



Short- versus long-course therapy in gram-negative bacilli bloodstream infections

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Abstract

Bacteremia due to gram-negative bacilli (GNB) is one of the most frequent causes of admission and prolongation of hospital stay. Nevertheless, optimal duration of antibiotic treatment is not clearly established. We designed an observational, prospective study of a cohort of adult patients with uncomplicated GNB bacteremia. They were classified according to the duration of treatment in short (7–10 days) or long (> 10 days) course. Mortality and bacteremia recurrence rate were evaluated, and propensity score for receiving short-course treatment was calculated. A total of 395 patients met eligibility criteria including 232 and 163 who received long- and short-course therapy, respectively. Median age was 71 years, 215 (54.4% male) and 51% had a urinary source. Thirty-day mortality was 12%. In multivariate analysis by logistic regression stratified according to propensity score quartile for receiving short-course therapy showed no association of duration of treatment with 30-day mortality or 90-day recurrence rate. Based on the results observed in our cohort, short-course therapy could be as safe and effective as longer courses.

Keywords Bloodstream infection therapy · Gram-negative bacteremia · Shorter therapy · Antimicrobial stewardship

Background

Bloodstream infections (BSI) due to gram-negative bacilli (GNB) are one of the most frequent causes of admission and prolongation of hospital stay [1, 2]. Moreover, mortality rate can reach 40% in more severe cases [3]. Some authors have identified inadequate empirical treatment as one of the main factors associated with a worse prognosis [4, 5], but optimal treatment duration for this type of infections has not been clearly defined.

Recommendations about treatment duration of some guidelines vary between “at least 7 days” or “7–14 days” in cases of catheter-related bacteremia due to GNB [6, 7]. However, there are no specific guidelines on the optimal management of GNB BSI in adult patients. This lack of solid evidence is reflected in the great variability in real clinical practice in terms of treatment duration of these patients [8]. The main factor that contributes to extend the duration of antimicrobial treatment is the concern about infection recurrence. This risk varies according to reported series between 3 and 28% depending on the type of patient and hospital setting analyzed [9–12].

In a meta-analysis published in 2011 of 24 randomized clinical trials including patients with BSI, a similar cure and survival rates were observed among those who received short- and long-course treatments [13]. Recently, several retrospective series of GNB BSI have been published, analyzing the efficacy and impact on the outcome of treatment duration [10, 14–16]. They achieved mixed results regarding the efficacy and safety of short- versus longer-course treatments.

The aim of our study was to compare evolution and prognosis of a prospective cohort of patients with uncomplicated bacteremia due to GNB according to the duration of therapy.

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Methods

All patients over 18 years old with GNB bacteremia were collected and evaluated prospectively and consecutively in our center between October 1, 2015 and October 1, 2016. Only uncomplicated bacteremia (excluding patients with deep-seated infections such as not-drained intra-abdominal or pelvic abscesses and/or those in which a treatment duration exceeding 28 days was expected) were included in the analysis. They were classified according to the duration of treatment in short (7–10 days) or long (> 10 days) course. Only the first episode of GNB bacteremia of each patient was included in the analysis.

Setting

University Hospital Complex of Vigo is a 1300-bed tertiary care hospital which attends a potential population of 600,000 inhabitants, located in the northwest of Spain.

Exclusion criteria included polymicrobial bloodstream infection defined as the isolation of more than one microorganism in blood cultures (excluding potential contaminants as coagulase-negative *Staphylococci*), patients who received less than 7 days of treatment or those in which treatment was expected to exceed 28 days, those who died while receiving antibiotic therapy for the BSI episode, and patients who did not receive at least one agent with in vitro activity against the microorganism isolated from the time of extraction of blood cultures until the finish of therapy.

Definitions

Source of bacteremia was defined based on Centers for Disease Control and Prevention criteria [17]. Site of infection acquisition was divided into community-acquired, healthcare-associated, and hospital-acquired [18]. The Charlson comorbidity index was determined at admission [19]. Patients were classified as having sepsis or septic shock as described elsewhere in Sepsis-3 consensus [20]. Pitt bacteremia score was calculated at the moment of blood cultures extraction [21].

Immunosuppression was defined as presence of severe neutropenia (neutrophil count < 500/mm³), solid organ or hematopoietic stem cell transplantation, high-dose corticosteroid therapy (equivalent to prednisone 16 mg/day for > 15 days), and uncontrolled human immunodeficiency virus infection (< 200 CD4/mm³).

Appropriate empiric therapy was considered when at least one in vitro active drug was administered within 24 h after drawing blood cultures and before susceptibility report was available. Definitive antibiotic therapy was defined as the antibiotic treatment administered after the susceptibility results were known. Source control was considered adequate if it was performed within 1 week of index blood cultures (surgical

procedures to drain an abscess or to treat an obstructive focus at any site including, among others, urinary tract, biliary tract, and surgical site).

Clinical cure was defined as resolution of signs and symptoms of infection within 7 days of treatment initiation. Recurrence was defined as either subsequent BSI or primary site infection due to the same microorganism as in the initial episode. Recurrent primary site infection was considered only if patients had local symptoms of infection at the same initial primary site. Primary outcome was 30-day mortality defined as all-cause mortality within 30 days after index blood cultures. Secondary outcome was 90-day recurrence (within 90 days after index blood cultures). We choose these time periods in accordance with previously reported studies [10, 14].

Microbiological methods

Isolations in blood cultures or in other clinical samples of all GNB were processed in the Laboratory of Microbiology of the University Hospital Complex of Vigo according to the current standardized procedures. The antibiotic susceptibility was determined by the automatic method VITEK2 (BioMérieux, France), which includes combinations of cephalosporins with clavulanic acid for the detection of extended-spectrum β -lactamases. For confirmation, a phenotypic method with double Etest strip and/or modified double disk was used. The detection of carbapenemases was carried out following the EUCAST protocol: meropenem disk diameter < 25 mm or minimum inhibitory concentration > 0.12 mg/L in all Enterobacteriaceae. Confirmation was carried out with chromID medium CARBA SMART (BioMérieux, rancid) and the type of carbapenemase by PCR (Cepheid Xpert Carba-R.) There was no change in the method used for the identification of microorganisms or analysis of antibiotic susceptibility during the study period.

Statistical analysis

The statistical package SPSS v24.0 (SPSS, Chicago, IL) was used to analyze the data. Continuous variables were compared using Student's *t* test or Mann-Whitney *U* test and were described as mean \pm standard deviation (SD) or as median and interquartile range (IQR) according to whether the distribution of the variables was normal or non-normal. Chi-squared test (χ^2) and Fisher's exact test were used to compare categorical variables. A multivariate analysis using a Cox regression model was carried out to identify factors that could influence the variables of the study. All variables with a *p* value < 0.20 in the univariate analysis were included in the multivariate analysis. Variables with a *p* value two-sided < 0.05 were considered statistically significant.

Propensity scores (PS) were calculated using a multivariable logistic regression model in which the dependent variable was a binary indicator of antibiotic duration. Covariates included in generating the propensity score included age, preexisting conditions (end-stage liver disease, end-stage renal disease, structural lung disease, congestive heart failure with an ejection fraction of < 45%, diabetes, immunosuppression), Pitt bacteremia score, adequate empirical treatment, and adequate source control. The 1:1 nearest neighbor matching without replacement was performed with a caliper width of 0.25. The PS was used first as a covariate in the multivariate analysis and then to perform stratified analysis according to PS quartiles.

Ethics

The study was approved by the Local Ethics Committee (2017/336) which waived the need to obtain written informed consent. STROBE recommendations were followed.

Results

During the study period 395 patients met eligibility criteria (see Fig. 1), including 167 in the short and 232 in the long-course therapy group, respectively. Median treatment duration was 10 days (interquartile range [IQR], 7–9) in the short group and 14 days (IQR, 11–18) in the long-course therapy group. In the second group, one patient with an episode of acute prostatitis was included, in which his treating physician decided to complete 27 days of treatment, despite the recommendation of our local antibiotic treatment guidelines in which 2–3 weeks of treatment for this type of infection is recommended.

The main demographic, clinical, treatment, and outcome characteristics of both groups of patients are shown in Table 1. Regarding to the antibiotic treatment, the most

frequent empirical therapy was a combination of β -lactam plus β -lactamase inhibitor in 139 cases (35%), followed by a carbapenem in 89 patients (22.5%), a third-generation cephalosporin in 88 (22%), and a fluoroquinolone in 22 cases (5.5%). Microorganisms isolated in both group of patients are shown in Table 2. Other isolates with low frequency were *Prevotella oralis* (4 patients), *Stenotrophomonas maltophilia* (3), *Acinetobacter baumannii* (2), *Burkholderia cepacia*, and *Hafnia alvei* (1).

An adequate source control (in the remaining patients, it was considered that no specific intervention was necessary, for example, in cases of acute diverticulitis with millimeter abscesses or acute cholangitis with resolution of symptoms without the need for endoscopic retrograde cholangiopancreatography) was achieved in 32/40 patients with biliary tract infection, 24/28 with an abdominal source, and in 30/49 of catheter-related, without statistically significant differences comparing short- and long-course therapy groups.

The outcome was similar between both groups without differences in 7-day clinical cure rate, 30-day mortality, or 90-day recurrence (Table 1). The recurrence rate was very low in both groups (4% and 3% in short- and long-course groups, respectively). Table 3 shows the main characteristics of patients with and without 30-day mortality. Univariate and multivariate analyses of risk factors associated are shown in Table 4. Multivariate analysis was performed including all variables with a *p* value higher than 0.20 in univariate analysis and only Charlson index > 2 points (HR 2.70 [95% CI 1.34–5.41]) and a urinary source of infection (HR 0.44 [95% CI 0.18–0.77]) were independent 30-day mortality associated factors.

We then stratified the patients in both groups (short and long) according to propensity score quartiles for receiving short-course treatment and performed 30-day mortality analysis (Fig. 2). Short-course therapy showed no higher mortality in any strata of patients with all comparisons within quartiles with *p* values > 0.20.

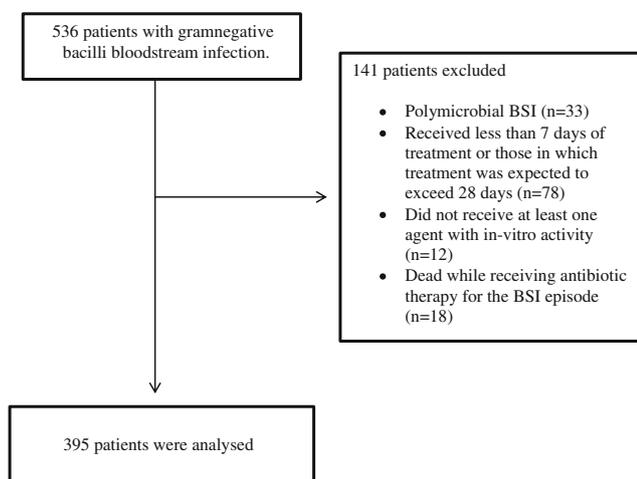


Fig. 1 Study flow chart

Discussion

In patients with uncomplicated GNB bacteremia, we have observed that short-treatment course (< 10 days) have not been associated with an increased risk of therapeutic failure, measured as 30-day mortality and/or 90-day recurrence rate.

To date, there have been few studies comparing different treatment durations in this type of infections [10, 14–16]. Most of them found that the recurrence and/or mortality rate were not different with both treatment durations [10, 15]. Chotiprasitsakul et al. [15] have recently published a propensity score-matched cohort in which they observed that short antibiotic treatment courses achieve similar outcomes as longer ones with

Table 1 Baseline characteristics of patients according to treatment duration

	Short-course therapy (<i>n</i> = 163)	Long-course therapy (<i>n</i> = 232)	<i>p</i>
Demographics			
Age, median [IQR]	74 [26–94]	70 [18–105]	0.18
Male sex, <i>n</i> (%)	78 (48)	137 (59)	0.02
Comorbidities, <i>n</i> (%)			
Chronic heart failure	14 (9)	23 (10)	0.65
Chronic respiratory disease	20 (12)	28 (12)	0.95
Chronic kidney disease	13 (8)	28 (12)	0.18
Neoplasia	48 (29)	77 (33)	0.43
Immunosuppression	30 (20)	55 (24)	0.20
SOT	8 (5)	14 (6)	0.88
HSCT	16 (10)	25 (11)	0.91
Charlson index > 2, <i>n</i> (%)	62 (38)	100 (43)	0.31
Acquisition of infection, <i>n</i> (%)			
Community-acquired	81 (50)	97 (42)	0.55
Hospital-acquired	43 (27)	75 (32)	0.72
Severity of infection, <i>n</i> (%)			
Pitt-score > 4	5 (3)	13 (6)	0.23
Septic shock	6 (4)	16 (7)	0.17
Source of BSI, <i>n</i> (%)			
Urinary tract	91 (56)	111 (48)	0.09
Biliary tract	16 (10)	40 (18)	0.03
Respiratory tract	20 (12)	16 (7)	0.04
Catheter-related	20 (12)	29 (12)	0.92
Abdominal	9 (5)	17 (7)	0.44
Others	7 (4)	19 (8)	0.06
Treatment characteristics			
Source control procedure, <i>n</i> (%)	38 (23)	48 (21)	0.88
Appropriate empirical treatment, <i>n</i> (%)	135 (83)	191 (82)	0.89
Days of treatment, median [IQR]	10 [7–9]	14 [11–18]	0.001
Outcome, <i>n</i> (%)			
Clinical cure at day 7	128 (78)	186 (80)	0.79
30-day mortality	23 (14)	23 (10)	0.31
90-day recurrence	7 (4)	8 (3)	0.66

IQR interquartile range, SOT solid organ transplantation, HSCT hematopoietic stem cell transplantation, BSI bloodstream infection, ESBL extended-spectrum beta-lactamase, CPE carbapenemase-producing Enterobacteriaceae

a trend of higher risk of multidrug resistant gram-negative microorganism subsequent infections in the group of patients receiving prolonged courses of antibiotic therapy. Moreover, recently, they were presented at the 28th ECCMID congress preliminary results of a non-inferiority randomized controlled trial comparing 7 versus 14 days of treatment for GNB bloodstream infections [22]. Although final data has to be analyzed, according to it, short-course treatment seems to be at least as safe and effective as longer courses. Also, a study performed in pediatric population did not found differences in terms of prognosis comparing long and short treatment courses [23].

On the other hand, in the paper by Nelson et al. [14] which included patients with uncomplicated GNB bloodstream infections, it was observed that those who received antibiotic treatment ≤ 10 days presented a higher risk of therapeutic failure (mortality and/or recurrence) despite adjustment for propensity score for receive a short-course treatment. In this work, a high rate of patients received > 14 days of treatment (29%) despite the fact that patients with intra-abdominal or pelvic abscess were excluded and also an adequate source control was achieved in > 95% of patients. In addition, 70% of patients presented a urinary source of infection (higher rate than that observed in our series) and that hardly could explain the better outcome achieved with longer treatment courses in the aforementioned study.

Table 2 Microbiological data of both groups of patients

Microorganism, <i>n</i> (%)	Short-course group (<i>n</i> = 167)	Long-course group (<i>n</i> = 232)
<i>Escherichia coli</i>	101 (60)	123 (53)
ESBL	20 (12)	34 (15)
<i>Klebsiella</i> sp.	20 (12)	41 (18)
CPE	6 (4)	11 (5)
<i>Pseudomonas aeruginosa</i>	5 (3)	12 (5)
<i>Proteus</i> sp.	4 (2)	10 (4)
<i>Serratia marcescens</i>	8 (5)	7 (3)
<i>Enterobacter</i> sp.	7 (4)	11 (5)
<i>Citrobacter</i> sp.	4 (2)	3 (1)

ESBL extended-spectrum beta-lactamase, CPE carbapenemase-producing Enterobacteriaceae

According to some authors [11, 24], bacteremia due to multidrug resistant microorganisms could be associated with a higher rate of recurrence. Nevertheless, nor in our series, with a 4% of CPE GNB, neither in the work of Giannella et al. [10] with an elevated ESBL microorganism rate (close to 30%) was observed this association.

Our work included patients with severe immunosuppression, such as hematopoietic stem cell or solid organ transplantation, that were not included in by other authors [15]. In the study of Giannella et al. [10], it was observed that immunosuppression was an independent risk factor for relapse within

Table 3 Comparison of patients with and without 30-day mortality

	Died (<i>n</i> = 46)	Survivors (<i>n</i> = 349)	<i>p</i>
Age, median [IQR]	75 [45–96]	71 [18–105]	0.01
Male sex, <i>n</i> (%)	27 (58)	188 (54)	0.54
Comorbidities, <i>n</i> (%)			
Chronic heart failure	6 (13)	31 (9)	0.36
Chronic respiratory disease	12 (26)	36 (10)	0.002
Chronic kidney disease	7 (15)	34 (9)	0.25
Neoplasia	16 (35)	109 (31)	0.62
Immunosuppression	12 (26)	73 (21)	0.42
Charlson index > 2, <i>n</i> (%)	28 (61)	134 (38)	0.004
Acquisition of infection, <i>n</i> (%)			
Community-acquired	7 (15)	172 (49)	0.001
Hospital-acquired	23 (50)	95 (27)	0.03
Severity of infection			
Pitt Score > 4	6 (13)	12 (3)	0.003
Septic shock	7 (15)	15 (4)	0.002
Source of BSI, <i>n</i> (%)			
Urinary tract	14 (30)	189 (54)	0.02
Biliary tract	6 (13)	50 (14)	0.88
Respiratory tract	9 (19)	27 (7)	0.01
Catheter-related	11 (24)	38 (11)	0.03
Abdominal	2 (4)	24 (7)	0.22
Microbiological characteristics, <i>n</i> (%)			
ESBL strain	13 (28)	43 (12)	0.04
CPE strain	4 (9)	13 (4)	0.11
Treatment characteristics, <i>n</i> (%)			
Source control procedure	11 (24)	75 (21)	0.77
Appropriate empirical treatment	37 (80)	289 (83)	0.69
Short-course therapy	23 (50)	140 (40)	0.20

IQR interquartile range, BSI bloodstream infection, ESBL extended-spectrum beta-lactamase, CPE carbapenemase-producing Enterobacteriaceae

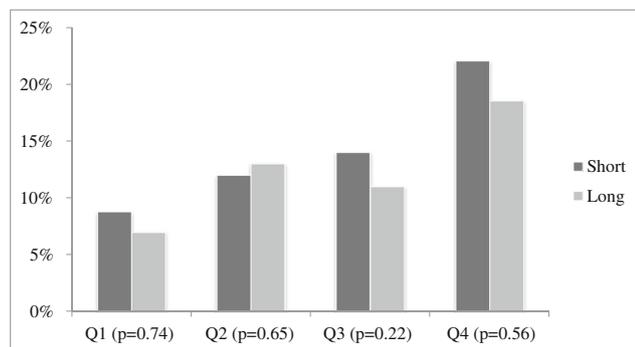
Table 4 Thirty-day mortality risk factors in univariate and multivariate analyses

	Univariate		Multivariate	
	RR (95% CI)	<i>p</i>	HR (95% CI)	<i>p</i>
Chronic respiratory disease	2.06 (1.46–6.45)	0.02	1.39 (0.88–4.40)	ns
End-stage renal disease	1.56 (0.69–4.00)	ns	1.11 (0.55–6.44)	ns
Liver cirrhosis	1.36 (0.59–5.79)	ns	1.28 (0.66–3.89)	ns
Immunosuppression	1.33 (0.65–2.70)	ns	1.28 (0.65–3.78)	ns
Charlson index > 2	2.49 (1.32–4.68)	0.004	2.70 (1.34–5.41)	0.003
Hospital acquired	1.88 (1.18–5.44)	0.01	1.78 (0.88–4.88)	ns
Pitt Score > 4	1.21 (1.09–8.83)	0.03	1.14 (0.64–5.77)	ns
Urinary source	0.37 (0.19–0.71)	0.002	0.44 (0.18–0.77)	0.004
CPE isolation	2.46 (0.76–7.89)	ns	1.55 (0.78–8.77)	ns
Adequate empirical treatment	0.85 (0.39–1.86)	ns	0.83 (0.55–5.61)	ns
Short-course treatment	0.67 (0.36–1.24)	ns	0.75 (0.43–3.44)	ns

90 days. Due to the low number of relapses in our cohort, we have not been able to demonstrate this association.

Thirty-day all-cause mortality rate in our cohort reach 14% and 10% in the short- and long-course groups, respectively. It is higher in the study by Nelson et al. [14], which found a 90-day mortality of 8% and 3% in the short- and long-treatment groups, respectively. This could be explained because in that work, patients with in-hospital mortality and those with length of hospital stay > 14 days were excluded. Moreover, our series included patients with a higher degree of comorbidity (immunosuppression of 20% versus 10%), higher nosocomial acquisition rate of infection (30% versus 10%), a greater number of patients with a non-urinary source of infection (50% versus 30%), and a lower rate of adequate empirical antibiotic treatment (81% versus 95%).

We also performed an analysis of subgroup of patients with catheter-related bacteremia in which a high 30-day mortality rate (11/49, 22%) was observed. All deaths were unrelated to the infection but due to underlying condition (mostly advanced hematological and solid organ malignancies). Catheter removal was performed in 7/11 patients who died.

**Fig. 2** Thirty-day mortality stratified according to Propensity Score quartile for receiving short-course therapy

In the rest of patients, antibiotic lock-therapy was initiated in addition to systemic treatment.

Our study has some limitations. On the one hand, it is a unicentric study with a smaller sample size than some previously published retrospective studies. However, we believe that this has allowed us to homogenize the clinical management, diagnosis, and treatment of our entire cohort. Furthermore, differences in the specific antimicrobial agent used to complete the treatment could not be demonstrated because the number of patients treated with a particular antibiotic was too low to make comparisons. Despite the prospective design, we do not have information on the incidence of infection by multiresistant microorganisms once the follow-up period has ended, so the impact of the duration of treatment on the incidence of infections due to multiresistant microorganisms is uncertain.

In summary, short-course therapy could be as safe and effective as longer courses for uncomplicated bloodstream infections due to GNB. New information is expected based on clinical trials currently underway, but until then, our results reinforce the current trend towards a shorter duration of antibiotic treatments.

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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 Committee (2017/336) which waived the need to obtain written informed consent.

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References

- Goto M, Al-Hasan MN (2013) Overall burden of bloodstream infection and nosocomial bloodstream infection in North America and Europe. *Clin Microbiol Infect* 19:501–509
- Suljagić V, Cobeljić M, Janković S et al (2005) Nosocomial bloodstream infections in ICU and non-ICU patients. *Am J Infect Control* 33:333–340
- Menashe G, Borer A, Yagupsky P et al (2001) Clinical significance and impact on mortality of extended-spectrum beta lactamase-producing Enterobacteriaceae isolates in nosocomial bacteremia. *Scand J Infect Dis* 33:188–193
- Retamar P, López-Prieto MD, Rodríguez-López F et al (2014) Predictors of early mortality in very elderly patients with bacteremia: a prospective multicenter cohort. *Int J Infect Dis* 26:83–87
- Battle SE, Bookstaver PB, Justo JA, Kohn J, Albrecht H, Al-Hasan MN (2017) Association between inappropriate empirical antimicrobial therapy and hospital length of stay in gram-negative bloodstream infections: stratification by prognosis. *J Antimicrob Chemother* 72:299–304
- Mermel LA, Allon M, Bouza E et al (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* 49:1–45
- Chaves F, Garnacho-Montero J, Del Pozo JL et al (2018) Executive summary: diagnosis and treatment of catheter-related bloodstream infection: clinical guidelines of the Spanish Society of Clinical Microbiology and Infectious Diseases (SEIMC) and the Spanish Society of Intensive Care Medicine and Coronary Units (SEMICYUC). *Enferm Infecc Microbiol Clin* 36(2):112–119
- Corona A, Bertolini G, Ricotta AM et al (2003) Variability of treatment duration for bacteraemia in the critically ill: a multinational survey. *J Antimicrob Chemother* 52:849–852
- Cattaneo C, Antoniazzi F, Tumbarello M, Skert C, Borlenghi E, Schieppati F et al (2014) Relapsing bloodstream infections during treatment of acute leukemia. *Ann Hematol* 93(5):785e90
- Giannella M, Pascale R, Toschi A et al (2018) Treatment duration for *Escherichia coli* bloodstream infection and outcomes: retrospective single-Centre study. *Clin Microbiol Infect* 24:1077–1083
- Sanz-Garcia M, Fernandez-Cruz A, Rodriguez-Creixems M, Cercenado E, Marin M, Munoz P et al (2009) Recurrent *Escherichia coli* bloodstream infections: epidemiology and risk factors. *Medicine (Baltimore)* 88(2):77e82
- Maslow JN, Mulligan ME, Arbeit RD (1994) Recurrent *Escherichia coli* bacteremia. *J Clin Microbiol* 32(3):710e4
- Havey TC, Fowler RA, Daneman N (2011) Duration of antibiotic therapy for bacteremia: a systematic review and meta-analysis. *Crit Care* 15:R267
- Nelson AN, Justo JA, Bookstaver PB, Kohn J, Albrecht H, Al-Hasan MN (2017) Optimal duration of antimicrobial therapy for uncomplicated gram negative bloodstream infections. *Infection* 45(5):613–620
- Chotiprasitsakul D, Han JH, Cosgrove SE et al (2018) Comparing the outcomes of adults with Enterobacteriaceae bacteremia receiving short-course versus prolonged-course antibiotic therapy in a multicenter, propensity score-matched cohort. *Clin Infect Dis* 66(2):172–177
- Havey TC, Fowler RA, Pinto R et al (2013) Duration of antibiotic therapy for critically ill patients with bloodstream infections: a retrospective cohort study. *Can J Infect Dis Med Microbiol* 24:129–137
- Horan TC, Andrus M, Dudeck MA (2008) CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. *Am J Infect Control* 36:309–332
- Friedman ND, Kaye KS, Stout JE et al (2002) Health care-associated bloodstream infections in adults: a reason to change the accepted definition of community-acquired infections. *Ann Intern Med* 137(10):791e7
- Charlson ME, Pompei P, Ales KL, MacKenzie CR (1987) A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 40:373–383
- Singer M, Deutschman CS, Seymour CW et al (2016) The third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA* 315(8):801–810
- Rhee JY, Kwon KT, Ki HK et al (2009) Scoring systems for prediction of mortality in patients with intensive care unit-acquired sepsis: a comparison of the Pitt bacteremia score and the acute physiology and chronic health evaluation II scoring systems. *Shock* 31:146–150
- ClinicalTrials.gov Duration of antibiotics for the treatment of Gram-negative bacilli bacteremia. NCT01737320
- Park SH, Milstone AM, Diener-West M, Nussenblatt V, Cosgrove SE, Tamma PD (2013) Short versus prolonged courses of antibiotic therapy for children with uncomplicated gram-negative bacteraemia. *J Antimicrob Chemother* 69:779–785
- Shields RK, Clancy CJ, Gillis LM et al (2012) Epidemiology, clinical characteristics and outcomes of extensively drug-resistant *Acinetobacter baumannii* infections among solid organ transplant recipients. *PLoS One* 7(12):e52349