

Multi Drug Resistant *Shigella flexneri* – An Emerging Threat to Community***Deepak Juyal, Vikrant Negi, Munesh Sharma, Neelam Sharma**

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ABSTRACT

Shigellosis remains to be a considerable public health problem in many parts of the world and is endemic in India. Among the different studies conducted across India the isolation rate of *Shigella* varies from 2-6%, with *Shigella flexneri* to be the most prevalent serogroup. Unlike other acute diarrheal illness that require adequate fluid replacement (oral or intravenous), shigellosis additionally needs antimicrobial therapy to curtail the duration of illness and to prevent transmission to the close contacts. But like many other bacterial pathogens the frequency of antibiotic resistance among *Shigella* species is on the rise, and emergence of multi drug resistance (MDR) *Shigella* is a growing concern globally. The third generation cephalosporins and the fluoroquinolones are the mainstay of treatment in MDR cases, however emergence of strains resistant to even these drugs have been reported worldwide and also from various parts of India. Additionally strains of *Shigella* spp. that produce extended spectrum β -lactamase (ESBL), conferring resistance to third generation cephalosporins have also been reported thus limiting the treatment options for clinicians.

We here report a case of 43 years old man suffering from diarrhea due to MDR strain of *Shigella flexneri* found resistant to all cephalosporins (1st, 2nd, and 3rd generation) and fluoroquinolones, susceptible only to meropenem, cefoperazone-sulbactam and piperacillin-tazobactam. Though the patient was treated successfully, but spread of such clones may pose a greater threat to the community and a comprehensive strategy for resistance control involving regulation of drug availability, antimicrobial drug quality assurance and discouraging antimicrobial abuse needs to be evolved.

Keywords: Ceftriaxone, diarrhea, ESBL, shigellosis

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INTRODUCTION

Shigellosis is an important public health problem in developing countries and is responsible for significant morbidity and mortality [1, 2]. About 125 million cases of *Shigella* infection occur annually in Asia, of which approximately 14000 are fatal [3]. *Shigella* infections can range from mild self limiting diarrhea to severe dysentery with frequent passage of blood and mucus, high fever, cramps, tenesmus and in rare cases bacteremia. Though oral rehydration is the principal means of management but antibacterial treatment may be necessary as the organism possess entero-invasive properties [1]. Prompt and appropriate therapy shortens the duration of clinical

symptoms and prevents the disease transmission to others. But like many other bacterial pathogens the frequency of antibiotic resistance among *Shigella* species is on the rise, and emergence of multi drug resistance (MDR) *Shigella* is a growing concern globally [4-6]. In severe shigellosis caused by MDR strain, ceftriaxone is an effective drug of choice, however recently the ceftriaxone resistant strains of *Shigella* species have also been reported thus limiting the treatment options for clinicians [1, 7].

We here report a case of 43 years old man suffering from diarrhea due to MDR strain of *Shigella flexneri* found resistant to all

cephalosporins (1st, 2nd, and 3rd generation) and fluoroquinolones, susceptible only to meropenem, cefoperazone-sulbactam and piperacillin-tazobactam. To the best of our knowledge this is the first case of ESBL positive MDR strain of *Shigella flexneri* reported from our hospital.

CASE REPORT

A 43 years old male was admitted to our hospital with the history of abdominal pain, vomiting, loose stools with mucus and fever since one week. He was referred to our tertiary care center from a peripheral hospital where he was treated for loose stools, but failed to respond to therapy for five days. He had a history of being hypertensive for last six years. On examination patient was febrile (39.2°C), blood pressure was 130/90mm of Hg and pulse rate was 98 beats/min. Abdomen was distended and firm without any organomegaly. His cardiovascular and respiratory system examination was unremarkable.

Laboratory investigations revealed hemoglobin; 11.9 gm/dl, total leukocyte count; 11400cells/mm³, differential leukocyte count; 79% polymorphs, 12% lymphocytes, 7% monocytes and 2% eosinophils, platelet count; 180000 cells/mm³, erythrocyte sedimentation rate; 45 mm in the first hour and random blood sugar; 130mg/dl. Kidney function and renal function tests were normal. Stool sample (for routine examination, culture and sensitivity) and two blood samples (for culture and sensitivity) were sent to microbiology laboratory.

On routine examination the stool guaiac test was positive, numerous fecal leukocytes

and red blood cells were seen per high power field. No ova, cyst and trophozoite were found. On the basis of this report a provisional diagnosis of acute febrile enterocolitis was made and patient was empirically started on ciprofloxacin 400 mg Q12H, metronidazole 500 mg Q8H and intravenous (IV) rehydration therapy. Stool culture was put up on Xylose lysine decarboxylase (XLD) media and selenite F enrichment broth from which subculture was done on Mac Conkey agar (MA) after six hours. The plates were incubated at 37°C for 24 hours, after which a heavy growth of, red colored colonies on XLD (figure 1a) and non lactose fermenting colonies on MA (figure 1b) were seen. Standard microbiological methods were followed for the isolation and identification of diarrheal pathogens. On the basis of battery of biochemical tests and serotyping by *Shigella* antisera (Denka Sieken, Japan), the organism isolated from stool culture was identified as *Shigella flexneri*. Antibiotic susceptibility was determined by Kirby-Bauer disc diffusion method in accordance with Clinical Laboratory Standards Institute (CLSI) guidelines [8]. The isolate was found resistant to ampicillin, cotrimoxazole, chloramphenicol, nalidixic acid, ciprofloxacin, ceftriaxone and was sensitive to meropenem, cefoperazone-sulbactam and piperacillin-tazobactam. Extended spectrum β -lactamase production (ESBL) production was detected by combined disc diffusion method applying ceftazidime (30 μ g) and ceftazidime plus clavulanate (30 μ g + 10 μ g) discs as per CLSI guidelines [8] and the isolate was found positive for ESBL production (**Figure 2**).

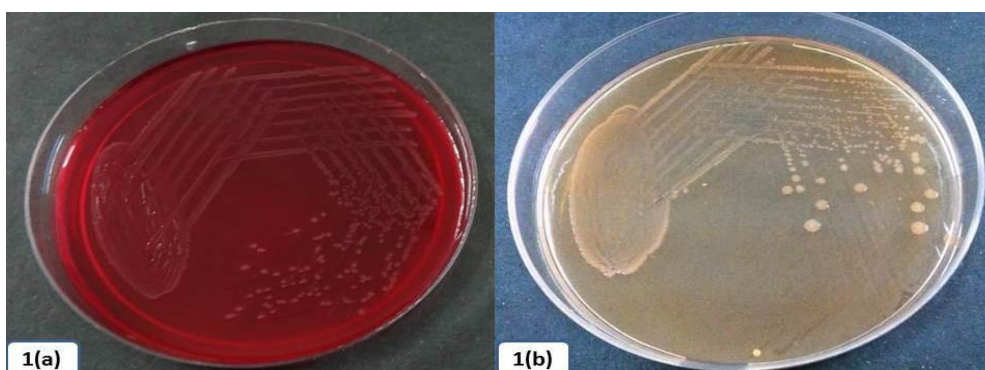


Figure 1: Growth of *Shigella flexneri* on (a) Xylose lysine decarboxylase agar showing red colored colonies; (b) Mac Conkey agar showing non lactose fermenting colonies

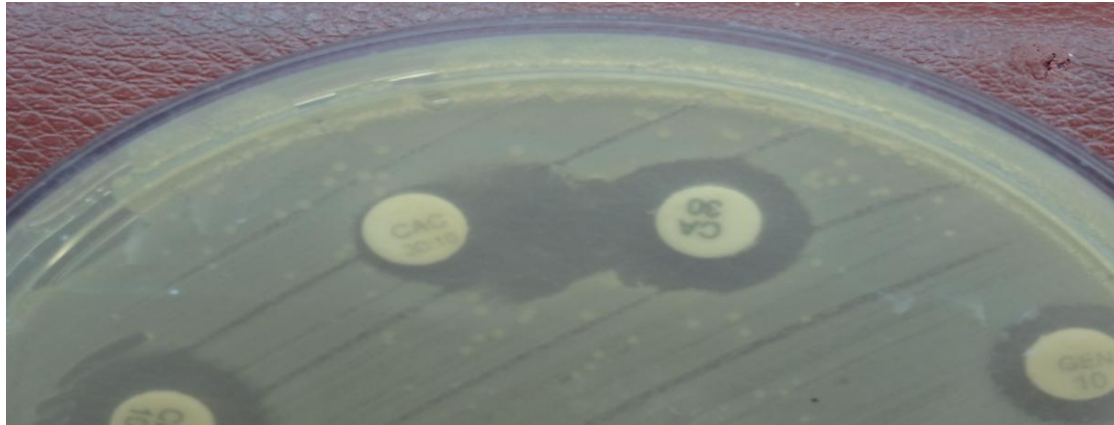


Figure 2: A positive double disc diffusion test for ESBL detection showing an increased zone of inhibition towards the clavulanic acid disc

By this time the patient did not showed any improvement and continued to pass loose stool with mucus. Considering the MDR status of the isolate and lack of clinical improvement, therapy was now changed to meropenem 1 g Q8H (IV) along with supportive measures. The patient showed remarkable clinical improvement and within 24 hours fever deffervescence, relief from abdominal discomfort and improvement in frequency and consistency of stool was seen. During all this time the blood culture of the patient remained negative. The patient showed complete recovery at the time of discharge and no further incidence of abdominal symptoms occurred during his stay.

DISCUSSION

Shigellosis remains to be a considerable public health problem in many parts of the world and is endemic in India. Among the different studies conducted across India the isolation rate of *Shigella* varies from 2-6% [1,5,6,9], with *Shigella flexneri* to be the most prevalent serogroup [1,9-11]. Unlike other acute diarrheal illness that require adequate fluid replacement (oral or intravenous), shigellosis additionally needs antimicrobial therapy to curtail the duration of illness and to prevent transmission to the close contacts. The World Health Organization (WHO) currently recommends ciprofloxacin (or other fluoroquinolones) to be considered as a first line antibiotic for the treatment of shigellosis and discourages the use of nalidixic acid even in the areas where it is still effective against *Shigella*. In addition

ceftriaxone, pivemecillinam (amdinocillin pivoxil) and azithromycin are considered as alternative drugs for treatment of shigellosis [12]. However similar to other pathogenic enteric bacteria, strains of *Shigella* spp. that are resistant to ciprofloxacin have been described [13]. Additionally strains of *Shigella* spp. that produce ESBL, conferring resistance to third generation cephalosporins have also been reported [2, 14].

The emergence of MDR strains of *Shigella* spp. over the last two decades clearly highlights the problem of MDR pathogenic enteric bacteria and makes the treatment selection more problematic. In India antimicrobial resistance in the genus *Shigella* is more common than in any other enteric bacteria [15]. The third generation cephalosporins and the fluoroquinolones are the mainstay of treatment in MDR cases, however emergence of strains resistant to even these drugs have been reported worldwide [2,14,17] and also from various parts of India [1,6,9,16].

Although the antimicrobial resistance is a well described phenomenon in the genus *Shigella* but diarrheal disease caused by an ESBL positive MDR Strain of *Shigella* spp. is still uncommon and to isolate such strain from a patient without any previous history of diarrheal illness or previous antibiotic exposure is a matter of concern. In the rural setting as of ours, the impact can be serious due to the acute nature of illness, possibility of the horizontal transfer of resistance to other enteric pathogens and due to the non availability of efficient and structured

healthcare facilities to the public. Though the patient was treated successfully, but spread of such clones may pose a greater threat to the community and make the situation bleaker with limited therapeutic options as many clinicians empirically prescribe fluoroquinolones or ceftriaxone (a third generation cephalosporin) for infections like diarrhea and urinary tract infections. To the best of our knowledge this is the first ESBL positive MDR strain of *Shigella flexneri* to be reported from our center.

CONCLUSION

Emergence of ESBL producing MDR *Shigella* spp. is a cause of great concern not only at local level but at regional level also, as it poses a therapeutic challenge for clinicians. This report emphasizes on reinforcement of active and effective surveillance program to detect various MDR isolates. Widespread selective pressure and efficient dissemination channels for MDR organisms are major factors that may contribute to the rapid emergence and spread of resistant organisms. A comprehensive strategy for resistance control involving regulation of drug availability, antimicrobial drug quality assurance and discouraging antimicrobial abuse needs to be evolved.

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