THE WHO ESSENTIAL MEDICINES LIST ANTIBIOTIC BOOK

Improving antibiotic AWAREness
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INTRODUCTION

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

Aim and Scope

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

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

Methodology

The antibiotic treatment recommendations outlined in this Handbook are based on reviews of the evidence undertaken for the 2017, 2019 and 2021 updates of the EML and EMLc. The EML/EMLc provide a list of safe and effective antibiotics that should be available and affordable for patients globally. The EML Handbook provides guidance on how to best use these antibiotics 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
The detailed reviews on the optimal choice of antibiotics to be used for each specific clinical infection were based on a standardised analysis by experts in evidence-based medicines from McMaster University (Hamilton, Canada) of systematic reviews, meta-analyses and clinical practice guidelines.

Details regarding the evidence underlying the recommendations and the methodology can be found here:
- https://apps.who.int/iris/handle/10665/259481
- https://apps.who.int/iris/handle/10665/330668

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

Structure

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

Each chapter on a clinical infection includes:
- **Background information.** The pathophysiology, epidemiology, global burden, most common pathogens and how to make the clinical diagnosis, including assessing disease severity.
- **Diagnostic tools.** As the availability of diagnostic tools varies considerably in different settings, the empiric antibiotic recommendations are based on clinical signs and symptoms. Relevant diagnostic tests (including imaging and laboratory tests) are suggested based on the WHO’s Essential *in-vitro* Diagnostics List (EDL) (4). The list of tests
provided for each infection is not based on a formal assessment of their predictive value, but as a general guide of tests that could be clinically helpful, where available.

- **Treatment.** Guidance is given where appropriate for “No Antibiotic Care” including symptomatic management for low-risk patients with minor infections that do not need antibiotic treatment. First- and second-choice antibiotic options are then given where relevant based on the EML/c and AWaRe system as well as other WHO guidance documents.
- Guidance on which infections may most benefit from **targeted clinical microbiology surveillance** to help inform both local and national empiric antibiotic guidance.

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

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

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

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

Background

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

AWaRE

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

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

Watch antibiotics are broader-spectrum antibiotics, generally with higher costs and are recommended only 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 (e.g. upper urinary tract infections).

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

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

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

1. No Antibiotic Care - safely reducing antibiotic use

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).

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

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

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

<table>
<thead>
<tr>
<th>Infection (in alphabetical order)</th>
<th>Can it be safely treated without antibiotics?</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute diarrhoea</td>
<td>Yes, in the great majority of cases (unless there is significant bloody diarrhoea)</td>
<td>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.</td>
</tr>
</tbody>
</table>
### Are antibiotics needed?

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

#### Think D8 – before prescribing!

**Box 5 – Points to always consider when prescribing**

1. **Diagnose** – what is the clinical diagnosis, is there evidence of a significant bacterial infection?
2. **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.

2. Improving Access use and reducing inappropriate oral Watch antibiotics

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

The 68th World Health Assembly in May 2015 endorsed a global action plan to tackle antimicrobial 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

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

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

Oral Watch antibiotics use globally is increasing. They are now very commonly taken by patients in primary health care for minor infections (fever/cough/diarrhoea) in both high-income
countries (HIC) and low- and middle-income countries (LMIC). Reducing the inappropriate use of both oral and intravenous Watch antibiotics is a critical strategy for the global control of antibiotic resistance, while ensuring vulnerable populations have continued or, where appropriate, improved “access to Access” antibiotics.

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

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

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

b Only oral antibiotic options are reported here.

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

3. Reducing the use of Not Recommended antibiotics

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 use 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/10665/327953)

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

4. Improving AWaRe-ness!

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

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

<table>
<thead>
<tr>
<th>Group</th>
<th>Responsibility</th>
<th>Examples of practical actions</th>
</tr>
</thead>
</table>
| Health care policy-makers and relevant programme managers | • The unnecessary use of antibiotics should be discouraged  
• Focus on promoting the use of Access antibiotics where appropriate  
• Ensure local access to and availability of antibiotics in the national EML at the appropriate cost, quality and in the correct formulation  
• Make sure that the national EML is regularly updated and whenever adequate aligned with the model lists  
• Undertake regular surveillance of antibiotic use at all levels, including by AWaRe group (e.g. Access/Watch ratio) | • Review national and local guidance documents and compare them with the Handbook  
• Disseminate new guidance to all levels of the health care services  
• Review provision of Access antibiotics, cost, quality, sustainability and barriers to use  
• Develop a monitoring programme for antibiotic use across all levels of health care provision, including the ratio of Access and Watch antibiotics  
• Regularly review national EML and align to model list where synergies exist  
• Disseminate data back to providers on antibiotic use appropriately and regularly |
| Physicians                                  | • Be AWaRe of the Handbook and focus clinical care on DB!  
• Diagnosis – which infection  
• Decisions – are antibiotics needed  
• Drug (medicine) – which antibiotic  
• Dose – at what dose  
• Duration – for how long  
• Delivery – what formulation  
• Document – in the notes  
• Discussion – with patient  
• Know which infections could be managed with antibiotics in your setting  
• Know which signs and symptoms would require hospital referral | • Review national and local guidance documents and compare them with the Handbook  
• “Adapt or adopt” EML guidance  
• Assist with developing and implementing educational programmes  
• Develop local tools for monitoring local patterns of antibiotic use and disseminate data appropriately and regularly  
• Act as local champions of the Handbook |
| Pharmacists                                 | • Be AWaRe of the Handbook  
• Do not provide antibiotics without a prescription  
• Discourage self-medication with antibiotics  
• Monitor relative use of Access and Watch antibiotics | • Review, adapt or adopt the Handbook in line with local guidance document  
• Ensure in-pharmacy availability of the commonest infection chapters of the Handbook and summaries of Access and Watch lists  
• Monitor local patterns of antibiotic use as Access/Watch ratios and disseminate data appropriately and regularly |
| Professional societies                      | • Be aware of AWaRe and of the Handbook  
• Contribute to awareness campaigns  
• Educate health care workers about AWaRe | • Disseminate new guidance to all levels of the health care services |
| Nurses | • Be AWaRe of Handbook and advise or prescribe accordingly | • Review, adapt or adopt the Handbook in line with local guidance documents |
| Community health workers | • Know which infections could be managed with antibiotics or with symptomatic treatment alone in your setting | • Review local availability of antibiotics |
| | • Know which signs and symptoms would require medical referral | • Review practices and procedures that are non-compliant with the Handbook |
| | • Be AWaRe of the Handbook | • Monitor patterns of antibiotic use |
| Patients | • Be aware of AWaRe | • Act as champions for the better use of antibiotics |
| | • Avoid using leftover antibiotics | • Promote antibiotic-related educational activities for patients |
| | • Avoid asking for antibiotics over the counter in pharmacies and asking physicians to prescribe them | |
| | • Avoid stockpiling leftover antibiotics | |
| | • Contribute to awareness campaigns (e.g. with family members, the community) | |

Substandard and falsified medicinal antibiotics

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

Community health care workers

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

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

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

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

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

Dosing

Wherever appropriate the same dose is given for each antibiotic for all infections to help local procurement and prescribing. In the Hospital Facility section, guidance is also given on when to consider Step Down from intravenous to oral antibiotics, encouraging the early discharge of patients from hospital when clinically appropriate.
Guidance on dose adjustments for abnormal kidney and liver function is not covered, and the summary of product characteristics should be consulted. Also detailed information on antibiotic administration, for example the use of continuous or prolonged infusion times of beta-lactams in multidrug-resistant infections is not covered as this is beyond the scope of this Handbook (14, 15).

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

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

Dosing in Children

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

Treatment duration

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

Allergy to antibiotics

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

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

Definitions

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

<table>
<thead>
<tr>
<th>Type A (or on-target) adverse reaction*: characteristics</th>
<th>Type B (or off-target) adverse reaction*: characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Pharmacologically predictable</td>
<td>- Pharmacologically unpredictable</td>
</tr>
<tr>
<td>- Dose / level dependent</td>
<td>- Non-dose dependent</td>
</tr>
<tr>
<td>- Non-immune mediated</td>
<td>- Often immunologically mediated hypersensitivity reactions(b) (IgE or T-cell mediated)</td>
</tr>
<tr>
<td>- Less influenced by genetic factors</td>
<td>Examples: skin reactions, angioedema or anaphylaxis (immune-mediated)</td>
</tr>
</tbody>
</table>

Example: side-effects such as antibiotic-associated diarrhoea, acute tubular necrosis due to aminoglycosides

\(a\) On-target (or augmented) means the effects are related to the primary mechanism of action of the medicine. Off-target means the effects are not related to the primary mechanism of action of the medicine.
These reactions are immunologically mediated. They can be immediate (< 4 hours), intermediate (4–24 hours) or delayed (> 24 hours) reactions based on when symptoms appear after the administration of the antibiotic.

**Epidemiology**

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

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

This over-diagnosis of allergy has important consequences because incorrectly labelling a patient as allergic to an antibiotic often results in the unnecessary use of alternative antibiotics. These alternatives may be less effective for the infection being treated and may expose the patient to other (sometimes more toxic) side-effects.

Unfortunately, most patients with a history of allergy to antibiotics are not evaluated to confirm the existence (or persistence) of the allergy.

**Cross-reactivity**

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

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

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

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

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

Clinical presentation

Signs and symptoms of antibiotic allergy can vary in severity, ranging from mild reactions that can be safely managed in an outpatient setting with or without need for symptomatic treatment (e.g. antihistamines) to severe reactions that require hospitalization and even admission to intensive care. Immediate and delayed reactions can be severe or non-severe. Gastrointestinal symptoms and headache are not usually due to an allergic reaction but rather to an intolerance of the antibiotic that can vary in intensity from person to person or to *Clostridioides difficile* infection in case of diarrhoea.

Most cases of allergic reactions to antibiotics are not severe and often present as mild skin reactions (most commonly mild rash, hives and itching) with no systemic symptoms. Severe reactions are rare but can become life-threatening. They can be immediate or delayed after administration of the antibiotic.

- **Immediate** severe reactions should be suspected if there is airway involvement, bronchospasm, wheezing, angioedema (swelling of the tissue under the skin with or without hives) or anaphylaxis. Usually, these reactions develop less than 4 hours after taking the antibiotic.
- **Delayed** severe reactions should be suspected in patients who have taken an antibiotic and present with severe skin symptoms (e.g. a painful blistering rash) and fever, joint pain or signs of organ involvement (e.g. hepatitis). Thrombocytopenia (low platelet count), haemolytic anaemia (destruction of red blood cells) and signs and symptoms of hepatitis or nephritis in severe cases are suggestive of organ involvement. Usually, these reactions develop more than 24 hours after taking the antibiotic.

Allergy evaluation

All patients who are labelled as allergic should be carefully evaluated, if possible, by an allergy specialist, and their antibiotic allergy risk level should be determined. When evaluating a patient,
a full history of their allergy should be taken from the patient with details of past reactions, including timing relative to antibiotic administration (immediate, intermediate, delayed or unknown) and treatment received (if any). Patients can be classified in three risk categories for allergy to antibiotics: low, moderate, and high risk; see Table 3 for examples. Detailed documentation of all elements of the allergy is crucial. The patient should be educated about what types of antibiotics to avoid (if any) and should be provided, if possible, with written information such as an “allergy” passport.

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

<table>
<thead>
<tr>
<th>Allergy risk category</th>
<th>Examples</th>
</tr>
</thead>
</table>
| Low risk              | • Patients with a history of isolated symptoms consistent with intolerance of an antibiotic, such as nausea, vomiting, diarrhoea or headache  
• Patients with a history of mild skin reactions  
• Patients with a history of unknown reactions a long time ago without features of immediate IgE-mediated reactions  
• Patients with a family history of antibiotic allergy |
| Moderate risk         | • Patients with a history of urticaria or other pruritic (itchy) rashes  
• Patients with a history of reactions that look like IgE-mediated reactions but with no history of anaphylaxis |
| High risk             | • Patients with a history of severe or life-threatening reaction (immediate or delayed) to an antibiotic (e.g. anaphylaxis)  
• Patients with a positive skin test  
• Patients with recurrent reactions or reactions to multiple antibiotics |


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

In settings where allergy testing, specialist advice or treatment for anaphylaxis are not available, then pragmatic decisions should be based on a detailed history of any reported possible penicillin allergy. A rapid risk assessment needs to be done, including the medical importance of the infection the patient is presenting with (i.e. benefit-risk assessment in that patient and also whether an antibiotic is really needed) and the availability of alternative antibiotics with similar effectiveness. Please see the relevant infection chapters and symptomatic non-antibiotic treatment of minor infections within chapters.
Patients with a definite history of immediate collapse, breathing difficulties or severe facial swelling within a few minutes to 1–2 hours of taking a penicillin class of antibiotic are likely to have had a true anaphylactic reaction. If any alternative antibiotics are available, they should be preferred. Patients who have only had gastrointestinal symptoms or a rash appearing a few days after receiving an antibiotic of the penicillin group and who have shown no signs of becoming seriously unwell are generally less likely to develop severe anaphylaxis if they receive such antibiotics again in the future. Therefore, if one of these antibiotics is the most appropriate and available treatment option, these patients can be given it and advised to stop it if they develop a new skin rash, especially if the onset is rapid, the rash is raised and itchy and/or accompanying symptoms are present (e.g. shortness of breath).
PRIMARY HEALTH CARE
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 [link]
- COVID-19 pandemic: [link]
- Therapeutics and COVID-19: living guideline, 24 September 2021. [link]

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

**Microbiology epidemiology**

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

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

<table>
<thead>
<tr>
<th>Respiratory viruses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhinovirus</td>
</tr>
<tr>
<td>Influenza virus (A and B)</td>
</tr>
<tr>
<td>Parainfluenza virus</td>
</tr>
<tr>
<td>Coronavirus (including SARS-CoV-2)</td>
</tr>
<tr>
<td>Respiratory syncytial virus (RSV)</td>
</tr>
<tr>
<td>Metapneumovirus</td>
</tr>
<tr>
<td>Adenovirus</td>
</tr>
</tbody>
</table>

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

**Clinical presentation**

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

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

Patients with pneumonia are usually:
• clinically unwell and with systemic signs of infection (e.g. fever, increased heart rate, increased respiratory rate, focal chest signs)
• short of breath
• have cough with sputum production

Please refer to the chapter on community-acquired pneumonia for the typical clinical presentation of patients with pneumonia.
In patients with pre-existing chronic obstructive pulmonary diseases (COPD), please refer to the chapter on this condition.

**Laboratory tests**

I. **Patient microbiology tests**

No microbiology test is usually required.

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

II. **Other tests**

In the great majority of cases of bronchitis, laboratory tests are not needed.
In uncertain cases some experts advocate the use of biomarkers of infection (C-reactive protein, procalcitonin) to differentiate viral bronchitis from bacterial pneumonia but these add costs and can also result in inappropriate prescribing due to the limited sensitivity and specificity of these tests.

III. **Using microbiology surveillance data**

As antibiotics are not recommended no routine microbiology surveillance is required.
Surveillance of circulating respiratory viruses can be useful to predict and follow epidemics and outbreaks (e.g. SARS-CoV-2, influenza virus, respiratory syncytial virus).

**Imaging**

Imaging is usually not needed.
“No antibiotic care”

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

Table 2 Medicines to consider for symptomatic treatment of acute bronchitis

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Formulation</th>
<th>Dose and frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibuprofen</td>
<td>Oral liquid: 200 mg/5 mL Tablet: 200 mg; 400 mg; 600 mg</td>
<td>Adults: 200–400 mg given every 6 to 8 hours (maximum dose of 2.4 g a day)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Children:</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Pain control / Antipyretic treatment: 5–10 mg/kg given every 6 to 8 hours</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6–&lt;10 kg: 50 mg given every 8 hours</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10–&lt;15 kg: 100 mg given every 8 hours</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15–&lt;20 kg: 150 mg given every 8 hours</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20–&lt;30 kg: 200 mg given every 8 hours</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥30 kg: Use adult dose</td>
</tr>
<tr>
<td>Paracetamol (acetaminophen)</td>
<td>Oral liquid: 120 mg/5 mL; 125 mg/5 mL Tablet: 100 mg to 500 mg</td>
<td>Adults: 500 mg–1 g given every 4 to 6 hours (maximum dose of 4 g a day)</td>
</tr>
<tr>
<td></td>
<td>Suppository: 100 mg</td>
<td><strong>Children:</strong></td>
</tr>
<tr>
<td></td>
<td>Tablet: 100 mg to 500 mg</td>
<td>• Pain control/ Antipyretic treatment: 10–15 mg/kg given every 6 hours</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3–&lt;6 kg: 60 mg given every 6 hours</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6–&lt;10 kg: 100 mg given every 6 hours</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10–&lt;15 kg: 150 mg given every 6 hours</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15–&lt;20 kg: 200 mg given every 6 hours</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20–&lt;30 kg: 300 mg given every 6 hours</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥30 kg: Use adult dose</td>
</tr>
</tbody>
</table>

*a* Not for children <3 months.

*b* Not recommended for use as an anti-inflammatory as it has not been proven to have such an effect.

*c* In patients with hepatic impairment or cirrhosis, maximum daily dose should be 2 g.

Antibiotic treatment

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

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**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](https://apps.who.int/iris/handle/10665/81170)

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3. Definition

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

4. Pathophysiology

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

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

**Microbiology epidemiology**

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

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

**Otitis media caused by possible antibiotic-resistant pathogens**

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

**Clinical presentation**

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

I. Patient microbiology tests

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

II. Other tests

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

III. Using microbiology surveillance data

There is no role for routine surveillance for resistant pathogens.

Otoscopy

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

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

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

Imaging

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

“No antibiotic care”

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

Non-severe cases usually have mild symptoms, often pain in one ear, and mild fever (< 39.0 °C which improves with antipyretics). A watchful waiting approach with symptomatic management
(i.e. analgesics and antipyretics) is appropriate (Table 2). Watchful waiting involves careful monitoring of the child by caregivers, with instructions to seek care in case of worsening of fever, pain or persistence of the symptoms.

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

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

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Formulation</th>
<th>Dose and frequency</th>
</tr>
</thead>
</table>
| Paracetamol (acetaminophen)  | Oral liquid: 120 mg/5 mL; 125 mg/5 mL  
Suppository: 100 mg  
Tablet: 100 mg to 500 mg | Adults: 500 mg–1 g given every 4 to 6 hours (maximum dose of 4 g a day)  
Children:  
• Pain control/ Antipyretic treatment: 10–15 mg/kg given every 6 hours  
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                    | Oral liquid: 200 mg/5 mL  
Tablet: 200 mg; 400 mg; 600 mg | Adults: 200–400 mg given every 6 to 8 hours (maximum dose of 2.4 g a day)  
Children:  
• Pain control / Antipyretic treatment: 5–10 mg/kg given every 6 to 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 |

Notes:  
^Not recommended for use as an anti-inflammatory as it has not been proven to have such an effect.  
^bIn patients with hepatic impairment or cirrhosis, maximum daily dose should be 2 g.  
^cNot for children < 3 months.

Antibiotic treatment

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

- In cases with severe symptoms (e.g. systemically very unwell, severe ear pain, fever ≥ 39.0 °C)
- In immunosuppressed children (because of the higher risk of complications)
- In cases with bilateral acute otitis media in children under 2 years
There is no clear consensus on offering antibiotic treatment in non-severe cases of recurrent acute otitis media (i.e. three or more episodes in the previous 6 months or four or more episodes in the previous year), in non-severe cases presenting with otorrhoea and in non-severe cases in neonates.

Table 3 Empiric antibiotic treatment for acute bacterial otitis media

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

<table>
<thead>
<tr>
<th></th>
<th>Adults</th>
<th>Children</th>
<th>Total treatment duration(36-38)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First choice</td>
<td>Amoxicillin (oral): 500 mg given every 8 hours</td>
<td>Amoxicillin (oral) 40-50 mg/kg/dose given every 12 hours</td>
<td>5 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>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</td>
<td></td>
</tr>
<tr>
<td>Second choice</td>
<td>Amoxicillin+clavulanic acid (oral): 500 mg + 125 mg given every 8 hours</td>
<td>Amoxicillin+clavulanic acid* (oral) 40-60 mg/kg/dose of amoxicillin component, given every 12 hours OR 30 mg/kg/dose given every 8 hours</td>
<td>5 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>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</td>
<td></td>
</tr>
</tbody>
</table>

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

*Oral liquid must be refrigerated after reconstitution.

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

Prevention

Prevention of otitis media is like prevention of upper respiratory tract infections. All strategies (e.g. hand hygiene) that help prevent upper respiratory tract infections can be useful in preventing otitis media including vaccination against *Streptococcus pneumoniae* and...
Haemophilus influenzae type b for all children (39, 40). For countries considering vaccination programmes for influenza, vaccination of high-risk groups could also be considered (e.g. young children) (41).
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)


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.
Epidemiology

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

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

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

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

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

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

Microbiology epidemiology

Most (> 80%) cases of pharyngitis are caused by a viral infection (respiratory viruses have been identified in 25–45% of cases; less frequently, the Epstein–Barr virus or other viruses of the herpesvirus family or SARS-CoV-2 are the cause). A minority of cases of pharyngitis are caused by bacteria, mainly *Streptococcus pyogenes* (group A *Streptococcus*). Other streptococci (group C and G) have also been implicated as causes of pharyngitis. Other infectious causes that need to be considered are acute HIV-infection and other sexually transmitted infections (syphilis, gonorrhoea), acute toxoplasmosis and diphtheria. Rarely, the cause of pharyngitis is non-infectious (e.g. exposure to pollution, allergens and smoking).
Table 1 Pathogens most frequently associated with pharyngitis (in descending order of frequency)

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

Pharyngitis caused by antibiotic-resistant pathogens

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

Clinical presentation

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

Scoring symptoms of pharyngitis

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

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

In LMIC, other scores could be considered that have been specifically validated in these settings(53).
Table 1 Centor score for the clinical assessment of pharyngitis

<table>
<thead>
<tr>
<th>Relevant signs and symptoms</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever &gt; 38 °C</td>
<td>1</td>
</tr>
<tr>
<td>No cough</td>
<td>1</td>
</tr>
<tr>
<td>Tender anterior lymphadenitis</td>
<td>1</td>
</tr>
<tr>
<td>Tonsillar exudates</td>
<td>1</td>
</tr>
<tr>
<td>Total score</td>
<td>Likelihood of <em>S. pyogenes</em> infection (%)</td>
</tr>
<tr>
<td>0</td>
<td>1–2.5</td>
</tr>
<tr>
<td>1</td>
<td>5–10</td>
</tr>
<tr>
<td>2</td>
<td>11–17</td>
</tr>
<tr>
<td>3</td>
<td>28–35</td>
</tr>
<tr>
<td>≥ 4</td>
<td>51–53</td>
</tr>
</tbody>
</table>

Centor score 0 – 1 – 2

- *S. pyogenes* pharyngitis unlikely
- Give symptomatic treatment only

Centor score 3 – 4 – 5

- Score suggestive of *S. pyogenes* pharyngitis
- In countries with a low prevalence of rheumatic fever, antibiotic treatment can be withheld even in cases of likely *S. pyogenes* pharyngitis
- 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.

Laboratory tests

I. Patient microbiology tests

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

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

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

<sup>a</sup>
RDT: rapid diagnostic test.

Community and health settings without laboratories are settings such as health posts and centres, doctors’ offices, outreach clinics, ambulatory care. These tests are also assumed to be available at health care facilities with laboratories.

Possible specimens include: throat swab.

- In the case of a low likelihood of S. pyogenes as the causative pathogen (this corresponds to a Centor score of 0 to 2; see Table 1 for Centor scoring): rapid antigen test or throat culture are usually not needed.

- In the case of a higher likelihood of S. pyogenes as the causative pathogen (i.e. Centor score 3–4): rapid antigen test or throat culture could be considered, especially in countries where rheumatic fever and rheumatic heart disease are important problems. (Note: WHO recommends the use of a rapid antigen test as part of the strategy for primary prevention of rheumatic fever through the effective treatment of streptococcal pharyngitis(50)).

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

II. Other tests

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

III. Using microbiology surveillance data

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

Imaging

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

“No antibiotic care”

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

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Formulation</th>
<th>Dose and frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paracetamol (acetaminophen)</td>
<td>Oral liquid: 120 mg/5 mL; 125 mg/5 mL&lt;br&gt;Suppository: 100 mg&lt;br&gt;Tablet: 100 mg to 500 mg</td>
<td>Adults: 500 mg–1 g given every 4 to 6 hours (maximum dose of 4 g a day)&lt;sup&gt;b&lt;/sup&gt;&lt;br&gt;Children:&lt;br&gt;• Pain control / Antipyretic treatment: 10–15 mg/kg given every 6 hours&lt;br&gt;3–&lt;6 Kg: 60 mg given every 6 hours&lt;br&gt;6–&lt;10 Kg: 100 mg given every 6 hours&lt;br&gt;10–&lt;15 Kg: 150 mg given every 6 hours&lt;br&gt;15–&lt;20 Kg: 200 mg given every 6 hours&lt;br&gt;20–&lt;30 Kg: 300 mg given every 6 hours&lt;br&gt;≥30 Kg: Use adult dose</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>Oral liquid: 200 mg/5 mL&lt;br&gt;Tablet: 200 mg; 400 mg; 600 mg</td>
<td>Adults: 200–400 mg given every 6 to 8 hours (maximum dose of 2.4 g a day)&lt;br&gt;Children:&lt;br&gt;• Pain control / Antipyretic treatment: 5–10 mg/kg given every 6 to 8 hours&lt;br&gt;6–&lt;10 Kg: 50 mg given every 8 hours&lt;br&gt;10–&lt;15 Kg: 100 mg given every 8 hours&lt;br&gt;15–&lt;20 Kg: 150 mg given every 8 hours&lt;br&gt;20–&lt;30 Kg: 200 mg given every 8 hours&lt;br&gt;≥30 Kg: Use adult dose</td>
</tr>
</tbody>
</table>

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

Antibiotic treatment

Most cases of pharyngitis are of viral origin and do not benefit from antibiotics. When bacterial pharyngitis is suspected or proven, the decision to give antibiotic treatment is usually based on the likelihood of *S. pyogenes* infection and on the local prevalence or patient history of rheumatic fever. Options to consider are reported in Table 4. Second choice options reported in Table 4 should only be considered in patients allergic to first-choice options. In the case of clarithromycin, the prevalence of macrolide resistance in the setting where the patient acquired the infection should be considered since macrolide resistance among *S. pyogenes* is high in certain countries.

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

- Patients treated in settings with a low prevalence of rheumatic fever. **Antibiotic treatment is not needed in most cases.** Antibiotics could be considered in some patients who have a high likelihood of pharyngitis caused by *S. pyogenes* (i.e. Centor score 3–4). However even with a Centor score of 3 or 4, antibiotic treatment is not necessary in most
cases. Antibiotic treatment reduces sore throat pain only by around one day (which can alternatively be managed by regular analgesia).

- Antibiotic treatment could be discussed with patients or their caregivers on a case-by-case basis, weighing the benefits (e.g. reduced transmission and slight reduction in duration of symptoms) and risks (e.g. side-effects of antibiotics, effect on the intestinal microbiota)(55). Relief of symptoms or prevention of suppurative complications is not considered an indication for antibiotic treatment. The rationale is that most suppurative complications are not severe and can be readily recognized and treated.

- Patients treated in settings with a medium to high prevalence of rheumatic fever and rheumatic heart disease or patients with a history of rheumatic fever or rheumatic heart disease. Antibiotic treatment is usually given if the likelihood of \textit{S. pyogenes} pharyngitis is high (i.e. Centor score 3–4). The rationale is to prevent rheumatic fever or its recurrence. However, after 21 years of age, the risk of rheumatic fever is usually lower.

\textit{Table 4 Empiric antibiotic treatment in patients with a high likelihood of S. pyogenes pharyngitis}

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

<table>
<thead>
<tr>
<th></th>
<th>Adults</th>
<th>Children</th>
<th>Total treatment duration(56, 57)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First choice</strong></td>
<td>Phenoxy methylpenicillin (oral): 500 mg (800,000 IU(^a)) given every 6 hours OR Amoxicillin (oral): 500 mg given every 8 hours</td>
<td>Phenoxy methylpenicillin (oral): 15 mg/kg/dose (24,000 IU/kg/dose(^3)) given every 6 hours OR Amoxicillin (oral) 40–50 mg/kg/dose given every 12 hours</td>
<td>5(^b) or 10(^c) days depending on the local prevalence or previous history of rheumatic fever</td>
</tr>
<tr>
<td><strong>Second choice</strong></td>
<td>Clarithromycin (oral): 500 mg given every 12 hours OR Cefalexin (oral): 500 mg given every 8 hours</td>
<td>Clarithromycin (oral): 7.5 mg/kg/dose given every 12 hours OR Cefalexin (oral): 25 mg/kg/dose given every 12 hours</td>
<td>5 days</td>
</tr>
</tbody>
</table>

\(^a\) 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 \(\geq\) 30 kg: Use adult dose
20-<30 kg: 625 mg given every 12 hours
≥ 30 kg: Use adult dose

IU: International units.

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

‘Units of the potassium salt.

b In settings with a low prevalence of rheumatic fever or in patients with no history of rheumatic fever or rheumatic heart disease.

c 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.

d 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.

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

**Prevention**

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

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

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


Other causes of bacterial pharyngitis: diphtheria

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

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)

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/10665/322970](https://apps.who.int/iris/handle/10665/322970)

Definition

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

Pathophysiology

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

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

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

Microbiology epidemiology

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

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

<table>
<thead>
<tr>
<th>Respiratory viruses (most cases)*</th>
<th>Bacteria (rarely)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza virus (A and B)</td>
<td>Streptococcus pneumoniae</td>
</tr>
<tr>
<td>Respiratory syncytial virus</td>
<td>Haemophilus influenzae</td>
</tr>
<tr>
<td>Parainfluenza virus</td>
<td>Very rarely:</td>
</tr>
<tr>
<td>Rhinovirus</td>
<td>Moraxella catarrhalis</td>
</tr>
<tr>
<td>Coronavirus (including SARS-CoV-2)</td>
<td>Streptococcus pyogenes (group A Streptococcus)</td>
</tr>
<tr>
<td></td>
<td>Staphylococcus aureus</td>
</tr>
</tbody>
</table>

*Note: about 98% of cases are caused by respiratory viruses.

Sinusitis caused by antibiotic-resistant pathogens

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

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

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

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

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

Acute bacterial sinusitis should be suspected in two situations:

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

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

Laboratory tests

I. Patient microbiology tests

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

II. Other tests

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

III. Using microbiology surveillance data

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

Imaging

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

“No antibiotic care”

The goal of treatment is to improve symptoms. Antibiotics have only minimal effect on the duration of symptoms in most cases and current evidence suggests that even without antibiotic treatment, most cases in healthy patients resolve within 1–2 weeks(59).
Most guidelines recommend using disease severity (i.e. duration and intensity of symptoms) to
direct treatment.

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

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

Table 2 Medicines to consider for symptomatic treatment of acute sinusitis

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Formulation</th>
<th>Dose and frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Paracetamol</strong> (acetaminophen)</td>
<td>Oral liquid: 120 mg/5 mL; 125 mg/5 mL Suppository: 100 mg Tablet: 100 mg to 500 mg</td>
<td>Adults: 500 mg–1 g every 4–6 hours (maximum dose of 4 g a day)(b) Children: Pain control/Antipyretic treatment: 10–15 mg/kg every 6 hours 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</td>
</tr>
<tr>
<td><strong>Ibuprofen</strong></td>
<td>Oral liquid: 200 mg/5 mL Tablet: 200 mg; 400 mg; 600 mg</td>
<td>Adults: 200–400 mg every 6–8 hours (maximum dose of 2.4 g a day) Children: 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</td>
</tr>
</tbody>
</table>

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

Antibiotic treatment

Antibiotic treatment is not required in the great majority of cases.
Antibiotic treatment could be considered in certain cases: severe onset of symptoms, patients with underlying comorbid diseases or in those at increased risk of complications (see antibiotic options in Table 3). Severe onset is defined as fever ≥ 39.0 °C and purulent nasal discharge or facial pain for at least 3–4 consecutive days (61). The decision to treat with antibiotics in patients with chronic comorbid diseases should always be made on a case-by-case basis. Relevant comorbid conditions to consider include, for example, chronic malignancies and immunodeficiency.

Antibiotic treatment could also be considered in cases with “red flag” signs and symptoms suggestive of a complicated infection, such as systemic toxicity, persistent fever ≥ 39.0 °C, periorbital redness and swelling, severe headache and altered mental status.

**Table 3 Empiric antibiotic treatment for bacterial sinusitis**

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

<table>
<thead>
<tr>
<th>Adults</th>
<th>Children</th>
<th>Total treatment duration (62)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Amoxicillin (oral):</strong> 1 g given every 8 hours OR <strong>Amoxicillin+clavulanic acid (oral):</strong> 500 mg + 125 mg given every 8 hours</td>
<td><strong>Amoxicillin (oral):</strong> 40–50 mg/kg/dose given every 12 hours 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: 750 mg given every 12 hours 20–&lt;30 kg: 1000 mg given every 12 hours ≥ 30 kg: Use adult dose OR <strong>Amoxicillin+clavulanic acid (oral):</strong> 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</td>
<td>5 days</td>
</tr>
</tbody>
</table>

Notes: All dosages are for normal renal and hepatic function.
Oral liquid must be refrigerated after reconstitution.

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

**Prevention**

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

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

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.

**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](https://apps.who.int/iris/handle/10665/149782)
- Oral health. [https://www.who.int/news-room/fact-sheets/detail/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](https://apps.who.int/iris/handle/10665/230643)
6 Definitions (presented in alphabetical order)

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

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

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

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

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

**Gingivae (gums)**: soft tissue covering the alveolar bone.
**Noma (cancrum oris / gangrenous stomatitis):** an acute necrotizing disease that destroys the soft tissues and bones of the mouth and face as it progresses from necrotizing ulcerative gingivitis.

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

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

This includes:

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

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

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

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

**Pathophysiology**

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

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

Accumulation of dental plaque around the gingival margin of teeth (at the gumline) and in periodontal pockets (below the gumline) can stimulate an inflammatory response. In some
people this can lead to immune-mediated destruction of the periodontal structures (e.g. gums or alveolar bone) which support the teeth. Progressive destruction of these periodontal tissues may lead to teeth becoming mobile and eventually to tooth loss.

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

**Epidemiology**

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

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

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

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

**Microbiology epidemiology**

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

<table>
<thead>
<tr>
<th>“Normal” resident oral microbiota</th>
<th>Bacteria associated with caries</th>
<th>Bacteria associated with periodontal disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptococcus spp.</td>
<td>Streptococcus spp.</td>
<td>Anaerobes (most cases):</td>
</tr>
<tr>
<td>Actinomyces spp.</td>
<td>(e.g. <em>Streptococcus mutans</em>)</td>
<td><em>Prevotella</em> spp.</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Porphyromonas</em> spp.</td>
</tr>
</tbody>
</table>

*A A richly diverse group of pathogens, including both aerobic bacteria and anaerobes.

*b Mostly acidogenic bacteria

Clinical presentation (presented in alphabetical order)

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

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

Dental abscess

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

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

If this is left untreated, there is a high risk of spread to vital structures of the head and neck or systemic spread of the infection that can then lead to sepsis. Signs that the infection has spread include cellulitis around the eye or throat (causing difficulties swallowing or breathing e.g. Ludwig’s angina), fever (> 38.0 °C), malaise, tachycardia (increased heart rate) and lymphadenopathy. This must be treated as a medical emergency.
A periodontal abscess (less common) is usually a localised accumulation of pus in the periodontal tissues (gums and alveolar bone supporting the tooth) which can be readily drained by professional cleaning of the periodontal pocket or by extraction of the tooth.

Dental caries progression to pulpal disease

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

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

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

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

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

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

Noma

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

Pericoronitis

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

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

- **Gingivitis** is characterized by redness and swelling of the gums due to the build-up of food debris and microbial biofilm. It is usually painless, but bleeding when toothbrushing is common. Halitosis may be present. In its early stages, gingivitis is reversible with good oral hygiene. Severe forms of gingivitis are known but are rare.

- One of the most severe form is **necrotizing ulcerative gingivitis** which is characterized by severe pain and inflamed ulcerated gums that bleed easily, necrosis of the interdental papillae, foul breath and a bad taste in the mouth. It may also be accompanied by systemic symptoms, such as fever $>38^\circ$C, malaise and lymphadenopathy.

- **Periodontitis** is an inflammatory disease characterized by the progressive destruction of the alveolar bone which supports the teeth. It is often a hidden disease as it is generally painless and progresses below the gums. Halitosis may be present. In case of periapical periodontitis, soreness while biting can occur due to a devitalised (dead) tooth. The disease process of periodontitis occurs over time (usually years) and people often only become aware of it when their teeth start to move or fall out; a more aggressive destruction of the bone may sometimes be seen. Oral health professionals use special probes when carrying out periodontal screening to enable early diagnosis and treatment of periodontitis. Addressing risk factors, including effective cleaning of the periodontal tissues (under the gums), smoking cessation and good diabetic control are essential. Antibiotics are only appropriate for the treatment of aggressively destructive conditions; antibiotics are not appropriate for chronic periodontitis.

Laboratory tests

I. **Patient microbiology tests**

Routine microbiology tests are not required in most cases of dental infection but can be considered in severe cases requiring hospitalization, when culture and sensitivity testing can help in the selection of an appropriate antibiotic for example if cellulitis (e.g. Ludwig’s angina) is
spreading to vital structures or if sepsis is suspected. Please also refer to the chapter on sepsis if suspected.

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

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

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

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

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

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

Treatment
Dental bacterial infections are rarely self-limiting and may rapidly become life threatening. Most dental infection and pain is amenable to treatment by removal of the cause and drainage of the infection using a dental procedure, such as extraction of the tooth. Removal of the cause of the infection using a dental procedure is usually the quickest and safest way of resolving the problem. This is essential to avoid the risk of rapidly spreading potentially life-threatening infection. Antibiotics are normally only required for the treatment of spreading infections.
“No antibiotic care”

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

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

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

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

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

**Table 2 Medicines to control acute dental pain**

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Formulation</th>
<th>Dose and frequency</th>
</tr>
</thead>
</table>
| Ibuprofen\(^a\) | Oral liquid: 200 mg/5 mL; Tablet: 200 mg; 400 mg; 600 mg | Adults: 200–400 mg given every 6 to 8 hours (maximum dose of 2.4 g a day)  
Children:  
- Pain control / Antipyretic treatment: 5–10 mg/kg given every 6 to 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 |
| Paracetamol (acetaminophen)\(^b\) | Oral liquid: 120 mg/5 mL; 125 mg/5 mL; Suppository: 100 mg; Tablet: 100 mg to 500 mg | Adults: 500 mg–1 g given every 4 to 6 hours (maximum dose of 4 g a day)\(^c\)  
Children:  
- Pain control/Antipyretic treatment: 10–15 mg/kg given every 6 hours  
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 |

\(^a\)Not for children < 3 months, or for people with hypersensitivity to aspirin or any other NSAID (nonsteroidal anti-inflammatory drug), or for people with a history of gastro-intestinal bleeding or ulceration.  
\(^b\)Not recommended for use as an anti-inflammatory as it has not been proven to have such an effect. Warning: overdose is relatively common among people with severe dental pain.  
\(^c\)In patients with hepatic impairment or cirrhosis, maximum daily dose should be 2 g.
**Oral antiseptics**

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

**Dental procedures**

Dental procedures are usually the quickest and safest solutions for dental pain and infection. Commonly performed dental procedures are briefly described in Table 3. Detailed information on these procedures is beyond the scope of this chapter.

*Table 3 Commonly performed procedures for certain dental diseases*

<table>
<thead>
<tr>
<th>Dental disease</th>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abscess</td>
<td>1. Apical abscess</td>
</tr>
<tr>
<td></td>
<td>Source control through:</td>
</tr>
<tr>
<td></td>
<td>• Tooth extraction;</td>
</tr>
<tr>
<td></td>
<td>• Pulp extirpation (drainage of pus and removal of necrotic pulp tissue by drilling through the tooth into the pulp) followed by root canal treatment;</td>
</tr>
<tr>
<td></td>
<td>or</td>
</tr>
<tr>
<td></td>
<td>• Soft tissue incision and drainage followed by tooth extraction or root canal treatment.</td>
</tr>
<tr>
<td></td>
<td>2. Periodontal abscess</td>
</tr>
<tr>
<td></td>
<td>Source control through:</td>
</tr>
<tr>
<td></td>
<td>• Tooth extraction;</td>
</tr>
<tr>
<td></td>
<td>or</td>
</tr>
<tr>
<td></td>
<td>• Drainage of any pus collection by professional cleaning of the periodontal tissues.</td>
</tr>
<tr>
<td>Apical periodontitis/ pulpal necrosis</td>
<td>Source control through:</td>
</tr>
<tr>
<td></td>
<td>• Tooth extraction;</td>
</tr>
<tr>
<td></td>
<td>or</td>
</tr>
<tr>
<td></td>
<td>• Pulp extirpation (drainage of pus and removal of necrotic pulp tissue by drilling through the tooth into the pulp) followed by root canal treatment</td>
</tr>
<tr>
<td>Dental caries (decay) / reversible pulpitis</td>
<td>Removal of caries and restorative filling.</td>
</tr>
<tr>
<td></td>
<td>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.</td>
</tr>
<tr>
<td>Dry socket (alveolar osteitis)</td>
<td>Reassurance that this is a common yet painful outcome.</td>
</tr>
<tr>
<td></td>
<td>Irrigation of the socket with saline.</td>
</tr>
<tr>
<td>Pericoronitis</td>
<td>Source control through:</td>
</tr>
<tr>
<td></td>
<td>• Tooth extraction;</td>
</tr>
</tbody>
</table>
Drainage of any pus collection by irrigation under the operculum (flap of gum over the erupting tooth) with saline.

Pulpitis (when irreversible)

<table>
<thead>
<tr>
<th>Source control through:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Tooth extraction;</td>
</tr>
<tr>
<td>or</td>
</tr>
<tr>
<td>• Pulp extirpation (removal of the inflamed pulp and treatment of the root canal)</td>
</tr>
</tbody>
</table>

Necrotizing ulcerative gingivitis

<p>| |</p>
<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Regular tooth brushing with a fluoride-containing toothpaste and use of an interdental brush or dental floss to remove plaque</td>
</tr>
<tr>
<td>• Professional cleaning around the teeth and periodontal tissues to remove the mineralized material known as scale, tartar or calculus</td>
</tr>
<tr>
<td>• Smoking cessation advice</td>
</tr>
</tbody>
</table>

Acute necrotising ulcerative gingivitis can often be resolved by procedures alone – antibiotics are often not required.

Antibiotic treatment

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

Antibiotic treatment is required only for few dental conditions.

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

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

Antibiotic treatment is essential in patients with severe, spreading dental infections. Severe cases include those with systemic signs of infection (e.g. facial swelling, inability to open the mouth, severe pain, fever > 38.0 °C, tachycardia). Even when necessary, antibiotics should only be used to complement surgical source control (e.g. drainage of the abscess or tooth extraction).

Antibiotic use could also be considered in severely immunocompromised patients (including patients with uncontrolled diabetes) because they have a higher risk of complications. When antibiotic treatment is considered necessary, empiric use of amoxicillin or phenoxymethylpenicillin as indicated in Table 4 is considered appropriate. Using two antibiotics (e.g. amoxicillin and metronidazole) as adjunctive treatment is not necessary in the vast majority of cases.

The Handbook does not include alternative antibiotic options in cases of allergy to first-choice antibiotics which in the case of dental infections, where only penicillin options are recommended by this Handbook, may be considered problematic by some prescribers. However, even though allergies to antibiotics (particularly to beta-lactams) are frequently self-reported or indicated in health records, in most cases (> 95%), these patients do not have a true immunologically-
mediated allergy and it is very likely that they can safely tolerate the medicine if re-exposed to it. Please refer to the chapter on allergies to antibiotics for more information about this aspect.

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

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

<table>
<thead>
<tr>
<th>Adults</th>
<th>Children</th>
<th>Total treatment duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Amoxicillin</strong>&lt;sup&gt;a&lt;/sup&gt; (oral): 500 mg given every 8 hours OR <strong>Phenoxymethylpenicillin</strong>&lt;sup&gt;a&lt;/sup&gt; (oral): 500 mg (800,000 IU)&lt;sup&gt;b&lt;/sup&gt; given every 6 hours</td>
<td><strong>Amoxicillin</strong> (oral)&lt;sup&gt;b&lt;/sup&gt; 40-50 mg/kg/dose given every 12 hours OR <strong>Phenoxymethylpenicillin</strong> (oral): 15 mg/kg/dose (24,000 IU/kg/dose)&lt;sup&gt;b&lt;/sup&gt; given every 6 hours</td>
<td>3 days, if adequate source control is achieved; otherwise 5 days&lt;sup&gt;c&lt;/sup&gt; Patients should be reassessed before the end of treatment to check the resolution of the infection.</td>
</tr>
</tbody>
</table>

IU: International units.

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

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

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

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

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

**Prevention**

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

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

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

Preventing the accumulation of dental plaque is important for preventing dental diseases such as dental caries or periodontal disease.
Where people are unable to perform adequate oral hygiene themselves, regular professional
dental cleaning may be necessary to maintain oral health.

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

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

**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

**Definition**

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

**Pathophysiology**

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

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

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

Microbiology epidemiology

Pathogens that can cause lymphadenitis are listed in Table 1.

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

<table>
<thead>
<tr>
<th>Viruses</th>
<th>Bacteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most cases:</td>
<td>Most cases:</td>
</tr>
<tr>
<td>Epstein–Barr virus</td>
<td><em>Staphylococcus aureus</em> (including MRSA strains)</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td><em>Streptococcus pyogenes</em> (group A <em>Streptococcus</em>)</td>
</tr>
<tr>
<td>Respiratory viruses</td>
<td>More rarely*:</td>
</tr>
<tr>
<td>More rarely:</td>
<td>Anaerobes</td>
</tr>
<tr>
<td>HIV</td>
<td><em>Bartonella henselae</em> (mostly following cat bites or scratches)</td>
</tr>
<tr>
<td></td>
<td><em>Chlamydia trachomatis</em> (serovars L1, L2 and L3 which cause lymphogranuloma venereum)</td>
</tr>
<tr>
<td></td>
<td><em>Corynebacterium diphtheriae</em></td>
</tr>
<tr>
<td></td>
<td><em>Francisella tularensis</em></td>
</tr>
<tr>
<td></td>
<td><em>Haemophilus ducreyi</em></td>
</tr>
<tr>
<td></td>
<td><em>Neisseria gonorrhoeae</em></td>
</tr>
<tr>
<td></td>
<td><em>Rickettsia spp.</em></td>
</tr>
</tbody>
</table>

MRSA: methicillin-resistant *Staphylococcus aureus*.

*Pathogens associated with chronic lymphadenitis such as mycobacteria are not included.

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

Clinical presentation

Lymphadenitis is a noticeable enlargement (> 1–2 cm) of a lymph node. Acute onset, unilateral involvement, fluctuance and fluid that drains from the lymph node to the skin suggest a bacterial cause. Tenderness and inflammation are frequently associated with infectious causes. Fever (> 38.0 °C) and other signs and symptoms of systemic disease may be present, accompanied by
cellulitis. Viral respiratory infections, infectious mononucleosis (caused by Epstein–Barr virus or
cytomegalovirus), (acute) HIV infection and mycobacterial infections (mostly tuberculosis) always
need to be considered when diagnosing the cause of acute lymphadenitis based on clinical history
and findings. As the first step, it is important to identify the cause of the enlargement. Location
of the enlarged lymph node and accompanying signs and symptoms of infection (e.g. skin lesion,
pharyngitis, signs and symptoms of a sexually transmitted disease) can help establishing the
diagnosis. History and physical examination usually help in the diagnosis and guide the
investigation and treatment.

Laboratory tests

I. Patient microbiology tests

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

II. Other tests

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

III. Using microbiology surveillance data

Routine surveillance is not helpful to inform empiric guidance.

Biopsy

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

Imaging

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

Antibiotic treatment

In certain cases, a watchful waiting approach, without antibiotics is indicated when follow-up is
feasible and the patient is not severely ill or a malignancy is not suspected. This approach is
reasonable because the condition is frequently self-limiting—for example, mild cervical lymphadenitis is usually caused by a viral infection of the upper respiratory tract, especially in children.

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

*Table 1 Empiric antibiotic treatment for bacterial lymphadenitis*[^1]

<table>
<thead>
<tr>
<th>Adults</th>
<th>Children</th>
<th>Total treatment duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Amoxicillin+clavulanic acid</strong> (oral): 500 mg + 125 mg every 8 hours OR <strong>Cefalexin</strong> (oral): 500 mg every 8 hours</td>
<td><strong>Amoxicillin+clavulanic acid</strong> (IV/oral): 40–50 mg/kg per dose of amoxicillin component, every 12 hours OR 30 mg/kg/dose given every 8 hours</td>
<td>5 days</td>
</tr>
</tbody>
</table>

**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  
**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  
20–<30 kg: 625 mg given every 12 hours  
≥ 30 kg: Use adult dose

OR  
**Cloxacillin** or **flucloxacillin** (oral): 500 mg given every 8 hours

**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 12 hours  
20–<30 kg: 750 mg given every 12 hours  
≥ 30 kg: Use adult dose

OR  
**Cloxacillin** or **flucloxacillin** (IV/oral):  
- Neonates: 25–50 mg/kg/dose given every 12 hours  
- Children: 25 mg/kg/dose given every 6 hours

**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

[^1]: Table 1 reference
Notes: All dosages are for normal renal and hepatic function.

86 a Patient history is key in order to adapt treatment if necessary (e.g. lymphadenitis in the context of cat scratch
87 fever caused by Bartonella henselae would require a different antibiotic treatment).
88 b Oral liquid must be refrigerated after reconstitution as clavulanic acid is rapidly metabolized in high ambient
89 temperatures.
90 c Cloxacillin (or dicloxacillin or flucloxacillin) has a narrower spectrum of antibacterial activity compared to
91 amoxicillin+clavulanic acid and cefalexin while maintaining good efficacy in cases of mild skin infections. Therefore,
92 from an antibiotic stewardship perspective, it would be the preferred option whenever possible. Cloxacillin,
93 dicloxacillin and flucloxacillin are preferred for oral administration because of better bioavailability (i.e. the extent
94 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.
Bacterial eye infections
(excluding trachoma – see separate chapter)

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.

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](https://apps.who.int/iris/handle/10665/81170)

Definition

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

It should be noted that many conditions presented in this chapter could also be of non-infectious origin (e.g. systemic inflammatory diseases affecting other parts of the body or in case of
conjunctivitis allergies or toxic irritants), but non-infectious eye conditions are beyond the scope of this chapter.

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

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

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

Pathophysiology

Eye infections can result either from external contamination through direct inoculation of the pathogen into the eye/s (exogenous transmission) or from dissemination of the pathogen through the bloodstream from a distant site of infection (endogenous transmission). Exogenous transmission can occur by contact with infected secretions (mostly by rubbing the eye/s with contaminated hands) or as a result of a penetrating eye injury; this includes eye surgery where bacteria from the flora could be “introduced”. The use of contact lenses and eye contact with water (e.g. during swimming) are also risk factors for exogenous transmission. In addition, certain
sexually transmitted infections (e.g. gonococcal and chlamydial infections) can be transmitted from infected mothers to their child during vaginal delivery. Endogenous transmission occurs when pathogens are spread through the bloodstream from other sites of infection (e.g. in case of endocarditis, urinary tract infections, abdominal abscesses, meningitis, indwelling catheters), mainly in high-risk patients (e.g. immunocompromised patients, people who inject drugs).
Blepharitis

Definition

<table>
<thead>
<tr>
<th>TYPE OF EYE INFECTION</th>
<th>ANATOMICAL LOCATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blepharitis/Hordeolum</td>
<td>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)</td>
</tr>
</tbody>
</table>

Epidemiology

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

Microbiology epidemiology

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

<table>
<thead>
<tr>
<th>TYPE OF EYE INFECTION</th>
<th>MOST COMMON CAUSATIVE PATHOGENS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blepharitis (usually not of infectious origin)</td>
<td>Bacteria: mostly Staphylococcus aureus and coagulase-negative Staphylococci Mites: <em>Demodex folliculorum</em>(^a), <em>Demodex brevis</em>(^b)</td>
</tr>
</tbody>
</table>

\(^a\) *Demodex folliculorum* has been identified in 30% of patients with chronic anterior blepharitis but is also found with approximately the same prevalence in asymptomatic persons. However, it is clearly a contributing factor in some patients as evidenced by the improvement seen in response to eradicative therapy.

\(^b\) *Demodex brevis*, has been associated with posterior blepharitis.

Clinical presentation

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

Blepharitis is more common in adults than in children, but children can have dramatic episodes of anterior and/or posterior blepharitis, often characterized by more conjunctival and corneal findings(71, 72).
Blepharitis related to *Demodex* infestation characteristically presents with cylindrical dandruff or “sleeves” on the eyelashes (73). Patients with hordeolum usually present with a tender swelling of the eyelid/s with a lash at its apex.

**Laboratory tests**

I. **Patient microbiology tests**

Microbiology tests are usually not needed.

II. **Other tests**

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

III. **Using microbiology surveillance data**

Routine surveillance is not helpful to inform empiric guidance.

**Imaging**

Imaging is usually not needed.

**Antibiotic treatment**

Antibiotic treatment is usually not needed. Good eyelid hygiene is the most important treatment and cases usually resolve without further measures. Warm compresses 5 to 10 minutes twice to four times per day, lid massage and washing and use of preservative-free artificial tears four to eight times per day can also help. Patients with severe or refractory symptoms may require additional therapies but this is beyond the scope of this chapter.
Conjunctivitis

Definition

<table>
<thead>
<tr>
<th>TYPE OF EYE INFECTION</th>
<th>ANATOMICAL LOCATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conjunctivitis</td>
<td>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)</td>
</tr>
</tbody>
</table>

Epidemiology

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

Microbiology epidemiology

Table 2 Pathogens most frequently associated with conjunctivitis (in descending order of frequency)

<table>
<thead>
<tr>
<th>TYPE OF EYE INFECTION</th>
<th>MOST COMMON CAUSATIVE PATHOGENS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conjunctivitis(74)</td>
<td>Viruses: most infectious cases are of viral origin, mostly adenovirus, rarely herpes simplex virus</td>
</tr>
<tr>
<td></td>
<td>Bacteria(75):</td>
</tr>
<tr>
<td></td>
<td>• In children: <em>Staphylococcus aureus</em>, <em>Streptococcus pneumoniae</em>, <em>Haemophilus influenzae</em>, <em>Moraxella catarrhalis</em>.</td>
</tr>
<tr>
<td></td>
<td>• In adults: <em>Staphylococcus aureus</em></td>
</tr>
</tbody>
</table>

Consider *Chlamydia trachomatis* (serovars D-K) and *Neisseria gonorrhoeae* in the context of sexually transmitted infections or in neonates after vaginal delivery from infected mothers. *Chlamydia trachomatis* (serovars A-C) can cause trachoma. Trachoma is covered in a separate chapter.

Clinical presentation

Patients with conjunctivitis (including cases of viral origin) usually present with a red, watery and itchy eye. They often describe a feeling of “sand in the eye” with no pain (if there is pain, this usually indicates corneal involvement) and have normal vision. In cases of bacterial infection, a thick purulent discharge from the eye is usually present. Patients may refer to all discharge as
“pus”, however, in bacterial conjunctivitis the complaint of discharge predominates, while in viral and allergic conjunctivitis patients report a burning and gritty feeling or itching. In most cases, conjunctivitis is a mild self-limiting condition.

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

**Laboratory tests**

I. Patient microbiology tests

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

II. Other tests

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

III. Using surveillance microbiology data

Routine surveillance is not helpful to inform empiric guidance.

**Imaging**

Imaging is usually not needed.

**Antibiotic treatment**

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

Urgent referral of the patient to an ophthalmologist, if available, should be considered when hyperacute bacterial conjunctivitis (mostly caused by *Neisseria gonorrhoeae*) is suspected because of the risk for rapid progression to corneal perforation.
### Table 3 Empiric antibiotic treatment for bacterial conjunctivitis

<table>
<thead>
<tr>
<th>Type of eye infection</th>
<th>Antibiotic treatment</th>
<th>Total treatment duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial conjunctivitis (children and adults)</td>
<td><strong>Gentamicin</strong> (eye drops): 0.3%, 1 drop in the affected eye given every 6 hours OR <strong>Ofloxacin</strong> (eye drops): 0.3% 1 drop in the affected eye given every 6 hours OR <strong>Tetracycline</strong> (eye ointment): 1% 1 cm in the affected eye given every 6 hours</td>
<td>5 days</td>
</tr>
<tr>
<td>Gonococcal conjunctivitis (adults, adolescents)</td>
<td><strong>Ceftriaxone</strong> (IM): 250 mg AND <strong>Azithromycin</strong> (oral): 1 g</td>
<td>Single dose</td>
</tr>
<tr>
<td>Gonococcal ophthalmia neonatorum (i.e. gonococcal conjunctivitis of the newborn)</td>
<td><strong>Ceftriaxone</strong> (IM): 50mg/kg</td>
<td>Single dose</td>
</tr>
<tr>
<td>Chlamydial ophthalmia neonatorum (i.e. chlamydial conjunctivitis of the newborn)</td>
<td><strong>Azithromycin</strong> (oral): 20 mg/kg given once a day</td>
<td>3 days</td>
</tr>
<tr>
<td>Ocular prophylaxis (topical treatment for the prevention of both gonococcal and chlamydial ophthalmia neonatorum)</td>
<td><strong>Erythromycin</strong> 0.5% eye ointment OR <strong>Tetracycline</strong> 1% eye ointment</td>
<td>Antibiotic needs to be applied to both eyes soon after birth (single dose)</td>
</tr>
</tbody>
</table>

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

IM: intramuscular; IV: intravenous.

*Concurrent treatment with azithromycin for chlamydial infection is usually recommended.

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

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

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

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

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)

Epidemiology

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

Microbiology epidemiology

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

<table>
<thead>
<tr>
<th>TYPE OF EYE INFECTION</th>
<th>MOST COMMON CAUSATIVE PATHOGENS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endophthalmitis</td>
<td>Bacteria:</td>
</tr>
<tr>
<td></td>
<td><strong>Most cases:</strong></td>
</tr>
<tr>
<td></td>
<td>Coagulase-negative Staphylococci</td>
</tr>
<tr>
<td></td>
<td><strong>Less frequently:</strong></td>
</tr>
<tr>
<td></td>
<td><em>Staphylococcus aureus</em>&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td><em>Streptococcus</em> spp.&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td><em>Klebsiella</em> spp. (more frequent in Asia)</td>
</tr>
<tr>
<td></td>
<td><em>Bacillus cereus</em> (mostly in case of penetrating trauma)</td>
</tr>
<tr>
<td></td>
<td><strong>Fungi</strong>:&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>mostly <em>Candida albicans, Fusarium</em> spp., <em>Aspergillus</em> spp.</td>
</tr>
</tbody>
</table>

<sup>a</sup>*Streptococcus viridans* is more frequently encountered in case of post-intravitreal injection endophthalmitis compared to post-cataract endophthalmitis(82).
In temperate climates, fungal endophthalmitis is usually endogenous and caused by *Candida* spp. In tropical regions, fungal endophthalmitis is often due to molds and is usually exogenous in origin.

**Clinical presentation**

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

**Laboratory tests**

I. **Patient microbiology tests**

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

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

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

II. **Other tests**

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

III. **Using microbiology surveillance data**

Routine surveillance is not helpful to inform empiric guidance.

**Imaging**

Imaging is usually not needed.
Antibiotic treatment

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

With bacterial endophthalmitis treatment, there are two common approaches:

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

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

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

Table 6 Empiric antibiotic treatment for bacterial endophthalmitis

<table>
<thead>
<tr>
<th>Type of eye infection</th>
<th>Antibiotic treatment</th>
<th>Total treatment duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial endophthalmitis</td>
<td><strong>Intravitreal injection:</strong> Vancomycin 1 mg + ceftazidime 2.25 mg</td>
<td>Intravitreal antibiotics: single dose (if no clinical improvement after 48 hours, the intravitreal injection can be repeated)</td>
</tr>
<tr>
<td></td>
<td><strong>ADD Systemic treatment</strong> (in case of endogenous infection)</td>
<td>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).</td>
</tr>
<tr>
<td></td>
<td>Adults: Ceftriaxone (IV): 2g given once a day AND Vancomycin (IV): 15-20mg/kg given every 12 hours</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Neonates and children: Ceftriaxone (IV): 80 mg/kg/dose given once a day AND Vancomycin (IV):</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Neonates: 15 mg/kg/ dose, given every 12 hours • Children: 15 mg/kg/dose, given every 8 hours</td>
<td></td>
</tr>
</tbody>
</table>

Systemic antibiotics alone are not effective in treating bacterial exogenous endophthalmitis. Whether systemic antibiotics provide any
benefit in these cases as adjunctive therapy to intravitreal antibiotics is still debatable.

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

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

Definition

<table>
<thead>
<tr>
<th>TYPE OF EYE INFECTIONS</th>
<th>ANATOMICAL LOCATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keratitis</td>
<td>Infection of the cornea (i.e. the transparent covering of the eye)</td>
</tr>
</tbody>
</table>

Epidemiology

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

Microbiology epidemiology

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

<table>
<thead>
<tr>
<th>TYPE OF EYE INFECTION</th>
<th>MOST COMMON CAUSATIVE PATHOGENS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keratitis(85, 86)</td>
<td><strong>Fungi</strong>: mostly <em>Fusarium</em> spp., <em>Aspergillus</em> spp.</td>
</tr>
<tr>
<td></td>
<td><strong>Bacteria</strong>: <em>Pseudomonas</em> spp (contact lenses), <em>Staphylococcus epidermidis</em>, <em>Staphylococcus aureus</em>, <em>Streptococcus pneumoniae</em></td>
</tr>
<tr>
<td></td>
<td><strong>Viruses</strong>: mostly herpes simplex virus (usually type 1), varicella zoster virus</td>
</tr>
<tr>
<td></td>
<td><strong>Parasites</strong>: <em>Acanthamoeba</em> (contact lenses)</td>
</tr>
</tbody>
</table>

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

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

Laboratory tests

I. Patient microbiology tests

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

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

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

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

II. Other tests

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

III. Using microbiology surveillance data

Routine surveillance is not helpful to inform empiric guidance.

Imaging

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

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

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

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

Table 9 Empiric antibiotic treatment for bacterial keratitis

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

\(^a\)A fluoroquinolone is usually given to patients who wear contact lenses because *Pseudomonas aeruginosa* is often the causative pathogen.

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

ACCESS Antibiotics are indicated in green, WATCH antibiotics in yellow and RESERVE antibiotics in red.
Orbital cellulitis

Definition

<table>
<thead>
<tr>
<th>TYPE OF EYE INFECTIONS</th>
<th>ANATOMICAL LOCATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orbital cellulitis</td>
<td>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.</td>
</tr>
</tbody>
</table>

Epidemiology

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

Microbiology epidemiology

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

<table>
<thead>
<tr>
<th>TYPE OF EYE INFECTION</th>
<th>MOST COMMON CAUSATIVE PATHOGENS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orbital cellulitis</td>
<td>Bacteria:</td>
</tr>
<tr>
<td></td>
<td>• In adults: <em>Staphylococcus aureus</em>, <em>Streptococcus</em> spp., <em>Bacteroides</em> spp.</td>
</tr>
<tr>
<td></td>
<td>• In children: <em>Haemophilus influenzae</em> (rare in vaccinated children(88)).</td>
</tr>
<tr>
<td></td>
<td>• Following eye trauma: <em>Pseudomonas aeruginosa</em> and <em>Escherichia coli</em></td>
</tr>
<tr>
<td></td>
<td>• Following a dental abscess: polymicrobial infection (including anaerobes)</td>
</tr>
<tr>
<td></td>
<td>Fungi:</td>
</tr>
<tr>
<td></td>
<td>• Mostly in immunocompromised patients (e.g. diabetes, chemotherapy, HIV infection): zygomycetes (e.g. <em>Mucor</em>) and <em>Aspergillus</em> spp.</td>
</tr>
</tbody>
</table>

*Fungal infections are rare but they should be considered in immunocompromised patients including patients with poorly controlled diabetes.

Clinical presentation

Patients with orbital cellulitis typically have unilateral local signs of inflammation around the affected eye. The eyelids are usually swollen, red, warm and tender. Sometimes fever is present (> 38.0°C). These findings are also present in cases of periorbital cellulitis (see below); however, in addition to these symptoms, patients with orbital cellulitis present with restricted extraocular motility with pain on attempted eye movement, conjunctival chemosis (i.e. swelling) and injection as critical sign. Usually this condition is accompanied by protrusion of the eye (i.e. proptosis), and loss of vision may be present(89). Signs of optic neuropathy (e.g. afferent
pupillary defect, dyschromatopsia) may be present in severe cases. In neglected cases orbital cellulitis may lead to cavernous sinus thrombosis, brain abscess or even death.

**Laboratory tests**

I. Patient microbiology tests

Blood cultures and cultures of samples collected can be considered.

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

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

*Possible specimens (depending on the type of infection) include: conjunctival swabs, corneal scrapings or corneal biopsy, aqueous or vitreous humour aspirate.

II. Other tests

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

III. Using microbiology surveillance data

Routine surveillance is not helpful to inform empiric guidance.

**Imaging**

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

**Antibiotic treatment**

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

Patients with orbital cellulitis should be admitted to the hospital and an infectious disease physician and an otorhinolaryngology specialist should be consulted. Most patients with uncomplicated orbital cellulitis can be treated with antibiotics alone(90, 91).
Surgery for source control (e.g. drainage of purulent collections) may be needed in severe and complicated cases (e.g. in case of abscess) in combination with systemic antibiotic treatment (92, 93). Surgery is almost always indicated in patients with intracranial extension of the infection.
Periorbital (or preseptal) cellulitis

Definition

<table>
<thead>
<tr>
<th>TYPE OF EYE INFECTIONS</th>
<th>ANATOMICAL LOCATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Periorbital (or preseptal) cellulitis</td>
<td>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)</td>
</tr>
</tbody>
</table>

Epidemiology

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

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

<table>
<thead>
<tr>
<th>TYPE OF EYE INFECTION</th>
<th>MOST COMMON CAUSATIVE PATHOGENS</th>
</tr>
</thead>
</table>
| Periorbital (or preseptal) cellulitis | Bacteria:  
  *Staphylococcus aureus* (including MRSA)  
  *Streptococcus pneumoniae*  
  *Haemophilus influenzae* (rare in vaccinated children[88])  
  *Moraxella catarrhalis*  
  Anaerobes (suspect if there is a history of animal or human bite or if necrosis is present)  
  **Viruses:**  
  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). |

Clinical presentation

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

I. Patient microbiology tests

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

II. Other tests

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

III. Using surveillance microbiology data

Routine surveillance is not helpful to inform empiric guidance.

Imaging

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

Antibiotic treatment

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

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

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

Children younger than one year of age, patients who cannot cooperate fully for an examination, who are severely ill or in case of no noticeable improvement or worsening after 24 to 48 hours of oral antibiotics should generally be admitted to the hospital and managed according to the recommendations for orbital cellulitis.
### Table 14 Empiric antibiotic treatment for periorbital (or preseptal) cellulitis

<table>
<thead>
<tr>
<th>Adults</th>
<th>Children</th>
<th>Total treatment duration</th>
</tr>
</thead>
</table>
| **Amoxicillin+clavulanic acid (IV):** 1 gr + 200 mg given every 8 hours  
Oral: 500 mg + 125 mg given every 8 hours | **Amoxicillin+clavulanic acid (IV/oral):** 40-50 mg/kg/dose of amoxicillin component given every 12 hours  
Oral 30 mg/kg/dose given every 8 hours | 10-14 days (depending on the severity) |
| OR | OR | |
| **Cefalexin (oral):** 500 mg given every 8 hours | **Cefalexin (oral):** 25 mg/kg/dose given every 12 hours | |
| OR | OR | |
| **Cloxacillin or flucloxacillin (IV):** 2 gr given every 6 hours  
Oral: 500 mg given every 8 hours | **Cloxacillin or flucloxacillin (IV/oral):**  
• Neonates: 25-50 mg/kg/dose, given every 12 hours  
• Children: 25 mg/kg/dose, given every 6 hours | |
| **Total treatment duration** | | |
| 10-14 days (depending on the severity) | | |

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

IV: intravenous.
It should be noted that these specific recommendations are not included in the EML/c(4, 5). The options presented are based on what is recommended for mild skin and soft tissues infections.

Oral liquid must be refrigerated after reconstitution as clavulanic acid is rapidly metabolized in high ambient temperatures.

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

Definition

**TYPE OF EYE INFECTIONS**  **ANATOMICAL LOCATION**

<table>
<thead>
<tr>
<th>Uveitis</th>
<th>Infection of the uvea, which is composed of:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Iris (colored ring-shaped part of the eye behind the cornea)</td>
</tr>
<tr>
<td></td>
<td>• 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)</td>
</tr>
<tr>
<td></td>
<td>• Choroid (this is a vascular layer)</td>
</tr>
</tbody>
</table>

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.

Epidemiology

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

Microbiology epidemiology

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

<table>
<thead>
<tr>
<th>TYPE OF EYE INFECTION</th>
<th>MOST COMMON CAUSATIVE PATHOGENS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uveitis</td>
<td><strong>Bacteria:</strong></td>
</tr>
<tr>
<td></td>
<td>• <em>Bartonella henselae</em> (with cat-scratch disease)</td>
</tr>
<tr>
<td></td>
<td>• <em>Mycobacterium tuberculosis</em></td>
</tr>
<tr>
<td></td>
<td>• <em>Treponema pallidum</em> (with neurosyphilis)</td>
</tr>
<tr>
<td></td>
<td><strong>Parasites:</strong></td>
</tr>
<tr>
<td></td>
<td><em>Toxoplasma gondii</em></td>
</tr>
<tr>
<td></td>
<td><strong>Viruses:</strong></td>
</tr>
<tr>
<td></td>
<td><em>cytomegalovirus</em>, <em>herpes simplex virus</em></td>
</tr>
</tbody>
</table>

Consider individual risk factors and presentation to identify the most likely causative pathogen.

Ocular tuberculosis usually results from haematogenous dissemination of the infection from pulmonary or extra-pulmonary sites.
Clinical presentation

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

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

Laboratory tests

I. Patient microbiology tests

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

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

<table>
<thead>
<tr>
<th>Diagnostic test</th>
<th>Purpose of the test</th>
<th>Settings where the test should be available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microscopy (Gram stain) and culture&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Microbial morphology and detection and identification of bacterial species for selection of appropriate antibiotic regimens</td>
<td>Healthcare facilities with clinical laboratories</td>
</tr>
</tbody>
</table>

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

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

II. Other tests

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

III. Using microbiology surveillance data

Routine surveillance is not helpful to inform empiric guidance.

Imaging

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

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

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

**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*

<table>
<thead>
<tr>
<th>Box 1 Other relevant WHO documents (please check regularly for updates)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Trachoma. <a href="https://www.who.int/news-room/fact-sheets/detail/trachoma">https://www.who.int/news-room/fact-sheets/detail/trachoma</a></td>
</tr>
<tr>
<td>• Trachoma control: a guide for programme managers <a href="https://apps.who.int/iris/handle/10665/43405">https://apps.who.int/iris/handle/10665/43405</a></td>
</tr>
</tbody>
</table>

**Definition**

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

**Microbiology epidemiology**

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

**Pathophysiology**

*Chlamydia trachomatis* infection spreads via the hands through direct contact with contaminated people or objects. Flies can also spread the infection by transporting contaminated eye and/or nose secretions from infected to non-infected people. Chronic inflammation of the conjunctiva caused by repeated infections over the years can cause inversion of the eyelashes that can lead
to permanent corneal damage through formation of scars on the cornea (the transparent front part of the eye – see Figure). This can eventually lead to vision impairment and blindness(97).

Epidemiology

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

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

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

- Surgery to treat advanced diseases;
- Antibiotics to clear infection;
- Facial cleanliness; and
- Environmental improvement to reduce transmission.

In 1996, WHO established the alliance for the global elimination of trachoma, whose goal was to eliminate trachoma as a public health problem by 2020. In addition, in 1998, the World
Health Assembly adopted a resolution on trachoma to urge WHO Member States to implement measures to target the elimination of trachoma (100). As of July 2020, 13 out of 30 countries that are implementing the SAFE strategy have achieved the WHO elimination targets. As part of the elimination strategy, data reported to WHO for 2019 indicate that about 92,000 people had corrective surgery for trichiasis and 95 million people received antibiotic treatment (i.e. 57% of 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 ≥ 10% (see the section on clinical presentation for the classification of trachoma), or
- the prevalence of trachomatous trichiasis in people aged ≥ 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 ≥ 15 years is < 0.2%
- there is evidence that the health system can identify and manage cases of trachomatous trichiasis.

**Clinical presentation**

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

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

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

The grading system includes:
- Trachomatous inflammation, follicular – five or more follicles of > 0.5 mm on a specific area of the upper tarsal conjunctiva
- Trachomatous inflammation, intense – papillary hypertrophy and inflammatory thickening of the upper tarsal conjunctiva obscuring more than half the deep tarsal vessels
- Trachomatous conjunctival scarring – grossly visible scars on the tarsal conjunctiva
- Trachomatous trichiasis – at least one ingrown eyelash touching the globe of the eye or evidence of epilation (eyelash removal)
- Corneal opacity – corneal opacity blurring part of the pupil margin.
Laboratory tests

I. Patient microbiology tests

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

Table 1 Microbiology tests to consider if trachoma is suspected as indicated in the WHO EDL

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

*Possible specimens: conjunctival swabs.

II. Other tests

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

III. Using microbiology surveillance data

Routine surveillance is not helpful to inform empiric guidance.

Imaging

When trachoma is suspected, imaging is not usually needed.

Treatment

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

If trichiasis has already developed, surgery is needed to prevent blindness by stopping the eyelashes continuing to erode the cornea.

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

Table 2 Empiric antibiotic treatment for trachoma

<table>
<thead>
<tr>
<th>Adults and children</th>
<th>Total treatment duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Azithromycin</strong> (oral): 20 mg/kg (maximum 1 g)</td>
<td>Single dose (azithromycin)</td>
</tr>
</tbody>
</table>
OR
Azithromycin (eye drops)\(^a\) 1.5%, 1 drop administered to both eyes every 12 hours
OR
Tetracycline (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)

3 days (topical treatment with azithromycin)
6 weeks (topical treatment with tetracycline)

Notes: Antibiotic treatment is mostly given once a year for at least three years as part of mass drug administration programmes in endemic areas.
\(^a\)Azithromycin eye drops may be as effective as oral azithromycin.(105).
ACCESS antibiotics are indicated in green, WATCH antibiotics in yellow and RESERVE antibiotics in red.

Prevention

For prevention of trachoma, please refer to the epidemiology section where the WHO SAFE strategy is described.
Community-acquired pneumonia – Mild

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, phenoxyethylpenicillin) 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).

**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](https://apps.who.int/iris/handle/10665/81170)
- Revised WHO classification and treatment of pneumonia in children at health facilities: evidence summaries. [https://apps.who.int/iris/handle/10665/137319](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](https://apps.who.int/iris/handle/10665/310970)
- Guidelines for treatment of drug-susceptible tuberculosis and patient care, 2017 update. [https://apps.who.int/iris/handle/10665/255052](https://apps.who.int/iris/handle/10665/255052)

Definition

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

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

**Epidemiology**

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

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

**Microbiology epidemiology**

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

In children aged 2 months to 5 years, pneumonia is more likely to be of viral origin (e.g. respiratory syncytial virus, influenza and parainfluenza virus). The most important bacterial pathogen in children under 5 years is *Streptococcus pneumoniae*. In older children *S. pneumoniae* is still common but “atypical bacteria” such as *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* may occur (“atypical bacteria” have intrinsic resistance to beta-lactam antibiotics and cannot by visualized by Gram staining). *Haemophilus influenzae*, *Moraxella catarrhalis* and *Staphylococcus aureus* also cause CAP in some children (Table 1).
In adults, viruses are common causes of CAP (Table 1), either by directly causing pneumonia or by favouring superinfection with bacteria. Among bacteria, the most common causative agents are *Streptococcus pneumoniae*, followed by “atypical bacteria” (see definition in the paragraph above) such as *Mycoplasma pneumoniae*, *Chlamydia pneumoniae* and *Legionella pneumophila*. *Haemophilus influenzae*, *Moraxella catarrhalis* and *Staphylococcus aureus* are also quite common (Table 1).

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

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

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

**a**“Atypical” bacteria remain colourless with Gram staining. They also have intrinsic resistance to beta-lactams.

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

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

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

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

Antimicrobial resistance is a potential problem with all pathogens associated with CAP. Clinically relevant high-level beta-lactam resistance in *Streptococcus pneumoniae* is though still rare.
globally. Resistance to macrolides in *Streptococcus pneumoniae* and *Mycoplasma pneumoniae* 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.**

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

**Clinical presentation**

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

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

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

**Laboratory tests**

I. **Patient microbiology tests**

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

II. **Other tests**

In mild cases, laboratory tests are usually not needed. If available, point-of-care testing for C-reactive protein (CRP) could be considered in adult patients if there is diagnostic uncertainty.
In general, CRP has good negative predictive value, and a negative test can be used to help rule out bacterial pneumonia (unless the pre-test probability is high or the clinical presentation is severe).

### III. Using microbiology surveillance data

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

### Imaging

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

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

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

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

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

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

### Table 4 CURB-65 criteria and scoring, and treatment decisions

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of confusion (new onset)</td>
<td>1</td>
</tr>
<tr>
<td>Urea &gt; 19 mg/dL (or &gt; 7 mmol/L)a</td>
<td>1</td>
</tr>
<tr>
<td>Respiratory rate &gt; 30 breaths/min</td>
<td>1</td>
</tr>
</tbody>
</table>
Systolic blood pressure < 90 mmHg (<12 kPa) or diastolic blood pressure ≤ 60 mmHg (<8 kPa) | 1
---|---
Age ≥ 65 years | 1
CURB-65 score / CRB-65 score | Where to treat
0–1 | Candidate for outpatient treatment
Low 30-day mortality risk (< 1.5%)
2 | Consider inpatient treatment
30-day mortality risk ≈ 10%
Consider adding clarithromycin (see Table 6)
If tests are available, consider testing for atypical pathogens (e.g. *Legionella* spp., *Mycoplasma* spp.)
≥ 3 | Inpatient treatment (consider admission to intensive care)
High 30-day mortality risk (≈ 20%)
Consider adding clarithromycin (see Table 6)
Consider testing for atypical pathogens (e.g. *Legionella* spp., *Mycoplasma* spp.)

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

*R* Urea is not required for the calculation of the CRB-65 score, a modification of the CURB-65 score that does not require the execution of laboratory tests.

**Ruling out tuberculosis**

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

**Symptomatic care**

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

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

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

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

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

<table>
<thead>
<tr>
<th>First choice</th>
<th>Adults</th>
<th>Total treatment duration ([117, 118])</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin (oral)</td>
<td>1 g given every 8 hours</td>
<td></td>
</tr>
</tbody>
</table>
Table 7 Empiric antibiotic treatment for mild cases of community-acquired pneumonia in children (from the WHO document “Revised WHO classification and treatment of childhood pneumonia at health facilities”)(112)

<table>
<thead>
<tr>
<th>Pneumonia (fast breathing and/or chest indrawing)</th>
<th>Children</th>
<th>Total treatment duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>(treat at home with oral antibiotic)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amoxicillin (oral): 40-50 mg/kg/dose given every 12 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral weight bands:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-6 kg: 125 mg given every 12 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-&lt;10 kg: 250 mg given every 12 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10-&lt;15 kg: 500 mg given every 12 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15-&lt;20 kg: 750 mg given every 12 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20-&lt;30 kg: 1000 mg given every 12 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥30 kg: Use adult dose</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

Notes: All dosages are for normal renal and hepatic function.
ACCESS antibiotics are indicated in green, WATCH antibiotics in yellow and RESERVE antibiotics in red.

Prevention

Vaccination can prevent many cases of CAP. Available vaccines are active against pneumococcal infection, *Haemophilus influenzae* type b disease and influenza and several vaccines against SARS-CoV-2 are available. Vaccines are never 100% effective and because they are serogroup-specific, they do not protect against all strains of bacteria or viruses. Duration of protection is also variable. As a result, even vaccinated people can develop CAP. *Haemophilus influenzae* type b conjugate vaccines and pneumococcal conjugate vaccines should be included in all routine infant immunization programmes as they have been very successful in reducing invasive disease and in many countries, rates of pneumococcal resistance. Countries should consider the inclusion of yearly seasonal influenza vaccination for high-risk populations (pregnant women, elderly...
people, patients with chronic medical conditions and health care workers) in their vaccination plan.
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 surveillance, prevention and control of chronic respiratory diseases: a comprehensive approach. [https://apps.who.int/iris/handle/10665/43776](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](https://apps.who.int/iris/handle/10665/310970)


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).
Pathophysiology

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

Epidemiology

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

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

Microbiology epidemiology

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

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

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

Clinical presentation

An exacerbation of COPD should be suspected in cases of recent and sustained worsening of dyspnoea and cough with increased sputum production compared with the baseline of patients with COPD (i.e. chronic bronchitis, emphysema and asthma). Symptoms can overlap with those of pneumonia; however, tachycardia, tachypnoea at rest and crepitations that persist (i.e. that do not clear) after coughing suggest pneumonia.
The decision to hospitalize a person with exacerbation of COPD should be guided by the severity of symptoms, assessment of comorbidities and availability of home support.

**Laboratory tests**

I. Patient microbiology tests

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

II. Other tests

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

III. Using microbiology surveillance data

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

**Imaging**

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

“**No antibiotic care**”

The core treatment of an exacerbation episode consists of supplementary oxygen and short-acting inhaled beta₂-agonists (with or without anticholinergics). Most guidelines currently recommend using systemic steroids because they help improve lung function and shorten time to recovery.

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

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

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

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

<table>
<thead>
<tr>
<th></th>
<th>First choice</th>
<th>Second choice</th>
<th>Total treatment duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild to moderate cases</td>
<td>Amoxicillin (oral): 500 mg given every 8 hours</td>
<td>Cefalexin (oral): 500 mg given every 12 hours OR Doxycycline (oral): 100 mg given every 12 hours</td>
<td>5 days</td>
</tr>
<tr>
<td>Severe cases</td>
<td>Amoxicillin+clavulanic acid (oral) 500 mg + 125 mg given every 8 hours</td>
<td>-</td>
<td>5 days</td>
</tr>
</tbody>
</table>

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

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

Prevention

Appropriate measures to prevent further exacerbations include smoking cessation, reduced indoor air pollution, use of long-acting inhaled beta₂-agonists (with or without anticholinergics) and vaccination (against influenza and *Streptococcus pneumoniae* infection) (39, 41). Currently, there is no clear consensus on the prophylactic use of antibiotics (e.g. macrolides) in patients with severe COPD and frequent episodes of exacerbation (130). For specific preventive measures for chronic respiratory diseases, refer to the WHO publication on global surveillance, prevention and control of chronic respiratory diseases (131).
Infectious diarrhoea / gastroenteritis

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

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.

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

- Diarrhoeal disease [internet]. ([https://www.who.int/news-room/fact-sheets/detail/diarrhoecal-disease](https://www.who.int/news-room/fact-sheets/detail/diarrhoeal-disease)

Definition

Acute diarrhoeal disease (also known as gastroenteritis) is a disease characterized by acute onset (usually defined as duration < 14 days) of diarrhoea. Diarrhoea is defined as the passage of unusually loose or watery stools occurring at least 3 times a day (or more frequent than is normal for the individual). Consistency (how liquid/runny) rather than frequency (how often) is the most
important factor to consider and frequent passing of formed stool is not diarrhoea. In breastfed babies, frequent loose “pale” stools are not considered diarrhoea(132). Most cases of acute diarrhoea have an infectious origin, but non-infectious causes are also possible (e.g. adverse effects of medicines, including antibiotics and cytotoxic chemotherapy; endocrine diseases, inflammatory bowel diseases, irritable bowel syndrome). Acute diarrhoea can be further subclassified as **watery diarrhoea** or **bloody diarrhoea** (i.e. presence of visible blood in the stool).

**Pathophysiology**

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

**Epidemiology**

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

**Microbiology epidemiology**

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

<table>
<thead>
<tr>
<th>Table 1 Pathogens most frequently associated with acute infectious diarrhoea in children (in descending order of frequency)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Viruses (most cases)</strong></td>
</tr>
<tr>
<td>Low-income settings</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>High-income settings</td>
</tr>
</tbody>
</table>
Diarrhoea is the most common complication in measles.

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

<table>
<thead>
<tr>
<th>Viruses (most cases)</th>
<th>Bacteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-income settings</td>
<td>Norovirus</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>High-income settings</td>
<td>Norovirus</td>
</tr>
<tr>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
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<tr>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3 Pathogens most frequently associated with persistent (14-29 days) or chronic (> 30 days) infectious diarrhoea in HIV patients (in descending order of frequency)

<table>
<thead>
<tr>
<th>Viruses</th>
<th>Parasites</th>
<th>Fungi (rarely)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytomegalovirus</td>
<td>Cryptosporidium spp., Microsporidium spp., Cystoisospora belli</td>
<td>Histoplasma capsulatum, Coccidioides spp., Penicillium spp.</td>
</tr>
</tbody>
</table>

It should be noted that in these cases, patients often receive unnecessary antibiotic treatment.

Rarely in the context of disseminated infections in patients with low CD4 count.

Clinical presentation

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

Five common clinical presentations can help identify cases that require specific treatment and management:

1. Patients with **watery diarrhoea**: in these patients, the most likely cause is viral (mostly rotavirus and norovirus). A mild fever and vomiting may also occur. The main risk is severe dehydration and management is symptomatic (e.g., fluid replacement).

2. Patients with **bloody diarrhoea** (dysentery or invasive diarrhoea with damage to the intestinal mucosa): in these patients, the most likely cause are bacteria, mostly *Shigella* spp., *Campylobacter* spp., *Salmonella* spp. or enterotoxigenic *Escherichia coli* (ETEC).
These cases may benefit from antibiotic treatment. In addition to dehydration these infections can be complicated by sepsis and malnutrition. *Schistosoma* (only *Schistosoma mansoni* and *Schistosoma japonicum*, the intestinal species) and *Entamoeba histolytica* can rarely also cause bloody diarrhoea weeks or months after the infection (often these infections are responsible for chronic rather than acute bloody diarrhoea).

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

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

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

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

**Table 4 Classification of dehydration**

| Severe dehydration (at least two signs from the list on the right must be present) | • Lethargy and/or unconsciousness  
• Sunken eyes  
• Inability to drink  
• Skin pinch goes back very slowly (≥ 2 seconds) |
|---|---|
| Some dehydration (at least two signs from the list on the right must be present) | • Restlessness, irritability  
• Sunken eyes  
• Drinks eagerly, is thirsty |
| No dehydration | Too few signs to classify as some or severe dehydration |


**Laboratory tests**

I. **Patient microbiology tests**

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

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

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

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

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

RDT: rapid diagnostic test.

Possible specimens include: stool and rectal swab.

**II. Other tests**

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

**III. Using microbiology surveillance data**

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

**Imaging**

Routine imaging is not needed for acute diarrhoeal disease.

**“No antibiotic care”**

Rehydration is the main treatment for acute diarrhoeal disease (oral or intravenous). In children, treating any diarrhoea with an oral rehydration solution (ORS) is recommended. An oral rehydration solution is composed of clean water, sugar and salt (“make-at-home” ORS is composed of 1L water, 6 tablespoons of sugar, 1/2 tablespoon of salt, more information available in the EML/c - https://list.essentialmeds.org/recommendations/1112). In addition, zinc tablets
(10–20 mg/day) for 10–14 days are usually recommended to shorten the duration and severity of symptoms (3).

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

**Antibiotic treatment**

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

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

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

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

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

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

<table>
<thead>
<tr>
<th></th>
<th>Adults</th>
<th>Children</th>
<th>Total treatment duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First Choice</strong></td>
<td><strong>Ciprofloxacin</strong> (oral): 500 mg given every 12 hours</td>
<td><strong>Ciprofloxacin</strong> (oral): 10-20 mg/kg/dose given every 12 hours</td>
<td>3 days</td>
</tr>
<tr>
<td></td>
<td>Oral weight bands:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3–&lt;6 kg: 50 mg given every 12 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>6–&lt;10 kg: 100 mg given every 12 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>10-&lt;15 kg: 150 mg given every 12 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>15-&lt;20 kg: 200 mg given every 12 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>20-&lt;30 kg: 300 mg given every 12 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥ 30 kg: Use adult dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Second Choice</strong></td>
<td><strong>Oral options</strong></td>
<td><strong>Oral options</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Azithromycin (oral): 500 mg given once a day</td>
<td>Azithromycin (oral): 10 mg/kg/dose given once a day</td>
<td>Azithromycin: 4 days</td>
</tr>
</tbody>
</table>
followed by 250 mg given once a day for 3 days
OR
Cefixime\(^c\) (oral): 400 mg given once a day
OR
Sulfamethoxazole+trimethoprim\(^c,d\) (oral): 800 mg + 160 mg given every 12 hours

**Parenteral option**
Ceftriaxone\(^c\) (IV/IM): 1 g given once a day

**Cefixime\(^c\)** (oral): 10 mg/kg/dose given once a day

OR
Sulfamethoxazole+trimethoprim\(^c,d\) (oral): 20 mg/kg + 4 mg/kg given every 12 hours

Oral weight bands
(mg of the sulfamethoxazole/trimethoprim component):
3–<6 kg: 100 mg/20 mg given every 12 hours
6–<10 kg: 200 mg/40 mg given every 12 hours
10–<15 kg: 400 mg/80 mg given every 12 hours
15–<20 kg: 400 mg/80 mg given every 12 hours
20–<30 kg: 400 mg/80 mg given every 12 hours
≥ 30 kg: Use adult dose

**Parenteral option**
Ceftriaxone\(^c\) (IV/IM): 80 mg/kg/dose given once a day

<table>
<thead>
<tr>
<th>Parenteral option</th>
<th>Ceftriaxone: 3 days</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cefixime: 3 days (adults), 5 days (children)</td>
</tr>
<tr>
<td></td>
<td>Sulfamethoxazole +trimethoprim: 5 days</td>
</tr>
</tbody>
</table>

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

\(^a\) If symptoms do not resolve within 24–48 hours of treatment, consider *Entamoeba histolytica* or *Giardia intestinalis* as possible causes and provide appropriate treatment.

\(^b\) Azithromycin is preferred in case of high prevalence of ciprofloxacin resistance among bacteria frequently associated with acute infectious diarrhoea (e.g. *Salmonella* spp., *Shigella* spp.).

\(^c\) Cefixime, ceftriaxone and sulfamethoxazole+trimethoprim are not active against *Campylobacter* spp.

\(^d\) Ideally, sulfamethoxazole+trimethoprim should only be used if local data suggest susceptibility or if the isolated strain is susceptible. As per WHO 2005 guidelines, this antibiotic should not be used empirically when shigellosis is suspected (132).

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

**Table 7 Empiric antibiotic treatment for cholera**

Antibiotic treatment for cholera should only be considered in the context of an outbreak and not based on the degree of dehydration. The rationale of giving an antibiotic during outbreaks is to reduce transmission but the cornerstone of treatment remains rehydration.
Doxycycline (oral): 300 mg, single dose (or 100 mg given every 12 hours for 3 days if single dose is not tolerated)

**Second choice**

Ciprofloxacin (oral): 1 g, single dose

Ciprofloxacin (oral): 10-20 mg/kg, single dose

OR

Doxycycline (oral):

- <45 Kg (<12 years): 2 to 4 mg/kg, single dose
- >45 Kg (>12 years): 300 mg, single dose

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

Azithromycin is preferred because of the decreasing susceptibility of cholera to tetracyclines and fluoroquinolones. Because of the long half-life of azithromycin, it should only be recommended for outbreak situations, where single-dose treatment is especially useful.

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

**Prevention**

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

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

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


Definition

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

Microbiology epidemiology

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

Pathophysiology

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

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

**Clinical presentation**

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

**Laboratory tests**

**I. Patient microbiology tests**

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

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

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

\(^b\) The gold standard for diagnosis but it is often not feasible to do.

\(^c\) Low sensitivity and not useful in the early phase (1\(^{st}\) week) of disease when the test is often negative.

II. Other tests

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

III. Using microbiology surveillance data

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

Imaging

Routine imaging is not needed.

Antibiotic treatment

In cases of enteric fever, antibiotic treatment should be started promptly because delays are associated with higher risk of complications and severe disease. In general, antibiotic treatment is given to shorten the duration of symptoms and to reduce the risk of complications, such as intestinal perforation and chronic carriage (chronic carriers are asymptomatic persons who continue to harbor the pathogen for months or even years after their initial infection and can transmit the infection). Fever usually decreases slowly, after around 3–5 days of effective treatment. Mild cases can be treated as outpatients with oral treatment, while severe cases should be treated as inpatients with systemic intravenous treatment.
The choice of oral antibiotic if possible, should be based on the sensitivity of the isolated pathogen. When choosing empiric treatment, the local prevalence of fluoroquinolone resistance should be considered because of the increasing number of resistant isolates, mostly in Asia(141). In these settings, a third-generation cephalosporin or azithromycin are appropriate options because resistance to these antibiotics is still low in most settings (< 5% for ceftriaxone and only sporadic cases with resistance to azithromycin). Of note, antibiotics that were widely used in the 1980s and 1990s but fell in disuse because of resistance or toxicity concerns (e.g. ampicillin, chloramphenicol and sulfamethoxazole+trimethoprim) are again effective in some settings (mostly in Asia). However, the empiric use of these “old” first options for treatment is discouraged because it could prompt a rebound of multidrug-resistant organisms.

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

**Combination treatment**

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

**Table 2 Empiric antibiotic treatment for enteric fever**

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

**Severe cases**
Ceftriaxone\(^b\) (IV): 2 g given once a day

Ceftriaxone\(^b\) (IV): 80 mg/kg/dose given once a day

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

\(^a\)It should be noted that there is no clearly defined prevalence of resistance in a certain setting that defines low versus high risk of fluoroquinolone resistance.

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

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

Prevention

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

<table>
<thead>
<tr>
<th>Box 1 Other relevant WHO documents (please check regularly for updates)</th>
</tr>
</thead>
</table>

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

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

Pathophysiology

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

Epidemiology

Bacterial skin infections occur worldwide and can affect all age groups; erysipelas is more
frequent in children and elderly patients. In 2013, skin diseases (not limited to bacterial
infections) were the fourth leading cause of non-fatal diseases(147). Cellulitis, the most common
skin infection, accounted for 0.04% (4 in 10,000) of the overall burden of all diseases combined
in 2013. It was the only skin condition that showed a significant decrease (−13.2%) between 2005
and 2013 in disability-adjusted life years (DALYs), a proxy for morbidity and mortality; this
decrease was attributed to reduced mortality(147). In 2017, the Global Burden of Disease study reported 43 million new cases of cellulitis worldwide(31). Diabetes, peripheral arterial disease, HIV infection and other causes of immunosuppression are risk factors for severe skin infections.

Microbiology epidemiology

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

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

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

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

Clinical presentation (only mild cases are covered)

Table 2 Glossary for skin lesions

<table>
<thead>
<tr>
<th>Type of skin lesion</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bulla</td>
<td>Large fluid-filled blister</td>
</tr>
<tr>
<td>Papule</td>
<td>Small, elevated lesions that can be palpated</td>
</tr>
<tr>
<td>Pustule</td>
<td>Small blister or pimple</td>
</tr>
<tr>
<td>Vesicle</td>
<td>Small fluid-filled blister</td>
</tr>
</tbody>
</table>
**Impetigo**

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


**Erysipelas**

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


**Cellulitis**

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

**Laboratory tests**

**I. Patient microbiology tests**

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

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

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

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

<table>
<thead>
<tr>
<th>Diagnostic test</th>
<th>Purpose of the test</th>
<th>Settings where the test should be available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tissue swab culture</td>
<td>Initial step to detect and identify bacterial and fungal species for selection of appropriate antibiotic regimens</td>
<td>Health care facilities with clinical laboratories</td>
</tr>
</tbody>
</table>

**II. Other tests**

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

**III. Using microbiology surveillance data**

Routine surveillance is not helpful in informing empiric guidance.

**Imaging**

Routine imaging of mild cases of impetigo, erysipelas and cellulitis is not necessary. However, initial imaging (e.g. ultrasound, X-ray) may be considered if an abscess or subdermal involvement
are suspected. In these cases, management often requires a surgical approach (e.g. incision and
drainage in case of abscess).

Topical treatment

(only for localized non-bullous impetigo)

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

Antibiotic treatment

(widespread impetigo, erysipelas and cellulitis)

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

<table>
<thead>
<tr>
<th>Adults</th>
<th>Children</th>
<th>Total treatment duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin+clavulanic acid (oral): 500 mg + 125 mg given every 8 hours OR Cefalexin (oral): 500 mg given every 8 hours OR Cloxacillin or flucloxacillin (oral): 500 mg given every 8 hours</td>
<td>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</td>
<td>5 days d</td>
</tr>
</tbody>
</table>
20-<30 kg: 1000 mg of amoxicillin/dose given every 12 hours
\[ \geq 30 \text{ kg: Use adult dose} \]

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
- 20-<30 kg: 625 mg given every 12 hours

\[ \geq 30 \text{ kg: Use adult dose} \]

OR

Cloxacillin* or Flucloxacillin (oral):

- Neonates: 25-50 mg/kg/dose given every 12 hours
- Children: 25 mg/kg/dose given every 6 hours

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

\[ \geq 30 \text{ kg: Use adult dose} \]

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

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

bOral liquid must be refrigerated after reconstitution as clavulanic acid is rapidly metabolized in high ambient temperatures.

cThe WHO Pocket book of hospital care for children(23) suggests amoxicillin plus cloxacillin. However, cloxacillin can be safely used as a single antibiotic option because it has good activity against both methicillin-susceptible Staphylococcus aureus and Streptococcus pyogenes (often referred to as group A Streptococcus). Amoxicillin alone is not suitable because it has variable activity against methicillin-susceptible Staphylococcus aureus.

dThe optimal duration of antibiotic treatment is not known(150); duration is often individualized based on clinical response.

ACCESS antibiotics are indicated in green, WATCH antibiotics in yellow and RESERVE antibiotics in red.
Burn wound-related infections

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.

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

- Burns (Fact sheet)

Definition

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

Pathophysiology

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

Epidemiology

Burn wounds are an important public health problem in low- and middle-income countries where they are among the leading causes of disability-adjusted life years (DALYs) lost. An estimated 180,000 deaths every year are caused by burns and most occur in LMIC (151). Infections
(including but not limited to the skin) are the most frequent complications encountered in patients with burn injuries and are the leading cause of death in patients with severe wounds. Skin infections (e.g. cellulitis) are in general the first infections to occur, usually in the first week of the injury.

Microbiology epidemiology

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

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

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

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

Clinical presentation

Diagnosis of a burn wound infection requires clinical examination. For this reason, burn wounds should be monitored for signs of infection, such as increased pain and redness or swelling of the area surrounding the wound. Redness alone may represent inflammation and does not necessarily indicate infection. Signs of invasive infection (e.g. change in the colour of the wound, signs of sepsis) should also be carefully monitored. Please also refer to the chapter on sepsis if suspected. Patients with burn injuries may also develop other complications dependent on their supportive care such as pneumonia, urinary tract infections or catheter-related infections.
Laboratory tests

I. Patient microbiology tests

In mild cases of infection of a burn wound where there are no signs of systemic infection, routine testing (including wound cultures) is not required. These tests are not needed because identifying the causative pathogen in mild cases will not benefit the patient as it will not change management. In severe cases, blood cultures can be considered. Please also refer to the chapter on sepsis if suspected.

II. Other tests

Routine testing in mild cases with no signs of systemic infection is not required. In addition, because of the inflammatory response associated with the burn itself, results of laboratory tests (e.g. biomarkers of infection) may be of limited help.

In severe cases, certain laboratory tests can be considered to make an initial assessment of the patient and to help guide the duration of antibiotic treatment. Please also refer to the chapter on sepsis if suspected.

III. Using microbiology surveillance data

Targeted clinical surveys of blood stream infection isolates at a local unit level may be helpful to inform empiric guidance. Empiric guidance should not usually be informed by routine surface culture skin swabs.

Imaging

Routine imaging is not required unless a complication is suspected.

Management

Irrigation and debridement of necrotic tissue to prevent infection of the burn wound is suggested. Appropriate daily cleaning and dressing of the wound are the cornerstone of treatment.

Infection control procedures should be meticulously observed to prevent transmission of multidrug-resistant organisms.

Topical treatment

Local antiseptics could be considered based on local protocols.
Preventive antibiotic use

Routine use of antibiotics to prevent infection in burn wounds should be avoided if there are no signs of systemic infection or in otherwise healthy patients. Use of antibiotics as a preventive treatment is controversial because there is no clear evidence that it can prevent infection (153, 154). In addition, such use can lead to colonization with resistant microorganisms, so caution is needed.

Antibiotic treatment

Empiric treatment of mild infections should include antibiotics with good activity against the most likely pathogens (Staphylococcus aureus and Streptococcus spp.). Antibiotic options are shown in Table 2. Empiric treatment against community-acquired methicillin-resistant Staphylococcus aureus (MRSA) may be considered and should be based on local prevalence of invasive isolates and individual patient risk factors (e.g. known MRSA colonization).

It is important to note that because hospital-acquired multidrug-resistant organisms are frequently found in burn units the results of microbiology cultures should where possible guide antibiotic treatment. Empiric use of RESERVE group antibiotics should, however, generally be avoided. Please also refer to the chapter on sepsis if suspected.

Table 2 Empiric antibiotic treatment for mild burn wound infections

It is important to note that only infected wounds should be treated with antibiotics.

<table>
<thead>
<tr>
<th>Adults</th>
<th>Children</th>
<th>Total treatment duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Amoxicillin+clavulanic acid</strong> (oral): 500 mg + 125 mg given every 8 hours</td>
<td><strong>Amoxicillin+clavulanic acid</strong> (oral): 40-50 mg/kg/dose of amoxicillin component given every 12 hours OR 30 mg/kg/dose given every 8 hours</td>
<td>5 days</td>
</tr>
<tr>
<td>OR <strong>Cefalexin</strong> (oral): 500 mg given every 8 hours</td>
<td>Oral weight bands: 3–6 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</td>
<td></td>
</tr>
<tr>
<td>OR <strong>Clindamycin</strong> or <strong>Clavuloxin</strong> (oral): 500 mg given every 8 hours</td>
<td>OR</td>
<td></td>
</tr>
</tbody>
</table>


**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
- 20-<30 kg: 625 mg given every 12 hours
- ≥ 30 kg: Use adult dose

**OR**

**Cloxacillin** or **Flucloxacillin** (oral):
- Neonates: 25-50 mg/kg/dose given every 12 hours
- Children: 25 mg/kg/dose given every 6 hours

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

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

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

Oral liquid must be refrigerated after reconstitution as clavulanic acid is rapidly metabolized in high ambient temperatures.

The **WHO Pocket book of hospital care for children** suggests amoxicillin plus cloxacillin; however, cloxacillin can be safely used as a single antibiotic option since it has good activity against both methicillin-susceptible *Staphylococcus aureus* and *Streptococcus pyogenes*. Amoxicillin alone is not suitable because it has variable activity against methicillin-susceptible *Staphylococcus aureus*.

ACCESS antibiotics are indicated in green, **WATCH** antibiotics in yellow and RESERVE antibiotics in red.
Wound and bite-related infections

This chapter does not include severe infections, surgical wounds and management of bites from poisonous animals or arthropods (insects, ticks, mites).

Please refer to the specific chapters about other skin and soft tissue infections – burn wounds, impetigo / erysipelas / cellulitis, necrotizing fasciitis, pyomyositis - if these infections are suspected.

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.

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

- 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](https://apps.who.int/iris/handle/10665/254583)
Skin wounds include any traumatic injury characterized by damage to and exposure of deeper skin tissue. Examples of skin wounds include those caused by human or animal bites or burns, traffic road injuries, gun shots and stab wounds. The severity of the clinical findings can vary from mild wounds with no systemic involvement to severe infections including tetanus (infection by *Clostridium tetani*) and gas gangrene (infection by gas producing bacteria such as *Clostridium perfringens*).

Skin wounds predispose to infection because they facilitate entry of pathogens from the patient’s own skin microbiota and the environment into the wound. With bites, pathogens from the oral cavity of the biting animal can also penetrate the skin.

### Epidemiology

#### Traumatic wounds

Road traffic injuries occur worldwide but the majority of deaths (>90%) occur in low and middle-income countries (157, 158). Overall each year about 1.3 million people die as a result of road traffic accidents with many more suffering from non-fatal injuries (between 20 and 50 million people)(157, 158). In young people (under 30 years of age), this is the leading cause of death.

In 2016, the Global Burden of Disease study reported about 251,000 deaths from firearm injuries globally (outside of war settings), the majority caused by homicides (64%), followed by suicides (27%) and unintentional firearm deaths (9%)(159). Overall, the global age-standardized rate of firearm deaths decreased by about 0.9% per year between 1990 and 2016 with differences between countries (159). Most firearm injury deaths occur among people aged 20 to 24 years(159).

#### Bite wounds

Human and animal bites occur worldwide; most cases are caused by animals (dogs in > 90% of cases)(160). Less frequently, bites are caused by other mammals such as cats, rodents (e.g. rats,
mice) and bats. In certain countries (e.g. in Africa and in South-East Asia), snake and monkey bites are also frequently reported. Children are more likely to have animal bites (161). The risk of developing a bacterial infection from a dog bite is unclear and depends on many different factors related to the patient (i.e. the person bitten), the characteristics of the bite (depth, location) and the initial management of the bite. However, available data suggest that in 10–20% of cases of dog bites, the wound will become infected (161, 162). In comparison, wounds caused by cat bites have a higher risk of becoming infected (up to 50%) because of the deeper penetration of their teeth (161, 162).

Animal bites are a significant risk factor for transmission of rabies, especially in settings where prophylaxis with rabies vaccine in domestic and wild animals is not routinely given. The Global Burden of Disease study estimated 13.400 new cases of rabies worldwide in 2017 (31). Deaths from rabies and dog bites are a problem mostly in low- and middle-income countries where post-exposure treatment and appropriate access to health care may be lacking (160).

Small rodents are vectors of numerous pathogens and are a reservoir for many zoonotic diseases. Rodents (mostly rats) are also responsible for an appreciable proportion of bites to humans (163). Rat bites primarily affect people (mostly children < 5 years) living in poorer conditions in rat-infested environments, including in high-income countries. Most bites occur on the face and hands and usually occur at night while sleeping. Although rare, rat bites can cause severe infections, such as rat-bite fever (caused by *Streptobacillus moniliformis* or *Spirillum minus*). Tetanus infection can also be caused by bites and it should be considered in patients who have not been immunized against the infection. In 2019, almost 15.000 cases of tetanus were reported globally (164).

### Microbiology epidemiology

#### Traumatic wounds

In most cases, infections from traumatic wounds are polymicrobial with a mix of human skin microbiota and environmental organisms (Table 1).

**Table 1: Pathogens most frequently associated with traumatic skin wounds in descending order of frequency (except bites, presented in another table)**

<table>
<thead>
<tr>
<th>Bacteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most cases&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td><em>Streptococcus</em> spp.</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em> (including MRSA strains)</td>
</tr>
<tr>
<td>More rarely</td>
</tr>
<tr>
<td>Anaerobes</td>
</tr>
<tr>
<td>Enterobacterales</td>
</tr>
<tr>
<td><em>Enterococcus</em> spp.</td>
</tr>
<tr>
<td><em>Clostridium tetani</em> (soil contaminant)</td>
</tr>
</tbody>
</table>

MRSA: methicillin-resistant *Staphylococcus aureus*.

<sup>a</sup>Mostly Gram-positive pathogens from the skin microbiota.
## Bite wounds

In infections from bites, causative pathogens may also be from the animal/human oral microbiota with differences among species (Table 2) (8,9).

### Table 2 Pathogens most frequently associated with bites

<table>
<thead>
<tr>
<th>Species causing the bite</th>
<th>Pathogens</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Human</strong></td>
<td><strong>Commonly isolated pathogens</strong>&lt;br&gt;Anaerobes from the oral microbiota such as <em>Prevotella</em> and <em>Fusobacterium</em> spp..&lt;br&gt;<em>Streptococcus</em> spp..&lt;br&gt;<em>Staphylococcus aureus</em>&lt;br&gt;<strong>Other non-bacterial pathogens that can be transmitted through human bites</strong>&lt;br&gt;Hepatitis B virus&lt;br&gt;Hepatitis C virus&lt;br&gt;HIV</td>
</tr>
<tr>
<td><strong>Cat</strong></td>
<td><strong>Commonly isolated pathogens</strong>&lt;br&gt;Anaerobes such as <em>Bacteroides</em> spp., <em>Cutibacterium</em> spp., <em>Fusobacterium</em> spp., <em>Peptostreptococcus</em> spp. and <em>Prevotella</em> spp..&lt;br&gt;<em>Pasteurella multocida</em>&lt;br&gt;<em>Staphylococcus aureus</em>&lt;br&gt;<strong>Other bacterial pathogens that can be transmitted through cat bites</strong>&lt;br&gt;<em>Bartonella henselae</em> (agent of cat-scratch disease)&lt;br&gt;<em>Francisella tularensis</em> (agent of tularemia)&lt;br&gt;<strong>Other non-bacterial pathogens that can be transmitted through cat bites</strong>&lt;br&gt;Rabies virus&lt;br&gt;<strong>Soil contaminants</strong>&lt;br&gt;<em>Clostridium tetani</em></td>
</tr>
</tbody>
</table>
### Dog

**Commonly isolated pathogens**
- Anaerobes such as *Bacteroides* spp., *Cutibacterium* spp., *Fusobacterium* spp., *Peptostreptococcus* spp. and *Prevotella* spp.
- *Capnocytophaga canimorsus*
- *Pasteurella multocida*
- *Staphylococcus aureus*

**Other pathogens that can be transmitted through dog bites**
- *Francisella tularensis* (agent of tularemia)
- *Leptospira* spp.
- Rabies virus

**Soil contaminants**
- *Clostridium tetani*

### Monkey

**Anaerobes such as Bacteroides spp., Cutibacterium spp., Fusobacterium spp., Peptostreptococcus spp. and Prevotella spp.**

- *Streptococcus* spp.
- *Staphylococcus aureus*

**Other non-bacterial pathogens that can be transmitted through monkey bites**
- Hepatitis B virus (macaques)
- Herpes B virus
- Monkeypox virus
- Rabies virus

**Soil contaminants**
- *Clostridium tetani*
<table>
<thead>
<tr>
<th>Rodent(^a) (e.g. mice, rats)</th>
<th><em>Pasteurella multocida</em></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Other bacterial pathogens that can be transmitted through rodent bites</strong></td>
<td></td>
</tr>
<tr>
<td><em>Francisella tularensis</em> (agent of tularemia)</td>
<td></td>
</tr>
<tr>
<td><em>Leptospira</em> spp.</td>
<td></td>
</tr>
<tr>
<td><em>Spirillum minor</em> (agent of rat-bite fever in Asia)</td>
<td></td>
</tr>
<tr>
<td><em>Streptobacillus moniliformis</em> (agent of rat-bite fever in North America)</td>
<td></td>
</tr>
<tr>
<td><strong>Other non-bacterial pathogens that can be transmitted through rodent bites</strong></td>
<td></td>
</tr>
<tr>
<td>Rabies virus</td>
<td></td>
</tr>
<tr>
<td>Monkeypox virus</td>
<td></td>
</tr>
<tr>
<td><strong>Soil contaminants</strong></td>
<td></td>
</tr>
<tr>
<td><em>Clostridium tetani</em></td>
<td></td>
</tr>
<tr>
<td>Reptile (e.g. crocodiles, lizards, snakes, turtles)</td>
<td>Anaerobes such as <em>Prevotella</em> and <em>Fusobacterium</em> spp.</td>
</tr>
<tr>
<td>Enterobacterales</td>
<td></td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td></td>
</tr>
<tr>
<td><em>Salmonella</em> spp.</td>
<td></td>
</tr>
<tr>
<td><strong>Soil contaminants</strong></td>
<td></td>
</tr>
<tr>
<td><em>Clostridium tetani</em></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Mammals.

### Clinical presentation

(only mild cases are covered)

Wounds range in severity from minor superficial abrasions to deep wounds with involvement and destruction of the deep tissues. An infection may or may not be present at the time of clinical evaluation. Usually signs and symptoms of infection appear > 12 hours after the injury. Superficial infections may manifest with signs and symptoms of cellulitis characterized by redness, swelling, warmth, lymphangitis and pain of the area surrounding the wound. Fever (> 38.0 °C) may be present. Patients should also be carefully monitored for signs of invasive infection (e.g. change in colour of the wound due to necrosis and signs of sepsis).
Laboratory tests

I. Patient microbiology tests

In mild cases with no signs of systemic infection, routine testing (including wound cultures) is not required. These tests are not needed because identifying the causative pathogen in mild cases is rare even when microbiologic tests are performed, most infections are polymicrobial and microbiologic results will not affect management of the condition in most cases.

II. Other tests

Routine testing in mild cases with no signs of systemic infection is not required.

III. Using microbiology surveillance data

Routine surveillance is not helpful in informing empiric guidance.

Imaging

Routine imaging is not required. Imaging may be considered in certain cases based on the size and depth of the wound, particularly if a complication such as development of an abscess or necrotizing infection is suspected.

“No antibiotic care”

Initial management of wounds

It is important to provide rapid and appropriate treatment of a wound after an injury has occurred to minimize the risk of infection. For prevention and management of wound infections, please refer to the 2013 WHO guidance publication (155).

Adequate cleaning and debridement are the cornerstone of initial treatment. It is important to thoroughly wash and flush the wound for about 15 minutes with soap or detergent and a lot of clean water, followed by debridement and immobilization of the wound.

Post-exposure prophylaxis

Traumatic wounds

After any wound, the risk of tetanus needs to be promptly evaluated to provide adequate post-exposure prophylaxis by vaccination +/- passive immunization using tetanus immunoglobulin when needed according to local / international recommendations.

- For tetanus post-exposure prophylaxis, please refer to the most recent WHO position paper (2017)(165).
Bite wounds

With animal bites, in addition to the risk of tetanus, the risk of rabies needs also to be rapidly evaluated based on the exposure category to provide adequate post-exposure prophylaxis when needed (Table 3).

- For rabies post-exposure prophylaxis, please refer to the most recent WHO position paper (2018)(166).

With human bites, the risk of hepatitis B and C virus and HIV transmission needs also to be evaluated and post-exposure prophylaxis offered when applicable(167, 168).

**Table 3 Risk of rabies exposure according to the type of contact with the animal suspected of having rabies(166)**

<table>
<thead>
<tr>
<th>Categorya</th>
<th>Type of contact</th>
<th>Risk of exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category I</td>
<td>Touching or feeding animals, animal licks on intact skin</td>
<td>No exposure</td>
</tr>
<tr>
<td>Category II</td>
<td>Nibbling of uncovered skin, minor scratches or abrasions without bleeding</td>
<td>Exposure</td>
</tr>
<tr>
<td>Category III</td>
<td>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</td>
<td>Severe exposure</td>
</tr>
</tbody>
</table>

aThe category of exposure determines the indicated post-exposure prophylaxis procedure.

Preventive antibiotic use

Routine use of antibiotics to prevent infection of the wound is not required in most cases (unless there are systemic signs of infection in which case antibiotics would be used as treatment and not as prophylaxis) and should be discouraged.

Preventive antibiotic use may be considered in very few specific cases where the potential risk of infection is judged to outweigh the risk of “overusing” antibiotics.

This includes:

- Wounds in high-risk clinical areas (e.g. face, hands, areas near a joint)

There is though no clear evidence that use of antibiotic can prevent the infection after wounds (including bite wounds). In addition, such use exposes the patient to the negative effects of antibiotic use (alteration of the intestinal microbiota; selection of resistant microorganisms).
Antibiotic treatment

If signs and symptoms of infection are present, empiric treatment should include antibiotics with good activity against the most likely pathogens (*Staphylococcus aureus* and *Streptococcus* spp. and anaerobic organisms). With animal bites, the type of animal should also be considered (Table 2), but in general, empiric treatment against both aerobic and anaerobic bacteria is required, since most infections are caused by multiple pathogens (polymicrobial infections). Empiric treatment against community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) is usually not required. If cellulitis around the wound develops, refer to the chapter on bacterial impetigo, erysipelas and cellulitis. Antibiotic options for empiric treatment are indicated in Table 4.

**Table 4 Empiric antibiotic treatment for mild infections from traumatic wounds and bites**

It is important to note that only infected wounds should be treated with antibiotics.

<table>
<thead>
<tr>
<th>Adults</th>
<th>Children</th>
<th>Total treatment duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Amoxicillin + clavulanic acid</strong>&lt;sup&gt;a&lt;/sup&gt; (oral): 500 mg + 125 mg given every 8 hours OR <strong>Cefalexin</strong> (oral): 500 mg given every 8 hours OR <strong>Cloxicillin</strong> or <strong>Flucloxacillin</strong> (oral): 500 mg given every 8 hours</td>
<td><strong>Amoxicillin + clavulanic acid</strong>&lt;sup&gt;a&lt;/sup&gt;,&lt;sup&gt;c&lt;/sup&gt; (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 OR <strong>Cefalexin</strong> (oral): 25 mg/kg/dose given every 12 hours 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</td>
<td>3 days (preventive treatment of wounds at high risk of infection) 5 days (treatment of infected wounds)</td>
</tr>
</tbody>
</table>
OR

<table>
<thead>
<tr>
<th>Cloxacillin$^a$ or flucloxacillin (oral):</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Neonates: 25-50 mg/kg/dose given every 12 hours</td>
</tr>
<tr>
<td>• Children: 25 mg/kg/dose given every 6 hours</td>
</tr>
</tbody>
</table>

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

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

$^a$ Amoxicillin+clavulanic acid is the preferred choice for bite wounds because it gives a better coverage of anaerobes.

$^b$ Cloxacillin does not provide good activity against anaerobic bacteria (therefore it is not the preferred option for the treatment of infected bite wounds). Cloxacillin (or dicloxacillin or flucloxacillin) has a narrower spectrum of antibacterial activity compared to amoxicillin+clavulanic acid and cefalexin while maintaining good efficacy in cases of mild skin infections. Therefore, from an antibiotic stewardship perspective, it would be the preferred option whenever possible (except for bite wounds). Cloxacillin, dicloxacillin and flucloxacillin are preferred for oral administration because of better bioavailability (i.e. the extent at which the medicine enters systemic circulation, thereby accessing the site of action).

$^c$ Oral liquid must be refrigerated after reconstitution as clavulanic acid is rapidly metabolized in high ambient temperatures.

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

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)

- WHO guideline for the laboratory diagnosis of sexually transmitted infections including HIV, 2013 (https://apps.who.int/iris/handle/10665/85343)

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

Chlamydial urogenital infection is a sexually transmitted infection caused by certain biovars of the bacterium *Chlamydia trachomatis*.

Microbiology epidemiology

Chlamydial urogenital infection is caused by *Chlamydia trachomatis*, an intracellular Gram-negative bacterium. There are several strains of *Chlamydia trachomatis* and not all are associated with sexually transmitted infections (see the chapter on trachoma). Chlamydial urogenital infections associated with sexually transmitted infection are mostly genital tract biovars (serovars D to K) and, more rarely, lymphogranuloma venereum biovar (serovars L1, L2, L3). Lymphogranuloma venereum is an ulcerative disease extending to regional lymph nodes (often the inguinal and anorectal area) and is more common in men (see below). It is endemic in many tropical and sub-tropical regions, in other settings infection is most commonly seen among men who have sex with men.

Pathophysiology

*Chlamydia trachomatis* infects the mucosa of the urogenital tract during sexual contact and produces a local inflammatory response that causes vaginal, urethral or anal discharge. Invasive infections caused by more invasive serovars of *Chlamydia trachomatis* can also spread to regional lymph nodes.

Epidemiology

Chlamydial urogenital infection is one of the most common sexually transmitted infections worldwide, including in low-income settings where it is probably underreported(169, 170). Young sexually active adults are at particularly high risk. Undiagnosed and untreated, chlamydial urogenital infections can lead to complications such as pelvic inflammatory disease (infection of the upper female reproductive tract), ectopic pregnancy and infertility in women(171, 172). Maternal infection can cause serious health problems to the child such as preterm birth, low birth weight or conjunctivitis. The 2021 WHO Global progress report on HIV, viral hepatitis and sexually transmitted infections reported an estimated 128 million new chlamydial infections in 2020 among adults aged 15 to 49 years of age(173).

Clinical presentation

Signs and symptoms of chlamydial infection mostly overlap with those of gonococcal infection. In most cases the infection is asymptomatic, and it is therefore impossible to determine how long a person has been infected. Even in the absence of symptoms, infected individuals can transmit the infection.
When symptoms occur (usually 1-2 weeks after being infected), particularly in men, the most common clinical presentation is acute urethritis characterized by profuse usually clear urethral discharge and dysuria. Most women with chlamydial cervical infection are asymptomatic. The ones who may be symptomatic have vaginal discharge, dyspareunia (painful intercourse) and dysuria. Several women may have lower abdominal pain or pelvic tenderness because of ascending infection, causing pelvic inflammatory disease.

In both sexes (but in males more than females), symptoms of acute proctitis with pain, pruritus, discharge and bleeding of the rectum may occur. Pharyngitis (mostly manifesting as a mild sore throat) and conjunctivitis are other conditions that usually coexist with genital infection.

**Lymphogranuloma venereum** is characterized by inguinal or femoral lymphadenopathy (usually unilateral) with or without an associated primary lesion. The classic lesion is a transient, ulcerative lesion or a papule usually located on the genitalia or rectum. In many cases the lesion may remain unnoticed (e.g. it may be completely asymptomatic in women when located on the cervix or the infection can sometimes present with symptoms of acute urethritis in men). Rectal exposure can cause proctitis with pain, pruritus, discharge and bleeding of the rectum.

**Laboratory tests**

**I. Patient microbiology tests**

Molecular testing has greatly improved the detection of *Chlamydia trachomatis* (and *Neisseria gonorrhoeae*) among both symptomatic and asymptomatic men and women and has become the recommended reference standard technology to diagnose and screen populations for *C. trachomatis* and *N. gonorrhoeae* (Table 1 also indicates the types of specimens that can be used for this purpose).

For more comprehensive information on the diagnosis of chlamydial infection, please refer to the most recent WHO guideline for the laboratory diagnosis of sexually transmitted infections – most recent version at publication of this Handbook was issued in 2013 (174). Please check the WHO website regularly for possible updates. Patients with chlamydial urogenital infection should be offered testing for HIV and other sexually transmitted infections (e.g. hepatitis B, hepatitis C, gonococcal infection and syphilis). Test of cure (i.e. testing after the end of treatment) could be considered in pregnant women 3-4 weeks after the end of treatment. Tests to consider when chlamydial infection is suspected are listed in Table 1. Additional tests for other sexually transmitted infections that could be considered when chlamydial urogenital infection is confirmed or suspected are shown in Table 2. Surveillance including etiologic studies of STI syndromes will be important to inform local and national guidance.

If symptoms persist at review, partner notification and treatment history should be checked. People with recurrent or persistent infection, should be referred to a centre with laboratory capacity to diagnose *Neisseria gonorrhoeae, Chlamydia trachomatis, Mycoplasma genitalium* and *Trichomonas vaginalis* and to test for antibiotic-resistant *N. gonorrhoeae* and *M. genitalium*. 


**Table 1 Microbiology tests to consider when chlamydial infection is suspected as indicated in the WHO EDL (54)**

<table>
<thead>
<tr>
<th>Diagnostic test</th>
<th>Purpose of the test</th>
<th>Settings where the test should be available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Qualitative test for <em>Chlamydia trachomatis</em> and <em>Neisseria gonorrhoeae</em> infections (i.e. nucleic acid amplification test) $^{a,b}$</td>
<td>To diagnose chlamydial and/or gonorrhoeal urogenital disease and extragenital infection</td>
<td>Healthcare facilities with clinical laboratories</td>
</tr>
<tr>
<td><strong>This is the recommended reference standard</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microscopy ($^{c}$)</td>
<td>To assess microbial morphology, and presence or absence of white blood cells</td>
<td>Healthcare facilities with clinical laboratories</td>
</tr>
<tr>
<td>Gram stain of vaginal and urethral discharge will usually show the presence of leukocytes (&gt;10 leukocytes/high power field for urethral discharge and &gt;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 (<em>Neisseria gonorrhoeae</em> is an intracellular diplococcus) with the presence of &gt;5 leukocytes/high power field in the context of urethral discharge in a man, can be presumed to suggest non-gonococcal urethritis.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Culture $^{c,d}$</td>
<td>Initial step to detect and identify bacterial species for selection of appropriate antibiotic regimens</td>
<td>Healthcare facilities with clinical laboratories</td>
</tr>
<tr>
<td>Rarely performed</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$^{a}$Usually chlamydial and gonococcal infections are tested at the same time since their clinical presentations are very similar.

$^{b}$Possible specimens are: 1) among women, a vulvovaginal specimen, which may be self-collected. An endocervical swab can also be an alternative but requires a speculum. First-catch urine is another option, but the sensitivity and specificity tend to be lower in women 2) Among men, first catch urine or urethral swabs are appropriate. Anorectal and pharyngeal samples are also adequate. For anorectal samples among men who have sex with men, *Chlamydia* genovar testing for lymphogranuloma venereum should be done to guide the appropriate treatment regimen for lymphogranuloma venereum.

$^{c}$Possible specimens are: urethral swabs, endocervical swabs, vaginal swabs, rectal swabs, oropharyngeal swabs, conjunctival swabs. Note: urine samples are not good specimens for microscopy and culture.

$^{d}$Consider culture if symptoms persist despite adequate treatment (note: urine samples are not good specimens for culture). Processing *C. trachomatis* for culture requires highly experienced laboratories and technicians and is complex, laborious and time-consuming to be of economic value. It is rarely performed in middle- or high-income countries nowadays except for special purposes.
Table 2 Additional tests for other sexually transmitted infections to consider in patients with confirmed or suspected chlamydial urogenital infection as indicated in the WHO EDL (54)

<table>
<thead>
<tr>
<th>Infection</th>
<th>Diagnostic test</th>
<th>Purpose of the test</th>
<th>Settings where the test should be available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gonorrhoea</td>
<td><em>Neisseria gonorrhoeae</em> nucleic acid amplification test</td>
<td>To diagnose gonorrhoeal urogenital disease and extragenital infection</td>
<td>Health care facilities with clinical laboratories</td>
</tr>
<tr>
<td>HIV</td>
<td>Anti-HIV-1 and -HIV-2 antibody (RDT)</td>
<td>Self-testing to screen for HIV</td>
<td>Community settings and health facilities without laboratories a</td>
</tr>
<tr>
<td>HIV</td>
<td>Anti-HIV-1 and -HIV-2 antibody (RDT and immunoassay)</td>
<td>To screen for HIV infection</td>
<td>Community settings and health facilities without laboratories a (RDT)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Healthcare facilities with clinical laboratories (immunoassay)</td>
</tr>
<tr>
<td>HIV</td>
<td>Combined anti-HIV-1/HIV-2 antibody and p24 antigen</td>
<td>To screen for HIV infection</td>
<td>Community settings and health facilities without laboratories a (RDT)</td>
</tr>
<tr>
<td></td>
<td>(RDT and immunoassay)</td>
<td></td>
<td>Healthcare facilities with clinical laboratories (immunoassay)</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Hepatitis B virus surface antigen (RDT, immunoassay)</td>
<td>To screen for acute and chronic hepatitis B virus infection in people aged &gt; 12 months</td>
<td>Community settings and health facilities without laboratories a (RDT)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Healthcare facilities with clinical laboratories (immunoassay)</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>IgM-specific antibodies to hepatitis B core antigen (immunoassay)</td>
<td>To aid in the diagnosis of acute HBV infection in the context of outbreak investigation</td>
<td>Healthcare facilities with clinical laboratories</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>Anti-hepatitis C antibody (RDT, immunoassay)</td>
<td>To screen for hepatitis C virus infection in people aged &gt; 18 months</td>
<td>Community settings and health facilities without laboratories a (RDT)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Healthcare facilities with clinical laboratories (immunoassay)</td>
</tr>
<tr>
<td>Syphilis</td>
<td>Antigens to <em>Treponema pallidum</em> (RDT)</td>
<td>To diagnose or help to diagnose <em>Treponema pallidum</em></td>
<td>Community settings and health facilities without laboratories a</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Syphilis and HIV</td>
<td>Combined antibodies to <em>Treponema pallidum</em> and to HIV-1 and HIV-2 (RDT)</td>
<td>To diagnose or help to diagnose HIV and/or <em>Treponema pallidum</em></td>
<td>Community settings and health facilities without laboratories a</td>
</tr>
<tr>
<td>(combined test)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Trichomoniasis

Microscopy

To assess microbial morphology, and presence or absence of white blood cells

Healthcare facilities with clinical laboratories

RDT: rapid diagnostic test.

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.

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).

II. Other tests

When chlamydial urogenital infection is suspected, laboratory tests other than microbiology are not usually needed.

III. Using microbiology surveillance data

Routine surveillance is not helpful to inform empiric guidance.

Imaging

When chlamydial urogenital infection is suspected, imaging is not usually needed.

Antibiotic treatment

Antibiotic treatment is always indicated when the infection is diagnosed. Table 3 gives recommendations taken from the most recent WHO guidelines on the treatment of chlamydial infections – most recent version at publication of this Handbook was issued in 2016 (175). Please check the WHO website regularly for possible updates. Recommendations in the EML overlap with the 2016 WHO guidelines (azithromycin or doxycycline are the recommended treatment options) but fewer treatment alternatives are included in the EML(4).

Table 3 Empiric antibiotic treatment for chlamydial urogenital infections as indicated in the most recent WHO guidelines(175)

<table>
<thead>
<tr>
<th>Type of chlamydia infection</th>
<th>Treatment</th>
<th>Total treatment duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncomplicated urogenital infection</td>
<td><strong>Doxycycline</strong>&lt;sup&gt;1&lt;/sup&gt; (oral): 100 mg given every 12 hours OR <strong>Azithromycin</strong> (oral): 1 g</td>
<td>7 days (doxycycline) Single dose (azithromycin)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anorectal infection</td>
<td><strong>Doxycycline</strong>&lt;sup&gt;1&lt;/sup&gt; (oral): 100 mg given every 12 hours</td>
<td>7 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection in pregnant women</td>
<td><strong>Azithromycin</strong> (oral): 1 g</td>
<td>Single dose</td>
</tr>
</tbody>
</table>
Lymphogranuloma venereum<sup>d</sup>  
**First choice**  
Doxycycline (oral): 100 mg given every 12 hours  
**Second choice**  
Azithromycin (oral): 1 g given once a day  

<table>
<thead>
<tr>
<th><strong>Ophthalmia neonatorum</strong>&lt;sup&gt;e&lt;/sup&gt; (i.e. chlamydial conjunctivitis)</th>
<th><strong>Azithromycin (oral): 20 mg/kg given once a day</strong></th>
<th><strong>21 days</strong></th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th><strong>Ocular prophylaxis</strong>&lt;sup&gt;f&lt;/sup&gt; (topical treatment for the prevention of both gonococcal and chlamydial ophthalmia neonatorum)</th>
<th><strong>Erythromycin (eye ointment): 0.5%</strong></th>
<th><strong>Antibiotic needs to be applied to both eyes soon after birth (single dose)</strong></th>
</tr>
</thead>
</table>

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

<sup>a</sup>Alternatives indicated in the WHO 2016 guidelines but not included the EML for this indication: tetracycline (oral): 500 mg every 6 hours; erythromycin (oral): 500 mg every 6 hours; ofloxacin (oral): 200–400 mg every 12 hours. The recommended duration of treatment is 7 days for all three options.

<sup>b</sup>According to recent data doxycycline is more effective than azithromycin and could be given priority if adherence to treatment is not of concern (176-178).

<sup>c</sup>Alternatives indicated in the WHO 2016 guidelines but not included in the EML for this indication: amoxicillin (oral): 500 mg every 8 hours; erythromycin (oral): 500 mg every 12 hours. The recommended duration of treatment is 7 days for both options.

<sup>d</sup>Alternatives indicated in the WHO-2016 guidelines but not included in the EML for this indication: erythromycin (oral): 50 mg/kg per day divided in 4 doses for 14 days. This option should be considered only when doxycycline or azithromycin are not available.

<sup>e</sup>Alternatives indicated in the WHO 2016 guidelines but not included in the EML for this indication: erythromycin (oral): 50 mg/kg per day divided in 4 doses for 14 days.

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

Access antibiotics are indicated in green, Watch antibiotics in yellow and Reserve antibiotics in red.

If symptoms persist at review:

- check partner notification and treatment history; and
- for people with recurrent or persistent urethral discharge, refer to a centre with laboratory capacity to diagnose *N. gonorrhoeae*, *C. trachomatis*, *M. genitalium* and *T. vaginalis* and test for antimicrobial-resistant *N. gonorrhoeae* and *M. genitalium*.

**Prevention**

Important elements of prevention include counselling and behavioural approaches including comprehensive sexuality education, pre- and post-test counselling, safe sex and risk reduction counselling and promoting consistent use of condoms. Interventions targeting high-risk groups (e.g. men who have sex with men, transgender people, sex workers, people who inject drugs)
may be considered. Also consider offering pre-exposure prophylaxis for HIV to people at high risk for HIV infection. Sexual partners should always be informed of the infection and treated (179). Reporting of this infection to health authorities according to local regulations should also be done.
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/fact-sheets/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 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.

Definition

Gonococcal infection is a sexually transmitted infection caused by the bacterium *Neisseria gonorrhoeae*.

Microbiology epidemiology

*Neisseria gonorrhoeae*, the organism causing gonorrhoea, is a Gram-negative bacterium. The bacterium easily develops resistance to antibiotics which has led to infections that are difficult to treat. As a result, resistance to antibiotics used for treatment (including third-generation cephalosporins) is a serious problem worldwide. Therefore, in 2012, WHO launched a global action plan to control the spread and impact of resistance in *Neisseria gonorrhoeae* (180).

Data on *Neisseria gonorrhoeae* resistance are collected through the WHO Global Antimicrobial Resistance Surveillance System (GLASS) and the WHO Global Gonococcal Antimicrobial Surveillance Programme (GASP network) and are regularly published (181, 182) (183, 184).

Pathophysiology

*Neisseria gonorrhoeae* usually enters the mucosa (mostly of the genital tract) during sexual contact. Because of its many virulence factors, this bacterium can adapt to the local environment, evade immune response mechanisms and proliferate causing local inflammatory response and disease and, more rarely, systemic infection (i.e. gonococcal bacteremia). If left untreated, or if it is inappropriately treated, complications may occur. In particular in women, pelvic inflammatory disease (i.e. an infection of the upper female reproductive tract) with inflammation of the uterine tubes (i.e. salpingitis), endometrium (i.e. endometritis) or abscess formation in the ovary/ovaries and tubes can occur. In men, complications include epididymitis and periurethritis with abscess formation. These complications can lead to infertility.

Disseminated gonococcal infection can occur as a result of bacteremia secondary to mucosal infection (mostly of the genital tract) and can lead to arthritis, skin manifestations and other complications.

Infants of mothers with gonococcal infection can be infected at delivery, resulting in neonatal conjunctivitis manifesting as purulent ocular discharge and swollen eyelids. Untreated conjunctivitis may lead to scarring and blindness.

Epidemiology

Gonococcal infection is one of the most common sexually transmitted infections worldwide.
The 2021 WHO Global progress report on HIV, viral hepatitis and sexually transmitted infections reported an estimated 82 million new gonococcal infections in 2020 among adults aged 15 to 49 years of age (173).

The highest incidence of gonococcal infection is in the Africa and Western Pacific regions; this includes China and Australia among others (185). Gonococcal infection increases the risk of HIV infection by 2 to 3 folds.

Risk factors for gonococcal infection include HIV infection, young age, having multiple sexual partners or a new sexual partner, having partners with STIs, having had previous gonococcal infection and / or other STIs and several socioeconomic factors (e.g. low socioeconomic or educational level, substance abuse). Infection does not induce protective immunity therefore reinfection is possible. Resistance of Neisseria gonorrhoeae to antibiotics used to treat the infection is a concern (see the microbiology epidemiology section for more information about resistance) (183).

**Clinical presentation**

Signs and symptoms of gonococcal infection vary in men and women and overlap with those of chlamydial infection. Some people with gonococcal infection may be asymptomatic even though they can still transmit the infection. When symptoms occur (usually a few days after being infected), the most common clinical presentation in men is acute urethritis characterized by profuse mucopurulent urethral discharge and dysuria; testicular discomfort can also be present. In women mucopurulent vaginal discharge and dysuria are the most common symptoms. Several women may have lower abdominal pain because of ascending infection causing pelvic inflammatory disease. Gonorrhoea causes cervical infection that presents with cervical discharge, cervical ectopy and friability and easy bleeding on contact.

In both sexes (but in males more than females), symptoms of acute proctitis with pain, pruritus, discharge and bleeding of the rectum may occur. Pharyngitis (mostly manifesting as a mild sore throat) and conjunctivitis are other conditions that usually coexist with genital infection.

Rarely, the infection can disseminate (i.e. gonococcal bacteraemia) and this can typically lead to localized infection in one or more joints (i.e. gonococcal arthritis). Please refer to the Handbook chapter on septic arthritis for more information on this topic.

In pregnant women, the infection can be transmitted to the child during vaginal delivery. In newborns, gonococcal infection can present with acute ocular infection (i.e. conjunctivitis) or pharyngitis which manifest a few days after birth. Disseminated infection with septic arthritis (usually with multiple joints involved) can also occur in newborns.

**Laboratory tests**

I. Patient microbiology tests
Molecular testing has greatly improved the detection of *Neisseria gonorrhoeae* (and *Chlamydia trachomatis*) among both symptomatic and asymptomatic men and women and has become the recommended gold standard technology to diagnose and screen populations for *N. gonorrhoeae* and *C. trachomatis* (Table 2 also indicates the types of specimens that can be used for this purpose).

Culture of *N. gonorrhoeae* is still the standard method for performing antibiotic susceptibility testing. However, this organism is not easy to grow in the laboratory, requiring special training and a special culture medium. For this reason, culture of *N. gonorrhoeae* is not routinely performed as part of managing people with gonococcal infection in resource-limited settings.

*N. gonorrhoeae* can also be identified by light microscopy of Gram-stained samples and a presumptive diagnosis can be made if intracellular Gram-negative diplococci are observed in polymorphonuclear leukocytes, best seen when there is a urethral discharge. Gram-stained smears from the cervix are also considered positive for the presumptive diagnosis of gonorrhoea in women if intracellular Gram-negative diplococci are observed in polymorphonuclear leukocytes. Gram stain of urethral samples among women has low yield and may not be cost-effective.

For more comprehensive information on the diagnosis of gonococcal infection, please refer to the most recent WHO guideline for the laboratory diagnosis of sexually transmitted infections – most recent version at publication of this Handbook was issued in 2013(174). Please check the WHO website regularly for possible updates. Patients with gonococcal infection are also usually evaluated also for other sexually transmitted infections (e.g. chlamydial infection, hepatitis B, hepatitis C, HIV and syphilis).

Tests to consider when gonococcal infection is suspected are listed in Table 1. Additional tests for other sexually transmitted infections that could be considered when gonococcal infection is confirmed or suspected are shown in Table 2.

<table>
<thead>
<tr>
<th>Diagnostic test</th>
<th>Purpose of the test</th>
<th>Settings where the test should be available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Qualitative test for <em>Neisseria gonorrhoeae</em> and <em>Chlamydia trachomatis</em> infections (i.e. nucleic acid amplification test)(^a,b)</td>
<td>To diagnose gonorrhoeal and/or chlamydial urogenital disease and extragenital infection</td>
<td>Healthcare facilities with clinical laboratories</td>
</tr>
<tr>
<td><strong>This is the recommended reference standard</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microscopy (Gram stain)(^c)</td>
<td>To assess microbial morphology, and presence or absence of white blood cells</td>
<td>Healthcare facilities with clinical laboratories</td>
</tr>
<tr>
<td>Culture(^d) &lt;br&gt; Consider if symptoms persist despite adequate treatment and for surveillance purposes.</td>
<td>Initial step to detect and identify bacterial species for selection of appropriate antibiotic regimens</td>
<td>Healthcare facilities with clinical laboratories</td>
</tr>
</tbody>
</table>
Blood cultures
Consider if disseminated infection is suspected.

To detect bacterial bloodstream infections (sepsis)
Healthcare facilities with clinical laboratories

Table 2 Additional tests for other sexually transmitted infections to consider in patients with confirmed or suspected gonococcal infection as indicated in the WHO EDL (54)

<table>
<thead>
<tr>
<th>Infection</th>
<th>Diagnostic test</th>
<th>Purpose of the test</th>
<th>Settings where the test should be available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlamydial urogenital infection</td>
<td><em>Chlamydia trachomatis</em> nucleic acid amplification test</td>
<td>To diagnose chlamydial urogenital disease and extragenital infection</td>
<td>Healthcare facilities with clinical laboratories</td>
</tr>
<tr>
<td>HIV</td>
<td>Anti-HIV-1 and -HIV-2 antibody (RDT)</td>
<td>Self-testing to screen for HIV</td>
<td>Community settings and health facilities without laboratories&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>HIV</td>
<td>Anti-HIV-1 and -HIV-2 antibody (RDT and immunoassay)</td>
<td>To screen for HIV infection</td>
<td>Community settings and health facilities without laboratories&lt;sup&gt;b&lt;/sup&gt; (RDT)</td>
</tr>
<tr>
<td>HIV</td>
<td>Combined anti-HIV-1/HIV-2 antibody and p24 antigen (RDT and immunoassay)</td>
<td>To screen for HIV infection</td>
<td>Community settings and health facilities without laboratories&lt;sup&gt;c&lt;/sup&gt; (RDT)</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Hepatitis B virus surface antigen (RDT, immunoassay)</td>
<td>To screen for acute and chronic hepatitis B virus infection in people aged &gt; 12 months</td>
<td>Community settings and health facilities without laboratories&lt;sup&gt;d&lt;/sup&gt; (RDT)</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>IgM-specific antibodies to</td>
<td>To aid in the diagnosis of acute HBV infection</td>
<td>Healthcare facilities with clinical laboratories</td>
</tr>
</tbody>
</table>

<sup>a</sup> Usually gonococcal and chlamydial infections are tested at the same time since their clinical presentations are very similar.

<sup>b</sup> Possible specimens are: 1) among women, a vulvovaginal specimen, which may be self-collected. An endocervical swab can also be an alternative but requires a speculum. First-catch urine is another option, but the sensitivity and specificity tend to be lower in women 2) Among men, first catch urine or urethral swabs are appropriate. Anorectal and pharyngeal samples are also adequate. Nucleic acid amplification tests also perform well for pharyngeal and anorectal samples.

<sup>c</sup> Possible specimens are: urethral swabs, endocervical swabs and conjunctival swabs. Note: urine samples are not good specimens for microscopy.

<sup>d</sup> Possible specimens are: urethral swabs, endocervical swabs, vaginal swabs, rectal swabs, oropharyngeal swabs and conjunctival swabs. Note: urine samples are not good specimens for culture. Culture is the standard method for performing antibiotic susceptibility testing.
### Other tests

When gonococcal infection is suspected, laboratory tests other than microbiology are not usually needed. However, microscopy of vaginal or urethral secretions will usually show the presence of leukocytes (> 10 leukocytes/field).

### Using microbiology surveillance data

Monitoring antibiotic resistance in *Neisseria gonorrhoeae* is recommended to inform local, national and global guidance.

### Imaging

When gonococcal infection is suspected, imaging is not usually needed.

### Antibiotic treatment

The recommendations on antibiotic treatment reported here are based on the most recent WHO guidelines for the treatment of gonorrhoea– most recent version at publication of this Handbook was issued in 2016(77). Because of increasing antibiotic resistance to azithromycin in *N. gonorrhoeae* and *M. genitalium* and reduced susceptibility of *N. gonorrhoeae* to cephalosporins,
WHO is in the process of revising current treatment recommendations and dosages. Please check the WHO website regularly for possible updates.

All people (including pregnant women) diagnosed with gonorrhoea should receive adequate antibiotic treatment (see Table 3).

When choosing treatment, local resistance data should determine the choice of the most appropriate therapy and if data are not available, dual therapy (i.e. two antibiotics) should be given. If symptoms do not resolve within about 5 days of adequate antibiotic treatment, a resistant infection should be suspected, or an alternative diagnosis sought.

Table 3 Antibiotic treatment for gonococcal infection as indicated in the most recent WHO guidelines for the treatment of gonorrhoea (77)

<table>
<thead>
<tr>
<th>Type of gonococcal infection</th>
<th>Treatment</th>
<th>Total treatment duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genital and anorectal infections (dual therapy&lt;sup&gt;a&lt;/sup&gt;)</td>
<td>First choice Ceftriaxone (IM): 250 mg AND Azithromycin (oral): 1 g</td>
<td>Single dose</td>
</tr>
<tr>
<td></td>
<td>Second choice Cefixime (oral): 400 mg AND Azithromycin (oral): 1 g</td>
<td></td>
</tr>
<tr>
<td>Genital and anorectal infections (single therapy); if local resistance data confirm susceptibility to the antibiotic&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Ceftriaxone (IM): 250 mg</td>
<td>Single dose</td>
</tr>
<tr>
<td></td>
<td>Second choice Spectinomycin (IM): 2 g OR Gentamicin (IM): 240 mg</td>
<td></td>
</tr>
<tr>
<td>Oropharyngeal infections&lt;sup&gt;d&lt;/sup&gt; (dual therapy&lt;sup&gt;a&lt;/sup&gt;)</td>
<td>First choice Ceftriaxone (IM): 250 mg AND Azithromycin (oral): 1 g</td>
<td>Single dose</td>
</tr>
<tr>
<td></td>
<td>Second choice Cefixime (oral): 400 mg AND Azithromycin (oral): 1 g</td>
<td></td>
</tr>
<tr>
<td>Oropharyngeal infections&lt;sup&gt;d&lt;/sup&gt; (single therapy); if local resistance data confirm susceptibility to the antibiotic</td>
<td>Ceftriaxone (IM): 250 mg</td>
<td>Single dose</td>
</tr>
<tr>
<td>Gonococcal ophthalmia neonatorum&lt;sup&gt;e&lt;/sup&gt; (i.e. gonococcal conjunctivitis)</td>
<td>Ceftriaxone (IM): 50mg/kg OR Spectinomycin (IM): 25mg/kg</td>
<td>Single dose</td>
</tr>
<tr>
<td>Ocular prophylaxis&lt;sup&gt;f&lt;/sup&gt; (topical treatment for the prevention of both chlamydial and gonococcal ophthalmia neonatorum)</td>
<td>Erythromycin (eye ointment): 0.5%</td>
<td>Antibiotic needs to be applied to both eyes soon after birth (single dose)</td>
</tr>
<tr>
<td>Retreatment after treatment failure</td>
<td>Ceftriaxone (IM): 500 mg AND Azithromycin (oral): 2 g OR Cefixime (oral): 800 mg AND Azithromycin (oral): 2 g</td>
<td>Single dose</td>
</tr>
</tbody>
</table>
Consider treatment failure if symptoms persist after 5 days of adequate treatment

OR

- **Gentamicin (IM):** 240 mg AND **Azithromycin (oral):** 2 g

OR

- **Spectinomycin (IM):** 2 g AND **Azithromycin (oral):** 2 g

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

IM: intramuscular.

\[a\] Dual therapy should be given if no reliable local data on resistance are available.

\[b\] Alternatives indicated in the WHO 2016 guidelines but not included in the EML for genital and anorectal infections:

- single therapy with cefixime (oral) 400 mg single dose.

\[c\] The EML lists gentamicin (single dose) for this indication, however, this option is not recommended in the WHO 2016 guidelines (except for retreatment after treatment failure) (77). Unless new information supporting the use of gentamicin in gonococcal infections is provided, the 2023 Expert Committee might consider gentamicin for deletion for this indication.

\[d\] Do not use spectinomycin to treat cases of oropharyngeal infection.

\[e\] Alternative indicated in the WHO 2016 guidelines but not included in the EML for gonococcal ophthalmia neonatorum: kanamycin (IM): 25mg/kg.

\[f\] Alternatives indicated in the WHO 2016 guidelines but not included in the EML for the prevention of both chlamydial and gonococcal ophthalmia neonatorum: tetracycline hydrochloride (eye ointment): 1%; povidone–iodine (water-based solution. Do not use alcohol-based solutions): 2.5%; silver nitrate (solution): 1%; chloramphenicol (eye ointment): 1%.

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

Prevention

No effective vaccine against *Neisseria gonorrhoeae* is available. Prevention is therefore one of the key elements included in the WHO 2012 global action plan to control the spread and impact of antimicrobial resistance in *Neisseria gonorrhoeae* (180).

Important elements of prevention include counselling and behavioural approaches including comprehensive sexuality education, pre- and post-test counselling, safe sex and risk reduction counselling and promoting consistent use of condoms. Interventions targeting high-risk groups (e.g. men who have sex with men, transgender people, sex workers, people who inject drugs) and offering HIV pre-exposure prophylaxis to people at high risk for HIV infection may be considered. Sexual partners should always be informed of the infection and treated. Reporting 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)

- 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
human diseases include subspecies *pertenue* (the causative pathogen of yaws\(^{(186)}\)), subspecies *endemicum* (the causative pathogen of endemic syphilis or bejel) and subspecies *carateum* (the causative pathogen of pinta\(^{(187)}\)). This chapter will only address disease caused by *Treponema pallidum* subspecies *pallidum* (syphilis). Information about other treponematoses is available on the WHO website\(^{(186)}\).

Syphilis can be classified as “early” or “late” based on the time since becoming infected (usually infections of ≤ 2 years duration are defined “early” and infections of > 2 years are defined “late”) and “primary”, “secondary” or “tertiary” based on the clinical presentation. There is usually a long latent phase with no clinical manifestations between secondary and tertiary infection – the tertiary phase only develops in untreated or inadequately treated infections. Overlap between definitions exists with early infection including primary and secondary syphilis and late infection including the latent phase and tertiary syphilis.

The latent phase can also be divided into two phases – “early latent” and the “late latent”.

Early latent is usually defined as < 2 years after infection while late latent is defined as > 2 years. However, this distinction is difficult to apply because it is often impossible to establish the time of the initial infection.

![Figure 10.1: Schematic representation of the course of untreated syphilis](image)

**Microbiology epidemiology**

Syphilis is caused by *Treponema pallidum* subspecies *pallidum* a bacterium of the phylum Spirochaetes (other members of this phylum include e.g. *Leptospira* and *Borrelia*).

*Treponema pallidum* is characterized by slow growth, difficulty in culturing *in vitro*, and its thinness (0.2 μm compared to about 0.5 μm for a bacterium like *Escherichia coli*) which makes it difficult to see with conventional microscopy.
Resistance to penicillin has not yet been reported and therefore it remains the antibiotic of choice for the treatment of syphilis. Resistance to azithromycin has been reported in some settings (188).

**Pathophysiology**

Syphilis is usually acquired through sexual contact with infectious lesions on the mucosa or skin or, much more rarely, through the bloodstream. The infection can also be transmitted from the mother to her fetus because *Treponema pallidum* subspecies *pallidum* can cross the placenta and cause fetal death and congenital infection.

With sexual transmission, once *Treponema pallidum* subspecies *pallidum* enters the subcutaneous tissue, infection develops within 2-6 weeks (usually about 3 weeks) with formation of an ulcerative lesion that occurs at the site of inoculation. Usually, the immune system is able to control the early infection and, even if left untreated, the primary ulcerative lesion (i.e. chancre) resolves. However, dissemination of *Treponema pallidum* through the bloodstream can occur at the time of primary infection and this can result over time in secondary or tertiary syphilis in the absence of adequate treatment. In particular, tertiary syphilis has a long incubation period (up to years or decades after the initial infection) and develops in about a third of patients with untreated syphilis. In 2017, 370,000 prevalent cases of tertiary syphilis were reported worldwide but this number is probably an underestimation of the true burden of the disease (31).

Congenital syphilis can occur as a result of vertical transmission of the pathogen from an infected mother to the fetus. The risk of transmission depends on a combination of factors including maternal titers of non-treponemal tests (see Table 1 for an explanation about tests), timing and adequacy of maternal treatment, and stage of maternal infection. The estimated number of total cases of congenital syphilis worldwide in 2016 was 661,000 (or 473 per 100,000 live births) (189).

**Epidemiology**

Syphilis is a common curable sexually transmitted infection, and its incidence is increasing globally. WHO estimates 7 million new cases in 2020 (173). Although other bacterial sexually transmitted infections occur more frequently (for example, in 2020 more than 82 million new cases of gonorrhoea and about 128 million new cases of chlamydial infection were reported (173), syphilis has an important public health impact because of the potential serious consequences if left untreated, including maternal transmission to the fetus resulting in congenital syphilis and fetal death and complications such as neurosyphilis and cardiovascular syphilis.

Moreover, as for other sexually transmitted infections, syphilis affects quality of life and increases the risk of transmitting or acquiring other sexually transmitted infections including HIV; This HIV risk is of particular concern because sexually transmitted infections characterized by the presence of ulcerative lesions have the highest risk of HIV transmission (190).

The risk factors for syphilis include having multiple sexual partners or a new sexual partner, having partners with STIs, having had a previous STI, and several socioeconomic factors (e.g. low socioeconomic or educational level, substance abuse, young age) (191, 192). Lack of access to adequate prenatal care is an important risk factor for congenital syphilis.
Clinical presentation

Signs and symptoms vary depending on the stage of the disease (early or late).

Early syphilis has the following signs and symptoms.

- Primary infection (localized disease): characterized by the presence of a localized non-painful ulcerative lesion (i.e. chancre) with indurated margins, usually associated with local lymphadenopathy. The lesion is usually located on the genitalia, mouth or rectum but other locations are possible depending on the site of inoculation. The lesion is often asymptomatic and can remain unnoticed particularly among women. If left untreated, the lesion usually resolves within a few weeks without leaving a scar.

- Secondary infection (disseminated disease): characterized by skin and mucosal manifestations. Generally, a maculopapular non-irritant rash appears which is usually diffuse and extends bilaterally over the trunk and the extremities. A characteristic feature is the involvement of the palms of the hands and soles of the feet. The mucous membranes of the mouth and perineum can also show lesions (mostly flat lesions) that are highly infectious. Systemic manifestations (e.g. fever > 38.0°C, generalized lymphadenopathy and malaise) are usually present. Neurologic manifestations (e.g. meningitis), hepatitis and ocular involvement can also occur in this phase.

Late syphilis has the following signs and symptoms.

- Tertiary syphilis (disseminated disease): this can occur as the result of an untreated early syphilis after a period of latency (with no clinical manifestations) that may last years – usually tertiary syphilis develops more rapidly in patients with HIV. In this phase different organ systems can be affected particularly: the cardiovascular system (typically with signs and symptoms of aortitis), the skin, soft tissues and bones (typically with granulomatous or nodular lesions also known as gummas) and the central nervous system (typically with symptoms of progressive dementia, psychiatric syndrome and tabes dorsalis characterized by problems with coordination of movements, pain radiating from the spine and impaired response of the pupils to light).

Congenital syphilis: infection during pregnancy can lead to spontaneous abortion or premature birth. Most babies with congenital syphilis are asymptomatic at birth but when symptoms are present, they usually develop days or weeks after birth. These symptoms often include anaemia, thrombocytopenia, rash (maculopapular, desquamative rash particularly over the palms, soles, mouth and anus), generalized lymphadenopathy, hepatomegaly and jaundice, nasal discharge (that may turn bloody), painful osteitis (mostly in long bones) and teeth abnormalities. The cerebrospinal fluid is abnormal, indicating neurological disease, in up to half of all babies. Of note, neurological consequences can be expressed later in life and this should always be considered in case of congenital syphilis.
Laboratory tests

For more comprehensive information on diagnosis of syphilis, please refer to the most recent WHO guideline for the laboratory diagnosis of sexually transmitted infections – the most recent version at publication of this Handbook was issued in 2013 (174). Please check the WHO website regularly for possible updates.

I. Patient microbiology tests

In patients with suspected syphilis, microbiology tests can support the diagnosis (Table 1). Certain microbiology tests are also used to screen asymptomatic pregnant women. For screening during pregnancy please refer to the most recent WHO guideline on syphilis screening and treatment for pregnant women – the most recent version at publication of this Handbook was issued in 2017 (193).

Direct detection methods

These methods can be used to detect the pathogen in specimens obtained from skin or tissues lesions (Table 1). This includes dark-field microscopy (where Treponema pallidum from lesions of primary syphilis can be observed. Of note a negative dark-field result does not exclude syphilis) and nucleic acid amplification tests (to detect T. pallidum-specific DNA sequences). Direct detection is considered the “gold standard” but it is much less frequently used today because it is more time consuming than serological tests.

Serological tests

Two types of serological tests can be done, treponemal and nontreponemal tests (Table 1).

- Treponemal tests detect antibodies to treponemal antigens and usually remain positive after infection even after successful treatment. These tests include: fluorescent treponemal antibody absorption (FTA-ABS) test, Treponema pallidum particle agglutination (TPPA) assay and Treponema pallidum haemagglutination (TPHA) assay.
- Non-treponemal tests detect antibodies that react to lipids (e.g. cardiolipin released during cellular damage that occurs in response to Treponema Pallidum). These are qualitative and quantitative tests that can also be used to monitor response to treatment because their titers tend to decline after adequate treatment and may become negative (i.e. nonreactive) over time. These tests include: rapid plasma reagin (RPR) test, Venereal Disease Research Laboratory (VDRL) test).

Initially, a two-step approach is used to test for syphilis (both types of tests – treponemal and non-treponemal- need to be positive to confirm the diagnosis). In order to increase access and ensure same-day treatment, WHO recommends the use of a rapid treponemal test followed (if positive) by a non-treponemal test.

However, starting with a non-treponemal test and confirm positive results with a treponemal test is also appropriate.
All serological tests for syphilis (non-treponemal and treponemal tests) are negative in the early phase of primary syphilis, taking 1–4 weeks after the chancre appears to become reactive. Both treponemal and non-treponemal tests are reactive in secondary or tertiary syphilis (Table 2). Non-treponemal tests can rarely give false positive results (e.g. during pregnancy or during an acute febrile illness). Tables 2, 3 and 4 can be used to help with the interpretation of results of serological tests.

Additional tests for other sexually transmitted infections that could be considered when syphilis is confirmed or suspected are shown in Table 5.

Table 1 Microbiology tests to consider when syphilis is suspected as indicated in the WHO EDL (54)

<table>
<thead>
<tr>
<th>Diagnostic test</th>
<th>Purpose of the test</th>
<th>Settings where the test should be available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microscopy of specimens obtained from skin and tissues lesions*</td>
<td>To assess microbial morphology</td>
<td>Healthcare facilities with clinical laboratories</td>
</tr>
<tr>
<td>Antibodies to <em>Treponema Pallidum</em> (RDT)</td>
<td>To diagnose or help to diagnose <em>Treponema pallidum</em></td>
<td>Community settings and health facilities without laboratories</td>
</tr>
<tr>
<td>Combined antibodies to <em>Treponema pallidum</em> and to HIV-1 and HIV-2 (RDT)</td>
<td>To diagnose or help to diagnose <em>HIV</em> and/or <em>Treponema pallidum</em></td>
<td>Community settings and health facilities without laboratories</td>
</tr>
<tr>
<td>Non-treponemal test: rapid plasma reagin (RPR)</td>
<td>To screen for syphilis and monitor effectiveness of treatment</td>
<td>Healthcare facilities with clinical laboratories</td>
</tr>
<tr>
<td>Non-treponemal test: venereal disease research laboratory (VDRL)²</td>
<td>To screen for syphilis and monitor effectiveness of treatment and also to screen for, diagnose and confirm neurosyphilis³</td>
<td>Healthcare facilities with clinical laboratories</td>
</tr>
<tr>
<td>Treponemal test: <em>Treponema pallidum</em> haemagglutination (TPHA)⁴</td>
<td>To confirm syphilis and diagnose early and late syphilis</td>
<td>Healthcare facilities with clinical laboratories</td>
</tr>
<tr>
<td>Treponemal test: <em>Treponema pallidum</em> particle agglutination (TPPA)⁴</td>
<td>To confirm syphilis and diagnose early and late syphilis</td>
<td>Healthcare facilities with clinical laboratories</td>
</tr>
</tbody>
</table>

RDT: rapid diagnostic test.

*Nucleic acid amplification tests (e.g. PCR) of specimens obtained from skin and tissues lesions could also be considered if available.

²Community and health settings without laboratories are defined as community and health facilities such as health posts and centres, doctors' offices, outreach clinics and ambulatory care. These tests are also assumed to be available at healthcare facilities with laboratories.

³If neurosyphilis is suspected (this can occur at any stage of infection including in the first few months) the VDRL test can also be performed on the cerebrospinal fluid in the presence of a positive syphilis serology. The test has a high specificity (i.e. few false positive results) but a low sensitivity (i.e. many false negative results). Examination of the cerebrospinal fluid is recommended in case of clinical evidence of neurological involvement and is also highly desirable in all patients with syphilis of more than two years duration or of uncertain duration in order to evaluate the possible presence of asymptomatic neurosyphilis(194).

⁴Treponemal tests usually remain positive after the infection has been cleared.
Table 2 Reactivity of non-treponemal serological tests by stage of syphilis and effect of treatment


Table 3 Reactivity of treponemal serological tests by stage of syphilis and effect of treatment

**Table 4 Possible interpretation of combinations of non-treponemal and treponemal test results**

<table>
<thead>
<tr>
<th>Non-treponemal test (RPR or VDRL)</th>
<th>Treponemal test (FTA-ABS, TPPA, TPHA, RDT)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>Positive</td>
<td>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.</td>
</tr>
<tr>
<td>Negative</td>
<td>Positive</td>
<td>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.</td>
</tr>
<tr>
<td>Positive</td>
<td>Negative</td>
<td>Usually this can be considered a false positive result (e.g. during pregnancy).</td>
</tr>
<tr>
<td>Negative</td>
<td>Negative</td>
<td>Usually the diagnosis of syphilis can be excluded.</td>
</tr>
</tbody>
</table>

FTA-ABS: fluorescent treponemal antibody absorption; RDT: rapid diagnostic test; RPR: rapid plasma reagin; TPHA: Treponema pallidum haemagglutination; TPPA: Treponema pallidum particle agglutination; VDRL: Venereal Disease Research Laboratory.

**Table 5 Additional tests for other sexually transmitted infections to consider in patients with confirmed or suspected syphilis as indicated in the WHO EDL (54)**

<table>
<thead>
<tr>
<th>Infection</th>
<th>Diagnostic test</th>
<th>Purpose of the test</th>
<th>Settings where the test should be available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlamydia urogenital infection and gonococcal infection</td>
<td>Qualitative test for <em>Chlamydia trachomatis</em> and <em>Neisseria gonorrhoeae</em> infections (i.e. nucleic acid amplification test)</td>
<td>To diagnose chlamydial and/or gonorrhoeal urogenital disease and extragenital infection</td>
<td>Healthcare facilities with clinical laboratories</td>
</tr>
<tr>
<td>HIV</td>
<td>Anti-HIV-1 and -HIV-2 antibody (RDT)</td>
<td>Self-testing to screen for HIV</td>
<td>Community settings and health facilities without laboratories*</td>
</tr>
<tr>
<td>HIV</td>
<td>Anti-HIV-1 and -HIV-2 antibody (RDT and immunoassay)</td>
<td>To screen for HIV infection</td>
<td>Community settings and health facilities without laboratories* (RDT)</td>
</tr>
<tr>
<td>HIV</td>
<td>Combined anti-HIV-1/HIV-2 antibody and p24 antigen (RDT and immunoassay)</td>
<td>To screen for HIV infection</td>
<td>Community settings and health facilities without laboratories* (RDT)</td>
</tr>
</tbody>
</table>
### II. Other tests

When primary syphilis is suspected, blood tests other than serology are not usually needed. However, in case of secondary or tertiary syphilis, laboratory tests may be required. If signs and symptoms of neurological disease (i.e. neurosyphilis) are present, a lumbar puncture to test the cerebrospinal fluid is indicated if available (Table 6).

**Table 6 Laboratory tests (other than microbiology) to consider when late syphilis is suspected as indicated in the WHO EDL (54)**

<table>
<thead>
<tr>
<th>Diagnostic test</th>
<th>Purpose of the test</th>
<th>Settings where the test should be available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basic CSF Profile (CSF leukocyte count&lt;sup&gt;a&lt;/sup&gt;, CSF differential leukocyte count and CSF protein&lt;sup&gt;b&lt;/sup&gt; and glucose)</td>
<td>To aid in the diagnosis of neurosyphilis</td>
<td>Health care facilities with clinical laboratories</td>
</tr>
</tbody>
</table>

RDT: rapid diagnostic test.

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

**Notes:**

<sup>b</sup>CSF leukocyte count: usually > 5 white blood cell / μl (> 0.01X10<sup>9</sup>/L), higher cut-off > 20 cell / μl in HIV positive patients (> 0.02X10<sup>9</sup>/L) even though this is not a specific finding of neurosyphilis.

<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 neurosyphilis.
CSF glucose levels: glucose concentrations are usually decreased but not a specific finding of neurosyphilis.

III. Using microbiology surveillance data

Routine surveillance is not helpful to inform empirical guidance.

Imaging

When syphilis is suspected, imaging is not usually needed unless a complication of late syphilis is suspected.

Antibiotic treatment

All patients (including pregnant women) diagnosed with syphilis should receive a full course of antibiotic treatment (Table 6). Serological response to treatment can be assessed by repeating a non-treponemal quantitative test (ideally the same type of non-treponemal test used at the time of diagnosis) to detect a reduction in titre. A four-fold reduction (or higher) in titres should be seen to confirm an adequate response to treatment for early syphilis (usually with repeated assessments at 3, 6 and 12 months after the end of treatment).

In case of early syphilis (primary or secondary), the partners of infected people should also be treated if they have had sexual relations with the infected person in the 90 days before the person was diagnosed with syphilis. If more than 90 days have elapsed, serological testing is usually suggested and treatment is given accordingly.

The antibiotic treatment recommendations reported here (Table 6) are aligned with the most recent WHO guidelines for the treatment of syphilis – most recent version at publication of this handbook was issued in 2016 (195).

Table 6 Antibiotic treatment for syphilis by stage of the disease as indicated in the most recent WHO guidelines for the treatment of syphilis (195)

<table>
<thead>
<tr>
<th>Type of infection</th>
<th>Treatment</th>
<th>Total treatment duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early syphilis (adults and adolescents)</td>
<td>First choice Benzathine benzylpenicillin() (IM): 2.4 million IU (1.8 g)</td>
<td>benzathine benzylpenicillin: single dose</td>
</tr>
<tr>
<td>Early syphilis includes primary, secondary and early latent syphilis of no more than 2 years duration</td>
<td>Second choice Procaine benzylpenicillin (IM): 1.2 million IU (1.2 g) given once a day</td>
<td>benzathine benzylpenicillin: one dose per week for 3 consecutive weeks (e.g. on days 1, 8 and 15)</td>
</tr>
<tr>
<td>Late syphilis or unknown stage (adults and adolescents)</td>
<td>First choice Benzathine benzylpenicillin() (IM): 2.4 million IU (1.8 g)</td>
<td>benzathine benzylpenicillin: one dose per week for 3 consecutive weeks (e.g. on days 1, 8 and 15)</td>
</tr>
<tr>
<td>This includes infection of more than 2 years duration without evidence of</td>
<td>Second choice</td>
<td></td>
</tr>
<tr>
<td>Treponemal infection (i.e. asymptomatic infection)</td>
<td><strong>Procaine benzylpenicillin</strong> (IM): 1.2 million IU (1.2 g) given once a day</td>
<td>The interval between doses should not exceed 14 days</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td><strong>Congenital syphilis</strong>&lt;br&gt;Infants with confirmed disease or infants who are clinically normal but whose mother had untreated or inadequately treated syphilis&lt;sup&gt;c&lt;/sup&gt;</td>
<td><strong>Benzylpenicillin</strong> (IV): 50 000-75 000 IU /kg/dose (30-45 mg/kg/dose) given every 12 hours&lt;br&gt;OR&lt;br&gt;<strong>Procaine benzylpenicillin</strong> (IM): 50 000 IU/kg (50 mg/kg) per day</td>
<td>If intravenous access is available, aqueous benzylpenicillin should be preferred over procaine benzylpenicillin. 10-15 days</td>
</tr>
<tr>
<td></td>
<td><strong>Neurosyphilis</strong>&lt;sup&gt;d&lt;/sup&gt;</td>
<td><strong>Benzylpenicillin</strong>&lt;sup&gt;e&lt;/sup&gt; (IV): 2–4 million IU (1.2 - 2.4 g) given every 4 hours&lt;br&gt;OR&lt;br&gt;<strong>Procaine benzylpenicillin</strong>&lt;sup&gt;f&lt;/sup&gt; (IM): 1.2 million IU (1.2 g) given once a day AND&lt;br&gt;<strong>Probenecid</strong> (oral): 500 mg given every 6 hours</td>
</tr>
<tr>
<td>Syphilis in pregnancy</td>
<td><strong>Early syphilis</strong>: <strong>Benzathine benzylpenicillin</strong> (IM): 2.4 million IU (1.8 g)&lt;br&gt;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.</td>
<td><strong>Early syphilis</strong>: single dose</td>
</tr>
<tr>
<td></td>
<td><strong>Late syphilis or unknown stage</strong>: <strong>Benzathine benzylpenicillin</strong> (IM): 2.4 million IU (1.8 g)&lt;br&gt;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 placental barrier).</td>
<td><strong>Late syphilis or unknown stage</strong>: 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</td>
</tr>
</tbody>
</table>
placental barrier completely, therefore only the mother is treated).

Notes: All dosages are for normal renal and hepatic function.
IM: intramuscular; IV: intravenous; IU: international units.

a Alternative options in case of allergy to penicillin (or stock-outs) are indicated in the WHO 2016 guidelines but not included in the EML for this indication. These are: doxycycline (oral) 100 mg every 12 hours (except in pregnant women) for 14 days or ceftriaxone 1 gr (IM) for 10-14 days (195); in special circumstances (i.e. when susceptibility is likely, based on local epidemiology) azithromycin 2 gr (oral) as a single dose can be given. If penicillin cannot be used, doxycycline is the preferred choice (except in pregnant women) because of its lower cost and oral administration (195).

b An alternative option, in case of allergy to penicillin (or stock-outs), is indicated in the WHO 2016 guidelines but this option is not included in the EML for this indication. This option is: doxycycline (oral) 100 mg every 12 hours (except in pregnant women) for 30 days (195).

c If the mother was adequately treated and the infant is clinically normal, close monitoring of the infant is suggested or if treatment is provided, the WHO 2016 guidelines indicate benzathine benzylpenicillin 50 000 IU/kg (37.5 mg) per day single dose IM as an option.

d From the 2003 WHO guidelines on management of sexually transmitted infections (194).

e Alternative options are indicated in the WHO 2003 guidelines for non-pregnant patients allergic to penicillin but they are not included in the EML. These options are: doxycycline (oral): 200 mg every 12 hours; tetracycline (oral): 500 mg every 6 hours. Treatment duration is 30 days in both cases.

f Some authorities recommend adding benzathine benzylpenicillin, 2.4 million IU (1.8 g) by intramuscular injection, in three consecutive doses once weekly, after completing this regimen, but there are no data to support this approach. Benzathine benzylpenicillin, 2.4 million IU (1.8 g) by intramuscular injection does not give adequate therapeutic levels in the cerebrospinal fluid (195).

Legend: ACCESS antibiotics are indicated in green, WATCH antibiotics in yellow and RESERVE antibiotics in red

Prevention

Sexual transmission typically occurs only during primary, secondary and early latent infection. Mother-to-child transmission, however, has been documented to occur up to several years after the initial infection (195).

Prevention of infection is a key strategy; no effective vaccine against Treponema pallidum is yet available therefore other preventive measures can be used.

The main elements of prevention include: comprehensive sexuality education, pre- and post-test counselling, safe sex and risk reduction counselling and promoting consistent use of condoms. Interventions targeting groups who have a higher risk of infection (e.g. men who have sex with men, transgender people, sex workers, people who inject drugs, indigenous communities, persons in prisons) should be considered. Offering HIV pre-exposure prophylaxis to people at high risk for HIV infection may be considered.

Access of pregnant women to early and adequate prenatal care, including screening at first visit and immediate treatment initiation if needed are key to prevent congenital syphilis. Sexual partners should always be informed of the infection and treated (179); Reporting of this 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)

- WHO guideline for the laboratory diagnosis of sexually transmitted infections including HIV, 2013. https://apps.who.int/iris/handle/10665/341412
- 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.*
Microbiology epidemiology

Trichomoniasis is caused by *Trichomonas vaginalis*, an anaerobe flagellated protozoan.

Pathophysiology

*Trichomonas vaginalis* infects the mucosa of the urogenital tract during sexual contact and produces a local inflammatory response that causes vaginal or urethral discharge.

Epidemiology

Trichomoniasis is the most prevalent sexually transmitted infection worldwide with an estimated 156 million new cases in 2020 as reported by WHO(173).

The infection most commonly affects women older than 40 years of age. As for other sexually transmitted infections, the risk of acquiring or transmitting HIV is higher in cases of trichomoniasis and the infection is associated with adverse outcomes in pregnancy (e.g. preterm delivery, premature rupture of membranes, low birth weight)(197). If left untreated, trichomoniasis can persist for months or years and in pregnant women, it can be transmitted to the baby during delivery. Common risk factors for infection include multiple sex partners, a history of having other sexually transmitted infections (e.g. HIV) and substance abuse.

Clinical presentation

Most cases of trichomoniasis are asymptomatic, especially in men, or have mild symptoms. In women, symptoms include acute onset of vaginal inflammation and discharge (usually characterized by a bad smell and with a frothy appearance), dysuria and pelvic pain. In men, symptomatic infection usually presents with urethral discharge, dysuria and testicular discomfort or pain. Epididymitis and prostatitis can also occur in a minority of cases.
Laboratory tests

For more comprehensive information on the diagnosis of trichomoniasis, please refer to the most recent WHO guideline on the laboratory diagnosis of sexually transmitted infections – the most recent version at publication of this Handbook was issued in 2013 (174). Please check the WHO website regularly for possible updates.

I. Patient microbiology tests

All people with trichomoniasis are also usually evaluated for other sexually transmitted infections (e.g. chlamydial infection, gonococcal infection, hepatitis B and hepatitis C, HIV and syphilis).

Tests to consider when trichomoniasis is suspected are indicated in Table 1.

Molecular assays such as nucleic acid amplification tests have the highest sensitivity of all diagnostic methods to detect \( T.\) \textit{vaginalis} but they are not currently widely available as rapid point-of-care tests. However, if available, they should be used. Vaginal swabs are the samples of choice, but endocervical samples and urine can be used for some assays.

Historically, trichomoniasis has been diagnosed by performing wet mount microscopy. Although this is not the gold standard technique, a wet mount is frequently used because it is quick, inexpensive and easy to perform. However, to have a good chance of successfully identifying the motile trichomonads, the slide should be read within 10 minutes of collection since trichomonads quickly lose their motility. Non-motile cells cannot be diagnosed as trichomonads (due to possible misidentification, e.g. a non-motile trichomonad is difficult to differentiate from the nucleus of a vaginal epithelial cell).

Culture of \( T.\) \textit{vaginalis}, which has a higher sensitivity than the wet mount microscopic examination, was the cornerstone for detecting \( T.\) \textit{vaginalis} before the advent of point-of-care antigen tests and nucleic acid amplification tests. Although a culture medium is commercially available, cultures of samples from women with trichomoniasis are usually positive in the first three days of inoculation, but they have to be incubated for up to seven days to rule out infection. Routine culture methods detecting \( T.\) \textit{vaginalis} are no longer widely performed.

Additional tests for other sexually transmitted infections that could be considered when trichomoniasis is confirmed or suspected are shown in Table 2.

Table 1 Microbiology tests to consider when trichomoniasis is suspected as indicated in the WHO EDL (54)

<table>
<thead>
<tr>
<th>Diagnostic test</th>
<th>Purpose of the test</th>
<th>Settings where the test should be available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microscopy(^{a,b})</td>
<td>To assess microbial morphology and presence or absence of white blood cells</td>
<td>Healthcare facilities with clinical laboratories</td>
</tr>
<tr>
<td>Culture(^b)</td>
<td>Initial step to detect and identify bacterial species for selection of appropriate antibiotic regimens</td>
<td>Healthcare facilities with clinical laboratories</td>
</tr>
</tbody>
</table>
If available, nucleic acid amplification tests for *Trichomonas vaginalis* could be considered, especially if the microscopy examination is negative. Nucleic acid tests for trichomoniasis are not listed in the third version of the EDL.

Possible specimens are: urethral swabs, endocervical swabs, vaginal swabs.

### Table 2  Additional tests for other sexually transmitted infections to consider in patients with confirmed or suspected trichomoniasis as indicated in the WHO EDL (54)

<table>
<thead>
<tr>
<th>Infection</th>
<th>Diagnostic test</th>
<th>Purpose of the test</th>
<th>Settings where the test should be available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlamydial urogenital infection and gonococcal infection</td>
<td>Qualitative test for <em>Chlamydia trachomatis</em> and <em>Neisseria gonorrhoeae</em> infections (i.e. nucleic acid amplification test)</td>
<td>To diagnose chlamydial and/or gonococcal urogenital disease and extragenital infection</td>
<td>Healthcare facilities with clinical laboratories</td>
</tr>
<tr>
<td>HIV</td>
<td>Anti-HIV-1 and -HIV-2 antibody (RDT)</td>
<td>Self-testing to screen for HIV</td>
<td>Community settings and health facilities without laboratories^a</td>
</tr>
<tr>
<td>HIV</td>
<td>Anti-HIV-1 and -HIV-2 antibody (RDT and immunoassay)</td>
<td>To screen for HIV infection</td>
<td>Community settings and health facilities without laboratories^a (RDT)</td>
</tr>
<tr>
<td>HIV</td>
<td>Combined anti-HIV-1/HIV-2 antibody and p24 antigen (RDT and immunoassay)</td>
<td>To screen for HIV infection</td>
<td>Healthcare facilities with clinical laboratories (immunoassay)</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Hepatitis B virus surface antigen (RDT, immunoassay)</td>
<td>To screen for acute and chronic hepatitis B virus infection in people &gt; 12 months</td>
<td>Community settings and health facilities without laboratories^a (RDT)</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>IgM-specific antibodies to hepatitis B core antigen (immunoassay)</td>
<td>To aid in the diagnosis of acute HBV infection in the context of outbreak investigation</td>
<td>Healthcare facilities with clinical laboratories</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>Anti-hepatitis C antibody (RDT, immunoassay)</td>
<td>To screen for hepatitis C virus infection in people &gt; 18 months</td>
<td>Community settings and health facilities without laboratories^a (RDT)</td>
</tr>
</tbody>
</table>
### Syphilis

| Antibodies to *Treponema pallidum* (RDT) | To diagnose or help to diagnose *Treponema pallidum* | Community settings and health facilities without laboratories

| Syphilis and HIV combined test | Combined antibodies to *Treponema pallidum* and HIV-1/HIV-2 (RDT) | To diagnose or help to diagnose HIV and/or *Treponema pallidum* | Community settings and health facilities without laboratories

---

**RDT:** rapid diagnostic test.

**a**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.

**b**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).

### II. Other tests

When trichomoniasis is suspected, laboratory tests (other than microbiology) are not usually needed.

### III. Using microbiology surveillance data

Routine surveillance is not helpful to inform empiric guidance.

### Imaging

When trichomoniasis is suspected, imaging is not usually needed.

### Antibiotic treatment

Antibiotic treatment is always indicated when trichomoniasis is diagnosed (Table 3), including in asymptomatic patients to stop transmission. Sexual partners should also be tested and treated if infected.

*Table 3: Antibiotic treatment for trichomoniasis as indicated in the most recent WHO guidelines for the management of symptomatic sexually transmitted infections (196)*

**Please check the WHO website regularly for possible updates**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Total treatment duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Metronidazole</strong> (oral) 2 g</td>
<td>Single dose</td>
</tr>
<tr>
<td>or</td>
<td></td>
</tr>
<tr>
<td><strong>Metronidazole</strong> (oral) 400 or 500 mg given every 12 hours</td>
<td>7 days</td>
</tr>
</tbody>
</table>

---

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

**a**If compliance is not a problem, consider giving 500 mg (oral) every 12 hours for 7 days. Evidence supports better cure rates with a 7-day course of treatment compared with a single dose (198).

**Legend:** ACCESS antibiotics are indicated in green, WATCH antibiotics in yellow and RESERVE antibiotics in red.
Prevention

No effective vaccine against *Trichomonas vaginalis* is available. Prevention of infection is therefore a key strategy. Important elements of prevention include counselling and behavioural approaches including comprehensive sexuality education, pre- and post-test counselling, safe sex and risk reduction counselling and promoting consistent use of condoms. Interventions targeting high-risk groups (e.g. men who have sex with men, transgender people, sex workers, people who inject drugs) may be considered. Offering HIV pre-exposure prophylaxis to people at high risk for HIV infection may be considered.

Sexual partners should always be informed of the infection and treated (179). Reporting of this infection to health authorities according to local regulations should also be done.
Urinary Tract Infection - Lower

Focus on community-acquired acute cystitis

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

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](https://apps.who.int/iris/handle/10665/81170) (23)

Definition

Lower urinary tract infections (UTI) are acute infections in which only the lower part of the urinary tract is affected (e.g. the bladder - cystitis). These infections are often classified as either complicated or uncomplicated based on the presence of risk factors that make them more difficult to treat.

Complications can occur with lower UTIs because of certain patient-related risk factors. While there is no universally accepted definition of what constitutes a complicated UTI, lower UTIs in individuals with certain conditions of the urinary tract (e.g. anatomical anomalies and kidney stones) are generally complicated. Infections in pregnant women are also usually included in this category. Examples of factors that may increase the risk of a complicated lower UTI are shown in 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

Pathophysiology

Lower UTIs occur when pathogens (usually ascending the urethra from the perineal area) reach the bladder and overcome the host defences, which leads to parenchymal damage and an inflammatory response. Microorganisms in the urine do not inevitably lead to infection. Infection will depend on the interaction between the organism (for example, because of virulence factors of the pathogen), the patient (who may have more infections because of underlying diseases) and the environment (for example, the presence of a urinary catheter).

Epidemiology

Lower UTIs are very common worldwide and can affect people of any age. According to the Global Burden of Disease study, in 2017 there were an estimated 274 million new cases of UTIs (lower and upper) globally, combining all ages and both sexes(31).

The incidence of UTIs is highest in women and increases with age (e.g. UTIs increase after menopause) and frequency of sexual activity. These infections are particularly common in women because of the anatomy of their lower urinary tract; women have a shorter urethra than men and so microorganisms colonizing the skin of the perineal area can more easily reach the bladder. However, after 65 years of age, rates of lower UTIs in men and women tend to be more similar(199). It is estimated that more than 50% of women experience at least one episode of lower UTI in their lifetime. After a first episode, the risk of recurrence in young women has been estimated to be about 70% within a year(200). Risk factors for UTIs include anatomical and functional abnormalities of the urinary tract (e.g. conditions that predispose to incomplete emptying of the bladder, renal insufficiency and urinary incontinence). Defective host immune factors (e.g. poorly controlled diabetes or neutropenia) and instrumentation of the urinary tract (e.g. urinary catheters and stents) are also predisposing factors.

Microbiology epidemiology

Lower UTIs are usually caused by bacteria that are part of the human intestinal microbiota, most frequently Escherichia coli. In clinical practice a causative pathogen is usually only identified in more severe cases when urinary cultures are obtained. Pathogens that most frequently cause UTIs are shown in Table 1. Data on causative organisms from LMIC are limited; however, if a difference exists in the proportion of less common pathogens, it is unlikely to affect management. In Africa and the Middle East Schistosoma haematobium can present with haematuria and signs of a UTI, particularly in children.
Table 1 Pathogens most frequently associated with urinary tract infections (in descending order of frequency)

- Enterobacterales (including multidrug-resistant strains such as those producing ESBL’s)
  - *Escherichia coli* (responsible for > 80% of cases)
  - *Klebsiella pneumoniae*
  - *Proteus mirabilis*
- Coagulase-negative Staphylococci
  - *Staphylococcus saprophyticus* (in young women)
- *Streptococcus agalactiae* (group B *Streptococcus*)
- *Enterococcus* spp.
- *Pseudomonas aeruginosa*\(^a\) (including multidrug-resistant strains such as those producing ESBL)
- *Acinetobacter baumannii*\(^a\) (including multidrug-resistant strains such as those producing ESBL)

ESBL: extended-spectrum beta-lactamases.

\(^a\)Especially in patients with recent antibiotic exposure.

Clinical presentation

Classical symptoms of lower UTIs include a combination of acute (< 1 week) dysuria, increased urinary urgency and frequency, lower abdominal pain or discomfort, and sometimes gross haematuria (i.e. blood can be seen in the urine). In women, vaginal discharge or irritation should be excluded before concluding a diagnosis of lower UTI. In elderly patients with pre-existing urinary symptoms (e.g. urinary incontinence), the evaluation may be more difficult. However, the most reliable symptoms in these cases are still acute urinary changes compared with the baseline. Atypical symptoms, such as falls and altered mental status, are unreliable. In addition, cloudy and smelly urine alone are not reliable signs of a UTI.

In children, symptoms can include vomiting, low grade fever, increased urgency, frequency, dysuria, new incontinence, smelly urine or lower abdominal pain and discomfort.

Laboratory tests

I. Patient microbiology tests

In symptomatic patients at a higher risk of complications and in children, a urine culture may be performed (Table 2). The rationale is to confirm the diagnosis and to adjust empiric treatment based on susceptibility results.

In children a clean catch specimen is difficult to obtain but is preferred to a urine specimen obtained with a bag. Positive urine cultures in patients without symptoms (asymptomatic bacteriuria) are frequent and not indicative of bacterial cystitis. Except for very selected cases (e.g. pregnant women, before invasive urologic interventions) asymptomatic bacteriuria should not be treated with antibiotics.
Table 2 Microbiology tests to consider for diagnosis of lower urinary tract infections as indicated in the WHO EDL (54)

<table>
<thead>
<tr>
<th>Diagnostic test</th>
<th>Purpose of the test</th>
<th>Setting where the test should be available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine culture⁴</td>
<td>Initial step to detect and identify bacterial and fungal species for selection of appropriate antibiotic regimens</td>
<td>Health care facilities with clinical laboratories</td>
</tr>
</tbody>
</table>

⁴A positive urine culture in an asymptomatic patient indicates bacterial colonization and does not require treatment except in pregnant women or in patients undergoing urological procedures in which bleeding is anticipated. Bacterial colonization of the urine is a common finding especially in women, in the elderly (both sexes) and in individuals with underlying urological abnormalities. Of note, the absence of urine leucocytes has a good negative predictive value but the positive predictive value of leukocyturia is poor.

II. Other tests

A urinalysis (dipstick or microscopy) may be done to detect the presence of bacteriuria and pyuria (Table 3), while blood tests are not generally used to confirm infection (tests results would be normal in case of lower UTI). In a symptomatic patient, leukocyturia (>10 leukocytes/µL, 10 M/l), the presence of leukocyte esterase and/or positive nitrites are indirect signs of infection. Of note, leukocyturia or presence of leukocyte esterase without symptoms is not an indication for antibiotic treatment.

Table 3 Laboratory tests to consider for diagnosis of lower urinary tract infections as indicated in the WHO EDL (54)

<table>
<thead>
<tr>
<th>Diagnostic test</th>
<th>Purpose of the test</th>
<th>Setting where the test should be available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinalysis test strips</td>
<td>To detect urinary tract infections</td>
<td>Community settings and health facilities without laboratories⁵</td>
</tr>
</tbody>
</table>

⁵Community and health settings without laboratories are settings such as health posts and centres, doctors’ offices, outreach clinics and ambulatory care. These tests are also assumed to be available at health care facilities with laboratories.

III. Using microbiology surveillance data

Empiric guidance given by the Handbook would ideally be guided by recent local clinically relevant microbiology surveillance data. This would include clinical microbiology surveys of urine culture data from patients with lower urinary tract infection in the primary care/community setting (not hospital out-patient clinic data which likely over estimate the prevalence of resistance). These surveys would ideally include information on the current and previous recent antibiotic treatment, clinical disease severity, patient risk factors and clinical outcomes. The focus would be on significant urine bacterial isolates resistant to EML/c recommended antibiotics such as nitrofurantoin.
Imaging

Initial imaging (e.g. ultrasound) of the urinary tract is not needed to diagnose a lower UTI. Imaging to investigate possible underlying abnormalities of the urinary tract could be considered, mostly in children and male patients.

Antibiotic treatment

Antibiotic treatment is usually given empirically if there are compatible signs and symptoms of a UTI AND a positive test (urinalysis or urine culture). If diagnostic tests cannot be performed, treatment may be given based on clinical presentation alone. If a urine culture is performed, empiric treatment should be reassessed once the results of susceptibility testing are available.

Clinical improvement should be within 48–72 hours of starting treatment. In general, antibiotics shorten the duration of symptoms by about 2 days (201). Efforts to reduce patient self-medication with antibiotics should be made as it is still very common in some settings (202).

Local patterns of antimicrobial resistance (mostly to E. coli) should be considered when available but interpreted with caution. In most cases, the summary prevalence of resistance reported by hospital microbiology laboratories will probably not be representative of first infections in the primary healthcare setting and may overestimate “true” prevalence of resistance for lower UTIs because of selection bias.

Most urine cultures are done on patients who have relapsed after their first empiric treatment and are being re-treated or have underlying reason for a higher risk of resistant infections. Most lower UTIs in patients who are not at risk of complications are still caused by pathogens that are susceptible to commonly used antibiotics. However, patterns of resistance based on good quality local data when available and on individual risk factors (e.g. previous urine culture results and recent antibiotic exposure) should be considered (203-205). In particular, E. coli may have varying levels of resistance to first-choice antibiotics (206) and resistance is associated with higher rates of clinical failure (9).

Nitrofurantoin for 5 days is the main antibiotic recommended for acute cystitis. However, the paediatric formulation (syrup) may not be widely available and is currently expensive, even in high-income settings. Nitrofurantoin still has activity against most isolates producing extended-spectrum beta-lactamases (ESBL) (207).

Different empiric antibiotic options for treating lower UTIs are indicated in Table 4;

Treatment duration is influenced by the antibiotic used, the age and sex of the patient, and for women by the presence of pregnancy.

Table 4 Empiric antibiotic treatment for lower urinary tract infections

<table>
<thead>
<tr>
<th>Adults</th>
<th>Children</th>
<th>Total treatment duration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Nitrofurantoin</strong> (oral):</td>
<td><strong>Nitrofurantoin</strong> (oral) 2-4 mg/kg/dose given every 12 hours</td>
<td>5 days</td>
</tr>
<tr>
<td>----------------------------</td>
<td>-------------------------------------------------------------</td>
<td>-------</td>
</tr>
<tr>
<td>• 100 mg given every 12 hours (modified-release formulation)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• 50 mg given every 6 hours (immediate-release formulation)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Sulfamethoxazole+trimethoprim</strong> (oral):</th>
<th><strong>Sulfamethoxazole+trimethoprim</strong> (oral)</th>
<th>3 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>800 mg + 160 mg given every 12 hours</td>
<td>4 mg/kg (of trimethoprim component), every 12 hours</td>
<td></td>
</tr>
<tr>
<td>Oral weight bands:</td>
<td>Oral weight bands:</td>
<td></td>
</tr>
<tr>
<td>(mg of sulfamethoxazole/trimethoprim component)</td>
<td>(mg of sulfamethoxazole/trimethoprim component)</td>
<td></td>
</tr>
<tr>
<td>3-&lt;6 kg: 100mg/20 mg given every 12 hours</td>
<td>3-&lt;6 kg: 100mg/20 mg given every 12 hours</td>
<td></td>
</tr>
<tr>
<td>6-&lt;10 kg: 200mg/40 mg given every 12 hours</td>
<td>6-&lt;10 kg: 200mg/40 mg given every 12 hours</td>
<td></td>
</tr>
<tr>
<td>10-&lt;15 kg: 400mg/80 mg given every 12 hours</td>
<td>10-&lt;15 kg: 400mg/80 mg given every 12 hours</td>
<td></td>
</tr>
<tr>
<td>15-&lt;20 kg: 400mg/80 mg given every 12 hours</td>
<td>15-&lt;20 kg: 400mg/80 mg given every 12 hours</td>
<td></td>
</tr>
<tr>
<td>20-&lt;30 kg: 400mg/80 mg given every 12 hours</td>
<td>20-&lt;30 kg: 400mg/80 mg given every 12 hours</td>
<td></td>
</tr>
<tr>
<td>≥ 30 kg: Use adult dose</td>
<td>≥ 30 kg: Use adult dose</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Trimethoprim</strong> (oral):</th>
<th><strong>Trimethoprim</strong> (oral)</th>
<th>3 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>200 mg given every 12 hours</td>
<td>4 mg/kg, every 12 hours</td>
<td></td>
</tr>
<tr>
<td>Oral weight bands:</td>
<td>Oral weight bands:</td>
<td></td>
</tr>
<tr>
<td>3-&lt;6 kg: 20 mg given every 12 hours</td>
<td>3-&lt;6 kg: 20 mg given every 12 hours</td>
<td></td>
</tr>
<tr>
<td>6-&lt;10 kg: 40 mg given every 12 hours</td>
<td>6-&lt;10 kg: 40 mg given every 12 hours</td>
<td></td>
</tr>
<tr>
<td>10-&lt;15 kg: 80 mg given every 12 hours</td>
<td>10-&lt;15 kg: 80 mg given every 12 hours</td>
<td></td>
</tr>
<tr>
<td>15-&lt;20 kg: 80 mg given every 12 hours</td>
<td>15-&lt;20 kg: 80 mg given every 12 hours</td>
<td></td>
</tr>
<tr>
<td>20-&lt;30 kg: 80 mg given every 12 hours</td>
<td>20-&lt;30 kg: 80 mg given every 12 hours</td>
<td></td>
</tr>
<tr>
<td>≥ 30 kg: Use adult dose</td>
<td>≥ 30 kg: Use adult dose</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Amoxicillin+clavulanic acid</strong> (oral):</th>
<th><strong>Amoxicillin+clavulanic acid</strong> (oral)</th>
<th>3–5 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>500 mg + 125 mg given every 8 hours</td>
<td>40-50 mg/kg/dose of amoxicillin component, given every 12 hours</td>
<td></td>
</tr>
<tr>
<td>OR 30 mg/kg/dose given every 8 hours</td>
<td>OR 30 mg/kg/dose given every 8 hours</td>
<td></td>
</tr>
<tr>
<td>Oral weight bands:</td>
<td>Oral weight bands:</td>
<td></td>
</tr>
<tr>
<td>3-&lt;6 kg: 250 mg of amoxicillin/dose given every 12 hours</td>
<td>3-&lt;6 kg: 250 mg of amoxicillin/dose given every 12 hours</td>
<td></td>
</tr>
<tr>
<td>6-&lt;10 kg: 375 mg of amoxicillin/dose given every 12 hours</td>
<td>6-&lt;10 kg: 375 mg of amoxicillin/dose given every 12 hours</td>
<td></td>
</tr>
<tr>
<td>10-&lt;15 kg: 500 mg of amoxicillin/dose given every 12 hours</td>
<td>10-&lt;15 kg: 500 mg of amoxicillin/dose given every 12 hours</td>
<td></td>
</tr>
<tr>
<td>15-&lt;20 kg: 750 mg of amoxicillin/dose given every 12 hours</td>
<td>15-&lt;20 kg: 750 mg of amoxicillin/dose given every 12 hours</td>
<td></td>
</tr>
<tr>
<td>20-&lt;30 kg: 1000 mg of amoxicillin/dose given every 12 hours</td>
<td>20-&lt;30 kg: 1000 mg of amoxicillin/dose given every 12 hours</td>
<td></td>
</tr>
<tr>
<td>≥ 30 kg: Use adult dose</td>
<td>≥ 30 kg: Use adult dose</td>
<td></td>
</tr>
</tbody>
</table>

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

*a* Resistance to sulfamethoxazole+trimethoprim is high in many settings ([208, 209]). It is ineffective against isolates producing extended-spectrum beta-lactamases (ESBL). Not recommended in the first trimester of pregnancy.

*b* Amoxicillin+clavulanic acid: *Escherichia coli* resistance rates to amoxicillin+clavulanic acid are lower than to amoxicillin alone. This combination still has activity against some ESBL-producing isolates and it can be considered an acceptable option, particularly in young children.

*c* Oral liquid must be refrigerated after reconstitution as clavulanic acid is rapidly metabolized in high ambient temperatures.
In general, shorter treatments are indicated for children or non-pregnant women (3-5 days depending on the antibiotic) while longer treatments are indicated for pregnant women (usually 5 days) or men (usually 7 days).

“Access” antibiotics are highlighted in green, “watch” antibiotics in yellow and “reserve” antibiotics in red.

“No antibiotic care”

Analgesic treatment should be complementary to antibiotic treatment to relieve pain associated with lower UTIs (Table 5). In young women who are not pregnant, clinically well, with a mild infection and who may wish to avoid or delay antibiotic treatment, symptomatic treatment alone (with a back-up antibiotic prescription) could be considered.

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Formulation</th>
<th>Dose and frequency</th>
</tr>
</thead>
</table>
| Paracetamol (acetaminophen)
| Oral liquid: 120 mg/5 mL; 125 mg/5 mL Suppository: 100 mg Tablet: 100 mg to 500 mg | Adults: 500 mg–1 g every 4–6 hours (maximum dose of 4 g a day)³
Children: | Pain control/ Antipyretic treatment: 10–15 mg/kg 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
| Oral liquid: 200 mg/5 mL Tablet: 200 mg, 400 mg, 600 mg | Adults: 200–400 mg every 6–8 hours (maximum dose of 2.4 g a day)
Children: | Pain control (mild pain): 5–10 mg/kg every 6–8 hours
Antipyretic treatment 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 |

³Not recommended for use as an anti-inflammatory as it has not been proven to have such an effect.

²In patients with hepatic impairment or cirrhosis, maximum daily dose should be 2 g.

³Not for children < 3 months.
HOSPITAL
FACILITY
Sepsis in adults

(including septic shock)

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.

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-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](https://apps.who.int/iris/handle/10665/334216)
- 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](https://apps.who.int/iris/handle/10665/310970)
Definition

In some patients with infection, a dysregulated host immune response to the infection contributes to the severity of the disease and organ dysfunction. These patients are at increased risk of death and severe sequelae and should be identified and treated rapidly. The definition of sepsis has remained a challenge because sepsis is not a single entity (the pathogens and primary sites of infection causing sepsis, for example, vary widely) but a continuum of many different clinical presentations.

Because of the serious clinical consequences of sepsis (see section on epidemiology), many attempts have been made to provide clinicians with simple and easy-to-use criteria for identifying 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.

Compared with previous definitions (SEPSIS-1 in 1991 and SEPSIS 2 in 2001), SEPSIS-3 removed the criteria for “systemic inflammatory response syndrome (SIRS)” from the definition because the criteria lacked specificity (SIRS referred to an exaggerated inflammatory response of the body to a noxious cause characterized by a combination of symptoms such as fever or hypothermia, increased heart and / or respiratory rate and increased white blood cell count). SEPSIS-3 also dropped the term severe sepsis because the concept of non-severe sepsis was not helpful (all sepsis being a severe disease) and could be misleading reducing the attention in providing rapid and effective treatment. Instead, SEPSIS-3 differentiates only between sepsis and septic shock. Septic shock is defined as a type of sepsis in which underlying circulatory and cellular and/or metabolic abnormalities are severe enough to substantially increase mortality(211). Patients with septic shock have persistent hypotension that requires vasopressor medication to maintain a mean arterial pressure of 65 mmHg or more and a level of serum lactate more than 2 mmol/L (> 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.
The criteria to identify sepsis according to SEPSIS-3 are difficult to apply in LMIC because severity is based on criteria and tests that may not be routinely available in these settings; for example, the use of inotropes, and determination of arterial oxygen partial pressure, bilirubin levels, creatinine concentrations and platelet counts. Furthermore, the SOFA score (see definition below) has been validated mostly in high-income settings and its performance in LMIC, where causes of sepsis rarely encountered in most high-income settings (e.g. dengue and malaria) are frequent and HIV infection is more prevalent, is unclear.

To implement the SEPSIS-3 definition, clinical and laboratory signs are graded to give an overall score (called the Sequential Organ Failure Assessment (SOFA) score) and an acute change of two or more points in the baseline score is proposed to identify organ dysfunction due to infection and predict the short-term mortality risk (210).

The SOFA score (range 0–24) includes six parameters – two clinical and four laboratory ones. Each parameter can have a value from 0 to 4 (Table 1). The baseline SOFA score can be assumed to be zero in patients with no known pre-existing organ dysfunction.

### Table 1 Sequential Organ Failure Assessment (SOFA) score

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>PaO2 mmHg (kPa)/FiO2 (%)</td>
<td>0</td>
</tr>
<tr>
<td>MAP mmHg (kPa) and catecholamine doses needed</td>
<td></td>
</tr>
<tr>
<td>(µg/kg/min for ≥ 1 h)</td>
<td></td>
</tr>
<tr>
<td>Platelets (x 10^3/µL, x 10^9/L)</td>
<td></td>
</tr>
<tr>
<td>Bilirubin mg/dL (mmol/L)</td>
<td></td>
</tr>
<tr>
<td>Glasgow coma scale</td>
<td></td>
</tr>
<tr>
<td>Creatinine mg/dL (µmol/L)</td>
<td></td>
</tr>
<tr>
<td>Urine output (mL/day)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameter</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>PaO2 mmHg (kPa)/FiO2 (%)</td>
<td>≥ 400 (53.3)</td>
<td>&lt; 400 (53.3)</td>
<td>&lt; 300 (40)</td>
<td>&lt; 200 (26.7)</td>
<td>&lt; 100 (13.3)</td>
</tr>
<tr>
<td>MAP mmHg (kPa) and catecholamine doses needed</td>
<td>MAP ≥ 70 (9.3)</td>
<td>MAP &lt; 70 (9.3)</td>
<td>Dopamine &lt; 5</td>
<td>Dopamine 5.1–15</td>
<td>Dopamine &gt; 15</td>
</tr>
<tr>
<td>(µg/kg/min for ≥ 1 h)</td>
<td></td>
<td></td>
<td>Or dobutamine any dose</td>
<td>Or epinephrine (adrenaline)/ norepinephrine ≤ 0.1</td>
<td>Or epinephrine/ norepinephrine &gt; 0.1</td>
</tr>
<tr>
<td>Platelets (x 10^3/µL, x 10^9/L)</td>
<td>≥ 150</td>
<td>&lt; 150</td>
<td>&lt; 100</td>
<td>&lt; 50</td>
<td>&lt; 20</td>
</tr>
<tr>
<td>Bilirubin mg/dL (mmol/L)</td>
<td>&lt; 1.2 (20)</td>
<td>1.2–1.9 (20–32)</td>
<td>2.0–3.4 (33–101)</td>
<td>3.5–4.9 (300–440)</td>
<td>&gt; 5.0 (440)</td>
</tr>
<tr>
<td>Glasgow coma scale</td>
<td>15</td>
<td>13–14</td>
<td>10–12</td>
<td>6–9</td>
<td>&lt; 6</td>
</tr>
<tr>
<td>Creatinine mg/dL (µmol/L)</td>
<td>&lt; 1.2 (110)</td>
<td>1.2–1.9 (110–170)</td>
<td>2.0–3.4 (171–299)</td>
<td>3.5–4.9 (300–440)</td>
<td>&gt; 5.0 (440)</td>
</tr>
<tr>
<td>Urine output (mL/day)</td>
<td>&lt; 500</td>
<td>&lt; 200</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FIO2: fractional inspired oxygen; PaO2: arterial oxygen partial pressure; MAP: mean arterial pressure.

The Glasgow coma scale is a clinical scale used to measure a person's level of consciousness based on the assessment of three parameters: eye opening response (max 4 points assigned), best verbal response (max 5 points assigned) and best motor response (max 6 points assigned). The total score can range from 3 (completely unresponsive) to 15 (responsive). Scores below 8 usually indicate a comatose state. To calculate the Glasgow coma scale, several online calculators exist.

A simplified quick version of the SOFA score called qSOFA (Table 2) exists that only includes three clinical criteria (mental status, blood pressure and respiratory rate) and an increase by two points can be used at the bedside for early identification of sepsis even in low-resource settings (213). A retrospective analysis of cohort studies conducted in 17 hospitals in 10 LMIC in sub-Saharan Africa, Asia and the Americas found that a high qSOFA score identified patients with infections.
who were at an increased risk of death (beyond the risk they had based on their baseline risk factors), with some variability among cohorts (214).

Table 2 qSOFA (quick Sequential Organ Failure Assessment) scoring

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory rate</td>
<td>≥ 22 breaths/min</td>
</tr>
<tr>
<td>Altered mental status</td>
<td>Glasgow coma scale &lt; 15&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>≤ 100 mmHg (≤ 13.3 kPa)</td>
</tr>
</tbody>
</table>

<sup>a</sup>The Glasgow coma scale is a clinical scale used to measure a person's level of consciousness based on the assessment of three parameters: eye opening response (max 4 points assigned), best verbal response (max 5 points assigned) and best motor response (max 6 points assigned). The total score can range from 3 (completely unresponsive) to 15 (responsive). Scores below 8 usually indicate a comatose state. To calculate the Glasgow coma scale, several online calculators exist.

Pathophysiology

Sepsis is a serious and complex clinical condition caused by the complicated interplay between an infectious agent and a dysregulated systemic immunological response by the patient, potentially resulting in multiple organ dysfunction and possibly death. Risk factors for sepsis mostly overlap with those that predispose patients to infection (e.g. very old and very young, immunosuppression due to HIV, cancer or medications, cirrhosis, alcohol abuse, poorly controlled diabetes, indwelling catheters and malnutrition). Genetic factors are also implicated in the likelihood of developing sepsis in patients with an infection (215).

Epidemiology

Sepsis is an important global health problem that can be difficult to diagnose and manage, especially in low-income settings (216, 217). According to the Global Burden of Disease study, about 49 million new cases of sepsis occurred worldwide in 2017, a decrease of almost 19% compared with 1990 (218). The most common underlying cause of sepsis is still diarrhoeal disease (9 million attributable cases in 2017). The number of sepsis-related deaths decreased worldwide (a 29% decrease compared with 1990) but deaths were still high (11 million in 2017) with the highest burden in sub-Saharan Africa. The most common underlying cause of sepsis-related death was lower respiratory tract infections (1.8 million attributable deaths in 2017). Children were more affected by sepsis than adults; in 2017, 20 million new cases of sepsis were in children < 5 years of age (see the chapter on sepsis in children and neonates). However, a second peak in incidence in older adults was reported. About one in four cases of sepsis is estimated to be hospital-acquired with high mortality rates (219).

Sepsis can also develop during pregnancy or in the first weeks after delivery. This form of sepsis is called maternal sepsis. In 2017, about 12 million new cases of maternal sepsis were reported (218). In the period 2003–2009, sepsis was the third leading cause of maternal death worldwide (10.7% of all maternal deaths or about 260 000 deaths) after haemorrhage and
hypertensive disorders(220). Based on results of the global maternal sepsis study from more than 700 facilities in 52 countries, 70 pregnant women per 1000 live births in the study cohort were hospitalized with an infection, mostly of bacterial origin (77% of those where a pathogen was identified)(221). Infections with severe maternal outcomes (e.g. death) were frequent, 11 per 1000 live births; however, large variations existed across countries – 15 per 1000 live births in low- and middle-income countries and 0.6 per 1000 in high-income countries(221). Infections originated most often from the genital (endometritis and chorioamnionitis) or urinary tract followed by skin, respiratory and abortion-related infections(221).

Infections with antibiotic-resistant bacteria are an increasingly important cause of sepsis worldwide with important implications for the management, especially in settings with limited resources. Antibiotic resistance can affect patient outcomes, increasing short-term mortality, mostly because in these cases effective antibiotic treatment active against the resistant pathogen may not be available or given late. In a 2015 European study, 170 disability-adjusted life years (DALYs, a proxy for morbidity and mortality) per 100 000 population were due to infections caused by antibiotic-resistant bacteria, of which about 70% were caused by bloodstream infections(222).

In 2017, the World Health Assembly adopted a resolution on sepsis to urge WHO Member States to implement measures to reduce the burden of sepsis by increasing efforts to improve sepsis prevention, diagnosis and treatment, including through increased research, training of health care professionals and public awareness campaigns(223).

Microbiology epidemiology

Sepsis can originate from any type of infection (bacterial, viral, fungal and protozoal) in any organ system. Infections can be community-acquired (CAI) or hospital acquired (HAI) (or health care-associated). The bacterial pathogens associated with sepsis will vary widely depending on the primary site of infection, geography and place of acquisition (community/hospital see table 3).

The mortality from sepsis is higher with infections caused by multi-drug resistant bacteria, which are commonly identified in HAI.

Table 3: Pathogens most frequently identified in blood cultures in patients with sepsis (also refer to Box 2 about bacteremia)

<table>
<thead>
<tr>
<th></th>
<th>Bacteria</th>
<th>Viruses</th>
<th>Parasites</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Community setting</strong></td>
<td><em>Escherichia coli, Klebsiella pneumoniae</em> and other Enterobacterales (including multidrug-resistant strains such as those producing ESBL and carbapenemases)</td>
<td><em>Staphylococcus aureus</em> (including MRSA)</td>
<td><strong>In endemic settings or after travel to endemic settings:</strong> Plasmodium spp. (pathogen causing malaria)</td>
</tr>
<tr>
<td></td>
<td><strong>In endemic settings or after travel to endemic settings:</strong> Respiratory viruses such as Influenza virus and SARS-CoV-2</td>
<td><strong>In endemic settings or after travel to endemic settings:</strong> Viruses causing viral haemorrhagic fevers (e.g. dengue, yellow fever, Ebola virus disease, Lassa fever, Marburg virus disease)</td>
<td><strong>In endemic settings or after travel to endemic settings:</strong> Plasmodium spp. (pathogen causing malaria)</td>
</tr>
</tbody>
</table>

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**Streptococcus pneumoniae**  
(including penicillin non-susceptible strains)  

*Salmonella* spp. (including *Salmonella Typhi* and *Paratyphi*)  

*Streptococcus pyogenes*  
(group A *Streptococcus*)  

*Neisseria meningitidis*  
(including strains resistant to third-generation cephalosporins)  

*Burkholderia pseudomallei*  
(pathogen causing melioidosis)

| Hospital setting | *Acinetobacter baumannii* and *Pseudomonas aeruginosa*  
(including multidrug-resistant strains such as those producing ESBL and carbapenemases)  

*Escherichia coli, Klebsiella pneumoniae* and other *Enterobacterales*  
(including multidrug-resistant strains such as those producing ESBL and carbapenemases)  

*Staphylococcus aureus*  
(including MRSA)

| Maternal sepsis | *Listeria monocytogenes*  

*Streptococcus agalactiae*  
(group B *Streptococcus*)

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**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.
Patients with sepsis usually present with non-specific signs and symptoms. The most frequent symptoms include fever (> 38.0 °C) or hypothermia (< 36.0 °C), some degree of respiratory distress (e.g. increased respiratory rate), tachycardia, acute altered mental status (e.g. disorientation and agitation) and hypotension. Oliguria (i.e. reduced urine output) may also be present.

Sepsis may be more difficult to diagnose in countries where vector-transmitted diseases (e.g. malaria and dengue) are endemic; therefore, sepsis should always be considered if there are any signs and symptoms of sepsis in these settings.

As outlined above, bacteraemia (i.e. the detection of bacteria in blood cultures) may be present depending on the type of pathogen, the primary site of infection and whether antibiotic treatment was administered before obtaining blood cultures. However, bacteraemia is not always found in patients with sepsis and on the other hand most patients with bacteraemia do 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.

**Sepsis of unknown origin**: treatment is based on the most probable clinical situation. Patients should be carefully examined to localize a source of infection, including pressure ulcers, deep-seated abscesses and indwelling vascular and urinary catheters. In n patients with central lines, the possibility of a central line-associated bloodstream infection should be considered with a positive blood culture and no other apparent source of infection. Bloodstream infections can also be associated with peripheral vascular lines.

### Laboratory tests

#### 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.

Microbiology tests help establish a definitive diagnosis of sepsis and identify the causative pathogen and underlying infection. Isolating a pathogen from a normally sterile body site (e.g. blood, cerebrospinal fluid) that is compatible with the clinical signs and symptoms usually confirms diagnosis. However, the causative pathogen is not identified in a substantial proportion of cases especially in patients pre-treated with antibiotics.

Tests to consider when sepsis of bacterial origin is suspected include those listed in Table 4. Ideally, these tests should be done before starting antibiotic treatment.
Table 4 Microbiology tests to consider when sepsis of bacterial origin is suspected depending on the most likely source of infection as indicated in the WHO EDL (54)

<table>
<thead>
<tr>
<th>Suspected underlying infection</th>
<th>Diagnostic test</th>
<th>Purpose of the test</th>
<th>Settings where the test should be available</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cases where sepsis is suspected</td>
<td>Blood cultures</td>
<td>To detect bacterial bloodstream infections (sepsis)</td>
<td>Health care facilities with clinical laboratories</td>
</tr>
<tr>
<td>Lower respiratory tract infection</td>
<td>Sputum microscopy (Gram stain)</td>
<td>To assess microbial morphology and adequacy of the specimen for culture by identifying white blood cells and squamous epithelial cells</td>
<td>Health care facilities with clinical laboratories</td>
</tr>
<tr>
<td>Lower respiratory tract infection</td>
<td>Sputum culture</td>
<td>Initial step to detect and identify bacterial and fungal species for selection of appropriate antibiotic regimens</td>
<td>Health care facilities with clinical laboratories</td>
</tr>
<tr>
<td>Meningitis</td>
<td>Cerebrospinal fluid Gram stain and bacterial culture</td>
<td>Initial step to detect and identify bacterial and fungal species for selection of appropriate antibiotic regimens</td>
<td>Health care facilities with clinical laboratories</td>
</tr>
<tr>
<td>Meningitis</td>
<td>Cerebrospinal fluid microscopy</td>
<td>To assess microbial morphology, number of white blood cells and red blood cells</td>
<td>Health care facilities with clinical laboratories</td>
</tr>
<tr>
<td>Diarrhoeal disease, enteric fever*</td>
<td>Stool culture</td>
<td>Initial step to detect and identify bacterial species for selection of appropriate antibiotic regimens</td>
<td>Health care facilities with clinical laboratories</td>
</tr>
<tr>
<td>Abscess (e.g. in the context of intra-abdominal infections, skin and soft-tissue infections, dental infections)</td>
<td>Culture of abscess and/or fluid collections that can be drained</td>
<td>Initial step to detect and identify bacterial and fungal species for selection of appropriate antibiotic regimens</td>
<td>Health care facilities with clinical laboratories</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>Urine culture</td>
<td>Initial step to detect and identify bacterial and fungal species for selection of appropriate antibiotic regimens</td>
<td>Health care facilities with clinical laboratories</td>
</tr>
</tbody>
</table>

*If enteric fever is suspected, note that stool cultures have a low sensitivity and are not useful in the early phase (first week) of the disease when the test is often negative.

II. Other tests

Laboratory tests can be used to complement the clinical examination and history. Tables 5 and 6 indicate the tests that could be considered to make an initial assessment of the patient and to help guide the duration of antibiotic treatment. Additional laboratory tests may be considered based on local availability.
### Table 5 Laboratory tests (other than microbiology) to consider when sepsis is suspected to identify a bacterial infection as indicated in the WHO EDL (54)

<table>
<thead>
<tr>
<th>Diagnostic test</th>
<th>Purpose of the test</th>
<th>Settings where the test should be available</th>
</tr>
</thead>
<tbody>
<tr>
<td>White blood count</td>
<td>To help in the diagnosis of infections</td>
<td>Health care facilities with clinical laboratories but also in primary care settings</td>
</tr>
<tr>
<td>C-reactive proteina</td>
<td>To detect inflammation as an indicator of various conditions (e.g. sepsis)</td>
<td>Health care facilities with clinical laboratories</td>
</tr>
<tr>
<td>Procalcitonina</td>
<td>To guide antibiotic therapy or discontinuation in sepsis</td>
<td>Only in tertiary health care facilities</td>
</tr>
</tbody>
</table>

*Biomarkers (C-reactive protein and procalcitonin) may help determine whether an infection is caused by bacteria and regular serial measurement of these biomarkers can also help decide when antibiotic therapy can be stopped* (224) (225, 226). It is important to note that the probability of sepsis based on the patient’s initial clinical assessment before testing (pre-test probability) needs to be considered. If the pre-test probability is high, inflammatory markers in the normal range do not rule out sepsis.

### Table 6 Laboratory tests (other than microbiology) to consider when sepsis is suspected to identify organ dysfunction as indicated in the WHO EDL (54)

<table>
<thead>
<tr>
<th>Diagnostic test</th>
<th>Purpose of the test</th>
<th>Settings where the test should be available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilirubin</td>
<td>To detect or monitor liver disease, bile duct disorders and red cell destruction (SOFA score calculation)</td>
<td>Community settings and health facilities without laboratories&lt;br&gt;</td>
</tr>
<tr>
<td>Blood pH and gases</td>
<td>To assess lung function and metabolic or kidney disorders, and monitor oxygen therapy (SOFA score calculation (for PaO2/FiO2))</td>
<td>Health care facilities with clinical laboratories</td>
</tr>
<tr>
<td>Blood urea nitrogen</td>
<td>To assess kidney function (CURB-65 score calculation) if pneumonia is suspected</td>
<td>Health care facilities with clinical laboratories</td>
</tr>
<tr>
<td>Complete blood count</td>
<td>To detect a wide range of disorders, including infections</td>
<td>Health care facilities with clinical laboratories</td>
</tr>
<tr>
<td>Creatinine</td>
<td>To monitor kidney function for management of severe infections (i.e. sepsis) and to adjust antimicrobial regimen (SOFA score calculation)</td>
<td>Health care facilities with clinical laboratories</td>
</tr>
<tr>
<td>Electrolytes</td>
<td>To monitor fluid, electrolyte and acid–base balance</td>
<td>Health care facilities with clinical laboratories</td>
</tr>
<tr>
<td>Glucose</td>
<td>To diagnose intermediate hyperglycaemia and hypoglycaemia</td>
<td>Community settings and health facilities without laboratories&lt;br&gt;</td>
</tr>
<tr>
<td>Haemoglobin</td>
<td>To diagnose and monitor anaemia (e.g. malaria and viral haemorrhagic fevers)</td>
<td>Community settings and health facilities without laboratories&lt;br&gt;</td>
</tr>
</tbody>
</table>
**III. Using microbiology surveillance data**

Empiric guidance given by the Handbook could be reviewed and adapted based on local clinically relevant microbiology surveillance data. For example, clinically relevant isolates for this infection would be blood culture data of significant isolates from patients with confirmed sepsis.

**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.

When sepsis is suspected and respiratory distress is present, a chest X-ray (or lung ultrasound) is indicated to confirm a lower respiratory tract infection. If an abdominal source of infection is suspected, in settings where it is available, a computed tomography scan of the abdomen could be considered (e.g. to confirm an intra-abdominal infection). A low-dose computed tomography scan is an acceptable option, including in pregnant women(227). However, because abdominal ultrasound is more widely available, it can be a very helpful alternative depending on the exact site of infection. If sepsis caused by an infection of the urinary tract is suspected, initial imaging (e.g. ultrasound) of the urinary tract or during follow-up could be considered if an outflow obstruction (e.g. because of urolithiasis) or an abscess are suspected.

**Treatment**

Treatment of sepsis includes treatment of the underlying infection and life-saving interventions such as fluid resuscitation and vital organ support which are beyond the scope of this Handbook. For more specific guidance on treating sepsis, please refer to the 2016 international guidelines for management of sepsis and septic shock(228). Please also consult a 2016 review on the pathophysiology and clinical management of sepsis(229).
Antibiotic treatment

(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.

When selecting empiric antibiotic treatment, several factors should be considered, such as the most likely site of primary infection, the infecting pathogens, and the local pattern of antimicrobial resistance. Comorbidities of the patient including malnutrition and immunosuppression (e.g. due to HIV or neutropenia) and other factors, such as known colonization and/or previous infection with multidrug-resistant organisms, are also important factors to consider. Many variables must be considered to provide the best treatment to patients with sepsis.

Table 7 outlines suggested empiric treatment regimens for common primary sites of infection. In many infections (e.g. necrotizing fasciitis and intra-abdominal infections), source control (e.g. drainage of an abscess, surgical debridement) is essential.

If the pathogen causing the infection is identified and once its antibiotic susceptibilities are known, antibiotics should be reviewed and modified accordingly. However, even if enough suitable samples have been obtained and tested, a pathogen is identified only in a minority of patients with sepsis(230). When no pathogen is identified, antibiotic treatment should be guided by available laboratory results and clinical response. If an alternative cause of a non-bacterial cause of sepsis has been identified, the possibility to stop treatment should be evaluated.

Treatment duration is often decided on an individual basis according to clinical response and (if available) changes in laboratory markers of infection.

Simplify empiric treatment to a more narrow-spectrum antibiotic based on culture results or based on rapid clinical improvement when no microbiology test results are available. In general, the intravenous (IV) route is preferred, for the initial phase of treatment.

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

In patients with suspected sepsis of bacterial origin, a risk assessment based on clinical factors needs to be done followed by appropriate tests and investigations to choose the best empiric antibiotic treatment. Patient-level and setting-level risk factors for infections caused by resistant bacteria need to be carefully considered.

- Low-risk patients: patients with no clinical risk factors for adverse outcomes. These patients have a low risk of infections caused by multidrug-resistant bacteria.
**High-risk patients**: patients with major pre-existing comorbidities or immunosuppressed and/or previous colonization or infection with a resistant pathogen. These patients have a higher risk of infections caused by multidrug-resistant bacteria.

**Table 7 Empiric antibiotic treatment for community-acquired sepsis of bacterial origin in adults**

<table>
<thead>
<tr>
<th>Most probable source of infection</th>
<th>Empiric antibiotic treatment</th>
<th>Total treatment duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical sepsis of unknown origin</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td><strong>Ceftriaxone</strong>&lt;sup&gt;b&lt;/sup&gt; (IV): 2 g given once a day OR <strong>Cefotaxime</strong>&lt;sup&gt;b&lt;/sup&gt; (IV): 2 g given every 8 hours AND <strong>Gentamicin</strong>&lt;sup&gt;c&lt;/sup&gt; (IV): 5 mg/kg given once a day OR <strong>Amikacin</strong>&lt;sup&gt;c&lt;/sup&gt;: 15 mg/kg given once a day</td>
<td>7 days (but duration depends on the patient’s underlying disease, the causative pathogen (if any identified later on) and clinical progression)</td>
</tr>
<tr>
<td><strong>Enteric fever</strong></td>
<td><strong>Ceftriaxone</strong>&lt;sup&gt;d&lt;/sup&gt; (IV): 2 g given once a day</td>
<td>10 days</td>
</tr>
<tr>
<td><strong>Intra-abdominal infection</strong></td>
<td><strong>First choice</strong></td>
<td>Generally 7 days. Duration depends on type of infection, whether adequate surgical source control was achieved and on clinical recovery. Please refer to specific chapters of the Handbook based on the suspected underlying infection</td>
</tr>
<tr>
<td></td>
<td><strong>Ceftriaxone</strong> (IV): 2 g given once a day AND <strong>Metronidazole</strong> (IV): 500 mg given every 8 hours OR <strong>Cefotaxime</strong> (IV): 2 g given every 8 hours AND <strong>Metronidazole</strong> (IV): 500 mg given every 8 hours OR <strong>Piperacillin+tazobactam</strong>&lt;sup&gt;e&lt;/sup&gt; (IV): 4 g + 500 mg given every 6 hours</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Second choice</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Meropenem</strong> (IV): 2 g given every 8 hours</td>
<td></td>
</tr>
<tr>
<td><strong>Meningitis</strong></td>
<td><strong>First choice</strong></td>
<td>10 days&lt;sup&gt;g&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td><strong>Ceftriaxone</strong> (IV): 2 g given every 12 hours OR <strong>Cefotaxime</strong> (IV): 2 g given every 6 hours</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Second choice</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Ampicillin</strong> (IV): 2 g given every 4 hours OR <strong>Amoxicillin</strong> (IV): 2 g given every 4 hours</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Chloramphenicol</strong>&lt;sup&gt;h&lt;/sup&gt; (IV): 1 g given every 6 hours OR <strong>Benzylpenicillin</strong> (IV): 4 million international units (2.4 g) given every 4 hours</td>
<td></td>
</tr>
<tr>
<td><strong>Lower respiratory tract infection</strong></td>
<td><strong>Ceftriaxone</strong> (IV): 2 g given once a day OR <strong>Cefotaxime</strong> (IV): 2 g given every 8 hours AND <strong>Clarithromycin</strong> (IV): 500 mg given every 12 hours</td>
<td>5 days</td>
</tr>
</tbody>
</table>
### Skin and soft tissue infection

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>Dosage</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftriaxone (IV):</td>
<td>2 g given once a day</td>
<td>7 days</td>
</tr>
<tr>
<td>AND Metronidazole (IV):</td>
<td>500 mg given every 8 hours</td>
<td></td>
</tr>
<tr>
<td>(In case of necrotizing fasciitis, use this treatment option only if <em>Streptococcus pyogenes</em> infection has been excluded first)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Piperacillin+tazobactam (IV):</td>
<td>4 g + 500 mg given every 6 hours</td>
<td></td>
</tr>
<tr>
<td>AND Clindamycin (IV):</td>
<td>900 mg given every 8 hours</td>
<td></td>
</tr>
<tr>
<td>If MRSA is suspected, ADD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vancomycin (IV):</td>
<td>15–20 mg/kg given every 12 hours</td>
<td></td>
</tr>
</tbody>
</table>

### Urinary tract infection

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>Dosage</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftriaxone (IV):</td>
<td>1 g given once a day</td>
<td>7 days</td>
</tr>
<tr>
<td>OR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefotaxime (IV):</td>
<td>1 g given every 8 hours</td>
<td></td>
</tr>
<tr>
<td>AND Amikacin (IV):</td>
<td>15 mg/kg given once a day</td>
<td></td>
</tr>
</tbody>
</table>

Notes: All dosages are for normal renal and hepatic function. Dose adjustments may be required in patients with septic shock.

IV: intravenous.

If the source of the infection is determined please follow infection-specific guidance.

Gentamicin and amikacin are alternative options. The choice can be made based on local availabilities.

Amikacin is still effective against isolates producing extended-spectrum beta-lactamases (ESBL) and is considered an appropriate carbapenem-sparing option in settings where ESBL-producing isolates are very prevalent.

Some countries may have problems of increasing ceftriaxone resistance.

In patients considered at risk of infections with ESBL-producing Enterobacterales, piperacillin+tazobactam does not provide adequate activity against many ESBL-producing isolates. In these cases, meropenem can be considered.

Meropenem should be considered only in settings with a high prevalence of ESBL-producing Enterobacterales.

Duration differs in the context of epidemics as indicated by WHO (231) and also depending on the pathogen identified.

Use chloramphenicol only when no other choice is available.

Ceftriaxone and metronidazole is the preferred option if the suspected source of infection is polymicrobial (type 1) necrotizing fasciitis but it is also an adequate option in case of severe cellulitis.

Piperacillin+tazobactam (or penicillin) and clindamycin is the preferred option if the suspected source of infection is necrotizing fasciitis caused by *Streptococcus pyogenes* but it is also an adequate option in case of severe cellulitis.

Alternative antibiotics to consider based on local resistance data are piperacillin+tazobactam and carbapenems.

Amikacin is still effective against ESBL-producing isolates and is considered an appropriate carbapenem-sparing option in settings where ESBL-producing isolates are prevalent.

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

### Prevention

Any infection can progress to sepsis; therefore, preventing sepsis requires either preventing the infection or preventing the progression of the infection to sepsis.

Factors that contribute to preventing infections in the community include: vaccinations (Table 8), adequate nutrition and healthy living environments (including access to safe water and sanitation). It is beyond the scope of this chapter to address in detail these topics.
Table 8 Vaccinations to consider for prevention of certain infections

<table>
<thead>
<tr>
<th>Vaccination</th>
<th>Population where the vaccine should be considered</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meningococcal vaccination(232)</td>
<td>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. 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.</td>
</tr>
<tr>
<td>Pneumococcal vaccination(39)</td>
<td>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).</td>
</tr>
<tr>
<td><em>Salmonella</em> Typhi vaccination(144)</td>
<td>Individuals living in countries with a high burden of enteric fever or antimicrobial-resistant <em>Salmonella</em> Typhi should be vaccinated with typhoid conjugate vaccines. Vaccination should also be offered during outbreaks.</td>
</tr>
</tbody>
</table>

*References are to WHO position papers that support the evidence for vaccination.*
Sepsis in neonates (<28 days) and children (28 days–12 years)

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

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-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](https://apps.who.int/iris/handle/10665/334216)

Definition
Because of differences in the microbiology, sepsis in children is often classified into neonatal sepsis (newborns < 28 days) and pediatric sepsis (28 days–12 years).

Neonatal sepsis
There is no universally accepted definition of neonatal sepsis and definitions vary among studies(233). However, the term is used to describe a serious systemic condition of infectious origin (most commonly bacterial) associated with a combination of clinical and laboratory signs that occurs in the first month of life.

Neonates are much more likely to have a primary bloodstream infection with no underlying source of infection identified. Furthermore, because of differences in the host (neonates have reduced immune responses) and the way the pathogen can be acquired (e.g. exposure to maternal pathogens at birth or in utero), the sepsis definitions currently used for adults and older children are not specifically designed for use in young infants(234, 235).

Neonatal sepsis has historically been categorized based on either the timing of clinical disease onset (Early Onset Sepsis [EOS] or Late Onset Sepsis [LOS]) or based on where the infection was likely acquired (Community Acquired Infection [CAI] –or Hospital Acquired Infection [HAI]) (Box 1). The aim of these categorizations is to predict the most likely causative pathogens and guide empiric treatment. However, these categorizations have become less helpful as more infants worldwide are born in health care facilities and are exposed to multidrug-resistant pathogens in the early neonatal period either acquired from their mother or through nosocomial acquisition in the health facility or hospital.

Box 1 Commonly used classifications of neonatal sepsis

By timing of onset
- early onset* (occurring ≤ 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

*A range of different post-natal ages have been used to define EOS, including less than 3, 5 or 7 days of life.

In settings with limited access to any laboratory tests, an alternative clinical definition used by the WHO is “possible Serious Bacterial Infection” (pSBI) (236, 237). This definition is based on the presence of multiple clinical signs. If at least one of the signs is present, the neonate or young
infant requires prompt treatment with antibiotics. Relevant signs to consider include difficulty
feeding, history of convulsions, movement only when stimulated, respiratory rate > 60
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).

Clinical signs and symptoms are important predictors of neonatal sepsis, as well as perinatal risk factors (e.g. prematurity/gestational age). Several scores exist that measure severity of sepsis and help predict short-term mortality, but these are virtually all derived in the high-income setting. Scores are used to promptly identify neonates who would benefit the most from optimal antibiotic treatment and supportive care.

Because of its simplicity, one of the most frequently used scores is the Score for Neonatal Acute Physiology–II (SNAP-II score) (238). This score was developed in 2001 to predict outcomes (usually short-term mortality) in cases of possible neonatal sepsis. It should be noted, however, that this score has not been extensively validated in LMIC and therefore there is no clear consensus on its use. Some evidence exists from LMIC settings that SNAP-II scores differ significantly in neonates with sepsis who survive or die in the short-term irrespective of gestational age (239). The SNAPPE-II score is an extension of the SNAP-II score which includes additional perinatal parameters (238).

**Sepsis in children beyond neonatal age**

The WHO Integrated Management of Childhood Illnesses (WHO-IMCI) defines sepsis as “a diagnosis of exclusion, characterized by the presence of acute fever (> 39.0 °C) and severe illness when no other cause is found” (indicating that it is possibly caused by an infection)(23). The definition outlined above (in the section about neonatal sepsis) of possible Serious Bacterial Infection can also be used beyond neonatal age to children under 5 years.

Other paediatric sepsis definitions in use include:

- International Pediatric Sepsis Consensus Conference, 2005(240). Suspected or proven infection caused by any pathogen or clinical syndrome associated with a high probability of infection AND systemic inflammatory response syndrome. Systemic inflammatory response syndrome is defined as abnormal temperature or white blood cell count AND one of the following age-adjusted signs: tachycardia or bradycardia, tachypnoea and/or mechanical ventilation(241).
Paediatric adaptation of the Sepsis-3 adult sepsis definition, including the paediatric version of the Sequential Organ Failure Assessment (pSOFA) score (Table 3) (242).

**Table 3 Paediatric Sequential Organ Failure Assessment (pSOFA) score**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Score</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PaO2 mmHg (kPa)/FiO2 (%)</strong></td>
<td></td>
<td>≥ 400 (53.3)</td>
<td>&lt; 400 (53.3)</td>
<td>&lt; 300 (40)</td>
<td>&lt; 200 (26.7)</td>
<td>&lt; 100 (13.3)</td>
</tr>
<tr>
<td><strong>MAP mmHg (kPa) by age group (in months) and catecholamine doses needed (µg/kg/min for ≥ 1 h)</strong></td>
<td></td>
<td>≥ 46 (6.1)</td>
<td>&lt; 46 (6.1)</td>
<td>Dopamine &lt; 5 OR Dobutamine any dose</td>
<td>Dopamine 5.1–15 OR Epinephrine (adrenaline)/norepinephrine ≤ 0.1</td>
<td>Dopamine &gt;15 OR epinephrine/norepinephrine &gt; 0.1</td>
</tr>
<tr>
<td><strong>&lt; 1</strong></td>
<td></td>
<td>≥ 55 (7.3)</td>
<td>&lt; 55 (7.3)</td>
<td>As above</td>
<td>As above</td>
<td>As above</td>
</tr>
<tr>
<td><strong>1–11</strong></td>
<td></td>
<td>≥ 60 (8)</td>
<td>&lt; 60 (8)</td>
<td>As above</td>
<td>As above</td>
<td>As above</td>
</tr>
<tr>
<td><strong>12–23 (1–2 years)</strong></td>
<td></td>
<td>≥ 62 (8.2)</td>
<td>&lt; 62 (8.2)</td>
<td>As above</td>
<td>As above</td>
<td>As above</td>
</tr>
<tr>
<td><strong>24–59 (2–5 years)</strong></td>
<td></td>
<td>≥ 65 (8.6)</td>
<td>&lt; 65 (8.6)</td>
<td>As above</td>
<td>As above</td>
<td>As above</td>
</tr>
<tr>
<td><strong>60–143 (6–11 years)</strong></td>
<td></td>
<td>≥ 67 (8.9)</td>
<td>&lt; 67 (8.9)</td>
<td>As above</td>
<td>As above</td>
<td>As above</td>
</tr>
<tr>
<td><strong>144–216 (12–18 years)</strong></td>
<td></td>
<td>≥ 150 (20)</td>
<td>&lt; 150</td>
<td>&lt; 100</td>
<td>&lt; 50</td>
<td>&lt; 20</td>
</tr>
<tr>
<td><strong>Platelets (x 10^3/µL, x 10^9/L)</strong></td>
<td></td>
<td>&lt; 1.2 (20)</td>
<td>1.2–1.9 (20–32)</td>
<td>2–5.9 (33–101)</td>
<td>6.0–11.9 (102–204)</td>
<td>&gt; 12.0 (204)</td>
</tr>
<tr>
<td><strong>Bilirubin mg/dL (mmol/L)</strong></td>
<td></td>
<td>15</td>
<td>13–14</td>
<td>10–12</td>
<td>6–9</td>
<td>&lt; 6</td>
</tr>
<tr>
<td><strong>Glasgow coma scale</strong></td>
<td></td>
<td>&lt; 0.8 (71)</td>
<td>0.8–0.9 (71-80)</td>
<td>1.0–1.1 (88-97)</td>
<td>1.2–1.5 (110-133)</td>
<td>≥ 1.6 (141)</td>
</tr>
<tr>
<td><strong>Creatinine mg/dL (µmol/L) by age group (months)</strong></td>
<td></td>
<td>&lt; 0.3 (26)</td>
<td>0.3–0.4 (26-35)</td>
<td>0.5–0.7 (44-62)</td>
<td>0.8–1.1 (71-97)</td>
<td>≥ 1.2 (110)</td>
</tr>
<tr>
<td><strong>&lt; 1</strong></td>
<td></td>
<td>0.4–0.5 (35)</td>
<td>0.6–1.0 (53-88)</td>
<td>1.1–1.4 (97-124)</td>
<td>≥ 1.5 (133)</td>
<td>≥ 2.3 (203)</td>
</tr>
<tr>
<td><strong>12–23 (1–2 years)</strong></td>
<td></td>
<td>0.6–0.8 (53)</td>
<td>0.9–1.5 (79-133)</td>
<td>1.6–2.2 (141-195)</td>
<td>≥ 2.6 (230)</td>
<td></td>
</tr>
</tbody>
</table>
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**

<table>
<thead>
<tr>
<th>Age group</th>
<th>Heart rate (beats/min)</th>
<th>Respiratory rate (breaths/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 month–1 year</td>
<td>&gt; 160 or &lt; 90</td>
<td>&gt; 34</td>
</tr>
<tr>
<td>2–5 years</td>
<td>&gt; 140</td>
<td>&gt; 22</td>
</tr>
<tr>
<td>6–12 years</td>
<td>&gt; 130</td>
<td>&gt; 18</td>
</tr>
<tr>
<td>13–18 years</td>
<td>&gt; 110</td>
<td>&gt; 14</td>
</tr>
</tbody>
</table>

**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.

### Pathophysiology

Sepsis is an acute life-threatening condition characterized by organ dysfunction/s due to a dysregulated host response to infection and to the direct effect of the pathogen (243). A combination of factors contributes to the clinical manifestation and severity of sepsis. Severity of sepsis depends on a combination of the amount and virulence of the pathogen and the immune status of the host (e.g. immunological immaturity or dysfunction in preterm neonates, severe malnutrition, HIV infection). In addition, the timing of exposure to the pathogen plays an
important role in neonates. In this age group, early onset sepsis is usually associated with in utero infections (e.g. chorioamnionitis) or infections caused by pathogens that colonize the maternal genital tract and that can be acquired during delivery. Late onset sepsis is more commonly associated with postnatal acquisition of community- or health care-associated pathogens.

Sepsis in neonates has a nonspecific clinical presentation and many neonates with suspected sepsis who receive antibiotics do not have sepsis and do not have any significant infection. This should be considered when sepsis is suspected to avoid overdiagnosis and overtreatment.

Beyond the neonatal age, sepsis in children can also be a primary bacterial bloodstream infection (e.g. meningococcal or pneumococcal sepsis), most commonly community-acquired. Sepsis in children may also be the result of an underlying infection in a particular site (pyelonephritis, intra-abdominal infection or meningitis) or a health care-acquired infection.

**Epidemiology**

In 2015, about 6 million children under 5 years of age were estimated to have died, mostly in sub-Saharan Africa and southern Asia(108). Neonates account for about half of the deaths in this age group. Overall about 2.7 million neonates died in 2015 and of these, about 400 000 were estimated to be the result of sepsis or meningitis (and 517 000 children under age 5 years died from sepsis or meningitis). Sepsis is the third leading cause of death in neonates after prematurity and birth asphyxia, both of which are associated with maternal infections such as chorioamnionitis(108). Premature birth (< 37 weeks of gestation) and low birth weight are the main risk factors for neonatal sepsis and are associated with higher mortality. In early onset sepsis, additional risk factors are intra-amniotic infections (i.e. chorioamnionitis), prolonged rupture of the membranes (e.g. > 18 hours) and maternal rectovaginal colonization with specific pathogens (such as Group B Streptococci - GBS). Neonates with underlying disease such as congenital malformations, or those undergoing invasive procedures, or those with central or peripheral catheters, surgical procedures or those with prolonged hospital stays are also at increased risk of sepsis.

**Microbiology epidemiology**

Sepsis can be caused by a variety of pathogens including fungi and viruses, although it is most commonly caused by bacteria(243). Differences in causative pathogens may be present based on the age of the child, presence or absence of underlying comorbidities and type of comorbidity and geographical location (e.g. children in high-income versus low- and middle-income settings) (Table 4 and Table 5). Pathogens most frequently associated with sepsis in neonates and children beyond the neonatal age are shown in Tables 5 and 6.

*Table 4 Pathogens most frequently identified in blood cultures in neonates 28 days or younger with sepsis (also refer to Box 3 about bacteremia)*

<table>
<thead>
<tr>
<th>Setting</th>
<th>Infection acquired in the community</th>
<th>Infection acquired in hospital</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low- and middle-income</td>
<td>Most common:</td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Escherichia coli</em></td>
<td><em>Klebsiella spp.</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Escherichia coli</em></td>
</tr>
</tbody>
</table>
### High-income

**Most common:**
- *Escherichia coli* (including multidrug-resistant strains such as those producing ESBL)

- *Staphylococcus aureus* (including MRSA)

**More rarely:**
- *Streptococcus agalactiae* (group B *Streptococcus*)
- *Streptococcus pyogenes* (group A *Streptococcus*)
- *Streptococcus pneumoniae*

**Gram-negative bacteria other than *E. coli* and *Klebsiella* spp.:**
- *Acinetobacter* spp.
- *Enterococcus* spp.

**Notes:**

- As indicated in the definition section, the distinction between neonatal sepsis acquired in the community-and in the hospital is usually used in low- and middle-income settings, but neonatal sepsis can also be classified as early or late onset based on the time of onset of sepsis (counting days after delivery). The purpose of both classifications is to help identify the most likely causative pathogens, however, overlap may exist in some settings (e.g. *Acinetobacter* spp. is associated with early onset sepsis in some settings).
- Hospital-acquired infections have a higher risk of being caused by multidrug-resistant organisms.
- Only bacteria are listed in the table. Other pathogens to consider are viruses (mostly herpes simplex virus and enteroviruses) and fungi (mostly *Candida* spp.).

### Table 5 Pathogens most frequently identified in blood cultures in children older than 28 days with sepsis (also refer to Box 3 about bacteremia)

<table>
<thead>
<tr>
<th>Setting</th>
<th>Infection acquired in the community</th>
<th>Infection acquired in hospital</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low- and middle-income</td>
<td>Gram-negative bacteria (mostly <em>Escherichia coli</em>, <em>Klebsiella</em> spp.) (including multidrug-resistant strains such as those producing ESBL and carbapenemases)</td>
<td><em>Klebsiella</em> spp., <em>Escherichia coli</em></td>
</tr>
<tr>
<td></td>
<td><em>Acinetobacter</em> spp. (including multidrug-resistant strains such as those producing ESBL and carbapenemases)</td>
<td></td>
</tr>
</tbody>
</table>

Notes: As indicated in the definition section, the distinction between neonatal sepsis acquired in the community-and in the hospital is usually used in low- and middle-income settings, but neonatal sepsis can also be classified as early or late onset based on the time of onset of sepsis (counting days after delivery). The purpose of both classifications is to help identify the most likely causative pathogens, however, overlap may exist in some settings (e.g. *Acinetobacter* spp. is associated with early onset sepsis in some settings). Hospital-acquired infections have a higher risk of being caused by multidrug-resistant organisms. Only bacteria are listed in the table. Other pathogens to consider are viruses (mostly herpes simplex virus and enteroviruses) and fungi (mostly *Candida* spp.).
**Clinical presentation**

The clinical presentation can vary according to the age of the child but usually signs and symptoms are non-specific. In general, to identify the underlying clinical infection, knowledge of local patterns of infections is helpful. Dengue and malaria related sepsis should also be considered in endemic settings(244).

Neonates with sepsis commonly present with a combination of hypo- or hyperthermia (temperature > 38.0 °C or < 35.5 °C), severe chest indrawing, tachycardia, poor feeding, reduced spontaneous movements, hypotension and vomiting. More rarely irritability, diarrhoea, abdominal distention and/or seizures may be present. Fast breathing alone is not a strongly predictive sign of sepsis.
In children beyond neonatal age, the most frequent signs and symptoms include fever (> 38.0 °C), respiratory symptoms, tachycardia, acute altered mental status, hypotension and vomiting. 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

### Laboratory tests

#### I. Patient microbiology tests

Microbiology tests help establish a definitive diagnosis of sepsis and identify the causative pathogen and underlying infection. Isolating a pathogen from a normally sterile body site (e.g. blood, cerebrospinal fluid) that is compatible with the clinical signs and symptoms usually confirms diagnosis. A septic screen in young infants would normally include culture of blood, urine and cerebrospinal fluid, and a chest X-ray may be considered.

Diagnostic tests should be guided by the suspected primary site of infection and will be different for pneumonia, meningitis or sepsis of unknown origin. Please also refer to specific chapters of the handbook based on the suspected underlying infection.

Tests to consider when sepsis of bacterial origin is suspected are indicated in Table 6. Ideally, these tests should be done before starting antibiotic treatment, but should not significantly delay in treatment in a very unwell child.

**Table 6 Microbiology tests to consider when sepsis in suspected depending on the most likely source of infection as indicated in the WHO EDL (54)**
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>a</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

<sup>a</sup>Additional tests may be considered in endemic settings or after travel to endemic settings (e.g. malaria, viruses causing viral haemorrhagic fevers).

<sup>b</sup>Even though cerebrospinal fluid culture is rarely done, it is a very important test to perform.

<sup>c</sup>If enteric fever is suspected, note that stool cultures have a low sensitivity and are not useful in the early phase (first week) of disease when the test is often negative.

II. Other tests

Laboratory tests can be used to complement the clinical examination and history to determine the likelihood of an underlying bacterial infection (Table 7) and the presence and severity of acute organ dysfunction (Table 8). Both tables include tests that can be considered based on local laboratory availability and local protocols.

Table 7 Laboratory tests (other than microbiology) to consider when sepsis in suspected to identify a bacterial infection as indicated in the WHO EDL (54)

<table>
<thead>
<tr>
<th>Diagnostic test</th>
<th>Purpose of the test</th>
<th>Settings where the test should be available</th>
</tr>
</thead>
<tbody>
<tr>
<td>White blood count</td>
<td>To help in the diagnosis of infections</td>
<td>Health care facilities with clinical laboratories and also in primary care settings</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>To detect inflammation as an indicator of various conditions (e.g. sepsis)</td>
<td>Health care facilities with clinical laboratories</td>
</tr>
<tr>
<td>Procalcitonin&lt;sup&gt;a&lt;/sup&gt;</td>
<td>To guide antibiotic therapy or discontinuation in sepsis</td>
<td>Only in tertiary and higher health care facilities</td>
</tr>
</tbody>
</table>
Procalcitonin is not widely available and has only moderate accuracy for the diagnosis of sepsis in neonates with suspected sepsis at the cut-off of 2.0–2.5 ng/mL; different cut-offs in neonates with early versus late onset sepsis may be necessary. Procalcitonin may possibly have a higher sensitivity and specificity than C-reactive protein, A combination of both tests may improve the accuracy of diagnosis of neonatal sepsis. A combination of both tests may improve the accuracy of diagnosis of neonatal sepsis.

Table 8 Laboratory tests (other than microbiology) to consider when sepsis is suspected to identify organ dysfunction as indicated in the WHO EDL (54)

<table>
<thead>
<tr>
<th>Diagnostic test</th>
<th>Purpose of the test</th>
<th>Settings where the test should be available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilirubin</td>
<td>To detect or monitor liver disease, bile duct disorders and red cell destruction</td>
<td>Health care facilities with clinical laboratories</td>
</tr>
<tr>
<td>Blood pH and gases</td>
<td>To assess lung function, metabolic or kidney disorders and monitor oxygen therapy</td>
<td>Health care facilities with clinical laboratories</td>
</tr>
<tr>
<td>Blood urea nitrogen</td>
<td>To assess kidney function</td>
<td>Health care facilities with clinical laboratories</td>
</tr>
<tr>
<td>Creatinine</td>
<td>To monitor kidney function for management of severe infections (i.e. sepsis,) and to adjust antimicrobial regimen</td>
<td>Health care facilities with clinical laboratories</td>
</tr>
<tr>
<td>Electrolytes</td>
<td>To monitor fluid, electrolyte and acid–base balance</td>
<td>Health care facilities with clinical laboratories</td>
</tr>
<tr>
<td>Glucose</td>
<td>To diagnose intermediate hyperglycaemia and hypoglycaemia</td>
<td>Health care facilities with clinical laboratories and also in primary care settings</td>
</tr>
<tr>
<td>Platelet count</td>
<td>To diagnose thrombocytopenia or thrombocytosis</td>
<td>Health care facilities with clinical laboratories</td>
</tr>
<tr>
<td>Whole blood lactate</td>
<td>To assess metabolic acidosis</td>
<td>Health care facilities with clinical laboratories</td>
</tr>
</tbody>
</table>

III. Using surveillance microbiology data

Targeted clinical microbiology surveys of neonates and children with confirmed sepsis, including clinical presentation and infection focus, underlying disease, blood stream isolate and resistance phenotype, antibiotic treatment and clinical outcome, may be helpful at a local and national level to inform empiric guidance.

Imaging

If available, imaging studies should be guided by the suspected primary site of infection as for microbiological sampling. Please also refer to specific chapters of the handbook based on the suspected underlying infection. When sepsis is suspected and respiratory distress is present, a chest X-ray is indicated to confirm a lower respiratory tract infection that may not always be clinically obvious.
If an abdominal source of infection is suspected, an abdominal ultrasound could be considered. As an alternative and if available, a computed tomography scan of the abdomen could also be considered; however, limiting exposure to radiation should always be considered, especially in young children. If sepsis caused by an infection of the urinary tract is suspected, initial imaging (e.g. ultrasound) of the urinary tract or during follow-up could be considered if an outflow obstruction or collection are suspected.

**Antibiotic treatment**

Antibiotic treatment should be started as soon as possible when sepsis is suspected. Performance and results of laboratory and microbiology tests should not delay the first dose of antibiotic treatment.

Even though the presence of perinatal risk factors (prematurity, prolonged rupture of membranes) often leads to early empiric antibiotic use in babies, there is good evidence that these risk factors alone do not reliably predict neonatal sepsis. Therefore, antibiotic treatment should generally be started in newborn infants based on a combination of clinical and laboratory signs. In neonates with significant risk factors for infection (e.g. membranes ruptured > 18 hours before delivery, mother had fever > 38.0 °C before delivery or during labour, or amniotic fluid was foul smelling or purulent), prophylactic antibiotics (ampicillin and gentamicin) should be given for only 2 days. The neonate should be reassessed after 2 days and treatment be continued only if there are signs of sepsis or a positive blood culture(236).

Empiric treatment (see Table 9) should always cover the most probable causative pathogens:

- In neonates: Gram-negative bacteria, *Staphylococcus aureus*, *Group B Streptococcus*.
- In children beyond the neonatal age: Gram-negative bacteria, *Streptococcus pneumoniae*, *Staphylococcus aureus* and *Neisseria meningitidis*.

Simplify empiric treatment to a more narrow-spectrum antibiotic based on culture results if a pathogen is isolated. When no organism is identified, antibiotic treatment should be guided by available laboratory results and clinical response. In low-risk neonates in the primary health care setting simplification of empiric antibiotic regimens is being implemented, including two doses of parenteral gentamicin combined with oral amoxicillin.

In malaria-endemic areas, it is often difficult to rule out sepsis in a child with shock or severe illness and decreased alertness, particularly where parasitaemia is common. In all such cases, empiric parenteral broad-spectrum antibiotics should be started immediately, together with antimalarial treatment (248).

*Table 9 Empiric antibiotic treatment for community-acquired sepsis of bacterial origin in neonates and children*
<table>
<thead>
<tr>
<th>First choice&lt;sup&gt;a&lt;/sup&gt;</th>
<th><strong>Ampicillin</strong> (IV): 50 mg/kg/dose</th>
<th><strong>Amoxicillin</strong> (oral): 50 mg/kg/dose given every 12 hours AND <strong>Gentamicin</strong> (IM):</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Given every 12 hours (1st week of life)</td>
<td>• Neonates: 5 mg/kg/dose given once a day</td>
</tr>
<tr>
<td></td>
<td>• Given every 8 hours (&gt;1st week of life)</td>
<td>• Children: 7.5 mg/kg/dose given once a day</td>
</tr>
<tr>
<td></td>
<td>AND</td>
<td><strong>Gentamicin</strong> (IV):</td>
</tr>
<tr>
<td></td>
<td>• Neonates: 5 mg/kg/dose given once a day</td>
<td>• Neonates: 5 mg/kg/dose given once a day</td>
</tr>
<tr>
<td></td>
<td>• Children: 7.5 mg/kg/dose given once a day</td>
<td>• Children: 7.5 mg/kg/dose given once a day</td>
</tr>
<tr>
<td></td>
<td>OR</td>
<td><strong>Benzylpenicillin</strong> (IV): 50,000 IU/kg/dose (30 mg/kg/dose) given every 8 hours</td>
</tr>
<tr>
<td></td>
<td>AND</td>
<td><strong>Gentamicin</strong> (IV):</td>
</tr>
<tr>
<td></td>
<td>• Neonates: 5 mg/kg/dose given once a day</td>
<td>• Neonates: 5 mg/kg/dose given once a day</td>
</tr>
<tr>
<td></td>
<td>• Children: 7.5 mg/kg/dose given once a day</td>
<td>• Children: 7.5 mg/kg/dose given once a day</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Second choice&lt;sup&gt;b&lt;/sup&gt;</th>
<th><strong>Ceftriaxone</strong>&lt;sup&gt;c&lt;/sup&gt; (IV): 80 mg/kg/dose given once a day</th>
<th><strong>Amikacin</strong>&lt;sup&gt;e&lt;/sup&gt; (IV): 16 mg/kg/dose given once a day</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>No specific option is indicated in the EML/c as second choice option when referral to hospital is not possible.</td>
</tr>
<tr>
<td></td>
<td>OR</td>
<td><strong>Cefotaxime</strong> (IV): 50 mg/kg/dose given every 8 hours</td>
</tr>
<tr>
<td></td>
<td>OR</td>
<td><strong>Cloxacillin</strong>&lt;sup&gt;d&lt;/sup&gt; or flucloxacillin (IV):</td>
</tr>
<tr>
<td></td>
<td>• Neonates: 25–50 mg/kg/dose given every 12 hours</td>
<td><strong>Age restriction: use only in neonates of &gt; 41 weeks corrected gestational age.</strong></td>
</tr>
<tr>
<td></td>
<td>• Children: 25 mg/kg/dose given every 6 hours</td>
<td><strong>Ceftriaxone should not be used in neonates with hyperbilirubinaemia and should not be administered with calcium.</strong></td>
</tr>
<tr>
<td></td>
<td>AND</td>
<td><strong>Amikacin</strong>&lt;sup&gt;e&lt;/sup&gt; (IV): 16 mg/kg/dose given once a day</td>
</tr>
</tbody>
</table>

For the treatment of neonatal sepsis, an update of WHO guidelines is ongoing as to the date of publication of this Handbook, please regularly check the WHO website for news on this topic.

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

IM: intramuscular; IV: intravenous; MSSA: methicillin-susceptible *Staphylococcus aureus*; MRSA: methicillin-resistant *Staphylococcus aureus*.

<sup>a</sup>To cover for *Listeria monocytogenes* and Gram-negative bacteria.

<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).

<sup>c</sup>Ceftriaxone should not be used in neonates with hyperbilirubinaemia and should not be administered with calcium.

<sup>d</sup>Cloxacillin is a useful second-choice option when an infection caused by *Staphylococcus aureus* is suspected; the presence of extensive skin pustules, abscess or omphalitis (i.e. infection of the umbilicus and/or surrounding tissues) may suggest a staphylococcal infection. Of note, in community setting with high prevalence of MRSA, vancomycin should be considered instead of cloxacillin.
Amikacin can be used when gentamicin is not available. Amikacin would mostly be used as a treatment for infections caused by Gram-negative bacteria and when antibiotic-resistant bacteria are suspected.

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

Prevention

Sepsis rates can be reduced by preventing infection and by preventing the progression of infection to sepsis. Infections can be prevented in the community with good hygiene, safe water and sanitation, safe food preparation, good nutrition and vaccinations (Table 10). In hospitals, adequate infection prevention and control practices are key to prevent infections – to prevent neonatal sepsis, infection prevention and control practices in neonatal units and labour rooms are essential. The main ways to prevent the progression of infections to sepsis include prompt and adequate medical care including appropriate antibiotic treatment of the underlying infection.

Table 10 Vaccinations to consider to prevent certain infections

<table>
<thead>
<tr>
<th>Vaccination*</th>
<th>Population where the vaccine should be considered</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemophilus influenzae type b vaccination (40)</td>
<td>All children should be vaccinated with Haemophilus influenzae type b conjugate vaccines.</td>
</tr>
<tr>
<td>Meningococcal vaccination(40, 232)</td>
<td>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. 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.</td>
</tr>
<tr>
<td>Pneumococcal vaccination(39)</td>
<td>All children should be vaccinated with pneumococcal conjugate vaccines.</td>
</tr>
<tr>
<td>Salmonella Typhi vaccination (144)</td>
<td>Individuals living in countries with a high burden of enteric fever or a high burden of antimicrobial resistant Salmonella Typhi should be vaccinated with typhoid conjugate vaccines; vaccination should also be offered during outbreaks.</td>
</tr>
</tbody>
</table>

*References are to WHO position papers that support the evidence for vaccination.
Bacterial meningitis

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.

Definition

Meningitis is an acute inflammation of the meninges, the membranes lining the brain and spinal cord. It can be infectious or non-infectious in origin (e.g. associated with autoimmune disease) and can be associated with high morbidity and mortality, even if treated promptly.
8 **Pathophysiology**

The pathogens that cause meningitis can colonize the upper respiratory tract and from there invade the bloodstream and get access to the central nervous system through the ventricular choroid plexus or can access the meninges by local spread. Because the central nervous system lacks effective immune defences, organisms can multiply rapidly, cause direct tissue injury to the meninges and produce an inflammatory response that contributes to neurological symptoms.

14 **Epidemiology**

Meningitis is found worldwide and can affect individuals of all ages, although some differences exist across geographic regions. Mortality is highest in children under 5 years of age. Outbreaks of meningococcal meningitis mostly occurring during cooler and drier seasons are a serious threat, especially in the so-called meningitis belt, an area in the peri-Saharan African region stretching from Senegal in the West to Ethiopia in the East. Although deaths from meningitis have overall decreased by about 20% between 1990 and 2016 (from an estimated 403 000 to about 318 000 a year), the burden of bacterial meningitis is still high, especially in LMIC despite an increase in immunization programmes(249). According to data from the Global Burden of Disease study, in 2017, there were around 5 million new cases of meningitis (considering all ages and both sexes combined)(31). Almost half of the cases were of viral origin (2.4 million cases). In the same year, the number of new cases of acute pneumococcal (about 440 000) and meningococcal (about 400 000) meningitis were similar, while *Haemophilus influenzae* accounted for an estimated 262 000 new cases(31).

Tuberculous meningitis is more common in settings with a high prevalence of tuberculosis (TB) especially among patients living with HIV. In settings where TB is endemic, children and young adults are more at risk of TB meningitis (dissemination of primary infection from the lungs to the central nervous system) while in setting with a low prevalence of TB, adults are most at risk (reactivation of a latent TB infection)(250).

The incidence and mortality of meningitis are higher in countries with limited resources. In 2016, >90% of new cases of meningitis and >80% of deaths (about 270 000 deaths) occurred in countries with a low to middle socioeconomic index (as defined by the Global Burden of Disease study group)(249). In 2016, the highest mortality was reported for central and western sub-Saharan African regions (about 110 000 deaths). Nevertheless, of the 10 countries with the highest absolute number of meningitis deaths in 2016, four were located outside of the meningitis belt (Afghanistan, China, India and Pakistan). About 7% of new meningitis cases and 4% of deaths in 2016 occurred in countries with a high or middle-to-high socioeconomic index (249).

42 **Microbiology epidemiology**

Viral meningitis (usually benign and mainly caused by enteroviruses and arboviruses) and non-infectious causes (e.g. autoimmune or neoplastic diseases or as a side-effect of certain medicines) can mimic the signs and symptoms of bacterial meningitis. Therefore, it is important to consider
these causes in the differential diagnosis. The most frequently implicated bacteria (beyond neonatal age) are *Streptococcus pneumoniae*, *Neisseria meningitidis* and *Haemophilus influenzae* (serotype b and non-typeable strains). The most likely causative bacteria may differ across age groups (e.g. meningitis due to *Haemophilus influenzae* mainly affects children) and in patients with immune system deficiencies (e.g. increased risk of *Listeria monocytogenes*, increased risk of meningitis caused by encapsulated bacteria such as *N. meningitidis* and *S. pneumoniae* in patients with asplenia or hyposplenia) as shown in Table 1.

Tuberculous meningitis should also be considered in the differential diagnosis in patients living in or coming from areas where tuberculosis (TB) is endemic especially if the onset of disease is not acute.

In patients with severe immunosuppression (e.g. with advanced HIV disease), cryptococcal meningitis and cerebral toxoplasmosis should also be considered, although the clinical presentation of these two infections is usually less acute than bacterial meningitis. In patients living in or visiting areas where malaria is endemic, cerebral malaria should also be included in the differential diagnosis. Although most cases of meningitis are community-acquired, the infection can also be health care-associated (e.g. after neurosurgical interventions and after lumbar puncture). In that case, the most likely pathogens are *Staphylococcus aureus* or aerobic Gram-negative bacilli, including multidrug-resistant strains. For prevention of health care-associated meningitis refer to the WHO global guidance on prevention of surgical site infections(251).

Table 1 Pathogens most frequently associated with bacterial meningitis (in descending order of frequency)

<table>
<thead>
<tr>
<th>Neonates (0–2 months)</th>
<th>Children and adolescents</th>
<th>Non-immunocompromised adults</th>
<th>Immunocompromised adults or adults &gt; 50 years</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Streptococcus agalactiae</em> (group B <em>Streptococcus</em>)</td>
<td><em>Escherichia coli</em></td>
<td><em>Listeria monocytogenes</em></td>
<td><em>Streptococcus pneumoniae</em></td>
<td><em>Streptococcus suis</em></td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td></td>
<td></td>
<td><em>Neisseria meningitidis</em></td>
<td><em>Listeria monocytogenes</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Haemophilus influenzae</em> type b and non-typeable strains</td>
<td><em>Neisseria meningitidis</em></td>
<td></td>
</tr>
</tbody>
</table>
immunosuppressed patients (HIV)

Cerebral malaria
(in patients living or travelling to endemic settings)

*Staphylococcus aureus* or *Gram-negative bacteria*\(^d\), including multidrug-resistant strains after neurosurgical interventions

---

<table>
<thead>
<tr>
<th><strong>Meningitis caused by antibiotic-resistant pathogens</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Data on the proportion of penicillin- and third-generation cephalosporin-resistant <em>Streptococcus pneumoniae</em> isolates causing meningitis are scarce in most countries with a high incidence of bacterial meningitis; however, whenever available, they should guide empiric antibiotic treatment. Currently, because of the potential risk of penicillin-resistance in <em>Streptococcus pneumoniae</em> isolates and because meningitis is a very serious and potentially fatal disease, a third-generation cephalosporin is recommended for empiric treatment. Isolates with intermediate or complete resistance to ceftriaxone have rarely been described (mainly in patients with prolonged or multiple exposures to beta-lactam antibiotics in the previous three months) and some experts suggest adding intravenous vancomycin or rifampicin empirically to provide effective treatment for these isolates. Meningitis caused by multidrug-resistant Gram-negative bacteria is also reported.</td>
</tr>
</tbody>
</table>

---

<table>
<thead>
<tr>
<th><strong>Clinical presentation</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>In adults, meningitis should be suspected in the case of acute onset (&lt; 48 hours) of</td>
</tr>
<tr>
<td>• fever (&gt; 38.0 °C) <strong>AND/OR</strong></td>
</tr>
<tr>
<td>• headache and/or change in mental status and/or confusion <strong>AND/OR</strong></td>
</tr>
<tr>
<td>• neck stiffness.</td>
</tr>
</tbody>
</table>

**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).

A haemorrhagic rash may also be present, especially in cases of meningitis caused by *Neisseria meningitidis* (although such a rash is not specific for meningococcal infection). Notably with *S. pneumoniae* foci of infection outside the CNS, such as otitis media, sinusitis, pneumonia and endocarditis, are also often observed.

Because bacterial meningitis is a serious illness and clinical and epidemiological features alone cannot always reliably differentiate bacterial and viral origin, all severe cases should be treated as if they were bacterial until this has been excluded or a viral cause has been clearly identified.

For the diagnosis of meningitis in children and neonates, refer to the latest edition of the WHO Pocketbook of hospital care for children(23). In neonates, the clinical presentation is less typical and symptoms are usually non-specific. Neonates often present with a combination of fever, poor feeding, lethargy, drowsiness, vomiting, irritability, seizures or a full fontanelle. Neck stiffness is very uncommon.

**Laboratory tests**

I. **Patient microbiology tests**

Whenever possible, certain microbiology tests should be considered (Table 2); ideally samples should be obtained before antibiotic treatment is started. The rationale for these tests is to establish the diagnosis and identify the pathogen as this affects treatment.

*Table 2 Microbiology tests to consider for the diagnosis of meningitis as indicated in the the WHO EDL (54)*

<table>
<thead>
<tr>
<th>Diagnostic test</th>
<th>Purpose of the test</th>
<th>Settings where the test should be available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood cultures</td>
<td>To detect bacterial and fungal bloodstream infections (sepsis)</td>
<td>Health care facilities with clinical laboratories</td>
</tr>
<tr>
<td>CSF microscopy (Gram stain)</td>
<td>To assess microbial morphology, number of white blood cells and red blood cells</td>
<td>Health care facilities with clinical laboratories</td>
</tr>
<tr>
<td>CSF culture</td>
<td>Initial step to detect and identify bacterial and fungal species for selection of appropriate antibiotic regimens</td>
<td>Health care facilities with clinical laboratories</td>
</tr>
<tr>
<td>Cryptococcal antigen test (CSF, blood)</td>
<td>To screen and diagnose cryptococcal meningitis in people living with advanced HIV disease</td>
<td>Health care facilities with clinical laboratories and also in primary care settings</td>
</tr>
<tr>
<td><em>M. tuberculosis</em> DNA (CSF)</td>
<td>To diagnose active TB and simultaneously or sequentially detect rifampicin resistance</td>
<td>Health care facilities with clinical laboratories</td>
</tr>
</tbody>
</table>

CSF: cerebrospinal fluid.

*If blood is taken before starting antibiotic treatment, blood cultures are often positive in cases of bacterial meningitis (up to 75% of cases)(252, 253).
II. Other tests

In the presence of compatible signs and symptoms, a definitive diagnosis of bacterial meningitis requires examination of cerebrospinal fluid. Therefore, whenever possible and if no contraindications are present (such as increased bleeding risk, risk of herniation or a skin infection at the site of the puncture), a lumbar puncture should be done before starting antibiotic treatment. However, doing a lumbar puncture should never delay giving antibiotic treatment when bacterial meningitis is suspected (if available at least blood cultures should be taken before starting treatment). In settings where computer tomography is available, certain patients may benefit from a scan of the head before the lumbar puncture because of the risk of cerebral herniation after removing cerebrospinal fluid at the lumbar level if elevated intracranial pressure is suspected. Computer tomography scanning should never delay the start of antibiotic treatment. If available, imaging is indicated in patients with focal neurological signs, decreased level of consciousness or coma or a history of central nervous system disease or recent onset of seizures (< 1 week) or severe immunosuppression (e.g. advanced HIV disease).

Laboratory tests to consider when meningitis is suspected are given in Table 3. In the specific context of epidemics, also consult the WHO meningitis epidemics guidelines(231).

In bacterial meningitis, the characteristics of cerebrospinal fluid vary widely (and may be normal or only slightly altered in neonates); however, certain findings suggest a probable bacterial cause. In particular, the following characteristics of the cerebrospinal fluid suggest bacterial meningitis:

- high opening pressure during lumbar puncture (reference range, 80-200 mm H₂O or 8-20 cm H₂O)
- turbid appearance of CSF
- elevated CSF white cell count (often several hundreds to several thousands WBC/mm³ or >0.1 to >1 X 10⁶/L)
- elevated CSF percentage of neutrophils (> 80%)
- elevated CSF protein (> 45 mg/dL or > 0.45 g/L)
- low CSF glucose (< 40 mg/dL or < 2.2 mmol/L)
- low cerebrospinal fluid / plasma glucose ratio (≤ 0.4)

Table 3: Laboratory tests that could be considered for the diagnosis of meningitis as indicated in the WHO EDL (54)

<table>
<thead>
<tr>
<th>Diagnostic test</th>
<th>Purpose of the test</th>
<th>Settings where the test should be available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basic CSF Profile (CSF leukocyte count, CSF differential leukocyte count and CSF protein and glucose)</td>
<td>To aid in the diagnosis of bacterial, mycobacterial, fungal and viral meningitis</td>
<td>Health care facilities with clinical laboratories</td>
</tr>
<tr>
<td>Complete blood count</td>
<td>To detect a wide range of disorders, including infections</td>
<td>Health care facilities with clinical laboratories</td>
</tr>
<tr>
<td>Blood glucose</td>
<td>To diagnose hyperglycaemia/hypoglycaemia</td>
<td>Health care facilities with clinical laboratories but also in primary care settings</td>
</tr>
</tbody>
</table>
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

CSF: cerebrospinal fluid.

### III. Using surveillance microbiology data

Targeted periodic clinical surveillance including risk factors, resistance of key pathogens and outcomes may be helpful to inform empiric guidance at a national level.

#### Tuberculosis meningitis

TB meningitis should always be considered in the differential diagnosis in high-risk patients and in settings where TB is endemic. TB meningitis can have an acute presentation and, similar to bacterial meningitis, its diagnosis cannot be made or excluded only on the basis of clinical presentation. Since TB meningitis is a serious disease, prompt diagnosis and treatment are essential(116).

#### Use of corticosteroids

The rationale for the use dexamethasone in cases of meningitis is to reduce the inflammatory response and the risk of neurological sequelae (e.g. hearing loss) and death. The use of adjunctive steroids is suggested only in high-income settings, where it has a proven benefit. Current evidence failed to show any significant benefit both in terms of mortality and sequelae in patients in low-income countries(254-256). In high-income countries, dexamethasone can be given before or at the time of the first antibiotic dose if bacterial meningitis is suspected and continued if *Streptococcus pneumoniae* is confirmed. The recommended dose is 0.15 mg/kg of dexamethasone every 6 hours. Steroids are not recommended in neonatal meningitis.

#### Antibiotic treatment

Antibiotic treatment should be started as soon as possible when bacterial meningitis is suspected (Table 4). The first dose of antibiotic treatment should not be delayed until the results of the lumbar puncture are available. The choice of empiric antibiotic treatment should take into account the age of the patient, presence of immunosuppression and local prevalence of *Streptococcus pneumoniae* isolates resistant to third-generation cephalosporins. The patient risk of *Listeria* meningitis should also be taken into account (e.g. pregnant women, patients who are immunosuppressed or > 50 years of age) because ceftriaxone (and cefotaxime) do not cover this pathogen and ampicillin should be used in these cases.

As a general rule, empiric treatment in children other than neonates (< 2 months) and in adults should always cover all three of the main causative pathogens (*Haemophilus influenzae*, *Neisseria meningitidis* and *Streptococcus pneumoniae*).
If a pathogen is isolated and its susceptibilities are known, antibiotics should be reviewed and modified accordingly. When no pathogen is identified, the duration of antibiotic treatment should be guided by available laboratory results and clinical response.

**Step-down** to oral treatment is less commonly used in meningitis management, where the treatment is mainly parenteral where possible to maximise CSF penetration.

**Table 4 Empiric antibiotic treatment for bacterial meningitis**

<table>
<thead>
<tr>
<th></th>
<th>Adults</th>
<th>Children (not neonates)</th>
<th>Neonates (&lt; 2 months)</th>
<th>Total treatment duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First choice</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ceftriaxone (IV):</td>
<td></td>
<td>Ceftriaxone (IV):</td>
<td>Ampicillin (IV):</td>
<td>Unconfirmed pathogen:</td>
</tr>
<tr>
<td>2 g given every 12</td>
<td></td>
<td>100 mg/kg given once a</td>
<td>50 mg/kg/dose given</td>
<td>10 days (adults and</td>
</tr>
<tr>
<td>hours</td>
<td></td>
<td>day</td>
<td>every 12 hours (1st</td>
<td>children)</td>
</tr>
<tr>
<td>OR Cefotaxime (IV):</td>
<td></td>
<td>OR Cefotaxime (IV):</td>
<td>50 mg/kg/dose given</td>
<td>3 weeks (neonates)</td>
</tr>
<tr>
<td>2 g given every 6</td>
<td></td>
<td>50 mg/kg/dose given</td>
<td>every 8 hours</td>
<td></td>
</tr>
<tr>
<td>hours</td>
<td></td>
<td>every 8 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>AND Gentamicin (IV):</td>
<td>5 mg/kg given once a</td>
<td>Confirmed pneumococcal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7.5 mg/kg given once a</td>
<td>day (1st week of life)</td>
<td>meningitis: 10–14 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>day (1st week of life)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>AND Gentamicin (IV):</td>
<td>5 mg/kg given once a</td>
<td>Confirmed meningococcal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7.5 mg/kg given once a</td>
<td>day (1st week of life)</td>
<td>meningitis: 5–7 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>day (1st week of life)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>OR Ceftriaxone (IV):</td>
<td>100 mg/kg given once a</td>
<td>In epidemics, specific</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100 mg/kg given once a</td>
<td>day</td>
<td>WHO recommendations on</td>
</tr>
<tr>
<td></td>
<td></td>
<td>day</td>
<td></td>
<td>duration apply (231)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OR Cefotaxime (IV):</td>
<td>50 mg/kg/dose given</td>
<td>Confirmed Listeria</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12 hours (1st week of</td>
<td>every 12 hours (&gt;1st</td>
<td>meningitis: 21 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>life) and given every</td>
<td>week of life)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>6 hours (1st week of</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>life)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>AND Gentamicin (IV):</td>
<td>5 mg/kg given once a</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>7.5 mg/kg given once a</td>
<td>day (1st week of life)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>day (1st week of life)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>OR Ampicillin (IV):</td>
<td>50 mg/kg/dose given</td>
<td>Same as above</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8 hours</td>
<td>every 8 hours</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>OR Amoxicillin (IV):</td>
<td>40–50 mg/kg/dose</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>40 mg/kg/dose given</td>
<td>given every 12 hours</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>every 8 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>OR Chloramphenicol (IV):</td>
<td>25 mg/kg/dose given</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>6 hours</td>
<td>every 6 hours</td>
<td></td>
</tr>
</tbody>
</table>

*a* Chloramphenicol

*b* Chloramphenicol
<table>
<thead>
<tr>
<th>(IV): 4 million IU (2.4 g) given every 4 hours</th>
<th>OR</th>
<th>Benzylpenicillin (IV): 100 000 IU/kg/dose (60 mg/kg/dose) given every 6 hours</th>
</tr>
</thead>
</table>

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

IM: intramuscular; IV: intravenous; IU: international units.

*Chloramphenicol should only be used when no other option is available because of toxicity (the most serious adverse event is bone marrow depression).

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

### Prevention

#### Vaccination and post-exposure prophylaxis

Primary prevention of bacterial meningitis relies on vaccination and antibiotic prophylaxis for close contacts of cases. Vaccination is a successful intervention to prevent bacterial meningitis. Available vaccines are active against meningococcal, pneumococcal and *Haemophilus influenzae* type b disease. Vaccines are never 100% effective and they do not protect against all strains of a bacterial pathogen. Duration of protection is also variable. As a result, even vaccinated people can develop bacterial meningitis. WHO recommendations for routine immunizations and the WHO roadmap towards defeating meningitis by 2030 are available online (257, 258).

### Meningococcal vaccination (232, 259)

Appropriate large-scale meningococcal vaccination programmes in countries with a 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 should be in place. In countries of the meningitis belt, all individuals aged 1–29 years (including pregnant women) should be vaccinated with the meningococcal A conjugate vaccine.

In countries with a low incidence of meningococcal disease (< 2 cases per 100 000 population/year), vaccination is recommended 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 different meningococcal serogroups.

### Pneumococcal vaccination (39)

The inclusion of pneumococcal conjugate vaccines in childhood immunization programmes worldwide is recommended.

### *Haemophilus influenzae* type b vaccination (40)

The inclusion of *Haemophilus influenzae* type b conjugate vaccines in childhood immunization programmes worldwide is recommended.
Post-exposure antibiotic prophylaxis in case of meningococcal meningitis

Post-exposure antibiotic prophylaxis should be considered in the following situations:

- outside of the African meningitis belt for all close contacts within the household
- in the African meningitis belt for close contacts in non-epidemic situations.

Ciprofloxacin (usually 500 mg oral, single dose) is the antibiotic of choice, and ceftriaxone can be used in alternative (usually 250 mg IM single dose in adults and 125 mg IM single dose in children) (260).
Community-acquired pneumonia – Severe

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

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**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](https://apps.who.int/iris/handle/10665/81170)
- Revised WHO classification and treatment of pneumonia in children at health facilities: evidence summaries: [https://apps.who.int/iris/handle/10665/137319](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 (108), 85 - 103. [https://apps.who.int/iris/handle/10665/310970](https://apps.who.int/iris/handle/10665/310970)

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Definition

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

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

**Epidemiology**

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

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

**Microbiology epidemiology**

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

In children aged 2 months to 5 years, pneumonia is more likely to be of viral origin (e.g. respiratory syncytial virus, influenza and parainfluenza virus). The most important bacterial pathogen in children under 5 years is *Streptococcus pneumoniae*. In older children *S. pneumoniae* is still common but “atypical bacteria” such as *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* may occur (“atypical bacteria” have intrinsic resistance to beta-lactam antibiotics and cannot be visualized by Gram staining). *Haemophilus influenzae*, *Moraxella catarrhalis* and *Staphylococcus aureus* also cause CAP in some children (Table 1).
In adults, viruses are common causes of CAP (Table 1), either by directly causing pneumonia or by favouring superinfection with bacteria. Among bacteria, the most common causative agents are *Streptococcus pneumoniae*, followed by “atypical bacteria” (see definition in the paragraph above) such as *Mycoplasma pneumoniae*, *Chlamydia pneumoniae* and *Legionella pneumophila*. *Haemophilus influenzae*, *Moraxella catarrhalis* and *Staphylococcus aureus* are also quite common (Table 1).

However, determining the cause of bacterial pneumonia is difficult in all age groups and no causative pathogen is identified in most cases, even if extensive microbiological tests are performed. Furthermore, there may be important geographic differences in the cause of pneumonia; for example, *Burkholderia pseudomallei* is a cause of CAP in South-East Asia, while *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.

The type of sample (upper respiratory versus lower respiratory origin, blood cultures), the test characteristics (sensitivity, specificity, predictive values), the local epidemiology, clinical presentation and if available other laboratory test results always need to be considered when deciding whether a positive result for a pathogen likely identifies the causative pathogen.

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

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

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

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

<sup>c</sup>*Mycoplasma pneumoniae* and *Chlamydia* spp. are more frequent in children > 5 years (compared with younger children) and in young adults.
Up to 50% of cases of pneumonia in children < 5 years are caused by a virus (most commonly respiratory syncytial virus)

**Community-acquired pneumonia caused by antibiotic-resistant pathogens**

Antimicrobial resistance is a potential problem with all pathogens associated with CAP. Clinically relevant high-level beta-lactam resistance in *Streptococcus pneumoniae* is though still rare globally. Resistance to macrolides in *Streptococcus pneumoniae* and *Mycoplasma pneumoniae* is highly prevalent in some settings (110, 111). It is important to note that also in the hospital setting parenteral penicillin/amoxicillin/ampicillin Access antibiotics achieve sufficient antibiotic 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.**

**Clinical presentation**

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

Well-established clinical features of CAP include a combination of: new onset (less than 2 weeks) of symptoms, worsening cough with or without sputum production, dyspnoea (difficulty in breathing), tachypnoea (abnormal respiratory rates to diagnose rapid breathing vary with age), reduced oxygen saturation, crepitations on lung auscultation, or chest pain or discomfort without an alternative explanation. Fever ≥ 38.0 °C for 3–4 days is usually present but may be absent, especially in the elderly. Extrapulmonary features such as confusion or disorientation may be the main symptoms in elderly people, immunosuppressed patients and malnourished children. Severe pneumonia with respiratory distress, sepsis requiring intensive care and intravenous antibiotic treatment has a high associated mortality.

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

**Laboratory tests**

**I. Patient microbiology tests**

In severe cases the following tests could be considered to guide antimicrobial treatment (Table 2):

- blood cultures (ideally before starting antibiotic treatment)
- sputum microscopy and culture (ideally before starting antibiotic treatment)
• urinary antigens for *Legionella pneumophila* and *Streptococcus pneumoniae*.

Additionally, in selected cases, the following tests could also be considered (Table 2):

• rapid molecular test for *Mycobacterium tuberculosis* in sputum

• nucleic acid amplification test for influenza virus in a nasopharyngeal sample to help decide on antiviral treatment and for infection prevention and control purposes (e.g. to prevent transmission to other patients)

• nucleic acid amplification test or antigen test for SARS-CoV-2 depending on the current epidemiology

• HIV testing in LMIC settings and in case of recurrent and severe pneumonia

Routine use of nasopharyngeal swab for nucleic acid tests for respiratory viruses other than influenza or SARS-CoV-2 is usually not needed.

*Table 2 Microbiology tests to consider if community-acquired pneumonia is suspected as indicated in the WHO EDL (54)*

<table>
<thead>
<tr>
<th>Diagnostic test</th>
<th>Purpose of test</th>
<th>Setting where the test should be available</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood cultures</td>
<td>To detect bacterial bloodstream infection</td>
<td>Health care facilities with clinical laboratories</td>
<td>Not routinely needed but suggested in severe cases&lt;sup&gt;a&lt;/sup&gt; Some guidelines suggest blood culture also in cases of recent antibiotic exposure (&lt; 3 months) or if MRSA or <em>Pseudomonas aeruginosa</em> infection is suspected</td>
</tr>
<tr>
<td>Sputum microscopy (Gram stain)</td>
<td>To assess microbial morphology and adequacy of the specimen for culture by identifying white blood cells and squamous epithelial cells</td>
<td>Health care facilities with clinical laboratories</td>
<td>Not routinely needed but suggested in severe cases&lt;sup&gt;a&lt;/sup&gt; Some guidelines suggest sputum microscopy also in cases of recent antibiotic exposure (&lt; 3 months) or if MRSA or <em>Pseudomonas aeruginosa</em> infection is suspected</td>
</tr>
<tr>
<td>Sputum culture</td>
<td>Initial step to detect and identify bacterial and fungal species for selection of appropriate antibiotic regimens</td>
<td>Health care facilities with clinical laboratories</td>
<td>Not routinely needed but suggested in severe cases&lt;sup&gt;a&lt;/sup&gt; Some guidelines suggest sputum culture also in cases of recent antibiotic exposure (&lt; 3 months) or if suspicion of MRSA or <em>Pseudomonas aeruginosa</em> infection is suspected</td>
</tr>
<tr>
<td>Test Type</td>
<td>Purpose</td>
<td>Setting</td>
<td>If <em>Mycobacterium tuberculosis</em> infection is suspected</td>
</tr>
<tr>
<td>--------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------</td>
<td>------------------------------------------------------</td>
</tr>
<tr>
<td>Sputum rapid molecular test for <em>Mycobacterium tuberculosis</em></td>
<td>To diagnose active tuberculosis and detect rifampicin resistance</td>
<td>Health care facilities with clinical laboratories</td>
<td>Not routinely needed but suggested in severe cases. 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 legionelllosis or recent travel.</td>
</tr>
<tr>
<td>Urinary antigens for <em>Legionella pneumophila</em> and <em>Streptococcus pneumoniae</em></td>
<td>To diagnose legionellosis and pneumococcal pneumonia</td>
<td>Health care facilities with clinical laboratories but also in primary care settings</td>
<td>Not routinely needed but suggested during the influenza season.</td>
</tr>
<tr>
<td>Nasopharyngeal swab for nucleic acid amplification test for influenza viruses</td>
<td>To diagnose seasonal influenza infection</td>
<td>Health care facilities with clinical laboratories but also in primary care settings</td>
<td>Not routinely needed but suggested depending on the epidemiologic situation.</td>
</tr>
<tr>
<td>SARS-CoV-2 Antigen</td>
<td>To diagnose COVID-19</td>
<td>Community settings and health facilities without laboratories</td>
<td>Not routinely needed but suggested depending on the epidemiologic situation.</td>
</tr>
<tr>
<td>Upper respiratory specimens (e.g. nasopharyngeal or nasal swab)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SARS-CoV-2 nucleic acid amplification test</td>
<td>To diagnose COVID-19</td>
<td>Health care facilities with clinical laboratories</td>
<td>Not routinely needed but suggested depending on the epidemiologic situation.</td>
</tr>
<tr>
<td>Upper respiratory specimens (e.g. nasopharyngeal and oropharyngeal) and lower respiratory specimens (e.g. BAL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasopharyngeal swab for nucleic acid amplification test for respiratory viruses other than influenza viruses or SARS-CoV-2 (e.g. respiratory syncytial virus)</td>
<td>To diagnose respiratory viruses other than influenza or SARS-CoV-2</td>
<td>Health care facilities with clinical laboratories</td>
<td>Not routinely needed but suggested in severe cases.</td>
</tr>
<tr>
<td>Anti-HIV-1 and -HIV-2 antibody (RDT) or Combined anti-HIV-1/HIV-2 antibody and p24 antigen (RDT)</td>
<td>To diagnose HIV infection</td>
<td>Community settings and health facilities without laboratories</td>
<td>Please consult the WHO consolidated guidelines on HIV testing services (261).</td>
</tr>
</tbody>
</table>

**Notes:**

- *a* BAL: bronchoalveolar lavage; MRSA: methicillin-resistant *Staphylococcus aureus*; NAT: nucleic acid test; RDT: rapid diagnostic test.
II. Other tests

In severe cases, several tests could be considered based on local availability (Table 3) to determine disease severity, help differentiate bacterial and viral aetiologies and determine treatment duration (and IV to oral switch) during follow up.

Table 3 Laboratory tests to consider if community-acquired pneumonia is suspected as indicated in the WHO EDL (54)

<table>
<thead>
<tr>
<th>Diagnostic test</th>
<th>Purpose of test</th>
<th>Setting where the test should be available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood urea nitrogen (BUN)</td>
<td>To assess kidney function&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Health care facilities with clinical laboratories</td>
</tr>
<tr>
<td>White blood cell count</td>
<td>To help in the diagnosis of infection</td>
<td>Health care facilities with clinical laboratories</td>
</tr>
<tr>
<td>Blood pH and gases</td>
<td>To assess lung function and metabolic or kidney disorders, and monitor oxygen therapy</td>
<td>Health care facilities with clinical laboratories</td>
</tr>
<tr>
<td></td>
<td>To measure blood pH, O&lt;sub&gt;2&lt;/sub&gt; and CO&lt;sub&gt;2&lt;/sub&gt;, serum bicarbonate, and anion gap</td>
<td></td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>To detect inflammation as an indicator of various conditions</td>
<td>Health care facilities with clinical laboratories</td>
</tr>
<tr>
<td>Procalcitonin</td>
<td>To guide antibiotic therapy or discontinuation in sepsis and lower respiratory tract infection</td>
<td>Only in tertiary care facilities</td>
</tr>
</tbody>
</table>

<sup>a</sup>Required for the CURB-65 score calculation.

III. Using microbiology surveillance data

In the great majority of episodes of CAP in the hospital setting, parenteral antibiotics produce an exposure sufficient to treat most resistant isolates.

Routine clinical microbiology samples for CAP are biased towards more severe forms of CAP where more invasive sampling is performed (such as bronchoalveolar lavage) and microbiology results are therefore not representative for the general population with CAP.

Therefore, routine clinical microbiology surveillance of CAP in the hospital setting does not help to inform local empiric guidance.
Imaging

When severe CAP is suspected clinically, a chest radiograph is needed because other conditions have similar clinical features and antibiotics may be avoided if the chest radiograph does not suggest bacterial pneumonia. Furthermore, chest radiographs can be difficult to interpret, especially those of elderly people, and many other conditions (such as heart failure) can mimic infectious infiltrates. In addition, the absence of a visible infiltrate does not always rule out pneumonia, e.g., in dehydrated patients. As with any test, the pre-test probability of pneumonia based on clinical picture and laboratory tests if available and the likelihood of alternative diagnoses need to be considered when interpreting chest radiographs. It should also be noted that the radiographic pattern cannot be used to accurately predict the microbial cause and does not reliably distinguish typical from atypical or viral pathogens.

Scores to determine disease severity and guide treatment decisions

The WHO recommends that children that meet the criteria of severe pneumonia should be admitted to hospital. As a general rule for children, hospitalization is indicated in cases of severe illness (e.g., cough and severe respiratory distress, marked tachypnoea and tachycardia) and/or if the child is unable to take oral therapy.

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

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

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

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of confusion (new onset)</td>
<td>1</td>
</tr>
<tr>
<td>Urea &gt; 19 mg/dL (or &gt; 7 mmol/L)</td>
<td>1</td>
</tr>
<tr>
<td>Respiratory rate &gt; 30 breaths/min</td>
<td>1</td>
</tr>
<tr>
<td>Systolic blood pressure &lt; 90 mmHg (&lt;12 kPa) or diastolic blood pressure ≤ 60 mmHg (&lt;8 kPa)</td>
<td>1</td>
</tr>
</tbody>
</table>
Age ≥ 65 years

<table>
<thead>
<tr>
<th>CURB-65 score / CRB-65 score</th>
<th>Where to treat</th>
</tr>
</thead>
</table>
| 0–1                         | Candidate for outpatient treatment  
Low 30-day mortality risk (< 1.5%) |
| 2                           | Consider inpatient treatment  
30-day mortality risk ≈ 10%  
Consider adding clarithromycin (see Table 6)  
If tests are available, consider testing for atypical pathogens (e.g. *Legionella spp.*, *Mycoplasma spp.*) |
| ≥ 3                         | Inpatient treatment (consider admission to intensive care)  
High 30-day mortality risk (≈ 20%)  
Consider adding clarithromycin (see Table 6)  
Consider testing for atypical pathogens (e.g. *Legionella spp.*, *Mycoplasma spp.*) |

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

*Urea is not required for the calculation of the CRB-65 score, a modification of the CURB-65 score that does not require the execution of laboratory tests.

### Ruling out tuberculosis

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

### Symptomatic care

Patients with severe CAP should receive appropriate oxygen therapy. Routine treatment with corticosteroids is usually not needed unless otherwise indicated. (262-265).

### Antibiotic treatment

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

Empiric treatment should be guided by the age of the patient, severity of symptoms, presence of comorbidities and previous antibiotic treatment. In certain cases (e.g. immunosuppressed patients), the epidemiology of antibiotic resistance for common pathogens causing CAP in the setting in which the patient is being treated could be considered.

Clinical improvement should be evident within 48–72 hours of starting antibiotic therapy. If there is no response to treatment, a complication (such as empyema) should be considered. Duration of treatment should be guided by measures of clinical improvement (e.g. resolution of fever); usually 5 days of treatment are adequate for adults and 3-5 days in children.

**Simplify** empiric treatment to a more narrow-spectrum antibiotic based on culture results or based on rapid clinical improvement when no microbiology test results are available.

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

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

<table>
<thead>
<tr>
<th>First choice</th>
<th>Adults</th>
<th>Total treatment duration (117, 118)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ceftriaxone</strong> (IV/IM): 2 g given once a day (IV), 1 g given once a day (IM)</td>
<td>5 days (consider longer treatment and / or investigate for complications if the patient is not clinically stable at day 5)</td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cefotaxime</strong> (IV/IM): 2 g given every 8 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td>if CURB-65 ≥ 2 CONSIDER ADDING</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Clarithromycin</strong>&lt;sup&gt;b&lt;/sup&gt; (oral or IV): 500 mg given every 12 hours</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Second choice</th>
<th>Adults</th>
<th>Total treatment duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Amoxicillin+clavulanic acid</strong> (IV): 1 g + 200 mg given every 8 hours (a higher dose could be considered: 1 g + 200 mg given every 6 hours)</td>
<td>5 days</td>
<td></td>
</tr>
<tr>
<td>if CURB-65 ≥ 2 CONSIDER ADDING</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Clarithromycin</strong>&lt;sup&gt;b&lt;/sup&gt; (oral or IV): 500 mg given every 12 hours</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

IM: intramuscular; IV: intravenous; IU: international units.

<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 be painful to give as intramuscular injection.

<sup>b</sup>The rationale of adding clarithromycin to beta-lactam is to cover for possible atypical bacteria. Azithromycin could be used as an alternative when clarithromycin is not available but there are increasing concerns about its potential for the emergence and spread of antibiotic resistance because of its long half-life. Erythromycin could also be considered but it is associated with higher toxicity (diarrhoea is frequently associated with its use). Macrolides have good bioavailability and there is no need to use the intravenous route if the patient has a function gastrointestinal tract.

ACCESS antibiotics are indicated in green, WATCH antibiotics in yellow and RESERVE antibiotics in red.
**Table 7 Empiric antibiotic treatment for severe cases of community-acquired pneumonia in children (from the WHO document “Revised WHO classification and treatment of childhood pneumonia at health facilities”)**

<table>
<thead>
<tr>
<th>Severe pneumonia (pneumonia with any danger sign(^a), which requires referral to facility/hospital, admission and injectable therapy)</th>
<th>Children</th>
<th>Total treatment duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ampicillin</strong> (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) <strong>AND</strong> <strong>Gentamicin</strong> (IV/IM):  • Neonates: 5 mg/kg/ dose given once a day  • Children: 7.5 mg/kg/ dose given once a day</td>
<td><strong>5 days</strong>  (consider longer treatment if the patient is not clinically stable at day 5)</td>
<td></td>
</tr>
<tr>
<td><strong>Ampicillin can be replaced by</strong> <strong>Amoxicillin</strong> (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) <strong>OR</strong> <strong>Benzylpenicillin</strong> (IV): 50,000 IU/kg (30 mg/kg) given every 8 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>If no clinical response to ampicillin AND gentamicin after 48-72 hours change to second line:</strong> <strong>Cefotaxime</strong> (IV/IM): 50 mg/kg/ dose given every 8 hours <strong>OR</strong> <strong>Ceftriaxone</strong> (IV/IM): 80 mg/kg/ dose given once a day</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Note:</strong>  • if HIV-positive and greater than 1 month of age <em>(Pneumocystis jirovecii pneumonia is a risk)</em>, add empiric sulfamethoxazole+trimethoprim: 8 mg/kg trimethoprim and 40 mg/kg sulfamethoxazole, given every 8 hours for 3 weeks  • Severe pneumonia, particularly in school age children, may rarely be caused by <em>Mycoplasma pneumoniae</em>, which is unresponsive to beta-lactams and would be usually treated with macrolides, for example clarithromycin.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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\(^a\)Not able to drink, persistent vomiting, convulsions, lethargic or unconscious, stridor in a calm child or severe malnutrition.

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

IM: intramuscular; IV: intravenous; IU: international units.

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

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

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.

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

Hospital-acquired pneumonia (HAP) is an acute illness affecting the lungs caused by pathogens present in the hospital setting and presenting 48 hours or more after admission. If pneumonia develops while the patient is on a ventilator, HAP is also called ventilator-associated pneumonia (VAP). Of note, the cut-off of 48 hours after admission is arbitrary and chosen for convenience and surveillance purposes. Depending on the situation (particularly in non-ventilated patients), even pneumonias occurring several days to weeks after hospitalisation can be caused by pathogens similar to community-acquired pneumonia while nosocomial pathogens can be acquired and cause infection in patients hospitalized for less than 48 hours.

Pathophysiology

Colonization of the oropharynx by bacteria from the hospital environment, aspiration of secretions into the lower respiratory tract and compromised host defense mechanisms are all
implicated in the pathogenesis of HAP. Pathogens can also reach the lung alveoli through the
blood or by direct spread (e.g. from an infection of the pleural or intra-abdominal space).
Secretions may become contaminated with bacteria (including with multidrug-resistant strains)
during patient care despite infection prevention and control efforts. Inhalation of pathogens
(mostly viruses) is another mechanism of infection to consider especially during epidemic
seasons or during pandemics such as COVID-19.

The presence of an endotracheal tube represents a major risk factor for pneumonia (ventilator-
associated pneumonia) because the mechanisms that usually prevent the microaspiration of
secretions into the lower respiratory tract are bypassed and also because biofilms (where
bacteria can survive and multiply) can form on the internal and external surfaces of the tracheal
cannula.

**Epidemiology**

Hospital-acquired infections are frequent across the world (around a quarter of all hospital
antibiotic prescriptions were for healthcare-associated infections (HAI) in a 2015 global point
prevalence survey in hospitals in more than 50 countries(266)) and HAP is an important HAI. The
incidence of HAP can vary between hospitals, depending on the patient population being
evaluated and the case definition used. However, the incidence is overall higher in mechanically
ventilated patients treated in intensive care units than in non-ventilated patients not requiring
intensive care(267).

Risk factors for HAP in non-ventilated patients include (i) patient-related factors such as
swallowing dysfunction and severe underlying medical conditions (e.g. immunosuppression,
chronic lung disease); and (ii) treatment-related factors such as mechanical ventilation (for VAP)
and feeding through a nasogastric tube because their presence can lead to aspiration of
oropharyngeal secretions into the lower respiratory tract. These conditions are particularly
common in elderly and frail patients(268). HAP is associated with higher in-hospital mortality
than community-acquired pneumonia, and VAP is the form of HAP with the highest mortality
(268, 269).

**Microbiology epidemiology**

HAP may be caused by the same pathogens found in community-acquired pneumonia or by
multidrug-resistant pathogens (Table 1). In general antibiotic resistance is more prevalent in
hospital-acquired strains but the frequency of multidrug-resistant pathogens varies between
hospitals and different patient populations. Usually, the risk of infection with multidrug-resistant
pathogens is increased in patients with HAP because they have often been exposed to different
regimens of antibiotics before developing HAP. The risk increases with prolonged hospitalization
(higher risk of transmission, more antibiotic use) especially if in a critical care setting and in
intubated patients. It is important to note that most data on the microbiological etiology of HAP
comes from ventilated patients in an intensive care setting because samples from the lower
respiratory tract can be relatively easily obtained. In contrast, in non-ventilated patients
bronchoalveolar lavage is associated with a risk of respiratory deterioration and non-invasive
sampling techniques are often not sufficient to obtain an accurate microbiological diagnosis of etiologic agents in pneumonia.

Table 1 Pathogens most frequently associated with hospital-acquired pneumonia (in descending order of frequency)

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>Viruses</th>
<th>Fungi</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptococcus pneumoniae</td>
<td>Influenza virus (A and B)</td>
<td>Mostly Aspergillus spp. in severely immunosuppressed patients or ventilated patients with influenza</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>Other respiratory viruses (including SARS-CoV-2)</td>
<td></td>
</tr>
<tr>
<td>Staphylococcus aureus (including MRSA)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gram-negative bacteria including Pseudomonas aeruginosa and Acinetobacter baumannii (including multidrug-resistant strains such as those producing ESBL and carbapenemases)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaerobes (mostly associated with aspiration of a large amount of secretions)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Legionella pneumophila</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Clinical presentation

The clinical manifestations are the same as in all other forms of pneumonia: new or worsening cough with or without sputum production, dyspnoea (difficulty in breathing), tachypnoea (cut-off points for rapid breathing vary with age), reduced oxygen saturation, crepitations on lung auscultation, or chest pain or discomfort without an alternative explanation. Fever ≥ 38.0 °C is usually present but may be absent, especially in elderly people.

In ventilated patients, pneumonia is usually suspected in those with increased secretions, reduced oxygen saturation and a new lung infiltrate on a chest-radiograph.

HAP and VAP may progress to sepsis and septic shock. Please refer to the sepsis chapter if this is suspected.

It is important to note that accurate diagnosis of HAP is difficult in the absence of a good reference standard. Pulmonary infiltrates on chest X-ray may be caused by a variety of non-infectious conditions and the clinical presentation may be very non-specific. There is considerable
interobserver variability among specialists in the diagnosis of HAP. It is important to consider the possibility of over diagnosis of HAP and think about stopping antibiotic treatment if HAP is ruled out or an alternative diagnosis can be made.

**Laboratory tests**

I. **Patient microbiology tests**

The following tests could be considered to guide antimicrobial treatment (Table 2):

- blood cultures (ideally before starting antibiotic treatment)
- microscopy and culture of respiratory samples (ideally before starting antibiotic treatment)
  - Respiratory sampling can be done using invasive or non-invasive methods depending on the patient’s condition (e.g. if the patient is mechanically ventilated or not) and local availability. Invasive methods include bronchoalveolar lavage (BAL) and blind bronchial sampling (usually called mini-BAL). Non-invasive methods include spontaneous expectoration of sputum, sputum induction, nasotracheal suctioning or endotracheal aspiration.
- urinary antigens for *Legionella pneumophila* and *Streptococcus pneumoniae*.

Additionally, in selected cases, the following tests could be useful (Table 2):

- nucleic acid amplification test for influenza virus in a nasopharyngeal sample to help decide on antiviral treatment and for infection prevention and control purposes (e.g. to prevent transmission to other patients).
- nucleic acid amplification test or antigen test for SARS-CoV-2 depending on the current epidemiology.

However, most patients will not have culture data to guide antibiotic treatment. In addition, in people with HAP, the respiratory tract is often colonized with bacteria and a positive culture may indicate colonization rather than an acute infection especially if the sample was obtained by non-invasive methods.

*Table 2 Microbiology tests to consider if hospital-acquired pneumonia is suspected as indicated in the WHO EDL (54)*

<table>
<thead>
<tr>
<th>Diagnostic test</th>
<th>Purpose of test</th>
<th>Setting where the test should be available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood cultures</td>
<td>To detect bacterial bloodstream infection</td>
<td>Health care facilities with clinical laboratories</td>
</tr>
<tr>
<td>Respiratory sample microscopya</td>
<td>To assess microbial morphology and adequacy of the specimen for culture by identifying white blood cells and squamous epithelial cells</td>
<td>Health care facilities with clinical laboratories</td>
</tr>
<tr>
<td>(Gram stain)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Respiratory sample culture\(^a\)

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 *Legionella pneumophila* and *Streptococcus pneumoniae*

To diagnose legionellosis and pneumococcal pneumonia

Health care facilities with clinical laboratories

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


\(^a\)Respiratory sampling can be done using invasive or non-invasive methods depending on the patient’s condition (e.g. if the patient is mechanically ventilated or not) and local availability. Invasive methods include bronchoalveolar lavage (BAL) and blind bronchial sampling (usually called mini-BAL) while non-invasive methods include spontaneous expectoration, sputum induction, nasotracheal suctioning or endotracheal aspiration.

\(^b\)This test is not in the current WHO EDL (54).

## II. Other tests

A number of tests could be considered based on local availability to determine disease severity, help differentiate bacterial and viral causes and determine treatment duration (and the move from intravenous to oral treatment) during follow up (Table 3). Please also refer to the chapter on sepsis if suspected.

**Table 3 Laboratory tests to consider if hospital-acquired pneumonia is suspected as indicated in the WHO EDL (54)**

<table>
<thead>
<tr>
<th>Diagnostic test</th>
<th>Purpose of test</th>
<th>Setting where the test should be available</th>
</tr>
</thead>
<tbody>
<tr>
<td>White blood cell count</td>
<td>To help in the diagnosis of infection</td>
<td>Health care facilities with clinical laboratories</td>
</tr>
<tr>
<td>Blood pH and gases</td>
<td>To assess lung function and metabolic or kidney disorders, and monitor oxygen therapy</td>
<td>Health care facilities with clinical laboratories</td>
</tr>
<tr>
<td></td>
<td>To measure blood pH, O(_2) and CO(_2), serum bicarbonate, and anion gap</td>
<td></td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>To detect inflammation as an indicator of various conditions, e.g. sepsis</td>
<td>Health care facilities with clinical laboratories</td>
</tr>
<tr>
<td>Procalcitonin</td>
<td>To guide antibiotic therapy or discontinuation in sepsis</td>
<td>Only in tertiary care facilities</td>
</tr>
</tbody>
</table>

III. Using microbiology surveillance data

Routine microbiology surveillance of isolates associated with HAP and their antibiotic susceptibilities could help informing local empiric guidance. Therefore, empiric guidance given by the Handbook could be reviewed and adapted based on local clinically relevant microbiology surveillance data.

However, clinically relevant isolates for this infection would be local hospital blood culture and bronchoalveolar lavage (BAL) fluid cultures data from patients in intensive care diagnosed with HAP/VAP. Caution should be taken with surveillance of routine respiratory sampling culture data from patients with HAP/VAP due to the high rates of colonisation seen in many settings.

Imaging

When HAP (or VAP) is suspected clinically, a chest radiograph should be obtained. HAP (or VAP) presents with clinical signs and symptoms along with a new or worsening pulmonary infiltrate on a chest radiograph and leukocytosis.

A chest radiograph is needed because other conditions have similar clinical features and antibiotics may be avoided if the chest radiograph does not suggest bacterial pneumonia. Chest radiographs can be difficult to interpret and to correlate with the clinical presentation (especially in elderly people where the clinical presentation is usually non-specific), and many other conditions (such as heart failure) can mimic infectious infiltrates. Therefore, caution is warranted to avoid over diagnosis and overtreatment with antibiotics. It should also be noted that the radiographic pattern cannot be used to accurately predict the microbial etiology.

Antibiotic treatment

Empiric treatment should be guided by the severity of symptoms (scoring systems to evaluate disease severity exist but they are beyond the scope of this chapter) and by risk factors for multidrug-resistant infections. In particular, individualized assessment should be done based on risk factors such as previous antibiotic treatment (e.g. in the 90 days preceding the infection), prolonged hospital stay, particularly in the intensive care unit (>5 days), previous colonization with multidrug-resistant pathogens and a high local prevalence of multidrug-resistant pathogens (among potential causative pathogens of HAP such as Staphylococcus aureus, Gram-negative bacteria including Pseudomonas aeruginosa).

Antibiotic options to consider for empiric treatment in patients with HAP (non-VAP) are given in Table 4. Treatment should always be tailored to culture results once these become available.

Empiric treatment in patients with VAP should be chosen considering the time from ICU admission/intubation to symptom onset. In ventilated patients (like in non-ventilated patients that develop HAP), infections that develop early (e.g. a few days after admission) are unlikely to be caused by multidrug-resistant pathogens or Pseudomonas aeruginosa and could safely be
treated with amoxicillin+clavulanic acid. On the other end, an antibiotic with a larger spectrum of activity (and active against *Pseudomonas aeruginosa*) is preferable in case of a longer time interval between admission to hospital and onset of symptoms.

There are some areas of uncertainty about empiric treatment for HAP.

- Adding vancomycin to the first-choice antibiotic options as an empiric treatment when methicillin-resistant *Staphylococcus aureus* (MRSA) infection is suspected (e.g. in settings with a high prevalence of *Staphylococcus aureus* isolates that are methicillin resistant and in patients known to be colonized by MRSA).

- The need for double coverage against *Pseudomonas* to improve coverage in severely ill patients with VAP (e.g. septic shock, or in need of ventilatory support) because of the risk of infection caused by *Pseudomonas aeruginosa* isolates resistant to an antibiotic used for monotherapy. The need for double coverage could therefore be considered in severely ill patients with VAP on a case-by-case basis based on local antibiotic resistance data and the personal history of the patient (e.g. known respiratory colonization with multidrug-resistant *Pseudomonas aeruginosa*, particularly in patients with underlying chronic lung disease).

**Simplify** empiric treatment to a more narrow-spectrum antibiotic based on culture results or based on rapid clinical improvement when no microbiology test results are available.

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

### Table 4 Empiric antibiotic treatment for hospital-acquired pneumonia (not for ventilator-associated pneumonia)

<table>
<thead>
<tr>
<th>Adults</th>
<th>Children</th>
<th>Total treatment duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Amoxicillin+clavulanic acid</strong> (IV): 1 g + 200 mg given every 8 hours</td>
<td><strong>Amoxicillin+clavulanic acid</strong> (IV/oral) 40-50 mg/kg/dose of amoxicillin component, given every 12 hours OR 30 mg/kg/dose given every 8 hours</td>
<td>7 days</td>
</tr>
<tr>
<td>OR</td>
<td>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</td>
<td>Reassess the diagnosis and consider longer treatment if the patient is not clinically stable at day 7</td>
</tr>
<tr>
<td><strong>Ceftriaxone</strong> (IV/IM): 2 g given once a day (IV), 1 g given once a day (IM) OR <strong>Cefotaxime</strong> (IV/IM): 2 g given every 8 hours</td>
<td>OR</td>
<td></td>
</tr>
<tr>
<td><strong>Piperacillin+tazobactam</strong> (IV): 4 g + 500 mg given every 6 hours</td>
<td>OR</td>
<td></td>
</tr>
</tbody>
</table>
Ceftriaxone (IV/IM): 80 mg/kg/dose given once a day
OR
Cefotaxime (IV/IM): 50 mg/kg/dose given every 8 hours
OR
Piperacillin+tazobactam (IV): 100 mg/kg/dose of piperacillin component, given every 8 hours

Notes: All dosages are for normal renal and hepatic function.
IM: intramuscular; IV: intravenous.

a Amoxicillin+clavulanic acid can be used in certain circumstances with low-risk of multidrug-resistant infections (e.g. short hospitalization before symptom onset and if no prior antibiotic exposure).

b The reason for giving a lower dose when the ceftriaxone is given IM (rather than IV) is that a larger volume would be painful to give as intramuscular injection.

c Piperacillin+tazobactam offers anti- Pseudomonas coverage (which the other options do not). Risk of Pseudomonas aeruginosa is higher in patients with recent antibiotic exposure and especially in patients with known previous respiratory colonization by P. aeruginosa and underlying lung diseases.

d Oral liquid must be refrigerated after reconstitution as clavulanic acid is rapidly metabolized in high ambient temperatures.

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

Prevention

A detailed discussion of the prevention of HAP and VAP is beyond the scope of this chapter; however, general key principles are presented. Some measures such as vaccination against pathogens that can commonly cause pneumonia overlap with those presented in the chapter on community-acquired pneumonia. Specific measures that apply to the hospital setting include: maintaining mobility, good oral and dental care, maintaining adequate nutritional support in hospital, elevating the head of the bed to reduce the chances of aspirating respiratory secretions into the lower lungs, avoiding intubation or reducing its duration as much as possible and good hand hygiene (this applies to patients and staff or family caregivers that come into contact with patients during the hospital stay). In addition, in the intensive care unit, locally adapted bundles of interventions to prevent VAP are usually in place and include, for example, maintaining adequate endotracheal tube cuff pressure, minimizing sedation and assessing regularly if the endotracheal tube can be removed in order to extubate patients as soon as it is safe to do so.

Selective oral decontamination (SOD) and/or selective decontamination of the digestive tract (SDD) can also be considered based on local ICU protocols. These preventive measures have been extensively studied to prevent hospital-acquired infections and their rationale is to reduce the bacterial burden of the upper (with SOD) and lower (with SDD) digestive tract through the administration of non-absorbable antibiotics (topical antibiotics applied to the oropharynx for SOD and non-absorbable antibiotics administered through nasogastric tube for SDD). Evidence exists that these practices can help reducing the incidence of VAP but there is a significant concern about the risk of selecting resistant bacteria.
Intra-abdominal infections - Acute cholecystitis and cholangitis

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.

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


Definition

Acute cholecystitis is an acute inflammation of the gallbladder and acute cholangitis is an acute inflammation in the bile duct system. Both conditions are classified as uncomplicated when there is no involvement of the peritoneal cavity and the inflammation is confined to the organ involved (i.e., no perforation, no abscess, no diffuse peritonitis). The conditions are classified as complicated when the inflammation extends to the peritoneal cavity with subsequent peritonitis or when an abscess is present.
Pathophysiology

In acute cholecystitis, a gallstone obstructing the cystic duct for prolonged periods of time and causing inflammation of the gallbladder is the most frequent cause (> 90%). Acalculous cholecystitis, where there is no evidence of gallstones or cystic duct obstruction, is uncommon, especially in adults. Rarely, certain parasites (e.g. the worm *Ascaris lumbricoides*) can also cause gallbladder perforation.

In acute cholangitis, the most common cause is choledocholithiasis (i.e. gallstones in the bile duct). Infection occurs when bacteria travel up the biliary tract from the intestine or via the portal venous system. Another cause may be obstruction by tumours (e.g. pancreatic cancer) or parasites (e.g. the liver fluke *Fasciola hepatica*). In addition, congenital biliary strictures or strictures following inflammation or infection can cause acute cholangitis.

In both cholecystitis and cholangitis, if bacterial contamination or chemical irritation (usually due to leakage of sterile fluids that are irritants to the peritoneum; for example, bile or blood) of the peritoneal cavity occur, peritonitis develops. Abdominal abscesses (i.e. the presence of a collection of infected fluid in the peritoneal cavity) can also form as a result of a complicated infection.

Epidemiology

Acute cholecystitis is a common surgical emergency worldwide. The incidence of acute cholecystitis is declining where cholecystectomy (surgical removal of the gallbladder) has become a common procedure in cases of recurrent attacks of biliary colic (i.e. intermittent pain in the upper abdomen, usually on the right side). Acute cholecystitis mostly affects adults; children are rarely affected. The disease is more prevalent in men and elderly people. Obesity and diabetes are also well-known risk factors. Short-term 30-day mortality is about 5% in severe cases and 1% in mild cases.

Acute cholangitis is a condition associated with high mortality if left untreated. It is a rare disease in children. Choledocholithiasis and malignant obstruction by tumours are the most common causes of cholangitis and their risk factors overlap.

Microbiology epidemiology

The most common pathogens involved in acute cholecystitis or cholangitis are Gram-negative bacilli and anaerobic bacteria from the intestinal microbiota (Table 1). Infections are often caused by more than one pathogen and may include fungal pathogens, especially in patients that have recently received antibiotic treatment. Certain parasites need to be considered in the differential diagnosis of abdominal pain in endemic settings.

Table 1 Pathogens most frequently associated with acute cholecystitis and cholangitis (in descending order of frequency)

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>Fungi</th>
<th>Parasites</th>
</tr>
</thead>
</table>

243
Enterobacterales (mostly *Escherichia coli*) and other Gram-negative bacteria such as *Pseudomonas aeruginosa* and *Acinetobacter baumannii* (including multidrug-resistant strains such as those producing ESBL and carbapenemases)

*Streptococcus* spp. (e.g. of the *Streptococcus anginosus* group - old name: *Streptococcus milleri*)

*Enterococcus* spp.

*Anaerobes* (mostly *Bacteroides* spp.)

Mostly *Candida albicans*

*Ascaris lumbricoides* *Fasciola hepatica*

ESBL: extended-spectrum beta-lactamases.

**Clinical presentation**

Acute cholecystitis should be considered as a possible diagnosis in all cases of acute abdominal pain, especially if the pain is predominantly located in the right upper quadrant.

Acute cholangitis should be considered a possible diagnosis in all cases presenting with abdominal pain, fever and jaundice (i.e. yellow color of the skin and sclera due to increased levels of bilirubin).

Fever (> 38.0 °C), chills, nausea and vomiting may be present, mostly in complicated infections. Severe pain, diffuse rebound tenderness on sudden release of pressure on the abdomen and abdominal muscular defence are usually present in case of peritonitis. Hypotension and signs of organ hypoperfusion (e.g. reduced urine output) may be present in cases of organ failure and are a medical and/or surgical emergency. Please also refer to the chapter on sepsis if suspected.

**Laboratory tests**

### I. Patient microbiology tests

In mild cases, routine microbiology tests are not usually needed and basing antibiotic treatment on pathogens cultured from the abdominal cavity at the time of operation is not recommended. Blood cultures and other microbiology tests could be considered in severely ill patients in order to adjust empiric antibiotic treatment once the results of susceptibility tests are available (see Table 2).

**Table 2 Microbiology tests to consider in severe cases of acute cholecystitis or cholangitis as indicated in the WHO EDL (54)**

<table>
<thead>
<tr>
<th>Diagnostic test</th>
<th>Purpose of the test</th>
<th>Setting where the test should be available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood cultures</td>
<td>To detect bacterial bloodstream infections (sepsis)</td>
<td>Health care facilities with clinical laboratories</td>
</tr>
</tbody>
</table>
II. Other tests

Laboratory tests can be used to complement the clinical examination and medical history. Based on availability, Table 3 indicates tests that could be considered in the patient’s initial assessment and to help guide the duration of antibiotic treatment.

Table 3 Laboratory tests (other than microbiology) that may help assess the severity of disease and identify a bacterial infection as indicated in the WHO EDL (54)

<table>
<thead>
<tr>
<th>Diagnostic test</th>
<th>Purpose of the test</th>
<th>Setting where the test should be available</th>
</tr>
</thead>
<tbody>
<tr>
<td>White blood cell count</td>
<td>To help in the diagnosis of infections</td>
<td>Health care facilities with clinical laboratories</td>
</tr>
<tr>
<td>Aspartate aminotransferase</td>
<td>To assess liver function</td>
<td>Health care facilities with clinical laboratories</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>To detect or monitor liver disease, bile duct disorders and red cell destruction</td>
<td>Health care facilities with clinical laboratories</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>To aid in diagnosis of hepatobiliary diseases</td>
<td>Health care facilities with clinical laboratories</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>To detect inflammation as an indicator of various conditions, e.g. sepsis</td>
<td>Health care facilities with clinical laboratories</td>
</tr>
<tr>
<td>Procalcitonin</td>
<td>To guide antibiotic therapy or discontinuation in sepsis</td>
<td>Only in tertiary care facilities</td>
</tr>
</tbody>
</table>

III. Using microbiology surveillance data

Routine surveillance of pathogens cultured from the abdominal cavity is not recommended. Empiric guidance given by the Handbook could be reviewed and adapted based on local clinically relevant microbiology surveillance data. For example, clinically relevant isolates for this infection would be blood culture data from patients on surgical wards with intra-abdominal infections.

Imaging

Imaging is helpful to confirm cholecystitis and cholangitis. An abdominal ultrasound should always be considered when these conditions are suspected. Where available, a computed tomography (CT) scan of the abdomen may also be considered, especially if complications are suspected or the diagnosis is uncertain.
Treatment of acute cholecystitis

Patients with suspected or confirmed acute cholecystitis should be promptly referred for surgical consultation. Eliminating the source of infection and the ongoing contamination of the peritoneal cavity (e.g. in case of perforation) is the most important surgical intervention. Cholecystectomy (i.e. removal of the gallbladder) is the only definitive treatment and an antibiotic should be given until the gallbladder is removed(275). After surgery, in uncomplicated cases, antibiotic treatment can be stopped provided the source of infection was adequately controlled and there is good clinical recovery. In severe cases (i.e. critically ill patients), 5 days of antibiotic treatment are usually adequate, provided there is good clinical recovery and the source of infection was adequately controlled and eliminated with surgery(276).

Treatment of acute cholangitis

Biliary drainage is the main surgical intervention for acute cholangitis and antibiotic treatment should be given in all cases irrespective of severity. Antibiotic treatment should be given until drainage procedures are done and continued for a total of 5 days once control of the source of infection has been achieved(276). Shorter courses of antibiotics (e.g. 3 days) have been evaluated in observational studies (and in a systematic review) and were not associated with a higher occurrence of complications; however, this practice remains controversial because the evidence is not strong(277, 278).

Antibiotic treatment

Empiric antibiotic treatment should be chosen based on the severity of symptoms (mild or severe), considering local prevalence of resistance, particularly isolates producing extended-spectrum beta-lactamases since the prevalence can vary greatly in different settings(279) (Table 4). Individual risk factors for resistant pathogens (e.g. recent antibiotic treatment, colonization with resistant pathogens) should also be considered.

Simplify empiric treatment to a more narrow-spectrum antibiotic based on culture results or based on rapid clinical improvement when no microbiology test results are available.

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

If signs and symptoms persist, abdominal imaging is suggested, or an alternative extra-abdominal source of infection should be considered.

Table 4 Empiric antibiotic treatment for acute cholecystitis or cholangitis

Mild cases are defined as patients who are not critically ill with no signs of sepsis or septic shock. Severe cases are defined as patients who are critically ill with signs of sepsis or septic shock.
<table>
<thead>
<tr>
<th>Severity</th>
<th>Adults</th>
<th>Children</th>
<th>Total treatment duration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>First choice</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild cases</td>
<td><strong>Amoxicillin+clavulanic acid</strong> (oral): 875 + 125 mg given every 8 hours</td>
<td><strong>Amoxicillin+clavulanic acid</strong> (IV/oral): 40-50 mg/kg/dose of amoxicillin component given every 12 hours OR 30 mg/kg/dose given every 8 hours</td>
<td></td>
</tr>
<tr>
<td></td>
<td>OR</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Ceftriaxone</strong> (IV): 2 g given once a day AND <strong>Metronidazole</strong> (IV/oral): 500 mg given every 8 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>OR</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Cefotaxime</strong> (IV): 2 g given every 8 hours AND <strong>Metronidazole</strong> (IV/oral): 500 mg given every 8 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Second choice</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Ciprofloxacin</strong> (oral): 500 mg given every 12 hours AND <strong>Metronidazole</strong> (IV/oral): 500 mg given every 8 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Ciprofloxacin has excellent oral bioavailability and the IV route should be reserved for patients with impaired gastrointestinal function)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Uncomplicated cases treated with cholecystectomy: stop after surgery if adequate control of the source of infection has been achieved and symptoms have resolved.
- Children: 7.5 mg/kg/dose given every 8 hours

Oral weight bands:
3–<6 kg: 30 mg given every 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

**OR**

**Ampicillin (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

**AND**

**Gentamicin (IV):**
- Neonates: 5 mg/kg given once daily
- Children: 7.5 mg/kg given once daily

**AND**

**Metronidazole**

Oral/IV:
- Neonates: 7.5 mg/kg/dose given every 12 hours (for IV starting with a loading dose of 15 mg/kg)
- Children: 7.5 mg/kg/dose given every 8 hours

Oral weight bands:
3–<6 kg: 30 mg given every 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

**Second choice**

**Ciprofloxacin (IV/oral):** 10-20 mg/kg/dose, given every 12 hours

Oral weight bands:
3–<6 kg: 50 mg given every 12 hours
### Severe cases

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First choice</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Piperacillin+tazobactam</strong> (IV):</td>
<td>4 g + 500 mg given every 6 hours</td>
</tr>
<tr>
<td>OR</td>
<td></td>
</tr>
<tr>
<td><strong>Ceftriaxone</strong> (IV):</td>
<td>2 g given once a day AND <strong>Metronidazole</strong> (IV/oral): 500 mg given every 8 hours</td>
</tr>
<tr>
<td>OR</td>
<td></td>
</tr>
<tr>
<td><strong>Cefotaxime</strong> (IV):</td>
<td>2 g given every 8 hours AND <strong>Metronidazole</strong> (IV/oral): 500 mg given every 8 hours</td>
</tr>
<tr>
<td><strong>Second choice</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Ampicillin</strong> (IV):</td>
<td></td>
</tr>
<tr>
<td><strong>Gentamicin</strong> (IV):</td>
<td></td>
</tr>
<tr>
<td><strong>Metronidazole</strong> Oral/IV:</td>
<td></td>
</tr>
</tbody>
</table>

### Acute cholecystitis: 5 days in total if adequate control of the source of infection has been achieved with surgery and symptoms have resolved.

### Acute cholangitis: 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.

- **Ciprofloxacin** has excellent oral bioavailability and the IV route should be reserved for patients with impaired gastrointestinal function.
- **Metronidazole** (IV/oral):
  - Neonates: 7.5 mg/kg/dose given every 12 hours (for IV starting with a loading dose of 15 mg/kg)
  - Children: 7.5 mg/kg/dose given every 8 hours

Oral weight bands:
- 3<6 kg: 30 mg given every 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
| **Meropenem**<sup>a</sup>(IV): 2 g given every 8 hours | • Children: 7.5 mg/kg/dose given every 8 hours  
Oral weight bands:  
3-<6 kg: 30 mg given every 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  
**OR**  
**Piperacillin+tazobactam** (IV): 100 mg/kg/dose of piperacillin component given every 8 hours  
**Second choice**  
**Meropenem**<sup>a</sup>(IV): 20 mg/kg/dose given every 8 hours |

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

<sup>a</sup>Meropenem should not be considered for routine use for all severe cases but only in complicated cases (i.e. abscess and/or peritonitis) in settings with a high prevalence of extended-spectrum beta-lactamase (ESBL)-producing *Enterobacterales* or in patients with known prior colonization, treated with multiple antibiotic courses or at risk of infections with pathogens resistant to the first-choice option. Empiric use of a “Reserve” antibiotic could be considered exceptionally in very selected cases of seriously ill patients failing to respond to carbapenems or that have previously been treated for infections caused by carbapenem-resistant pathogens or that are known to be colonized with multidrug-resistant Gram-negative bacteria known to be susceptible to the selected “Reserve” antibiotic. Please refer to the corresponding chapter for the definition and list of “Reserve” antibiotics included in the EML/c.

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

ACCESS antibiotics are indicated in green, WATCH antibiotics in yellow and RESERVE antibiotics in red.
Intra-abdominal infections -
Liver abscess - pyogenic

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.

Definition

A pyogenic liver abscess is defined as a collection of pus within the liver.

Pathogenesis

A pyogenic liver abscess develops when a biliary infection spreads directly to the liver or when a complicated intra-abdominal infection spreads to the liver via the portal circulation. In cases of systemic infection, the infection may also spread to the liver via the bloodstream.

Epidemiology

Pyogenic liver abscess is the most common type of visceral abscess. It is frequently associated with male sex and diabetes. Pyogenic liver abscess is more common in South-East Asia probably due to the different epidemiology of certain causative pathogens (e.g. *Klebsiella pneumoniae*). Underlying hepatobiliary or pancreatic diseases (e.g. malignancy, cirrhosis, recent abdominal or biliary surgery) are common risk factors. Abscess rupture is a rare but severe complication associated with a high mortality if not treated immediately.

Microbiology epidemiology

Most cases of liver abscess are caused by enteric Gram-negative bacteria and anaerobes and most cases involve more than one pathogen (Table 1). A hypervirulent strain of *Klebsiella pneumoniae* is an increasingly common cause of liver abscess in Asia. *Burkholderia*
pseudomallei (a Gram-negative bacterium found in soil and water and transmitted by inhalation or ingestion or inoculation) is also a cause of liver abscess in endemic countries (mostly in South-East Asia and in Australia).

Parasites, notably Entamoeba histolytica (acquired by ingestion of contaminated food or water), are another frequent cause of liver abscess in endemic settings (Indian subcontinent, Africa, and Central and South America)(285, 286).

Table 1 Pathogens most frequently associated with liver abscess (in descending order of frequency)

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>Fungi</th>
<th>Parasites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterobacterales (mostly Escherichia coli, Klebsiella pneumoniae, Enterobacter spp.) including multidrug-resistant strains such as those producing ESBL and carbapenemases Staphylococcus spp. Streptococcus spp. (e.g. of the Streptococcus anginosus group - old name: Streptococcus milleri) Enterococcus spp. Anaerobes (mostly Bacteroides spp.)</td>
<td>Candida spp.(^c) Entamoeba histolytica(^d)</td>
<td></td>
</tr>
</tbody>
</table>

ESBL: extended-spectrum beta-lactamases.

In Asia, Klebsiella pneumoniae is currently the main cause of liver abscess.

Burkholderia pseudomallei is an important cause of liver abscess in South-East Asia and northern Australia.

Often in combination with bacteria.

This pathogen is not a cause of pyogenic abscess but needs to be considered in the differential diagnosis, especially in patients who live or have travelled to settings where Entamoeba histolytica is endemic.

Clinical presentation

Pyogenic liver abscess should be considered as in all cases of fever (> 38.0 °C) and abdominal pain (mostly localized in the right upper abdominal quadrant). Vomiting, nausea, anorexia, malaise and jaundice are other common symptoms.

Laboratory tests

I. Patient microbiology tests

Whenever possible, a microbiology sample should be obtained (see Table 2) to guide antibiotic treatment. Ideally, the sample should be obtained before antibiotic treatment is started. The
reason for doing microbiology tests is to determine the type of pathogen causing infection and its resistance profile in order to provide adequate treatment.

Table 2: Microbiology tests to consider when a liver abscess is suspected (including testing for Entamoeba histolytica) as indicated in the WHO EDL (54)

<table>
<thead>
<tr>
<th>Diagnostic test</th>
<th>Purpose of test</th>
<th>Setting where the test should be available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood cultures</td>
<td>To detect bacterial bloodstream infections (sepsis)</td>
<td>Health care facilities with clinical laboratories</td>
</tr>
<tr>
<td>Microscopy and culture of abscess or pus aspirate</td>
<td>Initial step to detect and identify bacterial and fungal species for selection of appropriate antibiotic regimens</td>
<td>Health care facilities with clinical laboratories</td>
</tr>
<tr>
<td>Microscopy of stool sample for Entamoeba histolytica</td>
<td>To diagnose Entamoeba histolytica</td>
<td>Health care facilities with clinical laboratories</td>
</tr>
<tr>
<td>Antigen or nucleic acid amplification test (i.e. polymerase chain reaction) of abscess aspirate material for Entamoeba histolytica</td>
<td>To diagnose Entamoeba histolytica</td>
<td>–d</td>
</tr>
<tr>
<td>Serology for Entamoeba histolytica</td>
<td>To diagnose Entamoeba histolytica</td>
<td>–d</td>
</tr>
</tbody>
</table>

Entamoeba histolytica is not a cause of pyogenic abscess but a cause of liver abscess that needs to be considered in the differential diagnosis in endemic settings. However, patients with amoebic liver abscess usually have no bowel symptoms; therefore, stool testing (microscopy or antigen) has a low sensitivity and is of limited usefulness for diagnosis.

Antigen or nucleic acid amplification testing of abscess aspirate material for Entamoeba histolytica could be considered where available. Diagnosis is often difficult in low- and middle-income countries due to limited laboratory resources and the fact that most patients present after a failed course of antibiotic treatment for pyogenic abscess (therefore the yield of any microbiology tests is lower) (7,9).

Serology is a useful test in the diagnosis of invasive amoebiasis and is positive in more than 90% of patients with the disease. A positive serology combined with a compatible clinical presentation suggests active disease. However, in endemic settings, a positive result is more difficult to interpret since serology can remain positive for months and even years after resolution of the infection. Therefore, past and current infections become difficult to distinguish. With negative results, if the clinical suspicion of invasive amoebiasis is still strong, serology could be repeated after 1 week.

This test is not in the WHO EDL (54).

II. Other tests

Laboratory tests can be used to complement the clinical examination and medical history even though they are not specific for the diagnosis. Table 3 indicates tests that could be considered in the patient’s initial assessment. Please also refer to the chapter on sepsis if suspected.

Table 3: Laboratory tests (other than microbiology) to consider if pyogenic liver abscess is suspected as indicated in the WHO EDL (54)

| Diagnostic test                                      | Purpose of the test                                      | Setting where the test should be available       |
### Laboratory Tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Purpose</th>
<th>Settings</th>
</tr>
</thead>
<tbody>
<tr>
<td>White blood count</td>
<td>To help in the diagnosis of infections</td>
<td>Health care facilities with clinical laboratories</td>
</tr>
<tr>
<td>Aspartate aminotransferase</td>
<td>To assess liver function</td>
<td>Health care facilities with clinical laboratories</td>
</tr>
<tr>
<td>Alanine aminotransferase</td>
<td>To assess liver function</td>
<td>Health care facilities with clinical laboratories</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>To detect or monitor liver disease</td>
<td>Community settings and health facilities without laboratories^a</td>
</tr>
<tr>
<td>Direct and indirect bilirubin</td>
<td>To detect or monitor liver disease, bile duct disorders and haemolytic anaemia, and to differentiate between these causes of jaundice</td>
<td>Health care facilities with clinical laboratories</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>To aid in the diagnosis of hepatobiliary diseases</td>
<td>Health care facilities with clinical laboratories</td>
</tr>
</tbody>
</table>

^aCommunity and health settings without laboratories are settings such as health posts and centres, doctors’ offices, outreach clinics and ambulatory care. These tests are also assumed to be available at health care facilities with laboratories.

### III. Using microbiology surveillance data

There is no role for routine surveillance to inform empiric guidance.

### Imaging

Imaging is very helpful in the diagnosis of pyogenic liver abscess. An abdominal ultrasound should always be considered when this condition is suspected. In settings where it is available, a computed tomography (CT) scan of the abdomen may also be considered, especially if complications are suspected or the diagnosis is uncertain.

### Treatment

Early control of the source of infection through drainage of the abscess is usually required when feasible in addition to antibiotic treatment, especially for large (> 5 cm) abscesses. Drainage is recommended because larger abscesses have a higher risk of rupture.

Drainage techniques include:

- Percutaneous drainage (image-guided procedure that is usually performed by an interventionist radiologist where available): a drain – usually a pigtail catheter – is inserted through the skin into the abscess and left in place until the collection is drained.
- Surgical drainage: this is done either as a conventional open procedure (i.e. laparotomy) or by laparoscopy.

In both cases, the drainage procedure is also important for diagnostic purposes to identify the type of pathogen causing the abscess and its resistance profile. Abscess material should therefore be obtained for culture when the drain is posed or the abscess is surgically removed.
Antibiotic treatment

In patients who are clinically stable, targeted treatment based on the results of microbiology tests is always preferred. In particular, infections caused by Enterobacterales producing extended-spectrum beta-lactamases (ESBL) or carbapenemases need to be considered in patients with history of hospitalisation or previously colonised or infected with these resistant pathogens as their prevalence varies greatly in different settings.

In more severe cases, empiric treatment is given, taking into account the most probable type of causative pathogen (including the possibility of *Entamoeba histolytica* infection) and local prevalence of resistance (especially for ESBL- and carbapenemase-producing isolates). Individual risk factors for resistant pathogens (e.g. recent antibiotic treatment, colonization or previous infections with resistant isolates) should also be considered.

The total duration of treatment is usually long (weeks) and depends on whether control of the source of infection is achieved and on the causative pathogen. Therefore, early control of the source of infection and identification of the causative pathogen are encouraged. In most cases, at least 4 weeks of antibiotic treatment are needed with follow-up imaging to monitor response and define treatment duration.

Longer duration of treatment is required in cases of liver abscess caused by *Burkholderia pseudomallei* (usually 2 weeks of IV treatment followed by > 3 months of oral treatment with sulfamethoxazole+trimethoprim to eradicate the infection and prevent relapse or recurrence).

In cases of amoebic liver abscess, a 10-day course of treatment (with oral metronidazole) is usually adequate.

**Simplify** empiric treatment to a more narrow-spectrum antibiotic based on culture results or based on rapid clinical improvement when no microbiology test results are available. In general, the intravenous (IV) route is preferred for the initial phase of treatment.

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

Oral step-down therapy can be considered quickly for mild cases after adequate drainage and confirmed microbiology and susceptibility.

If signs and symptoms persist, abdominal imaging is suggested, or an alternative extra-abdominal source of infection should be considered.

*Table 4 Empiric antibiotic treatment for pyogenic or amoebic liver abscess*

In clinically stable patients, targeted treatment based on the results of microbiology tests is preferred.

**Mild cases** are defined as patients who are not critically ill with no signs of sepsis or septic shock.

**Severe cases** are defined as patients who are critically ill with signs of sepsis or septic shock.
<table>
<thead>
<tr>
<th>Severity</th>
<th>Adults</th>
<th>Children</th>
<th>Total treatment duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild cases</td>
<td><strong>First choice</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Amoxicillin+clavulanic acid</strong>:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(IV): 1g + 200 mg given every 8 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oral: 875 + 125 mg given every 8 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>OR</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Ceftriaxone</strong> (IV): 2 g given once a day</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>AND <strong>Metronidazole</strong> (IV/oral): 500 mg given every 8 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>OR</td>
<td></td>
<td></td>
</tr>
<tr>
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<td><strong>Cefotaxime</strong> (IV): 2 g given every 8 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>AND <strong>Metronidazole</strong> (IV/oral): 500 mg given every 8 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Second choice</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Ciprofloxacin</strong> (oral): 500 mg given every 12 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>(Ciprofloxacin has excellent oral bioavailability and the IV route should be reserved for patients with impaired gastrointestinal function)</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>AND <strong>Metronidazole</strong> (IV/oral): 500 mg (IV/oral) given every 8 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>First choice</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Amoxicillin+clavulanic acid</strong> (IV/oral)b:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>40-50 mg/kg per dose of amoxicillin component, every 12 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>OR 30 mg/kg/dose given every 8 hours</td>
<td></td>
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<tr>
<td></td>
<td>Oral weight bands:</td>
<td></td>
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<tr>
<td></td>
<td>3-&lt;6 kg: 250 mg of amoxicillin dose given every 12 hours</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>6-&lt;10 kg: 375 mg of amoxicillin/dose given every 12 hours</td>
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<tr>
<td></td>
<td>10-&lt;15 kg: 500 mg of amoxicillin/dose given every 12 hours</td>
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<tr>
<td></td>
<td>15-&lt;20 kg: 750 mg of amoxicillin/dose given every 12 hours</td>
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<tr>
<td></td>
<td>20-&lt;30 kg: 1000 mg of amoxicillin/dose given every 12 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥ 30 Kg: Use adult dose</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>OR</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td><strong>Ceftriaxone</strong> (IV): 80 mg/kg/dose given once a day</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>AND <strong>Metronidazole</strong> (IV/oral):</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Neonates: 7.5 mg/kg/dose given every 12 hours (for IV starting with a loading dose of 15 mg/kg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Children: 7.5 mg/kg/dose given every 8 hours</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Oral weight bands:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3-&lt;6 kg: 30 mg given every 8 hours</td>
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<td></td>
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<tr>
<td></td>
<td>6-&lt;10 kg: 50 mg given every 8 hours</td>
<td></td>
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<tr>
<td></td>
<td>10-&lt;15 kg: 100 mg given every 8 hours</td>
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<tr>
<td></td>
<td>15-&lt;20 kg: 150 mg given every 8 hours</td>
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<tr>
<td></td>
<td>20-&lt;30 kg: 200 mg given every 8 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥ 30 Kg: Use adult dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>At least 4 weeks if adequate control of the source of infection is achieved (follow-up imaging is usually performed to guide treatment duration).</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Children

- **Children**: 7.5 mg/kg/dose given every 8 hours

  **Oral weight bands:**
  - 3–<6 kg: 30 mg given every 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

**OR**

- **Ampicillin (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

- **Gentamicin (IV):**
  - Neonates: 5 mg/kg given once daily
  - Children: 7.5 mg/kg given once daily

**AND**

- **Metronidazole**
  - Oral/IV:
    - Neonates: 7.5 mg/kg/dose given every 12 hours (for IV starting with a loading dose of 15 mg/kg)
    - Children: 7.5 mg/kg/dose given every 8 hours

  **Oral weight bands:**
  - 3–<6 kg: 30 mg given every 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

**Second choice**

- **Ciprofloxacin (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
*(Ciprofloxacin has excellent oral bioavailability and the IV route should be reserved for patients with impaired gastrointestinal function)*

**AND Metronidazole** (IV/oral):
- Neonates: 7.5 mg/kg per dose given every 12 hours (for IV starting with a loading dose of 15 mg/kg)
- Children: 7.5 mg/kg per dose given every 8 hours

**Oral weight bands:**
- 3–<6 kg: 30 mg given every 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

Severe cases

<table>
<thead>
<tr>
<th>First choice</th>
<th>Second choice</th>
</tr>
</thead>
</table>
| **Piperacillin-tazobactam** (IV): 4 g + 500 mg given every 6 hours **OR** **Ceftriaxone** (IV): 2 g given once a day **AND** **Metronidazole** (IV/oral): 500 mg given every 8 hours **OR** **Cefotaxime** (IV): 2 g given every 8 hours **AND** **Metronidazole** (IV/oral): 500 mg given every 8 hours | **Ampicillin** (IV): **First choice**
- Neonates: 5 mg/kg given once daily
- Children: 7.5 mg/kg given once daily **AND** **Gentamicin** (IV):
  - Neonates: 5 mg/kg/dose given every 12 hours
  - Beyond first week of life: 50 mg/kg/dose given every 8 hours **AND** **Metronidazole** Oral/IV:
  - Neonates: 7.5 mg/kg/dose given every 12 hours (for IV starting with a loading dose of 15 mg/kg)
  - Children: 7.5 mg/kg/dose given every 8 hours **OR**

At least 4 weeks if adequate control of the source of infection is achieved (follow-up imaging is usually performed to guide treatment duration).
| Amoebic liver abscess | Metronidazole (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) | Metronidazole (oral<sup>c</sup>): 10-15 mg/kg/dose given every 8 hours | 10 days of metronidazole Followed by 7 days of paromomycin |

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

The EML/c currently does not have specific recommendations for antibiotic treatment of pyogenic or amoebic liver abscess; therefore the options presented in the table are extrapolated from the recommended treatment for complicated intra-abdominal infections.

Meropenem should not be considered for routine use in all severe cases but only in complicated cases in settings with a high prevalence of extended-spectrum beta-lactamase (ESBL)-producing Enterobacterales or in patients with known prior colonization, treated with multiple antibiotic courses or at risk of infections with pathogens resistant to the first choice option. Empiric use of a “Reserve” antibiotic could be considered exceptionally in very selected cases of seriously ill patients failing to respond to carbapenems or that have previously been treated for infections caused by carbapenem-resistant pathogens or that are known to be colonized with multidrug-resistant Gram-negative bacteria known to be susceptible to the selected “Reserve” antibiotic. Please refer to the corresponding chapter for the definition and list of “Reserve” antibiotics included in the EML/c.

When *Burkholderia pseudomallei* is suspected empiric use of meropenem or imipenem could be considered, although the preferred option is ceftazidime.

Oral liquid must be refrigerated after reconstitution as clavulanic acid is rapidly metabolized in high ambient temperatures.

If the patient is unable to tolerate oral treatment or in severe infections, intravenous metronidazole should be given (dose in adults: 500 mg every 8 hours).

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)

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.
Epidemiology

Acute appendicitis is a common surgical emergency worldwide, especially in children and young adults. The yearly incidence of appendicitis has been declining in western European and North American countries since the 1990s and has stabilized in the past 20 years to about 100–150 cases per 100 000 person-years. However, increasing trends are reported in Asia, South America and the Middle East with the incidence of appendicitis higher than in many western European and North American countries. In 2017, there were an estimated 19 million new cases worldwide. The lifetime risk of appendicitis reported in the literature varies across countries, ranging from about 2% in Africa to 16% in South Korea. Mortality attributable to appendicitis has declined and with prompt diagnosis and management, mortality is now < 1% in uncomplicated cases in most settings. Complicated cases or cases in the elderly are associated with a higher mortality.

Microbiology epidemiology

The most common pathogens involved in appendicitis are Gram-negative bacilli and anaerobes from the intestinal microbiota (Table 1). Infections are often caused by more than one pathogen and may include fungal pathogens, especially in patients that have recently received antibiotic treatment. Certain parasites need to be considered in the differential diagnosis of abdominal pain in endemic settings.

Table 1 Pathogens most frequently associated with complicated acute appendicitis (in descending order of frequency)

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>Fungi</th>
<th>Parasites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterobacterales (mostly <em>Escherichia coli</em>) and other Gram-negative bacteria such as <em>Pseudomonas aeruginosa</em> and <em>Acinetobacter baumannii</em> (including multidrug-resistant strains such as those producing ESBL and carbapenemases) <em>Streptococcus</em> spp. (e.g. of the <em>Streptococcus anginosus</em> group - old name: <em>Streptococcus milleri</em>) <em>Enterococcus</em> spp. Anaerobes (mostly <em>Bacteroides</em> spp.)</td>
<td>Mostly <em>Candida albicans</em> Mostly Enterobius vermicularis ([pinworm]) can contribute by causing obstruction of the appendix</td>
<td></td>
</tr>
</tbody>
</table>

ESBL: extended spectrum beta-lactamases.

Clinical presentation

Acute appendicitis should be considered as a possible diagnosis in all cases of acute abdominal pain, especially if the pain is in the right lower quadrant or is moving from the periumbilical area
to the right lower quadrant. Nausea and vomiting are usually present. Fever (> 38.0 °C) and rigors can be present.

Severe pain, diffuse rebound tenderness on sudden release of pressure on the abdomen and abdominal muscular tensing are usually present in cases of peritonitis. Hypotension and signs of organ hypoperfusion (e.g. reduced urine output) may be present in cases of organ failure and are a medical and/or surgical emergency. Please also refer to the chapter on sepsis if suspected.

Laboratory tests

I. Patient microbiology tests

Routine microbiology tests are not usually needed and basing antibiotic treatment on pathogens cultured from the abdominal cavity at the time of operation is not recommended but certain microbiology tests could be considered in severely ill patients to adjust empiric antibiotic treatment once the results of antibiotic susceptibility tests are available (see Table 2).

In more severe cases blood cultures should be taken and samples from the abdominal cavity may be useful in certain situations such as severely immunocompromised patients or patients known to be colonized with multidrug-resistant organisms or in patients presenting with septic shock.

Table 2 Microbiology tests to consider in severe cases of appendicitis as indicated in the WHO EDL (54)

<table>
<thead>
<tr>
<th>Diagnostic test</th>
<th>Purpose of the test</th>
<th>Setting where the test should be available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood cultures</td>
<td>To detect bacterial bloodstream infections (sepsis)</td>
<td>Health care facilities with clinical laboratories</td>
</tr>
<tr>
<td>Microscopy and culture of abscess fluid material when this can be drained</td>
<td>Not routinely recommended, but may be used in specific cases to identify bacterial and fungal species for selection of appropriate antibiotic regimens</td>
<td>Health care facilities with clinical laboratories</td>
</tr>
</tbody>
</table>

II. Other tests

Laboratory tests can be used to complement the clinical examination and medical history. Based on availability, Tables 3 and 4 indicate tests that could be considered in the patient’s initial assessment and to help guide the duration of antibiotic treatment.

Table 3 Laboratory tests (other than microbiology) that may help identify an alternative cause of abdominal pain that could mimic appendicitis as indicated in the WHO EDL (54)

<table>
<thead>
<tr>
<th>Diagnostic test</th>
<th>Purpose of the test</th>
<th>Setting where the test should be available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy test</td>
<td>In the context of suspected appendicitis the purpose of the test is to exclude an ectopic pregnancy</td>
<td>Community settings and health facilities without laboratories^</td>
</tr>
<tr>
<td>Urinalysis test (dipstick)</td>
<td>To exclude a urinary tract infection</td>
<td>Community settings and health facilities without laboratories^</td>
</tr>
</tbody>
</table>
Community and health settings without laboratories are settings such as health posts and centres, doctors’ offices, outreach clinics and ambulatory care. These tests are also assumed to be available at health care facilities with laboratories.

Table 4 Laboratory tests (other than microbiology) that may help assess the severity of disease and identify a bacterial infection as indicated in the WHO EDL (54)

<table>
<thead>
<tr>
<th>Diagnostic test</th>
<th>Purpose of the test</th>
<th>Setting where the test should be available</th>
</tr>
</thead>
<tbody>
<tr>
<td>White blood cell count</td>
<td>To help in the diagnosis of infections</td>
<td>Health care facilities with clinical laboratories</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>To detect inflammation as an indicator of various conditions, e.g. sepsis</td>
<td>Health care facilities with clinical laboratories</td>
</tr>
<tr>
<td>Procalcitonin</td>
<td>To guide antibiotic therapy or discontinuation in sepsis</td>
<td>Only in tertiary care facilities</td>
</tr>
</tbody>
</table>

III. Using microbiology surveillance data

Routine surveillance of pathogens cultured from the abdominal cavity is not recommended. Empiric guidance given by the Handbook could be reviewed and adapted based on local clinically relevant microbiology surveillance data. For example, clinically relevant isolates for this infection would be blood culture data from patients on surgical wards with intra-abdominal infections.

Imaging

Imaging is helpful to confirm acute appendicitis. An abdominal ultrasound should always be considered when this condition is suspected. Where available a computed tomography (CT) scan of the abdomen may also be considered, especially if complications are suspected or the diagnosis is uncertain.

Treatment

Surgery to eliminate/control the source of infection (e.g. abscess, perforated appendix) and reduce contamination of the peritoneal cavity (e.g. in cases of perforation) are the foundation of treatment. Patients with suspected or confirmed appendicitis should be promptly referred for surgical consultation and antibiotic treatment should be started quickly.

Uncomplicated cases treated with antibiotics alone

Treating appendicitis with antibiotics alone is controversial – and not recommended by WHO for children – mostly because of the higher risk of recurrences within a year (292-294). However, this approach can be considered in adults in certain cases if close monitoring is possible, given that 1 in 3 patients treated this way will experience a recurrence within 2 years (295). Patient preference should be one element considered when deciding the approach (avoidance of surgery versus higher risk of recurrence with antibiotics).
When antibiotic treatment alone is offered, the suggested duration of treatment is 7 days provided there is a good clinical response with resolution of symptoms. Patients should be re-evaluated to assess the need for surgical intervention if they do not improve on antibiotics alone.

As stated above, in children with acute appendicitis, WHO discourages this approach in the WHO Pocket book of hospital care for children: “appendectomy should be done as soon as possible to prevent perforation, peritonitis and abscess formation. It is better to operate and be wrong about the diagnosis than to delay and have peritonitis occur”(23).

Antibiotic treatment

In general, empiric antibiotic treatment should be chosen based on the severity of symptoms (mild or severe), considering local prevalence of resistance, particularly isolates producing extended-spectrum beta-lactamases, since prevalence can vary greatly among different settings (Table 5). Individual risk factors for resistant pathogens (e.g. recent antibiotic treatment, colonization with resistant pathogens) could also be considered.

Simplify empiric treatment to a more narrow-spectrum antibiotic based on culture results or based on rapid clinical improvement when no microbiology test results are available. It should be noted that anaerobes are difficult to culture and anaerobic coverage should usually be continued even if no anaerobes are detected in microbiologic samples.

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

If signs and symptoms persist, abdominal imaging is suggested, or an alternative extra-abdominal source of infection should be considered.

Table 5 Empiric antibiotic treatment for acute appendicitis

<table>
<thead>
<tr>
<th>Severity</th>
<th>Adults</th>
<th>Neonates and Children</th>
<th>Total treatment duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild cases</td>
<td>First choice</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Amoxicillin+clavulanic acid(^a) (oral): 875 + 125 mg given every 8 hours</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>OR</td>
<td></td>
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<tr>
<td></td>
<td>Ceftriaxone (IV): 2 g given once a day AND</td>
<td></td>
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<tr>
<td></td>
<td>Metronidazole (IV/oral): 500 mg given every 8 hours</td>
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<tr>
<td></td>
<td>OR</td>
<td></td>
<td></td>
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<tr>
<td>Severe cases</td>
<td>First choice</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Amoxicillin+clavulanic acid(^a) (IV/oral): 40-50 mg/kg/dose of amoxicillin component given every 12 hours OR 30 mg/kg/dose given every 8 hours</td>
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<td></td>
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<tr>
<td></td>
<td>Oral weight bands: 3-&lt;6 kg: 250 mg of amoxicillin/dose given every 12 hours</td>
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</tr>
</tbody>
</table>

Uncomplicated cases treated with appendectomy: stop antibiotics after surgery if adequate control of the source of infection has been achieved and symptoms have resolved.

Complicated cases treated with appendectomy: 5 days if adequate control of the source of infection has been achieved and symptoms have resolved.
**Cefotaxime (IV):** 2 g given every 8 hours  
**AND**  
**Metronidazole (IV/oral):** 500 mg given every 8 hours  

**Second choice**  
**Ciprofloxacin (oral):** 500 mg given every 12 hours  
**AND**  
**Metronidazole (IV/oral):** 500 mg given every 8 hours  

*(Ciprofloxacin has excellent oral bioavailability and the IV route should be reserved for patients with impaired gastrointestinal function)*

<table>
<thead>
<tr>
<th>Weight Range</th>
<th>Drug Combination</th>
<th>Dosage Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-&lt;10 kg</td>
<td>Amoxicillin</td>
<td>375 mg given every 12 hours</td>
</tr>
<tr>
<td>10-&lt;15 kg</td>
<td>Amoxicillin</td>
<td>500 mg given every 12 hours</td>
</tr>
<tr>
<td>15-&lt;20 kg</td>
<td>Amoxicillin</td>
<td>750 mg given every 12 hours</td>
</tr>
<tr>
<td>20-&lt;30 kg</td>
<td>Amoxicillin</td>
<td>1000 mg given every 12 hours</td>
</tr>
<tr>
<td>≥ 30 Kg</td>
<td>Use adult dose</td>
<td></td>
</tr>
</tbody>
</table>

**Uncomplicated cases treated with antibiotics alone:** 7 days with close clinical monitoring and re-evaluation for surgery if symptoms do not resolve.

**Ceftriaxone (IV):** 80 mg/kg/dose given once a day  
**AND**  
**Metronidazole (IV/oral):**  
- Neonates: 7.5 mg/kg/dose given every 12 hours (for IV starting with a loading dose of 15 mg/kg)  
- Children: 7.5 mg/kg/dose given every 8 hours  

Oral weight bands:  
- 3-<6 kg: 30 mg given every 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

**OR**  
**Cefotaxime (IV):** 50 mg/kg/dose given every 8 hours  
**AND**  
**Metronidazole (IV/oral):**  
- Neonates: 7.5 mg/kg/dose given every 12 hours (for IV starting with a loading dose of 15 mg/kg)
<table>
<thead>
<tr>
<th>Children: 7.5 mg/kg/dose given every 8 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral weight bands:</td>
</tr>
<tr>
<td>3–&lt;6 kg: 30 mg given every 8 hours</td>
</tr>
<tr>
<td>6–&lt;10 kg: 50 mg given every 8 hours</td>
</tr>
<tr>
<td>10–&lt;15 kg: 100 mg given every 8 hours</td>
</tr>
<tr>
<td>15–&lt;20 kg: 150 mg given every 8 hours</td>
</tr>
<tr>
<td>20–&lt;30 kg: 200 mg given every 8 hours</td>
</tr>
<tr>
<td>≥ 30 Kg: Use adult dose</td>
</tr>
</tbody>
</table>

**OR**

- **Ampicillin**
  - 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

- **Gentamicin**
  - Neonates: 5 mg/kg given once daily
  - Children: 7.5 mg/kg given once daily

- **Metronidazole**
  - Oral/IV:
    - Neonates: 7.5 mg/kg/dose given every 12 hours (for IV starting with a loading dose of 15 mg/kg)
    - Children: 7.5 mg/kg/dose given every 8 hours

**Second choice**

- **Ciprofloxacin** (IV/oral): 10-20 mg/kg/dose given every 12 hours

<table>
<thead>
<tr>
<th>Oral weight bands:</th>
</tr>
</thead>
<tbody>
<tr>
<td>3–&lt;6 kg: 50 mg given every 12 hours</td>
</tr>
<tr>
<td>6–&lt;10 kg: 100 mg given every 12 hours</td>
</tr>
<tr>
<td>10–&lt;15 kg: 150 mg given every 12 hours</td>
</tr>
<tr>
<td>Severe cases</td>
</tr>
<tr>
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</table>
### Second choice

**Meropenem** (IV): 2 g given every 8 hours

**OR**

**Piperacillin-tazobactam** (IV): 100 mg/kg/dose of piperacillin component given every 8 hours

**Second choice**

**Meropenem** (IV): 20 mg/kg/dose given every 8 hours

### Notes:

All dosages are for normal renal and hepatic function.

*a* Prevalence of resistance to amoxicillin-clavulanic acid among *Escherichia coli* isolates is high in some settings and this option should be considered taking local microbiology data into consideration where available.

*b* Oral liquid must be refrigerated after reconstitution as clavulanic acid is rapidly metabolized in high ambient temperatures.

*c* Meropenem should not be considered for routine use for all severe cases but only in complicated cases (i.e. abscess and/or peritonitis) in settings with a high prevalence of extended-spectrum beta-lactamase (ESBL)-producing Enterobacterales or in patients with known prior colonization, treated with multiple antibiotic courses or at risk of infections with pathogens resistant to the first-choice option.

Empiric use of a “Reserve” antibiotic could be considered exceptionally in very selected cases of seriously ill patients with peritonitis failing to respond to carbapenems or that have previously been treated for infections caused by carbapenem-resistant pathogens or that are known to be colonized with multidrug-resistant Gram-negative bacteria known to be susceptible to the selected “Reserve” antibiotic. Please refer to the corresponding chapter for the definition and list of “Reserve” antibiotics included in the EML/c.

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

### Uncomplicated cases treated with appendectomy

In patients with uncomplicated appendicitis, antibiotic treatment can be stopped once surgery is performed provided adequate control of the source of infection was achieved and symptoms have resolved. The rationale for stopping antibiotics is that in these cases the source of infection is considered to have been eliminated with surgery.

### Complicated cases treated with appendectomy

In patients with complicated appendicitis, **5 days** of total antibiotic treatment are usually adequate, provided there is good clinical recovery, and the source of infection was eliminated with surgery(296-298).
Intra-abdominal infections - Acute diverticulitis

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

Definition

Acute diverticulitis is the acute inflammation of diverticula (sac-like protrusions of the wall of the colon) that can cause severe abdominal pain. Acute diverticulitis is usually classified as uncomplicated when there is no involvement of the peritoneal cavity and the inflammation is localized to the diverticula (e.g. no perforation, no abscess, no diffuse peritonitis). When the inflammation extends to the peritoneal cavity or when an abscess is present, the condition is considered complicated.

Pathophysiology

In cases of acute diverticulitis, the first step in the pathogenesis is the formation of diverticula (i.e. diverticulosis). Diverticula are sac-like protrusions of the colonic wall. The mechanism leading to diverticulitis of the colon is the erosion of the wall of the diverticula by increased intraluminal pressure. If bacterial contamination and chemical irritation (usually due to leakage of sterile fluids that are irritants to the peritoneum; for example, bile or blood) of the peritoneal cavity occur, peritonitis develops. Intraabdominal abscesses (i.e. the presence of a collection of infected fluid in the peritoneal cavity) can also form as a result of a complicated diverticulitis.

Epidemiology

Acute diverticulitis is common in high-income countries and mostly affects adults older than 50 years; its incidence increases with age. The condition is less frequent in many low- and middle-income countries, probably because of differences in the fibre content of diets. The overall risk of developing acute diverticulitis in patients with diverticulosis is low (299, 300) and most cases
(> 80%) are uncomplicated. Nonetheless, acute diverticulitis is still a common cause of colonic resection (301).

Microbiology epidemiology

The most common pathogens involved in acute diverticulitis are Gram-negative bacilli and anaerobic bacteria from the intestinal microbiota (Table 1). Infections are often caused by more than one pathogen and may include fungal pathogens, especially in patients pre-treated with antibiotics. Certain parasites need to be considered in the differential diagnosis of abdominal pain in endemic settings.

Table 1 Pathogens most frequently associated with acute diverticulitis (in descending order of frequency)

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>Fungi</th>
<th>Parasites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterobacterales (mostly <em>Escherichia coli</em>) and other Gram-negative bacteria such as <em>Pseudomonas aeruginosa</em> and <em>Acinetobacter baumannii</em> (including multidrug-resistant strains such as those producing ESBL and carbapenemases)</td>
<td>Mostly <em>Candida albicans</em></td>
<td><em>Enterobius vermicularis</em> (pinworm)</td>
</tr>
<tr>
<td><em>Streptococcus</em> spp. (e.g. of the <em>Streptococcus anginosus</em> group - old name: <em>Streptococcus milleri</em>)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Enterococcus</em> spp.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaerobes (mostly <em>Bacteroides</em> spp.)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ESBL: extended-spectrum beta-lactamases.

Clinical presentation

Acute diverticulitis should be considered as possible diagnosis in all cases of acute pain in the left lower abdominal quadrant. It should be noted that while left lower diverticulitis is more prevalent in European countries and North America, right lower diverticulitis is more common in Asia.

Fever (>38.0 °C), chills, nausea and vomiting may be present, mostly in complicated diverticulitis. Severe pain, diffuse rebound tenderness on sudden release of pressure on the abdomen and abdominal muscular defence are usually present in cases of peritonitis. Hypotension and signs of organ hypoperfusion (e.g. reduced urine output) can be present in cases of organ failure and are a medical and /or surgical emergency. Please also refer to the chapter on sepsis if suspected.
Laboratory tests

I. Patient microbiology tests

In mild cases, routine microbiology tests are not usually needed and basing antibiotic treatment on pathogens cultured from the abdominal cavity at the time of operation is not recommended. Certain microbiology tests (see Table 2) could be considered in severely ill patients to adjust empiric antibiotic treatment once the results of antibiotic susceptibility tests are available.

Table 2 Microbiology tests to consider in severe cases as indicated in the EDL (54)

<table>
<thead>
<tr>
<th>Diagnostic test</th>
<th>Purpose of the test</th>
<th>Setting where the test should be available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood cultures</td>
<td>To detect bacterial bloodstream infections (sepsis)</td>
<td>Health care facilities with clinical laboratories</td>
</tr>
<tr>
<td>Microscopy and culture of abscess fluid material</td>
<td>First step to detect and identify bacterial and fungal species for selection of appropriate antibiotic regimen</td>
<td>Health care facilities with clinical laboratories</td>
</tr>
</tbody>
</table>

II. Other tests

Laboratory tests can be used to complement the clinical examination and medical history. Based on availability, Table 3 indicates several tests that could be considered in the patient’s initial assessment and to help guide the duration of antibiotic treatment.

Table 3 Laboratory tests (other than microbiology) that may help assess the severity of disease and the identification of a bacterial infection as indicated in the WHO EDL (54)

<table>
<thead>
<tr>
<th>Diagnostic test</th>
<th>Purpose of the test</th>
<th>Setting where the test should be available</th>
</tr>
</thead>
<tbody>
<tr>
<td>White blood cell count</td>
<td>To help in the diagnosis of infections</td>
<td>Health care facilities with clinical laboratories</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>To detect inflammation as an indicator of various conditions (e.g. sepsis)²</td>
<td>Health care facilities with clinical laboratories</td>
</tr>
<tr>
<td>Procalcitonin</td>
<td>To guide antibiotic therapy or discontinuation in sepsis</td>
<td>Only in tertiary care facilities</td>
</tr>
</tbody>
</table>

²A cut-off value of 150–170 mg/L for C-reactive protein is sometimes used to discriminate between mild/uncomplicated cases and severe/complicated cases (302, 303).

III. Using microbiology surveillance data

Routine surveillance of pathogens cultured from the abdominal cavity is not recommended. Empiric guidance given by the Handbook could be reviewed and adapted based on local clinically relevant microbiology surveillance data. For example, clinically relevant isolates for this infection would be blood culture data from patients on surgical wards with intra-abdominal infections.
Imaging

Imaging is helpful to confirm acute diverticulitis. In settings where computed tomography (CT) scanning is available, a CT scan of the abdomen is the best imaging method to confirm acute diverticulitis and grade its severity. However, because ultrasound is more widely available, abdominal ultrasound can also be considered a valid alternative.

Treatment

Patients with suspected or confirmed complicated acute diverticulitis or with recurrent attacks should be promptly referred for surgical consultation.

Uncomplicated cases

In immunocompetent patients with uncomplicated diverticulitis (i.e. localized diverticular inflammation) and no signs of systemic inflammation, antibiotic treatment is usually not needed and in these patients uncomplicated diverticulitis can be considered a self-limiting condition where antibiotics do not offer a benefit in terms of clinical resolution and recurrence (304, 305).

Antibiotic treatment

In patients with complicated acute diverticulitis or in uncomplicated cases requiring antibiotic treatment (e.g. cases that did not resolve spontaneously after 2-3 days without antibiotic treatment) or cases in severely immunosuppressed patients, empiric antibiotic treatment should be chosen based on the severity of symptoms (mild or severe), taking into account local prevalence of resistance, particularly isolates of Enterobacterales producing extended-spectrum beta-lactamases, since the prevalence can vary greatly among settings (Table 4). Individual risk factors for resistant pathogens (e.g. recent antibiotic treatment, colonization with resistant pathogens) should also be considered. In settings where resistance to carbapenems is highly prevalent, alternative antibiotic options including Reserve antibiotics – see chapter – could be considered in severely ill patients who are deteriorating. In complicated cases (i.e. presence of perforation or abscess), empiric antibiotic treatment should be started as soon as the diagnosis is suspected and could be stopped 4 days after control of the source of infection is achieved provided there is good clinical recovery.

Patients with small abscesses (< 5 cm) or pericolic gas are usually treated with systemic antibiotic treatment alone provided close clinical follow up is possible and there is a good clinical response and symptoms have resolved (306).

In patients with large abscesses (e.g. percutaneous drainage of abscesses > 5 cm) and patients with peritonitis, control of the source of infection (e.g. colonic resection), in addition to systemic antibiotic treatment, is needed.

Simplify empiric treatment to a more narrow-spectrum antibiotic based on culture results or based on rapid clinical improvement when no microbiology test results are available.
Step-down to oral treatment is based on improvement of symptoms and signs of infection and the ability to take oral antibiotics allowing discharge of the patient home when clinically appropriate.

If signs and symptoms persist, abdominal imaging is suggested, or an alternative extra-abdominal source of infection should be considered.

**Table 4 Empiric antibiotic treatment in case of acute diverticulitis**

**Mild cases** are defined as patients who are not critically ill with no signs of sepsis or septic shock.

**Severe cases** are defined as patients who are critically ill with signs of sepsis or septic shock.

<table>
<thead>
<tr>
<th>Severity</th>
<th>Adults</th>
<th>Total treatment duration</th>
</tr>
</thead>
</table>
| Mild cases (these can be uncomplicated cases that did not resolve spontaneously after 2-3 days without antibiotics or complicated cases with mild symptoms) | **First choice** Amoxicillin+clavulanic acid (oral): 875 mg + 125 mg given every 8 hours  
OR Ceftriaxone (IV): 2 g given once a day AND Metronidazole (IV/oral): 500 mg given every 8 hours  
OR Cefotaxime (IV): 2 g given every 8 hours AND Metronidazole (IV/oral): 500 mg given every 8 hours | Continue for 4 days after control of the source of infection is achieved provided that there is good clinical recovery.  
(Ciprofloxacin has excellent oral bioavailability and the IV route should be reserved for patients with impaired gastrointestinal function) |
| Severe cases | **First choice** Piperacillin+tazobactam (IV): 4 g + 500 mg given every 6 hours  
OR Ceftriaxone (IV): 2 g given once a day AND Metronidazole (IV): 500 mg every 8 hours  
OR Cefotaxime (IV): 2 g given every 8 hours AND Metronidazole (IV/oral): 500 mg every 8 hours |  |
| **Second choice** Meropenem (IV): 2 g given every 8 hours |  |

Notes: All dosages are for normal renal and hepatic function.
Meropenem should not be considered for routine use for all severe cases but only in complicated cases (i.e. abscess and/or peritonitis) in settings with a high prevalence of extended-spectrum beta-lactamase (ESBL)-producing Enterobacterales or in patients with known prior colonization, treated with multiple antibiotic courses or at risk of infections with pathogens resistant to the first choice option. Empiric use of a “Reserve” antibiotic could be considered exceptionally in very selected cases of seriously ill patients failing to respond to carbapenems or that have previously been treated for infections caused by carbapenem-resistant pathogens or that are known to be colonized with multidrug-resistant Gram-negative bacteria known to be susceptible to the selected “Reserve” antibiotic. Please refer to the corresponding chapter for the definition and list of “Reserve” antibiotics included in the EML. ACCESS antibiotics are indicated in green, WATCH antibiotics in yellow and RESERVE antibiotics in red.
Intra-abdominal infections-

*Clostridioides difficile* infection

**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.

**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)

**Definition**

*Clostridioides difficile* (formerly *Clostridium difficile*) infection is an infection of the colon caused by the bacterium *C. difficile*. The infection occurs mostly in patients with current or recent antibiotic use. For surveillance purposes *C. difficile* infection is usually classified as either health care-associated or community-associated based on where the infection was acquired, which is determined from the timing of onset of symptoms in relation to last contact with any health care setting.

**Microbiology epidemiology**

*C. difficile* is a Gram-positive anaerobic spore-forming bacterium that is widely present in the environment, especially in hospitals and long-term care facilities where spores can persist in the environment for months. Toxigenic and non-toxigenic strains exist but *C. difficile* infection is only
associated with toxigenic strains. Of these strains, BI/NAP1/027 is particularly virulent and in recent years has caused outbreaks, especially in North America.

**Pathophysiology**

*C. difficile* infection is acquired through the ingestion of toxigenic spores of the Gram-positive bacterium *C. difficile*. Spores are present in stools of symptomatic patients and asymptomatic carriers. Once ingested, the spores can colonize the colonic mucosa, germinate into vegetative bacteria, multiply and produce toxins (toxin A and/or B, binary toxin). In most cases, patients remain asymptomatic. However, if disruption of the normal colonic mucosa and intestinal microbiota occurs (e.g. after exposure to antibiotics or cytotoxic chemotherapy) and if there is no adequate antibody response to *C. difficile* toxins, clinical disease can occur. This disease ranges in severity, from mild diarrhoea to life-threatening pseudomembranous colitis and toxic megacolon. Not all strains of *C. difficile* produce toxins. Recurrent infections are a frequent problem, especially in elderly and immunocompromised patients, and the risk of relapse increases with each episode.

**Epidemiology**

*C. difficile* infection is the most frequent cause of health care-associated infectious diarrhoea and is associated with prolonged hospital stay and increased costs (307, 308). Common risk factors for *C. difficile* infection (CDI) include age ≥ 65 years, recent use of antibiotics and previous hospital admission (309). Almost all antibiotics can increase the risk of infection but clindamycin, cephalosporins and fluoroquinolones have been most consistently associated with increased risk of CDI (the risk may vary across time and settings based on the resistance / susceptibility of *C. difficile* to certain antibiotics). Cytotoxic chemotherapy can also increase the risk of infection because inflammation of the intestinal mucosa (i.e. mucositis) is often present. Patients regularly exposed to health care settings (e.g. patients on dialysis) are also at increased risk.

In young children (especially under 2 years of age), clinical disease is rare, probably because cellular receptors to *C. difficile* toxins develop later in life; therefore, young children are often asymptomatic carriers.

**Clinical presentation**

The most common symptom of *C. difficile* infection is diarrhoea, usually defined as the presence of at least three unformed or liquid stools in 24 hours (with no other plausible cause), or more than what is normal for that individual. Abdominal pain, cramping and fever may also be present. Signs of severe disease include marked leukocytosis (e.g. white blood cell count > 15 × 10⁹/L or 15 000/μL), severe abdominal pain, high fever and organ dysfunction (e.g. elevated serum creatinine, decreased serum albumin).

Rarely, *C. difficile* infection can present with signs and symptoms of toxic megacolon. Patients with this presentation often do not have diarrhoea but have signs of acute surgical abdomen
and/or sepsis and may need to be admitted to the intensive care unit. The absence of diarrhea does therefore not exclude CDI. Severe cases may require a colectomy for source control.

**Laboratory tests**

I. **Patient microbiology tests**

Where available, a stool test in a symptomatic patient to detect toxigenic *C. difficile* (or toxin production) could be considered if the patient has no other reasons for diarrhea (e.g. recent use of laxatives). The rationale is that, if infection is detected, an effective treatment can be provided, other antibiotics should be stopped if possible and infection control measures can be put in place (or reinforced) to limit transmission. Testing is not usually recommended in infants because of the high prevalence of colonization (i.e. “colonization” here refers to the presence of *C. difficile* in the stool without causing disease).

Even though the current version of the WHO EDL (54) does not include specific tests for *C. difficile* detection, Table 2 suggests tests that could be considered based on local availability.

Currently, no single test is completely reliable in diagnosing *C. difficile* infection and the best diagnostic approach to use is controversial (310). For both approaches it is important to limit testing to patients with a sufficiently high pre-test probability of CDI (diarrhea, risk factors such as current or recent antibiotic use). The two following approaches are commonly used and could be considered based on local available tests and laboratory protocols.

- Starting with a highly sensitive test (nucleic acid amplification test or glutamate dehydrogenase test depending on local availability) that can detect the presence of *C. difficile*. Then confirm positive results with a test that can detect toxin production such as the toxin A/B enzyme immunoassay. It should be noted that if the toxin production test is negative, the patient could be colonized with *C. difficile* and therefore an alternative reason for diarrhea should be sought.

- Starting with two tests at the same time (glutamate dehydrogenase test and toxin A/B enzyme immunoassay). If both tests are positive, *C. difficile* infection can be reliably confirmed; if both are negative, *C. difficile* infection can be excluded. If the results conflict, then symptomatic patients should be treated if the pre-test probability of *C. difficile* infection is sufficiently high (e.g., recent antibiotic exposure, absence of alternative causes of diarrhea).

Repeat testing during the same episode and test of cure are not needed and should be avoided.

**Table 2 Microbiology tests to consider if *C. difficile* infection is suspected (no test for *C. difficile* is listed in the third version of the EDL, 2021)**

<table>
<thead>
<tr>
<th>Type of test</th>
<th>Purpose of the test</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Culture</td>
<td>To detect toxigenic <em>C. difficile</em> strains</td>
<td>Usually NAAT (culture would be the gold standard but it is complex to perform and has a long turnaround time). With NAAT, the main disadvantage is the high</td>
</tr>
<tr>
<td>Nucleic acid amplification test (NAAT)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
• GDH (glutamate dehydrogenase) antigen test
  To detect *C. difficile* 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 *C. difficile* infection.

• Cytotoxicity assay
• Toxin A/B enzyme immunoassay (EIA)
  To detect *C. difficile* 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).

"NAAT detect the presence of the gene for the toxin not its expression."

### II. Other tests

Routine (non-microbiologic) laboratory testing is not always needed. However, for severe cases, certain tests could be considered (see Table 1) to assess disease severity.

**Table 1 Laboratory tests to consider if *C. difficile* infection is suspected as indicated in the WHO EDL (54)**

<table>
<thead>
<tr>
<th>Diagnostic test</th>
<th>Purpose of the test</th>
<th>Setting where the test should be available</th>
</tr>
</thead>
<tbody>
<tr>
<td>White blood cell count</td>
<td>To help in the diagnosis of infections</td>
<td>Health care facilities with clinical laboratories</td>
</tr>
<tr>
<td>Creatinine</td>
<td>To monitor kidney function for management of severe infections (i.e. sepsis) and adjustment of the antimicrobial regimen</td>
<td>Health care facilities with clinical laboratories</td>
</tr>
<tr>
<td>Electrolytes</td>
<td>To monitor fluid, electrolytes and acid–base balance</td>
<td>Health care facilities with clinical laboratories</td>
</tr>
</tbody>
</table>

### III. Using pooled microbiology data

Resistance to metronidazole, vancomycin, and multiple other antibiotics has been reported.

**Imaging**

Imaging is usually not needed unless a complication is suspected. In these cases, a computed tomography scan of the abdomen could be considered.

**“No antibiotic care”**

Rehydration (oral or intravenous) should always be recommended in patients with diarrhoea. Anti-diarrhoea medicines are not routinely required because they do not prevent dehydration and do not improve nutritional status(132).
Antibiotic treatment

It is important to discontinue any other antibiotics except those treating the *C. difficile* infection as soon as possible.

Symptomatic patients diagnosed with *C. difficile* infection should promptly receive adequate antibiotic treatment as indicated in Table 3. Whenever possible, it is also important to stop any other antibiotic that could have favoured *C. difficile* infection by disrupting the microbiota in the colon. If it is necessary to continue the antibiotic treatment (e.g. because of a clearly documented or high suspicion of a concomitant infection) it is advisable to select antibiotics with lower risk of selecting *C. difficile* infection (avoid ceftriaxone, fluoroquinolones, clindamycin).

Oral treatment with metronidazole is appropriate for a first episode of mild to moderate severity. This antibiotic also is suggested because of concerns that oral vancomycin could favour selection of vancomycin-resistant enterococci (VRE) in the intestinal microbiota and that the oral formulation may be unavailable or too expensive to consider in some low-resource settings (311, 312). However, in severe cases of infection, the current evidence supports the use of oral vancomycin rather than metronidazole, in part because of its benefit in reducing recurrent episodes (311-313). Treatment of recurrent episodes (usually defined as *C. difficile* infection within 8 weeks of a previous episode) with antibiotics or faecal microbiota transplantation is beyond the scope of this chapter.

Table 3 Antibiotic treatment for a first episode of *C. difficile* infection

It is important to discontinue any other antibiotics except those treating the *C. difficile* infection as soon as possible.

<table>
<thead>
<tr>
<th>Adults</th>
<th>Neonates and children</th>
<th>Total treatment duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First choice</strong></td>
<td><strong>First choice</strong></td>
<td></td>
</tr>
<tr>
<td><em>Metronidazole</em> (oral): 500 mg given every 8 hours</td>
<td><em>Metronidazole</em> (oral):</td>
<td></td>
</tr>
<tr>
<td><strong>Second choice</strong></td>
<td><strong>Second choice</strong></td>
<td></td>
</tr>
<tr>
<td><em>Vancomycin</em> (oral): 125 mg given every 6 hours</td>
<td><em>Vancomycin</em> (oral):</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Neonates: 7.5 mg/kg/dose given every 12 hours</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Children: 7.5 mg/kg/dose given every 8 hours</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oral weight bands:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3-&lt;6 kg: -30 mg given every 8 hours</td>
<td>10 days</td>
</tr>
<tr>
<td></td>
<td>6-&lt;10 kg: 50 mg given every 8 hours</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10-&lt;15 kg: 100 mg given every 8 hours</td>
<td></td>
</tr>
<tr>
<td></td>
<td>15-&lt;20 kg: 150 mg given every 8 hours</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥ 30 Kg: Use adult dose</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Children: 5-10 mg/kg/dose given every 6 hours</td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---------------------------------------------</td>
<td></td>
</tr>
</tbody>
</table>

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

*Oral vancomycin is preferable to metronidazole in severe cases. If needed, the dose could be increased to 500 mg given every 6 hours. In severe fulminant cases, intravenous metronidazole could be added to treatment with oral vancomycin.

ACCESS antibiotics are indicated in green, WATCH antibiotics in yellow and RESERVE antibiotics in red.
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 defences, which leads to tissue damage and an inflammatory response. Pathogens in the urine do not inevitably lead to infection. Infection will depend on the interaction between the pathogen (for example the presence of specific virulence factors in the pathogen), the host (who may be more or less likely to have infections because of, for example, underlying diseases) and the local conditions within the urinary tract (for example, because of abnormalities of the urinary tract or the presence of foreign material such as a urinary catheter). Furthermore, it is important to note that urine can also become contaminated during sampling so that the presence of 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 estimated 274 million new cases of UTIs globally (upper and lower), combining all ages and both sexes(31).
30 The incidence of UTIs is highest in women and increases with age (e.g. UTIs increase after menopause) and frequency of sexual activity. These infections are particularly common in women because of the anatomy of their lower urinary tract; women have a shorter urethra than men and so microorganisms colonizing the skin of the perineal area can more easily reach the bladder. Risk factors for UTIs include anatomical and functional abnormalities of the urinary tract (e.g. conditions that predispose to incomplete emptying of the bladder, renal insufficiency and urinary incontinence). Defective host immune factors (e.g. poorly controlled diabetes or neutropenia) and instrumentation of the urinary tract (e.g. urinary catheters and stents) are also predisposing factors.

41 Microbiology epidemiology
42 Most UTIs are caused by enteric Gram-negative bacteria, most frequently *Escherichia coli*, which is responsible for about 80% of cases in children and adults. Other causative pathogens are shown in Table 1. Data on causative pathogens from low- and middle-income countries are limited.
Table 1 Pathogens commonly causing upper urinary tract infections (in descending order of frequency)

<table>
<thead>
<tr>
<th>Most cases</th>
<th>Enterobacterales (including multidrug-resistant strains such as those producing ESBL and carbapenemases)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• <em>Escherichia coli</em> (&gt; 80% of cases)</td>
<td>• <em>Escherichia coli</em> (&gt; 80% of cases)</td>
</tr>
<tr>
<td>• <em>Klebsiella pneumoniae</em></td>
<td>• <em>Klebsiella pneumoniae</em></td>
</tr>
<tr>
<td>• <em>Proteus mirabilis</em></td>
<td>• <em>Proteus mirabilis</em></td>
</tr>
<tr>
<td>• Other Enterobacterales</td>
<td>• Other Enterobacterales</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>More rarely</th>
<th><em>Enterococcus spp.</em></th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Streptococcus agalactiae</em> (group B <em>Streptococcus</em>)</td>
<td><em>Streptococcus agalactiae</em> (group B <em>Streptococcus</em>)</td>
</tr>
<tr>
<td></td>
<td><em>Staphylococcus aureus</em> (rare in uncomplicated UTIs, often in patients with urinary catheters)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Additionally in patients with recent antibiotic exposure, hospitalization, or instrumentation of the urinary tract (e.g. insertion of a catheter)</th>
<th><em>Pseudomonas aeruginosa</em></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><em>Acinetobacter baumannii</em></td>
</tr>
<tr>
<td></td>
<td>(including multidrug-resistant strains such as those producing ESBL and carbapenemases)</td>
</tr>
</tbody>
</table>

ESBL: extended-spectrum beta-lactamases.

Clinical presentation

Classical symptoms of pyelonephritis include flank pain, costovertebral angle tenderness, nausea and vomiting, fever (> 38.0 °C) and signs of systemic illness. Symptoms of cystitis (dysuria, suprapubic tenderness, increased urgency and frequency) may or may not be present.

Severity of signs and symptoms may range from mild disease (e.g. no nausea or vomiting, low-grade fever) that can be safely managed in an outpatient setting with oral antibiotic treatment to severe cases that require hospitalization and intravenous treatment to septic shock requiring admission to intensive care.

In younger children symptoms are often non-specific, including high fever, irritability, vomiting and diarrhoea. In older children (e.g. over 2 years of age) abdominal pain, urgency, frequency and dysuria are more common.

Laboratory tests

I. Patient microbiology tests

A urine culture should be done where possible, ideally before starting antibiotic treatment. The rationale is to confirm the diagnosis and to adjust empiric treatment based on susceptibility results.
• Urine culture is considered positive when bacteria are above a certain cut-off (cut-off of concentration of bacteria in the urine (e.g. ≥10^5 microorganisms/mL of urine) in symptomatic patients.
• Minimum cut-offs to diagnose an infection can vary by laboratory.
• Lower cut-offs are often used to diagnose infections in females compared with males or 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).

For patients requiring hospitalization, a blood culture should be done where possible before starting antibiotic treatment to guide treatment.

Table 2 summarizes the microbiology tests that can be done to diagnose upper urinary tract infections.

<table>
<thead>
<tr>
<th>Diagnostic test</th>
<th>Purpose of the test</th>
<th>Settings where the test should be available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine culture</td>
<td>Initial step to detect and identify bacterial and fungal species for selection of appropriate antimicrobial regimens</td>
<td>Health care facilities with clinical laboratories</td>
</tr>
<tr>
<td>Blood cultures</td>
<td>To detect bacterial bloodstream infections (sepsis)</td>
<td>Health care facilities with clinical laboratories</td>
</tr>
</tbody>
</table>

II. Other tests

A urinalysis (dipstick or microscopy) may be done to detect the presence of bacteriuria and/or indirect signs of infection (leukocyturia and nitrites). In a symptomatic patient, leukocyturia (> 10 leukocytes/μL, 0.01x10^9/L), the presence of leukocyte esterase and/or positive nitrites are indirect signs of infection.

In patients with a severe clinical presentation and when sepsis of urinary origin is suspected, a white blood cell count may be done to support the diagnosis of bacterial infection as well as testing for biomarkers of infection (e.g. C-reactive protein). Table 3 summarizes the laboratory tests that can be done to assist with the diagnosis of upper urinary tract infections.
Table 3 Laboratory tests to consider for the diagnosis of upper urinary tract infections as indicated in the WHO EDL (54)

<table>
<thead>
<tr>
<th>Diagnostic test</th>
<th>Purpose of the test</th>
<th>Settings where the test should be available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinalysis test strips</td>
<td>To detect urinary tract infections</td>
<td>Community settings and health facilities without laboratories(^a)</td>
</tr>
<tr>
<td>Urine microscopy</td>
<td>Presence or absence of: white blood cells, red blood cells; presence of casts and crystals in urine</td>
<td>Health care facilities with clinical laboratories</td>
</tr>
<tr>
<td>White blood cell count(^b)</td>
<td>To aid in the diagnosis of infections</td>
<td>Health care facilities with clinical laboratories</td>
</tr>
<tr>
<td>C-reactive protein(^b)</td>
<td>To detect inflammation as an indicator of various conditions, e.g. sepsis</td>
<td>Health care facilities with clinical laboratories</td>
</tr>
<tr>
<td>Procalcitonin(^b)</td>
<td>To guide antibiotic therapy or discontinuation in sepsis</td>
<td>Only in tertiary care facilities</td>
</tr>
</tbody>
</table>

\(^a\)Community and health settings without laboratories are settings such as health posts and centres, doctors’ offices, outreach clinics and ambulatory care. These tests are also assumed to be available at health care facilities with laboratories.

\(^b\)Only in severe cases when sepsis of urinary origin is suspected.

III. Using microbiology surveillance data

Empiric guidance given by the Handbook could be reviewed and adapted based on local clinically relevant microbiology surveillance data. For example, clinically relevant isolates for this infection would be blood and urine culture data from patients being treated in the hospital with community acquired upper urinary tract infections. Data on severity of clinical presentation, underlying patient risk factors, previous and current antibiotic treatment, current microbiology and clinical outcome would help to inform the development of local guidance.

Imaging

Initial imaging (e.g. ultrasound) of the urinary tract could be done in severely ill patients or during follow-up if an outflow obstruction or a fluid collection (i.e. abscess) is suspected. Routine imaging of all cases of upper UTI is not necessary.

Table 4 Medicines to consider for pain control of upper urinary tract infections

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Formulation</th>
<th>Dose and frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paracetamol (acetaminophen)(^a)</td>
<td>Oral liquid: 120 mg/5 mL; 125 mg/5 mL Suppository: 100 mg Table: 100 mg to 500 mg</td>
<td>Adults: 500 mg–1 g every 4–6 hours (maximum dose of 4 g a day)(^b)</td>
</tr>
</tbody>
</table>

\(^a\)Only in severe cases when sepsis of urinary origin is suspected.
### Antibiotic treatment

The primary goal of empiric antibiotic treatment is to provide effective and timely treatment for the main bacterial pathogens in upper UTI, most commonly *E. coli*. The choice of empiric treatment should be based on the severity of symptoms (mild/moderate or severe). Many upper UTIs can be managed with oral antibiotics in the outpatient setting (315).

#### Mild/moderate cases (adults and children)

Mild/moderate cases of upper UTI are defined as patients who are not critically ill and there are no clinical signs of systemic sepsis or septic shock. In these cases, a 7-day treatment course with oral ciprofloxacin should be considered if there is no nausea and vomiting, for adults (Table 5). For young children it is clinically more difficult to make a clear distinction between upper and lower UTIs, with fever and general systemic signs of infection seen in both groups. If systemic intravenous treatment is required, a third-generation cephalosporin (ceftriaxone or cefotaxime) is an option. Clinical improvement should be evident within 48–72 hours of starting treatment. If no improvement is seen in that time, a complication (such as an abscess) should be considered and investigated by imaging and the susceptibility of bacteria isolated in the urine culture should be reviewed.

**Step-down** to oral treatment is based on improvement of symptoms and signs of infection and the ability to take oral antibiotics allowing discharge of the patient home when clinically appropriate.
Severe cases (adults and children)

Severe cases of upper UTIs are defined as patients who are critically ill, with sepsis and/or septic shock. Please also refer to the chapter on sepsis if suspected. These cases should be treated rapidly with systemic antibiotics. A third-generation cephalosporin (ceftriaxone or cefotaxime) or gentamicin or amikacin (Table 5) for 7 days, for both children and adults is recommended (316, 317). Clinical improvement is usually evident within 48–72 hours of starting treatment when a switch to oral antibiotics should be considered.

Simplify empiric treatment to a more narrow-spectrum antibiotic based on culture results or based on rapid clinical improvement when no microbiology test results are available.

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

Settings with high rates of resistant isolates

Enterobacterales can develop resistance to antibiotics through different mechanisms (e.g. production of extended-spectrum beta-lactamases (ESBL), AmpC beta-lactamases and carbapenemases). Resistance to beta-lactam antibiotics, e.g. in ESBL producing strains, is often associated with resistance to other classes of antibiotics, such as fluoroquinolones. Although resistance is higher in hospital-acquired strains, it is also present in community-acquired infections. Specific thresholds for when not to use particular antibiotics are given in some guidelines; however, these lack a strong evidence base with no clear rationale for the suggested cut-offs. Therefore, local knowledge of the prevalence of resistance to antibiotic classes used to treat UTIs should be considered, as well as individual risk factors (e.g. previous infection or colonization with a resistant pathogen) and severity of clinical presentation.

In hospital settings where resistance to first-choice antibiotics (see Table 5) is highly prevalent and in severely ill patients who are clinically acutely deteriorating, piperacillin + tazobactam or a carbapenem could be considered, even though the EML/c does not explicitly recommend these options. Empiric use of a “Reserve” antibiotic could be considered exceptionally in very selected cases of seriously ill patients failing to respond to carbapenems or that have previously been treated for infections caused by carbapenem-resistant pathogens or that are known to be colonized with multidrug-resistant Gram-negative bacteria known to be susceptible to the selected “Reserve” antibiotic. Please refer to the corresponding chapter for the definition and list of “Reserve” antibiotics included in the EML/c.

**Table 5 Empiric antibiotic treatment for upper urinary tract infections**

<table>
<thead>
<tr>
<th>Upper UTI</th>
<th>Adults</th>
<th>Children</th>
<th>Total treatment duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild to moderate cases</td>
<td>Ciprofloxacin (oral): 500 mg given every 12 hours</td>
<td>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</td>
<td>7 days</td>
</tr>
<tr>
<td></td>
<td><em>(Ciprofloxacin has excellent oral bioavailability and the IV)</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe cases</td>
<td>Oral weight bands:</td>
<td>OR</td>
<td>Ciprofloxacin (IV/oral):</td>
</tr>
<tr>
<td>--------------</td>
<td>--------------------</td>
<td>----</td>
<td>-------------------------</td>
</tr>
<tr>
<td>Ceftriaxone (IV/IM): 1 g given every 24 hours</td>
<td>3-&lt;6 kg: 250 mg given every 12 hours</td>
<td>10-20 mg/kg/dose given every 12 hours</td>
<td>10-20 mg/kg/dose given every 12 hours</td>
</tr>
<tr>
<td>OR</td>
<td>6-&lt;10 kg: 375 mg given every 12 hours</td>
<td>6-&lt;10 kg: 100 mg given every 12 hours</td>
<td>6-&lt;10 kg: 100 mg given every 12 hours</td>
</tr>
<tr>
<td>Cefotaxime (IV/IM): 1 g given every 8 hours</td>
<td>10-&lt;15 kg: 500 mg given every 12 hours</td>
<td>10-&lt;15 kg: 150 mg given every 12 hours</td>
<td>10-&lt;15 kg: 150 mg given every 12 hours</td>
</tr>
<tr>
<td>AND/OR</td>
<td>15-&lt;20 kg: 750 mg given every 12 hours</td>
<td>15-&lt;20 kg 200 mg given every 12 hours</td>
<td>15-&lt;20 kg 200 mg given every 12 hours</td>
</tr>
<tr>
<td>Gentamicin (IV): 5 mg/kg given once a day</td>
<td>20-&lt;30 kg: 1000 mg given every 12 hours</td>
<td>20-&lt;30 kg: 300 mg given every 12 hours</td>
<td>20-&lt;30 kg: 300 mg given every 12 hours</td>
</tr>
<tr>
<td>AND/OR</td>
<td>≥ 30 Kg: Use adult dose</td>
<td>≥ 30 Kg: Use adult dose</td>
<td>≥ 30 Kg: Use adult dose</td>
</tr>
<tr>
<td>Amikacin (IV): 15 mg/kg given once a day</td>
<td>(Ciprofloxacin has excellent oral bioavailability and the IV route should be reserved for patients with impaired gastrointestinal function)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Notes: All dosages are for normal renal and hepatic function.
158 Resistance to quinolones is increasing including in low-and middle-income countries and in children (318-320).
Resistance to sulfamethoxazole+trimethoprim is high in many settings (213, 214). It is ineffective against isolates producing extended-spectrum beta-lactamases (ESBL).

Amoxicillin+clavulanic acid: *Escherichia coli* resistance rates to amoxicillin+clavulanic acid are lower than to amoxicillin alone. This combination still has activity against some ESBL-producing isolates and it can be considered an acceptable option, particularly in young children.

Resistance to third-generation cephalosporins is increasing including in LMIC and in children (318-320). In very sick patients, gentamicin (or amikacin) can be given in combination with ceftriaxone (or ceftaxime). Amikacin and gentamicin are still effective against isolates producing ESBL and are considered appropriate carbapenem-sparing options in settings where ESBL-producing isolates are very prevalent. Use of aminoglycosides can be associated with nephrotoxicity and/or ototoxicity (especially when used for more than 7 days).

**ACCESS** antibiotics are highlighted in green, **WATCH** antibiotics in yellow and **RESERVE** antibiotics in red.
Acute bacterial osteomyelitis

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
4. In general, the intravenous route is preferred for initial treatment but rapid oral step down is increasingly used
5. Duration of treatment in children is usually shorter than in adults

Dead bone, which is usually present in chronic infections, needs to be removed surgically for antibiotic treatment to be successful.

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


Definition

Osteomyelitis is an infection of the bone characterized by inflammation and bone destruction. Infection can be classified according to how the pathogen spreads in the body (via the bloodstream or by local spread from nearby tissue) or the duration of symptoms (acute or chronic). Acute infections develop and evolve over days or weeks while chronic infections evolve over months or years. Chronic infections are also characterized by the presence of dead bone fragments (sequestrum).

Both classifications have implications for the management of osteomyelitis. For example, the pathogens infecting bone by local spread are more variable than those infecting bone via the bloodstream. In addition, dead bone, which is usually present in chronic infections, needs to be removed surgically for antibiotic treatment to be successful.

Pathophysiology

Bacteria can reach the bone from a source of infection by spreading through the bloodstream or by local spread or by direct inoculation (e.g. following trauma, bone surgery, prosthetic joint implantation, pressure or decubitus ulcers or diabetic foot infections). The infection can affect a
single portion of the bone or can extend to the surrounding soft tissue. Infections can rapidly lead to destruction of the affected bone.

The pathophysiology of osteomyelitis differs between children and adults; osteomyelitis caused by spread through the bloodstream is much more common in children (mostly <5 years of age) where it usually affects long bones (mostly the tibia and femur) because the bones are more heavily vascularized in children. In adults, spread of the infection via the bloodstream is less common; nonetheless, it can occur (e.g. as a metastatic infection of infective endocarditis) and in most cases if osteomyelitis is caused, it concerns the vertebra and intervertebral disc (vertebral osteomyelitis). However, in the adult population dissemination by local spread (e.g. after trauma) is far more common.

Epidemiology

Risk factors for osteomyelitis are those associated with bacteraemia (e.g. presence of indwelling vascular catheters, injection drug use, haemodialysis) and those making the bone vulnerable to infection (e.g. bone surgery, open bone fracture, presence of foreign material such as prosthetic joint implants, sickle-cell disease, diabetes, impaired bone vascularization).

Acute osteomyelitis in children is more frequent in low-and middle-income countries and more common in boys than in girls. If left untreated or managed late, acute osteomyelitis can leave children with long-term disability.

The global burden of osteomyelitis is still high, mostly in low-and middle-income countries where the disease disproportionately affects the young and where delays in diagnosis and adequate management can lead to acute forms evolving into chronic osteomyelitis, which is very difficult to treat.

Most cases globally develop after a post-traumatic event (e.g. infections in open fractures following road traffic incidents). In addition, in high-income settings, diabetes (which can lead to foot osteomyelitis; not specifically addressed in this chapter) and spinal interventions (which can lead to vertebral osteomyelitis) contribute to the burden of disease.

Microbiology epidemiology

The most frequent pathogens associated with acute osteomyelitis in children and adults are shown in Tables 1 and 2, respectively.

Table 1 Most frequent pathogens associated with acute osteomyelitis in children (in descending order of frequency)

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Most common way of spreading</th>
<th>Patients most at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>Bloodborne or local spread</td>
<td>Mostly no risk factor identified – consider penetrating injuries or recent surgical procedures or patients with bite wounds.</td>
</tr>
</tbody>
</table>
**Streptococcus spp.** (mostly *S. pyogenes* - often called group A *Streptococcus* and less commonly *S. pneumoniae*). *Streptococcus agalactiae* is a potential pathogen for neonates.

**Kingella kingae** (a species of anaerobic Gram-negative bacilli)

**Haemophilus influenzae** type b

**Salmonella spp.**

**Enterobacterales**

**Pseudomonas aeruginosa**

**Table 2 Most frequent pathogens associated with acute osteomyelitis in adults** (in descending order of frequency)

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Most common way of spreading</th>
<th>Patients most at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Staphylococcus aureus</em> (including MRSA)</td>
<td>Bloodborne or local spread</td>
<td>Mostly no risk factor identified – consider penetrating injuries, recent surgical procedures, patients with bite wounds or injection drug use.</td>
</tr>
<tr>
<td><em>Staphylococcus</em> spp. other than <em>S. aureus</em></td>
<td>Bloodborne or local spread</td>
<td>Patients with recent prosthetic joint implants or arthroscopy or patients with bite wounds.</td>
</tr>
<tr>
<td><em>Streptococcus</em> spp.</td>
<td>Bloodborne or local spread</td>
<td>Splenic disfunction</td>
</tr>
<tr>
<td>Less frequent pathogens (in alphabetical order)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaerobes</td>
<td>Local spread</td>
<td>Patients with bite wounds or recent abdominal surgery. Diabetic foot infection.</td>
</tr>
<tr>
<td><em>Bartonella</em> spp.</td>
<td>Bloodborne</td>
<td>Patients with cat bite wounds</td>
</tr>
<tr>
<td><em>Brucella</em> spp.</td>
<td>Bloodborne</td>
<td>Patients with occupational or domestic exposure to infected animals (e.g. farmers, sheep herder, veterinarians) or ingestion of contaminated food (mostly dairy products).</td>
</tr>
<tr>
<td><em>Candida</em> spp.</td>
<td>Bloodborne or local spread</td>
<td>Immunosuppressed patients, patients with invasive devices, patients who inject drugs (hematogenous spread) or patients with deep wounds (dissemination by local spread)</td>
</tr>
<tr>
<td><em>Cryptococcus</em> spp.</td>
<td>Bloodborne</td>
<td>Immunosuppressed patients.</td>
</tr>
</tbody>
</table>
| Enterobacterales                         | Bloodborne or local spread   | Patients with decubitus (pressure) ulcers, diabetic foot infections and burn wounds (especially if the wound}
**Clinical presentation**

Osteomyelitis can occur alone or in combination with septic arthritis.

Acute osteomyelitis is characterized by gradual onset of localized pain and/or tenderness with a combination of redness, swelling, pain and warmth of the affected area. Fever (> 38.0 °C) and other signs of systemic infection (e.g. tachycardia, leukocytosis) may be present. In the context of osteomyelitis involving the vertebral spine, hip and pelvis, pain is usually the main symptom. In children where acute osteomyelitis often involves the femur and tibia, difficulty and/or 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.

**Laboratory tests**

I. **Patient microbiology tests**

Determining the causative pathogen of osteomyelitis is important to target antibiotic treatment because the number of potential causative pathogens is large and antibiotic resistant pathogens (e.g. MRSA) are not infrequent; this makes it difficult to define appropriate empiric treatment. Duration of treatment may be long (increasing the risk of side-effects of the antibiotic therapy). Whenever possible, a microbiology sample should therefore be obtained to guide antibiotic treatment (Table 3).

*Table 3 Microbiology tests to consider when osteomyelitis is suspected as indicated in the WHO EDL (54)*

<table>
<thead>
<tr>
<th>Diagnostic test</th>
<th>Purpose of the test purpose</th>
<th>Settings where the test should be available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood culture</td>
<td>To detect bacterial bloodstream infections (sepsis)</td>
<td>Health care facilities with clinical laboratories</td>
</tr>
</tbody>
</table>
Bone biopsy for microscopy and culture

A

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)

Initial step in detection and identification of bacterial and fungal species for selection of appropriate antibiotic regimens

Health care facilities with clinical laboratories

Samples should be tested for special pathogens (e.g. mycobacteria, fungi, Brucella spp.) if compatible clinical/epidemiological features are evident.

II. Other tests

Laboratory tests can be used to complement the clinical examination and history. Table 4 gives several tests that could be considered in the initial patient assessment to differentiate between bacterial and reactive viral infections and to help guide the timing of changing to oral treatment and total duration of antibiotic treatment.

Table 4 Laboratory tests (other than microbiology) to identify a bacterial infection, as indicated in the WHO EDL (54)

<table>
<thead>
<tr>
<th>Diagnostic test</th>
<th>Purpose of the test</th>
<th>Settings where the test should be available</th>
</tr>
</thead>
<tbody>
<tr>
<td>White blood count</td>
<td>To help in the diagnosis of infections</td>
<td>Health care facilities with clinical laboratories</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>To detect inflammation as an indicator of various conditions</td>
<td>Health care facilities with clinical laboratories</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate</td>
<td>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</td>
<td>Community settings and health facilities without laboratories*</td>
</tr>
<tr>
<td>Procalcitonin</td>
<td>To guide antibiotic therapy or discontinuation in sepsis</td>
<td>Only in tertiary care facilities</td>
</tr>
</tbody>
</table>

Community health settings without laboratories are settings such as health posts and centres, doctors’ offices, outreach clinics and ambulatory care. These tests are also assumed to be available at health care facilities with laboratories.

Additional tests that could be considered mostly to help exclude other bone diseases in adults (e.g. metastatic or metabolic bone disease) include calcium, phosphate and alkaline phosphatase. The rationale is that these tests are usually normal in case of osteomyelitis by they are usually abnormal in other bone diseases.

III. Using microbiology surveillance data

Routine clinical microbiology surveillance is generally not helpful in informing empiric guidance.
Imaging

Initial imaging with an X-ray is important when bone infections are suspected. However, a normal X-ray on admission does not rule out acute osteomyelitis but it can help exclude alternative diagnoses (e.g. a fracture or a malignant condition). In an X-ray, changes such as soft tissue swelling, periosteal thickening and/or elevation and lytic lesions are often found later than clinical disease. An X-ray could also help identify a sequester (dead bone) that needs to be removed surgically. Where available, a computer tomography (CT) scan or magnetic resonance imaging (MRI) could also be considered in certain patients (e.g. diagnostic uncertainty with X-ray). MRI has a high degree of sensitivity and specificity to detect bone changes (especially in the early phase). Nuclear imaging (e.g. bone scan or bone scintigraphy) could also be considered as an alternative where available.

Surgical treatment

In adults, no surgical intervention is required in most cases of acute osteomyelitis that are diagnosed and managed early in the course of illness. These cases can be treated with an antibiotic alone with good bone penetration. However, in certain cases of acute osteomyelitis (and always in case of chronic infections), surgical debridement of the bone may be required to reduce the risk of complications because of impaired local vascularization (e.g. avascular necrosis of the bone, permanent bone damage) and to remove “dead” bone and clean the surrounding soft tissue.

In children, acute osteomyelitis is usually treated with medical management alone (i.e. no 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.

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.

In adults empiric treatment is sometimes required (e.g. in severely ill patients requiring immediate treatment or when it is not possible to obtain a clinical sample for microbiological examination). In these cases, the choice of the antibiotic needs to be based on the pathogens most commonly identified in this type of infections (see Table 5). In addition, empiric treatment
against community-acquired MRSA could be considered in some cases based on individual risk factors (e.g. MRSA colonization) and on the local prevalence of community-acquired MRSA.

Duration of treatment is usually long (weeks) but it differs in acute or chronic infections. Duration is also influenced by the presence, absence or removal of foreign bodies (including dead bone), the type of causative organism and its resistance profile and the use of antibiotics with an optimal antibiotic spectrum (i.e. based on microbiology results) and good bone penetration.

Total treatment duration of about 3 weeks is usually adequate in patients with uncomplicated disease and good clinical recovery, while complicated disease may require 6 weeks of treatment. Uncomplicated infections are those with symptoms for < 14 days, no underlying disease, no penetrating trauma and no need for extensive surgical intervention.

Imaging studies are usually not useful to determine the duration of treatment.

Simplify empiric treatment to a more narrow-spectrum antibiotic based on culture results or rapid clinical improvement if culture results unavailable. Historically, the intravenous route has always been preferred, at least in the initial phase of treatment.

Step down to oral antibiotics at home is increasingly being used early in the treatment course (e.g. in the first week) when the disease is uncomplicated (322). Step down to oral treatment is based on improvement of symptoms and signs of infection, improved clinical function and the ability to take oral antibiotics with good bone penetration, especially in adults (e.g. clindamycin).

**Table 5 Empiric antibiotic treatment for osteomyelitis**

<table>
<thead>
<tr>
<th></th>
<th>Adults</th>
<th>Children and neonates</th>
<th>Total treatment duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>First choice</td>
<td><strong>Cloxacillin</strong> or <strong>flucloxacinil</strong> (IV): 2 g given every 6 hours</td>
<td><strong>Cloxacillin</strong> or <strong>flucloxacinil</strong> (IV/oral):  • Neonates: 25-50 mg/kg/dose given every 12 hours  • Children: 25 mg/kg/dose given every 6 hours  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</td>
<td>3 weeks&lt;sup&gt;a&lt;/sup&gt; (in children with uncomplicated infections) 4-6 weeks&lt;sup&gt;f&lt;/sup&gt; (in adults)</td>
</tr>
<tr>
<td>Second choice</td>
<td><strong>Amoxicillin+clavulanic acid</strong> (IV): 1g + 200 mg given every 8 hours OR <strong>Cefazolin</strong> (IV): 2 g given every 8 hours OR <strong>Ceftriaxone</strong>&lt;sup&gt;b&lt;/sup&gt; (IV): 2 g given once a day OR</td>
<td><strong>Amoxicillin+clavulanic acid</strong> (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&lt;sup&gt;d&lt;/sup&gt;: 3-&lt;6 kg: 250 mg of amoxicillin/dose given every 12 hours</td>
<td>Same as above</td>
</tr>
<tr>
<td>Antibiotic</td>
<td>Dosage</td>
<td></td>
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<tr>
<td>------------</td>
<td>--------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefotaxime&lt;sup&gt;a&lt;/sup&gt; (IV)</td>
<td>2 g given every 8 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td>Clindamycin&lt;sup&gt;c&lt;/sup&gt; (IV/oral): 600 mg given every 8 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-&lt;10 kg:</td>
<td>375 mg of amoxicillin/dose given every 12 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10-&lt;15 kg:</td>
<td>500 mg of amoxicillin/dose given every 12 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15-&lt;20 kg:</td>
<td>750 mg of amoxicillin/dose given every 12 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20-&lt;30 kg:</td>
<td>1000 mg of amoxicillin/dose given every 12 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 30 Kg:</td>
<td>Use adult dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td>Cefazolin (IV): 25 mg/kg/dose given every 12 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td>Ceftriaxone&lt;sup&gt;b&lt;/sup&gt; (IV): 80 mg/kg/dose given once a day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td>Cefotaxime&lt;sup&gt;b&lt;/sup&gt; (IV): 50 mg/kg/dose given every 8 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td>Clindamycin&lt;sup&gt;c&lt;/sup&gt; (IV/oral):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Neonates:</td>
<td>5 mg/kg/dose given every 8 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Children:</td>
<td>10 mg/kg/dose given every 8 hours</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> If cloxacillin is unavailable, any other IV anti-staphylococcal penicillin could be used (e.g. dicloxacillin, flucloxacillin, nafcillin, oxacillin).<br><br>Notes: All dosages are for normal renal and hepatic function.<br><br>As mentioned in the text, empiric treatment should be avoided whenever possible in adults because there are many potential causative pathogens and high levels of resistance (e.g. methicillin-resistant *Staphylococcus aureus*) making it difficult to specify appropriate empiric treatment. In children there is usually less variability in the most likely causative pathogens (in children the disease is mostly caused by spread of *Staphylococcus* spp. and *Streptococcus* spp. through the bloodstream) and therefore empiric treatment is common practice.<br><br>In neonates, empirical antibiotic therapy should also cover Enterobacterales because infections caused by Gram-negative bacteria can occur in neonates (but *Staphylococcus aureus* remains the most common pathogen). Therefore, in neonates, empiric use of cefotaxime (or ceftriaxone) is appropriate (ceftriaxone should be avoided in infants with hyperbilirubinemia). In older children, bone infections caused by Enterobacterales are very rare.<br><br><sup>b</sup>Ceftriaxone or cefotaxime is preferred if *Salmonella* spp. or Enterobacterales infection is suspected. In neonates, cefotaxime is recommended in these cases.<br><br><sup>c</sup>Clindamycin is still an acceptable option when community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) is suspected or detected if antimicrobial susceptibility tests show that MRSA is sensitive to clindamycin or in settings where MRSA maintains high levels of susceptibility to clindamycin. Clindamycin can also be used when changing from the IV to the oral route, and in patients allergic to penicillin. In case of MRSA isolates resistant to clindamycin and in settings where the prevalence of community-acquired MRSA is high, the use of vancomycin could be considered when *Staphylococcus aureus* is suspected. Oral options to consider to complete the course of treatment in case of MRSA or MSSA infections could be sulfamethoxazole+trimethoprim and doxycycline.<br><br><sup>d</sup>Oral liquid must be refrigerated after reconstitution as clavulanic acid is rapidly metabolized in high ambient temperatures.
Three weeks of treatment (usually starting with 3–5 days IV treatment and then changing to oral treatment) are now commonly used in children with acute bloodborne osteomyelitis based on response to fever, ability to move the limb and reduction in levels of C-reactive protein (if available).

Longer treatments may be required if implants or foreign material are present or in case of inadequate control at the source of infection (e.g., where there is an abscess that has not been adequately drained).

ACCESS antibiotics are highlighted in green, WATCH antibiotics in yellow and RESERVE antibiotics in red.
**Septic arthritis**

**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.

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


**Definition**

Septic arthritis is an infection of one or several joints usually of bacterial origin. Infections can be classified based on the causative pathogen (gonococcal or non-gonococcal), on the type of affected joint (large or small joint) and on the concomitant presence or absence of osteomyelitis.

**Pathophysiology**

In case of septic arthritis, bacteria can reach the joint through dissemination through the bloodstream, by local spread or by direct inoculation from a contiguous infected bone or soft tissue (e.g. local spread following trauma or bites, bone surgery, prosthetic joint implantation, pressure and decubitus ulcers, diabetic foot infections)(323). Dissemination through the bloodstream is more common both in children and adults. Once bacteria gain access into the joint space, they can adhere to the articular cartilage, produce an inflammatory response and promote cartilage destruction within hours. If left untreated, septic arthritis can rapidly lead to destruction of the cartilage. It therefore needs to be rapidly diagnosed and treated.
Epidemiology

Septic arthritis is associated with substantial morbidity (e.g. adverse joint outcomes) and a low mortality (323, 324). People at risk of septic arthritis are people with a higher risk of bacteremia (e.g. those with indwelling vascular catheters, injection drug users, patients on hemodialysis) and those with a higher likelihood of the joint becoming infected (e.g. patients with rheumatoid arthritis, diabetes, sickle-cell disease and prosthetic joints and other foreign material). Post-surgical infections are common in adults. Community-acquired infections are quite rare in adults while they are common in children.

In children, septic arthritis is more frequent in low- and middle-income countries and in boys more than girls; if left untreated or managed late, septic arthritis can leave children with long-term disability.

Gonococcal arthritis, characterized by dissemination of the infection through the bloodstream, is a rare complication of gonorrhoea that mostly affects women.

Microbiology epidemiology

A large variety of pathogens can cause septic arthritis with some differences between children and adults (Table 1 and Table 2).

**Table 1 Pathogens most frequently associated with acute septic arthritis in children (in descending order of frequency)**

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Most common mechanism of dissemination</th>
<th>Patients most at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Staphylococcus aureus</em> (including MRSA)</td>
<td>Bloodborne or by local spread</td>
<td>Usually, no risk factors are identified but consider after penetrating injuries or recent surgical procedures, and in patients with bite wounds</td>
</tr>
<tr>
<td><em>S. pyogenes</em> (group A <em>Streptococcus</em>) and less commonly <em>S. pneumoniae</em></td>
<td>Bloodborne</td>
<td>Mostly no risk factors are identified but consider penetrating injuries or recent surgical procedures</td>
</tr>
<tr>
<td><em>Streptococcus agalactiae</em> (group B <em>Streptococcus</em>)</td>
<td>Bloodborne</td>
<td>Young children, usually with milder clinical disease</td>
</tr>
<tr>
<td><em>Kingella kingae</em> (a species of anaerobic Gram-negative bacilli)</td>
<td>Bloodborne</td>
<td>Young children not vaccinated against <em>Haemophilus influenzae</em> type b</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em> type b</td>
<td>Bloodborne</td>
<td>Children with sickle-cell disease</td>
</tr>
<tr>
<td>Non-typhoidal <em>Salmonella</em> spp.</td>
<td>Bloodborne</td>
<td>Neonates and immunosuppressed children</td>
</tr>
<tr>
<td>Enterobacterales</td>
<td>Bloodborne</td>
<td></td>
</tr>
</tbody>
</table>

MRSA: methicillin-resistant *Staphylococcus aureus*. 
### Table 2 Pathogens most frequently associated with acute septic arthritis in adults

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Main dissemination mechanism</th>
<th>Patients most at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Staphylococcus aureus</em> (including MRSA)</td>
<td>Bloodborne or by local spread</td>
<td>Patients with penetrating injuries or who underwent surgical procedures. Patients with bite wounds or intravenous drug injection</td>
</tr>
<tr>
<td><em>Staphylococcus</em> spp. other than <em>Staphylococcus aureus</em></td>
<td>Bloodborne or by local spread</td>
<td>Patients that underwent implantation of prosthetic joint implants or arthroscopy. Patients with bite wounds</td>
</tr>
<tr>
<td><em>Streptococcus</em> spp.</td>
<td>Bloodborne or by local spread</td>
<td>Splenic dysfunction</td>
</tr>
<tr>
<td><strong>Less frequent (in alphabetical order)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaerobes</td>
<td>By local spread</td>
<td>Patients with bite wounds</td>
</tr>
<tr>
<td><em>Bartonella</em> spp.</td>
<td>Bloodborne</td>
<td>Patients with cat bite wounds</td>
</tr>
<tr>
<td><em>Brucella</em> spp.</td>
<td>Bloodborne</td>
<td>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</td>
</tr>
<tr>
<td><em>Candida</em> spp.</td>
<td>Bloodborne or by local spread</td>
<td>Immunosuppressed patients, patients with invasive devices, patients who inject drugs (hematogenous spread) or patients with deep wounds (dissemination by local spread)</td>
</tr>
<tr>
<td><em>Cryptococcus</em> spp</td>
<td>Bloodborne</td>
<td>Immunosuppressed patients</td>
</tr>
<tr>
<td>Enterobacterales</td>
<td>Bloodborne or by local spread</td>
<td>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</td>
</tr>
<tr>
<td><em>Histoplasma</em> spp</td>
<td>Bloodborne</td>
<td>Immunosuppressed patients</td>
</tr>
<tr>
<td><em>Neisseria gonorrhoeae</em></td>
<td>Bloodborne</td>
<td>Mostly women with disseminated gonococcal infection</td>
</tr>
<tr>
<td><em>Mycobacterium tuberculosis</em></td>
<td>Bloodborne</td>
<td>Immunosuppressed patients because of the risk of reactivation of tuberculosis</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>Bloodborne or by local spread</td>
<td>Immunosuppressed patients and people who inject drugs</td>
</tr>
</tbody>
</table>

MRSA: methicillin-resistant *Staphylococcus aureus*.

#### Clinical presentation

Septic arthritis can occur alone or in combination with osteomyelitis.
Septic arthritis is characterized by acute onset (usually a few days, but up to 2 weeks) of joint pain (moderate to severe) and reduced range of motion with redness, swelling and warmth of the joint. The condition may be less evident when “deep” joints such as the hip, shoulder or sacroiliac joint are affected. In most cases, one single joint is affected (often the knee). Involvement of more than one joint (polyarticular infection) is more common with underlying rheumatoid arthritis. Other signs of systemic infection (e.g. fever >38.0°C, tachycardia, increased biomarkers of inflammation) are usually present.

In certain situations (e.g. septic arthritis of multiple joints), it is important to exclude an extraarticular source of infection (e.g. endocarditis).

In young children permanent destruction of the joint cartilage and long-term disability can occur rapidly, therefore rapid diagnosis and prompt empiric antibiotic treatment are essential.

In case of gonococcal arthritis, typical signs and symptoms of septic arthritis (mostly affecting one or a few joints and usually the knees and ankles) are usually accompanied by skin manifestations (e.g. rash, small papules on the trunk and distal extremities). Often patients with gonococcal arthritis have no signs or symptoms of cervicitis or urethritis.

**Laboratory tests**

I. **Patient microbiology data**

Determining the causative pathogen of septic arthritis is important for targeting antibiotic treatment because the number of potential causative pathogens is large (making it difficult to select empiric treatment) and treatment duration may be long (increasing the risk of side effects from the antibiotic therapy).

Whenever possible a microbiology sample should therefore be obtained to guide antibiotic treatment (Table 3). Ideally microbiology tests results should be obtained before starting antibiotic treatment, however because cartilage destruction can occur within hours, tests should never delay the start of antibiotic treatment.

*Table 3 Microbiology tests to consider when septic arthritis is suspected, as indicated in the WHO EDL (54)*

<table>
<thead>
<tr>
<th>Diagnostic test</th>
<th>Purpose of the test</th>
<th>Settings where the test should be available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synovial fluid for microscopy and culture*</td>
<td>Initial step to detect and identify bacterial and fungal species for selection of appropriate antibiotic regimens</td>
<td>Healthcare facilities with clinical laboratories</td>
</tr>
<tr>
<td>Blood cultures</td>
<td>To detect bacterial bloodstream infections (sepsis)</td>
<td>Healthcare facilities with clinical laboratories</td>
</tr>
<tr>
<td>Microscopy and culture of deep samples collected at debridement in case of prosthetic joint implant</td>
<td>Initial step to detect and identify bacterial and fungal species for selection of appropriate antibiotic regimens</td>
<td>Healthcare facilities with clinical laboratories</td>
</tr>
</tbody>
</table>
Examination for particular pathogens (e.g. mycobacteria, fungi, *Brucella* spp.) should be done if clinical/epidemiological features are compatible. In cases of gonococcal arthritis, the culture of the synovial fluid is usually negative.

II. Other tests

Laboratory tests can be used to complement the clinical examination and history and may help decide between bacterial septic arthritis and a viral reactive arthritis. Tables 4 and Table 5 list tests that could be considered in the initial assessment of the patient to help make a diagnosis and guide the duration of antibiotic treatment.

Table 4 Laboratory tests (other than microbiology) to consider to identify a bacterial joint infection, as indicated in the WHO EDL (54)

<table>
<thead>
<tr>
<th>Diagnostic test</th>
<th>Purpose of the test</th>
<th>Settings where the test should be available</th>
</tr>
</thead>
<tbody>
<tr>
<td>White blood count</td>
<td>To help in the diagnosis of infections</td>
<td>Healthcare facilities with clinical laboratories but also in primary care settings</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>To detect inflammation as an indicator of various conditions</td>
<td>Healthcare facilities with clinical laboratories</td>
</tr>
<tr>
<td>Procalcitonin</td>
<td>To guide antibiotic therapy or discontinuation in sepsis</td>
<td>Only in tertiary care facilities</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate</td>
<td>To detect inflammation as an indicator of various conditions when C-reactive protein is not available</td>
<td>Community settings and health facilities without laboratories*</td>
</tr>
</tbody>
</table>

*Community and health settings without laboratories are settings such as health posts and centres, doctors’ offices, outreach clinics and ambulatory care. These tests are also assumed to be available at health care facilities with laboratories.

Table 5 Synovial fluid examination

<table>
<thead>
<tr>
<th>Diagnostic test</th>
<th>Purpose of the test</th>
<th>Settings where the test should be available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synovial fluid: white cell count and crystals</td>
<td>To detect the presence or absence of white blood cells and crystals</td>
<td>Healthcare facilities with clinical laboratories</td>
</tr>
</tbody>
</table>

*With septic arthritis, it is helpful to know the number of white blood cells in the synovial fluid and microscopy should also be done to investigate alternative diagnoses such as gout or chondrocalcinosis. Compared to non-infectious arthritis, acute bacterial infections are characterized by a much higher white cell count in the synovial fluid (usually > 20 000 cells/μL [20 G/L]) with > 90% being neutrophils.

III. Using microbiology surveillance data

Due to the wide number of pathogens identified, there is no role for routine surveillance cultures to inform empiric guidance.
Imaging

Initial imaging with an ultrasound is useful when joint infections are suspected to detect joint effusion and synovial swelling due to the presence of increased intra-articular fluid. Magnetic resonance imaging (MRI) could also be considered, if available, in certain patients particularly when concomitant osteomyelitis is suspected, because MRI is more sensitive and specific in detecting bone changes.

Treatment

Prompt surgical drainage of any purulent material (aspiration) and washing of the joint (lavage) is a key part of the management of septic arthritis since antibiotics alone are usually not sufficient to control the source of the infection (at least in adults). Aspiration and lavage can reduce the risk of complications (e.g. permanent cartilage destruction, joint deformity and instability, 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.

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.

When patients require empiric treatment (mostly young children or severely ill patients or when it is impossible to obtain a clinical sample for microbiological examination), the choice should be based on the most probable pathogens in this type of infection (mostly Staphylococcus aureus and Streptococcus spp.; see Table 6). In addition, empiric treatment against community-acquired methicillin-resistant Staphylococcus aureus (CA-MRSA) or Neisseria gonorrhoeae may be considered in certain cases based on individual risk factors (e.g. known MRSA colonization) and compatible clinical and epidemiological features.

The duration of treatment is long (several weeks, except for gonococcal arthritis that requires shorter treatment) and is influenced by: the duration of symptoms (acute or chronic), the presence, absence or removal of foreign bodies (including devitalized bone if concomitant osteomyelitis is present), the type of causative pathogen and its resistance profile and the
The concomitant presence of osteomyelitis (and therefore the availability of antibiotics with good bone penetration).

The total treatment duration is generally 3 weeks in children and 4-6 weeks in adults. In case of gonococcal arthritis, a shorter treatment duration (10-14 days) is adequate.

**Simplify** empiric treatment to a more narrow-spectrum antibiotic based on culture results or rapid clinical improvement if culture results unavailable. Historically, the intravenous route has always been preferred at least in the first week of treatment. However, recent evidence suggests that a change to oral antibiotics in the first week of treatment can be used for patients with uncomplicated disease.

**Step down** to oral treatment is based on improvement of symptoms and signs of infection, improvement in joint function and the ability to take oral antibiotics allowing discharge of the patient home when clinically appropriate.

*Table 6 Empiric antibiotic treatment for septic arthritis*

<table>
<thead>
<tr>
<th></th>
<th>Adults</th>
<th>Children</th>
<th>Total treatment duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First choice</strong></td>
<td><strong>Cloxacillin or Flucloxacillin</strong></td>
<td><strong>Cloxacillin or Flucloxacillin</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2g given every 6 hours</td>
<td>(IV):</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Neonates: 25-50 mg/kg/dose given every 12 hours</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Children: 25 mg/kg/dose given every 6 hours</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Oral weight bands:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3-&lt;6 kg: 125 mg given every 6 hours</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>6-&lt;10 kg: 250 mg given every 6 hours</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>10-&lt;15 kg: 500 mg given every 6 hours</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>15-&lt;20 kg: 750 mg given every 6 hours</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥ 30 Kg: Use adult dose</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Second choice</strong></td>
<td><strong>Amoxicillin + Clavulanic acid</strong></td>
<td><strong>Amoxicillin + Clavulanic acid</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1g + 200 mg given every 8 hours</td>
<td>(IV):</td>
<td></td>
</tr>
<tr>
<td></td>
<td>OR</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Cefazolin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(IV): 2 g given every 8 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>OR</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Ceftriaxone</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(IV): 2g given once a day</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>OR</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Cefotaxime</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(IV): 2 g given every 8 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>OR</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Oral weight bands:*

- 3-<6 kg: 125 mg given every 6 hours
- 6-<10 kg: 250 mg given every 6 hours
- 10-<15 kg: 500 mg given every 6 hours
- 15-<20 kg: 750 mg given every 6 hours
- ≥ 30 Kg: Use adult dose

*Children: 3 weeks*

*Adults: 4-6 weeks (contingent on clinical response)*
<table>
<thead>
<tr>
<th>Clindamycin&lt;sup&gt;a&lt;/sup&gt; (IV/oral): 600 mg given every 8 hours</th>
<th>≥ 30 Kg: Use adult dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR Cefazolin&lt;sup&gt;b&lt;/sup&gt; (IV): 25 mg/kg/dose given every 12 hours</td>
<td></td>
</tr>
<tr>
<td>OR Ceftriaxone&lt;sup&gt;b&lt;/sup&gt; (IV): 80 mg/kg/dose given once a day</td>
<td></td>
</tr>
<tr>
<td>OR Cefotaxime&lt;sup&gt;b&lt;/sup&gt; (IV): 50 mg/kg/dose given every 8 hours</td>
<td></td>
</tr>
<tr>
<td>OR Clindamycin&lt;sup&gt;c&lt;/sup&gt; (IV/oral):</td>
<td></td>
</tr>
<tr>
<td>• Neonates: 5 mg/kg/dose given every 8 hours</td>
<td></td>
</tr>
<tr>
<td>• Children: 10 mg/kg/dose given every 8 hours</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Clindamycin is still an acceptable option when community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) is suspected if antimicrobial susceptibility tests show that MRSA is sensitive to clindamycin. In neonates, clindamycin is recommended in these cases. Patients allergic to penicillin. For severe disease potentially caused by MRSA, vancomycin can be considered in settings with high prevalence of community-acquired MRSA, even though this is not a recommendation included in the current EML/c (4, 5). In case of MRSA and based on susceptibility results, alternative oral options that could be considered to complete the course of treatment include sulfamethoxazole+trimethoprim and doxycycline. Oral liquid must be refrigerated after reconstitution as clavulanic acid is rapidly metabolized in high ambient temperatures.

<sup>b</sup>Ceftriaxone or cefotaxime is preferred in cases of suspected *Salmonella* spp. infection or Enterobacterales infection or gonococcal arthritis. In neonates, cefotaxime is recommended in these cases.

<sup>c</sup>Clindamycin is still an acceptable option when community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) is suspected if antimicrobial susceptibility tests show that MRSA is sensitive to clindamycin or in settings where MRSA maintains high levels of susceptibility to clindamycin (i.e. suspicion should be based on local prevalence of community-acquired MRSA). Clindamycin can also be used when changing from the IV to oral route, and in patients allergic to penicillin. For severe disease potentially caused by MRSA, vancomycin can be considered in settings with high prevalence of community-acquired MRSA, even though this is not a recommendation included in the current EML/c (4, 5). In case of MRSA and based on susceptibility results, alternative oral options that could be considered to complete the course of treatment include sulfamethoxazole+trimethoprim and doxycycline. Oral liquid must be refrigerated after reconstitution as clavulanic acid is rapidly metabolized in high ambient temperatures.

Notes: All dosages are for normal renal and hepatic function. As mentioned in the text, targeted treatment is preferable whenever possible in adults (because of the large number of potential causative pathogens) while in children empiric treatment is often given. In neonates, empirical antibiotic therapy should also cover Enterobacterales because infections caused by Gram-negative bacteria can occur (but *Staphylococcus aureus* remains the most common pathogen). Therefore, in neonates, empiric use of cefotaxime (or ceftriaxone) is appropriate (ceftriaxone should be avoided in infants with hyperbilirubinemia). In older children, joint infections caused by Enterobacterales are very rare. If cloxacillin is unavailable, any other IV antistaphylococcal penicillin could be used (e.g. dicloxacillin, flucloxacillin, nafcillin, oxacillin). Ceftriaxone or cefotaxime is preferred in cases of suspected *Salmonella* spp. infection or Enterobacterales infection or gonococcal arthritis. In neonates, cefotaxime is recommended in these cases. Clindamycin is still an acceptable option when community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) is suspected if antimicrobial susceptibility tests show that MRSA is sensitive to clindamycin or in settings where MRSA maintains high levels of susceptibility to clindamycin (i.e. suspicion should be based on local prevalence of community-acquired MRSA). Clindamycin can also be used when changing from the IV to oral route, and in patients allergic to penicillin. For severe disease potentially caused by MRSA, vancomycin can be considered in settings with local high prevalence of community-acquired MRSA, even though this is not a recommendation included in the current EML/c (4, 5). In case of MRSA and based on susceptibility results, alternative oral options that could be considered to complete the course of treatment include sulfamethoxazole+trimethoprim and doxycycline. Oral liquid must be refrigerated after reconstitution as clavulanic acid is rapidly metabolized in high ambient temperatures. Shorter duration (10-14 days) in cases of gonococcal arthritis. ACCESS antibiotics are highlighted in green, WATCH antibiotics in yellow and RESERVE antibiotics in red.
Skin and soft tissue infections - Necrotizing fasciitis

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)

Definition

Necrotizing fasciitis is a life-threatening necrotizing infection of the deep soft tissues that specifically affects the muscular fascia (the fascia is the connective tissue surrounding the muscle). The disease is caused mostly by bacteria and is characterized by acute and fulminant (severe and sudden onset) necrosis with tissue destruction and signs of systemic toxicity.

Necrotizing fasciitis can be classified based on the causative pathogen; type 1 or polymicrobial necrotizing fasciitis (caused by multiple pathogens) or type 2 or monomicrobial necrotizing fasciitis (caused by a single pathogen); the presence or absence of gas in tissues (polymicrobial infections are more often associated with the presence of gas); the site of the infection (e.g. leg, head and neck, perineum); or the risk of a poor outcome (high versus low or moderate risk).

Necrotizing fasciitis affecting the perineum is also called Fournier gangrene.

Pathophysiology

In necrotizing fasciitis, bacteria can reach the muscular fascia by local spread through a skin lesion or a break in the skin barrier (e.g. wounds, bites, injection of drugs, surgery) or through a breach in the mucosal barrier (usually in the intestine, e.g. the source could be a diverticulum or a malignancy, or in the oropharynx). Infections can thus be both exogenous (i.e. pathogens that enter the body from the environment) and endogenous (i.e. pathogens that naturally reside in the body). However, often a clear place of entry is not identified. Bacteria can also reach the muscular fascia via the bloodstream, although this is less common.
Necrotizing fasciitis is characterized by tissue damage with necrosis and inflammatory fluid accumulation along the fascia and between muscle groups. The muscle is usually not affected; however, sometimes muscular abscesses can form. Legs and arms are the most commonly affected sites.

Epidemiology

Necrotizing fasciitis is a rare but life-threatening disease. Polymicrobial forms occur most frequently in older adults and/or individuals with underlying comorbidities (mostly diabetes(325), peripheral vascular disease, immunosuppression) or traumatic or surgical wounds. Intravenous drug injection is also a risk factor. Monomicrobial forms can occur at any age, including in otherwise healthy individuals, and they are the most common form in children(326). Toxic shock syndrome is a rare life-threatening complication of necrotizing fasciitis due to toxin production by Streptococcus pyogenes (often referred to as group A Streptococcus) or Staphylococcus aureus and can also be the cause of septic shock when these pathogens are involved.

Microbiology epidemiology

The most common pathogens causing monomicrobial necrotizing fasciitis are listed in Table 1.

<table>
<thead>
<tr>
<th>Pathogens most frequently associated with necrotizing fasciitis (in descending order of frequency)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Monomicrobial (single pathogen)/Type 2</strong></td>
</tr>
<tr>
<td>Streptococcus pyogenes (group A Streptococcus)</td>
</tr>
<tr>
<td>Streptococcus agalactiae</td>
</tr>
<tr>
<td>Streptococcus dysgalactiae (mostly in elderly people and patients with chronic illness)</td>
</tr>
<tr>
<td><strong>Monomicrobial (multiple pathogens)/Type 1</strong></td>
</tr>
<tr>
<td>Bacteroides spp.</td>
</tr>
<tr>
<td>Clostridium perfringens</td>
</tr>
<tr>
<td>Peptostreptococcus spp. or oral anaerobic organisms when the head and/or neck are affected</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
</tr>
<tr>
<td>Aeromonas hydrophila (exposure to fresh water)</td>
</tr>
<tr>
<td>Vibrio vulnificus (exposure to seawater)</td>
</tr>
</tbody>
</table>

MSSA: methicillin-susceptible Staphylococcus aureus; MRSA: methicillin-resistant Staphylococcus aureus.
Adults
Necrotizing fasciitis is usually characterized by acute onset of pain out of proportion to physical findings in the affected area and rapid onset of systemic signs – for example, fever > 38.0 °C, tachycardia, and increased biomarker levels (leukocytosis, C-reactive protein and procalcitonin)(327).

Signs and symptoms of skin and soft tissue infections (i.e. redness, skin discoloration, swelling, induration (hardening of soft tissue) and warmth of the affected area) are usually present when pathogen entry is through the skin. However, at least initially, the overlying skin often appears only minimally affected, and skin changes – typically bullae and necrosis – only become apparent as the infection progresses.

In cases of necrotizing fasciitis of the perineum (Fournier gangrene), severe pain is accompanied by signs of necrosis in the perineal area (often the scrotum in men). Rapid progression of the infection to the abdominal wall and gluteal muscles is possible.

While in patients with cellulitis, skin abnormalities are the usual symptoms, in patients with necrotizing fasciitis, severe pain (often disproportionate to skin changes) is the characteristic symptom, at least in the initial phase. A definitive diagnosis requires the direct visualization of necrotic tissue in the muscular fascia through surgical exploration.

Children
Necrotizing fasciitis is very rare in children but may occur as a complication of varicella (chickenpox) or can be associated with a compromised immune system. Most characteristics described for adults also apply to children, but certain specific features exist(328). For example, in neonates and infants, the torso is often affected, while in older children the arms and legs and the face are affected.

Laboratory tests
I. Patient microbiology tests
Whenever possible, a microbiology sample of the affected tissue should be obtained to guide antibiotic treatment (e.g. samples can be collected at the time of surgical exploration). This will allow the causative pathogen(s) to be determined so that adequate antibiotic treatment can be given (e.g. single versus multiple causative pathogens). Blood cultures should also be obtained, ideally before antibiotic treatment is started (Table 2).

Table 2 Microbiology tests to consider in a patient with suspected necrotizing fasciitis as indicated in the WHO EDL (54)

<table>
<thead>
<tr>
<th>Diagnostic test</th>
<th>Purpose of the test</th>
<th>Setting where the test should be available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood cultures</td>
<td>To detect bacterial and fungal bloodstream infections (sepsis)</td>
<td>Health care facilities with clinical laboratories</td>
</tr>
</tbody>
</table>
Microscopy and culture of deep samples of tissue collected at debridement\(^a\) | Initial step in detection and identification of bacterial and fungal species for selection of appropriate antibiotic regimens | Health care facilities with clinical laboratories

\(^a\)Intraoperative tissue samples should also be sent for histopathology examination.

### II. Other tests

Laboratory tests can be used to complement clinical examination and history. Tables 3 and 4 give several tests that could be considered in the initial assessment of the patient suspected of having necrotizing fasciitis and to help guide the length of antibiotic treatment. Please also refer to the chapter on sepsis if suspected.

**Table 3 Laboratory tests (other than microbiology) to consider to identify a bacterial infection as indicated in the WHO EDL (54)**

<table>
<thead>
<tr>
<th>Diagnostic test</th>
<th>Purpose of the test</th>
<th>Setting where the test should be available</th>
</tr>
</thead>
<tbody>
<tr>
<td>White blood count</td>
<td>To help in the diagnosis of infections</td>
<td>Health care facilities with clinical laboratories but also in primary care settings</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>To detect inflammation as an indicator of various conditions, e.g. sepsis</td>
<td>Health care facilities with clinical laboratories</td>
</tr>
<tr>
<td>Procalcitonin</td>
<td>To guide antibiotic therapy or discontinuation in sepsis</td>
<td>Only in tertiary health care facilities</td>
</tr>
</tbody>
</table>

**Table 4 Laboratory tests (other than microbiology) to consider in a patient with suspected necrotizing fasciitis as indicated in the WHO EDL (54)**

<table>
<thead>
<tr>
<th>Diagnostic test</th>
<th>Purpose of the test</th>
<th>Setting where the test should be available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete blood count</td>
<td>To detect a wide range of disorders, including infections</td>
<td>Health care facilities with clinical laboratories</td>
</tr>
<tr>
<td>Creatinine</td>
<td>To monitor kidney function for management of severe infections (i.e. sepsis,) and adjustment of the antimicrobial regimen</td>
<td>Health care facilities with clinical laboratories</td>
</tr>
<tr>
<td>Electrolytes</td>
<td>To monitor fluid, electrolyte and acid–base balance</td>
<td>Health care facilities with clinical laboratories</td>
</tr>
<tr>
<td>Glucose</td>
<td>To diagnose intermediate hyperglycaemia and hypoglycaemia</td>
<td>Community settings and health facilities without laboratories</td>
</tr>
<tr>
<td>Haemoglobin</td>
<td>To diagnose and monitor anaemia Clinical marker for certain severe infections</td>
<td>Community settings and health facilities without laboratories</td>
</tr>
</tbody>
</table>

\(^a\) If sepsis is suspected, additional tests may be needed (please refer to the chapter on sepsis).

### III. Using microbiology surveillance data

There is no role for routine surveillance to inform empiric guidance.
Imaging

Imaging should not delay surgical exploration (or surgical inspection) since surgery is still the most reliable tool to diagnose and treat necrotizing fasciitis. If available, ultrasound imaging may help in the diagnosis of necrotizing fasciitis and to evaluate the extent to which the tissue is affected and the presence or absence of gas and fluid along the muscular fascia. A computed tomography scan of the affected area could also be considered.

Management

Prompt surgical removal of the necrotic tissue through drainage and debridement is the cornerstone of treatment of necrotizing fasciitis. Delays in this step are usually associated with higher mortality. Antibiotic treatment is a complementary measure to adequate surgical source control of the infection. Intravenous immunoglobulin is occasionally used when shock is a complication in necrotizing fasciitis and therefore toxic shock syndrome (mostly due to *S. pyogenes* or *S. aureus*) is suspected; however, the effect of the use of high cost intravenous immunoglobulin on mortality is unclear.

Antibiotic treatment

Because of the seriousness of necrotizing fasciitis and the speed at which it can progress, empiric antibiotic treatment should be given immediately when necrotizing fasciitis is suspected, the antibiotics should cover both Gram-positive bacteria (including methicillin-resistant *Staphylococcus aureus*) and anaerobic pathogens (Table 5).

In patients at higher risk of a Gram-negative bacterial infection (e.g. patients with severe immunosuppression), additional empiric medicines should be considered that have activity against these pathogens. Simplify empiric treatment to a more narrow-spectrum antibiotic based on culture results or rapid clinical improvement if culture results unavailable. Step-down to oral treatment is based on improvement of symptoms and signs of infection and the ability to take oral antibiotics allowing discharge of the patient home when clinically appropriate.

Table 5 Empiric antibiotic treatment for suspected or confirmed necrotizing fasciitis

<table>
<thead>
<tr>
<th>Adults</th>
<th>Children</th>
<th>Total treatment duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Piperacillin+tazobactam</em> (IV): 4 g + 500 mg given every 6 hours AND <em>clindamycin</em> (IV): 900 mg given every 8 hours</td>
<td><em>Piperacillin+tazobactam</em> (IV): 100 mg/kg/dose of piperacillin component given every 8 hours AND <em>clindamycin</em> (IV):</td>
<td>2–3 weeks</td>
</tr>
</tbody>
</table>
OR (only if *Streptococcus pyogenes* necrotizing fasciitis has been excluded):  
**Ceftriaxone** (IV): 2 g given once a day  
AND **metronidazole** (IV): 500 mg given every 8 hours

ADD **Vancomycin** (IV) if MRSA is suspected:  
15-20 mg/kg given every 12 hours

- Neonates: 5 mg/kg/dose given every 8 hours  
- Children: 10 mg/kg/dose given every 8 hours

OR (only if *Streptococcus pyogenes* necrotizing fasciitis has been excluded):  
**Ceftriaxone** (IV): 80 mg/kg given once a day  
AND **metronidazole** (IV/oral):

- Neonates: 7.5 mg/kg/dose given every 12 hours  
- Children: 7.5 mg/kg/dose given every 8 hours

Oral weight bands:  
3-<6 kg: 30 mg given every 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

ADD **Vancomycin** (IV) if MRSA is suspected:  
- Neonates: 15 mg/kg/dose given every 12 hours  
- Children: 15 mg/kg/dose given every 8 hours

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

**IV:** intravenous, **MRSA:** methicillin-resistant *Staphylococcus aureus.*

*Ceftriaxone* has the ability to suppress the expression of virulence factors in *Staphylococcus aureus* (i.e. it has an anti-toxin effect).

Knowledge on the most appropriate duration of treatment is limited. Therefore, duration is often individualized based on clinical response, on the success of surgical source control and, if available, changes in laboratory markers of infection. Usually total treatment duration is about 2–3 weeks.

**ACCESS** antibiotics are highlighted in green, **WATCH** antibiotics in yellow and **RESERVE** antibiotics in red.
Skin and soft tissue infections - Pyomyositis

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

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


Definition

Pyomyositis is an infection of a skeletal muscle caused by bacteria usually accompanied by abscess formation.

Pathophysiology

In pyomyositis, bacteria reach the muscle from another source of infection spread by the bloodstream. Once bacteria reach the muscle, an inflammatory reaction develops with initial swelling of the muscle and progressive abscess formation and increasing oedema. The process may take days to few weeks for the signs of systemic infection to appear and the presence of a pus collection large enough to be drained to become clinically evident.

Epidemiology

Most cases of pyomyositis occur in tropical countries often in young children (< 5 years of age) or in adults (aged 20–45 years), and males are more affected than females. History of trauma or muscle strain are usually present. HIV, malnutrition and malignancies may be risk factors in the tropics, even though most patients are otherwise healthy. In non-tropical countries, the disease is more common in adults with underlying severe medical conditions (e.g. immunosuppressed patients)(331).
Clinical presentation

Pyomyositis is characterized by acute onset (usually days to a few weeks) of localized muscle pain with cramping usually in the lower limbs or in the gluteal muscles (although any muscle can be affected) with a fever > 38.0 °C. Swelling and induration (hardening of soft tissue) of the affected area are also usually present when the disease becomes clinically evident. Other signs of systemic infection (e.g. tachycardia, increased biomarker levels such as leukocytosis, C-reactive protein and procalcitonin) are usually present. Abscess can form within days to weeks. Complications of bacteraemia (e.g. septic emboli, septic arthritis and endocarditis) can occur. The patient should always be monitored for signs of severe clinical progression (e.g. signs of sepsis or septic shock). Please also refer to the chapter on sepsis if suspected.

Microbiology epidemiology

Most cases (> 90%) of pyomyositis are caused by *Staphylococcus aureus* including methicillin-resistant *Staphylococcus aureus* (MRSA) strains or by *Streptococcus* spp. (mostly *Streptococcus pyogenes* often referred to as group A *Streptococcus*) (Table 1). *Escherichia coli* can sometimes be implicated, especially in patients with cancer. *Mycobacteria* (*Mycobacterium tuberculosis* and certain non-tuberculous mycobacteria) can also be responsible for this infection.

Table 1 Pathogens most frequently associated with pyomyositis (in descending order of frequency)

<table>
<thead>
<tr>
<th>Most cases</th>
<th>Staphylococcus aureus (including MRSA)</th>
<th>Streptococcus pyogenes (group A Streptococcus)</th>
</tr>
</thead>
<tbody>
<tr>
<td>More rarely</td>
<td><em>Escherichia coli</em> (mostly in patients with cancer)</td>
<td><em>Mycobacterium tuberculosis</em> and certain non-tuberculous mycobacteria</td>
</tr>
</tbody>
</table>

MRSA: methicillin-resistant *Staphylococcus aureus*.

Laboratory tests

I. Patient microbiology tests

Microbiology tests (cultures of blood and abscess material) can be done to determine the causative pathogen and its resistance profile, ideally before starting antibiotic treatment (Table 2). In patients with severe disease, microbiology tests should however not delay antibiotic treatment.

Table 2 Microbiology tests to consider in a patient with suspected pyomyositis as indicated in the WHO EDL (54)

<table>
<thead>
<tr>
<th>Diagnostic test</th>
<th>Purpose of the test</th>
<th>Settings where the test should be available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood cultures</td>
<td>To detect bacterial and fungal bloodstream infections (sepsis)</td>
<td>Health care facilities with clinical laboratories</td>
</tr>
</tbody>
</table>
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

II. Other tests

Laboratory tests can be used to complement the clinical examination and history. Table 3 indicates tests that could be considered in the initial assessment of the patient and to help guide the duration of antibiotic treatment.

*Table 3 Laboratory tests (other than microbiology) to consider to identify a bacterial infection as indicated in the WHO EDL (54)*

<table>
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<tr>
<th>Diagnostic test</th>
<th>Purpose of the test</th>
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<tr>
<td>C-reactive protein</td>
<td>To detect inflammation as an indicator of various conditions, e.g. sepsis</td>
<td>Health care facilities with clinical laboratories</td>
</tr>
<tr>
<td>Procalcitonin</td>
<td>To guide antibiotic therapy or discontinuation in sepsis</td>
<td>Only in tertiary and higher health care facilities</td>
</tr>
</tbody>
</table>

III. Using microbiology surveillance data

There is no role for routine surveillance to inform empiric guidance.

Imaging

Initial imaging with an X-ray is important when pyomyositis is suspected to locate the site and extent of the infection, any bony involvement or to exclude an alternative diagnosis. However, if available, magnetic resonance imaging or a computed tomography scan could also be considered because they have greater sensitivity (compared to conventional X-ray) in identifying muscle swelling (i.e. inflammation) and the presence of infected tissue.

Ultrasound is helpful, if available, to detect the presence of an abscess (and to guide its drainage).

Management

Prompt drainage of the abscess (if present) is important for adequate control of the source of infection and is complementary to antibiotic treatment. If extensive muscle necrosis is present or if it is not possible to drain the collection of pus percutaneously, surgery may be necessary.
**Antibiotic treatment**

Targeted antibiotics based on microbiology tests are preferred in the treatment of pyomyositis. However, when patients require immediate treatment (e.g. are severely ill) or when it is impossible to obtain a clinical sample for microbiological examination, the choice of antibiotic should be based on the pathogens most commonly seen in this type of infection (*Staphylococcus aureus* and *Streptococcus* spp.) In addition, empiric treatment against community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) may be considered in some cases based on individual risk factors (e.g. known MRSA colonization) and on the local prevalence of CA-MRSA. In these cases, some international guidance documents suggest using vancomycin (332).

Intravenous antibiotics may be needed at least in the first phase of treatment.

Treatment duration is long (usually 2–3 weeks) and is influenced by the clinical and radiological response and by the adequacy of drainage of the abscess, if present. Shorter duration of treatment (2 weeks) could be considered in otherwise healthy patients and when adequate source control is achieved (i.e. the abscess is well drained). Longer duration (3 weeks) could be considered if source control is inadequate or in patients with underlying diseases.

**Simplify** empiric treatment to a more narrow-spectrum antibiotic based on culture results or rapid clinical improvement if culture results unavailable.

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

**Table 3 Empiric antibiotic treatment for pyomyositis**

<table>
<thead>
<tr>
<th>Adults</th>
<th>Children</th>
<th>Total treatment duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Amoxicillin+clavulanic acid</strong> (IV): 1g + 200 mg given every 8 hours OR <strong>Cefalexin</strong> (oral): 500 mg given every 8 hours OR <strong>Cloxacillin</strong> or <strong>flucloxacillin</strong> (IV): 2g given every 6 hours</td>
<td><strong>Amoxicillin+clavulanic acid</strong> (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-&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</td>
<td><strong>2–3 weeks</strong></td>
</tr>
<tr>
<td>Antibiotic</td>
<td>Dosage</td>
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<td>------------</td>
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</tr>
<tr>
<td>Cefalexin</td>
<td>(oral) 25 mg/kg per dose every 12 hours</td>
<td></td>
</tr>
<tr>
<td>Oral weight bands:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-&lt;6 Kg: 125 mg given every 12 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-&lt;10 Kg: 250 mg given every 12 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10-&lt;15 Kg: 375 mg given every 12 hours</td>
<td></td>
<td></td>
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<tr>
<td>15-&lt;20 Kg: 500 mg given every 12 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20-&lt;30 Kg: 625 mg given every 12 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 30 Kg: Use adult dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OR Cloxacillin or Flucloxacillin (IV/oral):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neonates: 25-50 mg/kg/dose given every 12 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children: 25 mg/kg/dose given every 6 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral weight bands:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-&lt;6 kg: 125 mg given every 6 hours</td>
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<tr>
<td>6-&lt;10 kg: 250 mg given every 6 hours</td>
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<td></td>
</tr>
<tr>
<td>10-&lt;15 kg: 250 mg given every 6 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15-&lt;20 kg: 500 mg given every 6 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20-&lt;30 kg: 750 mg given every 6 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 30 Kg: Use adult dose</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

IV: intravenous.

*It should be noted that these specific recommendations are not included in the EML and were extrapolated from EML recommendations for skin and soft tissue infections.*

Vancomycin is not listed as first choice because in most settings methicillin-resistant *Staphylococcus aureus* is not a frequent cause of community-acquired infections.

Oral liquid must be refrigerated after reconstitution as clavulanic acid is rapidly metabolized in high ambient temperatures.

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

This chapter focuses on empiric treatment of suspected or confirmed bacterial infections in patients with neutropenia (including neutropenic sepsis) but it does not cover antiviral or antifungal treatment or antibiotic prophylaxis for patients with afebrile neutropenia, which are beyond the scope of this chapter.

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/μL (< 0.5 × 10^9 cells/L) with treatment duration adapted based on the clinical response irrespective of the neutrophil count

Definition

Febrile neutropenia is a severe condition that can be caused by common Gram-positive and Gram-negative bacteria, fungi and other opportunistic pathogens. Febrile neutropenia occurs mostly in patients with neoplastic diseases who are receiving cytotoxic myelosuppressive chemotherapy.

Two elements need to be considered in defining febrile neutropenia: fever and neutropenia.

For fever, there are no universally accepted temperature cut-offs and slightly different cut-offs are used in different centers. Generally, a pragmatic definition of fever is > 38.0°C. A more precise definition is used by the Infectious Diseases Society of America in their 2010 Clinical Practice Guideline for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer(333) which is:

- A single oral temperature measurement of ≥38.3°C or
- A temperature of ≥38.0°C sustained over 1 hour.

There is less variation in definition of neutropenia, which is defined as a temporary reduction of the absolute neutrophil count; an absolute neutrophil count of < 1000 cells (sometimes < 1500)/μL (< 1.0 × 10^9 cells/L) is considered indicative of neutropenia. Neutropenia can be classified as severe when the absolute neutrophil count is < 500 cells/μL (< 0.5 × 10^9 cells/L) (also called agranulocytosis) and profound when absolute neutrophil count is <100 cells/μL (< 0.1 x 10^9 cells/L).
Febrile neutropenia can be characterized according to identification of the causative pathogen and source of infection as:

1) microbiologically proven infection (i.e. the causative pathogen is identified)
2) clinical source of infection diagnosed but no pathogen identified (e.g. pharyngitis)
3) unexplained fever (no pathogen identified and no clear source of infection)
4) non-infectious fever (e.g. medicine-induced)

Unexplained fever with no focus or positive culture is the most common scenario observed in clinical practice.

Pathophysiology

Neutropenia (i.e. decreased number of circulating neutrophils) can develop as the result of a reduced production of neutrophils by the bone marrow, or increased peripheral destruction or sequestration at localized inflammatory sites. Once neutrophils decrease below a certain threshold, the risk of developing infections increases. Severity and duration of neutropenia are independent risk factors for serious infection (i.e. the risk is higher with longer and more profound neutropenia).

It is beyond the scope of this chapter to describe how cytotoxic chemotherapies and cancer affect the immune system and predispose to infection. As well as a reduced absolute neutrophil count, patients with cancer and on cytotoxic chemotherapy often also have dysfunctional lymphocytes or immunoglobulin deficiencies, impaired natural barriers to infection (e.g. mucositis) and malnutrition that additionally weaken their ability to control infections. Furthermore, the presence of invasive devices (e.g. intravascular catheters) is an additional risk factor for infection to consider.

Epidemiology

Neutropenia is the most common complication of cytotoxic cancer treatment that can lead to treatment delays and reductions in the chemotherapy dose (334). The risk of developing febrile neutropenia depends on: the type of underlying tumor (e.g. very high in patients with acute leukemia and lower in patients with solid tumors); the type and dose of chemotherapy used; and individual risk factors (e.g. older age, advanced stage of disease, comorbidities, other concomitant myelotoxic medications)(335). The risk of developing severe infection depends on the duration and severity of neutropenia; therefore, initial risk assessment is an important step to identify patients at low or high risk of developing serious complications (e.g. complications requiring hospitalization or prolonging hospitalization). As well as the physician’s assessment, several scoring systems exist (e.g. Multinational Association of Supportive Care in Cancer (MASCC) score) to help predict this risk (336). These systems usually include a combination of factors such as general clinical status of the patient, presence of comorbidities, age and whether the patient is hospitalized or not. However, no system can distinguish patients at low or high risk of infection with complete accuracy(337).
Low-risk patients are those expected to have a shorter duration of severe neutropenia (≤ 7 days) and have no comorbidities (other than cancer) or renal or hepatic dysfunction. High-risk patients are expected to remain neutropenic for longer periods (> 7 days) or are those with ongoing comorbidities (other than cancer) and renal or hepatic dysfunction.

Neutropenia is also common in children receiving myelosuppressive treatment especially for acute lymphoblastic leukemia or lymphoma (the most common forms of cancer in childhood(338)) and for acute myeloid leukaemia, or after haemopoietic stem cell transplantation or treatment for certain aggressive solid tumors (e.g. neuroblastoma)(339, 340).

**Microbiology epidemiology**

A fever of infectious origin in a patient with neutropenia is most likely caused by bacteria that colonize the patient’s own skin and bowel, including multi drug-resistant organisms such as extended-spectrum beta-lactamase (ESBL)-producing or carbapenemase-producing Gram-negative bacteria (Table 1). These patients often receive broad-spectrum antibiotics while in hospital and are therefore at increased risk of antibiotic-resistant infections. Furthermore, certain pathogens (e.g. fungi) become more frequent with longer duration of neutropenia.

**Table 1 Pathogens most frequently associated with febrile neutropenia (in descending order of frequency)**

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>Viruses</th>
<th>Fungi</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Staphylococcus epidermidis</em></td>
<td>Cytomegalovirus</td>
<td><em>Candida</em> spp.</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em> (including MRSA)</td>
<td>Human herpesvirus 6</td>
<td></td>
</tr>
<tr>
<td><em>Streptococcus</em> spp.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other Gram-positive bacteria (e.g. <em>Enterococcus</em> spp. including VRE)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enterobacterales (including multidrug-resistant strains such as those producing ESBL and carbapenemases)</td>
<td>(consider viruses in high-risk patients mostly because of reactivation of latent infections)</td>
<td></td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td></td>
<td><em>Aspergillus</em> spp. (in case of prolonged neutropenia)</td>
</tr>
<tr>
<td>Anaerobes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Notes: the risk of multidrug-resistant pathogens should always be carefully considered in patients with neutropenia because often infections in these patients are health care-associated.

Most data come from tertiary care centers located in high-income settings.

**Clinical presentation**

Apart from fever, other accompanying signs and symptoms of febrile neutropenia vary greatly depending on the underlying infection (e.g. pneumonia, urinary tract infection, skin infection, meningitis, colitis). Bacteraemia (i.e. the detection of bacteria in blood cultures) may be present.
Because patients with neutropenia fail to produce effective inflammatory responses, they can sometimes present with few clinical findings and no fever despite infection.

A detailed clinical examination should always be done to help identify the site of infection. Skin changes (e.g. rash, ulcers, signs of vascular infection), changes in the oral mucosa and pharynx (e.g. ulcers inside the mouth, dental disease, thrush), abnormalities in the perineal and perirectal area, symptoms and signs of typhlitis (inflammation of the cecum) and colitis with abdominal pain, diarrhoea and sometimes rectal bleeding often due to mucositis should therefore always be carefully investigated.

Clinical progression to severe disease or death can be very rapid (over a few hours); therefore, the presence of any signs of sepsis or septic shock should always be carefully monitored. Please also refer to the chapter on sepsis if suspected.

### Laboratory tests

#### I. Patient microbiology tests

Whenever possible a microbiology sample (e.g. blood cultures) should be obtained – ideally before antibiotic treatment is started – because results of the test can help establish the diagnosis and treatment can be adapted accordingly.

Tests to consider depend on the most likely primary site of infection and should therefore be adapted based on the clinical presentation (see Table 2). Some tests should always be performed (indicated as routine tests in Table 1) while others could be considered in certain cases, including for surveillance purposes and based on local availability. Additional tests not presented in the table but that could be considered, especially in high-risk patients, include tests to diagnose invasive fungal infections (e.g. *Aspergillus* galactomannan antigen screening) and those for other viral infections (e.g. nucleic acid amplification test for cytomegalovirus).

*Table 2 Microbiology tests to consider when febrile neutropenia is suspected depending on the most likely source of infection as indicated in the WHO EDL* (54)

<table>
<thead>
<tr>
<th>Test priority</th>
<th>Diagnostic test</th>
<th>Purpose of the test</th>
<th>Settings where the test should be available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Routine</td>
<td>Blood cultures</td>
<td>To detect bacterial and fungal bloodstream infections (sepsis)</td>
<td>Healthcare facilities with clinical laboratories</td>
</tr>
<tr>
<td>Routine</td>
<td>Bone culture</td>
<td>Initial step to detect and identify bacterial and fungal species for selection of appropriate antibiotic regimens</td>
<td>Healthcare facilities with clinical laboratories</td>
</tr>
<tr>
<td>Consider in certain cases</td>
<td>Sputum microscopy (Gram stain)</td>
<td>To assess microbial morphology and adequacy of the specimen for culture by identifying white blood cells and squamous epithelial cells</td>
<td>Healthcare facilities with clinical laboratories</td>
</tr>
<tr>
<td>--------------------------</td>
<td>-------------------------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------</td>
<td>--------------------------------------------------</td>
</tr>
<tr>
<td>Consider in certain cases</td>
<td>Sputum culture</td>
<td>Initial step to detect and identify bacterial and fungal species for selection of appropriate antibiotic regimens</td>
<td>Healthcare facilities with clinical laboratories</td>
</tr>
<tr>
<td>Consider in certain cases (including for infection control purposes)</td>
<td>Nasopharyngeal swab for nucleic acid amplification test for influenza&lt;sup&gt;a&lt;/sup&gt;</td>
<td>To diagnose seasonal influenza infection</td>
<td>Healthcare facilities with clinical laboratories but also in primary care settings</td>
</tr>
<tr>
<td>Consider in certain cases (including for infection control purposes)</td>
<td>Nasopharyngeal swab for nucleic acid amplification test or antigen test for SARS-CoV-2</td>
<td>To diagnose COVID-19</td>
<td>Healthcare facilities with clinical laboratories (NAT) and primary care settings (antigen test)</td>
</tr>
<tr>
<td>Consider in certain cases</td>
<td>Aspergillus antigen test</td>
<td>To diagnose invasive aspergillosis in immunocompromised patients</td>
<td>Healthcare facilities with clinical laboratories</td>
</tr>
<tr>
<td>Consider in certain cases</td>
<td>Cerebrospinal fluid microscopy</td>
<td>To assess microbial morphology, number of white blood cells and red blood cells</td>
<td>Healthcare facilities with clinical laboratories</td>
</tr>
<tr>
<td>Consider in certain cases</td>
<td>Cerebrospinal fluid Gram stain and bacterial culture</td>
<td>Initial step to detect and identify bacterial and fungal species for selection of appropriate antibiotic regimens</td>
<td>Healthcare facilities with clinical laboratories</td>
</tr>
<tr>
<td>Consider in certain cases</td>
<td>Stool culture</td>
<td>Initial step to detect and identify bacterial species for selection of appropriate antibiotic regimens</td>
<td>Health care facilities with clinical laboratories</td>
</tr>
<tr>
<td>Consider in certain cases</td>
<td>&lt;i&gt;Clostridioides difficile&lt;/i&gt; testing (usually nucleic acid amplification test)</td>
<td>To diagnose &lt;i&gt;C. difficile&lt;/i&gt; infection</td>
<td>—&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

CSF: cerebrospinal fluid; NAAT: nucleic acid amplification test.
Testing for respiratory viruses other than influenza (e.g. respiratory syncytial virus) could be considered based on availability and local epidemiology.

This test is not in the EDL (54).

II. Other tests

Laboratory tests to consider if febrile neutropenia is suspected depend on the most likely source of infection and are shown in Table 2.

Table 2 Laboratory tests to consider when febrile neutropenia is suspected as indicated in the WHO EDL (54)

<table>
<thead>
<tr>
<th>Diagnostic test</th>
<th>Purpose of the test purpose</th>
<th>Settings where the test should be available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete blood count</td>
<td>To detect a wide range of disorders (severity of neutropenia, anemia, thrombocytopenia), including infections</td>
<td>Healthcare facilities with clinical laboratories</td>
</tr>
<tr>
<td>C-reactive proteina</td>
<td>To detect inflammation as an indicator of various conditions (e.g. sepsis)</td>
<td>Healthcare facilities with clinical laboratories</td>
</tr>
<tr>
<td>Procalcitoninb</td>
<td>To guide antibiotic therapy or discontinuation in sepsis</td>
<td>Only in tertiary care facilities</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>To detect or monitor liver disease</td>
<td>Community settings and health facilities without laboratoriesb</td>
</tr>
<tr>
<td>Creatinine</td>
<td>To monitor kidney function for management of severe infections (i.e. sepsis) and to adjust antimicrobial regimens</td>
<td>Healthcare facilities with clinical laboratories</td>
</tr>
<tr>
<td>Electrolytes</td>
<td>To monitor fluid, electrolyte and acid-base balance</td>
<td>Healthcare facilities with clinical laboratories</td>
</tr>
<tr>
<td>Blood pH and gases</td>
<td>To assess lung function, metabolic or kidney disorders and monitor oxygen therapy</td>
<td>Healthcare facilities with clinical laboratories</td>
</tr>
<tr>
<td>Whole blood lactate</td>
<td>To assess metabolic acidosis, sepsis and dehydration</td>
<td>Community settings and health facilities without laboratoriesb</td>
</tr>
</tbody>
</table>

Measurement of biomarkers on admission (C-reactive protein and procalcitonin) might help identify high-risk patients and predict severe outcomes (e.g. sepsis) (341-343)
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 assumed to be available at health care facilities with laboratories.

III. Using microbiology surveillance data

Empiric guidance given by the Handbook could be reviewed and adapted based on local clinically relevant microbiology surveillance data. This would include blood culture data from local haemato-oncology patients, ideally risk stratified by underlying diagnosis.

Imaging

Imaging based on clinical presentation should be considered in the patient’s initial assessment to identify the source of infection. If there is no clinical improvement and the fever does not resolve with treatment in a few days, additional imaging could be considered (e.g. computed tomography scan of the lungs and sinuses, and other tests based on clinical suspicion) to expand diagnostic work-up or to exclude a complicated infection such as invasive fungal disease.

Treatment

This chapter focuses on antibiotic treatment of suspected or confirmed bacterial infections but it does not cover antiviral or antifungal treatment. It also does not cover prophylaxis with granulocyte colony-stimulating factors (i.e. growth factors that stimulate the bone marrow to produce more neutrophils) such as filgrastim listed on the EML since 2015 for the treatment of acquired neutropenia.

The use of granulocyte colony-stimulating factors for therapeutic purposes (i.e. in febrile patients) is controversial and guidelines vary in their recommendations. Evidence shows that their use in combination with antibiotics does not reduce mortality (compared with antibiotics alone), however granulocyte colony-stimulating factors could be considered in certain patients because their use is associated with shorter hospital stay and duration of antibiotic use (reduced by 1-2 days) most likely due to the faster neutrophil recovery.

It is important that source control is achieved as early as possible, this includes drainage of any abscesses and removal or change of invasive devices such as central venous catheters, where appropriate.

Antibiotic treatment

Patients with neutropenia who develop fever should promptly receive antibiotic treatment even when a clear site of infection is not identified.

Low-risk patients can be managed in an outpatient setting if adequate monitoring and follow-up is available and if they are able to tolerate oral treatment. High-risk patients (or patients where close follow-up is not feasible) require hospitalization and initial intravenous treatment to start with.
The choice of empiric treatment should always consider a combination of factors, including the most likely site of primary infection and the infecting pathogens (including risk of viral and invasive fungal infections) and the local pattern of antimicrobial resistance. Other factors, such as known colonization or previous infection with multidrug-resistant organisms and recent antibiotic exposure (including antibiotic prophylaxis) are also important factors to consider. Recommended empiric antibiotic options are given in Table 3.

Simplify empiric treatment to a more narrow-spectrum antibiotic based on culture results or rapid clinical improvement if culture results unavailable.

Step down to oral antibiotics is suggested when the patient has made a good clinical response, the fever has settled and the patient can tolerate oral antibiotics.

Table 3 Initial empiric antibiotic treatment for febrile neutropenia (absolute neutrophil count: < 500 cells/μL; < 0.5 × 10^9 cells/L) based on the patient’s initial risk assessment

This table refers to empiric treatment not to treatment escalation in case of persistent fever which is beyond the scope of the chapter.

<table>
<thead>
<tr>
<th>Patient risk</th>
<th>Adults</th>
<th>Children</th>
<th>Total treatment duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk (expected duration of neutropenia &lt; 7 days, no major comorbidities, no organ dysfunction, possible outpatient treatment)</td>
<td><strong>Amoxicillin+clavulanic acid</strong> (oral): 500 mg+125mg given every 8 hours <strong>CONSIDER ADDING</strong> <strong>Ciprofloxacin</strong> (oral): 500 mg given every 12 hours</td>
<td><strong>Amoxicillin+clavulanic acid</strong> (oral) 40-50 mg/kg/dose of amoxicillin component given every 12 hours OR 30 mg/kg/dose given every 8 hours <strong>CONSIDER ADDING</strong> <strong>Ciprofloxacin</strong> (oral) 10-20 mg/kg/dose given every 12 hours</td>
<td>7 days</td>
</tr>
</tbody>
</table>

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

**CONSIDER ADDING** **Ciprofloxacin** (oral) 10-20 mg/kg/dose given every 12 hours

Oral weight bands:
<table>
<thead>
<tr>
<th>Weight Range</th>
<th>Dosage</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-&lt;6 kg</td>
<td>50 mg given every 12 hours</td>
<td></td>
</tr>
<tr>
<td>6-&lt;10 kg</td>
<td>100 mg given every 12 hours</td>
<td></td>
</tr>
<tr>
<td>10-&lt;15 kg</td>
<td>150 mg given every 12 hours</td>
<td></td>
</tr>
<tr>
<td>15-&lt;20 kg</td>
<td>200 mg given every 12 hours</td>
<td></td>
</tr>
<tr>
<td>20-&lt;30 kg</td>
<td>300 mg given every 12 hours</td>
<td></td>
</tr>
<tr>
<td>≥ 30 Kg</td>
<td>Use adult dose</td>
<td></td>
</tr>
</tbody>
</table>

**First choice**: Piperacillin+Tazobactam (IV): 4g + 500 mg given every 6 hours

**Second choice**: Meropenem (<sup>a</sup>): 1g given every 8 hours

**CONSIDER ADDING**: Amikacin (<sup>b</sup>): 15 mg/kg given once a day

**AND/OR**: Consider adding Vancomycin (<sup>c</sup>): 15-20 mg/kg given every 12 hours

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

<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.

<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 empirical 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.

Until clinical signs of infection have resolved, including absence of fever for at least 48 hours.

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.
Consider adding vancomycin in combination with piperacillin–tazobactam or meropenem when methicillin-resistant *Staphylococcus aureus* (MRSA) is suspected (e.g. patients with MRSA colonization) or where a line infection is strongly suspected (because of the risk of multidrug-resistant coagulase-negative *Staphylococcus* infection). 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.

Oral liquid must be refrigerated after reconstitution as clavulanic acid is rapidly metabolized in high ambient temperatures.

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

Antibiotic treatment for patients with febrile neutropenia may require adjustments in dose and frequency of administration because pharmacokinetic and pharmacodynamic parameters could be altered in these patients and renal and hepatic toxicity related to chemotherapy is common (347).

If the causative pathogen is identified, once susceptibilities are known, antibiotics should be reviewed and modified accordingly. However, even if adequate microbiological sampling is performed, a pathogen is often not identified.

If fever persists (e.g. patient still has a temperature 48-72 hours after the start of antibiotic treatment) and there is no clinical improvement, further diagnostic tests (e.g. imaging) could be performed to identify the source of infection (if this is still unclear) or to assess whether a local complication has developed (e.g. a fluid collection). In addition, a resistant pathogen or an invasive fungal disease should be considered as they could be responsible for the prolonged fever.

Duration of treatment will mostly depend on the clinical response (e.g. resolution of fever and clinical recovery) and (if identified) on the infectious site and the causative pathogen.

Continuation of antibiotic treatment until neutrophil recovery (absolute neutrophil count > 500 cells/μL; > 0.5 × 10^9 cells/L) is controversial with guidelines varying in their recommendations. Evidence suggests that discontinuation of antibiotics based on a clinical assessment (e.g. if the clinical recovery is good and no source is identified or if an infection has been adequately treated and irrespective of the neutrophil count), can safely reduce exposure to antibiotics (348, 349).
Surgical prophylaxis

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)

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


Definition of terms used in this chapter

Definitions are taken from the 2018 WHO publication: Global guidelines for the prevention of surgical site infections (251).

Antibiotic prophylaxis: prevention of infectious complications by administering an effective antimicrobial agent before exposure to contamination during surgery.

Surgical procedure: an operation where at least one incision (including laparoscopic incisions) is made through the skin or mucous membrane, or a reoperation through an incision that was left open after a previous operative procedure and takes place in the operating room.

Surgical site infection: “an infection that occurs after surgery in the part of the body where the surgery took place. Surgical site infections can sometimes be superficial infections involving the skin only. Other surgical site infections are more serious and can involve tissues under the skin, organs or implanted material”.

Surgical site infection is also defined as an infection that occurs up to 30 days after an operation and affects:

(i) the skin and subcutaneous tissue of the surgical incision (superficial incisional); and/or
(ii) the deep soft tissue (for example, fascia or muscle) of the incision (deep incisional) and/or
(iii) any part of the anatomy (for example, organs and spaces) other than the incision that was opened or manipulated during an operation (organ/space).

**Surgical wound:** a wound created when an incision is made with a scalpel or other sharp cutting device and then closed in the operating room by suture, staple, adhesive tape, or glue and bringing the skin edges together.

**Categories of surgical wound:**

- **Clean:** an uninfected surgical wound in which no inflammation is found, and which is not in the respiratory, alimentary, genital or urinary tracts. In addition, clean wounds are usually closed and, if necessary, drained with closed drainage. Surgical incisional wounds that are done after non-penetrating (blunt) trauma should be included in this category if they meet the criteria.

- **Clean-contaminated:** a surgical wound in the respiratory, alimentary, genital or urinary tracts which was made under controlled conditions and without unusual contamination. Operations involving the biliary tract, appendix, vagina and oropharynx are included in this category, provided no evidence of infection or major (i.e. significant) break in sterile technique is found.

- **Contaminated:** open, fresh, accidental wounds. Also included in this category are: operations with major break in sterile technique (e.g. open cardiac massage) or substantial spillage (of gastrointestinal contents) from the gastrointestinal tract; and incisions in which acute, non-purulent inflammation is found, including necrotic tissue, without evidence of purulent drainage (e.g. dry gangrene).

- **Dirty or infected:** old traumatic wounds with retained dead tissue and those that involve existing clinical infection or perforated viscera. Such wounds suggest that the organisms causing postoperative infection were present at the site of the surgery before the operation.

**Epidemiology**

The percentage of surgical site infections varies depending on the type of surgical procedure. For example, in 2017 in 13 European countries reporting data on > 600 000 surgical procedures, the overall percentage of infections per 100 operations ranged from 0.5% after knee prosthesis surgery to 10.1% after colon surgery(350). For most types of surgery more than 80% of patients received antibiotic prophylaxis. The only exception was cholecystectomy for which a lower percentage of patients received antibiotic prophylaxis – 44.1% in case of laparoscopic and 65.9% in case of open cholecystectomy(350).

Another study included data collected in 2016 from more than 12 000 patients from 66 countries with different human development indices (HDI); 10.2% of patients were from countries with a low HDI. Overall, 12.3% of patients undergoing gastrointestinal surgery developed a surgical site infection within 30 days. However, statistically significant differences in the incidence of surgical site infections were found based on the HDI. In particular, the incidence of surgical site infections was 9.4% in countries with a high HDI, 14.0% in countries with a medium HDI and 23.2% in those.
with a low HDI. Patients in countries with a low HDI were 1.6 times more likely to develop an infection than countries with a higher HDI(351). Variation in infection rates was also found after caesarean sections with rates of infections ranging from 3% to 11% in high-income countries compared to 3% to 24% in low- and middle-income countries(352).

Surgical site infections and surgical prophylaxis to prevent them are a frequent cause of antibiotic use in hospitals. The 2015 Global Point Prevalence Survey on antibiotic use (reporting data from 303 hospitals in 53 countries) reported that on the day of the survey, 1.6% of admitted patients were receiving antibiotics for a postoperative surgical site infection(266). Of note, 34.4% of adult inpatients were receiving at least one antibiotic on the day of the survey. Of all total antibiotic prescriptions, 17.8% were for surgical prophylaxis. The most frequently prescribed antibiotic was cefazolin (prescribed in 27.5% of patients receiving surgical prophylaxis). Prolonged surgical prophylaxis (> 1 day) was common in all regions, ranging from 40.6% in Oceania to 86.3% in eastern Europe(266).

**Microbiology epidemiology**

The pathogens causing surgical site infections vary based on the type of surgical procedure (Table 1).

**Table 1 Pathogens most frequently associated with surgical site infections by anatomical site of the procedure**

<table>
<thead>
<tr>
<th>Type of procedure</th>
<th>Pathogens most frequently associated with surgical site infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac procedures</td>
<td><em>S. aureus</em> and coagulase-negative staphylococci</td>
</tr>
<tr>
<td>Cardiac device insertion procedures</td>
<td><em>S. aureus</em> and coagulase-negative staphylococci</td>
</tr>
<tr>
<td>(e.g. pacemaker implantation)</td>
<td><em>S. aureus</em> and coagulase-negative staphylococci</td>
</tr>
<tr>
<td>Non-cardiac thoracic procedures</td>
<td><em>S. aureus</em> and coagulase-negative staphylococci</td>
</tr>
<tr>
<td>(e.g. pulmonary resection)</td>
<td><em>H. influenzae</em></td>
</tr>
<tr>
<td></td>
<td><em>Enterobacter cloacae</em></td>
</tr>
<tr>
<td></td>
<td><em>Klebsiella pneumoniae</em></td>
</tr>
<tr>
<td></td>
<td><em>Acinetobacter</em> spp.</td>
</tr>
<tr>
<td></td>
<td><em>Pseudomonas aeruginosa</em></td>
</tr>
<tr>
<td></td>
<td><em>Moraxella catarrhalis</em></td>
</tr>
<tr>
<td>Gastroduodenal procedures</td>
<td><em>S. aureus</em> and coagulase-negative staphylococci</td>
</tr>
<tr>
<td></td>
<td><em>Enterococcus</em> spp.</td>
</tr>
<tr>
<td></td>
<td>Enterobacterales</td>
</tr>
<tr>
<td></td>
<td>Anaerobes (<em>Bacteroides</em> spp.)</td>
</tr>
<tr>
<td>Biliary tract procedures</td>
<td>Enterobacterales</td>
</tr>
<tr>
<td></td>
<td>Anaerobes</td>
</tr>
<tr>
<td></td>
<td><em>Enterococcus</em> spp.</td>
</tr>
<tr>
<td></td>
<td><em>Streptococcus</em> spp.</td>
</tr>
<tr>
<td></td>
<td><em>S. aureus</em> and coagulase-negative staphylococci</td>
</tr>
<tr>
<td>Appendectomy</td>
<td><em>Escherichia coli</em></td>
</tr>
<tr>
<td></td>
<td>Anaerobes (<em>Bacteroides fragilis</em>)</td>
</tr>
<tr>
<td>Small intestine procedures</td>
<td>Enterobacterales</td>
</tr>
<tr>
<td></td>
<td>Anaerobes</td>
</tr>
<tr>
<td></td>
<td><em>Enterococcus</em> spp.</td>
</tr>
<tr>
<td></td>
<td><em>Streptococcus</em> spp.</td>
</tr>
</tbody>
</table>
### Antibiotic Prophylaxis

The choice of the antibiotic should be based on the type of surgical procedure because not all procedures are associated with the same risk of developing infection.

In general, antibiotic prophylaxis before surgery, where the most likely pathogens causing infection are Gram-positive bacteria, should consist of intravenous first- or second-generation cephalosporins (cefazolin or, as an alternative second choice, cefuroxime). These surgeries include clean procedures such as cardiac and vascular surgery but also procedures that involve the placement of a prosthesis or implant.

If additional pathogens (e.g., anaerobes) could cause infection (e.g., in abdominal procedures), antibiotic prophylaxis should be adapted accordingly. In these cases, cefazolin in combination with metronidazole would be an appropriate option.

In patients known to be colonized with methicillin-resistant *Staphylococcus aureus* (MRSA) and who will have a skin incision, vancomycin prophylaxis (in addition to the routine recommended antibiotic prophylaxis) may be justified. This is recommended because vancomycin alone is less effective than cefazolin (the antibiotic recommended as prophylaxis in most surgical procedures) against methicillin-sensitive *Staphylococcus aureus* (and because vancomycin has no activity against Gram-negative bacteria). It should be noted that in patients colonized with MRSA, procedure-specific preventive measures other than antibiotic prophylaxis (e.g., nasal

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Suspected Pathogens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hernia repair procedures</td>
<td><em>Enterococcus</em> spp., <em>Streptococcus</em> spp., <em>S. aureus</em> and coagulase-negative staphylococci</td>
</tr>
<tr>
<td>Colorectal procedures</td>
<td><em>Escherichia coli</em>, Anaerobes (Bacteroides fragilis)</td>
</tr>
<tr>
<td>Head and neck procedures</td>
<td><em>Streptococcus</em> spp., <em>S. aureus</em> and coagulase-negative staphylococci, Enterobacterales, Anaerobes (from the oral microbiota)</td>
</tr>
<tr>
<td>Neurosurgical procedures</td>
<td><em>S. aureus</em> and coagulase-negative staphylococci, Gram-negative bacteria</td>
</tr>
<tr>
<td>Gynaecological procedures</td>
<td><em>Streptococcus agalactiae</em> (group B streptococcus), <em>Staphylococcus aureus</em>, <em>Enterococcus</em> spp., Anaerobes</td>
</tr>
<tr>
<td>Ophthalmic procedures</td>
<td><em>S. aureus</em> and coagulase-negative staphylococci</td>
</tr>
<tr>
<td>Orthopaedic procedures</td>
<td><em>S. aureus</em> and coagulase-negative staphylococci</td>
</tr>
<tr>
<td>Urological procedures</td>
<td>Enterobacterales (mostly <em>Escherichia coli</em>), <em>Enterococcus</em> spp.</td>
</tr>
<tr>
<td>Vascular procedures</td>
<td><em>S. aureus</em> and coagulase-negative staphylococci</td>
</tr>
</tbody>
</table>

Note: This list is based on data from high-income settings and aims to give a general overview (353). The distribution of the pathogens most frequently associated with surgical site infections may vary in other settings.
decolonization with mupirocin ointment, skin antisepsis) may be beneficial but such measures are not specifically addressed in this chapter. Please refer to the WHO guidelines for the prevention of surgical site infections(251) for information on such preventive measures.

In the context of patients known to be colonized with multidrug-resistant Gram-negative bacteria (e.g. bacteria producing extended-spectrum beta-lactamases or carbapenemases), the WHO guidelines acknowledged a lack of high-quality evidence to make recommendations on the need to include other antibiotics for prophylaxis to cover these pathogens(251). However, certain factors, such as the closeness of the likely reservoir of these bacteria to the operative site or characteristics of the patient could help to make decision on a case-by-case basis.

Table 2 Antibiotic prophylaxis before surgical procedures

<table>
<thead>
<tr>
<th>Type of procedure</th>
<th>First choice</th>
<th>Second choice</th>
</tr>
</thead>
</table>
| **Clean procedure**<sup>a</sup> | Cefazolin (IV):  
• Children: 50 mg/kg - single dose  
• Adults: 2 g<sup>b</sup> - single dose | Cefuroxime (IV):  
• Children: 50 mg/kg - single dose  
• Adults: 1.5 g – single dose |
| **Clean contaminated procedure**<sup>e</sup> (except bowel surgery and urological procedures) | Cefazolin (IV):  
• Children: 50 mg/kg - single dose  
• Adults: 2 g<sup>b</sup> - single dose | Cefuroxime (IV):  
• Children: 50 mg/kg - single dose  
• Adults: 1.5 g – single dose |
| **Contaminated procedure**<sup>d</sup> | Cefazolin (IV):  
• Children: 50 mg/kg - single dose  
• Adults: 2 g<sup>b</sup> - single dose  
AND Metronidazole (IV):  
• Children: 7.5 mg/kg - single dose  
• Adults: 500 mg - single dose | Amoxicillin+clavulanic acid (IV):  
• Children: 40-50 mg/kg of amoxicillin component – single dose  
• Adults: 2 g + 200 mg – single dose  
OR Gentamicin<sup>f</sup> (IV):  
• Neonates: 5 mg/kg – single dose  
• Children: 7.5 mg/kg – single dose  
• Adults: 5 mg/kg – single dose  
AND Metronidazole (IV):  
• Children: 7.5 mg/kg - single dose  
• Adults: 500 mg - single dose |
| **Bowel surgery**<sup>e</sup> | Cefazolin (IV):  
• Children: 50 mg/kg - single dose  
• Adults: 2 g<sup>b</sup> - single dose  
AND Metronidazole (IV):  
• Children: 7.5 mg/kg - single dose  
• Adults: 500 mg - single dose | Amoxicillin+clavulanic acid (IV):  
• Children: 40-50 mg/kg of amoxicillin component – single dose  
• Adults: 2 g + 200 mg – single dose |
| **Urologic procedures** | Cefazolin (IV): | Gentamicin<sup>f</sup> (IV): |
• Children: 50 mg/kg - single dose
• Adults: 2 g b - single dose
• Neonates: 5 mg/kg – single dose
• Children: 7.5 mg/kg – single dose
• Adults: 5 mg/kg – single dose

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

IV: intravenous.
a Surgical procedures where the respiratory, alimentary, genital or urinary tracts are not entered.
b Higher doses of cefazolin (e.g. 3g) may be required in obese patients (> 120 kg).
c 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.
d Operations with major (i.e. significant) interruptions in sterile technique (e.g. open cardiac massage) or substantial spillage from the gastrointestinal tract.
e Bowel surgery includes appendectomy, small intestine and colorectal surgical procedures.
f 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.

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

Timing of antibiotic prophylaxis before surgery

According to the previously cited WHO guidelines, the antibiotic should be given 120 minutes or less before incision (251).

Duration of antibiotic prophylaxis

Antibiotic prophylaxis should not be continued after surgery for the purpose of preventing surgical site infections including in the presence of a surgical wound drain(251). This is because one dose of the prophylactic antibiotic should cover the entire period of potential contamination (i.e. from time of the incision until final closure of the wound) in most cases and continuing prophylaxis does not offer additional benefit in reducing the incidence of surgical site infections compared with discontinuing it (354). At the same time, limiting the duration to one single dose reduces the risk of selecting resistant bacteria in the patient’s own microbiota and the risk of developing *Clostridioides difficile* infections.

Only in certain cases may a further dose of antibiotic be required, such as for prolonged surgical procedures (exceeding about 2 times the half-life of the antibiotic) or when there is major blood loss. If redosing is necessary, the half-life of the antibiotic should be considered (e.g. giving a second dose of cefazolin four hours after the initial preoperative dose in long surgeries) (Table 3).

Table 3 Half-life of the antibiotics recommended for surgical prophylaxis in the WHO EML(355)

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Half-life (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin–clavulanic acid</td>
<td>1–2</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>1–2</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>1–2</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>2–3</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>6–8</td>
</tr>
</tbody>
</table>
RESERVE ANTIBIOTICS
Overview

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.

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

- https://aware.essentialmeds.org/groups

The Reserve group of antibiotics includes antibiotics that still have significant levels of activity against some of the multidrug-resistant bacteria listed in the WHO priority pathogen list including bacteria which are resistant to most or all of the EML antibiotics in the Access and Watch groups (Table 1).

In addition, all Reserve antibiotics are categorized as either “high priority” or “highest priority” in the WHO list of critically important antimicrobials (356). This list is intended for public health and animal health authorities who should ensure that critically important antibiotics for humans are also used sensibly in veterinary medicine. Use of any Reserve antibiotics in animals should be avoided wherever possible.

Reserve antibiotics can either be older off-patent antibiotics that have been reintroduced into clinical practice (e.g., polymyxin B, colistin, fosfomycin) or new antibiotics that have been recently licensed for the treatment of multidrug-resistant bacteria. It is important to note that not all antibiotics that have activity against strains of multidrug-resistant bacteria have been included in the EML (355). Between 2017 and 2021, the list of Reserve antibiotics was updated, and some antibiotics were removed and others added to this group. Only antibiotics listed on the EML/EMLc are considered essential for all health systems.

The EML needs to be continually updated as more evidence on the antibiotics in the list and new antibiotics become available. The list of Reserve antibiotics in the 2021 EML is closely aligned with the WHO analysis of the clinical antibacterial pipeline (357) which assesses how antibacterial drugs in the development pipeline address the WHO priority pathogens list. Ideally an antibiotic under development will progress through the pipeline and, after licensing, would be considered for listing in the EML as a Reserve antibiotic.
The overarching principle for listing an antibiotic as a Reserve antibiotic in the EML is evidence of its utility to effectively treat an important clinical infection for which the currently available treatment options are very limited, with a clear global unmet public health need. Other important considerations are strong evidence that the antibiotic has: better efficacy, safety and durability (low likelihood of selection of resistance on treatment) than comparable drugs; low impact on the microbiome; and simplicity of administration. There is therefore likely to be a range of Reserve antibiotics that cover different serious clinical infections. These antibiotics would include, for example, systemic antibiotics targeted at particular multidrug-resistant phenotypes (e.g. carbapenem-resistant organisms) or targeted at important pathogens (e.g. *Pseudomonas* spp. or *Acinetobacter* spp.). Equally, there is an important unmet clinical need for active oral drugs that can be used as targeted treatment of multidrug-resistant pathogens (e.g. *Klebsiella* spp.). This focus on public health emphasizes the importance for Reserve antibiotics to have phenotypic and genotypic activity that is globally relevant. For example, Reserve antibiotics that are active against carbapenem-resistant pathogens should ideally also have activity against the most common genetic types identified in low and middle-income countries (e.g. metallo-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.

Reserve antibiotics are considered “last-resort antibiotics” which are still effective for the treatment of specific patient populations. There is a complex balance between using Reserve antibiotics effectively in sick patients where needed and their overuse leading to a rapid decline in their effectiveness. The great majority of Reserve antibiotics are intravenous and used in the hospital facility setting. There is wider use of Reserve antibiotics in HIC’s than LMIC’s, raising clear concerns about equity of access to Reserve antibiotics which are generally more expensive than Access or Watch antibiotics.

Therefore, these antibiotics should be available for clinical care when needed but used only in certain situations where their use is likely to have clear clinical benefits. Reserve antibiotics are ideally used for targeted treatment once the multidrug-resistant bacteria are confirmed (e.g. following laboratory identification of the pathogen from a blood culture and susceptibility testing demonstrating wide multidrug resistance but sensitivity to a Reserve antibiotic). However, high
quality rapid culture and sensitivity data are often not available in many settings. The Handbook focuses on empiric treatment when diagnostic test results, including microbiological cultures, are not available. Reserve antibiotics could be considered for empiric therapy in very selected cases where a multidrug-resistant pathogen as the cause of the infection can be strongly suspected based on the clinical infection, local microbiology, previous treatment or known colonization with a multidrug-resistant pathogen.

Reserve antibiotics are not listed as first- or second-choice options for any of the infections included in this Handbook. However, to help with the appropriate use of Reserve antibiotics, a comment about their potential role for empiric therapy has been added to specific chapters where they are most likely to be used (e.g. severe hospital-acquired infections or severe infections in heavily antibiotic experienced patients). The risks and benefits of treatment need to be carefully considered in high-risk patient populations with multidrug-resistant infections with high associated mortality. Some antibiotics on the Reserve list have substantial toxicity but may still be used for treatment if there are no / few other treatment options and the risk of death / permanent sequelae due to the infection are high. Focussing the optimal use of Reserve antibiotics is complex and difficult at both a patient and country level, but control of the use of Reserve antibiotics is critical to maintaining their future effectiveness. For example, Colistin in South Africa is only authorised for use following specific criteria and approval from the Medicines 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.

Prescribers need to recognise the very limited data available on the clinical efficacy of most Reserve antibiotics in treating multidrug-resistant infections. Regulatory approval is usually obtained through non-inferiority trials (usually in complicated UTI trials) containing few high-risk patients with multidrug-resistant infections. Therefore, the effectiveness of these new molecules on multidrug-resistant isolates is often based on in vitro data or case reports and retrospective observational studies with high inherent risk of bias. Furthermore, recruitment of patients with carbapenem-resistant pathogens into pathogen-focused or limited-population trials has been difficult, which has led to estimates of clinical efficacy based on small studies. Strategic comparative public health focused (rather than regulatory) trials for multidrug-resistant infections that directly compare multiple agents in high-risk populations for clinical efficacy, toxicity, resistance and health economic outcomes are urgently needed to inform the urgent unmet public health priorities in this critical area.
Table 1 Reserve antibiotic expected activity against third-generation cephalosporin and carbapenem-resistant bacteria based on the type of beta-lactamase produced

<table>
<thead>
<tr>
<th>Type of beta-lactamase</th>
<th>ESBL&lt;sup&gt;a&lt;/sup&gt;</th>
<th>KPC Carbenemase</th>
<th>NDM, VIM, IMP Carbenemase</th>
<th>AmpC Cephalosporinase</th>
<th>OXA-48 Oxacillinase</th>
<th>Expected activity against non-fermenters&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ambler Class&lt;sup&gt;c&lt;/sup&gt;</td>
<td>A Serine-beta-lactamase</td>
<td>A Serine-beta-lactamase</td>
<td>B Metallo-beta-lactamases</td>
<td>C Cephalosporinase</td>
<td>D Oxacillinase</td>
<td>+ Acinetobacter baumannii + Pseudomonas aeruginosa</td>
</tr>
<tr>
<td>Ceftazidime-avibactam</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>? Acinetobacter baumannii</td>
</tr>
<tr>
<td>Cefiderocol</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>(NOTE: higher mortality has been reported with carbapenem-resistant Acinetobacter baumannii infections)</td>
</tr>
<tr>
<td>Fosfomycin (IV)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Meropenem–vaborbactam</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Plazomicin</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Polymyxin B and colistin</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

Expected activity: + active; ? possibly active; - not or insufficiently active.

<sup>a</sup>ESBL (extended-spectrum beta-lactamases) are a group of different beta-lactamases.

<sup>b</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.

<sup>c</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.
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.
Spectrum of activity

Cefiderocol is only active against aerobic Gram-negative bacteria. Specifically, it is active against many carbapenem-resistant Enterobacterales, *Pseudomonas aeruginosa* and *Acinetobacter baumannii* clinical isolates. Cefiderocol has no, or only limited, activity against Gram-positive or anaerobes.

In vitro, cefiderocol inhibits the activity of extended-spectrum beta-lactamases (ESBL) and of certain types of carbapenemase, in particular *Klebsiella pneumoniae* carbapenemases (KPC), OXA-48 beta-lactamases and metallo-beta-lactamases (MBL) such as New Delhi metallo-beta-lactamases (NDM), Verona integron-encoded (VIM), or Imipenem-Resistant Pseudomonas (IMP) metallo-beta-lactamases.

Of note, cefiderocol is one of the few Reserve antibiotics with reported activity against metallo-beta-lactamases. The other such antibiotics are colistin/polymyxin B, fosfomycin and aztreonam combined with avibactam (in the form of ceftazidime+avibactam).

*Table 1 Cefiderocol expected activity against third-generation cephalosporin and carbapenem-resistant bacteria based on the type of beta-lactamase produced*

<table>
<thead>
<tr>
<th>Type of beta-lactamase</th>
<th>ESBLa</th>
<th>KPCb</th>
<th>NDM, VIM, IMPb</th>
<th>AmpC</th>
<th>OXA-48b</th>
<th>Expected activity against non-fermentersc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ambler classd</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A Serine-beta-lactamases</td>
<td>+</td>
<td>+</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+ (NOTE: higher mortality has been reported with carbapenem-resistant <em>Acinetobacter baumannii</em> infections)</td>
</tr>
<tr>
<td>B Carbapenemase</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C Cephalosporinase</td>
<td></td>
<td></td>
<td></td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>D Oxacillinase</td>
<td></td>
<td></td>
<td></td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>

*Expected activity:* + active; ? possibly active; - not or insufficiently active.

aESBL (extended-spectrum beta-lactamases) are a group of different beta-lactamases.
bCarbapenemases.
cNon-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.
dThe 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.
Clinical efficacy

As of the date of publication of this Handbook, three randomized clinical trials have assessed the efficacy and safety of cefiderocol in adults. The results of these trials provide evidence that cefiderocol is not inferior to carbapenems for the treatment of infections caused by Gram-negative bacteria (not specifically multidrug-resistant) particularly for complicated urinary tract infections (358, 360), hospital-acquired pneumonia including ventilator-associated pneumonia (358, 361) and bloodstream infections or sepsis(358).

One study that enrolled 150 patients with confirmed carbapenem-resistant Gram-negative infection and compared cefiderocol to the best available therapy reported higher mortality in the cefiderocol group, which appeared to be driven by a worse outcome in the subgroup of patients with *Acinetobacter baumannii* infections(358). Mortality at day 28 was 24.8% (25/101) in the cefiderocol group versus 18.4% (9/49) in the best available therapy group (difference 6.4%, 95% confidence interval: −8.6% to 19.2%). The statistically significant difference persisted at day 49 – 34/101 [33.7%] in the cefiderocol group versus 10/49 [20.4%] in the best available therapy group; difference 13.3%, 95% CI: −2.5% to 26.9%.

A possible explanation given by the authors for this difference was that, despite randomization, a higher mortality risk was present at the time of randomization in the cefiderocol group (e.g. more patients were in the intensive care unit or had experienced shock in the month preceding randomization). The increase in mortality remains, however, a major concern in this patient population and requires further investigation in clinical trials.

Although very small numbers of patients with metallo-beta-lactamase-producing Enterobacteriales were included in these trials, outcomes in this group of patients was favourable. As of the date of publication of this Handbook, cefiderocol is being assessed in phase 2 trials (i.e. trials that assess safety and effectiveness in small groups of patients) in children and good evidence about its efficacy and safety in the pediatric setting is lacking.

Toxicity

Cefiderocol has a good safety profile similar to other beta-lactams and is well tolerated. In clinical trials, side-effects were described in proportions similar to those experienced by patients in control groups. Gastrointestinal issues (e.g. diarrhoea) are those more commonly reported side-effects.

Dose

Cefiderocol requires dose adjustments in cases of renal impairment. Renal function should be closely monitored and doses adjusted accordingly. Dose adjustments are not covered in the Handbook. Please also refer to the chapter on dosing for more information.
Table 2 Cefiderocol suggested doses

<table>
<thead>
<tr>
<th>Dose in adults</th>
<th>Dose in children</th>
<th>Dose in neonates</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 g given every 8 hours</td>
<td>There is no data for children or neonates</td>
<td>There is no data for children or neonates</td>
</tr>
</tbody>
</table>

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

Indication for the use of cefiderocol as a Reserve antibiotic

I. Targeted treatment

Cefiderocol could be considered in the following situations.

- 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.

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.

II. Empiric treatment

- For empiric use exceptionally in very selected cases of seriously ill patients with invasive infections (e.g. patients with sepsis / septic shock) including:
  - 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.
  - Patients who have previously been treated for infections caused by carbapenem-resistant bacteria that are susceptible only to cefiderocol.
  - Patients who are known to be colonized with carbapenem-resistant bacteria found to be susceptible only to cefiderocol.
To help prescribers identify clinical scenarios where empiric use of Reserve antibiotics could exceptionally be considered, suggestions are given in the relevant chapters of the Handbook for certain infections (only for infections where empiric use could potentially be adequate on a case-by-case basis).

New resistance to cefiderocol in Enterobacterales, Pseudomonas and Acinetobacter

Most Gram-negative bacteria are susceptible to cefiderocol. However, as of the date of publication of this Handbook, few data are available about resistance. Most evidence comes from two laboratory surveillance studies that tested the in vitro activity of cefiderocol in more than 30,000 Gram-negative aerobic isolates (years 2014-2017) and showed that cefiderocol was effective at low minimum inhibitory concentrations for more than 99% of isolates (362, 363). An increase in minimum inhibitory concentrations to cefiderocol has emerged on treatment in a small proportion of patients in trials.

Data on resistance to cefiderocol are currently not reported by the Global Antimicrobial Resistance Surveillance System (GLASS).

Duration

Treatment duration varies according to indication and should be as short as possible, usually between 7-14 days.
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.
Ceftazidime+avibactam also has some antistreptococcal activity, very limited anti-staphylococcal activity and no anti-enterococcal activity. Its activity against anaerobes varies: *Clostridium* spp. are resistant and *Bacteroides* spp. show unpredictable susceptibility.

Table 1  Ceftazidime+avibactam expected activity against third-generation cephalosporin and carbapenem-resistant bacteria based on the type of beta-lactamase produced

<table>
<thead>
<tr>
<th>Type of beta-lactamase</th>
<th>ESBL&lt;sup&gt;a&lt;/sup&gt;</th>
<th>KPC&lt;sup&gt;b&lt;/sup&gt;</th>
<th>NDM, VIM, IMP&lt;sup&gt;b&lt;/sup&gt;</th>
<th>AmpC</th>
<th>OXA-48&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Expected activity against non-fermenters&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ambler class&lt;sup&gt;d&lt;/sup&gt;</td>
<td>A Serine-beta-lactamases</td>
<td>A Serine-beta-lactamases</td>
<td>B Metallo-beta-lactamases</td>
<td>C Cephalosporinase</td>
<td>D Oxacillinase</td>
<td>-</td>
</tr>
<tr>
<td>Ceftazidime-avibactam</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>? Acinetobacter baumannii + Pseudomonas aeruginosa</td>
</tr>
</tbody>
</table>

Expected activity: + active; ? possibly active; - not or insufficiently active.

<sup>a</sup>ESBL (extended-spectrum beta-lactamases) are a group of different beta-lactamases.

<sup>b</sup>Carbapenemases.

<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.

<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.

Clinical efficacy

Several clinical trials have assessed the efficacy and safety of ceftazidime+avibactam in adults and provide evidence that it is not inferior to carbapenems for the treatment of infections caused by Gram-negative bacteria particularly for: complicated urinary tract infections (365, 366); complicated intra-abdominal infections in combination with metronidazole (366-368); and hospital-acquired pneumonia (369). Of note, in the majority of trials the infection being caused by multidrug-resistant organisms was not an inclusion criterion. In children, as of the date of publication of this Handbook, ceftazidime+avibactam has been assessed in phase 2 trials (i.e. trials that assess safety and effectiveness in small groups of patients) for both the treatment of complicated urinary tract infections, compared with cefepime (370) and in combination with metronidazole for the treatment of complicated intra-abdominal infections, compared with meropenem(371).

In both studies, ceftazidime+avibactam was well tolerated with a safety profile similar to that of ceftazidime alone and appeared effective in children with complicated urinary or intra-abdominal infections caused by Gram-negative pathogens.
Toxicity

Ceftazidime+avibactam is well tolerated and has side effects similar to those previously reported for ceftazidime alone. The most frequent side-effects are diarrhoea, nausea and vomiting.

Dose

Ceftazidime+avibactam requires dose adjustments in cases of renal impairment. Renal function should be closely monitored, and doses adjusted accordingly.

Please also refer to the chapter on dosing for more information.

Table 2 Ceftazidime+avibactam suggested doses

<table>
<thead>
<tr>
<th>Dose in adults</th>
<th>Dose in children</th>
<th>Dose in neonates</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5 g (2 g ceftazidime + 500 mg avibactam) given every 8 hours</td>
<td>62.5 mg/kg (max 2.6 g) given every 8 hours</td>
<td>62.5 mg/kg given every 8 hours</td>
</tr>
</tbody>
</table>

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

Indication for the use of ceftazidime+avibactam as a Reserve antibiotic

I. Targeted treatment

Ceftazidime+avibactam could be considered:

- As a last-resort option for the targeted treatment of severe invasive infections (e.g., septic shock with positive blood culture) caused by laboratory-confirmed carbapenem-resistant Enterobacterales or *Pseudomonas aeruginosa* (not *Acinetobacter baumannii*) including infections caused by strains producing certain carbapenemases that have tested susceptible to this antibiotic;
  - Ceftazidime+avibactam is not indicated for infections caused by strains producing metallo-beta-lactamases (sometimes ceftazidime+avibactam is combined with aztreonam for these strains but the evidence remains limited).
  - If ceftazidime+avibactam is used to treat intra-abdominal infections, it should be used as part of a combination treatment because it lacks activity against anaerobic organisms—therefore it is usually used in combination with metronidazole.
  - To preserve its effectiveness (i.e. to prevent the development of resistance), ceftazidime+avibactam should not be used to treat infections caused by isolates only producing extended-spectrum beta-lactamases or by ceftazidime-resistant bacteria when there are other options available.
II. Empiric treatment

Ceftazidime+avibactam could be considered for empiric use exceptionally in very selected cases of seriously ill patients with invasive infections (e.g., patients with sepsis / septic shock without microbiologic documentations) suspected to be caused by a multidrug-resistant pathogen (e.g. severe hospital-acquired infections or infections in heavily antibiotic experienced patients including carbapenems) such as in the following situations:

- Patients who have not responded to carbapenems if other causes of treatment failure have been excluded first and there is a strong suspicion that the infection is caused by carbapenem-resistant bacteria. Since ceftazidime+avibactam is not active against metallo-beta-lactamases conveying carbapenem resistance, it is important to know the most prevalent genotypic variants that are circulating for aerobic Gram-negative bacteria in the setting where the patient acquired the infection. 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 source control, sub-optimal dose of the antibiotic or impossibility of the antibiotic to reach an adequate concentration at the site of infection. This is always important to consider before changing or adding new antibiotics.

- Patients who have previously been treated for infections caused by carbapenem-resistant bacteria.

- Patients who are known to be colonized with carbapenem-resistant bacteria found to be susceptible to ceftazidime+avibactam.

To help prescribers identify clinical scenarios where empiric use of Reserve antibiotics could exceptionally be considered, suggestions are given in the relevant chapters of the Handbook for selected infections (only for infections where empiric use could potentially be adequate on a case-by-case basis).

New resistance to ceftazidime+avibactam in Enterobacterales and Pseudomonas aeruginosa

Most Klebsiella pneumoniae carbapenemase-producing Enterobacterales and Pseudomonas aeruginosa are still susceptible to ceftazidime+avibactam; the proportion of isolates resistant to ceftazidime+avibactam is low (higher for Pseudomonas aeruginosa) with variability across geographical regions (372, 373). Data on resistance to ceftazidime+avibactam are currently not reported by the Global Antimicrobial Resistance Surveillance System (GLASS). Resistance is often associated with previous exposure to ceftazidime+avibactam(374).
Duration

Treatment duration varies according to indication and should be as short as possible, usually between 7-14 days.
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-
producing strains is variable (Table 1). Fosfomycin’s activity against *Pseudomonas aeruginosa* is variable.

*Table 1* Fosfomycin expected activity against third-generation cephalosporin and carbapenem-resistant bacteria based on the type of beta-lactamase produced

<table>
<thead>
<tr>
<th>Type of beta-lactamase</th>
<th>ESBL&lt;sup&gt;a&lt;/sup&gt;</th>
<th>KPC&lt;sup&gt;b&lt;/sup&gt;</th>
<th>NDM, VIM, IMP&lt;sup&gt;b&lt;/sup&gt;</th>
<th>AmpC</th>
<th>OXA-48&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Expected activity against non-fermenters&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ambler class&lt;sup&gt;d&lt;/sup&gt;</td>
<td>A Serine-beta-lactamases</td>
<td>A Serine-beta-lactamases</td>
<td>B Metallo-beta-lactamases</td>
<td>C Cephalosporinase</td>
<td>D Oxacillinase</td>
<td>-</td>
</tr>
<tr>
<td>Fosfomycin (IV)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>?</td>
</tr>
</tbody>
</table>

**Expected activity**: + active; ? possibly active; - not or insufficiently active.

<sup>a</sup>ESBL (extended-spectrum beta-lactamases) are a group of different beta-lactamases.

<sup>b</sup>Carbapenemases.

<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.

<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.

**Clinical efficacy**

Fosfomycin (IV) could be considered for the treatment of certain severe infections when other antibiotics cannot be used or are not effective. It is usually used as part of combination treatments, mostly because of concerns about the emergence of resistance when used alone. The benefits of combination treatment compared with monotherapy in terms of better clinical efficacy are unclear as there is limited clinical evidence(376, 377).

Few clinical trials have assessed the efficacy and safety of fosfomycin (IV) in adults. Fosfomycin has been assessed for the treatment of complicated urinary tract infections and the results showed that fosfomycin was not inferior to piperacillin+tazobactam(378). Another non-inferiority trial which compared fosfomycin with meropenem and ceftriaxone has recently been completed and results are expected(379). Fosfomycin has also been evaluated for the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) bacteraemia and endocarditis in combination with daptomycin and this combination was more effective than daptomycin alone (380).

Other evidence in support of the use of fosfomycin for difficult-to-treat *Staphylococcus aureus* infections (including MRSA) exists but it is anecdotal and inconclusive. This evidence is mostly from observational and *in-vitro* studies, including results from a clinical trial comparing fosfomycin (in combination with imipenem) to vancomycin alone for the treatment of
complicated MRSA bacteraemia and endocarditis but this study failed to reach an adequate sample size (381).

In children, the evidence is even more limited. One pharmacokinetic and safety trial has recently been completed of fosfomycin as an empiric treatment in neonatal sepsis (382).

The use of fosfomycin for other indications (e.g. bone and joint infections, healthcare-associated pneumonia, meningitis and abdominal infections) relies on evidence from case reports or other observational and in vitro studies which is therefore less robust.

Toxicity

Fosfomycin is well tolerated. However, use of the IV formulation can be associated with sodium overload related to the sodium salt formulation (this could be of concern in patients with heart failure) and hypokalaemia (therefore potassium levels should be regularly monitored).

Dose

The optimal IV dose needs still to be clearly defined. Usually doses vary with the severity of the disease and the patient’s renal function. Dose adjustments are necessary in cases of renal impairment.

Please also refer to the chapter on dosing for more information.

Table 2 Fosfomycin (IV) suggested doses

<table>
<thead>
<tr>
<th>Dose in adults</th>
<th>Dose in children</th>
<th>Dose in neonates</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 g given every 8 hours</td>
<td>200-400 mg/kg/day divided every 6 to 8 hours</td>
<td>200mg/kg/day divided every 8 hours</td>
</tr>
<tr>
<td>(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)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

Indication for the use of intravenous fosfomycin as a Reserve antibiotic

I. Targeted treatment

Fosfomycin (usually as part of combination therapy to reduce the risk of the development of resistance) could be considered:

- As a last-resort option for the targeted treatment of severe infections caused by laboratory-confirmed carbapenem-resistant Enterobacterales or Pseudomonas aeruginosa (including strains producing carbapenemases) that have been shown to be susceptible to this antibiotic.
Caution is needed with infections caused by *Pseudomonas aeruginosa* because the activity of fosfomycin against this pathogen is variable.

- Fosfomycin could also be considered as a last-resort option for difficult-to-treat infections caused by *Staphylococcus aureus* (including MRSA) and *Enterococcus* spp. (including vancomycin-resistant strains). However, the current version of the EML/EMLc does not include this use.

### II. Empiric treatment

- Usually as part of combination therapy, fosfomycin could be considered for empiric use in selected cases of seriously ill patients with invasive infections (e.g. patients with sepsis / septic shock) suspected to be caused by a multidrug-resistant pathogen (e.g. severe hospital-acquired infections or infections in heavily antibiotic experienced patients including carbapenems) such as in the following situations:
  - Patients who have not responded to carbapenems if other causes of treatment failure have been excluded first and there is a strong suspicion that the infection is caused by a carbapenem-resistant Enterobacterales (fosfomycin does not reliably treat *Acinetobacter* spp. and its activity against *Pseudomonas auruginosa* is variable). 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 source control, sub-optimal dose of the antibiotic or impossibility of the antibiotic to reach an adequate concentration at the site of infection. This is always important to consider before changing or adding new antibiotics.
  - Patients who have previously been treated for infections caused by carbapenem-resistant Enterobacterales. In certain settings *Klebsiella pneumoniae* may be resistant to fosfomycin; therefore, local knowledge of susceptibility profiles for aerobic Gram-negative bacteria is crucial(383). Fosfomycin does not reliably treat *Acinetobacter* spp. and its activity against *Pseudomonas auruginosa* is variable.
  - Patients who are known to be colonized with carbapenem-resistant pathogens found to be susceptible to fosfomycin.

To help prescribers identify clinical scenarios where empiric use of Reserve antibiotics could exceptionally be considered, suggestions are given in the relevant chapters of the Handbook for selected infections (only for infections where empiric use could potentially be adequate on a case-by-case basis).

### New resistance to fosfomycin in Enterobacterales

Cross-resistance is uncommon because of the unique structure and mechanism of action of fosfomycin. Both chromosomal-mediated and plasmid-mediated (i.e. transmissible) resistance
can occur. Resistance can rapidly develop *in vitro*, but in clinical practice resistance is still uncommon, although it is increasing (384).

Data on resistance to fosfomycin are currently not reported by the Global Antimicrobial Resistance Surveillance System (GLASS).

**Duration**

Treatment duration varies according to indication and should be as short as possible, usually between 7-14 days.
Linezolid

https://list.essentialmeds.org/medicines/345

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

Linezolid is a synthetic antibiotic of the oxazolidinone class which has been in clinical use since the early 2000s for the treatment of infections caused by Gram-positive bacteria resistant to other antibiotics. Its current indications in the EML/EMLc (355, 364) include infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Staphylococcus aureus* (VRSA) and vancomycin-resistant *Enterococcus* spp. (VRE) and multi-drug resistant *Mycobacterium tuberculosis*.

Administration

Linezolid is currently available as an intravenous (IV) formulation (injection for IV administration: 2 mg/mL in 300 mL bag) and as an oral formulation (tablet: 400 mg; 600 mg). A neonatal or pediatric formulation is also available (powder for oral liquid: 100 mg/5 mL). Generic versions of linezolid are available.

Mechanism of action

Linezolid acts by binding to the 50S unit of the bacterial ribosome, inhibiting the synthesis of bacterial proteins.

Spectrum of activity

Linezolid is mainly active against aerobic Gram-positive bacteria. In particular it is active against most clinical isolates of vancomycin-resistant *Enterococcus*, MRSA and penicillin non-susceptible pneumococci. In addition, linezolid has some bactericidal activity against *Mycobacterium tuberculosis* including extensively drug-resistant strains and certain non-tuberculous mycobacteria.

Linezolid is not indicated for the treatment of Gram-negative infections. Even though linezolid has some *in vitro* activity against certain Gram-negative and anaerobic bacteria, clinical data are limited, and its use is not recommended for the treatment of these pathogens.
Clinical efficacy

Several clinical trials have assessed the efficacy and safety of linezolid compared to vancomycin for the treatment of MRSA infections in general (385) and for skin and soft tissue infections in particular (including those caused by MRSA) (386). Linezolid was associated with better short-term survival compared to daptomycin for the treatment of bloodstream infections caused by vancomycin-resistant Enterococcus spp. (387-389). However, linezolid’s overall superiority to daptomycin is less clear because a large cohort study showed greater treatment failure and short-term mortality with linezolid than daptomycin (390). As to health care-associated pneumonia, the results of a systematic review and meta-analysis did not show a clear benefit of linezolid for clinical cure or microbiological eradication when compared to vancomycin or teicoplanin, and linezolid was associated with more side-effects (391).

Linezolid can also be used as part of a longer regimen (longer than the standard TB treatment duration) for the treatment of patients with multidrug- and rifampicin-resistant tuberculosis (MDR/RR-TB) as indicated in WHO guidelines available at https://apps.who.int/iris/handle/10665/311389).

Toxicity

Linezolid is generally well tolerated; however, it can cause myelosuppression (mostly thrombocytopenia but also anaemia or leukopenia), which is usually reversible when linezolid is stopped. Therefore, a complete blood cell count should be done weekly, especially in high-risk patients (e.g., those with pre-existing myelosuppression, concomitant use of medicines that cause bone marrow suppression). As with any other medicine, interactions with other medicines should be checked before prescribing linezolid; this topic is, however, not addressed in the handbook. Severe optic neuropathy can occur rarely, particularly if linezolid is used for over 28 days. Patients should be advised to report all new visual symptoms. Peripheral neuropathy is also rarely associated with the (prolonged) use of linezolid. The risk of side-effects increases with prolonged use (usually > 4 weeks), which should be avoided unless there are no alternatives.

Dose

Linezolid does not require dose adjustments in case of renal impairment.

Please also refer to the chapter on dosing for more information.

Table 1: Linezolid suggested doses

<table>
<thead>
<tr>
<th>Dose in adults</th>
<th>Dose in children</th>
<th>Dose in neonates</th>
</tr>
</thead>
<tbody>
<tr>
<td>400 to 600 mg given every 12 hours</td>
<td>10 mg/kg given every 8 hours</td>
<td>10 mg/kg given every 12 hours (1st week of life) or every 8 hours (&gt;1st week of life)</td>
</tr>
</tbody>
</table>

Notes: All dosages are for normal renal and hepatic function.
**Indication for the use of Linezolid as a Reserve antibiotic**

Linezolid can be considered when:

- Oral treatment for MRSA is necessary and other less expensive oral alternatives to linezolid are not indicated or likely to be ineffective due to resistance or toxicity concerns.
  - Oral treatment may be necessary when maintaining access to parenteral treatment is difficult or for switching from IV to oral treatment when the patient could be discharged from hospital before the planned treatment course is completed.
  - In case of documented hypersensitivity to vancomycin.

- In case of severe renal impairment.
- In case of infections caused by vancomycin-resistant (or –intermediate) *Enterococcus* spp. or *Staphylococcus aureus*.
- In very selected cases of seriously ill patients with invasive infections that are known to be colonized with vancomycin-resistant *Enterococcus* spp. or *Staphylococcus aureus*.
- Linezolid can also be considered as a second-line option for the treatment of mycobacterial infections, including extensively drug-resistant *Mycobacterium tuberculosis* and is specifically mentioned in WHO guidelines (392).

When using linezolid, the risk of side-effects (mostly thrombocytopenia), especially with prolonged use, should always be taken into account. Because of this and because of the risk of emergence of resistance, linezolid use as Reserve antibiotic should be limited to well-defined patient populations and be as short as possible.

**New resistance to linezolid in Gram-positive bacteria**

Resistance to linezolid in usually susceptible Gram-positive bacteria most commonly arises through mutations in the bacterial 23S ribosomal RNA but it can also be transmitted through plasmids. Resistance can develop in the absence of prior treatment with linezolid and also after short periods of exposure to the antibiotic and should be carefully monitored.

Resistant isolates of enterococci, staphylococci and streptococci have been reported worldwide but their proportion remains low and in general, most Gram-positive bacteria are still susceptible to linezolid (393). Selection for resistance could be favoured by suboptimal dosing of the antibiotic especially in severely ill patients where volumes of distribution may be higher leading to low plasma levels (394).

Data on resistance to linezolid are currently not reported by the Global Antimicrobial Resistance Surveillance System (GLASS).
Duration

Treatment duration varies according to indication and should be as short as possible. Prolonged treatment (> 4 weeks) should be avoided whenever possible because of increased risk of toxicity (see above).
Meropenem+vaborbactam

https://list.essentialmeds.org/medicines/396

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

Meropenem+vaborbactam is a combination of a carbapenem (meropenem) and a new non-beta-lactam beta-lactamase inhibitor (vaborbactam). Its current indications in the EML/EMLc (355, 364) include infections caused by certain strains of carbapenem-resistant Enterobacterales, Acinetobacter baumannii and Pseudomonas aeruginosa (but its activity varies) depending on the type of carbapenemase produced and the resistance mechanism.

The addition of vaborbactam has no additional advantage over meropenem alone for most strains of Acinetobacter baumannii and Pseudomonas aeruginosa.

Administration

Meropenem+vaborbactam is currently only available as intravenous formulation (powder for injection: 1 g + 1 g in vial) and it should be infused over 3 hours.

Mechanism of action

Meropenem+vaborbactam acts by inhibiting bacterial enzymes responsible for the cell wall synthesis, primarily penicillin-binding proteins. Vaborbactam targets the site of certain serine beta-lactamases (Ambler class B) and inactivates them, thus protecting meropenem from degradation.

Spectrum of activity

Meropenem+vaborbactam has a broad-spectrum of action including Gram-positive aerobic bacteria, Gram-negative aerobic bacteria and anaerobic bacteria. In particular, vaborbactam inhibits the activity of extended-spectrum beta-lactamases, AmpC beta-lactamases, Klebsiella pneumoniae carbapenemases, and thus preserves the activity of meropenem against many multidrug-resistant Gram-negative bacteria. However, vaborbactam does not inhibit the activity of metallo-beta-lactamases and OXA-48 beta-lactamases and therefore meropenem is not active against strains expressing these beta-lactamases.
Table 1 Meropenem+vaborbactam expected activity against third-generation cephalosporin and carbapenem-resistant bacteria based on the type of beta-lactamase produced

<table>
<thead>
<tr>
<th>Type of beta-lactamase</th>
<th>ESBL&lt;sup&gt;a&lt;/sup&gt;</th>
<th>KPC&lt;sup&gt;b&lt;/sup&gt;</th>
<th>NDM, VIM, IMP&lt;sup&gt;b&lt;/sup&gt;</th>
<th>AmpC</th>
<th>OXA-48&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Expected activity against non-fermenters&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ambler class&lt;sup&gt;d&lt;/sup&gt;</td>
<td>A Serine-beta-lactamase</td>
<td>A Serine-beta-lactamase</td>
<td>B Metallo-beta-lactamases</td>
<td>C Cephalosporinase</td>
<td>D Oxacillinase</td>
<td>-</td>
</tr>
<tr>
<td>Meropenem–vaborbactam</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Expected activity: + active; ? possibly active; - not or insufficiently active.

<sup>a</sup>ESBL (extended-spectrum beta-lactamases) are a group of different beta-lactamases.

<sup>b</sup>Carbapenemases.

<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.

<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.

Clinical efficacy

The TANGO I trial demonstrated that the efficacy and safety of meropenem+vaborbactam in adults was non-inferior to piperacillin-tazobactam for the treatment of complicated urinary tract infections (395). The TANGO II trial (77 patients) demonstrated improved clinical cure and decreased short-term mortality and nephrotoxicity than the best-available therapy for the treatment of infections caused by proven or suspected carbapenem-resistant Enterobacterales (396).

Toxicity

Meropenem+vaborbactam is well tolerated and has side-effects similar to those previously reported for meropenem alone. However, meropenem+vaborbactam is less damaging to the kidneys than other antibiotics used to treat infections caused by carbapenem-resistant Enterobacterales.

Dose

Dose adjustments are required in cases of renal impairment. In children, the optimal dose is unknown because of limited paediatric-specific pharmacokinetics and pharmacodynamic data(397). Please also refer to the chapter on dosing for more information.
### Table 2 Meropenem+vaborbactam suggested doses

<table>
<thead>
<tr>
<th>Dose in adults</th>
<th>Dose in children</th>
<th>Dose in neonates</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 g (2 g + 2 g vaborbactam) given every 8 hours</td>
<td>Currently not licenced for children</td>
<td>Currently not licenced for neonates</td>
</tr>
</tbody>
</table>

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

### Indication for the use of meropenem+vaborbactam as a Reserve antibiotic

#### I. Targeted treatment

Meropenem+vaborbactam could be considered:

- As a last-resort option for the targeted treatment of severe infections caused by laboratory-confirmed *Klebsiella pneumoniae* carbapenemase-producing Enterobacterales (not indicated in cases of metallo-beta-lactamases and OXA-48 production).
- In the treatment of infections caused by bacteria resistant to ceftazidime+avibactam
  - Based on the results of available trials, meropenem+vaborbactam could be considered in cases of severe complicated urinary tract and intra-abdominal infections and for hospital-acquired pneumonia when other antibiotics cannot be used or are not effective.

#### II. Empiric treatment

- Meropenem+vaborbactam could be considered for empiric use exceptionally in very selected cases of seriously ill patients with invasive infections (e.g. patients with sepsis / septic shock) suspected to be caused by a multidrug-resistant pathogen (e.g. severe hospital-acquired infections or infections in heavily antibiotic experienced patients including carbapenems) such as in the following situations:
  - Patients who have not responded to carbapenems if other causes of treatment failure have been excluded first and there is a strong suspicion that the infection is caused by a carbapenem-resistant pathogen. 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 source control, sub-optimal dose of the antibiotic or impossibility of the antibiotic to reach an adequate concentration at the site of infection. This is always important to consider before changing or adding new antibiotics.
  - Patients who have previously been treated for infections caused by carbapenem-resistant pathogens.
  - Patients who are known to be colonized with carbapenem-resistant pathogens found to be susceptible to meropenem+vaborbactam.
To help prescribers identify these specific situations where empiric use of meropenem+vaborbactam could exceptionally be considered, suggestions are given in the relevant chapters of the Handbook for selected infections (only for infections where empiric use could be considered on a case-by-case basis).

New resistance to meropenem+vaborbactam in Enterobacterales

Most *Klebsiella pneumoniae* carbapenemase-producing Enterobacterales are still susceptible to meropenem+vaborbactam with very few reports of resistant strains\(^\text{398}\). Data on resistance to meropenem+vaborbactam are currently not reported by the Global Antimicrobial Resistance Surveillance System (GLASS).

Duration

Treatment duration varies according to indication and should be as short as possible, usually between 7-14 days.
**Plazomicin**

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

Plazomicin is a new semisynthetic aminoglycoside derived from sisomicin, an older aminoglycoside(399). Its current indications in the EML/EMLc (355, 364) include infections caused by carbapenem-resistant Enterobacterales.

**Administration**

Plazomicin is currently only available as intravenous or intramuscular formulations (Injection: 500 mg/10 mL).

**Mechanism of action**

Plazomicin acts by binding to the 30S unit of the bacterial ribosome thus inhibiting the start of the synthesis of bacterial proteins.

**Spectrum of activity**

Plazomicin is mainly active against Gram-negative aerobic bacteria including extended-spectrum beta-lactamase-producing Enterobacterales, carbapenem-resistant (including carbapenemase-producing) Enterobacterales (Table 1) and bacteria producing aminoglycoside-modifying enzymes (AME).

### Table 1: Plazomicin expected activity against third-generation cephalosporin and carbapenem-resistant bacteria based on the type of beta-lactamase produced

| Type of beta-lactamase | ESBL &nbsp;&nbsp;&nbsp;&nbsp;&nbsp;<sup>a</sup> | KPC &nbsp;&nbsp;&nbsp;&nbsp;&nbsp;<sup>b</sup> | NDM, VIM, IMP &nbsp;&nbsp;&nbsp;&nbsp;&nbsp;<sup>b</sup> | AmpC &nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbsp;&nbs

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<sup>a</sup> ESBL: Extended-spectrum beta-lactamase

<sup>b</sup> KPC: Klebsiella pneumoniae carbapenemase

<sup>c</sup> NDM, VIM, IMP: New Delhi metallo-beta-lactamase, Verona integron-encoded metallo-beta-lactamase, Imipenem-hydrolyzing metallo-beta-lactamase

<sup>d</sup> AmpC: Ampicillin-resistant cephalosporinase

<sup>e</sup> OXA-48: Oxacillinase

<sup>f</sup> Expected activity against non-fermenters: -
Serine-beta-lactamases | Serine-beta-lactamase | Metallo-beta-lactamases
---|---|---
Plazomicin | + | + | ?

**Expected activity:** + active; ? possibly active; - not or insufficiently active.

**ESBL (extended-spectrum beta-lactamases)** are a group of different beta-lactamases.

**Carbapenemases.**

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. For plazomicin some *in vitro* studies have shown activity against *Pseudomonas aeruginosa* similar to amikacin(400).

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.

Susceptibility to plazomicin among strains producing metallo-beta-lactamases can be >50%.

### Clinical efficacy

Plazomicin can be considered as salvage therapy for otherwise untreatable carbapenem-resistant Gram-negative infections.

Efficacy has been demonstrated only for the treatment of complicated urinary tract infections in adults which showed non-inferiority to meropenem(401).

Very limited evidence exists for the treatment of other types of infections and for its use in children. Plazomicin has also been compared with colistin as part of combination therapy for the treatment of severe infections caused by carbapenem-resistant Enterobacterales (e.g. bacteraemia and health care-associated pneumonia)(402). The results of the study indicated that plazomicin reduced short-term mortality and disease-related complications, but the trial was stopped early because of major difficulties with enrolling patients. The study therefore provides only descriptive statistics and findings and as such its results are inconclusive.

### Toxicity

Plazomicin can cause damage to the kidneys and ears as with other aminoglycosides. The risk of nephrotoxicity is higher in older patients (>65 years) and in patients with pre-existing renal impairment; therefore, creatinine levels should be monitored regularly.

### Dose

Weight-based once-daily dosing is used. No paediatric dosing is currently available.

Please also refer to the chapter on dosing for more information.

**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 |

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

**Indication for the use of plazomicin as a Reserve antibiotic**

**I. Targeted treatment**

Plazomicin could be considered:
- As a last-resort option for the targeted treatment of severe infections (mostly urinary tract infections) caused by laboratory-confirmed carbapenem-resistant Enterobacterales including infections caused by strains producing carbapenemases that have been shown to be susceptible to this antibiotic.
  - An important advantage of plazomicin is that it only needs to be given once a day, while other Reserve antibiotics that have a comparable spectrum of activity require multiple daily doses.
  - To preserve its effectiveness (i.e. to prevent the development of resistance), it should not be used to treat Enterobacterales isolates that only produce extended-spectrum beta-lactamases when other choices are available.
- For infections caused by Gram-negative bacteria resistant to other aminoglycosides (e.g. gentamicin or amikacin).

**II. Empiric treatment**

- For empiric use exceptionally in very selected cases of seriously ill patients with invasive infections (e.g. patients with sepsis/septic shock caused by infections of the urinary tract if used as monotherapy while in other situations plazomicin like other aminoglycosides would most likely be used in combination with other antibiotics) suspected to be caused by a multidrug-resistant pathogen (e.g. severe hospital-acquired infections or infections in heavily antibiotic experienced patients including carbapenems) such as in the following situations:
  - Patients who have not responded to carbapenems if other causes of treatment failure have been excluded first and there is a strong suspicion that the infection is caused by carbapenem-resistant bacteria. 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. abscess), inadequate source control, sub-optimal dosing of the antibiotic or impossibility of the antibiotic to reach an adequate concentration at the site of infection. This is always important to consider before changing or adding new antibiotics.
  - Patients who have previously been treated for infections caused by carbapenem-resistant bacteria.
Patients who are known to be colonized with carbapenem-resistant bacteria found to be susceptible to plazomicin.

To help prescribers identify clinical scenarios where empiric use of Reserve antibiotics could exceptionally be considered, suggestions are given in the relevant chapters of the Handbook for selected infections (only for infections where empiric use could potentially be adequate on a case-by-case basis).

**New resistance to plazomicin in Enterobacterales**

The main mechanisms of resistance overlap with some of those for other aminoglycosides. In particular ribosomal modifications of the target site within the ribosome can prevent plazomicin from binding to its target, and alterations to uptake and efflux pumps can decrease the antibiotic concentration at the site of action. However, unlike other aminoglycosides, plazomicin maintains activity against most aminoglycoside-modifying enzymes – enzymes that can reduce the affinity of the antibiotic for its ribosomal target through a mechanism that is different from ribosomal modifications. Plasmid-mediated resistance (i.e. transmissible resistance) has also been described.

Data on resistance to plazomicin are currently not reported by the Global Antimicrobial Resistance Surveillance System (GLASS).

**Duration**

Treatment duration varies according to indication and should be as short as possible.
Polymyxin B and colistin (polymyxin E)

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).

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
example not being available in many countries. The oral non-absorbable formulation of colistin (colistin sulfate) is not currently included in the EML/EMLc (355, 364) and therefore is not covered in this chapter.

**Mechanism of action**

Polymyxin B and colistin act by disrupting the bacterial cell membrane through interaction with lipopolysaccharide (LPS) present in the membranes of Gram-negative bacteria thus leading to cell lysis however the exact mechanism is unknown.

**Spectrum of activity**

Polymyxin B and colistin have the same antibacterial spectrum and both are active only against aerobic Gram-negative bacteria with no activity against anaerobes, Gram-positive bacteria and Gram-negative cocci (e.g. *Neisseria* spp.). Polymyxins are active against many clinical isolates of carbapenem-resistant Enterobacterales, *Acinetobacter* spp. and *Pseudomonas aeruginosa* clinical isolates (including many of the isolates producing carbapenemases –Table 1).

*Table 1 Polymyxins expected activity against third-generation cephalosporin and carbapenem-resistant bacteria based on the type of beta-lactamase produced*

<table>
<thead>
<tr>
<th>Type of beta-lactamase</th>
<th>ESBL(^a)</th>
<th>KPC(^b)</th>
<th>NDM, VIM, IMP(^b)</th>
<th>AmpC</th>
<th>OXA-48(^b)</th>
<th>Expected activity against non-fermenters(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ambler class(^d)</td>
<td></td>
<td>A</td>
<td>B</td>
<td>C</td>
<td>D</td>
<td></td>
</tr>
<tr>
<td></td>
<td>A Serine-beta-lactamases</td>
<td>A Serine-beta-lactamase</td>
<td>B Metallo-beta-lactamases</td>
<td>C Cephalosporinase</td>
<td>D Oxacillinase</td>
<td>-</td>
</tr>
<tr>
<td>Polymyxin B and colistin</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

**Expected activity:** + active; ? possibly active; - not or insufficiently active.

\(^a\)ESBL (extended-spectrum beta-lactamases) are a group of different beta-lactamases.

\(^b\)Carbapenemases.

\(^c\)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.

\(^d\)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.

**Clinical efficacy**

Polymyxin B and colistin can be considered as salvage therapy for otherwise untreatable infections caused by carbapenem-resistant Gram-negative bacteria.
For severe infections, they are usually given as part of combination therapy often with high-doses of carbapenems (but only if the minimum inhibitory concentration of carbapenems is ≤ 8-16 mg/L) or in combination with other antibiotics depending on the type of infection and in vitro susceptibility (404).

However, the only currently available randomized clinical trial did not show that combination therapy was superior to colistin monotherapy for short-term clinical success – at least for infections caused by extensively drug-resistant Acinetobacter spp.; it is unclear whether this also applies to carbapenemase-producing Enterobacterales (405). Evidence from observational studies is available but should be interpreted with caution due to the inherent methodological limitations (406, 407).

Polymyxin B and colistin were approved for use decades ago and were therefore not subjected to the same development process that would be required for the approval of a new antibiotic today. This point should be kept in mind when interpreting data about their efficacy and safety (e.g., current products of polymyxins may be less nephrotoxic than those initially used (408)). There are recently licensed Reserve group beta-lactam / beta-lactamase inhibitor combinations (ceftazidime/avibactam, meropenem/vaborbactam) or siderophore-antibiotics (ceftiderocol), available that some experts consider preferable over polymyxins because of their better safety profile and potentially better efficacy, although the evidence for this is weak and access and affordability of these new antibiotics is a major issue in many LMIC settings.

### Toxicity

The use of polymyxin B and colistin can cause kidney damage (colistin being more likely to cause damage than polymyxin B) and, more rarely, neurotoxicity (e.g., paresthesia). The side effects are reversible in most cases and are associated with the cumulative dose and duration of therapy and use of concomitant medicines with similar toxicities.

### Dose

Great care must be taken to avoid dosing errors with polymyxin B and colistin. Errors can arise because doses can be given in different units on labels (409-411).

Polymyxin B doses can be given in international units (IU) or milligrams but the colistin dose can be given as:

- IU of colistimethate
- mg of colistimethate
- mg of colistin base activity.

For example, a dose of 1 million IU of colistin corresponds to 80 mg of colistimethate and to 34 mg of colistin base activity.

When using polymyxins, it is crucial to start therapy with a loading dose followed by maintenance dose after 12-24 hours. The reason is to achieve more rapidly plasma concentrations that may
be effective. In addition, for colistin (but not for polymyxin B), dose adjustments are necessary in cases of renal impairment (412).

Few data are available for dosing in children. Current evidence suggests that doses approved by regulatory agencies may be suboptimal for many children due to interpatient variability (412). Please also refer to the chapter on dosing for more information.

### Table 2 Polymyxin B suggested doses

<table>
<thead>
<tr>
<th></th>
<th>Dose in adults</th>
<th>Dose in children</th>
<th>Dose in neonates</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Loading dose</strong></td>
<td>2.5 mg/kg</td>
<td>2.5 mg/kg</td>
<td>2.5 mg/kg</td>
</tr>
<tr>
<td></td>
<td>(25.000 IU/kg)</td>
<td>(25.000 IU/kg)</td>
<td>(25.000 IU/kg)</td>
</tr>
<tr>
<td><strong>Maintenance dose</strong></td>
<td>1.5 mg/kg</td>
<td>1.5 mg/kg</td>
<td>1.5 mg/kg</td>
</tr>
<tr>
<td>(start 12 hours after the loading dose)</td>
<td>(15.000 IU/kg)</td>
<td>(15.000 IU/kg)</td>
<td>(15.000-45.000 IU/kg/day)</td>
</tr>
<tr>
<td></td>
<td>given every 12 hours</td>
<td>given every 12 hours</td>
<td>divided every 12 hours</td>
</tr>
<tr>
<td></td>
<td>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)</td>
<td>In children &lt; 2 years of age: 1.5-4.5 mg (15.000 - 45.000 IU)/kg/day divided every 12 hours</td>
<td></td>
</tr>
</tbody>
</table>

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

### Table 3 Colistin suggested doses

**Doses expressed in mg of colistin base activity (CBA) and in International Units (IU) of colistimethate**

<table>
<thead>
<tr>
<th></th>
<th>Dose in adults</th>
<th>Dose in children</th>
<th>Dose in neonates</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Loading dose</strong></td>
<td>300 mg of CBA / 9 Million IU of colistimethate</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Maintenance dose</strong></td>
<td>150 mg given every 12 hours / 4.5 Million IU given every 12 hours</td>
<td>2.5-5 mg (75 000 – 150 000 IU)/kg/day divided in 2 to 4 doses</td>
<td></td>
</tr>
<tr>
<td>(start 12 hours after the loading dose)</td>
<td>Maximal daily dose should not exceed 300 mg of CBA or 9 (to 12) million IU</td>
<td>2.5-5 mg (75 000 – 150 000 IU)/kg/day divided in 2 to 4 doses</td>
<td></td>
</tr>
</tbody>
</table>

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

*34 mg of colistin base activity correspond to 1 million IU of colistimethate and to 80 mg of colistimethate.
Indication for the use of polymyxins as a Reserve antibiotic

I. Targeted treatment

Polymyxin B or colistin could be considered, usually as part of a combination therapy:

- As a last-resort option for the targeted treatment of severe infections caused by laboratory-confirmed carbapenem-resistant Gram-negative bacteria including infections caused by carbapenemase-producing strains that have been found to be susceptible to these antibiotics
  - If available, polymyxin B is usually preferred to colistin because it has better pharmacokinetic characteristics and less potential to cause kidney damage.
  - The only situation where the use of colistin is preferred is for the treatment of urinary tract infections because colistin reaches higher concentrations in urine compared to polymyxin B (the prodrug colistimethate is excreted primarily by the kidneys while polymyxin B is mainly eliminated through nonrenal pathways however the fraction of colistimethate being converted to colistin in the urine remains unclear (413)).

II. Empiric treatment

- For empiric use exceptionally in selected cases of seriously ill patients with invasive infections (e.g., patients with sepsis/septic shock) suspected to be caused by a multidrug-resistant pathogen (e.g., severe hospital-acquired infections or infections in heavily antibiotic experienced patients including carbapenems) such as in the following situations:
  - Patients who have not responded to carbapenems if other causes of treatment failure have been excluded first and there is a strong suspicion that the infection is caused by a carbapenem-resistant pathogen. 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 source control, sub-optimal dose of the antibiotic or impossibility of the antibiotic to reach an adequate concentration at the site of infection. This is always important to consider before changing or adding new antibiotics.
  - Patients who have previously been treated for infections caused by carbapenem-resistant pathogens susceptible to polymyxins.
  - Patients who are known to be colonized with carbapenem-resistant pathogens found to be susceptible to polymyxins.

To help prescribers identify clinical scenarios where empiric use of Reserve antibiotics could exceptionally be considered, suggestions are given in the relevant chapters of the Handbook for
selected infections (only for infections where empiric use could potentially be adequate on a case-by-case basis).

**New resistance to polymyxins in Enterobacterales, Pseudomonas and Acinetobacter**

Some technical challenges exist to identify resistance to polymyxin B and colistin (e.g. polymyxins diffuse poorly in diffusion-based assays such as disk-diffusion tests and broth microdilution, which is the recommended method, is impractical and rarely used in most laboratories)(414). Resistance can be related to chromosomal mutations that lead to changes in the bacterial membrane that impair the ability of polymyxin B and colistin to bind to their target. Plasmid-mediated resistance (i.e. transmissible resistance) due to mobilized colistin resistance (*mcr*) genes is also being increasingly described (415, 416).

Unfortunately, data on resistance to colistin and polymyxin B are currently not reported by the Global Antimicrobial Resistance Surveillance System (GLASS).

**Duration**

Treatment duration varies according to indication and should be as short as possible, usually between 7-14 days.
# FORMULARY

## ADULTS

All dosages are for normal renal and hepatic function.

<table>
<thead>
<tr>
<th>Antibiotic (alphabetic order)</th>
<th>Dose</th>
<th>Indication for the use of the antibiotic in the Handbook</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>IV: 15 mg/kg/dose given once daily</td>
<td>Febrile neutropenia (high risk) Sepsis (unknown origin) Upper UTI (severe)</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>Oral: <strong>Lower dose</strong>: 500 mg given every 8 hours <strong>Higher dose</strong>: 1 gram given every 8 hours</td>
<td><strong>Lower dose</strong>: Pharyngitis Acute otitis media COPD exacerbations (mild) Dental infections <strong>Higher dose</strong>: Acute sinusitis CAP (mild)</td>
</tr>
<tr>
<td>Amoxicillin+clavulanic acid</td>
<td>Oral: <strong>Lower dose</strong>: 500mg + 125 mg given every 8 hours <strong>Higher dose</strong>: 875mg + 125 mg given every 8 hours</td>
<td><strong>Lower dose (oral)</strong>: Acute otitis media Acute sinusitis COPD exacerbations (severe) UTI (lower) SSTI (mild) Febrile neutropenia (low risk) <strong>Higher dose (oral)</strong>: CAP (mild) IAI (mild) <strong>Lower dose (IV)</strong> Bone and joint infections CAP (severe)) HAP Periorbital cellulitis Pyomyositis <strong>Higher dose (IV)</strong> Surgical prophylaxis</td>
</tr>
<tr>
<td>Ampicillin/Ampicillin</td>
<td>IV: 2 grams given every 4 hours</td>
<td>Meningitis</td>
</tr>
</tbody>
</table>
### Azithromycin
- **Oral:**
  - **Lower dose:** 500 mg given once daily
  - **Higher dose:** 1 gram (single dose)
- **Lower dose**
  - Enteric fever (mild)
  - Infectious acute diarrhoea
- **Single dose**
  - Chlamydia infection
  - Cholera
  - Gonococcal infection
  - Trachoma

### Benzylpenicillin
(Only for IV use)
- **IV:** 4 million international units (2.4 g) given every 4 hours
  - Meningitis
  - Neurosyphilis
- **Synonyms are aqueous benzylpenicillin, benzylpenicillin potassium, benzylpenicillin sodium, crystalline penicillin, penicillin G potassium, and penicillin G sodium**

### Benzathine benzylpenicillin
(Only for IM use)
- **IM:** 2.4 million international units (1.8 g)
  - Syphilis
  - (the number of doses depends on the stage of the infection)

### Procaine benzylpenicillin
(Only for IM use)
- **IM:** 1.2 million international units (1.2 g) given once daily
  - Syphilis
  - Neurosyphilis

### Cefalexin
- **Oral:** 500 mg given every 8 hours
  - COPD exacerbations (mild)
  - Periorbital cellulitis
  - Pharyngitis
  - Pyomyositis
  - SSTI (mild)

### Cefazolin
- **IV:** 2 grams given every 8 hours or single dose
  - Bone and joint infections
  - Surgical prophylaxis (single dose)

### Cefiderocol
- **IV:** 2 grams given every 8 hours

### Cefixime
- **Oral:** 400 mg given once daily
  - Infectious acute diarrhoea
  - Gonococcal infection (single dose)

### Cefotaxime
- **IV:**
  - **Lower dose:** 1 g given every 8 hours
  - **Higher dose:** 2 g given every 8 hours
  - **Highest dose:** 2g given every 6 hours
  - **Lower dose (3 g/day):**
    - Upper UTI (severe)
  - **Higher dose (6 g/day):**
    - Bone and joint infections
    - CAP (severe)
    - HAP
    - IAI (mild and severe)
    - Bone and joint infections
    - Sepsis (unknown origin)
  - **Highest dose (8 g/day):**
    - Meningitis

### Ceftazidime+avibactam
- **IV:** 2 grams ceftazidime + 500 mg avibactam given every 8 hours
<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>IV / IM:</th>
<th>Single dose:</th>
<th>Lower dose (1 g/day):</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ceftriaxone</strong></td>
<td>Single dose: 250 mg</td>
<td>Gonococcal infection</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lower dose: 1 gram given once daily</td>
<td></td>
<td>Infectious acute diarrhoea (severe)</td>
</tr>
<tr>
<td></td>
<td>Higher dose: 2 grams given once daily</td>
<td></td>
<td>Upper UTI (severe)</td>
</tr>
<tr>
<td></td>
<td>Highest dose: 2 grams given every 12 hours</td>
<td></td>
<td>Bone and joint infections</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High dose (2g/day):</td>
<td>CAP (severe)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Endophthalmitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Enteric fever (severe)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HAP</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>IA (mild and severe)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Necrotizing fasciitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sepsis (unknown origin)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Highest dose (4 g/day):</td>
<td>Meningitis</td>
</tr>
<tr>
<td><strong>Cefuroxime</strong></td>
<td>IV: 1.5 grams (single dose)</td>
<td>Surgical prophylaxis</td>
<td></td>
</tr>
<tr>
<td><strong>Ciprofloxacin</strong></td>
<td>Oral: 500 mg given every 12 hours</td>
<td>Upper UTI (mild)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 gram (single dose)</td>
<td>Infectious acute diarrhoea</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>IA (mild)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Enteric fever</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Febrile neutropenia (low risk)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cholera (single dose)</td>
<td></td>
</tr>
<tr>
<td><strong>Chloramphenicol</strong></td>
<td>IV: 1 gram given every 6 hours</td>
<td>Meningitis</td>
<td></td>
</tr>
<tr>
<td><strong>Clarithromycin</strong></td>
<td>Oral: 500 mg given every 12 hours</td>
<td>Pharyngitis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IV: 400 mg given every 12 hours</td>
<td>CAP (severe)</td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Clarithromycin has excellent oral bioavailability and the intravenous route should be reserved for patients with impaired gastrointestinal function.</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Clindamycin</strong></td>
<td>IV/oral: 600 mg given every 8 hours</td>
<td>Lower dose: Bone and joint infections</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Higher dose</strong>: 900 mg given every 8 hours</td>
<td>Higher dose: Necrotizing fasciitis</td>
<td></td>
</tr>
<tr>
<td><strong>Cloxacillin or Flucloxacillin</strong></td>
<td>Oral/IV: 500 mg given every 8 hours</td>
<td>Lower dose: SSTI (mild)</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Higher dose</strong>: 2 grams given every 6 hours</td>
<td>Higher dose: Bone and joint infections</td>
<td></td>
</tr>
<tr>
<td><strong>Doxycycline</strong></td>
<td>Oral:</td>
<td>CAP (mild)</td>
<td></td>
</tr>
<tr>
<td>Antibiotic</td>
<td>Dosage</td>
<td>Indications</td>
<td></td>
</tr>
<tr>
<td>------------</td>
<td>--------</td>
<td>-------------</td>
<td></td>
</tr>
<tr>
<td><strong>Gentamicin</strong></td>
<td>IV: 5 mg/kg given once daily</td>
<td>Sepsis (unknown origin) Surgical prophylaxis Upper UTI (severe)</td>
<td></td>
</tr>
<tr>
<td><strong>Fosfomycin (IV)</strong></td>
<td>IV: 6 grams given every 8 hours (range 12-24 grams per day depending on the indication)</td>
<td>Empiric use should be exceptional (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)</td>
<td></td>
</tr>
<tr>
<td><strong>Linezolid</strong></td>
<td>IV/Oral: 400 to 600 mg given every 12 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Meropenem</strong></td>
<td>IV: <strong>Lower dose</strong>: 1 gram given every 8 hours <strong>Higher dose</strong>: 2 grams given every 8 hours</td>
<td><strong>Lower dose</strong>: Febrile neutropenia (high risk) <strong>Higher dose</strong>: IAI (severe) Febrile neutropenia (high-risk)</td>
<td></td>
</tr>
<tr>
<td><strong>Meropenem+vaborbactam</strong></td>
<td>IV: 2 grams of meropenem + 2 grams of vaborbactam given every 8 hours</td>
<td>Empiric use should be exceptional (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)</td>
<td></td>
</tr>
<tr>
<td><strong>Metronidazole</strong></td>
<td>Oral/IV: <strong>Single dose</strong>: 500 mg, 2 grams <strong>Lowest dose</strong>: 500 mg given every 12 hours <strong>Lower dose</strong>: 500 mg given every 8 hours <strong>Higher dose</strong>: 750 mg given every 8 hours</td>
<td>Single dose: Surgical prophylaxis (500 mg) Trichomoniasis (2 gr) <strong>Lowest dose</strong>: Trichomoniasis <strong>Lower dose</strong>: C. difficile infection IAI (mild and severe) Necrotizing fasciitis <strong>Higher dose</strong>: Amoebic abscess</td>
<td></td>
</tr>
<tr>
<td><strong>Nitrofurantoin</strong></td>
<td>Oral: 100 mg given every 12 hours (modified release) 50 mg given every 6 hours (immediate release)</td>
<td>UTI (lower)</td>
<td></td>
</tr>
<tr>
<td><strong>Phenoxyethylpenicillin</strong></td>
<td>Oral: 500 mg (800,000 international units*) given every 6 hours 100 mg given every 12 hours 300 mg (single dose)</td>
<td><strong>Single dose</strong>: Pharyngitis CAP (mild) Dental infections</td>
<td></td>
</tr>
<tr>
<td><strong>Piperacillin+tazobactam</strong></td>
<td>IV: 4 grams + 500 mg q6h</td>
<td>HAP IAI (severe) Necrotizing fasciitis Febrile neutropenia (high-risk)</td>
<td></td>
</tr>
<tr>
<td>---------------------------</td>
<td>--------------------------</td>
<td>---------------------------------------------------------------</td>
<td></td>
</tr>
</tbody>
</table>

| **Plazomicin** | 15 mg/kg/dose give once daily | **Empiric use should be exceptional** (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:** Loading dose: 2.5 mg/kg (25,000 international units/kg) Maintenance dose: 1.5 mg/kg (15,000 international units/kg) given every 12 hours | **Empiric use should be exceptional** (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)** | **Loading dose:** 300 mg of colistin base activity / 9 million international units (IU) of colistimethate **Maintenance dose:** 150 mg / 4.5 million IU given every 12 hours | **Empiric use should be exceptional** (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: C. difficile infection (higher dose for severe cases) |

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

1. All dosages are for normal renal and hepatic function.

<table>
<thead>
<tr>
<th>Antibiotic (alphabetic order)</th>
<th>Dose</th>
<th>Indication for the use of the antibiotic in the Handbook</th>
</tr>
</thead>
</table>
| Amikacin                      | IV: 15 mg/kg/dose given once daily | Febrile neutropenia (high risk)  
Sepsis (unknown origin)  
Upper UTI (severe) |
| Amoxicillin                   | Oral: 40-50 mg/kg/dose given every 12 hours  
**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  
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 | Pharyngitis  
Acute otitis media  
Dental infections  
Acute sinusitis  
CAP (mild)  
Sepsis (referral to hospital not possible) |
| Amoxicillin+clavulanic acid | Oral/IV:  
40-50 mg/kg/dose (amoxicillin component) given every 12 hours  
OR  
30 mg/kg/dose given every 8 hours  
**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  
*Oral liquid must be refrigerated after reconstitution.* | 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 |
<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Route</th>
<th>Dosage Details</th>
<th>Conditions</th>
</tr>
</thead>
</table>
| **Ampicillin/Amoxicillin** | 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 | Meningitis  
Sepsis  
IAI mild and severe  
CAP          |
|                      | Oral:                  |                                                                               | Lower dose:  
Infectious acute diarrhoea  
Higher dose:  
Enteric fever (mild)  
Cholera (single dose)  
Trachoma (single dose)          |
|                      | Synonyms are aqueous benzylpenicillin, benzylpenicillin potassium, benzylpenicillin sodium, crystalline penicillin, penicillin G potassium, and penicillin G sodium | IV:  
- Lower dose: 50 000-75 000 IU/kg/dose (30-45 mg/kg/dose) given every 12 hours  
- Higher dose: Severe CAP / Sepsis 50.000 IU/kg/dose (30 mg/kg/dose) given every 8 hours  
Meningitis  
100 000 IU/kg/dose (60 mg/kg/dose) given every 6 hours | Lower dose:  
Congenital syphilis  
Higher dose:  
Severe CAP  
Sepsis  
Meningitis          |
| **Procaine benzylpenicillin** | IM:                    | 50 000 IU (50 mg) / kg per day                                                | Congenital syphilis          |
|                      | Oral:                  | 25 mg/kg/dose given every 12 hours                                            | Periorbital cellulitis  
Pharyngitis  
Pyomyositis  
SSTI (mild)          |
|                      | IV/IM:                 | 25 mg/kg/dose given every 12 hours                                            | Bone and joint infections  
Surgical prophylaxis          |
|                      | 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  
20–<30 kg: 625 mg given every 12 hours  
≥ 30 kg: Use adult dose | Bone and joint infections  
Surgical prophylaxis          |
|                      | There is no data for children or neonates |                                                                               | Bone and joint infections  
CAP (severe)  
HAP  
IAI (mild and severe)  
Sepsis (unknown origin)  
Meningitis          |
| **Cefixime**         | Oral:                  | 10 mg/kg/dose given once daily                                                | Infectious acute diarrhoea  
Upper UTI (severe)  
Bone and joint infections  
CAP (severe)  
HAP  
IAI (mild and severe)  
Sepsis (unknown origin)  
Meningitis          |
<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Dose</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftazidime+avibactam</td>
<td>IV/IM: 62.5 mg/kg (Max 2 grams ceftazidime + 500 mg avibactam) given every 8 hours</td>
<td>Lower dose: Infectious acute diarrhoea (severe)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>URTI (severe)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bone and joint infections</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CAP (severe)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Endophthalmitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Enteric fever (severe)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HAP</td>
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<tr>
<td></td>
<td></td>
<td>IAI (mild and severe)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Necrotizing fasciitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sepsis (unknown origin)</td>
</tr>
<tr>
<td></td>
<td><strong>Higher dose:</strong></td>
<td>Meningitis</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>IV / IM:</td>
<td>Infectious acute diarrhoea (severe)</td>
</tr>
<tr>
<td></td>
<td><strong>Lower dose:</strong></td>
<td>URTI (severe)</td>
</tr>
<tr>
<td></td>
<td>80 mg/kg/dose given once daily</td>
<td>Bone and joint infections</td>
</tr>
<tr>
<td></td>
<td><strong>Higher dose:</strong></td>
<td>CAP (severe)</td>
</tr>
<tr>
<td></td>
<td>100 mg/kg given once daily</td>
<td>Endophthalmitis</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>IV: 50 mg/kg (single dose)</td>
<td>Surgical prophylaxis</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>Oral: 10-20 mg/kg/dose given every 12 hours</td>
<td>Upper UTI (mild)</td>
</tr>
<tr>
<td></td>
<td><strong>Weight bands:</strong></td>
<td>Infectious acute diarrhoea (severe)</td>
</tr>
<tr>
<td></td>
<td>3-&lt;6 kg: 50 mg given every 12 hours</td>
<td>IAI (mild)</td>
</tr>
<tr>
<td></td>
<td>6-&lt;10 kg: 100 mg given every 12 hours</td>
<td>Enteric fever</td>
</tr>
<tr>
<td></td>
<td>10-&lt;15 kg: 150 mg given every 12 hours</td>
<td>Febrile neutropenia (low risk)</td>
</tr>
<tr>
<td></td>
<td>15-&lt;20 kg: 200 mg given every 12 hours</td>
<td>Cholera (single dose)</td>
</tr>
<tr>
<td></td>
<td>20-&lt;30 kg: 300 mg given every 12 hours</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥ 30 kg: Use adult dose</td>
<td></td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>IV/IM: 25 mg/kg/dose given every 6 hours</td>
<td>Meningitis</td>
</tr>
<tr>
<td></td>
<td><strong>Use chloramphenicol only when no other option is available due to toxicity concerns</strong></td>
<td></td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Oral: 7.5 mg/kg/dose given every 12 hours</td>
<td>Pharyngitis</td>
</tr>
<tr>
<td></td>
<td><strong>Clarithromycin has excellent oral bioavailability and the intravenous route should be reserved for patients with impaired gastrointestinal function.</strong></td>
<td></td>
</tr>
<tr>
<td>Clindamycin</td>
<td>IV/oral:</td>
<td>Bone and joint infections</td>
</tr>
<tr>
<td></td>
<td>• Neonates: 5 mg/kg/dose given every 8 hours</td>
<td>Necrotizing fasciitis</td>
</tr>
<tr>
<td></td>
<td>• Children: 10 mg/kg/dose given every 8 hours</td>
<td></td>
</tr>
<tr>
<td>Antibiotic</td>
<td>Dosage and Administration</td>
<td>Indications</td>
</tr>
<tr>
<td>------------</td>
<td>-----------------------------</td>
<td>-------------</td>
</tr>
</tbody>
</table>
| **Cloxacillin or Flucloxacillin** | **Oral/IV:**  
  - Neonates: 25-50 mg/kg/dose given every 12 hours  
  - Children: 25 mg/kg/dose given every 6 hours | SSTI (mild)  
  Bone and joint infections  
  Periorbital cellulitis  
  Pyomyositis  
  **Weight bands:**  
  - 3–<6 kg: 125 mg given every 6 hours  
  - 6–<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 |
| **Doxycycline** | **Oral:**  
  - <45 kg (<12 years): 2-4 mg/kg  
  - >45 kg (>12 years): 300 mg | Cholera (single dose) |
| **Gentamicin** | **IV:** 5 mg/kg given once daily | Sepsis (unknown origin)  
  Surgical prophylaxis  
  Upper UTI (severe)  
  IAI (mild and severe) |
| **Fosfomycin (IV)** | **IV:**  
  - Neonates: 200 mg/kg/day divided every 8 hours  
  - Children: 200-400 mg/kg/day divided every 6 to 8 hours | Empiric use should be exceptional (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) |
| **Linezolid** | **IV/Oral:**  
  - First week of life: 10 mg/kg given every 12 hours  
  - Beyond first week of life: 10 mg/kg given every 8 hours | Febrile neutropenia (high risk)  
  IAI (severe) |
| **Meropenem** | **IV:** 20 mg/kg/dose given every 8 hours |  |
| **Meropenem-vaborbactam** | Currently not licensed for use in children or neonates |  |
| **Metronidazole** | Oral/IV:  
- Neonates: 7.5 mg/kg/dose given every 12 hours (starting with a loading dose if used IV: 15 mg/kg)  
- Children: 7.5 mg/kg/dose given every 8 hours  
**Weight bands:**  
3-<6 kg: 30 mg given every 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  
**Higher dose:**  
10-15 mg/kg/dose given every 8 hours | IAI (mild and severe)  
Necrotizing fasciitis  
*C. difficile* infection  
**Higher dose:**  
Amoebic abscess  
**Single dose:**  
Surgical prophylaxis |
| **Nitrofurantoin** | Oral: 2-4 mg/kg/dose given every 12 hours | UTI (lower) |
| **Phenoxybenzylpenicillin** | Oral: 15 mg/kg/dose (24,000 international units*/kg/dose) given every 6 hours  
*Units of the potassium salt | Pharyngitis  
Dental infections |
| **Piperacillin-tazobactam** | IV: 100 mg/kg/dose of piperacillin component given every 8 hours | HAP  
IAI (severe)  
Necrotizing fasciitis  
Febrile neutropenia (high-risk) |
| **Plazomicin** | No data for children or neonates |  |
| **Polymyxin B** | IV:  
**Loading dose:** 2.5 mg/kg of colistin base activity (25,000 IU/kg)  
**Maintenance dose:**  
<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 | **Empiric use should be exceptional** (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)** | IV: 2.5-5 mg of colistin base activity/kg/day divided in 2-4 doses | **Empiric use should be exceptional** (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: 20 mg/kg of sulfamethoxazole+ 4 mg/kg of trimethoprim given every 12 hours  
**Weight bands:**  
3–<6 kg: 100 mg + 20 mg given every 12 hours  
6–<10 kg: 200 mg + 40 mg given every 12 hours  
10–<30 kg: 400 mg + 80 mg given every 12 hours  
≥ 30 kg: Use adult dose | UTI (lower)  
Infectious acute diarrhoea |
| --- | --- | --- |
| **Trimethoprim** | Oral: 4 mg/kg given every 12 hours  
**Weight bands:**  
3–<6 kg: 20 mg given every 12 hours  
6–<10 kg: 40 mg given every 12 hours  
10–<30 kg: 80 mg given every 12 hours  
≥ 30 kg: Use adult dose | UTI (lower) |
| **Vancomycin** | 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 | IV:  
Endophthalmitis  
Febrile neutropenia 9high risk)  
Necrotizing fasciitis (if MRSA suspected)  
Oral:  
*C. difficile* infection (higher dose for severe cases) |

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

| AMR | **Antimicrobial resistance.**  
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.  
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.  
Infection with antimicrobial-resistant pathogens makes infections harder to treat and increases the risk of disease spread, severe illness and death. |
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Antibiotic resistance</td>
<td>Antibiotic resistance is a subset of antimicrobial resistance that specifically refers to bacteria becoming resistant to antibiotics (medicines that act against bacteria).</td>
</tr>
</tbody>
</table>
| AWaRe | **Access, Watch and Reserve system.**  
AWaRe is the WHO classification of antibiotics introduced by WHO as part of the 2017 Model List of Essential Medicines.  
According to AWaRe there are three categories of antibiotics:  
- Access antibiotics that have a narrow spectrum of activity and a good safety profile in terms of side effects.  
- 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.  
- Reserve antibiotics that are last-choice antibiotics used to treat multidrug-resistant infections.  
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. |
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>BAL</td>
<td>Bronchoalveolar lavage. 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.</td>
</tr>
<tr>
<td>CAP</td>
<td>Community-acquired pneumonia. CAP is differentiated from Healthcare-associated pneumonia (HAP) in which antibiotic-resistant pathogens are more frequent.</td>
</tr>
<tr>
<td>Carbapenemases</td>
<td>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.</td>
</tr>
<tr>
<td>CDI</td>
<td>Clostridioides difficile infection. CDI is an infection of the colon caused by the bacterium <em>C. difficile</em> that occurs mostly in patients with current/recent antibiotic use and with regular exposure to healthcare settings.</td>
</tr>
<tr>
<td>COPD</td>
<td>Chronic obstructive pulmonary diseases. 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).</td>
</tr>
<tr>
<td>COVID-19</td>
<td>Coronavirus disease of 2019. 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.</td>
</tr>
<tr>
<td>CRP</td>
<td>C-reactive protein. CRP is a laboratory test used to detect inflammation as an indicator of various conditions and to monitor response to treatment.</td>
</tr>
</tbody>
</table>
| **DALYs** | **Disability-adjusted life years.**  
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 |
| **EDL** | **Essential in vitro Diagnostics List.**  
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) |
| **EIA** | **Enzyme immunoassay.**  
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 *Clostridioides difficile* infection |
| **EML** | **Model Essential Medicines List.**  
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 |
| **EMLc** | **Model Essential Medicines List for children.**  
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.
<table>
<thead>
<tr>
<th><strong>ESBL</strong></th>
<th><strong>Extended-spectrum beta-lactamase.</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>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)</td>
<td></td>
</tr>
</tbody>
</table>

| **Genotypic resistance** | **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** |

<table>
<thead>
<tr>
<th><strong>GDH</strong></th>
<th><strong>Glutamate dehydrogenase.</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>GDH is a constitutive enzyme produced by all strains of <em>Clostridiodes difficile</em> and it is easily detected in stool samples. In this Handbook it is specifically mentioned as one of the tests to diagnose <em>Clostridiodes difficile</em> infection</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>GLASS</strong></th>
<th><strong>Global Antimicrobial Resistance and Use Surveillance System.</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>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</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>HIC</strong></th>
<th><strong>High-income countries.</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>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></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>HIV</strong></th>
<th><strong>Human Immunodeficiency Virus.</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>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</td>
<td></td>
</tr>
</tbody>
</table>

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<thead>
<tr>
<th><strong>IM</strong></th>
<th><strong>Intramuscular injection.</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>IM is a technique used to deliver a medication deep into the muscles</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>IV</strong></th>
<th><strong>Intravenous injection / infusion.</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>IV is a technique used to deliver a medication into a vein</td>
<td></td>
</tr>
</tbody>
</table>
| KPC          | *Klebsiella pneumoniae* carbapenemase.  
|             | KPC is the most common Class A carbapenemase |
| LMIC        | **Low- and middle-income countries.**  
|             | Countries with lower- and middle-income economies according to the World bank classification available at https://datahelpdesk.worldbank.org/knowledgebase/articles/906519 |
| MRSA        | **Methicillin-resistant *Staphylococcus aureus***.  
|             | MRSA strains are resistant to methicillin and other beta-lactam antibiotics due to the presence of the mecA gene producing a different penicillin-binding protein with lower affinity for beta-lactam antibiotics. |
| Microbiota  | Collective term for the microorganisms that live in or on the human body |
| NAAT        | **Nucleic acid amplification test.**  
|             | 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) |
| Non-fermenters | Bacteria that cannot catabolize glucose and thus are unable to ferment. The most relevant in this context are *Acinetobacter baumannii* and *Pseudomonas aeruginosa* |
| 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          | **Pharmacodynamics.**  
|             | Pharmacodynamics: the molecular, biochemical and physiologic effects of medicines and their mechanisms of action - what the medicine does to the body |
| PK          | **Pharmacokinetics.**  
|             | Pharmacokinetics: the dynamics of absorption, distribution, metabolism and elimination of medicines by the body - what the body does to the medicine |
| **RDT** | **Rapid diagnostic test.**  
|         | RDTs are diagnostic assays designed for use at the point-of-care |
| **SAGE-IVD** | **Strategic Advisory Group of Experts on In Vitro Diagnostics.**  
|         | 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** | **Severe acute respiratory syndrome coronavirus 2.**  
|         | SARS-CoV-2 is the new coronavirus that causes COVID-19 |
| **STI** | **Sexually transmitted infection.**  
|         | STIs are infections passed from one person to another during sex or intimate contact |
| **WHO** | **World Health Organization** |
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