Gentamicin

Essential medicine status

Section: 6. Anti-infective medicines > 6.2. Antibacterials > 6.2.1. Access group antibiotics

EMLc | ATC codes: J01GB03

Indication	Neonatal meningitis ICD11 code: KA65.4
INN	Gentamicin
Medicine type	Chemical agent
Antibiotic groups	A ACCESS
List type	Core (EML) (EMLc)
Formulations	Parenteral > General injections > unspecified: 10 mg per mL in 2 mL vial (as sulfate) (EMLc) ; 40 mg per mL in 2 mL vial (as sulfate) (EMLc)
EML status history	First added in 2021 (TRS 1035)
Sex	All
Age	Newborn (< 1 month)
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Patents have expired in most jurisdictions Read more about patents.
Wikipedia	Gentamicin
DrugBank	Gentamicin

Expert Committee recommendation

The Committee noted that sepsis and meningitis are responsible for a substantial proportion of global neonatal mortality, and that the availability of empiric antibiotic treatment options is critical to reduce this burden. Gentamicin is currently included on the EMLc for the treatment of neonatal sepsis. The Committee noted that gentamicin, in combination with a beta-lactam, is recommended as first-line treatment of suspected or proven neonatal meningitis in several WHO and other international guidelines. To ensure alignment of the EMLc with these recommendations, the Expert Committee therefore recommended extending the indications for gentamicin on the EMLc to include empiric antibiotic treatment of neonatal meningitis as a first-choice option. The Committee recognized the importance of the availability of lower strength formulations of gentamicin for the dosing of paediatric patients.

Background

Gentamicin is currently included in the EML and EMLc for multiple other indications. The combination of gentamicin and a beta-lactam is listed as first choice for: acute malnutrition in infants, children or adolescents; severe community-acquired pneumonia in children; and sepsis in neonates and children. Gentamicin is also listed as second choice for surgical prophylaxis in children and adults, and for gonococcal infection. Reviews of the evidence for empiric antibiotic treatment options for meningitis and sepsis (not limited to neonates) had been prepared by the Department of Health Research Methods, Evidence and Impact, McMaster University, Canada, and were considered by the Expert Committee in 2017 (1). The evidence assessed in the 2017 reviews forms the basis for the current application. Neonatal meningitis occurs 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 (these two syndromes usually overlap and it is often impossible to separate the two clinically) (2). The 2016 Global Burden of Disease study

estimated that almost 20 000 neonates (i.e. children < 1 month of age) died of meningitis in 2016. However, authors of the Global Burden of Disease study acknowledged that the diagnosis is difficult and this could result in an underestimation of the burden of disease of neonatal meningitis (3). In general, the incidence and mortality of meningitis are higher in resource-constrained countries. Risk factors for neonatal meningitis include preterm birth, low birth weight, maternal peripartum infections or and delivery-associated risk factors such as prolonged rupture of membranes or traumatic delivery (4). The causative pathogens differ from those commonly found in older children and adults with infectious meningitis. Streptococcus agalactiae (a group B streptococci) and Escherichia coli are the most frequent bacteria causing neonatal meningitis. Streptococcus agalactiae is still the most frequent cause of neonatal meningitis despite a decline in cases over the years in settings where maternal screening and intrapartum antibiotic prophylaxis of mothers with a positive screening test for group B streptococcus is done as part of prenatal care. Streptococcus pneumoniae and Listeria monocytogenes, bacteria commonly encountered in meningitis in older children and adults, are also pathogens in neonatal meningitis (5).

Summary of evidence

The clinical presentations of neonatal sepsis and neonatal meningitis overlap and are difficult to differentiate. The 2017 McMaster review of systematic reviews, meta-analyses and guidelines published between 1996 and 2016 included studies on sepsis in children < 5 years. This evidence is considered relevant for neonatal meningitis. Systematic reviews and meta-analyses Two Cochrane systematic reviews were included in the McMaster review (6,7). The first (two randomized controlled trials, 127 participants) compared single to combination regimens for suspected early neonatal sepsis, but results on 28-day mortality were indeterminate because of the small sample size (risk ratio (RR) 0.75, 95% confidence interval (CI) 0.19 to 2.9) (6). The second systematic review examined antibiotic regimens for late onset sepsis in neonates (one randomized controlled trial, 24 participants) and compared beta-lactams alone with beta-lactams combined with aminoglycosides. The results were also inconclusive (RR 0.17 for mortality before discharge, 95% CI 0.01 to 3.23; the same as the results for treatment failure) because of the small sample size (7). Guidelines The 2012 United Kingdom clinical guidelines on antibiotics for the prevention and treatment of early-onset neonatal infection advise using 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 (8). These guidelines were updated in April 2021 and have kept the same recommendations (9). Although not formally a guideline, a policy report by the Committee on Fetus and Newborn of the American Academy of Pediatrics published in 2012 recommends ampicillin and an aminoglycoside (usually gentamicin), for treatment of infants with suspected early-onset sepsis (10). If Gram-negative meningitis is diagnosed, cefotaxime in combination with an aminoglycoside is recommended. The 2018 update, has kept the combination of ampicillin and gentamicin as the first choice for the empiric treatment of early-onset sepsis (11). 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.

Guidelines

Several WHO documents provide guidance on the management of neonatal meningitis/sepsis and recommend gentamicin in combination with a beta-lactam (ampicillin, ceftriaxone or cefotaxime) for empiric treatment. The 2017 WHO recommendations on newborn health (12) includes the following recommendations for the choice of empiric antibiotics for suspected neonatal sepsis or serious bacterial infections when referral is not feasible. • 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 clinically evident severe infection when referral is not feasible: o Option 1: Intramuscular gentamicin 5–7.5 mg/kg (for low-birth-weight infants, gentamicin 3–4 mg/kg) once daily for 7 days, and twice daily oral amoxicillin, 50 mg/kg per dose for 7 days. Close follow-up is essential. (Strong recommendation, moderate quality of evidence). o Option 2: Intramuscular gentamicin 5–7.5 mg/kg (for low-birth-weight infants, gentamicin 3–4 mg/kg) once daily for 2 days, and twice daily oral amoxicillin, 50 mg/kg per dose for 7 days. Close follow-up is essential. A careful assessment on day 4 is essential. (Strong recommendation, low quality of evidence). The 2015 WHO guideline for managing serious bacterial infection in young infants when referral is not feasible (13) includes the following recommendations: Young infants 0–59 days old who have any sign of critical illness (at presentation or developed during treatment of severe clinical infection) should be hospitalized after prereferral treatment with antibiotics. (Strong recommendation, very low-quality evidence (standard of care)). Although no comparative trials are available showing the relative efficacy and safety of treatments, 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 7 days): • twice daily intramuscular ampicillin and once daily intramuscular gentamicin • once daily intramuscular ceftriaxone with or without once daily intramuscular gentamicin • twice daily intramuscular benzylpenicillin and once daily intramuscular gentamicin • once daily intramuscular procaine benzylpenicillin and once daily intramuscular gentamicin. The 2013 WHO pocket book of hospital care for children (14) includes the following recommendations for treatment of meningitis in neonates. • 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: o Ampicillin (intravenous/intramuscular) 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 (intravenous/intramuscular) 5 mg/kg per dose once a day (1st week of life), 7.5 mg/kg once a day (after 1st week of life). o If ampicillin is unavailable alternative options are ceftriaxone 50–100 mg/kg per dose, once a day, or cefotaxime 50 mg/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.

Committee considerations

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 for the current application. Gentamicin has regulatory approval globally and is widely available

EML recommendations: Neonatal meningitis

First choice	Second choice
gentamicin	meropenem

1. The selection and use of essential medicines. Report of the WHO Expert Committee, 2017 (including the 20th WHO Model List of Essential Medicines and the 6th WHO Model List of Essential Medicines for Children). Geneva: World Health Organization; 2017 (WHO Technical Report Series, No. 1006; https://apps.who.int/iris/handle/10665/259481, accessed 13 August 2021).
2. WHO Department of maternal, newborn, child and adolescent health and ageing. Data portal. Maternal and newborn – mortality/causes of death [internet]. Geneva: World Health Organization (https://www.who.int/data/maternal-newborn-child-adolescent-ageing/maternal-and-newborn-data/maternal-and-newborn---mortality-causes-of-death, accessed 13 August 2021).
3. Global, regional, and national burden of meningitis, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 2018;17(12):1061–82.
4. Ku LC, Boggess KA, Cohen-Wolkowiez M. Bacterial meningitis in infants. Clin Perinatol. 2015;42(1):29–45, vii-viii.
5. Furyk JS, Swann O, Molyneux E. Systematic review: neonatal meningitis in the developing world. Trop Med Int Health. 2011;16(6):672–9.
6. Mtitimila EI, Cooke RW. Antibiotic regimens for suspected early neonatal sepsis. Cochrane Database Syst Rev. 2004;(4):CD004495.
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8. National Institute for Health and Care Excellence. Neonatal infection (early onset): antibiotics for prevention and treatment. Clinical guideline [CG149]. London: National Institute for Health and Care Excellence; 2012 (https://www.nice.org.uk/guidance/cg149, accessed 13 August 2021).
9. National Institute for Health and Care Excellence. Neonatal infection: antibiotics for prevention and treatment. NICE guideline [NG195]. London: National Institute for Health and Care Excellence; 2021 (https://www.nice.org.uk/guidance/ng195, accessed 13 August 2021).
10. Polin RA, Committee on Fetus and Newborn. Management of neonates with suspected or proven early-onset bacterial sepsis. Pediatrics. 2012;129(5):1006–15.
11. Puopolo KM, Benitz WE, Zaoutis TE, Committee on Fetus and Newborn; Committee on Infectious Diseases. Management of neonates born at ≤ 34 6/7 weeks' gestation with suspected or proven early-onset bacterial sepsis. Pediatrics. 2018;142(6):e20182896.
12. WHO recommendations on newborn health: guidelines approved by the WHO guidelines review committee. Geneva: World Health Organization; 2017 (https://apps.who.int/iris/handle/10665/259269, accessed 13 August 2021).
13. Guideline: Managing possible serious bacterial infection in young infants when referral is not feasible. Geneva: World Health Organization; 2015 (https://www.who.int/publications/i/item/9789241509268, accessed 13 August 2021).
14. Pocket book of hospital care for children: guidelines for the management of common childhood illnesses. Second edition. Geneva: World Health Organization; 2013 (https://apps.who.int/iris/handle/10665/81170, accessed 13 August 2021).