Best Practice

CLINICAL EVIDENCE

Infectious disease: diarrhea

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QUESTIONS: What are the effects of empiric antibiotic treatment in travelers' diarrhea? What are the effects of empiric antibiotic treatment in community-acquired diarrhea?

Summary points

- In randomized controlled trials, empirically treating travelers' diarrhea with antibiotics reduces the length of illness by 1 or 2 days
- In randomized controlled trials of community-acquired diarrhea, the use of ciprofloxacin reduces the duration of diarrhea by 1 or 2 days; in trials of the use of other antibiotics, no evidence of benefit was found or reported on time to cure
- In some randomized controlled trials, treatment prolonged the excretion of organisms and was associated with the development of resistant organisms

INTERVENTIONS

Empiric antibiotic treatment
Fluid replacement
Antimotility agents
Absorbent agents
Antisecretory agents
Bismuth subsalicylate

Definition

Diarrhea is defined as watery or liquid stools, usually with an increase in stool weight above 200 g per day and an increase in daily stool frequency.

Incidence/prevalence

An estimated 4 billion (4×10^9) cases of diarrhea occurred worldwide in 1996, resulting in 2.5 million deaths.[1] In developing countries, diarrhea is reported to cause more deaths in children younger than 5 years than any other condition.[1] In the United States, which has a low incidence, the estimated incidence of infectious intestinal disease is 0.44 episodes per person per year, or 1 episode per person every 2.3 years, resulting in about 1 consultation with a physician per person every 28 years.[2] The epidemiologic features of travelers' diarrhea (people who have crossed a national boundary) are not well known. The incidence is higher in travelers to developing countries but varies widely by location and season of travel.[3]

Etiology

The cause depends on geographic location, standards of food hygiene, sanitation, water supply, and season. The commonly identified causes of sporadic diarrhea in adults in developed countries include *Campylobacter, Salmonella,* and *Shigella* species; *Escherichia coli; Yersinia* species; protozoa; and viruses, but no pathogens are identified in more than half of patients. In returning travelers, about 80% of cases are caused by bacteria, such as enterotoxigenic *E coli*; *Salmonella, Shigella, Campylobacter,* and *Vibrio* species; enteroadherent *E coli*; and *Yersinia* and *Aeromonas* species.

Prognosis

Few studies have examined which factors predict poor outcome in adults. In developed countries, death from infectious diarrhea is rare, although serious complications causing admission to a hospital, such as severe dehydration and renal failure, sometimes occur. People older than 74 years and those in long-term care have an increased risk of death.[4]

Aims

To reduce the infectious period, length of illness, risk of dehydration, risk of transmission to others, and rates of severe illness and to prevent complications and death.

Outcomes

The time from the start of treatment to the last loose stool; the number of loose stools per day; relief of cramps, nausea, and vomiting; rate of hospital admission; incidence of

severe illness; duration of excretion of organisms; and presence of bacterial resistance.

Methods

We did a literature search for systematic reviews and relevant randomized controlled trials using the Cochrane Library, MEDLINE, and EMBASE (December 1999) and an appraisal of *Clinical Evidence* in June 1999. Trial quality was assessed on allocation concealment and inclusion of all randomly allocated participants. Trials were excluded if they did not meet epidemiologic quality criteria. Most trial participants had moderate to severe diarrhea, usually defined as acute diarrhea lasting less than a week; more than 3 loose stools in 24 hours or more than 2 in 8 hours; and symptoms of an enteric illness such as nausea, vomiting, and cramps.

QUESTION: How effective is empiric antibiotic treatment in patients with travelers' diarrhea?

OPTION: EMPIRIC ANTIBIOTIC TREATMENT

Empiric treatment with antibiotics shortened illness duration in adults with diarrhea acquired overseas. Treatment was associated in some people with a prolonged presence of bacterial pathogens in the stool and the development of resistant strains.

Benefits

We found no systematic review. Fifteen randomized controlled trials[5-19] were found (a total of 2,251 travelers) that compared the empiric use of 1 or more antibiotics versus placebo. Eight trials evaluated quinolones,[5-12] 2 evaluated the combination of trimethoprim and sulfamethoxazole (cotrimoxazole),[6,13-15] and 1 each evaluated trimethoprim,[14] aztreonam,[16] bicozamycin,[17] pivmecillinam,[18] and rifaximin.[19] Seven trials studied US students older than 18 years visiting Guadalajara, Mexico, during summer months. The other 8 were in different locations. Entry criteria varied among trials, and treatment duration ranged from a single dose to 5 days. All trials found a

Table 1 *Effects of empiric antibiotic treatment of travelers' diarrhea: results of placebo-controlled trials*

Drug and dosage	No. of participants	Mean duration of diarrhea from start of treatment		Difference between means (95% confidence interval)*
		Placebo group	Intervention group	
Ofloxacin, 300 mg bid for 3 d[9]	232	56 h	28 h	−28 h (−40.5 to −15.5 h)
Ofloxacin, 300 mg bid for 5 d[9]	232	56 h	39 h	−17 h (−31.2 to 2.8 h)
Ciprofloxacin, 500-mg single dose[11]	83	53.5 h	24.8 h	−28.7 h (−40.2 to −17.2 h)
Bicozamycin, 500 mg qid for 5 d[7]	148	63.7 h	28.2 h	−35.5 h (−48.1 to −22.9 h)
Norfloxacin, 400 mg bid for 5 d[5]	511	4 d†	3 d†	NA
Ciprofloxacin, 500 mg bid for 5 d[6]	181	81 h	29 h	−52 h
TMP-SMX, 160/800 mg bid for 5 d[6]	181	81 h	20 h	−61 h
Ciprofloxacin, 250 mg bid for 3 d[7]	15	60 h	26 h	−34 h
Norfloxacin, 400 mg bid for 3 d[8]	94	4.4 d	3.2 d	−1.2 d
Norfloxacin, 400 mg bid for 3 d[10]	106	3.3 d	1.2 d	−2.1 ds
TMP-SMX, 160/800 mg bid for 6 d[13]	110	92.8 h	29.2 h	−63.6 h
Trimethoprim, 200 mg bid for 5 d[13]	110	92.8 h	30.7 h	−62.1 h
TMP-SMX, 160/800 mg bid for 3 d[15]	134	59 h	24 h	−35 h
TMP-SMX, 310/1,600-mg single dose[15]	227	58 h	28 h	−30 h
TMP-SMX, 160/800 mg bid for 3 d[15]	227	58 h	36 h	−22 h
Aztreonam, 100 mg tid for 5 d[16]	191	84 h	44 h	−40 h

bid = twice a day; d = day; h = hour; qid = 4 times a day; TMP-SMX = trimethoprim and sulfamethoxazole; NA = not available; tid = 3 times a day.
*If available from published data.
†Median duration of posttreatment diarrhea.

reduced duration of diarrhea, ranging from 1 to 2.5 days, but confidence intervals were not available from published data in 7 of the trials (table 1). The largest trial, in which 70% of the 598 participants had a history of recent travel, reported a 1-day improvement in the median duration of diarrhea, from 4 to 3 days (no confidence intervals available).[5]

Harms

Adverse effects varied by agent, with incidence in the trials ranging from 1.7%[7] to 18%.[11] Common reported harms were gastrointestinal symptoms (cramps, nausea, anorexia), dermatologic symptoms (rash), and respiratory symptoms (cough, sore throat). In the largest trial,[5] people with salmonella infection treated with norfloxacin had significantly prolonged excretion of *Salmonella* species in stool compared with those given placebo (median time to clearance of *Salmonella* species from stool was 50 days in the group given norfloxacin compared with 23 days in the placebo group). In addition, 6 of 9 *Campylobacter* organisms isolated after treatment had developed resistance to norfloxacin. One small trial[7] reported that 4 of 8 participants treated with ciprofloxacin developed resistant organisms at 48 hours (difference from placebo group, 50%; 95% confidence interval, 15%-85%). One trial reported 3 cases of continued excretion of *Shigella* species in people treated with trimethoprim-sulfamethoxazole. The organisms in 2 of these became resistant to the drug. The participants were clinically well. Other trials did not find posttreatment resistance or did not report it.[8]

Comment

Studies were generally well conducted. All but 1[8] were double-blind. Participant blinding through the use of identical placebo was used and well described in 10 of the studies and probably adequate in the remaining 5, although not as clearly stated. However, only 1 study reported using an appropriate statistical method for analyzing time to event outcomes.[15] Several trials reported surrogate end points, such as change in fecal consistency,[19] rather than the primary outcome of interest.[12,18,19]

QUESTION: How effective is empiric antibiotic treatment of those with community-acquired diarrhea?

OPTION: EMPIRIC ANTIBIOTIC TREATMENT

In randomized controlled trials, the use of ciprofloxacin reduces the duration of diarrhea developed in the community by 1 or 2 days. Trials of other empiric treatments with antibiotics either found no effect or did not report data on time to cure.

Benefits

We found no systematic review. We found 9 randomized controlled trials in 8 reports[20-27] (1,760 participants)

Table 2 *Effects of empiric antibiotic treatment of community-acquired diarrhea: results of placebo-controlled trials*

Drug and dosage	No. of participants	Mean duration of diarrhea from start of treatment		Difference between means (95% confidence interval)*
		Placebo group	Intervention group	
Lomefloxacin, 400 mg/d for 5 d[23]	84	3.2 d	4.4 d	1.2 d (0.1 to 2.5 d)
Ofloxacin, 400-mg single dose[26]	117	3.4 d	2.5 d	−0.9 d (−1.8 to 0.0 d)
TMP-SMX, 800/160 mg bid for 3 d[21]	287	30.2 h	24.4 h	−5.8 h
Cloquinol, 250 mg tid for 3 d[21]	287	30.2 h	25.5 h	−4.7 h
Enoxacin, 400 mg bid for 5 d[21]	137	44.9 h	38.9 h	−6 h
TMP-SMX, 160/800 mg bid for 5 d[21]	137	44.9 h	42.3 h	−2.6 h
Ciprofloxacin, 500 mg bid for 5 d[24]	162	2.9 d	1.5 d	1.4 d
Ciprofloxacin, 500 mg bid for 5 d[25]	173	3.4 d	2.4 d	1 d
TMP-SMX, 160/800 mg bid for 5 d[25]	173	3.4 d	NA	NA
Ciprofloxacin, 500 mg bid for 5 d[27]	85	4.6 d	2.2 d	−2.4 d

d = day; TMP-SMX = trimethoprim and sulfamethoxazole; bid = twice a day; h = hour; tid = 3 times a day; NA = not available.
*If available from published data.

comparing the use of 1 or more antibiotics with placebo (table 2). Trials were conducted at 12 sites in 11 countries. Four trials were conducted in developed countries, and the others took place in developing countries. The largest study, a multicenter trial of fleroxacin, included 332 adult inpatients.[20] Eight trials evaluated quinolones,[20-27] 4 evaluated trimethoprim-sulfamethoxazole,[21,22,25] and 1 evaluated cloquinol.[21] Entry criteria varied between trials, and treatment duration ranged from a single dose to 5 days. In 3 trials, antibiotics reduced illness duration[24,27] or decreased the number of liquid stools by 48 hours,[20] whereas in 5, illness duration was not reduced.[21-23,26] In 1 trial, the illness duration after ciprofloxacin was reduced but not after trimethoprim-sulfamethoxazole.[25]

Harms

Adverse effects varied by agent. In 1 trial of lomefloxacin, 33% of treated participants reported adverse effects compared with 2.7% in the placebo group (absolute risk increase, 31%; 95% confidence interval, 17%-46%). Two were withdrawn from the trial after developing anaphylactoid reactions.[23] In the same trial, 18% of treated participants developed organisms resistant to lomefloxacin.[23] In the multicenter trial of ciprofloxacin and trimethoprim-sulfamethoxazole, 5 people with *Campylobacter* species isolated from stool (2 treated with ciprofloxacin, and 3 treated with trimethoprim-sulfamethoxazole) developed organisms resistant to respective agents.[25] In the largest trial, 3 deaths occurred, 2 people treated with fleroxacin and 1 person who received placebo. Two of the deaths occurred from hypovolemic shock (1 with fleroxacin, and 1 with placebo).[20]

Comment

The main pathogenic organisms found in each study varied, which may partly explain variations in effect. Reported outcomes varied between trials, precluding direct comparisons or a summary of treatment effect on the basis of published reports.

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