ClinicalEvidence

Amoebic dysentery

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ABSTRACT

INTRODUCTION: Amoebic dysentery is caused by the protozoan parasite Entamoeba histolytica. It is transmitted in areas where poor sanitation allows contamination of drinking water and food with faeces. In these areas, up to 40% of people with diarrhoea may have amoebic dysentery. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical question: What are the effects of drug treatments for amoebic dysentery in endemic areas? We searched: Medline, Embase, The Cochrane Library and other important databases up to July 2006 (BMJ Clinical Evidence reviews are updated periodically, please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 11 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: emetine, metronidazole, ornidazole, paromomycin, secnidazole, and tinidazole.

QUESTIONS

INTERVENTIONS

DRUG TREATMENTS

Likely to be beneficial

Unknown effectiveness

Unlikely to be beneficial

To be covered in future updates

Effects of interventions to prevent recurrence/transmission in endemic areas

Effects of interventions in immunocompromised people

Diiodohydroxyquin (iodoquinol)

Quinfamide

Concomitant antibiotics in fulminating amoebic colitis

Furazolidone

Dicholoroacetanilide derivates (furamide, clefamide, quifamide, and etofamide)

Teclozan

Diloxanide

Footnote

*No placebo controlled RCTs. Categorisation based on consensus and evidence of similar effectiveness among these drugs.

Key points

- Invasive infection with the parasite *Entamoeba histolytica* can be asymptomatic, or can cause diarrhoea with blood and mucus, abdominal pains and fever.

  Amoebic dysentery is transmitted in areas where poor sanitation allows contamination of drinking water and food with faeces. In these areas, up to 40% of people with diarrhoea may have amoebic dysentery.

  Fulminant amoebic dysentery is often fatal. Other complications include perforation of the colon, colonic ulcers, amoeboma, or chronic carriage.

- Ornidazole may be effective at curing amoebic dysentery compared with placebo, but can cause nausea and vomiting.

  We don't know whether tinidazole is better than placebo, but it seems to be more effective than metronidazole at reducing symptoms and clearing the infection, with fewer adverse effects.

  Secnidazole and tinidazole may be as effective as ornidazole at curing amoebic dysentery in children.

- We don't know whether emetine or paromomycin are beneficial in treating amoebic dysentery.

DEFINITION

Amoebic dysentery is caused by the protozoan parasite *Entamoeba histolytica*. Invasive intestinal parasitic infection can result in symptoms of fulminant dysentery, such as fever, chills, bloody or mucous diarrhoea, and abdominal discomfort. The dysentery can alternate, with periods of constipation or remission. This review focuses on amoebic dysentery only, and includes populations with both suspected and documented disease in endemic areas where levels of infection do not exhibit wide fluctuations through time. [1] The term amoebic dysentery encompasses people described

as having symptomatic intestinal amoebiasis, amoebic colitis, amoebic diarrhoea, or invasive intestinal amoebiasis. Extraintestinal amoebiasis (e.g. amoebic liver abscess) and asymptomatic amoebiasis are not covered.

INCIDENCE/ PREVALENCE

We found no accurate global prevalence data for *E histolytica* infection and amoebic dysentery. Estimates on the prevalence of *Entamoeba* infection range from 1–40% of the population in Central and South America, Africa, and Asia, and from 0.2–10.8% in endemic areas of developed countries such as the USA. [2] [3] [4] [5] However, these estimates are difficult to interpret, mainly because infection can remain asymptomatic or go unreported, [6] and because many older reports do not distinguish *E histolytica* from the non-pathogenic, morphologically identical species *Entamoeba dispar*. Development and availability of more sophisticated methods (such as the enzyme-linked immunosorbent assay [ELISA] based test) to differentiate the two species might give a more accurate estimate of its global prevalence. [7] Infection with *E histolytica* is a common cause of acute diarrhoea in developing countries. One survey conducted in Egypt found that 38% of people with acute diarrhoea in an outpatient clinic had amoebic dysentery. [8]

AETIOLOGY/ RISK FACTORS

Ingestion of cysts from food or water contaminated with faeces is the main route of *E histolytica* transmission. Low standards of hygiene and sanitation, particularly those related to crowding, tropical climate, contamination of food and water with faeces, and inadequate disposal of faeces, all account for the high rates of infection seen in developing countries. [9] [10] It has been suggested that some animals, such as dogs, pigs, and monkeys, may act as reservoir hosts to the protozoa, but this has not been proven. In resource rich countries, risk factors include communal living, oral and anal sex, compromised immune system, and migration or travel from endemic areas. [9] [11] [12]

PROGNOSIS

Amoebic dysentery may progress to amoeboma, fulminant colitis, toxic megacolon and colonic ulcers, and may lead to perforation. [13] Amoeboma may be mistaken for colonic carcinoma or pyogenic abscess. Amoebic dysentery may also result in chronic carriage and the chronic passing of amoebic cysts. Fulminant amoebic dysentery is reported to have 55–88% mortality. [14] [15] It is estimated that more than 500 million people are infected with *E histolytica* worldwide. [10] Between 40 000 and 100 000 will die each year, placing this infection second to malaria in mortality caused by protozoan parasites. [16]

AIMS OF INTERVENTION

To reduce the infectious period, length of illness, risks of dehydration, risks of transmission to others, and rates of severe illness; to prevent complications and death, with minimal adverse effects.

OUTCOMES

Mortality; quality of life; severity of diarrhoea (duration, time to formed stools, number of loose stools per day, stool volume); rate of complications (i.e. amoeboma, extension to pleural cavity, chronic cyst carriage); length of hospital stay; rate of hospital admission; relief from symptoms (i.e. cramps, nausea, vomiting); therapeutic cure (defined as absence of parasites in stools, disappearance of symptoms, and healing of ulcers); failure of treatment (defined as either persistence of symptoms or persistence of parasites, or both); and adverse effects of treatment.

METHODS

BMJ Clinical Evidence search and appraisal July 2006. Additional searches were carried out using these websites: NHS Centre for Reviews and Dissemination (CRD), Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment (HTA), Turning Research into Practice (TRIP), and National Institute for Health and Clinical Excellence (NICE) clinical guidelines. Abstracts of the studies retrieved were assessed independently by two information specialists using pre-determined criteria to identify relevant studies. Study design criteria for inclusion in this chapter were: published systematic reviews and RCTs in any language. RCTs could be from 'open' studies upwards and there was no minimum trial size, loss to follow up or length of follow up required. In addition we use a regular surveillance protocol to capture harms alerts from organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA), which are continually added to the review as required. We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 8).

QUESTION What are the effects of drug treatments for amoebic dysentery in endemic areas?

OPTION METRONIDAZOLE

Treatment failure

Compared with tinidazole Metronidazole may be less effective in reducing symptoms or in clearing parasites at 30 days compared with tinidazole (very low-quality evidence).

Adverse effects
Compared with tinidazole Metronidazole may be more likely to cause adverse effects compared with tinidazole (very low-quality evidence).

Note
We found no direct information about whether metronidazole is better than no active treatment. We found no clinically important results about metronidazole compared with secnidazole, omidazole, emetine, or paromomycin in people with amoebic dysentery.

For GRADE evaulation of interventions for amoebic dysentery, see table, p 8 .

Benefits: We found no systematic review.

Metronidazole versus placebo:
We found no RCTs.

Metronidazole versus tinidazole:
We found nine RCTs [17] [18] [19] [20] [21] [22] [23] [24] [25] (see table 1, p 7). Seven RCTs [17] [18] [19] [20] [22] [23] [24] found that metronidazole increased failure rate (defined as persistence of symptoms or parasites after 30 days) compared with tinidazole, although two of the RCTs did not assess significance. [22] [24] One RCT [21] found similar failure rates for metronidazole and tinidazole at 6 days (see table 1, p 7), whereas another [25] found no failures for both groups at 30 days. Neither of these two RCTs performed assessments of significance. [21] [25] It is not clear whether two of the RCTs involved the same group of people or different groups sampled from the same population. [19] [20] The quality of many of the RCTs was difficult to assess because details of methods were often not described.

Metronidazole versus secnidazole, ornidazole, emetine, or paromomycin:
We found no RCTs.

Harms: **Metronidazole versus tinidazole:**
Six RCTs [17] [19] [20] [22] [23] [24] found fewer adverse effects (nausea, vomiting, abdominal pain, bitter taste, diarrhoea, generalised weakness, furry tongue, dark urine, loss of appetite, blurring of vision, headache, sleep disturbance, vertigo, skin rash, dysuria) for tinidazole compared with metronidazole, although the differences reached statistical significance only in two RCTs (see table 1). [19] [20] One RCT found that fewer individuals overall reported adverse effects with metronidazole, but a greater number of these reported events were of a more severe nature (categorised as moderate). [18] No significance assessment was performed. One RCT found equal numbers of adverse effects in both the metronidazole and tinidazole groups. [25] One RCT did not report adverse effects (see table 1, p 7). [21]

Comment: None.

OPTION SECNIDAZOLE

Treatment failure
Compared with ornidazole Secnidazole may be no more effective at 10 days in clearing parasites in children with amoebic dysentery compared with ornidazole (low-quality evidence).

Note
We found no direct information about whether secnidazole is better than no active treatment. We found no clinically important results about secnidazole compared with metronidazole, omidazole, emetine, or paromomycin in people with amoebic dysentery.

For GRADE evaulation of interventions for amoebic dysentery, see table, p 8 .

Benefits: We found no systematic review.

Secnidazole versus placebo:
We found no RCTs.

Secnidazole versus ornidazole:
We found one RCT (102 children with amoebic dysentery). [26] It found similar rates of failure to clear parasites for secnidazole (30 mg/kg daily for 3 days) and ornidazole (15 mg/kg daily for 10 days) by 10 days after treatment ended (10/42 [24%] with ornidazole *v* 19/60 [32%] with secnidazole; significance assessment not performed).

Secnidazole versus metronidazole, tinidazole, emetine, or paromomycin:
We found no RCTs.

Harms:

Secnidazole versus ornidazole:
The RCT found no adverse effects with either secnidazole or ornidazole. [26]

Comment: None.

OPTION ORNIDAZOLE

Treatment failure
Compared with placebo Ornidazole may be more effective in clearing parasites at 8–10 days compared with placebo (low-quality evidence).

Compared with secnidazole Ornidazole may be as effective in clearing parasites at 10 days in children with amoebic dysentery compared with secnidazole (low-quality evidence).

Compared with tinidazole Ornidazole may be as effective in eradicating parasites at 4 weeks in children with amoebic dysentery compared with tinidazole (very low-quality evidence).

For GRADE evaulation of interventions for amoebic dysentery, see table, p 8 .

Benefits: We found no systematic review.

Ornidazole versus placebo:
We found one RCT (55 people aged 5–92 years with amoebic dysentery). [27] It found that ornidazole (500 mg three times daily for 3 days) reduced failure rate compared with placebo (AR for failure to clear parasites after 8–10 days: 7/35 [20.0%] with ornidazole *v* 20/20 [100%] with placebo; significance assessment not performed).

Ornidazole versus tinidazole:
We found one RCT (40 children aged 1–13 years with amoebic dysentery). [28] It found similar treatment failure rate between ornidazole (50 mg/kg daily for 3 days) and tinidazole (50 mg/kg daily for 3 days; AR for failure to eradicate parasites after 4 weeks: 0/18 [0%] with ornidazole *v* 1/17 [5.9%] with tinidazole; significance assessment not performed). Most of the children in the RCT also had helminthiasis (presence of ascaris, trichuris, or ancylostoma: 17/20 [85%] in the tinidazole group *v* 18/20 [90%] in the ornidazole group), which may have masked the clinical outcomes. [28]

Ornidazole versus secnidazole:
See benefits of secnidazole, p 3 .

Ornidazole versus metronidazole, ornidazole, emetine, or paromomycin:
We found no RCTs.

Harms:

Ornidazole versus placebo:
Nausea and vomiting were more common with ornidazole than with placebo (AR for adverse events: 3/35 [8.6%] with ornidazole *v* 0/20 [0%] with placebo; significance assessment not performed). [27]

Ornidazole versus tinidazole:
The RCT reported mild vomiting in one person with ornidazole. [28]

Ornidazole versus secnidazole:
See harms of secnidazole, p 3 .

Comment: None.

OPTION TINIDAZOLE

Treatment failure
Compared with metronidazole Tinidazole may be more effective in reducing symptoms or clearing parasites at 30 days compared with metronidazole (very low-quality evidence).

Compared with ornidazole Tinidazole may be as effective at 4 weeks in eradicating parasites in children with amoebic dysentery compared with ornidazole (very low-quality evidence).

Adverse effects

Compared with metronidazole Tinidazole may be less likely to cause adverse effects compared with metronidazole (very low-quality evidence).

Note
We found no direct information about whether tinidazole is better than no active treatment. We found no clinically important results about tinidazole compared with secnidazole, emetine, or paromomycin in children with amoebic dysentery.

For GRADE evaulation of interventions for amoebic dysentery, **see table, p 8 .**

Benefits: We found no systematic review.

Tinidazole versus placebo:
We found no RCTs.

Tinidazole versus metronidazole:
See benefits of metronidazole, p 2 .

Tinidazole versus ornidazole:
See benefits of ornidazole, p 4 .

Tinidazole versus secnidazole, emetine, or paromomycin:
We found no RCTs.

Harms: **Tinidazole versus metronidazole:**
See harms of metronidazole, p 2 .

Tinidazole versus ornidazole:
See harms of ornidazole, p 4 .

Comment: None.

OPTION EMETINE

We found no direct information about emetine in the treatment of people with amoebic dysentery. We found no clinically important results about emetine compared with metronidazole, tinidazole, secnidazole, ornidazole, or paromomycin in the treatment of people with amoebic dysentery.

For GRADE evaulation of interventions for amoebic dysentery, **see table, p 8 .**

Benefits: We found no systematic review or RCTs comparing emetine versus placebo, metronidazole, tinidazole, secnidazole, ornidazole, or paromomycin.

Harms: We found no RCTs.

Comment: None.

OPTION PAROMOMYCIN

We found no direct information about paromomycin in the treatment of people with amoebic dysentery. We found no clinically important results about paromomycin compared with metronidazole, tinidazole, secnidazole, ornidazole, or emetine in the treatment of people with amoebic dysentery.

For GRADE evaulation of interventions for amoebic dysentery, **see table, p 8 .**

Benefits: We found no systematic review or RCTs comparing paromomycin versus placebo, metronidazole, tinidazole, secnidazole, ornidazole, or emetine.

Harms: We found no RCTs.

Comment: None.

GLOSSARY

Amoeboma A granulomatous lesion of the caecum or ascending colon caused by localised chronic *E histolytica* infection.
Enzyme linked immunosorbent assay [ELISA] A testing method using immune responses to detect substances such as hormones, bacterial antigens and antibodies.

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low-quality evidence Any estimate of effect is very uncertain.

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Competing interests: Elizabeth Martínez is employed as Therapeutic Category Head, by United Laboratories Inc.

Disclaimer

TABLE 1 **Findings of RCTs comparing metronidazole versus tinidazole (see text, p 2).**

		Failure rates*		Adverse effects	
Ref	**Population**	**Tinidazole *v* metronidazole**	**p value**	**Tinidazole *v* metronidazole**	**P value**
[17]	60 people aged 16–55 years	2/27 (7%) *v* 12/29 (41%)	< 0.01	14/27 (52%) *v* 22/29 (76%)	Significance assessment not performed
[18]	60† people, mean age 30.5 years (range not reported)	1/29 (3%) *v* 12/27 (44%)	< 0.01	15/29 (52%) *v* 10/27 (37%)‡	Significance assessment not performed
[19]	60 hospitalised people aged 16–60 years§	3/30 (10%) *v* 14/30 (47%)	< 0.01	8/30 (27%) *v* 16/30 (53%)	P < 0.05
[20]	60 hospitalised people aged 16–60 years§	3/29 (10%) *v* 14/30 (47%)	< 0.01	8/29 (28%) *v* 16/30 (53%)	P < 0.05
[21]	225 people aged 12–65 years¶	78/123 (63%) *v* 60/102 (59%)	Significance assessment not performed	Not reported	Significance assessment not performed
[22]	60 people aged 16–50 years	7/30 (23%) *v* 8/30 (27%)	Significance assessment not performed	2/30 (7%) *v* 9/30 (30%)	Significance assessment not performed
[23]	60 people aged 20–50 years	1/30 (3%) *v* 6/30 (20%)	< 0.05**	6/30 (20%) *v* 7/30 (23%)	Significance assessment not performed
[24]	66 people aged 10–60 years††	2/22 (9.1%) with tinidazole 2 g for 3 days *v* 2/21 (9.5%) with tinidazole 2 g for 2 days *v* 4/23 (17.4%) with metronidazole 2 g for 2 days	Significance assessment not performed	6/22 (27%) *v* 4/21 (19%) *v* 14/23 (61%)	Significance assessment not performed
[25]	60 people‡‡	0/30 tinidazole 2 g for 3 days (0%) *v* 0/30 (0%)	Significance assessment not performed	9/30 (30%) *v* 9/30 (30%)	Significance assessment not performed

*Failure rates defined as persistence of symptoms or parasites after 30 days in seven trials [17] [18] [19] [20] [22] [23] [24] and as persistence of parasites after 6 days in one trial. [21] † Entamoeba histolytica present in stools.‡ These figures may be misleading because a greater number of the more severe adverse events were reported in the metronidazole group. [18] § It is not clear whether these RCTs involved the same group of people or different groups sampled from the same population. [19] [20] ¶ Participants in one RCT were randomised into four treatment groups: branded metronidazole, branded tinidazole, generic metronidazole, and generic tinidazole. [21] **This RCT reported that tinidazole significantly reduced failure rates; however, recalculation showed no significant difference (P greater-than or equal to 0.10). [23] †† The results presented here for this RCT are pooled for the branded and generic preparations of each drug. [24] Participants in the RCT were randomised into three treatment groups: tinidazole 2 g for 3 days, tinidazole 2 g for 2 days, and metronidazole 2 g for 2 days. The results for this RCT are presented in that order.‡‡ The age interval was not specified, but 11 people were under 20 years old.

TABLE **GRADE evaluation of interventions for Amoebic dysentery**

Important outcomes	**Cure rates, treatment failure, symptom relief, adverse effects**								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of drug treatments for amoebic dysentery in endemic areas?									
9 (at least 711 people) [17] [18] [19] [20] [21] [22] [23] [24] [25]	Treatment failure	Metronidazole *v* tinidazole	4	–2	–1	0	0	Very low	Quality points deducted for incomplete reporting of results and methodological flaws. Consistency point deducted for conflicting results
8 (477) [17] [18] [19] [20] [21] [22] [23] [24]	Adverse effects	Metronidazole *v* tinidazole	4	–2	–1	0	0	Very low	Quality points deducted for incomplete reporting of results and methodological flaws. Consistency point deducted for conflicting results
1 (102) [26]	Treatment failure	Secnidazole *v* ornidazole	4	–2	0	0	0	Low	Quality points deducted for incomplete reporting of results and sparse data
1 (55) [27]	Treatment failure	Ornidazole *v* placebo	4	–2	0	0	0	Low	Quality points deducted for incomplete reporting of results and sparse data
1 (40) [28]	Treatment failure	Ornidazole *v* tinidazole	4	–2	0	–1	0	Very low	Quality points deducted for incomplete reporting of results and sparse data. Directness point deducted for inclusion of population with additional diseases

Type of evidence: 4 = RCT; 2 = Observational; 1 = Non-analytical/expert opinion.
Consistency: similarity of results across studies.
Directness: generalisability of population or outcomes.
Effect size: based on relative risk or odds ratio.