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## Importance of Antimicrobial Absorption in the Treatment of Acute Infectious Diarrheal Diseases

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### Introduction

Antibiotic therapy is a mainstay of treatment for acute infectious diarrheal diseases, but several factors limit the utility of many anti-diarrheal antimicrobials. The emergence of widespread bacterial resistance may be the most important limitation of many of the antibiotics previously useful for infectious diarrheal illness.<sup>1-4</sup> For example, the finding of high-level resistance to trimethoprim and sulfamethoxazole (minimum inhibitory concentration 90, or MIC<sub>90</sub>, 512 to >1024 µg/mL) among enterotoxigenic *E. coli*, enteroaggregative *E. coli*, *Salmonella* species, and *Shigella* species isolated in 1997 from patients with travelers' diarrhea in India, Mexico, Jamaica, or Kenya led investigators to conclude that "trimethoprim or sulfamethoxazole should not be considered active against enteropathogens causing travelers' diarrhea and should not currently be recommended for empirical treatment of travelers' diarrhea regardless of the region of the world."<sup>3</sup> Quinolone resistance to enteric pathogens is also increasing rapidly worldwide<sup>4</sup>—a development that is worrisome because of the first-line role of quinolones in treating serious, life-threatening bacterial infections. Besides resistance, suboptimal tolerability and safety and the potential for drug interactions can reduce the utility of antimicrobials for infectious diarrheal illness.

These shortcomings have led to calls to develop new treatment options for acute infectious diarrheal diseases.<sup>2</sup> The use of nonabsorbable, orally

administered antibiotics has been advocated as one new approach that may overcome some of the limitations of currently available therapies. A nonabsorbed, orally administered antibiotic could offer several advantages including (1) ability to achieve high concentrations in the intestinal lumen to eradicate causative pathogens; (2) lack of systemic toxicity; (3) low potential for allergic reactions; and (4) benign tolerability and safety profiles. Furthermore, lack of activity outside the gastrointestinal tract would limit the use of the nonabsorbed antibiotic to enteric infections. Such circumscribed use of the antibiotic may limit the development of bacterial resistance relative to that observed with antibiotics used for extra-intestinal as well as enteric infections.

Besides having these potential advantages, a nonabsorbed antibiotic has the potential disadvantage of being ineffective for invasive enteric infections such as dysentery. The degree to which nonabsorbed antibiotics are effective for invasive enteric infections has been assessed in several studies conducted over a period of 35 years. This paper reviews the results of these studies and considers the utility of nonabsorbed antibiotics for invasive enteric infections.

### Neomycin

In an early study, the clinical and bacteriologic efficacy of the poorly absorbed antibiotic neomycin, given orally, was compared with that of the absorbable antibiotic ampicillin in children with severe acute *Shigella*

dysentery requiring hospitalization.<sup>5</sup> Acute *Shigella* dysentery is characterized by bacterial invasion of the cells of the inflamed colon such that the invading bacteria are poorly exposed to luminal antibiotic. This experiment thus constituted a rigorous test of antibiotic efficacy in invasive enteric infection. Neomycin was chosen because it had been previously shown to be effective in treating enteropathogenic *E. coli* infections. The latter infection, like acute *Shigella* dysentery, is an invasive infection; however, it differs from acute *Shigella* dysentery in that bacteria are thought to be less likely to be localized intracellularly. Ampicillin was chosen because of its previously proven efficacy in shigellosis.

Fifteen (15) patients received neomycin, and 15 patients received ampicillin. Each drug was given as a loading dose of 50 mg/kg/day, and subsequent doses of 100 mg/kg/day were administered every six hours orally for five total days. The results show that bacteriologic failure (defined as cultures positive more than 48 hours after initiation of therapy) was observed in 87% of patients receiving neomycin compared with 13% of those receiving ampicillin. Clinical failure (defined as persistence of diarrhea beyond five days after initiation of therapy, removal of the patient from the study, or both) was observed in 60% of patients receiving neomycin compared with 13% of those receiving ampicillin. All *Shigella* strains were susceptible to neomycin and ampicillin *in vitro*. Despite the *in vitro* susceptibility of shigellae to neomycin, then, clinical and bacteriologic efficacy was poor compared with ampicillin. On the basis of these data, the authors concluded that nonabsorbable antibiotics are suboptimal for acute shigellosis.

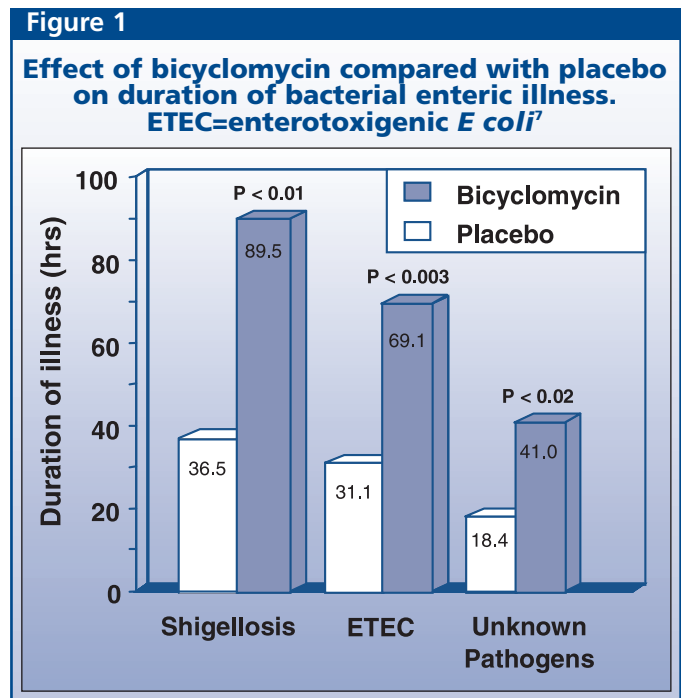
### Bicyclomycin

This pattern of results with neomycin was not replicated in a study 6 years later of the poorly absorbed antibiotic bicyclomycin (bicozamycin) in monkeys that had developed lethal infection after inoculation with *Shigella flexneri* 2a.<sup>6</sup> Only 3% of an oral dose of bicyclomycin is absorbed. Bicyclomycin and the control medication kanamycin, which is known to be effective for shigellosis, were given orally at a dose of 40 mg/kg/day for five days beginning 24 hours after rectal inoculation with *Shigella*. The results show that seven of seven monkeys treated with bicyclomycin survived, and stool cultures were negative in an average of  $7.0 \pm 1$  days. One of the five monkeys treated with kanamycin died on day 12, and the average time for negative stool cultures in the kanamycin group was  $9.3 \pm 2.7$  days. Five of seven monkeys control monkeys that were untreated (i.e., received neither bicyclomycin or kanamycin) died within 11 days. The animals had very high concentrations of the unchanged antibiotics in the feces. The authors concluded that the data demonstrate the therapeutic efficacy of the nonabsorbable bicyclomycin in severe *Shigella* infections.

The assessment of bicyclomycin was extended to humans in a randomized, double-blind study of 140 adults with travelers' diarrhea acquired while visiting Guadalajara, Mexico.<sup>7</sup> Patients received either oral bicyclomycin (500 mg qid) or placebo for three days. Some of the patients were infected with invasive organisms. *Shigella* infections were present in 25 patients, 13 of whom were treated with bicyclomycin. *Salmonella* infections were present in six patients, four of whom were treated with bicyclomycin. Infections attributed to enterotoxigenic *E. coli*

were present in 49 patients, 31 of whom were treated with bicyclomycin.

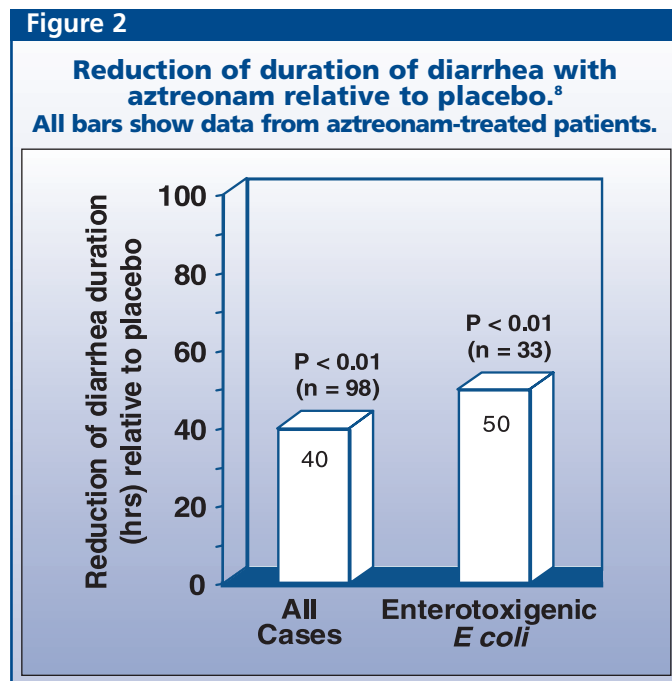
The results show that bicyclomycin was effective at reducing the duration of diarrhea regardless of whether it was caused by pathogens associated with invasive infection. The duration of diarrhea from all causes was  $29.2 \pm 27.3$  hours in the bicyclomycin group compared with  $63.7 \pm 46.1$  hours in the placebo group. For patients with *Shigella* infections, the duration of diarrhea was 36.5 hours in the bicyclomycin group compared with 89.5 hours in the placebo group (Figure 1).<sup>7</sup> For patients with infections with toxigenic *E. coli*, the duration of diarrhea was 31.1 hours compared with 69.0 hours in the placebo group (Figure 1). A similar pattern of results was observed for cases in which the pathogen could not be identified (Figure 1). The small number of patients infected with *Salmonella* did not allow for firm conclusions. However, bicyclomycin was associated with negative stool cultures in 5 of 5 patients on day 3 whereas none of the 5 placebo-treated patients was culture-negative on day 3. Stool cultures were negative on day 3 in 12 of 13 patients with *Shigella* infection compared with 3 of 12 patients in the placebo group. None of the 140 patients in this study required hospitalization, and no side effects were noted. These data suggest that bicyclomycin is effective for bacterial enteric illness caused by invasive pathogens. While the *Shigella* infection in this study was not as severe as the infection in the monkey studies, the results of the studies are consistent in showing efficacy of bicyclomycin against *Shigella*. The authors concluded that the data establish the need to re-evaluate the belief that nonabsorbable antibiotics are ineffective against invasive enteropathogens.<sup>7</sup>



### Aztreonam

In 1992, another nonabsorbable antibiotic, aztreonam, was assessed in enteric bacterial illness.<sup>8</sup> Aztreonam is not absorbed from the intestinal tract and has excellent broad-spectrum coverage that includes enteric pathogens. In a

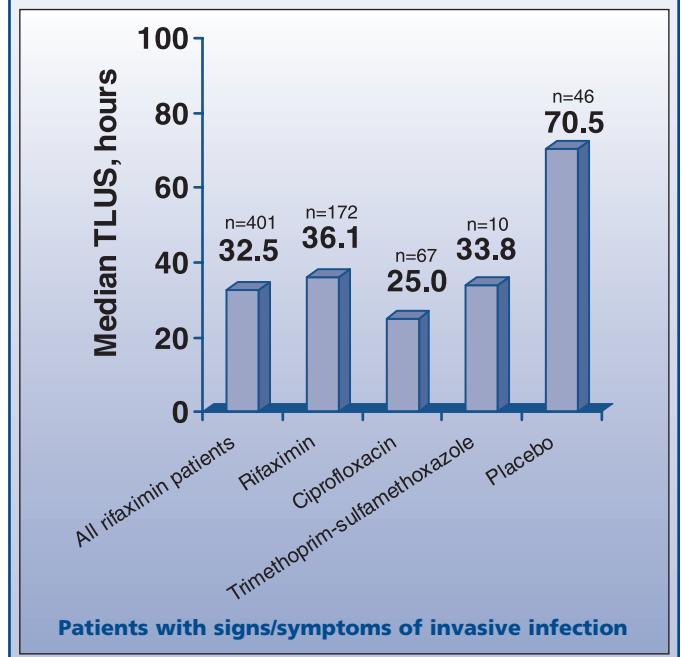
randomized, double-blind study in patients with travelers' diarrhea acquired during travel from the United States to Mexico, 98 patients received oral aztreonam 100 mg tid for five days, and 93 patients received placebo. The results demonstrate that aztreonam compared with placebo significantly shortened the duration of illness of any cause and illness attributed to enterotoxigenic *E coli* (Figure 2).<sup>8</sup> The number of patients infected with *Shigella* was too few to draw conclusions. Patients with fecal leukocytes, a finding suggestive of invasive infection, had a duration of illness comparable to those without fecal leukocytes when treated with active drug. None of these patients, apparently, had shigella dysentery. Possibly, the early treatment may have prevented its appearance. Like bicyclomycin, aztreonam can effectively control enteric illness caused by any of several bacteria.



### Rifaximin

Rifaximin, another nonabsorbed antibiotic, has been extensively evaluated for treating bacterial diarrheal diseases. The efficacy of rifaximin in travelers' diarrhea was assessed in three large clinical trials, which demonstrate that rifaximin was superior to placebo and comparable to ciprofloxacin or trimethoprim-sulfamethoxazole at conferring clinical improvement and eradicating causative pathogens in travelers' diarrhea.<sup>9-11</sup> To determine whether rifaximin is effective for invasive infection, data from patients who had signs or symptoms suggestive of more invasive infection (i.e., temperature exceeding 100.0°F, blood in stool, mucus in stool, or leukocytes in stool) in these three studies 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 3).<sup>12</sup> 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).

**Figure 3**  
**Median time to last unformed stool (hours) in all rifaximin-treated patients (n=401) and in the subset of patients with signs or symptoms suggestive of invasive infection in three controlled clinical trials of rifaximin for travelers' diarrhea<sup>12</sup>**



These data suggest that rifaximin is as effective among patients with invasive infection as it is among patients whose infection appears to be confined to the gastrointestinal tract. To further explore the utility of rifaximin for invasive infection, a controlled clinical trial of rifaximin in patients with dysentery is being conducted in Mexico and Peru. Whether or not rifaximin can control severe invasive infections such as *Shigella* dysentery has yet to be determined. Rifaximin did eradicate *Shigella* from patients in these clinical trials, but none of the patients had severe disease requiring hospitalization.

### Conclusions

Although early results with neomycin were unpromising, several nonabsorbed or poorly absorbed antibiotics have been demonstrated effective for enteric bacterial illness, including that caused by pathogens associated with invasive disease. The degree to which nonabsorbed 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 belief that nonabsorbable antibiotics are ineffective against invasive pathogens has not been substantiated. Several nonabsorbed or poorly absorbed antibiotics have been demonstrated effective for infections caused by *Shigella* and enterotoxigenic *E coli*. The efficacy of nonabsorbed or poorly absorbed antibiotics against invasive organisms may be enhanced by early treatment. Early treatment of enteric infections, including those cases caused by *Shigella* species, may eradicate bacteria before they have entered the protective intracellular environment and established necrotic foci that protect them from an antibiotic in the intestinal lumen.

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**Target Audience:** practicing physicians, infectious disease physicians, physicians specializing in travel medicine, clinical microbiologists, pharmacists, public health authorities, and others interested in the diagnosis and management of enteric infections and the growing problem of antimicrobial resistance in enteric infections

**Learning Objectives:** After reading this publication, the reader should be able to:

- Understand the importance of intestinal absorption of antibacterial drugs used to treat enteric infections.
- Discuss current thinking about the role of non-absorbable antibiotics for the treatment of enteric infections.

### CME Self Assessment Examination

Volume VI, Issue 5

See instructions and pertinent information on the reverse before requesting credit.

1) Which of the following is a potential advantage of a non-absorbable orally administered antibiotic for the treatment of infectious bacterial diarrheal disease?

- a) Lack of systemic toxicity
- b) Achieves high concentrations in the intestinal lumen
- c) Good tolerability and safety profile
- d) Low potential for allergic reactions
- e) All of the above

Answer: \_\_\_\_\_

2) Which of the following non-absorbable antibiotics has been shown to be more effective than placebo in treating travelers' diarrhea?

- a) Bicyclomycin
- b) Aztreonam
- c) Rifaximin
- d) A and c
- e) A, b, and c

Answer: \_\_\_\_\_

3-5) For each of the following questions numbered 3-5, answer **T** if the statement is **TRUE** and **F** if the statement is **FALSE**:

- 3) \_\_\_\_\_ Early experience with neomycin for treatment of severe shigella infections in children suggested that non-absorbable antibiotics might be ineffective in treating severe invasive enteric infections.
- 4) \_\_\_\_\_ Ciprofloxacin, rifaximin, and trimethoprim-sulfamethoxazole were comparable in clinical outcome measures and in eradicating known causal pathogens in several clinical trials of treatment of travelers' diarrhea
- 5) \_\_\_\_\_ The degree to which non-absorbable antibiotics are effective in severe invasive enteric disease has not been determined.

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