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A Review on Management of Acute Gastroenteritis and the Role of Antibiotics

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Abstract

One of the most common diseases is diarrhea. An overview of epidemiology, management, and current treatments for acute diarrhea is presented, as well as a review of the most important pathogens. Following a description of the general principles of diarrhea therapy, the most important bacterial gastrointestinal infections are described in terms of targeted antimicrobial therapy, including Salmonellosis, Shigellosis, Campylobacter, as well as *Escherichia coli*, Yersiniosis, and Cholera infections. There has been an increase in the incidence and severity of diarrhea caused by toxigenic *Clostridium difficile* strains. Therefore, new aspects of treatment will be described in detail for these infections. It is still important to treat infectious diarrhea with symptomatic therapy. Patients with severe illness, such as high frequency of stools, fever, bloody diarrhea, underlying immune deficiencies, advanced age, or significant comorbidities, may benefit from empirical antibiotic therapy. Resistance to fluoroquinolones is on the rise, in particular. Infections caused by Shiga toxin-producing *E. coli* (STEC), *C. difficile* infections (CDI), and severe Colitis should not be treated with motility inhibitors. CDI recurrence can be reduced by fidaxomicin, a macrocyclic antibiotic. Additionally, there is increasing evidence that fecal microbiota transplantation is a successful treatment option for multiple recurrences of CDI. As a result, acute diarrhea is still primarily treated with supportive measures. It is not evidence-based to prescribe antibiotics for acute diarrhea.

Keywords: Antibiotics, Community-acquired diarrhea, Diarrhea, Gastroenteritis, Travelers' diarrhea

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Introduction

Even in industrialized countries, acute infectious diarrhea remains a common health problem. Adults in Germany suffer from 0.95 episodes of acute gastrointestinal illness per year, according to recent data. The USA reported a similar rate. When assessing patients with acute diarrhea, one of the dilemmas is determining when to test for aetiological agents and when to initiate antimicrobial therapy. We review the management of acute gastroenteritis (GE) in adults in industrialized countries with a special focus on antibiotics. Managing persistent and chronic diarrhea, nosocomial diarrhea, and acute GE in resource-limited countries is beyond the scope of this article. There are two epidemiological settings in which acute GE can occur: community-acquired diarrhea and travelers' diarrhea [1].

Diarrhea is usually defined as the passage of three or more unformed stools per day or the passage of more than 250 g of unformed stool per day, often accompanied by symptoms of nausea, vomiting, or abdominal cramps. On the basis of duration, diarrhea can be divided into acute (lesser than 14 days), persistent (between 14 - 29 days), or chronic (greater than or equal to30 days) (Figure 1) [2].

Epidemiology of travelers' diarrhea and community-acquired diarrhea

The percentage of travelers with travelers' diarrhea in resource-restricted nations varies between 25% and 54%. As a result of ingestion of contaminated foods or drinks in the first 3 weeks of travel, it is most commonly acquired. Travelers who followed the advice 'boil it, cook it, peel it, or forget it' and those who engaged in more adventurous eating habits had similar incidences of diarrhea [3, 4].

The majority of travelers have self-limiting illnesses; <1% require hospitalization. 80% of travelers' diarrhea cases are caused by bacterial enteropathogens. Enterotoxigenic *E. coli*, enteroinvasive *E. coli* (EAEC) are implicated in the majority of cases, followed by *Campylobacter, Salmonella* and *Shigella*. It is uncommon for parasitic agents to cause acute travelers' diarrhea but should be suspected in cases of chronic or subacute symptoms [2, 5]. Whereas in community-acquired diarrhea, the leading cause of bacterial diarrheal illness includes *Campylobacter*, EAEC. During 2012 - 2014, Campylobacter infections were reported more frequently than infections caused by non-typhoidal Salmonella (70 per 100000 vs 26 per 100000). Salmonellosis cases have also decreased over the past few years, most likely as a result of veterinary control programs, particularly in poultry. In industrialized countries, EAEC is also recognized as an important cause of community-acquired diarrhea [6]. Furthermore, *C. difficile* has emerged as a major cause of community-acquired diarrheal illness. The transmission of *C. difficile* has been proposed as a possible source of community-associated infections, but the evidence needed to confirm or refute this hypothesis is lacking. Pathogens such as Yersinia species, non-cholera Vibrio species, and STEC strains [7].

Management of acute GE

Most patients with acute diarrhea can manage their illness and do not seek medical attention. An attending physician should

assess patients with significant diarrheal symptoms, such as profuse, dehydrating, febrile or bloody diarrhea, by obtaining a comprehensive history that includes epidemiological as well as clinical information [2, 8]. Clinical features that are relevant to diagnosis include the onset of illness, the frequency of bowel movements, dysenteric symptoms (fever, tenesmus, blood, or mucus in the stool), and associated symptoms such as nausea, vomiting, and abdominal pain. There are several important epidemiological factors to consider, such as previous international travel, antibiotic treatment, chemotherapy, immunosuppressive conditions, work at a daycare center, and consumption of unsafe foods (e.g. raw meat, eggs, and shellfish). It is important to examine the patient's hydration status and abdominal tenderness during a directed physical examination [9].

In most cases of non-severe illnesses, it is not necessary to determine the precise cause of diarrhea. An illness lasting longer than one day with fever, recent antibiotic use, longer duration of symptoms, hospitalization, immunosuppression, diarrhea in elderly patients, or symptoms of dehydration (defined as dry mucous membranes, decreased urination, tachycardia, postural hypotension, or lethargy) should lead to the evaluation of fecal specimens for Salmonella, Campylobacter, and Shigella. STEC testing should be added to stool examinations in cases of bloody stools [10-12]. Testing for *C. difficile* is recommended if the patient has a history of antibiotic intake, chemotherapy, or hospitalization. Community-acquired cases of CDI do occur without typical risk factors. Most of the time, the bacterial pathogen is detected in the first or second sample. Therefore, multiple cultures are not useful. Despite the low bacterial yields obtained in stool cultures (1.5 - 3%), the information obtained is important both for the individual patient and for public health [2, 13].

PCR-based diagnostic methods have evolved into novel tools that are often capable of detecting multiple enteropathogenesis in a single test in the past decade. The advantages of these techniques are high sensitivity, and, in the case of automated multiplex systems, a very short turnaround time compared to conventional cultures [14]. It is important to note, however, that detecting a pathogen's nucleic acid does not automatically indicate that it is causing clinical symptoms. It is possible for the patient to be an asymptomatic carrier, or the nucleic acid of the pathogen may be detected even if it is no longer viable [15]. In the future, PCR-based methods followed by culture could be used in conjunction to detect resistance patterns. To determine when to initiate antimicrobial therapy, a patient's history and symptoms should be considered rather than laboratory results alone. When patients have fever or symptoms indicative of systemic inflammatory response syndrome, additional diagnostic evaluations such as serum chemistry analysis, complete blood count, and blood cultures may be required [16, 17].

It is still common for family physicians to encounter pediatric acute GE on a day-to-day basis. There continue to be significant health risks associated with it, including vomiting, diarrhea, and dehydration. According to estimates, children under five years of age experience 1.5 to 2.5 episodes of diarrhea per year as a result of acute GE. More than 280 US children die from GE each year. In the United States alone, GE is responsible for approximately 10% of hospitalizations among children under five. Over $2 billion is estimated to be spent annually on hospital and outpatient care. Pediatric acute GE has attracted considerable attention and effort worldwide for the past two decades. A special emphasis has been placed on developing and promoting affordable, easy-to-use oral rehydration solutions (ORS) for the treatment of dehydration, the leading cause of morbidity and mortality among children. Although ORS are proven safe and effective, they

Table 1: Summary of randomized controlled trials evaluating the efficacy of ondansetron in acute GE [3].

Setting	No.	Age	Inclusion criteria	Antiemetic agent	Route/dose of ondansetron	Outcomes	Side effects	Follow-up
Inpatient	36	6 month - 8 years	GE and >2 × emesis within 1 h	Ondansetron/Metoclopramide (0.3 mg/kg iv)/isotonic saline	IV/0.3 mg/kg single dose	Vomiting episodes and ORT failure	Increase in diarrhea	24 h
Emergency department (ED)	145	6 month - 12 years	GE with >5 × vomiting in the preceding 24 h	Ondansetron (syrup)	Per OS/1.6 mg (6 month - 1 year); 3.2 mg (1 - 3 year); and 4 mg (4 - 12 year) Q8H up to 6 doses	Vomiting episodes, receipt of IVF, hospital admission, and diarrheal episode	Increase in diarrhea	24 h
ED	107	1 month - 22 years	GE and >3 × vomiting in the preceding 24 h, requiring IV rehydration	Ondansetron	IV/0.15 mg/kg single dose	Vomiting episodes, hospital admission, duration of vomiting, diarrhea episodes, and return to ED and need for readministration of IVF	No increase in diarrhea	5 - 7 days
ED	137	6 month - 12 years	GE with >3 × emesis within past 24 h, mild to moderate dehydration, and failed oral hydration	Onsansetron/Dexamethasone (1 mg/kg)/isotonic saline	IV/0.15 mg/kg single dose	Hospital admission, ORT tolerance, and degree of dehydration	Not assess the severity of diarrhea	1 - 2 days
ED	214	6 month - 10 years	GE with mild to moderate dehydration and >1 × vomiting in the preceding 4 hours	Ondansetron (orally dissolving tablet)	Per OS/2 mg (8 - 15 kg); 4 mg (15 - 30 kg); and 8 mg (>30 kg) single dose	Vomiting episodes, receipt of IVF, and admission to the hospital	Increase in diarrhea	1 - 2 weeks
ED	106	1 - 10 years	GE with mild to moderate dehydration and failed oral rehydration attempt	Ondansetron (orally dissolving tablet)	Per OS/0.15 mg/kg single dose	Vomiting episodes, receipt of IVF, hospital admission, diarrheal episodes, and return visit to ED	No increase in diarrhea	1 week
ED	109	5 month - 8 years	GE with mild to moderate dehydration, >4 × vomiting in 6h and >4 × diarrhea in 24 h	Ondansetron (syrup)	Per OS/0.2 mg/kg Q8H for 3 doses	Vomiting episodes, receipt of IVF, hospital admission, diarrheal episodes, and return visit to ED	Increase in diarrhea	24 h

remain underutilized, and GE management continues to vary greatly in developed countries [18-22]. There is evidence that some physicians are unaware of the current oral rehydration standards. Dehydrated pediatric patients are not always treated with oral rehydration therapy (ORT), even by physicians who are familiar with these guidelines. Children with little or no dehydration may be treated with ORS, and children with moderate dehydration may be treated with intravenous (IV) rehydration therapy [23-28]. Children with vomiting may be withheld ORS or other feedings inappropriately. It was in 1996 that the American Academy of Pediatrics (AAP) formulated and published a practice parameter on acute GE in children in an effort to improve physicians' understanding of the management of GE and to uniformize treatment approaches and costs. Following an extensive review of the relevant literature, the AAP issued recommendations regarding rehydration methods, refeeding during and after rehydration, and the use of antidiarrheal agents for symptom control (Table 1) [29-33].

Therapy for travelers' diarrhea and community-acquired diarrhea

Rehydration is the first step in treating acute diarrheal illnesses, which can be accomplished with oral electrolyte solutions or intravenous fluids (IVF). In most cases, antibiotic therapy is not necessary because the illness is usually self-limiting. Before considering antimicrobial therapy, unintended and potentially harmful consequences must be carefully weighed. In some cases, however, empirical and specific antimicrobial therapy may be considered. Identifying local patterns of resistance is crucial for reducing the number of treatment failures [34, 35].

Experimental models suggest that fluoroquinolones increase the production and release of STEC toxins during treatment with antibiotics in patients with suspected or proven STEC infections. Antibiotics may increase the risk of HUS, although some studies have suggested that antibiotic treatment does not increase the risk [11, 36, 37]. There is a correlation between antibiotic use and HUS risk, including a large, prospective study among 259 children. STEC infection should be suspected in patients with bloody diarrhea, abdominal pain, or tenderness without a fever. Antibiotics are not currently recommended for patients with little or no fever who may have STEC infection in an outbreak of bloody diarrhea. Single cases of acute febrile bloody diarrhea are more likely to be caused by *Campylobacter* spp. or *Shigella* spp., depending on the epidemiological setting. It is likely that empirical antimicrobial therapy will benefit these patients [12-14].

Travelers' diarrhea: The majority of travelers' diarrhea patients have self-limiting illnesses, and only 1% require hospitalization. Diarrhea with more than four stools per day, fever, and blood or mucus in the stool, however, requires antibiotic treatment [2, 15-18]. Traditionally, ampicillin, trimethoprim-sulfamethoxazole, and doxycycline have been used to treat bacterial infections [26]. These substances, however, have been reported to have high levels and frequencies of resistance, making them inappropriate for use as empirical treatments. Travelers are currently advised to take ciprofloxacin, azithromycin, and rifaximin as self-medication. Globally, enteropathogens are increasingly resistant to fluoroquinolones, particularly Campylobacter isolates from Southeast Asia and Europe. Rifaximin, a non-absorbed rifamycin, was shown to be effective in treating travelers' diarrhea. As a prophylactic agent, it has also been used successfully by travelers from the United States visiting Mexico. Despite the fact that rifaximin is not absorbed, it has been shown that rifampin-resistant staphylococci emerge following its intake. In patients at risk for staphylococcal foreign-body infections, rifaximin should be used cautiously due to its association with treatment failure. The use of azithromycin, a modern macrolide antibiotic, was more effective than levofloxacin in Thailand for treating travelers' diarrhea [19, 20, 31, 38, 39].

In a study conducted in Turkey, azithromycin and loperamide were compared with levofloxacin and loperamide. Although administration of 1000 mg once daily for 3 days was more effective than 500 mg once daily for 3 days, the single-dose regimen was associated with mild nausea more frequently [21, 22, 32, 33].

Community-acquired diarrhea: A Swedish study showed that norfloxacin treatment reduced diarrheal symptoms to some extent, although the effect was restricted to very ill patients. The use of norfloxacin did, however, delay the elimination of Salmonella and result in the development of resistance in Campylobacter. Among otherwise healthy patients with non-severe diarrhea caused by non-typhoidal Salmonella, antimicrobial therapy did not reduce the period of illness. Further, antimicrobial therapy increased the period of time during which Salmonella was detected in stools. Patients with non-severe non-typhoidal Salmonellosis who are otherwise healthy do not require antimicrobial therapy [23-27].

Campylobacter infections were three times more common in Europe in 2012 than nontyphoidal Salmonella infections [28]. The prevalence of ciprofloxacin resistance in human Campylobacter isolates in some EU states was 44%, while the prevalence of erythromycin resistance was <5%. In contrast, only 5 - 13% of non-typhoidal Salmonella isolates in Europe in 2011 were resistant to ciprofloxacin [29, 30, 34]. According to a recent study, approximately one-fifth of Campylobacter cases in the USA are associated with international travel in the week before symptoms develop. In international travel-associated cases, 60% of Campylobacter isolates were resistant to fluoroquinolones, compared to 13% in non-travel related cases [35, 36]. While fluoroquinolones may not be the first-line empirical therapy for community-acquired diarrhea in European countries, they may be effective in non-travel-associated cases in the United States. When treating international travel-associated cases in the USA and community-acquired cases in Europe, azithromycin seems reasonable [37, 40].

For selected patient groups, empirical antibiotic therapy is recommended: six or more stools per day, fever and bloody diarrhea or fever alone, symptoms persisting for more than a week, or immunocompromised status. There are several treatment options available in Europe, including azithromycin, fluoroquinolones, and trimethoprim-sulfamethoxazole. Fluoroquinolones and trimethoprim-sulfamethoxazole should not be used during pregnancy. Antimicrobial therapy may be required in some patients with an established infectious cause of acute diarrhea [41]. Recently, a summary of the treatment options was published.

Conclusion

It is not necessary to administer antibiotics to most patients with acute GE because the illness is usually self-limiting. In cases of community-acquired diarrhea, empirical antimicrobial therapy may be considered in selected patient groups, such as those with fever and bloody diarrhea or febrile diarrheal illness, or those with symptoms lasting more than one week. Antimicrobial therapy is recommended in cases of moderate and severe travelers' diarrhea. The ability to identify local patterns of resistance is crucial to reducing treatment failures. Whereas treatment of GE in children always includes the following pillars:

- The use of oral rehydration as a treatment for dehydration.
- Hypotonic ORS.
- Fast oral rehydration over 3 to 4 h.
- Rapid realimentation with normal feeding.

- Continuation of breast feeding at all times.
- Use of special formula is unjustified.
- Use of diluted formula is unjustified.
- Supplement with ORS for ongoing losses.

The usage of antiemetic medications in selected patients may be another essential pillar.

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Conflict of Interest

None.

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