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Bacteraemia in haemodialysis patients—not always *Staphylococcus aureus*

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Infections have been a major complication in patients with end-stage renal disease (ESRD) ever since maintenance haemodialysis was introduced. However, the problem is not limited to dialysis patients alone. An estimated glomerular filtration rate (eGFR) <45 mL/min 1.73 m^2 leads to strongly enhanced rates of hospitalization for infectious complications [1] and the risk of infection increases linearly with decreasing renal function, at least in patients aged 65 years or older. This is most likely a consequence of impaired immune function occurring with the retention of uraemic toxins. Deficient function has been described for neutrophils, monocytes and T-lymphocytes [2, 3]. In particular, granulocytes have impaired phagocytic activity [4], a finding with major relevance for bacterial infections. In addition, many patients with chronic renal failure have diabetes mellitus or receive immunosuppressive therapy for autoimmune diseases. Quite expectedly, the number of genitourinary infections increases with decreasing renal function. However, pulmonary infections are even more frequent and also bacteraemia contributes measurably [1].

The risk for blood-stream infection (BSI) is enhanced in patients with chronic kidney disease (CKD) not on dialysis. A Canadian study [5] evaluated a clinical laboratory database and found that CKD 4 tripled the risk of bacteraemia compared to individuals with eGFR >60 mL/min 1.73 m^2. While *Escherichia coli* was the predominant pathogen in CKD 3, *Staphylococcus aureus* took over in CKD 4 [5]. These aspects need to be kept in mind when reading the literature on blood stream infections in dialysis patients.

There are numerous publications pointing to high rates of BSI in haemodialysis patients [6–8]. The majority of them show a predominant role of *S. aureus* to the risk of bacteraemia [7]. Among the most important determinants for BSI is the type of dialysis access—whether a catheter or a fistula is in use [6, 8]. Central venous catheters (CVCs) associate with an 8-fold increase in the risk for bacteraemia [6]. This may be an important factor contributing to the enhanced mortality risk that the DOPPS study found for patients being treated by catheter rather than fistula [9]. A recent large analysis confirmed impressively that starting dialysis treatment with a catheter rather than a fistula strongly predicts the risk of bacteraemia [10]. In addition, starting with a catheter also predicts continued use of a catheter as dialysis access at 1 year. More than 13% of all patients had at least one positive blood culture within 1 year of dialysis initiation, the risk being 3-fold higher in catheter compared to fistula patients [10]. Interestingly, the probability of catheter-related bacteraemia seems to be age-related [11]. Surprisingly, the elderly had lower rates of BSI than the younger patients, which might be related to less physical activity in the former.

Still, the problem of BSI may be largely underestimated in every day clinical work. Dialysis doctors see single cases and since BSI remains an infrequent incident they usually do not have a feeling for the incidence in their dialysis programme. Nevertheless, it is alarming that cardiologists already identified haemodialysis as an important predisposing condition for the development of bacterial endocarditis [12]. Again, *S. aureus* is

described as the causing pathogen in between 40 and 80% of cases (reviewed in [13]). Furthermore, the detection of BSI depends on the decision to take blood cultures in a patient. In out-patient dialysis the diagnosis may not always be made since ESRD patients rarely develop fever. Episodes of unspecific infection may be treated by antibiotics without establishing the formal diagnosis of BSI. Even in an ICU setting, Karch *et al.* [14] showed that the rate of documented BSI depends on the frequency of blood cultures on a particular ward. They demonstrated that ICU wards taking <80–90 blood cultures per 1000 patient-days miss relevant numbers of BSI cases. If this occurs in the ICU, how many BSI cases are then missed in out-patient haemodialysis? Of course, these patients will mostly be treated; however, sometimes with delay, potentially with suboptimal antibiotic regime, and they will not be recognized and entered into statistics on BSI in dialysis.

Blood stream infections due to dialysis access contamination can be addressed effectively by hygienic precautions [15–17]. Among them, hand hygiene is the most important single measure. Optimal work flow organization and regular (re-)training can improve compliance of staff with hand hygiene [18] and thus reduce bacteraemia rates. In addition, rather simple interventions such as disinfection of a catheter exit with chlorhexidine and catheter hub disinfection by 70% alcohol can reduce blood stream infection and the need for antibiotic therapy [17]. These measures already achieve significant benefit particularly for patients with central venous catheters. They are complemented by the use of antibacterial catheter lock solutions (meta-analysis in [19]). Thus, part of the problem is obviously preventable.

In this issue, Murray and coworkers [20] present extensive data on Gram-negative bacteraemia in dialysis patients. They used data covering more than 500 000 haemodialysis days and comprehensive microbiological data on blood stream infection occurring during nearly 3 years of observation. Up until now, Gram-negative bacteraemia has been studied less thoroughly than Gram-positive. It is important to pay attention to this problem for several reasons, as beautifully illustrated by the Murray study. First, Gram-negative BSI is not actually rare. Although earlier data from the group [21] showed that Gram-positive infection is still in the lead, the rate of 0.175 events per 1000 HD days is a relevant order of magnitude. According to this incidence, medium sized dialysis centres treating 100 patients will observe 2–3 cases annually. Second, the prognosis of Gram-negative BSI is unfavourable, 3 months mortality accounted for 28.6%. And third, Gram-negative pathogens in blood culture raise suspicion of causes other than catheter contamination. Only 23% of all BSI episodes could be related to the dialysis access and even in patients with CVC nearly 2/3 of the infections were attributed to non-access related causes.

Gram-negative BSI is often caused by soft tissue or foot ulcer infection; urinary and intra-abdominal sources have to be considered as well. This may explain the dubious prognosis. The high comorbidity of dialysis patients and the arteriosclerotic and atherosclerotic vascular alterations allow for complications such as foot ulcer or mesenteric ischaemia that promote the risk of bacteraemia, particularly in the presence of immune incompetence.

Gram-negative BSI deserves particular attention since in recent years the rate of antibiotic resistance has increased. While rates of methicillin resistant *S. aureus* remained stable or start to decrease in many countries at least in Europe [22], multiresistant Gram negatives are on the rise. Although the study of Murray does not yet provide evidence for a relevant resistance problem (only 6/99 bacterial isolates were carriers of extended spectrum beta lactamases and no carbapenem resistance was reported) multiresistant gram negatives already emerge in dialysis patients as well [23]. Recent studies [24] showed high colonization rates of dialysis patients with multiresistant Gram-negative pathogens. Risk factors for such colonization are the widespread use of antibiotics and contact with healthcare institutions and/or hospitalization. Thus, haemodialysis patients are a typical risk group for the acquisition of such pathogens. The increasing prevalence will probably lead to more resistant BSI and influence the choice of empiric antibacterial therapy in the future.

In summary, Gram-negative BSI should receive more attention in dialysis patients. First, the diagnosis should be formally made whenever possible. Therefore, deliberate use of blood cultures in patients with rather unspecific symptoms is advocated. They will provide microbiological information to guide antibacterial therapy. This is the second consequence of alertness to Gram-negative bacteraemia: use antimicrobial drugs as target-oriented as possible. Blood stream infection—even with CVC in use—is not always caused by *S. aureus*. Empiric therapy should start with Gram-positive and Gram-negative coverage and then be narrowed down as soon as the identification of the relevant pathogen and its antimicrobial resistance profile becomes available. And third, further alertness should be promoted by BSI statistics to be maintained by individual dialysis facilities or—preferably—covering multiple single dialysis centres in regional collaboration.

CONFLICT OF INTEREST STATEMENT

The author does not have conflicts of interest regarding this paper. The results presented in this paper have not been published previously in whole or part, except in abstract format.

(See related article by Murray *et al.* Gram-negative bacteraemia in haemodialysis. *Nephrol Dial Transplant* 2015; 30: 1202–1208.)

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