European Heart Journal (2007) **28**, 2307–2312
doi:10.1093/eurheartj/ehm278

Review

Infective endocarditis in chronic haemodialysis patients: an increasing clinical challenge

Gaetano Nucifora[1]*, Luigi P. Badano[1], Pierluigi Viale[2], Pasquale Gianfagna[1], Giuseppe Allocca[1], Domenico Montanaro[3], Ugolino Livi[1], and Paolo M. Fioretti[1]

[1]*Cardiopulmonary Science Department, Azienda Ospedaliero-Universitaria di Udine, P.le S. Maria della Misericordia, 15, 33100 Udine, Italy;* [2]*Clinic of Infective Diseases, Azienda Ospedaliero-Universitaria di Udine, P.le S. Maria della Misericordia, 15, 33100 Udine, Italy; and* [3]*Nephrology and Haemodialysis Unit, Azienda Ospedaliero-Universitaria di Udine, P.le S. Maria della Misericordia, 15, 33100 Udine, Italy*

Received 9 March 2007; revised 19 May 2007; accepted 7 June 2007; online publish-ahead-of-print 26 July 2007

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

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.

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 survey[9] 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.

* Corresponding author. Tel: +39 0432552441; fax: +39 0432482353.
E-mail address: gnucifora@cardionet.it

Patients with ESRD have an increased incidence of degenerative heart valve disease, which is a major risk factor for IE.[11] Calcific aortic stenosis,[11] mitral annular calcification with consequent mitral regurgitation, and/or stenosis[11] and bioprosthetic valve degeneration[12] 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.[13] 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 uraemia associated with ESRD.[11]

Episodes of bacteraemia during HD are relatively common; they develop at an estimated rate of one episode per 100 patient-care months.[1,14] They are primarily the result of frequent intravascular access through arteriovenous fistula, vascular graft, or indwelling vascular catheter[14] 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).[15] 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.[16]

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 prognosis of IE in this setting is significantly better than in HD patients.[3,17]

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.[14]

Staphylococcus aureus is the main cause of vascular access-related bacteraemia among patients receiving long-term HD (up to 75% of cases);[18] this event could be explained by the high prevalence of *S. aureus* carriage among HD patients. Over 50% of dialysis patients are indeed carriers of *S. aureus*, with the nose as the reservoir, and nasal carriage of *S. aureus* has been shown to be a major risk factor for subsequent infection.[19]

Staphylococcus aureus blood-stream infections are responsible for a high rate of septic complications, when compared with other organisms;[20,21] particularly, *S. aureus* is the predominant causative pathogen of IE (up to 80% of cases)[1,4,22–24] (*Table 1*), much more frequently, therefore, than in the general population. Strains of *S. aureus* that infect HD intravascular devices are indeed particularly virulent and usually resistant to thrombin-induced platelet microbicidal protein; these strains are more likely to disseminate in the bloodstream, causing bacteraemia and IE.[25] Furthermore, the number of methicillin-resistant *S. aureus* (MRSA) isolated in this group of patients is increasing with time, reaching 50% of all *S. aureus* strains in the year 2002 in a recent study.[23]

Diagnosis

The clinical presentation of IE in the HD population is often difficult to distinguish from that of an uncomplicated access infection.[18]

Furthermore, the diagnosis of IE in HD patients using the Duke criteria[26,27] 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.[1,4,22] 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 uraemia-related impaired cellular host defence.[4] Although the absence of fever has high negative predictive value for a diagnosis of IE in the general population,[26] 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 Type of organism associated with infective endocarditis in haemodialysis patients in previously published series

	Nori *et al.*[24]	Spies *et al.*[23]	Doulton *et al.*[22]	Maraj *et al.*[4]	McCarthy and Steckelberg[1]
Episodes of IE in series	$n = 54$	$n = 40$	$n = 30$	$n = 30$	$n = 17$
Staphylococcus aureus	40%	50%	63%	80%	40%
MRSA	20%	15%	7%	23%	
Coagulase-negative *Staphylococcus*	22%	12%	13%	3%	10%
Enterococcus species	33%	23%	10%	7%	20%
Streptococcus species			10%	3%	25%
Gram-negative species	13%	10%			
Candida species		3%		3%	
Aspergillus species					5%
Negative blood culture	2%	10%			

MRSA, methicillin-resistant *Staphylococcus aureus*.

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

Presence of new-onset congestive heart failure
Presence of stigmata of endocarditis
Development of HD-related hypotension, particularly in a previously hypertensive patient
Prior or repeated past episodes of IE
Prior valvular surgery
Typical 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

HD, haemodialysis; IE, infective endocarditis.

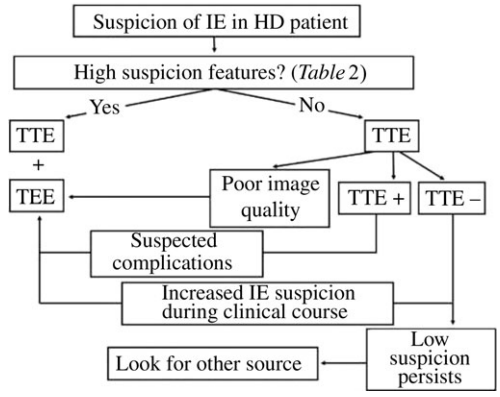


Figure 1 Echocardiography algorithm for suspected infective endocarditis in chronic haemodialysis patients. HD, haemodialysis; IE, infective endocarditis; TEE, transoesophageal echocardiography; TTE, transthoracic echocardiography.

erythrocyte sedimentation and anaemia, are already present in ESRD, whereas others, such as haematuria, may be specifically absent.[28]

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 hypotension, particularly in a previously hypertensive patient, prior or repeated past episodes of IE or prior valvular surgery), whenever typical organisms for IE (i.e. *S. aureus*, coagulase-negative *Staphylococcus*, *Enterococcus* species, and *Streptococcus* species) are the causative pathogen or bacteraemia is relapsing after antibiotic discontinuation, regardless of the causative pathogen.[1,6,18,23,29] TEE should also be considered in patients with HD catheters because of the high risk of IE of this group of patients,[18] and in TTE-positive cases, if there is suspicion of valvular and perivalvular complications. TEE is rarely necessary when these high-risk features are not present and TTE is negative with good quality images, since it does not give significant additional information.[29]

Although vascular access is the likely source of bacteraemia in most cases, right-sided heart valves IE is unusual in the HD population.[18] 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 perioperative 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]

Table 3 Clinical and echocardiographic prognostic factors for early and late mortality among haemodialysis patients with infective endocarditis

Early mortality	Late mortality
Septic embolism	Age >65 years
Mitral valve involvement	Diabetes as cause of ESRD
Vegetation size >2 cm^3 at TEE	Cerebrovascular accident/transient ischaemic attack
	Mitral valve involvement (especially if mitral annular calcification or severe mitral valvular regurgitation)
	IE related to MRSA and VRE

Data from McCarthy and Steckelberg,[1] Maraj *et al.*,[4] Nori *et al.*,[24] and Shroff *et al.*[31]

ESRD, end-stage renal disease; MRSA, methicillin-resistant *Staphylococcus aureus*; TEE, transoesophageal echocardiography; VRE, vancomycin-resistant *Enterococcus* sp.

In particular, screening for occult infection of the arteriovenous grafts, which represent a potential source of bacteraemia, should be always performed before kidney transplantation, especially if the candidate carries a history of previous bacteraemia or fever of unknown origin.[36,37] Surgical resection of the graft and appropriate antimicrobial treatment could be lifesaving, avoiding bloodstream infections that may become life-threatening with immunosuppression.[37]

Treatment

Even if current guidelines for treatment of IE in the general population are suitable also for chronic HD patients,[18] 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.[38,39]

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 through plasma level of about 15–20 mg/L without toxicity.[40,41]

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.[42,43]

A controversial issue concerns the removal of HD catheters in patients with IE.[44–47] 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 bacteraemia.[6,17,18] If 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.[6]

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.[48,49] 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.[1,23,24,30] 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.[50] Since acute renal failure due to IE is a strong predictor for 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.[50]

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.[51,52] 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,[53] 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.[51,52]

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

1. McCarthy JT, Steckelberg JM. Infective endocarditis in patients receiving long-term hemodialysis. *Mayo Clin Proc* 2000;**75**:1008–1014.

2. Brescia MJ, Cimino JE, Appel K, Hurwich BJ. Chronic hemodialysis using venipuncture and a surgically created arteriovenous fistula. *N Engl J Med* 1966;**275**:1089–1092.
3. Abbott KC, Agodoa LY. Hospitalizations for bacterial endocarditis after initiation of chronic dialysis in the United States. *Nephron* 2002;**91**: 203–209.
4. Maraj S, Jacobs LE, Kung SC, Raja R, Krishnasamy P, Maraj R, Braitman LE, Kotler MN. Epidemiology and outcome of infective endocarditis in hemodialysis patients. *Am J Med Sci* 2002;**324**:254–260.
5. Moreillon P, Que YA. Infective endocarditis. *Lancet* 2004;**363**:139–149.
6. Hoen B. Infective endocarditis: a frequent disease in dialysis patients. *Nephrol Dial Transplant* 2004;**19**:1360–1362.
7. Lamas CC, Eykyn SJ. Hospital acquired native valve endocarditis: analysis of 22 cases presenting over 11 years. *Heart* 1998;**79**:442–447.
8. Cabell CH, Jollis JG, Peterson GE, Corey GR, Anderson DJ, Sexton DJ, Woods CW, Reller LB, Ryan T, Fowler VG Jr. Changing patient characteristics and the effect on mortality in endocarditis. *Arch Intern Med* 2002; **162**:90–94.
9. Hoen B, Alla F, Selton-Suty C, Beguinot I, Bouvet A, Briancon S, Casalta JP, Danchin N, Delahaye F, Etienne J, Le Moing V, Leport C, Mainardi JL, Ruimy R, Vandenesch F. Changing profile of infective endocarditis: results of a 1-year survey in France. *JAMA* 2002;**288**:75–81.
10. Strom BL, Abrutyn E, Berlin JA, Kinman JL, Feldman RS, Stolley PD, Levison ME, Korzeniowski OM, Kaye D. Risk factors for infective endocarditis: oral hygiene and nondental exposures. *Circulation* 2000;**102**: 2842–2848.
11. Umana E, Ahmed W, Alpert MA. Valvular and perivalvular abnormalities in end-stage renal disease. *Am J Med Sci* 2003;**325**:237–242.
12. Fishbein MC, Gissen SA, Collins JJ Jr, Barsamian EM, Cohn LH. Pathologic findings after cardiac valve replacement with glutaraldehyde-fixed porcine valves. *Am J Cardiol* 1977;**40**:331–337.
13. Madu EC, D'Cruz IA, Wall B, Mansour N, Shearin S. Transesophageal echocardiographic spectrum of calcific mitral abnormalities in patients with end-stage renal disease. *Echocardiography* 2000;**17**:29–35.
14. Powe NR, Jaar B, Furth SL, Hermann J, Briggs W. Septicemia in dialysis patients: incidence, risk factors, and prognosis. *Kidney Int* 1999;**55**: 1081–1090.
15. Sexton DJ. Vascular access infections in patients undergoing dialysis with special emphasis on the role and treatment of *Staphylococcus aureus*. *Infect Dis Clin North Am* 2001;**15**:731–742. vii.
16. Stevenson KB, Adcox MJ, Mallea MC, Narasimhan N, Wagnild JP. Standardized surveillance of hemodialysis vascular access infections: 18-month experience at an outpatient, multifacility hemodialysis center. *Infect Control Hosp Epidemiol* 2000;**21**:200–203.
17. Fernandez-Cean J, Alvarez A, Burguez S, Baldovinos G, Larre-Borges P, Cha M. Infective endocarditis in chronic haemodialysis: two treatment strategies. *Nephrol Dial Transplant* 2002;**17**:2226–2230.
18. Maraj S, Jacobs LE, Maraj R, Kotler MN. Bacteremia and infective endocarditis in patients on hemodialysis. *Am J Med Sci* 2004;**327**:242–249.
19. Wertheim HF, Melles DC, Vos MC, van Leeuwen W, van Belkum A, Verbrugh HA, Nouwen JL. The role of nasal carriage in *Staphylococcus aureus* infections. *Lancet Infect Dis* 2005;**5**:751–762.
20. Engemann JJ, Friedman JY, Reed SD, Griffiths RI, Szczech LA, Kaye KS, Stryjewski ME, Reller LB, Schulman KA, Corey GR, Fowler VG Jr. Clinical outcomes and costs due to *Staphylococcus aureus* bacteremia among patients receiving long-term hemodialysis. *Infect Control Hosp Epidemiol* 2005;**26**:534–539.
21. Troidle L, Eisen T, Pacelli L, Finkelstein F. Complications associated with the development of bacteremia with *Staphylococcus aureus*. *Hemodial Int* 2007;**11**:72–75.
22. Doulton T, Sabharwal N, Cairns HS, Schelenz S, Eykyn S, O'Donnell P, Chambers J, Austen C, Goldsmith DJ. Infective endocarditis in dialysis patients: new challenges and old. *Kidney Int* 2003;**64**:720–727.
23. Spies C, Madison JR, Schatz IJ. Infective endocarditis in patients with end-stage renal disease: clinical presentation and outcome. *Arch Intern Med* 2004;**164**:71–75.
24. Nori US, Manoharan A, Thornby JI, Yee J, Parasuraman R, Ramanathan V. Mortality risk factors in chronic haemodialysis patients with infective endocarditis. *Nephrol Dial Transplant* 2006;**21**:2184–2190.
25. Fowler VG Jr, McIntyre LM, Yeaman MR, Peterson GE, Barth RL, Corey GR, Wray D, Bayer AS. In vitro resistance to thrombin-induced platelet microbicidal protein in isolates of *Staphylococcus aureus* from endocarditis patients correlates with an intravascular device source. *J Infect Dis* 2000;**182**:1251–1254.
26. Durack DT, Lukes AS, Bright DK. New criteria for diagnosis of infective endocarditis: utilization of specific echocardiographic findings. Duke Endocarditis Service. *Am J Med* 1994;**96**:200–209.
27. Li JS, Sexton DJ, Mick N, Nettles R, Fowler VG Jr, Ryan T, Bashore T, Corey GR. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *Clin Infect Dis* 2000;**30**:633–638.
28. Vijayvargiya R, Veis JH. Antibiotic-resistant endocarditis in a hemodialysis patient. *J Am Soc Nephrol* 1996;**7**:536–542.
29. Wu EB, Witherspoon ML, Gillmore JD, Pattison JM, Chambers JB. The role of transesophageal echocardiography in patients with chronic renal failure at low and high risk of endocarditis. *J Heart Valve Dis* 1997;**6**:249–252.
30. Ruiz M, Sanchez MP, Dominguez JC, Pineda SO, Penas ER, Rubio MD, Ortega MD, Belsue FV. Infective endocarditis in patients receiving chronic hemodialysis: clinical features and outcome. *J Heart Valve Dis* 2005;**14**:11–14.
31. Shroff GR, Herzog CA, Ma JZ, Collins AJ. Long-term survival of dialysis patients with bacterial endocarditis in the United States. *Am J Kidney Dis* 2004;**44**:1077–1082.
32. d'Udekem Y, David TE, Feindel CM, Armstrong S, Sun Z. Long-term results of surgery for active infective endocarditis. *Eur J Cardiothorac Surg* 1997;**11**:46–52.
33. Alexiou C, Langley SM, Stafford H, Lowes JA, Livesey SA, Monro JL. Surgery for active culture-positive endocarditis: determinants of early and late outcome. *Ann Thorac Surg* 2000;**69**:1448–1454.
34. Bauernschmitt R, Jakob HG, Vahl CF, Lange R, Hagl S. Operation for infective endocarditis: results after implantation of mechanical valves. *Ann Thorac Surg* 1998;**65**:359–364.
35. Aksoy O, Sexton DJ, Wang A, Pappas PA, Kourany W, Chu V, Fowler VG Jr, Woods CW, Engemann JJ, Corey GR, Harding T, Cabell CH. Early surgery in patients with infective endocarditis: a propensity score analysis. *Clin Infect Dis* 2007;**44**:364–372.
36. EBPG Expert Group on Renal Transplantation. European Best Practice Guidelines for Renal Transplantation (part 1). *Nephrol Dial Transplant* 2000;**15**(Suppl. 7):1–85.
37. Nassar GM, Ayus JC. Infectious complications of old nonfunctioning arteriovenous grafts in renal transplant recipients: a case series. *Am J Kidney Dis* 2002;**40**:832–836.
38. The Hospital Infection Control Practices Advisory Committee. Recommendations for preventing the spread of vancomycin resistance: recommendations of the Hospital Infection Control Practices Advisory Committee (HICPAC). *Infect Control Hosp Epidemiol* 1995;**16**:105–113.
39. Smith TL, Pearson ML, Wilcox KR, Cruz C, Lancaster MV, Robinson-Dunn B, Tenover FC, Zervos MJ, Band JD, White E, Jarvis WR. Emergence of vancomycin resistance in *Staphylococcus aureus*. Glycopeptide-Intermediate *Staphylococcus aureus* Working Group. *N Engl J Med* 1999;**340**:493–501.
40. Kitzis MD, Goldstein FW. Monitoring of vancomycin serum levels for the treatment of staphylococcal infections. *Clin Microbiol Infect* 2006;**12**: 92–95.
41. Pea F, Viale P. The antimicrobial therapy puzzle: could pharmacokinetic-pharmacodynamic relationships be helpful in addressing the issue of appropriate pneumonia treatment in critically ill patients? *Clin Infect Dis* 2006;**42**:1764–1771.
42. Wang G, Hindler JF, Ward KW, Bruckner DA. Increased vancomycin MICs for *Staphylococcus aureus* clinical isolates from a university hospital during a 5-year period. *J Clin Microbiol* 2006;**44**:3883–3886.
43. Drees M, Boucher H. New agents for *Staphylococcus aureus* endocarditis. *Curr Opin Infect Dis* 2006;**19**:544–550.
44. Lentino JR, Baddour LM, Wray M, Wong ES, Yu VL. *Staphylococcus aureus* and other bacteremias in hemodialysis patients: antibiotic therapy and surgical removal of access site. *Infection* 2000;**28**:355–360.
45. Marr KA, Sexton DJ, Conlon PJ, Corey GR, Schwab SJ, Kirkland KB. Catheter-related bacteremia and outcome of attempted catheter salvage in patients undergoing hemodialysis. *Ann Intern Med* 1997;**127**:275–280.
46. Capdevila JA, Segarra A, Pahissa A. Catheter-related bacteremia in patients undergoing hemodialysis. *Ann Intern Med* 1998;**128**:600.
47. Mokrzycki MH, Zhang M, Cohen H, Golestaneh L, Laut JM, Rosenberg SO. Tunnelled haemodialysis catheter bacteraemia: risk factors for bacteraemia recurrence, infectious complications and mortality. *Nephrol Dial Transplant* 2006;**21**:1024–1031.
48. Horstkotte D, Follath F, Gutschik E, Lengyel M, Oto A, Pavie A, Soler-Soler J, Thiene G, von Graevenitz A, Priori SG, Garcia MA, Blanc JJ, Budaj A, Cowie M, Dean V, Deckers J, Fernandez BE, Lekakis J, Lindahl B, Mazzotta G, Morais J, Oto A, Smiseth OA, Lekakis J, Vahanian A, Delahaye F, Parkhomenko A, Filipatos G, Aldershvile J, Vardas P. Guidelines on prevention, diagnosis and treatment of infective endocarditis executive summary; the task force on

infective endocarditis of the European Society of Cardiology. *Eur Heart J* 2004;**25**:267–276.
49. Baddour LM, Wilson WR, Bayer AS, Fowler VG Jr, Bolger AF, Levison ME, Ferrieri P, Gerber MA, Tani LY, Gewitz MH, Tong DC, Steckelberg JM, Baltimore RS, Shulman ST, Burns JC, Falace DA, Newburger JW, Pallasch TJ, Takahashi M, Taubert KA. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications: a statement for healthcare professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, and the Councils on Clinical Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia, American Heart Association: endorsed by the Infectious Diseases Society of America. *Circulation* 2005;**111**: e394–e434.
50. Horstkotte D, Piper C. Chronic hemodialysis: high risk for manifestation of infective endocarditis with poor outcome. *J Heart Valve Dis* 2005; **14**:8–10.
51. Lucke JC, Samy RN, Atkins BZ, Silvestry SC, Douglas JM Jr, Schwab SJ, Wolfe WG, Glower DD. Results of valve replacement with mechanical and biological prostheses in chronic renal dialysis patients. *Ann Thorac Surg* 1997;**64**:129–132.
52. Kaplon RJ, Cosgrove DM III, Gillinov AM, Lytle BW, Blackstone EH, Smedira NG. Cardiac valve replacement in patients on dialysis: influence of prosthesis on survival. *Ann Thorac Surg* 2000;**70**:438–441.
53. Landefeld CS, Goldman L. Major bleeding in outpatients treated with warfarin: incidence and prediction by factors known at the start of outpatient therapy. *Am J Med* 1989;**87**:144–152.

Clinical vignette

doi:10.1093/eurheartj/ehm100
Online publish-ahead-of-print 4 May 2007

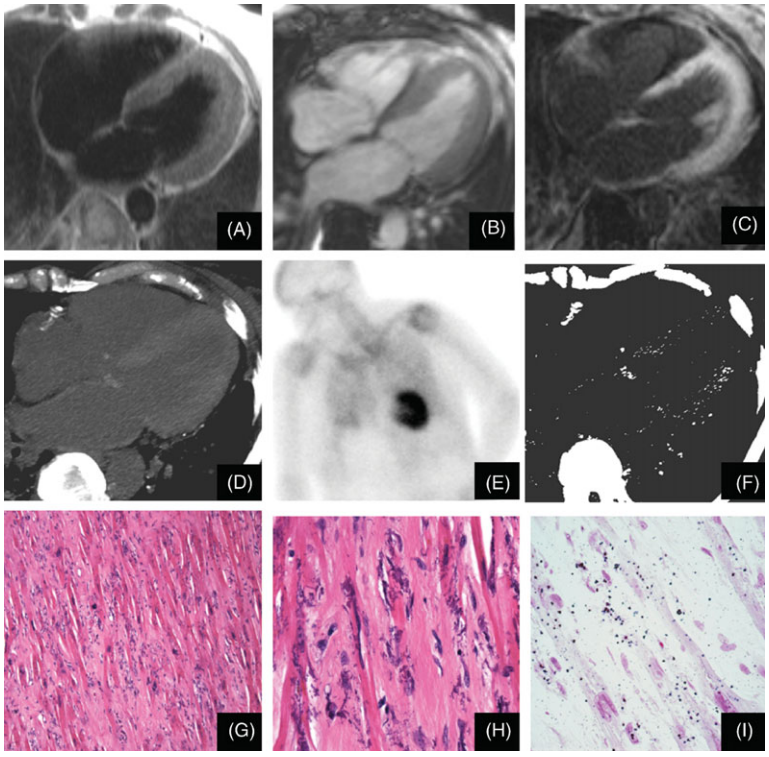
A stone heart: fatal cardiac microcalcification

Cynthia J. Lee[1,2], Cristina Ramirez[1,2], and Louise E.J. Thomson[1,2]*

[1]Division of Nuclear Medicine, Department of Imaging, Cedars-Sinai Medical Center, 8700 Beverly Boulevard, Room 1258, Los Angeles, CA 90048, USA and [2]Department of Anatomic and Clinical Pathology, Cedars-Sinai Medical Center, Los Angeles, CA 90048, USA

* Corresponding author. Tel: +1 310 423 0755; fax: +1 310 423 0811. *E-mail address*: louise.thomson@cshs.org

Marked cardiac uptake of ^{99m}Tc-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 ventricular 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 ^{99m}Tc-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).