV/IM:                      50 mg/kg/dose given every 8 hours</p>	<p>Upper UTI (severe)                      Bone and joint infections                      CAP (severe)                      HAP                      IAI (mild and severe)                      Sepsis (unknown origin)                      Meningitis</p>

<b>Ceftazidime+avibactam</b>	IV/IM: 62.5 mg/kg (Max 2 grams ceftazidime + 500 mg avibactam) given every 8 hours	
<b>Ceftriaxone</b>	IV / IM: <b>Lower dose:</b> 80 mg/kg/dose given once daily  <b>Higher dose:</b> 100 mg/kg given once daily	<b>Lower dose:</b> Infectious acute diarrhoea (severe) Upper UTI (severe) Bone and joint infections CAP (severe) Endophthalmitis Enteric fever (severe) HAP IAI (mild and severe) Necrotizing fasciitis Sepsis (unknown origin)  <b>Higher dose:</b> Meningitis
<b>Cefuroxime</b>	IV: 50 mg/kg (single dose)	Surgical prophylaxis
<b>Ciprofloxacin</b>	Oral: 10-20 mg/kg/dose given every 12 hours  <b>Weight bands:</b> 3-<6 kg: 50 mg given every 12 hours 6-<10 kg: 100 mg given every 12 hours 10-<15 kg: 150 mg given every 12 hours 15-<20 kg: 200 mg given every 12 hours 20-<30 kg: 300 mg given every 12 hours ≥ 30 kg: Use adult dose	Upper UTI (mild) Infectious acute diarrhoea IAI (mild) Enteric fever Febrile neutropenia (low risk) Cholera (single dose)
<b>Chloramphenicol</b>	IV/IM: 25 mg/kg/dose given every 6 hours  <i>Use chloramphenicol only when no other option is available due to toxicity concerns</i>	Meningitis
<b>Clarithromycin</b>	Oral: 7.5 mg/kg/dose given every 12 hours  <i>Clarithromycin has excellent oral bioavailability and the intravenous route should be reserved for patients with impaired gastrointestinal function.</i>	Pharyngitis
<b>Clindamycin</b>	IV/oral: • Neonates: 5 mg/kg/dose given every 8 hours • Children: 10 mg/kg/dose given every 8 hours	Bone and joint infections Necrotizing fasciitis

<p><b>Cloxacillin</b> or <b>Flucloxacillin</b></p>	<p>Oral/IV:</p> <ul style="list-style-type: none"> <li>• Neonates: 25-50 mg/kg/dose given every 12 hours</li> <li>• Children: 25 mg/kg/dose given every 6 hours</li> </ul> <p><b>Weight bands:</b>                      3-&lt;6 kg: 125 mg given every 6 hours                      6-&lt;15 kg: 250 mg given every 6 hours                      15-&lt;20 kg: 500 mg given every 6 hours                      20-&lt;30 kg: 750 mg given every 6 hours                      ≥ 30 kg: Use adult dose</p>	<p>SSTI (mild)                      Bone and joint infections                      Periorbital cellulitis                      Pyomyositis</p>
<p><b>Doxycycline</b></p>	<p>Oral:</p> <ul style="list-style-type: none"> <li>• &lt;45 kg (&lt;12 years): 2-4 mg/kg</li> <li>• &gt;45 kg (&gt;12 years): 300 mg</li> </ul>	<p>Cholera (single dose)</p>
<p><b>Gentamicin</b></p>	<p>IV: 5 mg /kg given once daily</p>	<p>Sepsis (unknown origin)                      Surgical prophylaxis                      Upper UTI (severe)                      IAI (mild and severe)</p>
<p><b>Fosfomycin (IV)</b></p>	<p>IV:</p> <ul style="list-style-type: none"> <li>• Neonates: 200 mg/kg/day divided every 8 hours</li> <li>• Children: 200-400 mg/kg/day divided every 6 to 8 hours</li> </ul>	<p><b>Empiric use should be exceptional</b> (e.g. seriously ill patients with risk factors for carbapenem-resistant infections or failing to respond to carbapenems when other causes of treatment failure have been excluded)</p>
<p><b>Linezolid</b></p>	<p>IV/Oral</p> <ul style="list-style-type: none"> <li>• First week of life: 10 mg/kg given every 12 hours</li> <li>• Beyond first week of life: 10 mg/kg given every 8 hours</li> </ul>	
<p><b>Meropenem</b></p>	<p>IV: 20 mg/kg/dose given every 8 hours</p>	<p>Febrile neutropenia (high risk)                      IAI (severe)</p>
<p><b>Meropenem+vaborbactam</b></p>	<p>Currently not licensed for use in children or neonates</p>	

<p><b>Metronidazole</b></p>	<p>Oral/IV:  <ul style="list-style-type: none"> <li>• Neonates: 7.5 mg/kg/dose given every 12 hours (starting with a loading dose if used IV: 15 mg/kg)</li> <li>• Children: 7.5 mg/kg/dose given every 8 hours</li> </ul> <p><b>Weight bands:</b>                      3-&lt;6 kg: 30 mg given every 8 hours                      6-&lt;10 kg: 50 mg given every 8 hours                      10-&lt;15 kg: 100 mg given every 8 hours                      15-&lt;20 kg: 150 mg given every 8 hours                      20-&lt;30 kg: 200 mg given every 8 hours                      ≥ 30 kg: Use adult dose</p> <p><b>Higher dose:</b>                      10-15 mg/kg/dose given every 8 hours</p> </p>	<p>IAI (mild and severe)                      Necrotizing fasciitis  <i>C. difficile</i> infection</p> <p><b>Higher dose:</b>                      Amoebic abscess  <b>Single dose:</b>                      Surgical prophylaxis</p>
<p><b>Nitrofurantoin</b></p>	<p>Oral: 2-4 mg/kg/dose given every 12 hours</p>	<p>UTI (lower)</p>
<p><b>Phenoxymethylpenicillin</b></p>	<p>Oral: 15 mg/kg/dose (24,000 international units*/kg/dose) given every 6 hours</p> <p>*Units of the potassium salt</p>	<p>Pharyngitis                      Dental infections</p>
<p><b>Piperacillin-tazobactam</b></p>	<p>IV: 100 mg/kg/dose of piperacillin component given every 8 hours</p>	<p>HAP                      IAI (severe)                      Necrotizing fasciitis                      Febrile neutropenia (high-risk)</p>
<p><b>Plazomicin</b></p>	<p>No data for children or neonates</p>	
<p><b>Polymixin B</b></p>	<p>IV:  <b>Loading dose:</b> :2.5 mg/kg of colistin base activity (25 000 IU/kg)  <b>Maintenance dose:</b>                      &lt;2 years: 1.5-4.5 mg/kg/day (15 000-45 000 IU/kg/day) divided every 12 hours                      ≥2 years: 1.5 mg/kg (15 000 IU/kg) given every 12 hours</p>	<p><b>Empiric use should be exceptional</b> (e.g. seriously ill patients with risk factors for carbapenem-resistant infections or failing to respond to carbapenems when other causes of treatment failure have been excluded)</p>
<p><b>Polymyxin E (colistin)</b></p>	<p>IV:                      2.5-5 mg of colistin base activity/kg/day divided in 2-4 doses</p>	<p><b>Empiric use should be exceptional</b> (e.g. seriously ill patients with risk factors for carbapenem-resistant infections or failing to respond to carbapenems when other causes of treatment failure have been excluded)</p>

<p><b>Sulfamethoxazole+trimethoprim</b></p>	<p>Oral: 20 mg/kg of sulfamethoxazole+ 4 mg/kg of trimethoprim given every 12 hours  <b>Weight bands:</b>                      3-&lt;6 kg: 100 mg + 20 mg given every 12 hours                      6-&lt;10 kg: 200 mg + 40 mg given every 12 hours                      10-&lt;30 kg: 400 mg + 80 mg given every 12 hours                      ≥ 30 kg: Use adult dose</p>	<p>UTI (lower)                      Infectious acute diarrhoea</p>
<p><b>Trimethoprim</b></p>	<p>Oral: 4 mg/kg given every 12 hours  <b>Weight bands:</b>                      3-&lt;6 kg: 20 mg given every 12 hours                      6-&lt;10 kg: 40 mg given every 12 hours                      10-&lt;30 kg: 80 mg given every 12 hours                      ≥ 30 kg: Use adult dose</p>	<p>UTI (lower)</p>
<p><b>Vancomycin</b></p>	<p>IV:                      • Neonates: 15 mg/kg/dose given every 12 hours                      • Children: 15 mg/kg/dose given every 8 hours                       Oral: 5-10 mg/kg/dose given every 6 hours</p>	<p>IV:                      Endophthalmitis                      Febrile neutropenia (high risk)                      Necrotizing fasciitis (if MRSA suspected)                       Oral:  <i>C. difficile</i> infection (higher dose for severe cases)</p>

3 **ACCESS** antibiotics are indicated in green, **WATCH** antibiotics in yellow and **RESERVE** antibiotics in red.

# 1 GLOSSARY

<p>AMR</p>	<p><b>Antimicrobial resistance.</b></p> <p>Antimicrobial resistance is the ability of bacteria, viruses, fungi and parasites to resist the effects of antimicrobial medicines that kill susceptible organisms or keep them from growing.</p> <p>Antimicrobial resistance predates the use of antimicrobials in human medicine and many bacteria, viruses, fungi and parasites are intrinsically resistant to some antimicrobials. Microorganisms can, however, also become resistant to antimicrobials for example by being exposed to antimicrobials.</p> <p>Infection with antimicrobial-resistant pathogens makes infections harder to treat and increases the risk of disease spread, severe illness and death.</p>
<p>Antibiotic resistance</p>	<p>Antibiotic resistance is a subset of antimicrobial resistance that specifically refers to bacteria becoming resistant to antibiotics (medicines that act against bacteria)</p>
<p>AWaRe</p>	<p><b>Access, Watch and Reserve system.</b></p> <p>AWaRe is the WHO classification of antibiotics introduced by WHO as part of the 2017 Model List of Essential Medicines.</p> <p>According to AWaRe there are three categories of antibiotics:</p> <ul style="list-style-type: none"> <li>- Access antibiotics that have a narrow spectrum of activity and a good safety profile in terms of side effects.</li> <li>- Watch antibiotics that are broader-spectrum antibiotics and are recommended as first-choice options for patients with more severe clinical presentations or for infections where the causative pathogens are more likely to be resistant to Access antibiotics.</li> <li>- Reserve antibiotics that are last-choice antibiotics used to treat multidrug-resistant infections.</li> </ul> <p>This classification can be used to give an indirect indication of the appropriateness of antibiotic use, e.g. WHO has defined a target that at least 60% of global antibiotic consumption at the national level should be from the Access group.</p>

BAL	<p><b>Bronchoalveolar lavage.</b></p> <p>BAL is a diagnostic method for the evaluation of diseases of the lower respiratory tract. It is an invasive procedure in which a bronchoscope is passed through the mouth or nose into the lungs, with a measured amount of fluid introduced and then collected for examination. In this Handbook BAL is mentioned as a method for the collection of specimens of respiratory secretions from the lower respiratory tract in case of pneumonia</p>
CAP	<p><b>Community-acquired pneumonia.</b></p> <p>CAP is differentiated from Healthcare-associated pneumonia (HAP) in which antibiotic-resistant pathogens are more frequent</p>
Carbapenemases	<p>Carbapenemases are beta-lactamases, enzymes that can break the beta-lactam ring (an essential component of beta-lactam antibiotics) and make penicillins, cephalosporins, monobactams and carbapenems ineffective</p>
CDI	<p><b><i>Clostridioides difficile</i> infection.</b></p> <p>CDI is an infection of the colon caused by the bacterium <i>C. difficile</i> that occurs mostly in patients with current/recent antibiotic use and with regular exposure to healthcare settings</p>
COPD	<p><b>Chronic obstructive pulmonary diseases.</b></p> <p>COPD is a disease characterized by persistent respiratory symptoms and airflow limitation due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases (e.g. tobacco smoking)</p>
COVID-19	<p><b>Coronavirus disease of 2019.</b></p> <p>COVID-19 is a disease caused by a new coronavirus called SARS-CoV-2. WHO first learned of this new virus on 31 December 2019, following a report of a cluster of cases of 'viral pneumonia' in Wuhan, People's Republic of China.</p>
CRP	<p><b>C-reactive protein.</b></p> <p>CRP is a laboratory test used to detect inflammation as an indicator of various conditions and to monitor response to treatment.</p>

DALYs	<p><b>Disability-adjusted life years.</b></p> <p>DALYs are an indicator used to assess the overall burden of disease. It is a time-based measure that combines years of life lost due to premature mortality and years of healthy life lost due to disability. One DALY represents the loss of the equivalent of one year of full health</p>
EDL	<p><b>Essential in vitro Diagnostics List.</b></p> <p>The EDL is a list of in vitro diagnostics that are recommended by WHO and that was first published in 2018. The list is not prescriptive with respect to which specific tests should be used and at what level of care. Rather, it can be used as a reference for programme and laboratory managers, procurement and reimbursement officers who are developing or updating their own national lists of essential diagnostics The list is updated every year based on proposed additions and changes submitted to WHO by stakeholders and reviewed by the Strategic Advisory Group of Experts on In Vitro Diagnostics (SAGE-IVD)</p>
EIA	<p><b>Enzyme immunoassay.</b></p> <p>EIA is a laboratory test that uses enzyme labelled antibodies and antigens to detect proteins. In this Handbook it is specifically mentioned as one of the tests to diagnose <i>Clostridioides difficile</i> infection</p>
EML	<p><b>Model Essential Medicines List.</b></p> <p>The EML is a list of minimum medicine needs for a basic health-care system that are recommended by WHO and that was first published in 2003. The list includes the most efficacious, safe and cost-effective medicines for priority conditions selected on the basis of current and estimated future public health relevance, and potential for safe and cost-effective treatment. The list is updated every two years based on proposed additions and changes submitted to WHO by stakeholders and reviewed by the WHO Expert Committee on the Selection and Use of Essential Medicines</p>
EMLc	<p><b>Model Essential Medicines List for children.</b></p> <p>The EML/c is a list of minimum medicine needs for a basic health-care system that are recommended by WHO for children up to 12 years of age and that was first published in 2007.</p>

ESBL	<p><b>Extended-spectrum beta-lactamase.</b></p> <p>ESBLs are a group of beta-lactamases, enzymes that can break the beta-lactam ring (an essential component of beta-lactam antibiotics) and make penicillins, cephalosporins and monobactams ineffective (but not carbapenems)</p>
Genotypic resistance	<p>A type of resistance determined by methods of antimicrobial susceptibility testing that detect resistance genes which may be an important information for choosing the correct antibiotic and also for epidemiologic / surveillance reasons. Genes may however not always be expressed, and different gene products may interact so that there is an imperfect correlation between genotypic and phenotypic resistance. Ideally both methods are used in combination for multidrug-resistant organisms</p>
GDH	<p><b>Glutamate dehydrogenase.</b></p> <p>GDH is a constitutive enzyme produced by all strains of <i>Clostridioides difficile</i> and it is easily detected in stool samples. In this Handbook it is specifically mentioned as one of the tests to diagnose <i>Clostridioides difficile</i> infection</p>
GLASS	<p><b>Global Antimicrobial Resistance and Use Surveillance System.</b></p> <p>GLASS is the WHO surveillance system for antimicrobial resistance launched in 2015 to collect official national data in selected bacterial pathogens causing common infections in humans</p>
HIC	<p><b>High-income countries.</b></p> <p>Countries with high-income economies according to the World bank classification available at <a href="https://datahelpdesk.worldbank.org/knowledgebase/articles/906519">https://datahelpdesk.worldbank.org/knowledgebase/articles/906519</a></p>
HIV	<p><b>Human Immunodeficiency Virus.</b></p> <p>HIV is an infection that attacks the body's immune system, specifically white blood cells called CD4 cells. This weakens a person's immunity against infections such as tuberculosis, fungal infections, severe bacterial infections and some cancers.</p>
IM	<p><b>Intramuscular injection.</b></p> <p>IM is a technique used to deliver a medication deep into the muscles</p>
IV	<p><b>Intravenous injection / infusion.</b></p> <p>IV is a technique used to deliver a medication into a vein</p>

KPC	<p><b><i>Klebsiella pneumoniae</i> carbapenemase.</b></p> <p>KPC is the most common Class A carbapenemase</p>
LMIC	<p><b>Low- and middle-income countries.</b></p> <p>Countries with lower- and middle-income economies according to the World bank classification available at <a href="https://datahelpdesk.worldbank.org/knowledgebase/articles/906519">https://datahelpdesk.worldbank.org/knowledgebase/articles/906519</a></p>
MRSA	<p><b>Methicillin-resistant <i>Staphylococcus aureus</i>.</b></p> <p>MRSA strains are resistant to methicillin and other beta-lactam antibiotics due to the presence of the <i>mecA</i> gene producing a different penicillin-binding protein with lower affinity for beta-lactam antibiotics.</p>
Microbiota	Collective term for the microorganisms that live in or on the human body
NAAT	<p><b>Nucleic acid amplification test.</b></p> <p>NAAT is a laboratory technique used to detect a particular nucleic acid sequence to identify virus or bacteria in different biological samples. There are several ways of amplification, one of the most commonly used is the polymerase chain reaction (PCR)</p>
Non-fermenters	Bacteria that cannot catabolize glucose and thus are unable to ferment. The most relevant in this context are <i>Acinetobacter baumannii</i> and <i>Pseudomonas aeruginosa</i>
Phenotypic resistance	A type of resistance determined by methods of antimicrobial susceptibility testing such as disk diffusion, broth microdilution, and agar dilution and considered the “reference standard”. Susceptibility / resistance is determined based on the ability of defined concentrations of antibiotics to inhibit growth. It can generally not determine the cause of the resistance (e.g. beta-lactamases versus efflux pumps), an information that may be relevant for choosing the correct antibiotic
PD	<p><b>Pharmacodynamics.</b></p> <p>Pharmacodynamics: the molecular, biochemical and physiologic effects of medicines and their mechanisms of action - what the medicine does to the body</p>
PK	<p><b>Pharmacokinetics.</b></p> <p>Pharmacokinetics: the dynamics of absorption, distribution, metabolism and elimination of medicines by the body - what the body does to the medicine</p>

RDT	<b>Rapid diagnostic test.</b> RDTs are diagnostic assays designed for use at the point-of-care
SAGE-IVD	<b>Strategic Advisory Group of Experts on In Vitro Diagnostics.</b> SAGE-IVD is an advisory body to WHO on matters of global policies and strategies related to IVDs (including those related to the EDL)
SARS-CoV-2	<b>Severe acute respiratory syndrome coronavirus 2.</b> SARS-CoV-2 is the new coronavirus that causes COVID-19
STI	<b>Sexually transmitted infection.</b> STIs are infections passed from one person to another during sex or intimate contact
WHO	<b>World Health Organization</b>

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