Staphylococcal and streptococcal infections

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Abstract

Staphylococcal and streptococcal infections are common infectious diseases and can range from mild, superficial skin infections to severe, life-threatening systemic infections. *Staphylococcus aureus*, group A streptococcus, and *Streptococcus pneumoniae* are the three major pathogens. The prevalence of invasive infections caused by community-associated meticillin-resistant *S. aureus* and group A streptococci appears to be increasing. The emergence of drug resistance (e.g. meticillin and glycopeptide resistance in *S. aureus*, macrolide resistance in group A streptococci and penicillin resistance in *S. pneumoniae*), is causing concern and could threaten successful treatment. *Streptococcus suis* has emerged as an important human pathogen.

Keywords community-acquired MRSA; group A streptococci; group B streptococci; *Staphylococcus aureus*; *Streptococcus bovis*; *Streptococcus pneumoniae*; *Streptococcus suis*; viridans streptococci

What's new?

- The first case of vancomycin-resistant *Staphylococcus aureus* (VRSA) in Europe has recently been reported
- The role of Panton–Valentine leucocidin (PVL) in the pathogenesis of community-acquired meticillin-resistant *S. aureus* infections is debatable
- Bacterial whole-genome sequencing is more discriminatory than conventional typing methods for *S. aureus*, and is useful in defining and tracking outbreaks
- Synergistic gentamicin is associated with nephrotoxicity and of no benefit in *S. aureus* bacteraemia and endocarditis

Staphylococci

The genus *Staphylococcus* currently contains 48 species, all of which are part of the normal skin and mucous membrane flora of humans and animals. *Staphylococcus aureus* is the most important pathogen, causing a range of pyogenic infections and toxin-mediated illnesses in normal hosts. Other species are collectively termed the 'coagulase-negative staphylococci'. These are generally considered non-pathogenic, apart from *Staphylococcus lugdunensis*, which can cause invasive infections similar to *S. aureus*, *Staphylococcus epidermidis* and *Staphylococcus haemolyticus*, which cause nosocomial (hospital-associated) bacteraemia and device-related infections, and *Staphylococcus saprophyticus*, which is a common cause of urinary tract infection.

Staphylococcus aureus

S. aureus is carried in the anterior nares of 20–40% of adults, depending on seasonal and local epidemiological factors. Some groups (e.g. medical staff, persons with type 1 diabetes mellitus, haemodialysis patients, injection-drug users) appear to be particularly susceptible to colonization with *S. aureus*. Carriers transfer the organism to the skin, where trauma can provide a portal of entry, leading to local, deep, or systemic infection. The global spread of meticillin-resistant *S. aureus* (MRSA), which is intrinsically resistant to all β-lactam antibiotics, is a major concern.[1] Over the past few years, infections caused by community-associated MRSA (CA-MRSA) in previously healthy people have emerged as a significant clinical problem, particularly in the USA.[2] The emergence of isolates with reduced susceptibility or resistance to vancomycin was first described in the 1980s. These include vancomycin-intermediate *S. aureus* (VISA), heterogeneous VISA (hVISA) and vancomycin-resistant *S. aureus* (VRSA).[3] hVISA strains appear to be susceptible to vancomycin but contain a subpopulation of cells resistant to vancomycin. To date, 12 cases of VRSA have been described in the USA[4] and one in Europe.[5] The mechanism of resistance appears to be plasmid-mediated transfer of the *vanA* gene cluster from enterococci, rather than clonal dissemination of a single VRSA strain.

Pathogenesis: *S. aureus* has several putative determinants of pathogenicity, including cell wall constituents, surface proteins, toxins and enzymes, and specific cell wall-bound adhesins. It secretes enzymes, including catalase, coagulase, clumping factor, hyaluronidase, β-lactamases and DNase, and produces extracellular toxins, some of which are directly cytotoxic (haemolysins, leukocidins) and some of which act as superantigens, causing polyclonal proliferation of T cells (toxic shock syndrome toxin-1 (TSST-1), enterotoxins, epidermolytic toxins). Panton–Valentine leucocidin (PVL) is a cytotoxin that causes leucocyte destruction and tissue necrosis. Although there is an epidemiological association between CA-MRSA infections and PVL production, the role of PVL in the pathogenesis and spread of infection remains uncertain.[6] Host factors that predispose particularly to *S. aureus* infection include inborn defects in neutrophil function, diabetes mellitus, and the presence of foreign material. Nasal carriers are more likely to develop nosocomial bacteraemia, though the associated mortality may be lower.

Microbiology: *S. aureus* grows rapidly in both aerobic and anaerobic conditions on blood agar and other non-selective solid

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media. Most strains are β-haemolytic. Microscopically, *S. aureus* is apparent as Gram-positive cocci that tend to form clusters on solid media. Identification is usually confirmed by positive catalase, coagulase and DNase tests. Typing is performed by molecular methods (e.g. pulsed-field gel electrophoresis, multilocus sequence typing, SCC*mec* typing or *spa* typing) although bacterial whole-genome sequencing has been found to be more discriminatory.[7]

Clinical manifestations: *S. aureus* is a major cause of skin and soft-tissue infections including impetigo, ecthyma (ulcerative pyoderma), folliculitis, furuncles, carbuncles, erysipelas, cellulitis and necrotizing fasciitis (see Skin and soft tissue infections *Medicine* **41**(12), pages 709-715). Over the past few years, outbreaks of CA-MRSA infection have been reported in children, Alaskan natives, Pacific islanders, prisoners, sports teams and military personnel.[2] CA-MRSA has become the most common cause of skin and soft-tissue infections presenting to emergency departments in the USA.[8]

The incidence of *S. aureus* bacteraemia and the proportion of bacteraemic episodes caused by MRSA have also increased over the past few years.[9] *S. aureus* bacteraemia can be divided into two categories: community-acquired (onset <2 days post-hospital admission) and hospital-acquired (onset ≥2 days after hospital admission). Metastatic infections such as endocarditis, pericarditis, pneumonia, pulmonary abscesses, empyema, septic bursitis, septic arthritis, pyomyositis and discitis osteomyelitis can occur (Figures 1 and 2). The diagnosis is confirmed by cultures of blood and appropriate clinical specimens. Patients with *S. aureus* bacteraemia should have an echocardiogram to exclude endocarditis. Investigations for metastatic infection should be guided by symptoms (e.g. magnetic resonance imaging of the spine to exclude osteomyelitis and discitis).

Management: treatment of *S. aureus* infections depends on the nature of the primary focus and the presence or absence of metastatic infection. Flucloxacillin is the drug of choice in meticillin-sensitive *S. aureus* (MSSA) infections, whereas vancomycin (or teicoplanin or daptomycin) is used in MRSA infections and penicillin-allergic patients. The role of the newer Gram-positive antimicrobial agents (e.g. linezolid, ceftobiprole) in the treatment of MRSA infections remains to be established.

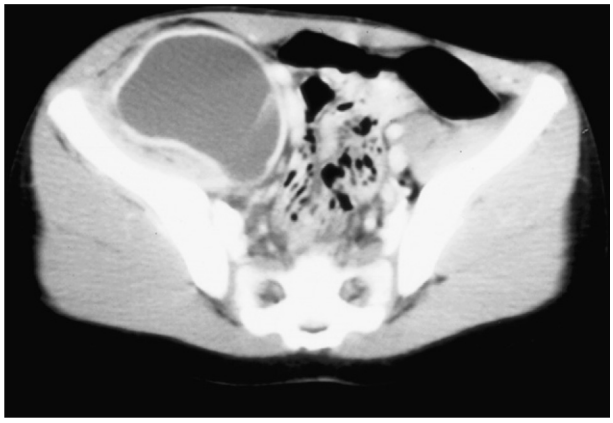

Figure 1 Psoas abscess caused by *Staphylococcus aureus*.

Aminoglycosides exhibit synergistic activity against *S. aureus in vitro* and are often used in endocarditis, although one study has shown no evidence of benefit.[10] Skin and soft-tissue infections usually respond to 7–14 days of antibiotic therapy. Deeper infections, such as deep abscesses, septic arthritis or osteomyelitis, often require drainage of the focus and more prolonged antimicrobial therapy (e.g. 4–6 weeks). Catheter-related bacteraemia is treated by removal of the catheter and 14 days' intravenous therapy. Bacteraemia of unknown source or endocarditis is treated with a minimum of 4 weeks' intravenous therapy. The treatment of endocarditis is discussed elsewhere (see Infective endocarditis in adults *Medicine* **41**(12), pages 689-692). In prosthetic device-related infection, the device should be removed and the infection treated with prolonged (4–6 weeks) intravenous therapy. In cases where the device cannot be removed (e.g. vascular graft infection), oral suppressive antimicrobial therapy (including rifampicin, if the isolate is susceptible) should be continued indefinitely.

Toxin-mediated diseases: *S. aureus* can also cause a number of toxin-mediated diseases, such as food poisoning, scalded skin syndrome, and toxic shock syndrome. Staphylococcal food poisoning presents with vomiting and diarrhoea within hours of ingestion of foods containing enterotoxin-producing bacteria.

Treatment is symptomatic

Staphylococcal scalded skin syndrome is caused by epidermolytic toxin-producing *S. aureus* and is usually seen in children. Clinical presentation ranges from bullous impetigo to severe, generalized, exfoliative dermatitis with systemic upset. It is usually treated with intravenous antibiotics, supportive skin care and careful management of fluid and electrolyte losses.

Toxic shock syndrome is caused by toxic shock syndrome toxin-1 (TSST-1) and other related staphylococcal enterotoxins. The menstrual form is associated with tampon use, the non-menstrual form with vaginal infections, contraceptive devices, abortion, childbirth and surgical procedures. The clinical case definition includes fever, hypotension, desquamating rash and involvement of three or more organ systems. Management requires aggressive fluid resuscitation, removal of any tampon, and parenteral anti-staphylococcal antibiotics.

Coagulase-negative staphylococci

Coagulase-negative staphylococci (CoNS) are skin commensals. Although they are often dismissed as culture contaminants, they are becoming increasingly recognized as pathogens.[11] *S. saprophyticus* is a common cause of community-acquired urinary tract infection. *S. lugdunensis* causes invasive infections similar to *S. aureus*. *S. epidermidis* causes nosocomial bacteraemia and prosthetic device-related infections. Other species that have been associated with infection include *S. haemolyticus*, and *Staphylococcus schleiferi*. These organisms adhere to prosthetic material and become embedded in an exopolysaccharide matrix, forming a biofilm. The biofilm protects the organisms from phagocytic cells and reduces the penetration of antibiotics.

Microbiology: coagulase-negative staphylococci grow rapidly aerobically and anaerobically on blood agar and other non-