Emergence of Multidrug-Resistant *Shigella* in Iran

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**ABSTRACT**

Acute infectious diarrhea is a major cause of morbidity and mortality in Iran especially during the warm season, with shigellosis recognized as a particular cause of acute bloody diarrhea. In view of increasing antibiotic resistance, this study was conducted to determine the prevalence of multidrug-resistant (MDR) *Shigella* in Kashan Hospital, Kashan, Iran.

The prevalence of multidrug-resistant (MDR) *Shigella* in Kashan Hospital, Kashan, Iran. The study was performed in 734 patients with acute diarrhea who were treated from 2002 to 2003. After admission and registration of demographic characteristics, the fecal specimens were studied by culturing and serotyping according to the recommendation of the National Committee for Clinical Laboratory Standards (NCCLS). The antibiotic susceptibility was done by the disk diffusion method (Kirby-Bauer). The results were presented by a descriptive analysis. The prevalence of shigellosis was reported as 7.6 percent (56 of 734). Thirty-four (60%) of the isolates belonged to *Shigella flexneri*, 14.3 percent were *S. dysenteria*, 25 percent were *S. boydii*. The highest rate of antibiotic resistance were found in cephalothin (78.6%), followed by sulfamethoxazole-trimethoprim (SXT) (58.9%), and ampicillin (38.9%). Furthermore, the results showed that 21 (61.6%) of *S. flexneri* were resistant to cephalothin and (SXT), 3 (8.8%) resistant to three antibiotics (cephalothin, SXT, and ampicillin), and 2 (5.9%) resistant to four antibiotics (cephalothin, SXT, ampicillin, and chloramphenicol). In conclusion, these results confirm that MDR strains of *Shigella* are present in Kashan, Iran and emphasize the importance of maintaining this surveillance in order to determine the local susceptibility patterns for appropriate empirical antibiotic treatment in patients with acute infectious diarrhea. *(J Infect Dis Antimicrob Agents 2006;23:15-9.)*

**INTRODUCTION**

Acute infectious diarrhea is a major cause of morbidity and mortality, especially in developing countries.1-4 The use of oral rehydration therapy has markedly decreased the mortality, but antimicrobial agents are usually employed to treat acute bloody
diarrhea, as occurs with shigellosis, to the decrease the
duration of the episode and the period of infectiousness,
as well to prevent the complications and death. An
appropriate use of antimicrobials in patients with
bloody diarrhea depends on the physician’s knowledge
of the relative frequency of enteropathogens and
their susceptibility to these drugs. Accordingly,
a continuous surveillance of the resistance patterns of
enteropathogens is needed to select the appropriate
antimicrobial agent. Unfortunately, in Kashan, Iran,
limited financial and laboratory resources generally
preclude the use of accurate stool cultures and
antimicrobial drug susceptibility testing to guide the
empirical therapy. Hence, an empirical therapy is often
used without supporting data, and a decision usually
depends on the clinical experience of the physician.

Sulfamethoxazole-trimethoprim (SXT) and
ampicillin are less expensive antimicrobial agents, and
are widely available for the treatment of bloody diarrhea
at Iranian hospitals and health care centers at no cost
to patients. However, an antibiotic treatment of patients
with suspected shigellosis, especially in children, has
been complicated by the occurrence of drug resistance
since the 1940, when strains of *Shigella* resistant to
SXT were first recognized in Japan, and later in other
parts of the world. Thus, the traditional therapeutic
agents such as ampicillin and SXT have lost much of
their effectiveness over the last decade, because the
resistance patterns are changing constantly and vary
among different parts of the world.

The aim of the present study was to determine
the antimicrobial resistance patterns of 56 *Shigella*
strains isolated from patients with acute diarrhea in
Kashan University Hospital, Iran.

**MATERIAL & METHODS**

**Patients and bacterial isolates**

From 2002 to 2003, 56 *Shigella* strains were
isolated from patients with acute diarrhea who were
treated at Kashan University Hospital, Kashan, Iran.
Freshly excreted fecal specimens were collected from
each patient, inoculated into the Cary Blair medium,
and transported to the Central Laboratory of Kashan
within three hours of the inoculation. Slides of fecal
specimens were stained with Gram stain and methylene
blue, and were examined for fecal leukocytes using light
microscopy. All strains were isolated from unrelated
cases of acute diarrhea. Isolation, identification, and
serotyping of *Shigella* species were performed according
to the standard procedures.

**Antimicrobial Agents**

Nine antimicrobial agents including SXT, ampicillin,
cephalothin, ceftriaxone, ceftizoxime, chloramphenicol,
nalidixic acid, ciprofloxacin, gentamycin were obtained
from Patan Tab Company, Iran.

**Susceptibility testing methods**

Susceptibility test was done by the disk diffusion
method (Kirby-Bauer). The results were presented
by a descriptive analysis.

**RESULTS**

The prevalence of shigellosis in patients with
acute diarrhea was reported as 7.6 percent (56 of 734),
with 34 (60.7%) of the isolates belonging to *Shigella*
flexneri, 8 (14.3%) belonging to *S. dysenteriae*, and
14 (25%) belonging to *S. boydii*. The results show
that all of *Shigella* were susceptible to ciprofloxacin,
gentamycin, ceftizoxime, and were mostly resistant to
cephalothin (78.6%) and SXT (58.9%) (Table 1).

The antimicrobial resistance phenotypes of
*Shigella* included a resistance to two antibiotics
(cephalothin and SXT) in 35 (62.21%), a resistance to
three antibiotics (cephalothin, SXT, and ampicillin) in 9
(61.1%), and a resistance to four antibiotics (cephalothin,
SXT, ampicillin, and chloramphenicol) in 4 (7.1%) isolates.

All eight isolates of *S. dysenteriae* were susceptible to all nine antibiotics tested. Of 34 *S. flexneri*, 27 (79.2%) were resistant to two antibiotics (cephalothin and SXT), 3 (8.8%) to three antibiotics (cephalothin, SXT, and ampicillin), 4 (11.8%) to four antibiotics (cephalothin, SXT, ampicillin, and chloramphenicol). Of 14 *S. boydii*, 8 (57.1%) were resistant to two antibiotics, 6 (42.9%) were resistant to three antibiotics (Table 2).

**DISCUSSION**

In our study, the prevalence of shigellosis was 7.6 percent, and the frequently isolated species were *S. flexneri* (60.7%), followed by *S. dysenteriae* (14.3%), and *S. boydii* (25%). Multidrug-resistant (MDR) *Shigella* has been reported in several parts of the world. Our study also demonstrates a high prevalence of *Shigella* with resistance to the first-line therapeutic agents including cephalothin, SXT, and ampicillin, as reported in Bulgaria, the United States, Canada, and in several other countries. Shahid and colleagues as well as Tauxe and colleague have found that an increased resistance to SXT is directly related to an extensive use of this drug. In Iran, SXT is frequently prescribed as an empirical therapy for shigellosis and other diarrhea of suspected bacterial origin. It is probable that its extensive use would lead

### Table 1. Antimicrobial susceptibility results of all 56 isolates of *Shigella*.

<table>
<thead>
<tr>
<th>Antimicrobial agents</th>
<th>Total (%) of <em>S. dysenteriae</em> (N=8)</th>
<th>Total (%) of <em>S. flexneri</em> (N=34)</th>
<th>Total (%) of <em>S. boydii</em> (N=14)</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciprofloxacin</td>
<td>8 (100)</td>
<td>34 (100)</td>
<td>14 (100)</td>
<td>56 (100)</td>
</tr>
<tr>
<td>Cephalothin</td>
<td>8 (100)</td>
<td>4 (11.8)</td>
<td>-</td>
<td>12 (21.4)</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>8 (100)</td>
<td>34 (100)</td>
<td>14 (100)</td>
<td>56 (100)</td>
</tr>
<tr>
<td>Nalidixic acid</td>
<td>8 (100)</td>
<td>32 (94.1)</td>
<td>14 (100)</td>
<td>96.4 (54)</td>
</tr>
<tr>
<td>Ceftizoxim</td>
<td>8 (100)</td>
<td>34 (100)</td>
<td>14 (100)</td>
<td>56 (100)</td>
</tr>
<tr>
<td>Sulfamethoxazole-trimethoprim</td>
<td>8 (100)</td>
<td>4 (11.8)</td>
<td>11 (78.6)</td>
<td>23 (41.1)</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>8 (100)</td>
<td>26 (76.5)</td>
<td>14 (100)</td>
<td>48 (85.7)</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>8 (100)</td>
<td>25 (73.5)</td>
<td>-</td>
<td>33 (58.9)</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>8 (100)</td>
<td>34 (100)</td>
<td>11 (78.6)</td>
<td>53 (94.6)</td>
</tr>
</tbody>
</table>

### Table 2. Number of resistant frequency of multidrug resistance according to the species of *Shigella*.

<table>
<thead>
<tr>
<th>Antimicrobial agents</th>
<th>Total (%)</th>
<th><em>S. dysenteriae</em> N (%)</th>
<th><em>S. flexneri</em> N (%)</th>
<th><em>S. boydii</em> N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>8 (14.3)</td>
<td>8 (100)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>35 (62.5)</td>
<td>0</td>
<td>27 (79.2)</td>
<td>8 (57.1)</td>
</tr>
<tr>
<td>3</td>
<td>9 (16.1)</td>
<td>0</td>
<td>3 (8.8)</td>
<td>6 (42.9)</td>
</tr>
<tr>
<td>4</td>
<td>4 (7.1)</td>
<td>0</td>
<td>4 (11.8)</td>
<td>0</td>
</tr>
</tbody>
</table>
the emergence of resistant *Shigella* in our hospital. A study in Caracas reported that 86 percent of *Shigella* isolated from patients with diarrhea in two health care centers, were resistant to SXT.\(^{14}\) This finding is in accordance with our study.

It is important to note that the resistance to ampicillin among *Shigella* has grown steadily over the past 25 years, along with an indiscriminate use of this drug.\(^{2,5,6,11}\) Indeed, 38.9 percent of the total isolates of *Shigella* in our study were resistant to ampicillin, which in accordance with a study of Flores and coleaguses.\(^{16}\) The high resistance rates of *Shigella* to cephalothin, SXT, and ampicillin are shown in our study, in accordance with others sties in Iran.\(^{17,18}\) No resistance to nalidixic acid among *Shigella* was observed in our study, and its use in controlled clinical trials has been shown to be effective against shigellosis, mainly in terms of clinical response. Nalidixic acid is not readily available in Kashan, Iran and is thus used occasionally in clinical practice. Its use should be promoted, rather than SXT or ampicillin, as the first-line agent for the empirical treatment of patients with suspected shigellosis. All *Shigella* isolates in our study were susceptible to ciprofloxacin, a 4-fluoroquinolone. Other studies have confirmed an excellent in vitro activity of 4-fluoroquinolone against Shigella.\(^{5,13,16,17,19,20}\) It has been recommended as an alternative therapeutic choice for pediatric patients with shigellosis, because all quinolones are contraindicated due to their potential chondrotoxicity.\(^{5,14}\) The broad-spectrum of cephalosporin may be another therapeutic option. It has recently been suggested that ceftriaxone may be used in children with *Shigella* dysentery.\(^{21}\) Varson and colleagues compiled the results from eleven studies which demonstrated that ceftriaxone was active against more than 500 *Shigella* isolates tested worldwide.\(^{22}\) The results obtained in our study indicated that ceftriaxone is very active in vitro against Shigella.

MDR strains of *Shigella* are now considered a public health problem,\(^{6,7,10,22}\) and the results obtained in our study support this statement. According to the susceptibility of *Shigella* isolated in our community, it is clear that cephalothin, SXT, and ampicillin are not good choice for the empirical treatment. Physicians should be aware of the increasing antimicrobial resistance of *Shigella*. Because the resistance patterns vary according to the specific location, routine antimicrobial resistance monitoring is mandatory and thus becomes an essential part of any diarrhea control program that advocates empirical antimicrobial therapy.

We conclude that MDR strains of *Shigella* are circulating in Kashan, Iran. We emphasize the importance of keeping these strains under surveillance in order to evaluate the local susceptibility patterns. At the same time, the empirical antibiotic treatment for patients with suspected shigellosis should be changed accordingly.

**ACKNOWLEDGEMENT**

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