Original research article

JVA The Journal of Vascular Access

The Journal of Vascular Access
1–6

DOI: 10.1177/1129729819875323
journals.sagepub.com/home/jva
SAGE

High success rate in salvage of catheter-related bloodstream infections due to *Staphylococcus aureus*, on behalf of project group of Italian society of nephrology

Salvatore Mandolfo[1], Adriano Anesi[2], Milena Maggio[2], Vanina Rognoni[2], Franco Galli[3] and Giacomo Forneris[4]

Abstract

Background: Catheter-related bloodstream infections caused by *Staphylococcus aureus* represent one of the most fearful infections in chronic haemodialysis patients with tunnelled central venous catheters. Current guidelines suggest prompt catheter removal in patients with positive blood cultures for *S. aureus*. This manoeuvre requires inserting a new catheter into the same vein or another one and is not without its risks.

Methods: A protocol based on early, prompt diagnosis and treatment has been utilized in our renal unit since 2012 in an attempt to salvage infected tunnelled central venous catheters. We prospectively observed 247 tunnelled central venous catheters in 173 haemodialysis patients involving 167,511 catheter days.

Results: We identified 113 catheter-related bloodstream infections (0.67 episodes per 1000 days/tunnelled central venous catheter). Forty were caused by *S. aureus*, including 19 by methicillin-resistant *S. aureus* (79% saved) and 21 by methicillin-sensitive *S. aureus* (90% saved), of which 34 (85%) were treated successfully. Eight recurrences occurred and six (75%) were successfully treated. A greater than 12 h time to blood culture positivity for *S. aureus* was a good prognostic index for successful therapy and tunnelled central venous catheter rescue.

Conclusion: Our data lead us to believe that it is possible to successfully treat catheter-related bloodstream infection caused by *S. aureus* and to avoid removing the tunnelled central venous catheter in many more cases than what has been reported in the literature. On the third day, it is mandatory to decide whether to replace the tunnelled central venous catheter or to carry on with antibiotic therapy. Apyrexia and amelioration of laboratory parameters suggest continuing systemic and antibiotic lock therapy for no less than 4 weeks, otherwise, tunnelled central venous catheter removal is recommended.

Keywords

Catheter-related bloodstream infections, central venous catheter, methicillin-resistant *Staphylococcus aureus*, methicillin-sensitive *Staphylococcus aureus*

Date received: 21 September 2018; accepted: 16 August 2019

Introduction

Tunnelled central venous catheters (tCVCs) represent an increasingly frequent type of vascular access in patients with stage 5 chronic kidney disease (CKD) undergoing haemodialysis (HD) treatment.[1] The main complications involve catheter-related bloodstream infections (CRBSIs). In the literature, the incidence of CRBSI ranges from 0.6 to 7 episodes per 1000 catheter days.[2] The majority of CRBSI associated

[1]Renal Unit, Ospedale Maggiore, Lodi, Italy
[2]Aziende Socio Sanitarie Territoriale Lodi, Lodi, Italy
[3]Bioengineering Laboratories (BEL), Cantù, Italy
[4]Department of Clinical and Biological Sciences, University of Turin, Turin, Italy

Corresponding author:
Salvatore Mandolfo, Renal Unit, Ospedale Maggiore, 26900 Lodi, Italy.
Email: mandolfo@alice.it

isolates are Gram-positive organisms (52%–84%), with *Staphylococcus aureus* ranging between 21% and 43% in most series and methicillin-resistant *Staphylococcus aureus* (MRSA) being reported in approximately 12%–38%.[3] CRBSI caused by *S. aureus* represents one of the most fearful infections since it is associated with the most severe complications (septic metastases), the highest mortality rates and costs of all the CRBSI. In case of positive blood culture (BC) for *S. aureus*, current guidelines suggest the immediate removal of the tCVC. An over the wire exchange may be considered should no other site for central venous catheter (CVC) insertion be available or should CVC insertion be a major risk factor.[4–7] The removal or the exchange of a tCVC, however, may not be always a simple manoeuvre and can create difficulties when providing subsequent dialysis treatments.

The aim of this article is to review the literature supporting the early removal of the tCVC in case of CRBSI caused by *S. aureus*, and to describe a diagnostic and therapeutic protocol we have adopted in order to try to salvage the tCVC.

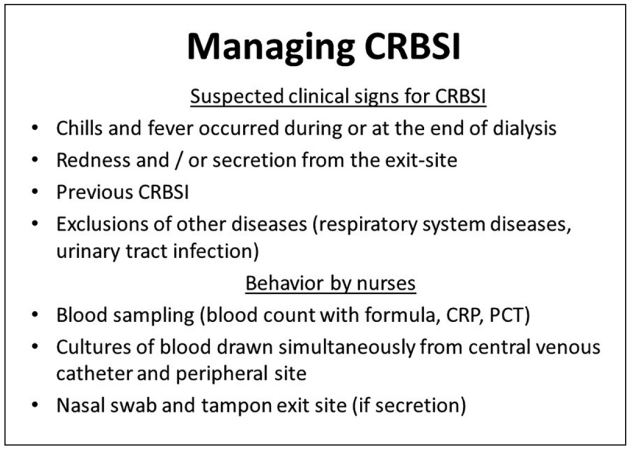

Figure 1. Managing CRBSI.

Materials and methods

Between January 2012 and December 2017, 247 tCVCs were placed in 173 chronic HD patients (mean age: 70.2 ± 13 years). The sites of insertion were the internal jugular vein (right 90%, left 6%) and the right femoral vein (4%). The majority of tCVCs (92%) were double-lumen catheters. tCVCs were the first choice of vascular access in 24% of incident patients. Clinical comorbidities, ageing, limited life expectancy, inadequate peripheral arteries or veins, poor availability of a vascular surgeon and last but not least the 'patient's will' were the reasons for this choice. In 70% of cases, tCVC was the second choice following the failure of arteriovenous fistula (AVF) or peritoneal dialysis. In 6% of cases, the tCVC was used as a bridge for an AVF. A protocol describing all aspects of preventive nursing care and early diagnosis of catheter infections was carefully standardized in our unit. Figure 1 shows the factors that led to the suspicion of a CRBSI and how our nurses acted in these cases. Figure 2 shows the therapeutic approach that was taken while waiting for the results of BCs. It is based on empirical therapy for Gram-positive and Gram-negative coverage, and is quite similar to the recommendations of the

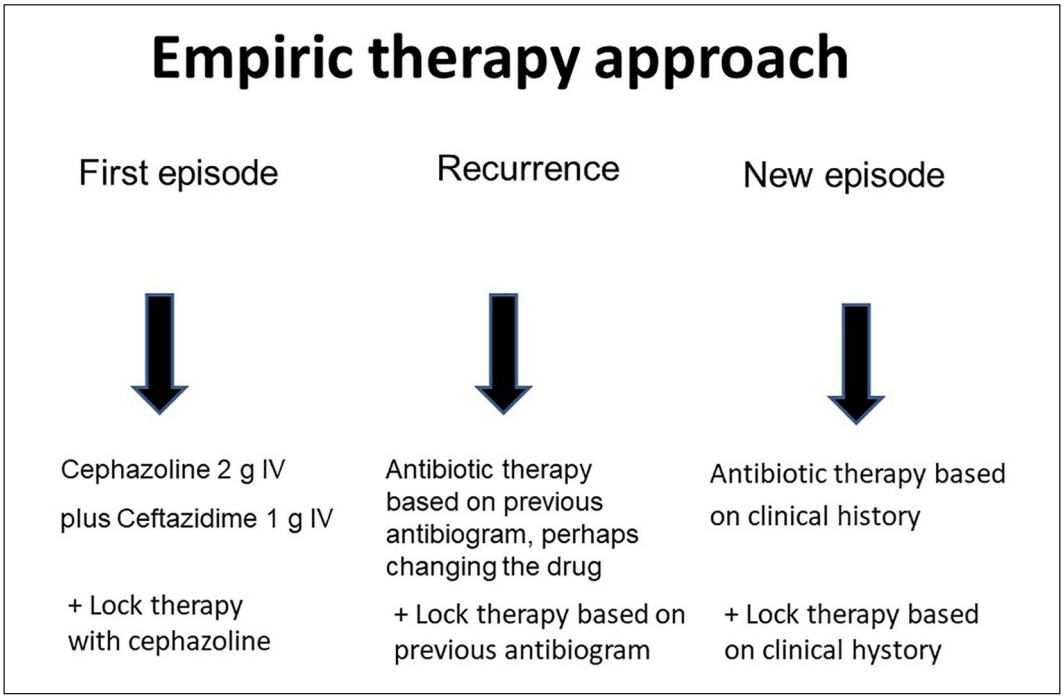

Figure 2. Empiric therapy approach.

International Society for Peritoneal Dialysis (ISPD) guidelines.[8] We did not include vancomycin as part of the empirical therapy in order to avoid the possibility of developing vancomycin-resistant *S. aureus*,[9] as recommended by the global antimicrobial resistance surveillance system (GLASS) report.[10] On the basis of the Infectious Diseases Society of America (IDSA) guidelines[4] for the diagnosis of sepsis and CRBSI, two BC sets for aerobic and anaerobic bacteria (BD Bactec™ PLUS/F Aerobic and Anaerobic medium, Becton Dickinson Diagnostics, Sparks, MD) were filled with 8–12 mL of blood that was collected from the HD circuit and from a peripheral vein, respectively. When peripheral vein sampling was not feasible, the sample was taken from the venous catheter hub.[11] BC bottles were incubated within 1 h from collection and bacteria growth detection was carried out for 5 days using the BD Bactec™ 9240 system (Becton Dickinson). Any BCs that flagged positive were removed from the instrument, then a bacterioscopist examination of Gram-stained smears was performed and the results were immediately reported to the nephrologist. Bacterial identification and antimicrobial susceptibility were routinely obtained by matrix-assisted laser desorption ionization-time of flight (MALDI-TOF) mass spectrometry (Vitek® MS, bioMérieux, Marcy l'Étoile, France) and the Vitek® 2 instrument (bioMérieux), respectively. Isolates characterized by borderline susceptibility to vancomycin were further evaluated by Etest® strips (bioMérieux) to confirm vancomycin minimal inhibitory concentration (MIC) values. *S. aureus* ATCC 29213 was used as control. Susceptibility results were interpreted based on European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints.[12] Since 2016, traditional Gram staining has been supported by methods based on molecular biology and mass spectrometry that significantly reduce the amount of time required to identify the etiologic agent, thus leading to treatment optimization in CRBSI. Whenever Gram-positive cocci were observed in the Gram stain, rapid detections of MRSA and methicillin-sensitive *Staphylococcus aureus* (MSSA) were performed using GeneXpert MRSA/SA BC® real-time polymerase chain reaction (PCR) (Cepheid, Sunnyvale, CA). In selected cases, such as fungi or polymicrobial flora in the Gram stain, FilmArray® Blood Culture Identification (BCID) Panel (BioFire Diagnostics LLC, Salt Lake City, UT) was used for rapid diagnosis. Based on the experience of other studies, we developed an in-house method capable of identifying microorganisms from positive BCs using mass spectrometry (MALDI TOF), which allowed us to obtain results in less than 1 h and to reduce the costs of the test.[13] Criteria for the diagnosis of CRBSI were a BC from the catheter hub turning positive at least 2 h before the peripheral BC (different time to positivity (DTTP). These criteria have been questioned in the literature.[14] Therefore, we also considered the time of BC positivity (time to positivity (TTP)). Growth of *S. aureus* in less than 12 h was considered a predictor of bad outcome.[15] We also recorded when the first symptoms appeared and the beginning of the empirical therapy. We defined early diagnosis as the start of empirical therapy within 6 h of the appearance of suspicious symptoms. We distinguished between the first episode of CRBSI and recurrence. Recurrence was defined as CRBSI occurring with the same organism within 6 weeks after the end of the previous therapy. The presence of prosthetic materials (i.e. heart valves, pacemakers) was also verified. Chest X-rays, urine cultures and sampling of any wounds or skin lesions were also performed to rule out other infectious sources. As soon as the lab reported the growth of MRSA or methicillin-resistant *Staphylococcus epidermidis* (MRSE), therapy with systemic vancomycin (loading dose 25–30 mg/kg/dry body weight) and lock therapy with vancomycin[6] were immediately started. Ceftazidime was discontinued and therapeutic serum concentrations (15–20 mg/L) of vancomycin were achieved within the next few days. In case of MSSA or methicillin-sensitive *Staphylococcus epidermidis* (MSSE), we continued administering systemic and alanine aminotransferase (ALT) cefazolin and discontinued ceftazidime. Patients whose antibiograms were ready after 24–48 h were shifted from vancomycin to daptomycin (6 mg/kg/day) when higher MIC levels of vancomycin (1.5–2 mcg/mL) were observed among MRSA isolates. Over the following 48–72 h, the patient was always hospitalized and monitored by clinical and laboratory parameters including C-reactive protein (CRP) and procalcitonin (PCT). On the third day, we decided whether to continue antibiotic therapy or to remove the catheter on the basis of the patient's clinical status (fever), haemodynamic parameters (blood pressure), laboratory parameters (white blood cells (WBCs), CRP and PCT) and transthoracic echocardiogram. A transoesophageal echocardiogram was performed only when endocarditis was suspected. The patients and their family members were informed about all the procedures that were being attempted in order to save the catheter.

Clinical results

During an observation period involving 167,511 catheter days, 113 CRBSI episodes were observed (incidence of 0.67 per 1000 catheter days). No tunnel infections were observed. We isolated 61 Gram-positive cases, 50 Gram-negative cases and two polymicrobial flora ones among our patients. Forty episodes of CRBSI caused by *S. aureus* (35%) were also observed, of which 34 were successfully treated (85%). Concerning methicillin resistance and sensitivity, we isolated 19 episodes of MRSA and 21 of MSSA that were successfully treated in 79% and 90% of cases, respectively. Figure 3 shows the clinical outcome of all episodes of CRBSI caused by *S. aureus*. We observed eight recurrences (22%), six (75%) of which were treated successfully. Table 1 reports clinical and laboratory parameters. In all the tCVCs we salvaged, the TTP was above 12 h.

The protocol failed in six cases (four MRSA and two MSSA) and the tCVCs were replaced. Two cases were related to delayed diagnosis (the patients were hospitalized at least 48 h after their first symptoms), two cases failed due to recurrences, one to the association of CRBSI and dysfunction and one case to polymicrobial flora (MRSA and *Escherichia coli*). Before replacing the tCVCs, we observed three patients with endocarditis, two of whom were patients with recurrence and one was an in-patient who had a delayed diagnosis. All the patients with endocarditis were MRSA positive and were discharged after 23.6 ± 3.8 days. No other significant complications were reported.

Discussion

Current guidelines recommend that in case of CRBSI caused by *S. aureus*, the infected catheter should always be promptly removed and a temporary catheter should be

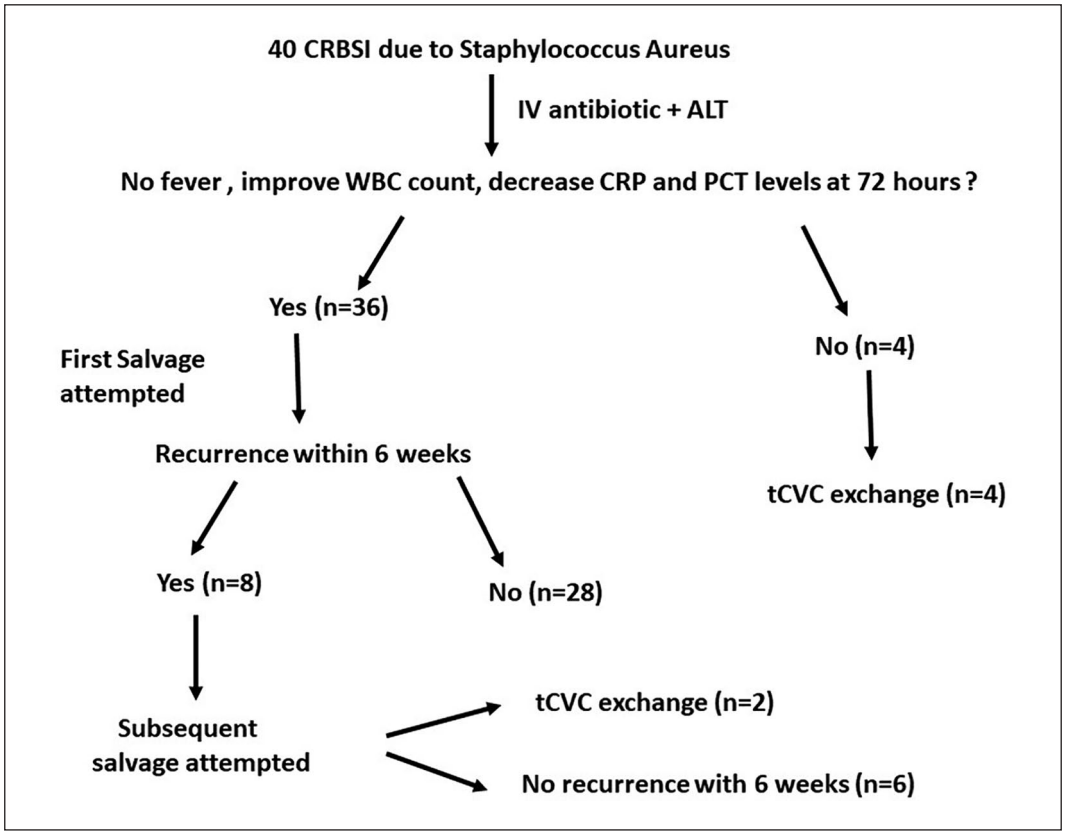

Figure 3. Clinical outcome of all episodes of CRBSI due to *Staphylococcus aureus*.

Table 1. Clinical and laboratory parameters at baseline and at the third day.

Baseline	Normal range	tCVC saved (N = 34)	tCVC replaced (N = G)	p value
Fever > 38° (%)	36.1–37.2°C	100%	100%	
White blood cell	5000–10,000/mL	11,200 ± 2400	12,700 ± 1800	0.08
C-reactive protein	0–10 mg/L	73.7 ± 18.8	85.8 ± 17.4	0.07
Procalcitonin	<0.15 µg/L	5.5 ± 1.7	6.7 ± 1.2	0.06
Time to positivity (TIP)	0 h	16.7 ± 2.8	9.2 ± 3.4	<0.000
Third day	tCVC saved (N = 34)	tCVC replaced (N = G)		p value
Fever > 38° (%)	0%	63%		<0.000
White blood cell	9100 ± 1400	12,300 ± 1400		<0.000
C-reactive protein	18.7 ± 4.4	64.2 ± 21		<0.000
Procalcitonin	2.6 ± 0.8	5.8 ± 1.2		<0.000

tCVC: tunnelled central venous catheters.

Table 2. Attempt of tCVC salvage reported in literature.

Authors (reference)	No. of patients	Success (%) for *Staphylococcus aureus*	Therapy loading dose	Vancomycin therapy scheme and recurrence
Vardhan et al[16]	23	MSSA 25% MRSA 12%	Vancomycin1 g Gentamicin 3 mg/kg ALT	Vancomycin therapy standardized for 2 weeks Recurrence not reported
Poole et al[17]	120	SA 40%	Vancomycin 20 mg/kg Ceftazidime 1 g ALT	Vancomycin 500 mg for eight HD sessions Recurrence not reported
Fernandez–Hidalgo et al[18]	98	SA 55%	Vancomycin 2 g Ciprofloxacin or Amikacin 2 g ALT	Vancomycin therapy standardized for 10–14 days Recurrence not reported for SA tCVC used for HD only in 37 patients
Maya et al[19]	113	SA 41%	Vancomycin 20 mg/kg – MRSA Cefazolin 1 g – MSSA ALT	Vancomycin 500 mg for 3 week Recurrence 27 (37%) within 3 months
Ashby et al[20]	133	SA 78%	Vancomycin 0.5–1 g According to body weight No ALT	Vancomycin monitoring concentration Recurrence 7 (39%) within 6 months

MSSA: methicillin-sensitive *Staphylococcus aureus*; MRSA: methicillin-resistant *Staphylococcus aureus*; HD: haemodialysis; ALT: alanine aminotransferase.

inserted into another anatomical site.[4–7] This strong recommendation is based on several articles in the literature regarding attempts at tCVC salvage, which are shown in Table 2. Systemic antibiotic therapy, that is also associated with ALT, has a 12%–55% success rate. Ashby et al.[20] reported a 78% success rate for *S. aureus*, but 39% recurrence within 6 months, at which point they suggest catheter replacement. Removal and replacement of tCVC is a manoeuvre that is not without its risks. Recently, Beathard et al.[21] reported very low complication rates during tCVC exchange. However, the presence of a fibrin sleeve or endovascular leads (pacemakers, implantable cardioverter-defibrillators (ICDs)), underlying central vein stenosis[22] or more rarely, an unexpected stuck catheter[23] may render any procedure more difficult. In these circumstances, it is fundamental to refer the patient to the interventional radiologist for angioplasty or stenting procedures before placing a new tCVC. In our renal unit, the prevalence of tCVCs (40%) is higher than the average Italian rates.[24] A few years ago, we described our experience and reported the 5-year outcome of tCVCs at our centre.[25]The placement of a large number of tCVCs requires a great deal of caution in their use, and accurate protocols for CRBSI are discussed and reviewed regularly with our staff. It is our opinion that the low incidence of CRBSI we have observed to date (0.67 per 1000 catheter days) is the result of our teamwork. Since 2017, we have improved our protocol by adding a nasal swab to test for MRSA/MSSA in all patients who undergo tCVC insertion or who have had a CRBSI. However, we currently have no data regarding any advantages on the outcome. In this study, we describe a protocol based both on early and prompt diagnosis and on therapy to save the tCVC. We believe that the 90% and 79% rates of successfully cleared MSSA and MRSA, respectively, are very good. A possible reason why the success of catheter salvage is better in this study than in the literature may be our organization and close cooperation with the microbiologists (empirical therapy is started within 6 h and germs are isolated within 24 h). Very recently, Nekidi et al. reported a case series in which three MSSA and two MRSA related CRBSI were successfully treated with optimized systemic antibiotics and antibiotic lock therapy. The authors highlight the role of pharmacist in this type of treatment.[26] The main weakness of our study is the choice of the time to recurrence. A 6-week period might be considered too short. *S. aureus* CRBSI is associated with a four-fold greater risk of recurrence or septic death within 3 months, with regard to microbiologic isolates.[27] Maya et al.[19] described 27 recurrences and one severe complication within 90 days. Ashby et al.[20] reported seven recurrences over 8 months of follow-up and no complications after tCVC salvage. We observed eight recurrences and a 75% success rate. The episodes of endocarditis in patients with MRSA recurrence make us reflect on the fact that the safety of treating recurrences remains to be defined.

On the basis of our data, we believe that a higher percentage of CVC removals can be avoided in *S. aureus* CRBSI cases (especially MSSA) than previously reported if early diagnosis is made and treatment is started within 6 h. Nonetheless, within the third day, the decision concerning either the removal of the tCVC or the continuation with antibiotic therapy must be carefully evaluated. Persistent bacteraemia after 72 h of antimicrobial therapy to which the pathogen is susceptible, severe sepsis, haemodynamic instability, recurrences, endocarditis, polymicrobial flora, or CRBSI associated with dysfunction are all circumstances for which tCVC removal is recommended.

Finally, we suggest an update of the current guidelines, which should always distinguish between MRSA and MSSA, to avoid administering vancomycin as empirical therapy. This is needed to prevent the development of *S. aureus* vancomycin resistance. Moreover, in cases of MRSA positivity, monitoring serum concentrations of vancomycin appears to be fundamental. Several factors remain to be defined; for instance, we suggest recording time of positivity, reporting when the first symptoms are observed, and the lag time before starting empirical therapy.

A randomized, controlled, clinical trial to investigate catheter salvage in patients with CRBSI caused by either MRSA or MSSA may be indicated.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship and/or publication of this article.

References

1. Noordzij M, Jager KJ, Van der Veer SN, et al. Use of vascular access for hemodialysis in Europe: a report from the ERA-EDTA Registry. *Nephrol Dial Transplant* 2014; 29(10): 1956–1964.
2. Beathard GA and Urbanes A. Infection associated with tunneled hemodialysis catheters. *Semin Dial* 2008; 21(6): 528–538.
3. Lok CE and Mokrzycki MH. Prevention and management of catheter-related infection in hemodialysis patients. *Kidney Int* 2011; 79(6): 587–598.
4. Mermel LA, Allon M, Bouza E, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 update by the Infectious Diseases Society of America. *Clin Infect Dis* 2009; 49(1): 1–45.
5. Allon M. Treatment guidelines for dialysis catheter–related bacteremia: an update. *Am J Kidney Dis* 2009; 54(1): 13–17.
6. Vanholder R, Canaud B, Fluck R, et al. Diagnosis, prevention and treatment of hemodialysis catheter-related bloodstream infections (CRBSI): a position statement of European Renal Best Practice (ERBP). *NDT Plus* 2010; 3(3): 234–246.
7. Ibeas J, Roca-Tey R and Vallespín J. Spanish clinical guidelines on vascular access for hemodialysis. *Nefrologia* 2017; 37(Suppl. 1): 1–191.
8. Kam-Tao Li P, Chun Szeto C, Piraino B, et al. ISPD guidelines/recommendations. *Perit Dial Int* 2016; 36: 481–508.
9. Mc Guiness WA, Malachowa N and De Leo F. Vancomycin resistance in *Staphylococcus aureus*. *Yale J of Biol Med* 2017; 90: 269–281.
10. Sirijatupath R, Srpanidkulchai K and Boonyasiri A. Implementation of global antimicrobial resistance surveillance system (GLASS) in patients with bacteraemia. *PLoS ONE* 2018; 13(1): e0190132.
11. Johns TS and Mokrzycki MH. Optimal approach for the diagnosis of hemodialysis catheter-related bacteremia. *Clin J Am Soc Nephrol* 2016; 11(5): 756–758.
12. http://www.eucast.org
13. Fiori B, D'Inzeo T, DiFlorio V, et al. Performance of two resin containing blood culture media in detection of bloodstream infections and in direct matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) broth assays for isolate identification: clinical comparison of the BacT/Alert Plus and Bactec Plus systems. *J Clin Microbiol* 2014; 52(10): 3558–3567.
14. Kaasch AJ, Rieg S, Hellmich M, et al. Differential time to positivity is not predictive for central line-related *Staphylococcus aureus* bloodstream infection in routine clinical care. *J Infect* 2014; 68(1): 58–61.
15. Marra AR, Edmond MB, Forbes BA, et al. Time to blood culture positivity as a predictor of clinical outcome of *Staphylococcus aureus* bloodstream infection. *J Clin Microbiol* 2006; 44(4): 1342–1346.
16. Vardhan A, Davies G, Daryanami I, et al. Treatment of hemodialysis catheter-related infections. *Nephrol Dial Transplant* 2002; 17: 1149–1150.
17. Poole CV, Carlton D, Bimbo L, et al. Treatment of catheter related bacteraemia with an antibiotic lock protocol: effect of bacterial pathogen. *Nephrol Dial Transplant* 2004; 19(5): 1237–1244.
18. Fernandez Hidalgo N, Almirante B, Calleya R, et al. Antibiotic-lock therapy for long-term intravascular catheter-related bacteremia: results of an open, non-comparative study. *J Antimicrob Chemother* 2006; 57: 1172–1180.
19. Maya ID, Carlton D, Estrada E, et al. Treatment of dialysis catheter-related *Staphylococcus aureus* bacteremia with an antibiotic lock: a quality improvement report. *Am J Kidney Dis* 2007; 50(2): 289–295.
20. Ashby D, Power A, Singh S, et al. Bacteremia associated with tunneled hemodialysis catheters: outcome after attempted salvage. *Clin J Am Soc Nephrol* 2009; 4(10): 1601–1605.
21. Beathard GA, Urbanes A and Litchfield T. Changes in the profile of endovascular procedures performed in freestanding dialysis access centers over 15 years. *Clin J Am Soc Nephrol* 2017; 12(5): 779–786.
22. Agarwal AK. Central vein stenosis. *Am J Kidney Dis* 2013; 61(6): 1001–1015.
23. Forneris G, Savio D, Quaretti P, et al. Dealing with stuck hemodialysis catheter: state of the art and tips for the nephrologist. *J Nephrol* 2014; 27(6): 619–625.
24. Vascular access in use by country – DOPPS 5, 2012–2014, https://www.dopps.org
25. Mandolfo S, Acconcia P, Bucci R, et al. Hemodialysis tunneled central venous catheters: five-year outcome analysis. *J Vasc Access* 2014; 15(6): 461–465.
26. El Nekidy WS, Soong D, Kadri A, et al. Salvage of hemodialysis catheter in *Staphylococcal bacteremia*: case series, revisiting the literature, and the role of the pharmacist. *Case Rep Nephrol Dial* 2018; 8(2): 121–129.
27. Mokrzycki MH, Zhang M, Cohen H, et al. Tunnelled hemodialysis catheter bacteraemia: risk factors for bacteraemia recurrence, infectious complications and mortality. *Nephrol Dial Transplant* 2006; 21: 1024–1031.