Background

Diarrhea is common. Very common. If you live in Latin America, you’ll get it 3 times a year. If in North America, you’ll get it twice a year – or more. Diarrhea is decreasing in the developing world, and deaths are down ~30% from 2005 to 2015. But diarrhea deaths are increasing in the USA (up ~25%, but still very low) – likely due to increasing Clostridium difficile (“C diff”) overgrowth from all the antibacterial antibiotics that we prescribe, sometimes without a good reason.

Even with research-grade cultures, we can only identify causative organisms in ⅓-¾ of cases. Diarrhea microbes are everywhere. You can get Salmonella from your pet turtle or from eating poorly-prepared beef jerky or from raw or rare beef or from Thanksgiving dinner. You can get drug-resistant Campylobacter from raw milk from your herdshare. You can get C difficile from simply being a carrier (about 10% are carriers) and taking an antibiotic. In the developing world, you can get travelers’ diarrhea from the best restaurants. Even weird bugs like Cyclospora can occasionally infect you. You can get Vibrio from eating Gulfcoast oysters, though the 2010 Gulf oil spill temporarily fixed 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 a water park like SandCastle. Good news, though: there were cases that 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.

A lot of diarrhea is viral – Rotavirus is most well-known, though its fame is fading: since the year 2000, many infants have been immunized against it. Rotavirus causes a week of diarrhea, and sometimes severe dehydration. Norovirus (AKA Norwalk Agent, AKA “24-hour stomach flu”) is responsible for clustered epidemics of vomiting and diarrhea worldwide, and when it hits the elderly or those with chronic illness, can kill. Like C diff, alcohol-based hand cleaners don’t kill Norovirus, you’ll need soap and water. Norovirus is very contagious (wear a mask and gloves when you go see someone who might have Norovirus), and causes diarrhea and vomiting for 1-3 days, usually just 24 hours.

The organisms that cause diarrhea in industrialized vs. developing countries, if you look at Figure

<table>
<thead>
<tr>
<th>Diarrhea Differences: Industrialized vs. Developing Countries</th>
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<tbody>
<tr>
<td><strong>Clinical Type</strong></td>
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<tr>
<td>--------------------</td>
</tr>
<tr>
<td>Watery diarrhea</td>
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<tr>
<td>Dysentery</td>
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<tr>
<td>Protracted diarrhea (&gt;14 days)</td>
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<tr>
<td>Severe purging with rice-water stool</td>
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<tr>
<td>Hemorrhagic colitis</td>
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</tbody>
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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, and giving lots of normal saline can cause a hyperchloremic acidosis), 4-8 mg IV
A couple of reviews\textsuperscript{6,54} list the constituents (tables on next page) of oral rehydration solutions; highlighted in yellow are the more common ones. Chicken broth has lots of sodium, but not much carbohydrate. Add some rice (rice is good, see below) 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 homemade chicken soup with matzo balls. (Someone already researched chicken soup for colds, but not for diarrhea and not with matzo.)

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 spit it out. Indeed, ORS induces a fair
bit of vomiting, and studies show that less-concentrated oral fluids are better,35-38 at least if you have diarrhea that’s not as bad as cholera. (Cholera is characterized by copious salty “rice-water” stool.) Reduced-osmolarity fluids seem to reduce diarrhea volume. In 2002, the WHO reduced the osmolarity of its standard ORS, and a review provides a table with the original and revised WHO formulas (right, below). Recently, there has been interest in improving the original ORS. Adding zinc39 (particularly in malnourished children in the developing world), rice flour40 or honey41 to the ORS makes it more effective, but short-chain polysaccharides do not.39

I usually recommend Gatorade or equivalent, not because it’s a good rehydration solution (too much sugar, and it has sucrose as well as 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. Chicken-rice soup is a good alternative. As for running and biking and the like, I recommend alternating Gatorade and water rather than diluting Gatorade half-and-half with water as some recommend. Half strength Gatorade is yucky.

Early refeeding shortens diarrhea.42 It is traditional to recommend the BRAT diet (bananas, rice, applesauce, toast), but there is no evidence for it, and it is no longer recommended. Instead, an eat-whatever-you-want approach is recommended.43

It is also traditional to avoid milk products due to the loss of sugar-absorbing enzymes from the brush border of the intestinal villi, making people lactose-intolerant for a few days after diarrhea. There is evidence for this, at least in infants with certain kinds of diarrhea (e.g., enteropathogenic E coli).44 It’s also seen in about 1 of 10 patients with rotavirus diarrhea.45 There are recommendations to continue feeding infants lactose, unless they show signs of intolerance,46 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,47 such as the sucrose found in fresh fruit and fruit juice, and in 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.48

There is, however, evidence that adding more complex carbohydrates to rehydration solutions helps, as discussed above.

We know almost nothing about the bacterial contents of the human gut – it varies massively between people, and even from hour to hour based on what we eat and who knows what else.49 Nonetheless, there are many recommendations to eat lots of yoghurt and buttermilk. They have essentially no lactose left after the Lactobacillus or other bacterial cultures have done their fermentation. It’s thought that the live bacterial cultures will help replace missing gut bacteria with an appropriate strain of bacteria. You can get pills of Lactobacillus (e.g., Lactinex; for those who hate yoghurt) or yeast (e.g., Florastor). Sometimes these probiotic pills are criticized as, compared to yoghurt or buttermilk, most of the bacteria or yeast in the pills are dead. But there’s some evidence that even some kinds of dead bacteria have salutary effects on diarrhea.49 It seems that eating bacteria is good,50 and it’s better to eat some kinds of bacteria than others.51-52 But each brand of yoghurt and buttermilk uses a slightly different strain of bacteria, it may be that certain bacteria are better for certain people, and there are no wide-ranging comparative trials. I hate buttermilk, and I think Chobani yoghurt tastes best, so that’s what I recommend. Avoid pop, avoid milk and fruit sugars, drink Gatorade, and eat chicken-rice soup and

| 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) |
| Rehydrate | 75     | 20     | 65     | 30     | 139 (25) |
| Pedialyte | 45     | 20     | 35     | 30     | 139 (25) |
| Resol  | 50     | 20     | 50     | 34     | 111 (20) |
| Riceleyte | 50     | 25     | 45     | 34     | (30) |
| **Gatorade** | 23.5  | <1     | 17     | 13.4* | (40) |
| Coca-Cola | 1.6   | <1     | 13.4* | (100) |
| Apple juice | <1   | 25     | 13.4* | (120) |
| Orange juice | <1   | 50     | 13.4* | (120) |
| **Chicken broth** | 250   | 8      | 0      | 0      | 0      |

* Figures in parentheses represent grams of carbohydrate.

Oral Rehydration Solutions

| Table 1. Composition of commercial oral rehydration solutions (ORS) and commonly consumed beverages |
|---------------------------------|--------|--------|--------|--------|--------|
| **ORS** | **Carbohydrate (mmol)** | **Sodium (mmol/L)** | **Potassium (mmol/L)** | **Chloride (mmol/L)** | **Base (mmol/L)** |
| WHO (2002) | 13.6 | 75 | 20 | 65 | 30 | 218 |
| WHO (1975) | 20 | 90 | 20 | 65 | 30 | 311 |
| European Society of Pediatric Gastroenterology, Hepatology and Nutrition | 10 | 50 | 20 | 65 | 30 | 240 |
| Entalyte | 30 | 50 | 25 | 45 | 34 | 167 |
| Pedialyte | 25 | 45 | 20 | 35 | 30 | 210 |
| Naturalyte | 25 | 45 | 20 | NA | 48 | 265 |
| Pedialyte Electrolyte | 25 | 45 | 20 | NA | 30 | 250 |
| Celtray | 40 | 50-90 | 20 | NA | 30 | 220 |
| Commonly consumed beverages (not appropriate for diarrhea treatment) |
| Apple juice | 1.20 | 0.4 | 44 | 45 | 45 | 720 |
| Coca-Cola classic | 112 | 1.6 | NA | NA | 13.4 | 650 |
| Gatorade | 88.2 | 20 | 3.2 | 1.6 | NA | 249 |
| Gatorade-carbohydrate energy formula | 222.5 | 43 | 11.5 | NA | NA | 1.076 |

Oral Rehydration Solutions

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.
**Medications**

Lomotil (diphenoxylate + atropine) is still available by prescription only. Diphenoxylate is a meperidine (DEMEROL) derivative that slows diarrhea but has fewer 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 loperamide (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. It is not recommended for children under 3 years of age, based on good evidence that it doesn’t help. And, for traveler’s diarrhea, loperamide added to ciprofloxacin (CIPRO) doesn’t seem to help much compared to Cipro by itself. But it generally cuts acute diarrhea from 2 days to 1 day. A new anti-secretory medication called raccadotril is available in Europe and India (though not yet in the USA); it’s thought to be safe for infants, and some consensus recommendations recommend it over loperamide.

Loperamide is generally safe for acute diarrhea. Loperamide for dysentery used to be controversial because of concerns about prolonging illness, but it is now thought safe when combined with an antibiotic.

Kaolin and Pectin (Kaopectate, others) combined kaolin, an adsorbent clay, and pectin – the stuff that makes apple pie gel. It was marketed as an over-the-counter treatment for diarrhea. However, in 2003, the FDA found no evidence it was effective, and it was withdrawn. The company continued to use the well-known Kaopectate name, but now for bismuth subsalicylate.

Bismuth subsalicylate (Pepto-Bismol, others) has been available for many years. The liquid is well-known for its characteristic opaque shocking-pink appearance, and is moderately effective at lessening diarrhea, but not so much so as loperamide or antibiotics. The more-portable pills are fairly effective at preventing travelers’ diarrhea. Both pills and liquid turn the stools black, but guaiac-negative. It is considered safe, even for bloody diarrhea. It does contain salicylate, so those allergic to aspirin should not take it.

Quinolones (CIPRO=ciprofloxacin is the most-studied) have traditionally been the antibiotic of choice for infectious diarrhea. Empiric treatment with a quinolone is recommended not only for travelers’ diarrhea but for diarrhea seen in EDs in the industrialized world. Quinolones have wide coverage of the agents of diarrhea, though Campylobacter has been developing resistance, especially in Thailand. Quinolones also disturb gut flora less than other antibiotics, though C difficile overgrowth can come after quinolones. Though some still recommend 3 days of 500 mg PO twice daily, there is a fairly high cure rate with a single dose (e.g., 750 mg Cipro), and most recommend a single dose.

Given the increasingly-bad side effects of quinolone antibiotics such as Cipro (hypoglycemia, neuropathy, tendon rupture, aortic dissection and abdominal aortic aneurysm) the single dose is what I prescribe, when the patient can’t afford:

Rifaximin (Xifaxan), which is an essentially non-absorbed oral antibiotic (= no side effects or drug interactions), is used primarily in the 550 mg strength to treat hepatic encephalopathy. It is safe and as effective as oral Cipro for enterotoxigenic E coli, and there are some theoretical reasons to suspect it is superior: organisms are unlikely to develop resistance. Even in Mexico, where antibiotic resistance is increasing, resistance to rifaximin is still very low. However, it doesn’t treat invasive organisms, so don’t use it for people who seem pretty sick. The dose is 200 mg TID for three days, with a retail cost of over $100, though increasingly covered by insurance. And, given the bad side effects of Cipro, I now prescribe rifaximin (“may substitute half a 550-mg pill twice a day for 3 days if do not have the 200 mg pills”) with a backup prescription of 750 mg of Cipro by mouth once that says “fill and take only if the rifaximin is too expensive.”

Azithromycin (Zithromax) is recommended in areas with quinolone-resistant Campylobacter (e.g., those just returned from Thailand) and for the treatment of children and pregnant women. However, diarrhea from Thailand is starting to become resistant to azithromycin. The usual dose is 1000 mg single dose, though some recommend 500 mg, 1-3 doses (pediatric dose: 5 mg/kg/day for 3 days).

Bacterial resistance to these antibiotics is likely to get worse from widespread use of antibiotics in animal feed “to promote growth” despite some feeble attempts by the FDA to curtail this practice.
Travelers’ Diarrhea is basically the same as acute diarrhea in the ED here, except that the patient is traveling in (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 likely get the runs. Dr. David Shlim, the great guru of traveler’s diarrhea, says that the best protection against traveler’s diarrhea is to eat food that’s served piping hot, as heat kills diarrhea-causing bacteria.

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 rifaximin (or Cipro) and loperamide (IMODIUM).

When he presents on traveler’s diarrhea, Shlim shows this algorithm:

**Patient with Traveler’s Diarrhea ▶ Stool Microscopic Exam for Amebae (Optional) ▶ Prescribe Antibiotic**

**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 any non-urban area in North America) 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 metronidazole = FLAGYL 250 mg 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 send stool cultures.

**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 infamous O157:H7 and maybe other strains) may cause such bloody diarrhea. Especially in children, this can lead to hemolytic-uremic syndrome with kidney failure.

There is some evidence that treating such diarrhea with antibiotics makes hemolytic-uremic syndrome more likely. However, there is even one study that showed that azithromycin decreased mouse mortality from shiga-toxin E coli diarrhea. And, most bloody diarrhea is not shiga-toxin E coli. One 2001 prospective study showed that about 1% of bloody diarrhea is from E coli O157:H7 (~15% was Shigella, ~4% Campylobacter, ~4% Salmonella, and ~2% Shiga-toxin E coli, only maybe half of which was O157:H7). Therefore, in the ED treatment of dysentery, empiric antibiotics are appropriate even for bloody diarrhea, and in children, azithromycin remains the drug of choice. It’s standard to send stool cultures for bloody diarrhea, but it is also important that you ask the lab to culture for shiga-toxin E coli, as it is not tested for on routine stool cultures. If this multi-day test is the only one available, a consideration of likelihood of bloody diarrhea being shiga-toxin E coli, and of the risks of causing hemolytic-uremic syndrome and benefits of treating all bloody diarrhea with an antibiotic, still comes down on the side of giving the antibiotics. This may all change for the better, however. New rapid assays for shiga toxin (Alere Shiga Toxin Quik Chek, Meridian ImmunoCard STAT! EHEC) are starting to be available (but not where I work), and if you can get it done rapidly, it makes sense to test before starting antibiotics.

**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. Although deaths from diarrhea worldwide are decreasing, from about 2000-2010 the rates of death from diarrhea actually increased, mostly due to more frequent C diff infections. Turns out that trehalose, a common food additive, makes C diff produce more toxin.
However, with increasing recognition of *C. diff*, better cleaning and fewer antibiotics, the number of *C. diff* diarrhea deaths in the US (29,000 in 2011) is again going down. (Remember to wash your hands! Alcohol-based hand cleaners don't work for *C. diff*.)

The drug of choice for *C. difficile* are not rifaximin, ciprofloxacin (CIPRO) or azithromycin, but vancomycin 125 mg by mouth four times a day, or fidaxomicin 200 mg PO twice a day, for 10 days. Due to side effects, oral metronidazole (FLAGYL) is no longer recommended as first-line treatment.85 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 where there is known *C. diff*), 86,87 may be clues to *C. diff*. *C. diff* is always a possibility, even without known risk factors. A recent paper estimated that up to 10% of acute diarrhea (without vomiting) seen in the ED is *C. diff*.88 For patients with dysentery and *C. diff* risks, or who say “my diarrhea is really, really foul-smelling” or for whom a nurse says “smells like *C. diff*”, it seems reasonable to treat empirically with vancomycin.

In 2011, the FDA approved a new drug for *C. diff*, fidaxomicin (DIFICID). At least for bad cases, it works better than vancomycin.89 However, it costs about $2500 for a course, so it seems to be reserved for the sickest patients admitted to the hospital.

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, which also will rule out appendicitis, which is a rare but serious cause of diarrhea.

**Executive Summary**

- Divide diarrhea patients into sick and not-sick. Sick means dysentery (fever, or ongoing belly pain, or blood or mucus in stool), or HIV, or diarrhea for more than 2 days.
- 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 a developing country (“travelers’ diarrhea”) should they get an antibiotic.
- Those with dysentery, or who have HIV, or > 2 days’ diarrhea, should also get rifaximin 200 TID for 3 days with a backup of Cipro, 750 mg PO as a single dose, or maybe 500 mg PO daily for 3 days for sicker patients. 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*, use vancomycin empirically instead, 10 days of 125 mg PO QID.
- Only for those acute diarrhea patients with dysentery who also look pretty sick, have frankly bloody diarrhea or have HIV, should you send stool for culture and *C. diff* toxin assay.

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**References**

20. McNulty WS, *DuPont* HL,


