Antibiotic Resistance in Children with Bloody Diarrhea

Abdolkarim Hamedi*

Department of Pediatrics, School of Medicine, Imam Reza Hospital, Mashhad University of Medical Science, Mashhad, Iran

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Abstract- Shigellosis is an important public health problem, especially in developing countries. Antibiotic treatment of bacterial dysentery, aimed at resolving diarrhea or reducing its duration is especially indicated whenever malnutrition is present. First-line drugs include ampicillin and trimethoprim sulfamethoxazole(TMP-SMX); however multidrug-resistance has occurred and careful antibiotic selection must be considered in prescribing .When epidemiologic data indicate a rise in resistancy, fluoroquinolones may be used in adults and oral third-generation cephalosporins and nalidixic acid in children. All children (n=2400) with acute diarrhea who were admitted to the Pediatric department of Dr.sheykh Hospital Mashhad, Iran from March 2004 to March 2005 were selected and their stool culture were obtained, then positive cultures (312 cases,13%) were evaluated by antibiogram. This study showed that in heavily populated areas of IRAN like Mashhad, 97% shigella strain isolated from children with bloody diarrhea were sensitive to nalidixic acid, ciprofloxacin and cefixime and rarely susceptible to ampicillin and cotrimoxazole. There is increasing resistance of Shigella to most of the antibiotics in use, and for this reason, careful selection of antibiotics must use considered in each area. Development and use of new drugs are expensive and have severe limitations in the third world. Simple prophylactic alternatives are therefore, required, such as awareness of hygienic child care practices and early promotion of breast feeding. For treatment of shigellosis in infants Ceftriaxon, and in children Nalidixic Acid is recommended.

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Key words: Shigellosis, diarrhea, stool

Introduction

When penicillin was first developed in the 1940s, it was hailed as a miracle drug. However, increasing drug resistance has compromised the strength of penicillin and other antibiotics, the issue of escalating antibiotic resistance is considered to be one of the major public health threats of the 21st century (1). Furthermore, in 2001the National Antimicrobial Resistance Monitoring System (NARMS) found that drug-resistance was increasing (1). Two reasons for this observed increase were that the percentage of infections caused by resistant strains increased(2) and the number of drugs to which organisms are becoming resistant are increasing. Also NARMAS reported that 80% of Shigella isolates were resistant to ampicillin, in comparison to 78% in 1999 (2).
For this reason, careful consideration is needed in deciding when and which antibiotics to prescribe.

Shigella causes a broad spectrum of gastrointestinal illness, ranging from mild diarrhea to life-threatening dysentery. Severe complications are relatively common and include intestinal perforation, mega colon, septic shock, hemolytic-uremic syndrome, profound dehydration, hypoglycemia, hyponatremia, seizures, and encephalopathy (3). Shigella is spread rapidly person-to-person through fecal-oral and oral-anal contacts as well as indirectly through houseflies and contaminated fomites In developing countries. Shigellosis is a common childhood disease. Worldwide, it is estimated that Shigella causes greater than 650,000 deaths per year (4).

Antibiotic treatment is always indicated for Shigella infections. Antibiotic therapy for shigellosis has envolved since the 1960s as Shigella infections have become resistant to the drugs of choice from each era (5). Shigella spp. are a major cause of acute dysentery in children. Most severe infections require treatment with antibiotics, which leads to over use and misuse of many of the drugs. Knowledge is insufficient in Iran regarding the development of resistant strains to antibiotics. The aim of the present study was to determine the resistance of Shigella to fourteen antibiotics, including: Tetracyclin, Cotrimoxazol Amoxicilin, Ampicilin, Cephalexin

***Corresponding Author:** Abdolkarim Hamedi
Department of Pediatric, Imam Reza Hospital, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
Tel: +98 511 7615640, E-mail: AB-hamedi@mums.ac.ir

Kanamicin, Neomicin, Nitrofurantoin, Amikacin, Choloramphenicol, Gentamicin, Ciprofloxacin, Cefixime and Nalidixic acid, in stools of hospitalized children with bloody diarrhea.

Patients and Methods

All children (n=2400) with acute diarrhea who were admitted to the Dr. Sheykh Pediatrics Hospital of Mashhad University of Medical Science, Mashhad, Iran, from March 2004 to March 2005 were selected and their stool culturs were obtained. Their ages ranged from 1 month to 12 years and duration of bloody diarrhea was reported to be 1-3 days. Stool samples collected by rectal swabs were placed in standard Stuart's transport medium. Parental consent was obtained for collection of stool samples.

Cultivation of enteropathogens

Cultivation was carried out for the isolation of Shigella spp. on deoxycholate citrate agar (Oxoid, Unipath Ltd., Basingstoke, United Kingdom) incubated at 37-8C for 18-24 hr. Prior to cultivation on brilliant green agar (Oxoid, Unipath) for the isolation of Salmonella, enrichment was provided in Rappaport broth (Merck, Darmstadt, Germany) for 24 hr. Brilliant green agar plates were incubated at 37-8C for 48 hr (5). Blood-free selective (BFS) medium was used.

Identification of isolates

Identification was done by biochemical and serologic tests for Shigella and Salmonella. The following biochemical media and tests were used:

Kligler's Iron agar slants, motility-indole-urea-agar, Koser citrateagar, phenylalanine agar, and fermentation of sugars. Shigella isolates were serologically grouped by a slide agglutination test using commercially available polyvalent O antisera for S.dysenteriae,S.flexneri,S. boydii, and S. sonnei (Burroughs WellcomeCo., Research Triangle Park, NC), Sensitivity of Shigella spp. to ampicillin, cotrimoxazole,and nalidixic acid and etc was performed using the KirbyBauer disk diffusion method. Broth cultures (4-5 hr) of Shigella isolates were plated on Mueller Hinton agar, commercial antibiotic disks (BBL, Cockeysville, MD) were applied, and the zone of inhibition was measured after 24 hr of incubation at 37 degree C.

Results

Of 2400 admitted children with diarrhea, 312 cases (13%) had positive culture for some of the micro organisms. In this study the most common bacteria that cultured was the specious of shigella 98 cases (31.4%).The most rare organism was camplibacter jejuni.2-5 years old babies were the more with positive stool culture for shigella. 90 cases with positive culture for shigellosis had bloody diarrhea (91.8%).

Different type of shigella (98 cases) cultured follow for antibiograme. Regarding the species distribution of Shigella strains, S. flexneri 68(69.3%) was more frequent than S. dysenteriae 10(10.2%), S. boydii 3(3.06%), and S. sonnei 7(7.1%) and unknown10 (10.2%) the rate of sensetivity in different antibiotics is follow. Nalidixidacid, ciprofloxacin, cefixime (97%) gentamicin (81%) chloramphenicol (42%) Amikacin (40%), nitrofourantoin (39%) neomycin (29%), kanamycin (26%) Cephalexin (23%) ampicillin (17%) amoxicillin (14%), co-trimoxazole (12%). The most resistency rates in antibiotics were in Tetracyclin (93%) and Co-trimoxazole (88%).

Tabels 1. Shigella sensitivity&resistency with different antibiotics

Antibiotic	Sensitivity percentage	Resistency Percentage
Tetracyclin	7	93
Co-trimoxazole	12	88
Amoxicillin	14	86
Ampicillin	17	83
Cephalexin	23	77
Amikacin	40	60
Choloramphenicol	42	58
Gentamicin	81	19
Ciprofluxacin	97	3
Cefixime	97	3
Nalidixic acid	97	3

Table 2. Ditribution of shigella typing in study

Shigella type	Number	Percentage
Flexeneri	67	68.3
Dysentric	11	11.2
Sonei	7	7.1
Boydi	3	3.06
Unknown	10	10.2
Total	98	100

Table 3. Distribution of patients (shigellosis) on age

Age	Number	Percentage
<1 years	1	1.02
1-2 years	5	5.1
>2 years	92	93.8

Shigellosis in infancy is very rare (1-24 months)

Table 4. Distribution of patients (shigellosis) on sex

Sex	Number	%
Male	42	42.8
Female	56	57.1

Discussion

Shigellosis is an important public health problem, especially in developing countries (5). Isolates with resistance to first line drugs have been reported throughout the world (6), third generation cephalosporin's and quinolones are mainstays of treatment (7). Shigella flexneri resistant to third generation cephalosporins in a clinical isolate is a rare finding, and this has been reported for the first time in Pakistan (8). Determined for 2491 Shigella isolates cultured in the medical laboratory of the Centre Hospitalized de Kigali, Rwanda, during 1983 to 1993. Overall, Shigella flexneri was the most frequent species, ranking before Shigella sonnei, Shigella boydii, and Shigella dysenteries (9). However, the relative frequency of the different Shigella spp. showed an important variability over time. S flexneri increased from 40% in 1983 to 68% of the isolates in 1993 whereas S. dysenteries Type decreased gradually from 30 to 0.5% of the isolates in 1992.

Antibiotic resistance makes some serious diseases and very difficult to treat, and new resistant strains emerge each year. Drug resistance and enteric infections food borne illnesses are estimated to cause approximately 76 million illnesses, 325,000 hospitalizations, and 5,000 deaths per year in the United States. Of these, bacterial enteric pathogens are estimated to cause about 6.5% of illnesses, 14% of hospitalizations, and 29% of deaths (6).Antimicrobial resistant infections are even more problematic because they increase the number of infections. The duration of disease treatment failure, the number of hospitalizations, and the number of deaths. Antibiotics are not recommended for treating all illnesses, but are used to prevent complications in people most at risk for serious disease (e.g. infants, persons with weakened immune systems, elderly). Antibiotics may be life-saving for thousands of people each year who have serious invasive infections, such as shigellosis.

Health experts are particularly concerned about antibiotic resistance in bacteria that cause certain serious infections and new resistant strains the epidemiology and antibiotic susceptibility of Shigella species changes over time. Updated susceptibility knowledge is necessary for appropriate empirical antibiotic treatment. Two hundreds and three Shigella strains, isolated from stool samples of diarrheic patients at the Central Health Laboratory in Sana'a, Yemen in 2 time periods (1993 and 2003) with a 10-year interval, were examined for stereotyping and drug resistance pattern (6). Resistance patterns of the strains to 12 commonly used antimicrobial agents and minimum inhibitory concentrations of the antibiotics were tested (10). Shigella flexneri (60%) was found to be the most common isolate of the total Shigella species, followed by Shigella dysenteriae (28.6%) and Shigella boydii (11.3%). In Shigella flexneri strains, Shigella flexneri 3 (30.5%) was the most prevalent serotype, followed by Shigella flexneri 6 (17.2%), and Shigella flexneri 1 (12.3%). All strains were found equally susceptible to cefotaxime, ceftriaxone, ciprofloxacin, and gentamicin, but more than 80% of the strains of 2003 were resistant to tetracycline, co-trimoxazole, and 52% of the same strains were resistant to ampicillin. Resistance to chloramphenicol was found in 61%, cefuroxime in 56.2%, and cephradine, 52% of the strains. Overall, Shigella species showed statistically significant increase in resistance against tetracycline, cephradine, trimethoprim/sulfamethoxazole, nalidixic acid, and aztreonam ($P<0.05$) over the 10 years period (11). This indicates decreased efficacy of co-trimoxazole and nalidixic acid for the empirical treatment of shigellosis in Sana'a, Yemen (6) most 55.2% of the strains were resistant to 4 drugs. In Karachi Out of 4688 stool samples received, 193 (4.1%) were positive for Shigella species. Shigella flexneri was the predominant serogroup (58%) followed by Shigella sonnei (16%), Shigella boydii (15%) and Shigella dysentriae being the least common11% (12). In one study from Tehran shigella was isolated frequently from children under 5 years of age, who were accounted for 55/7% of all isolates (13).

In the present study, 97% shigella strain isolated from children with bloody diarrhea were sensitive to nalidixic acid, ciprofloxacin and cefixime and rarely susceptible to ampicillin and cotrimoxazole, and others antibiotics.Recently resistance to cefixime to be increasing.

There is no suitable vaccine for the control of shigellosis and campylobacteriosis, despite many years of interest and research. Community outbreaks of shigellosis end when an appreciable percentage of high-risk hosts develop protective antibodies. If the safety and efficacy of Shigella vaccines can be established, their use in high-risk groups may be effective in preventing and controlling morbidity and mortality due to severe diarrhea in children.

In heavily populated areas of IRAN similar Mashhad, there is increasing resistance of shigella to

most of the antibiotics in use and for this reason select appropriate antibiotics must be considered in each area. Development and use of new drugs are expensive and have severe limitations in the third world. Simple prophylactic alternatives are therefore, required, such as awareness of hygienic child care practices and early promotion of breastfeed. For treatment shigellosis in infants Ceftriaxon,and in children Nalidixic Acid recommended. Conclusion: this is one of the first studies reporting an epidemiological pattern of Shigella species in Iran Mashhad with regard to serotypes and antibiotic resistance patterns. Based on these antibiotic resistance pattern findings, it is suggested that the commonly in use antibiotics including ampicillin, trimethoprim/ sulfamethoxazole, tetracycline, and chloramphenicol should not be used for empirical treatment of shigellosis.

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