Kidney Diseases

Review Article

Kidney Dis 2024;10:519–530
DOI: 10.1159/000540513

Received: January 20, 2024
Accepted: July 20, 2024
Published online: July 26, 2024

Infective Endocarditis in Patients Receiving Hemodialysis: A Current Review

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Keywords
Infective endocarditis · Hemodialysis · Risk factors · Management approach

Abstract
Background: Cardiovascular and infective complications are commonly observed in patients receiving hemodialysis (HD) with cardiovascular events and infection-related complications being the first and second leading causes of death. Infective endocarditis (IE) is characterized by inflammation of the endocardium caused by infection, typically affecting the cardiac valves and can be in acute, subacute, or chronic forms. It is a serious complication within the HD population due to their predisposition for both infection and valvular damage. Considering the frailty and burden of comorbidities in those receiving HD, management of IE in the HD population is very challenging. There has been continuous discussion and debate on optimizing the diagnostic and treatment approach of IE in this patient group to improve their clinical outcomes. Currently, reported outcomes are relatively poor and there are updates from numerous guidelines relating to advances in IE management. ***Summary:*** In this review, we will evaluate the evidence in relation to the epidemiology of HD-associated IE and discuss the important risk factors of IE in patients requiring dialysis. We will also evaluate the current recommendations regarding diagnosis and treatment for suspected or confirmed IE cases amongst HD patients and present the updated data regarding clinical outcomes relating to HD-associated IE. ***Key Messages:*** The incidence of IE in HD patients is expected to increase going forward as HD becomes more easily accessible alongside an emerging uptake of home HD. A more thorough insight into this topic is required to improve clinical practice relating to IE prevention and management in the HD population, given relatively poor clinical outcomes.

Introduction

There is an increased incidence of individuals diagnosed with kidney failure as our global and aging population continues to expand. As a result, the number of people needing kidney replacement therapy (KRT) is also increasing simultaneously. Hemodialysis (HD) initiation is more commonly observed in comparison to kidney transplantation and peritoneal dialysis in many instances, particularly for the elderly as a consequence of frailty, multi-morbidities and functional limitations which make them unsuitable to receive these other forms of kidney

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replacement therapies [1]. Whilst HD is generally safe and feasible for most patients, inevitably there are risks of complications with treatment. Cardiovascular disease and infection-related complications are considered the first and second leading causes of death in patients with kidney failure requiring HD [2, 3]. Infective endocarditis (IE) – the result of a combination of both – is one of the more serious complications observed within the HD population. IE is characterized by inflammation of the endocardium caused by infection, typically affecting the cardiac valves and can be in acute, subacute, or chronic forms [4, 5]. Various organisms are frequently associated with IE, such as *S. aureus* (including Methicillin-resistant *S. aureus* [MRSA]), coagulase-negative Staphylococci (*S. epidermidis*, S. lugdenensis), Streptococci (*S. viridans*, *S. bovis*), Enterococcus, Haemophilus species, *Aggregatibacter actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, *Kingella kingae* (HACEK) organisms and fungal infections. The major risk factors associated with IE are the presence of preexisting cardiac lesions (i.e., congenital heart disease, valvular heart disease including regurgitation, valve prolapse and degenerative valve disease, prosthetic valves), intravenous drug use, high-risk surgery, line infections, as well as HD [5, 6]. The modified Duke's criteria have traditionally been used to diagnose and prognosticate the severity of IE, and it is being continuously revised with other international guidelines proposing various measures to diagnose IE too as a source for comparison [7]. Evidence over the previous four decades have demonstrated HD in an acute and chronic setting to be associated with poorer clinical outcomes in IE, as well as being a risk factor [5, 8].

In this review, we will evaluate evidence relating to the epidemiology of HD-associated IE; details discussing important risk factors of IE to consider in patients requiring dialysis; current recommendations regarding diagnosis and treatment for suspected and confirmed IE cases amongst the HD patient population; and updated data regarding clinical outcomes relating to HD-associated IE.

Epidemiology of IE in HD Patients

The prevalence of IE in patients receiving HD was quoted as approximately 1.4% in a single-center retrospective analysis by Maraj et al. [9] in 2002. More recently, a systematic review and meta-analysis by Sadeghi et al. [10] in 2020 demonstrated the overall prevalence to be higher at 2.9%. The overall incidence of IE in HD patients was 70 times higher than the general population at 1,092 per 100,000 person-years in a large Danish population study comprising 10,612 patients who had received some form of KRT, ranging from HD to kidney transplantation, between 1996 and 2012 [11]. Also, an overall incidence of IE was reported as 201.4 per 100,000 person-years in a longitudinal cohort study in Taiwan looking at 68,426 dialysis patients between 1999 and 2007 [12].

In a study identifying outcomes of IE in 44,816 dialysis patients, Bhatia et al. [13] observed an increased incidence of IE in the dialysis cohort from 175 to 222 per 10,000 end-stage kidney disease (ESKD) patients between 2006 and 2011. This observational trend was similarly noted in the Danish population, where an increased incidence of IE in ESKD patients coincided with the increased incidence of KRT during the study period [11]. The increased incidence and prevalence of IE over the recent decade could be explained by the improved sensitivities in diagnostic tests for IE; unrestricted access to healthcare; and more ESKD patients being commenced and maintained on HD via indwelling central vascular catheters – which is an established risk factor associated with bacteremia. It is not surprising then that numerous studies have observed the incidence of IE was higher in HD patients when compared to those receiving peritoneal dialysis [11, 14].

Staphylococcus aureus (*S. aureus*) has been reported to be the dominant pathogen for IE in dialysis patients in several studies in different populations [13, 15–18]. This predominance could be explained by the fact that more than 50% of dialysis patients are typically carriers of *S. aureus* [19]. MRSA has also been shown to become the more prevalent strain in HD patients in recent studies [8, 16, 17]. Other organisms in descending order of predominance associated with IE in HD patients include Enterococcus species, Streptococcus, gram-negative species, and fungal strains [16, 20–22]. Interestingly, enterococcal IE has been shown to be linked with higher rates of recurrence of IE when compared to other organisms [23].

Risk Factors of IE in HD Patients

There are several reasons why the HD population have a higher risk of IE. ESKD patients are more prone to valvular calcifications secondary to the aberration of calcium-phosphorus homeostasis [24, 25]. HD patients are also more likely to go on developing degenerative heart disease 10–20 years earlier when compared to the general population [26]. In addition, the cardiovascular

system also undergoes different stresses and injuries during HD [3]. These conditions predispose chronic HD patients to valvular disease which further increases their vulnerability to developing IE. Whilst some studies have reported that preexisting aortic valve disease is a significant risk factor for chronic HD patients to develop IE [11, 25], other studies have identified mitral valve disease as the more common form of valvular disease pre-IE [17]. The mitral valve is also more frequently affected in IE when compared to the aortic valve [27].

Chronic HD patients are constantly exposed to pathogens due to the increased use of intravascular access for HD regardless of vascular catheters, fistulas, or grafts. Chaudry et al. [11] demonstrated that the incidence of IE in HD patients with central venous catheters (CVC) was twice as high as those with arteriovenous fistula (AVF) and that the increasing time of patients receiving HD via CVC also coincided with the increased incidence of IE. The higher rates of IE with HD patients on CVC when compared to AVF have also been observed in other smaller studies [28–30]. These results corresponded to other studies which demonstrated that CVC is associated with an increased risk of bloodstream infections [31–34]. Chronic HD patients who dialyze via AVF are also at a higher risk of developing IE compared to the general population; and the fact that most of the causative organisms in IE were skin commensals goes on to show that this could be a consequence of repeated puncture during dialysis [8].

Another point of consideration is the risks posed from use of non-tunneled versus tunneled HD catheters toward IE incidence. In a study conducted by Hajj et al. [35], it was observed that the risk of catheter-related infections was higher with non-tunneled catheters compared to tunneled catheters. However, these findings appear to contradict those from an observational study conducted by Bentata et al. [36], who reported in their cohort of 31 HD patients that non-tunneled catheters showed a weaker association with IE compared to tunneled catheters. Despite these discrepancies, the presence of a dialysis catheter inherently elevates the risk of catheter-related infections. The formation of thrombus and/or fibrin sheaths post-catheter insertion is proposed as the most culpable nidus for infection [37, 38].

Diabetes mellitus (DM) is a common comorbidity in chronic HD patients. It is also one of the risk factors for HD patients to develop IE and has been shown to be a significant predictor of all-cause death in chronic HD patients with IE [8, 12, 15, 39]. This could be explained by the defects and dysfunction of both the innate and adaptive immune response in diabetic patients [40]. Alongside hyperuricemia-induced immunosuppression in ESKD patients, this will increase the vulnerability of chronic HD patients to IE [41].

It has been shown that the presence of cardiac implantable devices in the HD population also increased their vulnerability to IE [42, 43]. Chou et al. [12] identified previous cerebrovascular events also being a risk factor for IE development. However, the reasons explaining for this observation remain very much unclear at present. Further studies are needed to determine the causative links between cerebrovascular disease and IE.

There has also been speculation historically regarding the risk of invasive dental procedures in patients undergoing HD in relation to increased IE incidence. Nevertheless, a cohort case-control study conducted by Yu et al. [44] using secondary data collected from the National Health Insurance Research Database of Taiwan of 19,602 HD patients has concluded that invasive dental treatment did not increase their risk of developing IE. HD patients in need of an invasive dental procedure should be encouraged to undergo treatment if their dentist deems it necessary.

Clinicians would also need to consider other potential iatrogenic risk factors of IE in HD patients, such as regular use of immunosuppression agents (e.g., corticosteroids, anti-cancer agents) leading to an immunocompromised state [9, 27, 45]. Whilst older age is an established risk factor of IE in HD populations, chronic liver disease (from both viral and non-viral causes) and malignancy should also be considered clinically significant risk factors associated with IE in HD patients, though as of present their epidemiology is less well-studied in HD cohorts specifically [10, 12, 39, 45–47]. Further observational data are needed.

Diagnostic Approach and Investigation of Suspected IE in HD Patients

Diagnosing IE in the general population is not straightforward given that sometimes IE may present as subacute disease with nonspecific symptoms [5, 8]. The diagnostic process is even more challenging in the HD population as initial presentation of IE is often difficult to differentiate from that of an uncomplicated infection. In Zhang et al.'s [48] study comparing HD and non-HD patients with IE, 90.5% of the HD patients had an initial presentation of fever. The European Society of Cardiology (ESC) 2015 and 2023 guidelines on IE both suggested that up to 90% of patients present with fever initially [49, 50]. However, Maraj et al. [9] reported fever as a less common presenting symptom in HD patients, ranging between 45 and 70%.

Table 1. Key points from recent society workgroup update recommendations on diagnostic approaches and investigation of suspected IE in HD patients

Source	Key update points
European Society of Cardiology 2015 and 2023 guidelines on Infective Endocarditis [49, 50]	• Advocates for greater reliance on newer and more detailed imaging techniques such as CT, MRI, and nuclear imaging, i.e., PET-CT to assist clinicians in confirming an IE diagnosis, even in more complex cases such as when patients require HD • Reinforces, however, that imaging in the form of TTE and TOE, positive blood cultures and assessment of clinical features should still remain the foundation to determine a diagnosis of IE along these newer imaging measures
2023 Duke-International Society for Cardiovascular Infectious Diseases Criteria for Infective Endocarditis [6]	• New microbiology diagnostic modalities were introduced in the criteria (enzyme immunoassay for Bartonella species, polymerase chain reaction, amplicon/metagenomic sequencing, in situ hybridization), alongside newer imaging options (PET-CT with 18F-fluorodeoxyglucose, cardiac CT), and inclusion of intraoperative inspection as a new major clinical criterion for diagnosis of IE in all patients • Greater expansion on the potential of other influencing predisposing factors of IE, such as transcatheter valve implants, endovascular cardiac implantable electronic devices, prior IE, etc., alongside the risks from HD
2019 National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) Guidelines for Vascular Access [54]	• Recommends the use of TTE to monitor and investigate for endocarditis in chronic HD patients who have a vascular access infection and are positive for *S. aureus*
2016 Canadian Society of Nephrology Vascular Access Workgroup Recommendations [55]	• Suggests that HD patients with *S. aureus* CRBSI should be considered for TTE

CRBSI, catheter-related bloodstream infections; CT, computed tomography; HD, hemodialysis; IE, infective endocarditis; MRI, magnetic resonance imaging; TOE, transoesophageal echocardiography; TTE, transthoracic echocardiography; PET-CT, positron emission tomography-computed tomography.

Table 1 summarizes key update points from numerous society workgroups over the past decade which have shaped current recommendations on diagnostic approach and investigation of suspected IE cases in HD patients. The 2015 and now the recently updated 2023 ESC guidelines on IE made several adjustments to the 2000 modified Duke's criteria, advocating for greater reliance on newer and more detailed imaging techniques such as computed tomography (CT), magnetic resonance imaging, and nuclear imaging, i.e., positron emission tomography-CT (PET-CT) to assist clinicians in confirming an IE diagnosis, whilst reinforcing imaging in the form of echocardiography, positive blood cultures and assessment of clinical features should remain the foundation to determine a diagnosis of IE along these new imaging measures [49–51]. Given the datedness of the previous modified Duke's criteria, the very recent 2023 Duke-International Society for Cardiovascular Infectious Diseases Criteria for IE sought to address these concerns and proposed significant changes [6]. There were new microbiology-based diagnostic modalities introduced in the criteria (enzyme immunoassay for Bartonella species, polymerase chain reaction, amplicon/metagenomic sequencing, in situ hybridization), imaging (PET-CT with 18F-fluorodeoxyglucose, cardiac CT), and inclusion of intraoperative inspection as a new major clinical criterion. The list of "typical" microorganisms causing IE was expanded and includes pathogens to be considered as typical only in the presence of intracardiac prostheses. The requirements for timing and separate venipunctures for blood cultures were removed. There was also greater clarification on additional predisposing conditions of IE (transcatheter valve implants, endovascular cardiac implantable electronic devices, prior IE, etc.) alongside the risks from HD. Nevertheless, with few specific comments regarding the handling of potential IE cases in the HD population in the past and current versions, there were numerous reviews which have questioned the validity of the Duke's criteria being applied for HD patients [52, 53].

There were retrospective studies investigating IE in the HD population which have applied the previous version of the modified Duke's criteria retrospectively to select their study populations however [9, 16, 21, 28]. Whilst there is greater recognition of the risks posed by dialysis and the importance of focusing on screening and optimizing diagnostic approach on IE in the 2023 ESC guidelines, it remains to be seen whether the 2023 Duke-International Society for Cardiovascular Infectious Diseases Criteria for Infective Endocarditis demonstrates improved applicability for the HD cohort [50].

Reviewing the nephrology guidelines which have commented on the diagnostic approach for suspected IE cases in HD, the 2019 National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) Guidelines for Vascular Access have recommended the use of transthoracic echocardiography (TTE) to monitor and investigate for endocarditis in chronic HD patients who have a vascular access infection and are positive for *S. aureus* [54]. Similar recommendations have also been made by the Canadian Society of Nephrology where HD patients with *S. aureus* catheter-related bloodstream infections should be considered for TTE [55]. It is not uncommon in clinical practice to have TTE reports stating that IE cannot be ruled out despite no lesions being seen on imaging. This could be explained by the fact that there is only 55% sensitivity in detecting native valve lesions, and results are largely affected by the size of the lesion [56]. Given the relatively low sensitivity, several studies have gone on to recommend that transesophageal echocardiography (TEE) should be performed in the HD population if one's initial presentation (i.e., acute heart failure, peripheral stigmata of endocarditis, cardiovascular instability, *S. aureus* bacteremia, relapses of bacteremia following antibiotic discontinuation) prompts a high clinical suspicion of IE already [16, 57–59]. A systematic review in 2014 by Holland et al. [60] recommended that TEE is preferred in selected patients who have *S. aureus* bacteremia with HD dependence as they are classed as a high-risk group in IE. The authors also pointed out, however, that the risk of major complications such as esophageal perforation from TEE remains and that there is no evidence suggesting that the increased sensitivity of TEE in identifying small valvular lesions could improve clinical outcomes [60].

Prevention and Treatment of IE in HD Patients

Optimizing prevention is important as part of the overarching management strategy of IE for the HD population. Given the high frequency and severity of IE in the HD cohort dialyzing via CVC, any patient with a suspected catheter-related bloodstream infection should be initiated on empirical broad-spectrum antibiotics after obtaining blood cultures and the antibiotic regime should be modified according to sensitivities once the culture results are back [54]. Immediate CVC removal is recommended in HD patients with proven bacteremia when they are clinically unstable, cultures are positive for common pathogens for IE, and when metastatic infections such as IE are present [54, 55, 61]. The administration of standard oral antibiotics as a prophylactic measure would typically be of prolonged duration for 4–6 weeks [49, 50]. Given the emergence of antibiotic resistance in the *S. aureus* strains, daptomycin has been deemed as an effective alternative antibiotic option prescribed in adjunct to conventional therapy [62, 63]. Other prophylactic measures to manage bacteriemia in HD patients to prevent IE may include prescription of line antibiotic locks and aiming for line salvage in such scenarios, though the extent of their efficacy to prevent IE still needs further determination. Based on updated guidance from the renal drug handbook and the ESC guidelines, Table 2 highlights antibiotic options for treatment of common bacteria in IE within the context of HD, in which antibiotic dose adjustments are factored in considering kidney function and dialysis modality [50, 64].

Timely surgical treatment of IE is indicated when patients have acute heart failure, uncontrolled infection and when there is a high risk of embolic complications. The key aims of surgical intervention will be to (i) remove the infected tissue and (ii) reconstruct defective cardiac structures including repair or replacement of the valves [49, 50]. Although there exists strong evidence for surgical treatment of IE, most of the studies are non-randomized and did not include ESKD and HD populations. Even with updates made in the 2023 ESC guideline in relation to more specific recommendations for timely surgical management of IE, an established guideline to guide surgical management of IE in the HD cohort is not yet available. The evidence on whether current indications for surgical treatment applies suitably to HD patients remain debatable given the intrinsic frailty and burden of comorbidities in this cohort [50]. Given past studies noting much poorer survival rates postoperatively in HD patients compared to non-HD populations, it is unsurprising to find there are substantially fewer HD patients receiving surgical treatment for IE compared to non-HD cohorts historically [39, 65–67]. The decision to perform invasive cardiothoracic surgery on a patient receiving HD requires meticulous consideration and preparation if it was decided to go ahead.

Table 2. Antibiotic options for treatment of common bacteria in IE with dose adjustments given suboptimal kidney function and HD considerations

Bacteria	Antibiotic options	Dose adjustment given suboptimal kidney function and HD considerations
MSSA	Flucloxacillin for 4–6 weeks	Nil
MRSA	Vancomycin for 4–6 weeks	Vancomycin – to be given toward end of HD based on trough levels, aiming for levels between 15 and 20 mg/L
	Daptomycin for 4–6 weeks	Daptomycin – to be given toward end of HD. To monitor CK levels
Streptococcus sp.	Penicillin or amoxicillin or ceftriaxone and gentamicin (for penicillin resistant streptococcus)	Nil changes to penicillin G or amoxicillin Ceftriaxone – 2 g toward end of each HD session Gentamicin to be dosed at 2 mg/kg every 48–72 h according to levels. Appropriate pre-dose trough level <1 mg/L. May worsen residual renal function as high risks of nephrotoxicity
Enterococcus sp.	Amoxicillin or Vancomycin and Gentamicin or	Nil changes to amoxicillin Vancomycin – to be given toward end of HD based on trough levels, aiming for levels between 15 and 20 mg/L Gentamicin to be dosed at 2 mg/kg every 48–72 h according to levels. May worsen residual renal function as high risks of nephrotoxicity
	Ceftriaxone *May be dependent on bacterial resistance requiring discussion with local ID specialist	Ceftriaxone – 2 g toward end of each HD session

CK, creatinine kinase; HD, hemodialysis; ID, infectious disease; MSSA, methicillin-sensitive staphylococcus aureus; MRSA, methicillin-resistant staphylococcus aureus.

Therefore, what was expanded from the 2023 ESC guideline which is significant in this context, is the need for a dedicated "endocarditis" multidisciplinary team in complex situations (such as this case where patients require HD) in which surgical management of IE is required [50]. This newly introduced Class I recommendation calls for the diagnosis and management of patients with complicated IE to be done at an early stage in a heart valve center with surgical capabilities and an endocarditis team to improve outcomes. For patients with uncomplicated IE managed at a referring center, there should be regular communication between the "endocarditis" team there and another team at a heart valve center to improve patient outcomes. The makeup of the "endocarditis" team will differ depending on the type of facility, and available manpower resources. Another key feature of the updated 2023 ESC guidelines is emphasis on the importance of patient perspective [50]. With the severity of IE, the complex and comprehensive diagnostics and treatment, as well as the long illness trajectory even following treatment, it would be important for clinicians to clearly inform patients on the challenges involved and ensure they have a role during the shared decision-making process to achieve patient-centered care [50].

Clinical Outcomes of IE in HD Patients

There are numerous complications of IE that have been commonly reported in HD populations (Table 3) [4, 13, 49, 50, 68, 69]. Acute heart failure is known to be the most common complication of IE and was found to be more common in non-HD patients than in HD patients [4, 49, 50]. Cerebrovascular complications as a result of embolism have also been more frequently observed in HD compared to non-HD patients [13, 70]. Although not statistically significant between HD and non-HD populations, these complications have been identified as the main causes of death [49, 50]. Otherwise, acute kidney injury; acute glomerulonephritis and arthritis resulting from the formation of immune complexes; pneumonia; and septic shock are also important clinical complications to identify and address in a timely manner [68, 69].

Overall, the clinical outcomes of IE in HD patients are recognized to be relatively much poorer compared to the non-HD population, and increased knowledge and advancements in diagnostics and management strategy did not appear to have improved survival rates over the past two decades [15]. Particularly, there is a significantly higher rate of in-hospital mortality during acute

Table 3. Commonly reported complications of IE in HD populations

Heart failure
• Local spread of infection in cardiac tissue leading to structural complications, i.e., Periannular abscess, chordal rupture, cusp or leaflet perforation
• Acute congestive heart failure
• Pericardial effusion
• Atrioventricular block
Embolic complications
• Ischemic stroke
• Mycotic aneurysm
• Septic pulmonary emboli
• Pulmonary infarct
• Splenic infarct
• Cerebral abscess
• Intracranial hemorrhage
Acute kidney injury
Formation of immune complexes leading to acute glomerulonephritis and arthritis
Pneumonia
Septic shock

treatment for HD compared to non-HD patients [4, 39, 71]. In itself, a large range in mortality rates during hospitalization was observed for HD patients receiving treatment for IE across study populations of different demographics, between 16.7 and 45.6% [10, 11, 13, 17]. Mortality typically peaks within the initial 30–60 days following diagnosis of IE in HD patients [52]. From their retrospective observational study, Liau et al. [17] reported a 3-year mortality of 33% for HD patients who were admitted into hospital with IE and survived their initial hospitalization. The authors noted heart failure with reduced ejection fraction as an independent risk factor for mortality in their study [17].

Nucifora et al. [52] identified risk factors which prognosticated mortality outcomes in HD patients with IE, in their review which included a summary of four original studies by Maraj et al. [9], Nori et al. [20], McCarthy and Steckelberg [59] and Shroff et al. [72]. DM as the primary cause of ESKD, cerebrovascular events, age >65 years, MRSA and vancomycin resistant-enterococci related IE were deemed to be associated with late-onset mortality; and large vegetation size of more than 2 cm^3 on TEE, evidence of septic embolism and mitral valve involvement was associated with early mortality [52]. The status of DM here as a prognosticating risk factor remains not fully established nonetheless, with conflicting results such as the study by Pericas et al. [8] highlighting no statistically significant associations between DM and mortality in HD patients with IE.

Despite one study by Jones et al. [73] showing the aortic value being more frequently affected in IE amongst HD patients, the majority of observational studies identified the mitral valve as being the more commonly affected valve out of the two in IE in the HD population [8, 17, 27, 30, 39, 70]. When the HD and non-HD populations with IE were compared, relapse rates of IE were found to be higher in the HD population [8, 74, 75]. This is most likely explained by concurrently higher rates of persistent bacteremia in the HD population, with this being a high-risk factor for IE development in maintenance HD patients [8, 74, 75].

There were no differences observed in 1-year mortality post-IE episode between HD patients who received surgical vs. medical management-only, according to a retrospective study conducted by Chaudry et al. [76]. Although Guo et al. [77] and Dohmen et al. [78] reported that mortality within 30 days of surgery for IE in the dialysis cohort was high at 14% and 42.2%, respectively, Raza et al. [65] noted overall survival outcomes in HD patients following IE-associated operations were higher compared to those who were managed only via medical treatment. Yet, perioperative mortality has been reported to be as high as 73% for HD patients undergoing valve replacement, and complications such as prosthetic valve endocarditis has been observed at significantly higher rates in the HD compared to non-HD cohorts [16, 66]. A systematic review and meta-analysis by Ting et al. [79] published in 2022 evaluated 13 studies which concluded surgical treatment of IE in HD patients were associated with better survival. There were a few studies which have also proposed the importance of early surgical intervention for significantly improved survival outcomes in carefully selected HD patients [15, 27, 52, 80]. To quantify risk assessment to determine appropriately suited HD patients for surgery, Rankin et al. [81] considered a simple point-based risk scoring system that stratified the risk of surgery for IE in HD patients based on the Society of Thoracic Society database between January 1994 and December 2003, in which a total of 1,862 valvular procedures was recorded in dialysis patients with IE. This scoring system was accurately predictive of in-hospital mortality and the predictors that were used here such as cardiogenic shock or salvage status, presence of a double valve, age ≥60 years, presence of an isolated mitral valve, body surface area >2.1 m^2, arrhythmia, active IE, and female sex was validated as similarly significant independent predictors of in-hospital mortality in the study conducted by Leither et al. [15] 6 years later.

Studies have also been conducted comparing outcomes in HD patients provided with bioprosthetic or

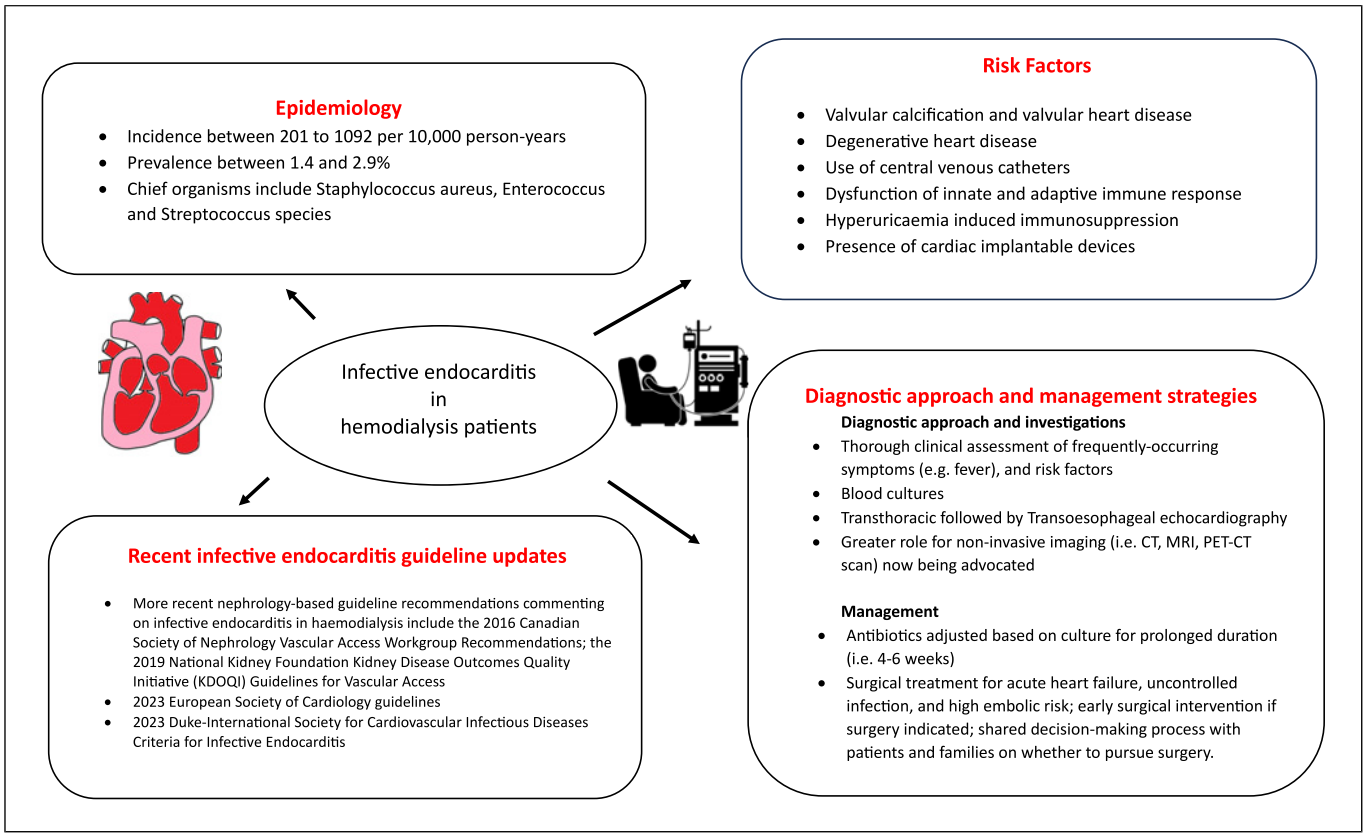

Fig. 1. Overview of IE in patients receiving hemodialysis. CT, computed tomography; MRI, magnetic resonance imaging; PET-CT, positron emission tomography-computed tomography.

mechanical valve replacements from surgical intervention for IE [15, 82, 83]. A systematic review and meta-analysis published by Chan et al. [84] found no significant survival differences between HD patients with IE receiving bioprosthetic or mechanical valve replacement but highlighted fewer postoperative complications with bioprosthetic valve replacement. This is likely explained by the fact that bioprosthetic valve degeneration is less common in the HD population given their relatively lower life expectancy and that the anticoagulation required for mechanical valves will put HD patients at a higher risk of bleeding [82, 83]. In another meta-analysis published in 2022 involving the evaluation of 24 studies, Chi et al. [85] concluded no significant survival differences between HD patients with IE receiving bioprosthetic or mechanical mitral valve replacement but demonstrated there was better survival in those receiving mechanical compared to bioprosthetic aortic valve replacement.

Beyond the prospects of survival in HD patients with IE, the risks of IE recurrence in HD patients following treatment also warrant attention. Recurrence of IE is typically categorized into relapse or reinfection. Relapse involves a repeat IE episode by the same microorganism within 6 months from the initial episode, whilst reinfection occurs due to a different microorganism at a later timepoint following the initial IE episode [86]. In the non-HD population, risk of IE recurrence ranges between 2 and 6%, where the patients experiencing IE recurrence would be at a higher risk of mortality and are more likely indicated for valve replacement surgery [49, 74, 87, 88]. Past studies suggest that IE relapse episodes are more prevalent amongst the HD population, in particular individuals with congenital heart disease and/or acute heart failure [8, 74, 75]. It has been emphasized that after treatment for IE, regular clinical follow-up with echocardiography monitoring is essential. Delivering patient education in regard to the risks of IE recurrence, highlighting preventative measures such as maintaining good oral health and practicing mandatory skin

hygiene for patients with tunneled dialysis catheters, and encouraging early symptom identification, are important aspects of management [49].

Conclusion

Figure 1 summarizes the key points and updates from our review on IE in the HD population. Given relatively poor clinical outcomes of IE in the HD population, a more thorough insight into this matter is essential to improve clinical practice in this scenario going forward. The incidence of IE in HD patients is expected to increase going forwards as HD becomes more easily accessible for ESKD patients, and with the increased popularity of home HD. Ideally, preventative measures to reduce hospital-acquired bacteremia and patient education regarding optimal care of their vascular access sites should be implemented prior to initiating patients on HD. There should be a lower threshold of raising alert in suspecting IE within the HD cohort and early identification of bacteremia with prompt source control, i.e., such as CVC removal should be considered alongside appropriate early imaging. With surgical management appearing to result in higher risks and mortality, a timely decision needs to be made within the multidisciplinary "endocarditis" team and with patients and families whether to operate or not, and to arrange HD patients with IE as early as possible for surgical intervention if this is deemed indicated to maximize positive clinical outcomes.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

This study was not supported by any sponsor or funder.

Author Contributions

Conceptualization: H.H.L.W. and R.C.; resources: H.H.L.W., U.D., and L.O.; writing – original draft preparation, U.D. and L.O.; writing – review and editing: H.H.L.W. and R.C.; visualization and project administration: H.H.L.W.; supervision: R.C., All authors have read and agreed to the published version of the manuscript.

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