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Characteristics and outcomes of *Fusobacterium nucleatum* bacteremia—a 6-year experience at a tertiary care hospital in northern Taiwan☆,☆☆

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Abstract

Fusobacterium nucleatum bacteremia is critical and not well defined. To identify the clinical characteristics and outcomes, we conducted a retrospective review of hospitalized patients from January 2004 to December 2009 at a tertiary center in northern Taiwan. Fifty-seven patients were enrolled. The mean age was 58.1 years, and the mean Pitt bacteremia score was 4.7. Males predominated (59.6%), and the overall 30-day mortality rate was up to 47.4%. Malignancy was the major comorbidity (26/57, 45.6%), especially oropharyngeal and gastrointestinal cancers (19/26, 73.1%). Pneumonia (17/57, 29.8%) was the most common presentation with high rates of respiratory failure (15/17, 88.2%) and mortality (11/17, 64.7%), followed by intra-abdominal infections (7/57, 12.3%). In multivariate analysis, higher Pitt bacteremia score, nosocomial infection, anemia, and intensive care unit stay were the independent factors for 30-day mortality. Nosocomial *F. nucleatum* bacteremia was a significant mortality predictor independent to other parameters of disease severities.

Keywords: Bacteremia; *Fusobacterium nucleatum*; Mortality; Pneumonia; Nosocomial

1. Introduction

Fusobacterium nucleatum is one of the most common species of fusobacteria in human infections and can be found in body cavities of humans (Bolstad et al., 1996; Henry et al., 1983; Huggan and Murdoch, 2008; Su et al., 2009). The body sites colonized by anaerobes including *F. nucleatum* contain many species of bacteria simultaneously, and disruption of anatomical barriers allows the penetration of many organisms, resulting in mixed infections involving multiple species of anaerobes combined with facultative or microaerophilic pathogens (Bennett and Eley, 1993; Bolstad et al., 1996; Henry et al., 1983; Huggan and Murdoch, 2008; Moore and Moore, 1994; Su et al., 2009). *F. nucleatum* may cause noninvasive, semi-invasive to invasive types of infections such as tropical skin ulcers (Falkler et al., 1989), peritonsillar abscesses (Jousimies-Somer et al., 1993), soft tissue and bone infections (Gonzalez-Gay et al., 1993), bacteremia and liver abscesses (Scoular et al., 1992), intrauterine infections (Chaim and Mazor, 1992), bacterial vaginosis (Hillier et al., 1993), urinary tract infections (Ribot et al., 1981), pericarditis and endocarditis (Shammas et al., 1993; Weber et al., 1999), and lung and pleuropulmonary infections (Johanson and Harris, 1980).

Fusobacterium bacteremia had a significant morbidity and mortality in humans, and accounted for less than 1% of all bacteremias in adults and <10% of anaerobic bacteremias (Bourgault et al., 1997; Brook, 2010; Su et al., 2009). Among them, *F. nucleatum* plays a major part of this rare disease. Since sporadic cases were reported (Bourgault et al., 1997; Huggan and Murdoch, 2008; Su et al., 2009), the studies for clinical characteristics of *F. nucleatum* bacteremia were limited and risk factors for mortality were not well understood. To investigate the clinical characteristics and outcomes and identify the risk factors for the mortality, we conducted a retrospective study of *F. nucleatum* bacteremia in Chang Gung Memorial Hospital-Taoyuan (CGMH-Taoyuan) from January 2004 to December 2009.

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☆☆ Research ethics: Our study has been approved by institutional review boards of CGMH-Taoyuan (No. 99-1078B).

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2. Methods

2.1. Setting

CGMH-Taoyuan is a university-affiliated hospital comprising 3500 beds and provides both primary and tertiary health care in northern Taiwan. A central microbiology laboratory is responsible for processing all clinical specimens. This study was reviewed and approved by the institutional review board of CGMH-Taoyuan.

2.2. Patients, study design, and definitions

All patients with positive blood cultures admitted to CGMH-Taoyuan between January 2004 and December 2009 were reviewed. The cases with at least one positive blood culture for *F. nucleatum* accompanied with fever or other clinical features compatible with systemic infection were enrolled. Data on demographic characteristics, underlying diseases, clinical features, sources of bacteremia, concurrent blood isolates of other bacterial species, susceptibility testing of blood isolates, laboratory and image findings, antibiotic regimens (14 days before the onset of *F. nucleatum* bacteremia and thereafter), length of hospital stay, Pitt bacteremia score, and outcomes were collected from the medical records of the enrolled patients using a standardized data collection form for analysis. If a single patient had multiple episodes of *F. nucleatum* bacteremia during the study period, only the first episode of bacteremia was included for analysis.

The Pitt bacteremia score was calculated to access the severity (Rhee et al., 2009). Pitt bacteremia score was calculated using the following criteria: (1) oral temperature: 2 points for a temperature of ≦ 35 °C or ≥40 °C, 1 point for a temperature of 35.1–36.0 °C or 39.0–39.9 °C, and 0 point for a temperature of 36.1–38.9 °C; (2) hypotension: 2 points for an acute hypotensive event with decreases in systolic and diastolic blood pressure of >30 and >20 mm Hg, respectively, use of intravenous vasopressor agents, or systolic blood pressure <90 mm Hg; (3) receipt of mechanical ventilation: 2 points; (4) cardiac arrest: 4 points; and (5) mental status: alert, 0 point; disoriented, 1 point; stuporous, 2 points; and comatose, 4 points. The underlying diseases included malignancy, renal insufficiency (defined as a serum creatinine level ≥1.4 mg/dL or the requirement of hemodialysis), diabetes mellitus, cerebral vascular accident, liver cirrhosis, heart failure, human immunodeficiency virus infection, and recent surgery (defined as surgical procedures performed within 3 months before the onset of infection). Polymicrobial bacteremia was defined as one or more additional bacterial species isolated from blood simultaneously with *F. nucleatum*.

Leukocytosis was defined as leukocyte count >10,000 cells/mm^3. Leukopenia was defined as leukocyte count <4000 cells/mm^3. Neutropenia was defined based on the absolute neutrophil count <500 cells/mm^3. Anemia was defined as hemoglobin <13 g/dL in men and <12 g/dL in women. Thrombocytopenia was defined as platelet count <150,000 cells/mm^3. Hepatic dysfunction was defined as one of the following: (1) elevated serum alanine transaminase, (2) elevated serum aspartate transaminase, or (3) elevated serum total bilirubin level. Fever was defined as body temperature ≥38 °C. Hypothermia was defined as body temperature <36 °C.

The sources of bacteremia were determined by the medical records, image studies, surgical findings, and microbiology evidence. The sources of bacteremia were classified into skin, soft tissue and bone, intra-abdominal sites, upper and lower respiratory tracts, central nerve system (CNS), and unknown primary site. Pneumonia probably caused by *F. nucleatum* was defined as *F. nucleatum* bacteremia with the concurrent pulmonary findings: (1) the presence of lower respiratory tract symptoms, such as cough, dyspnea or tachypnea (respiratory rate ≥30 breaths/min), crackles or bronchial breathing sounds on auscultation, pleuritic chest pain, purulent sputum, hypoxemia, or even respiratory failure requiring mechanical ventilation; (2) new onset of abnormal radiographic findings but without other significant bacteria isolated from sputum; and (3) no evidence of other infection foci. Nosocomial bacteremia was defined as bacteremia onset after 48 h of hospitalization.

Adequate definite antimicrobial treatment was defined as the empirical antibiotics effective in vitro against the offending pathogens, which had been used for at least 3 days. Adjunctive therapy was defined as concurrent therapy with operation or drainage. The 30-day mortality was recorded. Mortality occurred within 7 days of *F. nucleatum* bacteremia with profound shock, and multiple organ failure was defined as bacteremia-attributed mortality if there was no other identified cause for death.

2.3. Microbiology

Blood samples were inoculated into both aerobic and anaerobic broth media for processing in the Becton Dickinson BACTEC 9240 blood culture system. Gram-stained smears of colonies from the anaerobic and CO_2-incubated plates were examined for long slender Gram-negative rods, which were highly suspicious of *Fusobacterium* species. Each colony type from the anaerobic plate was subcultured in both aerobic and CDC anaerobic blood agar plates (BBL, Becton Dickinson, Cockeysville, MD) for overnight incubation to test aerotolerance. Kanamycin-vancomycin-colistin–laked blood agar was used for the differentiation of anaerobic, non–spore-forming Gram-negative bacilli. Morphology of colonies on CDC-anaerobe agar under light microscope was helpful in differentiation of the species of fusobacteria. Specifically, *Fusobacterium* species are resistant to vancomycin (5 μg) but sensitive to kanamycin (1000 μg) and colistin (10 μg), and they are usually catalase-negative, nitrate-negative, and 20% bile salt-negative, and indole-positive. *F. nucleatum* can be identified as