Benzylpenicillin

Essential medicine status

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

EMLc | ATC codes: J01CE01

Indication	Sepsis without septic shock ICD11 code: 1G40
INN	Benzylpenicillin
Medicine type	Chemical agent
Antibiotic groups	A ACCESS
List type	Core
Formulations	**Parenteral > General injections > unspecified:** 600 mg in vial powder for injection (=1 million IU as sodium or potassium salt) (EMLc) ; 3 g in vial powder for injection (=5 million IU as sodium or potassium salt) (EMLc)
EML status history	First added in 2023 (TRS 1049)
Sex	All
Age	Children (1 month - 12 years)
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Patents have expired in most jurisdictions Read more about patents.
Wikipedia	Benzylpenicillin
DrugBank	Benzylpenicillin

Expert Committee recommendation

The Expert Committee endorsed the inclusion on the EMLc of gentamicin, in combination with benzylpenicillin or ampicillin or amoxicillin, as the first-choice treatment for sepsis in neonates and children, and of ceftriaxone or cefotaxime as a second-choice treatment. The Committee recommended the addition of amikacin in combination with cloxacillin as a second-choice option for use in sepsis in neonates and children.

Background

Sepsis is a major global cause of morbidity and mortality in children. It is defined as “life-threatening organ dysfunction caused by a dysregulated host response to infection” (1). It can be caused by a wide variety of pathogens, although bacteria are responsible for most cases. The purpose of this review is to focus on empirical therapy for young children (age ≤5 years) presenting with sepsis or septic shock (where profound circulatory, cellular and metabolic abnormalities exist and contribute to a higher risk of mortality) (1).

Summary of evidence

Of the two reviews considered in the application from the McMaster Group, one (two randomized controlled trials (RCTs); 127 participants) compared single and combination treatment regimens for suspected early neonatal sepsis. Results for mortality within 28 days were inconclusive (risk ratio (RR) 0.75; 95% confidence interval (CI) 0.19–2.9) because of the limited sample size (2). A review that compared beta-lactams with beta-lactams plus aminoglycosides for late-onset sepsis in neonates (one RCT; 24 participants) also found no significant difference in mortality (RR 0.17; 95% CI 0.01–0.2) but this trial was severely underpowered (3).

Guidelines

The WHO Department of Maternal, Newborn, Child and Adolescent Health reviewed its existing guidelines for treatment of sepsis in children and neonates. This undertaking was informed by a systematic literature review of the current evidence of efficacy, safety and feasibility of antibiotic treatment options. Following expert consultation, the following recommendations were made for antibiotic treatment of sepsis in children and neonates: • Serious bacterial infection, hospitalized infants with community-acquired infection: gentamicin injection and benzylpenicillin or ampicillin injection for 7–10 days. • Serious bacterial infection, hospitalized infants, with risk of staphylococcal infection: cloxacillin injection and gentamicin injection for 10 days, continue with cloxacillin oral liquid or tablets for a total treatment duration of 21 days. • Possible severe bacterial infection (PSBI) in young infants when referral is not possible, fast breathing as the only sign of illness: amoxicillin oral liquid or tablets for 7 days. • PSBI in young infants when referral is not possible, clinical severe infection: Option 1: gentamicin IM injection once daily for 7 days and amoxicillin oral liquid or tablets twice daily for 7 days; Option 2: gentamicin IM injection once daily for 2 days and amoxicillin oral liquid or tablets twice daily for 7 days. • PSBI, young infants when referral is not possible, critically ill: ampicillin injection twice daily and gentamicin injection daily for 7 days. For early-onset infection, National Institute for Health and Care Excellence (NICE) guidelines suggest use of IV benzylpenicillin with gentamicin as the first-choice antibiotic regimen for empirical treatment of suspected infection unless local bacterial resistance patterns suggest use of a different antibiotic (4). Although not formally a guideline, the American Academy of Pediatrics recommendation is for ampicillin and an aminoglycoside, typically gentamicin, for treatment of infants with suspected early-onset sepsis (5). If Gram-negative meningitis is suspected, cefotaxime should be used instead of an aminoglycoside. WHO’s handbook of hospital care for children recommends ampicillin or penicillin and gentamicin as first-line antibiotic treatment for newborns with any signs of serious bacterial infection or sepsis (6). This handbook also specifies that use of cloxacillin and gentamicin should be considered if the clinical presentation suggests a higher risk of staphylococcal infection, such as extensive skin pustules, abscess or omphalitis in addition to signs of sepsis.

Rationale for antibiotic selection

The evidence from systematic reviews is extremely limited and essentially makes no contribution to the decision on which antibiotics should be on the EMLc. The guidelines suggest a penicillin (ampicillin, penicillin or IV benzylpenicillin) together with gentamicin to cover Listeria and Gram-negative organisms; these antibiotics were proposed as core agents for neonatal sepsis.

Committee considerations

For common community-acquired infections, the main focus has been on empirical treatment choices that are broadly applicable in most countries. Generally, alternatives for use in case of allergy were not considered. The Expert Committee considered the antibiotics proposed in the application from the WHO Department of Maternal, Newborn, Child and Adolescent Health, and selected first- and second-choice antibiotics for this indication, in line with the WHO guidelines, for inclusion on the EMLc. Recommended first- and second-choice antibiotics are reported above. The first-choice antibiotics are those generally recommended on the basis of available evidence and are usually narrow-spectrum agents. In particular, the Committee recommended the inclusion of cloxacillin and amikacin as potentially useful second-choice agents in infection suspected to be due to Staphylococcus aureus or gentamicin-resistant Gram-negative bacilli, respectively.

EML recommendations: Sepsis without septic shock

First choice	Second choice
gentamicin	cefotaxime
gentamicin	ceftriaxone
gentamicin	cloxacillin

1. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315(8):801–10.
2. Mtitimila EI, Cooke RW. Antibiotic regimens for suspected early neonatal sepsis. Cochrane Database Syst Rev. 2004;(4):CD004495.
3. Gordon A, Jeffery HE. Antibiotic regimens for suspected late onset sepsis in newborn infants. Cochrane Database Syst Rev. 2005;(3):CD004501.

4. Caffrey Osvald E, Prentice P. NICE clinical guideline: antibiotics for the prevention and treatment of early-onset neonatal infection. Arch Dis Child Educ Pract Ed. 2014;99(3):98–100.
5. Polin RA, Committee on Fetus and Newborn. Management of neonates with suspected or proven early-onset bacterial sepsis. Pediatrics. 2012;129(5):1006–15.
6. Pocket book of hospital care for children: guidelines for the managment of common illnesses with limited resources, second edition. Geneva: World Health Organization; 2013.