

Distribution of Coagulase-Negative Staphylococci and Antibiotic Resistance

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Coagulase-negative staphylococci (CoNS) are a typical group of microorganisms, and the recent advances in laboratory technology and medicine has dramatically modified their significance in medical practice. CoNS, which were previously classified as normal bacterial flora, have recently been reported to be associated with serious infectious diseases, such as surgical wound infection or periprosthetic joint infection. Representative CoNS include *Staphylococcus epidermidis*, *S. haemolyticus*, and *S. saprophyticus*, which are known to cause serious problems in biomaterial-based and prosthetic device infections, as well as to cause simple urinary tract infections in sexually active women. Over the last decade, the clinical isolation rate of CoNS has been increasing, and antibiotic resistance has also been occurring. This review aimed to investigate the incidence of CoNS infection and to use the results as basic data for the management of CoNS, with a focus on the isolation rate and antibiotic resistance in clinical surgery.

Key Words: Coagulase-negative staphylococci (CoNS), Sepsis, Identification, Antibiotic resistance

INTRODUCTION

Microorganisms are closely associated with humans. Humans have co-evolved with the trillions of microbes inhabiting the human body and creating complex, body-habitat-specific, adaptive ecosystems that are finely attuned to the constantly changing host physiology (Lloyd-Price et al., 2016). Among the numerous microorganisms, representative bacteria are the main taxa of living things. Bacteria, are commonly considered as normal flora, as they have a symbiotic relationship with humans under normal circumstances; however, they can become dangerous pathogens

when the immune function is not in its normal state, such as during surgery and treatment (Marple et al., 1990).

Coagulase-negative staphylococci (CoNS) are a group of staph bacteria, which generally exist as normal flora, although several of these bacteria are potential pathogens under reduced immunity in humans (Al Tayyar et al., 2015; Argemi et al., 2019). CoNS bacteria have long been regarded as culture contaminants. However, their infective role as pathogens has become important in recent years (Natsis and Cohen, 2018). There are about 45 types of known CoNS, and the representative strains are *Staphylococcus epidermidis*, *S. haemolyticus*, and *S. saprophyticus* (Grace et al., 2019). CoNS strains are frequently isolated in hospital environ-

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Table 1. Prevalence of CoNS in hospital environments

Previous studies (publication year)	Dziri et al. (2016)	Al Tayyar et al. (2015)	Azih and Enabulele (2013)	Keim et al. (2011)	Begum and Anbumani (2011)	Total, n (%)
Species	n (%)	n (%)	n (%)	n (%)	n (%)	
<i>Staphylococcus epidermidis</i>	2 (2.4)	122 (54.7)	16 (26.7)	70 (36.6)	49 (43.4)	259 (38.7)
<i>Staphylococcus haemolyticus</i>	38 (45.8)	52 (23.4)	17 (28.3)	33 (17.3)	19 (16.8)	159 (23.7)
<i>Staphylococcus saprophyticus</i>	30 (36.1)	7 (3.1)	11 (18.3)	5 (2.6)	4 (3.5)	57 (8.5)
<i>Staphylococcus warneri</i>	2 (2.4)	4 (1.8)	ND*	35 (18.3)	7 (6.2)	48 (7.2)
<i>Staphylococcus simulans</i>	1 (1.2)	2 (0.9)	6 (10.0)	21 (11.0)	5 (4.4)	35 (5.2)
<i>Staphylococcus hominis</i>	ND*	13 (5.8)	ND*	4 (2.1)	11 (9.7)	28 (4.2)
<i>Staphylococcus capitis</i>	ND*	8 (3.6)	ND*	4 (2.1)	7 (6.2)	19 (2.8)
<i>Staphylococcus sciuri</i>	2 (2.4)	ND*	ND*	15 (7.9)	ND*	17 (2.5)
<i>Staphylococcus xylosus</i>	4 (4.8)	2 (0.9)	6 (10.0)	3 (1.6)	1 (0.9)	16 (2.4)
<i>Staphylococcus cohnii</i>	2 (2.4)	ND*	ND*	ND*	9 (8.0)	11 (1.6)
<i>Staphylococcus lugdunensis</i>	ND*	9 (4.0)	ND*	ND*	1 (0.9)	10 (1.5)
<i>Staphylococcus auricularis</i>	ND*	4 (1.8)	ND*	1 (0.5)	ND*	5 (0.7)
<i>Staphylococcus chromogenes</i>	ND*	ND*	3 (5.0)	ND*	ND*	3 (0.4)
<i>Staphylococcus pasteurii</i>	1 (1.2)	ND*	ND*	ND*	ND*	1 (0.1)
<i>Staphylococcus arlettae</i>	1 (1.2)	ND*	ND*	ND*	ND*	1 (0.1)
<i>Staphylococcus schleiferi</i>	ND*	ND*	1 (1.7)	ND*	ND*	1 (0.1)
Total, n (%)	83 (12.4)	223 (33.3)	60 (9.0)	191 (28.5)	113 (16.9)	670 (100.0)

*ND: not detected

ments; the representative CoNS strains include *S. cohnii*, *S. warneri*, *S. sciuri*, *S. hominis*, *S. simulans*, *S. pasteurii*, *S. arlettae*, and *S. xylosus* (Table 1) (Al Tayyar et al., 2015; Houssaini et al., 2019; Dziri et al., 2016; Keim et al., 2011; Begum and Anbumani, 2011). Among the CoNS species associated with clinical disease, *S. epidermidis* is identified in infection associated with biomaterial-based and prosthetic devices. Meanwhile, *S. saprophyticus* causes simple urinary tract infection in sexually active women, and *S. haemolyticus* causes variable infection such as periprosthetic joint infections (PJI) and bacteremia (Eltwisy et al., 2020). In addition, identification of CoNS is of increasing importance in infection, as the isolation rate of CoNS from the blood of patients with risk factors has been increasing (Nickel and Costerton, 1992; Houssaini et al., 2019).

1. Importance of CoNS

In recent years, the use of devices such as intravascular catheters as well as the increase in invasive manipulation in

immunosuppressed patients, have been recognized as one of the important factors associated with nosocomial infections caused by bacteria (Supré et al., 2011). The frequency of CoNS infection has been increasing mainly due to bacteremia, catheter-related infections, endocarditis, and urinary tract infections; moreover, resistance to antibiotics, especially vancomycin, is a serious problem, as bacteria demonstrating severe resistance have been identified (Koksal et al., 2009; De Vecchi et al., 2018). A 2013 study for Azih et al., has reported that 105 CoNS were isolated from 79 clinical specimens, such as discharge from wounds, urine, and male genital infections, which could cause secondary infections, such as sepsis (Azih and Enabulele, 2013). These CoNS infections are usually internal or implanted foreign bodies that cause immune damage and are emerging as the cause of infectious diseases in both the community and hospital environment (Chu et al., 2008; Piette and Verschraegen, 2009).

Table 2. Prevalence of potential pathogens isolated from the blood culture in the Republic of Korea

Microorganism	No.	True pathogen (%)	Contaminated (%)	Reference
Coagulase-negative staphylococci	560	133 (23.8)	427 (76.2)	Chun et al., 2019
Viridans group <i>Streptococcus</i>	93	43 (46.2)	50 (53.8)	
<i>Bacillus</i> species	54	15 (27.7)	39 (72.3)	
<i>Corynebacterium</i> species	21	4 (19.0)	17 (81.0)	
<i>Micrococcus</i> species	14	0 (0.0)	14 (100.0)	
<i>Propionibacterium acnes</i>	8	0 (0.0)	8 (100.0)	
Total	750	195	555	

2. Distribution of CoNS in sepsis, surgical wound infection (SWI), and periprosthetic joint infection (PJI)

2.1. CoNS in Sepsis

Sepsis is one of the most common causes of death among hospitalized patients, and it can be caused by bacteria, fungi, or viruses (Rello et al., 2017). The causative agent of sepsis varies, but 11 pathogens are known as the major causative organisms (Liu et al., 2018). *S. aureus* and *Escherichia coli* are the most common causes; CoNS is also frequently isolated from blood, which in turn is considered contaminated, although no symptoms have been reported in such cases (Biedenbach et al., 2004). However, in developed countries, CoNS, such as *S. epidermidis* and *S. haemolyticus*, are indicated as the major pathogens involved in late-onset sepsis (Golińska et al., 2020) and are among the pathogenic bacteria implicated in catheter-related blood stream infection (CRBSI) (Osaki et al., 2020). According to one report, approximately 10% of the causative pathogens of sepsis are CoNS (Chun et al., 2015), and the most detected CoNS was *S. epidermidis* (20%), followed by *S. hominis*; *S. aureus* was detected at a rate of approximately 9% (Osaki et al., 2020). In Korea, in 13,519 blood cultures obtained from pediatric patients, 750 bacteria were identified, 560 (74.67%) of which were CoNS (Table 2). Indeed, the degree of contamination is high, and this finding is significant because contaminations are highly associated with diseases (Chun et al., 2019).

2.2. CoNS in surgical wound infection (SWI)

SWI is one of the complications in variable surgery, and the risk of SWI is 1.9 per 100 interventions (Hijas-Gómez et al., 2017). Also, SWI remains as the most common and

expensive hospital-acquired infection, accounting for 20% of cases (Campwala et al., 2019). During infection, pain, swelling, erythema, warmth, and impairment of function are consistently seen (Peel and Taylor, 1991).

In one study involving SWI patients, 82 samples were analyzed; CoNS were identified in 54.9% of the samples, especially methicillin-resistant CoNS (MR-CoNS) (13.4%) (Ahmed et al., 2021). In another study, *S. aureus* (53.2%) and CoNS (23.4%) were identified in 74 SWI patients (Liang et al., 2019). In yet another study, 31 of the 52 patients were confirmed to have bacterial growth, and 20 of them were infected with *S. epidermidis* (65%). These results suggest that in SWI patients, the proportion of CoNS is quite high, and this phenomenon remains a serious healthcare-associated infection (HAI) problem.

2.3. CoNS in periprosthetic joint infection (PJI)

PJI carries both a higher economic burden and greater morbidity and mortality compared with other aseptic complications (Gross et al., 2021). A PJI infection requires extended periods of hospitalization and re-operations and thus poses a significant financial burden (Li et al., 2020). Therefore, management of established PJI requires a combination of pathogen-specific antibiotics and surgical intervention (De Vecchi et al., 2018).

These PJIs are frequently caused by CoNS; importantly, antibiotic resistance among causative pathogens of PJI has been increasing (Veltman et al., 2019). A study involving 50 CoNS and 39 *S. aureus* infection cases has found that the CoNS were significantly more resistant to daptomycin and gentamicin and were more susceptible to rifampicin than *S. aureus* (De Vecchi et al., 2018). Another study reported

that in 106 PJI cases, 43 cases involved *S. aureus* and 32 involved streptococci infections; only 8 cases involved CoNS infections (Rakow et al., 2019). Another study involving 74 patients showed that PJI was caused by methicillin-resistant *S. aureus* (MRSA) (20.3%), methicillin-resistant *S. epidermidis* (MRSE) (32.4%), methicillin-susceptible *S. aureus* (MSSA) (18.9%), and methicillin-susceptible *S. epidermidis* (MSSE) (28.4%) (Hischebeth et al., 2019). These results suggested that in PJI, the major causative agents are gram-positive bacteria, especially *S. aureus* and CoNS. Moreover, the incidence of MRSE has been increasing; thus, MRSE must be diagnosed and treated promptly.

3. Distribution of antibiotic-resistant CoNS

As mentioned previously, the distribution of CoNS in various diseases as well as the incidence of antibiotic-resistant CoNS have been increasing. In addition, biofilm formation has been observed among CoNS, making them more difficult to treat because of their antibiotic resistance compared with non-biofilm bacteria (Saber et al., 2017). Methicillin resistance in staphylococci is caused by the expression of PBP2a (PBP') encoded by the *mecA* gene (Hanssen et al., 2004). According to one study, *S. epidermidis* is the most frequent isolate among methicillin-resistant CoNS (Schuster et al., 2018). Oxacillin resistance is often mediated by the *mecA* gene, which encodes a supplemental penicillin binding protein (PBP2a) with low affinity to semisynthetic penicillins (Archer and Niemeyer, 1994). The *mecA* gene is located on a mobile genetic element known as the staphylococcal cassette chromosome *mec* (SCC*mec*) that comprises the *mec* complex consisting of the *mecA* gene and its regulator genes *mecI* and *mecRI*, along with the *ccr* complex, which is responsible for integration (Pereira et al., 2020). Among the several MR-CoNS, *S. epidermidis* and *S. haemolyticus* were the most common species identified (Venugopal et al., 2019). Also, according to one study, *S. haemolyticus* isolates demonstrated the overall highest resistance rates (Tekeli et al., 2020). Another study investigated the antibiotic resistance and virulence factors of CoNS isolated from blood cultures. Among the 93 CoNS species, 86 were resistant to cefoxitin, and 49 displayed multi-antibiotic resistance (Al-Haqan et al., 2020). Also,

vancomycin-resistant CoNS is a recent health concern, especially in serious infections, such as bloodstream infections, as it may lead to failure of therapy (Mashaly and El-Mahdy, 2017). Therefore, early detection of antibiotic-resistant CoNS is important in order to effectively eliminate the bacteria that causes bloodstream infection.

CONCLUSION

The management of the CoNS plays an important role in controlling *S. aureus*-related infectious diseases in recent years. CoNS has a symbiotic relationship with humans in a normal environment, but it can become a dangerous pathogen when immune function is not normal, such as surgery or treatment. Besides, if CoNS are identified in blood cultures, it remains a serious healthcare problem whether infection or a contaminant (Muñoz-Gamito et al., 2020). Recently, it was confirmed that the treatment for surgical wound infection and the separation rate of CoNS from the joint around the prosthesis were increased, and the infection rate was also increased in septic patients. Also, the abuse and misuse of antibiotics, and antibiotic-resistant CoNS, which is caused when appropriate treatment was not conducted, are also becoming a problem in the community. After all, CoNS has been regarded as a contaminant, however its importance has increased in relation to various clinical diseases. Therefore, a research of CoNS on the distribution in variable diseases and antibiotic-resistant patterns are important to dissolve these situations. In addition, it is necessary to characterize the role of virulence factor and pathogenesis of CoNS in the host to identify the etiology in human.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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