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Comparison of community-onset *Staphylococcus argenteus* and *Staphylococcus aureus* sepsis in Thailand: a prospective multicentre observational study

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Abstract

Staphylococcus argenteus is a globally distributed cause of human infection, but diagnostic laboratories misidentify this as *Staphylococcus aureus*. We determined whether there is clinical utility in distinguishing between the two. A prospective cohort study of community-onset invasive staphylococcal sepsis was conducted in adults at four hospitals in northeast Thailand between 2010 and 2013. Of 311 patients analysed, 58 (19%) were infected with *S. argenteus* and 253 (81%) with *S. aureus*. Most *S. argenteus* (54/58) were multilocus sequence type 2250. Infection with *S. argenteus* was more common in males, but rates of bacteraemia and drainage procedures were similar in the two groups. *S. argenteus* precipitated significantly less respiratory failure than *S. aureus* (5.2% versus 20.2%, adjusted OR 0.21, 95% CI 0.06–0.74, p 0.015), with a similar but non-significant trend for shock (6.9% versus 12.3%, adjusted OR 0.46, 95% CI 0.15–1.44, p 0.18). This did not translate into a difference in death at 28 days (6.9% versus 8.7%, adjusted OR 0.80, 95% CI 0.24–2.65, p 0.72). *S. argenteus* was more susceptible to antimicrobial drugs compared with *S. aureus*, and contained fewer toxin genes although *pvl* was detected in 16% (9/58). We conclude that clinical differences exist in association with sepsis due to *S. argenteus* versus *S. aureus*.

Keywords: Prevalence, sepsis, *Staphylococcus argenteus*, *Staphylococcus aureus*, Thailand
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Introduction

Staphylococcus argenteus is a genetically divergent lineage of *Staphylococcus aureus* that received formal taxonomic classification in 2014 [1]. *S. argenteus* is mis-identified as *S. aureus* in

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clinical diagnostic laboratories using standard identification tests [2–4]. Multilocus sequence typing (MLST) makes a clear distinction between the two species, but the original PCR primers for *S. aureus* failed to amplify two of the seven loci in *S. argenteus* [2,5,6] and such isolates were often excluded by default. Although several of the earliest descriptions of *S. argenteus* were associated with remote communities [2–4], cumulative publications have since suggested that *S. argenteus* is globally distributed. This includes its isolation from humans or animals in Thailand, Cambodia, Indonesia, Fiji, New Zealand, Mayotte, Trinidad and Tobago, with additional evidence from the MLST database of its presence in Europe and Africa [2–12].

Discovering the existence of this new pathogenic species results in the need to determine whether *S. argenteus* and *S. aureus* should be distinguished apart in routine practice. This might be necessary if *S. argenteus* infection is associated with different clinical manifestations, severity or outcome, and/or requires different antimicrobial regimens. Data on clinical features of human *S. argenteus* infection are limited, but a study that defined the frequency of *S. argenteus* in three different clinical collections in northern Australia reported that this was predominantly associated with skin and soft-tissue infections, but rarely with bacteraemia [13]. *S. argenteus* has been reported to be more susceptible to oxidative stress and neutrophil killing *in vitro*, and less virulent in murine sepsis and skin infection models compared with *S. aureus* [13]. This raises the possibility that human *S. argenteus* infection may be associated with a milder course. Comparison between ten patients with invasive *S. argenteus* infection and 236 patients with invasive *S. aureus* infection reported that morbidity and death were comparable [6], but this study was underpowered. The presence of virulence genes in *S. argenteus* has not been subjected to detailed investigation. Several studies have reported that *S. argenteus* is negative for genes encoding Panton–Valentine leukocidin (PVL) [3,4,7,8,14,15], although a recent case report of two patients with PVL-positive *S. argenteus* infection [11] indicates that this species may acquire virulence factors. One study also detected the gene encoding staphylococcal enterotoxin B in all *S. argenteus* isolates cultured from villagers in the Amazonian forest [4].

Here, we describe a prospective, multicentre study of invasive staphylococcal infection that was initially reported by diagnostic laboratories to be due to *S. aureus*, in which around one-fifth of isolates were re-identified as *S. argenteus*. This allowed a comparison of patient characteristics and demography, features of infection and outcome, antimicrobial resistance profiles, and the presence of selected putative virulence determinants.

Methods

Study setting and design

A prospective cohort observational study of community-onset invasive staphylococcal infection was conducted in patients with sepsis at four hospitals across northeast Thailand between March 2010 and December 2013. Study sites were Sunpasitthiprasong Hospital, Ubon Ratchathani; Udon Thani Hospital, Udon Thani; Srinagarind Hospital, Khon Kaen; and Khon Kaen Hospital, Khon Kaen. Potential study patients were identified by daily screening at each hospital diagnostic microbiology laboratory for clinical samples that grew a pure culture identified by the routine microbiology laboratory as *S. aureus*. Invasive infection was defined as the isolation of *S. aureus* from a sample taken from a normally sterile site. Inclusion criteria were as follows: age at least 14 years (age of admission to adult wards), community-onset infection (positive culture taken within 2 days of hospital admission, or after 2 days when sampling was delayed from a patient admitted with suspected infection), and at least two of four systemic inflammatory response syndrome criteria met within 48 h of culture. These criteria are: (a) temperature >38°C or <36°, (b) heart rate >90 beats/min, (c) respiratory rate >20 breaths/min, P_{CO_2} <32 mmHg, or a requirement for mechanical ventilation, and (d) white blood count >12 000 cells/mL or <4000 cells/mL, or >10% band forms [16]. Exclusion criteria were other active co-infections, therapeutic immunosuppression with high-dose steroids or chemotherapy, and pregnancy. Patients were enrolled after providing written informed consent.

Clinical information was obtained from the medical records. Patients were followed until hospital discharge, during which time antimicrobial therapy, surgical drainage procedures, the development of shock requiring vasopressors or inotropes, or respiratory failure requiring mechanical ventilation were recorded. Mortality was ascertained 28 days from the day of admission. For patients discharged before 28 days, outcome was determined through telephone follow up. Patient residence was defined using http://mondeca.com/index.php/en/?option=com_content&view=article&id=206&Itemid=752, and the co-ordinates were mapped using ArcGIS software (https://www.arcgis.com). Ethical approval was obtained from the following Ethical and Scientific Review committees: Faculty of Tropical Medicine, Mahidol University (approval no. MUTM 2011-007-01); Sunpasitthiprasong Hospital, Ubon Ratchathani (approval no. 004/2553); Udon Thani Hospital, Udon Thani (approval no. 0027.102/2349); Khon Kaen Hospital, Khon Kaen; and Faculty of Medicine (Srinagarind Hospital), Khon Kaen University, Khon Kaen, Thailand (approval no. HE541113).

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