Increasing resistance to nalidixic acid in *Shigella* subgroups in a comparative study between 2001–2003 and 2004–2006

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ABSTRACT

Introduction: The *Shigella* spp. is an organism with an ongoing changing resistance pattern to different antibiotics, thus making its appropriate treatment difficult. Nalidixic acid has been one of the most common agents used for the treatment of shigellosis. Recently, some studies have reported an emerging resistance to this agent.

Methods: In this study, we compared the resistance of *Shigella* isolates during the period 2001–2003 with the period 2004–2006.

Results: *Shigella* spp. resistance was increased totally and in each subgroup, except for *Shigella sonnei*.

Conclusion: Our results showed an increasing resistance of the *Shigella* spp., thus identifying an emergent need for an alternative agent for the treatment of shigellosis in future.

Keywords: antimicrobial resistance, dysentery, nalidixic acid, *Shigella* spp., shigellosis

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INTRODUCTION

Shigellosis is one of the most common causes of dysentery in children, leading to significant mortality and morbidity. Knowing the antimicrobial resistance patterns of the *Shigella* spp. will enable appropriate treatment to be possible, leading to a decrease in the duration, severity and transmission of the disease. However, resistance and sensitivity patterns of *Shigella* subgroups change over time. Therefore, some of the antimicrobial agents that once were the best choice of treatment have lost their efficacy over time. Nalidixic acid is a member of fluoroquinolones that was frequently used in the treatment of shigellosis in the past, especially in children. Unfortunately, some studies have reported a growing resistance to this antibiotic recently.[1-9] In this study, we compared the resistance and sensitivity of the *Shigella* spp. and its subgroups to nalidixic acid at the Tehran Paediatrics Centre, a referral paediatrics hospital, between two periods, 2001–2003 and 2004–2006.

Table I. Prevalence of *Shigella* subgroups during the periods, 2001–2003 and 2004–2006.

Shigella subgroups	No. (%) in 2001–2003	No. (%) in 2004–2006
Shigella flexneri	88 (49.7)	38 (26.2)
Shigella sonnei	69 (39.0)	101 (69.7)
Shigella dysenteriae	15 (8.5)	4 (2.8)
Shigella boydii	5 (2.8)	2 (1.4)
Total	177 (100)	145 (100)

METHODS

From the 7,200 stool samples submitted to the Microbiology Laboratory of Tehran Paediatrics Centre, Iran, 322 *Shigella* isolates were identified, 177 isolates from March 2001 to February 2003, and 145 isolates from March 2004 to February 2006. Only one *Shigella* isolate per patient per diarrhoeal episode was included in the analysis. All stool samples were obtained from children under 12 years of age. Samples were inoculated on *Salmonella-Shigella* (SS) agar and eosin methylene blue agar, and incubated at 37°C for 1–5 days. The serotypes of all *Shigella* isolates were determined with commercially-variable polyclonal antisera against all *Shigella* serotypes. The *Shigella* strains were subcultured on McConkey agar plates, and serological tests were performed by the slide agglutination method. The susceptibilities of all isolates to different antibiotics were determined by the disc diffusion method, as recommended by the Clinical and Laboratory Standards Institute (formerly the National Committee for Clinical Laboratory Standards), with commercial antimicrobial discs. The antibiotic discs used in this study was nalidixic acid.[10,11] Results was interpreted as either sensitive, intermediate or resistant. In our study,

Table II. *Shigella* subgroups susceptibility pattern during the periods, 2001–2003 and 2004–2006.

Shigella subgroups	Prevalence in 2001–2003 (%)		Prevalence in 2004–2006 (%)	
	Sensitive	Resistant	Sensitive	Resistant
Shigella flexneri	89.9	10.1	86.9	13.1
Shigella sonnei	76.9	23.1	84.4	15.6
Shigella dysenteriae	81.3	18.8	75	25
Shigella boydii	100	0	50	50

we considered both intermediate and resistant results as resistant.

RESULTS

Among *Shigella* isolates obtained in 2001–2003, the most common subgroup was *Shigella* (*S.*) *flexneri* (49.7%, followed by *S. sonnei* (39.0%), *S. dysenteriae* (8.5%) and *S. boydii* (2.8%). In 2004–2006, the most prevalent subgroup was *S. sonnei* (69.7%), followed by *S. flexneri* (26.2%), *S. dysenteriae* (2.8%) and *S. boydii* (1.4%)(Table I). *Shigella* subgroups in 2001–2003 were 86.2% sensitive and 13.8% resistant to nalidixic acid, compared to results in 2004–2006 which was 84.5% and 15.5% for sensitivity and resistance, respectively. Susceptibility patterns according to each subgroup are shown in Table II.

DISCUSSION

Nalidixic acid has been one of the most appropriate antibiotics in the treatment of shigellosis for years because of its cost-effectiveness and accessibility. But antimicrobial therapy against shigellosis has become very limited because of its changing resistance pattern. Agents such as ampicillin, chloramphenicol and bactrim, which once were the choice for treatment of shigellosis, have lost their efficacy. Recently some degrees of resistance of *Shigella* subgroups to nalidixic acid have been reported from various parts of the world, especially in this region, indicating that these antibiotics is going to lose its effectiveness.[1-6,8,9,11] In one study on 184 *S. sonnei* isolates in Bangladesh, more than 60% of the strains were resistant to nalidixic acid.[2] In another study on *Shigella* serogroups in Iran, the total resistance of *Shigella* spp. to nalidixic acid was 4.87% (4.91% for *S. sonnei* and 6.25% for *S. flexneri*).[11] In our study, by comparing the susceptibility during two periods, 2001–2003 and 2004–2006, we showed that the sensitivity of the *Shigella* subgroups had decreased from 86.2% to 84.5%, and the resistance rate had increased from 13.8% to 15.5%, although this pattern was not similar among all subgroups, where *S. sonnei* sensitivity had increased.

Although our results were not statistically significant, it corroborated with other studies. In one Korean study, resistance to nalidixic acid showed a significant increase from 6% of the isolates obtained during the period 1980–1986 to 86% of the isolates obtained during the period 1998–2000.[4] In some other studies, resistance to nalidixic acid has been reported to be 60%–70%.[2,4] In another study, oral nalidixic acid failed clinically in 35% and microbiologically in 28.4% of 14 children, as compared with no clinical and microbiological failure in 25 children who were treated with oral azithromycin.[5] In a few studies, *S. sonnei* was the most common subgroup mentioned as being resistant to nalidixic acid.[2,4,7] Resistance to nalidixic acid first appeared in an *S. sonnei* isolate in 1997, and then in all *S. sonnei* isolates from 1998 to 1999. In the Korean study, 138 *S. sonnei* isolates were analysed in which nalidixic acid resistance was found in 86% of the isolates.[4] Significant nalidixic acid-resistant *S. dysenteriae* has been reported in some studies.[6,9,12] In our study, *S. dysenteria* and *S. boydii* showed the most change in the sensitivity pattern, although the changes were not statistically significant. However, we showed that the resistance rate of *Shigella* isolates is increasing in this region. Hence, resistance to nalidixic acid should be taken into account as a problem for the treatment of shigellosis in the near future. Another probable good option for treatment of shigellosis would be azithromycin, which has been reported in some studies as an alternative therapy.[5] Further investigation is required in this field.

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