Antimicrobial Resistance in Organisms Causing Diarrheal Disease

R. Bradley Sack, Mabhubur 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 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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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 \( \approx 50\% \) 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><em>V. cholerae</em> 01, 1991</th>
<th><em>V. cholerae</em> 01, 1992</th>
<th><em>V. cholerae</em> 01, 1993</th>
<th><em>V. cholerae</em> Bengal 0139, 1993</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetracycline</td>
<td>640 (4)</td>
<td>1,412 (68)</td>
<td>616 (53)</td>
<td>2,266 (0)</td>
</tr>
<tr>
<td>Trimethoprim-sulfamethoxazole</td>
<td>640 (13)</td>
<td>1,851 (78)</td>
<td>616 (85)</td>
<td>2,266 (100)</td>
</tr>
<tr>
<td>Furazolidone</td>
<td>344 (47)</td>
<td>873 (35)</td>
<td>616 (20)</td>
<td>2,266 (0.7)</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>264 (4)</td>
<td>881 (0.3)</td>
<td>616 (0)</td>
<td>2,266 (0)</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>0</td>
<td>0</td>
<td>29 (0)</td>
<td>111 (0)</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>15 (0)</td>
<td>78 (0)</td>
<td>25 (0)</td>
<td>335 (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 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 develop-

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>99</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>26.0</td>
<td>26.0</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>39.0</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 treat-
ment of shigellosis in children, is critically important. For fu-
ture control of antimicrobial resistance, some degree of regula-
tion 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 wa-
ter and sanitation, so that transmission of these enteric organ-
isms 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 diar-
rheal diseases are most important.

References

1. Tauxe RV, Puhr ND, Wells JG, Hargrett-Bean N, Blake PA. Antimicrobial
resistance of Shigella isolates in the USA: the importance of international
2. Bennish ML, Salam MA, Hossain MA, et al. Antimicrobial resistance of
Shigella isolates in Bangladesh, 1983–1990: increasing frequency of
strains multiply resistant to ampicillin, trimethoprim-sulfamethoxazole,
multidrug-resistance and transmission by water and seafood. Epidemiol
 Infect 1994;112:1–11.
prevent cholera deaths among Rwandan refugees in Goma, Zaire. Lancet
5. Murray BE, Mathewson JJ, DuPont HH, Ericsson CD, Reves RR. Emer-
gence of resistant fecal Escherichia coli in travelers not taking prophyl-
actic antimicrobial agents. Antimicrob Agents Chemother 1990;34:
515–8.
resistance pattern of heat-labile enterotoxin (LT) producing Escherichia
coli isolated from children with diarrhoea in Bangladesh: clonal relations-
ships among isolates with different resistant phenotypes. J Diarrhoeal
7. Salazar-Lindo E, Sack RB, Chea-Woo E, et al. Early treatment with eryth-
romycin of Campylobacter jejuni associated dysentery in children. J
in clinical isolates of Campylobacter jejuni. J Infect Dis 1992;165:
667–70.
9. Dworczynski A, Sokol B, Meisel-Mikolajczyk F. Antibiotic resistance of
10. Rao PS, Rajashekar V, Varghese GK, Shivandana PG. Emergence of
multidrug-resistant Salmonella typhi in rural southern India. Am J Trop