Cefixime

Section: 6. Anti-infective medicines > 6.2. Antibacterials > 6.2.2. Watch group antibiotics

EMLc | ATC codes: J01DD08

Indication	Infectious gastroenteritis or colitis without specification of infectious agent ICD11 code: 1A40.Z
INN	Cefixime
Medicine type	Chemical agent
Antibiotic groups	WATCH
List type	Core
Formulations	**Oral > Liquid:** 100 mg per 5 mL powder for oral liquid (EMLc) **Oral > Solid:** 200 mg (as trihydrate) ; 400 mg (as trihydrate)
EML status history	First added in 2017 (TRS 1006)
Sex	All
Age	Also recommended for children
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Patents have expired in most jurisdictions Read more about patents.
Wikipedia	Cefixime
DrugBank	Cefixime

Expert Committee recommendation

The Expert Committee noted that, in most circumstances of non-bloody and non-febrile diarrhoea, watchful waiting, symptom relief and no antibiotic treatment is the appropriate first-line treatment option. The Expert Committee endorsed the inclusion of the following medicines: • Invasive bacterial diarrhoea/dysentery: ciprofloxacin as first-choice therapy and ceftriaxone or cefixime or azithromycin or sulfamethoxazole + trimethoprim as second-choice therapy (EML and EMLc) • Cholera: azithromycin (EMLc) or doxycycline (EML) as first-choice therapy and ciprofloxacin or doxycycline (EMLc) as a second choice; doxycycline should be used only in severe/life-threatening cases • C. difficile infection: metronidazole as first-choice therapy. The Expert Committee recommended the addition of vancomycin (oral) as second-choice therapy for C. difficile infection.

Background

Diarrhoea is an alteration in bowel movement characterized by an increase in the water content, volume and/or frequency of stools. Acute infectious diarrhoea can result from multiple causes depending on the setting and can include traveller’s diarrhoea, for which therapy is typically empirical; it can also be cause-specific, e.g. cholera in epidemic settings. In this section, the focus is on empirical treatment in keeping with the other sections in which the major syndrome treated empirically is traveller’s diarrhoea. However, because of the burden of infectious diarrhoea in low- and middle-income countries, the systematic review evidence for cause-specific diarrhoea is also assessed. The potential benefits of antibiotics need to be weighed against increasing resistance rates, the risk of

superinfection, and the harm caused by Shiga-toxin-producing organisms, which can be triggered by antibiotic exposure. Empirical treatment is usually considered in the case of febrile traveller's diarrhoea. In non-travel-related diarrhoea, empirical treatment should be considered only in the case of severe/invasive disease. The following summary considers the review of acute infectious diarrhoea conducted by the McMaster group and the review of the cholera and dysentery (shigellosis) guidelines for paediatrics conducted by the WHO Department of Maternal, Newborn, Child and Adolescent Health.

Summary of evidence

A 2000 Cochrane review assessed the effect of oral antibiotics in traveller's diarrhoea (1). Twelve randomized controlled trials (RCTs) showed a greater cure by 72 hours for any antibiotics compared with placebo (odds ratio (OR) 5.90; 95% confidence interval (CI) 4.06–8.57). Patients who took antibiotics experienced more side-effects than those taking placebo (OR 2.37; 95% CI 1.50–3.75). Antibiotics reviewed included fluoroquinolones, + sulfamethoxazole + trimethoprim, ampicillin, azithromycin, aztreonam, bicozamycin, furazolidone, pivmecillinam, and trimethoprim alone. Although the authors had planned to compare the different antibiotics, this analysis was not carried out because of concerns about significant publication bias; it was therefore not possible to prioritize one antibiotic over the other. A Cochrane review of patients with cholera (39 RCTs or quasi-experimental studies; 4623 participants) confirmed that antibiotics reduce both duration of diarrhoea and stool volume compared with placebo or no treatment; however, the list of antibiotics considered in the active treatment arm was so long (tetracycline, doxycycline, norfloxacin, sulfamethoxazole + trimethoprim, azithromycin, erythromycin, chloramphenicol, ciprofloxacin, furazolidone, pivmecillinam) that no conclusions could be reached on the efficacy of specific drug classes (2). The authors provided head-to-head comparisons for duration of diarrhoea and clinical cure. Duration was more than a day less with a single dose of azithromycin than with ciprofloxacin (mean difference 32.4 hours; 95% CI 1.95–62.9) and clinical failure was less common (risk ratio (RR) 0.32; 95% CI 0.23–0.44). Similarly, tetracycline was found to be superior to sulfamethoxazole + trimethoprim (RR 0.56; 95% CI 0.34–0.92 for clinical failure). Another Cochrane review assessed non-typhoidal Salmonella infection (12 RCTs; 767 participants) and concluded that there was a lack of benefit with antibiotic treatment; however, the review did not compare the various antibiotics (3). Microbiological cure was significantly better with fluoroquinolones compared with placebo (RR 0.33; 95% CI 0.20–0.56), but this did not translate into a benefit in clinically important outcomes. A further Cochrane review of RCTs treating Shigella dysentery concluded that there was insufficient evidence to consider any class of antibiotic to be superior (4). Fluoroquinolones were compared with beta-lactams in six RCTs with no significant difference; however, in trials where >90% of participants had confirmed Shigella, beta-lactams were more effective than fluoroquinolones (RR 4.68; 95% CI 1.74–12.59). Two trials compared fluoroquinolones with macrolides and two compared sulfamethoxazole + trimethoprim with beta-lactams; both comparisons showed no difference between groups. Single trials of sulfamethoxazole + trimethoprim versus furazolidone, oral gentamicin versus nalidixic acid, and sulfonamides versus tetracyclines showed no significant differences. The confidence intervals around the risk estimates were very wide, however, and a potentially patient-relevant difference between these antibiotics can therefore not be ruled out. The evidence for both empirical therapy of traveller's diarrhoea and treatment of laboratory-confirmed diarrhoeal infection in low- and middle-income countries is extremely limited, and no data could be found favouring one antibiotic over another. Thus, recommendations are based on guidelines (see below). The exception is confirmed Shigella dysentery, for which beta-lactams appear to be superior to fluoroquinolones. For cholera, there is evidence that azithromycin is superior to fluoroquinolones. Sulfamethoxazole + trimethoprim should be avoided as it was found to be inferior to doxycycline.

Guidelines

Although some guidelines give detailed recommendations for organism-specific infections, the McMaster application summarized therapy for empirical treatment. The 2001 IDSA (Infectious Diseases Society of America) guidelines recommended fluoroquinolones for adults and sulfamethoxazole + trimethoprim for children with traveller's diarrhoea (5). A caveat is warranted, however, because of the increasing rates of fluoroquinolone-resistant Campylobacter infections. Moreover, patients with enterohaemorrhagic Escherichia coli infections should

not be treated with antibiotics because of the higher risk of haemolytic uraemic syndrome. For cholera, these guidelines recommend doxycycline or tetracycline or a single dose of a fluoroquinolone. For non-typhi species of Salmonella, antibiotics are not routinely recommended, but if the infection is severe or if the patient is <6 months or >50 years old or has prostheses, valvular heart disease, severe atherosclerosis, malignancy or uraemia, sulfamethoxazole + trimethoprim (if susceptible), a fluoroquinolone or ceftriaxone is recommended. For Shigella, the choices are sulfamethoxazole + trimethoprim, a fluoroquinolone, nalidixic acid, ceftriaxone and azithromycin. The NICE (National Institute for Health and Care Excellence) guidelines for children <5 years recommend antibiotics in this age group only if there is suspected bacteraemia, extra-intestinal spread, age <6 months with Salmonella, malnourished or immunocompromised children, children with C. difficile enterocolitis, giardiasis, dysenteric shigellosis, dysenteric amoebiasis or cholera (6). The American College of Gastroenterology guidelines recommend antibiotics – a fluoroquinolone, azithromycin or rifaximin – for traveller's diarrhoea only when the likelihood of bacterial pathogens is high enough to justify the potential adverse effects (7). For C. difficile infections, metronidazole and oral vancomycin are recommended (8). The WHO Department of Maternal, Newborn, Child and Adolescent Health reviewed its existing guidelines for treatment of dysentery (shigellosis) and cholera in children. The reviews were informed by systematic literature reviews of the current evidence on the efficacy, safety and feasibility of antibiotic treatment options. Following expert consultation, the following recommendations were made for antibiotic treatment of dysentery and cholera: Dysentery • 1st line: ciprofloxacin oral liquid or tablets 15 mg/kg twice daily for 3 days • 2nd line: IV/IM ceftriaxone injection 50–100 mg/kg for 2–5 days (to be used only when local strains of Shigella are known to be resistant to ciprofloxacin) • Alternative 2nd line: azithromycin oral liquid or capsules 12 mg/kg on day 1 then 6 mg/kg on days 2–4 (total course: 4 days) or cefixime oral liquid or tablets, 8 mg/kg per day. Cholera Doxycycline oral liquid or tablets 4 mg/kg as a single dose or erythromycin oral liquid or tablets 12.5 mg/kg four times daily for 3 days or ciprofloxacin oral liquid or tablets 10–20 mg/kg twice daily for 5 days or azithromycin oral liquid or capsules 20 mg/kg as a single dose (only in epidemics). In non-epidemic situations, antibiotics should be used only for children with severe dehydration.

Rationale for antibiotic selection

For traveller's diarrhoea, sulfamethoxazole + trimethoprim was proposed as a core antibiotic for both children and adults, if treatment is deemed necessary. Azithromycin and fluoroquinolones, although listed as alternatives in the IDSA guidelines, should be used only if no other more appropriate options are available because of resistance concerns as well as the potential for harm. Given the superiority of beta-lactams for treatment of confirmed Shigella dysentery, ceftriaxone was proposed as a core antibiotic. For cholera, azithromycin should be considered first-line treatment on the basis of the systematic review evidence, with doxycycline as another option as listed in guidelines. Metronidazole (oral treatment preferred) and oral vancomycin are listed as core antibiotics for treatment of C. difficile infections. Ofloxacin, norfloxacin and nalidixic acid were not proposed because of redundancy; other fluoroquinolones were proposed for several more indications across all syndromes. Rifaximin was not included on the basis of redundancy; other options are available that are also relevant for other indications. Based on recommendations from experts from low- and middle-income countries on the advisory panel, chloramphenicol is proposed for the preserved list as a last-resort option for typhoid fever if no other antibiotics are available. Sulfamethoxazole + trimethoprim, ciprofloxacin and erythromycin are not recommended for treatment of cholera based on data from systematic reviews.

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 applications for alignment with WHO guidelines and under the guiding principle of parsimony and selected first- and second-choice antibiotics for acute infectious diarrhoea for inclusion on the EML and/or EMLc. As a result, levofloxacin and erythromycin were excluded. Ciprofloxacin was preferred to levofloxacin (for parsimony, and to preserve levofloxacin as a treatment for multidrug-resistant tuberculosis). Recommended first- and second-choice antibiotics are reported below. The first-choice antibiotics are those generally recommended on the basis of available evidence and are usually

narrow-spectrum agents.

EML recommendations: Infectious gastroenteritis or colitis without specification of infectious agent

First choice

- ciprofloxacin

Second choice

- cefixime
- azithromycin
- sulfamethoxazole + trimethoprim
- ceftriaxone

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4. Christopher PR, David KV, John SM, Sankarapandian V. Antibiotic therapy for Shigella dysentery. Cochrane Database Syst Rev. 2010;(8):CD006784.
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6. Khanna R, Lakhanpaul M, Burman-Roy S, Murphy MS. Diarrhoea and vomiting caused by gastroenteritis in children under 5 years: summary of NICE guidance. BMJ. 2009;338:b1350.
7. Riddle MS, DuPont HL, Connor BA. ACG Clinical Guideline: Diagnosis, Treatment, and Prevention of Acute Diarrheal Infections in Adults. Am J Gastroenterol. 2016;111(5):602–22.
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