Infectious diarrhea can be caused by bacteria, viruses, and protozoa. When bacterial pathogens are involved, antibiotics are a mainstay of treatment because they alleviate symptoms and reduce duration of disease, prevent transmission of disease by eradicating pathogens from the stool, and arguably prevent long-term sequelae. These benefits notwithstanding, the use of antibiotics for bacterial diarrheal illness is associated with several challenges and limitations that should be borne in mind in therapeutic decision making. This paper discusses some of the challenges in the use of antibiotics for the management of bacterial diarrheal illness and considers the utility of nonabsorbed or poorly absorbed oral antibiotics in meeting these challenges. Nonabsorbed oral antibiotic therapy, unlike systemically available antibiotics, allows localized enteric targeting of pathogens and is associated with minimal risk of systemic toxicity or side effects. Provided that nonabsorbed antibiotics are as effective as systemically absorbed drugs for the target illness, their benign safety and tolerability profiles may render them more suitable than systemically available antibiotics for certain patient groups, such as young children, pregnant or lactating women, and the elderly, among whom side effects are a particular concern. The limited use of nonabsorbed oral antibiotics only for enteric infections should also limit the development of widespread resistance—a major limitation of current antibiotics for enteric infections. (Adv Stud Med. 2003;3(10A):S945-S950)
The primary reasons for prescribing an antibiotic for diarrheal illness include alleviating symptoms and reducing duration of disease; preventing transmission of disease by eradicating pathogens from the stool; and preventing sequelae. The value of antibiotic therapy in reducing symptoms and duration of bacterial diarrhea and the efficacy of antibiotics in eradicating pathogens from the stool are well documented. Bacterial agents cause no more than 15% to 20% of pediatric diarrhea in the United States, and antibacterial drugs are useful in only a subset of cases. Antibiotics are also helpful in treating protozoal diarrheal infections, such as those caused by Giardia and Cryptosporidium. The effects of antibiotic therapy on long-term sequelae of acute infectious diarrhea have not been systematically assessed in empirical studies; however, it is possible that by eradicating pathogens and thereby curing disease, antibiotic therapy would also prevent or reduce the severity of long-term sequelae.

These benefits of antibiotic therapy notwithstanding, the use of these agents for bacterial diarrheal illness is associated with several challenges and limitations that should be borne in mind in therapeutic decision making. This paper discusses some of the challenges in the use of antibiotics for the management of bacterial diarrheal illness and considers the utility of nonabsorbable antibiotics in meeting these challenges.

**Bacterial Resistance**

The progressive increase in resistance among enteric pathogens has been characterized as the most significant problem in the antibiotic treatment of infectious diarrhea. Bacterial resistance has rendered several classes of antibiotics, including the penicillins, the tetracyclines, and trimethoprim-sulfamethoxazole, ineffective for bacterial diarrhea in most parts of the world. Typically, widespread resistance to these antibiotics emerged within 10 years of their general use for bacterial diarrheal illness.Alarmingly, resistance to quinolones, currently the antibiotic standard of care for bacterial diarrhea, is rapidly increasing worldwide among common enteric pathogens, including Shigella, Campylobacter, and Salmonella. Resistance to macrolides, which are also prescribed for bacterial diarrhea, is also increasing. If previous resistance trends are any indication, quinolones and macrolides—like penicillins, tetracyclines, and trimethoprim-sulfamethoxazole before them—will be rendered ineffective for common diarrheal pathogens before the end of the decade.

It is hypothesized that restricting use of antibiotics can help to prevent the development of bacterial resistance in treated patients and in selected closed populations, such as in hospitals and day-care centers. Judicious prescribing of antibiotics—primarily by withholding them for nonserious bacterial illnesses or for illnesses in which a bacterial cause is uncertain—is commonly recommended as a means of restricting antibiotic use. For diarrheal illness, the use of nonabsorbable oral antibiotics with spectra of activity confined to common enteric pathogens may constitute a novel approach to judicious prescribing practice. Such antibiotics are useful only for enteric illnesses and presumably would not be prescribed for nonenteric illnesses. The circumscribed use of nonabsorbable antibiotics may result in limited selective pressure for the development of widespread bacterial resistance relative to the much higher pressure occurring with systemically available, broad-spectrum antibiotics used for infections affecting a variety of body systems.

Several nonabsorbable oral antibiotics have been shown to be effective in infectious diarrhea; one of these (rifaximin) is being developed for introduction in the United States. Rifaximin, which is less than 0.5% absorbed after oral administration, was first introduced more than 15 years ago in Italy for infec-

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**Table. Common Causes of Acute Infectious Diarrhea**

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>Viruses</th>
<th>Protozoa</th>
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<tbody>
<tr>
<td>Diarrheagenic</td>
<td>Rotavirus, Norwalk virus and</td>
<td>Giardia lamblia</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>other caliciviruses, Enteric</td>
<td>Entamoeba histolytica</td>
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<tr>
<td>Shigella</td>
<td>adenovirus, Astrovirus</td>
<td>Cryptosporidium</td>
</tr>
<tr>
<td>Salmonella</td>
<td>Small round viruses,</td>
<td>Cyclospora</td>
</tr>
<tr>
<td>Campylobacter</td>
<td>Coronavirus</td>
<td>Isospora</td>
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<tr>
<td>Yersinia</td>
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<tr>
<td>Clostridium difficile</td>
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<tr>
<td>Clostridium perfringens</td>
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<td>Staphylococcus aureus</td>
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<tr>
<td>Bacillus cereus</td>
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<tr>
<td>Vibrio species</td>
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<tr>
<td>Treponema pallidum</td>
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<tr>
<td>Neisseria gonorrhoeae</td>
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</tbody>
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Data from Park et al.
tious diarrhea and is now available in 13 countries. No clinically relevant resistance with rifaximin has been observed during clinical use for more than 15 years, during which 288 million rifaximin tablets have been prescribed. This finding contrasts with the development—in much shorter time spans than 15 years—of widespread resistance of enteric pathogens to systemically available antibiotics used for infections affecting multiple body systems. The circumscribed use of rifaximin for enteric infections may be partly responsible for the lack of clinically relevant resistance; that resistance to rifaximin is chromosomally mediated rather than plasmid mediated may also contribute. Among enteric pathogens, plasmid-mediated resistance, which can be transferred to bacteria within the same generation, generally develops much more rapidly and becomes more widespread than chromosomally mediated resistance, which is passed from bacterial generation to generation and requires selective environmental pressure. A third factor that may explain the lack of clinically relevant resistance to rifaximin is poorer viability of rifaximin-resistant mutants relative to nonresistant (wild-type) bacteria. In support of this possibility, resistance of enteric flora to rifaximin has been shown not to persist beyond 1 to 12 weeks (specific time dependent on species of bacteria) after cessation of therapy. Regardless of the mechanism of the lack of clinically relevant resistance to rifaximin, the available data suggest that the use of this nonabsorbable antibiotic may not be associated with the bacterial resistance that has reduced the effectiveness of other antibiotic therapies for infectious diarrhea.

There is no evidence of cross-resistance to other non-rifampicin classes of antibiotics.

Meeting the Needs of Special Patient Populations

Second to bacterial resistance, meeting the needs of special patient populations constitutes an important challenge in the management of infectious diarrhea. Ironically, the patient groups most susceptible to morbidity and mortality associated with enteric pathogens are the groups for which current antibiotics are least suited. Groups particularly vulnerable to adverse consequences of diarrheal illness include children, the elderly, pregnant and lactating women, and immunocompromised patients. These groups are also likely to tolerate the currently available antibiotics poorly.

The elderly, for example, are disproportionately affected by diarrheal illness. Mortality associated with diarrheal illness is higher in the elderly than in other age groups in the United States. Over a 9-year period in the United States, individuals older than 74 years of age accounted for approximately one half of mortality associated with diarrheal illness (51% of deaths). The majority of the remaining deaths occurred among those 55 to 74 years of age (27% of deaths) and younger than 5 years of age (11% of deaths). Elderly patients with severe diarrhea require treatment with fluid and electrolyte therapy. Many with bacterial infection may benefit by antibacterial therapy. Fluoroquinolones and other antibiotics for diarrheal illness are often not suitable for use in the elderly because of neurologic side effects. Similar considerations apply to diarrheal illness in children. Diarrhea-associated morbidity is especially high in children younger than 5 years of age. In the United States, approximately 11% of hospitalizations in this age group are attributed to diarrhea. Although death rates attributed to diarrheal illness are relatively low in US infants and children relative to infants and children in the developing world, diarrheal-associated death is estimated to constitute as much as 10% of the preventable postneonatal infant death in the United States. These statistics establish the substantial need for effective antimicrobials for this age group. (These considerations notwithstanding, bacterial enteropathogens cause only between 15% and 20% of pediatric diarrhea in the United States, an observation that underscores the fact that most children in the United States should not be treated with antibacterial agents.)

Fluoroquinolones are not yet licensed for use in children because of their potential to harm growing articular cartilage. Concern about effects on tendons and joints in children has limited their use in young patients, although data suggest that the actual risk of adverse joint and tendon effects is relatively low. The gastrointestinal side effects with other antibiotics, such as macrolides, limit their use in children.

Nonabsorbable oral antibiotic therapy, which lacks systemic toxicity and is associated with a low potential for allergic reactions, may be ideal for these patient...
populations, in whom tolerability is a particular concern. Nonabsorbable oral antibiotic therapy has been given safely to children and the elderly for the treatment of infectious diarrhea. Nonabsorbable oral antibiotic therapy has been given safely to children and the elderly for the treatment of infectious diarrhea. The tolerability profile of nonabsorbable therapy in these patient groups was benign and did not differ from that in studies in adult patients. Nonabsorbable antibiotic therapy would also presumably pose minimal risk when given to pregnant or lactating women, a possibility that has not been assessed in clinical studies. An oral suspension form of rifaximin is available in Europe and Mexico to treat children ages 2 years and older.

**Potential Limitations of Nonabsorbable Antibiotic Therapy**

Nonabsorbable oral antibiotic therapy thus will potentially help to meet important challenges in the management of infectious diarrhea. However, this approach is also associated with the potential limitation of lacking efficacy for diarrhea caused by invasive bacterial infection due to strains of *Shigella* and *Campylobacter*. Data collected more than 40 years ago with the poorly absorbed antibiotic neomycin suggested that this nonabsorbable antibiotic was not effective for invasive infection caused by *Shigella*. However, subsequent studies showed that other poorly absorbed or nonabsorbent antibiotics, including rifaximin, bicozamycin, and aztreonam, were effective in the presence of signs of a surrogate for invasive infection, fecal leukocyte-positive diarrhea.

To determine whether rifaximin is effective for invasive or intestinal inflammatory diarrheal illness, data from patients who had signs or symptoms suggestive of invasive or inflammatory infection, defined as having temperature exceeding 100°F, blood in stool, mucus in stool, or leukocytes in stool, in 3 controlled clinical trials of patients with infectious diarrhea were retrospectively assessed. The results show that the median time to last unformed stool for rifaximin-treated patients with signs or symptoms of invasive infection (36.1 hours, n = 172) did not differ from that for all rifaximin-treated patients (32.5 hours, n = 401; Figure). Furthermore, among patients with signs or symptoms of invasive infection, median time to last unformed stool was lower for all active treatments compared with placebo (n = 46) and was comparable among rifaximin-treated patients (n = 172) and patients treated with ciprofloxacin (n = 67) or trimethoprim-sulfamethoxazole (n = 10).

These data suggest that rifaximin is as effective among patients with intestinal invasive or inflammatory infection as it is among patients whose infection appears to be confined to the gastrointestinal tract. Whether rifaximin can control or treat the more severe forms of invasive infections, such as *Shigella* or *Campylobacter* dysentery, has yet to be determined. Rifaximin eradicated *Shigella* from patients in these clinical trials, but none of the patients had severe disease requiring hospitalization.

The degree to which nonabsorbent antibiotics are effective for severe invasive disease has not been studied, and—given that their activity is confined to the gastrointestinal tract—their use for severe invasive disease is not advised. However, the evidence considered in aggregate suggests that nonabsorbent antibiotics can sometimes be effective against invasive pathogens, particularly in mild disease. It has been suggested that the efficacy of antibiotics against invasive organisms may be enhanced by early treatment.

**Figure. Median Time from First Medication Dose Until Last Unformed Stool**

Median time from taking the first dose of medication until passage of the last unformed stool (hours) after which wellness is declared (TLUS) in all rifaximin-treated patients (n = 401) and in the subset of patients with signs or symptoms suggestive of invasive or inflammatory diarrhea (see text) in 3 controlled clinical trials of rifaximin for infectious diarrhea.
Emerging Challenges for Antibiotic Therapy: Bioterrorism

Bioterrorism involving bacterial pathogens is becoming an increasingly salient threat in the United States. Enteric pathogens may be attractive tools for the bioterrorist because few pathogens (generally) are required to produce disease, they are readily available, and they can cause serious infection and death in substantial proportions of exposed individuals. A Blue Ribbon Panel on Bioterrorism, which met in Washington, D.C., in late 2002, identified several enteric pathogens as potentially important bioterrorism weapons. They included the more virulent strains of Shigella (e.g., Shiga bacillus) and the diarrheagenic Escherichia coli. Antibiotics effective for acute and prophylactic management of bioterrorist attacks are being actively sought. The ideal antibiotic candidate for bioterrorism involving diarrheal illness would have broad-spectrum efficacy against enteric pathogens, would not be associated with widespread bacterial resistance or be prone to inducing persistent resistance, would be safe across the demographic spectrum of individuals potentially requiring therapy, and would be available in formulations suitable for administration to all age groups. Nonabsorbable oral antibiotic therapies, such as rifaximin, aztreonam, or bicozamycin, fulfill many of these characteristics and may prove with additional research to be important tools in antibioterrorism endeavors. (As of this writing, rifaximin is available in 13 countries and is being developed for introduction in the United States. Bicozamycin is not currently available for human use, and aztreonam is currently marketed for parenteral administration only.)

Conclusion

Nonabsorbable oral antibiotic therapy constitutes an important strategy for the antimicrobial management of infectious diarrhea; unlike systemically available antibiotics, it allows localized enteric targeting of pathogens and is associated with minimal or no risk of systemic toxicity or side effects. The benign safety and tolerability profiles of nonabsorbable oral antibiotic therapy may render it more suitable than systemically available antibiotic therapy for certain patient groups, such as young children, pregnant or lactating women, and the elderly, among whom side effects are a particular concern. The circumscribed use of nonabsorbable oral antibiotics for enteric infections may also limit the development of widespread resistance—a major limitation of current antibiotics for enteric infections.

References