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Pathogenicity and Antimicrobial Resistance in Coagulase-Negative Staphylococci

Debora Brito Goulart

Department of Veterinary Microbiology and Preventive Medicine, Iowa State University, Ames, IA, USA
Email: dgoulart@iastate.edu

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Abstract

The coagulase-negative staphylococci (CoNS) group was considered saprophytic or rarely pathogenic for many years. Since the first case of septicemia caused by CoNS, there has been a progressive increase in the prevalence of healthcare-associated infections caused by CoNS. The CoNS group has emerged as one of the main causes of nosocomial infections related to vascular catheters and prostheses, especially among immunocompromised patients. This gradual increase in infections is due to the change in the relationship between patients and procedures since CoNS are closely related to devices implanted in the human body. CoNS are successful in colonizing the host because they have several virulence mechanisms, such as biofilm formation and production of enzymes and toxins, in addition to several mechanisms of resistance to antimicrobials. Despite their great clinical relevance, few studies have focused on CoNS's pathogenicity and resistance to antimicrobials, which reveals the current need to better understand the factors by which this group became pathogenic to humans and other animals. This review aims to synthesize the aspects related to the pathogenicity and antimicrobial resistance in CoNS.

Keywords

Coagulase-Negative Staphylococci, Antimicrobial-Resistance, Biofilm, Nosocomial Infections, Pathogenesis, Beta-Lactams Antibiotics, Glycopeptide Antibiotics, Macrolide Antibiotics, Septicemia, Bacteremia

1. Introduction

Staphylococcus are microorganisms from the family *Micrococcaceae* that appear as Gram-positive cocci, with a diameter between 0.5 and 1.5 μm, grouped in grape-like clusters, but can also be seen isolated, in pairs, and short chains [1].

They have a fermentative metabolism that results in acid rather than gas and may thrive in a medium with high salt content (10% to 20% of sodium chloride) [2]. *Staphylococcus* are mesophilic microorganisms with a growth temperature of 7˚C to 48˚C, the optimum being 37˚C, and a pH in the range of 4 to 10, with optimum growth at pH between 6 and 7 [3]. *Staphylococcus* colonies can vary in color, from dull white to orange, when grown on a solid medium [4]. The carotenoid pigment can be seen in colonies grown on media containing starch or fatty acid [5]. Although *Staphylococcus* are non-spore-forming, they have great metabolic versatility and the ability to survive in different environments and conditions, such as desiccation, and tolerate most disinfectants well [6]. The staphylococcal genome consists of a single circular chromosome of approximately 2800 megabase pairs, with prophages, plasmids, transposons, insertion sequences, and other variable accessory genetic elements [7]. Some *Staphylococcus* strains produce coagulase, an enzyme that coagulates the plasma through the production of fibrin, allowing rapid bacterial agglutination and resistance to host defensive mechanisms such as opsonization and phagocytosis [8]. This characteristic divides the genus into two groups: Coagulase-positive staphylococci (CPS) and coagulase-negative staphylococci (CoNS). Importantly, only the species *S. aureus*, *S. delphini*, *S. intermedius*, *S. schleiferi coagulans*, and some strains of *S. hyicus* are coagulase producers [9]. They are ubiquitous, widely distributed in the environment, and part of the indigenous microbiota of the skin and mucous membranes of humans and other animals. Some species are associated with specific sites, such as the sebaceous glands [3] [10].

Staphylococcus are important pathogens for humans and animals (e.g., dogs, cats, rabbits, horses, cattle, pigs, poultry, and exotic species) and can be isolated as etiologic agents of various pathological processes, such as infections and intoxications [11] [12] [13]. Regarding the infectious processes, *Staphylococcus* are related to clinical manifestations such as pustules, boils, and impetigo, as well as more extensive and severe processes such as postsurgical infection, osteomyelitis, pneumonia, endocarditis, meningitis, bacteremia, and septicemia [9] [14]. Regarding intoxications, *Staphylococcus* are related to cellulitis, food poisoning, toxic shock syndrome, and scalded skin syndrome [15] [16] [17]. The species most commonly associated with human diseases are *S. aureus*, *S. epidermidis*, *S. haemolyticus*, *S. lugdunensis*, and *S. saprophyticus* [18] [19] [20] [21] [22]. Among the many existing human and animal pathogens, *Staphylococcus* are the most relevant in terms of multidrug resistance due to their intrinsic virulence and ability to cause various infections [23]. According to a systematic review and meta-analysis, although *Staphylococcus aureus* bacteremia mortality has decreased over the last three decades, more than one in four patients will die within three months due to antibiotic-resistant strains [24]. Notoriously, several nosocomial infections originate from CoNS, and for this reason, the resistance of these microorganisms to multiple antibiotics has increased [25] [26]. Importantly, greater attention must be directed to the control of nosocomial infections, aiming for the prudent use of antimicrobial drugs, antiseptics, and disinfectants,

to avoid selecting and disseminating resistant bacteria in the hospital environment.

2. History of the Genus *Staphylococcus*

In 1883, Alexander Ogston observed for the first time clustered cocci recovered from abscesses and related them as a cause of pyogenic diseases in humans [27]. In the following year, Rosenbach suggested a name for this arrangement visualized by Ogston: He called it *Staphylococcus* (from the Greek "staphyle" = bunch of grapes, and "cocos" = grain). Rosenbach was the first researcher to isolate and study the characteristics of the genus *Staphylococcus*, suggesting the names according to the observed color of the colonies—the orange ones were called *Staphylococcus pyogenes aureus*, and the white ones were called *Staphylococcus pyogenes albus* [28]. Interestingly, in 1905, Andrewes and Gordon proposed a classification based not only on the observed pigmentation but also on the pathogenicity of *Staphylococcus* in guinea pigs. As a result of this classification, four species were recognized: *Staphylococcus pyogenes* (orange or yellow, highly pathogenic), *Staphylococcus epidermidis albus* (white, small level of pathogenicity), *Staphylococcus salivarius* (non-pathogenic), and *Scurf staphylococci* (non-pathogenic) [29]. Nine different species of *Staphylococcus* were discovered between 1923 and 1948. However, there was still no correct distinction between the genera *Staphylococcus* and *Micrococcus*, with all the new species described being inserted in the latter genus. In the 1950s, a study suggested that the property of anaerobic growth and the production of acid from glucose was particular to the genus *Staphylococcus* and, therefore, this study was essential for the discrimination of the genera and definitive insertion of the genus *Staphylococcus* in the seventh edition of the Bergey Manual of Bacteriological Systematics [30] [31]. At the same time, two species—*Staphylococcus aureus* and *Staphylococcus epidermidis*—were recognized. Finally, there was a progressive increase in the number of new species in the 1970s, and the *Staphylococcus* genus currently has 52 species and 28 subspecies [32].

3. Coagulase-Negative Staphylococci (CoNS)

The CoNS group was considered saprophytic or rarely pathogenic for many years. Its clinical importance was only recognized when Smith and colleagues, in 1958, noticed some pathogenic potential in these microorganisms: These researchers reported the first published case of septicemia caused by CoNS [33]. Seven years later, Wilson and Stuart reported the presence of CoNS in wound infections [34]. During the 1980s, a wide range of infections, such as bacteremia, endocarditis, heart valve infections, pyoderma, mediastinitis, peritonitis, catheter-related infections, prosthetic device-related infections, and many others, were related to CoNS [35] [36] [37] [38]. After the 1980s, with the advancement of typing methods and molecular epidemiology, a more accurate assessment of the etiology of infections caused by CoNS was possible [39] [40]. Today, CoNS

have become one of the major pathogens responsible for nosocomial infections of the bloodstream, vascular catheters, and prostheses, especially among immunocompromised patients, such as those undergoing chemotherapy, drug users, patients with acquired immunodeficiency syndrome (AIDS) caused by human immunodeficiency virus (HIV) infection, and newborns [41] [42] [43] [44]. In a multicenter study Chinese children's cancer group, among patients with acute lymphoblastic leukemia due to chemotherapy, CoNS were the most frequent cause of sepsis, accounting for 20.1% of cases [45]. Among illicit drug users, a study revealed a 20% frequency of bone and joint infections caused by CoNS [46]. Among patients with AIDS, 7% of bloodstream infections are due to CoNS, and the mortality rate of these patients is approximately 10% [43]. Among newborns, CoNS is the most abundantly isolated group of microorganisms [47] [48]. In a study carried out at a university hospital in Malaysia, 1293 children were admitted over twenty months [49]. Of these children, 113 (8.7%) presented colonization by CoNS; of these 113 patients, 19 (16.8%) developed sepsis, providing an incidence of 1.5 per 100 admissions [49]. The most common sites of colonization were the nasopharynx, endotracheal tube, and eyes [49]. In a prospective study carried out in a North American hospital from 2004 to 2013, CoNS were the most commonly isolated microorganisms in newborns older than three days old, with a frequency of 31% [50]. Bloodstream infection caused by CoNS has a detrimental effect on the newborn's ability to recover and is associated with a significant increase in mortality and morbidity, as well as increased hospitalization and expenditures [51]. In a prospective study in hospitals in the U.S. between 1995 to 2002, CoNS were the most recovered microorganisms from bloodstream infections, representing 31.3% of cases and reaching a mortality rate of 20.7% [52]. Notoriously, an observational study carried out between 2007 and 2008 at the Virgen del Rocio Hospital in Spain reported that 95% of the bacteremia was due to CoNS [53]. This bloodstream infection was associated with patient factors, such as age and the presence of underlying disease [53].

3.1. Sources of CoNS in Bacteremia

The main question to be answered during the isolation of CoNS in blood cultures is whether the presence of CoNS is the cause of the infection or if it is a result of contamination. This criterion is crucial for the accurate diagnosis and treatment of the patient, particularly if blood cultures are positive for CoNS. A factor that helps this identification is the isolation of the same strain of CoNS in pure culture from the infected site and its subsequent isolation during the infection [32]. In order to determine the clinical significance of CoNS and, consequently, reduce erroneous classifications of bacteremia, the following algorithm was created: Two or more positive cultures for CoNS within five days or one positive culture accompanied by clinical signs of infection [54].

Interestingly, three hypotheses explain the potential sources of CoNS seen in bacteremia. The first hypothesis is based on the fact that when a mucosal injury

occurs due to chemotherapy, radiotherapy, or other factors, there is an increase in intestinal permeability and, thus, a translocation of CoNS through the mesenteric lymph nodes and, ultimately, to the bloodstream [55] [56]. The second hypothesis is based on the fact that CoNS may migrate from the skin to the tissue when a device like a catheter is inserted into the skin, and thus, microorganisms can reach the blood vessels and, ultimately, the bloodstream [57]. The third hypothesis relies on the fact that CoNS may contaminate the intravenous solution used in hospitals, so the bacteria directly migrate to the blood tissue [58].

3.2. Most Common Species of CoNS Found in Nosocomial Infections

In general, the species most commonly found in nosocomial infections is *S. epidermidis*, followed by *S. haemolyticus*, *S. hominis*, and *S. capitis* [53] [59] [60]. In a study carried out in a hospital in Belgium, 44.6% of bacteremia cases were due to *S. epidermidis*, surpassing *S. aureus* (39.3%) [61]. Regarding infections in newborns, *S. epidermidis* is the most common CoNS [62]. This microorganism beneficially colonizes the skin of neonates and prevents more virulent strains, such as *S. aureus*, from stabilizing in the environment [63]. However, multidrug-resistant newborn sepsis caused by *S. epidermidis* already occurred in neonatal intensive care units [64] [65]. A study showed that *S. epidermidis* strains that cause bloodstream infections have a different genetic profile from commensal strains, which suggests an adaptation of the strains in causing healthcare-associated infections [66]. *S. haemolyticus* is the second most common species isolated from blood cultures and is often resistant to a range of antimicrobials, especially glycopeptides [53] [67]. *S. haemolyticus* has been associated with endocarditis, septicemia, urinary tract infections, peritonitis, and bone and joint infections [68] [69]. *S. hominis* is the third most common species isolated from patients with nosocomial infections. This species is associated with bloodstream infections, sepsis, eye infections, endocarditis, peritonitis, and bone and joint infections [67] [70]. *S. capitis* is a human opportunistic pathogen, being related to 20% of cases of sepsis in newborns and occasionally to cases of endocarditis and meningitis associated with nosocomial infections [71]. Interestingly, other CoNS are important in causing hospital-related infections, including but not limited to *S. saprophyticus*, which is related to urinary tract infections in young women, and *S. lugdunensis*, which is implicated in arthritis, catheter infections, bacteremia, urinary tract infections, prosthetic joint infections, and endocarditis [20] [72]. According to a research done by Sabe and colleagues, *S. lugdunensis* behaves similarly to *S. aureus* in that it causes significant damage to heart valves during the development of endocarditis, necessitating surgical intervention [73]. Moreover, *S. lugdunensis* and *S. schleiferi* have recently emerged as potential pathogens in other animals, being agents of zoonoses [74].

3.3. Pathogenicity of CoNS

Staphylococcus has the ability to colonize and infect human hosts and other

animals through an arsenal of pathogenicity strategies that allow adhesion, invasion, persistence, and evasion of the immune, innate and adaptive systems [32] [68]. However, the virulence factors from CoNS are not fully elucidated, as they are in *S. aureus*. What is known so far is that a variety of mechanisms contribute to CoNS infection and persistence on biological or inert surfaces, with the capacity to form biofilms serving as the primary virulence factor [75] [76]. Concisely, the development of biofilm occurs in four steps: 1) rapid adhesion of bacteria to the surface, 2) proliferation and intercellular adhesion forming multiple layers of bacteria, 3) development of biofilm, and 4) detachment and dispersion of parts of the biofilm in other directions.

3.3.1. Biofilm

Adhesion is the initial event in biofilm formation and is a critical step for the successful colonization of CoNS on biotic and abiotic surfaces [77]. The interaction between bacteria and surfaces is mediated by physicochemical forces, such as hydrophobic interactions, van der Waals, and electrostatic interactions [78]. Such forces determine a greater or lesser bacterial attraction to the surface. A good example of the importance of chemical interactions for the initial establishment of adhesion is the fact that *S. epidermidis* strains with a mutation in an enzyme that catalyzes the insertion of D-alanine in the structure of teichoic acids (a constituent of the cell walls of Gram-positive bacteria) are deficient in producing biofilm on glass or polystyrene. Without the enzymatic activity, the bacterial cell continues to have a negative charge, and since the surface also has a negative charge, both repel each other [79]. Importantly, cell hydrophobicity and primary adhesion have been associated with bacterial surface proteins. The main components associated with this phase are autolysins and cell surface adhesins called Microbial Surface Components Recognizing Adhesive Matrix Molecules (MSCRAMM). AtlE autolysin, which is encoded by the chromosomal gene *atlE*, is the main adhesin of *Staphylococcus* [59]. The AtlE autolysin is a 115 kDa protein that degrades bacterial cell walls and is crucial for primary surface adhesion [80]. Although the exact method by which AtlE autolysin mediates adhesion is not fully understood, it is believed that the breakdown of the peptidoglycan results in the release of DNA to the extracellular environment, which has been demonstrated to be crucial in the early stages of the CoNS biofilm [32].

After the first step of initial adhesion, bacterial cells multiply and accumulate, forming several layers of bacteria, in a process where intercellular adhesion becomes of utmost importance, initiating the second step of biofilm formation. In this way, there is the production of polysaccharide molecules, such as Polysaccharide Intercellular Adhesion (PIA) and Polyglutamate (PGA) [32]. Acetylation of PIA/PGA residues introduces a positive charge to the molecule by releasing amine groups. As the bacterial surface is negatively charged, PIA/PGA supposedly acts as a "glue" that holds cells together through these electrostatic interactions [81]. The genes that produce PIA/PGA are organized into an operon called the *ica* operon (*ica ADBC*). The *ica* operon is composed of the structural genes

icaADBC and *icaR*, which are involved in the regulation of these genes [59]. The *icaA* and *icaD* locus code for an N-acetylglucosamine transferase, *icaB* for a deacetylase, while *icaC* for a PIA/PGA transporter [82]. In a murine model, PIA/PGA mutants were less virulent than the wild-type strain, corroborating the fact that these polysaccharides are important virulence factors in CoNS [83].

The third stage of biofilm formation consists of the development of the structure. A biofilm consists of cell aggregation, separated by channels with fluids that favor bacterial nutrition. The numerous cells that constitute the biofilm are embedded in an amorphous extracellular material (slime) that consists of a complex mixture of several sugars, constituents of cell walls, extracellular proteins, and teichoic acid [84]. This structure has immunomodulatory properties by directly stimulating the production of prostaglandins (PGs), inhibiting the function of T cells. The fourth and final stage of biofilm formation is based on the dissociation of a cell or a set of cells that once formed the biofilm. The dispersion of these cells is mediated by enzymatic action that cleaves the extracellular material responsible for facilitating intercellular adhesion [32].

Biofilm formation, essential for CoNS virulence, is controlled by the *quorum sensing* system, responsible for regulating gene expression in response to increased cell density [85]. Specific signaling molecules, commonly referred to as pheromones or autoinducers, are secreted by bacteria in order to communicate and sense the cell density [81] [86]. The main *quorum sensing* system of the genus *Staphylococcus*, named *agr* for the accessory gene regulator, consists of a system formed by two components for signal transduction (AgrA and AgrC), pheromone (AgrD) and AgrB, responsible for the development and export of the peptide formed after translational modifications. The effector molecule of the *agr* system is a regulatory RNA, called RNA III, whose synthesis is dependent on the activation of the *agr* system and is driven by the P3 promoter of the *agr* system [81].

Notoriously, the biofilm formed by *S. epidermidis* interferes with the action of antimicrobial agents by forming a barrier that makes antibiotic penetration difficult [87]. This was demonstrated in biofilms formed by *Pseudomonas aeruginosa* and *S. epidermidis*, concerning the action of ciprofloxacin and tobramycin, respectively [88] [89]. An important factor that could explain the influence of slime on antibiotic therapy would be the reduced growth rate of CoNS present in the biofilm, which enters the stationary phase of growth, probably because of the incomplete penetration of metabolic substrates, such as glucose and oxygen [90].

3.3.2. Other Virulence Factors

Studies involving electron microscopy reveal several virulence structures in CoNS. For example, a research group has shown a fimbriae-like structure in CoNS that assist in adherence [91]. A 140-kD extracellular protein has also been associated with the accumulation of *S. epidermidis* on surfaces [92], and hemagglutinin has been associated with adhesion to the surface of polymers [93]. CoNS can also produce lantibiotics, bacteriocins that have activity against other

Gram-positive bacteria [94]. In addition to the factors related to the production of biofilms and lantibiotics, studies report the detection of several metabolites, including enzymes and toxins, that contribute to the establishment of infection by CoNS [95] [96]. Staphylococcal enterotoxins are toxins of molecular size from 20 to 30 kD that interfere with intestinal function, causing emesis and diarrhea [97]. They are superantigens capable of stimulating T cell activation and proliferation without the need for antigen processing through the non-specific interaction of the major histocompatibility complex (*MHC*) class II [98]. Regarding the production of toxins by CoNS, there is a great deficiency in the literature since CoNS produce a small amount of toxins, and the available methods do not present adequate sensitivity for toxins detection [95] [99].

4. Antimicrobial Resistance

In addition to the important virulence factors present in CoNS, another eminent concern involving this bacterial group is its great loss of sensitivity to antimicrobials used in clinical practice observed during the last decades [26]. A large and dramatic increase in the number of resistant CoNS strains has been observed, especially in penicillin, oxacillin/methicillin, ciprofloxacin, clindamycin, erythromycin, and gentamicin [100]. The development of bacterial drug resistance emerged after the introduction of antimicrobials into veterinary and human medicine in the mid-1940s. Soon after the beginning of this practice, scientists questioned the use of antimicrobials in food-animal feed as growth promoters and their effect on human health [101]. This practice of adding antibiotics to food animals to accelerate their growth potentially favors the selective pressure for antibiotic-resistant genes resulting in multidrug-resistant bacteria [102] [103]. CoNS and *S. aureus* have received important attention as causative agents of intramammary infections in dairy cattle worldwide [104] [105]. Several studies on antimicrobial susceptibility in bovine mastitis caused by CoNS and *S. aureus* point to an increasing resistance pattern, especially for the most frequently used antibiotics, such as β-lactams [106] [107]. In humans, 80% to 90% of *Staphylococcus* strains produce beta-lactamases, and 60% to 80% of those are methicillin-resistant when isolated in hospitals, which results in resistance to all known beta-lactam antibiotics, leading to more frequent use of glycopeptides and a decrease in sensitivity to these antimicrobials [108]. As a result, treating infections becomes more challenging, restricting the therapeutic options to more toxic, costly, and challenging antibiotics. This prolongs the course of the disease and raises the risks of hospitalization due to potential bacteremia. Resistance genes can be spread via mobile genetic elements, such as plasmids and transposons, between different bacterial species, including those that cause human disease [109]. Furthermore, mobile genetic elements carry several resistance genes, and consequently, the acquisition of one of these elements can confer resistance to several antimicrobials, and resistance to different drugs can emerge when a single antimicrobial is used [110].

4.1. Resistance to β-Lactam Antibiotics

β-Lactam antibiotics inhibit the penicillin-binding proteins (PBPs) responsible for bacterial cell-wall biosynthesis [111]. Since penicillin was discovered, penicillin-resistant strains of *Staphylococcus* began to appear; the resistance phenotype is due to the production of penicillinases encoded by the *blaZ* gene located in mobile elements in the chromosomal DNA or plasmid [108]. The *blaZ* gene is controlled by the products of two adjacent genes, *blaR*1 antirepressor, and *bla*I repressor [109]. The signal required for β-lactamase synthesis is the breakdown of regulatory proteins Blal and BlaR1. Upon exposure to beta-lactams, BlaR1 cleaves itself [112]. This self-cleavage product functions as a protease to break the BlaI repressor, directly or indirectly, with the participation of another protein, BlaR2, allowing the synthesis of β-lactamase by blaZ [112]. Once *Staphylococcus* produce β-lactamases, the enzyme inactivates the antimicrobial through the hydrolytic destruction of the β-lactam ring [113]. These enzymes are predominantly extracellular, being synthesized when *Staphylococcus* are subjected to β-lactam antibiotics [114]. Based on amino acid sequences and enzymatic properties, four classes of beta-lactamases were determined: A, B, C, and D [115]. Classes A, C, and D comprise enzymes that contain serine at the active site, while class B contains metalloenzymes [116]. Class A enzymes comprise approximately 270 amino acid residues, such as those present in *S. aureus* and many of the β-lactamases encoded in plasmids of Enterobacteriaceae, such as TEM-1 and SHV-1 [117]. Class C includes enzymes of approximately 370 residues and generally encoded on the chromosome as *ampC* from Gram-negative bacteria. Class D comprises enzymes that preferentially hydrolyze methicillin and oxacillin, such as OXA-1, OXA-2, and PSE-2, encoded by plasmids. In beta-lactamases, serine plays an important role in catalysis by forming the acyl-enzyme complex when in contact with the antibiotic [118].

Another mechanism of resistance to methicillin and other β-lactam antibiotics is associated with the presence of the *mecA* gene, which encodes an additional penicillin-binding protein (PBP) [119]. The *mecA* gene is inserted into a mobile gene element called staphylococcal cassette chromosome mec (*SCC*mec). According to Saber and collaborators, eight types of cassettes (I to VIII) have already been described in CoNS [120]. The *SCC*mec cassette has two components; the *mecA* gene and the *ccr* gene complex. The *mecA* gene complex consists of *mecA*, the regulatory genes, and an associated insertion sequence. The *ccr* gene encodes a recombinase that mediates the integration and excision of *SCC*mec from the chromosome. The *ccr* gene and the other flanking genes constitute the *ccr* complex [120] [121]. Interestingly, the PBP2a, formed by the *mecA* gene, has a size of 78 kDa and considerably reduces the affinity for the β-lactam antimicrobial [122]. Therefore, β-lactam antibiotics cannot interact with PBP2a and become ineffective in lysing the microbial cell [123].

Regarding resistance to penicillin, oxacillin, and other antimicrobials of the β-lactam class, there has been a dramatic increase in the number of methicil-

lin-resistant CoNS (MRCNS) in hospitals around the world [124]. This fact is of extreme concern since such strains may also be resistant to other classes of antimicrobials [125]. A prospective observational study was done with 1166 orthopedic, spine, head, and neck surgeons from 75 countries to understand the prevalence of antibiotic-resistant bacteria among surgical professionals [126]. Interestingly, the researchers found 250 MRCNS strains, representing 21.4% of the total samples [126]. This finding is concerning because it indicates a potential spread across hospitals or the general population and alerts health professionals to the need to maintain preventative care practices in healthcare settings. In a case-control study with 1999 patients aimed to determine factors predicting deep sternal wound infections, 82 (4.1%) developed deep sternal wound infection [127]. Notoriously, CoNS were causal in 36 (44%) patients, with 25/36 (69%) being MRCNS [127]. A retrospective study conducted on 1739 *Staphylococcus* isolates from a hospital in China during 2001-2010 found high resistance rates for β-lactamases (94.0% and 73.7% for penicillin and oxacillin) and resistance percentages for cefoxitin, chloramphenicol, ciprofloxacin, clindamycin, erythromycin, gentamicin, trimethoprim–sulfamethoxazole, and tetracycline ranging from 83.9% to 19.4% [128]. A study conducted in a hospital in Brazil with 1017 patients found that CoNS was the most prevalent microorganism in hemoculture (15.87%), and 80% of these isolates were oxacillin-resistant [129].

4.2. Resistance to Glycopeptide Antibiotics

Glycopeptide antibiotics are used to treat infections caused by Gram-positive bacteria in cases of antimicrobial resistance or allergy to other antibiotics [130]. Since the discovery of glycopeptide antibiotics, their use has been limited; however, with the emergence of multidrug-resistant bacteria, these antibiotics are being used more frequently [114]. The first report of a plasmid mediating a high resistance to glycopeptide antimicrobials occurred in *Enterococcus* in 1988 [131]. The resistance mechanism to vancomycin is mediated by changes in cell wall peptides, specifically in the structure of N-acetylmuramic acid and N-acetylglucosamine, which, in this form, have much lower affinity for the antimicrobial molecule [132]. Vancomycin resistance is encoded by various genes (e.g., *van*A, *van*B, *van*B1, *van*B2, *van*C1, *van*C2, *van*C3, *van*D, *van*E, and *van*G) and it is suspected that its acquisition by staphylococci occurred from the contact with *Enterococcus faecalis*, normally resistant to vancomycin [133] [134]. *S. haemolyticus* was the first recognized vancomycin-resistant *Staphylococcus* [135]. There has been a lack of studies investigating the resistance rate of CoNS strains to vancomycin. A retrospective study in a single tertiary care center over eight years found no strain resistant to vancomycin among 308 patients with bacteremia caused by CoNS [136]. In Brazil, the first case of vancomycin-resistant CoNS was reported in 2005 in isolated samples of healthy carriers inside and outside the hospital environment [137]. Importantly, the vancomycin resistance rate remains low in hospitals worldwide and can still be considered a good the-

rapeutic option against CoNS [138].

4.3. Resistance to Other Antibiotics

Resistance to macrolides such as erythromycin and azithromycin in *Staphylococcus* is normally associated with resistance to other macrolides. Studies show that *Staphylococcus* may be carrier of the *ermA*, *ermB*, and *ermC* genes, which encode methylases, which in turn inactivate macrolide antibiotics [139]. In 2013, a prospective study done with low birth weight neonates in two neonatal intensive care units in Polish hospitals showed high rates of erythromycin resistance, with 90% of *S. epidermidis* and 100% of *S. haemolyticus* samples presenting resistance to this antimicrobial [64]. In a study done in Brazil evaluating the resistance of 16 CoNS isolated from blood cultures in 691 platelet concentrate storage bags, 62.5% of the samples were resistant to erythromycin [140].

The antimicrobials fusidic acid, fosfomycin, and rifampicin represent old treatment options currently being reintroduced into clinical practice [32]. Studies involving analysis of resistance against these antibiotic agents are incipient and often inconsistent. Regarding the molecular aspects of resistance to aminoglycosides, it is suggested that the resistance is due to the inactivating enzyme AAC(6')-APH(2") [32].

Resistance to fluoroquinolones has also been described for CoNS. This group of antimicrobials acts on the bacterial cell by modifying the structure of DNA gyrase necessary for supercoiling DNA. One of the proposed resistance mechanisms would be the spontaneous mutation of the gene that encodes the subunit A of DNA gyrase, causing the inhibitory action of these antimicrobials to no longer occur. Mutations in this gene have already been described in *S. epidermidis* resistant to ciprofloxacin and norfloxacin [125].

5. Conclusion

CoNS are clinical contaminants in immunosuppressed individuals who are submitted to the introduction of catheters and prostheses, causing serious infections. *S. aureus* is an important cause of food poisoning, pneumonia, and bacteremia and is one of the main causes of nosocomial infections. Since penicillin was introduced, penicillin-resistant strains of *Staphylococcus* began to emerge. This resistance occurs due to the production of a group of enzymes called β-lactamases that hydrolyze the antimicrobial, resulting in an inactive derivative. Today, the vast majority of S*taphylococcus* are resistant to penicillin. Due to penicillin's inefficiency in treating human and veterinary infections, antimicrobials resistant to β-lactamases such as oxacillin, methicillin, and cephalosporins were introduced into the market. Over the years, a dramatic increase in the number of resistant CoNS strains has been observed due to the selective pressure of antibiotic use and abuse. Future studies must be directed to the control of hospital infections, seeking the judicious use of antimicrobial drugs, antiseptics, and disinfectants, to avoid the selection and dissemination of resistant microorganisms in the hospital environment.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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