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SPECIALTY SECTION
This article was submitted to Molecular and Cellular Pathology, a section of the journal Frontiers in Cell and Developmental Biology

RECEIVED 16 July 2022
ACCEPTED 06 September 2022
PUBLISHED 03 October 2022

CITATION
Kouijzer JJP, Noordermeer DJ, van Leeuwen WJ, Verkaik NJ and Lattwein KR (2022), Native valve, prosthetic valve, and cardiac device-related infective endocarditis: A review and update on current innovative diagnostic and therapeutic strategies. *Front. Cell Dev. Biol.* 10:995508. doi: 10.3389/fcell.2022.995508

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Native valve, prosthetic valve, and cardiac device-related infective endocarditis: A review and update on current innovative diagnostic and therapeutic strategies

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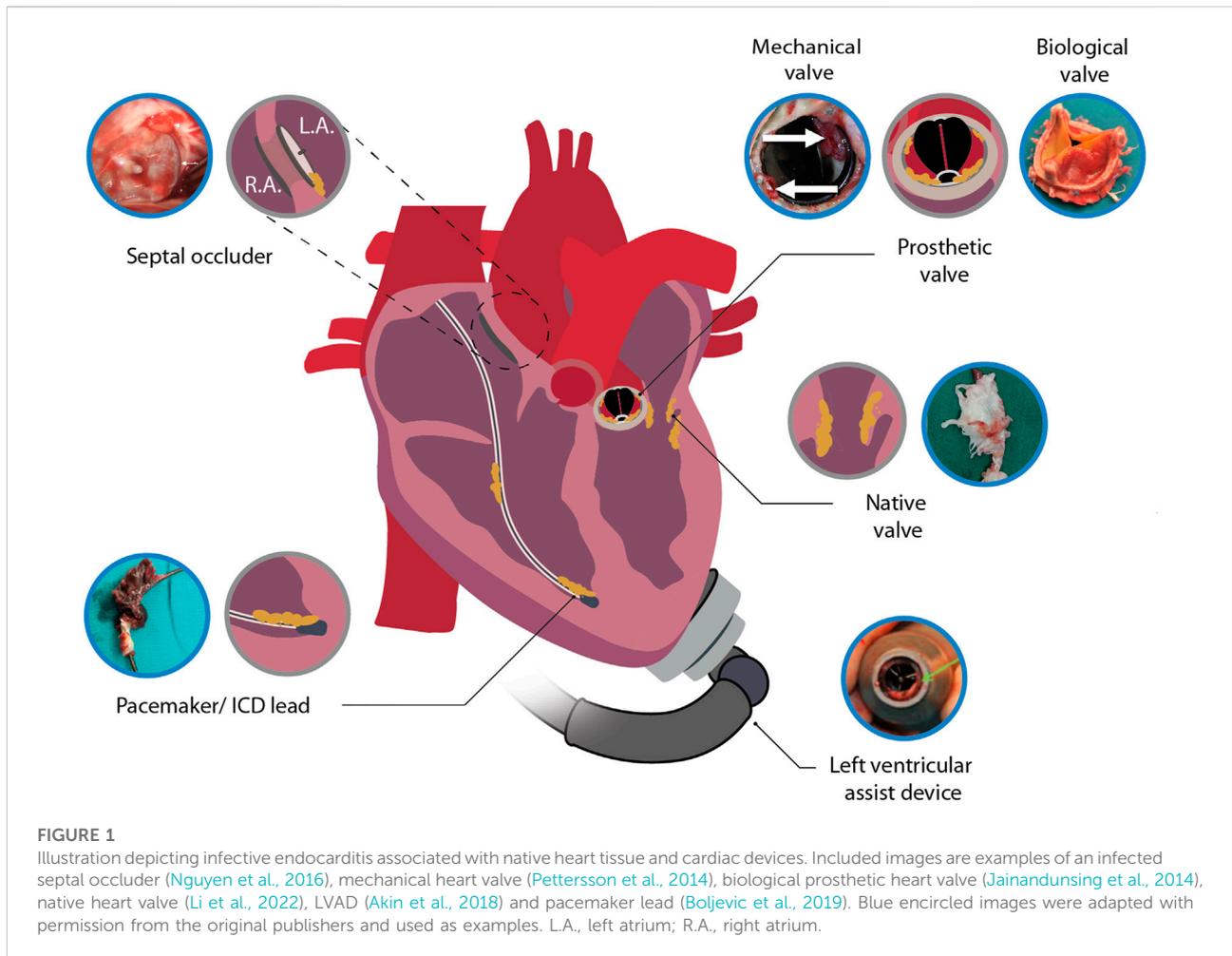
Infective endocarditis (IE) is a life-threatening microbial infection of native and prosthetic heart valves, endocardial surface, and/or indwelling cardiac device. Prevalence of IE is increasing and mortality has not significantly improved despite technological advances. This review provides an updated overview using recent literature on the clinical presentation, diagnosis, imaging, causative pathogens, treatment, and outcomes in native valve, prosthetic valve, and cardiac device-related IE. In addition, the experimental approaches used in IE research to improve the understanding of disease mechanisms and the current diagnostic pipelines are discussed, as well as potential innovative diagnostic and therapeutic strategies. This will ultimately help towards deriving better diagnostic tools and treatments to improve IE patient outcomes.

KEYWORDS

biofilm, cardiac device, diagnosis, infection, infective endocarditis, native valve, prosthetic valve, treatment

Introduction

This review provides an overview on native valve infective endocarditis (NVE), prosthetic valve (PVE) and cardiac device-related infective endocarditis (CDRIE) concerning epidemiology, pathogenesis, clinical presentation, diagnosis, causative microbes, and treatments with outcomes. Articles published within approximately the last 5 years (from 2016) were included for providing information pertaining to diagnosis, treatment, and outcomes. Literature published in the last 10 years (from 2011) was also included when more recent literature concerning symptoms, causative agents, and



treatment options was unavailable. The latter part of the review presents the current and new investigative developments with respect to IE, as well as briefly discusses potential new avenues for diagnostic pipelines, therapeutic strategies, and research methods.

Epidemiology and risk factors

Infective endocarditis (IE) is a life-threatening microbial infection of the native and prosthetic valves, endocardial surface, or indwelling cardiac device (Figure 1). Despite advances in diagnosis and management, IE is associated with high mortality (6–50% in-hospital mortality and 19–82% 5-year mortality) (Abegaz et al., 2017; Mistiaen, 2018; Habib et al., 2019; Suzuki et al., 2019; Witten et al., 2019; El Kadi et al., 2020; Huuskonen et al., 2021) which has not significantly improved over the last decades. The prevalence of IE, currently at 5–14.3 per 100,000 per year among the adult population (Thornhill et al., 2020; Williams et al., 2021), is increasing

(Keller et al., 2017; Ahtela et al., 2019; Shah A. S. V. et al., 2020) and in some countries has doubled over the past 10 years (van den Brink et al., 2017; Thornhill et al., 2020). This increase is largely attributed to the growing population with age-related degenerative valvular disease, chronic co-morbidities, and an increased need for invasive procedures and implanted cardiac devices (Forestier et al., 2016; Wu et al., 2019; Shah A. S. V. et al., 2020). Risk factors for developing IE include cardiac risks, such as degenerative valvular disease, congenital valvular abnormalities, rheumatic heart disease, atrial fibrillation, post cardiac transplant valvulopathy and/or indwelling cardiac devices, as well as non-cardiac risks, such as intravenous drug use, poor dentition, chronic liver disease, hemodialysis and/or advanced age (Bin Abdulhak et al., 2018; Yang and Frazee, 2018; Chambers and Bayer, 2020). Further risk factors specific for IE following aortic valve replacement (surgical or transcatheter) include younger age and male sex, as well as an elevated body mass index specific for surgical replacement and an elevated post-deployment gradient and self-expanding valves for transcatheter replacement (Cahill et al., 2022).

Pathogenesis

Concerning IE pathogenesis, bacteria possess several adherence factors that facilitate direct microbial attachment to the surfaces within the cardiovascular system, whether that be tissue or device (Cahill and Prendergast, 2016). IE development on native tissue is understood to be initiated by valvular endothelium damage or inflammation to which pathogens adhere directly or indirectly by fibrin deposition or the activated endothelial layer (Holland et al., 2016; Liesenborghs et al., 2019; Liesenborghs et al., 2020; Lerche et al., 2021). Activated endothelial cells can initiate the deposition of von Willebrand factor, which subsequently recruits platelets leading to the formation of fibrin. The presence of von Willebrand factor multimers and fibrin are believed to play an important role in the initial adherence of bacteria (Claes et al., 2014; Liesenborghs et al., 2019). For infection development on indwelling leads and devices, blood protein deposition and disturbed blood flow provide niches for bacterial adherence or contamination can occur with a patient's own skin flora at the time of implantation (Blomström-Lundqvist et al., 2020). Once adhered, bacteria encase themselves in a protective extracellular matrix, consisting of numerous bacterial and host components, such as fibrin, platelets, host and bacterial proteins, polysaccharides, and extracellular DNA. The combination of both the bacteria and extracellular matrix is called a biofilm, also commonly known as a vegetation in the clinical setting when it can be seen macroscopically. Biofilm confers several benefits for bacteria which impact treatment success, such as tight endothelial adherence and protection against the immune system and antimicrobial treatments (Werdan et al., 2014; Holland et al., 2016).

Clinical presentation

The clinical presentation of IE is diverse, ranging from severe infection to indolent with nonspecific symptoms (Cahill et al., 2017; Yang and Frazee, 2018). IE presentation can be divided into subacute and acute (Vincent and Otto, 2018; Ibrahim and Siddique, 2021). Subacute infection has a gradual development of disease over the course of weeks to months and is associated with nonspecific symptoms, such as fever, chills, sweats, dyspnea, and back pain. Acute infection has a more sudden onset that can become life-threatening within days and is associated with severe clinical signs, such as sepsis, stroke, and pulmonary and systemic embolization. Heart failure, with new-onset more common than worsening pre-existing, can also occur in acute IE infections due to severe valvular obstruction or insufficiency (Pericas et al., 2021). Subacute endocarditis is often marked by delayed diagnosis, up to 40 days with a median delay of 13 days (Nishiguchi et al., 2020). This is largely attributed to the nonspecific symptoms that prove difficult to pinpoint the disease and arrive at a definitive diagnosis of IE (Nishiguchi et al., 2020). The most reported presenting symptoms are summarized in Table 1. For NVE, PVE, and CDRIE, fever

and cardiac murmur were the most common. Further symptoms include cough, embolization, heart failure, sepsis, stroke, and immunologic phenomena, such as Osler's nodes, Janeway lesions, and Roth's spots, are rarely found. Subacute and acute presentation can be linked to the most relevant bacteria responsible for this type of presentation. The division of subacute infection is more often linked to streptococci and acute infection to staphylococci, with *S. aureus* most common (Talha et al., 2020). *S. aureus* has become the most common infecting bacteria causing IE and is associated with higher mortality, twice as long hospitalization times, and neurological complications (Tong et al., 2015; Das et al., 2022).

Diagnosis

For diagnostic classification, the modified Duke criteria are used, with diagnosis categories of definite (two major or one major and three minor), possible (one major and one minor or three minor) or rejected IE (Gomes et al., 2017; Horgan et al., 2020a). The major criteria include positive blood culture, positive echocardiography, and valvular regurgitation (Cahill and Prendergast, 2016; Vincent and Otto, 2018; Blomström-Lundqvist et al., 2020; Hubers et al., 2020). Additional criteria have been recommended in the diagnosis of CDRIE patients, which can be found in the European Heart Rhythm Association consensus statement (Blomstrom-Lundqvist et al., 2020). The sensitivity of the modified Duke criteria to provide a definite IE diagnosis is 80% in native valves, and 70% in cardiac devices (Cahill and Prendergast, 2016; Gomes et al., 2017). Concerning only heart valve associated IE, both native and prosthetic, the sensitivity has been reported to be 72% and specificity at 74% (Shrestha et al., 2017).

Microbiological diagnosis

Positive blood cultures remain crucial in the diagnosis of IE by demonstrating the presence of bacteria (Rajani and Klein, 2020). At least two positive blood cultures, from microorganisms typically known to cause IE, are required within at least 12 h between the first and last sample, or a set of three separate cultures obtained with at least 1 h between the first and last sample (Cahill and Prendergast, 2016; Liesman et al., 2017; Vincent and Otto, 2018; Blomström-Lundqvist et al., 2020; Hubers et al., 2020). In the case of no bacterial growth in combination with a high suspicion for IE, blood culture incubation should be prolonged and serological testing should be performed (Rajani and Klein, 2020). Tissue cultures are also used to determine the causative microorganism in patients with IE. Although blood and tissue cultures are considered the gold standard for pathogen identification, false negative results can occur (ranging from 2.5 to 31% (Brouqui and Raoult, 2001)). False negative test results are attributed to the use of antibiotic

TABLE 1 Presenting symptoms in IE.

Symptoms	Abscess	Chills	Cough	Dyspnea	Embolization	Fever	Heart failure	Inflammation in area	Janeway lesions	Malaise	Murmur	Osler nodes	Pulmonary infection	Roth spots	Sepsis	Stroke
NVE																
Babes et al. (2021)				Green		Green					Green					Red
De Camargo et al. (2019)					Orange	Green	Orange									
Habib et al. (2019)	Orange		Orange			Green			Red		Green	Red			Red	Red
Servy et al., 2014	Orange				Green		Orange		Red		Green	Red			Orange	Orange
CDRIE																
Granados et al. (2016)						Green	Orange	Orange							Red	
Habib et al. (2019)	Red		Orange		Orange	Green	Orange		Red		Green	Red		Red		Red
Jędrzejczyk-Patej et al. (2021)						Green		Orange					Orange			
Plonska-Gosciniak et al., 2019		Green	Orange	Red		Green	Orange	Red		Green			Orange		Red	
Saez et al., 2019			Orange	Orange	Orange	Green					Orange				Orange	Orange
PVE																
De Camargo et al. (2019)					Orange	Green	Orange									
Habib et al. (2019)	Orange		Orange		Orange	Green	Orange		Red		Green	Red			Red	Red
Selton-Suty et al., 2012	Orange		Orange		Orange	Green	Orange									Red
Undefined IE																
Ortiz-Bautista et al. (2017)		Green			Orange	Green	Orange				Green				Red	Red
Zaqout et al., 2020				Orange		Green	Orange			Orange					Red	Red

Green = common ($\geq 50\%$); orange = sometimes (10–50%); red = uncommon ($\leq 10\%$).

CDRIE, cardiac device-related infective endocarditis; IE, infective endocarditis; NVE, native valve endocarditis; PVE, prosthetic valve endocarditis.

TABLE 2 Diagnostic accuracy with reported sensitivity and specificity of various imaging modalities.

Imaging	All IE		NVE		CDRIE		PVE	
	Se (%)	Sp (%)	Se (%)	Sp (%)	Se (%)	Sp (%)	Se (%)	Sp (%)
TTE	71 (60–82)	57 ^a	84 (70–98)	93 ^a	17 ^a	100 ^a	63 (60–65)	79 (67–95)
TEE	81 (36–95)	70 (42–85)	94 (91–96)	78 (67–88)	67 ^a	100 ^a	84 (78–91)	67 (57–75)
[¹⁸ F]FDG PET/CT	81 (74–88)	86 (79–92)	36 (17–68)	97 (85–100)	82 (56–96)	90 (80–100)	91 (75–100)	67 (29–93)
WBC SPECT/CT	90 (86–100)	98 (95–100)	—	—	73 (60–84)	87 (74–100)	—	—
CT	53 (16–89)	84 (71–96)	49 (11–80)	77 (63–92)	75 ^a	86 ^a	73 (19–96)	78 (50–98)

^aOnly reported once since 2016.

CDRIE, cardiac device-related infective endocarditis; CT, computed tomography; [¹⁸F]FDG, 18F-fluorodeoxyglucose; IE, infective endocarditis; NVE, native valve endocarditis; PET, positron emission tomography; PVE, prosthetic valve endocarditis; Se, sensitivity; Sp, specificity; SPECT, single photon-emission computed tomography; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography; WBC, white blood cell. The values in this graph were obtained using the following references: (Cahill and Prendergast, 2016; Wang A. et al., 2018; Bin Abdulhak et al., 2018; DeSimone and Sohail, 2018; Doring et al., 2018; Karchmer et al., 2018; Vincent and Otto, 2018; Galar et al., 2019a; Ivanovic et al., 2019; Pettersson and Hussain, 2019; Slawinski et al., 2019; Horgan et al., 2020b; Blomström-Lundqvist et al., 2020; Chambers and Bayer, 2020; Galea et al., 2020; Hubers et al., 2020; Aguilera et al., 2021; Jędrzejczyk-Patej et al., 2021; Rezar et al., 2021).

therapy prior to blood sample collection, bacteria that are difficult to culture, fastidious or grow intracellular (Houpikian and Raoult, 2005). Further, results of blood cultures can be inconclusive due to contamination by commensal bacteria, a complex polymicrobial biofilm (Oberbach et al., 2017), or insufficient amounts of bacteria to culture. Negative blood cultures are found in approximately 24% of all IE cases, which is similar for NVE (25%), CDRIE (26%), and PVE (23%) (Hussein et al., 2016; Koneru et al., 2018; Calais et al., 2019; de Camargo et al., 2019; El Gabry et al., 2019; Habib et al., 2019; Heriot et al., 2019; Nesterovics et al., 2019; Płońska-Gościński et al., 2019; San et al., 2019; Witten et al., 2019; Bohbot et al., 2021; Duval et al., 2021; Jędrzejczyk-Patej et al., 2021; Michałowska et al., 2021; Pyo et al., 2021).

Considering false culture-negative potential, when suspicion of IE remains then other techniques are emerging as additional diagnostic tools. This includes serological and molecular techniques, to include broad-range polymerase chain reaction (PCR) analysis, next-generation sequencing (Oberbach et al., 2017; Kolb et al., 2019; Zeng et al., 2022), and mass spectrometry (Holler et al., 2011; Singhal et al., 2015). At the same time, false negative PCR results have been reported with positive cultures (Gauduchon et al., 2003; Breitkopf et al., 2005) and identifying new isolates with mass spectroscopy relies on pre-existing databases input. Since limitations exist for all identification tools, a multimodal diagnostic approach for pathogen identification would be best in the modified Duke criteria.

Imaging modalities

Transthoracic echocardiography (TTE) is the most common first-line imaging modality for IE and is used to visualize suspicious valvular insufficiencies, biofilms, and potential IE complications, such as abscess formation (Habib et al., 2015).

Recent reports on the sensitivity of TTE is 84% for native valve, 63% for prosthetic valve, and 17% for cardiac devices (Table 2) (Cahill and Prendergast, 2016; Sivak et al., 2016; Sekar et al., 2017; Bin Abdulhak et al., 2018; de Camargo et al., 2019; Pettersson and Hussain, 2019; Slawinski et al., 2019; Horgan et al., 2020b; Rezar et al., 2021). This reduced sensitivity of prosthetic valves and intracardiac devices can be explained by imaging challenges, such as artifacts induced by metal components (Chambers and Bayer, 2020; Hubers et al., 2020). If TTE is negative and a high level of suspicion for IE persists, then transesophageal echocardiography (TEE) should also be performed (Sedgwick and Scalia, 2016; Sordelli et al., 2019; Hubers et al., 2020). TEE provides a better characterization of local abnormalities and can detect valvular biofilms as small as 1 mm, whereas biofilms smaller than 5 mm have a reduced TTE sensitivity of 25% (Erbel et al., 1988; Cuervo et al., 2021). As shown in Table 2, TEE has a sensitivity of 67% for cardiac devices and 94% for native valves, which is 50 and 10% higher than TTE respectively (Sekar et al., 2017; Doring et al., 2018; Koneru et al., 2018; Galar et al., 2019b; Ivanovic et al., 2019; Slawinski et al., 2019; Horgan et al., 2020b; Galea et al., 2020; Sifaoui et al., 2020; Aguilera et al., 2021; Jędrzejczyk-Patej et al., 2021). Nevertheless, the reported sensitivity of TEE for cardiac devices is limited. A systemic review also highlights the importance of considering the pre-disposing valvular intervention and the valve used, where echocardiography could only detect IE in 34% of patients that had previously undergone a transcatheter pulmonary valve implantation, also known as percutaneous pulmonary valve implantation, with the Melody valve (Abdelghani et al., 2018). As neither TTE and TEE are 100% sensitive and if positive blood cultures persist, intracardiac echocardiography (ICE) may be considered (Abdelghani et al., 2018; Blomström-Lundqvist et al., 2020). ICE probes are used to diagnose CDRIE and have high image resolution and can be oriented in any direction within the heart (Ali et al., 2011; Narducci et al., 2013). However, the role of ICE

for NVE and PVE remains unclear, with limited supporting literature (Kolodner et al., 2007; Bouajila et al., 2017; Abdelghani et al., 2018; Yang et al., 2019) and cost/benefits need to be determined since it is more costly and invasive as well as not sustainable since each probe is single-use.

For CDRIE diagnosis, additional nuclear imaging techniques are recommended to increase the detection sensitivity from 56–88% to 78–98%, namely positron-emission tomography with 18F-fluorodeoxyglucose integrated with computed tomography (^{18}F FDG PET/CT) or radiolabeled white blood cell (WBC) single photon-emission computed tomography (SPECT) (Cahill and Prendergast, 2016; Blomström-Lundqvist et al., 2020). This imaging is recommended when echocardiography is negative and blood cultures are positive (Blomström-Lundqvist et al., 2020). These additional nuclear imaging techniques should also be used in patients with a suspicion of PVE, and abnormal activity around the implantation site is considered a major diagnostic criterion (Habib et al., 2015). The sensitivity of ^{18}F FDG PET/CT is 15% higher than echocardiography for cardiac devices (6% for prosthetic valves), and 58% lower for native valves (Guenther et al., 2015; Dell'Aquila et al., 2016; Fagman et al., 2016; Granados et al., 2016; Memmott et al., 2016; Salomäki et al., 2017; Sánchez-Enrique et al., 2018; Calais et al., 2019; de Camargo et al., 2019; Abikhzer et al., 2020; Gomes et al., 2020; Wang et al., 2020). Besides the poor detection accuracy in NVE, this imaging modality has possible false-negatives in patients with small biofilms, possible false-positives concerning early post-surgical prosthetic valve implantation (Rosenbaum et al., 2006) or when active thrombi, cardiac tumors, and atrial fibrillation are present, a complex preparation protocol, and limited availability in peripheral centers (Marchetta et al., 2017). Current guidelines stipulate that ^{18}F FDG PET/CT should only be considered for IE diagnosis when > 3 months have elapsed after valve implantation to prevent false positives from artefacts following surgery (Habib et al., 2015). Radiolabeled WBC imaging with SPECT/CT improves detection and identification of endocardial involvement in IE by differentiating superficial surgical site infections from true generator pocket infections (Erba and Slart, 2020). In addition, this imaging modality has a sensitivity of 73% in CDRIE patients which can improve the risk stratification of patients with CDRIE (Małecka et al., 2018; Calais et al., 2019; Holcman et al., 2019). Positive results of WBC SPECT/CT scans are associated with an increased in-hospital mortality rate and complete hardware removal (Małecka et al., 2018; Calais et al., 2019; Holcman et al., 2019). Despite these promising features, this technique also has limitations, to include long scan-time, complex preparation procedure, lower spatial resolution compared with PET/CT, and limited availability for appropriate hospital-wide implementation (Erba and Slart, 2020).

Other imaging modalities, such as cardiac CT with or without angiography, can be used after a negative

echocardiography to detect valvular complications, such as valvular regurgitation and paravalvular complications like abscesses or pseudoaneurysms (Vincent and Otto, 2018; Blomström-Lundqvist et al., 2020). CT can be advantageous because it has an improved spatial resolution compared to echocardiography that allows for the detection of infected valve manifestations, such as biofilms, leaflet thickening, valve perforation, valve aneurysm, and vascular complications like mycotic aneurysm, arterial emboli, and septic pulmonary infarcts (Vincent and Otto, 2018; Blomström-Lundqvist et al., 2020; Erba and Slart, 2020). However, Koneru et al. reported CT having a low sensitivity (16%) for all IE, and more specifically 11% in NVE and 19% in PVE, which is low compared to other papers which reported sensitivities of 89% for all IE, 57–80% in NVE, and 82–96% in PVE (Koneru et al., 2018; Hryniewiecki et al., 2019; Gomes et al., 2020; Sifaoui et al., 2020; Velangi et al., 2020; Michałowska et al., 2021). Overall, various imaging modalities fulfil an essential role in the evaluation and management of IE. A multimodality imaging approach in the evaluation of IE-suspected patients should be an early consideration to arrive at a definitive diagnosis.

Causative microbes

Staphylococci, streptococci, and enterococci bacterial species are estimated to account for ~80% of all cases (Cahill and Prendergast, 2016; DeSimone et al., 2019; Chambers and Bayer, 2020). Microorganism prevalence was evaluated based on all IE, NVE, CDRIE, PVE (Figure 2). *Staphylococcus aureus* accounts for 27% of NVE, followed by streptococci (26%), and enterococci (12%) (de Camargo et al., 2019; El Gabry et al., 2019; Habib et al., 2019; Heriot et al., 2019; San et al., 2019; Chambers and Bayer, 2020; Hubers et al., 2020; Bohbot et al., 2021; Duval et al., 2021; Pyo et al., 2021). Coagulase-negative staphylococci have a prevalence of 6.3% in NVE, which is in contrast to CDRIE with 25.2% (Hussein et al., 2016; Koneru et al., 2018; Calais et al., 2019; Habib et al., 2019; Nesterovics et al., 2019; San et al., 2019; Witten et al., 2019; Bohbot et al., 2021; Duval et al., 2021; Pyo et al., 2021). Microorganisms obtained from cultures of CDRIE patients were predominately staphylococci (54%), followed by streptococci (12%) and enterococci (5%) (Habib et al., 2015; Hussein et al., 2016; Koneru et al., 2018; Calais et al., 2019; Nesterovics et al., 2019; Płońska-Gościński et al., 2019; Witten et al., 2019; Jędrzejczyk-Patej et al., 2021). Staphylococci are considerably more prevalent in CDRIE compared to NVE (27%) and PVE (32%) (Hussein et al., 2016; Koneru et al., 2018; Calais et al., 2019; de Camargo et al., 2019; El Gabry et al., 2019; Habib et al., 2019; Heriot et al., 2019; Nesterovics et al., 2019; Płońska-Gościński et al., 2019; San et al., 2019; Witten et al., 2019; Bohbot et al., 2021; Duval et al., 2021; Jędrzejczyk-Patej et al., 2021; Michałowska et al., 2021; Pyo et al., 2021). Streptococci (25%) and enterococci (16%) also cause PVE (de Camargo et al., 2019;

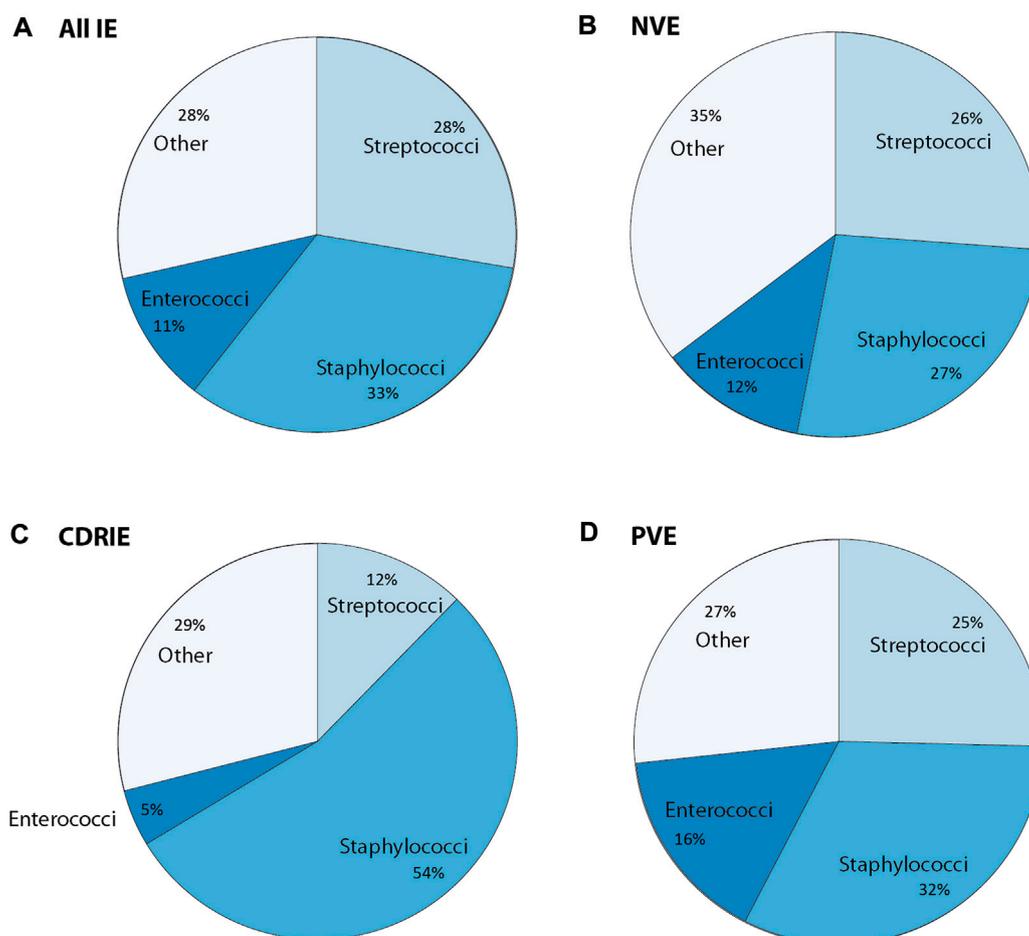


FIGURE 2

Overview of causative bacteria in infective endocarditis (IE) concerning (A) all IE cases, (B) native valve endocarditis (NVE), and (C) cardiac device related-infective endocarditis (CDRIE) that is further subdivided into (D) prosthetic valve endocarditis (PVE). Other refers to either other cultured or unidentified microorganisms. The values in this graph were obtained using the following references (Cahill and Prendergast, 2016; Wang A. et al., 2018; DeSimone and Sohail, 2018; DeSimone and Sohail, 2018; Babeş et al., 2021; Doring et al., 2018; Teoh and Hannan, 2018; Slawinski et al., 2019; Mateos Gaitán et al., 2020; Khalil and Soufi, 2022).

Habib et al., 2019; San et al., 2019; Duval et al., 2021; Michałowska et al., 2021; Pyo et al., 2021). Enterococci causing NVE and CDRIE tends to be more common in elderly or chronically ill patients (Cahill and Prendergast, 2016; Yang and Frazee, 2018). The elderly population and patients who undergo transcatheter aortic valve implantations, also known as percutaneous aortic valve implantation, are most at risk for enterococcal infections, particularly in combination with pre-existing comorbidities (Munita et al., 2012; DeSimone et al., 2021). For IE caused by enterococci, there has been an increasing temporal trend of approximately 5% per year (DeSimone et al., 2021).

Although less common, other microorganisms can be the cause of IE. This includes, though not limited to, *Haemophilus*, *Aggregatibacter*, *Cardiobacterium*, *Eikenella*, and *Kingella* species

known collectively as HACEK organisms, as well as *Coxiella burnetii*, aerobic gram-negative bacilli, and fungi (Chambers and Bayer, 2020; Hubers et al., 2020). HACEK are gram-negative bacteria and fastidious, i.e. difficult to culture (Wang F. et al., 2018). Fungal endocarditis is rare for both native valves and cardiac devices, and is associated more with CDRIE, particularly PVE (Ojha and Dhamoon, 2022). *Candida* and *Aspergillus* species are the primary causative fungal microbes, where *Candida albicans* is the most common overall (Shokohi et al., 2014; Yuan, 2016) and *Aspergillus* species more prevalent in PVE (Pasqualotto and Denning, 2006). Fungal endocarditis is extremely challenging to diagnosis and thus start appropriate treatment as it presents similarly to bacterial endocarditis (Wang F. et al., 2018; Ammannaya and Sripad, 2019), with 82% receiving a delayed or mistaken diagnosis, 28–77%

diagnosed only post-mortem, and a mortality rate of 72% (Seelig et al., 1974; Ellis et al., 2001; Yuan, 2016).

Treatment and outcomes

Management of IE patients consists largely of antimicrobial therapy and surgery. Without treatment, IE is considered to be fatal. Treatment focus is placed on preventing the development of complications, such as embolization and heart failure as well as progression from a local to a systemic infection (i.e., sepsis and septic shock) which has a four-fold increase in mortality risk (Werdan et al., 2014).

Antimicrobial therapy

Antimicrobial therapy is required in the management of IE focusing on antibiotics for a prolonged period. The choice of antibiotic and the duration of administration itself is based on the causative pathogen, potential antibiotic resistance, and type of infected material, whether native tissue, prosthetic valve, or cardiac device (Wang F. et al., 2018). Antimicrobial treatment of IE is extensively described in the European Society of Cardiology (ESC), American Heart Association (AHA), and Stichting Werkgroep Antibioticabeleid (SWAB) guidelines (Habib et al., 2015; Baddour et al., 2015; T.W. van der Vaart, 2019).

Rifampicin use remains controversial and is associated with diverse adverse effects, including hepatotoxicity, nephrotoxicity, and high-risk of drug interactions (Almatrafi et al., 2021). Studies have shown that rifampicin did not have a significant effect on mortality or bacteremia duration in patients with a *S. aureus* infection (not only IE) (Thwaites et al., 2018), and specifically for PVE with *S. aureus* rifampicin did not reduce mortality and those patients had longer hospital stays (Le Bot et al., 2021). However, rifampicin did lead to lower disease recurrence (Thwaites et al., 2018). In another study, the addition of gentamycin to vancomycin and rifampicin also did not result in lower mortality and the occurrence of new renal failure or worsening of previous failure was high both in patients treated with and without gentamicin (Ramos-Martínez et al., 2018). Worse outcomes could potentially be attributed to comorbidities and infection severity (Goenaga Sánchez et al., 2017). Regardless, additional clinical evidence is necessary so a definitive decision can be derived on if rifampicin and/or gentamycin should continue to be added to the treatment of PVE patients with *S. aureus* (Di Domenico et al., 2019).

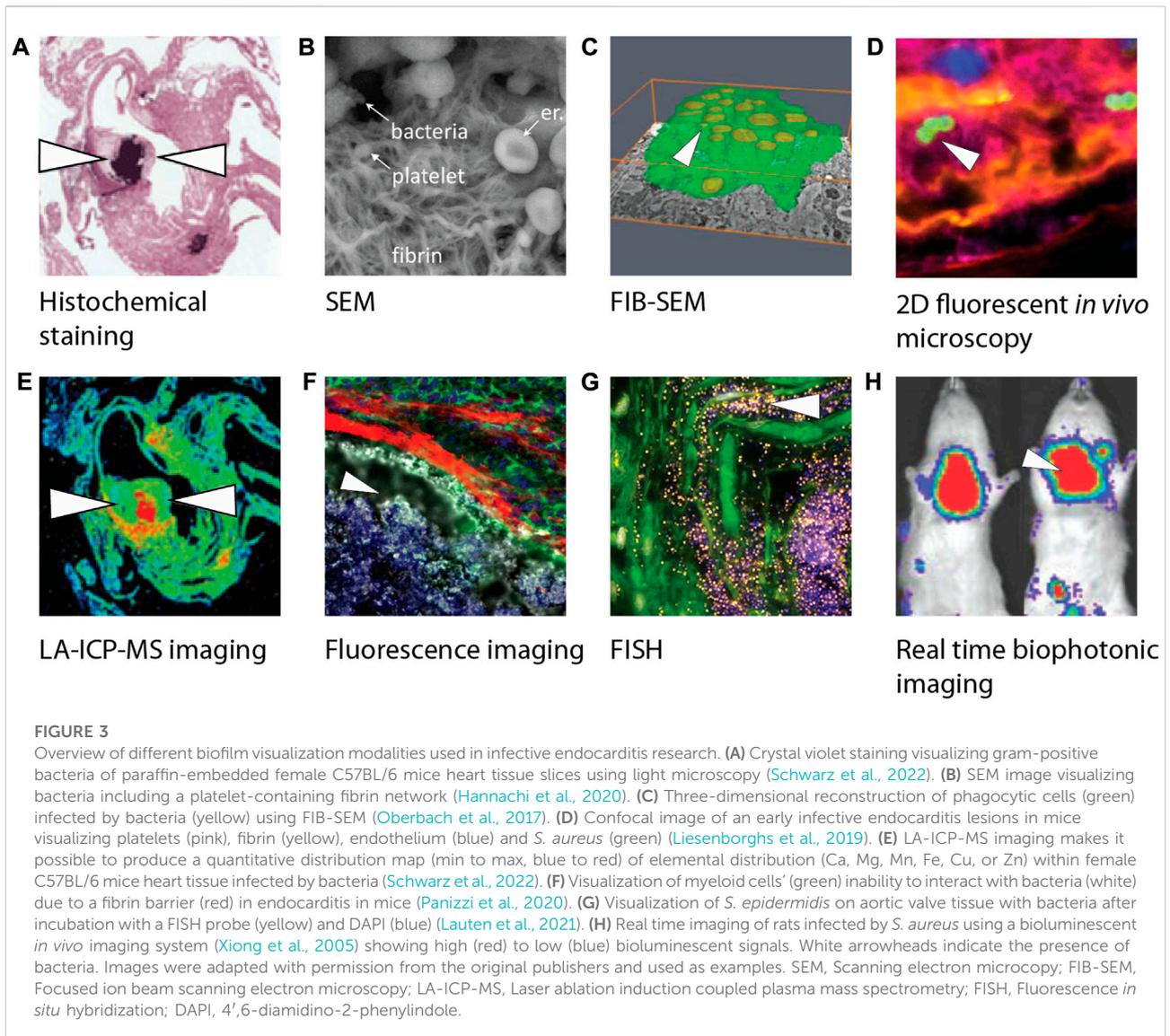
Another controversial topic in IE empirical treatment is antibiotic prophylaxis. The incidence of IE is increasing and although this is likely multifactorial, it has been suggested that the recent increases can be attributed to the change in prophylaxis guidelines (Pant et al., 2015). To prevent IE during at-risk procedures, such as invasive dental procedures

and implantable cardiac electronic device insertion, international guidelines changed from the routine use of a single-administration of an antibiotic shortly before procedures to only used in patients with a high-risk for poor IE outcomes. This patient population includes those having prosthetic or repaired valves, a previous IE diagnosis, or congenital heart disease (Wilson et al., 2007; Habib et al., 2009; Habib et al., 2015). The correlation between antibiotic prophylaxis and the incidence of IE before and after the updated AHA guidelines of 2007 was investigated (Thornhill et al., 2018). Patients were categorized based on their low, moderate, and high risk of developing IE. Data acquired from May 2003 to August 2015 revealed no increase of IE cases in the low-risk patient group. However, for the high- and moderate-risk patients groups increases were observed. Recently, a significant association between the use of prophylaxis and reduced IE incidence following invasive dental procedures (particularly extractions and oral-surgical procedures) was found (Thornhill et al., 2022). These data support AHA, ESC, and other guideline recommendations that prophylaxis before invasive dental procedures should continue for individuals with a high IE risk. In addition to prophylactic antibiotics, educating patients on the importance of good dental and skin hygiene and sterility during invasive procedures remain essential IE prevention methods. It should be noted that good hygiene is not only more difficult to achieve in developing countries, also the awareness of its importance in preventing IE has been reported to be inadequate not only in the general population, but also among general practitioners and specialists within the fields of cardiology (Maharaj and Parrish, 2012).

Surgery

When antimicrobial therapy fails, or other complications arise due to IE such as valve leakage or abscess, these patients often require surgery. At least 50% of IE patients are estimated to undergo surgery during hospitalization, and when stratified for tissue or device this is 54% for NVE, 46% for PVE, and 65–95% for CDRIE (Ortiz-Bautista et al., 2017; Habib et al., 2019; Roder et al., 2020). Surgery can be required however also cannot be a treatment option due to patient refusal, high surgical risk, neurological complications, or death before surgery (Ortiz-Bautista et al., 2017; Habib et al., 2019). In-hospital mortality following surgery was highest for PVE (up to 27%) when compared to NVE (16%) and CDRIE (8–15%) (Ortiz-Bautista et al., 2017; Habib et al., 2019; Nasso et al., 2021).

Surgery for NVE is generally performed due to valvular dysfunction or rupture, uncontrolled IE, heart failure, abscess, sepsis, as well as to prevent embolization (El Gabry et al., 2019; Chambers and Bayer, 2020; Pyo et al., 2021) and generally consists of valve replacement or repair, with valve replacement more frequent (Said et al., 2018; Witten et al.,



2019; Park et al., 2020). Concerning NVE surgical heart procedures, bioprostheses (35–40%) were utilized most, followed by mechanical prostheses (25–39%), repair (15–31%), and homograft placement (4–11%) (Said et al., 2018). The 1-year mortality rate following surgery for NVE is 4–22%, and a 5-year survival rate reported as 77% (El Gabry et al., 2019; Defauw et al., 2020; Park et al., 2020; Pyo et al., 2021; Weber et al., 2021). NVE comparative studies observed a higher 30-day mortality after valve replacement (8–17%) compared to valve repair (4–14%) (Toyoda et al., 2017; Defauw et al., 2020). Surgery for PVE is indicated for mobile or larger than 10 mm biofilms, heart failure, valvular dysfunction, abscess, persistent sepsis, acute renal failure, and evidence or high risk of embolic events (Pyo et al., 2021). Aortic valve procedures are performed most often (72%), followed by mitral (39%), tricuspid (9%) and pulmonary (3%) valves (Habib et al., 2019). Adverse outcomes

can occur in PVE surgical management, which include embolization (21%), acute renal failure (21%), new-onset dialysis (20%), stroke (13–19%), reoperation for bleeding (12–14%), low cardiac outcome syndrome (13%), heart failure (11%), and persistent fever (13%) (Pyo et al., 2021; Weber et al., 2021). Additionally, fungal endocarditis can occur up to 3 years following surgery (Shokohi et al., 2014). The post-surgical 30-day mortality for PVE is 14–20% and at 1-year 22–36% (Pyo et al., 2021; Weber et al., 2021), with 27% in-hospital mortality in patients with a prior aortic valve replacement (Nasso et al., 2021). For both NVE and PVE, the type of prosthesis (biological or mechanical) chosen is not associated with mortality while (longer) aortic cross-clamp times are a significant mortality predictor (Nasso et al., 2021).

Current valve replacement interventions can either be surgical or transcatheter. Transcatheter interventions were

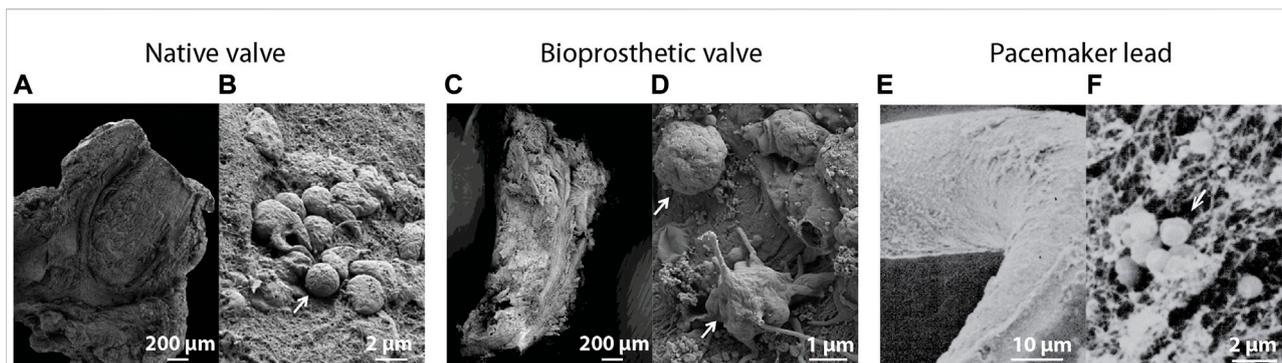


FIGURE 4

Scanning electron microscopic images of (A) an infected native heart valve with (B) a corresponding magnified image showing intact bacteria on the tissue surface (Oberbach et al., 2017). (C) Overview of an infected biological prosthetic valve with (D) a corresponding magnified image showing intact bacteria surrounded by a fibrous surface (Oberbach et al., 2017). (E) Visualization of a biofilm on the surface of a pacemaker lead with (F) a corresponding magnified image showing bacteria surrounded by a fibrillar substrate (Marrie and Costerton, 1984). White arrows indicate the presence of bacteria. Images were adapted with permission from the original publishers and used as examples.

only first approved by the FDA in 2012 for high-risk patients. Comparing surgical and transcatheter aortic valve replacement in England over 10 years, the surgical cohort had a higher IE incidence rate of 4.8 (2.4% cumulative) compared to 3.6 (1.5% cumulative) in the transcatheter cohort (Cahill et al., 2022). This significant higher IE risk was also found in another study (Lanz et al., 2021), however these two studies are in contrast to several others that found no significant differences (Kolte et al., 2018; Butt et al., 2019; Noriaki et al., 2019; Summers et al., 2019; Fauchier et al., 2020). For transcatheter pulmonary valve implantation, two valves have been approved: the Edwards Sapien valve and Medtronic Melody valve. The cumulative incidence of IE concerning the Melody valve was 3–25%, with 59% of cases occurring within the first 2 years after implantation (Abdelghani et al., 2018). In comparative and meta-analysis studies, the Sapien valve was found to have a significantly decreased cumulative IE incidence at 0–1% compared to the Melody valve at 5–24% (Hascoet et al., 2017; Lehner et al., 2019). In a single-center study in Munich, Germany, the incidence of IE was three times higher for the Melody valve (1.6%) compared to the surgical pulmonary valve replacement group (0.5%), however the estimated survival between the two groups did not significantly differ (Georgiev et al., 2020).

Most cases of CDRIE managed by surgery underwent surgical device removal (95%) (Ortiz-Bautista et al., 2017; Habib et al., 2019; Roder et al., 2020; Jędrzejczyk-Patej et al., 2021). Adverse effects of device removal include acute renal failure (21%), shock (15%), embolization (13%), and persistent fever (12%) (Habib et al., 2019). For implicated cardiac device drivelines, initial surgical management can include drainage and dead tissue debridement. When stratified for pacemakers and implantable cardioverter-defibrillators, 47–53% patients underwent percutaneous lead extraction, 41–53% surgical lead extraction, and 5%

percutaneous catheter extraction (Ortiz-Bautista et al., 2017; Habib et al., 2019; Roder et al., 2020; Jędrzejczyk-Patej et al., 2021). Device reimplantation occurs once a negative blood-culture is obtained, which in 77% of patients was after a median time of 13 days (Ortiz-Bautista et al., 2017). In a 13-year Danish nationwide study, following reimplantation, the mortality rate was 42% for pacemakers and 21% for cardioverter-defibrillators (Özcan et al., 2017), which is higher than the overall in-hospital mortality rate of CDRIE (Ortiz-Bautista et al., 2017; Habib et al., 2019).

Early surgery for IE patients, defined as emergency or within 48 h once an indication for surgery is established (Pettersson and Hussain, 2019), have improved outcomes without increasing the incidence of postoperative neurological complications (Samura et al., 2019) and is associated with lower in-hospital stroke rates and length-of-stays compared to late surgery (Kousa et al., 2020). For CDRIE, delayed extraction may also contribute to higher mortality (Kim et al., 2014). Following guidelines, the timing of surgery should be without delay after definitive diagnosis for NVE, PVE, and CDRIE (Pettersson and Hussain, 2019; Blomström-Lundqvist et al., 2020). However, there are conflicting studies that observed no difference in neurological outcomes and mortality between early and late surgery (Oh et al., 2016; Okita et al., 2016; Huuskonen et al., 2019; Kousa et al., 2020). Huuskonen et al. stated that patients receiving early surgery had a higher reoperation rate and greater recurrent mitral regurgitation (Huuskonen et al., 2019). Furthermore, early surgery has also been associated with a trend toward higher 6-month overall mortality compared with later surgery during hospitalization (Wang et al., 2019) and had higher rates of postoperative bleeding and pericardial effusion (Kousa et al., 2020). This could be due to earlier operated patients being significantly sicker at the time of surgery with a higher potential to have frail tissue due to active infection

(Huuskonen et al., 2019). Surgical decision and timing are important yet challenging factors in the management of IE and thus, should be deliberated as early as possible by a multispecialty clinical team that can consider factors such as comorbidities and neurological complications with a greater knowledge depth (Pettersson and Hussain, 2019; Habib et al., 2015; Wahadat et al., 2022).

Investigative research approaches

This part of the review is focused on the research techniques used to improve the understanding of IE pathogenesis and address the diagnostic and treatment challenges to improve or develop innovative strategies. Various techniques are utilized to investigate IE, as seen in Figure 3, and are thus discussed, including histopathology, microscopy, metagenomics, proteomics, and others.

Histopathological analysis

Histological staining of surgically excised cardiac tissue and valves in connection with IE, whether definitive or suspected IE, has been routinely performed for decades (Figure 3A). The subsequent histopathological analysis is used to confirm diagnosis or provide support for alternative disease. One study compiling the histopathological results of over 800 valves with definite IE (59% NVE) found 92% having evidence of inflammation and/or microorganisms (Ely et al., 2016). Not one single histological finding achieved this 92% accuracy, with 67% samples showing microorganisms, 62% chronic inflammation markers (neovascularization, lymphocytes, histiocytes, foamy histiocytes, or giant cells), and 56% acute inflammation marker (polymorphonuclear leukocytes). Fibrin deposits, which are implicated in the pathogenesis of IE, were found in 61% of cases and clustered together with microorganism presence. No significant connections were made between valve type, valve location, and microorganism presence.

Histopathological analysis is also performed in conjunction with CDRIE, however to a lesser extent given that mechanical devices themselves cannot be histologically processed. Lead-associated intracardiac masses in connection with positive blood cultures (*S. aureus*, *S. epidermidis*, and *Propionibacterium* species) that were histologically investigated were found to be primarily composed of fresh fibrin with inflammatory cell infiltration, mostly neutrophils (Chang et al., 2019; Miyagi et al., 2020). Although bacteria were not found histologically, the primary findings still support that intracardiac masses can be related to CDRIE since extracted masses without positive blood cultures only showed thickened endocardium and collagenous tissue (Miyagi et al., 2020). Biopsies of intracardiac masses obtained

using a triple-loop wire snare (Salaun et al., 2017) or a biptome with a steerable sheath (Chang et al., 2019) with access *via* the femoral vein, demonstrated their diagnostic value resulting in either the continuation or discontinuation of antibiotic therapy. Thus, biopsies of these masses for histopathological analysis should be considered during diagnosis to allow for accurate differentiation between thrombus and biofilm for correct and prompt treatment.

There are limitations to histopathological analysis, namely intra-inter pathologist variability and entire excised valves are not analyzed due to procedural and analytical tool constraints. 2D tissue sections of only a few micrometers thick of samples that can easily be larger than 10 mm can result in missing infection-indicating information, especially given the complexity and heterogenous make-up of IE biofilms. 3D histology techniques are in development and show histopathological promise (Eberle et al., 2014), though have yet to be evaluated for IE.

Microscopic evaluation and imaging

The adhesion and spatial orientation of bacterial biofilms can be observed with scanning electron microscopy (Litzler et al., 2007) (Figures 3B, 4). Additionally, it can be used to determine the efficiency of antibiotic treatment on biofilms cultured on different materials used for prosthetic implants and other medical devices, while simultaneously evaluating the matrix produced by the pathogen (Jahanbakhsh et al., 2020). Oberbach et al. aimed with their research to identify the biodiversity of bacteria species in three infected native and five prosthetic heart valves (Oberbach et al., 2017). Focused ion beam scanning electron microscopy (FIB-SEM) was used to investigate the micro-environment of the infected heart valves, and localization and distribution patterns of the causative bacteria were analyzed. FIB-SEM reconstructions visualized the intracellular and intramural localization of bacteria, which might contribute to the sensitivity of culture-based diagnostic characterization of bacteria causing IE (Figure 3C).

Fluorescence *in situ* hybridization (FISH) is a relatively new technique that can be used for the identification, location and spatial organization and activity of the pathogen causing IE by using oligonucleotides (specific sequences of RNA or DNA) (Lauten et al., 2021). However, it remains difficult to implement FISH as a diagnostic tool due to the need of technical and medical expertise as well as the lack of diagnostic quality control (Kikhney and Moter, 2021). In research, FISH can broaden the understanding of IE pathogenesis. For example, Lauten et al. created a pulsatile two-chamber circulation model to grow biofilms on porcine heart valves under physiological conditions. Microscopic evaluation of fixated samples was carried out using several FISH probes (Figure 3G). Results showed metabolic active bacterial formations on the heart valve. Similar colonization

patterns were observed between multiple samples. This *in vitro* infected heart valve model was compared to clinical IE samples and showed good comparability with these biofilms. Furthermore, the use of FISH with peptide nucleic acid probes (PNA) has previously been reported for the detection of *Coxiella burnetii* in heart valves and thrombi collected from patients with IE (Prudent et al., 2018). Compared to FISH using oligonucleotides, PNA FISH showed a higher sensitivity and specificity in clinical specimens (Prudent et al., 2018).

Although FISH can be used for the detection and characterization of bacteria in tissue sections, the manual assessment process can be time consuming. While tissue samples with fluorescent signal due to the binding of FISH probes can quickly be labeled as positive, a negative diagnosis requires a specialist to investigate the rest of the sample. Automated imaging analysis might be used for more efficient pathogen detection and aid specialists in identifying potential infected regions (Brunns et al., 2021).

Injected bacteria can be fluorescently labeled for detection using confocal microscopy post-mortem, or genetically modified by gene knock-out technology to investigate the function of specific genes in biofilm formation (Liesenborghs et al., 2019; Martini et al., 2020) (Figure 3D). The progression of the infection can also be monitored using cardiac magnetic resonance imaging, which Schwarz et al. used to reveal pronounced valve thickening, hypo-intensities, and masses on the heart valves of C57BL/6 mice within 24 h after *S. aureus* infection (Schwarz et al., 2021). Xiong et al. made use of an aortic IE rat model in combination with an engineered *S. aureus* isolate capable of bioluminescence (Figure 3H) (Xiong et al., 2005). Animals can serve as their own control without the need for sequential sacrifices at multiple timepoints.

Laser ablation inductivity coupled plasma mass spectrometry (LA-ICP-MS) was used on tissue slices of a heart from an IE mouse model (Schwarz et al., 2022) (Figure 3E). Three *S. aureus* isolates with specific adhesion deficiencies were used to investigate strain-specific patterns and were compared to sterile inflammation, and control samples. Element specific accumulations were quantified, and its distribution was compared between the experimental groups. Increased concentrations of calcium, magnesium, and zinc were observed in IE samples. LA-ICP-MS could distinguish between inflammation and infection and could be beneficial for characterizing tissue biopsies from patients suspected of IE.

Clinical metagenomics

Although culture-based methods are generally accepted as the gold standard for pathogen identification, a proper readout requires 24–72 h and can be inconclusive or give false negative results (2.5–31%) (Brouqui and Raoult, 2001). Clinical metagenomics is an emerging, culture-independent approach

utilizing nucleic acid sequencing that can identify infecting pathogens relatively quick (as quick as 6 h) with a high sensitivity (up to 96.6%) and specificity (up to 99%) (d'Humieres et al., 2021). Considering these advantages, proposals have been made for metagenomic techniques to be added as a routine diagnostic tool to the Modified Duke's criteria (Millar et al., 2001; Tak and Shukla, 2004).

Several metagenomic techniques exist. A broad-range PCR technique that can be combined with next generation sequencing called 16S rDNA or 16S rRNA analysis has been successfully used for bacterial detection (Oberbach et al., 2017; Boujelben et al., 2018; Armstrong et al., 2021). Currently, PCR in IE can only be used to determine which bacteria are on valve- and other infected tissue retrieved after surgical intervention. Thus, this approach to determine the causative bacteria cannot be used for patients who do not require surgical removal of the infected heart valves. Identification of the causative pathogen in blood samples by PCR is more challenging, possibly due to a low concentration of microorganism in the samples (Vollmer et al., 2010). A thorough review about using PCR to detect microorganisms in IE has been written by Faraji et al. (Faraji et al., 2018).

To identify the causative pathogen in culture-negative patients not requiring valve surgery, To et al. used cell-free plasma metagenomic next-generation sequencing (mNGS) to detect pathogens in cell-free plasma of pediatric IE patients (To et al., 2021). Despite prolonged antibiotic treatment, the causative pathogen was successfully identified in eight out of the ten subjects. Since excised tissue is no longer a requirement for this technique, the disadvantage of broad-range PCR techniques requiring valve tissue is resolved. Another study used mNGS to retrospectively analyze 49 IE patients (43 patients with NVE and nine patients with PVE), of which 28 (57.1%) had positive blood or valve cultures. The remaining 21 patients (42.9%) had negative culture results. For all patients, including culture-negative IE patients, receiving empirical antibiotic treatment, the causative IE pathogen could be detected with mNGS (Cai et al., 2021).

Similarly, Eichenberger et al. used microbial cell-free DNA (mcfDNA) extracted from plasma obtained from patients to detect IE (Eichenberger et al., 2022). Although the sensitivity of mcfDNA was comparable to blood cultures (both 87%), the duration of detection after antibiotic treatment was estimated to be 38.1 days compared to 3.7 days positive blood cultures. After surgical intervention, mcfDNA was declined rapidly and may potentially be used as a marker for IE infection burden. Another technique to detect the causative pathogen in IE is nanopore sequencing. Unlike PCR, this technique does not require the amplification of DNA or RNA before sequencing. Cheng et al. used NGS and nanopore sequencing to detect the causative pathogen and their resistance genes in several culture-negative IE patients (Cheng et al., 2018). With each sequencing technique, the researchers were able to identify the pathogens in excised infected valve tissue.

Lilje et al. used whole genome sequencing (WGS) in combination with genome-wide association studies (GWAS: SNP and k-mer analysis) to search for genetic differences between bacterial *S. aureus* isolates from patients with IE and patient with bacteremia. When comparing the clonal complexes (CCs) between the two groups, no significant association of specific CCs was found (Lilje et al., 2017). Also, SNP analysis could neither highlight any statistical overrepresentation in the IE or bacteremia patient isolates group, nor after k-mer analysis of all IE and bacteremia samples (Lilje et al., 2017).

Metagenomic analysis is projected to be used more routinely in the future to identify unusual or fastidious pathogens (bacterial, fungal or viral) due to its increased sensitivity compared to contemporary diagnostic modalities. However, of all sequencing data, approximately 5% is usable for the identification of pathogens (Cheng et al., 2018). Considering that the remaining 95% of the generated data can be accounted for by patient material, methods to reduce this percentage could further improve pathogen detection to aid in a more rapid and accurate antimicrobial IE treatment.

Proteomic analysis

Biofilms consist out of a plethora of different components, such as extracellular matrix components like fibrin and collagen, platelets, host immune cells and proteins produced by the pathogen. Mass spectrometry (MS) techniques can measure the presence of thousands of peptides in a single sample, which after bioinformatic analysis, can be assigned to specific proteins produced by the host or the causative pathogen. Martin et al. extensively described the proteome of native and bioprosthetic heart valve biofilms obtained from the clinic and noted a high abundance of fibrin and platelets in these biofilms (Martin et al., 2020). Of all proteins contributing to the biofilm (five on native heart valves, two on bioprosthetic heart valves and one from non-valvular complex IE), the 15 most abundant proteins of all examined biofilms made up for 57% of the samples proteomes and was similar between staphylococcal and non-staphylococcal biofilms. However, comparing the shared proteins in any combination of the non-staphylococcal biofilms (including both NVE and PVE) resulted in an average of 21% similarity, which is considerably less compared to the 56% shared proteins in staphylococcal biofilms. Furthermore, the amount of peptides overlapping between staphylococcal and non-staphylococcal biofilms was as high as 82%, which could be mostly explained by the contribution of host proteins from blood and neutrophils. New insights in the composition and formation of these biofilms might lead to new treatment opportunities and prospective biomarkers.

Different methods can also be combined for the identification of IE. Brinkman et al. used electro spray ionization MS on obtained PCR products for the identification of pathogens in

formalin-fixed paraffin-embedded heart valves. This technique was used in 83 cases of IE, of which 59 with NVE and 24 with PVE. This approach allowed for the correct detection of antibiotic resistance genes (*mecA* in staphylococcal IE and *vanA/B* in enterococcal IE) in all IE cases in which the susceptibility towards antimicrobials was known, while also identify the causative pathogen in 55% concordant to microbiology (Brinkman et al., 2013). In 34% no identification of the causative pathogen was possible, which could potentially be attributed to degradation of DNA during histological sample treatment with formalin, degrading DNA in its process (Srinivasan et al., 2002).

Currently the detection of IE biomarkers is not being used in the clinic. Biomarkers indicating the presence of IE could be of great value for early diagnosis and several mass spectrometry approaches are aiming to detect IE by finding potential biomarkers (Martin et al., 2020; Snipsoyr et al., 2020). One such biomarker is Osteoprotegerin, which could potentially be used to exclude IE in patients suspected to have IE (Snipsoyr et al., 2020). A major challenge is the verification of possible biomarkers due to inter-patient variability and the low sensitivity and specificity in blood samples, which can be attributed to high abundance of blood protein peptides. These highly abundant peptides may conceal the presence of peptides from low abundant proteins, which is often the case for biomarkers. This stresses the importance of finding optimal sample preparation and bioinformatic analysis techniques.

In vitro, *ex vivo*, and *in vivo* IE models

In vitro biofilm models have a wide-range of utility for infection research, such as high throughput screening of new drug treatments (Harrison et al., 2010), or for investigating (a-) synergism of antibiotics when combined with other therapies (Nair et al., 2016). However, infection models are often not developed specifically for IE. Although useful for initial experiments, *in vitro*, *ex vivo*, and *in vivo* biofilm-related models without an IE focus are not included in this review and the reader is referred to other extensive reviews (Coenye and Nelis, 2010; Lebeaux et al., 2013). Additionally, NVE model history and results are discussed at length by Lerche et al. (Lerche et al., 2021). This subsection will thus touch upon new literature as well as PVE and CDRIE and discuss controversies and considerations in IE model research.

To resemble early pathogenesis of IE, Lattwein et al. produced an *in vitro* infected blood clot model comprised out of human whole-blood clots retracted around silk sutures (Lattwein et al., 2018). Sterile clots were inoculated with a clinical *S. aureus* isolate. Blood clots were used to simulate the cardiac micro-thrombi to which bacteria adhere to before biofilm formation to better represent IE biofilms found in patients. After incubation, infected clots were placed in an flow system for treatment experiments.

A main disadvantage of *in vitro* models is the lack of a host immune system or blood pool proteins, resulting in a more artificial, non-representative IE biofilm model. Schwartz et al. aimed to create an *in vitro* NVE biofilm model which did not have this drawback (Schwartz et al., 2021). Their organoid-like model contained a leukocyte and platelet-rich fibrin patch system, which normally is applied to chronic wounds for treatment. This patch system thus represented damaged endothelium as a matrix for bacterial colonization. After formation of bacterial microcolonies by *S. aureus*, *Enterococcus faecalis* and *Streptococcus mitis*, increased antibiotic tolerance for all three pathogens was observed compared to its planktonic counterpart highlighting the importance of bacteria to form biofilms. The addition of host immune cells in this *in vitro* model is novel compared to other *in vitro* IE models and might in the future better predict personalized IE treatment outcomes.

IE model research has been performed focusing on the prevention of PVE and CDRIE after the implantation of prosthetic heart valves, catheter-associated biofilms and implantable cardiac devices (Litzler et al., 2007; Abdelhady et al., 2013). Litzler et al. investigated the adhesion of *S. aureus*, *S. epidermidis*, and *Pseudomonas aeruginosa* to three pyrolytic carbon mechanical heart valves, with and without silicon, using bioreactors (Litzler et al., 2007). The hydrophobicity, roughness, surface chemistry, electrostatic forces and surface free energy all seem to influence the adhesion of bacteria to the mechanical heart valves. The importance of the surface chemistry of biomaterials on biofilm formation has also been further investigated by MacKintosh et al. (MacKintosh et al., 2006). They highlighted the importance of using the correct media in *in vitro* set-ups. In their study, the use of serum promoted the adhesion and aggregation of *S. epidermidis* to charged surfaces. An *ex vivo* IE model using freshly excised porcine heart valve punch biopsies to study *Enterococcus faecalis* adherence has also been developed (Chuang-Smith et al., 2010). One major advantage of investigating bacterial adherence in *in vitro* and *ex vivo* set-ups, are the controlled environment and reproducibility of conditions, which is inherently less for clinical studies due to inter-individual differences.

Several factors are important to the pathogenesis of IE, such as a fully functional immune system and clotting cascade as well as flow conditions within the heart, are difficult to replicate *in vitro* and thus, in many cases findings should be confirmed using *in vivo* IE models. IE has been induced in mice (Liesenborghs et al., 2019; Schwarz et al., 2021), rats (Heraief et al., 1982; Xiong et al., 2005; Veloso et al., 2011; Augustin et al., 2013), rabbits (Durack et al., 1973; Crosby et al., 2016), pigs (Johnson et al., 1986; Christiansen et al., 2013), dogs (Highman et al., 1956), horses (Else and Holmes, 1972) and opossums (Vakilzadeh et al., 1970). *In vivo* IE models have been extensively used for wide-ranging research questions from pathogenesis to

treatment outcomes (Lerche et al., 2021). To induce NVE, a catheter-based approach is almost exclusively used to initially cause mechanical damage on aortic valves to create a non-bacterial thrombus and then subsequently bacteria are introduced intravenously (Augustin et al., 2013). In one murine NVE model that sought to mimic valvular inflammation-induced infection, the catheter was used to infuse histamine at the aortic valve site for 5 min while sustaining mechanical injury only during that time window (Liesenborghs et al., 2019). A controversial aspect of the catheter-based approach is that in many studies the catheter remained in place for the entirety of the experiments, i.e., from infection progression to sacrifice, and raises criticism on whether this more represents PVE or CDRIE than NVE (Sande, 1999; Schwarz et al., 2020). To address this, one study modified the catheter approach in four aspects to assess the influence of valvular damage and foreign material presence in mice, and although differences in infection were found, whether either approach best represents NVE or PVE was not concluded (Schwarz et al., 2020).

Another controversial aspect is that a large majority of IE *in vivo* studies used laboratory strains to induce infection. Laboratory-derived strains have been shown to possess genetic changes leading to phenotypic variation among entire strain pedigrees and loss of original and typical *in vivo* virulence (Baek et al., 2013). Furthermore, many of these commonly used laboratory strains were not derived from or known to be IE infections, for example *S. aureus* Newman isolated in 1952 from a human infection type unrecorded or *S. aureus* 6850 isolated during a human infection that progressed from skin abscess to osteomyelitis and sepsis. Schwarz et al. set out to research similarities between *in vitro* and *in vivo* behavior of two *S. aureus* strains (Schwarz et al., 2020). Conversely, the isolate with non-aggressive characteristics *in vitro* demonstrated to be the most “aggressive” by fast tissue destruction and immune cell infiltration *in vivo*, compared to the other isolate. It was concluded that the *in vitro* situation cannot directly be translated to the *in vivo* situation, and pathogenic interaction and immune response pathways should be evaluated in future research. However, it would be of interest if *in vivo* studies were repeated with *S. aureus* directly isolated from patients with recent definite IE or animal specific-derived IE strains (Trube et al., 2019) instead of laboratory strains.

Limitations of *in vivo* models do exist because ultimately animals are not a complete human representative. Pigs and rabbits are thought to have a close resembling cardiovascular and immune system to humans (Esteves et al., 2018; Pabst, 2020). The human immune system matches that of the pig by more than 80%, where this is only 10% in mice (Dawson, 2011) and further it is known that mice respond differently to bacterial toxins (Salgado-Pabón and Schlievert, 2014). Yet, mice and rats have been used extensively in IE research, most likely because rodents are less expensive and easier to genetically modify. Differences

between animal and human should always be taken into consideration when interpreting *in vivo* IE animal model results. Another consideration is that IE in humans is often accompanied by co-morbidities, such as diabetes mellitus. Hanses et al. used a diabetic rat model to characterize *S. aureus* endocardial biofilms and showed that IE was more severe in diabetic rats compared to non-diabetic rats (Hanses et al., 2014). The impact of other co-morbidities should also be further investigated considering that the increasing prevalence of IE is associated with the increasing elderly population that inherently have more co-morbidities that predispose them to IE.

Future directions

Several promising new strategies to increase diagnostic and therapeutic potential are under development. It must be noted that though many seem promising, most still require further verification for IE in human clinical trials. There is clinical trial support for switching from intravenous to combinational oral antibiotic therapy using two antibiotics with different mechanisms of action in stable left-sided IE patients (Bundgaard et al., 2019; Iversen et al., 2019). For mono- or combination therapy using approved new-generation (last 10 years) antibiotics against gram-positive bacteria, limited IE-focused clinical data exists or larger prospective trials are needed and thus, should only be considered if resistance, allergy, or clinical/microbiological failure is present (Bloem et al., 2021).

For diagnosis, a novel probe for PET/CT imaging that is specific for bacteria has shown preclinical promise in a *S. aureus*-induced aortic valve endocarditis CD-1 mouse model (Wardak et al., 2020). This $6''$ -[18F]Fluoromaltotriose probe, targeting the maltodextrin transporter, showed a 2.3 fold increase in tracer uptake in the aortic valve compared with the non-IE control group. After 20 days of antibiotic treatment with vancomycin, the probe signal returned to baseline values. The use of this probe could potentially be used as a diagnostic tool and for treatment monitoring in patients with IE.

Dabigatran, a thrombin inhibitor, has been extensively studied in preclinical IE *in vivo* studies with promising results (Lerche et al., 2021). Panizzi et al. was able to develop a targeted imaging agent based on this thrombin inhibitor (Panizzi et al., 2020). The radioisotope fluorine-18 was coupled to dabigatran to produce a PET imaging agent, or a fluorochrome was attached to synthesize a near-infrared imaging agent for intravital microscopy. With these new imaging methods, monoclonal antibodies raised against the virulence factors staphylocoagulase and von Willebrand factor-binding protein were shown to inhibit the conversion of fibrinogen into fibrin *in vivo* murine and porcine IE models (Panizzi et al., 2020). Direct thrombin inhibitors have been demonstrated to be safe in patients with *S. aureus* bacteremia (Peetermans et al., 2018) and lower the incidence of developing *S. aureus* bacteremia in

patients with atrial fibrillation on anticoagulants (Butt et al., 2021). These results are all encouraging, yet their efficacy and potential role, whether prophylactic and/or therapeutic, need to be clinically determined specific for NVE, PVE, and CDRIE.

Another potential theranostic avenue for IE, called sonobactericide (Lattwein et al., 2020), is focused on the removal of IE biofilms, non-invasively, using ultrasound-activated lipid-coated microbubbles (1–10 μ m in diameter), clinically approved as ultrasound contrast agents. Non-targeted microbubbles exposed to focused and unfocused ultrasound have been shown to be effective against *in vitro* biofilms produced from clinical IE *S. aureus* isolates (Lattwein et al., 2022). Ultrasound-induced microbubble displacement resulted in up to 84% biofilm degradation (Lattwein et al., 2022), whereas the infected clot *in vitro* IE model mentioned previously in section 6.5 required the addition of thrombolytics to sonobactericide with an efficacy up to 97% (Lattwein et al., 2018). Thrombolytics currently remain contraindicated for IE, however support exists for its use as a therapeutic agent (Lerche et al., 2021). Vancomycin-decorated microbubbles are also developed to specifically bind to the cell wall of gram-positive bacteria (Kouijzer et al., 2021). Proof-of-concept was demonstrated using a patient-derived IE. *S. aureus* isolate to culture biofilms under flow conditions (5 dyn/cm²). Theranostic potential was firstly demonstrated by the significant increase in signal detection with vancomycin-decorated microbubbles using a high-frequency pre-clinical ultrasound scanner. Secondly, very few targeted microbubbles (approximately 1–4) exposed to ultrasound under flow conditions were necessary to achieve a biofilm reduction of up to 28%. It is possible that a higher concentration could result in higher amount of reduction.

Anti-platelet therapy has promise as a potential adjuvant therapy in IE prevention. This therapy inhibits bacteria-platelet interactions and can thereby inhibit biofilm growth. The anti-platelet drug aspirin via its metabolite salicylic acid suppresses *S. aureus* virulence genes, which has been shown to interfere with biofilm formation in a rabbit model (Kupferwasser et al., 1999). However, this effect was not observed in a similar study performed in rats without using another anti-platelet drug, ticlopidine (Velooso et al., 2015). Clinical studies using aspirin in patients with a high IE risk remain to have contradicting results as clearly summarized in a mini review by Leeten et al. (Leeten et al., 2021). Another anti-platelet drug, ticagrelor, a reversible platelet adenosine diphosphate P2Y₁₂ receptor inhibitor, has shown bactericidal activity against multiple gram positive bacteria *in vitro*, including MSSA and MRSA (Lancellotti et al., 2019). The same study observed biofilm growth inhibition in mice with implants pre-infected with *S. aureus*. Further investigations are needed to determine if anti-platelet therapy is beneficial in the prevention and treatment of IE.

Another promising therapy, which in the future might be used as an adjuvant therapy for IE, is bacteriophage therapy (Plumet et al., 2022). A first-in-patient case study describes a LVAD patient with a persistent open-chest *S. aureus* device

infection (Aslam et al., 2019). The patient was successfully treated with AB-SA01 bacteriophages intravenously without any adverse effects. The safety of this AB-SA01 bacteriophage therapy was further examined in a single-arm non-comparative trial including 13 patients diagnosed with *S. aureus* bacteremia, six were also diagnosed with IE (four PVE patients) (Petrovic Fabijan et al., 2020). Eight of the included patients showed clinical improvement and in eleven patients inflammatory markers declined. Although these results show promise, it remains challenging to evaluate the precise effect of this adjuvant therapy since patients are simultaneously under high-concentration antibiotic therapy.

Recently, a bacteriophage-derived lysin was tested for safety and efficacy in a patient cohort with *S. aureus* blood stream infections, including patients with left- and right-sided IE. The tested lysin (cell wall hydrolase) called exebacase, is the first non-antibiotic antimicrobial direct lytic agent tested in a randomized, double-blind, placebo-controlled proof-of-concept study (Fowler et al., 2020). In the blood stream infections and right-sided endocarditis patient subgroup 80% were found to be clinical responders to the exebacase adjuvant therapy, which was 20.5% higher compared to antibiotics alone (59.5%) (Fowler et al., 2020). After 2 weeks, the clinical responder rate for methicillin-resistant *S. aureus* (MRSA) subgroup receiving exebacase and standard-of-care antibiotics was 42.8% higher compared to antibiotics alone. For the methicillin-sensitive *S. aureus* (MSSA) subgroups, the enhanced treatment effect with the addition of exebacase to the antibiotic regime was not observed. Conversely, an *in vitro* study comparing five MRSA and five MSSA isolates treated with antibiotics combined with exebacase observed synergistic enhancements for both MRSA and MSSA treatment groups (Watson et al., 2020). This underscores the importance of pathogenic interaction and immune response pathways in the (human) *in vivo* setting. In a study using an experimental rabbit MRSA IE model, four of the six animals treated with exebacase and daptomycin showed vegetation size reduction or stabilization (Shah S. U. et al., 2020). A similar rabbit MRSA IE model study using daptomycin and a different lysin, LSVT-1701, also found similar promising results (Huang David et al., 2021). Further studies should be done using multiple strains of MRSA as well as MSSA to better understand its potential for effective clinical application. Exebacase and other bacteriophage-derived products could potentially be a new adjuvant therapy for patients with MRSA IE, however further focused confirmation clinical studies are needed. Other possible future directions for IE treatment include, but not limited to, shockwave therapy (Gnanadhas et al., 2015; Qi et al., 2016), and hyperbaric oxygen therapy (Lerche et al., 2017).

Conclusion

Infective endocarditis (IE) is a life-threatening microbial infection of native and prosthetic heart valves, endocardial surface, and/or indwelling cardiac devices. Prevalence of IE is increasing and mortality remains high despite technological advances. Often IE literature focuses on native valve IE and/or prosthetic valve IE, cardiac device-related IE, or can be undefined. This review provides an updated overview of all three IE stratifications together and separately concerning clinical presentation, diagnosis, causative pathogens, treatment, and outcomes. Having all three stratifications in one review allows for clear visualization on the similarities and dis-similarities between each, which was found in all clinical domains and highlights the continued importance of stratifying based on infected material. Another strength of this review is that only recent literature was used, almost exclusively within the last 5 years, which the contents and discussion within then reflect current trends in IE infection management. Further, current and novel investigative developments and innovative strategies showing promise to improve diagnostic pipeline and therapeutic outcomes are discussed. Overall, the findings presented in this review provides an overview that will potentiate discussion on IE relating to the different infected materials, ultimately to help towards deriving better diagnostic strategies and treatment management.

Author contributions

JK and KL designed the structure of the review. JK, DN, and KL collected the necessary literature and wrote the manuscript draft. NV and WL contributed invaluable knowledge and comments. KL supervised the entire process from inception to submission. JK, DN, WL, NV, and KL all read, edited, and approved the final manuscript.

Funding

This project has received funding from the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation program (grant agreement 805308).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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