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Unusually virulent coagulase-negative *Staphylococcus lugdunensis* is frequently associated with infective endocarditis: a Waikato series of patients

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Abstract

Background *Staphylococcus lugdunensis*, a species of coagulase-negative staphylococci is associated with a wide variety of infections ranging from mild skin and soft tissue infections to serious infections which include brain abscess, chronic osteomyelitis and infective endocarditis. The aim of this study was to review cases of *S. lugdunensis* bacteraemia isolated from a New Zealand tertiary institution and describe the clinical presentation, diagnosis and treatment of the patients.

Methods All blood cultures reported positive for *S. lugdunensis* from the Microbiology Laboratory, Waikato Hospital, New Zealand between March 2006 to April 2011 were reviewed.

Results A total of 11 cases of *S. lugdunensis* bacteraemia were identified during the 5-year period. Three (27%) cases were due to infective endocarditis with one delayed diagnosis due to the failure of recognize the coagulase-negative *Staphylococcus*. Transthoracic or transoesophageal echocardiography was performed in 6 (55%) of the patients. One patient with endocarditis required early surgery and the other two were managed successfully with intravenous antibiotics. There was no in hospital mortality in the patients with endocarditis. The remaining 8 cases included 1 (9%) necrotizing fasciitis, 1 (9%) immunocompromised nosocomial multiple organism sepsis, 1 (9%) deep tissue infection requiring 6 weeks of intravenous antibiotics, 2 (18.5%) superficial skin infection, 1 (9%) nosocomial post-pacemaker insertion infection and 2 (18.5%) had fever of unknown origin. All isolates were sensitive to Flucloxacillin and Vancomycin. Overall the survival rate of the acute presentation and treatment was 91% (10/11).

Conclusion Three of our 11 patients (27%) with *S. lugdunensis* bacteraemia were diagnosed with infective endocarditis. Evaluation for endocarditis is therefore advised in patients who have positive blood culture for this organism.

Staphylococcus lugdunensis, a species of coagulase-negative staphylococcus (CoNS), was first described by Freney et al in 1988.[1] This organism is a rare contaminant in culture and commonly found on human skin. In addition this pathogen is associated with a wide variety of infections ranging from mild skin and soft tissue infections to serious infections such as brain abscess, septicaemia, chronic osteomyelitis and infective endocarditis.[2–4]

Case reviews have demonstrated that *S. lugdunensis* infective endocarditis is associated with a high mortality and early operation is often advised.[4–7] A positive blood culture for this pathogen is frequently an indication of invasive infection.

We report a case series of *S. lugdunensis* bacteraemia and clinical management and outcomes from our institution.

Methods

All blood cultures reported positive for *S. lugdunensis* at Waikato Hospital between March 2006 to April 2011 were retrospectively reviewed. Patient's presenting complaints, diagnosis, duration of antibiotics therapy and longer term outcomes were assessed. Microbiological data were retrieved from the laboratory database and antimicrobial susceptibility was recorded. All cases of infective endocarditis fulfilled the modified Duke's Criteria.[8]

Results

Eleven consecutive cases of *S. lugdunensis* bacteraemia were identified from our microbiology laboratory. The cases are summarised in Table 1. Overall, 3 (27%) patients had infective endocarditis, 1 (9%) patient had deep tissue infection, 1 (9%) had necrotizing fasciitis, 1 (9%) patient had multiple organism sepsis, 2 (18.5%) had skin infection, 1 (9%) had post-pacemaker insertion bacteraemia, and 2 (18.5%) had a diagnosis of fever of unknown origin.

Transthoracic or transoesophageal echocardiography was performed in 6 (55%) of the patients. All isolates were susceptible to Flucloxacillin and Vancomycin. The majority of patients were successfully managed with Flucloxacillin alone. Cephalosporin (intravenous Cefazolin and oral Cefaclor) were used successfully in one case where the patient had penicillin allergy.

All but one (91%) patient survived the acute presentation of bacteraemia. Mortality occurred in the patient who had nosocomial sepsis following pelvic radiotherapy, this patient progressed rapidly to multiorgan failure on the background of terminal metastatic prostate carcinoma. During the median follow-up period of 10 months, the cumulative mortality was 45%.

Case synopses

Endocarditis—Three cases (Case 4, 9, 11) of infective endocarditis related to *S. lugdunensis* were identified in our series. One patient had native aortic valve involvement, one had mechanical mitral valve involvement and the third case had native mitral valve vegetation identified on a long standing prolapsing mitral valve leaflet.

An 80-year-old woman (Case 4) who presented with fever, general malaise and rigors, subsequently had native aortic valve infective endocarditis associated with severe aortic regurgitation diagnosed. She was successfully managed with high dose intravenous Flucloxacillin for a total duration of 6 weeks. The presence of severe aortic regurgitation led to deterioration in cardiac function (ejection fraction). Surgical intervention was not recommended due to general frailty and co-morbidities. She died 9 months post admission due to cardiac failure.

Table 1. Summary of the patients with *Staphylococcus lugdunensis* bacteraemia including their clinical diagnosis, treatment and outcomes. TTE (transthoracic echocardiography), TOE (transoesophageal echocardiography), IV (intravenous)

Case No.	Date of Blood Culture	Patient Information.	Presenting Complaint	Diagnosis	TTE/TOE	Sensitivity/MIC	Treatment	Outcome	Survival, days from diagnosis to follow-up	Comments
1	21 Jul 2006	52yr, Female	Fever, left elbow carpet burn	Necrotizing fasciitis of left forearm	Nil	Flucloxacillin, Vancomycin	Surgical debridement of left forearm. Ceftriaxone 2g OD, Metronidazole 400mg IV TDS for 2 weeks.	Successful surgical and medical treatment.	Alive, 1745	
2	17 Jun 2007	71yr, Male	Painful left ankle, fever, confusion.	Left foot/ankle tenosynovitis	Both	Flucloxacillin, Vancomycin	IV Flucloxacillin 2g IV Q6hr for 1 week and discharged with 6g IV Flucloxacillin continuous infusion over 24hrs. Total duration 4 weeks.	Successful Medical Treatment	Death, 460	Death due to neutropenic sepsis with underlying multiple myeloma. Patient had negative transoesophageal echocardiography
3	9 Dec 2007	46yr, Male	24hrs fever, malaise and rigor	Sepsis ? source	Nil	Flucloxacillin, Vancomycin	IV Ceftriaxone 1g OD and Flucloxacillin 1g Q6hr for 2 days. Fever settled within 48hrs. Changed to oral Cefuroxime 500mg bd for 1 week.	Successful medical treatment	Alive, 1239	Source of infection was unclear.
4	28 Dec 2007	80yr, Female	Fever, rigors and general malaise	Native aortic valve endocarditis	Both	Flucloxacillin, Vancomycin. MIC Penicillin; 0.064ug/mL.	IV Flucloxacillin 2g IV Q6hr for 2 weeks and discharged with 6g IV Flucloxacillin continuous infusion over 24hrs. Total duration 6 weeks.	Successful immediate medical treatment. Severe AR with CHF.	Death, 287	Cause of Death: Cardiac Failure.
5	23 Jan 2008	84yr, Female	Rigors. Previous St Jude mitral valve replacement. Penicillin Allergy	Cellulitis of left leg	TTE	Cotrimoxazole, Flucloxacillin, Vancomycin	IV Cefazolin 1g TDS for 4 days then Cefaclor 250mg tds for 10 days.	Successful medical treatment	Alive, 1194	Echocardiography did not reveal obvious abnormality.

6	23 Mar 2008	26yr, Female	Fever during acute myeloid leukaemia chemotherapy	Neutropenic sepsis with multiple organism infection	TTE	Cotrimoxazole, Flucloxacillin, Vancomycin, Erythromycin	Voriconazole, Meropenem, Teicoplanin, Amikacine for 2 weeks.	Successful inpatient treatment.	Death, 98	Cause of Death: acute myeloid leukaemia. Nosocomial infection
7	25 Mar 2008	70yr, Female	Post pacemaker insertion transient fever	Pacemaker wound infection	Nil	Cotrimoxazole, Flucloxacillin, Vancomycin	Amoxycillin-Clavulanate 625mg po tds 1 week.	Successful medical treatment	Alive, 1132	Nosocomial infection
8	19 Aug 2009	77yr Male	Post radiotherapy fever for prostate cancer	Fever of unknown origin	Nil	Cotrimoxazole, Flucloxacillin, Vancomycin	Amoxycillin-Clavulanate 625mg po tds	Failed medical treatment, patient progressed to multi-organ failure for comfort care.	Death, 2	Nosocomial infection
9	20 Dec 2009	70yr, Male	Fever, shortness of breath. Previous St Jude mitral valve replacement	St Jude mitral valve endocarditis	Both	Cotrimoxazole, Flucloxacillin, Vancomycin	Flucloxacillin 2g q6hrly IV for 6 weeks. Rifampicin 300mg tds po 6 weeks. Gentamycin 4mg/kg in 3 divided IV doses for 2 weeks.	Successful medical treatment	Death, 115	Cause of Death: extensive subarachnoid haemorrhage
10	22 Oct 2010	39yr, Male	High fever, malaise	Skin infection from minor scratch	Nil	Cotrimoxazole, Flucloxacillin, Vancomycin	Ceftriaxone IV 1g OD and Flucloxacillin IV 2g q6hrly for 3 days then oral Flucloxacillin 500mg po tds for 1 week.	Successful medical treatment	Alive, 161	
11	13 Mar 2011	56yr, Male	4 weeks of fever, malaise, recent transient ischaemic attach. Mitral valve prolapse	Mitral valve endocarditis	Both	Flucloxacillin, Vancomycin	Flucloxacillin IV 2g q4hrly. Mitral valve surgery and St Jude mitral valve replacement on Day 3 post diagnosis due to ongoing fever and severe mitral regurgitation. 6 weeks of IV Flucloxacillin (6g over 24hrs)	Successful surgical treatment for severe mitral valve endocarditis	Alive, 49	Post-surgery right middle and lower lobe pneumonia.

A second case of endocarditis case was diagnosed in a 70-year-old man (Case 9) with a previous St Jude mitral valve replacement who presented with several days of fever. He was aggressively managed with intravenous Flucloxacillin (6 weeks), Gentamicin (2 weeks) and oral Rifampicin (6 weeks). He had good response to the medical treatment and transoesophageal echocardiography did not demonstrate significant valvular or para-valvular dysfunction. This patient died 4 months later due to an unrelated subarachnoid haemorrhage; computed tomography of the head did not show features to suggest mycotic aneurysm.

The final case of infective endocarditis was in a 56-year-old man (Case 11) with known mitral valve prolapse, associated with moderate mitral regurgitation under regular cardiology follow-up. He presented to the hospital 2 weeks prior with recent onset of fever and malaise which settled spontaneously. On that admission there was documented left hemiplegia, which resolved completely within several hours. A computed tomography scan of the brain did not reveal any acute lesions. A diagnosis of transient ischaemic attack (TIA) was made. On that particular admission, only a single blood culture was taken, and it grew a CoNS, which was not further identified at that time. Thus, based on the resolution of fever, it was believed that CoNS was a contaminant.

He subsequently returned to hospital with intermittent fever, rigors and abdominal pain; the working diagnosis communicated to the laboratory was suspected appendicitis or diverticulitis. This time, the first blood culture set grew two CoNS, one of which was identified as *S. lugdunensis*. A third set, taken 2 days later, grew only the *S. lugdunensis*. An urgent transthoracic echocardiography revealed a vegetation on the anterior mitral leaflet associated with severe mitral regurgitation which was confirmed on transoesophageal echocardiography. This patient underwent urgent mitral valve replacement surgery and a 6 week course of intravenous Flucloxacillin.

Other infections—A number of other infections including deep tissue infection, necrotising fasciitis, severe nosocomial systemic sepsis, superficial skin infection, post-pacemaker implantation bacteraemia, and fever of unknown origin have also been associated with *S. lugdunensis*.

The patient characteristics, diagnosis, antibiotics regime, duration, echocardiographic investigations and outcomes were summarized in Table 1. Flucloxacillin, Vancomycin, Amoxycillin-Clavulanate, second and third-generation of Cephalosporin monotherapy or combination had been used in treatment. Two of these eight patients died in the follow-up with associated comorbidities that resulted immunosuppression (Case 2 & 6, Table 1). One patient with end stage prostate cancer died in hospital due to nosocomial infection which progressed to multiorgan failure (Case 8, Table 1).

Discussion

S. lugdunensis infection, unlike sepsis due to other species of CoNS, is frequently aggressive and life threatening in nature.[9] In our single centre report of 11 patients with *S. lugdunensis* bacteraemia presenting over a 5-years period, this organism was associated with serious clinical infection in almost half of the cases. This observation is similar to other published experience, where *S. lugdunensis* is reported as a virulent

pathogen, causing invasive infection similar to *Staphyloccocus aureus*, particularly in the setting of infective endocarditis.[4,10-12]

In our series, 3 (27%) cases of *S. lugdunensis* bacteraemia were due to infective endocarditis which merits further discussion. The incidence of endocarditis in patients with *S. lugdunensis* bacteraemia is not well established. It is reported as high as 46% by Zinkernagel et al.[11] Other studies report a much lower incidence of infective endocarditis with *S. lugdunensis* bacteremia from 0 -7%.[12–14] Of note, in the presence of multiple positive blood cultures, systemic inflammatory response syndrome, sepsis or septic shock, the incidence of endocarditis was considerably higher in most series; 1 (17%) of 6 by Ebright et al and 4 (27%) of 15 by Choi et al.[12,14] In our series, both native and prosthetic valves proved susceptible to infection which is in concordance with other series. In addition, pacemaker lead infection, as described in our series, can result in infective endocarditis, which was not clinically suspected in our patient, although no echocardiography was undertaken.

Our series revealed that only 6 (55%) patients had echocardiogram performed with 4 (66%) of this cohort also undergoing transoesophageal echocardiography. The 2009 European Society of Cardiology (ESC) guidelines on the prevention, diagnosis and treatment of infective endocarditis recommends echocardiography in cases where infective endocarditis were highly suspected and/or in patients with *S. aureus* bacteriaemia.[15] Recommendation of echocardiography in patients with *S. lugdunenesis* bacteraemia, however, is not clear. Due to its aggressive nature and high association with infective endocarditis and devastating effects once intracardiac infection is established, we support, as a minimum, routine transthoracic echocardiography in this group of patients.

S. lugdunensis endocarditis is associated with a high mortality rate with frequent surgical intervention considered necessary. Anguera et al, in a series of 912 consecutive endocarditis, reported the overall mortality of *S. lugdunensis*, *S. aureus* and *Staphylococcus epidermidis* as 50%, 14.5% and 20% respectively; surgery was performed in 70%, 36.9% and 60% respectively. Although *S. lugdunensis* accounts for 1.1% cases of endocarditis in this series, the high mortality rate highlights the aggressive nature of this particular CoNS in the setting of endocarditis.[4] Liu et al, in their recent review of 67 cases of *S. lugdunensis* infective endocarditis from 1988 to 2008, documented that 82.5% of cases were left-sided valvular endocarditis, 78.7% occurred in native valves, with surgery performed in 66.7% of cases and a mortality rate of 38.8%.[5]

Unlike most of the CoNS, *S. lugdunensis* appears susceptible to a wide range of antibiotics including Penicillin, Cefazolin, Linezolid, Moxifloxacin, Nafcillin, Quinupristin-Dalfopristin, Rifampicin, Tetracycline, Trimethoprim-Sulfamethoxazole, and Vancomycin, using standard *in vitro* methods.[16] However, Linezolid and Vancomycin were not bactericidal. In a biofilm model, the activity of most antibiotics was severely reduced and Nafcillin (a congener of the Flucloxacillin used in our case series) increased the production of biofilm.[16]

The 2009 European Society of Cardiology guidelines on the prevention, diagnosis and treatment of infective endocarditis has acknowledged the aggressive nature of *S. lugdunensis* and the recommended treatment is the same for *Staphylococcus* species which involves 4–6 weeks of Flucloxacillin (or Oxacillin) with 3–5 days of

Gentamicin for native valve infection. For patients with prosthetic valve infection or Methicillin-resistant strains, addition of Rifampicin or the use of Vancomycin may be considered.[15] All isolates in our series were susceptible to Flucloxacillin and Vancomycin. Oral treatment with Cephalosporin (Cefuroxime & Cefaclor) in simple soft-tissue infection appeared to be effective in our case series. The high rate of susceptibility to beta-lactams in our series is in concordance with available data.[4,10,11] Multiple antibiotics resistance is rare in the literature and was not observed in our study.

One of the described cases of infective endocarditis had CoNS identified on the admission blood culture which was initially considered to be a contaminant. As a consequence, no further identification was carried out. It is recommended that three sets of blood cultures are performed in cases of suspected endocarditis as continuous bacteraemia occurs. Contamination usually only affects one sample. This particular patient presented as fever and transient ischaemia attack which retrospectively may have represented an embolic event secondary to infective endocarditis. On the second presentation to the hospital 2 weeks later, three sets of blood cultures demonstrated *S. lugdunensis* and the initial culture was then re-studied and confirmed to be the same organism. Reliable methods for identification of of *S. lugdunensis* have been well described.[1,17,18] *S. lugdunensis* colonies usually appear similar to other CoNS after 24 hrs incubation: small, white and non haemolytic. After 48 hrs, a faint yellow colour is often visible and they may resemble *S. aureus*. A high degree of skill and awareness is required for prompt recognition. Many laboratories use slide and rapid latex agglutination tests to distinguish *S. aureus* from CoNS but these kits do not detect staphylococcal coagulase itself. *S. lugdunensis* can be falsely identified as *S. aureus* due to the presence of clumping factor. In an experienced hand, phenotypic characteristics such as colony pleomorphism and beta-haemolysis are useful in detecting *S. lugdunensis*, in contrast to clumping and synergistic haemolysis, which characterize several CoNS species.[19] Bocher et al in their study found that, *S. lugdunensis* has a prominent beta-haemolysis and characteristic *Eikenella*-like odour 2 days after incubation on Columbia agar with 5% sheep blood; by combining with these features and colony pleomorphism they were able to increase the yield of *S. lugdunensis* identification by 11-fold in all types of cultures.[20]

Conclusion

S. lugdunensis bacteraemia is associated with infective endocarditis in one in three patients. Investigation for suspected endocarditis should include at least three sets of blood cultures, to distinguish contamination or transient bacteraemia from the continuous bacteraemia of endocarditis. Assessment for the presence of endocarditis with echocardiography should be considered strongly in all cases of S. lugdunensis bacteraemia.

Competing interests: None declared.

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