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EDITORIAL COMMENT

CoN(S) Nuevas Perspectivas

Insights Into Coagulase-Negative Staphylococcal Infective Endocarditis

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Infective endocarditis (IE) is a rare syndrome with an incidence of 10 to 20 cases per 100,000 person-years, but it carries a high mortality rate and significant clinical burden.[1] Historically, rheumatic heart disease was the primary risk factor associated with IE, particularly in low-income countries, where it remains prevalent and often manifests as streptococcal IE in young adults. More recently, however, an aging population with comorbidities such as valvular heart diseases, diabetes mellitus, and end-stage kidney disease has resulted in a substantial rise in the incidence of IE, particularly that due to staphylococci.[2] This increase is further driven by the expanded use of intravascular and both valvular and nonvalvular cardiovascular devices.

Coagulase-negative staphylococci (CoNS), traditionally regarded as low-virulence skin microbiota, have emerged as prominent pathogens in health care-associated infections because of their high propensity to cause intravascular and intracardiac device-associated bloodstream infections. Unlike *Staphylococcus aureus*, positive blood cultures for CoNS can be challenging to interpret clinically because they are common skin microbiota and the most common causes of blood culture contamination. Moreover, there are >40 species of CoNS, and most can cause human infections. Thus, the moniker "*Staph epi*" hardly addresses this group of staphylococci and their variability of virulence, which can be confusing to clinicians in the interpretation of microbiology laboratory results.

Confirmed CoNS bloodstream infection can serve as a significant marker for IE. In this regard, the 2023 Duke-International Society of Cardiovascular Infectious Diseases IE criteria included CoNS as a "typical pathogen" to cause IE, in cases involving intracardiac prosthetic materials, reflecting the rising incidence of prosthetic valve endocarditis caused by this organisms.[3]

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In a study reported in this issue of *JACC*, Palom-Grau et al[4] evaluated 1,951 definite staphylococcal IE episodes from a contemporary Spanish nationwide cohort, over a 15-year period, producing several noteworthy findings into the epidemiology, clinical characteristics, and outcomes of CoNS IE as well as *S. aureus* IE. First, staphylococcal IE accounted for nearly one-half of all IE cases, and this proportion remained stable over the study period. Notably, the incidence of CoNS IE was significantly higher than previously reported.[5] Compared with *S. aureus* IE, patients with CoNS IE were older and had more comorbid conditions, particularly those with prosthetic valves. Historically, CoNS have been primarily linked to prosthetic valve endocarditis and cardiovascular implantable electronic device infections because of their biofilm-forming ability; in contrast, CoNS causing native valve endocarditis (NVE) have been reported in only a small minority of patients with IE.[6] The present investigation, however, revealed that the proportion of NVE cases due to CoNS was markedly higher (36%) than had been described in earlier investigations and demonstrated a seismic shift in the clinical profile of CoNS IE.

Second, it is not surprising that *S. epidermidis* accounted for the largest proportion of IE cases, given

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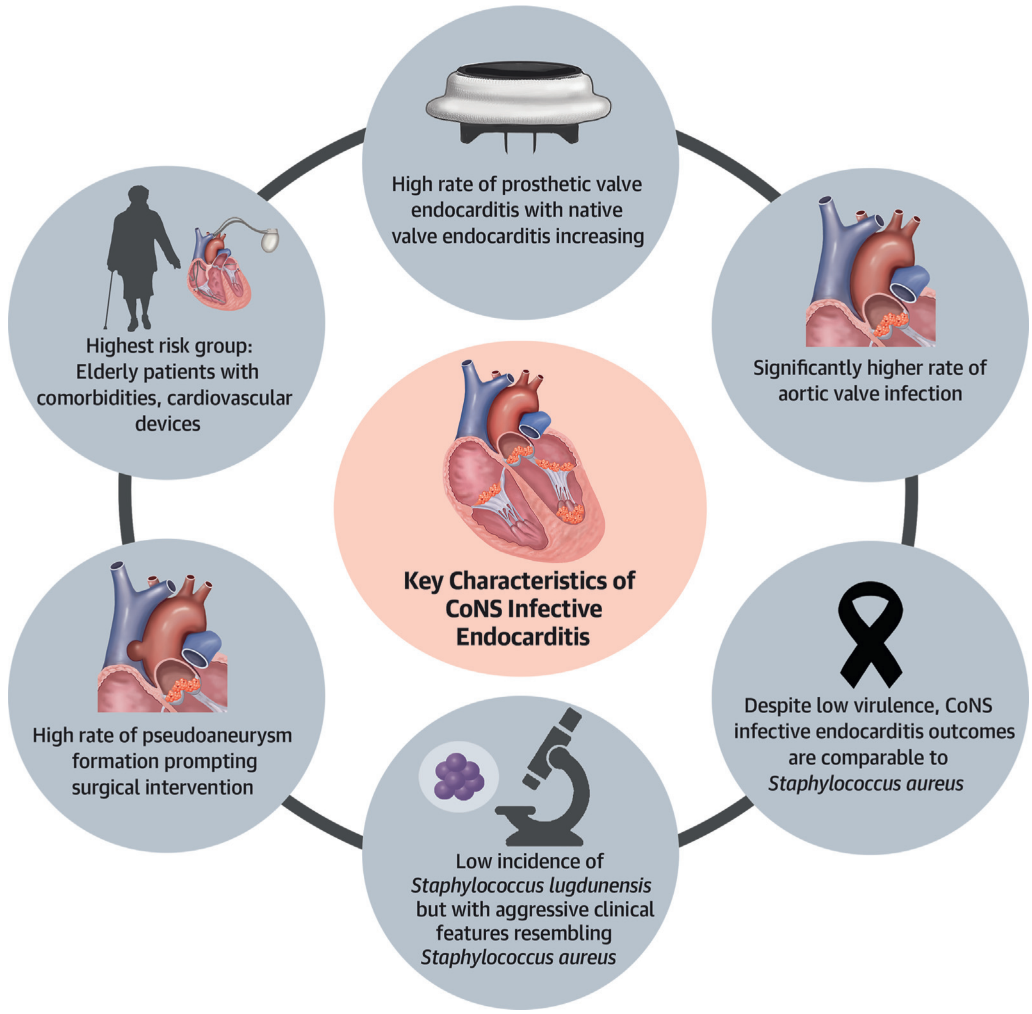
FIGURE 1 **Clinical Insights Into CoNS Infective Endocarditis**



Key clinical characteristics of coagulase-negative staphylococci (CoNS) infective endocarditis from the study of Palom-Grau et al.[4]

its high prevalence among CoNS species in clinical specimens, and it exhibited the highest rate (70%) of methicillin-resistant isolates, a rate comparable with that seen in isolates from the United States. The proportion of IE cases caused by *S. lugdunensis* was relatively low (6%). *S. lugdunensis* is recognized for its increased virulence compared with that of other CoNS, and is reflective of *S. aureus* in its pathogenicity, particularly in affecting native valves. This study showed that *S. lugdunensis* frequently affects patients undergoing hemodialysis and involves native valves, similarly to *S. aureus*. Moreover, recent findings[7] from our medical center highlighted the importance of *S. lugdunensis* in bloodstream infections, with 59% of patients who underwent echocardiography harboring underlying IE. Of note, the 2023 Duke-International Society of Cardiovascular Infectious Diseases IE criteria[3] added *S. lugdunensis* as a “typical pathogen” for IE because of its virulence.

Third, the clinical outcomes in the Spanish cohort deserve attention. In-hospital mortality for patients with CoNS and *S. aureus* IE were 33% and 37%, respectively, both alarmingly high, especially with CoNS NVE. One-year mortality (approaching 40%) was comparable with that observed in previous studies,[8] reflecting the persistent severity of IE and its potential for devastating outcomes. These results underscore the importance of early recognition, a multidisciplinary team approach, and referral to

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centers of excellence, as this study demonstrated that perivalvular abscess was associated with worse outcomes, making surgery a key protective factor, something that can be achieved only with a well-trained and well-equipped endocarditis team.

The prospective, uniquely large Spanish nationwide cohort is an invaluable tool for deepening our understanding of staphylococcal IE, as it captures granular data on clinically relevant variables in this low-incidence disease, particularly with the scarcity of robust randomized controlled trials in this field. Referral bias does exist in this type of study, though this is typically unavoidable when examining rare but severe illnesses that require coordinated, specialized care in a referral center. The replication of such comprehensive cohort studies elsewhere may be difficult because of various barriers, including prohibitive costs, complex coordination, requirement for longitudinal follow-up, the absence of standardized protocols, and a lack of specialized endocarditis teams, which lead to inconsistencies in IE care. Furthermore, there is often a lack of data from underrepresented populations which could exhibit different patterns of staphylococcal IE.

Important clinical insights (**Figure 1**) we have learned from this study are that CoNS IE is common in both community-acquired and nosocomial settings, particularly among elderly patients with comorbidities and multiple risk factors for IE. Clinicians should not overlook CoNS bloodstream infections, as they could be markers for IE, including native valves. Despite the theoretically lower virulence of CoNS, their clinical outcomes are comparable with those of *S. aureus* IE, with similarly high morbidity and mortality. A key challenge remains in distinguishing blood culture contamination, intravascular device colonization, uncomplicated bloodstream infection, and underlying IE caused by CoNS. With the advantage of a large, well-maintained cohort with comprehensive data, integrating generative artificial intelligence and machine learning into such data sets is expected. These advanced tools could help develop individualized, comprehensive risk scores and, in the future, accurately predict the likelihood of IE in the setting of bloodstream infection, solely on the basis of patient comorbidities and clinical characteristics, offering a true "IE con nuevas perspectivas."

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