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Prosthetic Joint Infections Due to Coagulase-Negative Staphylococci

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Abstract

Context: *Staphylococcus aureus* and coagulase-negative staphylococci (CoNS) are the most frequently isolated pathogens and are responsible for approximately two-thirds of joint replacement infections.
Evidence Acquisition: Although both belong to the staphylococci genus, there are several epidemiological and therapeutic differences between *S. aureus* and the heterogenous group of CoNS. In general, however, preventive and therapeutic recommendations for Prosthetic Joint Infection PJI due to CoNS do not differ from PJI caused by other pathogens.
Results: The main differences between the pathogens lie in the clinical presentation of PJI, the presumed origin of infection, and the presence of a higher proportion of methicillin-resistant strains leading to a limited choice of antibiotic agents.
Conclusions: Fortunately, due to its lower virulence as compared to its cousin *S. aureus*, PJI due to CoNS may display higher remission rates than *S. aureus*-caused PJI after combined surgical and medical management.

Keywords: Orthopedic Infections, Epidemiology, Coagulase-Negative Staphylococci, Treatment, Perioperative Antibiotic Prophylaxis, Prosthetic Joint

1. Context

The carriages of coagulase-negative staphylococci (CoNS) are 100% on any human skin. However, its close associate, *Staphylococcus aureus* can only found on 20% - 35% carriages of humans skin (1, 2). *Staphylococcus epidermidis* is the most prevalent organism among over 30 CoNS species (3). A positive culture for any microorganism of the CoNS group is very often regarded simply as a contaminant. However, with the presence of a foreign body such as an implant, CoNS must be considered as a potential causative pathogen (2, 4). Staphylococcal implant infections are difficult to treat because of their ability to both grow biofilms and to form small-colony variants (4, 5). Prosthetic joint infections (PJI) are the most concerned group in terms of the allocation of research funds. The consequences and treatment costs are higher compare to other orthopedic implant infections. The morbidity, and mortality rate is also much higher. Despite this level of concern, however, little is known about the differences between these two major families of staphylococci. This review attempts to contribute to the rectification of this lack of knowledge, by highlighting key elements of the clinical presentation, perioperative antibiotic prophylaxis, and general treatment of arthroplasty infections due to CoNS. This study is an update and complement of a former review issued seven years ago (4) in light of recent publications and new evidence on this subject.

2. Evidence Acquisition

2.1. Literature Review

We conducted a search of the literature on this topic using electronic resources such PubMed database and other internet sources in order to identify English, French, and German language publications with the MeSH terms “coagulase-negative staphylococci”, “orthopedic”, “infection”, “prosthetic”, “joint”, and “treatment” in different combinations. Results retrieved by PubMed were screened for pertinence and the presence of redundant information, with an emphasis on locating original evidence-based literature published within the last ten years. We selected papers based on their abstracts and from the reference lists in retrieved articles. Review articles were included if they summarized specific aspects of PJI treatment. Reference lists of identified articles were hand-searched to retrieve additional evidence-based literature. We concentrated on in vivo human data, by

excluding experimental publications and studies performed in animals.

3. Results

3.1. Epidemiology

S. aureus and CoNS are isolated in approximately two-thirds of PJIs (6, 7). Of approximately 600 cases of PJI treated over a 5-year period at the Mayo Clinic in Rochester, USA, 30% were due to *S. epidermidis* (8). Among 112 patients with PJIs in Oxford, UK, CoNS were the most frequently isolated pathogens (9), while the proportion of CoNS cases among all PJIs in our institution, the Geneva University Hospitals, peaks around 50% and has been constant over the last decade (2, 10, 11).

More interesting than the overall incidence rate of CoNS among PJIs is the antibiotic susceptibility pattern of the causative CoNS. Methicillin is a timeworn antibiotic that is no longer used in clinical treatment, but it still serves as a reference for susceptibility testing in the laboratory. Nowadays, the clinical antibiotics that are closest to methicillin are flucloxacillin or nafcillin (12). The proportion of methicillin-resistance cases among clinical isolates of CoNS is much higher than the corresponding proportion in *S. aureus* cases; the corresponding pathogen is called methicillin-resistant *S. aureus* (MRSA) (1). According to the National Nosocomial Infections Surveillance (NNIS) report issued in 1999, 80% of CoNS had become resistant to methicillin during the previous decade; resistance to gentamycin has risen to 60% - 70%, whereas resistance to rifampin has remained at 10% (13). Methicillin-resistant *S. epidermidis* (MRSE) is now the most commonly encountered variant of CoNS in many healthcare institutions (14, 15). Skin carriage of polyclonal (15, 16) methicillin-resistant *S. epidermidis* (MRSE) has been reported among healthcare workers (15, 17, 18) and orthopedic patients (15, 17, 19).

This rise in methicillin-resistance, however, is not ubiquitous. The authors of this review assessed secular trends of CoNS infections from 1995 to 2010 (2). The overall incidence of orthopedic CoNS-associated infection and implant-related procedures was 0.14% and 0.28% respectively. There were only non-significant changes in the absolute number and incidence of CoNS infections, and 75% of all episodes were due to methicillin-resistant strains. Importantly, this epidemiology was stable over 15 years, and methicillin-resistance did not influence the outcome, supported by the fact that there was a 93% remission rate after a median follow-up of 5 years (2). In a Swedish study, most patients in an orthopedic ward were colonized with methicillin-resistant CoNS within 14 days following admission (15). So far, it remains unclear whether patients become colonized with methicillin-resistant CoNS following hospital admission.

3.2. Pathogenesis of CoNS Arthroplasty Infections

PJI usually begins intraoperatively by bacterial contamination of the surgical site (or immediately thereafter) (20), by hematogenous microbial spread from a distant area of infection (21), or contiguously, by direct or lymphogenic spread from an adjacent infectious process (e.g. cellulitis). Of these various causes, lymphogenic spread of CoNS is likely insignificant due to the fact that these bacteria co-exist and colonize on the human skin without provoking cellulitis. The hematogenous route is theoretically possible in the case of substantial bacteremia, such as in central venous line infections. Regardless of the means of contamination, the most important aspect of the pathogenesis of foreign-body-associated infections is the ability of the bacteria to colonize the polymer surface by the formation of a thick, multilayered biofilm. Within biofilms, microorganisms are enclosed in a polymeric matrix and grow into organized, complex communities with structural and functional heterogeneity, resembling multicellular organisms (4). The formation of the biofilm may be divided into three steps. First, bacteria rapidly attach to surface. In the second step, after attachment, bacteria multiply and accumulate into multilayered cell aggregates, a process requiring intercellular adhesion. Finally, the biofilm grows and matures into a thick, structured layer. A mature biofilm contains fluid-filled channels to ensure the delivery of oxygen and nutrients to the bacterial cells located in the deeper layers of the biofilm (22). The initial interactions involve non-specific physiochemical forces such as van der Waals forces, hydrophobic interactions, and polarity (23). Virulence factors such as adhesive proteins, enzymes, and toxins also play a role in this process. Intercellular adhesion requires the synthesis of the polysaccharide intercellular adhesin (PIA) under the control of an intercellular adhesion (ica) operon (23). These components are considered part of the main genetic determinants involved in the accumulation phase of biofilm formation, even if ica- or PIA-negative biofilm forming *S. epidermidis* infections may occur (24). In the case of *S. epidermidis*, exposure to foreign bodies in vitro and in vivo induces a sharp increase in ica expression, which is significantly correlated with the ability of biofilm to form in contrast to ica-negative isolates.

Biofilms provide significant resistance to antibiotics and the innate host's defenses. This resistance does not involve common mechanisms such as drug-modifying enzymes, mutations, and efflux pumps. Rather, it is the result of the thick, acidic matrix through which antibiotics penetrate poorly. Additionally, bacteria in deep layers are metabolically inactive and have an inherent lack of susceptibility to antibiotics (22).

Group behavior is an important intercellular communication mechanism in bacteria. Small signaling molecules are released in the natural environment, which

trigger specific responses in a coordinated manner in neighboring bacteria of the same species. This is known as "quorum sensing", and plays an important role in biofilm formation in practically all staphylococci and other bacteria (25, 26). Moreover, small-colony variants of CoNS, a phenomenon well-recognized in *S. aureus*, can emerge. Small-colony variants represent a subpopulation that exhibits a slow growth rate, atypical colony morphology, and unusual biochemical characteristics, thus making it a challenge when clinical microbiologists attempt to identify them. The clinical consequences of this altered phenotype are the improved persistence in mammalian cells and a reduced susceptibility to antibiotics, which make them nearly ideal candidates for recurrences. Furthermore, foreign material itself inhibits neutrophil antibacterial activity (5). Because of those given above facts, these infections are difficult to treat.

3.3. Clinical presentation of CoNS PJIs

For every PJI, the formal definition of CoNS infection requires the presence of the same CoNS in more than one intraoperative tissue sample; in addition, there must be at least one sign of infection, such as local heat, redness, pain, pus, fistula, or implant loosening. However, there are symptoms specific to CoNS that are different from those caused by more virulent pathogens, such as *S. aureus*. For example, bacteremic PJI, often seen in *S. aureus* infection, is seldom encountered in CoNS PJI. Distinctively, CoNS usually cause gradual, insidious PJI, without fever, shivering, or sinus tracts. Their hallmark is slowly increasing pain and implant loosening, typically occurring between 3 to 24 months after arthroplasty (27).

Table 1 reveals other clinical differences between the groups of CoNS and *S. aureus* infections according to an internal evaluation in our hospital. In this analysis, 219 predominant CoNS infections were compared to 1052 orthopedic infections due to *S. aureus*. At least ten differences between the groups were statistically significant. CoNS were more often encountered among arthroplasty infections, and in female or older patients (less often in the soft tissue abscesses among females), while the underlying immune suppression was not a contributing factor. In contrast, *S. aureus* was more frequently associated with abscess formation, polymicrobial infections, and septic bursitis. Moreover, *S. aureus* infections were more virulent with significantly higher serum C-reactive protein levels (CRP) than CoNS infections, and were more likely to lead to bacteremic disease (Table 1).

Table 1. Orthopedic Infections Due to Coagulase-Negative Staphylococci Versus *S. aureus* [a,b]

	Coagulase-Negative staphylococci (n = 219)	*S. aureus* (n = 1052)	P Value[c]
Median age, y	64	53	0.001
Median C-reactive protein level, mg/L	45	79	0.001
Antibiotic duration prior to operating sampling, d	5	3	0.005
Female gender	86 (39)	292 (28)	0.001
Immune suppression[d]	69 (32)	372 (35)	NA
Diabetes mellitus	44 (20)	229 (22)	NA
Implant-associated infections	118 (54)	186 (18)	0.001
Arthroplasty infections	78 (36)	54 (5)	0.001
Spondylodesis infections	5 (2)	9 (1)	
Nail infections	5 (2)	23 (2)	
Plate infections	15 (7)	68 (6)	
Septic bursitis	10 (4)	304 (29)	0.001
Foot infections	30 (14)	157 (15)	NA
Shoulder infections	5 (2)	39 (4)	NA
Abscess formation	44 (20)	544 (52)	0.001
Bacteremia	13 (6)	135 (13)	0.004
Polymicrobial infection	30 (14)	178 (17)	0.001

[a] Abbreviation: NA, not available.
[b] Data are presented as No. (%) except for Median age, Median C-reactive protein level, and Antibiotic duration prior to operating sampling.
[c] Only significant P values ≤ 0.05 (two-tailed) are displayed.
[d] Immunosuppressive therapy, renal dialysis, cirrhosis Child C, human immunodeficiency virus infection, active malignancy, pregnancy, splenectomy, agranulocytosis.

3.4. Perioperative Antibiotic Prophylaxis

Prevention of surgical site infections in arthroplasty surgery is a major issue and must address challenges not encountered in other surgical disciplines: low inoculum for implant infections; pathogenicity of CoNS and other skin commensals; possible hematogenous origin; and long post-discharge surveillance periods. Among many preventive measures that have been recommended, only few are based on strong evidence, and there is insufficient data to show one's superiority over any other. This highlights the need for multimodal approaches involving active post-discharge surveillance, as well as stronger surveillance measures at every step of the care process. These steps range from pre-operative care to surgery and post-operative care, at the individual patient level to department-wide interventions targeting all healthcare-associated infections, including antibiotic stewardship.

The entire field of infection prevention would be beyond the scope of this review (20), and therefore our focus will be on the antibiotic prophylaxis of CoNS infections. Antimicrobial prophylaxis for arthroplasty surgery enables a reduction in surgical site infection rates down to 1-3% compared to 4% - 8% without antibiotics (20). Antibiotics should be started shortly before surgery in order to ensure high concentrations in the tissues at the time of possible contamination. First- and second-generation cephalosporins are generally used in surgery because of their strong intrinsic activity against staphylococci, few side effects, and lower costs (28). However, we also know that nosocomial CoNS are often resistant to methicillin and thus per definitionem to most cephalosporines (14, 16, 19, 29, 30). Despite this fact, neither routine MRSE screening nor systematic vancomycin prophylaxis, even for medical implants, should be warranted for several reasons (31). First, there are no randomized or prospective studies showing an overall benefit of glycopeptide, or combined glycopeptide, antibiotic prophylaxis. Second, a large proportion of CoNS may still be susceptible to cephalosporines. Third, there is an emergence of vancomycin-resistant strains among enterococci and CoNS (13). Fourth, the administration of vancomycin requires slow infusion in order to avoid excessive histamine liberation, which makes its use more difficult in a setting where the precise timing of administration is of the utmost importance (32). Fifth, a routine glycopeptide prophylaxis does not guarantee decreased infection rates due to methicillin-resistant staphylococci (33).

A review of four randomized trials comparing the prophylactic use of teicoplanin versus a cephalosporin in settings with a high prevalence of methicillin-resistance among *S. epidermidis* showed similar infection rates in both groups (34). This has been confirmed in a meta-analysis of seven randomized trials (35). Another review comparing the effectiveness of non-glycopeptide and glycopeptide antibiotic prophylaxis for surgery in endemic MRSA settings failed to show increased efficacy for the perioperative antibiotic prophylaxis of surgical site infection due to methicillin-resistant staphylococci (33). Economic indicative modeling also failed to substantiate a clear benefit of general vancomycin prophylaxis (36).

3.5. Treatment

There are no established guidelines for the treatment of CoNS prosthetic or implant-related infections due to the absence of randomized trials. Various therapy regimens have been used, including the surgical removal of all infected tissue and the prosthetic joint, or a combination of debridement and exchange of prosthetic components, with implant retention and the implantation of long-term antimicrobial therapy effective against biofilm microorganisms.

3.6. Antibiotics

The ideal antimicrobial agent should be active against slow-growing and biofilm-producing bacteria and possess good bone penetrating ability and oral bioavailability. Rifampin fulfills these requirements; it can penetrate phagocytes and kill intracellular bacteria (37). Rifampin should never be administered alone, however, because it may lead to the rapid emergence of rifampin-resistant staphylococci (4, 38). Given the ease of administration, oral bioavailability, safe side-effect profile, and relatively low cost, rifampin administered in combination with another molecule as a bi-therapy has proven to be the most potent choice in vivo (39, 40). This is supported by a prospective study conducted by Widmer et al. conducted on 11 patients with orthopedic implant infections in whom the device could not be removed; rifampin was used in combination with a beta-lactam antibiotic or ciprofloxacin. The authors report treatment success in 82% of this population (41).

Different antibiotics have been used in combination with rifampin, such as cotrimoxazol (31, 42), fusidic acid (31, 43, 44), tigecyclin (31, 45), daptomycin (31, 39, 46), linezolid (30, 44, 47), dalbavancin (31), minocyclin (42, 48), ofloxacin (49), ciprofloxacin (41, 50) and levofloxacin (51, 52). Table 2 gives an overview of the doses and regimens recommended in the literature, as well as those applied at our institution. It is important to note that the combination with rifampin is only applied in the presence of an implant. When the implant has been surgically removed, there is no need for combination therapy, and antibiotic administration can be carried out with a single agent. However, the monotherapeutic use of the following molecules is not evidence-based and should be avoided for various reasons in the treatment of staphylococcal PJI: fusidic acid, cotrimoxazol, minocyclin, and ciprofloxacin (53).

Table 2. Antibiotic Recommendations of Prosthetic Joint Infections due to Coagulase-Negative Staphylococci[a]

Arthroplasty Infection	
Antibiotic/Alternatives[b]	**Duration**
Parenteral Treatment	
Vancomycin + rifampin	
Teicoplanin	~ 2 weeks
Daptomycin	~ 2 weeks
Tigecycline	~ 2 weeks
Linezolid	~ 2 weeks
Oral Treatment	
Fusidic acid + rifampin	
Ciprofloxacin + rifampin	$2^{1/2}$ months
Levofloxacin + rifampin	$2^{1/2}$ months[c]
Doxycyclin + rifampin	$2^{1/2}$ months
Minocyclin + rifampin	$2^{1/2}$ months
Cotrimoxazole + rifampin	$2^{1/2}$ months

[a]Adapted from Uckay et al. (54)
[b]Drug doses: Vancomycin, 2 ×15 mg/kg iv or 30 mg/kg/d in continuous infusion, targeted serum vancomycinemia in steady state ~ 25 mg/L; Rifampin, 600 - 1200 mg/d, parenteral medication not necessary, always in combination, never alone (development of resistance), In absence of implants rifampin is not indicated, but may be used in combination therapy because of good bone penetration; Teicoplanin, 1st day 2 × 400 mg intravenously, from 2nd day 1 × 400 mg iv, it can also be given by intramuscular route, Teicoplanin and fusidic acid not available in the U.S.; Daptomycine, 6 - 10 mg/kg/d once daily, few data on human osteoarticular infections available; Tigecycline, 100 mg iv once, thereafter 2 × 50 mg/d iv, mostly experimental so far; Linezoli: 2 × 600 mg/d, in non-bacteremic cases, linezolid can be given orally, be aware of interactions with MAO-inhibitors, myelosuppression and polyneuropathy; Fusidic acid: 3 × 500 mg/d, always in combination (possible development of resistance during monotherapy); Ciprofloxacin, 2 × 500 mg/d, only if the MRSA is susceptible, this is rarely the case; Levofloxacin, 2 × 500 mg/d, only if the MRSA is susceptible, this is rarely the case; Doxycyclin, 2 × 100 mg/d; Minocyclin, 2 × 100 mg/d; Cotrimoxazole, 2 double-strength tablets (800 mg trimethroprim, 160 mg sulfadiaxozide) per day, may have failure when high inoculum.
[c]Total duration: 3 months. For knee joint prostheses, up to six months can be considered.

Polyclonal infections (55, 56) represent up to 32% of all CoNS cases in an orthopaedic patient population (57). As laboratories do not routinely perform antibiotic susceptibility testing for all strains, polyclonality could theoretically lead to insufficient antibiotic coverage, e.g., due to other unidentified methicillin-resistant strains with different sensitivity patterns. However, formally speaking, we were unable to show any difference in the cure rates or in the occurrence of methicillin-resistant infections between the groups of poly- and monoclonal CoNS infections (2).

3.7. Duration of Antibiotic Therapy

For PJI, antibiotics are initially administered intravenously for 2 weeks and followed by oral therapy, for a total treatment duration of 3 months in patients with retained hip prostheses, and 3 to 6 months in those with retained knee prostheses (although, as is also the case below, this duration is arbitrary and might be excessive). In the case of prosthesis removal, a 6-week total course of antibiotic therapy is considered sufficient (27, 58). The arbitrary limit of 6, 12, or 24 weeks is based solely on experts' opinions rather than on prospective trials. Following drug administration of a proper-length, antibiotics can be discontinued regardless of actual C-reactive protein (CRP) values or inflammatory parameters (59).

3.8. Surgery

For patients with an early postoperative or acute hematogenous infection, having experienced clinical symptoms for less than 3 weeks, debridement with implant retention is a reasonable option (7) when the prosthesis is stable, the soft tissue is in good condition, and an agent displaying activity against biofilm producing microorganisms is available. For multimorbid and elderly patients, debridement with suppressive antibiotic prescription is another option, but it does not target remission (it is used only for infection control). For all other cases, arthroplasty removal is strongly recommended (27).

3.9. One-Stage Exchange Revision

The one-stage exchange, in which the infected prosthesis is removed and a new one implanted in the same procedure, was first popularized in Europe. This technique has been recommended in immune-competent patients with an acute infection, sensitive to first-line antibiotics. Antibiotics should be administered post-operatively for a minimum of several weeks, if not months (60).

3.10. Two-Stage Exchange Revision

This process has become the standard procedure in North America and in many other countries. The interval between resection and re-implantation of the prosthesis is typically 6 weeks (6, 7, 27). In most instances, a temporary spacer made of antibiotic-loaded cement is inserted in the first stage and removed in the second in order to avoid soft tissue retraction and ensure a high concentration of the active principle in the vicinity of the residual joint space. However, while the activity of antibiotic-containing bone cement against CoNS has been proven in vitro (61), no specific data from large human studies exists to the best of our knowledge. Of particular note is the fact that most surgeons use spacers for mechanical reasons, facilitating re-implantation and postoperative mobilization.

3.11. Outcomes of Prosthetic Joint Infections due to CoNS

Clinical presentation of CoNS PJI is typically less virulent than other infections caused by microorganisms.

Therefore, one might assume that this lesser virulence might lead to higher remission rates after therapy. Unfortunately, this theoretical advantage is hampered by a higher proportion of methicillin-resistant strains among CoNS. Interestingly, though, few publications have addressed this issue. In an older study conducted by Kloos and al. back in 1994, patients with methicillin-sensitive infections showed higher implant survival rates than those who harbored methicillin-resistant strains (3). In our own institution, we compared PJI and other orthopedic implant infections due to methicillin-sensitive *S. aureus* (MSSA), MRSA, and coagulase-negative staphylococci (CoNS). Methicillin-resistance did not influence the physician's decision regarding the type of surgical procedure used, or the duration of antibiotic treatment. In the subgroup of arthroplasty infections, remission was achieved in 39% (7/18) of MRSA cases, 60% (15/25) of MSSA cases, and 77% (30/39) of CoNS episodes. In multivariate analysis, PJI and MRSA infections were inversely associated with an overall cure for all implants. CoNS infection and the insertion of a new implant were associated with higher cure results. Methicillin resistance, immune suppression, sex, age, duration of antibiotic therapy, one-stage revision, rifampin use, and total number of surgical interventions did not influence the cure rate (11).

4. Conclusions

In general, the preventive and therapeutic recommendations for PJI due to CoNS do not differ from other pathogens. The differences lie in the clinical presentation of PJI, the presumed origin of infection, and the presence of a higher proportion of methicillin-resistant strains leading to limited choices of antibiotic agents. Fortunately, due to its lower virulence compared to its cousin *S. aureus*, PJI due to CoNS is associated with higher remission rates after combined surgical and medical treatment. Ultimately, we have determined that it is very difficult to evaluate implant-related infections in small clinical studies or single centers. Hopefully, the future will harbor prospective and multicenter human cohort studies for the specific subset of patients with PJIs due to CoNS.

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