Susceptibilities of Hong Kong Isolates of Multiply Resistant *Shigella* spp. to 25 Antimicrobial Agents, Including Ampicillin plus Sulbactam and New 4-Quinolones

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Seventy-two percent of 129 shigella isolates from two Hong Kong hospitals were *Shigella flexneri*. Twenty-six percent were *S. sonnei*, and there was only one isolate each of *S. dysenteriae* and *S. boydii*. Ninety-six percent of the isolates were resistant to two or more antibiotics, and up to 11 resistances were seen in a single isolate. Fifty-seven percent or more of these isolates were resistant to ampicillin, streptomycin, tetracycline, chloramphenicol, and sulfamethoxazole; and up to twenty-three percent were resistant to kanamycin, trimethoprim, trimethoprim-sulfamethoxazole, and gentamicin. All the isolates were susceptible to amikacin, nalidixic acid, and the newer 4-quinolone agents; and all but one were susceptible to the cephalosporins tested. Only three isolates remained resistant to ampicillin in the presence of sulbactam. Ampicillin plus sulbactam or the newer 4-quinolone agents may be alternatives for the treatment of severe infections caused by multiply resistant shigellas.

The incidence of *Shigella* species resistant to ampicillin, tetracycline, chloramphenicol, and trimethoprim has increased considerably in many parts of the world (10, 13, 15, 18, 21, 26; R. M. Bannatyne, S. Toma, and R. Cheung, Letter, Lancet ii:173, 1984; K. Zaman, M. D. Yunus, A. H. Baqui, K. M. B. Hossain, and M. U. Khan, Letter, Lancet ii:796–797, 1983). Infection caused by *Shigella sonnei* is usually mild and does not require antimicrobial therapy, but *Shigella flexneri* infection is usually more severe, especially in children or the elderly, and treatment with appropriate antimicrobial agents may be required (24). Although shigellosis is endemic in Hong Kong, there has been no previous report from this area on the occurrence of *Shigella* spp. or their antimicrobial susceptibilities. This study reports the distribution of hospital isolates of *Shigella* spp. in Hong Kong and their susceptibilities to some common antimicrobial agents and newer agents, including ampicillin-sulbactam and the 4-quinolones.

MATERIALS AND METHODS

**Bacterial strains.** A total of 129 nontypable isolates of shigella were cultured from inpatients at two Hong Kong hospitals: 97 between June 1986 and March 1987 from Princess Margaret Hospital, an infectious diseases hospital; and 32 between May 1984 and March 1987 from The Prince of Wales Hospital, a general and teaching hospital. All were fecal isolates, identified by standard microbiological techniques (16) and confirmed to be *Shigella* spp. by the API 20E system (API System, S.A., Montalieu Vercieu, France). They were also serotyped with specific antisera (Wellcome Research Laboratories, Beckenham, England) (5).

**Antimicrobial susceptibility testing.** MICs of the following 25 agents were determined by the agar dilution method according to the procedures recommended by the National Committee for Clinical Laboratory Standards (20): ampicillin, tetracycline, chloramphenicol, kanamycin, nalidixic acid, sulfamethoxazole, trimethoprim, trimethoprim-sulfamethoxazole (1:19, wt/wt), and gentamicin (all from Sigma Chemical Co., St. Louis, Mo.); cefuroxime, cefazidime, and streptomycin (Glaxo Laboratories, Ltd., Greenford, England); amikacin (Bristol Laboratories, Syracuse, N.Y.); cefoperazone and sulbactam (Pfizer Inc., New York, N.Y.) in combination with ampicillin (1:1, wt/wt); cephalothin, cefamandole, and moxalactam (Eli Lilly & Co., Indianapolis, Ind.); ceftriaxone (Hoffmann-La Roche Inc., Nutley, N.J.); cefotaxime (Hoechst-Roussel Pharmaceuticals Inc., Frankfurt, Federal Republic of Germany); ciprofloxacin (Bayer AG, Wuppertal, Federal Republic of Germany); enoxacin (Warner-Lambert Co., Detroit, Mich.); pefloxacin (May & Baker, Dagenham, England); ofloxacin (Daichi Seiyaku Co., Tokyo, Japan); and norfloxacin (AB Astra, Sodertalje, Sweden). An MIC 2000 inoculator (Dynatech Laboratories, Inc., Alexandria, Va.) was used to transfer 10⁴ CFU per spot onto the agar plates. Mueller-Hinton agar (Oxoid Ltd., Basingstoke, England) was used for testing all agents except sulfamethoxazole, trimethoprim, and trimethoprim-sulfamethoxazole, for which Iso-Sensitest agar (Oxoid) was used. The MIC was taken as the lowest concentration which inhibited visible growth on the inoculation spot. *Escherichia coli* ATCC 25922 and NCTC 10418 and *Pseudomonas aeruginosa* ATCC 27853 were included as controls.

**RESULTS**

A total of 93 (72.1%) of the 129 shigella isolates were *S. flexneri* (33 were type 1, 48 were type 2, 8 were type 3, and 1 each was type 4 and 6 and x and y variant), and 34 (26.4%) were *S. sonnei*. There was only one isolate each of *Shigella dysenteriae* and *Shigella boydii* (both were type 2).
TABLE 1. Susceptibilities of 129 isolates of *Shigella* spp. to 25 antimicrobial agents

<table>
<thead>
<tr>
<th>Antimicrobial agent</th>
<th>MIC (mg/liter)</th>
<th>50%</th>
<th>90%</th>
<th>% Resistant*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Commonly used agents</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ampicillin</td>
<td>0.5–1,024.0</td>
<td>128.0</td>
<td>512.0</td>
<td>57.4 (8)</td>
</tr>
<tr>
<td>Ampicillin-sulbactam</td>
<td>0.5–32.0</td>
<td>4.0</td>
<td>8.0</td>
<td>2.3 (8)</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>8.0–1,024.0</td>
<td>256.0</td>
<td>&gt;1,024.0</td>
<td>96.9 (16)*</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>≤1.0–256.0</td>
<td>128.0</td>
<td>256.0</td>
<td>94.6 (4)</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>≤1.0–512.0</td>
<td>32.0</td>
<td>256.0</td>
<td>76.7 (8)</td>
</tr>
<tr>
<td>Kanamycin</td>
<td>1.0–1,024.0</td>
<td>4.0</td>
<td>16.0</td>
<td>9.3 (16)</td>
</tr>
<tr>
<td>Sulfamethoxazole</td>
<td>≤64.0–&gt;4,096.0</td>
<td>&gt;4,096.0</td>
<td>&gt;4,096.0</td>
<td>69.8 (256)</td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>0.125–&gt;128.0</td>
<td>0.25</td>
<td>&gt;128.0</td>
<td>23.3 (1)*</td>
</tr>
<tr>
<td>Trimethoprim-sulfamethoxazole</td>
<td>0.05/9.5–&gt;64/121.6</td>
<td>0.1/1.9</td>
<td>&gt;6.4/121.6</td>
<td>23.3 (0.8/15.2)*</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>0.25–&gt;16.0</td>
<td>1.0</td>
<td>&gt;16.0</td>
<td>17.8 (4)</td>
</tr>
<tr>
<td>Amikacin</td>
<td>1.0–8.0</td>
<td>4.0</td>
<td>8.0</td>
<td>0.0 (16)</td>
</tr>
</tbody>
</table>

| Cephalosporins                                           |                |         |         |             |
|-----------------------------------------------------------------------------------------------------------------------|
| Cephalothin                                               | 0.5–32.0       | 4.0     | 8.0     | 0.8 (8)     |
| Cefuroxime                                               | 1.0–8.0        | 4.0     | 8.0     | 0.8 (8)     |
| Cefamandole                                              | 0.25–16.0      | 0.5     | 2.0     | 0.8 (8)     |
| Ceftazidime                                              | 0.06–0.5       | 0.12    | 0.25    | 0.8 (8)     |
| Cefoperazone                                             | 0.03–16.0      | 0.12    | 1.0     | 0.8 (16)    |
| Ceftriaxone                                              | 0.015–0.12     | 0.03    | 0.06    | 0.8 (8)     |
| Cefotaxime                                               | 0.0075–0.12    | 0.06    | 0.12    | 0.8 (8)     |
| Meropenem                                                 | 0.03–1.0       | 0.12    | 0.25    | 0.8 (8)     |

| Quinolones                                               |                |         |         |             |
|-----------------------------------------------------------------------------------------------------------------------|
| Nalidixic acid                                            | 1.0–4.0        | 2.0     | 4.0     | 0.0 (16)    |
| Ciprofloxacin                                             | ≤0.00375–0.015 | 0.0075  | 0.015   | 0.0 (4)*    |
| Enoxacin                                                 | 0.03–0.12      | 0.06    | 0.06    | 0.0 (4)*    |
| Pefloxacin                                               | 0.03–0.12      | 0.06    | 0.06    | 0.0 (4)*    |
| Ofloxacinar                                              | 0.03–0.12      | 0.03    | 0.06    | 0.0 (4)*    |
| Norfloxacin                                               | 0.015–0.06     | 0.03    | 0.03    | 0.0 (4)     |

* 50% and 90% MICs for 50 and 90% of isolates, respectively.
* Percentage of isolates with MICs greater than the concentration in milligrams per liter is indicated in parentheses. Except for those marked with an asterisk, the breakpoints values are concentrations recommended for susceptible strains by the National Committee for Clinical Laboratory Standards (20).

Table 1 shows the antimicrobial susceptibility results for these shigellas, including the MIC ranges and the MICs for 50 and 90% of the isolates. Table 1 also shows the percentage of isolates resistant to the stated breakpoints, which in most cases are the National Committee for Clinical Laboratory Standards (20) MICs for susceptible strains. The incidences of resistance to different antimicrobial agents were similar in *S. flexneri* and *S. sonnei*: 57 to 97% of the isolates were resistant to ampicillin, streptomycin, tetracycline, chloramphenicol, and sulfamethoxazole, while 9 to 23% were resistant to kanamycin, trimethoprim, trimethoprim-sulfamethoxazole, and gentamicin. A single *S. flexneri* isolate with extensive multiple resistance was resistant to cephaplatin, cefamandole, and cefoperazone; otherwise, all the isolates were susceptible to the cephalosporins, amikacin, nalidixic acid, and the five new quinolones tested. Except for three strains, sulbactam reduced the ampicillin MICs for resistant isolates to within the susceptible range.

Ninety-five percent of *S. flexneri* isolates, all of the *S. sonnei* isolates, and both *S. dysenteriae* and *S. boydii* isolates were resistant to two or more antibiotics. Forty percent of isolates were resistant to four drugs, fourteen percent were resistant to five drugs, and nine percent were resistant to eight drugs (Table 2). The most frequent resistance patterns in *S. flexneri* isolates were ampicillin, streptomycin, tetracycline, and chloramphenicol; streptomycin, tetracycline, chloramphenicol, and sulfamethoxazole; and ampicillin, streptomycin, tetracycline, chloramphenicol, and sulfamethoxazole. In *S. sonnei* isolates, the most frequent patterns were streptomycin, tetracycline, and sulfamethoxazole; and ampicillin, streptomycin, tetracycline, chloramphenicol, and sulfamethoxazole.

**DISCUSSION**

Most of our shigella isolates were *S. flexneri*. A small proportion were *S. sonnei*, while *S. dysenteriae* and *S. boydii* were very uncommon. This distribution is similar to that seen in Bangladesh (15), India (12, 17), and Korea (3, 26); but in the United Kingdom, Western Europe, and the United States, *S. sonnei* still predominates (6, 22).

Antimicrobial resistance and multiple resistance were common in these Hong Kong isolates. A large proportion of isolates were resistant to ampicillin, but most of them reverted to susceptibility in the presence of sulbactam, indicating that β-lactamase was responsible for the ampicillin resistance. Ampicillin has been generally accepted as the drug of choice for the treatment of severe bacillary dysentery caused by susceptible organisms (8, 11, 14). The combination of sulbactam with ampicillin may be an effective alternative in areas where ampicillin-resistant shigella isolates now predominate, but no clinical studies of this combination have been reported.

The incidence of trimethoprim- and trimethoprim-sulfamethoxazole-resistant shigella isolates in Hong Kong is high but is lower than that found in neighboring countries (3, 17, 24).
Although trimethoprim has been recommended for the therapy of bacillary dysentery (28), its usefulness is now limited to areas where trimethoprim resistance has not yet developed. Even then, the use of trimethoprim-sulfamethoxazole for the treatment of shigellosis has been associated with the development of resistance (J. A. Frost, B. Rowe, and J. Vandeputte, Letter, Lancet ii:963, 1982).

The older cephalosporins had good in vitro activity against these shigella isolates, and the broad-spectrum cephalosporins were even more effective. Although shigella septicaemia is rare, it does occur in compromised patients, such as neonates and the immunosuppressed (1, 25), causing high morbidity and mortality. The cephalosporins may be reserved for these cases, especially when the causative organism is resistant to the usual drugs of choice.

Although shigella strains showing resistance to nalidixic acid have been isolated, resistance is not widespread and is not plasmid mediated (7). Malengreau et al. (19; M. Malengreau, Letter, Lancet ii:172, 1984) have reported the effective use of this drug in treating multiply resistant shigellosis in Central Africa. All our isolates were susceptible to nalidixic acid and to the newer 4-quinolones, among which ciprofloxacin was the most active. Other workers have also noted the high in vitro activity of ciprofloxacin against shigellas (2, 4, 9; Bannatyne et al., Lancet ii:173, 1984), and one study reported successful treatment of shigellosis with norfloxacin (23).

In Hong Kong, as elsewhere in East Asia, shigella isolates are now frequently multiply resistant to common therapeutic agents, such as ampicillin, sulfamethoxazole, and trimethoprim. However, they remain susceptible to nalidixic acid, the new 4-quinolones, and the combination of ampicillin with sulbactam.

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