ANNEXES TO CHAPTER 6

Clinical Question XXXII. Should empirical antibiotic treatment to cover gram-positive bacteraemia in haemodialysis patients who are tunnelled central venous catheter carriers initially be started with cefazolin (vancomycin if MRSA level > 15%) or daptomycin, associated with the treatment for gram-negatives, when the catheter is preserved?

No comparative studies of the above strategies for empirical antibiotic treatment of haemodialysis catheter-related bacteraemia were identified. Empirical treatment would imply acting before knowing the microorganisms involved, the choice of the antibiotic depending on the epidemiology of each unit, taking into account the sensitivity and resistance of their usual germs, the patient's risk factors (previous colonisation of the patient by a particular germ and/or his/her immune status) and the severity of the infection.

The recommendations contained in different clinical practice guidelines are discussed here.

The Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC) guidelines (Cisneros-Herreros 2007) state that the incidence of nosocomial bacteraemia is estimated at 6 episodes/1,000 admissions. The predominant bacteria are Gram-positive (65%) and, by microorganisms, coagulase-negative staphylococci (31%), S. aureus (20%) and Enterococcus spp. (9%) are the most common. They state that there are major differences between centres and even between different areas of the same hospital in nosocomial bacteraemia aetiology and sensitivity patterns, so knowledge of the local epidemiology is essential when selecting empirical antibiotic treatment. They therefore recommend that the microbiology department at each site compile and distribute reports, stratified by area and hospital department, with the frequency and sensitivity of the microorganisms isolated in blood cultures. They go on to say that methicillin-sensitive *S. aureus* and methicillin-resistant *S. aureus* (MRSA) are the main causes of bacteraemia in patients on haemodialysis. If the patient's clinical condition is stable, they consider vancomycin to be the empirical treatment of choice. In case of severe sepsis or septic shock, they recommend broadening the coverage against gram-negative bacilli, including *P. aeruginosa*.	
Guidelines for the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) infection were published in 2008 (Mensa 2008), drawn up by representatives of the Spanish Societies of Chemotherapy, Internal Medicine, Intensive Care Medicine, Critical and Coronary Care Units, Surgeons and Haematology and Haemotherapy, with the aim of standardising the treatment regimen for an infection that was often severe and was becoming increasingly more common and which, over the previous 5 years, had undergone significant changes in aspects that determined the choice of antibiotic.	

The changes alluded to involve: *a)* the emergence of community-acquired strains of MRSA, with no link to the strains of nosocomial origin and with a somewhat peculiar clinical behaviour; *b)* the evolution of the pattern of resistance of nosocomial MRSA towards recovery of sensitivity to various non-beta-lactam antibiotics (aminoglycosides, rifampicin and clindamycin, among others); *c)* advances in the understanding of the pharmacokinetic and pharmacodynamic parameters governing the efficacy of antimicrobials, including recognition of the importance of the minimum inhibitory concentration of vancomycin in the prognosis of MRSA infection treated with glycopeptides; *d)* implementation in the local microbiology laboratories of techniques for rapid identification of MRSA in clinical samples; *e)* the introduction of new antibiotics active against MRSA (linezolid, daptomycin, tigecycline); and *f)* clinical experience with the use of vancomycin in MRSA infections acquired in the phase III studies conducted with the new antibiotics. They argue that the use of vancomycin as initial empirical therapy for a serious infection probably caused by MRSA is not advisable in the following circumstances: a) when it is possible that the minimum inhibitory concentration of vancomycin is >1.5 mg/l (patient who received vancomycin during the previous month or nosocomial infection acquired in a centre/hospital where the prevalence of these strains is greater than 10% of the isolates); b) likely MRSA pneumonia; and c) infection in a patient with glomerular filtration rate less than 50 ml/min (age >65 years with serum creatinine >1.4 mg/dl) or on treatment with potentially nephrotoxic drugs.	
In relation to paediatric care, the Spanish Tapia guidelines (2012) state that empirical antibiotic therapy should cover mainly Gram-positive cocci, and recommend vancomycin in centres with a high prevalence of methicillin-resistant staphylococci. For sensitive germs, they argue that cloxacillin can be used as first choice. They point out that the safety of treatment with linezolid or daptomycin in children has not been established.	
The European Renal Best Practice guidelines (Vanholder 2010) state that to guide the empirical antibiotic treatment, it is of paramount importance that each haemodialysis centre maintains a database of all suspected and established cases of catheter-related bacteraemia, and of episodes of bacteraemia in general, the causal microorganisms,	

patterns of antibiotic susceptibility, the potential source (catheter-related, pneumonia, urinary tract, etc.) and outcomes after the treatment intervention. Consequently, each unit should have up-to-date knowledge of the epidemiology of catheter-related infections. Their recommendations are: • Haemodialysis units should register all the details on the epidemiology of catheter-related bacteraemia, as well as all episodes of bacteraemia (events, causal organisms with their sensitivity and changes in the response to treatment). • In general, antibiotics requiring only post-dialysis administration (vancomycin, teicoplanin, cefazolin, ceftazidime, daptomycin) should be opted for. • Vancomycin or teicoplanin as first choice for the empirical treatment of gram-positives where MRSA is highly prevalent.	
The Nottingham University Hospitals NHS Trust guidelines (Roe 2013) propose the following use of empirical antibiotics: • Vancomycin 20 mg/kg IV (rounded to the nearest number to 250 mg; maximum dose 2 g); administered at a maximum rate of 10 mg/minute (i.e. 1 g dose for 120 minutes, 1.5 g for 150 minutes, and 2 g for no less than 200 minutes). • Gentamicin 2 mg/kg IV given after dialysis (slow injection over at least 3 to 5 minutes if dose <160 mg or infusion over 60 minutes).	
The Infectious Diseases Society of America guidelines (Mermel 2009) recommend vancomycin for the empirical treatment of bacteraemia in hospital settings with a high prevalence of infection by methicillin-resistant Staphylococcus aureus (MRSA). In departments where cultures of MRSA show mostly minimum inhibitory concentrations of vancomycin >2 μg/ml, they propose the use of alternative agents, such as daptomycin. One of the authors of the guidelines published an update in August 2013 (Allon 2013) maintaining the previous recommendation to use vancomycin as empirical antibiotic to cover the Gram-positive bacteria, and considering daptomycin in patients with known allergy to vancomycin.	
Lock (2011) proposes vancomycin or teicoplanin for empirical therapy due to the high prevalence of MRSA in haemodialysis units. In cases where the minimum inhibitory concentration of vancomycin is above 2 μg/ml, they propose the use of daptomycin.	

Summary of evidence	
Comes from guidelines of professional organisations, which take into account the experience in different healthcare centres, stating the importance of adapting empirical treatment to the epidemiological conditions of the bacteraemia episodes in each haemodialysis unit, and the sensitivity and resistance of their habitual germs.	
Patients' values and preferences *No relevant studies related to this aspect have been identified.*	
Use of resources and costs *No relevant studies related to this aspect have been identified.*	
Recommendations [Proposal]	
Weak	The choice of empirical antibiotic to cover gram-positive microorganisms should be made according to the epidemiology of each individual dialysis unit, taking into account the sensitivity and resistance of their habitual germs, the patient's risk factors (previous colonisation of the patient by a particular germ, his/her immune status, parenteral nutrition) and the severity of the infection.
Weak	Use cefazolin as first choice for the empirical treatment of gram-positive bacteria where the prevalence of MRSA is low.
Weak	Use vancomycin (or teicoplanin) as first choice for the empirical treatment of gram-positive bacteria where MRSA is highly prevalent.
Weak	Use daptomycin for the empirical treatment of bacteraemia in adults in haemodialysis departments where the MRSA cultures show minimum inhibitory concentrations of vancomycin >2 μg/ml in more than 10% of isolates, and in patients with known allergy to vancomycin.
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Table 1. STUDIES EXCLUDED

Study	Cause for exclusion
APIC 2009	Does not make recommendations on empirical antibiotics in bacteraemia.
Chin 2012 CARI Guidelines	Does not make recommendations on empirical antibiotics in bacteraemia.
Ocharan-Corcuera 2010	Does not expressly address empirical treatment in cases of confirmed dialysis catheter-related bacteraemia.
O'Grady 2011	Does not make recommendations on empirical antibiotics in bacteraemia. Infection prevention guidelines.
Sarria 2012	Analyses the role of daptomycin in patients with chronic renal failure and infected with gram-positive bacteria, not as empirical therapy in bacteraemia.