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## **A Practical Guide to Diagnosis and Treatment of Infection in the Outpatient Setting** ***Diagnosis and Treatment of Infectious Diarrhea***

By Gary R. Skankey, MD, FACP, Infectious Disease, Las Vegas, NV

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As part (article V) of our effort to provide you information regarding appropriate antibiotic usage, Dr. Gary Skankey has graciously written an article for us on the practical diagnosis and treatment of diarrhea in the outpatient setting. The following is the introductory paragraph. The full article can be obtained via HealthX, or we can e-mail or fax the article directly to you. I hope you enjoy this interesting article:

Diarrhea is a condition frequently encountered by primary care physicians. The clinician must initially categorize the diarrhea: Is it acute or chronic? Is it small intestinal or colonic? Is it infectious or non-infectious? Categorization is done primarily on clinical grounds and is crucial as it will direct diagnostic tests and treatment. It is safe to say that more episodes of diarrhea are treated with antibiotics than need to be. The vast majority of infectious diarrheas are self limited and antimicrobials only serve to increase selective pressure on bacteria to develop more resistance without having any impact on clinical outcome.

**Definitions.** *Acute diarrhea* is diarrhea that lasts less than two weeks. *Persistent diarrhea* is defined as lasting longer than two weeks and *chronic diarrhea* continues past 30 days.

Sincerely,

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# A Practical Guide to Diagnosis and Treatment of Infection in the Outpatient Setting

## *Diagnosis and Treatment of Infectious Diarrhea*

By Gary R. Skankey, MD, FACP, Infectious Disease, Las Vegas, NV  
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Diarrhea is a condition frequently encountered by primary care physicians. The clinician must initially categorize the diarrhea: Is it acute or chronic? Is it small intestinal or colonic? Is it infectious or non-infectious? Categorization is done primarily on clinical grounds and is crucial as it will direct diagnostic tests and treatment. It is safe to say that more episodes of diarrhea are treated with antibiotics than need to be. The vast majority of infectious diarrheas are self limited and antimicrobials only serve to increase selective pressure on bacteria to develop more resistance without having any impact on clinical outcome.

**Definitions.** *Acute diarrhea* is diarrhea that last less than two weeks. *Persistent diarrhea* is defined as lasting longer than two weeks and *chronic diarrhea* continues past 30 days.

### ***Chronic Diarrhea***

We will only mention chronic diarrhea briefly here as the focus of this paper is on acute diarrhea. Most chronic diarrhea is due to non-infectious causes, such as inflammatory bowel disease, malabsorption syndromes, or irritable bowel syndrome. The latter may result from a prior bacterial enterocolitis, but is not itself a chronic infection.

In rare instances infection may present as a chronic diarrhea. Whipple's disease is caused by the recently described bacterium *Tropheryma whipplei* and is clinically characterized by abdominal pain, chronic diarrhea, weight loss and arthralgias. In rare cases CNS involvement or even endocarditis may occur. Diagnosis is made by electron microscopic examination of duodenal biopsy specimens and treatment is with long term (up to a year) trimethoprim/sulfamethoxazole.

Strongyloidiasis, caused by the helmenthic parasite *Strongyloides stercoralis*, can cause a chronic, waxing and waning diarrhea associated with chronic abdominal pain. Very few other illnesses here in the United States cause the prominent eosinophilia seen in this infestation. Strongyloides serology confirms the diagnosis.

Protozoan infection such as amebiasis and giardiasis may cause a persistent diarrhea and will be mentioned below.

### ***Acute Diarrhea***

**Etiology.** Acute diarrhea is usually caused by microorganisms. Cultures of stools from patients with acute diarrhea are positive only 5% of the time or less, which suggests that the majority of cases are viral. The more severe cases of diarrhea are caused by bacteria. Salmonella, Shigella, E. coli, Campylobacter, Yersinia, Listeria, and Vibrio are the genera most frequently involved. The most common causes of bloody infectious diarrhea are E. coli O157:H7 (enterohemorrhagic E. coli), Shigella, Campylobacter and Salmonella.

*Clostridium difficile* causes acute diarrhea in patients with recent hospitalization during which time they received antibiotics. Recently, increasing amounts of community acquired *C. difficile* infections have been seen, however, I have not seen any cases here in Las Vegas. Predisposing factors for development of community-acquired *C. difficile* are use of antibiotics, use of proton pump inhibitors and/or H2 blockers, and, oddly enough, use of NSAIDs (ASA excluded).

The patient's colon becomes colonized in the hospital by the organism when spores are carried to the patient on the unwashed hands of health care workers, on improperly cleaned instruments, or if the bed rails, beside table, or other parts of the patient's room have not been properly cleaned from the previous occupant. The organism proliferates when normal flora populations which compete for nutrients are reduced because of antibiotic use. A cytotoxin is produced which causes severe damage to the colonic mucosa leading to development of diarrhea, an intense inflammatory response including leukocytosis, and eventually development of pseudomembranes.

Norovirus (formerly Norwalk-like viruses) cause over 90% of all non-bacterial acute diarrheas in the USA. Enteric adenoviruses are a less common cause. Rotaviruses and astroviruses commonly cause diarrhea in children.

Protozoans are an uncommon cause of acute diarrhea in the United States, but as mentioned above, may be a cause of persistent diarrhea (> 2 weeks). *Entamoeba histolytica* is primarily seen in travelers to developing countries. Institutionalized people and homosexuals seem to have a higher rate of infection without a travel history. *Giardia lamblia*, also nicknamed *beaver fever*, causes infection after drinking creek water or other water sources contaminated with the organism. *Cryptosporidium parvum* has caused epidemics of acute diarrhea when public water supplies have been contaminated and causes a persistent diarrhea, usually recalcitrant to therapy, in AIDS patients.

*Dientamoeba fragilis*, *Endolimax nana*, and *Blastocystis hominis* are occasionally identified in stool specimens, but are believed to be saprophytic and generally do not cause disease, although some reports suggest that in rare cases they might.

Traveler's diarrhea is common in people recently returning from trips to less well developed countries. The most common cause is enterotoxogenic *E. coli* which secretes a four-subunit toxin similar to that of cholera. Other causes include salmonella, shigella, noroviruses, and *Entamoeba histolytica*.

Food poisoning exists in two types: toxin-mediated and invasive. Toxin mediated food poisoning in which diarrhea is usually also accompanied by vomiting, is most commonly caused by *Staphylococcus aureus*, *Clostridium perfringens* and *Bacillus cereus*. To emphasize, these organisms cause a *toxin-mediated* disease, therefore they do not constitute infection. The organism multiplies in the food, secretes a toxin into the food which is ingested by the individual which then causes illness.

**Clinical presentation.** Most acute diarrhea is mild enough that the patient may not seek medical attention. The following findings, which only occur in a minority of cases, should raise concern and encourage a physician to investigate further: 1) Presence of dehydration, 2) hematochesia, 3) fever, 4) greater than 6 liquid stools over a period of 24 hours, 5) duration of illness longer than 3 days, 6) severe abdominal pain, 7) recent hospitalization with use of antibiotics, 8) elderly or immune compromised patients. If these findings are not present, the patient can simply be assured that the diarrhea is self-limited and will resolve in a few days without the use of antibiotics.

**History.** A thorough history makes up 90% of the diagnosis of acute diarrhea. Certain questions must be asked: What are the bowel movements like?

- High volume, watery stools suggest small bowel disease (enteritis) and smaller volume with or without blood suggests colonic involvement (colitis).
- Organisms associated with colitis: *Campylobacter*, *Shigella*, *Salmonella*, *C. difficile*, *Yersinia*, *Vibrio parahaemolyticus*, enteroinvasive *E. coli*, *Entamoeba histolytica*, CMV.
- Organisms that enteritis: *Salmonella*, enterotoxogenic *E. coli*, *Vibrio cholerae*, *cryptosporidium*, *giardia*, *Rotovirus*, *norovirus*.
- The toxins of *staphylococcus*, *bacillus* and *clostridium* species affect the small bowel.

Have you been having fever?

- This suggests invasive bacteria, such as *Salmonella*, *Shigella*, and *Campylobacter*
- *C. difficile* can cause fever, but in my experience patients with colitis due to this organism are either afebrile or have low grade fever.
- Amebic dysentery and viral enterocolitis will also often be accompanied by fever.
- Be aware that many times inflammatory bowel disease flares are accompanied by fever.

Have you eaten any raw or undercooked meats, raw fish or unpasteurized dairy products?

- Consumption of raw oysters can transmit *Vibrio*.
- *Salmonella* and *Shigella* can be transmitted from raw dairy products and have been associated with consumption of undercooked meats along with *E. coli* H7:O157.

Has anyone else had the same symptoms especially after having eaten the same foods?

- If the answer to this is "yes", food poisoning must be a consideration.
- Toxin-mediated food poisoning has an "incubation period" of only a few hours, so if several people become ill the same day as eating the same food, we are probably not dealing with an infection

- Salmonella, Shigella, Campylobacter, and Yersinia all have a 3 – 5 day incubation period.
- Food poisoning and *C. difficile* should be considered in outbreaks in hospitals, long term acute care facilities and nursing homes.

Have you traveled outside the country lately?

- The average incubation period for most types of traveler’s diarrhea is 3 – 5 days, so travel prior to a couple of weeks before onset of symptoms is not likely to be related.
- The most common causes of traveler’s diarrhea are *E. coli*, Salmonella species, Shigella species, viruses (rotavirus), amoeba and Giardia.

Do you have pets at home, or have you have contact with any other animals?

- Salmonella has been transmitted from lizards and turtles.

Did you drink any creek or river water lately?

- Hikers and campers who develop diarrhea within a few days of returning to civilization may have Giardiasis.

**Physical examination.** Bowel sounds will usually be active or hyperactive. Mild abdominal tenderness may be present in most case. Invasive colitis may present with significant tenderness if inflammation is extensive. Watch for signs of dehydration (orthostatic hypotension, tenting of skin)

**Laboratory.** Laboratory work up is not indicated unless a patient’s symptoms are severe enough that antimicrobial therapy may be necessary.

Stool cultures can detect Salmonella, Shigella, Campylobacter, Yersinia and Vibrio. Since *E. coli* is a normal inhabitant of the colon, growth of the organism is usually not reported. However, a special test can detect for *E. coli* H7:O157. Remember that cultures are not 100% sensitive and may miss the organism.

Ova and parasites (O&P) examination of stool can detect amoeba and other protozoans. To enhance the test’s sensitivity, this should be performed on fresh stool, not much older than 30 minutes. The reliability of this test also depends on the skill of the technician. *It is not cost effective to order this routinely* as rates of parasitic diarrhea in the USA are very low. The test is indicated in cases of: 1) recent travel to developing countries, 2) a patient with persistent diarrhea (> 2 weeks), 3) a patient with significant exposure history (works in a day care center, recent backpacking expedition and drank creek water, known community waterborne outbreak), 4) a patient with bloody diarrhea and few or no fecal leukocytes. Routine O&P testing on all cases of diarrhea is otherwise not warranted.

Serologic tests on stool are available for detection of certain viral etiologies, such as Rotavirus. When stools are sent for detection of *C. difficile* an enzyme-linked assay is performed for *C. difficile*-secreted toxins, the organism is not cultured.

Fecal leukocytes may help diagnose acute invasive bacterial diarrhea. However, studies done looking at the sensitivity and specificity of this test show widely varying results. Presence of fecal leukocytes is very supportive of a diagnosis of inflammatory enterocolitis, however their absence does not rule it out.

Blood work is rarely of much help in diagnosing the cause of acute diarrhea since most cases of acute diarrhea are non-invasive and illicit no systemic response. An elevated white blood cell count in someone with fever, abdominal pain and diarrhea could be a clue that the patient has an invasive form of diarrhea. In my experience, *C. difficile* colitis is almost always associated with leukocytosis, to the extent that diarrhea with a normal white blood count virtually rules it out. Eosinophilia is particularly suggestive of strongyloides infestation. Interestingly, eosinophilia is usually not seen in cases of ameobiasis or giardiasis since when causing colitis the protozoan does not invade tissue to a significant extent.

**Treatment.** Since the majority of cases of acute diarrhea are self-limited, treatment is primarily supportive and is aimed at preventing or treating dehydration. Only the most severe cases require antimicrobial therapy. Unfortunately, as in the case of upper respiratory tract infections, when a patient takes the time and expense to see their doctor for their diarrhea they often expect to leave with a prescription for an antibiotic. *Physicians must resist giving in to those expectations by educating the patient.*

Acute bacterial diarrhea - Indications for instituting antimicrobial therapy empirically are: 1) fever accompanying diarrhea, 2) bloody or purulent stools, 3) the patient is immune compromised, 4) the patient has severe abdominal pain. Even in most of these cases, the illness is self-limited and antibiotics only serve to shorten the duration of illness by a day or two and decrease the severity of symptoms.

The standard regimen I see physicians ordering for empiric therapy of acute diarrhea is a fluoroquinolone (usually Levaquin 500 mg PO QD) plus metronidazole 500 mg PO TID, believing that this blanket covers all causes of diarrhea. Certainly, a fluoroquinolone is the drug of choice in treating *acute diarrhea when treatment is indicated*. Not only are most bacterial causes of diarrhea sensitive to them, but quinolones also attain high intracellular concentrations which is important in treating Salmonella infections which is primarily an intracellular infection. Metronidazole is usually not necessary unless the patient's history reveals a risk for *C. difficile* (recent hospitalization, recent antibiotics, etc.) or protozoan disease (international travel, backpacking, etc).

Ampicillin, in years past has been the drug of choice, is no longer adequate empiric therapy as *E. coli*, Salmonella species and Shigella species now have a high rate of resistance to it. These organisms are, with the uncommon exception, sensitive to quinolones. Campylobacter is innately resistant to beta-lactams, like penicillins or cephalosporins, but is sensitive to erythromycin and fluoroquinolones.

In proven cases where the patient has a clinical presentation that includes bloody diarrhea, abdominal pain, but little or no fever, and stool cultures reveal enterohemorrhagic *E. coli* (EHEC), antibiotics should actually be *avoided*. The infection is self limited so the antibiotics have little or no impact on the outcome, plus antibiotics are implicated in development of hemolytic-uremic syndrome, especially in children.

Acute protozoan diarrhea - 500 mg of metronidazole is adequate therapy for giardiasis, but 750 mg TID is necessary for treatment for amebiasis. Then, ten days of metronidazole must be followed by two weeks of paromomycin for 10 days or iodoquinol for 20 days to eradicate amoebic cysts from the gut.

Clostridium difficile diarrhea - Metronidazole is the drug of choice for treatment of *C. difficile* colitis. Oral vancomycin is second line. Metronidazole should be dosed at least 1 gm over a 24 hour period. So 250 mg PO QID or 500 mg PO TID are the recommended doses. The reason why metronidazole is the drug of choice over vancomycin is three-fold. First, metronidazole and vancomycin are equally effective in treating *C. difficile*. Vancomycin should be used primarily when metronidazole fails. Second, oral vancomycin is about one hundred times more expensive than metronidazole. Third, oral vancomycin promotes the development of VRE at a higher rate than metronidazole.

If oral vancomycin is used to treat *C. difficile*, in such cases as intolerance of or failure of metronidazole, the dose is 125 mg PO QID. The concentration in the gut of vancomycin at such a dose exceeds the MIC of *C. difficile* by about 1000-fold. All that is needed to kill an organism is a concentration that is 8-fold greater than the MIC, so this dose is entirely adequate. There is, therefore, no reason to dose vancomycin at 250 mg or 500 mg PO QID as I have seen done many times. Obviously, a concentration that is 2000-fold greater than the MIC does not kill the organism better than one that is 1000-fold greater. The only instance where a higher vancomycin dose might be given is in the case of a patient with a severe ileus which might not allow the PO antibiotic to reach the colon in sufficient quantities to exceed the MIC. Then, a higher dose might be more likely to reach the desired concentration there. Usually, these are patients who will be in the hospital and not the outpatient setting.

Relapsing C. difficile diarrhea – About 20% of *C. difficile* cases relapse and there are three reasons why this may happen: 1. metronidazole and vancomycin kill vegetative cells, but not the spores. Those spores may not be cleared out of the gut completely after antimicrobial therapy. 2. Patients with recurrent *C. difficile* do not make adequate secretory IgA specific for the organism. 3. Reinoculation is possible because the spores may survive on surfaces in the patients' surroundings for a very long time.

No one therapeutic approach to this problem has been proven superior. Approaches include:

- Long taper of metronidazole or vancomycin over several weeks
- Use of probiotics, like *Saccharomyces boulardii* or acidophilus to repopulate the colonic microflora and out compete *C. difficile*

- Pulse therapy – This is my favorite approach. The patient is treated with 2 to 3 weeks of metronidazole or vancomycin followed by several weeks of 5- or 7-day pulses of the antibiotic (5 days of antibiotics followed by 5 days off antibiotics repeated 6 to 8 times). The philosophy here is that the antibiotics kill vegetative cells, but not the spores. The antibiotic free periods allow the spores to germinate, then the next pulse of antibiotic kills those off. The hope is that after each pulse fewer and fewer spores are left until they are eventually cleared from the gut.
- Fecal enemas – This approach is used with great success outside the USA. The concept is to repopulate the patient's gut microflora that out competes *C. difficile* for nutrients. A family member or friend donates stool which is then filtered to remove particulate matter. The filtrate is then given as an enema. I have used this once or twice in-patients who failed all other attempts at putting a halt to recurrences of *C. difficile* and it worked.
- Intravenous immune globulin (IVIG) has shown some efficacy in preliminary studies, but more research is required before this can be recommended.

**Practice Guidelines for treatment of acute diarrhea: The following is recommended by the Infectious Disease Society of America. Empiric antibiotic therapy should only be given to the following groups of patients:**

1. Severe traveler's diarrhea with > 4 loose stools per day, fever, pus and blood in the stools.
2. > 8 stools per day, dehydration, that might require hospitalization
3. Immunocompromised patients
4. May also be *considered* in patients who have not recently traveled who have blood or pus in their stools (except EHEC), and fever.

**Recommended regimen: a fluoroquinolone for 3 to 5 days. Alternative drugs are erythromycin or Azithromycin.**

**To restate;** *antibiotic treatment is not necessary in the vast majority of cases as most cases of acute diarrhea, whether due to bacteria, viruses, or protozoans are self limited.*

**Prevention and Treatment of Traveler's Diarrhea.** If a patient wants advice regarding protection against development of traveler's diarrhea prior to visiting countries south of the boarder, the middle east, Africa or Southeast Asia, the best advice is to educate him/her on what steps to take to avoid exposure. They are:

1. Don't drink tap water, or drinks with ice, or brush your teeth with tap water – boil any water you drink or drink name brand bottled. Remember that the temperature of hot water coming out of a tap is not hot enough to kill microorganisms. Don't sing in the shower.
2. Don't eat raw fruit or vegetables that may have been washed by water. Peeled fruit is safe.
3. Don't eat any food from street vendors.
4. Don't eat any restaurant food unless it is served piping hot (assuring that enough heat was used to cook the food to kill pathogens).
5. Don't eat raw meat.
6. H2 blockers and proton pump inhibitors remove a very effective barrier to infection; gastric acid. Risk of infection increases in patients taking these drugs. Suggest to patients that they might stop taking these medications while on their trip if it will be a short one (1 – 2 weeks).

If a prophylactic medication is desired, recommend bismuth-subsalysalate (Pepto-Bismol) 2 to 4 tablets four times a day for the duration of the trip. Antibiotics should only be given prophylactically for patients with serious underlying medical conditions (diabetes, oxygen-dependent COPD, Parkinson's disease, congestive heart failure, etc) in whom dehydration from diarrhea could be potentially life threatening. Antibiotic of choice would be a quinolone.

As with all cases of acute diarrhea, the majority of cases of Traveler's Diarrhea are self limited and do not require use of antibiotics. Only the more severe cases should be treated. Otherwise, use of anti-motility drugs and hydration efforts are the mainstay of therapy.

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