Coagulase-negative staphylococci

Coagulase-negative staphylococci are the most frequent constituent of the normal flora of the skin and mucosae and at the same time among the most commonly isolated microorganisms in the microbiology laboratory. These microorganisms are often contaminants in clinical specimens, but are also recognized as causative agents of clinically significant infection, including bacteraemia and endocarditis.

Thus when coagulase-negative staphylococci are isolated from blood, other normally sterile body fluids, intravenous catheters, peritoneal dialysates or various tissues, this presents a potential interpretive challenge to both microbiologists and clinicians. In recent years, with the expansion in invasive procedures and devices, coagulase-negative staphylococci have become increasingly recognized as important agents of nosocomial infection.

Epidemiology and clinical significance

Coagulase-negative staphylococci rarely cause disease in immunocompetent hosts without prosthetic devices, the main risk factors for infection being foreign implanted devices and immunocompromise. In contrast to sepsis caused by *Staphylococcus aureus*, infections caused by coagulase-negative staphylococci typically manifest as less severe and subacute diseases that are infrequently associated with mortality. However, sepsis syndrome and fatal outcomes may occur in immunocompromised patients and/or infections with more aggressive strains such as *S. lugdunensis*.

Coagulase-negative staphylococci are the most common cause of nosocomial bloodstream infections, causing 30–40% of these infections (Rupp, 2004). Data from the National Nosocomial Infections Surveillance System collected between 1992 and 1997 revealed that coagulase-negative staphylococci were associated with 36% of all bloodstream isolates in intensive care units, making these the most common cause of nosocomial bloodstream infections (Richards et al, 1999). A survey from the Surveillance and Control of Pathogens of Epidemiologic Importance (SCOPE) database of nosocomial bloodstream infections in American hospitals between 1995 and 2002 also identified coagulase-negative staphylococci as the most common cause of hospital-acquired bloodstream infections, accounting for 31% of cases (Wisplinghoff et al, 2004).

Among patients with blood cultures positive for coagulase-negative staphylococci, the percentage with significant bloodstream infection ranges from 12–25% of cases (Kirchhoff and Sheagren, 1985; Herwaldt et al, 1996; Weinstein et al, 1997; Souvenir et al, 1998).

Distinguishing between a 'significant' isolate and the occurrence of a skin flora contaminant is important for clinical management. For example, if a patient with a central venous catheter has a single positive blood culture from which a coagulase-negative staphylococcus is isolated, interpretation of this finding is difficult, as this could represent contamination rather than catheter-related bloodstream infection. Additional cultures of blood samples obtained through the suspected catheter and from a peripheral vein should be performed when catheter-related bloodstream infection is suspected before the initiation of antimicrobial therapy and/or catheter removal, to confirm the diagnosis.

A high proportion of positive blood cultures performed on samples drawn from multiple sites remains the best indication for true catheter-related bloodstream infections caused by coagulase-negative staphylococci (Mermel et al, 2009). An incubation time to positivity of less than 25 hours has also been considered consistent with true bacteraemia (Yébenes et al, 2006; Martínez et al, 2007).

In addition, the 'differential time to positivity' test can be used to determine whether a vascular catheter is the source of bacteraemia (Gaur et al, 2003). Blood drawn from the suspect catheter should have a higher inoculum and become positive more quickly than blood obtained from a peripheral venepuncture. When the same amount of blood is inoculated, a 2-hour or more differential time is a sensitive and specific marker of catheter-associated bacteraemia (Gaur et al, 2003; Raad et al, 2004), although time to positivity estimates may not be available in all laboratories. To unequivocally confirm the diagnosis of catheter-related bloodstream infection, it is also important to demonstrate that the coagulase-negative staphylococci isolated from several sites are identical by genotyping. Techniques such as pulsed-field gel electrophoresis are ultimately more discriminatory than phenotypic methods in establishing the diagnosis of catheter-related bloodstream infection caused by coagulase-negative staphylococci, but they are costly and require highly skilled staff and specialist equipment (Casey et al, 2007a).

In addition to catheter-related bloodstream infections, coagulase-negative staphylococci cause prosthetic joint infections, prosthetic valve endocarditis and infection associated with other intracardiac devices, sternal wound infections associated with metal wires after cardiac surgery, vascular graft infections, postneurosurgical meningitis and ventriculoperitoneal shunt infections, peritoneal dialysis peritonitis and post-cataract endophthalmitis.

In ophthalmological practice, coagulase-negative staphylococci are major pathogens for post-cataract endophthalmitis causing 70% of cases (Durand, 2013), and 60% of infections following intravitreal injections of anti-vascular endothelial growth factor agents administered to treat neovascular macular degeneration (Durand, 2013).

Coagulase-negative staphylococci are also important aetiological agents of late onset neonatal sepsis. In a large retrospective cohort study conducted in 248 neonatal intensive care units in the USA from 1997–2009, 17 624 episodes of coagulase-negative staphylococci sepsis were identified among 16 629 very low birth weight (<1500 g) infants. Most episodes were classified as possible infections. Infants with lower birth weights and gestational age were more likely to have coagulase-negative staphylococci isolated during an episode of sepsis (Shane and Stoll, 2014).

Dr Miruna D David *is Consultant Microbiologist and* **Professor Tom Elliott** *is Consultant Microbiologist in the Microbiology Department, Queen Elizabeth Hospital Birmingham, University Hospitals Birmingham, Birmingham B15 2WB*

Correspondence to: Dr MD David (miruna.david@uhb.nhs.uk)

Microbiology and laboratory diagnosis

Staphylococci are Gram-positive cocci in clusters that produce catalase (*Figure 1*). In contrast to the coagulase-positive *S. aureus*, coagulase-negative staphylococci are so named because of their inability to clot plasma as a result of the lack of production of the secreted enzyme coagulase (*Figure 2*).

Although there are over 32 staphylococcal species (von Eiff et al, 2002), usually clinical laboratories do not identify individual species and report these isolates at group level, referring to them as coagulase-negative staphylococci. Current biochemical profile identification techniques are relatively slow and not always accurate, although with new technology such as matrix-assisted laser desorption/ionization laboratory users will increasingly encounter laboratory reports including the exact species name. The three commonest coagulase-negative staphylococci species are *S. epidermidis*, *S. haemolyticus* and *S. hominis*.

One particular species, *S. lugdunensis*, named after the city of Lyon where it was first discovered, stands out among coagulase-negative staphylococci as particularly virulent and has been called 'a wolf in sheep's clothing'. Catheter-related bloodstream infections caused by *S. lugdunensis* should be managed in a similar manner to those caused by *S. aureus* (Mermel et al, 2009), because of the risk of endocarditis and metastatic infection similar to *S. aureus*.

S. saprophyticus, identified in the laboratory through resistance to the antibiotic novobiocin, is a urinary pathogen and a leading cause of cystitis in young women.

Figure 1. Staphylococci Gram stain review (classical appearance in clusters).

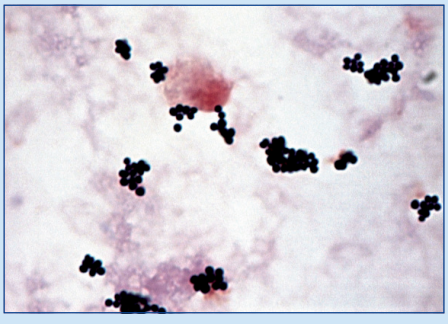
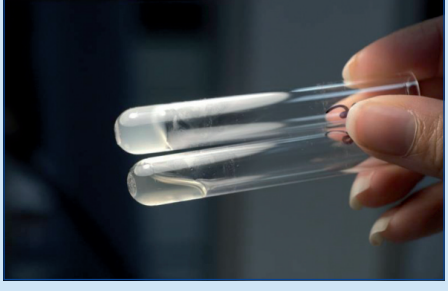


Figure 2. The coagulase test. The top tube is a positive test showing a clot. The bottom tube is negative as there has been no clot formation.



Pathogenesis

The most important virulence factor of coagulase-negative staphylococci is the ability to produce biofilm on the surface of prosthetic or other devices (*Figure 3*).

They can cause intravascular device infection following either colonization of the hub or migration from the patient's skin flora at the point of catheter insertion. Once the pathogens have overcome the mucocutaneous protective barriers, they adhere to certain biosynthetic materials (such as catheters) and proliferate, forming a thick multilayered community and causing local or systemic infection (Ziebuhr et al, 2006). The communities of microorganisms within the biofilm stick to each other and/or to surfaces by the production of an extracellular matrix that mostly consists of polysaccharides and proteins (Ziebuhr et al, 2006) and their persistence is implicated in the risk of recurrence of infection.

Treatment

The treatment of coagulase-negative staphylococcal infections depends on the severity and anatomical site, the presence of a foreign body or prosthetic device, the results of antimicrobial susceptibility testing and any restrictions posed by patient factors such as drug allergies and interactions. Before embarking on an antibiotic course, it is important to evaluate the evidence available in order to distinguish a genuine infection from a contaminated culture, to avoid unnecessary treatment.

Figure 3. Colour enhanced scanning electron microscope of Staphylococcus capitis.

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In general, infections can be treated with antibiotics alone, but in the case of severe sepsis, therapeutic failure or recurrent infection, any foreign body must be removed to facilitate cure.

The glycopeptide antibiotics (vancomycin and teicoplanin) are the usual initial drug of choice because coagulase-negative staphylococci are frequently resistant to beta-lactam antibiotics such as penicillin and flucloxacillin (Wielders et al, 2001; Casey et al, 2007b). For systemic treatment, they are only effective via the intravenous route and may require therapeutic drug monitoring. Glycopeptide resistance is emerging, so susceptibility cannot be automatically assumed, with up to 1% of isolates causing hospital-acquired bacteraemia in England between 1997 and 2002 being vancomycin resistant (National Nosocomial Infections Surveillance System, 2002). Teicoplanin resistance is more prevalent (Biavasco et al, 2000; Ma et al, 2011) and *S. haemolyticus* seems particularly predisposed to develop glycopeptide resistance (Vignaroli et al, 2006). In cases where prolonged treatment is required, such as prosthetic joint infections, suitable oral alternatives may include rifampicin, clindamycin, tetracycline and linezolid. Newer antibiotics such as daptomycin and tigecycline may be used in case of resistance or drug intolerance.

Although antibiotics are usually given systemically (intravenously or via the enteral route), local administration may be preferred in order to achieve high enough concentrations for optimal therapeutic effect in certain infections such as endophthalmitis (where antibiotics can be administered intravitreally), extraventricular drain infection (when vancomycin can be administered intrathecally), intraperitoneally (in cases of peritoneal dialysis peritonitis) or as an antibiotic lock solution in the case of central venous catheter infection. Antibiotic treatment of coagulase-negative staphylococci infection may be difficult because staphylococcal biofilm is almost impermeable to many antibiotics (Mah and O'Toole, 2001).

Complex infections are best discussed with the local microbiologist, when the treatment can be tailored to the individual patient, taking into account special 'drug–bug' associations and other properties such as drug bioavailability and activity on biofilms.

Prevention of coagulase-negative staphylococci infections

Given that cross-infection is possible as a source of nosocomial coagulase-negative staphylococci catheter-related bloodstream infections (Worthington et al, 2000), strategies to prevent coagulase-negative staphylococcal infections are the same as those for the prevention of hospital-acquired infections. These include attention to hand hygiene, meticulous patient skin care, limited use and manipulation of invasive devices. Guidelines for the prevention of intravascular catheter-related infections exist both in the UK and the USA (Mermel et al, 2009; Loveday et al, 2014).

Using antibiotic prophylaxis during surgery with foreign material implantation and antibiotic-impregnated venous catheters and ventriculoperitoneal shunts are other strategies to prevent such infections.

Ongoing surveillance is essential to monitor rates of infection and target measures appropriately.

Conclusions

Coagulase-negative staphylococci are large components of the normal resident flora on the skin and mucous membranes and, at the same time, some of the commonest microorganisms isolated in the microbiology laboratory. Although they are often contaminants, they can also cause a wide spectrum of nosocomial infections. When pathogenic, they tend to be low virulence microorganisms with the exception of species such as *S. lugdunensis*. Treatment usually involves antibiotics with Gram-positive spectrum activity such as glycopeptides or linezolid but recurrent infection may occur in the presence of persistent biofilm, necessitating removal of prosthetic devices where appropriate. BJHM

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KEY POINTS

- Coagulase-negative staphylococci are part of the skin flora and are commonly isolated in the microbiology laboratory, both as contaminants and as true pathogens.
- Several species exist, but most of the time speciation is not required for clinical management.
- They are generally low virulence microorganisms and their main pathogenic potential stems from the ability to form biofilms.
- Coagulase-negative staphylococci cause opportunistic infections especially in immunocompromised hosts and neonates, after surgery with foreign device implantation or in patients with indwelling devices and other prosthetic material.
- The majority of isolates are resistant to beta-lactams (such as flucloxacillin), hence treatment is usually with other agents such as glycopeptides.
- The removal of foreign material may be required especially in cases of severe sepsis, antibiotic treatment failure or relapsing infections.