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Limitations of Antimicrobial Therapy for Enteric Infections

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Introduction

Enteric illness is a common and costly problem that causes significant morbidity and mortality worldwide. In children in the United States, diarrhea is the cause of 1.5 million outpatient visits, 200,000 hospitalizations, and up to 300 deaths per year. In addition, diarrhea and dehydration are associated with more than 3000 deaths per year in the elderly. Direct medical costs are estimated to be \$250 million annually with an estimated \$1 billion total costs per year to society.¹⁻⁶ In a 2-year study of approximately 1 million children enrolled in 4 health maintenance organizations in the United States, diarrhea was associated with 6% of all hospitalizations and 4% of emergency department visits.⁷ Diarrhea was estimated to cause 1 in 57 children to be hospitalized and 1 in 21 to visit the emergency department during the first 5 years of life. About 76 million cases of foodborne illnesses occur per year in the United States, of which all but 300,000 manifest as acute gastroenteritis.⁷

Enteric infections generally are self-limited conditions that require only fluid and electrolyte therapy.⁸ However, patients with diarrhea associated with certain bacterial and protozoal agents may benefit from therapy with an antimicrobial agent.⁹ In some instances, specific antimicrobial therapy may reduce morbidity and mortality associated with enteric illnesses or prevent future complications, but antimicrobial

agents should be prescribed with an appreciation for their limitations. This manuscript considers the rationale for antimicrobial therapy of enteric infections and discusses limitations of current antimicrobial agents for enteric illness.

Rationale for Antimicrobial Therapy of Enteric Infections

The primary reasons for prescribing antimicrobial agents for enteric infections are listed in the **Table** (next page).

- Reduction of symptoms and duration of disease constitutes the main reason for treating a bacterial enteric infection with an antimicrobial agent.
- Antimicrobial therapy also is prescribed to prevent sequelae of acute enteric infections. Although enteric infections are often self-limiting and not associated with serious sequelae, complications can occur including dissemination of infection outside the intestinal tract. The effect of early antimicrobial therapy on Guillain-Barre syndrome, reactive arthritis, Reiter's syndrome, and other immune mediated sequelae is unknown.
- Antimicrobial therapy also is administered to people with diarrhea to eradicate fecal shedding and to prevent transmission of enteric pathogens. From a public health aspect, elimination of an enteric pathogen from stool is key in preventing spread of disease, particularly in child-care centers and institutional settings such as nursing homes and hospitals.

Table**Primary Reasons for Prescribing Antimicrobial Agents for Enteric Infections**

- To reduce symptoms and duration of disease
- To prevent serious sequelae
- To prevent mortality
- To eradicate fecal shedding
- To prevent pathogen transmission

Shortcomings of Antimicrobial Therapy for Enteric Infections

Benefits of antimicrobial therapy can be achieved for certain bacterial enteric infections, but antimicrobial therapy is not always appropriate. For many enteric pathogens including enteric viruses, benefits of antimicrobial therapy have not been demonstrated. While the clinical and bacteriologic benefits of antimicrobial therapy are well established for infections caused by *Clostridium difficile*, *Vibrio cholerae*, enterotoxigenic and enteroinvasive *Escherichia coli*, *Shigella* species, and *Salmonella typhi*, antimicrobial therapy is of limited or unknown value for enteric infections caused by *Aeromonas*, *Campylobacter jejuni*, intestinal salmonellosis, Shiga toxin-producing *E. coli* (STEC), and *Yersinia enterocolitica*. Even when antimicrobial therapy is of proven benefit, it may be associated with several shortcomings.

Limitation: Complexity of Identifying Causative Organisms

The complexity and cost of identifying enteric pathogens influence clinical practice. Rapid diagnostic methods are available for some enteric pathogens while many enteric bacteria require use of culture methodology. Organisms, such as *Campylobacter jejuni*, *Salmonella*, and *Shigella*, are identified via routine culturing techniques, but other important enteric organisms including *E. coli* O157:H7 in some health care settings are not routinely sought. Others including *V. cholerae*, *Y. enterocolitica*, *C. difficile*, and other STEC require consultation with laboratory personnel to ensure appropriate processing and testing. Selective testing of organisms and the long lag time for identification of enteric pathogens may necessitate empiric therapy.

Limitation: Narrow Spectrum of Antimicrobial Activity

Antimicrobial therapy for enteric infections often is empiric, necessitating use of a broad-spectrum antimicrobial agent in order to cover a range of suspected

pathogens. Many currently available antimicrobial agents do not cover a sufficiently broad range of pathogens for empiric therapy of all common enteropathogens. Narrow spectrum of activity may be an inherent property of the antimicrobial agent or can arise through development of bacterial resistance to the agent. For example, fluoroquinolones, which are a treatment option for acute infectious diarrhea caused by resistant *Shigella* species, are not ideal for empiric therapy because of their relatively poor activity against other common enteric pathogens including *C. jejuni*.¹⁰

Limitation: Bacterial Resistance

Bacterial resistance constitutes an important limitation of currently available antimicrobial agents for enteric infections. *Shigella* strains have become progressively resistant to multiple antimicrobial agents, initially to sulfonamides shortly after they become commercially available, then to tetracycline, ampicillin, chloramphenicol and streptomycin less than 10 years after each was introduced, and subsequently to TMP/SMX.⁹ Fluoroquinolones also are associated with widespread, increasingly prevalent bacterial resistance with reduced susceptibility noted in *Campylobacter*,¹⁰ *Salmonella*,¹¹ and *Shigella*.¹² Macrolide resistance is becoming increasingly common in certain parts of the world and resistant strains of *Salmonella* are common in retail ground meats.¹³

Limitation: Safety and Tolerability of Antimicrobial Agents

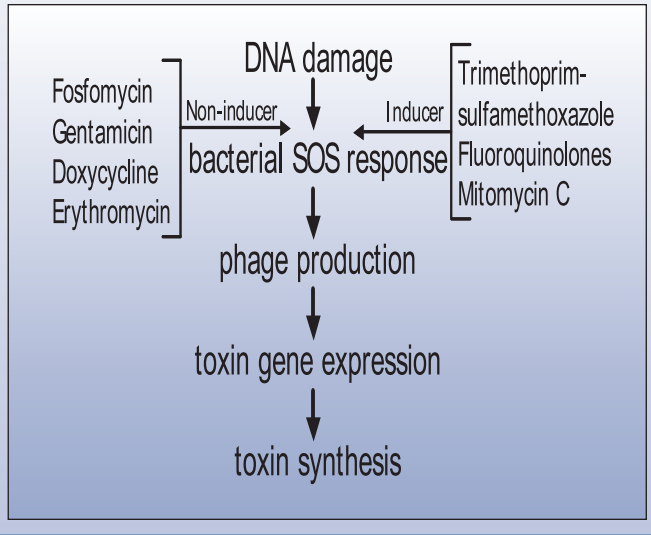
Safety and tolerability characteristics of many antimicrobial agents used for enteric infections have not been defined for all populations including children, pregnant and lactating women, and immunocompromised hosts. Quinolones are not licensed by the FDA for use in children or pregnant women because of their potential to harm cartilage. Drug interactions and adverse events also are concerns for the quinolones and other antimicrobial agents including trimethoprim/sulfamethoxazole. To be most useful for bacterial enteric infections, an antimicrobial agent should be sufficiently well-tolerated to be used confidently in special patient populations such as children, the elderly, pregnant women, and immunocompromised patients. These groups are most likely to tolerate medications poorly, and they also are uniquely susceptible to morbidity and mortality associated with enteric pathogens.

Limitation: Antibiotic-Mediated Enhancement of Bacterial Virulence Properties

Pathogenic organisms express specific virulence properties that enable them to overcome host defense mechanisms. For example, some bacteria produce enterotoxins; others produce protein synthesis-inhibiting cytotoxins, neurotoxins, or cytoskeleton-altering toxins. Some antimicrobial agents may enhance these virulence properties. In *in vitro* studies with STEC, exposure to trimethoprim-sulfamethoxazole, the fluoroquinolones, or mitomycin C has been associated with increased toxin synthesis whereas exposure to other antimicrobial agents such as fosfomycin, gentamicin, doxycycline, and erythromycin has not resulted in an increase in toxin synthesis.¹⁴ Toxin production associated with these antimicrobial agents is caused by bacterial DNA damage, which results in a bacterial SOS response that stimulates phage production, toxin gene expression, and increase in toxin synthesis (**Figure 1**).

Figure 1

Hypothesized mechanism of antimicrobial associated toxin synthesis by shigatoxin-producing *E. coli*¹⁴



Results of a clinical study show that antimicrobial-associated enhancement of bacterial virulence properties can have clinical consequences.¹⁵ The course of illness and characteristics of children infected with *E. coli* 0157:H7 treated with antimicrobial agents were compared with those of children infected with *E. coli* 0157:H7 and not treated with antimicrobial agents in a nonrandomized, prospective cohort study. One of the virulence properties of *E. coli* 0157:H7 is production of Shiga toxin, which is associated with development of hemolytic uremic syndrome in 10% of children with colitis due to the bacterium. Characterized by thrombocytopenia, hemolytic anemia, and renal dysfunction, the hemolytic uremic syndrome can be life threatening. The results of the study demonstrate that, although the subgroups of children receiving antimicrobial agents and children not receiving antimicrobial agents were comparable with respect to age and incidence of bloody diarrhea, children who had received an antimicrobial agent were more likely to develop hemolytic uremic syndrome than children who had not received an antimicrobial agent (78% versus 11%, odds ratio 14.25, 95% CI 3.62-56.1; **Figure 2**).

This study should be interpreted cautiously because children were not randomized and the subgroups were imbalanced (n=9 in antibiotic group and n=62 in group not receiving antimicrobial agents). A subsequent metaanalysis shows no relationship between antimicrobial therapy for STEC enteritis and risk of HUS.¹⁶ The inconsistency in results across studies highlights the need for additional research to explore the risks and benefits of using antimicrobial therapy to treat children with colitis due to STEC.

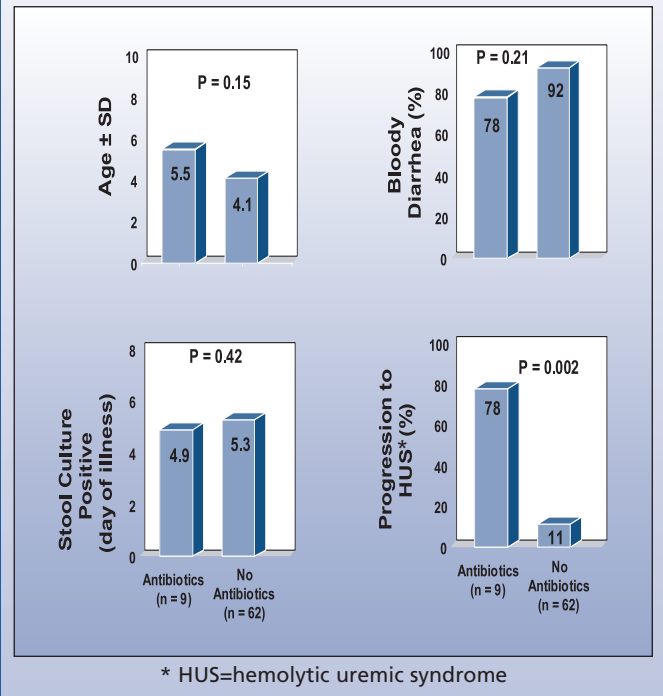
Limitation: Prolongation of the Carrier State

Besides enhancing bacterial virulence properties, antimicrobial agents can prolong the carrier state of the host. Antimicrobial agents are not recommended for intestinal infections caused by *Salmonella* because they prolong the carrier state. In a Cochrane database review, antimicrobial therapy for uncomplicated nontyphoidal *Salmonella* gastroenteritis did not significantly decrease the length of illness and was associated with an increased risk for relapse,

a positive culture after three weeks, and adverse drug reactions.¹⁷ By increasing the amount of time that organisms are excreted in stool, treatment with antimicrobial agents increases the risk of transmission of the infection.

Figure 2

Baseline and clinical characteristics of children infected with *E. coli* and either treated or not treated with an antimicrobial agent.¹⁵



Conclusions

In summary, while antimicrobial therapy of bacterial enteric infections can reduce morbidity and even save lives, it should be used appropriately and with an appreciation of limitations. In determining whether or not to use antimicrobial therapy, a physician should consider whether antimicrobial therapy has been proven effective for the causative pathogens as well as the potential consequences of withholding therapy for the patient. Withholding antimicrobial therapy for self-limiting illnesses in the interest of not contributing to the growing problem of bacterial resistance is an important consideration. In choosing among specific antimicrobial agents, a physician should consider factors such as spectrum of activity of the antimicrobial agents against likely causative pathogens; appropriateness of the antimicrobial agents for the specific patient in the context of the patient's age, other medication use, and clinical status; and the potential for adverse drug reactions or introducing other iatrogenic problems such as enhancement of bacterial virulence properties or prolongation of the carrier state.

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Target Audience: 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 limitations of antimicrobial therapy for enteric infections.
- List the current drugs available to treat enteric infections in children and young women.
- Discuss the problem of quinolone use in children and young women.

CME Self Assessment Examination

Volume VI, Issue 3

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

1. Which of the following statements about enteric infections in the United States is incorrect?
- Most foodborne illnesses manifest as acute gastroenteritis.
 - Most enteric infections will require antibiotic treatment.
 - Appropriate antibiotic use for some enteric infections may limit extraintestinal dissemination.
 - The effect of early antimicrobial therapy on immune mediated sequelae is unknown.

Answer: _____

2. Which of the following statements constitutes the primary reason for treating bacterial enteric infections in the United States?
- To limit fecal shedding and prevent transmission.
 - To prevent serious sequelae.
 - To prevent mortality.
 - To reduce symptoms and duration of disease.

Answer: _____

3-5. For each of the following statements 3-5, answer **T** if the statement is **true** and **F** if the statement is **false**:

- _____ Difficulties in rapid identification of enteric pathogens in clinical specimens may necessitate empiric therapy.
- _____ Bacterial resistance is increasing worldwide and may limit future therapeutic options.
- _____ Uncertainties about the safety of quinolones in pregnant women and children may limit their use in these populations.

6-10. For each of the following antibiotics, circle **N** if the antibiotic is a **non-inducer** and **I** if the antibiotic is an **inducer** of a bacterial SOS response.

- | | | |
|-----------------------------------|----------|----------|
| 6. Doxycycline | N | I |
| 7. Erythromycin | N | I |
| 8. Fluoroquinolones | N | I |
| 9. Gentamicin | N | I |
| 10. Trimethoprim-sulfamethoxazole | N | I |

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