

Emergency Medicine Grand Rounds

Keith Conover, M.D., FACEP
August, 2010

Acute Diarrhea

Background

Diarrhea is common. Very common.

If you live in Latin America, you'll likely have it 3 times a year. If you live in North America, you'll likely have it one or two times a year – or perhaps more often, as people tend to have diarrhea and not report it, so our figures may not be all that good.

Even with laboratory grade cultures, we can only identify causative organisms in 1/3-3/4 of cases.^{1,2}

The causative agents of diarrhea are everywhere. You can get *Salmonella* from your pet turtle³ or from eating poorly-prepared beef jerky⁴ or from raw or rare beef⁵ or from Thanksgiving dinner.⁶ You can get *C. difficile* from simply being a carrier (you have about a 10% chance of being a carrier, we think) and taking an antibiotic. When in the developing world, you can get travelers' diarrhea even from eating in the best restaurants.⁷ Even weird bugs like *Cyclospora* can occasionally infect you and cause diarrhea.⁸ You can get *Vibrio* diarrhea from eating Gulfcoast oysters,⁹ though the 2010 Gulf oil spill seems to be fixing this by making Gulfcoast seafood inedible.

Cryptosporidium is in the water, and even if you don't have HIV, you can get Crypto diarrhea from going to a water park like SandCastle.¹⁰ There is one bit of good news, though: there were case reports of what sounded like infectious diarrhea from being out skiing and eating "watermelon snow" (snow red from the algae *Chlamydomonas nivalis*). But then some people volunteered for a scientific study where they ate watermelon snow and nobody got sick. Really.¹¹

A lot of diarrhea is viral – *Rotavirus* is perhaps most well-known, though its fame is fast fading, as since the year 2000, many infants have been immunized against rotavirus. *Rotavirus* typically causes a week of diarrhea, sometimes causing

severe dehydration. A quick assay (Rotazyme and others) is often available to EDs, particularly pediatric EDs, to quickly assess for *Rotavirus*. Once known to be *Rotavirus*, there is no need for further testing, such as stool cultures, and treatment can focus on hydration. *Norovirus* (AKA Norwalk Agent) is responsible for clustered epidemics of diarrhea worldwide. It is extremely contagious, and typically causes diarrhea for 1-3 days.

The organisms that cause diarrhea in industrialized vs. developing countries, if you look at Figure 1 closely and are a lumpers rather than a splitter, are not that different, though enterotoxigenic *E. coli* and cholera and amebic dysentery are more common in the developing world.

Face it. Shit happens.

Diarrhea Stratification: Dysentery

Let's now stratify patients with diarrhea: sick vs not-so-sick. It makes a difference in how they should be treated. Patients who are not truly sick can be treated symptomatically. My standard ED treatment for diarrhea with dehydration, which is usually accompanied by anorexia or nausea, if not vomiting, is 1-2 liters of warm LR IV wide open (rapid room-temperature fluids make people chilled and uncomfortable), 4-8 mg IV Zofran, and 4 mg PO Imodium. But some patients will also do better with an antibiotic. So it's important to determine who needs an antibiotic.

Some (not emergency physicians) used to recommend stool cultures to stratify patients, delaying treatment until the results are back. However, sending \$100-\$600 worth of tests and not treating until these come back, despite the high false-negative rate mentioned above, is cruel and cost-ineffective. (Thus, the aphorism by Dr.

David Shlim: *Physicians are remarkably tolerant of others' diarrhea.*) The positive predictive value of dysentery symptoms for one of the "bad" bugs is only about 20% in one study.¹² Looking at this backwards, one can say that there is little correlation between the causative organism and the severity of diarrhea. The idea that need for antibiotic treatment should hinge on cultured organisms is difficult to defend. In some studies with laboratory-grade cultures (better than the clinical

"Physicians are remarkably tolerant of others' diarrhea."

cultures used at clinical labs), more people got better with an antibiotic than could be explained by the number of positive cultures. It's said (usually by emergency physicians) that by the time the results come back, the patient will either be dead or better. Or will have gone to seek care elsewhere. Reserve stool cultures and O+P for those who are truly sick, or do not respond to initial treatment. (An interesting sidelight: many hospital labs are now refusing to do stool studies on patients who have been in the hospital more than 3 days, as they have been shown to be useless.¹³) Rather than treating based on several-day-old information about the causative organism, the current paradigm is that it's the clinically sicker patients who need antibiotics.

Severe diarrhea is also known as dysentery, and is characterized by fever, or significant ongoing abdominal pain, or blood or mucus in the stool.*

It's patients with dysentery who need antibiotics. The sickest may need admission, but many with dysentery may be discharged home with antibiotic treatment.

Fecal testing for WBC, blood and lactoferrin do show some correlation with infectious agents.¹³⁻¹⁷ And, there is some correlation between the causative agent and whether people develop mild diarrhea or true dysentery. But there is no evidence that fecal WBC, fecal blood, or lactoferrin are better at determining who is sick (and needs an antibiotic) than the history and physical exam, or if they are better than a rectal exam to look for gross blood or mucus. Stool WBC has also been found unreliable for detecting *C. difficile*.¹⁸

There are recommendations that, as with travelers' diarrhea, acute diarrhea in the industrialized world – at least those with acute dysentery, or more than two days of diarrhea – should be



Table 2. Clinical Presentations and Likely Causes of Acute Diarrheal Disease in Outpatients

Clinical Type	Approximate Percentage of Patients	Likely Cause	
		Industrialized Countries	Less-developed Countries
Watery diarrhea	90	Rotavirus, other viruses	Rotavirus, Enterotoxigenic <i>Escherichia coli</i> , Enteropathogenic <i>E. coli</i> , <i>Campylobacter jejuni</i>
Dysentery	5 to 10	<i>Shigella</i> , Enteroinvasive <i>E. coli</i> , <i>Campylobacter jejuni</i>	<i>Shigella</i> , Enteroinvasive <i>E. coli</i> , <i>Campylobacter jejuni</i> , <i>Entamoeba histolytica</i>
Protracted diarrhea (>14 days)	3 to 4	Enteropathogenic <i>E. coli</i> , <i>Giardia</i> , <i>Yersinia</i>	Enteropathogenic <i>E. coli</i> , <i>Giardia</i>
Severe purging with rice-water stool	1 (higher in cholera-endemic areas)	<i>Salmonella</i> , Enterotoxigenic <i>E. coli</i>	<i>Vibrio cholerae</i> , Enterotoxigenic <i>E. coli</i>
Hemorrhagic colitis	<1?	Enterohemorrhagic <i>E. coli</i>	Enterohemorrhagic <i>E. coli</i>

Figure 1. Diarrhea Differences: Industrialized vs. Developing Countries

* Some reserve the term dysentery for bloody diarrhea, but this neither fits with dictionary definitions nor is useful.

treated empirically with an antibiotic. This does not prolong carrier states as previously thought. Again: those with acute dysentery – fever, significant abdominal pain, blood or mucus by history or by rectal exam (and I would add, who simply look sick and don't look better with rehydration) – and those who have had more than two days of diarrhea (exclusive of known Rotavirus in kids) – should be treated with antibiotics.¹⁹⁻²⁵

One final note: this division into “sick” and “not sick” leaves out the “sick-sick” patients who are critically ill and have diarrhea. Those sickest patients are beyond the scope of this handout.

Oral Rehydration and Food

You should give diet and oral rehydration recommendations to anyone who is well enough to go home. As some computer-generated discharge instructions are a bit behind the times, supplement them with some brief oral instructions.

Oral rehydration is key for cholera, and the World Health Organization's program to follow stool output with a bucket and a ruler, and to match it with equal amounts of Oral Rehydration Solution (ORS), has saved thousands of lives. ORS is useful for other watery diarrhea, as well.

A recent review article²⁶ provides a list of the constituents (Figure 2) of oral rehydration solutions; I've highlighted in yellow the more common ones. You will note that chicken broth has lots of sodium, but not much carbohydrates. Add some rice (rice is good, see above) and you have chicken rice soup, which I highly recommend for treatment of diarrhea. If anyone is looking for a great research topic, consider comparing Campbell's chicken-rice soup with a Jewish mother's home-made chicken soup with matzo balls.

Have you ever tasted ORS? Try it some time. You can get it from www.rei.com: search for “Oral Rehydration Salts.” Unless you're deathly ill, you may decide to skip it. Indeed, ORS induces a fair bit of vomiting, and studies show that less-concentrated oral fluids are better,²⁷⁻³⁰ at least if you have diarrhea that's not as bad as cholera (which is characterized by so-called “rice-water” stool). Reduced-osmolarity fluids seem to, at least in some studies, reduce diarrhea volume. In 2002, the WHO reduced the osmolarity of its standard ORS and a review article³¹ provides a table with the original and revised WHO formulas (Figure 3). Recently, there has been interest in improving the original ORS. For instance, the addition of rice flour to the ORS seems to make it more effective,³² as does the addition of honey.³³

I usually recommend Gatorade or equivalent, not because it's a good rehydration solution (too much sugar, and it's sucrose rather than the more easily-absorbed glucose; and not enough salt), but it's easily available at the grocery store and better than the other easily-available alternatives. As for running/biking etc., I recommend alternating Ga-

Rapid Oral Rehydration

Surprising to some is the rapid rate at which oral rehydration can be given. In cases of mild dehydration (3–5% body weight loss), the dosage is 50 ml/kg consumed over a period of 2–4 h. The dosage should be increased to 100 ml/kg over 2–4 h in patients with moderate dehydration (6–9% body weight loss). [Atia AN, Buchman AL. Oral rehydration solutions in non-cholera diarrhea: a review. *Am J Gastroenterol* 2009;104:2596-604] [That's 7 liters for a 70kg adult. –KC]

torade and water rather than diluting Gatorade half-and-half with water as some recommend. Half strength Gatorade tastes yucky.

Early refeeding shortens diarrhea.³⁴ It is traditional to recommend the BRAT diet (bananas, rice, apple-sauce, toast) for diarrhea, but there is no evidence for it, and it is no longer recommended. Instead, an eat-whatever-you-want approach is recommended.³⁵

It is also traditional to tell patients to avoid milk products due to the loss of lactase enzyme from the brush border of the intestinal villi,

making people lactose-intolerant for a few days after diarrhea. There is evidence of this, at least in infants with certain kinds of diarrhea (e.g., enteropathogenic *E coli*).³⁶ It's also seen in about 1 of 10 patients with rotavirus diarrhea.³⁷ There are recommendations to continue feeding infants lactose, unless they show signs of intolerance,³⁸ but it seems reasonable to tell adults, children and infants to avoid lactose for a day or two after an episode of acute diarrhea. Studies show that those with diarrhea-induced lactose intolerance also

are intolerant of other carbohydrates, particularly disaccharides,³⁹ such as the sucrose or fructose found in fresh fruit and fruit juice, and the high-fructose corn syrup found in many types of pop (or soda or Coke, see <http://popvssoda.com:2998/> and the map on the last page), and drinking soda may worsen diarrhea.³⁵ There is, however, evidence that adding more complex carbohydrates to rehydration solutions helps, as discussed above.

We know very little about the bacterial contents of the human gut – it varies widely between people, and even from hour to hour based on what we eat and who knows what else.⁴⁰ Nonetheless, there are many recommendations to eat lots of yoghurt and buttermilk. First, they have essentially no lactose left after the *Lactobacillus* or other bacterial cultures have done their fermentation. Secondly, it's also thought that the live bacterial cultures will help replace missing gut bacteria with an appropriate strain of bacteria.

One can also get pills of *Lactobacillus* for those who hate yoghurt. Sometimes these *probiotic* pills are criticized as, compared to yoghurt or buttermilk, most of the bacteria in the pills are dead. But there's some evidence that even dead bacteria of the right type have some salutary effects during diarrhea.⁴¹

Table 4. Composition of Oral Replacement Solutions for the Treatment of Diarrhea

Solution	Sodium mmol/L	Potassium mmol/L	Chloride mmol/L	Citrate mmol/L	Glucose* mmol/L
WHO solution	90	20	80	30	111 (20)
Rehydralyte	75	20	65	30	139 (25)
Pedialyte	45	20	35	30	139 (25)
Resol	50	20	50	34	111 (20)
Ricelyte	50	25	45	34	(30)
Gatorade	23.5	<1	17		(40)
Coca-Cola	1.6	<1		13.4 [†]	(100)
Apple juice	<1	25			(120)
Orange juice	<1	50		50	(120)
Chicken broth	250	8		0	0

* Figures in parentheses represent grams of carbohydrate.

[†] Rice syrup solid rather than glucose.

Figure 2. Oral Rehydration Solutions

Table 1. Composition of commercial oral rehydration solutions (ORS) and commonly consumed beverages

ORS	Carbohydrate (gm/l)	Sodium (mmol/l)	Potassium (mmol/l)	Chloride (mmol/l)	Base (mmol/l) ^a	Osmolarity (mosM/l)
WHO (2002)	13.5	75	20	65	30	245
WHO (1975)	20	90	20	80	30	311
European Society of Pediatric Gastroenterology, Hepatology and Nutrition	16	60	20	60	30	240
Entalyte ^b	30	50	25	45	34	167
Pedialyte ^c	25	45	20	35	30	250
Naturalyte ^d	25	45	20	NA	48	265
Pediatric Electrolyte ^e	25	45	20	NA	30	250
CeraLyte ^f	40	50-90	20	NA	30	220
Commonly used beverages (not appropriate for diarrhea treatment)						
Apple juice ^g	120	0.4	44	45	NA	730
Coca-Cola ^h classic	112	1.6	NA	NA	13.4	650
Gatorade ⁱ	58.3	20	3.2	11	NA	299
Gatorade carbohydrate energy formula ^j	222.5	43	11.5	NA	NA	1,076

Figure 3. Oral Rehydration Solutions

The evidence isn't strong, but it seems that eating bacteria is good,⁴² and it's better to eat some kinds of bacteria than others.⁴³ But each brand of yoghurt and buttermilk uses a slightly different strain of bacteria, and there are no wide-ranging comparative trials.

I hate buttermilk, and I think Stonyfield yoghurt tastes best, so that's what I recommend: avoid pop, avoid milk and fruit sugars, drink Gatorade, and eat chicken-rice soup and Stonyfield yoghurt.

Medications

Lomotil (diphenoxylate + atropine) is still available by prescription only. Diphenoxylate is a meperidine (Demerol) derivative that slows diarrhea but has few other narcotic effects; atropine was added to prevent abuse, but as a result, Lomotil has a fair number of drug interactions and side effects. There is really no good reason to prescribe Lomotil, now that Imodium is available. (I had a patient whose doctor prescribed Lomotil when Imodium didn't work; Lomotil didn't work either, and the side effects brought her to the ED.)

Imodium (loperamide) became available in ~1972, and has an established track record of safety, enough so that it later became **Imodium A-D**, available without a prescription.⁴⁴ Loperamide is not recommended for children under 3 years of age, based on good evidence that it doesn't help.⁴⁵ And, for traveler's diarrhea, loperamide added to Cipro doesn't seem to help much compared to Cipro by itself.⁴⁶ But it generally cuts acute diarrhea from 2 days to 1 day.⁴⁷

Loperamide is generally safe for acute diarrhea. The use of loperamide in dysentery used to be controversial because of concerns about prolonging illness, but it is now considered safe when combined with an antibiotic.^{23, 48, 49}

Quinolones (Cipro is the most-studied) have traditionally been the antibiotic of choice for infectious diarrhea.⁵⁰ Empiric treatment with a quinolone is recommended not only for travelers' diarrhea but for diarrhea seen in EDs in the industrialized world.²² Quinolones have wide coverage of the agents of diarrhea, though *Campylobacter* has been developing resistance recently, especially in Thailand. Quinolones also seem to disturb gut flora less than other antibiotics,⁵¹ though *C difficile* overgrowth is known to come from the use of quinolones. There have been several comparisons of dose and length of treatment, and though some still recommend 2-3 days of 500 mg PO daily, there is a fairly high cure rate with a single dose (e.g., 750 mg Cipro), and most recommend a single dose.⁵²⁻⁵⁵

Rifaximin, a minimally absorbed oral antibiotic, has recently been the subject of scientific investigations as a treatment for acute diarrhea. At least in preliminary studies it was found to be safe and as effective as oral Cipro for enterotoxigenic *E coli*, and there are some theoretical reasons to suspect it may prove superior: organisms are unlikely to develop resistance; however, it doesn't treat invasive organisms.⁵⁶⁻⁵⁹ The dose is 250 mg TID for three days. But as Sir William Osler said, tongue firmly in cheek, in 1901: *One should treat as many patients as possible with a new drug while it still has*

the power to heal. So I think many will continue to opt for Cipro for now.

Azithromycin is recommended in areas with quinolone-resistant *Campylobacter* (e.g., those

“One should treat as many patients as possible with a new drug while it still has the power to heal.”

just returned from Thailand)⁴⁷ and for the treatment of children and pregnant women. However – and now without tongue in cheek – azithromycin is starting to lose the power to heal diarrhea in Thailand.⁶⁰ The usual dose is 1000 single dose, though some recommend 500 mg, 1-3 doses (pediatric dose: 5 mg/kg/day for 3 days).⁶¹

Bacterial resistance to these antibiotics is likely from widespread use of antibiotics in animal feed.

Special Situations

Travelers' Diarrhea: is basically the same as acute diarrhea in the ED here, except that the patient is traveling to (or just returned from) the developing world. There's lots of diarrhea to catch in the developing world. And, just like kids in the developing world who haven't developed immunity yet, travelers from the industrialized world tend to get diarrhea. A lot. Of your group going on vacation, 25-50% will get the runs.

There are a couple of small but significant differences between acute diarrhea here and in the developing world. In the developing world, there are cholera epidemics, and enterotoxigenic *E coli* is more common. And even though enterotoxigenic *E coli* usually gives watery diarrhea instead of dysentery, it responds well to antibiotics, so they're recommended: Cipro; or, if you're pregnant or a kid, or if you're in Thailand where there are Cipro-resistant bugs, azithromycin (or, perhaps, rifaximin).

Another thing that's common (relatively) in the developing world is amebic dysentery. For this reason, a stool sent for amebae is appropriate if the patient has dysentery or isn't getting better with Cipro and Imodium.

Giardia: if a person complains of a couple weeks of intermittent abdominal cramping, lots of gas, and occasional loose stools, and tells you they were hiking in an area with a lot of beavers (pretty much anywhere in the Pennsylvania mountains) a week before this occurred, then you need to think of Giardia. Giardia is hard to diagnose, so for such a classic history, many recommend an empiric trial of antibiotics (tinidazole 2g PO x1, or Flagyl 250mg TID x 5d) rather than going through repeated testing that is required to definitively diagnose it. There are also occasional outbreaks of Giardia when it gets into a community's water supply, as happened in McKeesport, PA in 1984.

HIV: those with HIV are at higher risk for the usual causes of diarrhea, but also at risk for other causes, including cytomegalovirus (CMV), herpes simplex (HSV), and mycobacterium avium complex (MAC). Treating HIV patients with empiric antibiotics is warranted, given the predominance of “normal” causes of diarrhea, but sending stool studies is advised.

Bloody Diarrhea: for a while, people were saying you shouldn't give Imodium or antibiotics if there is frankly bloody diarrhea. (This doesn't mean streaks of blood, or a guaiac-positive rectal exam, but gross blood.) Shiga-toxin producing *E coli* (the famous O157:H7 and other strains) may cause such diarrhea, leading, especially in children, to hemolytic-uremic syndrome with renal failure. However, most bloody diarrhea is not shiga-toxin *E coli*,⁴⁹ and despite some opinions that antibiotics might make shiga-toxin *E coli* diarrhea worse, this has not been established, and there is even one study that showed that azithromycin decreased mouse mortality from shiga-toxin *E coli* diarrhea.⁶² Therefore, in the ED treatment of dysentery, empiric antibiotics are appropriate even for bloody diarrhea, but in children, azithromycin remains the drug of choice.

One should send stool cultures for bloody diarrhea, but it is also important to specifically ask the lab to culture for shiga-toxin *E coli*, as it is not tested for on routine stool cultures.⁴⁹

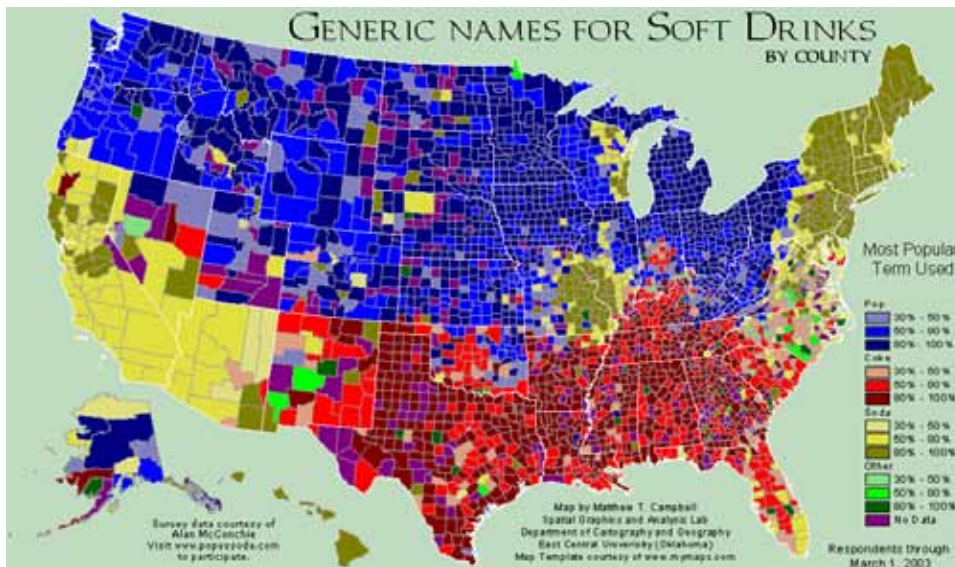
C difficile: The recent advent/recognition of community-acquired *C difficile* complicates things a bit. *C diff* used to be just in hospitalized patients on IV antibiotics, or those recently discharged from the hospital. But more recently we have recognized *C diff* as a problem with those prescribed oral antibiotics on an outpatient basis. Quinolones and clindamycin are known as significant offenders, but almost any antibiotic can knock down normal flora and allow *C diff* to bloom. There is also now community-acquired *C diff* with no prior antibiotics or other risk factors.⁶³

The drugs of choice for *C difficile*, however, are not Cipro or azithromycin, but oral Flagyl or vancomycin. Clues to *C diff* are especially-smelly diarrhea with a unique smell and often, a highly-elevated WBC. (I would love to see a trial of standard lab *C diff* toxin assays vs. a nurse who knows the smell of *C diff*.) Recent antibiotics, or a stint in a hospital or nursing home (especially a nursing home where there have been other cases of *C diff*),^{64, 65} may be clues to *C diff*. *C diff* is always a possibility, even without known risk factors. However, for patients with dysentery and *C diff* risks, it seems reasonable to check a WBC, and if normal or only mildly elevated, treat with Cipro or azithromycin. On the other hand, if you find a markedly elevated WBC, or the patient has characteristically-smelly diarrhea, you could treat with Flagyl while stool culture and stool *C*

Monkey Do

For some primates, especially when they have access to lots of fresh fruit, diarrhea is normal – they only have “normal” BMs when food is scarce. Constipation allows extraction of harder-to-digest components of food, at the risk of more toxicity to the colon (and the rest of the body) from toxins in the food. That's why doctors often recommend that those trying to lose weight eat a good diet that results in 2-3 bowel movements a day. I suppose if we subsisted on a diet of mostly fresh plums (the raw material from which one makes prunes) we'd probably have “normal” diarrhea too.

Take-home message: don't stand under fruit trees full of monkeys.



diff toxin assay are pending.

Others: there are a great variety of things that can cause diarrhea. Food poisoning from preformed Staph toxin in picnic food, or an allergic reaction to food, may present primarily as diarrhea. Although usually a bit more insidious, new-onset inflammatory bowel disease (Crohn's disease or ulcerative colitis) may present acutely – abdominal pain and tenderness in the right lower quadrant may represent terminal ileitis, which should be fairly easy to diagnose by abdominal CT.

Executive Summary

- Divide diarrhea patients into not-sick and sick. Sick means dysentery (fever, or ongoing belly pain, or blood or mucus in stool) or diarrhea for more than 2 days, or HIV.
- Those who are not-sick should use loperamide (Imodium AD) and get the diet recommendations above (Gatorade, chicken-rice soup, yoghurt). Only if they're just back from foreign travel to a developing country ("travelers' diarrhea") should they get an antibiotic.
- Those who are sick (dysentery or > 2 days' diarrhea or HIV) should also get Cipro, 750 mg PO single dose (maybe 500 mg PO daily x3 days for sicker patients), and if they can produce a stool sample, it is reasonable (though not required) to send it for O+P, culture, and *C diff* toxin assay. If pregnant, a kid, or just back from Thailand, 1000 mg single-dose of azithromycin PO, or 500 mg daily for 3 days (pediatric dose: 5 mg/kg/day for 3 days), is a reasonable alternative.
- If you suspect *C diff*, you may want to use Flagyl empirically instead, 10-14 days of 500 mg PO TID.

References

1. Biswas R, Lyon DJ, Nelson EA, Lau D, Lewindon PJ. Aetiology of acute diarrhoea in hospitalized children in Hong Kong. *Trop Med Int Health* 1996;1:679-83.
2. Sharp TW, Thornton SA, Wallace MR, et al. Diarrheal disease among military personnel during Operation Restore Hope, Somalia, 1992-1993. *Am J Trop Med Hyg* 1995;52:188-93.
3. Multistate outbreak of human *Salmonella typhimurium* infections associated with pet turtle exposure - United States, 2008. *MMWR Morb Mortal Wkly Rep* 2010;59:191-6.
4. Outbreak of Salmonellosis associated with beef jerky--New Mexico, 1995. *MMWR Morb Mortal Wkly Rep* 1995;44:785-8.
5. Outbreak of *Salmonella* serotype typhimurium infection associated with

cating raw ground beef--Wisconsin, 1994. *MMWR Morb Mortal Wkly Rep* 1995;44:905-9.

6. Salmonellosis associated with a Thanksgiving dinner--Nevada, 1995. *MMWR Morb Mortal Wkly Rep* 1996;45:1016-7.
7. Shlim DR. Looking for evidence that personal hygiene precautions prevent traveler's diarrhea. *Clin Infect Dis* 2005;41 Suppl 8:S531-5.
8. Huang P, Weber JT, Sosin DM, et al. The first reported outbreak of diarrheal illness associated with *Cytophora* in the United States. *Annals of internal medicine* 1995;123:409-14.
9. Altekruze SF, Bishop RD, Baldy LM, et al. *Vibrio gastroenteritis* in the US Gulf of Mexico region: the role of raw oysters. *Epidemiol Infect* 2000;124:489-95.
10. Outbreak of cryptosporidiosis associated with a splash park - Idaho, 2007. *MMWR Morb Mortal Wkly Rep* 2009;58:615-8.
11. Fiore DC, McKee DD, Janiga MA. Red snow: is it safe to eat? A pilot study. *Wilderness Environ Med* 1997;8:94-5.
12. Ismail R, Bakri A, Nazir M, Ryanto, Haridawati. Indicators for antibiotic therapy in invasive bacteria diarrhoea. *J Diarrhoeal Dis Res* 1994;12:208-13.
13. Siegel D, Cohen PT, Neighbor M, et al. Predictive value of stool examination in acute diarrhea. *Arch Pathol Lab Med* 1987;111:715-8.
14. Huicho L, Campos M, Rivera J, Guerrant RL. Fecal screening tests in the approach to acute infectious diarrhea: a scientific overview. *Pediatr Infect Dis J* 1996;15:486-94.
15. McNeely WS, Dupont HL, Mathewson JJ, Oberhelman RA, Ericsson CD. Occult blood versus fecal leukocytes in the diagnosis of bacterial diarrhea: a study of U.S. travelers to Mexico and Mexican children. *Am J Trop Med Hyg* 1996;55:430-3.
16. DuBois D, Binder L, Nelson B. Usefulness of the stool Wright's stain in the emergency department. *J Emerg Med* 1988;6:483-6.
17. Stoll BJ, Glass RI, Banu H, Huq MI, Khan MU, Ahmed M. Value of stool examination in patients with diarrhoea. *Br Med J (Clin Res Ed)* 1983;286:2037-40.
18. Marx CE, Morris A, Wilson ML, Reller LB. Fecal leukocytes in stool specimens submitted for *Clostridium difficile* toxin assay. *Diagn Microbiol Infect Dis* 1993;3:16-313-5.
19. Moss PJ, Read RC. Empiric antibiotic therapy for acute infective diarrhoea in the developed world. *J Antimicrob Chemother* 1995;35:903-13.
20. Quinolones in acute non-travellers' diarrhoea. *Lancet* 1990;336:282.
21. Dryden MS, Gabb RJ, Wright SK. Empirical treatment of severe acute community-acquired gastroenteritis with ciprofloxacin. *Clin Infect Dis* 1996;22:1019-25.
22. Goodman LJ, Trenholme GM, Kaplan RL, et al. Empiric antimicrobial therapy of domestically acquired acute diarrhea in urban adults. *Arch Intern Med* 1990;150:541-6.
23. Murphy GS, Bodhidatta L, Echeverria P, et al. Ciprofloxacin and loperamide in the treatment of bacillary dysentery. *Annals of internal medicine* 1993;118:582-6.
24. Noguerao A, Garcia-Polo I, Isasia T, et al. Early single dose therapy with ofloxacin for empirical treatment of acute gastroenteritis: a randomised, placebo-controlled double-blind clinical trial. *J Antimicrob Chemother* 1995;36:665-72.
25. Taylor DN, Houston R, Shlim DR, Bhaibulaya M, Ungar BL, Echeverria P. Etiology of diarrhea among travelers and foreign residents in Nepal. *Jama* 1988;260:1245-8.
26. Aranda-Michel J, Giannella RA. Acute diarrhoea: a practical review. *The American journal of medicine* 1999;106:670-6.
27. Santosham M, Fayad I, Abu Zikri M, et al. A double-blind clinical trial comparing World Health Organization oral rehydration solution with a reduced osmolarity solution containing equal amounts of sodium and glucose. *J Pediatr* 1996;128:45-51.
28. Multicentre evaluation of reduced-osmolarity oral rehydration salts solution. International Study Group on Reduced-osmolarity ORS solutions. *Lancet* 1995;345:282-5.
29. Mahalanabis D, Faruque AS, Hoque SS, Faruque SM. Hypotonic oral rehydration solution in acute diarrhoea: a controlled clinical trial. *Acta Paediatr* 1995;84:289-93.
30. Lin SL, Kong MS. Extremely low sodium hypotonic rehydration solution for young children with acute gastroenteritis. *Chang Gung Med J* 2001;24:294-9.

31. Atia AN, Buchman AL. Oral rehydration solutions in non-cholera diarrhea: a review. *Am J Gastroenterol* 2009;104:2596-604; quiz 605.
32. Molina S, Vettorazzi C, Peerson JM, Solomons NW, Brown KH. Clinical trial of glucose-oral rehydration solution (ORS), rice dextrin-ORS, and rice flour-ORS for the management of children with acute diarrhea and mild or moderate dehydration. *Pediatrics* 1995;95:191-7.
33. Abdurhman MA, Mekawy MA, Awadalla MM, Mohamed AH. Bee honey added to the oral rehydration solution in treatment of gastroenteritis in infants and children. *J Med Food* 2010;13:605-9.
34. Practice parameter: the management of acute gastroenteritis in young children. American Academy of Pediatrics, Provisional Committee on Quality Improvement, Subcommittee on Acute Gastroenteritis. *Pediatrics* 1996;97:424-35.
35. King CK, Glass R, Bresee JS, Duggan C. Managing acute gastroenteritis among children: oral rehydration, maintenance, and nutritional therapy. *MMWR Recomm Rep* 2003;52:1-16.
36. Moreira CR, Fagundes-Neto U. [Lactose intolerance in hospitalized infants with acute diarrhea due to classic enteropathogenic *Escherichia coli* (EPEC)]. *Arq Gastroenterol* 1997;34:262-9.
37. Szajewska H, Kantecki M, Albrecht P, Antoniewicz J. Carbohydrate intolerance after acute gastroenteritis--a disappearing problem in Polish children. *Acta Paediatr* 1997;86:347-50.
38. Meyers A. Modern management of acute diarrhea and dehydration in children. *Am Fam Physician* 1995;51:1103-18.
39. Karabouglu M, Sokucu S, Gokcay G, Ucsel R, Neyzi O. Carbohydrate malabsorption in acute diarrhea. *Indian Pediatr* 1994;31:1071-4.
40. Guarner F, Malagelada JR. Gut flora in health and disease. *Lancet* 2003;361:512-9.
41. Adams CA. The probiotic paradox: live and dead cells are biological response modifiers. *Nutr Res Rev* 2010;23:37-46.
42. Williams NT. Probiotics. *Am J Health Syst Pharm* 2010;67:449-58.
43. Heydariyan F, Kianifar HR, Ahanchian H, Khakshure A, Seyedi J, Moshirian D. A comparison between traditional yogurt and probiotic yogurt in non-inflammatory acute gastroenteritis. *Saudi Med J* 2010;31:280-3.
44. Ericsson CD, Johnson PC. Safety and efficacy of loperamide. *The American journal of medicine* 1990;88:10S-4S.
45. Li ST, Grossman DC, Cummings P. Loperamide therapy for acute diarrhea in children: systematic review and meta-analysis. *PLoS Med* 2007;4:e98.
46. Taylor DN, Sanchez JL, Candler W, Thornton S, McQueen C, Echeverria P. Treatment of travelers' diarrhea: ciprofloxacin plus loperamide compared with ciprofloxacin alone. A placebo-controlled, randomized trial. *Annals of internal medicine* 1991;114:731-4.
47. Hughes IW. First-line treatment in acute non-dysenteric diarrhoea: clinical comparison of loperamide oxide, loperamide and placebo. UK Janssen Research Group of General Practitioners. *Br J Clin Pract* 1995;49:181-5.
48. Adachi JA, Ostrosky-Zeichner L, DuPont HL, Ericsson CD. Empirical antimicrobial therapy for traveler's diarrhea. *Clin Infect Dis* 2000;31:1079-83.
49. DuPont HL. Clinical practice. Bacterial diarrhea. *N Engl J Med* 2009;361:1560-9.
50. Carlson JR, Thornton SA, DuPont HL, West AH, Mathewson JJ. Comparative in vitro activities of ten antimicrobial agents against bacterial enteropathogens. *Antimicrob Agents Chemother* 1983;24:509-13.
51. Reeves DS. The effect of quinolone antibacterials on the gastrointestinal flora compared with that of other antibacterials. *J Antimicrob Chemother* 1986;18 Suppl D:89-102.
52. Ericsson CD, DuPont HL, Mathewson JJ. Single Dose Ofloxacin plus Loperamide Compared with Single Dose or Three Days of Ofloxacin in the Treatment of Traveler's Diarrhea. *J Travel Med* 1997;4:3-7.
53. Petruccielli BP, Murphy GS, Sanchez JL, et al. Treatment of traveler's diarrhea with ciprofloxacin and loperamide. *J Infect Dis* 1992;165:557-60.
54. Bassily S, Hyams KC, el-Masry NA, et al. Short-course norfloxacin and trimethoprim-sulfamethoxazole treatment of shigellosis and salmonellosis in Egypt. *Am J Trop Med Hyg* 1994;51:219-23.
55. Salam I, Kataralis P, Leigh-Smith S, Farthing MJ. Randomised trial of single-dose ciprofloxacin for travellers' diarrhoea. *Lancet* 1994;344:1537-9.
56. Layer P, Andresen V. Review article: rifaximin, a minimally absorbed oral antibacterial, for the treatment of travellers' diarrhoea. *Aliment Pharmacol Ther* 2010;31:1155-64.
57. DuPont HL. Therapy for and prevention of traveler's diarrhea. *Clin Infect Dis* 2007;45 Suppl 1:S78-84.
58. Keenum AJ, Stockton MD. Rifaximin (Xifaxan) for traveler's diarrhea. *Am Fam Physician* 2005;72:2525-6.
59. DuPont HL, Jiang ZD, Ericsson CD, et al. Rifaximin versus ciprofloxacin for the treatment of traveler's diarrhea: a randomized, double-blind clinical trial. *Clin Infect Dis* 2001;33:1807-15.
60. Murphy GS, Jr., Echeverria P, Jackson LR, Arnes MK, LeBron C, Pitarangsi C. Ciprofloxacin- and azithromycin-resistant *Campylobacter* causing traveler's diarrhea in U.S. troops deployed to Thailand in 1994. *Clin Infect Dis* 1996;22:868-9.
61. DuPont HL, Ericsson CD, Farthing MJ, et al. Expert review of the evidence base for self-therapy of travelers' diarrhea. *J Travel Med* 2009;16:161-71.
62. Ohara T, Kojo S, Taneike I, et al. Effects of azithromycin on shiga toxin production by *Escherichia coli* and subsequent host inflammatory response. *Antimicrob Agents Chemother* 2002;46:3478-83.
63. Bauer MP, Goorhuis A, Koster T, et al. Community-onset *Clostridium difficile*-associated diarrhoea not associated with antibiotic usage--two case reports with review of the changing epidemiology of *Clostridium difficile*-associated diarrhoea. *Neth J Med* 2008;66:207-11.
64. Campbell RR, Beere D, Wilcock GK, Brown EM. *Clostridium difficile* in acute and long-stay elderly patients. *Age Ageing* 1988;17:333-6.
65. Bender BS, Bennett R, Laughon BE, et al. Is *Clostridium difficile* endemic in chronic-care facilities? *Lancet* 1986;2:11-3.