Clinical Infectious Diseases

MAJOR ARTICLE

Procalcitonin-guided Antibiotic Treatment in Patients With Positive Blood Cultures: A Patient-level Meta-analysis of Randomized Trials

Marc A. Meier,[1] Angela Branche,[2] Olivia L. Neeser,[1] Yannick Wirz,[1] Sebastian Haubitz,[1] Lila Bouadma,[3] Michel Wolff,[3] Charles E. Luyt,[4] Jean Chastre,[4] Florence Tubach,[5] Mirjam Christ-Crain,[6] Caspar Corti,[7] Jens-Ulrik S. Jensen,[8,9] Rodrigo O. Deliberato,[10] Kristina B. Kristoffersen,[11] Pierre Damas,[12] Vandack Nobre,[13] Carolina F. Oliveira,[14] Yahya Shehabi,[15,16] Daiana Stolz,[17] Michael Tamm,[17] Beat Mueller,[1,18] and Philipp Schuetz[1,18]

[1]Medical University Department, Kantonsspital Aarau, Switzerland; [2]Department of Medicine, University of Rochester, Rochester General Hospital, New York; [3]Service de Réanimation Médicale, Université Paris 7-Denis-Diderot, Assistance Publique–Hôpitaux de Paris (AP-HP), [4]Service de Réanimation Médicale, Université Paris 6-Pierre-et-Marie-Curie, and [5]Département d'Epidémiologie Biostatistique et Recherche Clinique, AP-HP, Hôpitaux Universitaires Paris Nord Val de Seine, France; [6]Division of Endocrinology, Diabetology and Clinical Nutrition, University Hospital Basel, Switzerland; [7]Department of Respiratory Medicine, Copenhagen University Hospital Bispebjerg, [8]Centre of Excellence for Health, Immunity and Infections, Department of Infectious Diseases and Rheumatology, Finsencentret, Rigshospitalet, University of Copenhagen, and [9]Department of Internal Medicine, Respiratory Medicine Section, Copenhagen University Hospital Herlev-Gentofte Hospital, Denmark; [10]Critical Care Unit, Hospital Israelita Albert Einstein, São Paulo, Brazil; [11]Department of Infectious Diseases, Aarhus University Hospital, Denmark; [12]Department of General Intensive Care, University Hospital of Liege, Domaine universitaire de Liège, Belgium; [13]Department of Intensive Care, Hospital das Clinicas and [14]Department of Internal Medicine, School of Medicine, Universidade Federal de Minas Gerais, Belo Horizonte, Brazil; [15]Critical Care and Peri-operative Medicine, Monash Health, and [16]School of Clinical Sciences, Faculty of Medicine Nursing and Health Sciences, Monash University, Melbourne, Victoria, Australia; and [17]Clinic of Pneumology and Pulmonary Cell Research, University Hospital Basel, and [18]Faculty of Medicine, University of Basel, Switzerland

Background. Whether procalcitonin (PCT)–guided antibiotic management in patients with positive blood cultures is safe remains understudied. We performed a patient-level meta-analysis to investigate effects of PCT-guided antibiotic management in patients with bacteremia.

Methods. We extracted and analyzed individual data of 523 patients with positive blood cultures included in 13 trials, in which patients were randomly assigned to receive antibiotics based on PCT levels (PCT group) or a control group. The main efficacy endpoint was duration of antibiotic treatment. The main safety endpoint was mortality within 30 days.

Results. Mean duration of antibiotic therapy was significantly shorter for 253 patients who received PCT-guided treatment than for 270 control patients (–2.86 days [95% confidence interval [CI], –4.88 to –.84]; $P = .006$). Mortality was similar in both arms (16.6% vs 20.0%; $P = .263$). In subgroup analyses by type of pathogen, we noted a trend of shorter mean antibiotic durations in the PCT arm for patients infected with gram-positive organisms or *Escherichia coli* and significantly shorter treatment for subjects with pneumococcal bacteremia. In analysis by site of infection, antibiotic exposure was shortened in PCT subjects with *Streptococcus pneumoniae* respiratory infection and those with *E. coli* urogenital infections.

Conclusions. This meta-analysis of patients with bacteremia receiving PCT-guided antibiotic management demonstrates lower antibiotic exposure without an apparent increase in mortality. Few differences were demonstrated in subgroup analysis stratified by type or site of infection but notable for decreased exposure in patients with pneumococcal pneumonia and *E. coli* urogenital infections.

Keywords. positive blood cultures; bacteremia; procalcitonin; antibiotic stewardship.

Duration of antibiotic therapy for patients hospitalized with confirmed or suspected infections often exceeds recommended lengths of treatment [1]. The resulting overuse in antibiotics is a key driver for the emergence of antibiotic-resistant bacteria and leads to potentially avoidable drug adverse events including *Clostridium difficile* infection [2]. Implementation of stewardship programs is an important measure to curb this trend [3]. Still, given the limitations of current diagnostic tools, clinicians are often reluctant to prescribe shorter antibiotic courses even when clinical improvement is evident. This is particularly true for patients with positive blood cultures. Using a biomarker that is a sensitive surrogate of bacterial infection as a supplement to clinical judgement may be one promising approach to reduce antibiotic overuse in the hospital setting [4, 5].

Recently, the US Food and Drug Administration approved the serum biomarker procalcitonin (PCT) to guide antibiotic therapy in patients with acute respiratory infections and sepsis [6]. Several clinical studies found that PCT levels decrease during recovery from acute bacterial infections and demonstrated that PCT kinetics have important prognostic value [7]. As a surrogate of host response to bacterial infections, PCT may therefore serve as an adjunct to traditional clinical and diagnostic parameters and help to gauge resolution to infection, thereby allowing for more individualized treatment [4].

Received 22 August 2018; editorial decision 15 October 2018; accepted 21 October 2018; published online October 25, 2018.

Correspondence: P. Schuetz, University Department of Medicine, Kantonsspital Aarau, Tellstrasse, CH-5001 Aarau, Switzerland (schuetzph@gmail.com).

Clinical Infectious Diseases® 2019;69(3):388–96

DOI: 10.1093/cid/ciy917

Several trials have now investigated the effects of PCT-guided use of antibiotics in patients with respiratory infections and sepsis [8, 9]. PCT guidance care resulted in shorter durations of antibiotic treatment and positive clinical outcomes, specifically a lower rate of antibiotic-related side effects and mortality [8]. Nevertheless, significant concerns remain about the effectiveness and safety of this approach in patients with infections associated with bacteremia, and physicians may be reluctant to reduce treatment duration in this patient population. Moreover, infectious diseases society guidelines in the United States and Europe currently recommend standard durations of therapy for most patients with confirmed bacteremia to guard against clinical outcomes such as endocarditis [10].

Because most individual PCT trials were underpowered to look at patients with bacteremia, there is currently no comprehensive analysis to close this knowledge gap. We therefore performed a secondary analysis of a patient level meta-analysis assessing clinical outcomes of PCT-guided care in patients with positive blood cultures, stratified by type of bacteria, to determine if duration of antibiotic therapy may be safely shortened from the standard prescribed length using PCT-guided algorithms [11, 12].

METHODS

Definition of Patient Population and Trial Selection

We performed a secondary analysis of an individual patient data meta-analysis of PCT-guided antibiotic stewardship trials focusing exclusively on patients with positive blood cultures [8, 9]. Trial selection and data collection were performed as originally described in a protocol published in the Cochrane Library [9] and the report was prepared according to Preferred Reporting Items for Systematic Review and Meta-analyses individual patient data guidelines [13, 14]. For this analysis, we included all patients with a clinical infection involving any organ system (eg, respiratory, abdominal, urogenital) who also had positive blood cultures. We did not include pediatric patients and trials not using PCT to guide initiation and duration of antibiotic treatment.

Trial Search and Data Collection

The search strategy for this review was updated in February 2018 in collaboration with personnel from the Cochrane collaboration and executed in all databases from the date of their inception to February 2018. All references were screened for eligibility. Databases searched included the Cochrane Central Register of Controlled Trials (January 2017, Issue 1), Medline Ovid (1966 to February 2017), and Embase (1980 to February 2017). We applied no language or publication restrictions.

Two authors (Y. W. and M. A. M.) independently assessed trial eligibility based on titles, abstracts, and full-text reports. Study protocols, case report forms, and unedited databases containing individual patient data were requested from investigators of all eligible trials. Data from each trial were first checked against reported results, and queries were resolved with the principal investigator, trial data manager, or statistician. Data were assessed in a consistent manner across all trials, with standard definitions and parameters, and thus mortality rates differed slightly from previous reports. In accordance with the Cochrane methodology, we used the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) approach to assess risk of selection bias, performance bias, detection bias, attrition bias, reporting bias, and other types of bias [15]. The grading was done by 2 authors (Y. W. and M. A. M.) and in case of conflicting results, grading was discussed with another author (P. S.) and within the meta-analysis group.

Patients and Endpoints

All patients with true-positive blood cultures randomized to PCT-guided care or the control group were eligible for inclusion in the analysis. We excluded 5 patients because their blood culture results were classified as likely to be a contaminant and not a true bacteremia. The main efficacy endpoint was duration of antibiotic treatment in days. The main safety endpoint was mortality within 30 days of randomization. For trials with a shorter follow-up period treatment failure at the time of hospital discharge was utilized as the measure of safety. Other secondary endpoints included length of hospital stay and length of intensive care unit (ICU) stay.

All trials included in the meta-analysis received approval from their institutional review boards and enrolled patients who provided informed consent.

Statistical Analysis

The statistical analysis was adapted from the previously published Cochrane Library study protocol [11] with special emphasis on patients with positive blood cultures. In brief, we calculated odds ratios (ORs) and 95% confidence intervals (CIs) using mixed multivariable hierarchical logistic regression model for all binary endpoints [16, 17]. Variables in the multivariate analysis included treatment arm, age, sex, and type of infection. To control for within-and between-trial variability, a "trial" variable was added to the model as a random effect. Corresponding linear regression models were fitted for length of stay, a continuous endpoint. Analyses followed the intention-to-treat principle by analyzing patients in groups to which they were randomized. We tested for predefined subgroup effects by type of bacteria overall and within specific types of infection by adding interaction terms to the model. All statistical analyses were performed using Stata version 15.1 (StataCorp, College Station, Texas).

Role of the Funding Source

There was no funding for this secondary analysis. The National Institute for Health Research provided a research grant for the initial Cochrane analysis. The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full

access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

Results of Systematic Search and Characteristics of Included Trials

Nine hundred ninety records were identified through the systematic literature search, 32 of which were eligible for analysis. We excluded 14 trials that had insufficient information on blood culture results, 1 trial with no positive cultures, and 4 trials with insufficient clinical data (Figure 1). Thus, we included 523 patients with positive blood cultures from 13 trials into the final analysis.

Data were obtained from trials performed in 7 countries including Switzerland, France, the United States, Denmark, Brazil, Belgium, and Australia (Table 1). Six trials were conducted in the emergency department (ED) and medical ward and 7 in the ICU. PCT algorithms used in the different trials were similar in design and recommended discontinuation of antibiotic therapy when PCT levels decreased to <0.25 μg/L in ED/medical ward trials and <0.5 μg/L in ICU trials [18]. Adherence to algorithms was variable, ranging from 46% to 100% (Addendum 1).

Baseline Characteristics

Baseline characteristics of individual patients were similar in PCT-guided and control groups. Half of the patients had a respiratory infection and 16% had a urinary tract infection. A total of 243 patients had gram-positive bacteria, with *Streptococcus pneumoniae* being the most common type, and 196 patients had gram-negative bacteria, with *Escherichia coli* most frequently identified (Table 2). The mean PCT value was ≤29.7 μg/L in subjects with gram-positive bacteremia compared to those with gram-negative bacteremia (23.1 ± 46.0 μg/L vs 45.3 ± 96.5 μg/L; $P = .004$).

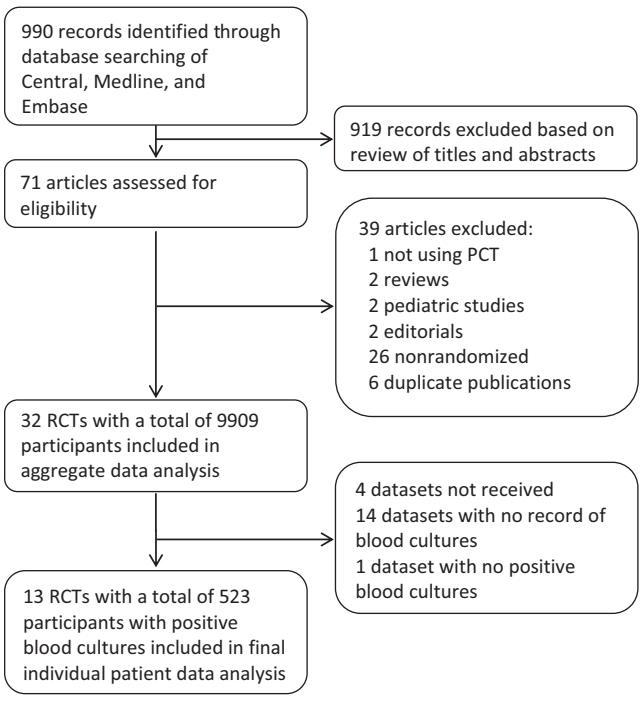

Figure 1. Study flowchart. Abbreviations: PCT, procalcitonin; RCT, randomized controlled trial.

Primary Efficacy Endpoint: Duration of Antibiotic Treatment

Duration of antibiotic treatment was significantly lower for patients in the PCT-guided treatment arm compared with control patients (12.7 ± 10.9 days vs 15.6 ± 12.8 days; adjusted difference, −2.86 [95% CI, −4.88 to −.84] days; $P = .006$). Despite large CIs in subgroup analysis, we found no evidence for a subgroup effect indicating variances from the overall effect by means of interaction testing stratified by pathogen identified (Table 3; Figure 2) or site of infection (ie, respiratory, urogenital, and abdominal infections) (P for interaction > .05 each). However, subgroup analysis revealed a more pronounced decrease in duration of antibiotic therapy for PCT group subjects with *S. pneumoniae* respiratory infections and bacteremia (adjusted difference, −4.75 [95% CI, −7.71 to −1.80]; P for interaction = .021) and all urogenital infections, most notably those secondary to *E. coli* (adjusted difference, −4.21 [95% CI, −7.98 to −.40]; P for interaction = .629; Table 4; Addendum 2).

Primary Safety Endpoint: Mortality

There were 42 deaths in 253 patients in the PCT-guided treatment arm (16.6%) vs 54 deaths in 270 control subjects (20.0%), resulting in an adjusted OR for mortality of 0.82 (95% CI, .57–1.16; $P = .263$; Table 3). Mortality rates differed by pathogen identified with the highest rates noted for patients with *S. aureus* bacteremia in both arms. Consistent with the overall finding, there were also no significant differences in 30-day mortality between PCT and control subjects in subgroup analysis by bacterial pathogen type or site of infection (P for interaction > .05 each; Tables 3 and 4; Figure 2; Addenda 2 and 3).

Length of Stay

Length of hospital stay was similar in PCT-guided and control group patients (mean, 22.5 ± 21.9 days vs 21.2 ± 24.0 days; adjusted difference, −1.48 [95% CI, −5.27 to 2.30] days; $P = .443$), as was length of ICU stay between the 2 arms (mean, 13.3 ± 14.6 vs 13.6 ± 16.4 days; adjusted difference, 0.55 [95% CI, −2.48 to 3.57] days; $P = .723$) (Table 3). This finding was conserved in subgroup analyses with no evidence for subgroup effects (P for interaction > .05 each; Table 4; Addenda 2 and 3).

DISCUSSION

In this meta-analysis of individual patient data from 523 subjects with positive blood cultures from 13 randomized trials, we found a significant decrease in antibiotic treatment duration with the use of PCT treatment algorithms. There was no evidence for effect modification by type of pathogen or

Table 1. Characteristics of Included Trials

First Author (Year)	Country	Setting, Type of Trial	Clinical Diagnosis	Type of PCT Algorithm and PCT Cutoffs Used (μg/L)	Patients Analyzed in Study, No.	Blood Culture–Positive Patients, No. (%)
Bouadma (2010)	France	ICU, multicenter	Suspected bacterial infections during ICU stay without prior AB (>24 h)	Initiation and duration; R against AB: <0.5 (<0.25); R for AB: >0.5 (>1.0)	621	108 (17.4)
Branche (2015)	US	ED, medical ward, single center	Lower ARI	Initiation and duration; R against AB: <0.25 (<0.1); R for AB: >0.25 (>0.5)	300	2 (0.9)
Christ-Crain (2004)	Switzerland	ED, single center	Lower ARI with radiographic confirmation	Initiation; R against AB: <0.25 (<0.1); R for AB: >0.25 (>0.5)	243	16 (9.8)
Christ-Crain (2006)	Switzerland	ED, medical ward, single center	CAP with radiographic confirmation	Initiation and duration; R against AB: <0.25 (<0.1); R for AB: >0.25 (>0.5)	302	30 (11.4)
Corti (2016)	Denmark	ED, single center	AECOPD	Initiation and duration; R against AB <0.25 (0.15)/80% decrease, R for AB >0.25	120	1 (1.5)
Deliberato (2013)	Brazil	ICU, single center	Septic patients with proven bacterial infection	Duration; R against AB: <0.5 or >90% drop	81	47 (58.0)
Kristoffersen (2009)	Denmark	ED, medical ward, multicenter	Lower ARI without radiographic confirmation	Initiation and duration; R against AB: <0.25; R for AB: >0.25 (>0.5)	210	12 (7.9)
Layios (2012)	Belgium	ICU, single center	Suspected infection	Initiation; R against AB: <0.5 (<0.25); R for AB: >0.5 (>1.0)	509	68 (13.4)
Nobre (2008)	Switzerland	ICU, single center	Suspected severe sepsis or septic shock	Duration; R against AB: <0.5 (<0.25) or >80% drop; R for AB: >0.5 (>1.0)	79	25 (31.6)
Oliveira (2013)	Brazil	ICU, multicenter	Severe sepsis or septic shock	Discontinuation; Initial <1.0: R against AB: 0,1 at day 4; Initial >1.0: R against: >90% drop	94	20 (21.3)
Schuetz (2009)	Switzerland	ED, medical ward, multicenter	Lower ARI with radiographic confirmation	Initiation and duration; R against AB: <0.25 (<0.1); R for AB: >0.25 (>0.5)	1359	83 (6.1)
Shehabi (2014)	Australia	ICU, multicenter	Suspected sepsis, undifferentiated infections	Duration; R against AB: <0.25 (<0.1) or >90% drop	394	79 (20.0)
Stolz (2009)	Switzerland, US	ICU, multicenter	VAP when intubated for >48 h	Duration; R against AB: <0.5 (<0.25) or >80% drop; R for AB: >0.5 (>1.0)	101	32 (31.7)

Abbreviations: AB, antibiotic; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; ARI, acute respiratory infection; CAP, community-acquired pneumonia; ED, emergency department; ICU, intensive care unit; PCT, procalcitonin; R, recommendation; US, United States; VAP, ventilator-associated pneumonia.

Table 2. Baseline Characteristics of Included Patients

Parameter	Control (n = 270)	PCT Group (n = 253)
Demographics		
Age, y, mean ± SD	64.3 ± 16.7	64.4 ± 16.9
Male sex	149 (55.2)	137 (54.2)
Focus		
Respiratory	126 (50.8)	119 (51.5)
Urinary	38 (15.3)	37 (16.0)
Abdominal	18 (7.3)	19 (8.2)
Skin/soft tissue	6 (2.4)	5 (2.2)
Central nervous system	2 (0.8)	3 (1.3)
Catheter related	2 (0.8)	5 (2.2)
Bloodstream	22 (8.9)	14 (6.1)
Other/unknown	34 (13.7)	28 (12.1)
Blood culture (gram-positive)		
Streptococcus pneumoniae	66 (27.8)	50 (23.0)
Streptococcus spp	22 (9.3)	20 (9.2)
Staphylococcus aureus	31 (13.1)	19 (8.8)
MRSA	1 (0.4)	2 (0.9)
CoNS	11 (4.6)	14 (6.5)
Other gram-positive bacteria	5 (2.1)	2 (0.9)
Blood culture (gram-negative)		
Escherichia coli	46 (19.4)	47 (21.7)
Other Enterobacteriaceae	26 (11.0)	32 (14.7)
Pseudomonas aeruginosa	11 (4.6)	9 (4.1)
Haemophilus influenzae	6 (2.5)	4 (1.8)
Neisseria meningitidis	2 (0.8)	2 (0.9)
Moraxella catarrhalis	0 (0.0)	3 (1.4)
Other gram-negative bacteria	6 (2.5)	2 (0.9)
Unspecified bacteremia	4 (1.7)	11 (5.1)
Vital signs		
Temperature, °C, mean ± SD	38.0 ± 1.2	38.1 ± 1.2
Sepsis score		
SOFA score	7.3 ± 3.9	7.6 ± 4.2
Laboratory assessments		
CRP day 0, mg/L, mean ± SD	259.8 ± 406.0	299.6 ± 537.9
PCT day 0, µg/L, mean ± SD	35.2 ± 82.6	24.3 ± 50.2
Creatinine, µmol/L, mean ± SD	99.3 ± 88.8	92.5 ± 84.2
Arterial pH, mean ± SD	7.44 ± 0.06	7.42 ± 0.10
Additional sepsis support		
Vasopressor use	90 (59.6)	87 (58.4)
Ventilator support	64 (42.1)	61 (40.4)
Renal replacement	193 (71.5)	182 (71.9)

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: CoNS, coagulase-negative staphylococci; CRP, C-reactive protein; MRSA, methicillin-resistant *Staphylococcus aureus*; PCT, procalcitonin; SD, standard deviation; SOFA, Sepsis-Related Organ Failure Assessment.

site of infection, although individual subgroups were mostly small with large CIs. Patients with respiratory infections and *S. pneumoniae* bacteremia demonstrated a more pronounced effect of PCT-guided care on antibiotic duration. In the safety assessment, there were no differences in mortality, length of hospital stay, or length of ICU stay noted between the PCT-guided care and control groups. Our results therefore demonstrate that PCT may be helpful in reducing antibiotic treatment durations in patients with bacteremia with no apparent harmful effects.

Procalcitonin treatment algorithms have been proposed as an adjunct to traditional clinical and diagnostic tools to guide antibiotic therapy in patients with respiratory infections and diagnostic uncertainty due to the absence of definitive microbiological diagnosis [19, 20]. This approach was found to reduce antibiotic exposure, side effects from antibiotics, and mortality in a recent meta-analysis of mostly European trials [8]. Current trials and aggregate data meta-analyses based on these trials, however, so far were not able to give conclusive evidence regarding the use of PCT in patients with bacteremia due to the low number of patients with bacteremia within each individual trial. To our knowledge, this is the first comprehensive analysis assessing the added value of PCT treatment algorithms in patients with bacteremia and thus closes an important knowledge gap.

For this analysis, we pooled individual patient data from different trials. Trials differed in regard to the patient population (eg, respiratory infection, general sepsis), setting (eg, ED, medical ward, ICU), and type of PCT protocol used (eg, recommendation regarding initiation vs stop of therapy), also with different cutoffs (eg, 0.25 µg/L in lower-risk settings vs 0.5 µg/L in higher-risk settings). We have previously compared different PCT protocols and found PCT to be most helpful when used for early stopping antibiotic treatment, particularly in the setting of high-risk patients such as patients with positive blood cultures, using the 0.25 µg/L cutoff for the ED setting and 0.5 µg/L for the ICU setting [18].

International guidelines recommend treatment durations of <8 days in patients with CAP [10]. However, no specific recommendations exist for bacteremic CAP patients. Common practice varies, though duration of therapy generally ranges from 10 to 14 days. Our subgroup analysis demonstrated significantly shorter duration of therapy for patients with *S. pneumoniae* lower respiratory infection and bacteremia in the PCT algorithm treatment arm compared to the control group. Since duration of therapy decreased from 15 to 11 days, PCT-guided care may boost provider confidence in defaulting to the lower end of the 10–14 days rather than continuing prolonged therapy. Interestingly, we saw similar results for patients with respiratory infections and bacteremia due to another common respiratory pathogen, *Haemophilus influenzae*, and conversely a trend to increased duration of therapy for subjects with *S. aureus* infection in the PCT-guided treatment arm compared to the control arm. Although our sample overall is large, the statistical power within most subgroups was limited. While these results did not reach statistical significance due to the small sample size, they illustrate the benefit of utilizing PCT to provide more individualized care rather than a standard duration of therapy recommendation, which may result in antibiotic overuse or premature discontinuation of therapy.

Table 3. Clinical Endpoints Stratified by Subgroup of Bacterial Subspecies

Endpoint	Control Group	PCT Group	Adjusted OR or Difference (95% CI)[a], *P* Value	*P* for Interaction
Overall	270	253		
Antibiotic therapy	15.6 ± 12.8	12.7 ± 10.9	**–2.86 (–4.88 to –.84), *P* = .006**	
30-d mortality, No. (%)	54 (20.0)	42 (16.6)	0.82 (.57–1.16), *P* = .263	
Length of hospital stay	22.5 ± 21.9	21.2 ± 24.0	–1.48 (–5.27 to 2.30), *P* = .443	
Length of ICU stay	13.3 ± 14.6	13.6 ± 16.4	0.55 (–2.48 to 3.57), *P* = .723	
Subgroup by Gram stain				
Gram-positive	136	107		
Antibiotic therapy	16.9 ± 14.3	12.2 ± 11.0	**–4.63 (–7.87 to –1.39), *P* = .005**	.151
30-d mortality, No. (%)	26 (19.1)	21 (19.6)	0.97 (.60–1.57), *P* = .899	.425
Length of hospital stay	21.9 ± 24.1	18.3 ± 18.3	–3.99 (–9.17 to 1.19), *P* = .131	.197
Length of ICU stay	12.6 ± 15.3	13.6 ± 18.3	1.00 (–4.57 to 6.58), *P* = .725	.971
Gram-negative	97	99		
Antibiotic therapy	13.6 ± 11.4	12.3 ± 10.8	–1.29 (–4.37 to 1.80), *P* = .415	.151
30-d mortality, No. (%)	21 (22)	16 (16)	0.77 (.43–1.37), *P* = .369	.425
Length of hospital stay	22.1 ± 20.5	24.4 ± 31.3	2.30 (–5.08 to 9.68), *P* = .541	.197
Length of ICU stay	12.7 ± 14.5	13.5 ± 17.4	1.75 (–2.76 to 6.25), *P* = .447	.971
Subgroup by bacterial species				
Streptococcus pneumoniae	66	50		
Antibiotic therapy	15.8 ± 7.6	11.3 ± 8.3	**–4.52 (–7.40 to –1.64), *P* = .002**	.393
30-d mortality, No. (%)	5 (8)	3 (6)	0.76 (.19–3.04), *P* = .703	.965
Length of hospital stay	15.1 ± 11.1	14.9 ± 11.7	–1.17 (–5.03 to 2.69), *P* = .552	.699
Length of ICU stay	9.2 ± 9.8	13.8 ± 16.7	4.59 (–6.48 to 15.7), *P* = .417	.495
Other *Streptococcus* spp	22	20		
Antibiotic therapy	16.6 ± 15.4	11.4 ± 7.8	–5.24 (–12.6 to 2.07), *P* = .160	.492
30-d mortality, No. (%)	6 (27)	3 (15)	0.55 (.16–1.91), *P* = .347	.484
Length of hospital stay	29.5 ± 28.7	16.4 ± 11.9	–13.1 (–26.3 to .12), *P* = .052	.082
Length of ICU stay	17.6 ± 23.4	8.4 ± 8.0	–10.0 (–20.9 to 0.88), *P* = .072	.059
Staphylococcus aureus	31	19		
Antibiotic therapy	19.1 ± 19.7	13.4 ± 8.3	–5.73 (–14.9 to 3.42), *P* = .220	.359
30-d mortality, No. (%)	12 (39)	9 (47)	1.33 (.65–2.73), *P* = .435	.337
Length of hospital stay	29.7 ± 34.7	19.7 ± 15.4	–10.1 (–26.3 to 6.18), *P* = .225	.160
Length of ICU stay	11.4 ± 12.1	13.0 ± 12.2	1.59 (–5.52 to 8.70), *P* = .662	.755
CoNS	11	14		
Antibiotic therapy	20.0 ± 25.9	17.5 ± 22.1	–2.50 (–20.6 to 15.6), *P* = .786	.935
30-d mortality, No. (%)	2 (18)	5 (36)	1.95 (.48–7.90), *P* = .348	.213
Length of hospital stay	28.5 ± 29.8	35.1 ± 35.9	5.33 (–19.8 to 30.4), *P* = .677	.376
Length of ICU stay	12.5 ± 12.1	23.3 ± 31.9	10.8 (–8.43 to 30.0), *P* = .272	.087
Escherichia coli	46	47		
Antibiotic therapy	15.2 ± 14.4	12.4 ± 9.0	–2.49 (–7.29 to 2.32), *P* = .310	.981
30-d mortality, No. (%)	8 (17)	5 (11)	0.61 (.22–1.73), *P* = .355	.540
Length of hospital stay	24.0 ± 20.8	22.1 ± 34.4	–1.94 (–13.4 to 9.52), *P* = .74	.882
Length of ICU stay	11.6 ± 14.6	9.9 ± 13.1	–0.29 (–5.84 to 5.25), *P* = .918	.492
Other Enterobacteriaceae	26	32		
Antibiotic therapy	10.2 ± 6.2	10.0 ± 7.8	–0.38 (–3.92 to 3.16), *P* = .832	.386
30-d mortality, No. (%)	7 (27)	5 (16)	0.58 (.21–1.61), *P* = .296	.461
Length of hospital stay	22.7 ± 22.5	23.0 ± 19.6	0.25 (–9.32 to 9.83), *P* = .958	.774
Length of ICU stay	14.8 ± 16.6	15.2 ± 17.5	0.05 (–8.39 to 8.50), *P* = .990	.976
Pseudomonas aeruginosa	11	9		
Antibiotic therapy	12.4 ± 7.5	16.4 ± 12.2	4.08 (–4.18 to 12.3), *P* = .333	.189
30-d mortality, No. (%)	5 (45)	3 (33)	0.73 (.24–2.27), *P* = .590	.749
Length of hospital stay	20.2 ± 21.0	39.7 ± 47.7	19.5 (–10.1 to 49.1), *P* = .197	.040
Length of ICU stay	14.6 ± 13.7	19.2 ± 20.8	4.60 (–11.4 to 20.6), *P* = .573	.558

Data are presented as mean ± SD unless otherwise indicated. Antibiotic therapy, length of hospital stay, and length of ICU stay are shown in days. Bold values denote statistical significance at the $P < .05$ level.

Abbreviations: CI, confidence interval; CoNS, coagulase-negative staphylococci; ICU, intensive care unit; OR, odds ratio; PCT, procalcitonin; SD, standard deviation.

[a]Multivariable hierarchical regression with outcome of interest as dependent variable and trial as a random effect.

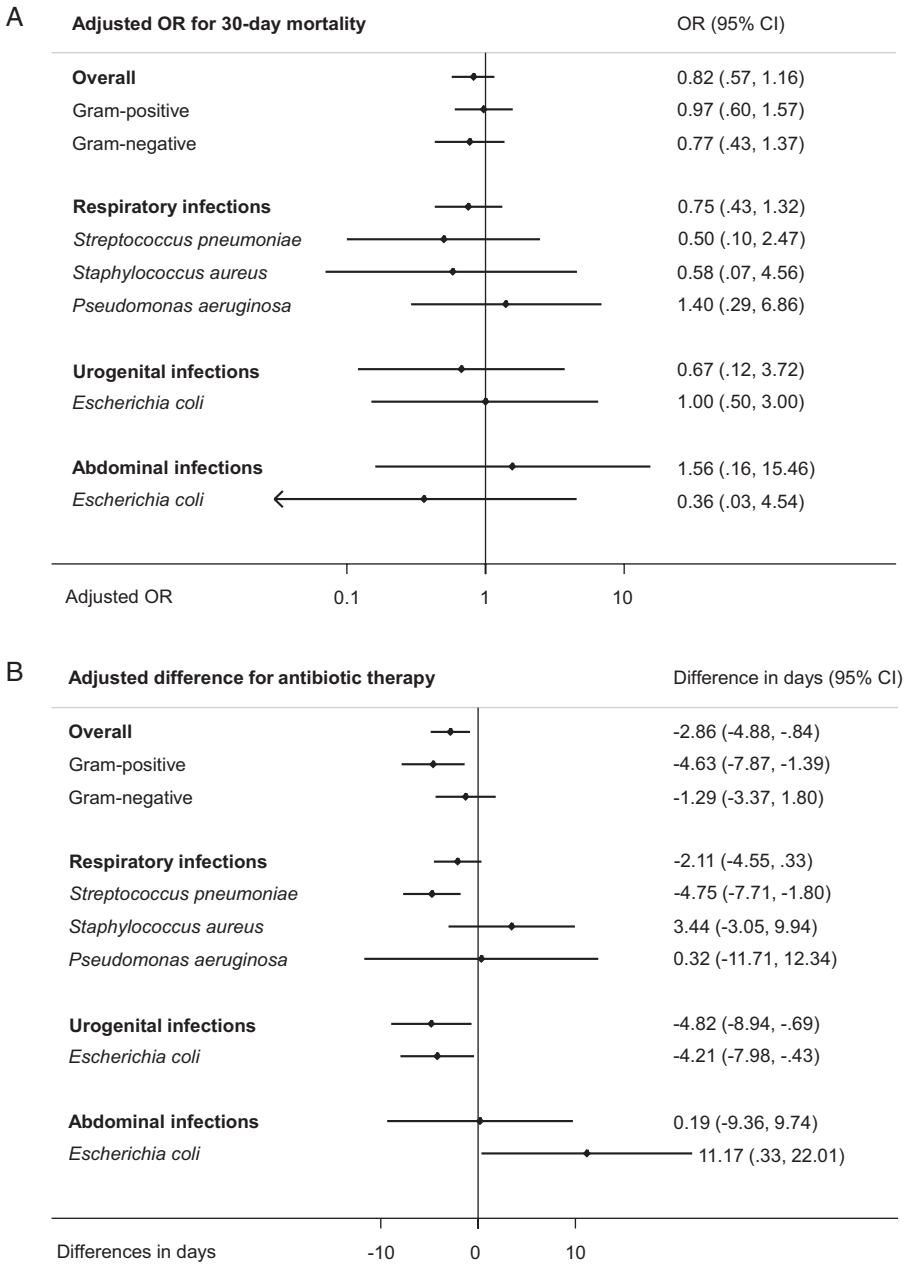

Figure 2. Forest plot showing 30-day mortality (*A*) and difference in antibiotic therapy (*B*). Abbreviations: CI, confidence interval; OR, odds ratio.

In a previous study, PCT-guided treatment of urinary tract infections showed a reduction in antibiotic exposure without apparent negative effects [21]. Sandberg et al showed noninferiority for 7 days of quinolone-based therapy in women with acute pyelonephritis regardless of bacteremia [22]. Current guidelines suggest a treatment time of 1–2 weeks for an uncomplicated gram-negative bacteremia [23, 24]. However, a new study evaluated a duration of 7 vs 14 days in gram-negative bacteremia and demonstrated noninferiority of the shorter treatment time [25]. Similarly, we noted a decrease in antibiotic duration in patients in the PCT treatment arm, without increased mortality and with shorter length of stay. Although this subgroup was limited by a rather small sample size, these findings support utilizing PCT treatment algorithms to guide therapy for patients with *E. coli* bacteremia and urogenital infections.

In abdominal infections, the appropriate treatment time largely depends on adequate source control. The results of the Trial of Short-Course Antimicrobial Therapy for Intraabdominal Infection showed similar results if using a fixed 4-day course of antibiotic treatment or a clinical and laboratory-driven course (median, 8 [interquartile range, 5–10] days) [26]. But this study did not focus on bacteremia. Our results did not show differences in antibiotic treatment duration or other clinical

Table 4. Clinical Endpoints Stratified by Bacterial Subspecies in Respiratory Infection

Endpoint	Control Group	PCT Group	Adjusted OR or Difference (95% CI)[a], *P* Value	*P* for Interaction
All respiratory infection	112	98		
Antibiotic therapy	14.2 ± 7.7	12.0 ± 10.4	–2.11 (–4.55 to .33), *P* = .090	
30-d mortality, No. (%)	19 (17.0)	15 (15.3)	0.75 (.43–1.32), *P* = .316	
Length of hospital stay	16.6 ± 14.0	19.9 ± 26.3	2.12 (–3.14 to 7.38), *P* = .429	
Length of ICU stay	15.7 ± 14.0	17.3 ± 18.3	1.58 (–5.42 to 8.57), *P* = .658	
Streptococcus pneumoniae	63	48		
Antibiotic therapy	15.9 ± 7.7	11.2 ± 8.2	**–4.75 (–7.71 to –1.80), *P* = .002**	**.021**
30-d mortality, No. (%)	5 (8)	2 (4)	0.50 (.10–2.47), *P* = .398	.568
Length of hospital stay	14.9 ± 11.1	14.7 ± 11.4	–1.31 (–5.21 to 2.59), *P* = .510	.258
Length of ICU stay	11.0 ± 11.3	14.1 ± 17.8	3.08 (–10.9 to 17.0), *P* = .664	.881
Staphylococcus aureus	12	9		
Antibiotic therapy	12.7 ± 8.1	16.1 ± 7.6	3.44 (–3.05 to 9.94), *P* = .299	.145
30-d mortality, No. (%)	6 (50)	4 (44)	0.58 (.07–4.56), *P* = .604	.867
Length of hospital stay	19.2 ± 16.0	22.1 ± 12.6	2.94 (–9.08 to 15.0), *P* = .631	.961
Length of ICU stay	12.9 ± 10.5	16.1 ± 10.3	3.24 (–6.19 to 12.7), *P* = .500	.792
Escherichia coli	7	10		
Antibiotic therapy	7.9 ± 5.0	10.0 ± 6.5	0.91 (–4.28 to 6.10), *P* = .731	.337
30-d mortality, No. (%)	0 (0)	1 (10)		
Length of hospital stay	16.9 ± 12.6	36.8 ± 68.1	–1.99 (–14.5 to 10.5), *P* = .756	.078
Length of ICU stay	32.5 ± 2.1	18.2 ± 15.1	–14.3 (–33.0 to 4.43), *P* = .135	.245
Pseudomonas aeruginosa	7	5		
Antibiotic therapy	16.3 ± 6.0	16.6 ± 16.6	0.32 (–11.7 to 12.3), *P* = .959	.643
30-d mortality, No. (%)	2 (29)	2 (40)	1.40 (.29–6.86), *P* = .678	.599
Length of hospital stay	28.3 ± 22.7	23.2 ± 20.5	–5.09 (–28.0 to 17.8), *P* = .663	.469
Length of ICU stay	23.2 ± 14.9	19.6 ± 17.1	–3.65 (–22.4 to 15.1), *P* = .702	.623
Haemophilus influenzae	5	4		
Antibiotic therapy	10.4 ± 3.9	6.2 ± 4.5	–4.15 (–8.99 to .69), *P* = .093	.734
30-d mortality, No. (%)	0 (0)	1 (25)		
Length of hospital stay	8.8 ± 5.3	25.0 ± 27.9	16.2 (–4.45 to 36.9), *P* = .124	.385
Length of ICU stay	9.5 ± 2.1	6.0 ± 4.0	–3.50 (–8.33 to 1.33), *P* = .156	.720
Others	18	22		
Antibiotic therapy	11.6 ± 7.5	13.2 ± 15.1	1.62 (–5.87 to 9.10), *P* = .672	.155
30-d mortality, No. (%)	6 (33)	5 (23)	0.69 (.25–1.90), *P* = .471	.575
Length of hospital stay	18.4 ± 17.8	21.3 ± 21.6	4.03 (–8.25 to 16.3), *P* = .520	.964
Length of ICU stay	16.4 ± 17.4	22.7 ± 25.7	6.24 (–9.76 to 22.2), *P* = .445	.424

Data are presented as mean ± SD unless otherwise indicated. Antibiotic therapy, length of hospital stay, and length of ICU stay are shown in days. Bold values denote statistical significance at the $P < .05$ level.

Abbreviations: CI, confidence interval; ICU, intensive care unit; OR, odds ratio; PCT, procalcitonin; SD, standard deviation.

[a]Multivariable hierarchical regression with outcome of interest as dependent variable and trial as a random effect.

outcomes between the PCT and control arms in patients with abdominal infections. However, this may be at least partially influenced by the inability to achieve source control and other confounding factors. Future research should more closely look at patients with abdominal infection to improve antibiotic management and reduce associated side effects.

The strengths of this meta-analysis include a predefined study protocol, a comprehensive search and retrieval of all relevant trials, and a network that permitted inclusion of individual patient data from most eligible trials. We also standardized outcome definitions across trials and performed appropriate subgroup and sensitivity analyses, thereby overcoming the limitation of previous meta-analyses with aggregated data to make more definitive conclusions. We are, to our knowledge, the first to look at the effect of PCT guidance in bacteremic patients. However, our study still has limitations. First, adherence to the PCT algorithm was variable among the studies, ranging from 44% to 100%. Adherence was closely related to the severity of infection with better adherence in low-risk populations, and lower adherence in high-risk trials. As seen in a very recent trial, low adherence may strongly interfere with effects of PCT protocols [27], making education of physicians regarding the benefits of utilizing PCT imperative. Second, we limited our analysis to immunocompetent adults, thereby impeding generalizability of our conclusions to other patient populations. Third, we had substantial heterogeneity in our patient population in regard to site of infection and pathogen identified. This also limits generalizability of results, particularly for our main

endpoint, mortality. Also, we were not able to look at safety endpoints other than mortality and length of stay due to the lack of such outcome data in our dataset. Finally, we did not include the recent Procalcitonin Antibiotic Consensus trial in our dataset as the study was not available at the time of analysis [27].

In conclusion, this pooled analysis of PCT-guided antibiotic management in patients with positive blood cultures from previous randomized trials showed lower antibiotic exposure without an apparent increase in mortality. Effects were most notable in patients with respiratory infections from common respiratory pathogens. PCT treatment algorithms thus offer the opportunity to provide more individualized care, particularly for patients with CAP independent of blood culture results.

Notes

Author contributions. P. S., M. A. M., O. L. N., and Y. W. performed the literature search, performed all analysis for this report, and wrote the first draft. All authors shared trial data, gave critical feedback to the manuscript, and approved the final version. P. S. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. P. S. and B. M. oversaw the study and act as guarantors. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Acknowledgments. We thank all researchers and patients involved in the individual trials for sharing their data. Data of the individual trials are available upon reasonable request based on the authorization of principal investigators of the trials.

Disclaimer. No personnel from the company or from the National Institute for Health Research (NIHR) were involved in the conduct of the analysis or in the preparation of the manuscript, and they had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Financial support. The NIHR provided a research grant for the initial Cochrane analysis; bioMérieux Inc provided an unrestricted research grant to conduct previous analyses with a similar dataset.

Potential conflicts of interest. A. R. F. has served on advisory boards for Novavax, Hologic, Gilead, and MedImmune, and has received research funding from AstraZeneca, Sanofi Pasteur, GlaxoSmithKline, and ADMA Biologics. C. C. has received an unrestricted grant of €2000 from Thermo Fisher Scientific, and has received nonfinancial support from bioMérieux for the ProToCOLD study. Y. S. has received unrestricted research grants from Thermo Fisher, bioMérieux, Orion Pharma, and Pfizer. D. S. and M. T. have received research support from Thermo Fisher. J.-U. S. J. declares that he was invited to the European Respiratory Society meeting 2016 by Roche Pharmaceuticals. M. C.-C., P. S., and B. M. have received support from Thermo Fisher and bioMérieux to attend meetings and fulfill speaking engagements. B. M. has also served as a consultant to bioMérieux and Thermo Fisher and received research support from Roche and Abbott. P. S. reports payments from Roche and Abbott. C. E. L. reports personal fees from Bayer Healthcare and MSD. M. W. has received grants from Janssen-Cilag, Merck Sharp & Dohme-Chibret, Gilead, Astellas, Sanofi, and Thermo Fisher. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Hecker MT, Aron DC, Patel NP, Lehmann MK, Donskey CJ. Unnecessary use of antimicrobials in hospitalized patients: current patterns of misuse with an emphasis on the antianaerobic spectrum of activity. Arch Intern Med **2003**; 163:972–8.
2. Huttner A, Harbarth S, Carlet J, et al. Antimicrobial resistance: a global view from the 2013 World Healthcare-Associated Infections Forum. Antimicrob Resist Infect Control **2013**; 2:31.
3. NICE antimicrobial stewardship: right drug, dose, and time? Lancet **2015**; 386:717.
4. Sager R, Kutz A, Mueller B, Schuetz P. Procalcitonin-guided diagnosis and antibiotic stewardship revisited. BMC Med **2017**; 15:15.
5. Mitsuma SF, Mansour MK, Dekker JP, et al. Promising new assays and technologies for the diagnosis and management of infectious diseases. Clin Infect Dis **2013**; 56:996–1002.
6. US Food and Drug Administration. FDA clears test to help manage antibiotic treatment for lower respiratory tract infections and sepsis. **2017.** Available at: https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm543160.htm.
7. Schuetz P, Birkhahn R, Sherwin R, et al. Serial procalcitonin predicts mortality in severe sepsis patients: results from the multicenter procalcitonin Monitoring Sepsis (MOSES) study. Crit Care Med **2017**; 45:781–9.
8. Schuetz P, Wirz Y, Sager R, et al. Effect of procalcitonin-guided antibiotic treatment on mortality in acute respiratory infections: a patient level meta-analysis. Lancet Infect Dis **2018**; 18:95–107.
9. Schuetz P, Wirz Y, Sager R, et al. Procalcitonin to initiate or discontinue antibiotics in acute respiratory tract infections. Cochrane Database Syst Rev **2017**; 10:CD007498.
10. Woodhead M, Blasi F, Ewig S, et al; Joint Taskforce of the European Respiratory Society and European Society for Clinical Microbiology and Infectious Diseases. Guidelines for the management of adult lower respiratory tract infections—full version. Clin Microbiol Infect **2011**; 17(Suppl 6):E1–59.
11. Schuetz P, Briel M, Christ-Crain M, et al. Procalcitonin to initiate or withhold antibiotics in acute respiratory tract infections (protocol). Cochrane Database Syst Rev **2008**; 4:CD007498.
12. Schuetz P, Muller B, Christ-Crain M, et al. Procalcitonin to initiate or discontinue antibiotics in acute respiratory tract infections. Cochrane Database Syst Rev **2012**; 9:CD007498.
13. Stewart LA, Clarke M, Rovers M, et al; PRISMA-IPD Development Group. Preferred reporting items for systematic review and meta-analyses of individual participant data: the PRISMA-IPD statement. JAMA **2015**; 313:1657–65.
14. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. J Clin Epidemiol **2009**; 62:e1–34.
15. Guyatt GH, Oxman AD, Vist GE, et al; GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ **2008**; 336:924–6.
16. Thompson SG, Turner RM, Warn DE. Multilevel models for meta-analysis, and their application to absolute risk differences. Stat Methods Med Res **2001**; 10:375–92.
17. Turner RM, Omar RZ, Yang M, Goldstein H, Thompson SG. A multilevel model framework for meta-analysis of clinical trials with binary outcomes. Stat Med **2000**; 19:3417–32.
18. Schuetz P, Bolliger R, Merker M, et al. Procalcitonin-guided antibiotic therapy algorithms for different types of acute respiratory infections based on previous trials. Expert Rev Anti Infect Ther **2018**; 16:555–64.
19. Schuetz P, Briel M, Christ-Crain M, et al. Procalcitonin to guide initiation and duration of antibiotic treatment in acute respiratory infections: an individual patient data meta-analysis. Clin Infect Dis **2012**; 55:651–62.
20. Müller F, Christ-Crain M, Bregenzer T, et al; ProHOSP Study Group. Procalcitonin levels predict bacteremia in patients with community-acquired pneumonia: a prospective cohort trial. Chest **2010**; 138:121–9.
21. Drozdov D, Schwarz S, Kutz A, et al. Procalcitonin and pyuria-based algorithm reduces antibiotic use in urinary tract infections: a randomized controlled trial. BMC Med **2015**; 13:104.
22. Sandberg T, Skoog G, Hermansson AB, et al. Ciprofloxacin for 7 days versus 14 days in women with acute pyelonephritis: a randomised, open-label and double-blind, placebo-controlled, non-inferiority trial. Lancet **2012**; 380:484–90.
23. 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**; 49:1–45.
24. Nelson AN, Justo JA, Bookstaver PB, Kohn J, Albrecht H, Al-Hasan MN. Optimal duration of antimicrobial therapy for uncomplicated gram-negative bloodstream infections. Infection **2017**; 45:613–20.
25. Chotiprasitsakul D, Han JH, Cosgrove SE, et al; Antibacterial Resistance Leadership Group. 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 **2018**; 66:172–7.
26. Sawyer RG, Claridge JA, Nathens AB, et al; STOP-IT Trial Investigators. Trial of short-course antimicrobial therapy for intraabdominal infection. N Engl J Med **2015**; 372:1996–2005.
27. Huang DT, Yealy DM, Filbin MR, et al; ProACT Investigators. Procalcitonin-guided use of antibiotics for lower respiratory tract infection. N Engl J Med **2018**; 379:236–49.