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# Cephalosporin resistant *Shigella flexneri* from a clinical isolate - a rare finding

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### Abstract

Shigellosis is an important public health problem, especially in developing countries. Antibiotic treatment of dysentery aimed at resolving diarrhea or reducing its duration, and to prevent transmission to other close contacts. Isolates with resistance to first line drugs have been reported throughout world, third generation cephalosporins and quinolones are mainstay of treatment. *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.

### Introduction

Infection due to *Shigella* species is an important cause of diarrhea worldwide and is responsible for significant morbidity and mortality in the underdeveloped world including Pakistan.<sup>1,2</sup> Frequency of antibiotic resistance among *Shigella* species is on the rise like many other bacterial pathogens.<sup>3</sup> Resistance to drugs frequently used in enteric infections like ampicillin, tetracyclines, chloramphenicol and co-trimoxazole has been reported in *Shigella flexneri* and *sonnei*.<sup>4</sup>

Production of  $\beta$ -lactamase enzymes is primarily responsible for the development of resistance against  $\beta$ -lactam antibiotics. Presence of TEM-1, OXA-1 and OXA-3  $\beta$ -lactamase have been reported in *Shigella* spp. rendering resistance to all 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> generation cephalosporins.<sup>5-7</sup> In a recent publication, Fortineau et al reported a case of bloody diarrhea in an Algerian boy caused by *Shigella flexneri*, resistant to all  $\beta$ -lactam drugs, and the isolate expressed extended spectrum  $\beta$ -lactamase (ESBL) production. The isolate was found to be containing SHV2  $\beta$ -lactam gene.<sup>1</sup> A similar SHV-2  $\beta$ -lactamase producing strain of *Shigella dysenteriae* has been reported from India, which was resistant to 3<sup>rd</sup> generation cephalosporins as well as to oxacillin and oxyiminocephalosporins.<sup>5</sup>

Another case report of vulvovaginitis in a prepubertal child due to *Shigella flexneri* has been published, the organism was susceptible to Cefixime, Amoxicillin/clavulanic acid and Levofloxacin in vitro but the patient remained unresponsive to the treatment with cefixime and amoxicillin/clavulanic acid for 10 and 14 days respectively and eventually responded to prolonged therapy with Ciprofloxacin.<sup>6</sup>

We report a case of an old man admitted into the hospital with the diagnosis of stroke and volvulus, *Shigella flexneri* was isolated from his stool sample, and found to be resistant to all 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> generation cephalosporins susceptible only to fluoroquinolones and imipenem.

### Case History

A 73 years old male with a 10-15 years history of hypertension, ischemic heart disease and chronic obstructive pulmonary disease, suddenly developed tonic colonic seizures during an outpatient visit. The patient was admitted after initial management. Previous history revealed transient attacks of unconsciousness for which he had frequently been admitted to the hospital.

Investigations showed a right frontal hematoma on CT scan. Considering a primary diagnosis of meningoencephalitis, intravenous ceftriaxone and acyclovir were initiated. Abdominal distension associated with severe abdominal pain developed on the 2<sup>nd</sup> day of admission and an abdominal X-ray revealed a sigmoid volvulus. Volvulus was decompressed by urgent sigmoidoscopy and a rectal tube was inserted. The loose stool found in the gut was sent for detail report (D/R) and culture and sensitivity. The patient continued to pass loose stools from rectal tube with the frequency of 3-4 times a day and also developed low-grade fever.

Stool D/R reported presence of moderate pus cells. Stool cultures were set up on standard microbiological culture media and standard microbiological methods were followed for the isolation of diarrheal pathogens.

The organism isolated from stool culture was biochemically identified by Analytic profile index (API) 20E (bio Murex, France) serotyped by anti-sera supplied by Denka Seiken Co., Japan and found to be *Shigella flexneri* Co., Type-2. Anti-microbial susceptibility was determined using disc diffusion in accordance with NCCLS guidelines. The isolate was found resistant to ampicillin, chloramphenicol, ceftriaxone, cefixime, and susceptible to ofloxacin and imipenem. Minimum inhibitory concentration (MIC) was also determined for ceftriaxone by using E-strip (AB Biodisk, Sweden) which was 32  $\mu$ g, suggestive of intermediate resistance.

Extended spectrum  $\beta$ -lactamase (ESBL) production was detected by combined disc diffusion method applying cefotaxime (30  $\mu$ g) and cefotaxime plus clavulanate

(30 µg + 10 µg) discs according to NCCLS. Our isolate was negative for ESBL production.

Injection imipenem was commenced and clinical response was observed. Within 24 hours fever deffervescence and improvement in the frequency and consistency of stool was seen. Simultaneously, his abdominal discomfort was relieved and rectal tube was removed.

Though the patient improved promptly after initiation of imipenem, he remained hospitalized for his primary illness and was later discharged. No further incidence of abdominal symptoms occurred during his stay.

## Discussion

Like many other pathogens multiple antibiotic resistant Shigellae has been on the rise. In countries like Pakistan the impact can be serious, due to the acute nature of illness in an infected population, spread of resistance to other enteric pathogens and also due to the non-availability of efficient and structured healthcare facilities to the public.

Being a tertiary care center, the Aga Khan University receives around 4,300 stool samples per annum for culture and sensitivity testing per year, and the average isolation rate of stool pathogens is 17% with Shigella 11% of all. To our knowledge this is the first isolate of Shigella flexneri found resistant to ceftriaxone and cefixime in the country.

Presence of toxic mega colon has been reported with Shigella dysenteriae isolates due to presence of Shigga toxin.<sup>7</sup> Shigella flexneri have been reported to possess very potent shigella enterotoxins (SHET 1 and 2),<sup>8</sup> but production of shigga toxin has not been reported. An association of sigmoid volvulus with presence of Shigella flexneri could not be confirmed, as colonic tissue sample was not submitted for routine microbiological culture. The presence of multidrug resistant shigella in a patient without a previous history of diarrheal illness, but with a history of multiple hospital admissions and previous antibiotic exposure may be the cause of antimicrobial resistance. A long-term carrier state could not be ruled out in this case.

Most cases of shigella dysentery are self-limiting and usually an antibiotic treatment is not recommended but cases in extreme of ages or in compromised patients may need effective and early therapy. Presence of cephalosporin resistant shigella may pose a great problem in the future, due to prevalence of isolates resistant to Ampicillin, Chloramphenicol, Tetracyclines and Cotrimoxazole (MDR). Cephalosporins are antibiotics of choice for severe and hospitalized cases, particularly in children where quinolones are not considered as treatment options by most clinicians. Recent reports of ESBL producing and quinolone resistant shigella from different parts of the world make the situation bleaker with limited treatment options.<sup>9,10</sup>

Therefore, this report again reinforces the need of active and effective surveillance program as matter of utmost priority at national level to detect various MDR isolates. At the same time it would assist the development of effective strategies which are needed for the control plans.

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