Staphylococcal and streptococcal infections

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Abstract

Staphylococci and streptococci are leading causes of healthcare and community-acquired bacterial infections worldwide. Within each genus, virulent species such as *Staphylococcus aureus*, *Streptococcus pyogenes* and *Streptococcus pneumoniae* are associated with diverse syndromes of superficial infection, invasive infection and exotoxin production. Within each genus, less virulent species such as coagulase-negative staphylococci and viridans streptococci are common harmless human commensals but are frequently cultured from clinical samples. For these organisms, differentiating opportunistic infection from contamination is a major diagnostic challenge. Infections by these species are typically associated with prosthetic material, and increasing use of implanted medical devices has lead to their rising importance as pathogens. Medically important staphylococcal species such as *Staph. aureus* and *Staphylococcus epidermidis* are frequently resistant to commonly used antibiotics. Clinicians should have a sound understanding of how staphylococci and streptococci cause the clinical syndromes they do and how they are treated.

Keywords Coagulase-negative staphylococci; MRCP; *Staphylococcus aureus*; *Streptococcus agalactiae*; *Streptococcus dysgalactiae*; *Streptococcus pneumoniae*; *Streptococcus pyogenes*; viridans streptococci

Key points

- Coagulase-negative staphylococci are increasingly important pathogens in the context of medical device infections
- *Staphylococcus aureus* bloodstream infection requires intensive investigation and management with specialist input to minimize risk of complications. Patients with deep foci of infection that cannot be removed, or with no identifiable focus of infection, are at highest risk of complications
- Clinical samples frequently yield low-virulence staphylococcal and streptococcal species; differentiating whether these are contaminants or pathogens requires thorough clinical evaluation of the patient
- Invasive β-haemolytic streptococcal infections have a high associated mortality
- Clindamycin is sometimes added to cell-wall-active agents such as β-lactams or glycopeptides to treat invasive β-haemolytic streptococcal infections, but resistance is >10% in some species
- Non-group A haemolytic streptococci are increasingly common causes of invasive human disease

Staphylococci

There are 77 currently recognized species and subspecies within the genus *Staphylococcus*. *Staphylococcus aureus* remains by far the most medically important and is distinguished by its production of coagulase.

Among coagulase-negative staphylococci (CoNS), *Staphylococcus lugdunensis* and *Staphylococcus saprophyticus* have particular pathogenic potential in device-related and genitourinary infections, respectively. *Staphylococcus epidermidis* and *Staphylococcus haemolyticus* are common commensals of human skin and mucosal surfaces. Their medical importance arises from the fact that they are common sample contaminants in diagnostic microbiology and common causes of device-related infection. With increasing use of implanted medical devices in elderly and frail patients, CoNS have been termed 'pathogens of medical progress'. CoNS are frequently resistant to many antibiotics. Accurate diagnosis and treatment of CoNS infection is thus an increasingly important medical problem.

Microbiology

Identification of staphylococci in the laboratory still relies heavily on microscopy and culture-based techniques. Staphylococci stain positive (purple) with Gram stain, and are spherical, non-motile, non-spore-forming bacteria seen down the microscope singly, in pairs or in grape-like clusters. 'Staphyl' comes from the Greek word for grapes. Staphylococci grow easily at 30–37°C on a wide variety of culture media in both aerobic and microaerophilic conditions. Colonies on solid agar are round and smooth, varying from white to golden yellow in colour.

Laboratory identification of *Staph. aureus* is still primarily based on phenotypic methods to detect the presence of enzymes such as catalase or coagulase and adhesins such as clumping factor or protein A (usually by commercial latex agglutination assays). Chromogenic agar allows identification through colour changes in response to phosphatase activity present in *Staph. aureus*. *Staph. aureus* is tolerant to high salt concentrations, so

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salt broth (5–7% NaCl) can be used for selective culture. Mass spectrometry (matrix-assisted laser desorption/ionization-time of flight (MALDI-TOF)) is increasingly being used for rapid organism identification in cultured isolates through molecular mass profiling of species-specific proteins.

Antibiotic susceptibility testing relies primarily on detection of growth in the presence of different antibiotics. Traditionally, this has been done by antibiotic diffusion on agar, but faster, automated, culture systems such as Vitek® (bioMerieux) and Phoenix™ (Becton Dickinson) are now widely used. Even with such systems, identification and susceptibility testing of *Staph. aureus* still typically takes >36 hours.

Molecular methods based on detection of *Staph. aureus*-specific genes such as nuclease (*nuc*), coagulase (*coa*) and protein A (*spa*) are now being used to detect *Staph. aureus* in clinical samples, and these are particularly used to screen patients for *Staph. aureus* carriage because they provide no susceptibility data.

Whole-genome sequencing is an emerging technology in diagnostic and public health microbiology. Although currently a reference laboratory tool, analysis of microbial whole-genome sequence data has the potential to provide organism identification, resistance and virulence data to guide management testing and transmission data for infection control purposes.

Pathogenesis

Staph. aureus: this colonizes as many as 40–60% of healthy people yet is also the cause of a diverse range of syndromes of infection. A general understanding of virulence mechanisms and the genetics behind them can help in understanding how *Staph. aureus* presents clinically.

Most of the *Staph. aureus* genome (2.8 Mbp) is made up of genes present in all strains (core genome), but around 10% is made up of genes that vary between strains (core variable genome) and 10–20% is mobile genetic elements that are gained and lost at high frequencies. These often encode virulence factors and antibiotic resistance genes. This sharing of mobile genes is not uniform, and *Staph. aureus* has evolved into distinct lineages, with most disease-causing isolates belonging to a small number of these. Their prevalence varies widely over time and geography for reasons that are generally unclear.

Staph. aureus virulence determinants take three major forms (Figure 1). Adhesins such as fibronectin-binding protein and collagen-binding protein are implicated in tissue adherence; others such as protein A and intracellular adhesion contribute to within-host survival through immune evasion and biofilm formation. *Staph. aureus* produces a range of enzymatic virulence factors involved in tissue destruction and immune evasion, such as exfoliative toxins and nucleases. It also produces cytolysin toxins (e.g. haemolysins, leucocidins) that destroy host cells. Finally, it produces a range of 'superantigen' toxins that cause massive polyclonal T cell activation, probably as an immune evasion strategy. Clinically, these toxins are associated with dramatic host reactions including enterotoxin-mediated food poisoning and toxic shock syndrome (TSS).

Understanding *Staph. aureus* pathogenesis has traditionally focused on its behaviour as a vegetative organism in the extracellular compartment, whether as a commensal of the skin/mucus membranes or a cause of invasive disease. It has long been known that, in some situations, nutritionally variant forms of *Staph. aureus* with altered growth, such as cell wall-deficient variants (L-forms) and small colony variants, can be identified from patients with chronic disease states such as cystic fibrosis and orthopaedic infections. It is now increasingly recognized that persister forms of *Staph. aureus*, which may involve intracellular infection, represent an important immune evasion mechanism and explain why a proportion of *Staph. aureus* infections recur after apparently curative treatment.

Coagulase-negative staphylococci: *Staph. lugdunensis* has emerged in recent years as an uncommon but virulent species. It is associated with clinical manifestations very like those of *Staph. aureus*, with which it shares many virulence determinants, although not exotoxin production or secreted coagulase. It has been particularly associated with native valve endocarditis.

Staph. saprophyticus expresses adhesins to genital tract epithelium and is part of the normal vaginal flora. It is responsible for a significant minority (around 15%) of cases of urinary tract infection among young women.

Staph. epidermidis and related species such as *Staphylococcus capitis* and *Staph. haemolyticus* are common commensals of human skin. Their medical importance arises from their tendency to contaminate medical devices, usually at the time of implantation, and set up complex biofilms that withstand clearance of infection by both host immune responses and antibiotic treatment. The complex pathogenesis of biofilm formation involves specific adhesins, production of extracellular polymers, intracellular persistence and mechanisms for biofilm detachment and seeding of infection. These mechanisms, coupled with often extensive antibiotic resistance, make CoNS device-related infections a very significant challenge in modern medicine.

Clinical manifestations and management of *Staph. aureus* infections

Superficial skin and soft tissue infections: *Staph. aureus* is the primary cause of pyoderma (impetigo, folliculitis, boils, carbuncles). Outbreaks of pyoderma are common in families, closed communities (e.g. barracks, prisons) and sports teams. Particular attention has been paid to specific strains such as so-called community-acquired meticillin-resistant *Staph. aureus*, which often encode Panton–Valentine leucocidin (PVL). The relationship between PVL and pyoderma is not clear, and many strains identified from such patients do not carry PVL genes. Infections usually respond well to oral antibiotic treatment but can require surgical drainage. The real clinical challenge is prevention of recurrence in individual patients and their close contacts.

Invasive *Staph. aureus* disease: *Staph. aureus* is one of the most common causes of bloodstream infection, and *Staph. aureus* bacteraemia (SAB) is associated with all-cause mortality in excess of 20% at 30 days. Unlike CoNS, *Staph. aureus* is rarely a contaminant of blood culture, so all patients with *Staph. aureus* identified in blood should be assessed very carefully and managed by infection specialists employing evidence-based care bundles.[1]

SAB has two notable features. First, it is able to metastasize in the blood and establish infection in almost any tissue, most notably the heart valves and musculoskeletal system, especially the spine. Second, infection tends to recur after apparently successful treatment. For these reasons, patients with SAB require

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