RAPID RISK ASSESSMENT

Multidrug-resistant *Staphylococcus epidermidis*

8 November 2018

Main conclusions and options for prevention and control

Several endemic multidrug-resistant *S. epidermidis* strains predominate across healthcare systems globally. Increases in the rate and breadth of resistance to multiple antimicrobial agents among these strains is a concerning trend that may limit treatment options for indwelling and prosthetic device infections that are already difficult to treat. Although there are a number of alternative antimicrobial agents that are active against staphylococci, clinical experience with these antimicrobial agents is still limited. Consequently, the precise significance for the therapeutic outcome in patients who have foreign devices (e.g. central vascular catheters, orthopaedic prosthetic devices and cerebrospinal fluid shunts) and surgical site infections of evolving resistance mechanisms that have been recently described in *S. epidermidis* is not yet fully characterised.

Further epidemiological studies of the geographical prevalence of multidrug-resistant *S. epidermidis* strains as a cause of invasive infection in susceptible patient populations as well as prospective in vitro, in vivo and clinical outcome correlation studies are needed to clarify their clinical impact on therapeutic outcomes of foreign-body infections However in the majority of cases of *S. epidermidis* infections, removal or replacement of the contaminated medical device is already required in addition to antimicrobial therapy.

Irrespective of the findings of further studies, the increasing resistance of *S. epidermidis* to multiple antimicrobial agents that are currently considered as first-line agents for the treatment of *S. epidermidis* infections highlights the need for prudent use of them and therefore the importance of antimicrobial stewardship. Treatment options should be guided by local epidemiological surveillance data and individual antimicrobial susceptibility test results for each patient's isolates. Ensuring consistent application of proper infection prevention and control practices, particularly during the insertion and use of medical devices, is crucial for prevention of infections by *S. epidermidis*. More information on antimicrobial susceptibility testing against newer antimicrobial agents with activity against *S. epidermidis,* as well as better evaluation of their effectiveness, is necessary for the optimal management of *S. epidermidis* infections.

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Public health issue

A recent article published in the journal Nature Microbiology, 'Global spread of three multidrug resistant lineages of *Staphylococcus epidermidis*', by J.Y.H. Lee et al. [1] reports a previously unrecognised international spread of near pandrug-resistant strains of *S. epidermidis* as a cause of infection in several countries including European Union (EU) Member States.

Consulted experts

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All experts have submitted declarations of interest and a review of these declarations did not reveal any conflict of interest.

Disease background information

Staphylococcus epidermidis is the most common species of coagulase-negative staphylococci (CoNS) and is the most common species of normal human skin microbiota. *S. epidermidis* is a Gram-positive bacterium and able to form biofilms. A frequent skin coloniser, *S. epidermidis* commonly contaminates clinical microbiology samples, but is also a frequent cause of healthcare-associated infection. Due to the propensity to form biofilms, *S. epidermidis* is a leading cause of infections related to medical devices, such as central venous line-associated bloodstream infections, prosthetic valve endocarditis and surgical site infections (e.g. hip and knee prosthetic joint infections). CoNS were the most frequently identified cause of central line-associated bloodstream infections in surveillance of healthcare-associated infections acquired in intensive care units in 11 European Union (EU) Member States in 2015 [2] and the second-most common organism isolated from hip and knee prosthetic joint infections in surveillance of surgical site infections in the European Union/European Economic Area (EU/EEA) [3].

Specific strains of *S. epidermidis* can become predominant in hospital settings and have been shown to spread within hospitals [4] and between hospitals and countries [5,6]. Multilocus sequence typing (MLST) studies have demonstrated that several lineages predominate globally, with the most common lineages being ST2, ST5 and ST23. The modes of transmission of *S. epidermidis* in hospital settings are not well characterised since it is a ubiquitous commensal of the human skin and only acts as an opportunistic pathogen.

Healthcare-associated strains of *S. epidermidis* produce extracellular biofilms that hinder the action of most antimicrobial agents and host immune response, thus making treatment of medical device infections challenging and often requiring the replacement or removal of the contaminated device for successful treatment of the infection. Antimicrobial agents are administered concomitantly with replacement or removal of the device. Healthcare-associated strains of *S. epidermidis* tend to be multidrug-resistant, with resistance to meticillin ranging from 75% to 90% [7–9]. Resistance to other antimicrobial agents, such as trimethoprim/sulfamethoxazole, clindamycin, fusidic acid and fluoroquinolones is also very high. The antimicrobial agent of choice for most infections caused by *S. epidermidis* is vancomycin. Strains with decreased susceptibility or with resistance to vancomycin and the presence of subpopulations resistant to vancomycin (heteroresistance) have been commonly reported [10–12]. Heteroresistance to glycopeptides is not detected with standard antimicrobial susceptibility testing techniques and requires special methods such as the gradient diffusion macromethod or population-analysis profiling area under the concentration-time curve [13]. However, the clinical significance of heteroresistance is unknown [14–16]. Rifampicin is often recommended for the treatment of infections involving prosthetic devices due to activity against staphylococci in biofilms. However, rifampicin should always be used in combination with other active antimicrobial agents due to the rapid development of resistance to rifampicin when used as monotherapy [17]. Resistance of *S. epidermidis* to rifampicin is also commonly reported [18]. Several other antimicrobial agents remain active in vitro against *S. epidermidis*, such as ceftaroline, ceftobiprole, dalbavancin, daptomycin, linezolid, oritavancin, quinupristin/dalfopristin, tedizolid, telavancin and tigecycline. However, resistance to linezolid is increasingly reported, having spread among major predominant healthcare-associated lineages, and can be plasmid-mediated [19–21]. Resistance to the other listed antimicrobial agents is still uncommon.

Due to the challenges of treatment of medical device infections, consistent application of periprocedural infection prevention measures is crucial [22].

Event background information

A comparative genomic study of 419 *S. epidermidis* clinical isolates from Australia, the EU (Belgium, Denmark, France, Germany, Ireland and the United Kingdom) and the US identified dual D471E and I527R *rpoB* gene mutations as a common mechanism related to rifampicin resistance and heteroresistance to glycopeptides that is prevalent among two common sequence types globally: ST2 and ST23 [1]. The study also describes an increasing prevalence of resistance to rifampicin among clinical *S. epidermidis* isolates from 2007 to 2017 in an Australian hospital and from 2012 and 2017 in a Belgian hospital. The study further confirmed the long-lasting predominance of a limited number of genetic lineages of multidrug-resistant *S. epidermidis* in hospital environments in Australia, the US and the above-mentioned EU Member States.

ECDC threat assessment for the EU

Several endemic multidrug-resistant *S. epidermidis* strains predominate across healthcare systems globally. Increases in the rate and breadth of resistance to multiple antimicrobial agents among these strains is a concerning trend that may limit treatment options for indwelling and prosthetic device infections that are already difficult to treat. Although there are a number of alternative antimicrobial agents that are active against staphylococci, clinical experience with these antimicrobial agents is still limited. Consequently, the precise significance for the therapeutic outcome in patients who have foreign devices (e.g. central vascular catheters, orthopaedic prosthetic devices and cerebrospinal fluid shunts) and surgical site infections of evolving resistance mechanisms that have been recently described in *S. epidermidis* is not yet fully characterised.

Further epidemiological studies of the geographical prevalence of multiresistant *S. epidermidis* strains as a cause of invasive infection in susceptible patient populations, as well as prospective in vitro, in vivo and clinical outcome correlation studies, are needed to clarify their clinical impact on therapeutic outcomes of foreign body infections. However, in the majority of cases of *S. epidermidis* infections, removal or replacement of the contaminated medical device is already required in addition to antimicrobial therapy.

Conclusions and options for prevention and control

The increasing resistance of *S. epidermidis* to multiple antimicrobial agents that are currently considered as first-line agents for the treatment of *S. epidermidis* infections highlights the need for prudent use of these agents and therefore the importance of antimicrobial stewardship. Treatment options should be guided by local epidemiological surveillance data and individual antimicrobial susceptibility test results for each patient's isolates. Ensuring consistent application of proper infection prevention and control practices, particularly during the insertion and use of medical devices, is crucial for prevention of infections by *S. epidermidis*. More information from antimicrobial susceptibility testing against newer antimicrobial agents with activity against *S. epidermidis,* as well as better evaluation of their effectiveness, is necessary for the optimal management of *S. epidermidis* infections.

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