2021 WHO Expert Committee on Selection and Use of Essential Medicines

Proposal to extend the indications for gentamicin on the EMLc to include acute bacterial meningitis in neonates

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1. Summary statement of the proposal for inclusion, change or deletion.

This application concerns the updating of the forthcoming WHO Model List of Essential Medicines for Children (EMLc) to add the new indication of acute bacterial meningitis in neonates to the existing listing for gentamicin.

The treatment options for neonatal meningitis of ampicillin in combination with gentamicin, and the use of ceftriaxone or cefotaxime as alternatives to ampicillin are recommended by several WHO guidelines. Ampicillin, ceftriaxone and cefotaxime are currently included on the EMLc for the treatment of acute bacterial meningitis related to their good CSF penetration, safety profile and coverage of the most common pathogens.

In neonates, the clinical presentation of meningitis is, however, less typical than in adults or in older children and symptoms are usually non-specific. Neonates with meningitis often present with a combination of fever, poor feeding, lethargy and/or reduced interaction with caregivers, vomiting, irritability, seizures and rash. Neck stiffness is uncommon.

These non-specific symptoms overlap with those of "neonatal sepsis" for which there is no universally accepted definition even though the term is most commonly used to describe a serious systemic condition of infectious origin (usually bacterial) that occurs in the first month of life, associated with a combination of clinical and laboratory signs.

Therefore, empiric treatment of neonatal meningitis and sepsis overlap, and meningitis should always be suspected in case of signs of serious bacterial infection. Globally, neonatal sepsis is often treated in settings where the infrastructure for obtaining a lumbar puncture is not available and it is not often possible to fully confirm clinically whether a neonate with signs of sepsis may have also developed meningitis.

2. Relevant WHO technical department and focal point (if applicable).
Maternal, Newborn, Child & Adolescent Health & Ageing

3. Name of organization(s) consulted and/or supporting the application.
Department of Health Research Methods, Evidence and Impact, McMaster University, Canada.

4. International Nonproprietary Name (INN) and Anatomical Therapeutic Chemical (ATC) code of the medicine.

INN	ATC
Gentamicin	J01GB03

5. Dose forms(s) and strength(s) proposed for inclusion; including adult and age-appropriate paediatric dose forms/strengths (if appropriate).
Dose forms and strengths as currently listed on the EMLc.

6. Whether listing is requested as an individual medicine or as representative of a pharmacological class.
The application is to add an indication to gentamicin as an individual medicine.

7. Treatment details (requirements for diagnosis, treatment and monitoring).
Recommendations concerning meningitis and serious bacterial infections in children from recent WHO guidelines are summarized below.

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WHO recommendations on newborn health (2017) (1):

The guideline refers to empiric antibiotics for suspected neonatal sepsis and to possible serious bacterial infections when referral is not feasible (the latter recommendation taken from the 2015 WHO guidelines for managing possible serious bacterial infection in young infants when referral is not feasible, cited below)

- Neonates with signs of sepsis should be treated with ampicillin (or penicillin) and **gentamicin** as the first line antibiotic treatment for at least 10 days. (Strong recommendation, low quality of evidence).
- Young infants 0–59 days old with clinical severe infection when referral is not feasible:
    - Option 1: **Intramuscular gentamicin** 5–7.5 mg/kg (for low-birth-weight infants gentamicin 3–4 mg/kg) once daily for seven days and twice daily oral amoxicillin, 50 mg/kg per dose for seven days. Close follow-up is essential. (Strong recommendation, moderate quality evidence).
    - Option 2: **Intramuscular gentamicin** 5–7.5 mg/kg (for low-birth-weight infants gentamicin 3–4 mg/kg) once daily for two days and twice daily oral amoxicillin,50 mg/kg per dose for seven days. Close follow-up is essential. A careful assessment on day 4 is mandatory. (Strong recommendation, low quality evidence).

Managing possible serious bacterial infection in young infants when referral is not feasible (2015) (2)

- Young infants 0–59 days old who have any sign of critical illness (at presentation or developed during treatment of clinical severe infection) should be hospitalized after pre-referral treatment with antibiotics. Strong recommendation based on very low-quality evidence (standard of care).
- Although there are no comparative trials available showing the relative efficacy and safety, in cases where hospitalization is not possible at all, critically ill children should be given one of the following treatment regimens until hospitalization becomes possible (up to seven days):

    1. twice daily intramuscular ampicillin and **once daily intramuscular gentamicin**
    2. once daily intramuscular ceftriaxone **with or without once daily intramuscular gentamicin**
    3. twice daily intramuscular benzyl penicillin and **once daily intramuscular gentamicin**
    4. once daily intramuscular procaine penicillin and **once daily intramuscular gentamicin**.

Pocket book of hospital care for children (2013) (3)

In relation to treatment of meningitis recommends:

- The first-line antibiotics are ampicillin and **gentamicin for 3 weeks**. Alternatively, give a third-generation cephalosporin, such as ceftriaxone or cefotaxime and gentamicin for 3 weeks.

The proposed dose and duration for the empiric treatment of neonatal meningitis is:

Ampicillin (IV/IM): 50 mg/kg per dose, twice a day (1st week of life), 50 mg/kg per dose, three times a day (>1st week of life) in combination with gentamicin (IV/IM): 5 mg/kg per dose once a day (1st week of life), 7.5 mg/kg once a day (after 1st week of life).

If ampicillin is unavailable alternative options are ceftriaxone 50-100 mg/kg per dose, once a day or cefotaxime 50mg/kg per dose, twice a day (1st week of life) and three times a day (after 1st week of life)

Treatment duration: 3 weeks if no pathogen is isolated.

8. Information supporting the public health relevance.

Epidemiological information on disease burden

Neonatal meningitis is found worldwide and according to estimates by WHO and the Maternal and Child Epidemiology Estimation group, 14% of all neonatal deaths in 2017 were due to meningitis or sepsis (4) (these two syndromes usually overlap and as previously mentioned it is often impossible to separate the two clinically). The Global Burden of Disease (GBD) study estimated in 2016 that almost 20.000 neonates (i.e. children <1 month of age) died of meningitis globally. However, authors of the GBD study acknowledged that the diagnosis is difficult and this could result in potential underreporting.

Risk factors include among others pre-term birth, low birth weight but also maternal peripartum infections or delivery-associated risk factors such as prolonged rupture of membranes or traumatic delivery.

Causative pathogens differ from those commonly found in older children and adults with infectious meningitis. In particular, *Streptococcus agalactiae* (group B streptococci) and *Escherichia coli* are those pathogens most frequently responsible for meningitis in this age group along with *Listeria monocytogenes* and *Streptococcus pneumoniae.* S*treptococcus agalactiae* remains the most frequent cause of neonatal meningitis despite a decline in new cases over the years in settings where maternal screening and intrapartum antibiotic prophylaxis of mothers with a positive screening test is performed as part of prenatal care.

The incidence and mortality of meningitis are higher in countries with limited resources (5).

Likely impact on the burden of disease

Treating neonates with suspected meningitis can prevent morbidity (high rates of neurological disabilities (6)) and mortality at the individual level. WHO data indicated that in 2016 approximately 395 000 neonates (<28 days) died due to sepsis or other infections worldwide (7). The same data indicate that only 142 neonates died of meningitis in the same year in contrast with data from the Global Burden of Disease study that report approximately 19 000 deaths in the same age group and in the same year (5). The Global Burden of Disease study also indicates that the peak age of incident meningitis is during the neonatal period and that rates of disabilities are also highest in the youngest (5, 6). In particular 5.8% of total (all ages) meningitis DALYs "were attributable to low birthweight and short gestation in 2016 with the highest rates of attributable DALYs occurring in the meningitis belt countries, Burundi, Malawi, Somalia, Zambia, and Afghanistan. All attributable burden was in neonates younger than 28 days" (5).

As stated above, it is often difficult to differentiate meningitis from sepsis or other serious bacterial infections in this age group due to symptoms overlap, therefore benefits of treating suspected meningitis overlap with the benefits of treating sepsis (or a possible serious bacterial infection). Published data show that neonatal possible serious bacterial infections remain a major cause of morbidity and mortality especially in the first days of life and in low-and middle-income countries (8).

9. Review of benefits: summary of evidence of comparative effectiveness.

Reviews of the evidence for empiric antibiotic treatment options for meningitis and sepsis prepared by the Department of Health Research Methods, Evidence and Impact, McMaster University, Canada, were considered by the Expert Committee in 2017 as part of a comprehensive review of antibiotics on the Model Lists (see Appendix).

The evidence presented in the 2017 reviews forms the basis for the current proposal.

10. Review of harms and toxicity: summary of evidence of safety.

The harms and toxicities of gentamicin are well known and have been reviewed extensively by the Expert Committee on previous occasions. Gentamicin has been included on the EML since 1977 and on the EMLc since 2007.

11. Summary of available data on comparative cost and cost-effectiveness of the medicine.

As gentamicin is already included on the Model Lists and in many national essential medicine lists, a review of the comparative costs and cost-effectiveness has not been undertaken.

12. Summary of regulatory status and market availability of the medicine.
Gentamicin has regulatory approval globally and is widely available.

13. Availability of pharmacopoeial standards (British Pharmacopoeia, International Pharmacopoeia, United States Pharmacopoeia, European Pharmacopeia).
Gentamicin is listed in multiple pharmacopoeias including the United States Pharmacopeia and European Pharmacopoeia.

14. References

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Appendix

Relevant extract from the Review of Antibacterial Medicines for the WHO Model List of Essential Medicines 2017 Update by the Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton Canada

- Sepsis in children
- Meningitis

The full Review is available at:
https://www.who.int/selection_medicines/committees/expert/21/applications/comprehensive_antibiotics_rev/en/

Sepsis in Children

Sepsis is a major global cause of morbidity and mortality in children. Defined as a systemic inflammatory response syndrome in the presence of a suspected or proven infection, it can be caused by a wide variety of pathogens, although bacteria are responsible for the vast majority of cases. The purpose of this chapter is to focus on the empiric therapy for young children (ag e≤ 5 years) presenting with sepsis or septic shock.

Synopsis of published evidence

We evaluated 11 reviews [88-98], of which only two were considered further [88, 89]. Eight reviews were excluded because they dealt with pre-term prophylaxis [91-98] and one was excluded because it focused on dosing for gentamicin [90]. Of the two included reviews, both had low scores (40% and 45%) [88, 89].

Of the two reviews considered, one (2 RCTs, 127 participants) compared single to combination regimens for suspected early neonatal sepsis, but had indeterminant results on mortality within 28 days (RR 0.75, 0.19 to 2.9) because of the limited sample size [88]. A review which examined antibiotic regimens for late onset sepsis in neonates (1 RCT, 24 participants), comparing beta-lactams to beta-lactams and aminoglycosides also was indeterminant (RR 0.17, 0.01 to 0.2) because it was severely underpowered [89].

Synopsis of guidelines

We retrieved 6 references to guidelines [28, 99-103]. However, we did not further consider one because it was the wrong topic (MRSA)[28], did not meet our criteria [99, 101, 103], and 1 did not focus on children [102]. We considered 1 guideline[100].

For early onset infection, the NICE guidelines, which had a rating of 75%, suggest use intravenous benzylpenicillin with gentamicin as the first-choice antibiotic regimen for empirical treatment of suspected infection unless local bacterial resistance patterns suggest using a different antibiotic [100]. Although not formally a guideline, the American Academy of Pediatrics recommends ampicillin and an aminoglycoside, typically gentamicin, for treatment of infants with suspected early onset sepsis [101]. If gram negative meningitis, cefotaxime should be used instead of an aminoglycoside. The WHO handbook recommends, for newborns with any signs of serious bacterial infection or sepsis, to give ampicillin or penicillin and gentamicin as first-line antibiotic

treatment [103]. This handbook also specify to consider using cloxacillin and gentamicin if the clinical presentation suggests a higher risk of staphylococcus infection, such as extensive skin pustules, abscess or omphalitis in addition to signs of sepsis.

Selection of antibiotics

The systematic review evidence is extremely limited and essentially does not contribute to deciding which antibiotics should be on the list. The guidelines suggest a penicillin (ampicillin, penicillin, or intravenous benzylpenicillin) along with gentamicin to cover listeria and gram negatives. As such, these antibiotics were recommned as core agent for neonatal sepsis.

Antibiotics selected as essential for neonatal sepsis:

Antibiotic	**Neonates**	**SR**	**CPG**	**EML**	**List**
Ampicillin			✓	+	C
OR Benzylpenicillin			✓	+	C
Gentamicin			✓		C

Meningitis

Acute bacterial meningitis is a medical emergency requiring prompt administration of antibiotics that penetrate will into inflamed meninges. Because of the severity of this infection, RCT evidence is limited and recommendations for antimicrobials are driven largely on susceptibility patterns of the most common pathogens along with experimental work in animal models.

Synopsis of published evidence

We evaluated eight reviews [138-145], of which 5 were not considered further (three were for prophylaxis[140, 144, 145], one for intraventricular therapy [139], one for a different study question [143]) and retained 3 ([138, 141, 142] where quality scores ranged from 63% to 70%. In a 2015 systematic review, chloramphenicol was compared to other antibiotics (2 penicllins, 2 cephalorins, and 1 tetracycline) (5 RCTs, 1,753 patients)[142]. Chloramphenicol was associated with higher mortality than other antibiotics (RR 1.27, 95% CI 1.00-1.60) (152). In contrast, an older, lower ranked 2007 Cochrane review (19 RCTs, 1496 patients) that compared third generation cephalosporins to treatment with penicillin or ampicillin-chloramphenicol found no difference for death (risk difference (RD) 0%; 95% CI -3% to 2%), risk of deafness (RD -4%; 95% CI -9% to 1%), or risk of treatment failure (RD -1%; 95% CI -4% to 2%)[138]. There was a reduced risk of culture positivity of CSF after 10 to 48 hours (RD -6%; 95% CI -11% to 0%) and an increase in the risk of diarrhoea between the groups (RD 8%; 95% CI 3% to 13%) with third generation cephalosporins versus penicillin/ampicillin-chloamphenicol.

A 2009 systematic review compared short course (4 to 7 days) to long-course (7 to 14 days) of antibiotics in children (5 RCTs 426 patients) and found no difference in clinical success (1.24, 95% CI 0.73 to 2.11), long-term neurological complications (OR 0.60, 95% CI 0.29 to 1.27) or long-term hearing impairment (OR 0.59, 95% CI 0.28 to 1.23) [141].

Synopsis of guidelines

We evaluated two guidelines [146, 147], with quality scores of 68% and 67% ,with concordance across domains. The NICE guidelines recommend ceftriaxone for patients aged 3 months and older while those younger should be treated with intravenous cefotaxime along with amoxicillin or ampicillin [147]. They also recommend that vancomycin should be added for those who have received prolonged or multiple exposure to antibiotics (within past 3 months) and for those with

travel outside of the UK. IDSA guidelines recommend ampicillin and cefotaxime or an aminoglycoside for children less than one month of age, vancomycin and ceftriaxone or cefotaxime for children older than 23 months to adults 50 years of age, and recommend adding ampicillin for those over 50 years for coverage of *Listeria monocytogenes* [146]. Vancomycin along with either cefepime, ceftazidime, or meropenem is recommended for patients with penetrating trauma, who are post-neurosurgery, or who have a cerebrospinal shunt in place.

Selection of antibiotics:

Systematic review evidence suggests that chlorampehnicol is associated with higher mortality than other antibiotics, as such, it is not listed as a core antibiotic. Ampicillin, ceftriaxone, and cefotaxime are listed for multiple indications and are categorized as core while aminoglycosides and vancomycin have more specific indications (e.g. by age or indication) and are therefore categorized as targted as are ceftazidime and meropenem.

Antibiotics selected as essential for meningitis:

Antibiotic	**Adults (per dose)**	**Paediatrics (per day)**	**SR**	**CPG**	**EML**	**List**
Ampicillin	2g IV	100-300mg/kg IV		✓	+	c
Ceftriaxone	2g IV	80-100mg/kg IV	✓	✓	+	c
Or cefotaxime		100-300mg/kg IV				
Ceftazidime	2g IV	100-150mg/kg IV		✓	+	T
Penicillin G	4 Mio U	0.15-0.3mg/kg IV	✓	✓	+	c
Meropenem	2g IV	120mg/kg IV		✓	-	T
Amikacin	15mg/kg IV	15-30mg/kg IV		✓	+	T
Or Gentamicin	5mg/kg IV	5-7.5mg/kg IV			+	

Vancomycin	15mg/kg IV	20-60mg/kg IV	✓	+	T

Duration of treatment depends on the type of pathogen and ranges from 7 days for *N*. *meningitidis* and *H*. *influenzae*, 14 days for streptococcal meningitis, and 21+ days for gram negative bacilli and *L*. *monocytogenes*.

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