Cefazolin

Essential medicine status

EMLc | ATC codes: J01DB04

Indication	Bacterial infection of joint ICD11 code: FA10.0
INN	Cefazolin
Medicine type	Chemical agent
Antibiotic groups	A ACCESS
List type	Core
Formulations	**Parenteral > General injections > unspecified:** 1 g in vial (as sodium salt) powder for injection
EML status history	First added in 2017 (TRS 1006)
Sex	All
Age	Also recommended for children
Age restriction	> 1 month
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Patents have expired in most jurisdictions Read more about patents.
Wikipedia	Cefazolin
DrugBank	Cefazolin

Expert Committee recommendation

The Expert Committee endorsed the inclusion of cloxacillin (with a square box) as first-choice therapy for empirical treatment of bone and joint infections and of ceftriaxone, cefotaxime, cefazolin, clindamycin, and amoxicillin + clavulanic acid as second-choice therapy. All inclusions apply to both the EML and EMLc.

Background

Bone and joint infections include infections of the native bone or joint, i.e. osteomyelitis and septic arthritis, as well as prosthetic joint infections (which are increasing in incidence as a result of the ever-greater number of joint replacements). Treatment is rarely empirical and targeted treatment based on microbiology is emphasized for this type of infection.

Summary of evidence

One Cochrane review compared antibiotics for treating chronic osteomyelitis in adults (1). There were only eight small randomized controlled trials (RCTs) with a total of 282 participants; these provided very limited information because a lack of power meant that no significant differences could be found between various combinations of oral and parenteral agents, and none of the comparisons met the definition of non-inferiority. Another review compared fluoroquinolones (ciprofloxacin, ofloxacin and pefloxacin) with various beta-lactams (imipenem + cilastatin, ampicillin + sulbactam, amoxicillin + clavulanic acid, cefazoline or ceftazidime, broad-spectrum cephalosporins or nafcillin in combination with an aminoglycoside) for osteomyelitis (7 RCTs; 411 participants) (2). There was no difference in treatment success between fluoroquinolones and beta-lactams (194 patients; odds ratio (OR) 0.99; 95% confidence interval (CI) 0.51–1.91); confidence intervals were wide and non-inferiority criteria were not met. Given the small size of the studies and the resultant wide confidence intervals, no conclusions could be drawn from the systematic reviews, and recommendations from clinical practice guidelines were needed to inform the

selection of antibiotics proposed for the EML.

Guidelines

Clinical practice guidelines from the Infectious Diseases Society of America (IDSA) provide recommendations for treatment of prosthetic joint infection (3). Where the prosthetic joint is retained after debridement, they recommend rifampicin in combination with pathogen-specific therapy: nafcillin, cefazolin or ceftriaxone for methicillin-susceptible staphylococci; vancomycin for methicillin-resistant staphylococci; penicillin or ampicillin for penicillin-susceptible Enterococcus spp; vancomycin for penicillin-resistant Enterococcus spp; cefepime or meropenem for Pseudomonas aeruginosa; cefepime or ertapenem for Enterobacter spp; an intravenous beta-lactam based on susceptibility or ciprofloxacin for Enterobacteriaceae; penicillin or ceftriaxone for beta-haemolytic streptococci, and penicillin or ceftriaxone for Propionibacterium acnes. An oral antibiotic, such as a fluoroquinolone (ciprofloxacin or levofloxacin), or sulfamethoxazole + trimethoprim, minocycline, doxycycline, or first-generation cephalosporin (e.g. cefalexin) or antistaphylococcal penicillins along with rifampicin is recommended for methicillin-susceptible S. aureus infections. Cephalexin, dicloxacillin, sulfamethoxazole + trimethoprim, and minocycline are recommended choices for chronic suppressive therapy (if required) following an initial treatment course. When the treatment is a 1-stage approach, a similar approach, i.e. pathogen-specific therapy with rifampicin followed by longer-term rifampicin plus a companion oral antibiotic, is recommended for patients with S. aureus infections. The IDSA guidelines for vertebral osteomyelitis suggest a combination of vancomycin and a third- or fourth-generation cephalosporin for empirical use if required, but the general approach is to identify and then target the pathogen (4). First-line antibiotics for vertebral osteomyelitis pathogens are the same as those for prosthetic joint infections, with the addition of ciprofloxacin for Salmonella spp.

Rationale for antibiotic selection

Based on the epidemiology of pathogens typically encountered in this type of infection, the application proposed the most appropriate antibiotics for possible empirical and targeted treatment. Empirical treatment should be avoided unless patients need immediate antibiotic treatment or if it is impossible to obtain a sample for microbiological examination. Choice of antibiotic for empirical treatment should be based on the pathogens deemed most likely to be involved. As treatment depends heavily on the identified pathogen, no distinction was made between core and targeted antibiotics: all antibiotics were proposed in a single group (i.e. core) for this indication. Of the antibiotics proposed in the guidelines, cefepime was not proposed for inclusion on the EML because of safety concerns (see summary for Febrile neutropenia) in settings where an alternative agent (meropenem) is available. However, cefepime is considered a niche antibiotic for treatment of otherwise beta-lactam-resistant pathogens, as a carbapenem-sparing agent. Ertapenem, in keeping with other syndromes, was also proposed as a niche antibiotic when broad Gram-negative coverage without coverage of P. aeruginosa is needed. Minocycline was not proposed because doxycycline was proposed for this and several other syndromes. Dicloxacillin, rather than nafcillin, is proposed as an antistaphylococcal penicillin because it is also proposed for several other syndromes. Finally, rifampicin was listed as a niche antibiotic specifically for treatment of rifampicin-susceptible staphylococci in the presence of a prosthetic joint. No data or guidelines specifically for children were identified and no recommendation for dosage in children was proposed.

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 various antibiotics proposed in the application under the guiding principle of parsimony and selected first- and second-choice antibiotics for this indication for inclusion on the EML and/or EMLc. The following antibiotics were excluded: • ampicillin, benzylpenicillin, levofloxacin, ciprofloxacin, sulfamethoxazole + trimethoprim, and doxycycline, since these antibiotics are used mostly for targeted therapy; • cephalexin because of redundancy; • vancomycin because MRSA is a frequent cause of community-acquired infections only in a minority of countries. The Committee recommended inclusion of cloxacillin (with a square box), and considered that any IV antistaphylococcal penicillin would be appropriate. For oral administration, cloxacillin, dicloxacillin and flucloxacillin are preferred because of their better bioavailability. 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.

EML recommendations: Bacterial infection of joint

First choice	Second choice

cloxacillin

cefazolin

clindamycin

amoxicillin + clavulanic acid

cefotaxime

ceftriaxone

1. Conterno LO, Turchi MD. Antibiotics for treating chronic osteomyelitis in adults. Cochrane Database Syst Rev. 2013;(9):CD004439.
2. Karamanis EM, Matthaiou DK, Moraitis LI, Falagas ME. Fluoroquinolones versus beta-lactam based regimens for the treatment of osteomyelitis: a meta-analysis of randomized controlled trials. Spine (Phila Pa 1976). 2008;33(10):E297–304.
3. Osmon DR, Berbari EF, Berendt AR, Lew D, Zimmerli W, Steckelberg JM et al. Diagnosis and management of prosthetic joint infection: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis. 2013;56(1):e1–25.
4. Berbari EF, Kanj SS, Kowalski TJ, Darouiche RO, Widmer AF, Schmitt SK et al. 2015 Infectious Diseases Society of America (IDSA) clinical practice guidelines for the diagnosis and treatment of native vertebral osteomyelitis in adults. Clin Infect Dis. 2015;61(6):e26–46.