



Infective endocarditis—whose baby? Everyone's!

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Ever since the seminal works of William Osler, the field of infective endocarditis (IE) has evolved serially and incrementally. There has been a keen tussle and a kind of tug of war, between the stakeholders—the offending microbial infective agent on one side and the defending host, backed by technology, on the other. Alas, the former seems to be getting one over the latter, with no evidence whatsoever of the fortunes reversing. Despite all advances, the overall mortality from IE keeps hovering around 20 to 25% in most series, and has remained thereabouts in the last 50 years.

Factors contributing to this stalemate are just as myriad as they are protean. The changing and ever-evolving epidemiology—advancing age of the host and nosocomial characterization, with virulent *Staphylococcus aureus* and fastidious organisms as the predominant offenders—takes the pole position. Matters are made worse with antimicrobial misuse and resistance, increasing numbers of indwelling and intravascular devices, the menace of “drug abuse” (especially opiates), and burgeoning population of immunosuppressed hosts (cancers, haemodialysis, etc.). The role of restrictive antibiotic prophylaxis of the National Institute for Health and Clinical Excellence (NICE) guidelines remains sub-judice, and may be a subject for revisit. The resurgence of viral infections, including the recent pandemic of coronavirus disease, 2019 (COVID-19), and transcatheter aortic valve implantation (TAVI)—associated IE are new kids on the block, vitiating the field, with the latter having “characteristics of healthcare-associated infections, with a high predominance of staphylococcal and enterococcal infections” [1]. Oral and gut microbiomes are interesting fields of investigation, calling for an in-depth exploration of their role in causation of IE. Sadly, even we, the medical professionals, have contributed significantly to the poor outcomes by delayed institution of antimicrobials, late referral to higher and better equipped hospitals, and “non-performance of

surgery when indicated” [1]. This profound spectral transition in IE not only is seen in the developed countries, but is now transgressing boundaries and replicating itself, in all its fury, even in the developing world.

Pari passu with changing epidemiology, clinical presentation has also changed hues. We traditionally taught our students to take history of prolonged low-grade fever as suggestive of IE. However, contemporary IE is more an acute, rather than a chronic indolent disease. Patients are presenting earlier with embolization and failure, a surrogate of virulence of the pathogens. Elderly, chronically ill, malnourished, and immunosuppressed hosts may stay afebrile and classical peripheral stigmata of IE are either disappearing or missed (especially in the dark skinned). All these should come with no surprise as the pathophysiology of IE too is evolving. Starting with endothelial injury or inflammation, it passes serially through non-bacterial sterile thrombosis due to fibrin-platelet interaction, colonization by microbes (aided by adhesins), and vegetation formation. The microbiome here plays a seminal role in deciding the course of the disease. “*Staphylococcus aureus* and *Staphylococcus epidermidis*, may move between single free-floating cells and multicellular biofilms. Cells bind to a surface and then multiply to form microcolonies during biofilm formation. They then create the extracellular matrix, which is made up of polysaccharides, proteins, and extracellular DNA and is a hallmark of biofilm formation” [2]. The evolution of this self-sustaining defence fortress by the offending pathogen of complex prophage-mediated biofilms and exudation of a surrounding matrix of macromolecules is the most common mechanism for implanted device-related antimicrobial resistance. Other less understood mechanisms like “nutritional immunity” affecting bacteria's health (e.g. role of manganese), with likely many more waiting to be unfolded, may also be influencing host-microbe interactions. No matter the mechanisms involved, IE leads to either valvular damage and consequent heart failure, embolization, or septic shock. It finally culminates into assisted/spontaneous remission or cure—if luck favours the brave patient; or mortality—if the microbe gets better of the weak host.

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Advancements in imaging technologies of 3D and 4D echocardiography, nuclear medicine, and positron emission tomography (PET) functional imaging play a seminal role in early detection and localisation of infective foci. The European Society of Cardiology has recommended nuanced use of ¹⁸F-fluorodeoxyglucose positron emission computed tomography (FDG-PET/CT) and radio-labelled white blood cell single-photon emission computed tomography (WBC-SPECT) in patients with suspected prosthetic valve endocarditis (PVE) [3]. They may even have a role in TAVI-associated IE, but their role in native valve endocarditis is sub-judice [4].

Though blood culture, echocardiography, and PET/SPECT-based imaging remain the primary diagnostic tools for IE, diversity of pathogens, with 10–20% being culture negative, has necessitated development of novel diagnostic modalities involving molecular pattern detection of these pathogens. The classical cytogenetics looking at fluorescent banding patterns, using trypsin-Giemsa for detection and characterization of chromosomal abnormalities, has yielded to newer molecular cytogenetic techniques like amplification and sequencing of the gene encoding the 16S ribosomal RNA (rRNA); broad-spectrum PCR (polymerase chain reaction), especially for hard to culture, anaerobic, or non-viable bacteria; fluorescence in situ hybridization (FISH); next-generation sequencing from blood; and Direct 16S rDNA PCR [5]. “The molecular techniques namely FISH, Quorum sensing detection, 16S rRNA PCR and metagenomic sequencing can overcome the limitations like diagnostic delay, false negatives/positives, and presence of non-culturable pathogens” [2]. Computer-assisted image analysis of FISH data [6] and ever so fast intruding “artificial intelligence” and “machine learning” are exciting developments meriting further explorations. However, FISH technique, though effective in diagnosing fastidious bacteria, is limited by the fact that it can only detect intact and viable bacteria. Moreover, “False-positive results could be caused by auto fluorescent particles that imitate bacteria, while false-negative results could be caused by autofluorescence masking the presence of bacteria in the sample. ...combining FISH with other diagnostic methods such as blood cultures, PCR, or immunohistochemistry is a viable choice” [2].

Management of IE calls for a personalized and multidisciplinary approach. The advent of precision medicine, complemented by advanced molecular diagnostic tools and genetic profiling, lends IE to tailored treatment plans with a view to optimizing outcomes. Timely and appropriate use of antimicrobial agents, coupled with meticulous surgical debridement, plays a pivotal role in preventing relapses and improving long-term prognosis. Modern surgical valve repair techniques, such as the Ross operation and the Ozaki procedure, exemplify the strides made in preserving native tissues and improving long-term

outcomes for patients. Minimally invasive approaches, including robot-assisted procedures, have been validated to minimize trauma, reduce recovery times, and enhance overall patient satisfaction. However, the timing of surgery in IE still remains unsettled, and should be individualised [1]. Benefits of early surgery, as shown by an anecdotal randomised controlled trial (RCT) [7], have not been replicated and even European and American guidelines are ambiguous in the face of lack of sufficient literature.

However, there seems to be no such ambiguity in matters of antimicrobial therapy. Notwithstanding the giant strides in diagnostics and surgical techniques, the importance of infection control and antibiotic stewardship cannot be overstated. “Sepsis is a medical emergency and life-threatening condition due to a dysregulated host response to infection, which is time-dependent and associated with unacceptably high mortality. Thus, when treating suspicious or confirmed cases of sepsis, clinicians must initiate broad-spectrum antimicrobials within the first hour of diagnosis” [8]. In a study of 4000 patients with sepsis and septic shock, there was a 2% increase in mortality for every hour of antibiotic delay [9], reconfirming the need for expediency in matters.

Infective endocarditis is a wily customer, providing formidable and daunting challenges to the medical fraternity. Given its heterogeneity and the multifactorial intricacies of the interplay between microorganisms and host tissues, a collaborative multidisciplinary approach is not just desirable, but in fact an absolute necessity for comprehensive management of IE [10]. It ensures early diagnosis, institution of appropriate antimicrobials, and a seamless transition to surgery, if indicated. Proof of the pudding lies in over 50% reduction in the hard end-point of 1-year mortality (from 18.2 to 8.2%; hazard ratio 0.41; 95% confidence interval 0.21–0.79; $p = 0.008$) [11]. The European Society of Cardiology and European Association for Cardio-Thoracic Surgery (ESC/EACTS) Guidelines accord Class IIa B recommendation for establishing an “Endocarditis Team” as a multidisciplinary strategy to the management of IE [12].

If “time is muscle” for myocardial infarction, it is in fact “life” in a case of IE. Early referral to a higher centre with facilities for advanced imaging and genetic and molecular testing, besides a team of dedicated professionals, is fundamental to a successful outcome. However, access to specialized cardiac care, particularly in resource-limited settings, remains a concern. Development of novel long half-life parenteral anti-microbials and oral and domiciliary antibiotic regimens are interesting propositions, which may help redress this inequity. The medical community must therefore continue its efforts to innovate, communicate, and build capacity.

Overall, IE is still a work under progress and this thematic issue is just yet another cog in that wheel. Hope it lives up to, and serves, the purpose of disseminating knowledge and

sensitising the medical profession to the complexities and perils of infective endocarditis.

Signing off with an impassioned plea and a clarion “call to action”.

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