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Antibiotics for the treatment of dysentery in children

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Background Ciprofloxacin, ceftriaxone and pivmecillinam are the antibiotics currently recommended by the World Health Organization (WHO) for the treatment of dysentery in children; yet there have been no reviews of the clinical effectiveness of these antibiotics in recent years.

Methods We reviewed all literature reporting the effect of ciprofloxacin, ceftriaxone and pivmecillinam for the treatment of dysentery in children in the developing countries. We used a standardized abstraction and grading format and performed meta-analyses to determine the effect of treatment with these antibiotics on rates of treatment failure, bacteriological failure and bacteriological relapse. The CHERG Standard Rules were applied to determine the final effect of treatment with these antibiotics on diarrhoea mortality.

Results Eight papers were selected for abstraction. Treatment with ciprofloxacin, ceftriaxone or pivmecillinam resulted in a cure rate of >99% while assessing clinical failure, bacteriological failure and bacteriological relapse.

Conclusions The antibiotics recommended by the WHO—ciprofloxacin, ceftriaxone and pivmecillinam—are effective in reducing the clinical and bacteriological signs and symptoms of dysentery and thus can be expected to decrease diarrhoea mortality attributable to dysentery.

Keywords Ciprofloxacin, ceftriaxone, pivmecillinam, diarrhoea, dysentery, morbidity, mortality, treatment

Background

Dysentery is a major cause of childhood morbidity and mortality in developing countries. Most dysentery cases in the tropics are caused by *Shigella*,[1] whereas dysentery in the developed countries is usually caused by *Salmonella*.[2] Death rates as high as 6.2% have been reported during epidemics of Shigella dysenteriae type 1.[3] The provision of effective anti-microbial therapy is important especially for reducing the prevalence of Shigella and other organisms causing dysentery in children. Decreasing the bacterial load excreted by a child with dysentery also reduces the probability of fecal–oral transmission to close contacts, such as neighbours, friends or members of the child's household.[4] Anti-microbial therapy is particularly important in developing countries, where prolonged diarrhoea episodes, including dysentery, can significantly decrease the growth and nutritional status in the affected children.[5,6]

The World Health Organization (WHO) recommends that all episodes of diarrhoea with blood in the stool be treated with antibiotics. The WHO currently recommends treatment with ciprofloxacin (a quinolone) or one of the three second-line antibiotics, pivmecillinam, azithromycin and ceftriaxone (a third-generation cephalosporin).[7] Here, we review the scientific evidence supporting the WHO-recommended antibiotics

ciprofloxacin, ceftriaxone and pivmecillinam for the effective treatment of dysentery.

Methods

We systematically reviewed all literature published between 1 January 1990 and 31 January 2009 to identify the studies describing the efficacy of ciprofloxacin, ceftriaxone and pivmecillinam for the treatment of dysentery in children aged ⩽5 years. Following CHERG Systematic Review Guidelines (ref. methods paper), we searched PubMed, Cochrane Libraries and all WHO Regional Databases, including literature published in other languages.

We limited the search to studies of antibiotic use in cases of bloody diarrhoea. Search terms included various combinations of 'ciprofloxacin', 'ceftriaxone', 'amdinocillin pivoxil', 'pivmecillinam', 'diarrhoea', 'infantile diarrhoea', 'dysentery', 'Shigella' and 'Salmonella'. Studies were included if they reported the effect of the antibiotics on severe morbidity as observed by decreased blood in the stool or the effect of the antibiotics on Shigella and/or Salmonella bacteraemia, in the stool of paediatric dysentery cases.

We abstracted data describing study identifiers and context, study design and limitations, intervention specifics and outcome effects, into a standardized abstraction form from any publications that met final inclusion and exclusion criteria (ref. methods paper). Outcome effects examined were categorized as 'clinical failure', 'bacteriologic failure' and 'bacteriologic relapse'. Clinical failure was defined as an absence of marked improvement in, or worsening of, illness with the presence of bloody mucoid stools, more than a trace of blood in stool, abdominal pain, tenesmus and/or fever. Bacteriological failure was defined as failure to clear an enteropathogen isolated from an individual on admission to the study, by the end of the treatment period. Bacteriological relapse was defined as the reappearance of an enteropathogen in stool after that enteropathogen was cleared by treatment.

Each study was assessed and graded according to the CHERG adaptation of the GRADE technique. Randomized trials received an initial score of 'high'. We deducted half a grade point for each study design limitation. One- to two-point grade increases were allotted to studies with statistically significant strong levels of association (>80% reduction). Any study with a very low final grade was excluded on the basis of inadequate study quality.

We conducted a meta-analysis and used the DerSimonian–Laird pooled relative risk and corresponding 95% confidence interval because there was heterogeneity in the study design. We also ran, but did not report, the Mantel–Haenszel pooled relative risk and corresponding 95% CI. All analyses were conducted using STATA 10.0 statistical software.[8]

We summarized the evidence by outcome, including qualitative assessments of the study quality and quantitative measures, according to the standard guidelines for each outcome.[9] We applied the CHERG Rules for Evidence Review[10] to the collective diarrhoea morbidity outcomes to estimate the effects of ciprofloxacin, ceftriaxone and pivmecillinam on eliminating severe morbidity due to diarrhoea in children with dysentery.

Results

We identified 586 titles from searches conducted in all databases (Figure 1). After screening titles and abstracts, we reviewed 31 papers for the identified outcome measures of interest. Because very few

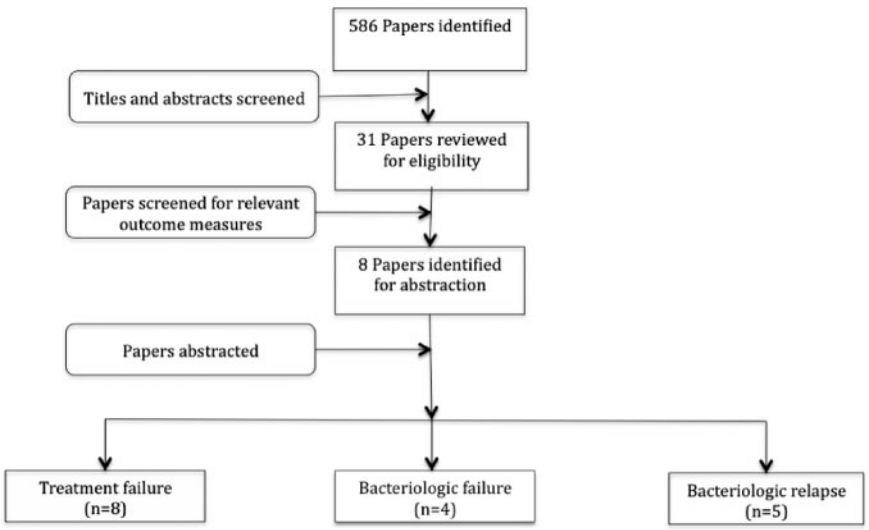

Figure 1 Synthesis of study identification to review effect of ciprofloxacin, ceftriaxone and pivmecillinam on diarrhoea treatment failure, bacteriological failure and bacteriological relapse

studies reported data exclusively for children aged ⩽5 years, we expanded our study population to include children aged up to 16 years. Eight papers were included in the final dataset with some papers contributing data for multiple antibiotics or more than one outcome measure (Supplementary Table 1). We found eight studies that reported on clinical failure (12 unique data points),[1,11–17] with most studies evaluating clinical failure status 3 days after treatment was initiated (range 3–6 days). Four studies reported on bacteriological failure (six unique data points),[11,14–16] and five reported on bacteriological relapse (seven unique data points)[10–12,14,15] (Table 1). All abstracted studies were randomized controlled treatment studies. We identified very few studies with limitations based on study design and execution.

In Table 1, we report the quality assessment of trials by study outcome as well as results from corresponding meta-analyses. Based on 12 data points from eight studies, treatment with one of the three antibiotics resulted in a clinical failure rate of 0.1% (95% CI −0.2 to 0.5%). Based on six datasets abstracted from four studies evaluated in this review, the effect size of antibiotic therapy on a child's relative risk of bacteriological failure is 0% (−0.1 to 0.1%). Seven datasets from five studies indicate that the effect size of antibiotic therapy on a child's relative risk of bacteriological relapse is 0.0% (−0.1 to 0.1%). Assuming treatment failure rate to be an extremely conservative proxy for dysentery deaths not preventable with prompt antibiotic treatment, it can be estimated that treatment of dysentery with ciprofloxacin, ceftriaxone or pivmecillinam will reduce diarrhoea mortality attributable to dysentery by 99% (Figure 2).

Table 1 Quality assessment of trials of antibiotics for the treatment of diarrhoea

	Quality assessment					Summary of findings		
				Directness		No. of events		
No. of studies (ref)	Design	Limitations	Consistency (based on the heterogeneity of the meta-analysis)	Generalizability to population of interest	Generalizability to intervention of interest	Intervention	Control	Pooled failure rate (95% CI)
Clinical failure: moderate outcome-specific quality								
Eight[1,11–17]	RCT	RCT but only able to use treatment failure rates (−0.5)	−0.5	5/12 data points from Israel	7/12 hospital based; 2/12 multicentre	82		0.1% (−0.2 to 0.5%)[a]
Bacteriological failure: moderate outcome-specific quality								
Four[11,14–16]	RCT	RCT but only able to use treatment failure rates (−0.5)	Borderline heterogeneity based on the meta-analysis ($P = 0.077$) (−0.5)	3/6 data points from Bangladesh	Generalizable	9		0% (−0.1 to 0.1%)[a]
Bacteriological relapse: moderate outcome-specific quality								
Five[11–13,15,16]	RCT	RCT but only able to use treatment failure rates (−0.5)	Consistent based on meta-analysis	3/7 data points from Israel	Generalizable	7		0% (−0.1 to 0.1%)

[a]Random effects meta-analysis.
RCT, Randomized controlled trial.

Discussion

Diarrhoeal disease, including dysentery, is a major cause of morbidity and mortality among children in developing countries. This systematic review of the literature summarizes the evidence supporting the use of the antibiotics recommended by WHO: ciprofloxacin, ceftriaxone and pivmecillinam. It also suggests that the bacteria isolated from a stool sample of a child with dysentery rarely relapses if the child has received full-course treatment with one of these antibiotics, and the disease-causing bacteria is sensitive to the antibiotic. Reducing a child's risk of bacteriological relapse is beneficial, because the likelihood of subsequent episodes of dysentery occurring in that child, and of transmission occuring to others, are reduced as a result.

The studies contibuting data in this review were conducted in middle- and low-income countries increasing their generalizability to paediatric populations in countries with the highest diarrhoea mortality rates. Extrapolating clinical failure to mortality, our meta-analyses indicate that >99% of dysentery deaths can be prevented with ciprofloxacin,

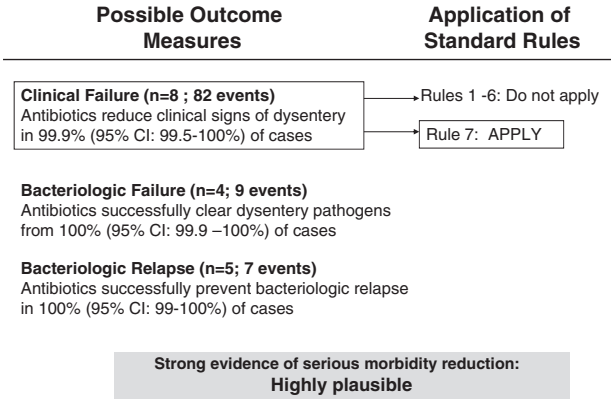

Figure 2 Application of the CHERG Guidelines for the effect of antibiotics on dystenteric morbidity and mortality

ceftriaxone or pivmecillinam treatment. For application in the Lives Saved Tool, it is essential to extrapolate severe morbidity to mortality, although this leap has many limitations. Children with functioning immune systems do not always progress to death as a result of dysentery. It is possible for some children to successfully fight the infection without antibiotics and make a full recovery. In addition, many children who present for medical care and are prescribed one antibiotic are put on a second-line treatment if the first choice fails, thus further reducing the treatment failure rate.

Nearly, all studies were conducted in a clinic or hospital, where staff could monitor treatment. In a community or outpatient setting, the therapeutic effect of the antibiotics reviewed here may not be as great as our analyses indicate, because caregivers may not comply with the dosage and duration specifications of the treatment. Caregivers may also fail to manage the dehydration that often accompanies diarrhoea, thereby increasing a child's risk of death.

The 99% reduction in diarrhoea mortality that we estimate is attributable to the treatment of dysentery with ciprofloxacin, ceftriaxone or pivmecillinam and assumes antibiotic susceptibility. The variability in the types of dysentery-causing organisms that occur worldwide[18] and their sensitivity to the antibiotics recommended for treatment by the WHO may decrease the generalizability of the findings presented in this review. Because bacteria that cause dysentery can acquire resistance to antibiotics, drugs used for treatment should be selected based on resistance patterns prevalent in the community. Future research with regard to site-specific antibiotic resistance may provide additional data and help refine recommendations for national or local planning.

There is strong evidence in favour of the continued use of the antibiotics recommended by WHO—ciprofloxacin, ceftriaxone and pivmecillinam—to reduce morbidity and mortality in children with dysentery.

Supplementary data

Supplementary data are available at *IJE* online.

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KEY MESSAGES

- The evidence supporting antibiotics for the treatment of dysentery includes 8 studies demonstrating a benefit on clinical and bacteriologic outcomes.
- Antibiotics for the treatment of diarrhea results in a cure rate of 99%.
- Antibiotics for the treatment of dysentery is critical to reducing dysentery deaths and should be easily accessible especially in areas where dysentery rates are high.

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