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Infective endocarditis: a frequent disease in dialysis patients

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The epidemiological profile of infective endocarditis (IE) has changed dramatically over the last few years [1]. Once a disease affecting young adults with previously well identified valve disease (mostly rheumatic disease), IE is now affecting older patients, a significant proportion of whom have no previously known valve disease and develop IE as the result of health-care associated procedures [2]. Actually, if IE was commonly classified in four categories, namely native valve IE, prosthetic valve IE, IE in i.v. drug users (IVDUs), and nosocomial IE, health-care associated IE should probably be added as a fifth category in the near future because of its increasing incidence. Within this new category, IE in chronic haemodialysis (HD) patients appears to be the most important subgroup [3,4].

Incidence and risk factors

The most convincing demonstration that HD patients are increasingly developing IE was provided recently by Cabell et al. [4] who performed trend analyses in the IE database of the Duke University Medical Center in the 1993–1999 period. Not only did they show that the overall proportion of HD patients in their sample of 329 IE patients was as high as 20%, but also that the proportion of HD patients increased from 6.7 to >20% over the 7 year study period. This was associated with a significant increase of Staphylococcus aureus IE from 10 to 68% (P-value for trend <0.001). Finally,
HD was the best predictor of *S. aureus* as the causative agent of IE. In a recent 1 year cross-sectional survey of IE in France [2], 13 of 390 patients were receiving chronic HD treatment. Based on these figures and on the number of HD patients in France (25 000–30 000), 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, Abbott et al. [3] also demonstrated that HD patients are at increased risk for IE compared with the general population. The incidence of IE in 1996 was 483 per 100 000 person-years in HD patients, while it was 6.5 per 100 000 person-years in the general US population. This difference accounted for an age-adjusted incidence ratio of IE in the HD population of 17.9 (95% CI 6.6–48.9) compared with the general population.

Three recent retrospective studies reporting all cases of IE diagnosed in HD patients from five dialysis centres concurred with the same two findings: (1) *S. aureus* is the predominant causative pathogen, being responsible for 40–80% of the cases; and (2) IE in HD patients has a poor prognosis, as illustrated by in-hospital and 1 year death rates ranging from 25 to 45% and 46 to 75%, respectively [5–7].

Another way to assess the risk of IE in HD patients is to evaluate the outcome of bacteraemia in this population. Marr et al. [8] prospectively followed up 445 HD patients for 18 months. Sixty-two patients developed 65 episodes of *S. aureus* bacteraemia, 15% of which were complicated with IE. Interestingly, this study showed that 53% of the patients with *S. aureus* bacteraemia had a dual-lumen tunnelled, cuffed catheter as a vascular access device. More recently, of 210 prospectively evaluated HD patients who developed *S. aureus* bacteraemia between 1994 and 2001, 36 patients (17.1%) developed an endocarditis [9]. Once again in this series, more than 55% of the patients were dialysed via tunnelled catheters. In another large prospective study of nearly 1000 HD patients, catheters, especially long-term implanted catheters, were found to be the most important risk factor of bacteraemia in HD patients, with a relative risk of 7.6 (95% CI 3.7–15.7) compared with arteriovenous fistula [10].

There are several potential explanations for the increased incidence of IE in HD patients. Ageing of dialysis population may act through the increased frequency of degenerative valve lesions. Likewise, valve calcifications, which are extremely frequent in HD patients, may also play a role [11]. However, the most important risk factor seems to result from an increased use of catheters instead of fistulas as vascular access devices [5,9,10].

**Clinical management**

How should these recent changes in the epidemiology of IE in HD patients impact their clinical management? I will try to address this question, focusing on the management of patients who develop *S. aureus* bacteraemia, which is both the most frequent situation, and that associated with the highest risk of complication, especially IE. The first two questions are: (1) should IE be searched for in every case of *S. aureus* bacteraemia, and (2) if yes, what is the optimal way to do so? In non-HD patients, Fowler et al. [12] showed that IE develops in 25% of patients with *S. aureus* bacteraemia and that transthoracic echocardiography (TTE) is only 33% sensitive for the diagnosis of IE, whereas the sensitivity of transesophageal echocardiography (TEE) is 100%, with a specificity of 99% [12]. They concluded that the use of TEE is essential to establish the diagnosis of IE and to detect associated complications and should therefore be considered as part of the early evaluation of patients with *S. aureus* bacteraemia. They also demonstrated that this strategy is cost-effective in determining the duration of therapy for intravascular catheter-associated *S. aureus* bacteraemia [13]. Some data support the use of the same strategy in HD patients [8,14]. In a small observational study of 32 patients with chronic renal failure, not all on HD treatment, TEE was found to contribute better than TTE, but only in patients with high pre-test risk of IE [15]. In order to select patients with the highest risk of complicated bacteraemia, it seems reasonable to recommend that HD patients who present with a bacteraemic infection should undergo TTE whenever *S. aureus* is the causative pathogen, bacteraemia is relapsing after antibiotic discontinuation, regardless of the causative pathogen; or a dialysis catheter that has not been removed was present at the onset of bacteraemia.

When coming to the treatment of IE in HD patients, I would like first to reinforce the existing guidelines for an adequate, restricted use of vancomycin and glycopeptides [16]. The main objective of these guidelines is to prevent the emergence of vancomycin-resistant Gram-positive cocci, on the other hand, Marr et al. [8] also showed that vancomycin alone may be less effective than when combined with another antistaphylococcal drug. Although vancomycin is easy to use in HD patients, due to its long half-life and low dialysability, one should keep in mind that it exerts only a slow bactericidal activity and is less active than β-lactams on methicillin-susceptible *S. aureus*. In addition, vancomycin-resistant *S. aureus* strains emerged in various clinical settings, including dialysis units. Therefore, vancomycin should be used only for the treatment of methicillin-resistant *S. aureus* infections. The minimum duration of antibiotic treatment of IE should be 28 days, inasmuch as a removable vascular access device has not been removed. Whether a dialysis catheter should be removed in patients with IE is still a controversial issue. In HD patients with IE, Lentino et al. [17] failed to evidence any benefit from vascular access removal, but catheters had been removed in 95% of the patients. Catheter salvage in HD patients presenting with bacteraemia was evaluated prospectively by Marr et al. [18]. Only one-third of the catheters were salvaged successfully and salvage was less likely to succeed in
patients with gram-positive bacteraemia than in patients with gram-negative bacteraemia, although the difference was not statistically significant. The authors concluded that antibiotic therapy without catheter removal is unlikely to eradicate catheter-related bacteraemia, but an attempted salvage may not increase the risk for complications. These results were disputed by Capdevila et al. [19] who claimed that they treated catheter-related bacteraemia without catheter removal with high success rates and no septic complications during extended follow-up. As long as no controlled trial has been performed to assess this issue, the decision to remove a dialysis catheter in HD patients with bacteraemia will still be made on an individual basis. If catheter salvage is attempted, a longer duration of antibiotic treatment is recommended, a high degree of suspicion for IE should be maintained, and repeat echocardiographic examination may be warranted. On the other hand, once IE is diagnosed in a HD patient the maintainance of a catheter should be exceptional and reserved for patients without alternative vascular access sites.

**Prevention**

With regard to prevention, each dialysis centre should have a critical reappraisal of its vascular access policy. Sandroni et al. [20] recently reminded us that originally there were only two indications for long-term catheters: access of last resort, and temporary access while awaiting the maturation of a newly created native fistula or vascular graft. They also listed a number of false ‘good reasons’ for substituting catheters for fistulas and concluded that ‘the possibility that every 55th patient with a tunnelled catheter might succumb to endocarditis should discourage us from expanding the indications for catheters’. However, because catheters are easy to insert, immediately usable and save lives, they will continue to be used. In return, strict adherence to hygiene rules and prevention guidelines [21] is mandatory. Mupirocin nasal ointments, which proved to significantly reduce the incidence of *S. aureus* bacteraemia in HD patients [22], might be used preferentially in patients with dialysis catheters.

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