Infective endocarditis in chronic haemodialysis patients: an increasing clinical challenge

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Infective endocarditis (IE) in chronic haemodialysis (HD) is significantly more common and causes greater morbidity and mortality than in the general population, being second only to cardiovascular disease as the leading cause of death in this group of patients. Because of the peculiarity of this group of patients, it has been recently proposed to add a fifth category (health-care associated and HD-associated IE) in the actually four categories classification of IE (namely, native valve IE, prosthetic valve IE, IE in e.v. drug users, and nosocomial IE). Given that rates of acceptance into HD are increasing (including a higher proportion of older patients in whom valvular calcification is virtually ubiquitous), and along with improved survival in HD patients, the incidence of IE in this subset of patients will probably increase with significant diagnostic and therapeutic implications. In particular cardiac, diagnostic, echocardiographic, and surgical expertises are required to correctly identify patients at higher risk and who may benefit from surgical treatment. The aim of this review is to clarify the peculiar features of chronic HD patients with regard to pathogenesis, diagnosis, current therapeutic options, and determinants of prognosis of IE.

KEYWORDS
Cardiac surgery; Echocardiography; Haemodialysis; Infective endocarditis; Prognosis

Introduction
The end-stage renal disease (ESRD) population is increasing rapidly. There are approximately 300,000 patients with ESRD who are on haemodialysis (HD) in the USA and the incidence is raising at a rate of 6–8% per year.1

Infective endocarditis (IE) in patients receiving HD has been reported for the first time in 1966.2 It is now well known that IE in HD is significantly more common and causes greater morbidity and mortality than in the general population, being second only to cardiovascular disease as the leading cause of death in this group of patients.1,3,4 Because of the peculiarity of this subset of patients, it has been recently proposed to add a fifth category (health-care associated and HD-associated IE) in the actually four categories classification of IE (namely, native valve IE, prosthetic valve IE, IE in e.v. drug users, and nosocomial IE).5,6

The aim of this review is to clarify the peculiar features of chronic HD patients with regard to pathogenesis, diagnosis, current therapeutic options, and determinants of prognosis of IE.

Epidemiology
Chronic HD patients are at increasingly high risk of IE. In a study of hospital-acquired native valve endocarditis, Lamas et al.7 reported that one-third of their patients with IE had ESRD, with the great majority receiving HD. More recently, Cabell et al.8 showed that the overall proportion of HD patients in their study population of 329 IE patients was as high as 20%, with an increased proportion of HD patients from 6.7 to 20% over the 7-year study period.

The risk of IE in ESRD patients is significantly higher than that in the general population. A 1-year IE French survey9 showed that the incidence of IE in HD patients was 1.7–2.0 cases/1000 patients, which is 50–60 times higher than the overall incidence of IE in France. Using the United States Renal Data System database, Abbott et al.3 found an age-adjusted incidence ratio of IE in the HD population of 17.9 compared with the general population. Similar data were reported by Strom et al.,10 who found a 16.9 relative risk of IE in HD patients over that in the general population.

Predisposing factors and microbiology
There are several potential explanations for the increased incidence of IE in HD patients.
Patients with ESRD have an increased incidence of degenerative heart valve disease, which is a major risk factor for IE. Calcific aortic stenosis, mitral annular calcification with consequent mitral regurgitation, and/or stenosis and bioprosthesis valve degeneration are extremely frequent in this group of patients. Furthermore, degenerative heart valve disease is premature since it appears to begin 10–20 years earlier than in the general population. The accelerated development of valvular calcification in ESRD patients is thought to be related to the abnormalities of calcium–phosphorus homeostasis in the setting of secondary hyperparathyroidism and to the chronic micro-inflammatory milieu of uremia associated with ESRD.

Episodes of bacteraemia during HD are relatively common; they develop at an estimated rate of one episode per 100 patient-care months. They are primarily the result of frequent intravascular access through arteriovenous fistula, vascular graft, or indwelling vascular catheter and may originate from either endogenous (i.e. patient’s own cutaneous flora, the major cause of staphylococcal infections in these patients) or exogenous sources (i.e. hands of personnel, contaminated equipment). A hierarchy of bacteraemia risk exists among various types of HD vascular access; it is less common in patients with native arteriovenous fistulae, while synthetic grafts, cuffed catheters, and uncuffed catheters yield a progressively increasing risk.

The prominent role of vascular access-related bacteraemia in chronic HD patients has been confirmed by recent reports that the frequency of IE is not increased among peritoneal dialysis patients when compared with the general population, and that the diagnosis of IE in this setting is significantly better than in HD patients. Patients with ESRD are inherently prone to bacteraemia and IE also as a result of an impairment of the immune system. Metabolic abnormalities associated with ESRD, malnutrition, and associated comorbidities, such as diabetes mellitus, may indeed impair polymorphonuclear cell function and granulocyte mobility, reducing cellular host defence and clearance of bacteria from the bloodstream. The clinical presentation of IE in the HD population is often difficult to distinguish from that of an uncomplicated access infection. The diagnosis of IE in HD patients using the Duke criteria could be problematic. The use of Duke criteria in this group of patients has indeed some limitations; first, they require the presence of bacteraemia in the absence of a removable focus of infection for diagnosing IE. However, many HD patients have a vascular access device in situ and hence a potential primary focus of infection precluding bacteraemia from being a major criterion. Second, fever, another component of the Duke criteria, is present less commonly in HD patients (45–70%) than in the general population (80–90%), probably due to ureaemia-related impaired cellular host defence. Although the absence of fever has high negative predictive value for a diagnosis of IE in the general population, it is not a useful diagnostic feature in HD patients.

Therefore, it is questionable to apply the Duke criteria in their strictest form to HD patients, since they could underdiagnose IE and significantly delay the time to diagnosis in these patients.

Furthermore, other signs commonly accompanying an infectious disease in the general population are not helpful in this subset of patients; some of these, such as increased

### Table 1

<table>
<thead>
<tr>
<th>Type of organism associated with infective endocarditis in haemodialysis patients in previously published series</th>
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<tbody>
<tr>
<td>Nori et al.</td>
</tr>
<tr>
<td>Episodes of IE in series</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
</tr>
<tr>
<td>MRSA</td>
</tr>
<tr>
<td>Coagulase-negative Staphylococcus</td>
</tr>
<tr>
<td>Enterococcus species</td>
</tr>
<tr>
<td>Streptococcus species</td>
</tr>
<tr>
<td>Gram-negative species</td>
</tr>
<tr>
<td>Candida species</td>
</tr>
<tr>
<td>Aspergillus species</td>
</tr>
<tr>
<td>Negative blood culture</td>
</tr>
</tbody>
</table>

MRSA, methicillin-resistant Staphylococcus aureus.
Infective endocarditis in HD patients

Table 2 High suspicion features for infective endocarditis mandating transoesophageal echocardiography after transthoracic echocardiography in chronic haemodialysis patients

<table>
<thead>
<tr>
<th>High suspicion features? (Table 2)</th>
<th>TTE</th>
<th>TEE +</th>
<th>Poor image quality</th>
<th>TTE</th>
<th>TEE +</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>TTE</td>
<td>TTE-</td>
<td>Suspected complications</td>
<td>Increased IE suspicion during clinical course</td>
<td>Low suspicion persists</td>
</tr>
</tbody>
</table>

HD, haemodialysis; IE, infective endocarditis.

Figure 1 Echocardiography algorithm for suspected infective endocarditis in chronic haemodialysis patients. HD, haemodialysis; IE, infective endocarditis; TEE, transoesophageal echocardiography; TTE, transthoracic echocardiography.

eythrocyte sedimentation and anaemia, are already present in ESRD, whereas others, such as haematuria, may be specifically absent.\(^1\)

These considerations further emphasize the importance of echocardiography in the assessment of HD patients with bacteraemia and suspected IE (Table 2 and Figure 1). Indeed, any HD patient suspected of having IE should be screened by transthoracic echocardiography (TTE). Owing to the increased sensitivity of transoesophageal echocardiography (TEE) over TTE in detecting vegetations and IE-related complications, TEE should be always performed after TTE in any chronic HD patient with high clinical suspicion features (i.e. presence of new-onset congestive heart failure, other stigmata of endocarditis, development of HD-related hypertension, particularly in a previously hypertensive patient, prior or repeated past episodes of IE or prior valvular surgery). Typically organisms for IE (i.e. Staphylococcus aureus, coagulase-negative Staphylococcus, Enterococcus species, and Streptococcus species) as causative pathogens Relapsing bacteraemia after antibiotic discontinuation, regardless of the causative pathogen Patients with HD catheters.

Table 3

<table>
<thead>
<tr>
<th>IE presence</th>
<th>TTE</th>
<th>TEE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>TTE</td>
<td>TEE</td>
</tr>
</tbody>
</table>

HD, haemodialysis; IE, infective endocarditis.

Although vascular access is the likely source of bacteraemia in most cases, right-sided heart valves IE is unusual in the HD population.\(^1\) The mitral valve (up to 50% of cases) and the aortic valve (up to 40% of cases) are the most commonly affected valves.\(^1,4,23\) Simultaneous involvement of the aortic and mitral valves is also relatively frequent, occurring in 20% of the cases.\(^23\) Alterations of laminar flow caused by degenerative left-sided heart valves disease might lead to an increased susceptibility for IE, explaining these findings.

Prognosis

Chronic HD patients with IE have a poorer early and late prognosis. Recently, Ruiz et al.\(^30\) found a significantly higher early and late mortality among HD patients when compared with patients not receiving HD (30 days mortality: 43 vs. 16%; 24 months mortality: 64 vs. 25%, respectively). Mortality rate was similar in the HD patients series studied by McCarthy and Steckelberg\(^1\) (30-day, 60-day, and 1-year mortality after a first episode of IE of 29, 47, and 65%, respectively), whereas Spies et al.\(^23\) found that the peri-operative mortality among HD patients requiring heart valve surgery was even higher (73%, 11/15). Moreover, survival rate of HD patients with IE have changed little in the past two decades, despite the improvement in medical and surgical therapy.\(^31\)

The first 30–60 days after the diagnosis of IE are associated with the highest mortality in patients receiving HD with IE. Therefore, this period requires the closest monitoring, during which time repeated echocardiography, adjustment of medications, surgery, if needed, and removal of infected grafts or catheters may be most beneficial in reducing mortality.\(^1\)

These data are impressive, since, in a non-selected population with IE, in-hospital mortality rate is 16%\(^5\) and mortality rates after surgery for active IE is 8–16%, with actuarial survival at 5 years of 75–76% and at 10 years of 61%.\(^32–34\)

Clinical and echocardiographic factors previously identified as having a prognostic role for early and late mortality among HD patients with IE are listed in Table 3. Moreover, valvular and perivalvular complications of IE, such as abscesses, pseudoaneurysms, leaflet destructions, and intracardiac shunts, should be also considered, since they have been shown to predict mortality in non-selected patients with IE.\(^35\)

Another inevitable issue concerns the decision to perform renal transplantation among HD patients with IE or history of previous IE. At present, no study has specifically addressed this issue; according to the European Best Practice Guidelines for Renal Transplantation, patients with sepsis or any form of potentially life-threatening infection should be excluded from transplantation until complete recovery in view of the deleterious effect of immunosuppressive treatment.\(^36\) Previous history of recurrent infections should not be considered an absolute contraindication to renal transplantation, despite the fact it could increase the risk of post-transplant morbidity and mortality.\(^36\)
In particular, screening for occult infection of the artery, as well as the potential source of bacteremia, should be always performed before kidney transplantation, especially if the patient carries a history of previous bacteremia or fever of unknown origin. Surgical resection of the graft and appropriate antimicrobial treatment could be lifesaving, avoiding bloodstream infections that may become life-threatening with immunosuppression.

**Treatment**

Even if current guidelines for treatment of IE in the general population are suitable also for chronic HD patients, some considerations should be done. Vancomycin should not be used for the treatment of methicillin-susceptible *S. aureus* IE, both for its lower bactericidal activity when compared with oxacillin or cefazolin and for its leading role in the selection of *S. aureus* strains with reduced sensitivity to glycopeptides and vancomycin-resistant Enterococci.

Conversely, when approaching a patient with MRSA-related IE, vancomycin (possibly in combination with rifampicin) is still the drug of choice, if there is the possibility to reach and maintain a trough plasma level of about 15–20 mg/L without toxicity.

Nevertheless, the growing problem of the rising incidence of *S. aureus* strains with increased vancomycin minimal inhibitory concentration may raise more concerns about the potential failure of treatment and confirms the need for further studies involving alternative drugs such as linezolid and daptomycin.

A controversial issue concerns the removal of HD catheters in patients with IE. Since controlled trials to assess this issue are still lacking, the decision to remove the HD catheter with delayed placement of a new catheter, or to exchange the infected catheter with a new catheter over a guidewire or to temporarily transfer the patient on peritoneal dialysis, should be more desirable, due to the risk of persistent catheter-related bacteremia.

catheter salvage is attempted (for example, in patients without alternative vascular access sites), a longer duration of antibiotic treatment and repeated echocardiographic examinations are recommended.

There is also debate on whether accepted indications for valve replacement in the general population are applicable to patients with ESRD, since prospective, randomized, and controlled trials comparing medical vs. surgical therapy in patients with IE and ESRD are lacking. High perioperative mortality has been observed in most observational studies, probably because patients selected for surgery had a more advanced stage of the disease, when serious complications had already set in. The surgical mortality rate further underscores the importance of early identification of HD patients at high risk of mortality (Table 3) and suggests that surgery for active IE in HD patients may be indicated much earlier than in patients without a kidney disease. Since acute renal failure due to IE is a strong predictor of a fatal outcome and most experts seriously consider surgery in this situation, irrespective of the presence or absence of other prognostically relevant factors, it has also been proposed that all HD patients should be considered as candidates for an urgent surgical intervention as soon as the diagnosis of acute IE has been made.

Another issue concerns which type of prosthesis should be implanted among HD patients undergoing cardiac valve replacement. From data of a few retrospective studies, bioprosthetic valves should be considered an effective option even among chronic HD patients. Because of the limited life expectancy of HD patients, bioprosthesis degeneration will in fact be uncommon. Furthermore, ESRD is a known major risk factor for major bleeding in patients treated with warfarin, making mechanical valves less desirable. Mechanical valves should be considered in young and otherwise healthy HD patients; older and patients with a relatively short life expectancy (most patients with ESRD) should be considered as candidates for bioprosthetic valves.

**Conclusion**

IE in HD is significantly more common and lethal than in the general population, the greatest mortality being observed within the first year of diagnosis. Given that rates of acceptance into HD are increasing (including a higher proportion of older patients in whom valvular calcification is virtually ubiquitous), and along with improved survival in HD patients, the incidence of IE in HD patients will probably increase with significant implications for the investigation and treatment of these patients. In particular, cardiac, diagnostic, echocardiographic, and surgical expertises are required to correctly identify patients at higher risk and who may benefit from surgical treatment.

**Conflict of interest:** none declared.

**References**


A stone heart: fatal cardiac microcalcification

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Marked cardiac uptake of 99mTc-methyl-diphosphonate was noted on a bone scan performed in a patient with end-stage renal failure, on long-term dialysis. Amyloidosis was considered a possible explanation for clinical features that included severe left ventricular hypertrophy, low-voltage ECG, atrial and ventricular arrhythmia. Cardiac magnetic resonance (CMR) imaging demonstrated an unusual pattern of delayed contrast hyperenhancement of the entire left myocardium, suggesting diffuse myocardial fibrosis. This pattern was not typical for amyloidosis. Non-contrast CT demonstrated diffusely increased Hounsfield units in the myocardium and unconventional windowing demonstrates patchy calcification in the myocardium.

The patient died of intractable ventricular arrhythmia. At autopsy, there were diffuse microcalcification and interstitial fibrosis of the left ventricular myocardium. Congo red staining for amyloid protein was negative and von Kossa stain for calcium was positive.

CMR and radionuclide pyrophosphate imaging may be abnormal in the setting of either cardiac amyloidosis or cardiac interstitial fibrosis owing to microcalcification. The risk of nephrogenic systemic fibrosis now precludes the use of gadolinium in severe renal failure; however, non-contrast CT may provide a means for non-invasive detection of microcalcification and assist in differentiating this condition from cardiac amyloidosis.

End-stage renal failure and dialysis may be associated with ectopic calcium deposition owing to elevated serum phosphorous and calcium-phosphate (Ca × P) product and elevated parathyroid hormone. Calcium-based phosphate binding therapy may contribute to hypercalcaemia. Diffuse cardiac microcalcification may cause intractable heart failure and malignant arrhythmia, but is most often diagnosed at autopsy.

The pre-contrast black blood (Panel A) and bright blood (Panel B) CMR demonstrate increased diastolic wall thickness of the left ventricle in the four-chamber view. The corresponding post-contrast-delayed hyperenhancement pattern (Panel C) is unusual with diffusely increased signal intensity in the left ventricular myocardium and normal null (dark appearance) of the right ventricular myocardium. The CT shows diffusely increased left ventricular Hounsfield units (Panel D), and when windowed unconventionally (Panel F), a speckled appearance of the myocardium can be appreciated. Abnormal visualization of soft tissue (left ventricular) uptake of 99mTc-methyl-diphosphonate is seen on the bone scan (Panel E). Haematoxylin and eosin stain of the left ventricle shows the extensive interstitial fibrosis with microcalcifications (Panels G and H), and the calcifications are evident as brown–black granules in intracellular and extracellular locations, von Kossa stain (Panel I).