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High Frequency of Strains Multiply Resistant to Ampicillin, Trimethoprim-Sulfamethoxazole, Streptomycin, Chloramphenicol, and Tetracycline Isolated from Patients with Shigellosis in Northeastern Brazil during the Period 1988 to 1993

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The occurrence and antimicrobial resistance pattern of *Shigella* isolates obtained from persons in community and hospital-based studies of diarrhea and matched controls in northeastern Brazil were studied. The isolation rate of *Shigella* spp. from patients with diarrhea during 1988 to 1993 varied from 4.5% (26 of 575) for the urban community of Gonçalves Dias to 6.7% (12 of 179) and 5.9% (7 of 119) for Hospital Infantil and Hospital Universitário, respectively. Of the 55 *Shigella* isolates (45 from patients with diarrhea, 8 from controls, and 2 undetermined) 73% (40 of 55) were *Shigella flexneri*, 16% (9 of 55) were *S. sonnei*, 7% (4 of 55) were *S. boydii*, and 4% (2 of 55) were *S. dysenteriae*. Of 39 *S. flexneri* strains, over half were resistant to ampicillin, trimethoprim-sulfamethoxazole, or both. Over 64% were resistant to streptomycin, chloramphenicol, and tetracycline. Overall, 82% of all *S. flexneri* isolates were resistant to four or more antimicrobial agents tested. As elsewhere, in the northeast of Brazil, ampicillin and trimethoprim-sulfamethoxazole are no longer reliable for treatment of *S. flexneri* infection. Most *Shigella* strains were resistant to four or more antimicrobial agents. Nalidixic acid was still useful for treatment of infections due to *S. flexneri*.

Dysentery caused by *Shigella* organisms constitutes an important health problem in industrialized as well as in less developed countries (14, 19, 23). Effective antimicrobial therapy for shigellosis reduces the duration and severity of the dysentery and can also prevent potentially lethal complications (17, 34, 35).

Several studies have reported shigellosis caused by strains of *Shigella* species that were resistant to ampicillin, trimethoprim-sulfamethoxazole (TMP-SMZ) or both drugs (6, 10, 20, 21, 24, 37, 39). Most infections with multiply resistant strains of *Shigella* species in the United States and Finland were associated with foreign travel, travel aboard a cruise ship, and day care centers (10, 18, 24, 36, 39). Isolates of *Shigella* species from patients returning from foreign travel in the United States and Finland showed a high rate of resistance to TMP-SMZ (18, 36, 39). Strains of *Shigella sonnei* and *S. flexneri* multiply resistant to ampicillin and TMP-SMZ plus other antibiotics were also observed in day care centers and on cruise ships in the United States.

Two studies from Bangladesh showed an increasing frequency of *Shigella* strains with multiple resistance to ampicillin, TMP-SMZ, and nalidixic acid (6, 20). Outbreaks of shigellosis caused by *Shigella* strains that were resistant to ampicillin, TMP-SMZ, or both drugs have been reported in other countries in Asia (4, 16, 27, 30), Africa (15), Central America (12), and Europe (8).

In this report we analyze for the first time the occurrence and antimicrobial resistance pattern of *Shigella* isolates obtained from persons with dysentery in northeastern Brazil that complicate the treatment of this infection.

Sources of *Shigella* strains. The occurrence and antimicrobial resistance pattern of *Shigella* isolates obtained from three groups of patients was determined. The first group of isolates was obtained from October 1989 to December 1992 during community surveys of diarrhea. Thirty-two isolates were obtained from the urban community of Gonçalves Dias (approximately 2,000 people), where the Clinical Research Unit at the Federal University of Ceará maintains surveillance in Fortaleza, the capital of the state of Ceará. The field surveillance team followed 184 cohort children by three weekly family visits (Monday, Wednesday, and Friday), recording diarrheal episodes and other diseases and nutritional practices and checking sample collections (stool and blood), after obtaining signed guardian consent. A total of 893 stool samples (575 from patients with diarrhea and 318 from controls) were cultured for *Shigella* species and examined for other enteric pathogens. Diarrhea was defined as the passage of three or more liquid stools per day. Control samples were collected from cohort children without diarrhea in the previous 2 weeks at 6-month intervals.

The second group of isolates was obtained from children <5 years old attending Hospital Infantil Albert Sabin, the major state pediatric hospital in Fortaleza (population, approximately 1.7 million people), during a study of diarrhea from August 1988 through October 1991. Patients from whom a stool sample for culture was obtained included all patients enrolled in the research study. A total of 216 stool samples were available for culture: 79 samples from patients with persistent diarrhea (duration, >14 and ≤30 days), 100 samples from patients acute diarrhea (duration, ≤14 days), and 37 samples from controls without diarrhea. Diarrhea was defined as above.

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The remaining isolates were collected from hospitalized patients (mostly adults) at Hospital Universitário Walter Cantídio, the major teaching hospital in the state of Ceará. The Hospital Infection Control Committee conducted a prospective study of the incidence and etiology of nosocomial diarrhea from July 1989 through February 1993. Prospective selective surveillance of the charts of patients at high risk for nosocomial infections, as identified by a risk factor indicator form completed by the resident physician (26), was conducted by nurses. Surveillance was based on thrice-weekly visits of all hospitalized patients inquiring about any diarrheal illness. A total of 233 stool samples, 114 from patients without diarrhea and 119 from inpatients with diarrhea, were examined for *Shigella* strains by standard procedures (13). In addition, 70 hospitalized controls were matched with 49 of the patients by age, sex, admission diagnosis, and duration of hospitalization. Patients with chronic inflammatory bowel diseases, bowel preparation, and laxative use were excluded from the study group.

Antimicrobial disk susceptibility tests. Stool samples from patients were examined by direct microscopy and cultured for enteric pathogens by standard methods (13). Non-lactose-fermenting colonies on MacConkey agar and XLD (xylose-lysine-desoxycholate) agar were screened biochemically by using the API 20E system (Analytab Products, New York, N.Y.) and typed by using commercially available antisera (Difco Laboratories, Detroit, Mich.). Isolates of *Shigella* spp. were tested for sensitivity to TMP-SMZ, ampicillin, ceftriaxone, nalidixic acid, ciprofloxacin, streptomycin, gentamicin, kanamycin, chloramphenicol, and tetracycline by the disk diffusion method of Bauer and colleagues (1) using commercial disks (Becton Dickinson, Cockeysville, Md.). Standard control strains of *Escherichia coli* (ATCC 25922), *Staphylococcus aureus* (ATCC 25923), and *Pseudomonas aeruginosa* (ATCC 27853) were used for monitoring the accuracy and precision of disk diffusion tests.

Statistical methods. The significance of differences in proportions was analyzed by the chi-square test, and Fisher's exact test was used when there was a cell with a number less than 5. Entry of data into the computer and the chi-square and Fisher exact tests were performed with Epi Info version 5.0 software (USD, Stone Mountain, Ga.), and P values less than 0.05 were considered statistically significant.

The isolation rates of *Shigella* spp. from diarrhea samples during 1988 to 1993 were 4.5% (26 of 575) for the community of Gonçalves Dias, 6.7% (12 of 179) for Hospital Infantil Albert Sabin (300 beds), and 5.9% (7 of 119) Hospital Universitário Walter Cantídio (220 beds) versus the corresponding control rates of 1.9% (6 of 318), 0% (0 of 114), and 5.4% (2 of 37). In the Hospital Infantil the isolation rates were 9% (9 of 100) and 3.8% (3 of 79) for patients with acute diarrhea and persistent diarrhea (duration, >14 days), respectively. Of the 55 *Shigella* sp. isolates available for testing (45 from patients with diarrhea, 8 from controls, and 2 from undetermined patients), 73% (40 of 55) were *S. flexneri*, 16% (9 of 55) were *S. sonnei*, 7% (4 of 55) were *S. boydii*, and 4% (2 of 55) were *S. dysenteriae*. *S. flexneri* was predominant in all three populations studied.

Figure 1 shows the resistance pattern, by year, of 39 *S. flexneri* isolates (one isolate was lost upon storage). The prevalence of resistance to ampicillin and TMP-SMZ was ≥50% in all four years studied. The rates of resistance to both ampicillin and TMP-SMZ were also high (50 to 90%). Because of the increasing resistance to ampicillin and TMP-SMZ, in 1991 nalidixic acid replaced ampicillin and TMP-SMZ as the drug of choice for empirical treatment of patients with suspected shigellosis attending the state hospitals. Following the lead of the Clinical Research Unit at Federal University of Ceará and the State Health Secretary, practitioners in the community also began to use nalidixic acid for the treatment of shigellosis. Although resistance to nalidixic acid among *Shigella* sp. isolates had never been a problem in these settings in 1991, we found two (10%) strains of *S. flexneri* to be resistant for the first time. Because *S. flexneri* represents 73% (40 of 55) of the total *Shigella* sp. isolates, the resistance patterns in all 54 strains of *Shigella* spp. tested (one *S. flexneri* strain was lost during storage) showed a pattern similar to that shown for *S. flexneri.*

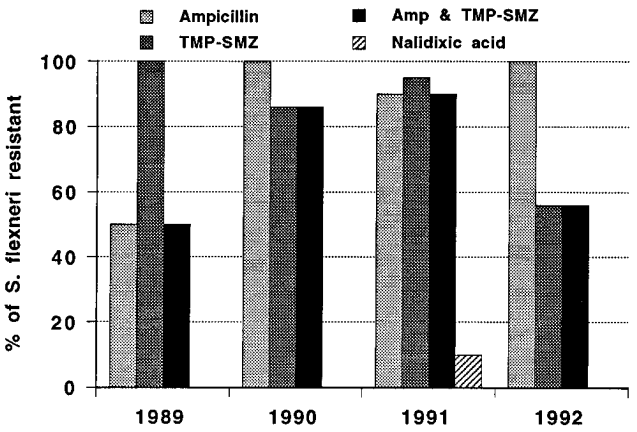

FIG. 1. The prevalence of resistance to ampicillin, TMP-SMZ, both ampicillin and TMP-SMZ, and nalidixic acid among 39 *S. flexneri* isolates from the community and two hospitals in Fortaleza, Brazil, between 1989 and 1992.

The susceptibility pattern by patient group for the 11 antimicrobial agents tested is shown in Fig. 2. Overall, the resistance patterns among the 21 available *S. flexneri* isolates in the community paralleled those of isolates from hospitalized patients. Of the 21 community isolates, 94% were resistant to ampicillin, 81% were resistant to TMP-SMZ, and 76% were resistant to both drugs. Resistance to ampicillin plus clavulanic acid decreased to 46% among *S. flexneri* isolates in the community. Eighty-six percent of 7 Hospital Universitário isolates and 91% of 11 Hospital Infantil isolates were resistant to TMP-SMZ. Resistance to ceftriaxone was very low (7%) for all isolates of *S. flexneri*. Two strains of *S. flexneri*, one from Hospital Infantil and another from Hospital Universitário, were resistant to nalidixic acid (Fig. 2). None of the 25 isolates tested were resistant to ciprofloxacin. Among the aminoglycosides, these isolates were commonly (93% [27 of 29]) resistant only to streptomycin. Sixty-two percent of 21 isolates in the community, 87% of 7 isolates in Hospital Universitário, and 91% of 11 isolates in Hospital Infantil were resistant to chloramphenicol. Overall, more than 95% of 39 *S. flexneri* isolates were resistant to tetracycline in the three groups of patients. Of all *S. flexneri* isolates tested, 82% were resistant to four or more antimicrobial agents tested.

The isolation rates of *Shigella* species in the three groups of patients with diarrhea studied in the northeast of Brazil varied between 4.5 and 6.7%, with the most prevalent species being *S. flexneri*, similar to the 4 to 13% rates from clinic and household surveys in Chile reported by Ferreccio et al. (14). Another study done in Teknaf, in the coastal area of Bangladesh, reviewed epidemiologic data on shigellosis over a 10-year period (1975 to 1984) (20). While the isolation rate of *Shigella* species in Matlab and Dhaka varied between 11 and 12%, in Teknaf the unusually high isolation rate of *Shigella* species was 19 to

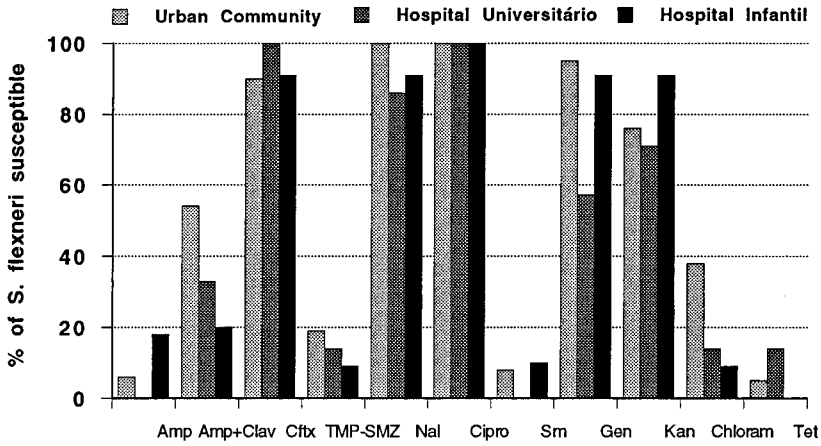

FIG. 2. Percent susceptible *S. flexneri* strains isolated in the community and at two hospitals in Fortaleza, Brazil, from 1988 to 1993. Amp, ampicillin; Clav, clavulanic acid; Cftx, ceftriaxone; Nal, nalidixic acid; Cipro, ciprofloxacin; Sm, streptomycin; Gen, gentamicin; Kan, kanamycin; Chloram, chloramphenicol; Tet, tetracycline.

42%, with *S. dysenteriae* type 1 being the predominant species. Kagalwalla et al. (21) studied 234 children with shigellosis in Saudi Arabia during a 6-year period. *S. flexneri* and *S. sonnei* accounted for 44 and 43% of the isolates, respectively. In Thailand, *S. flexneri* (83.5%) was the most common species isolated from 230 hospitalized children with shigellosis (38). In the United States, Lee et al. (22) from the Centers for Disease Control reviewed surveillance data on shigellosis for 1967 through 1988. Nationwide peaks were due predominantly to increases in the number of *S. sonnei* isolates.

Antimicrobial therapy is recommended for shigellosis because it can shorten the severity and duration of illness, reduce shedding of the organism, and prevent secondary complications and deaths (2, 3, 5, 7, 9, 34, 35). However, antimicrobial resistance has occurred among *Shigella* spp. since the 1940s, when sulfonamide resistance among *Shigella* organisms was first recognized in Japan (40). In this study, we found a strikingly high prevalence of multiple antibiotic resistance among *Shigella* isolates in northeastern Brazil. This had been seen in association with several different plasmids among shigellae, enterotoxigenic *E. coli*, and other enteric isolates in this area over 10 years ago (38). However, until 1991 ampicillin and TMP-SMZ had remained the drugs of choice for the treatment of patients with shigellosis. During 1989 to 1991 over 50% of isolates were already resistant to ampicillin, TMP-SMZ, or both drugs. In 1991, following the lead of the Clinical Research Unit at the Federal University of Ceará and the State Health Secretary, nalidixic acid was introduced as the drug of choice for treating patients with suspected shigellosis. In the same year, the routine use of nalidixic acid was followed by an increase (10%) in resistance to this agent. In 1992, resistance of all *S. flexneri* isolates to ampicillin and TMP-SMZ remained high. The rapid development of resistance following the routine use of nalidixic acid has occurred previously with *Shigella* species (28, 31) and strains of the *Enterobacteriaceae* that cause urinary tract infections (32). Our routine use of this agent is likely to eventually lead to high-level resistance among *Shigella* strains circulating in the northeast of Brazil. A high prevalence of ampicillin and TMP-SMZ resistance among *Shigella* species has also developed in Bangladesh (6), Guatemala (12), Saudi Arabia (22), Thailand (37), The Netherlands (39), and elsewhere (29).

The resistance patterns of *S. flexneri* strains isolated from patients at Hospital Universitário and Hospital Infantil and strains collected during an urban community survey in Gonçalves Dias were similar. This finding suggests that the high prevalence of resistance that we found in these hospitals is not simply a result of the use of antibiotics in both hospitals or of the selection of patients who had previously received, and failed to respond to, therapy with ampicillin or TMP-SMZ. It also demonstrates that multiple resistance extends into the urban community. This promiscuous multiple resistance has a wide geographic distribution, and the inappropriate use of antibiotics (therapy of insufficient duration or dosage or drugs prescribed without proper indications) in the northeast of Brazil may help to explain this problem. The use of the β-lactamase inhibitor clavulanic acid with ampicillin partially offsets the resistance observed with *S. flexneri* isolates from the urban community Gonçalves Dias and, to lesser extent, the isolates from Hospital Universitário but not in the ampicillin-resistant strains from Hospital Infantil. This suggests that the mechanism of resistance is at least in part due to β-lactamase production but that different strains of *S. flexneri* and types of ampicillin resistance are present in the hospitals.

Shigella isolates resistant to multiple drugs including ampicillin and TMP-SMZ are found in several parts of the world (6, 12, 21, 29, 37, 39). However, this multiple antimicrobial resistance has usually been sporadic and most often has occurred in association with an epidemic strain of either *S. dysenteriae* type 1 (4, 16) or *S. sonnei* (8, 10, 11). Although epidemics of infection due to multiply resistant *S. sonnei* have occurred in the United States, in a survey by the Centers for Diseases Control (Atlanta, Ga.) in 1985 and 1986 only 6% of all *Shigella* isolates were resistant to both ampicillin and TMP-SMZ (36). Infections with multiply resistant *Shigella* strains in the United States and Finland were often associated with foreign travel (18, 36). An exception to this pattern of only sporadic resistance to both ampicillin and TMP-SMZ has been observed in Thailand, where most endemic *S. flexneri* strains from patients in Bangkok hospitals are now resistant to both ampicillin and TMP-SMZ (27). In Bangladesh, the multiple resistance to ampicillin and TMP-SMZ is common among all four *Shigella* species and the majority of *S. dysenteriae* type 1 strains are also resistant to nalidixic acid (6). The experience in northeast Brazil showed that multiple resistance to ampicillin and TMP-SMZ is common among *S. flexneri* isolates, but these organisms had still remained sensitive to nalidixic acid.

The combined resistance of isolates to ampicillin and TMP-SMZ makes these antimicrobial agents unacceptable for empirical treatment of patients suspected of having shigellosis.

These agents had been the drugs of choice for treating patients with shigellosis. Overall, nalidixic acid is effective in the majority of patients with shigellosis who receive therapy at both hospitals and the urban community in the northeast of Brazil. Thus, the presumptive treatment for shigellosis in our hospitals and community areas has become nalidixic acid (25, 33). Indeed, in most developing countries, treatment of shigellosis must of necessity be empirical because facilities for routine culture of stool samples are not available. Currently, in the Clinical Research Unit program at the urban community and hospitals, patients with dysentery are now started on empirical therapy with nalidixic acid. Thus, the continuing evaluation of the antimicrobial resistance patterns among *Shigella* isolates is important in determining the appropriate treatment of this potentially serious illness.

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