Azithromycin

Essential medicine status

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

EMLc | ATC codes: J01FA10

Indication	Typhoid fever ICD11 code: 1A07
INN	Azithromycin
Medicine type	Chemical agent
Antibiotic groups	WATCH
List type	Core *also listed for single-dose treatment of trachoma and yaws
Formulations	Oral > Liquid: 200 mg per 5 mL oral liquid Oral > Solid: 250 mg (anhydrous) capsule ; 500 mg (anhydrous) capsule
EML status history	First added in 2019 (TRS 1021)
Sex	All
Age	Also recommended for children
Therapeutic equivalence	The recommendation is for this specific medicine
Patent information	Patents have expired in most jurisdictions Read more about patents.
Wikipedia	Azithromycin
DrugBank	Azithromycin

Expert Committee recommendation

The Expert Committee endorsed listing of ciprofloxacin, ceftriaxone and azithromycin as first-choice treatments for typhoid and paratyphoid (enteric) fever on the core list of the EML and EMLc. Ciprofloxacin is recommended as first-choice in settings with low prevalence of fluoroquinolone resistance, while ceftriaxone and azithromycin are recommended first-choice treatments in settings where there is a high prevalence of fluoroquinolone resistance. Ciprofloxacin, azithromycin and ceftriaxone are all classified as Watch group antibiotics (Section 6.2.2). Following the principle of parsimony, the Expert Committee did not recommend the addition of ofloxacin for this indication, noting that ofloxacin and ciprofloxacin have demonstrated similar clinical performance for this indication in clinical trials.

Background

Enteric fever, a bloodstream infection caused by Salmonella enterica serovars Typhi and Paratyphi, causes a major public health burden, especially in children and young adults in resource-limited settings. Recent estimates put the burden of enteric fever at 16 million cases and an estimated 150000 deaths per year (1). Resistance to first-line treatments (multidrug resistance (MDR) defined as resistance against chloramphenicol, ampicillin and trimethoprim/ sulfamethoxazole) and to fluoroquinolone antibiotics is now ubiquitous at the global level (2). Resistant infections cause high clinical failure rates and prolonged carriage, increasing the risk of complications (intestinal haemorrhage, gut perforation and encephalopathy) in the individual patient, and lead to continued transmission in families and their communities (3). There are now very few effective treatment options. Worryingly, extensively drug-resistant (XDR) S. Typhi strains, combining MDR, resistance to fluoroquinolones and third-generation cephalosporins, have recently been reported in Pakistan (4). The most recent WHO Guidelines for the diagnosis, treatment and prevention of typhoid were published in 2003, and are now outdated particularly in an era of widespread drug resistance (5). Antibiotic treatment and

sanitation have been the only widely used intervention aimed at reducing the burden of enteric fever. Vaccines have been underutilized. The recent decision of Gavi, the Vaccine Alliance, to support the introduction of the new typhoid conjugate vaccine, Typbar-TCV, into the routine immunization schedules of eligible countries will help, but may take many years to be fully implemented and effective in endemic countries (6). In addition to antimicrobial resistance, there are several issues in the management of enteric fever. The sensitivity of blood culture is low, only approximately 40% of patients with enteric fever will have a positive blood culture (5, 7). In low- and middle-income countries, blood culture facilities are often not available. There are no rapid tests with acceptable sensitivity and specificity (3, 5). Treatment is usually empirical.

Summary of evidence

The application identified two Cochrane systematic reviews that evaluated antibiotic treatment of typhoid fever. A 2011 Cochrane systematic review of 26 trials involving 3033 patients evaluated fluoroquinolones for treatment of typhoid and paratyphoid fever (8). The review did not include comparisons with antibiotics that are no longer recommended for use in enteric fever (e.g. norfloxacin due to its poor bioavailability). Antibiotic resistance is an important consideration for efficacy; an earlier version of this SR combined different generations of fluoroquinolones in one sub-group, stratified according to the prevalence of MDR and nalidixicresistant (NaR) strains (9). However, the updated version grouped studies by each fluoroquinolone individually. Results are presented as risk ratios (RR; 95%CI) for categorical data and mean difference (MD; 95%CI) for continuous data. Ciprofloxacin versus chloramphenicol Four trials (293 patients) compared ciprofloxacin to chloramphenicol, only one trial included children above 12 years of age, none of the trials reported the prevalence of MDR and NaR strains. For clinical failure, the results favoured ciprofloxacin (RR 0.24, 95%CI 0.07 to 0.82), although confidence intervals were wide, due to the small sample size (low quality evidence). Fever clearance time (FCT) (two trials; 147 patients) also favoured ciprofloxacin, the mean difference (MD) was −62.46 hours (95%CI −75.52 to −49.39) (moderate quality evidence). Small numbers of events occurred for microbiological failure (two trials, 142 patients; RR 0.05, 95%CI 0.00 to 0.81) (low quality evidence) and relapse (four trials, RR 0.15, 95%CI 0.02 to 1.15) (low quality evidence). The results for serious adverse events (two trials) were indeterminate (RR 0.99, 95%CI 0.18 to 5.52) (very low quality evidence) and for non-serious adverse events (four trials), the results were comparable (RR 1.00, 95%CI 0.61 to 1.64), but with wide confidence intervals (low quality evidence) (8). Ofloxacin versus chloramphenicol Four trials (247 patients) compared ofloxacin to chloramphenicol. The results for clinical failure were in favour of ofloxacin, but with wide confidence intervals (RR 0.15, 95%CI 0.03 to 0.64) (low quality evidence). Fever clearance time (two trials, 140 patients) followed the same trends as clinical failures, the MD was −75.85 hours (95%CI −88.52 to −63.17) (moderate quality evidence). Due to the small numbers of events, the results for microbiological failure (three trials, RR 0.16, 95%CI 0.02 to 1.07) (low quality evidence) and relapse (RR 0.14, 95%CI 0.01 to 2.65) (low quality evidence) were indeterminate. For serious adverse events (one trial), the RR was not estimable due to zero events. For non-serious adverse event (four trials), the results were comparable, with a RR of 1.06 and wide confidence intervals (95%CI 0.60 to 1.87) (low quality). The SR included one trial (252 patients) that compared gatifloxacin (which was not proposed in the application for EML listing), versus chloramphenicol (RR for clinical failure was 0.79, 95%CI 0.32 to 1.96) (7). Nonserious adverse events favoured gatifloxacin (RR 0.58, 95%CI 0.44 to 0.78). Ciprofloxacin/ofloxacin versus cotrimoxazole and ampicillin/amoxicillin The application reported comparisons of ciprofloxacin versus cotrimoxazole (two trials, 132 patients), ofloxacin versus cotrimoxazole (one trial, 99 patients), ofloxacin versus ampicillin (one trial, 40 patients), ofloxacin versus amoxicillin (one trial, 50 patients). However, due to the small sample sizes the results were indeterminate and the individual outcomes were assessed as low or very low quality. Therefore, cotrimoxazole and ampicillin/amoxicillin were not proposed in the application for EML listing. Ciprofloxacin/ofloxacin versus cefixime The comparisons of ciprofloxacin versus cefixime and ofloxacin versus cefixime were each based on one trial. Due to the weakness and low/very low quality of the evidence, cefixime was not proposed in the application for EML listing. A randomized controlled trial that compared gatifloxacin versus cefixime (158 patients), was stopped early by the Independent Data Safety and Monitoring Board due to the high number of failures (19/70) in the cefixime arm (RR 0.04, 95%CI 0.01 to 0.31) ($p<0.001$) (10). This trial was included in the SR but was not part of the comparisons evaluated in the application for inclusion in the EML. Ciprofloxacin versus ceftriaxone For this comparison, only one trial (42 adult participants) was available. Due to the very small number of patients, the result was indeterminate. There is no estimate for FCT and adverse events were not reported. The overall quality of the evidence was accessed as very low. More than 50% of strains were MDR. Ofloxacin versus ceftriaxone For this comparison, only one trial (47 adult participants) was available. More than 50% of strains were MDR, no NaR was reported. For clinical failure, a nonsignificant result in favour of ofloxacin was reported, (RR 0.09, 95%CI 0.01 to 1.46), the MD in FCT was −115 hours (95%CI −150.67 to −79.33). Ciprofloxacin versus azithromycin For this comparison, only one trial (64 participants) was available. Due to the small sample size (0 events in both

arms), clinical failure, microbiological failure and relapse were not estimable. The MD for FCT was −12 hours (95%CI −24.39 to 0.39). The quality of the evidence was low/very low. Ofloxacin versus azithromycin Two trials were available (213 patients) for this comparison. Clinical failure favoured azithromycin with a RR of 2.2 (95%CI 1.23 to 3.94) (high quality of evidence), the MD in FCT of 30.41 hours (95%CI −22.12 to 82.93) (moderate quality evidence) supported azithromycin. The higher failure rates in the ofloxacin arm in the more recent of the two trials, reflected the increasing prevalence of NaR S. typhi isolates in this region. The systematic review included one azithromycin trial (287 patients), that compared gatifloxacin to azithromycin (11). Gatifloxacin and azithromycin had similar high efficacy (RR for clinical failure 0.98, 95%CI 0.32 to 2.96) in this setting with high proportions of NaR S. typhi strains. A 2008 Cochrane systematic review of seven trials involving 773 patients evaluated azithromycin for treatment of uncomplicated typhoid and paratyphoid fever (12). The comparison azithromycin versus chloramphenicol (one trial, 77 patients) showed a benefit for azithromycin, but due to the small sample size and wide confidence intervals no inferences can be made (odds ratio (OR) for clinical failure 0.16, 95%CI 0.01 to 3.4 (low quality evidence)). Four trials (564 patients) compared azithromycin to the fluoroquinolones (including gatifloxacin) and were discussed above. Two trials (132 patients) compared azithromycin versus ceftriaxone. Clinical failure (OR 2.58, 95%CI 0.48 to 13.87) and FCT (MD 9.12 h. 95%CI −1.11 to 19.36) favoured ceftriaxone (moderate quality evidence). No data were available to assess adverse events. The application described a systematic search for randomized controlled trials (RCTs) in enteric fever to supplement evidence obtained from the two SRs. The majority of identified RCTs had small sample sizes, few events and lacked sufficient power to detect significant differences. Four trials with sample sizes greater than 30 patients in each arm were reviewed. Two trials had zero events for clinical failure. A trial of gatifloxacin versus ofloxacin (218 culture-positive patients) showed similar numbers of treatment failures in both arms (hazard ratio, HR 0.81, 95%CI 0.25 to 2.65), however the FCT was significantly shorter in the gatifloxacin arm (HR 1.59, 95%CI 1.16 to 2.18) in this setting with high NaR (13). Similar proportions of patients experienced adverse events, most of which were mild (Grade 1 or Grade 2). A trial of gatifloxacin versus ceftriaxone (116 culture-positive patients) showed similar number of failures in the intention-to-treat (ITT) patients, but in the culture-confirmed patients, the comparison favoured ceftriaxone (HR 0.24, 95%CI 0.08 to 0.73) (14). Treatment failure was associated with the emergence of high-level fluoroquinolone resistance in S.typhi, requiring the trial to be stopped. A similar number of non-serious adverse events occurred in each treatment group, and no serious events were reported.

Guidelines

The 2003 WHO guidelines on the diagnosis, treatment and prevention of typhoid fever (5) make the following recommendations for treatment of uncomplicated typhoid fever, based on susceptibility of infection: – Fully sensitive: a fluoroquinolone (ofloxacin or ciprofloxacin) as optimal therapy. Chloramphenicol, amoxicillin or sulfamethoxazole + trimethoprim are alternatives. – Multidrug resistance: a fluoroquinolone or cefixime as optimal therapy. Azithromycin or cefixime are alternatives. – Quinolone resistance: azithromycin or ceftriaxone as optimal therapy. Cefixime is an alternative. The 2012 WHO pocket book recommendations for management of common childhood conditions (15) make the following recommendations for the treatment of typhoid fever in children: – Children with typhoid fever should be treated with a fluoroquinolone (i.e. ciprofloxacin, gatifloxacin, ofloxacin and perfloxacin) as a first-line treatment for 7–10 days (strong recommendation, moderate quality evidence). – If response to treatment is poor, consider drug-resistant typhoid and treat with a second-line antibiotic such as a third-generation cephalosporin or azithromycin for 5–7 days (strong recommendation, moderate quality evidence). – Where drug resistance to antibiotics among salmonella isolates is known, follow national guidelines according to local susceptibility data (strong recommendations, moderate quality evidence).

Rationale for antibiotic selection

Although recommended in the 2003 WHO guidelines, ampicillin/amoxicillin and trimethoprim-sulfamethoxazole were not proposed in the application for inclusion in the EML for typhoid fever due to the lack of data showing any benefit over comparators based on evidence from the SRs identified. Chloramphenicol is recommended in the 2003 WHO guidelines but not in the 2012 WHO pocket book. There has been conflicting evidence from smaller trials, however, a large trial showed similar efficacy to gatifloxacin, a fourth-generation fluoroquinolone, but higher numbers of Grade 1 and 2 adverse events. Due to the need to monitor blood counts, the long treatment duration and the availability of alternative drugs, chloramphenicol was not proposed in the application for inclusion on the EML. The application proposed the inclusion of ofloxacin and ciprofloxacin on the EML and EMLc, supported by evidence from the SRs and clinical practice guidelines (CPGs). More clinical trials evaluating ofloxacin have been performed, however, ofloxacin is not currently included on the EML. As ciprofloxacin is currently listed and has similar clinical performance, for parsimony, ciprofloxacin only could be considered. Although included in the 2003 WHO guidelines, the evidence from the SRs did not support

listing of cefixime. In comparisons with fluoroquinolones, cefixime, showed higher number of failures and longer FCTs, however, in comparisons with chloramphenicol, it compared favourably. The application also proposed listing ceftriaxone and azithromycin on the EML and EMLc for typhoid fever, supported by evidence from SR and CPGs.

Committee considerations

The Expert Committee agreed that knowledge of the local resistance patterns for S.typhi and S. paratyphi strains was critical for making empiric treatment choices in the treatment of enteric fever, noting that there are reports of high rates of fluoroquinolone resistance in some settings. This is the first time the Expert Committee has considered resistance patterns in making specific recommendations for empiric treatment. 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 EMLc.

EML recommendations: Typhoid fever

First choice	Second choice
ciprofloxacin	
ceftriaxone	
azithromycin	

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