Infective Endocarditis in Patients With End-stage Renal Disease

Clinical Presentation and Outcome

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Background: Infective endocarditis is a common complication of vascular access in patients undergoing long-term hemodialysis. However, available data are either dated or gathered from small samples. The goal of this study was to investigate the clinical characteristics and outcome of infective endocarditis occurring in patients with end-stage renal disease.

Methods: Patients were identified by computerized discharge diagnosis and manual chart review at 3 major hospitals in Honolulu, Hawaii. The search covered an 11-year period, through December 2001. Modified Duke criteria were retrospectively applied. Patients fulfilling criteria for definite endocarditis were included in this study.

Results: Forty patients were identified. Average age was 59.4 years, and average duration of hemodialysis before endocarditis was 3.3 years; arteriovenous fistulas were the most commonly used access sites. Predominant organism was *Staphylococcus aureus* in 20 (50%) of the 40 cases. The mitral valve was affected in 29 cases (73%); aortic and mitral valve endocarditis was seen in 8 cases (20%). Overall in-hospital mortality was 52% (21/40). Patients with an unfavorable outcome more often had fever on admission, fewer negative blood cultures, and bivalvular infective endocarditis, and more often underwent valve replacement surgery. The perioperative mortality in patients undergoing valve replacement was 73% (11/15).

Conclusions: Mortality of infective endocarditis in patients with end-stage renal disease remains high and has been essentially unchanged during the past decade. If patients require valve replacement surgery, mortality is even higher. A randomized, controlled trial is needed to clarify whether the increased mortality is due solely to more severe disease in patients requiring valve replacement surgery.

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Patients with end-stage renal disease (ESRD) undergoing long-term hemodialysis are at increased risk of developing infective endocarditis (IE). This is thought to be secondary to transient bacteremia due to repetitive vascular access, either through permanent arteriovenous fistulas, artificial grafts, or indwelling, tunneled catheters. Two conditions that contribute to this risk are underlying valvular heart disease and the immunocompromised state resulting from uremia. The incidence of bacteremia is dependent on the type of vascular access and ranges from 1.6 to 7.7 per 1000 catheter-days in indwelling catheters, to 0.2 to 0.5 per 1000 catheter-days in native arteriovenous fistulas. Consequently, the incidence of IE has been described as 2% to 5% in patients regularly undergoing hemodialysis. Mortality in patients without renal disease is known to be high, relative to the causative organism. For example, IE caused by *Staphylococcus aureus* has a mortality of 25% to 47%. In patients undergoing hemodialysis, the outcome may be even worse, with reported mortality rates of 47% and 65% after 1 year.

With the number of patients undergoing long-term hemodialysis approaching an estimated 300,000, the morbidity and mortality associated with IE is an important health care management issue. The available data involving incidence and outcomes of IE as well as valvular distribution and causative organisms are either old or based on information gathered from small studies with samples of 17 to 20 patients. Further limitations of these early studies relate to the underrepresented group of patients with native arteriovenous fistulas, who represented only 12% and 5% of all patients with ESRD and concomitant IE reported to date, respectively.

The aim of this study was to overcome the limitations of the earlier studies by gathering a larger sample size, with better representations of vascular access.
fied Duke criteria were applied retrospectively. Major cri-

nal failure requiring hemodialysis, were excluded. The modi-

fied criteria. Nearly three quarters of the episodes involved the

mitral valve (29 patients [72%]); the average temperature on ad-

mission was 38.2°C. New murmurs were documented in

one third (14 patients). Sus-

pected portal of infection was the vascular access site in

nearly one third (14 patients), and embolic phenomena oc-

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blood cultures. Polymicrobial infections were seen in 13% and consisted of 2 patients with positive blood cultures for coagulase-negative Staphylococcus and Enterococcus or Candida glabrata, respectively. In 1 patient, MRSA and Pseudomonas aeruginosa grew from blood cultures, and 1 patient had blood cultures positive for MRSA, Klebsiella pneumoniae, and Enterobacter cloacae.

The 5 patients with IE caused by coagulase-negative Staphylococcus were defined in 4 cases by positive results of echocardiography, performed as TTE on 3 occasions. The remaining patient with coagulase-negative Staphylococcus IE had negative findings on TEE, but also had positive blood cultures for Enterococcus and fulfilled 3 minor criteria.

Vancomycin, gentamicin, and cefazolin were most often used, documented in 75%, 63%, and 28% of the cases, respectively. Vancomycin was administered empirically as a single dose in most of the cases, and was continued in patients who had MRSA-positive blood cultures. The remaining cases involving methicillin-sensitive S aureus were treated with either cefazolin or nafcillin.

**OUTCOME**

In-hospital mortality was 52%. Factors associated with an unfavorable outcome were fever on admission (86% vs 58%; P = .05), high white blood cell count (17.2 ± 7 × 10^3/µL vs 12.1 ± 5.4 × 10^3/µL; P = .02) (Table 3), dual-veal endocarditis (38% vs 5%; P = .01), valve replacement surgery (52% vs 21%; P = .04), and negative blood cultures (0% vs 21%; P = .04). Patients with an unfavorable outcome showed a trend toward longer periods of hemodialysis before the episode of IE (4.51 ± 5.9 years vs 1.89 ± 2.0 years; P = .08). Fifteen patients underwent valve replacement surgery after initial medical treatment. Eleven patients died after the procedure, representing an operative mortality of 73%.

**COMMENT**

To our knowledge, our data represent the largest series describing characteristics and outcomes of IE in patients receiving hemodialysis. We identified 40 cases of definite endocarditis in patients with ESRD admitted to our 3 centers during an 11-year period; available data describing the total number of patients with ESRD in Hawaii in 1991 show 1050 patients. This number has increased to 2012 patients in 2000, and data are not yet available beyond that year. Estimates of incidence are not appropriate with these numbers, as we likely have not identified every case of IE during this period.

Sixty percent of our patients had arteriovenous fistulas as an access site, with only 23% solely having a dual-lumen catheter in place. This distribution of vascular access is much more representative of the population of patients receiving long-term hemodialysis than has been described in earlier studies. Clearly, data from more “typical” patients undergoing hemodialysis are desirable. It has been proposed that bacteremia results from either migration of bacteria from the skin during vessel cannulation, or contamination of the catheter lumen; the latter more closely reflects line sepsis than pure hemodialysis-associated bacteremia, leading to 2 different potential mechanisms for bacteremia. This is an important
distinction, since, depending on the type of access and its mechanism of bacteremia, it might be possible to predict which of the different species of bacteria could be involved and provide guidance for therapy. A recently published, prospective study of bacteremia in patients with dual-lumen hemodialysis catheters showed that coagulase-negative *Staphylococcus* species were isolated in 39.5% of cases, and in 45% blood cultures were positive for gram-negative rods. This is consistent with data from our series in which 3 of the 4 patients with episodes involving gram-negative organisms were associated with temporary catheters. In our series, the 3 most commonly identified isolates were *S. aureus* at 50%, followed by *Enterococcus* at 23% and *Staphylococcus epidermidis* at 12%. This is consistent with data from McCarthy and Steckelberg as well as Robinson et al, who report similar findings.

This study confirms the predominance of *S. aureus* endocarditis in patients undergoing long-term hemodialysis. It has been recognized that in recent years *S. aureus* has been seen more commonly than *Streptococcus* species in the general population presenting with native valve endocarditis. In ESRD, this is due to frequent bacteremia and high virulence of *S. aureus*. The high incidence of IE caused by MRSA is consistent with the antibigrams from the hospitals involved in this study. The number of MRSA isolates continues to increase with time, reaching 50% of all *S. aureus* strains in the year 2002 in the participating hospitals. The high rate of vancomycin use reflects the awareness among community physicians of the significance of the risk of methicillin-resistant strains. When combined, *Enterococcus* species and *S. aureus* account for nearly three quarters of the isolates, making the use of vancomycin prudent.

Infective endocarditis caused by coagulase-negative *Staphylococcus* might be a difficult diagnosis to establish because this organism is frequently a contaminant of blood cultures. However, the 3 cases included in this study meet strict criteria for definite endocarditis and thus are legitimate.

The Duke criteria underwent a modification in 2000, when Li et al redefined the term possible endocarditis. Even though the initial Duke criteria were thought to be highly specific, there was an overrepresentation of cases defined as possible endocarditis, meaning one could neither conclude definite endocarditis nor reject a diagnosis of endocarditis by the criteria. As a result, the modified Duke criteria have a clearer definition of possible endocarditis. However, in the 2 studies by Robinson et al and McCarthy and Steckelberg addressing IE in ESRD, both included patients classified by the unmodified Duke criteria and included patients judged as having definite or possible endocarditis. This at least introduces the risk of including a fair number of patients who do not have IE. Not only did we apply the modified Duke criteria to define our group, we also included only patients judged to have definite endocarditis, probably increasing the yield of this study. However, we recognize that it remains questionable to what extent the Duke criteria are applicable to patients with ESRD. As mentioned by Robinson et al, the Duke criteria require the absence of removable foci. A large number of patients included in this and previous series had either PTFE grafts or some type of venous catheters, making the Duke criteria inaccurate to apply in their strictest form. Consequently, applying the modified Duke criteria to these patients might actually overestimate the incidence or occurrence of IE in patients with ESRD. Nevertheless, these patients are at greater risk of developing IE and their chance of having *S. aureus* endocarditis is higher than in the general population. As shown by Fowler et al in a study of 103 nondialysis patients with *S. aureus* bacteremia, the rate of IE was 25% in all patients and 23% in patients with indwelling catheters. This suggests that, at least in these cases of *S. aureus* bacteremia, the rate of IE was not overestimated in patients with indwelling catheters, which would support the applicability of the Duke criteria to patients receiving hemodialysis, regardless of their vascular access. Ultimately, these considerations become less important in daily practice, since hemodialysis is known to have an increased risk of bacteremic complications, and it might be prudent to overestimate the likelihood of IE rather than undervalue this life-threatening disease.

The mitral valve was the most commonly affected valve. Simultaneous involvement of the aortic and mitral valves was also relatively common, occurring in 20% of the cases. This is likely explained by mitral annular calcification, which has been shown to be associated with an increased susceptibility for IE. Valvular thickening of the aortic and mitral valves is also very common in ESRD and might lead, via alterations of laminar flow, to an increased susceptibility for IE.

In our series, right-sided endocarditis was seen in only 2 cases. This is consistent with most previous published data. To some extent, one would expect an increased frequency of tricuspid valve endocarditis in ESRD, considering the presumed pathogenesis of transient bacteremia due to cannulation of the vascular access, which is analogous to the mechanism involved with injection drug users, who commonly present with right-sided endocarditis. However, as suggested by Frontera and Gradon, there may be multiple additional factors.

Transeosophageal echocardiography was underutilized in our group (40%), compared with utilization rates of 63% and 80%, respectively, in the studies by McCarthy and Steckelberg and Robinson et al. The overall sensitivity for detecting vegetations via TTE has dropped below 60% in recent reports. Moreover, since TTE has a poor yield in detecting perivalvular extension, TEE should be the initial imaging strategy in these patients. This is consistent with the recommendations of the American Heart Association and American College of Cardiology, which state that initial TEE is essential to exclude IE in certain patients at risk, including those with possible *S. aureus* endocarditis, as well as providing greater prognostic information to monitor response to therapy. All the same, most centers have fairly low utilization rates of TEE. The most plausible explanation for the low utilization rate of TEE in our series is reluctance to perform this time-consuming procedure, or unawareness of certain recommendations and guidelines. This was the common scenario identified in quality control reviews, which led to the initiative “Get With the Guidelines” (American Heart Association).

Mortality in patients with ESRD who have IE is high. The in-hospital mortality of 32% in this study is comparable with a previously published 60-day mortality of 47%.
Cofactors identified in patients with an unfavorable outcome were higher temperature on admission, higher white blood cell counts, involvement of 2 valves, presence of negative blood cultures, and valve replacement surgery. Interestingly, with the exception of a trend toward a longer period receiving hemodialysis in the patients who died, no differences were seen in the amount or types of comorbidities, nor was there any difference in the bacterial spectrum. However, the higher rate of blood culture-negative endocarditis in the survival group suggests, presumably, involvement with HACEK organisms (Haemophilus species, Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, and Kingella species) and their associated lower virulence and more favorable outcomes.23 Surprisingly, the survivor group underwent significantly fewer valve replacements, and, comparing patients undergoing valve replacement with patients treated medically, the mortality almost doubled (40% vs 73%). However, the 2 groups were similar in regard to their baseline characteristics, with the exception of having a higher incidence of cerebrovascular disease and less frequent use of arteriovenous fistulas in the surgery group (data not shown). This finding might appear contradictory to findings in a recently published population-based survey, which showed improved mortality in patients undergoing surgery for IE.24 However, patients considered for valve replacement surgery either were not candidates for medical management to begin with or had undergone conservative treatment with antibiotics that failed, suggesting more severe disease in the patients considered for surgery. Nevertheless, these findings at least raise the question of whether accepted indications for valve replacement in the general population are applicable to patients with ESRD. About half of the patients who underwent valve replacement had acute valvar regurgitation with heart failure as indications for surgery, which follows a class I recommendation as outlined in the American Heart Association–American College of Cardiology guidelines.25 Considering the extremely high mortality of this condition if no valve replacement takes place, it seems reasonable to follow this guideline.26 The other half of the patients were sent to surgery because of either “persistent infection” or recurrent emboli, or because vegetations larger than 10 mm were seen during echocardiography. To what extent those indications justify the high risk of valve replacement surgery cannot be answered by our study. Whether this surprisingly high perioperative mortality solely reflects more severe disease in those patients can only be answered by a prospective, randomized, and controlled trial comparing medical vs surgical therapy in patients with IE and ESRD.

In summary, despite improved diagnostic maneuvers, more standardized antibiotic therapy, and more sophisticated valve replacement, the mortality of IE in ESRD remains high. In patients requiring valve replacement surgery, the mortality is even higher. Our study has some limitations. Because of its retrospective nature, we were able to extract only clearly documented data. The locations of the dual-lumen catheters were rarely documented; thus, we were unable to examine the correlation between insertion site of dual-lumen catheters and severity of infections.

A small minority of patients did not fulfill clear diagnostic criteria for vegetations by echocardiography. Nevertheless, these patients fulfilled the modified Duke criteria for definite endocarditis, based on blood culture results as the major criterion and the presence of at least 3 additional minor criteria. Furthermore, by excluding all patients for whom we could not document criteria for definite endocarditis by means of the modified Duke criteria, it is possible that some of the patients meeting the probable endocarditis criteria may have indeed had an episode of IE.

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