European Journal of Clinical Microbiology & Infectious Diseases (2019) 38:977–983
https://doi.org/10.1007/s10096-019-03545-8

ORIGINAL ARTICLE

A short course of antibiotic treatment is safe after catheter withdrawal in catheter-related bloodstream infections due to coagulase-negative staphylococci

Rafael San-Juan[1] · Iván Martínez-Redondo[1] · Mario Fernández-Ruiz[1] · María Ruiz-Ruigómez[1] · Laura Corbella[1] · Pilar Hernández-Jiménez[1] · Jose Tiago Silva[1] · Francisco López-Medrano[1] · Raúl Recio[2] · María Ángeles Orellana[2] · José María Aguado[1]

Received: 8 February 2019 / Accepted: 19 March 2019 / Published online: 28 March 2019

Abstract

CoNS is the main cause of catheter-related bloodstream infections (CRBSI). Current guidelines recommend catheter withdrawal followed by antibiotics for at least 5 days. We aimed to assess the efficacy and safety of a shorter course of antibiotherapy in patients with CoNS CRBSI. All proven cases of CoNS CRBSI at our institution (Jan 12/Dec 17) were retrospectively analysed. Comparison of clinical characteristics and outcomes between patients receiving a short (SC ≤ 3 days) versus long antibiotic course (LC > 3 days) was performed. Cox regression models predicting the risk for complications (including propensity score [PS] for treatment assignment as covariate) were designed to adjust baseline differences among both treatment groups. A total of 79 cases were included. Most patients (75.9%) showed clinical response at day 7 after catheter removal. Complications occurred in 3.8% (three cases of septic thrombophlebitis) with no cases of endocarditis. Microbiological relapse (MR) occurred in 13 patients (16.5%). SC and LC were administered to 25 (31.6%) and 54 (68.4%) patients, respectively, with no significant differences in MR-free survival between SC and LC groups (87.8 vs 86.3%; $P = 0.6$). In PS-adjusted Cox regression analyses, a tunnelled catheter as the source of CRBSI was the only independent risk factor for MR (hazard ratio, 5.71; 95% confidence interval, 1.6–21) whereas the duration of therapy had no apparent impact. Shortening antibiotic therapy to ≤ 3 days is not associated with a poorer outcome or a greater risk of MR in patients with CoNS CRBI with catheter withdrawal.

Keywords Coagulase-negative *Staphylococcus* · Catheter-related bloodstream infection · Short antibiotic course · Outcome · Relapse

Introduction

Intravascular catheters have become an essential element in current hospital care, and therefore, the number of hospitalised patients with these devices is continuously growing. Catheter-related bloodstream infection (CRBSI) is the most common associated complication of these type of devices and a major cause of morbidity, increasing length of stay and hospital costs [1]. According to the cross-sectional prevalence study of infections in Spain (EPINE), intravascular devices are responsible for almost half of hospital-acquired episodes of bacteraemia [2]. Coagulase-negative staphylococci (CoNS) are the most common cause of these infections (accounting for up to 40% of cases) [3]. Although most episodes typically show a benign course, current clinical practice guidelines [4–6] recommend at least a 5-day antibiotic course for uncomplicated CoNS CRBSI even if the catheter has been removed. However, there is scarce evidence supporting such recommendations, as there is no compelling data to determine the optimal duration of antibiotic therapy for intravascular device-related infections once the catheter has been withdrawn.

✉ Rafael San-Juan
rafasjg@yahoo.es

[1] Unit of Infectious Diseases, Instituto de Investigación Hospital "12 de Octubre" (imas12), University Hospital "12 de Octubre", Avenida de Córdoba, s/n, 28041 Madrid, Spain

[2] Department of Microbiology. University Hospital 12 de Octubre, Instituto de Investigación Hospital "12 de Octubre" (imas12), School of Medicine, Universidad Complutense, Madrid, Spain

We hypothesise that a short course of appropriate antibiotics may suffice for the treatment of uncomplicated CoNS CRBSI, provided that the catheter has been removed. Hence, the aim of this study was to assess the efficacy and safety of a short regimen of antibiotics (≤ 3 days) as compared to the standard longer course (> 3 days) in terms of microbiological relapse and other outcome parameters.

Material and methods

Study design and setting

The present retrospective, observational, single-centre study was conducted at a tertiary university-affiliated institution (Hospital "12 de Octubre") and included all patients admitted at our institution between January 1, 2012 and December 31, 2017 with a definite diagnosis of CoNS CRBSI in which intravascular catheter had been removed.

We collected patients' clinical data through electronic medical records and generated a database comprising the following variables: basic demographics; prognosis of the underlying disease (classified according to the McCabe and Jackson modified criteria [7] as rapidly fatal [when death was expected within 3 months], ultimately fatal [when death was expected within a period of > 3 months but < 5 years] and nonfatal [when life expectancy was > 5 years]); concurrent conditions (as assessed by the Charlson Comorbidity Index [8]); date of the first (i.e. incident) positive blood culture (BC); susceptibility pattern of CoNS (methicillin-resistant or methicillin-susceptible isolate); type of intravascular catheter; timing of catheter removal; duration of fever and bacteraemia since catheter withdrawal; Pitt bacteraemia score at CRBSI onset [9]; development of severe sepsis or septic shock; complicated bacteraemia (as defined below); antibiotic therapy administered (agent and duration); clinical or microbiological relapse; and all-cause and attributable mortality.

Study outcomes

The primary study outcome was microbiological relapse (defined by the presence of at least one positive BC for CoNS with the same antibiotic susceptibility pattern between day 7 and month 3 from the incident BC).

Secondary outcomes included:

- Clinical response (defined by the resolution of symptoms and significant reduction in inflammatory parameters, such as normalisation of white blood cell [WBC] count and/or reduction of ≥ 50% in C-reactive protein serum level from baseline]) at days 3 and 7 from the incident BC.
- Persistent bacteraemia at day 7 (defined by the presence of at least one new positive BC for CoNS within the first 7 days from the incident BC).
- All-cause and CRBSI-attributable mortality at 30 days from the incident BC

Other study definitions

We considered a definite diagnosis of CoNS CRBSI when the isolation of the same species (i.e. same antibiotic susceptibility pattern) of CoNS was reported in at least two different BC and in the catheter tip culture (≥ 15 colony-forming units by the Maki semiquantitative method) in the presence of suggestive symptoms and signs [5]. Polymicrobial cases were excluded from the study.

Septic thrombophlebitis was defined by persistent CoNS bacteraemia for > 72 h after the initiation of active antibiotic therapy associated with the documentation by Doppler ultrasound examination of a thrombus at the site of catheter insertion.

Short antibiotic course (SC) was defined if the patient did not receive in vitro active antibiotic for the incident episode of CoNS CRBSI or if appropriate therapy was administered for ≤ 3 days following catheter withdrawal. In contrast, long antibiotic course (LC) was defined as the administration of appropriate therapy for > 3 days after catheter withdrawal.

Microbiological methods

Blood cultures and catheter tips were processed and isolates of coagulase-negative *Staphylococcus* were identified according to standard techniques at the microbiology laboratory. In brief, blood samples were inoculated in the BacT/ALERT® FA aerobic and FN anaerobic bottles and incubated in the BacT/ALERT 3D (Biomerieux, France) for 5 days. Identification and susceptibility testing were performed using the MicroScan Walkaway® System (Beckman Coulter diagnostics, Indianapolis, USA) according to European Committee of Antimicrobial Susceptibility Testing (EUCAST) criteria. Catheter tip culture was performed by the Maki semiquantitative method considering significant ≥ 15 colony-forming units.

Statistical analysis

Student's unpaired *t* test was used to compare normally distributed continuous variables, the Mann-Whitney *U* test to compare continuous variables with non-normal distribution, and the chi-squared and Fisher exact tests to compare proportions, as appropriate.

To test the effect of SC and LC in the development of microbiological relapse, Kaplan-Meier event-free survival

curves were plotted and comparison between groups was performed by means of the log-rank test.

Multivariate adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) were also calculated by stepwise forward Cox proportional hazards models using the occurrence of microbiological relapse as the dependant variable and, as covariates, the number of days of effective treatment in a continuous manner and other clinically relevant variables along with those found to be significant at a P value < 0.05 by univariate analysis. In order to adjust for the potential imbalance between treatment groups (SC vs. LC), we previously performed a logistic regression model to determine the baseline factors associated with the assignment to standard course of antibiotic therapy (i.e. > 3 days). The goodness-of-fit of the resulting propensity score (PS) was assessed by means of the area under receiver operating characteristics curve (auROC) with 95% CI. Such PS for receiving LC was included as a covariate in the final multivariate Cox regression models analysing the risk factors for microbiological relapse.

All statistical tests were two-tailed and the threshold of statistical significance was set at a P value < 0.05. The statistical software SPSS v. 20.0 (IBM Corp., Armonk, NY, USA) was used to perform the calculations of the different analysis and graphics were generated with Prism v. 6.0 (GraphPad Software Inc., La Jolla, CA, USA). Variables with missing values over 20% were excluded from the final analysis.

Results

Demographics and clinical characteristics

A total of 83 patients fulfilled the inclusion criteria during the study period, although four of them were excluded due to the lack of relevant clinical data. Therefore, the final study cohort comprised 79 patients with diagnosis of definite CoNS CRBSI that were followed-up for a median of 589 days (interquartile range [IQR]1048 days). The majority of isolated CoNS strains were methicillin-resistant (68 isolates [86.1%]) whereas only 11 of them (13.9%) were methicillin-susceptible.

Eighteen patients (22.8%) were children, most of them admitted to the intensive care unit (ICU) or onco-haematological departments. Seven patients (8.9%) had heart valve prostheses or intracardiac devices. The majority of included cases of CoNS CRBSI were related to central venous catheters: temporary central venous catheter in 69 patients (87.4%) and tunnelled catheter in 5 (6.3%). The remaining sources of infection included peripheral vein catheters in four patients (5.1%) an arterial catheter in one (1.3%).

Fever was the most frequent clinical sign (67 patients [84.8%]), local signs of infection were present in 8 patients (10.1%), and 26 of them (32.9%) fulfilled sepsis criteria at CRBSI onset, with a mean Pitt score of 3.67. Severe sepsis and/or septic shock occurred in three patients (3.8%). A total of 69 patients (87.3%) received empiric antibiotic treatment effective against CoNS after catheter removal, which included glycopeptides (53.2%), daptomycin (22.8%), oxazolidinones (3.8%), antistaphylococcal β-lactams (2.5%) and other antistaphylococcal antibiotics (5.1%). The remaining 10 patients (12.7%) received no empiric treatment or the regimen administered was based on antimicrobial drugs with no in vitro activity against CoNS. The median duration of antibiotic therapy after catheter removal was 5 days (IQR 39 days).

The majority of patients (60 [75.9%]) presented clinical response at day 7 after catheter withdrawal. Follow-up BC during the first week after incident CRBSI episode were performed in 63 patients (79.7%). The occurrence of persistent CoNS bacteraemia beyond that point was demonstrated in 9 patients (11.4%).

Major complications occurred in three patients (3.8%) and exclusively comprised septic thrombophlebitis, whereas no cases of infective endocarditis were observed. All-cause 30-day mortality rate was 5.1% (4 patients), and no cases of death were considered to be attributable to CoNS CRBSI.

Microbiological relapse was globally reported in 13 patients (16.5%) after a median of 15 days (IQR 21 days) from the incident BC.

Comparison between short and long antibiotic courses

We compared patients within the two groups according to the duration of antibiotic therapy. As shown in Table 1, 25 patients (31.6%) received appropriate antibiotics for ≤ 3 days or no in vitro active therapy after catheter withdrawal (SC), whereas the remaining 54 patients (68.4%) were treated with active antibiotics against the isolated CoNS for > 3 days (LC).

Both groups were not entirely comparable. Patients treated with LC were significantly younger, with higher presence of paediatric population. Patients with higher clinical severity at presentation were more likely to receive LC, as suggested by the significantly higher mean Pitt score (4 vs. 2.52 for patients with LC and SC; P value < 0.01) and the higher rate of sepsis (44.4% [24/54] vs. 8% [2/25], respectively; P value < 0.001).

As shown in Table 2, the rates of clinical response at day 3 were significantly lower in patients included in the LC group (46.3% [25/54] vs. 88.0% [22/25] in the SC group; P value < 0.01), as was the rate at day 7 (66.7% [36/54] vs. 96.0% [24/25] for LC and SC, respectively; P value = 0.07). All nine patients with documentation of persistent ConNS bacteraemia at day 7 pertained to the LC group.

Regarding the primary outcome, the rate of microbiological relapse was similar in both groups (12.0% [3/25] for SC vs. 18.5% [10/54] for LC; P value = 0.84). As shown in Fig. 1, Kaplan-Meier curve comparison confirmed no significant differences in the probability of staying free of microbiological

Table 1 Demographics and clinical characteristics according to the duration of antibiotic therapy

	Total $N = 79$	Short course* (≤ 3 days) $n = 25$	Long course (> 3 days) $n = 54$	P value
Age (years); mean (SD)	53 (24.8)	61.9 (20.9)	39.8 (29)	< 0.01
Paediatric population (< 14 years); *n* (%)	18 (22.8)	1 (4)	17 (31.5)	0.02
Male/female (%)	53.2/46.8	64/36	48.1/51.9	0.6
Type of department; *n* (%)				
Surgical	34 (43.0)	13 (52.0)	21 (38.9)	0.4
Medical	19 (24.1)	7 (28.0)	12 (22.2)	0.78
Onco-haematological	15 (18.9)	1 (4.0)	14 (25.9)	0.04
ICU	11 (13.9)	4 (16.0)	7 (13.0)	0.99
Prognosis of underlying disease; *n* (%)				
Nonfatal	57 (72.2)	18 (72)	39 (72.2)	0.8
Finally fatal	10 (12.7)	4 (16)	6 (11.1)	0.8
Rapidly fatal	12 (15.2)	3 (12)	9 (16.7)	0.8
Prosthetic valve or intracardiac device; *n* (%)	7 (8.9)	3 (12)	4 (7.4)	0.9
Charlson Comorbidity Index; mean (SD)	2.52 (2.15)	2.84 (2.34)	1.93 (2.02)	0.08
Tunnelled intravascular catheter as source of CRBSI; *n* (%)	5 (6.3)	1 (4)	4 (7.4)	0.9
Type of CoNS; *n* (%)				
MS-CoNS	11 (13.9)	7 (28)	4 (7.4)	0.03
MR-CoNS	68 (86.1)	18 (72)	50 (92.6)	0.03
Pitt bacteraemia score at CRBSI onset; mean (SD)	3.67 (2.53)	2.52 (1.08)	4 (2.83)	< 0.01
Presence of fever at CRBSI onset; *n* (%)	67 (84.8)	23 (92)	44 (81.5)	0.38
Clinical severity at presentation; *n* (%)				
Sepsis	26 (32.9)	2 (8)	24 (44.4)	< 0.01
Severe sepsis	2 (2.5)	0 (0)	2 (3.7)	0.84
Septic shock	1 (1.3)	0 (0)	1 (1.9)	0.71
Complicated bacteraemia; *n* (%)	8 (10.2)	0 (0)	8 (14.8)	0.1
Control BC drawn in the first 7 days; *n* (%)	63 (79.7)	23 (92)	40 (61.2)	0.01
Clinical response; *n* (%)				
Day 3	47 (59.5)	22 (88.0)	25 (46.3)	<0.01
Day 7	60 (75.9)	24 (96.0)	36 (66.7)	0.07
Persistent bacteraemia at day 7; *n* (%)	9 (11.4)	0 (0.0)	9 (16.7)	0.1
Microbiological relapse; *n* (%)	13 (16.5)	3 (12)	10 (18.5)	0.84
All-cause 30-days mortality: *n* (%)	4 (5.1)	1 (4)	3 (5.6)	0.71

*Includes patients receiving no active antibiotic therapy for the incident episode of CoNS CRBSI. *BC*, blood culture; *CI*, confidence interval; *CRBSI*, catheter-related bloodstream infection; *MS-CoNS*, methicillin-sensitive coagulase-negative staphylococci; *MR-CoNS*, methicillin-resistant coagulase-negative staphylococci; *SD*, standard deviation

relapse between patients treated with SC or LC (microbiological relapse-free survival at day 100 after catheter withdrawal: 87.8% for SC vs. 86.3% for LC; log rang test P value = 0.6).

Potential effect short antibiotic courses on the risk for microbiologic relapse

Taking into account the presence of significant imbalances in baseline demographics and clinical characteristics between both treatment groups (SC and LC), we designed exploratory Cox regression models in order to analyse the effect of the duration of therapy including as a covariate the PS to receive LC. The auROC of the resulting PS for predicting LC was 0.71 (95% CI 0.59–0.82).

As shown in Table 3, receiving SC was not associated with the development of microbiological relapse, being the presence of a tunnelled catheter the only statistically significant variable in the univariate analysis (HR, 5.71; 95% CI 1.6–21; P value = 0.01).

Due to the low number of episode of CoNS CRBSI with microbiological relapsed ($n = 13$), we could not assess the potential impact of receiving SC by means of a single model adjusted for all the covariates found to be significant in the univariate analysis. We alternatively attempted an exploratory approach based on different models that incorporated a

Table 2 Study outcomes according to the duration of antibiotic therapy

	Total $N = 79$	Short course* (≤ 3 days) $n = 25$	Long course (> 3 days) $n = 54$	P value
Clinical response; *n* (%)				
Day 3	47 (59.5)	22 (88.0)	25 (46.3)	< 0.01
Day 7	60 (75.9)	24 (96.0)	36 (66.7)	0.07
Persistent bacteraemia at day 7; *n* (%)	9 (11.4)	0 (0.0)	9 (16.7)	0.1
Microbiological relapse; *n* (%)	13 (16.5)	3 (12)	10 (18.5)	0.84
All-cause 30-days mortality: *n* (%)	13 (16.5)	1 (4)	3 (5.6)	0.71

*Includes patients receiving no active antibiotic therapy for the incident episode of CoNS CRBSI

maximum of three variables at a time—always including the PS to receive LC as covariate. The only variable that was constantly retained in all multivariate exploratory models was again a tunnelled catheter as source of CRBSI, whereas receiving SC was not found to be related with the development of microbiological relapse (Table 3).

Discussion

This study investigated the clinical and microbiological outcome of a short antibiotic course or even no treatment as compared with the longer course of more than 3 days in episodes of CoNS CRBSI. The results suggest that patients who achieve clinical response at day 3 after catheter withdrawal do not clearly benefit from extending the antibiotic treatment, as the outcome (in terms of microbiological relapse) was not apparently worse with shorter courses of antibiotics.

It has been previously demonstrated the importance of catheter removal as an independent protective factor for bacteraemia recurrence in CoNS CRBSI [10, 11], but the role of antibiotic therapy is still uncertain [12]. Even so, clinicians are usually prone to maintain antibiotic therapy for more than 5 days, as currently recommended based on expert opinions in clinical practice guidelines [4, 5], and a recent trial applying this treatment schedule in CoNS bacteraemia demonstrated its

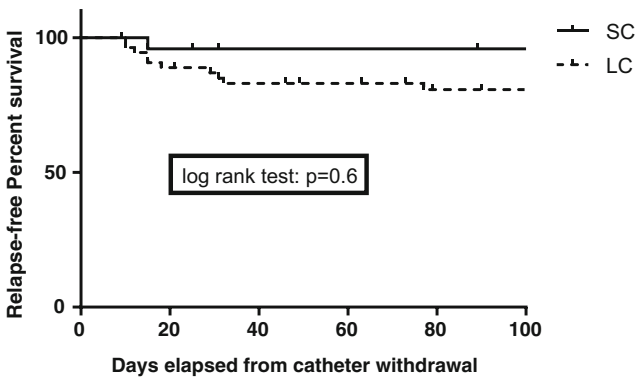

Fig. 1 Microbiological relapse-free Kaplan-Meier survival curves according to the duration of antibiotic therapy (SC or LC) in the overall study cohort

safety and efficacy [13]. This recommendation likely comes from extrapolating the potential risk of long-term complications demonstrated in other microorganisms causing CRBSI as *S. aureus* [14]. Our findings emphasise the overall benign course of CoNS infections, as has been already proposed by several previous studies [15, 16]. In fact, in our cohort, there were no cases of endocarditis (even among high-risk patients with intracardiac prosthetic devices) and none of the deaths that occurred during the study time was directly attributable to CoNS bacteraemia. Moreover, the rate of microbiological relapse after catheter withdrawal was very low among all included patients (16.5%), and a fair number of cases might have been related to new catheters inserted precisely for administering intravenous antibiotic therapy.

In fact, it is not uncommon to deal in clinical practice with patients with CoNS CRBSI with a removed catheter in which no empirical effective treatment had been administered and are nonetheless asymptomatic at the time of diagnosis. Although the 3-day criteria for defining short treatment is somehow arbitrary, it has a practical application as 72 h is a reasonable time point to establish the diagnosis of CoNS CRBSI and at which clinical response is expected. On the other hand, Hemels et al. [17] previously reported that, after catheter withdrawal, a short course of antibiotics (also defined by the 3-day criterion) was as effective as longer therapies in children with uncomplicated CoNS sepsis and was not associated with an increase in morbidity or sepsis relapse. Therefore, both studies support the possibility of shortening antibiotic therapy in uncomplicated low-risk episodes of CoNS CRBSI.

A potential benefit from reducing the number of days on therapy in these patients could be expected in terms of minimising antibiotic pressure, and therefore lowering the risk of development of bacterial resistance, especially considering the emergence of CoNS glycopeptides resistance [18]. On the other hand, the requirement for new intravascular catheter for extended antibiotic administration poses an additional risk for developing new episodes of CRBSI.

It is important to note that, in view of the present experience, SC should not be administered in patients with tunnelled intravascular catheter and CoNS CRBSI in which replacement

Table 3 Cox regression analysis for the development of microbiological relapse

	Univariate analysis			Multivariate analysis[b]		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Tunnelled catheter	5.77	1.5–21.1	0.008	5.71	1.6–21	0.01
Charlson Comorbidity score[a]	0.73	0.5–1.06	0.1	–	–	–
Local signs of phlebitis at insertion site	2.8	0.78–10.3	0.11	–	–	–
Sepsis at CRBSI onset	1.49	0.5–4.4	0.4	–	–	–
Pitt bacteraemia score[a]	1.02	0.83–1.26	0.87	–	–	–
SC (≤ 3 days of active antibiotic therapy)	0.62	0.17–2.27	0.47	–	–	–

[a] Per unitary increment

[b] Adjusted by the propensity score for treatment group assignment and the receipt of SC through exploratory multivariate models including a maximum of three variables. Only variables that were constantly retained in these models are shown and minimum HR values are depicted

CRBSI, catheter-related bloodstream infection; *HR*, hazard ratio; *SC*, short antibiotic course

is needed within a short period. Maintaining the patient under antibiotic therapy until catheter replacement seems to be a more reasonable approach in such scenario.

Our study has several limitations. Firstly, it is a retrospective study in which data collection relied on chart records. Secondly, due to its single-centre nature, the sample size was limited, which may have resulted in insufficient statistical power to demonstrated differences between SC and LC groups, although we did not find even a trend suggesting a protective effect of the duration of antibiotic therapy on the outcome. Finally, partially due do the retrospective nature of the study, comparability between both treatment groups was limited and significant differences in demographic and clinical characteristics were present. In order to minimise such biases that could have prevented us to find any prognostic impact of the treatment duration, we constructed various multivariate Cox regression models to analyse the potential effect of receiving SC in the development of microbiological relapse. On the other hand, we also included as adjusting covariate the propensity score for treatment assignment.

In conclusion, we suggest that catheter withdrawal should be considered as a curative measure by itself in most patients with CoNS CRBSI. Such intervention would allow restricting the use of prolonged antibiotic therapy to cases with poorer clinical response, those with a tunnelled catheter or those developing infective complications. In contrast to what has been reported for other pathogens such as *S. aureus*, long-term complications in CRBSI due to CoNS seem to be extremely rare. Nonetheless, further well-controlled prospective studies are warrant to ascertain the safety and efficacy of catheter removal as the only therapeutic intervention in CoNS CRBSI.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The study was approved by the local ethics research committee.

Informed consent In accordance with the local ethics research committee, informed consent was waived due to the retrospective nature of this study.

References

1. Wenzel RP, Edmond MB (2006) Team-based prevention of catheter-related infections. N Engl J Med 355(26):2781–2783
2. Sociedad Española de Medicina Preventiva SPeH (2017) Estudio EPINE-EPPS 2017, http://hws.vhebron.net/epine/Global/EPINE-EPPS%202017%20Informe%20Global%20de%20Espa%C3%B1a%20Resumen.pdf Cited May 2018 2018
3. Rogers KL, Fey PD, Rupp ME (2009) Coagulase-negative staphylococcal infections. Infect Dis Clin N Am 23(1):73–98
4. Chaves F, Garnacho-Montero J, Del Pozo JL, Bouza E, Capdevila JA, de Cueto M, Dominguez MA, Esteban J, Fernandez-Hidalgo N, Fernandez Sampedro M, Fortun J, Guembe M, Lorente L, Pano JR, Ramirez P, Salavert M, Sanchez M, Valles J (2018) Diagnosis and treatment of catheter-related bloodstream infection: clinical guidelines of the Spanish Society of Infectious Diseases and Clinical Microbiology and (SEIMC) and the Spanish Society of Spanish Society of intensive and Critical Care Medicine and Coronary Units (SEMICYUC). Med Int 42(1):5–36
5. Mermel LA, Allon M, Bouza E, Craven DE, Flynn P, O'Grady NP, Raad II, Rijnders BJ, Sherertz RJ, Warren DK (2009) 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 49(1):1–45
6. Corey GR, Stryjewski ME, Everts RJ (2009) Short-course therapy for bloodstream infections in immunocompetent adults. Int J Antimicrob Agents 34(Suppl 4):S47–S51
7. McCabe WR, Jackson GG (1960) Treatment of chronic pyelonephritis. III. Comparison of several drugs combined and one member of the combination, colistin. Am J Med Sci 240:754–763
8. Charlson ME, Sax FL, MacKenzie CR, Braham RL, Fields SD, Douglas RG Jr (1987) Morbidity during hospitalization: can we predict it? J Chronic Dis 40(7):705–712

9. Chow JW, Yu VL (1999) Combination antibiotic therapy versus monotherapy for gram-negative bacteraemia: a commentary. Int J Antimicrob Agents 11(1):7–12
10. Raad I, Davis S, Khan A, Tarrand J, Elting L, Bodey GP (1992) Impact of central venous catheter removal on the recurrence of catheter-related coagulase-negative staphylococcal bacteremia. Infect Control Hosp Epidemiol 13(4):215–221
11. Raad I, Kassar R, Ghannam D, Chaftari AM, Hachem R, Jiang Y (2009) Management of the catheter in documented catheter-related coagulase-negative staphylococcal bacteremia: remove or retain? Clin Infect Dis 49(8):1187–1194
12. Park SY, Kwon KH, Chung JW, Huh HJ, Chae SL (2015) Coagulase-negative staphylococcal bacteremia: risk factors for mortality and impact of initial appropriate antimicrobial therapy on outcome. Eur J Clin Microbiol Infect Dis 34(7):1395–1401
13. Holland TL, Raad I, Boucher HW, Anderson DJ, Cosgrove SE, Aycock PS, Baddley JW, Chaftari AM, Chow SC, Chu VH, Carugati M, Cook P, Corey GR, Crowley AL, Daly J, Gu J, Hachem R, Horton J, Jenkins TC, Levine D, Miro JM, Pericas JM, Riska P, Rubin Z, Rupp ME, Schrank J Jr, Sims M, Wray D, Zervos M, Fowler VG Jr, Staphylococcal Bacteremia I (2018) Effect of algorithm-based therapy vs usual care on clinical success and serious adverse events in patients with Staphylococcal Bacteremia: a randomized clinical trial. JAMA 320(12):1249–1258
14. Lalueza A, Morales-Cartagena A, Chaves F, San Juan R, Laureiro J, Lora-Tamayo J, Lopez-Medrano F, Orellana MA, Aguado JM (2015) Risk factors for metastatic osteoarticular infections after a long follow-up of patients with *Staphylococcus aureus* bacteraemia. Clin Microbiol Infect 21(11):1010 e1011-1015
15. Molina J, Penuela I, Lepe JA, Gutierrez-Pizarraya A, Gomez MJ, Garcia-Cabrera E, Cordero E, Aznar J, Pachon J (2013) Mortality and hospital stay related to coagulase-negative Staphylococci bacteremia in non-critical patients. J Infect 66(2):155–162
16. Olaechea PM, Alvarez-Lerma F, Palomar M, Insausti J, Lopez-Pueyo MJ, Martinez-Pellus A, Canton ML (2011) Impact of primary and intravascular catheter-related bacteremia due to coagulase-negative staphylococci in critically ill patients. Med Int 35(4):217–225
17. Hemels MA, van den Hoogen A, Verboon-Maciolek MA, Fleer A, Krediet TG (2012) Shortening the antibiotic course for the treatment of neonatal coagulase-negative staphylococcal sepsis: fine with three days? Neonatology 101(2):101–105
18. Yamada K, Namikawa H, Fujimoto H, Nakaie K, Takizawa E, Okada Y, Fujita A, Kawaguchi H, Nakamura Y, Abe J, Kaneko Y, Kakeya H (2017) Clinical characteristics of methicillin-resistant coagulase-negative Staphylococcal Bacteremia in a tertiary hospital. Intern Med 56(7):781–785