SECONDARY BACTERIAL INFECTION IN ADULT PATIENTS WITH PROLONGED AND SEVERE DENGUE FEVER

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ABSTRACT

INTRODUCTION
Generally, in dengue shock syndrome antibiotics are not advised. But unrecognised bacterial infection is likely to contribute to morbidity and mortality, probably because of increased vascular permeability.

OBJECTIVES
To assess the incidence of secondary bacterial infection in adult patients with prolonged and severe dengue fever.

METHODS
A prospective study was conducted recruiting patients with confirmed acute dengue infection who had prolonged fever (>5 days). Prior to institution of antibiotic therapy, two sets of blood cultures were taken from patients. Demographic, clinical, haematological and biochemical parameters were recorded. Severity of fever & associated symptoms assessed. Ultrasonography done to find out development of ascites and pleural effusions.

RESULTS
Sixty patients (60.0% males) with a mean age of 33.5 years (SD 12.1) were studied. The average duration of fever was 6.9 days (SD 1.6). Fifteen patients (25%) had bacterial isolates in their blood cultures; Staphylococcus aureus (n=3), coliforms (n=7), pseudomonas (n=2) and 3 had mixed growths. The culture positive group had severe body aches and joints paint at admission and high grade fever, third space fluid accumulation and significant drop in platelets compared to culture-negative group.

CONCLUSIONS
A quarter of dengue patients with prolonged fever had a bacterial isolate. Culture-positive patients appeared more ill with body aches and had higher degrees of fever during the course of the illness. Increased vascular permeability may predispose to bacterial seepage into blood. Although white cell count is not helpful in detecting bacteraemia in dengue fever, low platelet count and severe symptoms at presentation may be helpful.

KEYWORDS
Bacteraemia, Dengue fever, Infection.

INTRODUCTION: Dengue fever (DF) is a vector borne disease caused by 4 closely related dengue viruses (DENV 1–4).[1,2] Infection with DENV can also cause dengue haemorrhagic fever (DHF), a syndrome characterised by increased vascular permeability, plasma leakage, hypovolemia, and shock.[3,4] Dengue threatens more than 40% of the world's population, causing 50-100 million infections every year.[5,6] Dengue illness is characterised by a febrile phase, critical phase and the recovery phase. During the critical phase, there is an increase in vascular permeability resulting in leakage of fluid and plasma or leading to haemorrhage.

Although there is no specific treatment, early detection and timely intervention is the key in reducing mortality.[6] The febrile phase of dengue usually lasts for 5-7 days. Few studies have shown growth of bacteria in blood cultures suggesting secondary bacteraemia in patients with prolonged dengue fever, probably due to translocation of gut bacteria due to disruption of intestinal mucosal and vascular integrity.[7,8] One study showed serious methicillin-susceptible Staphylococcus aureus (MSSA) bacteraemia have been identified as occurring simultaneously with dengue virus infection.[9]

Furthermore, it has been shown that concurrent bacterial infection may cause lipopolysaccharide-mediated enhancement of virus replication and synergistic IFN alpha production resulting in disease progression during dengue virus infection.[10] Usually, guidelines recommend not to use antibiotics during any stages of dengue infection probably due to less or no evidence of secondary bacteraemia in patients with severe dengue.

However, it is important to understand the incidence, risk factors and predictors of bacterial infection in critical illness, because at least a proportion of patients with severe dengue may develop septic shock mimicking or complicating dengue shock resulting in a worse outcome and which may improve with timely antibiotic therapy. The aim of the study was to assess the prevalence of bacterial infection and identify risk factors and predictors of severe dengue fever patients with prolonged duration.

METHODS: A prospective study was conducted in the department of Medicine, Saptagiri Institute of Medical Sciences, Bangalore over a period of one-year period from March 2015 to February 2016. This study was approved by the ethical committee of Saptagiri Institute of Medical Sciences, Bangalore. Patients with antigenically or serologically confirmed dengue who were over 18 years of age and having prolonged fever (>5 days) were recruited. Patients who had received antibiotics prior to recruitment to the study were excluded.

An interviewer administered pre-tested questionnaire was developed to obtain demographic, clinical, biochemical and haematological data. They were obtained by direct interview and on site examination. Data related to fever were obtained from temperature. Body ache was assessed using a visual analogue scale numbered from 0 to 5, where 0 represented no body ache and 5 represented unbearable body ache as perceived by the patient. Once prolonged fever criteria were fulfilled, two sets of blood cultures were obtained using strict aseptic precautions prior to initiation of antibiotic therapy. Detection of third space fluid accumulation (TSFA) was done using bedside ultrasonography performed daily.

Demographic and clinical characteristics were tabulated between blood culture-positive and negative patients. Informed written consent was obtained from all participants.

	Total	Culture (+) ve	Culture (-) ve
	n=60	n=12	n=48
Age in Years,			
Mean (SD)	33.5(12.1)	31.8(14.3)	27.8(15.2)
Male (%)	36(60)	6(50)	20(41.6)

Table 1: Demographic Characteristics

Parameter	Total	Culture (+)ve	Culture (-)ve
	Number=60	Number=12	Number=48
	n (%)	n (%)	n (%)
Backache	60(100)	12(100)	48(100)
Retro-orbital Pain	25(41.6)	6(50)	19(39.6)
Abdominal Pain	23(38.3)	8(66.6)	15(31.25)
Vomiting	20(33.3)	7(58.3)	13(27.08)
Postural Dizziness	32(53.3)	10(83.3)	22(45.83)

Third Space Fluid Accumulation Present	28(46.6)	10(83.3)	18(37.5)
Maximum Recorded Fever Mean (SD)		103.2°F (1.7)	101.8(1.4)
Body Aches Score At Admission Mean (SD)		1.45(0.76)	1.37(0.81)
Body Aches Maximum Score Mean (SD)		3.06(0.45)	1.86(1.20)
Body Aches Score On Day 6 mean (SD)		2.42(0.92)	1.26(1.23)

Table 2: Clinical Features of Culture-Positive and Culture-Negative Groups

	Culture (+) ve	Culture (-) ve
	n=12	n=48
	Mean (SD)	Mean (SD)
WBC	9.1×10^9/L (1.5)	7.9×10^9/L (1.9)
Neutrophils	55.4(8)	49.2(7.8)
Platelets	30.5×10^9/L (12.8)	51.5×10^9/L (20.5)
PCV (% rise)	7.8 (13.2)	10.3(15.4)
AST (% rise)	217 (331.4)	133.7(254.2)
ALT (% rise)	197.6 (272.4)	145.2 (201.3)

Table 3: Maximum Values of Haematological and Biochemical Parameters

DISCUSSION: Of the patients who had prolonged fever, fifteen had positive cultures (25%) and twelve (20%) had a single organism isolate in the blood cultures. Age and sex distribution of culture-positive and culture-negative samples were comparable. Culture-positive group appeared to be more symptomatic with higher rate of abdominal pain, vomiting, and postural dizziness. The culture-positive group reported more severe body ache throughout the illness. Lee et al also found severe bone pain as one of the common clinical manifestations in patients with dual infections similar to our patients.[11] Maximum recorded fever was higher among the culture-positive patients.

Third space fluid accumulation was more among the culture-positive patients. It is possible that abnormal vascular permeability, the main cause for dengue shock syndrome, results in seepage of bacteria into blood stream. Seven out of the twelve patients were positive for Enterobacteriaceae similar to findings from other studies.[11,12] Like others have shown, the majority of bacteraemia isolates were Gram-negative.[11] Primary Gram-negative bacteraemia was postulated to be caused by the

breakdown of the intestinal mucosal barrier in severe dengue infections.[11]

This suggests that gut organisms may be responsible for bacteraemia. This could probably be due to disintegration of intestinal mucosal barriers in dengue haemorrhagic fever patients as reported previously.[7,8] Dengue haemorrhagic fever and dengue shock syndrome are characterised by rapid capillary plasma leakage followed by thrombocytopenia, clotting disorders, and hepatic changes showed by the increase of aspartate transaminase and glutamate transaminase.[13] There was no significant difference in white cell (WBC) and neutrophil counts between the two groups.

It has been shown that patients with dual infection are older, have prolonged fever, higher frequencies of acute renal failure, gastrointestinal bleeding, altered level of consciousness, unusual dengue manifestations and dengue shock syndrome.[11] However, except for prolonged fever and varying degrees of fluid leakage, our patients did not show such manifestations or complications. Lee et al in 2012 found bacteraemia as a significant cause of fatality in adult patients with dengue fever.[14]

CONCLUSIONS: According to our study, 25% of dengue patients with prolonged fever had bacteraemia. Culture-positive patients appeared to be more ill with body aches and had higher degrees of fever during the latter part of the illness. Although WBC is not helpful in detecting bacteraemia, lower platelet counts and severe symptoms seem to be helpful. We feel that institution of antibiotics should be considered in similar patients in order to reduce bacteraemia associated complications.

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