Journal of the American Heart Association

EDITORIAL

Infective Endocarditis Remains a Deadly Disease—It's Bad News, Especially When *Staphylococci* and *Enterococci* Are Involved: A Call to Action

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In this issue of the *Journal of the American Heart Association (JAHA)*, Østergaard and colleagues present data drawn from national registries across Denmark, providing clear insight to the common pathogens and associated outcomes following a first episode of infective endocarditis (IE).[1] Understanding the predictors of poor outcome and identifying modifiable patient- and disease-related factors are key to building an evidence-based approach to tackle the high morbidity and mortality associated with IE. Danish registries provide a unique opportunity to achieve this, with individual citizens traceable across pseudoanonymized national databases.

See Article by Østergaard et al.

The Danish National Patient Registry holds information on every hospital admission in Denmark since 1977, with *International Classification of Diseases, Tenth Revision (ICD-10)* coded diagnoses obtained from patient discharge paperwork. Although coding relating to IE is not without pitfalls, the authors identified patients with a first diagnosis of IE from 2010 to 2017 with a combination of *ICD-10* codes previously identified as having good positive predictive value for IE.[2] This allowed linking of patients with first-time IE to clinical, microbiological, and outcome registries, containing key demographic and comorbidity data. Over the 8 years of study, 4123 admissions with IE were included in analyses, with no significant difference in incidence. Outcome data were available for both inpatient stay and in the medium term, with a median follow-up period of 2.3 years (interquartile range 0.4–4.6 years). This allowed for identification of trends over time, accounting for captured patient characteristics and causative organism. Interestingly, in the more recent quartile of study, patients were older, had proportionally more prosthetic valve IE, and were more likely to have a past history of cancer and diabetes compared with earlier time periods.[1]

Staphylococci were the leading causative organism in IE (28.1%), followed by *Streptococci* (26.0%) and *Enterococci* (15.5%) with blood culture negative IE (BCNIE) accounting for 18.9% of cases.[1] This is in line with international registries showing falling rates of streptococcal IE and climbing staphylococcal and

Key Words: Editorials ■ blood stream infection ■ heart valve disease ■ infective endocarditis ■ mortality ■ nationwide study ■ organism ■ population study

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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enterococcal IE.[3,4] However, there was no temporal change in the proportion of IE secondary to these organisms in the period of study. This does, however, reflect the shift in causative organism over the past 20 years, associated with the climbing incidence of invasive procedures and a population with a longer life expectancy.[5–7] These relate not only to cardiac interventions with climbing rates of valve surgery, the evolution of transcatheter aortic valve implantation, and cardiac implantable devices but also to indwelling vascular catheters associated with dialysis and the management of cancer.[3,5]

Given the important role of viridans streptococci in IE, an increased population health focus on improving oral health and dental hygiene may also contribute to falling rates of streptococcal disease.[8,9] An inevitable impact of this change in causative organism has been a shift from subacute bacterial IE to rapid deterioration with an acute presentation for staphylococcal disease, in particular. This demands new treatment paradigms for the diagnosis and management of IE, with many patients seeking evaluation of fever later in their illness. This is despite guidance for patients deemed at high risk, including those with valvular heart disease, prosthetic heart valves, and previous IE; this has been particularly evident during the COVID-19 pandemic.[10–13] Although *Staphylococcus aureus* is a known predictor of poor outcome in IE, only 13.6% of patients underwent operative intervention in the current study, compared with 20.1% of those with streptococcal IE, 24.3% with enterococcal IE, and 21.1% with BCNIE.[1]

Despite high rates of morbidity and mortality, IE remains a rare disease, and this may explain in part why health care services are ill equipped to deliver rapid diagnostics to patients with IE that may well be life saving. This is highlighted in the current study, and other large international registries, where almost 1 in 5 cases were BCNIE (18.9%).[1,3,4] This is despite established diagnostic pathways to identify the causative pathogen in this scenario, including the use of 16S rDNA polymerase chain reaction technology.[3,12,13] This phenomenon is reflected in the current study, with a statistically significant decline in the proportion of BCNIE over the period of study from 24.1% in 2010 to 18.4% in 2017.[1] Further promising work continues in this area, with the emerging technologies of both metagenomics to identify bacterial DNA in resected valve tissue and proteomics to capture proteins pathognomonic of certain bacteria and fungi.[14,15] Critically, identifying the causative organism will allow more targeted therapeutics, reducing toxicity and improving outcomes for this group in particular.

The paradigm shift in the timing of surgery in IE has been adopted in international guidelines, with a move away from the concept of achieving sterility and operating late, toward early surgery to avoid heart failure, intractable sepsis, irreversible structural damage, and death.[12,13] This move led to reduced all-cause mortality in a large meta-analysis, favoring surgery before 7 days compared with 8 to 21 days, with an odds ratio (OR) of 0.61 (95% CI, 0.50–0.74), albeit with a possible higher rate of recurrence in the early surgery group.[16] The modern approach to the management of IE is to therefore actively identify the established indications for surgical intervention in every patient at the time of diagnosis, and regularly thereafter, as a part of a multidisciplinary expert IE team.[12,17,18] Despite this, the EuroENDO (European Infective Endocarditis) registry identified 69.3% of patients had an indication for surgery, with only 51.2% of patients actually undergoing surgical intervention; the remaining 18.1% had the highest rates of mortality.[3] Of those undergoing surgery, just 31.5% went to the operating theater emergently or urgently, with 32.0% operated beyond the first week and 36.5% electively. In the current study, the population statistics preclude identification of surgical indications; however operative rates declined steadily from 24.8% in 2010 to 2011 to 17.6% in 2016 to 2017.[1] If we are to reduce mortality in IE further, it is imperative we reconfigure our services to improve response times, training a cohort of cardiologists to identify IE early and manage it aggressively, and a further cohort of cardiac surgeons and anesthetists who operate upon these patients on a regular basis.

The most striking findings from Østergaard and colleagues however, relate to in-hospital versus medium-term mortality.

Overall in-hospital mortality was comparable to other European countries in the contemporary era at 18.7%, with highest mortality rates in *S. aureus* IE (28.2%) compared with just 11.1% in streptococcal IE.[1] This translated to an OR of 3.5 (95% CI, 2.7–4.4) for *S. aureus* IE, OR of 2.0 (95% CI, 1.5–2.6) for BCNIE, OR of 1.8 (95% CI, 1.2–2.7) for coagulase negative *Staphylococci* (CoNS), and OR of 1.5 (95% CI, 1.0–2.3) for enterococcal IE. A similar distribution of risk was seen for 1-year mortality, albeit ≈10% higher in absolute values.[1]

However, at a median follow-up of 2.3 years (interquartile range 0.4–4.6 years) mortality rates were astounding: 74.4% for enterococcal IE, 70.1% for *S. aureus*, 62.4% for BCNIE and coagulase negative *Staphylococci* IE, and 58.5% for streptococcal IE. This higher rate of mortality for patients with enterococcal disease, compared with *S. aureus*, was identified only when differentiating mortality at time from discharge compared with admission.[1] This suggests that although *S. aureus* IE is high risk at presentation, if patients survive their admission, they do better compared with their counterparts with enterococcal disease, who are older with more comorbidities.

To put these findings in context, mortality rates in observational studies of patients with heart failure

between 2000 and 2009 to 2010 show a 1-year mortality of 20% and a 5-year mortality of 53% to 67%.[19,20] Even without the anticipated real-world reduction in mortality with novel heart failure pharmacotherapy, the mortality in IE is significantly worse than in heart failure. Yet most countries spend very little on the organization of IE services in comparison with heart failure.

In conclusion, the present study highlights significant mortality in IE, with *Staphylococci* as the leading causative organism in an unselected cohort of patients with IE. When adjusting for inpatient mortality, the prognosis following enterococcal IE is also poor. Patient characteristics are important factors in relation to the causative organism, particularly in relation to intracardiac prosthetic material and indwelling long-term vascular catheters.

The very high rates of medium-term mortality are a serious concern, and as a community we must strive to identify and address modifiable risk factors to improve outcome. To achieve this, we must innovate in diagnostics, adopt a mindset of active consideration and adoption of early surgery, and develop robust pathways that facilitate working in expert teams.

ARTICLE INFORMATION

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Disclosures

None.

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