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Antibiotic profiles of *Shigella* and emergence of resistance: An editorial perspective

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This recently reported Health Alert as issued by the CDC informs of an extensively drug resistant Shigella (XDR). This is of serious concern because there exist limited treatment options and the resistance genes can spread to other enteric bacteria. I provide a summary of the CDC alert which is followed by an historical document from 2009 that details the struggles even then to provide the best care when choosing antimicrobial therapy.

It is interesting to note that in previous studies on Type III secretion systems with attributable virulence, the virulence factors were carried in both animal and plant genomes; the hrpn genes in the plant pathogen Erwinia were found in Shigella strains in addition to the IpaSip genes (on plasmids) carried by Salmonella and Shigella (data not shown). Genes encoding Type III secretion systems are clustered and homologous areas within the clusters can be targeted. In some the gene clusters are located on plasmids unique to the pathogen and not found in relatives. In other pathogens, the Type III clusters are located on the chromosome and appear to have been acquired during evolution by evidence that related nonpathogenic bacteria lack the pathogenesis island but share corresponding adjacent sequences. This is merely one example of the complexities of gene carriage of virulence factors.

Plasmid transfer among enteric bacteria in the gut has contributed in unlimited measure to the production of ESBL (extended spectrum beta lactamase) production in enteric bacteria and continues to transfer resistance to beta lactam engineered next generation antimicrobials. It is difficult to predict how quickly resistance can gather momentum among bacterial populations. We need to be fastidiously aware of the microbes' efficiency around survival in the presence of offending antimicrobials and especially cognizant of plasmid to chromosomal carriage.

Increase in extensively Drug-resistant shigellosis in the United States

Distributed via the CDC Health Alert Network

February 24, 2023, 11:30 AM ET

CDCHAN-00486

Summary

"The Centers for Disease Control and Prevention (CDC) has been monitoring an increase in extensively drug-resistant (XDR) *Shigella* infections (shigellosis) reported through national surveillance systems*. In 2022, about 5% of *Shigella* infections reported to CDC were caused by XDR strains, compared with 0% in 2015. Clinicians treating patients infected with XDR strains have limited antimicrobial treatment options. *Shigella* bacteria are easily transmissible. XDR *Shigella* strains can spread antimicrobial resistance genes to other enteric bacteria. Given these potentially serious public health concerns, CDC asks healthcare professionals to be vigilant about suspecting and reporting cases of XDR *Shigella* infection to their local or state health department and educating patients and communities at increased risk about prevention and transmission."

"In the United States, the percentage of *Shigella* infections caused by XDR strains reported to CDC increased from zero in 2015 to 5% in 2022 (Figure). Between January 1, 2015, and January 22, 2023, CDC received reports of 239 XDR *Shigella* isolates, with *Shigella sonnei* accounting for the largest percentage (66%) followed by *Shigella flexneri* (34%)*".

***CDC Health Alert Network-00486**

Retrospective look at resistance developing in real time

What follows is an unpublished article written for instructive purposes. It is presented here to illustrate that even with the awareness around the potential evolution of resistance, the choices were becoming more limited around the treatment of Shigella infections in children.

Retrospective antibiotic profiles of Shigella

Abstract

Between January 2008 and February 2009, the isolation rate of Shigella at St. Christopher's Hospital for Children increased from 0.37% for a 6-month period (Jan - June 2008) to 7.3% for the month of February 2009. This has provided us with the rare opportunity to assess the antimicrobial characteristics of Shigella in our local area. Tabulation of antimicrobial profiles of all isolates revealed that most were resistant to ampicillin (90%) and some (26%) were resistant to trimethoprim-sulfamethoxazole (SXT). All remained susceptible to ciprofloxacin, which, unfortunately, is not always useful for treatment in pediatric patients. Studies in countries where Shigella is endemic reflect emerging resistance to SXT, mecillinam, azithromycin, ceftriaxone, and cefixime. Studies performed at a 10-year interval in an endemic area, showed an increase in SXT resistance of 20% and an increase in nalidixic acid resistance (as a marker for ciprofloxacin resistance) of 32%.[1,2] Our new reporting scheme – SXT, ciprofloxacin (tested along with nalidixic acid as a screen for resistance), amoxicillin/clavulinate, and ceftriaxone - reflects the current trends, both locally and globally, in useful antimicrobial profiles for this organism.

Introduction

Shigellosis affects 165 million persons worldwide per year and causes 1.1 million deaths. Antimicrobial therapy limits the course of the illness and reduces its spread. Globally, Shigella is showing increasing resistance to useful antimicrobial agents. It is known that Shigella can be resistant to sulphonamides, tetracycline, ampicillin, SXT and nalidixic acid. More recently, resistance to mecillinam, azithromycin, ceftriaxone and cefixime has emerged in countries where the illness is endemic. These resistance patterns impose limitations on appropriate choices. Ciprofloxacin and amoxicillin/clavulinate remain viable alternatives (1,2). St. Christopher's Hospital for Children is experiencing an increase in the incidence of Shigella, reflective of spread throughout the Philadelphia region. The Shigella isolation rate from stools increased from 0.3% Jan-June 2008 to 7.3% in February 2009 at St Christopher's. The increase has not been traced to one source, but is attributed to person-to-person spread in close contact situations such as day care centers (3).

Objective

The objective in this presentation was to determine the antimicrobial profiles of the Shigella isolated at St. Christopher's Hospital for Children from January 2008 through February 2009 and to adjust our antimicrobial reporting scheme to better reflect resistance trends.

Patient population

Patients were seen in the Emergency Department at St. Christopher's between the ages of less than one and fourteen. Ten of the patients were admitted to the hospital for follow-up care and three were in the hospital with multiple diagnoses. Complications directly related to the virulence of their Shigella isolates included concomitant urinary tract infections with Shigella in two patients. The age by incidence of the children showed that most occurrences were in children between the ages of 1 and 6 years old, peaking between 2 and 5.

Frequency of isolation

Hospital-based studies, in most cases, reflect the levels of resistance that predominate in the community because Shigellosis is community acquired and cultures are taken on the day of admittance to the hospital.

Between January 2008 and February 2009, 50 Shigella species were isolated from 1945 stool specimens at St Christopher's. The graph below shows the comparative increase in incidence from January 2008 through February 2009. Between January and June 2008 only two Shigella isolates were recovered. From July 2008 through February 2009, 48 isolates were found with the highest concentration being in January and February of 2009. The incident increase went from 0.37% (Jan – Jun 2008) to 3.4% (July 2008 – Feb 2009) positive stool cultures for Shigella, with incidences in January (5.6%) and February (7.3%) being the highest.

Historically, the incidence of Shigella at St Christopher's has remained under 0.4% per year with the exception of the occasional outbreak. Since we continue to see an increase in the number of isolates, the antimicrobial profile needs to reflect current trends in efficacy.

Susceptibility profiles

Antibiotic susceptibilities reported at St. Christopher's include ampicillin, sulfamethoxazole/trimethoprim (SXT), and ciprofloxacin as recommended by the Clinical Laboratory Standards Institute (CLSI). (Ceftriaxone - reported but not released.) Although ciprofloxacin in the drug of choice with 100% *in vitro* susceptibility, it is not always recommended for use in pediatric patients.

Ninety percent of Shigella isolated showed resistance to ampicillin. Although 74% of the isolates at St Christopher's showed *in vitro* susceptibility to SXT, resistance to this antibiotic is emerging. It is interesting to note that in two cases of Shigellosis from St Christopher's, catheterized urine specimens grew *Shigella sonnei*, both resistant to SXT. Isolates from the stools of these two patients were also resistant to SXT. Ceftriaxone is not recommended for use in this infection due to its selective pressure in the evolution of beta-lactam resistance and the potential transfer of extended spectrum beta lactamase (ESBL) genes. A detailed breakdown of susceptibilities of St Christopher's isolates can be seen in Table 1.

Table 1 Shigella Susceptibilities St Christopher's Jan 2008 – Feb 2009

		S. sonnei	***S. flexneri***	***S. boydii***
MIC	Interpretation	n = 47	n = 2	n = 1
Amp ,<=2	S	1		1
Amp 4	S	3		
Amp 16	MS	1		
Amp >=32	R	42	2	
Cipro <=0.25	S	47	2	1
SXT <=1	S	25	1 (type6)	
SXT 2	S	11		
SXT >=16	R	11	1 (type 2)	
CAX	S	47	2	1

United States Data

In the United States, a 2006 review by the National Antimicrobial Resistance Monitoring System (NARMS) for Enteric Bacteria found evidence of large increases in resistance among all Shigella strains. Percent increases are listed below.[4]

- Ampicillin-resistant Shigella strains in the United States increased from 32% in 1986 to 67% in 1995 to 78% in 2002.
- SXT-resistant Shigella strains increased from 7% in 1986 to 35% in 1995 to 46% in 2002.
- One percent of *S. sonnei* and 2% of *S. flexneri* isolates were resistant to nalidixic acid as a ciprofloxacin resistance indicator, while one *S. flexneri* was resistant to ciprofloxacin in 2002.[4]

Global findings

Studies from areas in which Shigella is endemic reflect a transition in antibiotic use in the treatment of Shigella infections. Due to emergent resistance patterns, a limited few efficacious drugs remain available, based on *in vitro* susceptibilities. One such study was conducted in Chile by collaboration between several Chilean Universities and the Center for Vaccine Development, University of Maryland, Baltimore. It showed a spectrum of resistance to ampicillin (82%) and SXT (62%). Multi-resistance was described as resistance to three or more antibiotics and reached 51%. The most frequent multi-resistant pattern was resistance to ampicillin, SXT, chloramphenicol and tetracycline. All 155 isolates in this study showed *in vitro* susceptibility to nalidixic acid and to ciprofloxacin.[1]

In this Chilean study, isolates obtained between 1997 and 2001, showed increases in resistance to ampicillin and SXT and a decrease in resistance to amoxicillin /clavulinate (only 9% were resistant) when compared to previous isolates from 1995-1997.[1]

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In 2007, Johns Hopkins University and a medical facility in Bangladesh published information on the continued emergence of resistance in Shigella. They examined patterns of 266 isolates obtained during 2001 and 2002 and compared their susceptibility rates to isolates obtained in 1991 and 1992. In this more recent evaluation, resistance to nalidixic acid emerged. Rates of resistance to ampicillin, SXT and nalidixic acid increased to more than 50% in the isolates tested when compared to previous resistance rates in isolates from 1991 to 1992. Azithromycin resistance was observed for the first time in this study. Resistance to ceftriaxone and cefixime did not emerge (98% susceptible), but there remains some dispute about the clinical efficacy of cefixime in treating Shigellosis. Resistance rates to chloramphenicol and tetracycline remained high and unchanged when compared to previous data. Although *S. flexneri* is the most commonly isolated strain in countries other than the United States, and *S sonnei* is most commonly isolated in the U.S., resistance was seen in this study across all species (data not shown).

Cefixime was found to be effective in 78% of children with Shigellosis. Although no increase was seen in the MIC of ceftriaxone, ESBL-mediated TGC resistance was seen in Shigella in Bangladesh for the first time. R- plasmid-mediated resistance was transferable to *E. coli* K-12 and Shigella by conjugation. This suggests that ESBL could spread resistance to third-generation cephalosporins among Shigella and other enteric pathogens within communities. Two *S sonnei* resistant strains showed high-level resistance (>256 ug/mL) to ceftriaxone and the other Shigella species showed intermediate (24 ug/mL) resistance.[2]

It is not clear why Shigella exhibited high modal MIC's to azithromycin in Bangladesh. It is thought that the use of azithromycin for other infections, and the high carriage rate of Shigella in healthy individuals in Bangladesh, might contribute to the emergent resistance patterns.[2]

Although some physicians have chosen to use azithromycin in children, its efficacy and the emergence of resistance remain under investigation. It may be difficult to correlate *in vitro* resistance levels of Shigella to activity of this antibiotic in the bowel, since the intracellular concentration of azithromycin achieved in colonic cells and leukocytes exceeds serum concentrations by 100-fold. This concentration effect may be fatal for the bacteria regardless of the *in vitro* result. More studies are needed in this area to determine efficacy in the patient.[2]

Discussion and conclusions

Studies have shown that Shigella has developed resistance to many useful antibiotics on the global front, including mecillinam, azithromycin, ceftriaxone, and cefixime. Options for treatment are limited to fluoroquinolones in some countries. For the pediatric patient population, some physicians are choosing to use short courses of ciprofloxacin when appropriate.

S. sonnei shows 100% *in vitro* susceptibility to mecillinam globally and amoxicillin/clavulinate remains active against all species of Shigella. Ceftriaxone or cefixime remain viable alternatives, keeping in mind the risk for ESBL propagation.

At St. Christopher's Hospital for Children, several options still exist for treatment of Shigella. Seventy-four percent of our Shigella isolates showed susceptibility to SXT during this time period. Two patients had complicating urinary tract infections caused by *S sonnei* isolates that were resistant to SXT. Although Shigella is susceptible to ceftriaxone in high percentages, its use may potentate ESBL emergence. If ciprofloxacin is chosen for treatment, nalidixic acid should be tested to predict possible emergence of resistance to ciprofloxacin. Only 10% of the Shigella isolates during the time period showed susceptibility to ampicillin.

Keeping this evidence-based assessment in mind, our antimicrobial susceptibility reporting scheme for Shigella has changed in order to better reflect the current local trend in susceptibility patterns and the global emergence of resistance to a wider variety of antimicrobials, we have moved from (as recommended by CLSI)

Ampicillin, Ciprofloxacin, SXT, and (Ceftriaxone but hide) to SXT, Ciprofloxacin, Ceftriaxone, and Amoxicillin/Clavulinate.

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None.

Conflicts of interests

Author declare no conflict of interest..

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