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# Multidrug resistance of *Staphylococcus epidermidis*: An emerging threat to global health

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**ABSTRACT**

The threat of multidrug resistance in bacteria is a global issue projected to cause 10 million deaths by the year 2050. *Staphylococcus epidermidis*, which resides on human skin and is generally believed to be harmless, has evolved into a significant opportunistic pathogen. This bacterium has been reported as the etiological agent for various types of infections and its resistance against multiple drugs has challenged the treatment process. The impact is intensified with the possible role of *S. epidermidis* as a reservoir for antibiotic resistance genes, with the ability to transfer the genes between the various species of staphylococci, including *Staphylococcus aureus*, potentially creating new strains of multidrug-resistant bacteria. Hence, identifying and acknowledging the potential danger of the underrated *S. epidermidis* through this review will encourage more global effort to contain the advancement of antimicrobial resistance and subsequently the appropriate therapy for this bacterium.

## INTRODUCTION

The discovery of bacteria in the late 19th century has sparked the interest of mankind to search for preventive measures and therapeutic treatment for diseases caused by this group of microorganisms. This led to the discovery of antibiotics about half a century later, a turning point in human history that has brought about the revolution in medicine in controlling infectious diseases, thus saving millions of lives. Unfortunately, the effectiveness of these drugs has deteriorated due to the development of resistance in some bacteria strains against antibiotics. Such resistance is defined as the ability of the bacteria to survive in antibiotic concentrations that inhibit or kill others of the same species (Balaban *et al*., 2019).

In 2019, more than 1.2 million people died due to antibiotic-resistance bacterial infections, a number that is higher than the death by AIDS or malaria (Gregory, 2022) and the number is estimated to increase to 10 million by the year 2050 (Maillard *et al*., 2020; Strathdee *et al*., 2020). Hence, by the year 2050, death due to infections by antibiotic-resistant bacteria is expected to top the list, which exceeds the projected death due to cancer at 8.2 million (Dadgostar, 2019). In the US alone, reports from the Centers for Disease Control and Prevention's (CDC's) *antibiotic resistance threats stated that* more than 2.8 million antibiotic-resistant infections occur annually with more than 35,000 death (CDC, 2020).

Majority of *Staphylococcus* species is part of the normal microbiota of humans and play a major role in the spread of antibiotic resistance. The most prominent species of this group is *Staphylococcus aureus*, which causes a variety of human infections, such as bacteremia (Guo *et al*., 2020), endocarditis, osteomyelitis, and respiratory tract infection (Algammal *et al*., 2020). However, majority of commensal staphylococci species can be differentiated from *S. aureus by* their inability to produce the enzyme coagulase and are grouped together as the coagulase-negative staphylococci (CoNS). CoNS are known as nonpathogenic staphylococci that can be regularly found colonizing the skin and mucous membranes of humans and animals (Heilmann *et al*., 2019; Teixeira *et al*., 2019). The genus *Staphylococcus* has been expanded continuously, and to date, there are 41 main species and more than 20 subspecies of

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CoNS (Becker *et al*., 2020; França *et al*., 2021). Among the CoNS, *Staphylococcus epidermidis*, *Staphylococcus haemolyticus*, and *Staphylococcus lugdunensis* stand out as clinically significant species of growing importance (Chabi and Momtaz, 2019; Eladli *et al*., 2018).

The lifelong commensal relationship of a normal microbiota with its host can also be beneficial, with the normal microbiota contributing to the health and well-being of the host by preventing the colonization of more pathogenic species (Brown and Horswill, 2020; Eladli *et al*., 2018; Sharma *et al*., 2018). Commensal microbiota are known to contribute to host health and may play important roles in protecting the host against infections (O'Sullivan *et al*., 2018). *Staphylococcus epidermidis* plays a significant role in maintaining local homeostasis by balancing the skin's microflora composition of the host (Brown and Horswill, 2020; Eladli *et al*., 2018; Sharma *et al*., 2018). In addition, by producing antimicrobial peptides, *S. epidermidis* can inhibit the growth of some pathogenic bacterial strains, hence indirectly helping in protecting the host.

The concept of contextual pathogenicity of certain skin microbes was first mooted by Dr. Philip B. Price in 1983. This concept helps to describe the nature of the relationship of a commensal with its host as either mutualistic or as an opportunistic pathogen (Guo *et al*., 2019; Sharma *et al*., 2018). The ability of *S. epidermidis* to cause infection was first reported in the infection of aseptic wound in 1981 (Becker *et al*., 2020). Since then, *S. epidermidis* has emerged as one of the most important causative agents of nosocomial (Lopes *et al*., 2021) and medical device-related infections (Gómez-Sanz *et al*., 2019; Xu *et al*., 2020). The treatment of these infections is rendered difficult due to the ability of *S. epidermidis* to acquire resistance to multiple antibiotics. A great majority of *S. epidermidis* strains in hospital settings was found to be methicillin-resistant, or methicillin-resistant *S. epidermidis* (MRSE) (Peixoto *et al*., 2020; Teixeira *et al*., 2019). The situation is further complicated with the observation that many MRSE are also resistant to multiple antibiotics (Eladli *et al*., 2018; Namvar *et al*., 2017; Wang *et al*., 2016). As such, the proliferation of multidrug-resistant (MDR) phenotype within the MRSE strains highlights the clinical significance of MRSE and their ability to acquire antibiotic resistance (Lopes *et al*., 2021).

Comparative genomic analyses have indicated the potential role of *S. epidermidis* as an important reservoir for resistance genes that can be transferred between the different species of staphylococci from different hosts and environments (Xu *et al*., 2018a). Such ability can be a potential threat if the resistance genes are transferred to a more pathogenic strain like *S. aureus*, thus suggesting the likely contribution to the further expansion of antibiotic resistance and subsequently resisting drug therapy (Haaber *et al*., 2017). However, despite these developments, *S. epidermidis* has remained inadequately represented in scientific literature, as compared to its more famous sibling *S. aureus*.

### *Staphylococcus epidermidis*: duality nature as a commensal and a pathogen

*Staphylococcus epidermidis* is the most commonly isolated commensal species from the human epithelia (Brown and Horswill, 2020; Claudel *et al*., 2019). There is evidence that this bacterium's interaction with the human begins as early as in the *in utero* stage of pregnancy, as they can be detected in the amniotic fluid (Sabaté Brescó *et al*., 2017). From there on, *S. epidermidis* begins to colonize the newborn shortly after birth (Dong *et al*., 2018), and subsequently assumes its role as the predominant commensal on the human skin. Generally, this bacterium can be found not only on the human skin but also on the mucous membranes, thus indicative of a ubiquitous trait (Brown and Horswill, 2020; Dong *et al*., 2018; Espadinha *et al*., 2019).

In 1891, US pathologist, W. H. Welch first discovered *S. epidermidis* colonizing aseptic wounds (Becker *et al*., 2020). As this bacterium was initially inferred to be harmless, the occurrence of *S. epidermidis* in a variety of infections continued to be frequently regarded as contaminants (Weinstein *et al*., 1997). However, with the heightened medical significance of CoNS in the last two decades (Michalik *et al*., 2020), the opportunistic pathogen nature of *S. epidermidis* is now an accepted reality.

The concept of contextual pathogenicity of skin microbes shown in Figure 1 summarizes the duality nature of the relationship between the host and microflora, which can be either mutualistic or pathogenic. This duality nature depends on host factors such as homeostatic or normal conditions, barrier breaches, and immunosuppression (Chen *et al*., 2018). Under normal conditions, *S. epidermidis* is a commensal of the skin (Claudel *et al*., 2019), but in case of breached skin, the barrier can completely transform the behavior of bacterium into pathogenic (Brown and Horswill, 2020). However, in CoNS, like *S. epidermidis*, the lines between pathogenic and nonpathogenic are often blurred as the status of the host immune system can influence the disease onset and outcome (Heilmann *et al*., 2019). Hence, distinguishing invasive from commensal strains can be challenging for this bacterium since virulence factors can be present in both (Murugesan *et al*., 2018).

However, the host factors are interrelated with the current situation in the medical field, such as the rising number of immunosuppressive patients and the continuous increase in invasive treatments and indwelling medical devices (Becker *et al*., 2020). As the host factors combine with current medical progress, *S. epidermidis* is no longer just an opportunistic pathogen but has emerged as a clinically significant pathogen. The current therapeutic and prophylactic use of antibiotics against this clinically significant pathogen invokes high selective antibiotic pressure, which will later facilitate the emergence and dissemination of MDR isolates (Heilmann *et al*., 2019). The host factors of the *S. epidermidis* pathogenicity are also dependent on the advancement of activities outside the medical field, such as animal therapeutics and the usage of antibiotics in sewage agriculture and other industries, which will also aid in the transmission of resistance within the community (Xu *et al*., 2018b).

### Clinical significance of *S. epidermidis*

*Staphylococcus epidermidis* has been documented to cause a considerable range of diverse infections in humans, as shown in Table 1. *Staphylococcus epidermidis* was also implicated as an important pathogen in medical device-related infections, especially in hospital settings, due to the ability of this bacterium to form a biofilm structure that can attach to both biotic and abiotic surfaces. Hence, as the use of indwelling medical device increases, opportunistic infections by this bacterium via the medical device

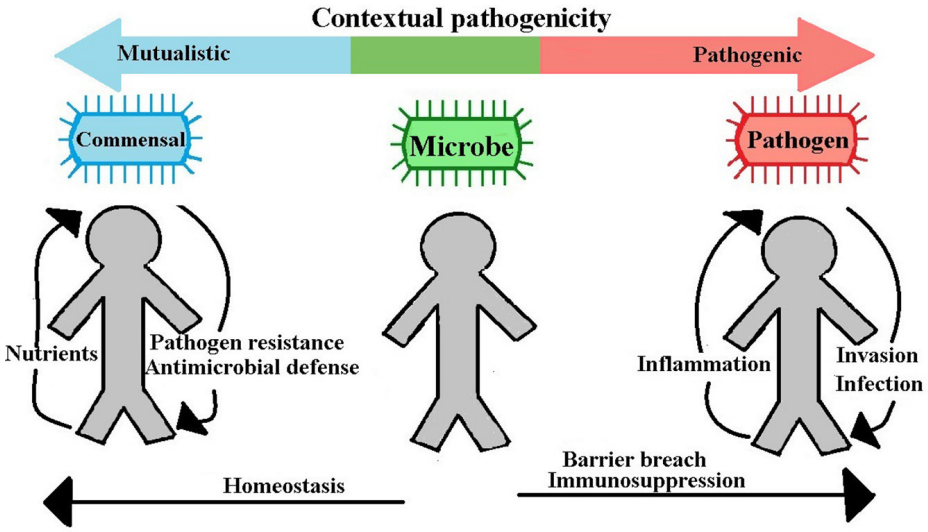


**Figure 1.** Contextual pathogenicity of microbes on human skin (adapted from Chen *et al*., 2018).

**Table 1.** The variety of *S. epidermidis* infections documented in humans.

| | Reference |
|---|---|
| **A) General infections** | |
| Wound infection | (Méric *et al*., 2018) |
| Bloodstream infection | (Pedroso *et al*., 2018) |
| Neonatal septicemia | (Dong *et al*., 2018; Sheikh *et al*., 2019) |
| Peritonitis | (Hwang *et al*., 2020) |
| Urinary tract infection | (Chabi and Momtaz, 2019) |
| **B) Medical device-related infections** | |
| Catheter-related bloodstream infections | (Ehlers *et al*., 2018; Farrington and Allon, 2019) |
| Orthopedic device-related infection | (Post *et al*., 2017; Sabaté Brescó *et al*., 2017) |
| Prosthetic valve endocarditis | (Borde *et al*., 2016; Eladli *et al*., 2018) |
| Ventriculoperitoneal shunt-related infections | (Albehair *et al*., 2021) |
| Ventricular-associated pneumonia | (Hotterbeekx *et al*., 2016) |

route has become a major clinical concern (Espadinha *et al*., 2019; Xu *et al*., 2020; Zalewska *et al*., 2021a).

The majority of infections caused by *S. epidermidis* is nosocomial in nature, especially bloodstream infections (Otto, 2017; Zhou *et al*., 2020) and neonatal septicemia (Dong *et al*., 2018; Sheikh *et al*., 2019). Despite its growing clinical significance, the identification of *S. epidermidis* is frequently dismissed and infections suspected to be due to this species is often grouped as CoNS instead. For example, in a surveillance study on bloodstream infections conducted in China, CoNS was reported as the most prevalent isolates at 30.6%, followed by *E. coli* at 20.4%, while *S. aureus* was recorded in 1.3% of the isolates (Bai *et al*., 2019). In another surveillance study of nosocomial bloodstream infections in Brazil, the most common organisms isolated were CoNS at 21.3%, followed by *Klebsiella* species at 15.7% and *S. aureus* at 10.6% (Pereira *et al*., 2013). In both studies, the species of CoNS contributing to the infections were not identified.

Infections caused by *S. epidermidis* are mainly related to immunocompromised patients and individuals with indwelling medical devices (Grace *et al*., 2019; Teixeira *et al*., 2019). Such infections, if not managed properly, may lead to undesirable clinical outcomes such as longer intensive care unit stays, prolonged hospitalization, additional treatment cost, and increase in mortality rates (Heilmann *et al*., 2019). In Canada, an elderly patient died due to *S. epidermidis* bacteremia (Kou *et al*., 2015). In a study on prosthetic valve endocarditis, *S. epidermidis* not only accounted for about 13% of the infections but also 24% of the mortality rate (Chabi and Momtaz, 2019). For *S. epidermidis* medical device-related infections, the infections are mostly chronic as the host immune response is often insufficient to clear the infection (Nguyen *et al*., 2017). In neonates, the immunocompromised and premature newborns are the most vulnerable to CoNS sepsis, with *S. epidermidis* being the most prevalent species isolated (Cheung and Otto, 2010).

**Antibiotic resistance in *S. epidermidis***

A penicillin-resistant strain of *S. epidermidis* was first isolated in the US from three fatal cases of subacute bacterial endocarditis in 1949 (Griffith and Levinson, 1949). To combat penicillin resistance, methicillin was introduced in 1959 to treat staphylococcal infections (Akpaka *et al*., 2017). However, in 1961, the first report of methicillin-resistant *S. aureus* (MRSA) was isolated from a nephrectomy wound of a patient (Jevons, 1961). Similarly, in the same year, the first MRSE strain was also isolated from children hospitalized in a pediatric hospital in the UK (Stewart, 1961). In *S. epidermidis*, the term "methicillin-resistant" in MRSE signifies strains with resistance to beta-lactam antibiotics, excluding the newest generation cephalosporins such as ceftaroline (Morris *et al*., 2017).

Treatment of MRSE has become more difficult due to the resistance of the bacterium against multiple antibiotics. *S. epidermidis* was reported to be resistant to antibiotic classes like macrolides, penicillins, aminoglycosides, and fluoroquinolones (Chabi and Momtaz, 2019; Nicolosi *et al*., 2020; Pedroso *et al*., 2018). Currently, the antibiotics used in the treatment of *S. epidermidis* infections include isoxazolyl penicillin ( Zalewska *et al*., 2021a), vancomycin (Asante *et al*., 2020), rifampicin (Becker *et al*., 2020; De Vecchi *et al*., 2018), clindamycin (Bora *et al*., 2018), and linezolid (Dortet *et al*., 2018). Isoxazolyl penicillin was a recommended first-line therapy for several medical device-related staphylococcal infections (Zalewska *et al*., 2021a). However, the common resistance to penicillins in *S. epidermidis* (Guo *et al*., 2019; Lopes *et al*., 2021) and the possible penicillin allergy resulted in vancomycin being the choice for most of the treatment of infections caused by this bacterium (Asante *et al*., 2020; Zalewska *et al*., 2021a). This, however, has led to cases of resistance or decrease susceptibility to vancomycin which has become more frequently reported (Castro-Orozco *et al*., 2019; European Centre for Disease Prevention and Control, 2018).

Linezolid was then used as a last-resort treatment for *S. epidermidis* infections. However, despite the initial trend for zero resistance of *S. epidermidis* against linezolid (Guo *et al*., 2019; Nicolosi *et al*., 2020; Peixoto *et al*., 2020), reports on the resistance to this antibiotic soon surfaced (Lopes *et al*., 2021; Xu *et al*., 2020). Not long after, the usage of linezolid was approved in the year 2000, the first linezolid-resistant case of *S. aureus* was reported in the USA in 2001 (Tsiodras *et al*., 2001). Between the years 2001 and 2002, a SENTRY Antimicrobial Surveillance Program in the US involving clinical samples from various infection sites reported 8 linezolid-resistant isolates from the 9833 Gram-positive tested isolates whereby 1 of the 8 isolates was identified as *S. epidermidis* (Mutnick *et al*., 2003).

Between the years 2004 and 2015, an outbreak of a clone of linezolid-resistant *S. epidermidis*, which was also a MRSE strain, was reported in a hospital in Italy (Morroni *et al*., 2016). A study conducted in the tertiary children's hospital in Poland between the year 2015 and 2017 reported 11 linezolid-resistant *S. epidermidis* isolates from pediatric ICUs patients whereby all the isolates were not only MRSE strains, but they also harbored type III staphylococcal cassette chromosome, a mobile genetic element (MGE) known as *SCCmec* (Kosecka-Strojek *et al*., 2020), which contributes to the multidrug-resistant characteristics of these strains. These findings suggest the role of MGE as the driving factor in the development of multidrug resistance in *S. epidermidis*.

**The role of MGEs in MDR *S. epidermidis***

One of the most important features of MGEs is that they can not only harbor antibiotic resistance genes together with many other genes conferring increased virulence and environmental persistence, but also be easily distributed between bacteria via horizontal gene transfer (Evans *et al*., 2020). Hence, MGE is not just a connecting bridge between the mutualistic and pathogenic nature of *S. epidermidis* whereby an acquisition of the virulent genes may turn this commensal into a pathogen, but it also serves a more important role as a directing passage of this bacterium into multidrug resistance.

SCC*mec* is one of the most important MGE in *Staphylococcus* (Monecke *et al*., 2016), which carries the *mec*A gene that characterizes the methicillin-resistant strains (Lopes *et al*., 2021).

Figure 2 shows a representative SCC*mec* element which comprises two main components, the *mec*A gene and the cassette chromosome recombinase *ccr* complex; and the interstitial regions in between are called the joining or the J regions. The *ccr* genes function in the integration and excision of SCC*mec* into and from the bacterial chromosome, while the J regions can carry additional genetic determinants, such as transposons, which may contain additional resistance genes (Rolo *et al*., 2017). Based on the various combinations of the *ccr* and *mec* gene complexes, 11 categories of SCC*mec* types are recognized in *S. aureus,* which is believed to be the origin of these genetic elements (França *et al*., 2021; Xu *et al*., 2020).

The *mec*A gene encodes a PBP2a protein with a low affinity to beta-lactam antibiotics including penicillins, cephalosporins, carbapenems, and monobactams (Xu *et al*., 2020). Hence, the *mec*A gene is the principal element in this cassette since it provides the staphylococci with the resistance ability to the extensive beta-lactam antibiotics (Rolo *et al*., 2017). The SCC*mec* may also carry additional antibiotic resistance genes through the insertion of other MGEs into the cassette such as

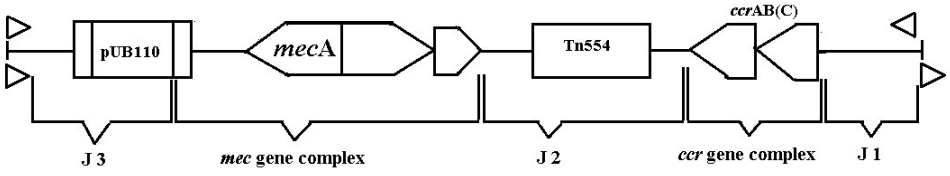


**Figure 2.** The main components of SCC*mec*.

Tn554 transposon, plasmid pT181, and pUB110 (Sansevere and Robinson, 2017). Hence, this provides an almost effortless path for MRSE strains to acquire additional multidrug resistance ability by the acquisition of these MGEs.

The methicillin resistance characteristic associated with the *mec*A gene is a critical factor that allows for the establishment of this bacterium as a nosocomial pathogen (Guo *et al*., 2019). It is estimated that as much as 75%–90% of all the *S. epidermidis* strains in hospital settings were MRSE strains, a proportion that is higher as compared to MRSA (Tang *et al*., 2020). These MRSE strains isolated from the hospital settings are also known as hospital-associated (HA) MRSE. Besides that, MRSE is also reported from other backgrounds such as community-associated (CA) and livestock-associated (LA) MRSE. However, as most CoNS are still viewed as minimally pathogenic in veterinary medicine (Morris *et al*., 2017), the study on LA-MRSE is scarce.

However, the significance and emergence of the CA-MRSE are increasing. A study in the UK reported that 61.9% of the community harbored MRSE isolates (Gómez-Sanz *et al*., 2019), while another study in Thailand recorded that all of the community *S. epidermidis* isolates were MRSE (Seng *et al*., 2017). Not only that, but the CA-MRSE may also cause moderate skin infection to severe necrotizing pneumonia, especially in persons with predisposing risk factors (Ekinci *et al*., 2018). For example, a case of CA-MRSE pyelonephritis in an immunocompetent child was reported in Japan in 2014 (Kanai *et al*., 2014).

Unfortunately, even though CA-MRSE strains, in general, do not cause serious infections, they may pose as an epidemiological concern in the health sector as these MRSE strains may persist as a genetic reservoir for the transmission of antibiotic resistance genes. The carrier of the CA-MRSE strains will also remain as a possible source of infections in the future where it may compromise the well-being of other patients in the same facility by transfer of the resistance. Although the significance of the CA-MRSE strains is clear, unfortunately, only a few studies have been conducted on this subject, and the majority of studies were focused generally on HA-MRSE instead (Gómez-Sanz *et al*., 2019; Seng *et al*., 2017; Xu *et al*., 2018b).

On the contrary, the incidence of HA-MRSE in nosocomial settings is evident. The percentage of HA-MRSE from nosocomial infections in most European and American countries was estimated to be around 75%–90% (Namvar *et al*., 2014). For example, a study in Portugal on *S. epidermidis* recorded that 79.1% of the isolates from patients in a tertiary care hospital were MRSE (Lopes *et al*., 2021). Studies on HA *S. epidermidis* in two South American countries, Columbia and Brazil, showed that 78.2% and 100% of the HA were MRSE, respectively (Castro-Orozco *et al*., 2019; Peixoto *et al*., 2020). Meanwhile, in a study in China in 2019, it was reported that 76.5% of the HA isolates were MRSE (Castro-Orozco *et al*., 2019; Xu *et al*., 2020). Another study in South Africa reported that all of the hospital-acquired isolates were MRSE (Ehlers *et al*., 2018). This exceptionally high recovery of MRSE in hospital settings certainly raises serious concerns.

However, the real threat is when some of the MRSE strains were found to be MDR as well. The high recovery of MRSE is further aggravated by the inclination of MRSE strains to develop an MDR phenotype, a phenomenon that is increasingly observed and reported in studies from various countries (Ehlers *et al*., 2018; Lopes *et al*., 2021; Peixoto *et al*., 2020). For example, a study in Brazil reported that 94.7% of the MRSE were also MDR (Peixoto *et al*., 2020). Another study in Portugal also recorded a high prevalence of MDR at 91.9% among their MRSE isolates (Lopes *et al*., 2021). Studies on *S. epidermidis* in South Africa and India reported that all the MDR strains isolated were also carriers of the *mec*A gene (Ehlers *et al*., 2018; Jena *et al*., 2017), which signifies MRSE (Lopes *et al*., 2021).

A bacterial strain is classified as MDR when it demonstrates resistance to three or more classes of antibiotics (Schmidt *et al*., 2018). The increase in the incidence of multidrug resistance in *S. epidermis* is evident from reports of MDR strains from all around the world (Imran *et al*., 2017), from either hospital or community settings, as shown in Table 2.

The data shown suggests that majority of the MDR *S. epidermidis* strain are HA or nosocomial in nature. Nevertheless, the proliferation of MDR *S. epidermidis* in the community should not be taken lightly as it may also cause diseases under permissible conditions (Ekinci *et al*., 2018). However, when the worldwide spread of these MDR *S. epidermidis* strains are coupled with the reduced pipeline of antibiotics, the treatment of the infections will be obstructed. Therefore, the infections caused by MDR strains are prone to associate with prolonged hospitalization and increased mortality (Kot *et al*., 2020).

**Antibiotic-resistant genes (ARG) and their association with MGEs**

Events like mutations or horizontal transfer of ARGs can change the nature of bacteria from being normal into resistant (Sánchez-Baena *et al*., 2021). However, as ARGs are often found on MGEs, like transposons and plasmids, it is more frequent for bacteria to acquire ARGs from the event of horizontal gene transfer (Checcucci *et al*., 2020; Sánchez-Baena *et al*., 2021) and become resistant rather than other events like mutations. In fact, one MDR strain is capable of carrying multiple ARGs conferring the resistance against a single antibiotic class such as *bla*, *mec*, and *amp* genes for penicillin resistance; *aad*, *arm*, and *aph* genes for resistance to aminoglycosides; and *mph*, *msr*, and *mac* genes for resistance to macrolides (Sánchez-Baena *et al*., 2021).

ARGs have been widely discovered within both pathogenic and commensal *S. epidermidis* whereby ARGs like *tet*K, *tet*M, *erm*A, *erm*B, *msr*B, and *mec*A are examples of resistance genes that are routinely discovered in this bacterium (Chabi and Momtaz, 2019). The association between ARGs and MGEs has been reported in *S. epidermidis* whereby the *tet*K and *erm*C were usually located on small multicopy plasmids, while the *tet*M and *erm*A genes were usually found on transposons (Chabi and Momtaz, 2019). However, the most prominent example will be the *mec*A gene located in SCC*mec*, which is harbored by many strains of *S. aureus*, *S. epidermidis*, and other CoNS species, and has a major role in the development of multidrug resistance (Rolo *et al*., 2017).

The association of the ARGs with a variety of MGEs not only explains the high mobility nature of ARGs in the development of MDR *S. epidermidis*, but also uncovers the potential of these ARGs to be spread widely to other species. The ability of MGEs to move horizontally to facilitate the spread of the ARGs was suggested to transverse taxonomic boundaries (Ebmeyer *et al*., 2021). For example, the *tet*M gene possesses the ability to confer an extensive host range of bacteria for tetracycline resistance (Zalewska *et al*., 2021b). As the *tet*M gene is also one of the

**Table 2.** Reports on MDR *S. epidermidis* from various countries.

| Country | Category | Reference |
|---|---|---|
| Sweden | HA | (Månsson *et al*., 2021) |
| United Kingdom | CA | (Xu *et al*., 2018a) |
| France | HA | (Dortet *et al*., 2018) |
| United Kingdom | HA and CA | (Cave *et al*., 2019) |
| Mexico | HA | (Cabrera-Contreras *et al*., 2019) |
| India | HA | (Talat *et al*., 2020) |
| Iran | HA | (Chabi and Momtaz, 2019) |
| Brazil | HA | (Peixoto *et al*., 2020) |
| Saudi Arabia | HA and CA | (Eladli *et al*., 2018) |
| China | HA | (Xu *et al*., 2020) |
| South Africa | HA | (Ehlers *et al*., 2018) |
| Portugal | HA | (Lopes *et al*., 2021) |
| Australia | HA | (Lee *et al*., 2018) |
| Germany | HA | (Post *et al*., 2017) |
| Iran | HA | (Sheikh *et al*., 2019) |

MDR: multidrug-resistant; HA: hospital-associated; CA: community-associated.

**Table 3.** ARG of the SCC*mec* elements and its corresponding antibiotic resistance.

| SCC*mec* elements | ARG | Antibiotic resistance | Reference |
|---|---|---|---|
| *mec* gene complex | *mec*A | Beta-lactams | (Xu *et al*., 2020) |
| Tn554 | *erm*A, *spc* | Erythromycin, clindamycin, streptogramin B, and spectinomycin | (Haaber *et al*., 2017) |
| pT181 | *tet*K | Tetracycline | (Haaber *et al*., 2017) |
| pUB110 | *aad*D, *ble* | Kanamycin, neomycin, paromomycin, tobramycin, and bleomycin | (Haaber *et al*., 2017) |

ARG: antibiotic resistance gene.

ARGs found in *S. epidermidis*, it means that this gene can be transferred to other bacteria regardless of the taxonomies through *S. epidermidis*. Therefore, this initiates the investigation on the potential trait of *S. epidermidis* as a gene reservoir, which may intensify the threat of multidrug resistance.

### Potential role of *S. epidermidis* as a gene reservoir

In addition to the surge of multidrug resistance, studies have also suggested the potential role of *S. epidermidis* as a reservoir for resistance genes (Otto, 2013; VanAken *et al*., 2021; Xu *et al*., 2018a). A study on a compiled data of about 1,800 genomes of CoNS suggested that CoNS may act as a crucial reservoir of transferable antimicrobial resistance genes and virulence determinants whereby the highest interspecies donation of recombined DNA was discovered in *S. haemolyticus*, *S. hominis*, *S. caprae*, *S. capitis*, and *S. Saprophyticus* (Smith and Andam, 2021). However, the transfer of resistance genes is not limited to occur within the member of CoNS as a study in the UK found that SCC*mec*, metal resistance, and SaPIn1 pathogenicity island elements were extensively exchanged between both clinical isolates of *S. epidermidis* and coagulase-positive *S. aureus* (Méric *et al*., 2015). The transfer of the resistance gene from *S. epidermidis* to *S. aureus* was also successfully exhibited *in vitro* involving clinical strains from different countries (Cafini *et al*., 2016). In addition, a MGE associated with gentamicin resistance called IS 256 is commonly found not only within clinical isolates of *S. epidermidis* and *S. haemolyticus*, but also in several virulent sequence types of the MRSA (Pain *et al*., 2019).

The presence of MGEs such as SCC*mec* in MRSE, the high incidence of MRSE in nosocomial settings, and the common proliferation of MDR strain within MRSE are among the factors that support the underlying reasons behind such suggestions. Besides that, the insertion of other MGEs, such as Tn554 transposon, plasmid pT181, and pUB110, contributes to the diverse range of ARGs found in SCC*mec* elements and their corresponding antibiotic resistance, as shown in Table 3 (França *et al*., 2021; Sansevere and Robinson, 2017). In addition, the *ccr* gene in the SCC*mec* mediates the integration and excision of the cassette to and from the chromosome (Pedroso *et al*., 2018; Rolo *et al*., 2017), assisting the transfer within staphylococci (Schmidt *et al*., 2018). Hence, the acquisition of SCC*mec* may not only introduce multidrug resistance within *S. epidermidis* but can also turn this bacterium into an MDR reservoir that can provide ARGs to other *Staphylococcus* since the cassette transfer may occur in both intra and interspecies of staphylococci (Xu *et al*., 2018a), especially into *S. aureus* (VanAken *et al*., 2021; Wang *et al*., 2019).

This finding is supported through the similarity between the high prevalence of SCC*mec* type IV in MRSE (Peixoto *et al*., 2020; Tang *et al*., 2020) and the increase in the prevalence of type IV SCC*mec* in *S. aureus* (Murugesan *et al*., 2019). In addition, high homology was also observed between the type IV cassette of both *S. epidermidis* and *S. aureus* (Cafini *et al*., 2017; Rossi *et al*., 2017). The junctions between IS 1272 and truncated *mec*R1 in the type IV

and type IV SCC*mec* are also identical in these two staphylococci (Otto, 2013; Wisplinghoff *et al*., 2003). In fact, the presence of type IV SCC*mec* was detected much earlier in *S. epidermidis* than it was detected in *S. aureus* (Wisplinghoff *et al*., 2003). All these findings point out on the high possibility of the transfer of SCC*mec* elements between CoNS like *S. epidermidis* toward *S. aureus*. This is also supported by the claim that CoNS may serve as a reservoir of resistance genes that can be transferred between both related and more pathogenic bacteria like *S. aureus*, which later may enhance its antimicrobial resistance (Rossi *et al*., 2017). Therefore, the threat of MDR in *S. epidermidis* is becoming more grievous as it does not only limit to the bacterium itself but may also involve other staphylococci, especially the highly pathogenic *S. aureus*.

## CONCLUSION

With the increase in antibiotic resistance and the emergence of MDR strains together with its potential role as a genetic reservoir of resistance genes, *S. epidermidis* can no longer be underestimated, as this original human skin commensal can become an emerging threat to global health. If left unchecked, the advent of multidrug resistance in *S. epidermidis* may rival that of a notorious threat like MRSA. This highlights the need to study the virulence signature of *S. epidermidis*, and with continuous surveillance as an emerging pathogen, the extent and evolution of the MDR strains of this bacterium can be monitored. As *S. epidermidis* is an ever-present commensal on human epithelia, good hygienic exercise in individuals and proper infection prevention and control practices in clinical sectors, especially in the use of medical devices, are crucial to mitigate the spread of this bacterium. In general, various coordinated actions and global approaches from various sectors are required to control this threat, thus optimizing the management of infections by *S. epidermidis*.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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## AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the international committee of medical journal editors (ICMJE) requirements/guidelines.

## ETHICAL APPROVALS

This study does not involve experiments on animals or human subjects.

## DATA AVAILABILITY

All data generated and analyzed are included within this research article.

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