Antimicrobial Resistance in Organisms Causing Diarrheal Disease

R. Bradley Sack, Mahbubur Rahman, M. Yunus, and Eradul H. Khan

Antimicrobial resistance is becoming increasingly important in the treatment of enteric infections, particularly those due to *Shigella*, *Vibrio cholerae*, enterotoxigenic *Escherichia coli* (associated with traveler’s diarrhea), and *Salmonella typhi*. The rate of antimicrobial resistance is highest in the developing world, where the use of antimicrobial drugs is relatively unrestricted. Of greatest immediate concern is the need for an effective, inexpensive antimicrobial that can be used safely as treatment for small children with dysentery due to *Shigella*, primarily *Shigella dysenteriae* type 1.

Acute infectious diarrheal diseases and acute respiratory diseases continue to be the two most frequent causes of childhood deaths in the developing world. Diarrheal diseases account for roughly 25% of all deaths in children younger than 5 years of age in these areas. The etiologic agents of acute diarrhea, of which at least 35 have been recognized, can now be determined in about 75% of episodes, when all diagnostic assays are employed. In the order of decreasing frequency, they are bacteria, viruses, and protozoa.

The application of oral rehydration therapy, which can be used to correct dehydration due to diarrheas of any etiology, has greatly decreased the number of deaths due to diarrhea worldwide. As a result of the use of this therapy, the percentage of deaths due to invasive diarrheas, for which antibiotic treatment is clearly indicated, has increased. Fortunately, most (~90%) acute diarrheal diseases can be effectively treated without antimicrobials. The presently accepted treatment of all acute infectious diarrheal diseases is rehydration, antibiotic treatment (when indicated), and nutritional therapy.

The acute diarrheal diseases for which antimicrobial therapy is clearly effective include shigellosis, cholera, traveler’s diarrhea (which is most frequently caused by enterotoxigenic *Escherichia coli* [ETEC]), and diarrhea due to *Clostridium difficile*. Antimicrobial therapy is also useful for diarrhea due to *Campylobacter jejuni*, but the diagnosis of this disease is usually made too late for antimicrobial therapy to be effective. The latter two types of diarrhea are probably important only in the developed world. Typhoid fever, although not primarily a diarrheal illness, sometimes presents as acute diarrhea. This illness is also a major public health problem in the developing world, and effective antimicrobials are required for its treatment.

Antimicrobial resistance in enteric pathogens is of greatest importance in the developing world, where the rate of diarrheal diseases is highest. Organisms of the same species, particularly *Shigella*, are more apt to be resistant when they are isolated in the developing world [1]. This circumstance is most likely related to the frequent unrestricted use of over-the-counter drugs without medical supervision.

We discuss herein antimicrobial resistance in organisms causing acute diarrheal diseases (*Shigella*, *Vibrio cholerae*, ETEC, *C. jejuni*, and *C. difficile*) and typhoid fever (*Salmonella typhi*). Data from the International Centre for Diarrhoeal Disease Research, Bangladesh, will be used to illustrate some of these issues.

### Antimicrobial Resistance in Specific Enteropathogens

*Shigella*. *Shigella* species are invasive organisms that clearly present the most pressing challenge for providing effective antimicrobial therapy. Over the past several decades, they have progressively become resistant to most of the widely used and inexpensive antimicrobials [2]. Sulfonamides, tetracycline, ampicillin, trimethoprim-sulfamethoxazole, nalidixic acid, and pivmecillinam have all in succession been used as first-line antimicrobial drugs in many parts of the world. At present, *Shigella dysenteriae* type 1, the most resistant of the species, has become resistant to nearly all of the above-mentioned drugs and is now uniformly susceptible only to the fluoroquinolones. Unfortunately, use of the fluoroquinolones as therapy for children is still not widely accepted because of the potential toxicity of these drugs.

The patterns of antimicrobial resistance in *Shigella* in Bangladesh are representative of those in many areas of the developing world. These patterns are shown in figure 1. The rate of antimicrobial resistance in *Shigella* species is increasing with time, and the increased rate among *S. dysenteriae* type 1 has become critical. There are also geographic differences in the resistance rates that can be quite striking, as is illustrated in...
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Figure 1. Patterns of antimicrobial resistance in *Shigella* species at the rural diarrhea treatment center in Matlab, Bangladesh, 1987–1992. Antimicrobials (ampicillin = ■; trimethoprim-sulfamethoxazole = □; nalidixic acid = □; and pivmecillinam = ■) were tested by the disk diffusion method.

Figure 2. Patterns of antimicrobial resistance in *Shigella dysenteriae* type 1 at rural (Matlab; ■) and urban (Dhaka; □) diarrhea treatment centers in Bangladesh during 1993. The differences in pivmecillinam susceptibilities were statistically significant (P < .001). TMP-SMZ = trimethoprim-sulfamethoxazole.

Figure 3. Patterns of antimicrobial resistance in *Shigella flexneri* at rural (Matlab; ■) and urban (Dhaka; □) diarrhea treatment centers in Bangladesh during 1993. TMP-SMZ = trimethoprim-sulfamethoxazole.

Of all the pathogens causing diarrhea, *Shigella* species are of most concern. New inexpensive antimicrobials that are safe as treatment for children are clearly needed.

*V. cholerae*. Although rehydration therapy is the mainstay of therapy for cholera, antimicrobials are important adjuncts to therapy; their use results in a marked decrease in overall stool volume and a decreased length of illness. For most of the past 30 years, tetracycline has been the drug of choice for treatment of cholera. From time to time, however, antimicrobial resistance in *V. cholerae* develops; since this resistance is largely plasmid-mediated and since vibrios do not stably carry plasmids, the resistance patterns fluctuate. Other drugs, such as furazolidone and erythromycin, are then used widely. Antimicrobial resistance in *V. cholerae* developed during a Latin American outbreak [3] and during a recent outbreak in Zaire [4]. On the other hand, the newly emerged cholera vibrio, O139 Bengal, is uniformly susceptible to tetracycline.

The patterns of antimicrobial resistance in *V. cholerae* O1 and *V. cholerae* O139 Bengal in Bangladesh again are representative of those occurring over the last several years (table 1). It can be noted that susceptibility patterns fluctuate somewhat from year to year. In the latter half of 1994, *V. cholerae* O1 again became primarily (80%) susceptible to tetracycline (data not shown).

*ETEC*. Although traveler’s diarrhea can be caused by a wide variety of etiologic agents, for about the last 20 years, it has been known that ETEC is the most common cause (sometimes accounting for ≥50% of recognized episodes). Furthermore, antimicrobial resistance in the normal fecal flora in travelers to the developing world frequently develops [5], even though diarrhea has not developed. Initially, doxycycline was the drug of choice for treatment of traveler’s diarrhea; as the rates of resistance in ETEC and *Shigella* have increased, trimethoprim-sulfamethoxazole and most recently the fluoroqui-
Table 1. Antimicrobial resistance in *Vibrio cholerae* isolated at the ICDDR,B laboratory in Dhaka, Bangladesh, 1991–1993.

<table>
<thead>
<tr>
<th>Antimicrobial agent(s)</th>
<th>No. of isolates tested (percent resistant) by year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><em>V. cholerae</em> 01, 1991</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>640 (4)</td>
</tr>
<tr>
<td>Trimethoprim-sulfamethoxazole</td>
<td>640 (13)</td>
</tr>
<tr>
<td>Furazolidone</td>
<td>344 (47)</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>264 (4)</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>0</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>15 (0)</td>
</tr>
</tbody>
</table>

NOTE. ICDDR,B = International Centre for Diarrhoeal Disease Research, Bangladesh.

nolones have now become the drugs of choice. Since the genes for the two enterotoxins from ETEC are also carried on plasmids, increasing antibiotic resistance could be linked to the transfer of enterotoxin genes to other enteric organisms.

ETEC is also known to be the most common bacterial cause of acute diarrhea in small children in developing countries [6]. However, these infections are not usually treated with antimicrobials, since the identification of ETEC is not easily made and since the benefits of antimicrobial therapy are thought to be marginal.

*C. jejuni.* The disease caused by *C. jejuni* is milder than that caused by *Shigella*, although *C. jejuni* is also an invasive organism. Studies have shown that antimicrobial therapy for children can be useful in shortening the course of illness [7]. However, laboratory identification at present is not rapid enough to allow the use of antimicrobial therapy (such as erythromycin) early in the course of illness, when it would be most effective. Furthermore, high-level resistance to the quinolones is now being reported [8].

*C. difficile.* Disease due to *C. difficile* usually follows the use of wide-spectrum antimicrobials as therapy for other infectious indications. The alteration of the microflora of the bowel allows this anaerobic organism to proliferate and produce its two enterotoxins, which are responsible for the diarrheal disease. Vancomycin and metronidazole are the therapeutic drugs of choice for *C. difficile* diarrhea. However, resistance to vancomycin has been described [9], and the choice of antibiotic drugs may have to be modified in the future.

**Antimicrobial Resistance in *S. typhi***

A number of antimicrobials have been used to treat typhoid fever effectively. Chloramphenicol, the drug initially found to be effective as treatment of typhoid fever, is still widely used, as are the alternate drugs ampicillin and trimethoprim-sulfamethoxazole. Recently, particularly in Southeast Asia, multidrug-resistant *S. typhi* strains have now been found; in cases of diarrheal disease due to these strains, use of the fluoroquinolones is required [10].

Again, the patterns of antimicrobial resistance in *S. typhi* in Bangladesh can be used to illustrate those in developing countries. The patterns of antimicrobial resistance during the last several years (table 2) show a marked increase in resistance rates and indicate that plasmids carrying several resistance genes have been acquired by *S. typhi* strains.

**Discussion***

The problem of antimicrobial resistance in organisms causing diarrheal diseases will continue to be ongoing in both devel-

Table 2. Prevalence of resistance to recommended drugs in *Salmonella typhi* (*n* = 1,145) isolated from blood at the ICDDR,B hospital in Dhaka, Bangladesh, 1989–1993.

<table>
<thead>
<tr>
<th>Year</th>
<th>No. of isolates tested</th>
<th>Ampicillin</th>
<th>Chloramphenicol</th>
<th>Co-trimoxazole</th>
<th>Ciprofloxacin</th>
<th>Ceftriaxone</th>
</tr>
</thead>
<tbody>
<tr>
<td>1989</td>
<td>71</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>1990</td>
<td>90</td>
<td>8.0</td>
<td>8.0</td>
<td>8.0</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>1991</td>
<td>231</td>
<td>26.0</td>
<td>26.4</td>
<td>26.4</td>
<td>ND</td>
<td>0</td>
</tr>
<tr>
<td>1992</td>
<td>309</td>
<td>41.0</td>
<td>41.0</td>
<td>41.0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1993</td>
<td>435</td>
<td>38.0</td>
<td>38.0</td>
<td>38.0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

NOTE. ICDDR,B = International Centre for Diarrhoeal Disease Research, Bangladesh; ND = not done.
oped and developing countries [11]. At present, the continued development of new antimicrobials, particularly those for treatment of shigellosis in children, is critically important. For future control of antimicrobial resistance, some degree of regulation of antimicrobial use is necessary, but obviously this regulation will be difficult to achieve. Other more indirect but highly relevant and applicable solutions include improving water and sanitation, so that transmission of these enteric organisms is diminished; development of vaccines to decrease the incidence of the diseases; and improving nutrition, an important risk factor for children in the developing world, in whom diarrheal diseases are most important.

References