Death from Multi-resistant shigelloses: a case study from Fiji

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Abstract

Death from Shigellosis is rare in developed countries, however it causes over a million deaths in developing countries worldwide annually. Death from shigellosis is rare in Fiji.[2] However, the global problem of emerging multi-drug resistance raises some issues about the management of Shigellosis in this country. Within Fiji, Shigella is a notifiable disease .The Fiji Ministry of Health recorded 68 cases of Shigella in 1996, 173 cases in 1997 and 334 cases in 1998 (no data available for 1999).[2] There was only one recorded death during this time - in 1998. Resistance to chloramphenicol occurred in 82% of cases. Shigella flexneri in Fiji remains sensitive to cephalothin and cefaclor.

The current antibiotic guidelines in Fiji[9], recommend that antibiotics be used only for cases of moderate and severe dysentery. Shigellosis was suspected soon after presentation however the patient was unable to take oral antibiotics and was treated with intravenous antibiotics (chloramphenicol and ampicillin), which were ineffective due to resistance of the organism. The current antibiotic guidelines for severe dysentry recommend chloramphenicol or nalidixic acid – the later not available in Fiji. However the only intravenous drugs that retain their sensitivity to Shigella - ceftriaxone and cephalothin, are expensive ($F 45.00 per vial' of ceftdaxone) and these are only available in large regional hospitals. (PHD 2006 Vol 13 No 2 Pages 111 - 114)

Introduction

Death from Shigellosis is rare in developed countries, however it causes over a million deaths in developing countries worldwide annually. Sixty nine percent of the deaths occur in children under 5 years of age.[1] Death from Shigellosis is rare in Fiji.[2] However the global problem of emerging multi-drug resistance raises some issues about the management of Shigellosis in this country. This case highlights some of the chemotherapy-related difficulties encountered during the management of severe shigellosis in Fiji.

Case study

Mr M, a previously fit and well 32 year old male, was admitted to Sigatoka District Hospital with a one day history of sudden onset of diarrhea, fever, chills and rigors. He had passed approximately 10 greenish, watery, bloodstained stools in the 24 hours prior to admission, with no history of abdominal pain or vomiting. There were no known contacts with diarrheal disease.

On presentation he was restless, confused, and hypotensive (BP 70/50mmHg), his temperature was 37.8° C. A provisional diagnosis of dehydration secondary to Shigellosis was made and he was given intravenous IV fluids and commenced the antibiotics chlormphenicol and ampicillin each in the dose of 500 mgm IV 6 hourly. Mr M. became profoundly hypotensive and hypoglycaemic several hours' later and required further IV fluids. After 24hrs of hospitalization the patient remained restless and unresponsive to voices with a BP of 100/70.

He was transferred to Lautoka hospital on the second day of admission. Lautoka is a large regional teaching hospital approximately two hours drive from Sigatoka. Upon admission to Lautoka hospital he was severely dehydrated and in septicaemic shock with likely Shigella gastroenteritis. The IV fluids, chloramphenicol, and ampicillin were continued. During the evening of the day of admission to Lautoka hospital, the patient continued to deteriorate developing hypokalaemia. Intravenous ceftriaxone was commenced and the other antibiotics were stopped. He developed Disseminated Intravascular Coagulopathy (DIC) with thrombocytopaenia and prolonged prothrombin time and this was treated with fresh frozen plasma.

The next day the patient continued to deteriorate and required intubation, ventilation and inotropic support because of persisting hypotension. Intravenous flucloxacillin and metronidazole were added. The patient then developed Acute Respiratory Distress

Syndrome (ARDS) and remained persistently hypotensive (BP 71/35) despite inotropic support.

Mr M became asystolic and died on the fourth day after his original admission to Sigatoka hospital. Blood cultures remained negative for pathogens throughout his admissions and stool specimen culture results were only available after the patient had died. Stool culture was positive for Shigella flexneri. Sensitivities revealed multi-drug resistance to ampicillin and chloramphenicol although the organism was sensitive to ceftriaxone.

Discussion

Shigella is an aerobic gram-negative bacilli which causes diarrhoeal disease in endemic and epidemic forms in poor and crowded communities. Man is the only known reservoir, for infection, which is spread by person-to-person contact from asymptomatic excreters and via contaminated water or food. Four serotypes of Shigella are responsible for bacillary dysentery - Shigella dysenteriae, flexneri, boydii and sonnei. Dysenteriae and flexneri are responsible for most infections in the tropics and have a case fatality rate of up to 20%.[4]

Infected patients may be asymptomatic or present with a spectrum of symptoms, from mild watery diarrhoea to severe bloody dysentery with extra-intestinal manifestations. The dysentery is characterized by invasion of the colonic mucosa with local spread of the infecting organism and death of intestinal epithelial cells. Extra-intestinal complications can include seizures, hyponatraemia and hypoglycaemia, septicaemia Reiter's syndrome, encephalopathy and haemolytic uraemic syndrome. An endotoxin is likely to play an important role in the systemic manifestations.(Shiga toxin) and bacteraemia is rare.[3]

Diagnosis is difficult in areas with poor laboratory facilities, as clinically it is often confused with other bloody diarrheas such as amoebic dysentery or campylobacter.[4] Diagnosis can only be confirmed by culture and identification from faecal specimens or rectal swabs. There is a facility within Fiji to send specimens from outlying hospitals to one of the government laboratories on the main island though, in the case of Shigella, this tends to be only done if a major outbreak is suspected. Stool specimens take approximately two to four days to process. Antibiotics are known to shorten the course of the illness and lower the mortality rate in severe cases, although a knowledge of local sensitivities is particularly important as there is increasing resistance to antibiotics in developing countries.[6,7,8,9]

The first multi-drug resistant outbreak occurred in central America from 1969 to 1972 with over

Table 1. Antibiotic resistance of Shigella species. Lautoka Hospital, Fiji. 1996-1999.

	Antibiotic	Cases-	Cases-	Cases-	Cases-
Shigella flexineri					
Total number of		23	90	37	19
	Ampicillin	14 (61%)	85 (94%)	35 (95%)	17 (89%)
	Doxycycline	11 (48%)	75 (83%)	28 (76%)	16 (84%)
	Chloramphenicol	10 (43%)	83 (92%)	32 (86%)	14 (74%)
	Cephalothin	1 (4%)	7 (8%)	1 (3%)	Not
	Trimethoprim	6 (26%)	28 (31%)	11 (30%)	Not
	Cefaclor	Not tested	Not tested	1 (3%)	1 (5%1)
	Nalidixic acid	Not tested	Not tested	1 (3%)	Not
Shigella sonnei					
Total number of		9	7	8	8
	Ampicillin	0	4 (57%)	1 (13%)	4 (50%)
	Doxycycline	0	2 (29%)	Not tested	Not
	Cephalothin	0	3 (43%)	Not tested	Not
	Trimethoprim	0	1 (14%)	1 (13%)	Not
	Cefaclor	Not tested	Not tested	Not tested	2 (25%)
Shigella dysenteriae					
Total number of		1	0	3	0
	Ampicillin	0		2 (67%)	
	Doxycycline	0		2 (67%)	
	Chloramphenicol	0		2 (67%)	
	Trimethoprim	0		2 (67%)	

10,000 deaths reported due to strains resistant to chloramphenicol, streptomycin, sulphonamides and tetracycline. Multi-drug resistance amongst all serotypes is an increasing problem worldwide, and there is some evidence that increased case fatality is associated with strains resistant to the antibiotics used initially.[10]

Until 1984, ampicillin was the drug of choice for severe dysentery and trimethoprim was used for resistant strains. Quinolones are currently widely recommended for use in developing countries as they continue to be efficacious, however they are prohibitively expensive and unsuitable for children.[5] Cephalothin and ceftriaxone remain effective although they are also expensive and no oral preparations are available.

Within Fiji, Shigella is a notifiable disease .The Fiji Ministry of Health recorded 68 cases of Shigella in 1996, 173 cases in 1997 and 334 cases in 1998 (no data available for 1999).[2] There was only one recorded death during this time - in 1998. However, the Depaitment of Medicine at Lautoka Hospital has recorded three deaths in young adults who presented with severe dysentery in the past 12 months, although a definitive diagnosis of shigellosis was only made in the case presented above. This may represent an increase in the number of cases or may simply be reflect- underreporting.

Resistance to Ampicillin occurred in 89% of cases with some evidence that the rates are increasing over time.

A review of the microbiology department records at Lautoka Hospital, (which services approximately 350,000 patients - approximately 40% of the total Fijian population), indicated a total of 169 cases of Shigella over the past four years, and 75% of these were Shigella flexneri. There were high levels of multi-drug resistance for all Shigella, subtypes (Table 1) and these resistance patterns in Fiji were similar to those found around the world and in other developing nations.[4,5,7] Resistance to Ampicillin occurred in 89% of cases with some evidence that the rates are increasing over time. Resistance to chloramphenicol occurred in 82% of cases. Shigella flexneri in Fiji remains sensitive to cephalothin and cefaclor.

The current antibiotic guidelines in Fiji[11], recommend that antibiotics be used only for cases of moderate and severe dysentery. The recommended regimes are: nalidixic acid 1 gm 6 hourly given orally, cefaclor SR 375mg 12 hourly given orally, or chloramphenicol 500mg 6 hourly IV although, naladixic acid is currently unavailable in Government Pharmacies. The guidelines also recommend that sensitivities be obtained because of the problem of drug resistance.

Conclusion

In the case of Mr D, several management problems can be identified. Shigellosis was suspected soon after presentation however the patient was unable to take oral antibiotics and was treated with intravenous antibiotics (chloramphenicol and ampicillin), which were ineffective due to resistance of the organism. The current antibiotic guidelines for severe dysentry recommend chloramphenicol or nalidixic acid – the later not available in Fiji. These guidelines do not adequately address the problem of emerging multi-drug resistance in Shigellosis, and do not provide clear information on treatment options and of the likely resistance of Shigella to Chloramphenicol. However the only intravenous drugs that retain their sensitivity to Shigella - ceftriaxone and cephalothin, are expensive ($F 45.00 per vial of ceftriaxone) and these are only available in large regional hospitals. This patient was not transferred to a large hospital for 24 hours despite his critical condition, and appropriate antibiotics were not started for 48 hours after his presentation.

Within Fiji the current statistics indicate that death from Shigellosis is extremely rare. Although there is some suggestion that this may be changing, it does not seem necessary to recommend that more finances be made available to provide intravenous ceftriaxone to the district hospitals. However, doctors should be made aware that the drugs available to them in the community will not cover Shigellosis and that if dysentery is severe then immediate transfer is required for proper treatment.

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"Never accept failure, no matter how often it visits you. Keep on going. Never give up. Never."
(Dr Michael Smurfit, Jefferson Smurfit)