Serious staphylococcal infections

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Staphylococcus aureus is a versatile pathogen that causes significant morbidity and mortality in the community and healthcare settings. It is capable of causing a broad spectrum of disease from mild skin and soft tissue infections (SSTIs) to severe life-threatening diseases such as bacteraemia, complicated SSTIs, osteomyelitis, infective endocarditis and toxic shock syndrome. Infection is usually endogenous in origin,[1] with approximately one-quarter of the population carrying one or more strains, principally in the nose, at any given time.

This article focuses on the diagnosis and management of life-threatening infections and emerging problems related to staphylococcal infections, including Panton-Valentine leucocidin (PVL)-associated disease, community-associated methicillin-resistant *S. aureus* (CA-MRSA) and vancomycin intermediate *S. aureus* (VISA).

Key Points

- ***Staphylococcus aureus* is a versatile pathogen capable of causing a broad spectrum of disease**
- **Clinical findings are often absent in infective endocarditis especially in early disease**
- **A high clinical index of suspicion for complications is required for any patient with *S. aureus* bacteraemia**
- **Flucloxacillin is the first-line treatment for methicillin-sensitive *S. aureus***
- **Panton-Valentine leucocidin-related disease may be severe and vigilance is required**

KEY WORDS: bacteriaemia, infective echocarditis, methicillin-resistant *Staphylococcus aureus*, Panton-Valentine leucocidin

Bacteraemia

S. aureus is a leading cause of community- and hospital-acquired bacteraemia. It is the third commonest cause of bacteraemia in Wales and rates worldwide have risen with the increased use of intravascular (iv) catheters.[2] The overall associated mortality of 20–40% has remained largely unchanged over several decades despite advances in medical care.[3] Higher mortality rates are seen in patients who develop complications as well as in the elderly and those with comorbidities.[4]

Complications

Diverse complications, often difficult to identify and frequently overlooked, are suffered by 11–53% of patients with *S. aureus* bacteraemia.[5] A high clinical index of suspicion for complications is therefore required in any patient with a *S. aureus* bacteraemia. Complications include infective endocarditis and metastatic seeding to almost any body site. Host risk factors associated with the development of complications in patients with bacteraemia include community acquisition of bacteraemia, absence of identifiable infective focus, presence of an indwelling foreign body and comorbidities such as malignancy and HIV.[6–9]

Complications are often occult and, as it is not practical to investigate every case of *S. aureus* bacteraemia extensively, clinicians have attempted to identify factors that predict their subsequent development (Table 1).[10,11] However, no risk factor or constellation of risk factors will reliably identify all individuals with – or who will develop – complications.

Infective endocarditis

Infective endocarditis (IE) is a feared complication of *S. aureus* bacteraemia, with an estimated incidence of 10–15%.[10] The risk of IE and its associated mortality are increased in the setting of iv drug use, iv catheter-related infection and predisposing cardiac abnormalities including prosthetic valves.[8,12]

Clinical findings are often absent in *S. aureus* endocarditis, particularly during early disease, leading to underdiagnosis of this complication.[13] Echocardiography is therefore often used to evaluate patients with *S. aureus* bacteraemia and is more sensitive than clinical findings alone.[14] Transthoracic echocardiography (TTE) is usually performed initially due to its widespread availability and non-invasive nature. However, transoesophageal echocardiography is superior to TTE and should be considered in all patients with *S. aureus* bacteraemia in whom there is a clinical suspicion of complicated disease (Table 1) or suspicion of IE.[15]

Metastatic infections

Bones, joints, meninges and prosthetic devices are particularly prone to metastatic seeding of *S. aureus* following bacteraemia. Many patients develop localising symptoms related to the metastatic focus within the first 48–72 hours of hospitalisation. However, complications go

Table 1. Predictors of complications in patients with *Staphylococcus aureus* bacteraemia.

- A time to blood culture positivity less than 14 hours
- Positive follow-up blood cultures 48–96 hours after the first positive blood culture result
- Persistent fever 72 hours after initial positive blood culture result
- Skin findings suggestive of an acute systemic infection
- A new or diastolic murmur

unnoticed in a subset of patients, resulting in inadequate therapy and subsequent increased morbidity and mortality. The development of localising symptoms and persistent fever should prompt further investigation for a deep focus of infection.

Osteomyelitis

In adults, haematogenous *S. aureus* osteomyelitis most often involves the vertebral bodies.[16] Patients over the age of 50 with community-acquired bacteraemia and no identifiable primary focus are at highest risk.[16]

Septic arthritis

The joint synovium is highly vascular and therefore susceptible to haematogenous infection. Septic arthritis usually involves a single joint but may be polyarticular in people with rheumatoid arthritis (RA). Patients with immunosuppression and/or RA are at particular risk.

Meningitis

S. aureus meningitis may occur as a result of *S. aureus* bacteraemia, usually in the context of overwhelming disseminated disease.[17] Lumbar puncture should be carried out in any patient with *S. aureus* bacteraemia who develops headache, neck stiffness or meningism.

Staphylococcus aureus virulence factors

The pathogenicity of *S. aureus* is related to a large number of virulence factors that include bacterial components such as surface-associated molecules. *S. aureus* also produces a number of secreted products, including superantigens, cytotoxins such as PVL, and secreted enzymes.

Toxic shock syndrome

Toxic shock syndrome (TSS) is an acute and potentially fatal condition characterised by several clinical and laboratory findings (Table 2).[18] TSS often develops from a site of colonisation rather than from infection and is related to the production of exotoxins.[19] In the early 1980s numerous cases were reported in North America related to the use of superabsorbent tampons. The proportion of cases related to menstruation has since dropped due to increased public awareness and altered composition of tampons.[20] Non-menstrual cases may be associated with localised infections, surgery or insect bites. There is a 5% overall case mortality for staphylococcal TSS.

Community-associated methicillin-resistant *Staphylococcus aureus*

MRSA is classically acquired during contact with hospitals or other healthcare institutions and is known as hospital-associated MRSA (HA-MRSA).[21] Recently, however, cases of MRSA in patients from the community with no exposure to healthcare institutions have emerged as a problem, particularly in the USA. These CA-MRSA strains are genotypically and phenotypically distinct from the strains associated with HA-MRSA. The community-acquired strains are often susceptible to a wider range of antibiotics, including ciprofloxacin, and resemble community strains of methicillin-sensitive *S. aureus* (MSSA). Most of them produce the PVL toxin.[22]

Panton-Valentine leucocidin

PVL toxin, first described in 1932, is encoded by a mobile phage that produces two gene products that assemble with each other to form a membrane-perforating complex that destroys white blood cells and causes tissue necrosis.[23] PVL-related disease, often associated with severe infections including necrotising pneumonia,[24] is not a new phenomenon.

Renewed interest in PVL-related disease in the UK and worldwide has developed from the emergence of community outbreaks of MRSA in the USA. Currently in the UK, PVL-related disease is mostly associated with MSSA. Although rare at present, with only a handful of reported MRSA-related clus-

Table 2. Clinical case definition of toxic shock syndrome (adapted from Ref 18).

Symptom or criterion	Description
Fear	Temperature >38.9°C
Rash	Diffuse macular erythroderma
Desquamation	1–2 weeks after onset of illness, particularly on palms and soles
Hypotension	Systolic blood pressure <90 mmHg for adults
Multisystem involvement (>2 systems involved):	
Gastrointestinal	Vomiting/diarrhoea at onset of illness
Muscular	Severe myalgia or creatine kinase at least twice ULN
Mucous membrane	Vaginal, oropharyngeal or conjunctival hyperaemia
Renal	Blood urea or creatinine at least twice ULN or urinary sediment with pyuria in absence of UTI
Hepatic	Total bilirubin, ALT or AST at least twice ULN
CNS	Disorientation or alteration in consciousness without focal neurology when fever and hypotension are absent
Laboratory criteria	Negative results on the following tests if performed: (i) blood, throat or CSF cultures (blood culture for *S. aureus* may be positive) (ii) Rocky Mountain spotted fever, leptospirosis or measles
Case classification:	
Confirmed	All six of the clinical findings above are present
Probable	Five of the six clinical findings above are present

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CNS = central nervous system; CSF = cerebrospinal fluid; ULN = upper limit of normal; UTI = urinary tract infection.

Table 3. Risk factors for Panton-Valentine leucocidin-related disease (the five 'Cs').

- Contaminated items
- Close contact, such as with contact sports (eg wrestling, rugby, judo)
- Crowding, such as in households, gyms, prisons and military training camps
- Cleanliness (lack thereof)
- Cuts and other compromised skin integrity

ters in the UK to date, ongoing vigilance is required for the emergence of this phenomenon. Risk factors for the acquisition of PVL *S. aureus* have been identified and are listed in Table 3.[25]

Investigation into PVL-related disease in the UK has uncovered a number of clusters and hot spots of infection and led to the development by the Department of Health of interim guidelines for its management.[26] It is important to recognise PVL-related disease through its clinical presentation as specific treatment regimens and decolonisation strategies are recommended. The clinical features suggestive of PVL *S. aureus* are given in Table 4.

Skin and soft tissue infections

Most SSTIs can be dealt with in the community using oral antibiotics. Wherever possible, therapy should be guided by antimicrobial susceptibility tests. Severe disease requires emergency admission for parenteral antibiotics. The current recommendations are combination therapy with iv clindamycin and linezolid to suppress PVL and alpha-toxin production, with rifampicin for intracellular clearance of staphylococci. In the intensive care setting, iv immunoglobulins should be considered because of their action in neutralising exotoxins and superantigens.

Vancomycin-intermediately and -fully resistant *Staphylococcus aureus*

VISA was first described in Japan in 1997. These isolates do not reliably respond to glycopeptide therapy and are not detected by routine microbiological methods. The mechanism of resistance is unclear but is probably related to the production of a thicker capsule. VISA should be suspected in any patient who has persistent *S. aureus* infection despite prolonged glycopeptide treatment. If suspected, the isolates should be referred to a reference laboratory for specialist testing. Isolates fully resistant to vancomycin have also been reported but remain rare.

Newer agents for staphylococcal infections

Flucloxacillin is the treatment of choice for MSSA infection and the parenteral glycopeptides remain the preferred therapy for MRSA in most situations. However, a number of new agents with efficacy against *S. aureus,* including MRSA, have been developed in recent years.

Oxazolidinone

Linezolid, an oxazolidinone, is a bacteriostatic agent discovered in 1987, with activity against Gram-positive organisms. It is an alternative to glycopeptides for the treatment of pneumonia and severe SSTI caused by MRSA. It is available in iv and oral preparations and is therefore suitable for outpatient treatment. It can cause bone marrow suppression, so full blood counts should be measured at least once a week while on therapy. Prolonged use has been associated with resistance, blood disorders and optic neuropathy. Licensed use is limited to a maximum of 28 days.

Daptomycin

A lipopeptide, daptomycin, is a rapidly bactericidal agent discovered in the 1980s with activity against Gram-positive organisms. It is licensed for the treatment of complicated SSTIs and has shown comparable efficacy to vancomycin in the treatment of bacteraemia and endocarditis caused by *S. aureus.*[27] It is not recommended for the treatment of pneumonia as it does not achieve sufficiently high concentrations in the respiratory tract and is inactivated by surfactant. Daptomycin can cause myalgia, muscle weakness and myositis. Creatine kinase should be measured before and regularly during treatment.

Tigecycline

A glycylcycline, tigecycline, is structurally related to the tetracyclines and has broad-spectrum activity. It has been approved

Table 4. Clinical features of Panton-Valentine leucocidin (PVL) *Staphylococcus aureus* disease (adapted from Ref 26).

Skin and soft tissue infections (often recurrent and may occur in clusters)	**Invasive infections** (may occur in young, immunocompetent host)
• Furunculosis, carbuncles, folliculitis, cellulitis • Cutaneous lesions >5 cm are not uncommon • Pain and erythema that seems out of proportion to severity of cutaneous findings may occur • Necrosis is an indicator of possible PVL *S. aureus* infection	Necrotising pneumonia suspect in patient with: – respiratory symptoms and sepsis following a flu-like illness – haemoptysis – hypotension – marked leucopenia – very high inflammatory markers – raised creatine kinase – numerous staphylococci seen on Gram film of sputum • Necrotising fasciitis • Osteomyelitis, septic arthritis and pyomyositis • Purpura fulminans

for the treatment of complicated SSTIs and complicated abdominal infections caused by multiple-antibacterial resistant organisms.

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