Is the routine use of antimicrobials useful for persistent diarrhoea in children under six in low and middle income countries?

A systematic review of randomized trials

FINAL DRAFT

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Abstract

Background: We conducted a systematic review to evaluate the effectiveness of antimicrobial treatment regimens for the treatment of persistent diarrhoea of unknown or non-specific aetiology in children under the age of six years in low and middle income countries.

Methods: We searched the electronic databases MEDLINE, EMBASE, LILACS, WEB OF SCIENCE, and the Cochrane Central Register of Controlled Trials (CENTRAL) to March 2007 for relevant randomized or quasi randomized controlled trials. We summarised the characteristics of the eligible trials, assessed their quality using standard criteria, and extracted relevant outcomes data. Where appropriate, we combined the results of different trials.

Results: We identified four eligible trials: 3 adequately concealed the allocation sequence, and one did not describe its allocation methods.

In two trials of oral gentamicin versus placebo, no difference was detected in either presence of diarrhoea at the end of one week (relative risk 1.04, 95% CI 0.78 to 1.38, 2 trials, 151 participants) or in weight gain.

In a trial that compared metranidazole vs. metranidazole+nalidixic acid vs. placebo, no difference was detected between metronidazole only and placebo (n=99) on diarrhoea at three, five or seven days. Outcomes with the combination of metranidazole and naladixic acid tended towards benefit over placebo, which showed borderline statistical significance for one outcome.

In a trial of sulphamethoxazole-trimethoprim versus placebo, significantly fewer children had diarrhoea at day seven (relative risk 0.4, 95% confidence interval 0.16 to 0.99, 55 participants), relating to an 82% cure rate in the antimicrobials group and 55% cure rate in the placebo group. There was a tendency for the illness to be shorter with the intervention (mean difference -2.3 days, 95% confidence interval -50.8 to 0.48), and total stool output was lower in the seven days following start of treatment (mean difference 179.4g, 95% confidence interval 18.6 to 340.2).

Conclusions: There is little evidence as to whether antimicrobials help treat persistent diarrhoea in young children in developing countries. No trials in HIV positive children were identified.

1 This review has not yet been refereed.
Background

In 2002, diarrhoea caused an estimated 13.2% of child deaths worldwide\(^1\), most in children under the age of five in developing countries\(^2\). In this group, around 3% to 19% of acute diarrhoea episodes become persistent\(^3\) and 50% of diarrhoea deaths are due to persistent diarrhoea\(^2\). As the number of deaths from acute diarrhoea reduces following widespread use of oral rehydration therapy, the contribution of persistent diarrhoea to overall diarrhoea mortality is increasing. Persistent diarrhoea may also adversely affect nutritional status; in one study, three months after a persistent diarrhoea episode, children had significantly lower weight for age and weight for height Z scores than three months before the episode\(^4\).

Children living in poor areas with poor hygiene and sanitation conditions and children with poor nutritional status are most at risk of developing persistent diarrhoea\(^3\). Children with HIV/AIDS are at particular risk; at initial presentation to hospital with HIV/AIDS, around 36-50%\(^5,6,7\) of children have persistent diarrhoea. Dysentery and more severe diarrhoeal illness are more likely to become persistent than milder episodes\(^3\). Previous antibiotic use and irrational use of antibiotics for acute diarrhoea are also risk factors\(^8\) for persistent diarrhoea.

Causes

The causes of persistent diarrhoea in populations are complex and poorly understood, and in individuals are often unknown. Pathogens associated with persistent diarrhoea are also found in healthy children without diarrhoea\(^9\). Some, such as Cryptosporidium, Giardia lamblia and enteroaggregative Escherichia coli (EAggEC) are thought to be particularly associated with persistent diarrhoea\(^3\) in some locations. Children with persistent diarrhoea and HIV infection may have different patterns of enteric pathogens than those without HIV\(^8\).

Treatment

When persistent diarrhoea is caused by giardiasis, the illness is likely to respond to appropriate treatment. Recent studies have, however, suggested that antimicrobial treatment may be useful in other cases of watery diarrhoea. For example, there have been promising trials looking at the use of nitazoxanide for children with diarrhoea associated with Cryptosporidium infection\(^9\), and ciprofloxacin for diarrhoea associated with enteroaggregative E coli in adults with AIDS\(^10\).

However, these are yet to be demonstrated in a systematic review or large scale trial in children with persistent diarrhoea. The use of antimicrobials should be approached with caution, due to potential problems of drug resistance and the potential reactions of some micro-organisms: entero-haemorrhagic E coli (EHEC) may release toxins more readily when a person is treated with certain types of antibiotics, causing potentially severe illness\(^11\).

Health workers in developing countries, where persistent diarrhoea is most common, often do not have access to sufficient high quality diagnostic laboratory facilities to be able to analyse stool samples for all children with diarrhoea. Therefore treatment often needs to be presumptive, based on symptoms and the mostly likely cause of the symptoms. The current recommendations of Integrated Management of Childhood Illness programme\(^12\) for treating persistent diarrhoea is that children with bloody diarrhoea are treated with antibiotics for Shigella, and children with watery diarrhoea not treated with antibiotics; other recommendations relate to diarrhoea in the acute phase, or where an organism has been found.

Given the lack of diagnostic facilities, and the consequent requirement that children presenting to health facilities with persistent diarrhoea receive only presumptive treatment; we conducted a systematic review to evaluate the effectiveness of antimicrobial treatment regimens for the treatment of persistent diarrhoea of unknown or non-specific aetiology in children under the age of six years in low and middle income countries. This review complements our related systematic review of the enteric pathogens associated with persistent diarrhoea in children.

\(^2\) The World Health Organization (WHO) defines diarrhoea as the passing of three or more loose stools (which take the shape of a container) within a 24 hour period. A new episode of diarrhoea can occur after two full days without diarrhoea. Episodes of diarrhoea lasting for less than 14 days are defined as acute, episodes starting as an acute episode but lasting for 14 or more days are defined as persistent.
Criteria for including studies in this review

Types of studies

Randomized controlled trials and quasi randomized controlled trials.

Types of participants

Children under the age of six years living in low or middle income countries with persistent diarrhoea that has lasted for more than 14 days. Trials including children of different ages or with diarrhoea of different durations (both acute and persistent) will be included provided that data relating only to results for children under the age of six with persistent diarrhoea can be extracted.

Types of intervention

Intervention: any antimicrobial treatment regimen plus usual care
Control: usual care

Types of outcome

Primary:
- Duration of diarrhoea

Secondary:
- Presence of diarrhoea at follow-up
- Need for hospitalisation
- Stool volume
- Death

Adverse events:
- Any adverse events

Search strategy for identification of studies

MEDLINE (1966 to March 2007) via the OVID interface (table 1 for strategy).
EMBASE (1980 to March 2007) via the OVID interface.
LILACS database - Latin American and Caribbean Health Sciences Literature (1982 to date) - via Virtual Health Library interface.
WEB OF SCIENCE (Science Citation Index Expanded – 1945 to present).
Cochrane Central Register of Controlled Trials (CENTRAL), published in The Cochrane Library.

The strategy was amended where necessary to search the other databases listed. No language restrictions were applied; however, it was not possible, given to time constraints for this review, to find interpreters for all the retrieved texts.

Methods of the review

Study selection

Two reviewers independently inspected titles and abstracts identified in the initial literature search in order to identify potentially relevant publications. All potentially relevant publications identified by at least one reviewer were obtained in full text format. One reviewer then applied the inclusion criteria to select which trials to include in the review, and scrutinised publications for duplication of trial results.
Assessment of methodological quality

Two reviewers independently assessed the methodological quality of the included trials, using a pro-forma as a guide. The methodological quality of the included trials was assessed in terms of generation of the allocation sequence and allocation concealment and reported as adequate, inadequate or unclear according to Juni 2001. We recorded who was blinded in each trial. We classified inclusion of randomized participants in the analysis as adequate if 80% or more of the participants are included in the analysis, unclear if not described, and inadequate if less than 80%. Any disagreements were resolved by discussion.

Characteristics of included trials

One reviewer summarised the characteristics of the included trials using a proforma as a guide. Information was extracted on the start date, participant characteristics, source of participants, number of participants, intervention, control and outcomes for each trial. We also noted any acknowledged sources of support for the trial.

Data extraction

One author extracted outcomes data for the intervention and control groups. For dichotomous data we extracted the number of participants with the outcome and the total number randomized to each group, and the total number analysed. For continuous data we extracted the number of participants in each group, the arithmetic mean and their standard deviations, where available.

Data analysis

For dichotomous data we calculated the relative risk and where appropriate combined results from different trials. Where continuous data were summarized by arithmetic means, we summarised the results using weighted mean difference (WMD). We stratified the analysis by class of antimicrobial used. We present adverse event data in a narrative summary.

There were not sufficient trials to conduct a sensitivity analysis to investigate the robustness of the results to the quality components.

Results

Studies identified

Four trials met our inclusion criteria. The initial search identified 378 publications, from which we selected 42 that appeared potentially relevant for retrieval of the full text. We were unable to assess three reports due to time constraints, one because it was not available within the UK, and two, published in Polish and Ukrainian respectively, because translators were not available within the available time period. Of the 39 papers that we were able to assess, three were reports of trials eligible for inclusion in the review. The reasons for the exclusion of the other 36 are summarised in Table 1. We identified one additional eligible trial through reading the reference lists of retrieved review articles.

Characteristics of included trials

The characteristics of the four included trials are summarised in Table 3, and also described below.

Location

Three studies were undertaken in the South East Asia region; two in India and one in Bangladesh. Another was undertaken in Guatemala in the Americas.

Dates of fieldwork

Two trials recruited participants during the period 1988 to 1990. Two trial reports did not provide dates for the fieldwork; these were published in 1995 and 1996 respectively.
Participants

Each study included children of a slightly different age range, the total age range being three months to four years. Three excluded children with diarrhoea lasting over a certain length of time (18 days, 4 weeks and 6 weeks respectively). Three trials excluded children with dysentery or blood in the stool, and the other excluded children with Shigella or Entamoeba histolytica, the main causes of dysentery. Two excluded children with signs of malnutrition, while another included only children who were underweight. Two trials excluded children with systemic infection, one excluded children who had taken antibiotics in the previous seven days. Two excluded children with specific enteric pathogens (Giardia lamblia and Entamoeba histolytica in one, Giardia lamblia, Entamoeba histolytica, Vibrio cholerae, Salmonella and Shigella another).

Comparisons

Two trials compared gentamicin and placebo, one compared metronidazole, with or without nalidixic acid, and placebo, and one compared sulphamethoxazole-trimethoprim and placebo. All antimicrobials were given orally for between five and seven days.

Settings

Two of the included trials were undertaken within a hospital setting and two were undertaken within the community, with children being treated by visiting nurses within their own homes.

Outcomes

All four trials reported on recovery from diarrhoea by the end of treatment, three trials at seven days after start of treatment, one trial at six days; one trial also assessed diarrhoea at three and five days. In addition, two trials reported on weight gain at different time intervals, one reported on various fluid intakes and outputs, three reported on stool output at various points (two by weight, one by number of stools), two reported on energy intake at various points, and one reported on duration of diarrhoea and hospital infections.

Sources of support

Two of the included trials were supported by the World Health Organization, one by the United States Agency for International Development and International Centre for Diarrhoeal Disease Research, and one did not mention a source of support. None acknowledged support from pharmaceutical companies.

Quality assessment

The methodological quality of the included studies was high. All four studies described blinding the participants to which group they were in, and following up over 80% of the randomized participants. Three studies also reported adequate generation of allocation sequence, allocation concealment and blinding of service providers and outcomes assessors. The remaining study was unclear on these methodological issues, but stated that it used randomization, and that it used coded antimicrobial and placebo preparations, which were identical in appearance. A summary of the methodological quality assessment for each study is presented in Table 4.

Outcomes

Oral gentamicin versus placebo

Two trials (Guatemala 1992 and India 1992) compared oral gentamicin (10mg/kg body weight in one trial and 50mg/kg body weight in the other) versus placebo. Both trials reported on diarrhoea at end of treatment (see Table 2 for definitions used). As there was no evidence of heterogeneity of results between trials, the data from the two trials was combined. We found no difference between the gentamicin and placebo groups in the number of children with diarrhoea at end of treatment (relative risk 1.04, 95% CI 0.78 to 1.38, 151 participants); around half the children in both groups recovered within six or seven days.
One trial also reported on weight gain at seven days after start of treatment, as a percentage of weight at one day. Weight gain was generally small in both groups: 1% in the gentamicin group and 1.4% in the placebo group; with no significant difference between groups. There were also no significant differences between groups in any reported measure of fluid intake, energy intake, or fluid output.

One trial reported no drug-related untoward effects. The other reported no clinical toxicity, and blood urea concentrations similar in the treatment and placebo groups.

Metronidazole plus nalidixic acid versus metronidazole alone and placebo alone

One trial (India 1996) included three groups: metronidazole plus nalidixic acid, metronidazole alone and placebo. There was no significant difference between the metronidazole plus nalidixic acid and metronidazole alone groups in the number of children with diarrhoea at three, five or seven days, although estimates were in favour of the metronidazole plus nalidixic acid group (at 5 days: relative risk 0.63, 95% confidence interval 0.35 to 1.12, 99 participants). Comparisons between metronidazole plus nalidixic acid versus placebo were very similar to metronidazole plus nalidixic acid versus metronidazole alone, with an identical relative risk and 95% confidence interval at five days.

The trial also reported mean number of days before recovery from diarrhoea. There was no significant difference between groups, although estimates were in favour of the group receiving metronidazole plus nalidixic acid; when compared with metronidazole alone (mean difference -1.4 days, 95% confidence interval -3.69 to 0.89, 99 participants) or placebo (mean difference -2.2 days, 95% confidence interval -5.01 to 0.61, 99 participants).

There were no differences in the mean number of stools in the previous 24 hours at three of five days; however at seven days the group receiving metronidazole and nalidixic acid had significantly fewer stools than the group receiving metronidazole alone (mean difference -1.10, 95% confidence interval -2.07 to -0.13), and fewer, but not significantly fewer, than the placebo group (mean difference -1.30, 95% confidence interval -2.75 to 0.15).

The trial showed no differences between groups in percentage weight gain at seven and 14 days. Adverse events were not mentioned in the trial report.

Sulphamethoxazole-trimethoprim versus placebo

One trial compared treatment with sulphamethoxazole-trimethoprim (Bangladesh 1995) with placebo. Significantly fewer children in the treatment group had diarrhoea seven days after treatment started (relative risk 0.4, 95% confidence interval 0.16 to 0.99, 55 participants). This related to an 82% cure rate in the antimicrobials group and 55% cure rate in the placebo group. Duration of diarrhoea also appeared to favour treatment, but the difference was not significant (mean difference -2.3 days, 95% confidence interval -50.8 to 0.48). Total stool output in the seven days following start of treatment was significantly lower in the treatment group (mean difference -179.4g, 95% confidence interval -340.20 to -18.60).

Participants in the treatment group had a significantly lower risk of acquiring infections while in hospital compared with placebo (relative risk 0.06, 95% confidence interval 0.01 to 0.54); while energy intake from the hospital diet was similar in both groups.

Adverse events were not mentioned in the trial report.

Conclusions

There is limited evidence as to whether antimicrobials help to reduce the duration of persistent diarrhoea or reduce its health impact in young children in developing countries. The available evidence suggests that gentamicin is probably not useful, while more promising results have been demonstrated for sulphamethoxazole-trimethoprim and metronidazole plus nalidixic acid. However, there is currently insufficient data to recommend the use of any kind of antibiotic in persistent diarrhoea of unknown cause, and more research is needed to evaluate presumptive treatment of persistent diarrhoea.
References

Included studies


Others


**Table 1: Search Strategy in MEDLINE**

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<td>6.</td>
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**Table 2: Reasons for excluding for reports initially identified as relevant**

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