Severe bacterial infections in haemodialysis patients

Infezioni batteriche gravi in pazienti emodializzati

Sebastiano Leone, Fredy Suter
Department of Medicine, Division of Infectious Diseases, Ospedali Riuniti, Bergamo, Italy

INTRODUCTION

Infections are today by far the most common complications affecting patients with chronic kidney disease and particularly those undergoing chronic haemodialysis. These patients are hospitalized with greater frequency than the general population and the number of hospitalizations has been shown to correlate with higher infection rates [1]. As for other types of infections, the most common microorganisms causing dialysis-related infections are becoming more resistant to antimicrobials [2, 3].

The greater risk of infection in this population is caused partially by impaired host immunity through uraemia that interferes with T-cell and B-cell dysfunction, macrophage phagocytosis, and antigen presentation [4]. More recently, convincing evidence has been accumulated about the chronic activation of the immune system in clinically relevant uremic states. As a result, many investigators believe that chronic activation with hyporesponsiveness may be the most accurate description of the immune dysfunction in uraemia [1].

This review will briefly discuss the most common infections in patients undergoing chronic haemodialysis, clinical relevance of antimicrobial resistance in these patients, and their therapeutic options.

Catheter-related blood-stream infections

Patients undergoing haemodialysis require a reliable vascular access to perform dialytic treatments. Approximately 20% of the US patients who undergo haemodialysis use a tunneled central vein catheter for vascular access, either while waiting for placement and maturation of a fistula or graft or because they have run out of options for a permanent vascular access [5]. The mean incidence of catheter-related bloodstream infections (CRBSIs) for non tunnelled catheters has been reported to be 5.0 episodes/1000 catheter-days and 3.5/1000 catheter-days for tunnelled cuffed catheters [6-9]. Among non tunnelled catheters, femoral catheters have the highest infection rates, compared with internal jugular and subclavian catheters [6-9]. CRBSIs may originate from endogenous or exogenous sources. The latter is thought to be the primary mode of infection in patients with surgically implanted tunnelled haemodialysis catheters, whereas the former is considered to be most common among patients with percutaneously placed temporary haemodialysis catheters.

The microorganisms most commonly associated with CRBSIs are Gram-positive cocci, different species of aerobic Gram-negative bacilli, and Candida albicans [10]. In a study on 101 chronic haemodialysis patients with permanent catheters, Saad showed that 45 infections (52.3%) were caused by Gram-positive cocci only, including Staphylococcus aureus, coagulase-negative staphylococci, and Enterococcus spp. Twenty-three infections (26.7%) were caused by Gram-negative rods only, including a wide variety of enteric organisms. Eighteen infections (20.9%) were polymicrobial. Thirty-nine of 86 episodes (45.3%) included at least one Gram-negative organism [9]. Similar findings were reported by Rocklin with 82% of infectious due to Gram-positive and only 7% to Gram-negative bacteria [11]. In contrast, other studies reported a wide variety of Gram-negative organisms isolated from 32% to 45% of CRBSIs [12, 13]. Metastatic complications occur in a large proportion of patients with CRBSI; these include...
infective endocarditis, osteomyelitis, septic arthritis, septic pulmonary embolism, and spinal epidural abscesses [14]. Infective endocarditis in haemodialysis patients is significantly more common and causes greater morbidity and mortality than in the general population. Currently, the incidence of infective endocarditis in haemodialysis patients is estimated to be 308/100000 patient-years, which is more than 50-fold higher than the 1.7-6.2 cases per 100,000 patient-years reported for the general population, and it carries an intolerably high rate of mortality approaching 50% [15-17]. In a retrospective analysis of data in haemodialysis patients, Maraj found 32 (1.4%) infective endocarditis on a total of 2,239 patients undergoing haemodialysis. Permanent and temporary venous dialysis catheters, arterio-venous (AV) grafts, and AV fistulae were used in 19 (59%), 12 (38%), and 1 (3%) patient respectively. The microorganism most commonly isolated was S. aureus and the mitral valve was the main site of infection. One-year mortality was 56.3% [18]. More recently, Rekik observed that S. aureus was the most common pathogen (11 out of 16 cases, 68.7%) [19]. In another study on infective endocarditis in haemodialysis patients, Nori showed that in-hospital mortality was high (37%) and valve replacement was required for 13 episodes (24%). Based on logistic regression analyses, mitral valve disease [P=0.002; OR 15.04; 95% CI 2.70-83.61] and septic embolism (P=0.0099; OR 9.56; 95% CI 1.72-53.21) were significantly associated with in-hospital mortality. Using the Cox proportional hazards model, mitral valve involvement (P=0.0008; HR 4.05; 95% CI 1.78-9.21) and infective endocarditis related to drug-resistant organisms such as methicillin-resistant S. aureus (MRSA) and vancomycin-resistant enterococci (VRE) (P=0.016; HR 2.43; 95% CI 1.18-5.00) were associated with a poorer out-

**Figura 1** - Management of CRBSIs among patients who are undergoing hemodialysis with tunneled catheters according to IDSA guidelines.
come after hospital discharge [20]. According to the Infectious Diseases Society of America (IDSA) guidelines, the management of CRBSI involves making decisions related to:
1) whether the CVC should be removed or retained with antibiotic catheter lock therapy;
2) the type of antimicrobial therapy, based on the type of organism and its resistance pattern;
3) the duration of antimicrobial therapy [21]. The Figure 1 show the management of CRBSIs among patients who are undergoing haemodialysis with tunnelled catheters according to IDSA guidelines.

**Methicillin-resistant Staphylococcus aureus**

MRSA was first described in 1961 and has become a worldwide problem [22]. MRSA is currently the most commonly identified antibiotic-resistant pathogen in US hospitals and contributes significantly to patient morbidity and mortality [23].

A meta-analysis, by Cosgrove, on the impact of methicillin resistance on mortality in *S. aureus* bacteraemia, described 31 studies on a total of 3963 patients with *S. aureus* bacteraemia. The analysis showed a significant increment in mortality associated with MRSA bacteraemia (OR, 1.93; 95% CI, 1.54-2.42; P<0.001) [24]. In another meta-analysis, Whitby observed that bacteraemia caused by MRSA was associated with significantly higher mortality rates than bacteraemia caused by Methicillin-Susceptible *S. aureus* (MSSA) (29% vs. 12%; P<0.001) [25].

Melzer reported that the proportion of patients whose death was attributable to MRSA was significantly higher than that for MSSA (11.8% vs. 5.1%; OR, 2.49; 95% CI, 1.46-4.24; P<0.001) [26]. Persons receiving dialysis are at high risk for infection with invasive MRSA compared with the general population, in whose rates of invasive MRSA have ranged from 0.2 to 0.4 infections per 1000 persons [27].

A recent survey of the Centre for Disease Control and Prevention (CDC) found that the overall incidence of invasive MRSA infection among dialysis patients was 45.2 cases per 1000 persons, indicating a 100-fold higher risk than for the general population. The majority (86%) of the infections were bloodstream infections, identified via positive blood culture. Approximately 85% of dialysis patients had an invasive device or catheter in place at the time of infection, and approximately 90% required hospitalization. The in-hospital mortality rate for MRSA-related hospitalization was 17% [28]. Because colonization with MRSA increases the risk of subsequent infection, eradication of nasal carriage would be beneficial [29]. In a meta-analysis, Tacconelli showed that the use of mupirocin reduced the rate of *S. aureus* infections by 68% (95% CI, 57%-76%) among all patients undergoing dialysis; risk reductions were 80% (95% CI, 65%-89%) among patients undergoing haemodialysis and 63% (95% CI, 50%-73%) among patients undergoing peritoneal dialysis. When data were stratified by type of infection, *S. aureus* bacteraemia was found to be reduced by 78% among patients undergoing haemodialysis, and peritonitis and exit-site infections were found to be reduced by 66% and 62%, respectively, in patients undergoing peritoneal dialysis [30].

**Vancomycin-resistant enterococci**

VRE have emerged as an important nosocomial pathogens. VRE were first described in 1987 in Europe, and within 10 years VRE were among the most feared pathogens in US hospitals. Studies dealing with the emergence of VRE in the United States revealed that most patients with VRE were in ICUs [31]. The clinical impact of vancomycin resistance is a controversial issue. In a study comparing the prognosis of patients with VRE vs. vancomycin susceptible enterococci (VSE) bacteraemia, clinical failure was higher for patients with VRE bacteraemia (60% vs. 40%, P<0.001) [32], but some studies failed to demonstrate a statistically significant association between vancomycin resistance and mortality [33]. DiazGranados performed a systematic literature review with a meta-analysis to analyse the impact of vancomycin resistance on mortality in VRE bacteremias. The authors described nine studies including a total of 1612 enterococcal bloodstream infections episodes. Analysis of the data showed that VRE patients were more likely to die than those with VSE bacteraemia (OR, 2.52; 95% CI, 1.9-3.4) [34].

In addition, colonised individuals could be at risk of developing severe infections. The National Surveillance of Dialysis-Associated Diseases, performed by the CDC, documented an increase in the percentage of dialysis centres reporting one or more patient harbouring VRE from 12% in 1995 to 30 in 2002 [35]. In a prospective study, D’Agata showed that 19% of patients who stayed in hospital ≥4 days acquired VRE and that a non-ambulatory status
was significantly associated with colonization at admission (OR, 9.7; 95% CI, 1.8-53; P=0.01), and vancomycin exposure was significantly associated with VRE acquisition (RR, 1.8; 95% CI, 1.1-2.9; P=0.02) [36]. Another study found a very similar incidence of VRE colonization (17.8%) in an outpatient population of haemodialysis and peritoneal dialysis patients. In this study, none of the patients who had not received vancomycin became colonized with VRE, while 26% of patients who had received vancomycin during the study period became colonized [37].

**Extended-spectrum β-lactamases in Enterobacteriaceae**

The first reports of ESβLs in Gram-negative bacilli came from Europe and were followed quickly by reports in the US. This type of antimicrobial resistance is now recognised worldwide. The influence of ESβLs production on clinical outcome is controversial. Several studies found no significant association between ESβLs production and treatment failure or crude mortality [38].

In contrast, Lautenbach, in a case-control study, observed that ESβLs-producing *Escherichia coli* or *Klebsiella pneumoniae* infections were associated with a significantly longer duration of hospital stay and greater hospital costs (P<0.01 and P<0.001, respectively). Mortality attributable to infection was greater in cases than in controls (15.2% vs. 9.1%; OR, 1.91; 95% CI, 0.49-7.42; P=0.35) (39). More recently, Schwaber and Carmeli performed a meta-analysis to examine the impact of ESβLs production on mortality and delay in effective therapy in *Enterobacteriaceae* bacteraemia. Crude RRs demonstrated a significantly increased risk of mortality in ESβLs-associated bacteraemia (pooled RR 1.85, 95% CI 1.39-2.47, P<0.001) and increased incidence of delay in effective therapy (pooled RR 5.56, 95% CI 2.94-10.51, P<0.001) [40]. There are few reports on ESβLs-producing *Enterobacteriaceae* in haemodialysis patients. However, ESβLs-producing *Enterobacteriaceae* peritonitis in peritoneal dialysis patients are associated with a higher risk of failure. In a retrospective study, Yip reviewed 88 episodes of *E. coli* peritonitis over a 10-year study period. Eleven of the 88 cases were caused by ESβLs-producing *E. coli*. Recent use of cephalosporins and gastric acid inhibitors were associated with the development of ESβLs-producing *E. coli* peritonitis. Compared with non-ESβLs-producing *E. coli* peritonitis, more cases in the ESβLs-producing *E. coli* group failed treatment (45.5% vs. 13.0%, P=0.02) and died of sepsis (27.3% vs. 3.9%, P=0.02). Peritoneal failure rate was higher in the ESβLs-producing *E. coli* group, although the difference was not statistically significant (18.2% vs. 3.9%, P=0.12) [41].

**The problem of glycopeptides**

Vancomycin has been reported to be the treatment of choice for staphylococcal septicaemia in haemodialysis patients. However, there is great controversy over the current utility of the backbone antimicrobials for treatment of MRSA infections, i.e., glycopeptides [42]. The poor pharmacokinetic/pharmacodynamic parameters of glycopeptides, with poor tissue distribution, slow cidal activity and high protein binding predict poor patient outcome even without the advent of resistant strains. These facts may explain the higher mortality of MRSA infections and the poorer outcome even of MSSA infections when treated with vancomycin.

Moreover, there is a growing body of evidence indicating that the glycopeptide MIC has a real impact on patient outcomes [43]. In a small study, Sakoulas found a statistically significant relationship between vancomycin treatment success and lower vancomycin MICs (≤0.5 μg/mL vs. 1.0 to 2.0 μg/mL; P=0.02) and the degree of killing (reduction in log₁₀ CFU/mL) by vancomycin over a 72 h incubation period *in vitro* (P=0.03). On bacteraemia due to MRSA isolates with vancomycin MIC ≤0.5 μg/mL, vancomycin was successful in 55.6% of cases whereas it was effective only in 9.5% of cases in which vancomycin MICs were 1 to 2 μg/mL [44]. In another study comparing infections caused by MRSA with a vancomycin MIC of ≥2 μg/mL with infections due to MRSA with a MIC of <2 μg/mL, the response rate was significantly lower (62% vs. 85%; P=0.02) and infection-related mortality was higher (24% vs. 10%) in the higher MIC group.

In addition, a high MIC for vancomycin was an independent predictor of poor response in multivariate analysis of these MRSA infections [45]. More recently, Soriano showed a significantly higher mortality for this disease when vancomycin was used empirically and the vancomycin MIC was 2 μg/mL [46]. In patient with bacteraemia, Lodise showed that vancomycin MICs of >1.5 μg/mL had a 2.4-fold increase in failure rates compared to MICs of
In a Poisson regression analysis, a vancomycin MIC of >1.5 µg/mL was independently associated with failure (ARR, 2.6; 95% CI, 1.3 to 5.4; P=0.01) [47]. Therefore, clinical MRSA strains with high vancomycin MIC values require aggressive empirical therapy to achieve trough concentrations ≥15 mg/L [48]. The Consensus of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists suggested that trough serum vancomycin concentrations in that range should achieve an AUC/MIC of ≥400 in most patients if the MIC is ≤1 mg/L. In order to achieve rapid attainment of this target concentration for seriously ill patients, a loading dose of 25-30 mg/kg can be considered. However, a targeted AUC/MIC of ≥400 is not achievable with conventional dosing methods if the vancomycin MIC is ≥2 µg/mL [49].

New therapeutic options

New agents with activity against multidrug-resistant (MDR) bacteria have been developed recently. Linezolid is the first member of a structurally unique class of antibiotics, the oxazolidinones. Linezolid inhibits formation of the 70S initiation complex by binding to the 50S ribosomal subunit near to the interface with the 30S subunit. It has a bacteriostatic or bactericidal effect depending on the organism and the concentration. Linezolid is active against most Gram-positive bacteria, including MDR bacteria, some Gram-negative species, Nocardia species, and mycobacteria species. Linezolid was approved for the treatment of uncomplicated and complicated skin and soft-tissue infections (cSSTIs), community-acquired and nosocomial pneumonia, and vancomycin-resistant E. faecium infections, including cases with concurrent bacteraemia.

Daptomycin, a new lipopeptide antibiotic, is highly bactericidal against the majority of Gram-positive human pathogens, including MRSA and VRE [50-52]. Daptomycin also remains bactericidal (99.9% kill within 24 h) against stationary phase cultures of both MSSA and MRSA. Its mechanism of action involves insertion into and disruption of the Gram-positive plasma membrane without entering the cytoplasm of the cell. The proposed mechanism involves a calcium-dependent binding of the lipophilic tail of daptomycin to the bacterial cell membrane. This results in potassium efflux, membrane depolarisation, cessation of macromolecular synthesis and cell death. Daptomycin has been approved for the treatment of bacteremia and right-sided endocarditis due to S. aureus (including MRSA) and cSSTIs [50-52]. Tigecycline is the first in a new class of antibiotics, the glycyclines. It is the 9-t-butylglycylamido derivative of minocycline. This addition in the 9-position enables the drug to overcome the two major mechanisms of tetracycline resistance: tetracycline-specific efflux pump acquisition and ribosomal protection. Tigecycline acts at the ribosomal level to inhibit protein synthesis. It is primarily bacteriostatic and is active against many Gram-negative bacilli and Gram-positive cocci, including MRSA, VRE, and ESβLs-producing E. coli and K. pneumoniae. It is active also against most anaerobic bacteria, as well as most atypical microorganisms. Tigecycline has been approved for use in patients with complicated intra-abdominal infections, and cSSTIs [50-52].

Finally, investigations of other drugs are at an advanced stage of development, including new glycopeptides (e.g. dalbavancin, oritavancin, and telavancin), new anti-MRSA β-lactams (e.g. ceftobiprole and ceftaroline), and new diaminopyrimidines (e.g. iclaprim) [53].

Key words: chronic kidney disease, haemodialysis, infections, MRSA, VRE, ESβLs.

Infections are today by far the most common complication affecting patients with chronic kidney disease and particularly those undergoing chronic haemodialysis. Numerous antimicrobial-resistant pathogens have emerged among patients with chronic kidney disease. These patients are hospitalized with greater frequency than the general population and the number of hospitalizations has been shown to correlate with higher infection rates. This review will briefly discuss the most common infections in patients undergoing chronic haemodialysis, the clinical relevance of antimicrobial resistance in these patients, and their therapeutic options.
REFERENCES


