New recommendations in the treatment of Gram-positive bacteraemia in dialysis patients

Claudio Ponticelli

Istituto Auxologico Italiano, Milan, Italy

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Introduction

There is a progressive increase in community and nosocomial infections caused by Gram-positive pathogens, which often result in bacteraemia resistant to antibiotics. Many Gram-positive bacteria, including coagulase-negative staphylococci, Staphylococcus aureus and enterococcus species, may colonize the skin, mucous membranes (particularly anterior nares) and lower bowel of most normal subjects. In general, these bacteria do not incur consequences to the host, as the intact cornified squamous epithelium can prevent their access to subcutaneous tissues and blood. Only when the skin or mucous membranes are disrupted, may staphylococci give rise to localized superficial abscesses. Cutaneous infections are often self-limited, because normal subjects can organize a primary defence based on neutrophils and opsonophagogytosis. Nevertheless, if bacteria invade the lymphatics and the blood, they can cause a number of life-threatening complications such as septic shock, endocarditis, pneumonia, osteomyelitis, etc. The leading pathogens are coagulase-negative staphylococci and S. aureus, followed by enterococcus species [1]. The coagulase-negative staphylococci such as Staphylococcus epidermidis have been considered as avirulent commensals in the past. However, in the last 30 years, they have been recognized to be one of the most frequent pathogens responsible for nosocomial infection, with a high rate of mortality. The development of bacteraemia is largely influenced by factors such as (i) the use of catheters that can disrupt the cutaneous barrier to Gram-positive pathogens; (ii) a heavy colonization at mucocutaneous sites, that is favoured by wounds, traumas, ulcers, etc; (iii) the virulence of the pathogen including its ability to produce enzymes and toxins, its capacity to persist intracellularly in phagocytes and its resistance to antibiotics and (iv) the inadequate immunological and inflammatory response of the host.

Gram-positive infection in dialysis patients

Dialysis patients are at increased risk of bacteraemia caused by Gram-positive pathogens. The risk of infection is similar in pediatric and adult patients. A US study reported a cumulative incidence of infection-related hospitalizations of 39.9% for children on haemodialysis versus 52.6% for adults and of 51.2% versus 51.8%, respectively for patients on peritoneal dialysis [3]. Some factors may predispose dialysis patients to infection. It is known that the immunological system is deficient in patients with uraemia, as a consequence of the accumulation of uraemic toxins, neutrophil dysfunction and hyperparathyroidism [4]. Chronic nasal carriers of S. epidermidis or other staphylococcal strains are at high risk of developing cutaneous abscesses and bacteraemia [5]. Uraemic patients frequently suffer from pruritus [6] and scratching may cause lesions that can alter the skin barrier. Contamination of dialysis or equipment may also predispose to infection [4]. However, the most important cause of bacteraemia is represented by vascular access for haemodialysis patients and by peritoneal catheter for patients on peritoneal dialysis. In haemodialysis patients with arteriovenous fistula, infection is relatively rare but it may be particularly severe as the bacteria have direct access to the blood. Conversely, infection is frequent in patients with central vein catheters or cannulae [7] that are largely used in patients with acute renal failure and in those with thrombosis or exhaustion of arteriovenous fistula or vascular graft [8–10]. In a study, 75% of episodes of S. aureus bacteraemia occurred in haemodialysis patients using a catheter versus 25% for patients using an arteriovenous graft or fistula [11]. In another study, more than 50% of patients using intravenous catheter developed an S. aureus bacteraemia [12]. The Center for Diseases Control and Prevention reported an incidence of invasive methicillin-resistant S. aureus (MRSA) infections of 45.2 cases per 1000 population in dialysis patients, versus 0.2–0.4 infections per 1000 in the general population. [13]. In a Swedish prospective study of all
cases of *S. aureus* infection, the most common predisposing factors were represented by haemodialysis with a relative risk (RR) of 291, and peritoneal dialysis with an RR of 204 [14]. A multicenter prospective study reported an incidence of bacteraemia of 0.93 per 100 patient-months. Four risk factors were identified: (i) catheter versus fistula as a vascular access (RR 7.6); (ii) history of bacteraemia (RR 7.3); (iii) immunosuppressive therapy (RR 3.0) and (iv) corpuscular haemoglobin (per 1 g/dl-increment RR 0.7). Long-term implanted catheters were the leading risk factor for bacteraemia [15].

The diagnosis of Gram-positive bacteraemia should be suspected in the presence of fever >38°C, chills, hypotension, tachycardia and/or hyperventilation. Increased procalcitonin levels, abnormal glucose and lactate levels and increased C reactive protein levels may confirm the diagnosis of bacteraemia. A definitive diagnosis is reached when culture from a vascular catheter and/or from a peripheral vein shows the presence of a Gram-positive pathogen. It should be remembered that in rare cases, the source of bacteraemia is not represented by catheter or fistulas but by pneumonia or urinary tract infection (Figure 1).

### Prevention of infection

To prevent infection, including MRSA, the recommended procedures are hand washing, using full-barrier precautions during the insertion of catheters and cleaning the skin with a disinfectant agent. For intravascular catheters, the femoral site should be avoided if possible. Specific prevention in dialysis patients requires meticulous exit-site care, both for vascular access and peritoneal catheter. Proper catheter placement, avoiding trauma to the exit-site and daily cleaning of the exit-site with a dedicated antimicrobial soap is essential for the longevity of the peritoneal dialysis catheter. Continuous monitoring of infection of the catheter exit site and review of every episode of infection to determine the root cause of the event should be routine in peritoneal dialysis programs [16]. Antibiotic cream and disinfectant agents including povidone-iodine, chlorhexidine and electrolytic chloroxidizing solutions are useful to keep the resident micro-organisms inhibited [17]. The use of 5-day courses of oral rifampin or topical mupirocin [18,19] has been proven to reduce the risk of staphylococcal infection in dialysis patients. Local application of mupirocin on exit-site vascular accesses or peritoneal catheters can also reduce the risk of *S. aureus* infections [19]. A retrospective study showed that there was a significant lower rate of catheter-associated bacteraemia in haemodialysis patients treated with aspirin than in those not treated with aspirin, while there was no difference with other bacteria [20]. A prospective randomized trial assessed the efficacy of antibiotic-lock therapy using vancomycin and gentamycin in preventing bacteraemia in haemodialysis patients. The incidence of tunnelled central catheter infection was significantly lower in the 33 patients assigned to antibiotic-lock therapy than in the 30 controls [21]. However, it is also possible that preventative antibiotic treatment may favour resistance.

The prognosis of *S. aureus* and other Gram-positive bacteraemias in dialysis patients is severe. Mortality ranges from 8 to 30% [11,22]. Infective endocarditis is a serious complication. The most frequently infected valve is mitral, followed by aortic and tricuspid valves. In a study on dialysis patients with infective endocarditis, the overall mortality was 49%; more patients who had valvular heart surgery survived than patients who did not [23]. Metastatic infection, discitis, osteomyelitis and myocardial abscesses are less frequent but serious complications. The risk of recurrent bacteraemia is frequent, particularly when catheters with abnormal exit sites are not removed [24,25].

### Antimicrobial treatment

Antibiotic treatment of Gram-positive bacteraemia is a big challenge for the clinician today, because an increasing number of strains are becoming antibiotic-resistant. Before the advent of antibiotics, more than 80% of patients with bacteraemia from staphylococci died. The discovery of penicillin cured most cases of bacteraemia caused by staphylococci. Soon, however, it appeared that *S. aureus* as well as coagulase-negative staphylococci could produce penicillinase able to inactivate the effects of penicillins. The availability of methicillin raised new hopes for the control of *S. aureus* infections. However, in non-dialysis patients, a mortality rate of 16% was recorded, even when bacteraemias were sustained by methicillin-sensitive *S. aureus* (MSSA) [26]. On the other hand, a few months after the introduction of this antibiotic, cases of methicillin-resistant strains were reported [27]. Within 5 years, the prevalence of MRSA was 35% and further increased in the following years. In the USA, it has recently been estimated that 95% of staphylococci strains are resistant to penicillin and more than 50% are methicillin-resistant [28,29]. Methicillin resistance is mainly related to the acquisition of novel DNA, which results in the production of a new penicillin-binding protein with low affinity for β-lactams, including methicillin [30]. Vancomycin, a glycopeptide antibiotic, has thus become the antibiotic of choice for the treatment of MRSA. Also largely used is teicoplanin, another glycopeptide with anti-staphylococcus activity similar to that of vancomycin, but with a longer half-life. These agents may cause side effects. Vancomycin and to a lesser extent teicoplanin can induce nephrotoxicity, which is of little importance for patients on chronic dialysis, but which can hamper recovery in patients with acute renal failure. Both agents may cause ototoxicity that can get enhanced when an aminoglycoside antibiotic is added. Measuring blood levels may be useful for assessing the efficacy and avoiding too high area-under-the-
curve levels, but even with blood monitoring, ototoxicity remains a problem [31]. Less frequent side effects are hepatotoxicity, neutropenia and anaphylactic reactions. Unfortunately, the large use of these agents has led to the development of strains of staphylococci and enterococci resistant or only partially sensitive to vancomycin and teicoplanin [32–34]. The mechanisms of resistance remain far from clear. The remarkable ability of these bacteria to acquire useful genes from various organisms may explain why some strains are capable of infecting humans of diverse genetic backgrounds, eliciting severe immune reactions [35]. It is possible that resistant strains may develop a thickened cell wall and/or an increase in glutamine-containing precursors. *Staphylococcus aureus* also proved to be able to develop resistance to other Gram-positive pathogens, such as enterococci, has become a threat to public health [39] and particularly to patients at high risk of staphylococcal bacteraemia, as are dialysis patients. There is therefore an urgent need for a new class of antibiotics with some fundamental characteristics that include bactericidal activity, low potential for the development of resistance, low potential for adverse events and no significant drug interaction. Three new antibiotics might meet these requirements, namely linezolid, daptomycin and tigecycline.

Linezolid is a synthetic antibacterial agent of the oxazolidinone class, which is particularly active on aerobic gram-positive bacteria. Linezolid inhibits bacterial protein synthesis by binding to a site on the bacterial 23 S ribosomal RNA of the 50 S subunit and prevents the formation of a functional 70 S initiation complex, which is an essential component of the bacterial translation process [40]. Linezolid is bacteriostatic against enterococci and staphylococci. Bone marrow suppression may occur with prolonged administration. Anaemia and thrombocytopenia are particularly frequent in patients with end-stage renal failure [41, 42]. Other risk factors for these complications are the pre-treatment severity score of infection and central-catheter related infections [42]. Attention should be paid to peripheral and optic neuropathy, which can be irreversible [43]. Rare cases of lactic acidosis have also been reported [44]. Angioedema and bullous skin disorders have also been reported. As an inhibitor of monoamine oxidase, linezolid may interact with adrenergic agents and cause hypertension. The elimination half-life of linezolid is 5–7 h, and twice-daily administration of 400–600 mg provides steady-state concentrations in the therapeutic range. Linezolid is mainly cleared by non-renal clearance of two inactive metabolites, an aminoethoxyacetic acid metabolite (metabolite A) and a hydroxylethyl glycine metabolite (metabolite B), and renal clearance of the parent compound. Approximately 50% of an administered dose appears in the urine as the two major metabolites, and approximately 35% appears as parent drug. Plasma linezolid concentrations in patients with mild to severe renal impairment are similar to those achieved in healthy volunteers. However, in patients with severe renal impairment, the exposure to the two primary metabolites was 7- to 8-fold higher than in patients with normal renal function. Therefore, linezolid should be used with caution in patients with severe renal insufficiency. [45] Both linezolid and the two metabolites are eliminated by haemodialysis [46]. Approximately 30% of a dose was eliminated in a 3-h dialysis session, beginning 3 h after the dose of linezolid was administered [47]; linezolid should therefore be given after haemodialysis. The clearance of linezolid with continuous venovenous haemodiafiltration is marginal and does not require supplemental dosing [48]. No information is available on the effect of peritoneal dialysis on the pharmacokinetics of linezolid. Cases of resistance to linezolid have been reported [49]. Resistance is probably determined by the co-expression of two genes cfr and ermB. A cfr methyltransferase, modifies adenosine in the large ribosomal subunit. When cfr is linked to ermB, a gene responsible for dimethylation of rRNA, resistance to all the antibiotics that target the large ribosomal subunit can develop [50].

Tigecycline is an intravenous antibiotic with a broad spectrum of antimicrobial activity, including activity against MRSA. Tigecycline is the first glycylcycline antibiotic to be approved by health authorities. Glycylcyclines are tetracycline antibiotics containing a glycylamido moiety attached to the 9-position of a tetracycline ring. Tigecycline is an analogue of minocycline, but the 9-glycylamido moiety extends its antibacterial activity. Tigecycline binds to the 30 S subunit of bacterial ribosomes and inhibits protein synthesis by preventing the incorporation of amino acid residues into elongating peptide chains [51]. *In vitro*, tigecycline exhibits bacteriostatic activity against a wide range of Gram-positive microorganisms, such as *Enterococcus faecalis* (vancomycin-susceptible isolates only), *S. aureus* (methycillin-susceptible and methicillin-resistant isolates). No cross-resistance has been reported between tigecycline and other antibiotics. In addition, tigecycline is not affected by resistance mechanisms, such as β-lactamases, target site modifications, macrolide efflux pumps or enzyme target changes [52]. Tigecycline is administered by intravenous (i.v.) infusion every 12 h, over 30–60 min. Clinical trials have shown that tigecycline (50 mg i.v. q12 h) in adults is safe and generally well tolerated for up to 11.5 days. Drug-related adverse events, which are typically mild to moderate in intensity and of limited duration, mainly include nausea and vomiting, that occur 1–2 days after administration. When co-administered with warfarin, warfarin clearance is diminished. Although tigecycline does not significantly alter warfarin’s effect on prothrombin time or international ratio [53], appropriate monitoring of anticoagulation tests is recommended during treatment. Plasma protein binding ranges from approximately 71–89% at concentrations used in clinical studies. Tigecycline is extensively distributed beyond the plasma volume and into the tissues. Almost 60% of the tigecycline dose is eliminated by biliary/fecal excretion, and 33% is excreted in urine. Approximately 22% of the total dose is excreted as unchanged tigecycline in urine [54, 55]. Overall, the primary route of elimination for tigecycline is biliary excretion of unchanged tigecycline and its metabolites. Glucuronidation and renal excretion are limited.
of unchanged tigecycline are secondary routes. The pharmacokinetic profile of tigecycline does not appear to be significantly altered in renal impairment, and tigecycline is not removed by haemodialysis. Thus, no dosage adjustment is necessary in patients with renal impairment or in patients undergoing haemodialysis [56]. The pharmacokinetics of tigecycline in patients younger than 18 years has not been established.

Daptomycin is a novel cyclic amino acid compound classified as a lipopeptide that derives from the fermentation of a soil organism, *Streptomyces roseosporus*. The lipophytic daptomycin tail enters the bacterial cell membrane and binds to the cytoplasmic membrane in a calcium-dependent manner. Daptomycin oligomerizes and disrupts the membrane causing potassium ion efflux and a rapid membrane depolarization. As a consequence there is an arrest of DNA, RNA and protein synthesis with rapid cell death [57]. The bactericidal effect of daptomycin is rapid. In *in vitro* studies showed that more than 99.9% of methicillin-resistant and methicillin-susceptible *S. aureus* died in less than 1 h [58,59]. Pharmacodynamic studies showed that the most effective dose coupled with minimal toxicity was a once-a-day i.v. administration at a dose of 4 mg/kg per day [60]. Acquisition of resistance to daptomycin occurs rarely in some strains of staphylococci, possibly as a result of the loss of a membrane protein ‘chaperone’ with which daptomycin interacts [61]. At present, no cross-resistance with other antibiotics has been observed. Clinical trials have shown daptomycin to be effective and well tolerated for the treatment of infection caused by staphylococci and other Gram-positive pathogens including enterococci, with equivalent clinical success rates and a similar safety profile to those of comparative agents [62,63]. Data from these studies suggest a trend towards shorter duration of therapy and faster resolution of symptoms with daptomycin [64]. Adverse events associated with glycopeptides, such as nephrotoxicity, otoxicity and hypersensitivity were uncommon with daptomycin. Constipation, diarrhoea and headache may occur. Skeletal muscle toxicity may develop. An increase of serum creatine-phosphokinase levels in 2.8% of patients has been reported in phase III trials [65]. Anecdotal cases of rhabdomyolysis have also been reported [66,67]. The risk of myopathy is closely related to the dosing interval rather than the dosage. Once-daily administration can minimize the potential for daptomycin-related skeletal-muscle effects [60]. Daptomycin plasma clearance is influenced by renal function. Among dialysis subjects, plasma clearance was approximately one-third that of healthy subjects [67]. Thus, it is recommended that the dose of 4 mg/kg be administered every 48 h in patients with a creatinine clearance <30 ml/min, including patients on haemodialysis or peritoneal dialysis. In a study, neither cefazolin nor vancomycin produced a bactericidal or a bacteriostatic effect versus MRSA or MSSA, in peritoneal dialysis fluid, while all concentrations of daptomycin were bactericidal against all organisms in peritoneal dialysis fluid and did not exhibit concentration-dependent activity in dialysis fluid. This agent appears therefore indicated for use in peritoneal dialysis-associated peritonitis, producing bacterial kill to a greater extent and at a higher rate than cefazolin or vancomycin [68]. During continuous haemofiltration, the extent of daptomycin’s trans-membrane clearance is dependent on haemodialfiltrate type, dialysate and ultrafiltration rates. Continuous haemofiltration with high ultrafiltrate or dialysate rates may result in substantial daptomycin clearances [69]. In an *in vitro* study, the efficacy of these new antibiotics was compared with that of vancomycin, minocycline and rifampin against MRSA. Daptomycin was the fastest in eradicating MRSA by biofilm, followed by minocycline and tigecycline. Rifampin given alone was the least effective, but when given in combination was more effective than each of the antibiotics given alone [70].

In summary, as a result of the high prevalence of resistance, treatment options for Gram-positive bacteremia in dialysis patients are limited, and the problem may be aggravated by the issue of safety. At present, the following steps may be recommended (Figure 2). A broad-spectrum antimicrobial therapy should be given early, within 1 h if the patient presents with a sepsis syndrome. If therapy is unsuccessful and a Gram-positive pathogen is identified, therapy can be narrowed to a specific antibiotic agent. A few cases may respond to semi-synthetic penicillins or cefazolin, but the glycopeptides, vancomycin or teicoplanin, are usually the first therapeutic option. Increasing resistance of Gram-positive pathogens and poor tissue penetration represent potential obstacles to a successful therapy with these agents. It has been suggested that these problems may be overcome by administration of vancomycin in much higher doses, but the efficacy of this approach remains to be determined, and can be loaded by irreversible toxicity in dialysis patients. Daptomycin, linezolid and tigecycline are effective alternatives to glycopeptides. However, to prevent the development of resistance, their use should be limited to cases that have not responded to previous treatments or to life-threatening infections. These agents are usually administered as monotherapy, but in resistant cases combination with rifampin may improve their efficacy. In case of successful treatment, the antibiotic(s) should be continued for at least 3 weeks [7].

**Fig. 2.** Algorithm for antibiotic treatment of Gram-positive bacteremia.

### Conclusions

Dialysis patients are particularly susceptible to Gram-positive bacteremia sustained by coagulase-negative staphylococci, *S. aureus* and enterococci. Vascular and peritoneal accesses are the main doors of entrance for pathogens...
and need a careful handling to prevent infection. Treatment of staphylococcus and enterococcus infection is particularly difficult, as more and more strains show resistance to methicillin, cephalosporins and glycopeptides. Newly approved agents are welcome additions to the increasingly narrow range of effective therapies. It should be remembered however, that the history of antimicrobial therapy has clearly demonstrated that the drugs used to treat infections are also responsible for making them more difficult to treat in future. The only way to keep antimicrobial agents useful is to use them appropriately and judiciously [71].

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