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Review

Procalcitonin-guided antibiotic therapy algorithms for different types of acute respiratory infections based on previous trials

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Abstract

Introduction

Although evidence indicates that use of procalcitonin to guide antibiotic decisions for the treatment of acute respiratory infections (ARI) decreases antibiotic consumption and improves clinical outcomes, algorithms used within studies had differences in PCT cut-off points and frequency of testing. We therefore analysed studies evaluating procalcitonin-guided antibiotic therapy and propose consensus algorithms for different respiratory infection types.

Areas covered: We systematically searched randomized-controlled trials (search strategy updated on February 2018) on procalcitonin-guided antibiotic therapy of ARI in adults using a pre-specified Cochrane protocol and analysed algorithms from 32 trials that included 10,285 patients treated in primary care settings, emergency departments (ED), and intensive care units (ICU). We derived consensus algorithms for use of procalcitonin by the type of ARI including community-acquired pneumonia, bronchitis, chronic obstructive pulmonary disease or asthma exacerbation, sepsis, and post-operative sepsis due to respiratory infection. Consensus algorithm recommendations differ with regard to timing of treatment (i.e., timing of initiation in low-risk patients or discontinuation in high-risk patients) and procalcitonin cut-off points for the recommendation/strong recommendation to discontinue of antibiotics (≤0.25/≤0.1 µg/L ED and inpatients, ≤0.5/≤0.25 µg/L in ICU patients, and reduction by ≥80% from peak levels in sepsis patients).

Expert commentary: Our proposed algorithms may facilitate safe and efficient implementation of procalcitonin-guided antibiotic protocols in diverse healthcare settings. Still, the decision about initiation and cessation of antibiotic treatment remains a clinical decision based on the patient assessment and the severity of illness and use of procalcitonin should not delay empirical treatment in high risk situations..

Keywords: procalcitonin, antibiotic stewardship, respiratory infection, pneumonia, systematic review

1. Introduction

Antibiotic overuse and the resulting increase in antimicrobial resistance among pathogenic bacteria, continues to be a major public health issue of global interest [1,2]. Acute respiratory tract infection (ARI) represents one of the leading causes of hospitalization [3]. Although >40% of ARI have a viral aetiology, intensive bacterial diagnostics and concerns about possible bacterial-viral coinfection prompt premature and/or inappropriate antibiotic prescriptions in a significant proportion of cases [4]. In light of this, using an accurate and rapidly quantifiable biomarker of bacterial infection has the potential to restrict antibiotic usage to only the most appropriate cases and thereby reduce antibiotic overconsumption.

Procalcitonin (PCT), a calcitonin-related protein expressed by human epithelial cells, is upregulated in response to bacterial infection and down-regulated in viral infection [5]. Its clinical utility as a diagnostic and prognostic aid in the context of respiratory infections has been evaluated and proven in several studies [6]. Randomized-controlled trials (RCTs) have reported significant reductions in antibiotic prescriptions and shorter treatment duration in patients with ARI when PCT treatment algorithms were used to guide initiation and/or duration of antibiotic therapy [7]. In a 2017 meta-analysis based on individual data from 6,708 patients, the use of PCT guided antibiotic therapy was associated with a 2.4-day reduction in antibiotic exposure (5.7 *versus* 8.1 days), a reduction in antibiotic-related side-effects (16.3% *versus* 22.1%), as well as a reduction in mortality (8.6% *versus* 10.0%) [8,9].

However, one impediment to the acceptance of PCT treatment algorithms in clinical practice is the absence of standard cut-off points. The aim of this systematic review was therefore to summarize data on PCT-guided treatment recommendations used in previous RCTs and define consensus algorithms for adults, stratified by type of acute respiratory tract illness and healthcare setting.

2. Methods

2.1 Trial selection

For this systematic review, trial selection and data collection were based on a protocol published in the Cochrane Library [8,10,11]. This report was prepared in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [12,13]. Results summarizing the effects of PCT use on antibiotic consumption and clinical outcomes have been previously published [8,9]. The aim of this analysis is to focus on the cut-off points for PCT-guided antibiotic treatment recommendations used in the trials included in the systematic review in order to formulate consensus algorithms specific for different types of acute respiratory infections.

2.2 Search strategy

The search strategy was updated on February 10, 2018 in collaboration with personnel from The Cochrane Collaboration. No language or publication restrictions were employed. We searched all databases from the date of their inception to February 10, 2017. All retrieved references were screened for eligibility. The databases searched were the Cochrane Central Register of Controlled Trials (CENTRAL; Issue 1 to February 10, 2017), MEDLINE (1966 to February 10, 2017), and Embase (1980 to February 10, 2017).

2.3 Types of studies and participants

To be included, RCTs were required to compare antibiotic treatment as a primary outcome in adult patients with acute respiratory infection for whom antibiotic decisions were made by utilizing a PCT treatment algorithm (PCT-guided antibiotic stewardship algorithm) versus standard of care. Paediatric trials and trials that did not use PCT to guide initiation and/or duration of antibiotic treatment were excluded. Data were collected from eligible trials that

included adults with a clinical diagnosis of an ARI (including community-acquired pneumonia [CAP], hospital-acquired pneumonia [HAP], ventilator-associated pneumonia [VAP], aspiration pneumonia, bronchitis, or exacerbation of chronic obstructive pulmonary disease [COPD], asthma, or pulmonary fibrosis), sepsis or septic shock, or febrile neutropenia with concomitant respiratory infection.

2.4 Data collection and analysis:

Two reviewers (YW and RS) independently assessed trial eligibility based on titles, abstracts, full-text reports, and further information obtained from trial investigators as needed. Two additional reviewers (RB and MM) reviewed all PCT algorithms in individual trials. Data were assessed in a consistent manner across all trials with standard definitions and parameters, resulting in slightly different mortality and adverse outcome rates in the meta-analysis than previous reported in the individual studies.

In accordance with the Cochrane method, the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) [14] approach was used to assess risk of selection bias, performance bias, detection bias, attrition bias, reporting bias, and other types of bias [8]. This analysis is listed in the **online supplementary material**.

Summary data on the PCT algorithm including types of protocols, PCT cut-off levels, and predefined overruling criteria were reported and consensus algorithms derived from trial data for the following specific types of respiratory tract infection: CAP, bronchitis, exacerbations of COPD and asthma, sepsis, and post-operative sepsis.

To derive consensus algorithms stratified by type of ARI, we studied all protocols and manuscripts included in our analysis with focus on types of patients and PCT cut-offs used in the individual trials, and discussed differences among protocols with all co-authors until

consensus was reached. All co-authors agreed to the proposed consensus PCT algorithms presented in this manuscript.

3. Results

3.1 Overall results of the systematic search

For the final analysis, we considered 32 RCTs that evaluated adults with different types of respiratory infections. They included a total of 10,285 patients (5,056 in the control group and 5,102 in the PCT group). **Table 1** summarizes the design of the trials including number of subjects and types of infection, the PCT cut-off points used for initiation or discontinuation of antibiotic treatment, protocol adherence rates, and clinical outcomes (antibiotic use and mortality) in the PCT versus control groups.

3.2 PCT algorithms by healthcare setting

There were two trials conducted in the primary care setting with a total of 1,008 patients with lower and upper respiratory tract infections [15,16]. Both studies were non-inferiority trials exploring clinical outcomes. A similar PCT algorithm was used in both trials, with a recommendation against antibiotic therapy in patients with PCT levels of <0.25 µg/L and a strong recommendation against antibiotic therapy if PCT levels were <0.1 µg/L. In the Briel study, physicians measured PCT repeatedly in a minority of patients who did not demonstrate improvement and for whom no antibiotics had been prescribed [15]. In the Burkhardt study, a single initial PCT levels was obtained on admission [16]. Both studies demonstrated significant reductions in antibiotic use and no differences in primary safety endpoints between the control and PCT groups. Mortality was very low in both trials.

In the emergency department (ED) and inpatient settings, 14 RCTs with a total of 3,889 patients were eligible for inclusion in our analysis [17-30]. All of the studies measured PCT on admission, five studies collected additional PCT measurements from patients in whom antibiotics were

withheld and 8 studies measured PCT both on admission and during follow-up to guide duration of treatment. All but two studies used initial PCT level obtained on admission to guide initiation of antibiotic therapy. PCT cut-off values of >0.25 µg/L and ≥0.5 µg/L were used in the majority of studies to recommend initiation or strongly recommend initiation of antibiotics, respectively. Similarly, most studies recommended against the use of antibiotics in patients with PCT levels <0.25 µg/L, with a strong recommendation if PCT was ≤0.1 µg/L. The Verduri study used <0.1 µg/L as a cut-off to recommend against antibiotic usage [30]. Two studies focused exclusively on making recommendations to discontinue antibiotics if patients had a PCT cut-off of <0.5 µg/L (Lima et al) or >90% decrease from peak levels (Lima et al and Ogasawara et al) [22,26].

Sixteen studies conducted in the ICU were eligible for inclusion and showed more heterogeneity with regard to patient diagnoses and PCT cut-offs used that in patients in other healthcare settings [31-46]. Thirteen studies evaluated patients with sepsis, one study enrolled patients with pulmonary fibrosis, one study focused on those with exacerbation of COPD and a final study examined the use of PCT in ICU patients with pneumonia. In most studies, patients received antibiotics empirically (without knowledge of PCT levels) and algorithms recommended cessation of antibiotics based on repeated PCT measurements. The majority of trials used recommended cessation of antibiotics at both a cut-off level (range of < 0.1 - 1.0 µg/L) or decrease of PCT from its peak value (range decrease of >50 - 90%).

3.3 Consensus recommendations for specific types of respiratory infections

Based on the data from the different trials included in our analysis, we have derived the following authors` consensus algorithms stratified by the type of respiratory infection.

For CAP (**Table 2**), initiation of antibiotic therapy is recommended when PCT levels are >0.25 µg/L. In patients already undergoing antibiotic therapy, PCT levels should be rechecked every 2–3 days and cessation of therapy should be considered in patients with a favourable clinical response and if PCT levels are either ≤0.25 µg/L or have dropped >80% from peak values. If

PCT levels do not decrease adequately, treatment failure (e.g., empyema, multi-resistant strains, or inadequate antibiotic therapy) should be suspected. If initial PCT levels are ≤0.25 µg/L, a bacterial infection is unlikely and other illnesses should be excluded (e.g., pulmonary embolism or heart failure). In patients with high suspicion of bacterial CAP or in high-risk patients, empiric antibiotic therapy is stil advised and PCT should be reassessed after 24–48 hours. Similarly, depending on results from other diagnostic tests (i.e., cultures) a longer antibiotic treatment duration may be needed despite a rapid decrease in PCT levels.

In patients presenting with bronchitis (**Table 3**), initiation of antibiotic therapy is discouraged if PCT levels are ≤0.25 µg/L. Antibiotics may still be considered in unstable patients or patients with strong clinical evidence of bacterial infection. If subsequent PCT levels are higher than initial admission values and antibiotic therapy should be started, PCT should be rechecked every 2–3 days to facilitate early discontinuation of antibiotics once PCT levels are <0.25 µg/L. In patients with exacerbation of COPD, initiation of antibiotic therapy is recommended if PCT levels are >0.25 µg/L. Levels should be rechecked every 2–3 days and antibiotics discontinued when patients responded favourably and repeat PCT values are ≤0.25 µg/L cut-off or have decreased >80% from the peak value.

If initial PCT levels are ≤0.25 µg/L or <0.1 µg/L, initiation of antibiotic therapy is discouraged and strongly discouraged, respectively, except in unstable patients and patients at high risk for adverse outcomes (e.g., patients with very severe COPD [i.e., Global Initiative for Chronic Obstructive Lung Disease [GOLD] stage IV]). For patients with exacerbation of asthma, a similar algorithm is recommended, with initiation of antibiotic therapy if PCT levels are >0.25 µg/L and cessation if the PCT value drops below 0.25 µg/L.

For patients with clinical suspicion of sepsis in the intensive care unit (ICU) setting (**Table 4**), PCT cut-off levels have to be adapted on a case-by-case basis. Importantly, all patients should receive empirical antibiotic therapy with no delay. If repeat PCT levels are ≤0.5 µg/L or decrease by ≥80%-90% relative to peak values and the patient shows a favourable clinical response, antibiotic therapy can safely be discontinued. Overruling of the algorithm may be necessary in patients showing lack of clinical improvement. Treatment failure should be considered if PCT levels do not decrease adequately. In patients with suspected post-operative sepsis, empiric antibiotic therapy should be initiated through initial PCT elevations may be due to non-infectious Systemic Inflammatory Response Syndrome (SIRS) secondary to surgical stress. However, follow-up PCT measurements may help with early discontinuation of antibiotics which should be considered if PCT levels decrease to <1.0 µg/L or by >65%–75% of peak values and the patient shows clinically a favourable response. If PCT levels do not decrease, treatment failure should be considered. Also, depending on results from other diagnostic tests (i.e., CT-scan, blood or urine cultures) a longer antibiotic treatment duration may be necessary in individual patients. While the focus of our analysis was the development of consensus algorithms for each type of respiratory infection, we also developed algorithms offering recommendations stratified by treatment setting (primary care settings, EDs, and ICUs). These algorithms are listed in the **online supplementary material**.

4. Discussion

4.1 Overall finding

Our aim in performing this systematic review was to derive consensus PCT algorithms for different types of respiratory infections based on previously published trial data. We analysed PCT protocols used in all 32 RCTs retrieved through a systematic literature search until February 2018 that focused on adult patients with respiratory infections treated in the primary care, ED, and ICU settings.

Despite some heterogeneity in the trial design and PCT algorithm recommendations, we found similar patterns in the use of PCT. First, the majority of trials focusing on low-risk patients (e.g., patients with bronchitis in the ED) utilized algorithms which recommended antibiotic initiation based on initial PCT levels. Trials that included high-risk patients (e.g., patients with CAP or sepsis), focused on early cessation of antibiotic therapy by monitoring serial PCT levels during the hospital course, with discontinuation recommendations based on a decrease in PCT levels below pre-specified cut-offs or by at least 80%–90% of peak levels.

Secondly, similar cut-off levels were used by most trials, with PCT levels <0.25 µg/L considered indicative of the absence of bacterial infection and leading to a recommendation against the use of antibiotics, and a strong recommendation against the use of antibiotics for PCT levels <0.1 µg/L in ED and hospitalized patients. In trials conducted in the ICU, after initial empirical antibiotic therapy was administered, PCT levels <0.5 µg/L were used to signal absence or resolution of bacterial infection and associated with a recommendation to discontinue antibiotics if a patient also showed clinical recovery. Levels <0.25 µg/L resulted in a strong recommendation against further antibiotic therapy. Importantly, monitoring of PCT over the course of treatment and cessation of antibiotics once levels dropped below 80%-90% of peak levels likely constitutes the safest and most effect use of PCT in ICU patients.

4.2 Limitations

Our review has limitations. We only included 32 studies that exclusively utilized a RCT study design in order to minimize bias. This might have led to an exclusion of relevant findings from observational research. We also did not include one trial that used PCT to escalate therapy.[47] The included RCTs had different sample sizes, and the quality of their findings was heterogeneous. Moreover, there were some differences with regard to the algorithms. Our recommendations pertaining to the PCT algorithms are therefore based on the cut-offs used by a majority of the studies. Also, we did not include very recent studies published after Febuary

2018 including ProACT, the HiTEMP study and BPCTrea.[48-50] ProACT is a large US based multicentre trial that did not find strong effects of PCT-guided therapy on clinical outcomes and antibiotic usage.[48] This negative result may be explained by lower antibiotic usage in control group patients and a very low adherence to the protocol in intervention group patients. As the ProACT investigators used a similar algorithm as was done in ProHOSP[7], we do not expect that inclusion of this trial would alter our recommendations regarding PCT algorithm. However, the trial importantly demonstrates the importance of educational efforts when introducing PCT into clinical practice to improve appropriate use of PCT and protocol adherence. The BPCTrea trial investigated the effects of PCT on antibiotic usage and mortality in COPD patient receiving intensive care. The HiTEMP study, finally, did not focus on ARI but general patients with fever in the emergency department.

Finally, we derived the PCT algorithms by consensus after discussing the different trials and PCT-cut-offs used within the group of authors. Therefore, the proposed algorithms reflect the opinion and experience of the coauthors based on review of all trials available at the time of manuscript preparation.

Importantly the concept of PCT-guided antibiotic management is based on both, a clinical assessment of a patients condition (i.e., to assess the pre-test probability for an infection in need of antibiotics) and additional use of the biomarker to come to a final decision about antibiotic management. Thus, in a patient with a high pre-test probability (e.g., a patient with sepsis or severe CAP), PCT use may not change the initial antibiotic management, but may improve monitoring of a patient and influences treatment duration. In a patient with low pre-test probability for a bacterial infection (e.g. bronchitis patient, outpatient ith only mild disease), PCT has a stronger influence on the initial management and, if low, may help to rule out bacterial infection. It is thus important that physicians become familiar with the PCT test and treatment algorithm to use this biomarker most efficiently.

4.3 Conclusions

In conclusion, this systematic review suggests that the use of PCT-guided algorithms to guide antibiotic therapy decisions in patients with respiratory tract infections may effectively be applied across a wide spectrum of clinical presentations and clinical settings. We propose PCT algorithms specific for different infection type which when implemented has the potential to improve antibiotic management in clinical practice and slow the development of antimicrobial resistance worldwide.

5. Expert commentary

Safe reduction in the use of antibiotics by use of different antibiotic stewardship tools is now an International priority to limit the increase threat of multi-resistant bacteria. Particularly patients presenting with different types of respiratory infections represent an important population where antibiotics are often misused due to lack of sensitive and specific diagnostics that help to rapidly and accurately rule-out bacterial infections. The use of PCT in this setting is promising with trials showing efficacy in regard to reduced antibiotic usage and improved clinical outcomes. Our proposed algorithms may facilitate safe and efficient implementation of PCT-guided antibiotic protocols in different healthcare settings. A key issue for PCT to improve clinical care is high adherence to algorithm as a very recent US trial – the ProACT – did not find a strong effects of PCT on antibiotic consumption. Ongoing educational efforts to improve protocol adherence is therefore key for such a strategy to work in real life. Also, we have now focused on patients with ARI and future trials should look into other types of infections and other patient populations (e.g., outpatients, pediatric patients). Most current trials have used high sensitive PCT assays done in core labs. With point of care (POC) technology now becoming more widely available, it will be important to understand how these rapid and cheaper assays are used best for patient care. Also, with other microbiological tests becoming available at moderate cost, the

combination of host-directed test (e.g., PCT) and pathogen-directed tests (e.g. PCR) may further improve the accuracy for prediction of bacterial aetiology of an infection.

6. Five year review

There needs to be more efforts for the clinical implementation of antibiotic stewardship tools, including PCT, into clinical routine to improve adherence and thus efficacy of these protocols. With more technological progress, it can be anticipated that novel pathogen-derived tools will help to better identify causative organisms in patients with respiratory infections. Also, technical progress may improve measurement of novel host-response markers at lower costs and thereby make it more appealing for routine care. Investing time and resources in the identification of both, host-response and pathogen-derived markers seems to be most promising.

7. Key issues:

- Several trials have shown that using procalcitonin to guide antibiotic decisions for the treatment of acute respiratory infections decreases antibiotic consumption and improves clinical outcomes
- Procalcitonin algorithms may be adapted to the type of infection and the clinical setting to be most effective and safe
- Procalcitonin algorithm recommendations differ with regard to timing of treatment (i.e., timing of initiation in low-risk patients or discontinuation in high-risk patients) and procalcitonin cut-off points for the recommendation/strong recommendation to discontinue of antibiotics (≤0.25/≤0.1 µg/L ED and inpatients, ≤0.5/≤0.25 µg/L in ICU patients, and reduction by ≥80% from peak levels in sepsis patients).

- Use of these algorithms may facilitate safe and efficient implementation of procalcitonin-guided antibiotic protocols in different healthcare settings.

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Declaration of interest

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Reference annotations
*** Of interest**
**** Of considerable interest**

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TABLE 1 Summary of randomized-controlled trials analysed

Author, year	Diagnosis	Total No. (Control/ PCT)*	PCT recommendation on admission		PCT monitoring for cessation		PCT protocol adherence		Effect on antibiotic use and outcome	
			Recommendation for initiation?	PCT cut-off (µg/L)	Antibiotic cessation?	PCT cut-off (µg/L) for cessation	% Adherence in trial	Overruling criteria by protocol	Antibiotic use (control *versus* PCT)	Mortality (control *versus* PCT)
Primary Care Settings										
Briel et al, 2008 [15]	Upper and lower ARI	458 (226/232)	Yes	>0.25 or increase of >50% from baseline value (strong recommendation if >0.5)	Yes	≤0.25 (<0.1 strong recommendation)	85%	Overruling permitted, but details not specified	Prescription: 97% vs 25% Duration (mean): 7.1 days *versus* 6.2 days	28-day mortality: 1/226 (0.4%) *versus* 0/232 (0%)
Burkhardt et al, 2010 [16]	Upper and lower ARI	550 (275/275)	Yes	≥0.25	No	Not available	87%	Overruling permitted in case of signs of infection, patient's request, results of chest radiography, purulent sputum, strong cough, purulent tonsillitis, or severe obstructive bronchitis	Prescription: 36.7% vs 21.5% Duration (mean): 7.7 days *versus* 7.8 days	28-day mortality: 0/275 (0%) *versus* 0/275 (0%)
Emergency department										

Author, year	Diagnosis	Total No. (Control/ PCT)*	PCT recommendation on admission		PCT monitoring for cessation		PCT protocol adherence		Effect on antibiotic use and outcome	
			Recommendation for initiation?	PCT cut-off (μg/L)	Antibiotic cessation?	PCT cut-off (μg/L) for cessation	% Adherence in trial	Overruling criteria by protocol	Antibiotic use (control *versus* PCT)	Mortality (control *versus* PCT)
Branche et al, 2015 [17]	ARI	300 (149/151)	Yes	≥0.25 (strong recommendation if ≥0.5)	Yes	<0.25 (strong recommendation if ≤0.1)	64%	Not reported	Duration (median): 4.0 days *versus* 3.0 days	Not available
Christ-Crain et al, 2004 [18]	ARI	243 (119/124)	Yes	>0.25 (strong recommendation if ≥0.5)	No	Not available	83%	Overruling permitted, but details not specified	Prescription: 83% vs 44% Duration (mean): 12.8 days *versus* 10.9 days	Overall mortality: 4/119 (3.4%) *versus* 4/124 (3.2%)
Christ-Crain et al, 2006 [19]	Pneumonia	302 (151/151)	Yes	>0.25 (strong recommendation if >0.5)	Yes	<0.25 (strong recommendation if <0.1) or if PCT drops ≥10 to <10% of peak level	87%	Overruling permitted, but details not specified	Prescription: 99% vs 85% Duration (mean): 12.9 days *versus* 5.8 days	Overall mortality: 20/151 (13.2%) *versus* 18/151 (11.9%)

Author, year	Diagnosis	Total No. (Control/ PCT)*	PCT recommendation on admission		PCT monitoring for cessation		PCT protocol adherence		Effect on antibiotic use and outcome	
			Recommendation for initiation?	PCT cut-off (μg/L)	Antibiotic cessation?	PCT cut-off (μg/L) for cessation	% Adherence in trial	Overruling criteria by protocol	Antibiotic use (control *versus* PCT)	Mortality (control *versus* PCT)
Corti et al, 2016 [20]	AECOPD	120 (58/62)	Yes	>0.25	Yes	≤0.25 or drop of 80% from peak value (strong recommendation if ≤0.15)	61.10%	Overruling permitted in case of respiratory or hemodynamic instability, infiltrate on chest X-ray, fever ≥38.5°C, or after consulting ProToCOLD team	Prescription: 67.2% *versus* 41.9% Duration (mean): 9.0 days *versus* 6.1 days	28-day mortality: 2/58 (3.4%) *versus* 1/62 (1.6%)
Kristoffersen et al, 2009 [21]	ARI	223 (113/110)	Yes	≥0.25 (strong recommendation if >0.5)	Yes	<0.25	59%	Overruling permitted, but details not specified	Prescription: 79% *versus* 85% Duration (mean): 6.8 days *versus* 5.1 days	Mortality during hospitalization: 1/107 (0.9%) *versus* 2/103 (1.9%)
Lima et al, 2016 [22]	Febrile neutropenia	62 (31/31)	No	Not available	Yes	<0.5 or >90% drop off peak value	44%	Overruling permitted, but details not specified	Duration (median): 8.0 days *versus* 9.0 days	28-day mortality: 2/31 (6.5%) *versus* 4/30 (13.3%)

Author, year	Diagnosis	Total No. (Control/ PCT)*	PCT recommendation on admission		PCT monitoring for cessation		PCT protocol adherence		Effect on antibiotic use and outcome	
			Recommendation for initiation?	PCT cut-off (μg/L)	Antibiotic cessation?	PCT cut-off (μg/L) for cessation	% Adherence in trial	Overruling criteria by protocol	Antibiotic use (control *versus* PCT)	Mortality (control *versus* PCT)
Long et al, 2009 [24]	Pneumonia	127 (64/63)	Yes	>0.25	Yes	<0.25	47.60%	Not reported	Prescription: 97% *versus* 86% Duration (median): 10 days *versus* 6 days	Overall mortality: 0/64 (0%) *versus* 0/63 (0%)
Long et al, 2011 [23]	Pneumonia	172 (86/86)	Yes	≥0.25	Yes	<0.25 (strong recommendation if <0.1)	100%	Not reported	Prescription: 97.5% *versus* 84.4% Duration (median): 7.0 days *versus* 5.0 days	Not available
Long et al, 2014 [25]	Exacerbation of Asthma	180 (90/90)	Yes	>0.25	No	Not available	Not reported	Overruling permitted, but details not specified	Prescription: 87.8% *versus* 48.9% Duration (median): 6.0 days *versus* 6.0 days	Not available

Author, year	Diagnosis	Total No. (Control/ PCT)*	PCT recommendation on admission		PCT monitoring for cessation		PCT protocol adherence		Effect on antibiotic use and outcome	
			Recommendation for initiation?	PCT cut-off (μg/L)	Antibiotic cessation?	PCT cut-off (μg/L) for cessation	% Adherence in trial	Overruling criteria by protocol	Antibiotic use (control *versus* PCT)	Mortality (control *versus* PCT)
Ogasawara et al, 2014 [26]	Pneumonia	105 (52/53)	No	Not available	Yes	<10% of PCT peak value	59%	Overruling permitted, but details not specified	Duration (median): 8.0 days *versus* 5.0 days	In-hospital mortality: 10/48 (21%) *versus* 5/48 (10%) Pneumonia relapse and death within 30 days: 18/48 (37.5%) *versus* 12/48 (25%)

Author, year	Diagnosis	Total No. (Control/ PCT)*	PCT recommendation on admission		PCT monitoring for cessation		PCT protocol adherence		Effect on antibiotic use and outcome	
			Recommendation for initiation?	PCT cut-off (µg/L)	Antibiotic cessation?	PCT cut-off (µg/L) for cessation	% Adherence in trial	Overruling criteria by protocol	Antibiotic use (control *versus* PCT)	Mortality (control *versus* PCT)
Schuetz et al, 2009 [27]	ARI	1381 (694/687)	Yes	>0.25 (strong recommendation if >0.5)	Yes	≤0.25 or high PCT (>10) and drop of PCT by 80% from initial level (strong recommendation if <0.1 or high PCT [>10] and drop of PCT by 90% from initial level)	46.30%	Overruling permitted in case of patients with immediate need for ICU admission, with respiratory or hemodynamic instability, with positive antigen test for *Legionella pneumophila*, after consulting with the study centre, and in patients with severe CAP and PCT values of <0.1µg/L or ≤0.25µg/L	Prescription: 87.7% *versus* 75.4% Duration (median): 8.7 days *versus* 5.7 days	Overall mortality: 33/688 (4.8%) *versus* 34/671 (5.1%)
Stolz et al, 2007 [28]	AECOPD	226 (113/113)	Yes	>0.25	No	Not available	73.30%	Overruling permitted, but details not specified	Prescription: 72% *versus* 40%	Mortality within 6 months: 9/106 (8.5%) *versus* 5/102 (4.9%)

Author, year	Diagnosis	Total No. (Control/ PCT)*	PCT recommendation on admission		PCT monitoring for cessation		PCT protocol adherence		Effect on antibiotic use and outcome	
			Recommendation for initiation?	PCT cut-off (μg/L)	Antibiotic cessation?	PCT cut-off (μg/L) for cessation	% Adherence in trial	Overruling criteria by protocol	Antibiotic use (control *versus* PCT)	Mortality (control *versus* PCT)
Tang et al, 2013 [29]	Exacerbation of Asthma	265 (133/132)	Yes	>0.25	No	Not available	Not reported	Not reported	Prescription: 74.8% *versus* 46.1%	Not available
Verduri et al, 2015 [30]	AECOPD	183 (90/93)	Yes	≥0.25 or ≥0.1–<0.25 and clinically unstable	Yes	<0.1	Not reported	Overruling permitted in case of clinical inappropriateness	Patients with ≥1 exacerbation: 27.78 *versus* 31.82	Mortality within 6 months: 2/90 (2.22%) *versus* 3/88 (3.41%)
ICU and Inpatient Settings†										
Annane et al, 2013 [31]	Sepsis	62 (31/31)	Yes	≥0.5 (strong recommendation if ≥5.0)	Yes	<0.5 (strong recommendation if <0.25)	63%	Overruling not permitted	Patients on Abx on day 5: 21/26 (81%) *versus* 18/27 (67%)	Overall mortality: 10/30 (33%) *versus* 7/31 (23%)
Bloos et al, 2016 [32]	Sepsis	1180 (593/587)	No	Not available	Yes	≤0.1 or >50% drop from previous level	49.60%	Overruling permitted, but details not specified	Abx exposure days per 1000 ICU days: 862 days *versus* 823 days	28-day mortality: 149/529 (28.2%) *versus* 140/547 (25.6%)

Author, year	Diagnosis	Total No. (Control/ PCT)*	PCT recommendation on admission		PCT monitoring for cessation		PCT protocol adherence		Effect on antibiotic use and outcome	
			Recommendation for initiation?	PCT cut-off (μg/L)	Antibiotic cessation?	PCT cut-off (μg/L) for cessation	% Adherence in trial	Overruling criteria by protocol	Antibiotic use (control *versus* PCT)	Mortality (control *versus* PCT)
Bouadma et al, 2010 [33]	Sepsis	630 (311/319)	Yes	≥0.5 (strong recommendation if ≥1.0)	Yes	<0.5 (strong recommendation if <0.25) or ≥80% drop from peak level	81%	Overruling permitted in case of continued antibiotics for clinically persistent infection, or patient deemed to have no infection	Abx-free days alive: 11.6 days *versus* 14.3 days Duration (mean): 9.9 days *versus* 6.1 days	28-day mortality: 64/314 (20.4%) *versus* 65/307 (21.2%)
Deliberato et al, 2013 [35]	Sepsis	81 (42/39)	No	Not available	Yes	<0.5 or >90% drop from peak level	Not reported	Overruling permitted, but details not specified	Duration (median): 11.0 days *versus* 10.0 days	Overall mortality: 4/39 (10.3%) *versus* 2/42 (4.8%)
de Jong et al, 2016 [34]	Sepsis	1575 (776/799)	No	Not available	Yes	≤0.5 or ≥80% drop from peak level	44%	Overruling permitted, but not specified	Abx-free days in first 28 days: 5.0 days *versus* 7.0 days Duration (median): 7.0 days *versus* 5.0 days	28-day mortality: 196/785 (25.0%) *versus* 149/761 (19.6%)

Author, year	Diagnosis	Total No. (Control/ PCT)*	PCT recommendation on admission		PCT monitoring for cessation		PCT protocol adherence		Effect on antibiotic use and outcome	
			Recommendation for initiation?	PCT cut-off (μg/L)	Antibiotic cessation?	PCT cut-off (μg/L) for cessation	% Adherence in trial	Overruling criteria by protocol	Antibiotic use (control *versus* PCT)	Mortality (control *versus* PCT)
Ding et al, 2013 [36]	Acute exacerbation of pulmonary fibrosis	78 (39/39)	Yes	>0.25	Yes	≤0.25	100%	Overruling not permitted	Prescription: 100% *versus* 79% Duration (median): 14.5 days *versus* 8.7 days	30-day mortality: 20/35 (57.1%) *versus* 21/33 (63.6%)
Hochreiter et al 2009 [37]	Sepsis	110 (53/57)	No	Not available	Yes	<1 or drop to 25-35% of initial level over 3 days	Not reported	Overruling permitted, but details not specified	Duration (mean): 7.9 days *versus* 5.9 days	Overall mortality: 14/53 (26.4%) *versus* 15/57 (26.3%)
Layios et al, 2012 [38]	Sepsis	509 (251/258)	Yes	>0.5 (strong recommendation if >1.0)	No	Not available	46.30%	Not reported	Abx treatment days of ICU days: 57.7% *versus* 62.6 % Abx defined daily dose/100 ICU days (mean): 141.1 days *versus* 147.3 days	Overall mortality: 53/251 (21.1%) *versus* 56/258 (21.7%)

Author, year	Diagnosis	Total No. (Control/ PCT)*	PCT recommendation on admission		PCT monitoring for cessation		PCT protocol adherence		Effect on antibiotic use and outcome	
			Recommendation for initiation?	PCT cut-off (μg/L)	Antibiotic cessation?	PCT cut-off (μg/L) for cessation	% Adherence in trial	Overruling criteria by protocol	Antibiotic use (control *versus* PCT)	Mortality (control *versus* PCT)
Maravić-Stojković et al, 2011 [39]	Sepsis	205 (103/102)	Yes	≥0.5	Yes	≤0.5	Not reported	Overruling permitted, but details not specified	Prescription: 49.0% *versus* 19.0%	Overall mortality: 8/103 (7.8%) *versus* 7/102 (6.9%)
Najafi et al, 2015 [40]	Sepsis	60 (30/30)	No	Not available	Yes	≤0.5, recheck after 12 hours 0.5-2, recheck after 8 hours	Not reported	Not reported	Exposure (total days): 320 days *versus* 128 days	In-hospital mortality: 4/30 (13.3%) *versus* 5/30 (16.6%)
Nobre et al, 2008 [41]	Sepsis	79 (40/39)	No	Not available	Yes	Baseline PCT ≥1: Re-evaluate on day 5 and stop if <0.25 or drop >90% from baseline value Baseline PCT <1: Re-evaluate on day 3 and stop if <0.1 and careful clinical evaluation rules out severe infection	81%	Overruling permitted, but details not specified	Duration (median): 9.5 days *versus* 6.0 days	28-day mortality: 8/40 (20.0%) versus 8/39 (20.5%)

Author, year	Diagnosis	Total No. (Control/ PCT)*	PCT recommendation on admission		PCT monitoring for cessation		PCT protocol adherence		Effect on antibiotic use and outcome	
			Recommendation for initiation?	PCT cut-off (μg/L)	Antibiotic cessation?	PCT cut-off (μg/L) for cessation	% Adherence in trial	Overruling criteria by protocol	Antibiotic use (control *versus* PCT)	Mortality (control *versus* PCT)
Oliveira et al, 2013 [42]	Sepsis	97 (47/50)	No	Not available	Yes	Initial PCT <1.0: <0.1 at day 4 or after 7 days of Abx therapy Initial PCT ≥1.0: ≥90% decrease or after 7days of Abx therapy	87.80%	Overruling permitted, but details not specified	Duration (mean): 7.2 days *versus* 8.1 days Duration (median): 6 days *versus* 7 days	28-day mortality: 15/45 (33.3%) versus 16/49 (32.7%)
Schroeder et al, 2009 [43]	Sepsis	27 (13/14)	No	Not available	Yes	≤1 or drop to 25-35% of initial value over 3 days	Not reported	Overruling permitted, but details not specified	Duration (mean): 8.3 days *versus* 6.6 days	Overall mortality: 3/13 (23.1%) *versus* 3/14 (21.4%)
Shehabi et al, 2014 [44]	Sepsis	400 (200/200)	No	Not available	Yes	<0.25 (and infection highly unlikely) or >90% drop from initial level (strong recommendation if <0.1)	97%	Overruling permitted, but details not specified	Abx-free days at day 28: 17 days *versus* 20 days Duration (median): 11 days *versus* 9 days	90-day mortality: 31/198 (16%) *versus* 35/196 (18%)

Author, year	Diagnosis	Total No. (Control/ PCT)*	PCT recommendation on admission		PCT monitoring for cessation		PCT protocol adherence		Effect on antibiotic use and outcome	
			Recommendation for initiation?	PCT cut-off (μg/L)	Antibiotic cessation?	PCT cut-off (μg/L) for cessation	% Adherence in trial	Overruling criteria by protocol	Antibiotic use (control *versus* PCT)	Mortality (control *versus* PCT)
Stolz et al, 2009 [45]	Pneumonia	101 (50/51)	No	Not available	Yes	<0.5 or >80% drop from initial level (strong recommendation if <0.25)	Not reported	Overruling permitted, but details not specified	Abx-free days alive: 9.5 days *versus* 13 days Duration (median): 15 days *versus* 10 days	28-day mortality: 12/50 (24.0%) *versus* 8/51 (15.7%)
Wang et al, 2016 [46]	AECOPD	194 (97/97)	No	Not available	No	Not available	82.3% (17 patients received Abx in the control group)	Overruling permitted, but details not specified	Treatment success within 10 days Abx use within 30 days of hospital discharge: 12 days *versus* 17 days	In-hospital or 30-day mortality: 2/96 (2.1%) *versus* 5/95 (5.63%)

*Total for all studies: 10,285 (Control: 5,056; PCT: 5,102)
†Mostly medical ICU patients, with some surgical ICU and general ward patients.

Abbreviations: Abx, antibiotics; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; ARI, acute respiratory infection; CAP, community-acquired pneumonia; CF, Cystic Fibrosis; CT, computed tomography; Dep., Department; ED, emergency department; FN, febrile neutropenia; ICU, intensive care unit; LRTI, lower respiratory tract infection; PSI, pneumonia severity index; RTI respiratory tract infection; TB, Tuberculosis; VAP, ventilator-associated pneumonia

TABLE 2 Consensus recommendations for procalcitonin-guided antibiotic therapy of community-acquired pneumonia

Evaluation at time of admission							
PCT cut-off	**<0.1 µg/L**		**≤0.25 µg/L**		**>0.25 µg/L**		**>0.5 µg/L**
Recommendation regarding use of antibiotics	Low PCT levels make a bacterial CAP unlikely. Initiation of antibiotics is advised in all patients that have strong suspicion of bacterial CAP or are clinically unstable (see below)				Initiation of therapy encouraged		Initiation of therapy strongly encouraged
Overruling the algorithm	Consider use of antibiotics if patients are clinically unstable, are at high risk for adverse outcome (e.g., PSI classes IV-V, immunosuppression), or have strong evidence of a bacterial pathogen						
Follow-up/other comments	Reassess patients' condition and recheck PCT level after 6–24 hours in all patients from whom antibiotics were withheld				Recheck PCT level every 2–3 days to consider early cessation of antibiotics		
Follow-up evaluation every 2–3 days							
PCT cut-off	**<0.1 µg/L**		**≤0.25 µg/L**		**>0.25 µg/L**		**>0.5 µg/L**
PCT kinetics	**>90%**		**>80%**				
Recommendation regarding use of antibiotics	Cessation of therapy strongly encouraged		Cessation of therapy encouraged		Cessation of therapy discouraged		Cessation of therapy strongly discouraged
Overruling the algorithm	Consider continuation of antibiotics if patients are clinically unstable						
Follow-up/other comments	Clinical re-evaluation as appropriate				Consider treatment to have failed if PCT level does not decrease adequately		

Abbreviations: PCT, procalcitonin; PSI, pneumonia severity index

TABLE 3 Consensus recommendations for procalcitonin-guided antibiotic therapy of bronchitis

Evaluation at time of admission							
PCT cut-off	**<0.1 µg/L**		**≤0.25 µg/L**		**>0.25 µg/L**		**>0.5 µg/L**
Recommendation regarding use of antibiotics	Initiation of therapy strongly discouraged		Initiation of therapy discouraged		Initiation of therapy encouraged		Initiation of therapy strongly encouraged
Overruling the algorithm	Consider alternative diagnosis, or use of antibiotics if patients are clinically unstable, there are signs of infection, infiltrate on chest X-ray, purulent sputum, strong cough, purulent tonsillitis, severe obstructive bronchitis, or have strong evidence of a bacterial pathogen						
Follow-up/other comments	Reassess patients' condition and recheck PCT level after 6–24 hours in all patients from whom antibiotics were withheld				Recheck PCT level every 2–3 days to consider early cessation of antibiotics		
Follow-up evaluation every 2 to 3 days							
PCT cut-off	**<0.1 µg/L**		**≤0.25 µg/L**		**>0.25 µg/L**		**>0.5 µg/L**
PCT kinetics	**>90%**		**>80%**				
Recommendation regarding use of antibiotics	Cessation of therapy strongly encouraged		Cessation of therapy encouraged		Cessation of therapy discouraged		Cessation of therapy strongly discouraged
Overruling the algorithm	Consider continuation of antibiotics if patients are clinically unstable						
Follow-up/other comments	Clinical re-evaluation as appropriate				Consider treatment to have failed if PCT level does not decrease adequately		

Abbreviation: PCT, procalcitonin

TABLE 4 Consensus recommendations for procalcitonin-guided therapy of sepsis in the intensive care unit setting

Evaluation at time of admission							
PCT cut-off	**<0.25 µg/L**		**≤0.5 µg/L**		**>0.5 µg/L**		**≥1 µg/L**
Recommendation regarding use of antibiotics	Low PCT levels make a bacterial sepsis unlikely, but initial use of antibiotics is advised in all patients possible bacterial sepsis				Initiation of therapy encouraged		Initiation of therapy strongly encouraged
Overruling the algorithm	Empirical antibiotic therapy recommended in all patients with clinical suspicion of infection						
Follow-up/other comments	Consider alternative diagnosis; reassess patients' condition and recheck PCT level every 2 days				Reassess patients' condition and recheck PCT level every 1–2 days to consider early cessation of antibiotics		
Follow-up evaluation every 1 to 2 days							
PCT cut-off	**<0.25 µg/L**		**≤0.5 µg/L**		**>0.5 µg/L**		**≥1 µg/L**
PCT kinetics	**>90%**		**>80%**				
Recommendation regarding use of antibiotics	Cessation of therapy strongly encouraged		Cessation of therapy encouraged		Cessation of therapy discouraged		Cessation of therapy strongly discouraged
Overruling the algorithm	Consider continuation of antibiotics if patients are clinically unstable						
Follow-up/other comments	Clinical re-evaluation as appropriate				Consider treatment to have failed if PCT level does not decrease adequately		

Abbreviation: PCT, procalcitonin