Journal of Infection (2014) 69, 145–153

BIA British Infection Association

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Bacteraemia due to *Streptococcus gallolyticus* subspecies *pasteurianus* is associated with digestive tract malignancies and resistance to macrolides and clindamycin

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Accepted 6 March 2014
Available online 15 March 2014

KEYWORDS
Streptococcus bovis;
Streptococcus gallolyticus;
Streptococcus infantarius;
Bacteraemia;
Endocarditis;
Digestive tract malignancies;
Macrolide and clindamycin resistance

Summary *Objectives:* This study was intended to delineate the association between digestive tract malignancies and bacteraemia due to *Streptococcus gallolyticus* subspecies *pasteurianus*.
Methods: We reviewed the medical records and microbiological results of patients with bacteraemia due to *Streptococcus bovis* during the period 2000–2012. Species and subspecies identification of isolates originally classified as *S. bovis* was confirmed by 16S rRNA sequencing and PCR restriction fragment length polymorphism (PCR-RFLP) assays. Minimum inhibitory concentrations of antimicrobial agents were determined by the broth microdilution method.
Results: Of the 172 *S. bovis* complex isolates obtained from 172 patients (age range, <1–94 years, median age, 66) with bacteraemia, 31 isolates were identified to be *S. gallolyticus* subspecies *gallolyticus*, 126 were *S. gallolyticus* subspecies *pasteurianus*, and 15 were shown to be *Streptococcus infantarius*. The majority ($n = 104$, 60%) of patients were male and had underlying malignancies ($n = 87$, 51%). Bacteraemia due to *S. gallolyticus* subspecies

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http://dx.doi.org/10.1016/j.jinf.2014.03.010

gallolyticus was significantly associated with endocarditis while *S. gallolyticus* subspecies *pasteurianus* was more likely to be associated with malignancies of the digestive tract, including gastric, pancreatic, hepatobiliary and colorectal cancers. Septic shock at presentation was the only factor associated with mortality among patients with bacteraemia due to either subspecies of *S. bovis*. Isolates of *S. gallolyticus* subspecies *pasteurianus* had higher rates of resistance to macrolides and clindamycin than isolates of *S. gallolyticus* subspecies *gallolyticus*.

Conclusion: Extensive diagnostic work-up for digestive tract malignancies and transesophageal echocardiogram should be investigated in patients with bacteraemia caused by *S. gallolyticus*.

Introduction

Strains of *Streptococcus bovis* complex are common commensal microorganisms found in the alimentary tract of animals and humans.[1] Both *Enterococcus* and *S. bovis* belong to the Lancefield group D; however, in contrast to *Enterococcus*, *S. bovis* can hydrolyse esculin and is viable in 40% bile.[2] *S. bovis* is divided into two biotypes based on mannitol fermentation: *S. bovis* biotype I strains are mannitol-positive and biotype II strains are mannitol-negative.[3] Biotype II/1 strains ferment starch and glycogen but do not produce β-glucuronidase or β-galactosidase, while biotype II/2 strains do not ferment starch or glycogen, but produce β-glucuronidase and β-galactosidase.[3] Previous studies have shown that *S. bovis* biotype I bacteraemia is strongly associated with the presence of endocarditis and colorectal malignancies.[4–7] However, *S. bovis* biotypes are not widely tested on a routine clinical basis. Therefore, most patients with bacteraemia due to strains of *S. bovis* undergo investigations for colon cancer and endocarditis.

Studies on the *S. bovis* complex using genetic-based classification methods, such as 16s rRNA gene and *sodA* gene (encoding manganese dependent superoxide dismutase) sequencing analysis, and PCR restriction fragment length polymorphism (PCR-RFLP) assays based on *groESL* sequences have revealed that the complex could be divided into six different DNA groups.[3,8–12] Further studies led to extensive taxonomic changes in this complex, and strains formerly known as *S. bovis* are now designated as different species. The two species most commonly associated with disease in humans are now known as *Streptococcus gallolyticus*, with the subspecies *gallolyticus* (formerly *S. bovis* biotype I) and *pasteurianus* (formerly *S. bovis* biotype II/2), and *Streptococcus infantarius* (formerly *S. bovis* biotype II/1), with the subspecies *coli* and the subspecies *infantarius* (*S. lutetiensis*).[10,11] Since the introduction of the new taxonomic classification of *S. bovis*, a number of case reports have shown that bacteraemia due to *S. gallolyticus* or its subspecies *gallolyticus* or *pasteurianus* is associated with the development of colon cancer.[13–15] No large-scale studies on the association between digestive tract malignancies and bacteraemia due to *S. gallolyticus* or its subspecies have been conducted.

In this study, we examined the clinical and microbiological characteristics as well as the outcomes associated with bacteraemia due to pathogens formerly known as *S. bovis*.

Materials and methods

Study settings and design

We included all blood isolates of *S. bovis* complex obtained from patients with bacteraemia during the period January 2000 to 31 December 2012 at the National Taiwan University Hospital (NTUH), a 2500-bed medical centre located in northern Taiwan. Patient characteristics, co-morbidities, immunosuppressive status, microbiologic parameters, and patient outcomes were recorded. Sites of infection were identified according to definitions of the Centers for Disease Control and Prevention.[16] If no infection focus could be identified, bacteraemia was classified as being primary bacteraemia. Neutropenia was defined as blood absolute neutrophil count less than 1500/μL at the onset of bacteraemia. Results from echographic, computed tomographic, and endoscopic examinations for colon lesions, endocarditis, and biliary pathology were collected. Colorectal cancer and adenoma (pre-malignant lesions) were defined as colorectal neoplasia. The 30-day crude mortality (defined as death within 30 days after admission) and bacteraemia associated mortality (defined as death occurring within 30 days after the onset of bacteraemia due to *S. bovis* before resolution of symptoms and signs without another explanation) were recorded.

Microbiology

All blood cultures were processed by the microbiology laboratory at the NTUH using the BACTEC system (Becton Dickson, Sparks, MD). The VITEK automated system (bioMerieux, Hazelwood, MO) was used for *S. bovis* and subspecies identification. Subspecies identification was confirmed by sequencing of both 16S rRNA and the *sod*A genes and PCR-RFLP assays of *groESL* gene with the restriction enzyme *Acl*I (New England BioLabs).[11,12] 16S rRNA gene PCR with universal primers (primer 8FPL [5′-AGAGTTTGATCCTGGCTCAG-3′] and primer 1492RPL [5′-GGTTACCTTGTTACGACTT-3′]), *sodA* PCR with degenerate primers (primer *dl* [5′-CCITAYICITAYGAYGCIYTIGARCC-3′] and primer *d2* [5′-ARRTARTAIGCRTGYTCCCAIACRTC-3′]), and forward primer ES5-29F (5′-TAAAACCHTTAGGHGAHCGWRTBGT-3′), together with the reverse primer, *Streptococcus bovis* EL1265R (5′-CAAGTTCAAGTTCAGCAACTTTTG-3′) were performed.[11,12]

Minimum inhibitory concentrations (MICs) of the isolates to various antimicrobial agents, including penicillin,