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Review of Antibacterial Medicines for the Treatment of Enteric Fever for the WHO Model List of Essential Medicines 2019 Update

Centre for Tropical Medicine and Global Health, University of Oxford, United Kingdom

**Essential Medicine List Application for Special Indication:**

**Typhoid and Paratyphoid Fever**

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Scope of work

The objective of this application is to review the available evidence on the efficacy and safety of antibiotic treatments for enteric fever (typhoid fever and paratyphoid fever) and add enteric fever as new indication for selected antibiotics listed in the current Essential Medicine List [1].

Introduction

Enteric fever, a bloodstream infection caused by *Salmonella enterica* serovars Typhi and Paratypi 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 150 000 deaths per year, causing 10 Mio DALYs [2]. 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 [3]. 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 [4] There are now very few effective treatment options. Worryingly, Extensively Drug Resistant (XDR) *S. Typhi* strains, combining MDR, resistance to fluoroquinolones and third-generation cephalosporines, have recently been reported in Pakistan [5]. The, current WHO Guidelines ‘Background document: The diagnosis, treatment and prevention of typhoid fever’ were last published in 2003, are clearly now outdated particularly in an era of widespread drug resistance [6].

Antibiotic treatment and sanitation have been the only widely used intervention aimed at reducing the burden of enteric fever. Vaccines have been underutilised. The recent decision of Gavi, the Vaccine Alliance, to support the introduction of the new typhoid conjugate vaccine, Typbar-TCV into the routine immunisation schedules of eligible countries will help, but may take many years to be fully implemented and effective in endemic countries [7].

Background to this application

The WHO Essential Medicine List (EML) lists the most efficacious and safe medicines, including antibiotics to treat illnesses that are considered high priority. The 20th EML, published in 2017, provided new guidance to optimise antibiotic use for many common infections and categorised antibiotics into three groups:
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ACCESS, WATCH, RESERVE. The choice of an effective antibiotics to treat patients is an important tool in the fight against antimicrobial drug resistance (AMR) and is part of the WHO Global Action [8]. The aim of this proposal is to add enteric fever as new indication for selected antibiotics included in the Essential Medicines List. We performed systematic reviews to evaluate the safety and efficacy of antibiotics that are recommended in national and international enteric fever treatment guidelines following the process outlined in the Guideline Development Handbook [9]. We believe that special attention should be paid to the impact of drug resistance on treatment, and the impact of sub-optimal treatment on individuals and on secondary transmission in the community.

This review was based on the syndrome-based approach that McMaster University performed for the 2017 EML update. It needs to be noted that the patterns of antimicrobial susceptibilities can differ from place to place and over time, and that knowledge about local resistance patterns is necessary to inform empiric treatment. Surveillance and sharing of antimicrobial resistance data is critical in order to combat resistance and to inform the correct choice of antibiotic treatment [8].

**General considerations regarding enteric fever trials**

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 [6, 10]. In low and middle income countries (LMICs), blood culture facilities are often not available. There are no rapid tests with acceptable sensitivity and specificity [4, 6]. Treatment is usually empirical.

The Cochrane Collaboration performed several systematic reviews evaluating the efficacy and safety of fluoroquinolones and azithromycin for the treatment of enteric fever [11, 12]. An issue that was consistently highlighted were the small sample sizes of randomised controlled trials (RCTs) and the lack of standardised outcome definitions, which made pooling of data in a meta-analysis difficult [13]. Earlier trails did not perform intention-to-treat analysis (ITT), but only reported the results for blood culture positive patients. All RCTs of antibiotics were conducted in patients with uncomplicated enteric fever. The majority of trials include typhoid fever patients only, since the proportion of S. Paratyphi A strains in Asia has increased only relatively recently. Typhoid and paratyphoid fever are clinically indistinguishable [14], there is no evidence of a different impact of treatment between the serovars and treatment recommendations.
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apply to both. We will use enteric fever as the more comprehensive term.

Synopsis of evidence from Systematic Reviews

Methods

Data searches for systematic reviews and meta-analyses of randomised controlled trials in enteric fever

We developed a comprehensive search syntax, combining systematic reviews, meta-analysis with randomised controlled trials AND enteric fever/typhoid fever/paratyphoid fever. We performed a systematic search in MEDLINE, Embase and the Cochrane Database of Systematic Reviews (Appendix Table 1 and Figure 1) from January 1990 to January 2018. We identified 218 articles. Two researchers (CD, SK) independently screened titles, abstracts and full texts. Screening at title and abstract level excluded 193 references, 25 full text articles were accessed for eligibility. We excluded 13 articles and reviewed 12 systematic reviews (SR). One SR was a duplication [15], two full texts could not be retrieved [16, 17], one article was a published protocol [18], one was an older review on chloramphenicol in infectious diseases [19], two references pertained to a Cochrane SR, that had been withdrawn [20, 21] and three were SR on fluoroquinolones for the treatment of enteric fever by the Cochrane Collaboration or their authors [13, 22, 23], which were superseded by the most recent version [11]. We retained two Cochrane SR for final assessment, one on FQ for the treatment of enteric fever [11] and one on azithromycin [24].

Quality assessment of outcomes reported in Systematic Reviews and Meta-analyses

We evaluated the quality of evidence for the following outcomes: clinical failure, fever clearance time (FCT), microbiological failure, relapse, serious adverse events and non-serious adverse events according to the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) criteria, as outlined in the WHO Handbook for Guideline Development [9]. We adopted the approach used for the Recommendations for Management of Common Childhood Conditions [25] in our assessment. Two researchers independently evaluated limitations of the study (in terms of study design, allocation, concealment, blinding and loss to follow-up), precision of results, consistency, generalizability and
Results

Effa 2011

The Cochrane SR on fluoroquinolones for treating typhoid and paratyphoid fever included 26 trails, involving 3033 patients [11]. The 2011 update does not include comparisons with antibiotics that are no longer recommended for use in enteric fever (e.g. norfloxacin due to its poor bioavailability).

An important consideration for efficacy is antibiotic resistance; an earlier version of this Cochrane SR combined different generations of fluoroquinolones in one subgroup, stratified according to the prevalence of MDR and nalidixic resistant (NaR) strains [13]. However, the most recent SR 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.

Outcomes: Fluoroquinolones versus first-line drugs

Ciprofloxacin versus chloramphenicol

Four trials (Gottuzzo 1992, Morelli 1992, Gasem 2003, Rizvi 2009*; 293 patients) compared ciprofloxacin to chloramphenicol, only one trial included children above 12 years (Rizvi, 2009), none of the trials reported the prevalence of MDR and NaR strains.

For clinical failure (4 trials, 293 patients) the results favoured ciprofloxacin (RR 0.24; 95% CI 0.07 to 0.82), confidence intervals were wide, due to the small sample size (low quality evidence). Appendix Table 3 shows the GRADE outcome assessment.

Fever clearance time (FCT) (2 trials; 147 patients) also favoured ciprofloxacin, the mean difference (MD) was -62.46 hours (95% CI, -75.52 to -49.39) (moderate quality).

Small numbers of events occurred for microbiological failure (two trials, 142 patients; RR 0.05; 0.00 to 0.81) (low quality evidence) and relapse (4 trials, RR 0.15; 0.02 to 1.15) (low quality evidence).

The results for serious adverse events (2 trials) were indeterminate (RR 0.99; 0.18 to 5.52) (very low quality
Evidence and for non-serious adverse events (4 trials), the results were comparable (RR 1.00; 0.61-1.64), but with wide confidence intervals (low quality evidence).

**Ofloxacin versus chloramphenicol**


The results for clinical failure (4 trials) were in favour of ofloxacin, but with wide confidence intervals (RR 0.15; 0.03 to 0.64) (low quality evidence). Fever clearance time (2 trials, 140 patients) followed the same trends as clinical failures, the MD was -75.85 hours (-88.52 to -63.17) (moderate quality evidence).

Due to the small numbers of events, the results for microbiological failure (3 trials, RR 0.16; 0.02 to 1.07) (low quality evidence) and relapse (RR 0.14; 0.01 to 2.65) (low quality evidence) were indeterminate.

For serious adverse events (1 trial), the RR was not estimable due to zero events. For non-serious adverse event (4 trials), the results were comparable with a RR of 1.06, with wide confidence intervals (0.60 to 1.87) (low quality).

*Rizvi performed a multi-arm study and compared ofloxacin, ciprofloxacin, chloramphenicol, cefixime and cotrimoxazole. None of the studies reported resistance.

The SR includes one trial (252 patients), that compared gatifloxacin, which is not part of this application, versus chloramphenicol (RR for clinical failure was 0.79; 0.32 to 1.96) [10]. Non-serious adverse events favoured gatifloxacin (0.58; 0.44 to 0.78).

**Ciprofloxacin/ofloxacin versus cotrimoxazole and ampicillin/amoxicillin**

We also tabulated the results (Appendix Table 3. GRADE outcome assessment) for the comparisons of ciprofloxacin versus cotrimoxazole (2 trials, 132 patients), ofloxacin versus cotrimoxazole (1 trial, 99 patients), ofloxacin versus ampicillin (1 trial, 40 patients), ofloxacin versus amoxicillin (1 trial, 50 patients), however, due to the small sample sizes the results were indeterminate and the individual outcomes were accessed as low or very low quality. We therefore did not add cotrimoxazole and ampicillin/amoxicillin to the list.
Ciprofloxacin/ofloxacin versus third-generation cephalosporines

Ciprofloxacin/ofloxacin versus cefixime

The comparisons of ciprofloxacin versus cefixime and ofloxacin versus cefixime were each based on one trial (Rizvi, 2007, Phuong, 1999). Due to the weakness and low/very low quality of the evidence, cefixime was not included here (Appendix Table 3. GRADE outcome assessment).

A RCT that compared the fourth generation fluoroquinolone gatifloxacin, which is not part of the EML, 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; 0.01 to 0.31) (p<0.001) [26]. This trial is included in the SR [11], but does not constitute part of the comparisons evaluated for inclusion in the EML list, due to the gatifloxacin arm.

Ciprofloxacin versus ceftriaxone

For this comparison, there was only one trial available (Wallace 1993; 42 participants, adults only). 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

One trial was available (Smith, 1994; 47 participants, adults only), More than 50% of strains were MDR, no NaR was reported. For clinical failure, they reported a non-significant result in favour of ofloxacin, (RR was 0.09, 0.01 to 1.46), the mean difference in FCT was -115 hours (-150.67 to -79.33).

Ciprofloxacin/ofloxacin versus azithromycin

Ciprofloxacin versus azithromycin

Only one trial (Girgis 1999, Egypt, 64 participants) was available for this comparison. 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 (-24.39 to 0.39). The quality of the evidence was low/very low.
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**Ofloxacin versus azithromycin**

Two trials were available (Chinh 2000; Parry 2007; 213 patients). Clinical failure favoured azithromycin with a RR of 2.2 (1.23 to 3.94) (high quality of evidence), the MD in FCT of 30.41 hours (-22.12 to 82.93) (moderate quality) supports azithromycin (Appendix Table 3. GRADE outcome assessment).

The higher failure rates in the ofloxacin arm in the more recent trial (Parry, 2007), reflected the increasing prevalence of NaR S. Typhi isolates in this region.

The SR includes one azithromycin trial (287 patients), that compared gatifloxacin to azithromycin [27]. Whilst gatifloxacin is not part of this application, gatifloxacin and azithromycin had similar high efficacy (RR for clinical failure 0.98 (0.32 to 2.96)) in this setting with high proportions of NaR S. Typhi strains.

**Effa 2008**

The Cochrane SR on azithromycin for treating uncomplicated typhoid and paratyphoid fever included 7 trials and 773 patients [12].

The comparison azithromycin versus chloramphenicol (Butler 1999; 77 patients) showed a benefit for azithromycin, but due to the small sample size and wide confidence intervals no inferences can be made (OR for clinical failure, 0.16 (0.01 to 3.4) (low quality evidence). Four trials (564 patients) compared azithromycin to the fluoroquinolones (this included gatifloxacin) and were discussed above.

Two trials (Frenck 2000, Frenck 2004; 132 patients) compared azithromycin versus ceftriaxone. Clinical failure (OR 2.58; 0.48 to 13.87) and FCT (MD 9.12 h; -1.11 to 19.36) favoured ceftriaxone (moderate quality evidence). No data were available to assess adverse events.

**Synopsis of evidence from Randomised Controlled Trials**

**Methods**

**Search strategy for randomised controlled enteric fever trials**

We performed systematic searches for enteric fever RCTs to supplement the evidence obtained from the SR. We searched PubMed from 1990 to October 2018 for all randomised controlled trials for the treatment
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of enteric fever, including the two MeSH terms “Typhoid Fever” or “Paratyphoid Fever”, with typhoid, paratyphoid, “enteric fever” or “enteric fevers” as text words.

Two investigators independently screened the identified 341 articles, and retained 44 enteric fever treatment trials (Appendix Figure 2. Flowchart of additional randomised controlled trials). We removed duplicate articles that were included in the SR and reports of antibiotics that were no longer in clinical use, ultimately retaining 12 RCTs for review. Two researchers independently abstracted the trial data (Appendix Table 7. Characteristics and outcomes of additional randomised controlled trials).

Quality assessment of randomised controlled trials

We used the Cochrane risk of bias assessment tool to assess the quality of the 12 RCTs. Appendix Table 6. Quality assessment of randomised controlled trials.

Results

In keeping with previous SR results, the majority of RCTs had small sample sizes, few events and had a lack of power to detect significant differences (Appendix Table 7. Characteristics and outcomes of additional randomised controlled trials). We selected four trials with a sample size of more than 30 patients in each arm for further review. Two of those had zero events for clinical failure (Tatli 2003, 72 patients and Girgis 1995, 93 patients). A larger 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 [28]. Similar proportions of patients experienced adverse events, most of which were mild (grade 1 or grade 2).

One larger, more recent trial (116 culture positive patients) compared gatifloxacon versus ceftriaxone; there were similar number of failures in the ITT patients, but in the culture confirmed patients, the comparison favoured ceftriaxone (HR 0·24; 95% CI 0·08 to 0·73) [29]. 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.
Synopsis of guidelines

Methods

Search strategy for Clinical Practice Guidelines

We performed a systematic review of Clinical Practice Guidelines (CPGs). The search strategy is listed in Appendix Table 8, publication dates were restricted from January 1990 to January 2019. Two investigators independently screened 321 articles. The Flow Chart is shown in Appendix Figure 3. We retained nine articles for full-text review and of those four for evaluation.

Quality assessment of Clinical Practice Guidelines

We used the AGREE (Appraisal of Guidelines, Research and Evaluation) II instrument to appraise the quality of CPGs [30]. Amongst other items, the CPG needed to contain an explicit methods section, which included the search strategy, state how decisions were made and potential conflicts of interest. Two researchers independently assessed the quality of the selected guidelines using the AGREE II score sheet. We evaluated the following five domains: scope and purpose, stakeholder involvement, rigor of development, clarity of presentation, editorial independence. Individual quality scores of the domain were added up and scaled as percentage of the maximum attainable score of the domain. We calculated mean percentages for each domain and these were used to arrive at an overall percentage score for the guideline.

Results

We evaluated four CPGs, but removed two due to low scores [31, 32]. The highest scoring CPG (88%) was the WHO Recommendations for Management of Common Childhood Conditions: Pocket Book Recommendations [25]. The WHO Background document: The diagnosis, treatment and prevention of typhoid fever, was published in 2003 and did not conform to the more formalised structure of contemporary guideline development (56%).

The recommendations of both guidelines are shown in Appendix Table 10.
Selection of antibiotics

Please note that knowing the local resistance pattern for *S. Typhi* and *S. Paratyphi* strains is critical for making empiric choices.

Although listed in an earlier CPG (WHO Guidelines), ampicillin/amoxicillin and trimethoprim-sulfamethoxazole were not included due to the lack of data showing any benefit over comparators (evidence from SR).

Chloramphenicol is recommended in the WHO treatment guidelines [6], but not in the pocket handbook [25]. 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 adverse events (grade 1 and 2). Due to the necessity to monitor blood counts, the long treatment duration, and the availability of alternative drugs, chloramphenicol is not listed for inclusion in the EML.

We are listing ofloxacin and ciprofloxacin supported by evidence from SR and CPG. More clinical trials evaluating ofloxacin have been performed, however, ofloxacin is not included in the EML. We therefore list ciprofloxacin, which has similar clinical performance.

Although included in the WHO guidelines [6], the evidence from the SR does not support listing cefixime. In comparisons with fluoroquinolones, cefixime showed higher number of failures and longer FCTs, however, in comparisons with chloramphenicol, it compared favourably.

We are listing ceftriaxone and azithromycin supported from evidence from SR and CPG.
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### Antibiotic EVIDENCE FROM CPG-WHO CPG-WHO EML Comments

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Adults</th>
<th>Children</th>
<th>SR</th>
<th>additional RCTs</th>
<th>Treatment Guidelines 2003</th>
<th>Pocket book 2012</th>
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</thead>
<tbody>
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<td></td>
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<td>✓</td>
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<td>✓</td>
<td>oral, divided into two daily doses</td>
<td>primary indication</td>
<td></td>
</tr>
<tr>
<td>Ofloxacin</td>
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<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>oral, divided into two daily doses NOT IN EML, CIPROFLOXACIN HAS SIMILAR CLINICAL PERFORMANCE WITHIN THE PHARMACOLOGICAL CLASS.</td>
<td>primary indication</td>
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<tr>
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<td></td>
<td>^</td>
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<td>✓</td>
<td>✓</td>
<td>intravenous, once daily dose</td>
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</table>

Treatment duration is 7 days

^Limited evidence in favour of antibiotics.
FDA warning

Both fluoroquinolones and azithromycin have black box warnings by the FDA. In 2016, the FDA enhanced warnings about the association of fluoroquinolones with disabling and potentially permanent side effects involving tendons, muscles, joints, nerves and the central nervous system. Because the risk of these serious side effects generally outweighs the benefits for patients with acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis and uncomplicated urinary tract infections, the FDA determined that fluoroquinolones should be reserved for use in patients with these conditions who have no alternative treatment options. The U.S. Food and Drug Administration (FDA) is warning the public that azithromycin (Zithromax or Zmax) can cause abnormal changes in the electrical activity of the heart that may lead to a potentially fatal irregular heart rhythm. Patients at particular risk for developing this condition include those with known risk factors such as existing QT interval prolongation, low blood levels of potassium or magnesium, a slower than normal heart rate, or use of certain drugs used to treat abnormal heart rhythms, or arrhythmias. This communication is a result of our review of a study by medical researchers as well as another study by a manufacturer of the drug that assessed the potential for azithromycin to cause abnormal changes in the electrical activity of the heart.
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