

Teaching Point
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Infective endocarditis in haemodialysis patients: 16-year experience at one institution

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Abstract

Objectives. To ascertain the characteristics, outcomes and correlates of mortality in chronic haemodialysis patients with confirmed infective endocarditis (IE).

Methods. Patients were identified by computerized discharge diagnosis and chart review of admissions to Saint Louis University hospital from January 1990 through January 2006. Modified Duke Criteria were retrospectively applied to confirm the diagnosis of IE. Survivors and non-survivors were compared to identify clinical correlates of IE mortality.

Results. We identified 59 patients with IE who had received dialysis for a mean duration of 52.9 ± 58.0 months prior to IE diagnosis. Dialysis access comprised 28 (47.5%) catheters, 26 (44.1%) arteriovenous grafts, 3 (5.1%) arteriovenous fistulas and 2 (3.4%) life sites. The causative organisms were MRSA in 15 (25%), MSSA 12 (20%), *S. Epidermidis* 10 (17%), Enterococci 8 (14%), multi-organism 6 (10%), gram negative 2 (3%) and VRE 1 (2%). Valves involved were mitral valve in 37 (63%), aortic valve in 10 (17%), tricuspid valve in 3 (5%) and multiple valves in 8 (13%) cases. Patient mortality was 28.8% ($n = 17$) during hospitalization, 37.9% ($n = 22$) at 30 days and 63.1% ($n = 36$) at 1 year. In multivariable logistic regression, the adjusted odds ratio of in-hospital mortality was 3.6-fold higher in those with IE and arteriovenous grafts ($P = 0.04$, 95% CI 1.04–12.27) compared to other forms of dialysis access.

Conclusion. Mortality of IE remains high, despite the availability of potent antibiotics. Patients with arteriovenous grafts who develop IE may face increased risk for in-hospital mortality, perhaps reflecting difficulty eradicating endovascular infection if a graft is involved.

Keywords: end-stage renal disease; haemodialysis; infective endocarditis; mortality

Introduction

The end-stage renal disease (ESRD) population is increasing rapidly in the United States. In 2004 the adjusted prevalence of ESRD reached 1542 per million population—5.4 times higher than that in 1980, and 1.4 times higher than that in 1994 [1]. Patients receiving long-term haemodialysis (HD) are at increased risk for infective endocarditis (IE) with an age-adjusted incidence ratio of 17.9 compared to the general population [2]. Conditions that may contribute to this risk are the immunocompromised state resulting from uraemia [3] and valve calcifications, which are extremely frequent in HD patients [4]. However, the most important risk factor seems to result from an increased use of other forms of dialysis access apart from native arteriovenous fistulas (AVFs) [5,6]. With the current number of patients undergoing long-term HD, the mortality associated with IE, illustrated by in-hospital mortality and 1-year mortality rates ranging from 25 to 45% and 46 to 75%, respectively [5,7,8], is an important health care management issue.

In view of these factors, we have reviewed our experience with IE in patients receiving long-term HD between 1990 and 2006 to ascertain the predominant patient characteristics, outcomes and correlates of mortality. This identification might allow us to intervene more aggressively at an earlier stage to improve the outcome of these patients.

Methods

Subjects and definitions

This study is a retrospective analysis of HD patients who had an index hospitalization for bacterial endocarditis after initiation of renal replacement therapy from January 1990 to January 2006, in Saint Louis University Hospital. After Institution Review Board's approval, patients hospitalized for bacterial endocarditis were identified from the electronic databases using International Classification of Diseases-9 (ICD-9) codes for ESRD (585.0) and IE (421.0). Modified Duke criteria were retrospectively applied to define IE, and only the definite IE cases were included, i.e. if a patient had

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Table 1. Baseline clinical characteristics of patients and IE episodes within the full cohort, and distributions of according to in-hospital survival

Trait	Full cohort <i>N</i> = 59 count (%)	Non-survivors <i>N</i> = 17 count (%)	Survivors <i>N</i> = 42 count (%)	<i>P</i> -value*
Male gender	28 (47%)	9 (52.9%)	19 (45.2%)	0.59
Age	57.3 ± 13.8	61.8 ± 14.72	55.5 ± 13.24	0.12
Race				0.30
Black	42 (71%)	14 (87.4%)	28 (66.7%)	
White	14 (24%)	2 (11.8%)	12 (28.6%)	
Other	3 (5%)	1 (5.9%)	2 (4.8%)	
Diabetes	35 (59%)	10 (58.8%)	25 (59.5%)	0.96
History of IVDU	4 (7%)	1 (5.9%)	3 (7.1%)	1.00
History of IE	6 (10.2%)	1 (5.9%)	5 (11.9%)	0.66
Serum albumin	2.6 ± 0.58	2.5 ± 0.58	2.75 ± 0.58	0.15
Access				
Catheter	28 (47.5%)	6 (35.3%)	22 (52.4%)	0.23
AVG	26 (44.1%)	11 (64.7%)	15 (35.7%)	0.04
AVF	3 (5.1%)	0 (0.0%)	3 (7.1%)	0.55
Life site	2 (3.4%)	0 (0.0%)	2 (4.8%)	1.00
Valvular involvement				
Native valve	58 (98%)	17 (100.0%)	40 (95.2%)	1.00
AV	10 (17%)	5 (29.4%)	5 (11.9%)	0.13
MV	37 (62.7%)	10 (58.8%)	27 (64.3%)	0.69
TV	3 (5.1%)	0 (0.0%)	3 (7.1%)	0.55
Multivalvular	8 (13.6%)	2 (11.8%)	6 (14.3%)	1.00
Organism				
MRSA	15 (25.4%)	6 (35.3%)	9 (21.4%)	0.33
MSSA	12 (20.3%)	6 (35.3%)	6 (14.3%)	0.08
VRE	1 (1.7%)	0 (0.0%)	2 (2.4%)	1.00
Enterococci	8 (13.6%)	2 (11.8%)	6 (14.3%)	1.00
Gram-negative bacteria	2 (3.4%)	0 (0.0%)	2 (4.8%)	1.00
Fungal	1 (1.7%)	0 (0.0%)	1 (2.4%)	1.00
Complications				
Septic emboli	17 (28.8%)	7 (41.2%)	10 (23.8%)	1.00
Brain emboli	9 (15.3%)	5 (29.4%)	4 (9.5%)	0.10
Valve replacement	7 (11.9%)	1 (5.9%)	6 (14.3%)	0.66

**P*-value from the chi-square test of difference in frequency distribution among survivors and non-survivors.

IVDU: intravenous drug use; AVG: arteriovenous graft; AVF: arteriovenous fistula; AV: aortic valve; MV: mitral valve; TV: tricuspid valve; MRSA: methicillin-resistant *Staphylococcus aureus*; MSSA: methicillin sensitive *Staphylococcus aureus*; VRE: vancomycin-resistant enterococci.

two major criteria, or one major and three minor criteria, or five minor criteria [9].

Demographic, clinical, echocardiographical and microbiological data were obtained from patients' charts or the institution's computerized medical records. The demographic data included the patient's age, sex, race, duration of dialysis prior to hospitalization, type of dialysis access, duration of access (i.e. the time interval between the placement of access and the time of hospitalization) and duration of hospitalization. Clinical data included history of diabetes mellitus, hypertension, coronary artery disease, intravenous drug use (IVDU), hepatitis B and hepatitis C serologies, HIV status, serum albumin level, organisms causing IE and echocardiographic findings. The primary outcome of interest was in-hospital death, as reported in hospital death records. Vital status of survivors of the initial hospitalization was ascertained at 1 month and 1 year after discharge by the computerized US death record index and hospital computerized medical records.

Statistical analysis

The frequencies of clinical characteristics of patients and IE episodes are reported as counts and proportions within the full cohort and sub-samples classified by in-hospital mortality. We compared differences in the distributions of

characteristics among IE patients who did and did not survive at the time points of interest by the chi-square test. We modeled adjusted associations of clinical characteristics with survival by multivariable logistic regression. Analyses were performed with SAS for Windows, version 9.1.

Results

For the 16-year period (1990–2006) studied, there were 132 cases with discharge diagnosis of IE and ESRD in the Saint Louis University Hospital database. After application of the modified Duke criteria, 59 long-term HD patients with hospitalization for bacterial endocarditis were identified and 73 were rejected. The patient's clinical and demographic data are shown in Table 1. The mean (± SD) patient age was 57.3 ± 13.8 years, 28 (47%) cases were men and 42 (71.2%) were African American. The mean duration of HD prior to IE was 52.9 ± 58.0 months. Comorbidities such as hypertension, diabetes and coronary artery disease were common in 55 (93%), 35 (59%) and 16 (27%) patients, respectively. A history of IVDU was present in 4 (7%) patients, and underlying hepatitis C existed in 11 (27%) patients. None of our patients had human immunodeficiency syndrome. Three (5%) patients were taking immunosuppressive medications.

The principal mode of dialysis access at the time of each episode of IE was as follows: 28 (47.5%) catheters,

Table 2. Multivariable model of correlates of in-hospital mortality including dialysis access, age, gender and diabetes status

Characteristic	Adjusted odds ratio (95% CI)	P-value
AVG versus other access modality	3.57 (1.04–12.27)	0.04
Age (per decade)	1.62 (0.95–2.75)	0.08
Male versus female gender	2.02 (0.54–7.50)	0.29
Diabetes versus no diabetes	0.70 (0.19–2.52)	0.58

26 (44.1%) synthetic arteriovenous grafts (AVGs), 3 (5.1%) AVFs and 2 (3.4%) LifeSites (Vasca, Inc., Tewksbury, MA, USA). Among the catheter patients, 26 (92.9%) had cuffed, tunneled catheters and 2 (7.1%) had un-cuffed catheters. Four patients with AVGs and two patients with AVFs had catheters as a secondary mode of dialysis access. In comparison, the prevalence of different types of dialysis accesses in Saint Louis area chronic dialysis units, in the past 5 years, has been in the following ranges: AVF, 20–28%; AVG, 41–49%; catheters, 23–38%, with a trend toward decreasing the prevalence of catheters and increasing AVFs.

Staphylococcus aureus was the causative organism in 27 (45%) patients [MRSA in 15 (25%) patients and MSSA in 12 (20%) patients]. The other cultured organisms are listed in Table 1.

All 59 patients underwent echocardiographic evaluation. Fifty (85%) patients were examined by means of both transthoracic echocardiography (TTE) and transoesophageal echocardiography (TEE). Seven (12%) patients had only TEE, and two (3%) had only TTE. Fifty-four (91%) patients fulfilled both major criteria. Four (7%) patients had negative blood cultures but fulfilled Duke criteria by having echocardiographic findings consistent with vegetations and three positive minor criteria. The remaining one (2%) patient with a negative echocardiogram had positive blood cultures and fulfilled three minor criteria. No case of IE was defined by five minor criteria. The mitral valve was the most commonly affected valve in 37 (63%) patients. The aortic valve was affected in 10 (17%) patients, and multiple valves were involved in 8 (13%) patients, Table 1.

Septic emboli related to IE were noted in 17 (29%) patients and 7 of those patients died during hospitalization. The sites of septic embolism were as follows: brain ($n = 9$), musculoskeletal ($n = 3$), lung ($n = 2$), multiple sites ($n = 2$) and spleen ($n = 1$). Seven (12%) patients underwent valve replacement or repair following an episode of IE.

Patient mortality was 28.8% ($n = 17$) during hospitalization, 37.9% ($n = 22$) at 30 days and 63.1% ($n = 36$) at 1 year. The clinical, microbiological and echocardiographic data were compared between survivors and non-survivors during hospitalization, at 30 days and 1 year after diagnosis. Clinical characteristics such as gender, age, ethnicity, history of diabetes and IVDU did not differ significantly according to survival status during hospitalization (Table 1). The type of cardiac valve affected by IE was not statistically different between groups stratified by mortality. The type of microorganisms did not differ significantly between survivors and non-survivors. Specifically, IE related to MRSA, and VRE did not increase in-hospital, 30-day or 1-year mortality.

AVGs were used more commonly among patients who died during the initial hospitalization as compared to those who survived (64.7 versus 35.7%, $P = 0.04$). This difference persisted on multivariable adjustment for baseline demographic traits, such that the adjusted odds of in-hospital death among patients with AVGs was 3.5-times that of patients with other forms of dialysis access ($P = 0.04$, OR 3.57, 95% CI 1.04–12.27) (Table 2)

There were no significant differences in the distributions of clinical traits in relation to mortality at 30 days or 1 year after discharge.

Discussion

This article outlines our institutional experience with definite IE patients receiving long-term HD. The unique attributes of our study compared with previous publications are that we identified 59 patients with definite IE, which makes it the largest reported series to the best of our knowledge, and that we have identified important in-hospital mortality risk factor in these patients. The current study also details the long-term survival trends over time in this group of patients.

Forty-seven percent of our patients with IE had venous catheters and 44% had AVGs. A similar distribution of the vascular access in IE patients was previously reported by Robinson *et al.* [10], who noted that 11 of 20 patients had central venous dialysis catheter and 8 of 20 patients had AVG. In their series and in our experience, it was extremely unusual for a patient with a native AVF to develop IE. Others have also reported a high prevalence of bacteraemia and IE in chronic dialysis patients receiving therapy with either a central venous catheter or an AVG, as opposed to a native AVF [5,10–17]. Our study was not designed to assess the risk factors for IE in HD patients. However, the disproportionately higher incidence of IE in patients with central venous catheters, as compared to patients with AVFs, suggests that central venous catheters may be an important risk factor for developing IE in HD patients.

Staphylococcus aureus remains the most common pathogen in this group of patients accounting for ~50% of all IE episodes [5,7,8,10,18]. This is consistent with our findings in which 45% of patients with IE had *S. aureus*, including the MRSA. Chang *et al.* [19] reported a higher mortality rate in patients with MRSA, as opposed to patients with MSSA. However, in the present study, the type of organism did not influence mortality, which is consistent with previous series by Nori *et al.* [20]. This observation may be explained by adequate and early use of broad-spectrum antibiotics in our patients.

Consistent with prior observations [5,8,10,18], the mitral and aortic valves are more susceptible to IE than the right-sided valves in the HD population. Sixty-three percent of our patients had mitral valve involvement and 17% had aortic valve involvement. The right-sided IE was relatively infrequent, occurring in 5% of our patient population.

On bivariate analysis, valve replacement surgery did not impact the in-hospital, 30-day and 1-year survival in our patients. A total of 7 (12%) patients underwent valve replacement or repair; 6 survived to the hospital discharge, same patients survived to 1 month post-diagnosis and only two survived to 1-year follow-up. Contrary to our observation, Spies *et al.* [18] reported a high perioperative mortality in dialysis patients who underwent valve replacement surgery for endocarditis. Outcomes in patients managed surgically in our study presumably reflect appropriate selection of this group, but a relatively small sample size could have also contributed to the lack of significant correlates on bivariate analysis.

The mortality rates we report, 28.8% ($n = 17$) during hospitalization, 37.9% ($n = 22$) at 30 days and 63.1% ($n = 36$) at 1 year, are similar to those found in other studies [5,7,8]. Some deaths occurring after hospital discharge may reflect incomplete treatment. Another possibility suggested by USRDS is that the risks of non-infectious causes of morbidity and mortality, such as myocardial infarction and congestive heart failure, are increased long term after hospitalization for infectious causes [21]. The first year after diagnosis of IE is associated with the highest mortality in patients receiving HD. Therefore, this period requires a closer monitoring.

In our study, the in-hospital mortality rate was 3.5-fold higher in those with AVGs ($P = 0.04$) compared to other forms of dialysis access. A similar observation was reported recently by Doulton *et al.* [8], who found that 68% of patients that died in their initial admission were dialyzed through a 'non-removable' dialysis access device (e.g. AVF or AVG). Robinson *et al.* [10] also reached similar conclusions. The more complex management involved when excising an infected AVG, occasional absence of physical findings of infected AVGs and the lower threshold on the part of nephrologists for removing infected HD catheters as compared with removing an infected AVGs, all may have contributed to increased mortality in this group of patients.

Conclusion

IE in patients receiving HD carries a poor prognosis, even in the current treatment era. Although the dual-lumen HD catheters have been previously reported to be the most common source of bacteraemia resulting in IE in dialysis patients, AVGs are commonly implicated and may be associated with a higher mortality. Therefore, patients with AVG-related bacteraemia must be treated aggressively at the first sign of bacteraemia. This includes organism-sensitive antimicrobial therapy and early consideration of graft removal. Additional studies are needed to identify

risk-reduction measures and develop additional treatment strategies for dialysis patients with endocarditis.

Conflict of interest statement. None declared.

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