Antibiotics for the Empirical Treatment of Acute Infectious Diarrhea in Children

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While the routine use of antibiotics for infectious diarrhea in children must be avoided, because it brings little benefit in most cases and is associated with the risk of increasing antimicrobial resistance, selected cases may require antimicrobial therapy, and the choice of the antimicrobial agent often has to be made empirically. Physicians prescribing antimicrobials in such a setting have not only to be aware of the most likely pathogens, but also of their characteristic antimicrobial susceptibility pattern and the safety profile of the various drugs. We reviewed the literature on the use of ampicillin, beta-lactamase inhibitors, trimethoprim-sulfamethoxazole, chloramphenicol, tetracyclines, nalidixic acid, fluoroquinolones, third-generation cephalosporins, macrolides, metronidazole and malabsorbed agents in the setting of acute infectious diarrhea, and we evaluated the available information, seeking to apply it to empirical use, highlighting clinically-useful pharmacological information and patients' and pathogens' characteristics that must be taken into account for decisions about antimicrobial therapy.
Key Words: Diarrhea, antibiotics, children, treatment.

Acute diarrhea remains one of the most important health issues worldwide, with high morbidity and mortality rates, accounting for more than two million deaths annually [1,2]. Acute diarrhea is the commonest infectious disease in developing countries, mostly affecting children younger than five years old. Whereas most cases of acute diarrhea are caused by virus, such as rotavirus and enteric adenovirus, and tend to present in a mild and self-limiting fashion, with the optimal treatment consisting solely of oral rehydration and nutritional support, practitioners in ambulatories or emergency rooms, especially in developing countries, are frequently faced with life-threatening presentations, characterized by signs of severe dehydration, toxemia, marked leucocytosis with high percentages of immature forms, high-grade fever, severe welfare depression, tenesmus, gross fecal blood loss and dissemination of infection. Supportive anti-dehydration therapy, associated with adequate nutritional support, is the cornerstone of therapy, regardless of the etiology and the severity of the process, and its prompt and early adoption is associated with a favorable outcome. Moreover, dehydration can simulate toxemia and mislead the clinical assessment of severity. As a consequence, volumetric expansion, electrolyte corrections and nutritional support should always be performed before any other therapeutic measure.

A few cases, however, may require antimicrobial therapy, because of the severity of the clinical picture or a patient's increased potential to develop complications, such as dissemination of the disease, sepsis or disseminated intravascular coagulation. Among those patients more prone to an unfavorable evolution are those receiving chemotherapy, HIV-positive, cirrhotics, diabetics, neonates, very young infants, the elderly, patients who have undergone organ transplantation or who have a lymphoproliferative disease, patients with sickle cell disease, or those with articular or cardiac valve prostheses. Additionally, the use of antibiotics is mandatory in severe cases of cholera, shigellosis and typhoid fever. Antimicrobial treatment tends to quicken the clinical resolution of diarrhea, prevent the progression of disease and reduce the severity of associated symptoms, such as fever, abdominal pain and vomiting. Furthermore, antimicrobial therapy decreases secondary cases, by halting person-to-person spread of most pathogens, which warrants special consideration for the use of antibiotics in the treatment of child-care workers, health professionals and workers in the catering industry or services. Prompt adoption of empirical antimicrobial therapy is also useful in the setting of febrile acute bloody diarrhea in young children and is currently recommended by the World Health Organization [3].

On the other hand, there are several arguments against the empirical use of antibiotics for acute infectious diarrhea. The most compelling of them is the fact that acute infectious diarrhea is typically a self-limiting disease, regardless of its etiology, with most cases resolving in less than three days [4]. Moreover, one must consider the low incidence of treatable pathogens among the causative agents of acute diarrhea (which are viruses in most cases), the possible occurrence of side effects, the potential development of resistant strains, the cost of treatment, and a possible noxious effects on the disease itself, as seen with enterohemorrhagic *E. coli* (EHEC) and non-typhoidal *Salmonella*. Additionally, virtually all oral antimicrobials are able to cause, or worsen, diarrhea because

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of their effect on gut microflora. Oral antimicrobials may also have their efficacy reduced by impaired intestinal absorption and enhanced intestinal motility.

The most severe drawback of widespread use of antimicrobials for the treatment of infectious diarrhea is the consequently rising rates of antimicrobial resistance, fostered by the unselected use of these drugs in patients with a mild presentation, with low risk for complications or who would recover well without antibiotics. This finding demonstrates the important role of doctors when they prescribe these drugs, especially to outpatients. Every case should be evaluated individually, considering the patient's age, nutritional status, risk for complications, characteristics of diarrhea with possible etiological agents, and the risks and benefits intrinsic to antimicrobial therapy. Laboratory information is particularly useful to help distinguish invasive enteropathogens (which may require antimicrobial therapy) from non-invasive agents, such as viruses (rotavirus, adenovirus, calicivirus, and astrovirus) and parasites (*Giardia lamblia*, *Entamoeba histolytica* and *Criptosporium* sp.).

Given the self-limiting nature of the disease, most patients with acute diarrhea do not require laboratorial evaluation and can be safely managed as outpatients. Severely ill patients may need hospitalization and further investigation, including complete blood counts, electrolyte dosing and stool culture. Rotavirus-associated diarrhea should always be excluded in such cases, given its propensity to cause severe and dehydrating pictures [5,6]. Blood culture may also be indicated in a few cases, depending on the severity and risk of hematogenic dissemination. Because of the low yield and extreme dependence on laboratory methods, the results of stool cultures should be carefully interpreted along with clinical findings. A negative culture by no means excludes the possibility of bacterial etiology in a patient with clinical signs of bacterial diarrhea. Additionally, a mixed infection may occur as well.

While stool cultures and antimicrobial testing of the isolates are the best way to select the most adequate antimicrobial regimen, the results are only available after 72 hours or more. In some instances, it is possible to wait for the result; often cases improve substantially during this interval and the use of antibiotics is no longer required when the results become available, even if enteropathogenic bacteria are identified. In severe cases, however, it is advisable to start antimicrobials empirically as soon as stools are collected for culture.

Since the use of antibiotics is associated with higher response rates if it is adopted early in the course of the disease, one is often not able to wait for the results of the stool culture before initiating antimicrobial therapy. Therefore, the decision to start antimicrobial therapy for acute diarrhea must be made solely on clinical grounds, and the choice of the antimicrobial agent has to be made empirically; it should consist of the narrowest antimicrobial spectrum possible that covers the most likely pathogens in each case. As soon as the results of the stool culture become available, the therapy may be altered according to the antimicrobial susceptibility pattern, favoring the use of narrower-spectrum, cheaper and/or safer drugs, if antimicrobial therapy remains necessary.

In order to decrease costs, as well as to reduce the possibility of increasing antimicrobial resistance among circulating strains, clinicians should choose the narrowest antibiotic regimen that adequately covers the predicted organisms for each case. Therefore, up-to-date knowledge of locally circulating strains and their antimicrobial susceptibility patterns is crucial. Clinicians must be wary of adopting antimicrobial susceptibility patterns reported by published studies from other countries, no matter how extensive and well designed they are, because the frequency of pathogens and their susceptibility patterns are highly variable from one part of the world to another. Certain clinical features may suggest specific etiological agents or help narrow the list of possible agents implicated, such as intense tenesmus with uncountable dejections, suggesting *Shigella*, right lower quadrant pain, suggesting *Yersinia*, or painless voluminous watery diarrhea without abdominal pain or fever, suggesting *Vibrio cholerae*. Severe bloody diarrhea in afebrile patients strongly suggests an EHEC-associated picture, especially if there is clustering of cases or a report of consumption of undercooked meat; the use of antibiotics should be avoided in such cases, because it increases toxin production and increases the risk of hemolytic-uremic syndrome [7,8]. In the case of patients who report the use of antibiotics during the weeks preceding an episode of diarrhea, one should examine the possibility of pseudomembranous colitis, caused by *Clostridium difficile*.

Despite the intrinsic limitations of stool cultures, laboratory investigation may also be helpful in judging the need for antibiotics for diarrheal patients. The detection of blood in the stools is a reliable indicator of invasive diarrhea, favoring the use of antibiotics if it is associated with other clinical or laboratorial hallmarks of invasive diarrhea. A simple enzyme-linked immunoabsorbent assay (ELISA) may identify rotavirus-associated cases of diarrhea and preclude the use of antibiotics. Also, the development of effective polymerase chain reaction-based techniques for stool analysis is expected to allow reliable early etiological diagnosis, guiding antimicrobial therapy, even in the absence of antimicrobial susceptibility testing, thus favoring the rational use of drugs. However, most clinical laboratories remain unable to identify enteropathogens, as the most sensitive methods remain restricted to a few research laboratories. Additionally, clinical laboratories are also unable to identify viral diarrheal pathogens other than rotavirus, and they normally cannot perform bacterial serotyping.

Ampicillin and Trimethoprim-Sulfamethoxazole

Ampicillin and trimethoprim-sulfamethoxazole (TMP-SMX) once were the drugs of choice for the empirical treatment of outpatients with acute infectious diarrhea, because of their efficacy, safety and affordability. With the passing of years, outbreaks of infectious diarrhea caused by *Shigella* or *Salmonella* strains resistant to one or both of them have been reported from all continents [9-18]. Even though these drugs may still be useful against some bacteria infecting outpatients or inpatients in various parts of the world, and though they have the obvious advantages of oral administration, the resistance of many pathogens has reached such high rates that their widespread empirical use can no longer be recommended [19-24], except when supported by detailed local knowledge of the sensibility pattern of circulating strains.

The association of ampicillin with the beta-lactamase inhibitor sulbactam provides enhanced antimicrobial activity, but increasing antimicrobial resistance to that association has also been documented, chiefly among *Shigella* spp. [20-25]. Additionally, ampicillin may fail clinically despite confirmed *in vitro* microbial susceptibility, because of its poor intracellular penetration. Amoxicillin is rapidly absorbed from the gastrointestinal tract, and therefore it is less effective than ampicillin for the treatment of infectious diarrhea.

TMP-SMX remains the drug of choice for the treatment of prolonged *Aeromonas* infections in most regions, though a 48% resistance rate has been reported from Taiwan [26]. That association may also remain an adequate choice for treating *Yersinia* infections, as no evidence of increasing resistance has been shown so far. However, one placebo-controlled study of TMP-SMX for the treatment of *Yersinia* infections showed no reduction in the duration of illness [27], though it decreased the duration of fecal shedding of the pathogen [28]. TMP-SMX may also remain an effective choice for the treatment of enterotoxigenic and enteropathogenic *E. coli* (ETEC and EPEC, respectively), in spite of growing resistance in several areas, chiefly among ETEC, which is a very common causative agent of travelers' diarrhea, especially in Latin America [29]. It may also remain a good choice for the treatment of cholera in children less than eight years old.

Chloramphenicol

Rising resistance rates, uncomfortable posology, and the risk of side effects, have contributed to the displacement of chloramphenicol as a good drug for the empirical treatment of acute diarrhea. Nevertheless, it still may be used empirically if typhoid fever is strongly suspected on clinical grounds, as long as it is supported by up-to-date knowledge of antimicrobial susceptibility pattern of locally circulating strains. The use of chloramphenicol for the treatment of typhoid fever is associated with reduced mortality and decreased incidence of life-threatening complications, but the need for a long two - three week regimen to prevent relapse and prolonged fecal shedding of pathogens is a significant drawback. Widespread plasmid-mediated resistance to chloramphenicol among typhoid *Salmonella* species became a clinical problem in the early 1970s [30,31], and both ampicillin and TMP-SMX were shown to be effective drugs to replace it until the late 1980s, when plasmid-mediated resistance to chloramphenicol, ampicillin and TMP-SMX was reported [32-34]. On the other hand, the re-emergence of chloramphenicol-susceptible strains has been reported from areas where the use of chloramphenicol had been avoided due to high resistance rates, possibly as a result of decreased selective pressure [35,36]. The occurrence of aplastic anemia is a very rare complication associated with the use of chloramphenicol, but it should always be kept in mind due to its potentially life-threatening severity [37,38].

Tetracyclines

In spite of their low cost and broad antimicrobial spectrum, the use of tetracyclines in pediatric patients is limited by permanent dental discoloration in children younger than eight years of age. The total dosage received appears to be the most important factor influencing the degree of staining, which has also been shown to depend upon the dosage and duration of therapy. Additionally, tetracyclines have been shown to cause enamel hypoplasia and reversibly impair bone growth. Because of these important side effects, tetracyclines have been progressively displaced by safer, equally effective drugs, for the treatment of most conditions in which they are likely to be effective. However, the benefits of therapy with a tetracycline can exceed the risks if alternative drugs are less efficacious or are associated with more significant side effects.

This is the case for cholera, for which the current standard antimicrobial therapy in adults is a single dose of fluoroquinolone, the use of which in children remains restricted. Oral tetracycline for three days or a single dose of doxycycline are the drugs of choice for the treatment of moderate to severe cases of cholera in patients older than eight years. Younger children may also profit from that therapy, in spite of the risk of dental staining, which has to be weighed against the benefits, i.e. decreases in the duration of diarrhea and in fluid replacement requirements. Whenever possible, the preferred tetracycline is doxycycline, because the risk of dental staining is less with this drug than with the other tetracyclines; in addition, it is given only twice a day. In the treatment of tetracycline-resistant strains, TMP-SMX has been used for children less than eight years of age who have cholera; ampicillin and macrolides may be reasonable alternatives.

Nalidixic Acid

Nalidixic acid, the only non-fluorinated quinolone available, was initially considered the best option to replace ampicillin and TMP-SMX [39,40]; but its widespread use was followed by increasing resistance in several countries, chiefly among *Shigella* spp. and, to a lesser extent, *Salmonella* [19,22,41-47]. However, in some regions there are still low rates of resistance, so it may still be a good option, especially because of its low cost and the possibility of oral use [23,48-51].

Besides increasing microbial resistance, two major problems for therapy with nalidixic acid are the regimen that should be used (four times a day for five days), which compromises compliance, and the fact that clinical and microbiological failure has been reported in 30% of patients infected with nalidixic acid-susceptible strains, possibly because of its poor cellular penetration when compared to fluorinated quinolones [39,52]. Nalidixic acid has been reported to damage juvenile weight-bearing joints in animal studies [53,54], but clinical studies have failed to demonstrate an association between the use of nalidixic acid and growth impairment or joint symptoms in humans, even with prolonged treatment [55,56].

Recently, resistance to nalidixic acid among *Shigella* and both typhoidal and non-typhoidal *Salmonella* has been shown to be a reliable predictive factor of clinically relevant decreased susceptibility to fluoroquinolones, which, on the other hand, cannot be considered fluoroquinolone resistance according to current guidelines [57-64].

Fluoroquinolones

The fluoroquinolones have become the drugs of choice for the empirical treatment of acute diarrhea in adults, because they are active against most of the common treatable enteropathogens, have excellent tissue and intracellular penetration, achieve high fecal concentrations, are suitable for oral administration, and have a favorable safety profile in adults [65,66]. The use of 500 mg ciprofloxacin twice a day for five days in the empirical therapy of acute diarrhea has been shown to decrease the duration of diarrhea, fecal shedding of pathogens, duration of fever and of other symptoms as well as total duration of illness, based on several randomized, placebo-controlled trials of various types of adult populations [67-71]. This decrease appears to be independent of the predominant pathogens that are isolated and of the rate of negative cultures from the study population, reflecting both the broad spectrum of activity of this drug and the low yield of stool cultures. Shorter three-day or even single-dose regimens of fluoroquinolones have been suggested to be effective for the treatment of shigellosis in adults and children [72-74]. Nevertheless, it is essential that clinicians be very selective in the cases in which they use fluoroquinolones, because the widespread unnecessary use of those drugs brings the risk of increasing microbial resistance to one of the few highly effective oral antimicrobial drugs currently available, as has been recently reported for some strains of *Shigella*, *Salmonella* and *Campylobacter* [75-80].

In children, though, there are several restrictions to the use of fluoroquinolones. Joint disorders observed in young experimental animals during experimental toxicity trials made pharmaceutical companies decide not to seek to extend fluoroquinolone indications to Pediatrics. Such side effects have also been noted in children participating on clinical trials [81-83] and, indeed, among all possible adverse effects of the use of fluoroquinolones, only musculoskeletal events are more common in children than in adults [84-87]. Based on the potential risks and benefits of prescribing fluoroquinolones to children, the American Academy of Pediatrics, as well as several experts, have suggested that fluoroquinolones only be prescribed for specific infections or as a second-line antibiotic, in the case of severe bacterial infections with proven resistance to safer drugs [88-92]. Therefore, it is not advisable to use fluoroquinolones for the empirical treatment of diarrhea in small children, though it may have a role in culture-oriented therapy. Further studies to precisely assess the cut-off age beyond which children may use fluoroquinolones safely are warranted.

Third Generation Cephalosporins

Since third generation cephalosporins have equally wide antimicrobial activity spectrum and fewer adverse effects than the fluoroquinolones, they have been considered by many the best drugs for the empirical treatment of severe acute infectious diarrhea in children; this is especially true for ceftriaxone, given the success rates similar to those achieved with the fluoroquinolones [83]. Ceftriaxone may be administered both intravenously and intramuscularly, typically for five days; but a two-day course has also been shown to be effective for shigellosis [93], but not for typhoid fever, which needs longer regimens [94]. Additionally, the clinical resolution of symptoms is typically slower with ceftriaxone than with ciprofloxacin, and more severe cases may require courses longer than five days. The effectiveness of ceftriaxone has been demonstrated in the treatment of both typhoid [95] and non-typhoid salmonellosis [96] and shigellosis [83,97], even with strains resistant to fluoroquinolones [98,99]. Besides the need for parenteral administration and the high cost, the major drawback of the widespread empirical use of ceftriaxone for the treatment of acute infectious diarrhea is the immediate danger of increasing microbial resistance to this useful drug. For all of these reasons, this drug should be reserved for very severe cases.

Cefixime is a third-generation cephalosporin that is administered orally; therefore, it may be an adequate drug for the treatment of outpatients. It is typically administered once or twice daily for five days, but it has been found that a two-day course is associated with rates of clinical cure similar to those achieved with a five-day course [100]. While a small trial found that therapy with cefixime failed in 47% of adults with shigellosis [101], others have reported high success rates with the use of cefixime for the treatment of childhood shigellosis and typhoid fever [95,102,103].

Azithromycin and Erythromycin

Oral azithromycin has been found to be a safe and effective alternative for the treatment of acute diarrhea due to a variety of etiologic agents, and it may be an interesting empirical choice due to its safety, comfortable once-daily posology and high cellular penetration. A five-day course of azithromycin has achieved similar cure rates and lower relapse rates than a five-day course of ceftriaxone in the treatment of uncomplicated typhoid fever in children and adolescents [104,105], and similar success rates have been found in a seven-day course comparison with chloramphenicol for the treatment of infections caused by chloramphenicol-susceptible strains [106]. Azithromycin, however, has the advantage of lower overall resistance rates. Azithromycin has also been compared with fluoroquinolones, and the results have indicated similar clinical and bacteriological effectiveness in cure and relapse rates and in defervescence in the treatment of typhoid fever caused by both sensitive and multidrug-resistant organisms [107,108]. It has also been observed that azithromycin can be more suitable than ofloxacin for the treatment of infections caused by nalidixic acid-resistant strains [108]. A single oral dose of 1 g has been shown to be as effective as a single 500 mg dose of levofloxacin in adults with traveler's diarrhea, achieving similarly high success rates [109].

While most cases of *Campylobacter*-associated diarrhea are self-limiting and do not require the use of antibiotics, patients with high fever, with bloody diarrhea, prolonged disease, pregnancy or those who are HIV-positive should be treated. Azithromycin has also been shown to be effective against *Campylobacter*-associated diarrhea in a region where fluoroquinolone-resistance is endemic [110], while erythromycin stearate is still considered the drug of choice for the treatment of *Campylobacter* enteritis in children, because of low overall resistance rates and lower cost. Erythromycin is also a good option for the treatment of severe cases of cholera in young children who should not take tetracyclines or fluoroquinolones. Additionally, resistance rates of *Vibrio cholerae* strains to tetracyclines, TMP-SMZ and ampicillin are high in several areas [111,112]. Azithromycin has been shown to be more effective for the treatment of shigellosis, than nalidixic acid [113] and cefixime [103] in children, and roughly as effective as ciprofloxacin in adults [114].

Metronidazole

Oral metronidazole is the first choice for the treatment of *Clostridium difficile* colitis, which is responsible for over 80% of antibiotic-associated cases of diarrhea, especially the most severe [115]. Such cases, however, account for only a small part of all cases of nosocomial diarrhea, which should not be empirically treated with metronidazole [116]. Several studies have found that the usual doses of metronidazole or vancomycin are equally efficacious against *C. difficile*-associated diarrhea, whereas some experts advocate the use of vancomycin for more severe cases [117,118]. As intravenous vancomycin is not satisfactorily efficacious against *C. difficile*, cases complicated by paralytic ileum or intestinal obstruction can be successfully treated with intravenous metronidazole, plus a vancomycin enema; but surgical evaluation is usually warranted. Therefore, the use of vancomycin may be avoided in order to prevent the selection of vancomycin-resistant strains, especially among enterococci.

Withdrawing the inciting antibiotic (generally a beta-lactam or a second or third generation cephalosporin) is a very important measure for the treatment of *C. difficile* colitis. Discontinuation of therapy is often enough to resolve mild presentations and must be accomplished as soon as possible in severe cases. Antimicrobial therapy is reserved for cases with increased severity or that persist after withdrawal of the inciting agent. Relapse is common a few weeks after clinical remission and frequently represents reinfection rather than therapeutic failure, so that the same antibiotic regimen can be used again. In spite of the efficacy of vancomycin, its use must be discouraged because of the ominous possibility of provoking the appearance of vancomycin-resistant strains.

Malabsorbed Agents

Because of concerns about growing resistance and side effects, great expectations have been raised for the use of antimicrobial agents that are not absorbed from the gastrointestinal tract and, therefore, tend to be associated with fairly low resistance rates and few adverse effects. Bicozamycin and oral aztreonam, albeit proven effective both *in vitro* and *in vivo*, have not become popular choices for the treatment of acute infectious diarrhea for a number of reasons [119-122].

The development of a broad-spectrum agent with such a favorable safety profile and a low tendency for increasing resistance would have a very positive impact, not only on the empirical treatment of severe diarrhea, but also on the therapy and prevention of travelers' diarrhea. Currently, rifaximin has been the focus of intense investigation, with exciting results. The effectiveness of rifaximin for the treatment of traveler's diarrhea has already been demonstrated in comparison with a placebo [123], with TMP-SMX [124] and with ciprofloxacin [125]. More data are needed to properly evaluate the efficacy of rifaximin for the treatment of severe invasive diarrhea.

Probiotics

Probiotics have been defined as living microorganisms that exert beneficial effects beyond their nutritional value upon ingestion in certain quantities [126]. Acid-lactic and non-pathogenic bacteria have been extensively used as probiotics, as has the non-pathogenic yeast *Saccharomyces boulardii*. Probiotic agents may be beneficial for the treatment of diarrhea through several mechanisms. These mechanisms vary from one agent to another; they include competition with enteropathogens for nutrition and adhesion, modification of bacterial toxins and/or their receptors and modulation of the

Table 1. Antimicrobial agents used most frequently for the treatment of acute infectious diarrhea

Drug	Posology	Remarks
Ampicillin	50-100 mg/Kg/day in four doses if weight under 20 Kg; for children above 20 Kg 250-500 mg four times a day if weight above 20 Kg	Empirical use not recommended unless supported by up-to-date knowledge of local susceptibility patterns. Combinations with beta-lactamase inhibitors may be especially useful for treating outpatients.
TMP-SMX	10/50 mg/Kg/day in 2 doses	Empirical use not recommended unless supported by up-to-date knowledge of local susceptibility patterns.
Chloramphenicol	50-100 mg/Kg/day in 4 doses	Currently, has its use limited to typhoid fever. Widespread resistance may render it not suitable for empirical use in many areas. Caution with aplastic anemia.
Tetracycline	20-50 mg/Kg/day in 4 doses	Do not use in children younger than 8 yrs-old. High resistance rates in several areas.
Doxycycline	2-4 mg/Kg/day in 1-2 doses*	Do not use in children younger than 8 yrs-old, unless as a last resort for severe cholera. Tetracycline preferred for young children.
Nalidixic acid	55 mg/Kg/day in 4 doses	Still useful in many areas of the world, despite high resistance rates in others. Affordability is a major advantage.
Ciprofloxacin	20-30 mg/Kg/day in 2 doses	No empirical use in children except in some individual cases strongly suspected of being caused by *Shigella sp.* or typhoid *Salmonella* resistant to safer agents. The commonest drug used in adolescents with bloody Traveler's diarrhea.
Ceftriaxone	50-100 mg/Kg/day in 1-2 doses	Safe and effective, but expensive. Reserve for use in cases of evident dissemination of disease. Avoid use in infants younger than 1 year.
Cefixime	7.5-10 mg/Kg/day in 1-2 doses	Safe and effective, but expensive. Reasonable choice for treating outpatients.
Azithromycin	5-12 mg/Kg/day in a single dose	Safe and effective, but expensive. Reasonable choice for treating outpatients.
Metronidazole	20-40 mg/Kg/day in 3 doses	Drug of choice for antibiotic-associated diarrhea.
Rifamixin	600 mg/day in 3 doses**	Promising drug for empirical therapy due to low tendency for side effects and raising antimicrobial resistance

* Adult dosing (100 mg twice a day) may be used if weight above 45 Kg. ** Adult dosing. No pediatric data.

host's immune response [127-131]. Several systematic reviews have addressed the role of probiotics in the treatment of acute diarrhea; generally it is agreed that probiotics reduce the duration of diarrhea when compared with a placebo, even though this may not be true for bacterial diarrhea [132-134]. There have been no reports of side effects so far. Further studies are warranted to determine exactly which probiotics are effective for each type of acute diarrhea. Additionally, several studies have investigated the role of probiotics for the prevention of community- and nosocomial-acquired diarrhea, antibiotic-associated diarrhea and travellers' diarrhea [135-138], but a discussion on those topics goes beyond the scope of this article.

Conclusion

There are plenty of antibiotics currently available for the treatment of acute infectious diarrhea in children (Table 1). While antibiotics are effective against most bacteria and may help shorten the duration of symptoms, it must always be kept in mind that antimicrobial therapy should be reserved for severe, prolonged or potentially complicated cases, as most patients respond fairly well to supportive therapy, and their indiscriminate use carries the danger of increasing antimicrobial resistance and brings no benefit to patients with mild presentations, as has been shown for uncomplicated salmonellosis [139]. Additionally, most diarrheal episodes affecting children are due to viruses, parasites, chemical agents and food intolerance, none of which requires antimicrobial therapy.

We reinforce the need for careful consideration of the use of antibiotics in the setting of acute diarrhea in children. The decision to start antimicrobial therapy should always be taken after adequate hydration and individual evaluation of various factors, including the likelihood of extra-intestinal dissemination of the infection and its severity. The empirical choice of the antimicrobial agent must be made individually for each case, considering the safety and the cost of the drugs, the pathogens most likely to be infecting the patient and up-to-date knowledge of the susceptibility pattern of locally circulating strains. In that context, large multicentric studies, such as SENTRY and RESISTNET [140,141], certainly play a role, but they do not replace smaller studies that more faithfully depict the situation in a given city or service.

We emphasize that most cases of acute diarrhea involve a self-limiting condition, requiring no more than supportive treatment with adequate hydration and nutrition that can be accomplished at home. The physician should make the patient's parents aware of warning signs that depict aggravation of the picture and the need for returning to the hospital for re-evaluation. The parents should also be informed about the routes of transmission of enteropathogens and about preventive measures.

While antibiotics may play a major part in reducing mortality among severely-ill patients, the ultimate approach against diarrhea in developing countries rests on the need for improving sanitary conditions, maintaining exclusive breastfeeding until the sixth month of life and developing safe and effective vaccines for immune prophylaxis, along with systematic parental education.

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