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ORIGINAL ARTICLE

# Risk factors for concurrent bacteremia in adult patients with dengue

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**Abstract** *Background/Purpose:* Bacteremia in dengue may occur with common exposure to pathogens in association with severe organ impairment or severe dengue, which may result in death. Cohort studies identifying risk factors for concurrent bacteremia among patients with dengue are rare.
*Methods:* We conducted a retrospective case—control study of adult patients with dengue who were admitted to the Department of Infectious Diseases at Tan Tock Seng Hospital, Singapore from 2004 to 2008. For each case of dengue with concurrent bacteremia (within the first 72 hours of admission), we selected four controls without bacteremia, who were matched on year of infection and dengue confirmation method. Conditional logistic regression was performed to identify risk factors for concurrent bacteremia.
*Results:* Among 9,553 patients with dengue, 29 (0.3%) had bacteremia. Eighteen of these patients (62.1%) had concurrent bacteremia. The predominant bacteria were *Staphylococcus aureus*, one of which was a methicillin-resistant strain. Dengue shock syndrome occurred more frequently and hospital stay was longer among cases than among controls. Three cases did not survive, whereas none of the controls died. In multivariate analysis, being critically ill at

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hospital presentation was independently associated with 15 times the likelihood of a patient with dengue having concurrent bacteremia.
*Conclusion:* Concurrent bacteremia in adult patients with dengue is uncommon but presents atypically and results in more deaths and longer hospital stay. Given the associated mortality, collection of blood cultures and empiric antibiotic therapy may be considered in patients who are critically ill.


## Introduction

Dengue is an arbovirus-borne infection that is widespread in tropical and subtropical regions.[1] A recent model by Bhatt et al[2] estimated that 390 million infections occur annually, with 96 million of these infections being clinically apparent. Despite the high rate of infection worldwide, there is no effective vaccine against dengue.[3,4] Clinical manifestations of dengue range from an asymptomatic infection to a mild, flu-like, self-limiting infection.[5] In adults, the infection can less commonly develop into the more severe and life-threatening forms, dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS). Close monitoring and timely administration of fluid therapy have improved outcomes from DHF and DSS globally.[5,6] More recently, the World Health Organization (WHO) proposed a new classification that better guides clinical management: dengue with warning signs, dengue without warning signs, and severe dengue.[5,7]

Only a few case series of concurrent bacteremia and dengue infection have been reported. Bacteremia in dengue may occur with common exposure to pathogens[8,9] in association with severe organ impairment[10] or severe dengue, resulting in death.[11–13] In addition, nosocomial infection may result from prolonged hospitalization for severe dengue and its complications.[11] Hypotheses on the pathogenesis of concurrent bacteremia in patients with dengue include disintegration of endothelial cells by antibodies against dengue nonstructural protein 1[14,15] and/or relative immunosuppression in patients with dengue.[11]

A recent cohort study was carried out by Lee et al[16] to identify the clinical characteristics and risk factors of patients with DHF and concurrent bacteremia. However, large cohort studies identifying risk factors for patients with dengue and concurrent bacteremia are rare. In this large cohort study of adult patients with dengue who were admitted to the Department of Infectious Diseases at Tan Tock Seng Hospital (TTSH), Singapore from 2004 to 2008, we aimed to (1) determine the prevalence of concurrent bacteremia in adult patients with dengue; (2) describe the clinical characteristics of adult patients with dengue and concurrent bacteremia; and (3) identify clinical and laboratory risk factors for concurrent bacteremia at the time of hospital presentation. This information would be clinically useful for doctors performing appropriate microbiological investigations of bacteremia and starting early empiric antibiotic therapy.

## Methods

### Patients

We conducted a retrospective study of laboratory-diagnosed dengue in adult patients who were admitted to the Department of Infectious Diseases at TTSH from January 1, 2004, to December 31, 2008.

Patients were diagnosed as having probable dengue based on the 1997 and 2009 WHO guidelines.[5,17] Dengue Real-time Reverse Transcription-Polymerase Chain Reaction, as described earlier,[18] or Panbio Rapid Dengue Duo Rapid Strip Test (Panbio Diagnostic, Queensland, Australia)[19,20] was performed at the Department of Laboratory Medicine, TTSH, according to the manufacturer's instructions, to confirm the diagnosis. Diagnosis of bacteremia was confirmed by a positive bacterial culture in the patient's blood sample obtained after admission to the hospital. In this study, "concurrent bacteremia" was defined as a positive bacterial blood culture within 72 hours of a patient's admission.[16] Blood culture was taken in the event of clinical deterioration despite treatment based on a standardized dengue care path.

For each case of dengue with concurrent bacteremia, we selected four controls among patients with dengue without clinical suspicion of bacteremia or without blood cultures collected or reported as negative by the Department of Laboratory Medicine, TTSH, matched on year of infection (a surrogate for predominant circulating dengue serotype) and dengue confirmation method. The selection generated all controls without collection of blood cultures. In brief, 29 patients had bacteremia from 2004 to 2008, among which 18 had blood samples collected for bacterial culture within 72 hours of admission. Although the other 11 patients yielded positive results for bacterial growth, blood samples were collected >72 hours after admission. Therefore, it was not possible to determine whether bacteremia was concurrent with dengue infection or was acquired nosocomially. An analysis identifying risk factors was carried out with 72 controls and 18 cases.

Demographics (age, sex, and ethnicity), comorbidities (diabetes mellitus, hypertension, hyperlipidemia, and cardiac diseases), dengue diagnosis classification, symptoms and signs at presentation (Table 1), parameters for laboratory investigation at presentation, types of intervention, dengue severity classification at hospital discharge, and clinical outcomes (Table 2) were extracted for comparison between cases and controls. The laboratory parameters