Antibiotics for treating salmonella gut infections

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A substantive amendment to this systematic review was last made on 13 November 1998. Cochrane reviews are regularly checked and updated if necessary.

Background: Antibiotic treatment of salmonella infections aims to shorten illness and prevent serious complications. There are also concerns about increasing antibiotic drug resistance.

Objectives: The objective of this review was to assess the effects of antibiotics in adults and children with diarrhoea who have salmonella.

Search strategy: We searched the Cochrane Infectious Diseases Group trials register, the Cochrane Controlled Trials Register, Medline, Science Citation Index, African Index Medicus, Lilacs, Extra Med and reference lists of relevant articles. We also contacted experts in the field.

Selection criteria: Randomised and quasi-randomised trials comparing antibiotic therapy with placebo or no antibiotic therapy for salmonella infections in symptomatic or asymptomatic adults or children. Typhoid and paratyphoid salmonella infections were excluded.

Data collection and analysis: Trial quality assessment and data were extracted independently by two reviewers.

Main results: Twelve trials involving 778 participants (with at least 258 infants and children) were included. There were no significant differences in length of illness, diarrhoea or fever between any antibiotic regimen and placebo. The weighted mean difference for length of illness was -0.07 days, 95% confidence interval -0.55 to 0.40; diarrhoea -0.03 days, 95% confidence interval -0.53 to 0.48; fever -0.45 days, 95% confidence interval -0.98 to 0.08. Antibiotic regimens resulted in more negative cultures during the first week of treatment. Relapses were more frequent in those receiving antibiotics, and there were more cases with positive cultures in the antibiotic groups after three weeks. Adverse drug reactions were more common in the antibiotic groups (odds ratio 1.67, 95% confidence interval 1.05 to 2.67).

Reviewers’ conclusions: There appears to be no evidence of a clinical benefit of antibiotic therapy in otherwise healthy children and adults with non-severe salmonella diarrhoea. Antibiotics appear to increase adverse effects and they also tend to prolong salmonella detection in stools.

Background

A wide range of different organisms cause acute diarrhoea. Non-typhoidal salmonella appears to be an important cause in some developing countries, resulting in epidemics. The highest incidence rates occur in children younger than 5 years, particularly those under one year, and individuals older than 70 years (Gomez 1998). In Thailand, 80% of cases classified as salmonella diarrhoea occurs in children under 2 years old (Sirinavin 1988). The organism is also a common cause of food poisoning in older children and adults.

Salmonella diarrhoea can cause: chronic diarrhoea, fluid & electrolyte disturbance, malnutrition, necrotising enterocolitis in young infants, and systemic and localised infections (Gomez HF 1998). About 2-45% of patients with salmonella diarrhoea develop bacteremia (Gomez 1998). This sometimes results in metastatic infections such as meningitis, osteomyelitis, septic arthritis, and less and less frequently any other localized infection such as aortitis, endocarditis, pyelonephritis, pneumonia (Gomez 1998). Salmonella meningitis is particularly important as it may also cause long term central nervous system damage. The incidence of bacteremia depends on host status and
salmonella serotypes, and the rate varies between studies and participants. Bacteremia complicating salmonella enteritis in AIDS was reported to be as high as 78% (Sperber 1987). All of these conditions are serious and life threatening and can occur without known diarrhoeal episodes although the gastrointestinal tract is the likely route of acquiring the organism. These complications are more likely to occur in young infants, old age and immunocompromised patients, and fatality rates are higher in these groups. A study in 172 children with extra-intestinal salmonella infection in Thailand (Sirinavin 1998) revealed that the overall case-fatality rate was 9.9%; 17% (95%CI 10.26) in immunocompromised patients, 3% (95%CI 0.12) in infants. For these reasons, aggressive treatment of salmonella diarrhoea with antibiotics is often recommended.

Salmonella carriers are people with salmonella in stool without diarrhoea. They are divided into groups: acute asymptomatic infection, transient or convalescent carriers, and chronic or persistent or permanent carriers. A study of Mexican infants showed that 74% of non-typhoidal salmonella infections were asymptomatic (Cravioto 1990). Transient carriers are those who continue excreting salmonella in stool after infection or diarrhoea for less than a year, usually not more than 3 months. Chronic or persistent carriers are those who excrete salmonella in stool for more than one year. Incidence of chronic carriers of non-typhoidal salmonella is less than 1% (Buchwald 1984).

Patients with schistosomiasis may have prolonged carrier stage, because salmonella can invade and multiply within the schistommasomes and are protected from the effects of antibiotics. Structural abnormalities of biliary and urinary systems can be causes of unsuccessful eradication of the intestinal organisms, since the organisms may be protected in the obstructed parts (Miller 1995, Gomez 1998).

Asymptomatic non-typhoidal salmonella infection and post-diarrhoeal carriers are not uncommon. It is thought to result in unpredictable salmonella sepsis in infants and immunocompromised hosts including AIDS patients. It can be a source of salmonella diarrhoea epidemics, especially when it occurs in public food handlers or nurseries. Their importance in terms of cross-infection depends very much on circumstances, e.g. in the developed world healthy adult carriers are probably not a risk whereas carriage among the faecally incontinent, e.g. infants and elderly, can be a major factor in spread of infection. Presence of salmonella in stools can mislead diagnosis of diarrhoea from other causes such as diarrhoea from virus, campylobacter, or other toxin diarrhoea.

Salmonella is one important cause of opportunistic infections in HIV/AIDS patients. It is a common cause of severe morbidity in these patients. Problems with eradication of salmonella intestinal colonization and prevention of extra-intestinal invasion need to be addressed.

Treatment policies

Antibiotics are commonly recommended early in the illness (Farthing et al 1996) and are widely used (80-90% of culture proven cases in Thailand). The rationale is that if given routinely, antibiotics will shorten the duration of diarrhoea and prevent the serious complications associated with the infection. However, there are doubts about the effectiveness of antibiotics for either presumed salmonella diarrhoea or for culture proven salmonella diarrhoea. In particular, it is not clear whether antibiotics given routinely actually shorten the duration of diarrhoea or prevent extra-intestinal invasion and infections. There have been reports that antibiotic administration prolonged salmonella excretion (Wistrom 1995).

It is well known that antibiotic administration in It is well known that antibiotic administration in any situation causes selective pressure resulting in increased antibiotic resistance. Antibiotics given to treat salmonella diarrhoea may induce resistance in non-salmonella intestinal organisms, especially in areas of endemic salmonellosis. Although quinolones may not cause resistance problems as readily as other drugs, it is well established that campylobacter can acquire resistance
during quinolone treatment with a single step mutation (Wistrom 1995). Ciprofloxacin-resistant bacteria, including salmonella, have occurred in some parts of the world (Wistrom 1995).

In some settings, antibiotics are given presumptively to all patients with clinically diagnosed infectious diarrhoea whilst awaiting culture results. These policies are often instituted in areas where bacteria (such as salmonella, shigella) are known to be causes of diarrhoea. In trials of these policies, outcomes across all patients entered into the study are important, not just the subgroup that turn out to be salmonella positive.

In other settings, antibiotics are given following diarrhoea culture results. Trials in these circumstances will give a good indication of efficacy of drugs against the organism, but will not be directly comparable with trials of presumptive treatment as the patients, setting and timing of treatment will be different.

In addition, some patients carry salmonella infection and are asymptomatic. This may be after an untreated or treated symptomatic diarrhoeal episode. They may be asymptptomatically identified by surveillance stool culture, for example during checks of food handlers, or in diarrhoeal epidemic investigation. These people continue to excrete the infective organism in their faeces. This can result in other people catching and developing the disease. The carriers are important sources of environmental and person-to-person spreading. Antibiotic treatment may make the situation worse if it actually prolongs the carrier stage and induces antibiotic-resistant strains. The role of antibiotics in eradicating the carrier state has not been fully documented (Asperilla 1990, Wistrom 1995).

Some patients may be asymptomatic carriers of salmonella whilst their diarrhoea is caused by some other infection, such as a virus, campylobacter, or pathogenic E.coli. Indeed, it is not always possible to be sure that diarrhoea with salmonella cultured in the stool actually means the salmonella is causing the symptoms. In evaluation of effectiveness of antibiotic therapy in patients with salmonella in the stool, randomisation will help tease out whether presumptive treatment policies are actually effective. However, the trials will not necessarily demonstrate whether salmonella is causing the illness or simply associated with some other infectious agent that is actually causing the diarrhoea.

Information about effectiveness of policies listed above may be apparent in trials of any antibiotic agent, although sensitivities of current organisms may vary in time and place.

**Drugs used**

Salmonellae are facultative intracellular pathogens that can reside within host phagocytes, such as macrophages and neutrophils. In order to effectively eradicate salmonellae from infected hosts, antibacterial drugs which also have intracellular activity may be needed.

Three groups of pharmacokinetically different antibiotics have been used to treat Salmonella diarrhoea and carriers of the organism:

1. The earliest group used are the non-absorbable drugs such as neomycin and colistin.
2. Later, absorbable drugs were used. These antibiotics are broad spectrum agents such as ampicillin, amoxycillin, chloramphenicol, tetracycline, and cotrimoxazole that do not have substantial intracellular activity.
3. New drugs that are absorbable, with potent intracellular activity, such as 5-fluoroquinolone compounds (norfloxacin, ofloxacin, fleroxacin, ciprofloxacin). It is claimed these are more effective because of their mode of biological action. Fluoroquinolone has been used recently but evidence of its clinical and clinical and bacteriological effectiveness remains limited.
The cost of these drugs varies considerably, so it is important to identify the most effective and cheapest option for treatment, particularly in developing countries where resources are severely limited and difficult for services and patients to afford.

Non-typhoidal salmonella, excludes S. typhi, S. paratyphi or S. paratyphi A, S. schottmulleri or S. paratyphi B, and S. hirschfeldii or S. paratyphi C which cause typhoid and paratyphoid fever. Management of these will be dealt with in a separate review.

Objectives
1. To assess the effects of a policy of routine antibiotics in patients with diarrhoea and salmonella cultured from the stool in relation to duration of diarrhoea, other gastrointestinal symptoms, fever, systemic complications, culture positivity at follow-up, emergence of resistant bacteria, and unwanted effects of therapy.

2. To assess the effects of antibiotics on participants with salmonella cultured in the stool but without symptoms.

The following hypotheses will be tested or explored, depending on the available data:

Antibiotics are effective in a subgroup of patients with severe clinical presentation of disease (severe diarrhoea and fever)

Antibiotics are effective in participants who are either immuno-compromised (HIV infection or immunosuppressive therapy), or very young (infants), or old ( >60 years).

Criteria for considering studies for this review

Types of studies
All randomised and pseudorandomised (alternate allocation) placebo (or no treatment) controlled trials were included.

Types of participants
Infants, children and adults with
a) diarrhoea, and with salmonella on culture.
b) asymptomatic salmonella infections (salmonella carriers).

Infections with Salmonella typhi which cause typhoid fever; and S.paratyphi (previously S paratyphi A), S.schottmulleri, S. hirschfeldii which cause paratyphoid fever were not included.

Types of intervention
Any oral antibiotic against placebo or no treatment.

Comparisons between antibiotics, provided there is evidence that antibiotics are effective against the organism.

Types of outcome measures
Studies will be included in comparison tables if there is an outcome in terms of at least one of the following:

1. Clinical outcomes

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Duration of illness
Duration of diarrhoea
Presence of diarrhoea at 2-4 days*, and 5-7 days
Duration of fever
Presence of fever at 2-4 days

Serious extraintestinal tract infection (bacteremia, meningitis, osteomyelitis, septic arthritis, pneumonia)*
Treatment is regarded as worthwhile if it reduced length of illness by at least 24 hours.

2. Bacteriological outcome

Prevalence of positive salmonella culture from stool in the first four days, five to seven days, 1-3 weeks, 3-6 weeks, and six weeks onwards

*indicates primary outcomes

Search strategy for identification of studies
See: Collaborative Review Group search strategy

The trials register of The Cochrane Infectious Diseases Group was searched for relevant trials (published, in press or in progress). The topic search terms used were diarrhoea/diarrhea. Full details of the CIDG methods and the journals hand-searched are published in The Cochrane Library in the section on Collaborative Review Groups.

The reviewer searched The Cochrane Controlled Trials Register, published on The Cochrane Library (1998, Issue 3). This is a compilation of about 160,000 published trials identified by hand-searching by various individuals within The Cochrane Collaboration. Full details of the sources and methods used are published in The Cochrane Library.

The following databases were also searched: MEDLINE 1980-1998;
Science Citation Index 1981-1998, using the search Science Citation Index 1981-1998, using the search strategy defined by the Cochrane Collaboration and detailed in appendix 5c of The Cochrane Handbook. African Index Medicus; LILACS. The specific topic search terms used were: explode “DIARRHEA”/ all subheadings explode “SALMONELLA” (not SALMONELLA TYPHI or SALMONELLA PARATYPHI)

Dates of latest searches:
Cochrane Infectious Diseases Group Trials Register: September 1998
CCTR: September 1998
MEDLINE: September 1998
Science Citation Index: August 1998
African Index Medicus: 27 August 1997

Organisations and individuals working in the field were contacted. These included staff at the World Health Organization and Centers for Disease Control, Atlanta.

External referees were asked to check the completeness of the search strategy, and to identify any additional unpublished, on-going or planned trials.

The reviewer also checked the citations of all the trials identified by the above methods.

Methods of the review
The reviewer applied the inclusion criteria to all potential trials. Where there was any doubt, a second person was consulted.

The first reviewer and one other person independently extracted the data using a standard form and any disagreement was resolved by discussion.

Quality of allocation concealment was assessed using the standard methods of the Cochrane Infectious Diseases Group (see editorial group details).
Alongside basic descriptive data for each included study, the following prespecified data were extracted from each study:

Participants: age, underlying diseases, the diagnostic criteria used whether the participants were episodic cases or part of an outbreak, duration and severity of illness. Interventions: description of each of the comparative regimens Numbers of participants in each group: numbers in stage randomisation, numbers excluded and evaluable. Outcomes: illness, fever, diarrhoea, and salmonella excretion Comments: sensitivity to the study drug in the study population.

Data extraction in some problematic situations:
SD, when not available, was estimated from range divided by four, or from SE.
Presence of salmonella in stools: when there was more than one result from the same study in one outcome category, the one with the higher combined positive salmonella cultures across groups was used. When they were equal, the one with higher numbers tested was chosen.
Trials that compared treatment with placebo based on the results of culture were examined. Patients were subgrouped by whether they were symptomatic or asymptomatic.
We aimed to conduct a subgroup analysis by risk into: a) low risk: children and adults; b) high risk: neonates and infants; c) high risk: immuno-compromised patients (HIV-positive or chemotherapy patients).

The primary analysis used an intention to treat, with patients recruited into trials following either policy outlined above. It was intended to group drugs by the three classes (non-absorbable, absorbable, absorbable with potent intracellular activity) and compared with placebo, initially, and then compared with each other provided there was evidence they were more effective than placebo. If effects were highly variable within an antibiotic type (some studies showing positive effects, and others not, with statistically significant heterogeneity) then a further subgroup analysis by individual antibiotic compound would be conducted.

A secondary analysis of studies in presumptive treatment examined the effects in the subgroup of patients with cultures positive for salmonella. Results from this subgroup were interpreted with caution. The size of this subgroup was calculated as a percentage of the total patients entered into the study.

Description of studies
Twelve trials met the inclusion criteria. Ten potential studies were excluded because they were not randomised clinical trials or the required outcome data could not be extracted (see table of excluded studies). Eleven studies were published in 1972-1996 and one in 1954. Six studies were in adolescents and adults (n=352), five in infants >6 weeks and children (n=258). One study included all ages (n=168, 0-2 y 64, 3-11 y 44, >11 y 60). One study (an extended abstract) did not specify ages. Almost all studies excluded pregnant patients and those with underlying diseases, previous antibiotic treatment, severe illness, and history of allergy to the group of study drug. One study included malnourished children (DGO 1974).

Thirteen studies were sporadic cases. Two studies concerned epidemics of salmonella diarrhoea: one in a military base (GC 1990), and one in hospital personnel (MAN 1991). All studies included symptomatic patients, but only three also included asymptomatic patients (GC 1990, MAN 1991,TP 1996). There were 62 asymptomatic participants in these 3 studies, out of the total of 855 participants (7.2%). Authors grouped symptomatic and asymptomatic patients together for bacteriological analysis, since there were no data available for subgroup analysis in the studies.
Duration of diarrhoea preceding entry to the study varied. In eleven studies, the history was short (<7 days). Two studies had very variable duration of diarrhoea: a range of 1-34 days (JDN 1980), and 5-18 days (GC 1990).

Studies were from all over the world: Europe and Scandinavia (6), North America (4), Australia (1). There were two international multicentred studies, one between countries in South America and Italy, and the other between countries in Asia, South America and Italy. There was one study from Colombia, and one from Egypt.

Salmonella serovars were reported in seven studies. Two outbreaks were caused by S.typhimurium (GC 1990), and S.java (MAN 1991). About 90% of cases were caused by S.enteritidis in two studies (CS 1993, TP 1996), and by S.typhimurium in one (WBM 1991). In two studies in infants and children (MK 1973, JDN 1980), S.typhimurium was the cause in 31% and 53% of the patients.

Randomisation was conducted on diarrhoeal patients prior to culture results in seven studies (CS1993, DGO1974, JW1992, KCH1972, MK 1973, SB 1994, TB 1993). Results were then stratified by culture status in six of these studies. Participants with positive salmonella accounted for 3-16% in six studies, but 39% and 46% in two studies in infants and children (DGO 1974, MK 1973). In two studies, patients who were culture negative were excluded from the analysis (CS 993, MK 1973).

Randomisation was conducted on the remaining six studies once culture results had been obtained (ASID 1970, GC 1990, JDN 1980, MAN 1991, TP 1996, WBM 1954). In three studies (ASID 1970, JDN 1980, WBM 1954) patients with diarrhoea had stool cultures taken, and treatment was not commenced until cultures were received. Then participants were randomised into groups if they were found to be salmonella positive. In the other 3 studies (GC 1990, MAN 1991, TP 1996), participants with positive stool culture for salmonella, with or without diarrhoea, were randomised into groups.

Ten studies included a placebo comparison, and three compared with no treatment (GC 1990, MK 1973, WBM 1954).

One study reported a few salmonella strains resistant to ampicillin which is the study drug (DGO 1974), while others were all susceptible before starting therapy.

Eight different drugs were investigated, including: norfloxacin (6), cotrimoxazole (5), ampicillin (4), ciprofloxacin (2), neomycin (1), chloramphenicol (1), amoxycillin (1), and fleroxacin (1). Various dose schedules were used.

Duration of treatment varied from 1-14 days. Two studies were single dose treatments (norfloxacin or fleroxacin), but all the rest were multiple doses. The bulk of treatment regimens were for five days (8 regimens). Three regimens were 10-14 days (chloramphenicol, norfloxacin, or ciprofloxacin), all others were 7 days or less.

The period of follow-up varied between 6 months and 5 days. In 6 studies, follow-up was less than fourteen days. It was 5-8 weeks in three studies, 3 months in three in three studies, 3 months in three studies and 6 months in two studies. However, in the longer periods of follow-up the number of evaluable patients dropped considerably.

Bacterial detection techniques varied between studies. It was not specified in 6 studies (ASID 1970, HLD 1987, JW 1992, MLJ 1989, TB 1993, TP 1996). In other studies, the common culture media for isolation of enteric bacilli and salmonella-shigella were used, including MacConkey, salmonella-shigella agar, xylose-lysine-deoxycholate agar, eosin-methylene-blue agar, and brilliant green agar. The time lag between stool or rectal swab specimen collection and culture media inoculation was not reported in most studies.
Methodological quality
Quality of randomisation varied considerably. Only 2 studies (JDN 1980, KCH 1972) reported concealment of allocation; 11 studies were described as randomised but no details of the concealment procedures were given; 2 studies used alternate allocation (KCH 1972, GC 1990).

Trials varied in when they randomised participants.
No studies reported on whether the analysis was by “intention to treat”.

Results
Clinical outcomes
Only 5 studies reported any clinical outcomes which were extractable for meta-analysis (CS 1993, MK 1973, WBM 1954, JDN 1980, TP 1996). No study reported serious complications associated with the infection, such as septicaemia, or any other extra-intestinal infection. However, patients with any other diseases and neonates (which were high-risk for serious complications), and those with serious illnesses, were excluded and most studies were small, with the largest study consisting of 75 patients.

In 2 studies (CS 1993, MK 1973) including 101 participants, patients who had diarrhoea for less than 24 hours were included. Duration of illness before randomisation was longer in the other 3 studies: 1-34 days (JDN 1980), 4-36 days (TP 1996) and 2-5 days (WBM 1954).

Four studies examined duration of illness. In three studies, the mean duration was 1.7-3.7 days, with no difference between the groups. In one study in children under two (WBM 1954), the illness was much longer, but there was no significant difference between the two groups (14.9 days (n=25) in the choramphenicol group, and 13.5 (n=26) in the control group).

Four studies examined duration of diarrhoea. In the comparisons of antibiotics with placebo, there was no direction of effect, and the meta-analysis across a total of 196 patients showed no effect. Two studies compared cotrimoxazole with placebo in a total of 68 patients, and one study compared ciprofloxacin with placebo in a total of 39 patients, with no evidence of an effect. Two studies in infants and young children (JDN 1980, WBM 1954) showed long duration of diarrhoea with averages of about 7-8 and 13-15 days.

Two studies examined the effect of antibiotic on duration of fever (CS 1993, MK 1973), 101 patients in total. No effect was demonstrated in either study.

Proportions of patients with diarrhoea on days 2-4 (n=46), and days 5-7 (n=140) after starting treatment were reported by one and two studies respectively. The differences between the comparative groups do not reach any statistically significant level.

There were 2 deaths in a study of ampicillin treatment compared with placebo (DGO 1974), in 110 malnourished infants and children having salmonella diarrhoea in Colombia in 1974. There was no detailed information on these 2 cases.

Proportions of clinical failure at the end of therapy were reported in 6 studies, and meta-analysis showed no effect of antibiotics although there was a tendency towards a better outcome in the control group (antibiotic 43/231, placebo 40/172, OR 0.60, 95%CI 0.35,1.05).

Clinical relapse also occurred in one study in 6/30 patients treated with ampicillin or amoxycillin while it did not occur in the placebo group (JDN 1980).

Bacteriological outcomes
Salmonella cultures were conducted in studies at varying Salmonella cultures were conducted in studies at varying periods after the start of treatment. Many studies excluded from follow-up
patients that had become culture negative (based on two to three consecutive negative cultures) so they could not detect patients who relapsed.

At day 2-4 after the start of treatment, there were fewer salmonella positive patients in the antibiotic group (antibiotic group: 37/143; control: 76/119; OR 0.14, 95% CI 0.08, 0.25). The studies included three using a 5-fluoroquinolone, one chloramphenicol, and one ampicillin.

At days 5-7, meta-analysis also showed fewer salmonella-positive patients in the antibiotic group (antibiotic group: 60/216; control 101/185; OR 0.30, 95% CI 0.20, 0.45). The effect was also detected in the study which examined neomycin, a non-absorbable agent.

At days 8-21, the pattern was even less clear. Two studies using quinolone regimens (TP 1996, MAN 1991) still demonstrated a tendency towards fewer salmonella positive patients in the antibiotic group. The courses of antibiotic administration in these two studies were 10 and 14 days while the other six were 1-7 days.

At days 22-42, meta-analysis showed that there were significantly more participants with positive cultures in the antibiotic group than the placebo group (antibiotic 62/174, placebo 50/157, OR 1.67, 95% CI 1.02, 2.75).

Five studies had follow-up of six weeks or more. There were also significantly more participants with positive culture in the antibiotic group than the placebo group (antibiotic 12/114, placebo 3/101, OR 3.82, 95% CI 1.31, 11.14). This was also the case in comparisons between 5-fluoroquinolone antibiotics and placebo (quinolones 11/86, control 3/89, OR 3.73, 95% CI 1.23, 11.34). The numbers were too small to derive information from comparisons between cotrimoxazole or ampicillin, amoxycillin and placebo.

Five of the studies investigated the resistance pattern of the persistent salmonella in stool and did not find strains resistant to the drugs used. One reported development of cotrimoxazole-resistant salmonella after cotrimoxazole or ciprofloxacin therapy (CS 1993).

Eight studies reported bacteriological relapse rates, which represented the numbers with positive cultures after 1-3 negative cultures. Meta-analysis showed that relapse was more common in the antibiotic group than the placebo group (OR 4.84, 95% CI 2.91, 8.05).

Adverse drug reaction (ADR)

Clinical adverse drug reactions were reported in 13 studies. Some studies reported ADR as overall events in all diarrhoeal patients randomised to comparative groups.

From meta-analysis, there is a higher proportion of adverse treatment effects in the antibiotic group than the control group (antibiotic 55/1040, placebo 25/823, OR 1.67, 95% CI 1.05, 2.67).

Candida skin rash occurred in 4 infants and children after treatment with ampicilllin. Adverse reactions in the cotrimoxazole group included: eyelid edema 1, skin rash 3, and nausea with epigastric pain 1. Adverse reactions in norfloxacin-treated participants included: urticaria 2, exacerbation of chronic eczema 1, severe headache and nausea 2. All four had to discontinue treatment. Five participants treated with ciprofloxacin had increased diarrhoea at the beginning of treatment. In 2 studies (JW 1992, TB 1993), proportions of participants with adverse effects (5-7%) showed no statistically significant differences between norfloxacin or fleroxacin therapy compared to placebo. The symptoms included headache, dizziness, or epigastric pain.

Summary of analyses

The figures and graphs in Cochrane Reviews display the Peto Odds Ratio and the Weighted Mean Difference by default. These are not always the methods used by reviewers when combining data in
their review. You should check the text of the review for a description of the statistical methods used.

**Discussion**

A number of studies, that appeared to be controlled trials, were not not randomised or did not provide data useful for this systematic review (see excluded references). In other studies, results were poorly presented: mean values were given without standard deviations, some only gave median values, or the data was presented in graphical form without figures. We have contacted the authors for additional data, but this problem highlights the need for researchers to report their data in full.

**Clinical effects**

Two studies in adults excluded from this review suggested that antibiotics shorten the length of diarrhoea (Pichler 1987, Mattila 1993). We were unable to include these studies or evaluate their conclusions as they provided insufficient statistical data (no SD or range).

Examination of included studies provided no evidence to support this hypothesis. Antibiotic therapy had no significant effect on the clinical course of salmonella gastroenteritis. This finding occurred consistently in treatment with non-absorbable or absorbable antibiotics, or antibiotics with potent intracellular activity.

Studies in this review were mostly in normal patients with mild to moderate diarrhoea. The potential impact of antibiotics on severe diarrhoeal illness caused by salmonella cannot be assessed, nor their potential role in immuno-compromised hosts (people with AIDS, or immuno-compromising conditions).

One of the potential risks of intestinal salmonellosis in young infants is extra-intestinal infection. No study in the placebo group was of sufficient size to study this outcome. None of the three studies included infants tested for bacteraemia, and all studies excluded infants with clinical sepsis. It is therefore difficult to know whether antibiotics have an impact on the risk of extra-intestinal infection in this population. There was no study of the effect of a 5-fluoroquinolone in infants and young children.

**Bacteriological effects**

The finding of early negative culture in the antibiotic group may be the result of true eradication, or the suppression effects of antibiotic present in the stool on cultured specimens. This is true of many studies of culture in the first week. In fact, ciprofloxacin has been found in stool tests for several weeks after a dose (Murray 1989). It is interesting that the two studies with long antibiotic administration (10 and 14 days) showed an apparent positive effect of antibiotics at 8-21 days while the other shorter regimens (<7days) did not.

This review demonstrated that long-term salmonella excretors were found more often in antibiotic treated groups than in those who did not receive antibiotics. This finding was also demonstrated in comparisons of 5-fluoroquinolones with placebo. Three excluded studies, where data extraction was not possible for meta-analysis, also showed prolonged excretion in antibiotic groups (Franzen 1973, Dixon 1965, Clementi 1975). Clinical responses were not evaluated in these three studies.

Persons with salmonella in stools may transmit the organism to others. Most antibiotics cause more negative cultures during treatment and for a certain period after that. Their role in preventing transmission is not established. There seems to be a relationship between duration of antibiotic treatment and duration of positive bacteriological effect. A duration of 21-28 or more days therapy is needed to eradicate carrier stage of S. typhi (Asperilla 1990). This may also be necessary for non-typhoidal intestinal salmonellosis. Evaluation of roles of antibiotics in non-typhoidal
salmonella carriers was not possible in this review because there were no subgroup analyses in reports.

Development of antibiotic-resistant salmonella was rarely detected after the treatment, but it did occur with co-trimoxazole therapy. Resistance of Campylobacter species to ciprofloxacin during treatment with one-step mutation has been reported in other studies on diarrhoeal treatment (Wistrom 1995). Ciprofloxacin-resistant intestinal bacteria do exist in certain populations, especially in developing countries. It is well known that that antibiotic selective pressure cannot be prevented when any antibiotic is used.

Response to therapy may vary with age, immunocompromising status, duration of diarrhoea before treatment, severity of illness, duration of antibiotic therapy. There was not enough data to evaluate the effects of these factors. But it appeared that antibiotic therapy of 1-14 days had no clinical benefit for normal patients with uncomplicated intestinal salmonella infection.

The high eradication rate reported in a study of norfloxacin in the treatment of enteritis (Dupont 1987) may be due to the fact that bacteriologic evaluation was soon (2-9 days) after therapy. Other reports of longer follow-up periods have shown either a high bacteriologic relapse rate or no effect on the elimination rate of salmonella after treatment with norfloxacin or ciprofloxacin (GC 1990, MAN 1991). Only studies including bacterial cultures collected for several weeks after the end of treatment seem to be valid for evaluation of bacteriologic cure.

**Reviewers’ conclusions**

**Implications for practice**

Antibiotic therapy has no positive clinical effect on the treatment of salmonella diarrhoea in healthy children and adults with non-severe diarrhoea. Adverse drug reactions, although minimal, do occur with antibiotic treatment. Antibiotic administration, therefore, should not be routinely recommended for this disease in children and adults. For patients with some underlying immunosuppressive disorder, current data are insufficient to guide management: this suggests that they are not indicated outside the context of a randomised, placebo controlled trial.

Antibiotic therapy has an apparent effect on stool cultures only in the early stages, but clinical impact and public impact has not been demonstrated. Antibiotic regimens of 1-14 days do not decrease the positive rates of intestinal salmonella after 2-3 weeks, but prolong salmonella excretion. Antibiotic-resistant organisms can occur during treatment and selective pressure will occur especially with frequent use. They are not useful for intestinal salmonella eradication and should not be recommended.

**Implications for research**

Effects of antibiotic therapy on salmonella intestinal infection in the high-risk group for extraintestinal invasion (infants, elderly, and immuno- compromised patients), and severe diarrhoea cannot be determined from this review and information should be obtained by further randomised, placebo controlled trials.

Effective measures to eradicate non-typhoidal salmonella carriers are needed. It is important to understand the pathogenic effects of non-typhoidal salmonella infection, and in what circumstances the organism causes symptoms.

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**Potential conflict of interest**
We certify that we have no affiliations with or involvement in any organisation or entity with a direct financial interest in the subject matter of the review (e.g. employment, consultancy, stock ownership, honoraria, expert testimony).

Characteristics of included studies

Table: Characteristics of included studies

Characteristics of excluded studies

Study : Aserkoff B 1969
Not a clinical trial.
It is a cohort study comparing any antibiotic treatment (ampicillin, chloramphenicol, tetracycline, and others) with no treatment, in a food-borne outbreak of S.typhimurium infection. (U.S.A.)

Study : Clementi KJ 1975
Not a randomised, controlled trial.
It is a three-phase trial which included 102 patients with acute salmonella enterocolitis or asymptomatic carriers. Treatment allocation is not reported. In the first phase, the compared treatment regimens were A. any antibiotics (ampicillin, chloramphenicol or tetracycline, or combination of these, n=6) and B. asymptomatic patients receiving no treatment (n=22). The second phase phase included:C. an antibiotic followed by cotrimoxazole (n=12) and D. cotrimoxazole (n=15). Duration of treatment was not reported. The choice of therapy depended on whether the case was discovered by a practicing physician or by the health unit. It was found that the mean (range) duration of carrier state were: A. 160 (72-381), B. 52.4 (15-114), C. 56.8 (6-156), D. 54.3 (7-170). (Alta, Canada)

Study : Dixon JMS 1965
Not a clinical trial.
A historical controlled study in UK comparing effect of any antibiotic treatment in a food-born outbreak in school by S. typhimurium in 1964 (n=67) with a previous result on no treatment in another school outbreak (n=64) by the same salmonella serotype in 1954. Treatments were given by 14 general practitioners on their individual judgement. Antibiotics used were: neomycin, streptomycin, ampicillin, tetracycline, and chloramphenicol. They were in different regimens, and some patients received 2-3 courses of treatment. However, it was found in complete follow-up groups that the treated group excreted salmonella for a longer period than the untreated group: week 4 - 90% and 55%, week 6 - 58% and 12%, week 10 - 28% and 3%, week 12 - 13% and 2%. (Suffolk and Wales, United Kingdom)

Study : Dryden MS 1996
No extractable outcome information
A randomised controlled trial in severe acute community-acquired gastroenteritis, comparing ciprofloxacin 500 mg bid x 5 days with a placebo. There were 27 patients with salmonella diarrhoea. The outcome assessment combined patients with salmonella and shigella diarrhoea together, which made it impossible to extract data on salmonellosis. (Hamshire, United Kingdom)

Study : Franzen C 1976
Not a randomised, controlled trial.
It is a trial comparing cotrimoxazole (dosage and duration are not available) and no treatment in 48 patients with Salmonella enteritidis outbreak in a school in Gothenburg. Methodology information is not adequately available for evaluation. Outcomes of trial were reported comparing cotrimoxazole (n=19) versus no treatment (n=29) as: mean days of diarrhea 7.7 and 7.2; mean days of fever 6.3 and 6.9; numbers of patients still excreting S.enteritidis after 6 weeks 11/19 (58%) and 12/29 (41%), after 10 weeks 4/19 (21%) and 3/29 (10%) respectively. (Gothenburg, Germany)

Study : Goodman LJ 1990
No extractable data for meta-analysis. No clinical outcome data for salmonellosis. Bacteriologic outcome was presented but not clearly defined.

It is a randomised, double-blinded study, comparing ciprofloxacin (500 mg) bid x 5 days with cotrimoxazole 160mg/800mg bid x 5 days or placebo for adults with diarrhoea, 13 had salmonella. Stool cultures were performed on day 3,6,14 from start of treatment. Definition of bacteriologic response (cured, failed, or relapse) was not presented. It assumed that bacteriologic cured = negative on day 3,6,14, failed = positive cultures on day 3,6,14, and relapsed = one negative followed by one positive. A table presented numbers with bacteriologic cure / failure or relapse for ciprofloxacin : cotrimoxazole : placebo were 2/0 : 1/3 : 1/6. (Chicago, Illinois, United States of America)

Study : Mattila L 1993
No extractable outcome data for meta-analysis. This is a randomised double-blind placebo-controlled study to evaluate clinical efficacy of norfloxacin for treatment of traveler’s diarrhoea in 106 Finnish tourists to Morocco. There were 23 patients with symptomatic S.enteritica intestinal infection, 10 treated with norfloxacin (400 mg Lexinor bid) and 13 with placebo for 3 days. Clinical outcomes were available as mean values without SD, range, nor 95%CI. The mean days of outcomes of treatment with norfloxacin versus placebo are: diarrhoea 1.8 and 5.0, P <0.01); fever (0.8 and 1.1, P >0.05). The statistical analysis is probably Mann-Whitney U-test (presented in methodology section but not available in the Table). Duration of diarrhoea was defined as the time to the last passage of unformed stool.

Duration of diarrhoea
Duration of diarrhoea in cases of treatment failure was the time from the beginning of study substance to cessation of diarrhoea after institution of therapy with the nonstudy medication (norfloxacin). (Helsinki, Finland)

Study : Pichler HET 1987
No extractable information for meta-analysis. A double-blind randomised controlled trial in patients with bacterial diarrhoea. Patients were included if they had more than 3 watery stools per day, and the duration of diarrhoea was less than 14 days. There were 37 patients with salmonella diarrhoea. The compared regimens are: ciprofloxacin 500mg bid for 5 days (n=16) versus placebo (n=21). The clinical outcome was presented as mean durations of diarrhoea without SD, range, or 95%CI; which were: ciprofloxin 1.9 days (n=16), and placebo 3.4 days (n=21), p Student t-test). Bacteriologic relapse rate in ciprofloxacin group was 4/16 (25%) at 1-3 weeks after treatment. There was no information for bacteriologic outcome in the placebo group with salmonellosis.

Definition of diarrhoeal cure was 3 watery stools per day or less. This was different from most other studies where endpoint was usually 0-1 loose stool per day.

(Vienna, Austria)

Study : Rodriguez RS 1983
Outcome data was not clearly presented, and too few cases (n=4). A randomized controlled, single-blind study in children (2-54 months) with acute invasive diarrhoea in Mexico. Randomization performed in 125 children with acute diarrhoea, 4 patients had salmonella as single pathogen and 3 had salmonella and one other pathogen. Treatment comparison included 5 days of furazolidone 7.5mg/kg/day, cotrimoxazole 8 mg/ 40 mg/kg/day, and no treatment. Totals of bacteriologic outcome of children with salmonella is not clear (all cases with salmonella or only those with salmonella as single pathogen), and the sample size is very small. (Mexico)

Study : Smith ER 1971
Not a clinical trial.
It is a cohort study which included 113 patients with S.typhimurium intestinal infection occurring in a hospital outbreak (student nurses, dietary workers, and in-patients) in Halifax, Nova Scotia, Canada. The study included (group A) ampicillin treated group (n=43) as a historical control, and pararell comparison in 70 participants (33 asymptomatic) between groups treated with (group B) cotrimoxazole 80mg/400 mg tid for 7 days (n=41), and (group C) no treatment (n=29). Percentages of positive stool cultures of group A:B:C were: week 1- 72: 66: 90 ; week 2- 46: 30:61; week 3-38:24:9; week 4- 26:21: 7. (Canada)

References

References to studies included in this review

ASID 1970 (Nm) {published data only}

CS 1993 (Cp,Co) {published data only}

DGO 1974 (Ap) {published data only}

GC 1990 (Nr) {published data only}

JDN 1980 (Ap,Ax) {published data only}

JW 1992 (Nr) {published data only}

KCH 1972 (Ap) {published data only}

MAN 1991 (Cp) {published data only}

MK 1973 (Ap,Co) {unpublished data only}

TB 1993 (Fx) {published data only}


* indicates the major publication for the study

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