Pros and cons of using biomarkers versus clinical decisions in start and stop decisions for antibiotics in the critical care setting

Werner C. Albrich & Stephan Harbarth

Intensive Care Medicine

ISSN 0342-4642

Intensive Care Med
DOI 10.1007/s00134-015-3978-8

Springer

Intensive Care Med
DOI 10.1007/s00134-015-3978-8

REVIEW

Werner C. Albrich
Stephan Harbarth

Pros and cons of using biomarkers versus clinical decisions in start and stop decisions for antibiotics in the critical care setting

Received: 29 March 2015
Accepted: 9 July 2015

Presented in part at the 54th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington, DC, 8 September 2014 (symposium abstract, L1915).

Essential gist: Antibiotic stewardship with PCT and CRP is safe and effective in ICUs, but short course therapy is also supported by non-biomarker studies.

W. C. Albrich (✉)
Division of Infectious Diseases and Hospital Epidemiology, Kantonsspital St. Gallen, Rorschacherstrasse 95, 9007 St. Gallen, Switzerland
e-mail: Werner.albrich@kssg.ch
Tel.: +41 71 494 2653

S. Harbarth
Division of Infectious Diseases and Hospital Epidemiology, Faculty of Medicine, Geneva University Hospitals, Geneva, Switzerland
e-mail: Stephan.harbarth@hcuge.ch

Abstract *Introduction:* Patients in the intensive care unit (ICU) frequently receive prolonged or even unnecessary antibiotic therapy, which selects for antibiotic-resistant bacteria. Over the last decade there has been great interest in biomarkers, particularly procalcitonin, to reduce antibiotic exposure. *Methods:* In this narrative review, we discuss the value of biomarkers and provide additional information beyond clinical evaluation in order to be clinically useful and review the literature on sepsis biomarkers outside the neonatal period. Both benefits and limitations of biomarkers for clinical decision-making are reviewed. *Results:* Several randomized controlled trials (RCTs) have shown the safety and efficacy of procalcitonin to discontinue antibiotic therapy in patients with severe sepsis or septic shock. In contrast, there is limited utility of procalcitonin for treatment initiation or withholding therapy initially. In addition, an algorithm using procalcitonin for treatment escalation has been ineffective and is probably associated with poorer outcomes. Little data from interventional studies are available for other biomarkers for antibiotic stewardship, except for C-reactive protein (CRP), which was recently found to be similarly effective and safe as procalcitonin in a randomized controlled trial. We finally briefly discuss biomarker-unrelated approaches to reduce antibiotic duration in the ICU, which have shown that even without biomarker guidance, most patients with sepsis can be treated with relatively short antibiotic courses of approximately 7 days. *Conclusions:* In summary, there is an ongoing unmet need for biomarkers which can reliably and early on identify patients who require antibiotic therapy, distinguish between responders and non-responders and help to optimize antibiotic treatment decisions among critically ill patients. Available evidence needs to be better incorporated in clinical decision-making.

Keywords Procalcitonin · CRP · Antibiotic stewardship · Short-course therapy · Sepsis · Respiratory tract infections

Introduction

Patients in intensive care units (ICUs) are prone to numerous infectious complications. In a large multinational point prevalence study, 51 % of ICU patients were considered infected and the prevalence of multidrug resistance was positively correlated with length of ICU stay [1]. Multiple factors contribute to this predisposition including the nature of patients' severe illness, underlying or ICU-acquired organ dysfunction, and local or systemic

Published online: 21 July 2015

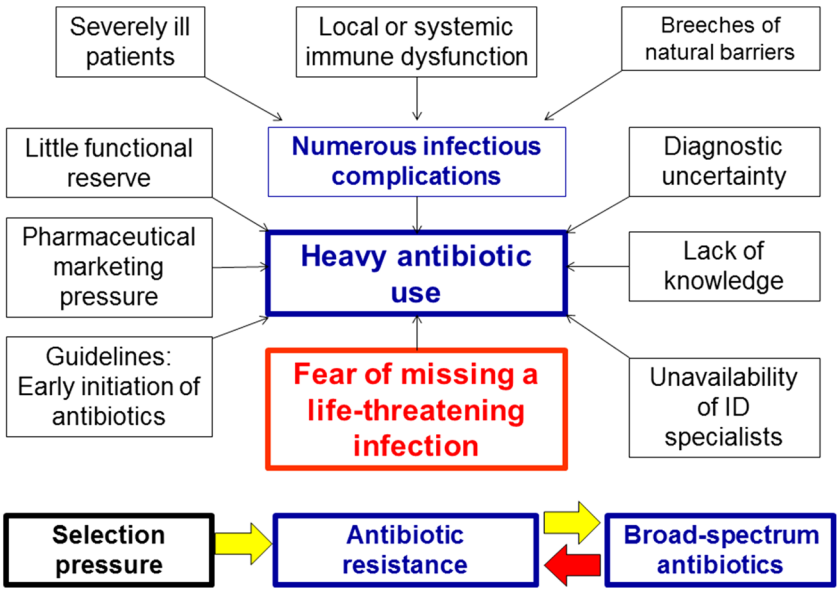

Fig. 1 Causes and consequences of heavy antibiotic use in the intensive care unit. *ID* infectious diseases

immune dysfunction [1]. Breeches in natural barriers due to invasive diagnostic and therapeutic procedures and catheters and tubes are frequent entry points or sources of life-threatening infections (Fig. 1). Frequently, clinicians face uncertainty in the early diagnosis and severity assessment of infections in the ICU caused by limited utility of the clinical examination, conventional radiology, or routine laboratory tests. Nevertheless, clinical judgement has been reported to have reasonable diagnostic accuracy (AUC = 0.77) for blood-culture-proven sepsis among pediatric ICU physicians in Boston and Zurich [2]. As a result of the lack of clear guidance in difficult clinical situations dealing with critically ill patients there is an inherent tendency for antibiotic overuse in the ICU setting. In the multicenter point prevalence EPIC II surveillance study, 71 % of patients were receiving antibiotics at the time of study [1]. This tendency is further supported by data indicating a significantly increased mortality if there was a delay of appropriate antibiotic initiation beyond 1 h after triage (33.2 vs. 10.5 %, $p = 0.02$) or after qualification for early goal-directed therapy (38.5 vs. 25.0 %, $p = 0.03$) in patients with severe sepsis or septic shock [3, 4]. Accordingly the most recent Surviving Sepsis Campaign guidelines strongly recommend initiation of antibiotics within 1 h of recognition of severe sepsis and septic shock [5]. Perhaps the most pressing reason for the frequent use of antibiotics in the ICU is the overarching fear of missing a life-threatening infection. In addition to their recommendation of timely initiation of appropriate antimicrobial therapy, the Surviving Sepsis Campaign guidelines state that antimicrobial regimens should be reassessed daily for potential de-escalation and suggest that low levels of procalcitonin or similar biomarkers might be used as one of several pieces of information to help to discontinue empiric antibiotics if there is no more evidence of infection [5].

Several strategies effectively reduce antibiotic consumption in the ICU through antibiotic stewardship programs, which consist mainly of restriction of antibiotic indications (i.e., withholding antibiotics), reducing duration of antibiotic therapy by effective source control, short-course therapy, individualization of treatment duration according to individual response, improved accuracy and shorter turnaround time of diagnostic tests (i.e., discontinuation of antibiotic therapy) and computer-based stop orders or checklists including criteria for the maintenance of antibiotic therapy [6]. In particular, treatment duration is largely based on expert opinion. Assessment of the treatment response remains challenging in septic ICU patients because of the poor diagnostic accuracy of clinical examination and poor correlation of microbiological eradication with clinical response [7], which is also affected by the immune response, underlying diseases, and other concomitant infectious or non-infectious complications [8]. Therefore, treatment duration should not be guided by success of pathogen eradication alone [7]. Not surprisingly, there are large variations in treatment duration, e.g., for ICU patients with bacteremia. For all of these challenges, biomarkers may be beneficial adjunctive tools and have shown promising results. However, sepsis is a highly complex pathophysiologic process in response to an infectious stimulus rather than a single disease: The host response involves such different pathways and cascades such as the complement system, coagulation system, pathways of leukocyte activation, and damage-associated molecular patterns all leading to a proinflammatory state while there are simultaneously signs of an anti-inflammatory response mediated by neuroendocrine regulation, impairment, and

apoptosis of immune cells. All this leads to the question whether the sepsis syndrome is not too complex to be reflected by individual biomarkers. The aim of this narrative review was to summarize the scientific literature on advantages and disadvantages of biomarker-guided decision-making regarding initiation and discontinuation of antibiotic therapy in critically ill patients in the ICU and to highlight some alternative approaches. We used the following search terms without language restriction in PubMed until January 2015 and searched personal files and references in identified articles: biomarker*, antibiotic*, "stewardship", guid*, "initiation", "discontinuation", "ICU", "intensive", critical*. Neonatal infections were excluded.

What to expect from a biomarker?

The World Health Organization (WHO) defines a biomarker as an objectively measured characteristic used as an indicator of a normal or pathologic biologic process or a pharmacological response. It has been suggested that biomarkers should be sensitive and specific, measurable with good precision and reproducibility, readily available, affordable, responsive to minor changes, and provide timely results [9]. Ideally biomarkers should be independent of comorbidities such as renal or hepatic dysfunction, should not be modified by renal replacement therapy or other medications (such as anti-inflammatory drugs), and the biomarker should not demonstrate an exhaustion or fatigue phenomenon in prolonged or successive infections. In addition, biomarkers are considered clinically useful if they provide additional information beyond the clinical evaluation, if they shorten the time to diagnosis or treatment decision, and show a large amplitude of variation [10].

Specificity challenges

There is a great overlap of biomarker values between different infectious (bacterial, viral, parasitic) and non-infectious etiologies in patients with the systemic inflammatory response syndrome (SIRS). This has been shown both for commonly used and widely available "sepsis biomarkers" (procalcitonin (PCT), C-reactive protein (CRP), white blood cell or neutrophil count) and for "sepsis biomarkers" that are still experimental and not commercially available in most settings [soluble urokinase-type plasminogen activator receptor (suPAR), soluble triggering receptor expressed on myeloid cells-1 (sTREM-1), and macrophage inhibitory factor (MIF)] [11]. PCT is a hormokine within the family of calcitonin gene-related peptides, which is hyperexpressed in parenchymatous organs in response to endotoxin or cytokines. In several head-to-head studies PCT has been found to have greater diagnostic accuracy than CRP, IL-6, IL-8, or lactate in adults to distinguish between bacterial sepsis and non-infectious etiologies of SIRS [12–14], whereas other studies have found greater utility of CRP than PCT [11, 15]. PCT allows one to distinguish bacterial superinfections in patients with viral pneumonia such as influenza [16]. PCT does not usually increase in fungal infections [17]. Therefore fungal etiologies should be considered in special patient populations with suspected sepsis and low PCT values, but at high risk of fungal superinfection. Common to all observational studies is the difficulty to define the etiology with certainty. Potential advantages of PCT over CRP include a more rapid increase within 3–12 h and an earlier peak within 24 h [18–20]. Despite a longer half-life of PCT (22–35 h) [19] than CRP (19 h) [21], PCT levels decrease faster than CRP when the infection resolves [17]. However, several relevant causes of false-positive and false-negative results have to be considered for both PCT and CRP [22]. For instance, the CRP response is blunted in fulminant hepatic failure, but overall the clinical relevance of renal dysfunction, chronic liver insufficiency, and corticosteroid treatment on PCT and CRP seems to be negligible [23]. As recently summarized, patients with chronic kidney disease and active infection have higher levels than those without infections [24]. PCT levels in the absence of bacterial infections are higher in patients with chronic kidney dysfunction than in those without and levels decrease after renal replacement therapy while the magnitude of these differences depends on the method used [24]. The increased PCT levels are likely primarily due to increased proinflammatory cytokines as a consequence of renal insufficiency and only slight changes in PCT clearance. However, the clinical relevance of this increase remains questionable [23] as patients with acute or chronic renal failure and patients requiring dialysis were included in randomized controlled trials (RCTs) without adaption of cutoff levels. For instance, 22.2 and 17.6 % of patients in the ProHOSP and the ProRATA RCTs had renal failure, respectively [23, 25], but chronic renal failure resulted in only 1.2 % higher PCT values in the ProHOSP study [23]. These results suggested that in at least this large RCT of 925 patients with community-acquired pneumonia (CAP) no adjustment of PCT cutoff values was necessary [23]. Other authors proposed different PCT cutoff values for patients with chronic kidney disease but these have not been prospectively tested [24]. Both CRP and PCT kinetics are independent of neutropenia [26, 27].

In a review of 178 sepsis biomarkers Pierrakos and Vincent found none of them specific or sensitive enough for diagnosis or prognosis in routine clinical practice with too much of an overlap between infectious and inflammatory conditions [28]. Therefore,

multimarker algorithms were recommended for sepsis diagnosis [11], but even those face specificity or sensitivity problems in addition to cost and increased complexity in the analysis and incorporation into clinical algorithms.

There is great controversy in the literature on the utility of PCT in the diagnosis of sepsis. Several meta-analyses arrive at different conclusions, which can be at least partly attributed to inclusion of studies with different assays yielding different functional sensitivities, different settings, quality of study design, and different and sometimes poorly chosen control groups [29–32].

Handling uncertainty in clinical decision-making

Knowledge of the medical literature has to be applied to the unique clinical situation for clinical decision-making. However, clinicians have to deal with varying levels of uncertainty since published data frequently does not correspond exactly to the clinical scenario. Therefore "gut feeling" and previous experience play important roles in clinical decision-making but are difficult to quantify. Classical biomarker studies evaluated—typically in case-control study designs—the values of biomarkers in cases with proven (i.e., culture-confirmed) sepsis and controls without signs of sepsis. However, the situations most in need of biomarker guidance such as patients with probable but not confirmed sepsis, localized infections without signs of systemic infection, or patients with unclassifiable syndromes were typically excluded from these studies [2]. Therefore, this data is frequently not applicable to real-life situations, which suffer from lack of diagnostic gold standards for sepsis [28]. Thus, the real impact of a diagnostic test should be evaluated on the basis on how it will change the pretest probability and reclassify "uncertain" situations using Bayes computations or if multiple tests are used multivariable logistic regression analysis (Fig. 2) [33]. The additional value of biomarkers was studied in patients with CAP, where addition of either PCT, high-sensitivity CRP, or both improved the diagnostic ability of clinical parameters [34]. In ICU patients with SIRS, the addition of PCT significantly increased diagnostic accuracy of a clinical diagnosis of sepsis (from AUC = 0.77 to 0.94, $p = 0.001$) even though it used an early-generation and relatively insensitive PCT assay [12] and excluded patients with SIRS-negative sepsis, who are increasingly recognized to represent a small proportion of patients with sepsis [35]. In contrast, despite reasonably good diagnostic accuracy of 0.85, PCT seems to lead to only modest improvements of post-test probabilities in those patients with unclear clinical status [30, 31].

Randomized controlled trials of biomarker-guided antibiotic stewardship

Several RCTs have been performed on antibiotic guidance in ICU patients using different PCT algorithms based on currently used sensitive assays [25, 36–40]. Nobre et al. demonstrated that an algorithm consisting of absolute PCT values and relative PCT decreases was able to decrease antibiotic duration for the first episode of severe sepsis and septic shock from 10 to 6 days [hazard ratio (HR) 1.9, 95 % CI 1.2–3.1; $p = 0.009$] and ICU length of stay from 5 to 3 days ($p = 0.03$) [38]. All patients received antibiotics initially. In the French five-center, seven-ICU ProRATA RCT of 621 non-surgical patients with suspected bacterial infection (73 % with a respiratory infection source), PCT-guided treatment initiation and discontinuation led to 23 % more antibiotic-free days alive (14.3 vs. 11.6 days, $p < 0.0001$) [25]. The algorithm reached non-inferiority regarding 28-day (21.2 vs. 20.4 %, aHR 0.89, 90 % CI 0.62–1.28) and 60-day mortality (30.0 vs. 26.1 %, aHR 1.09, 90 % CI 0.79–1.51). A limitation of this otherwise impressive study was the poor algorithm compliance of 53 % and exclusion of 52 % of screened patients. The non-significantly increased 60-day mortality was extensively discussed but several lines of reasoning argue against biological plausibility (late deaths were all non-infection related) and suggest rather a random effect as neither the slightly lower 28-day mortality in the PCT group nor the slightly higher 60-day mortality in the PCT group reached statistical significance. In general, adherence rates in RCTs were relatively low (47–84 %) and rates of exclusions prior to randomization high (38–84 %) [25, 37, 38, 40–43]. None of the many secondary outcomes in the ProRATA study (relapse, superinfection; ventilation days, SOFA score, length of stay, emergence of antibiotic resistance) were significantly different except from a higher SOFA score at day 28 (difference 0.6, 95 % CI 0.0–1.1) while there were slight baseline imbalances with a trend for sicker patients in the PCT group.

In a two-center RCT of 101 patients with ventilator-associated pneumonia (VAP), daily measurement of PCT and guidance of antibiotic initiation and discontinuation resulted in a reduction of overall antibiotic duration from 15 to 10 days ($p = 0.038$) and significantly more antibiotic-free days alive (13 vs. 9.5 days; $p = 0.049$) [40]. A major criticism was the duration of antibiotic therapy in the control group, which was almost twice as long as currently recommended (15 vs. 8 days) [44, 45]. However, it may also be argued that in real life many patients still receive longer antibiotic courses than recommended by guidelines, which would again strengthen the utility of PCT as it increases the confidence in stopping antibiotics outside of study conditions [46]. In contrast, during two recent multicenter studies on CAP (one evaluating the

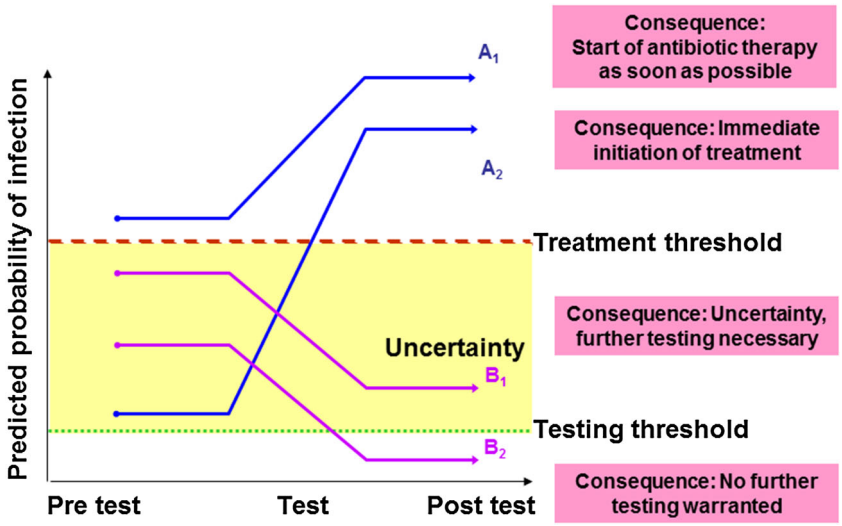

Fig. 2 The impact of test results on diagnostic certainty and treatment decisions. The post-test probability is a combined result of the pre-test probability and the test result. Four hypothetical scenarios are illustrated. A_1 The pre-test probability is already above the treatment threshold. The test result further increases the post-test probability, which should lead to start of antibiotic therapy as soon as possible. A_2 The pre-test probability is higher than the testing threshold but lower than the treatment threshold. Therefore further testing is indicated but no antibiotic therapy. The test result increases the post-test probability above the treatment threshold leading to immediate initiation of antibiotic therapy. B_1 The pre-test probability is higher than the testing threshold but lower than the treatment threshold. Therefore further testing is indicated but no antibiotic therapy. The test result lowers the post-test probability even more, but being still above the testing threshold further testing is required before a decision regarding antibiotics can be made. B_2 The pre-test probability is higher than the testing threshold but lower than the treatment threshold. Therefore further testing is indicated but no antibiotic therapy. The test result lowers the post-test probability below the testing threshold. No antibiotic therapy is given, no further testing warranted. (Modified with permission from [33])

effectiveness of antibiotic combination therapy [47], the other the efficacy and safety of prednisone [48]), the median antibiotic durations were longer than recommended by recent guidelines (10.0 and 9.0 days, respectively) even in Swiss centers which have had extensive training and experience with PCT. Recently, an Australian multicenter RCT tested very low PCT cutoffs of 0.1 μg/l to discontinue antibiotics for patients with suspected bacterial infection or sepsis [39]. The lack of effect in this study is not unexpected as the applied cutoff was much lower than cutoffs typically used in RCTs in critically ill patients, who have a high "background noise" of PCT irrespective of infections [12, 13, 49]. Based on previous observations that increasing PCT values predicted increased mortality [50], a PCT-guided antibiotic escalation algorithm was tested in a Danish randomized multicenter study against standard of care [36]. However, this algorithm resulted in a higher consumption of broad-spectrum antibiotics and a longer duration of antibiotic therapy (6 vs. 4 days) without improving survival. It rather led to longer stay in the ICU (by 1 day), 4.9 % per day more mechanical ventilation, and 21 % more renal failure, likely driven by more aminoglycoside use [36].

Of note, most algorithms excluded infections which require long-term antibiotic therapy including endocarditis, osteoarticular infections, abscesses, or empyema [25, 38].

PCT for initiation or discontinuation of antibiotics

In two RCTs initiation of antibiotics was determined on the basis of a PCT algorithm. In the ProRATA study, 30 % of patients in the PCT group had an initial PCT value less than 0.5 μg/l but antimicrobials were withheld in only 9 % as recommended by their algorithm [25]. In another multicenter open RCT in five Belgian ICUs, 15 % of episodes which ultimately were considered an infection had an initial PCT less than 0.25 μg/l and 34 % of episodes which were ultimately determined to be non-infectious had an initial PCT greater than 1 μg/l suggesting both limitations in sensitivity and specificity of their cutoffs, respectively. In turn, 18 % of episodes with an initial PCT greater than 1 μg/l were later classified as non-infectious and 54 % of episodes with an initial PCT less than 0.25 μg/l were treated with antibiotics (despite their recommendation) resulting both in overtreatment and low compliance, respectively. In this study, which exclusively guided antibiotic initiation and not discontinuation, the proportion of ICU days on antibiotics was not different between the PCT and the control group (63 vs. 58 %, $p = 0.11$) [37]. On the basis of these two studies, a single PCT measurement seems to be ineffective to withhold antimicrobial therapy in critically ill patients with a high pre-test probability of sepsis.

Table 1 PCT-guided duration of antibiotics in ICU in randomized clinical trials

References, number of patients (*n*)	Days alive without antibiotics in first 28 days			Duration of first antibiotic course (days)			Total duration of antibiotics (days)			DDD of prescribed antibiotics		
	PCT group	Control group	Relative difference	PCT group	Control group	Relative difference	PCT group	Control group	Relative difference	PCT group	Control group	Relative difference
[25], 621	14.3	11.6	0.23 $p < 0.001$	6.1	9.9	−0.38 $p < 0.001$						
[41], 110				5.9	7.9	−0.25 $p < 0.001$						
[38], 79	17.4	13.6	0.28 $p = 0.04$	6	10	−0.32 $p = 0.003$						
[42], 27				6.6	8.3	−0.21 $p < 0.001$						
[40], 101	13	9.5	0.37 $p = 0.049$				10	15	−0.33 $p = 0.038$			
[39], 394	20	17	3 $p = 0.18$	9	11	−0.18 $p = 0.74$				1200	1500	−0.2 $p = 0.001$

Adapted from [29, 30, 32, 43, 51]
DDD defined daily doses

In contrast, in all five studies in which antibiotic discontinuation was guided by PCT, antibiotic duration was significantly shorter in the PCT groups [25, 38, 40–43], for days alive off antibiotics, duration of first antimicrobial course, and total duration of antimicrobial administration (Table 1). Importantly, none of the studies reported any adverse outcomes as mortality, relapse rate, length of stay (LOS), and length of mechanical ventilation were similar between the groups. However, adherence rates to the algorithms varied between 47 and 84 % and there were relatively high proportions of eligible patients who were excluded prior to randomization.

PCT-guided antibiotic therapy: data from meta-analyses

Several meta-analyses and systematic reviews have recently been performed on the effectiveness of PCT in the ICU setting [29, 30, 32, 43, 51]. In an individual patient data meta-analysis, the PCT -algorithm led to shorter total antibiotic exposure compared with the control group in the subgroup of patients with acute respiratory infections in the ICU (8 vs. 12 days; $p < 0.001$) with no difference in mortality (PCT group 19.9 %; control group 23.8 %; aHR 0.84, 95 % CI 0.54–1.31) [51]. In a meta-analysis of seven RCTs with different PCT algorithms among ICU patients with severe sepsis and septic shock (regardless of source), three RCTs had a primary goal of antibiotic de-escalation, two had a goal of both de-escalation and escalation, and two had a primary goal of escalation [32]. Overall, there was a significantly increased antibiotic duration in the control groups (aHR 1.27, 95 % CI 1.01–1.53) without differences in mortality (hospital mortality: RR 0.91, 95 % CI 0.61–1.36; 28-day mortality: RR 1.02, 95 % CI 0.85–1.23) or LOS [32]. Another meta-analysis of ICU trials confirmed no difference in mortality in PCT-guided treatment versus controls (RR 0.95, 95 % CI 0.83–1.09) [30, 31].

The consistency of effectiveness and safety in individual studies and in meta-analyses suggests that these effects are true despite the considerable exclusion rates in some of these RCTs.

PCT in bacteremic and immunosuppressed patients

Data on bacteremic patients is rarely reported separately in RCTs on PCT guidance in the ICU. In the ProRATA study, the number of days without antibiotics was 2.9 and 2.8 days higher in the PCT groups compared to the control group for patients with and patients without bacteremia, respectively. The difference between bacteremic and

non-bacteremic patients was not significant ($p = 0.94$). Similarly, the effect was similar between patients with and patients without a microbiologically confirmed episode (2.8 vs. 2.4 days, $p = 0.78$). Mortality was not different depending on positivity of blood cultures ($p = 0.97$) [25].

The ProRATA study also assessed immunosuppressed patients in a subgroup analysis. The effect of more days without antibiotics was similar in immunosuppressed and non-immunosuppressed patients (3.6 vs. 2.5 days, $p = 0.48$). Again the difference in mortality was not significant between the study arms.

Pathogens with low virulence such as *Enterococcus faecium*, *Acinetobacter baumannii*, or coagulase-negative staphylococci, which frequently cause nosocomial infections and elicit only little systemic inflammatory responses, are associated with smaller increases of PCT levels [20, 52]. This has to be taken into account for decision-making and might explain the limited usefulness of PCT in patients with VAP [49]. No RCTs are available yet specifically for patients with postoperative meningitis or catheter-associated bloodstream infections [20] who probably require lower PCT cutoffs.

An economic analysis is beyond the scope of this review and is associated with many shortcomings as the cost of antibiotic resistance, which is possibly reduced in biomarker guidance owing to shorter treatment courses, is difficult to estimate. However, costs must not be restricted to assay procurement costs. It was estimated that a PCT-guided algorithm would lead to cost savings in patients with lower respiratory tract infections, including those who require ICU care [53].

Other biomarkers for antibiotic stewardship

Despite widespread and long-lasting use of C-reactive protein (CRP) in many ICUs throughout the world, until recently there were no prospectively tested cutoff values and no interventional data regarding safety and usefulness of CRP-based algorithms. In an open RCT in two Brazilian ICUs in patients with severe sepsis and septic shock, a CRP-based algorithm was compared to a PCT-guided algorithm, which was similar to a successfully tested algorithm [38, 54]. In analogy to the PCT group, the recommendations regarding discontinuation of antibiotic therapy in the CRP group were based on absolute CRP values (if initial CRP was less than 100 mg/l, antibiotic stop was recommended if CRP was less than 25 mg/L on day 4) or relative CRP changes (if initial CRP was at least 100 mg/l, antibiotic stop was recommended if CRP decreased by at least 50 % on day 5). Importantly, in patients in whom the infection had clinically resolved, antibiotics were discontinued in both groups regardless of CRP and PCT values by day 7 at the latest; only bacteremic and severely ill patients with initial SOFA scores above 10 were allowed to receive longer antibiotic courses. All primary (duration of antibiotic therapy; mean [median] 8.1 [7] days in PCT group vs. 7.2 [6] days in CRP group; $p = 0.25$ [0.06]) and secondary outcomes including total antibiotic exposure, clinical cure, mortality, and length of ICU and hospital stay were similar in both groups. In addition, these results support the hypothesis that 7 days represents a feasible and safe maximum antibiotic duration in recovering patients [54]. Important exclusions to this general rule still have to be clearly defined but bacteremia due to *Staphylococcus aureus*, deep-seated infections such as endocarditis, mediastinitis, empyema, bone and joint infections, and foreign-body-related infections should be treated according to generally accepted longer antibiotic courses. These infections are usually excluded from biomarker-guided algorithms. Despite the relatively small sample size of 94 patients, which requires replication in larger clinical trials, and a large number of prescreened but excluded patients, this is an important proof-of-concept study extending strategies developed with PCT to the less expensive and more widely available CRP. By discontinuing antibiotics on day 7 irrespective of biomarker levels in those patients who clinically responded and had no contraindications, this study successfully introduced a novel concept and should be considered a landmark trial shaking traditional practices. Based on this study, alternative algorithms for PCT and CRP have been published (Fig. 3, reprinted from [55]).

To the best of our knowledge, no other RCTs have been published on CRP or other biomarkers for antibiotic guidance in septic adult patients in the ICU.

Alternative approaches to biomarkers: clinical assessment and protocolized care

Surprisingly little systematically collected data is available regarding treatment duration for patients with bacteremia (as a general surrogate of sepsis) in the ICU. This is likely attributable to the heterogeneous group of diseases and syndromes, which results in a large variation of treatment durations [56]. Among 713 ICU patients with bacteremia identified in a prospective observational study over 6 months at a single London ICU, a satisfactory response was reported with short-course monotherapy (5–6 days, based on clinical response), which was employed routinely except for infections which specifically require longer treatment such as endocarditis or osteomyelitis [8]. The observed mortality (crude 45 % and attributable 24 %) did not differ from the expected mortality based on severity of illness. No long-term complications were seen and there were six relapses, all

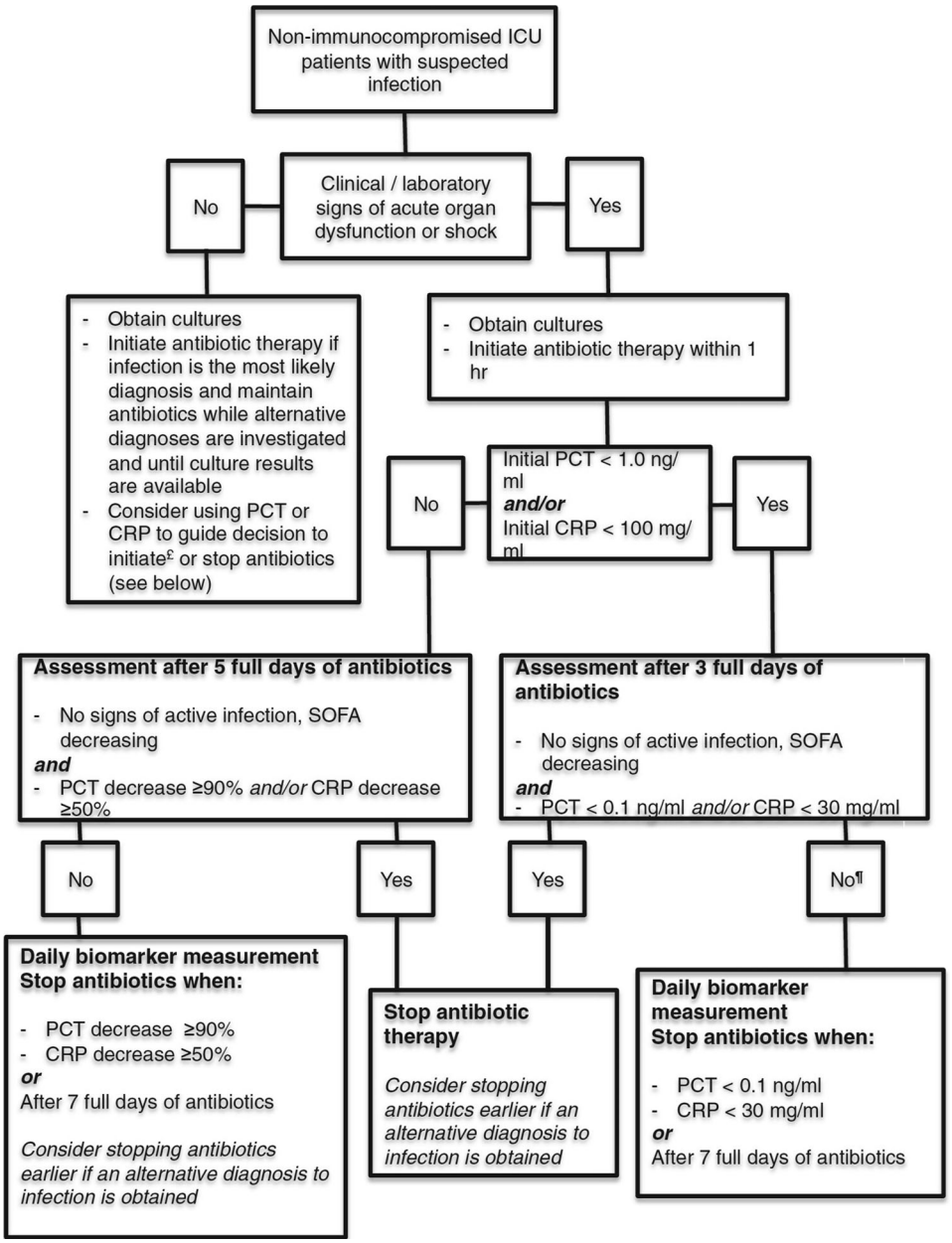

Fig. 3 Algorithms for CRP- and PCT-guided antibiotic therapy in critically ill patients (reprinted with permission from [55]). *SOFA* sequential organ failure assessment. £In critically ill patients, antibiotic discontinuation has been repeatedly shown to be safe and effective on the basis of biomarker levels (particularly PCT). Effectiveness and safety to initiate antibiotic is less well established in critically ill patients and should only be done if clinical status permits withholding antibiotics, i.e., in rare instances only. ¶In patients without signs of active infection and alternative explanations for increased biomarker levels and/or negative cultures, consider stopping antibiotics

due to Gram-negative pathogens, four of which were treated with combination therapy. In a systematic review and meta-analysis from 1947 to 2010 of antibiotic duration for patients with bacteremia, Havey et al. identified 24 RCTs, only one specific for bacteremia, and in total 227 patients with bacteremia [57]. Short therapy (5–7 days) resulted in similar clinical cure (risk ratio 0.88, 95 % CI 0.77–1.01), microbiological cure (risk ratio 1.05, 95 % CI 0.91–1.21), and survival (risk ratio 0.97, 95 % CI 0.76–1.23) as long antibiotic therapy (7–21 days). A preplanned subgroup analysis of *S. aureus* bloodstream infections was limited by small numbers, but demonstrated lower success with short course therapy (3/7, 42.9 %) compared to longer therapy (7/7, 100 %, $p = 0.02$) [57].

Even without the use of biomarkers, antibiotic duration for many infectious syndromes has been progressively shortened during recent years [45]. A recent RCT of patients with complicated intra-abdominal infections and adequate source control demonstrated similar success rates of a fixed duration of 4 ± 1 days of antibiotic therapy compared with continuing antibiotic therapy for 2 days after resolution of fever, leukocytosis, and ileus, which resulted in a median of 8 days [58]. Additional examples include current recommendations for duration of therapy for community-acquired

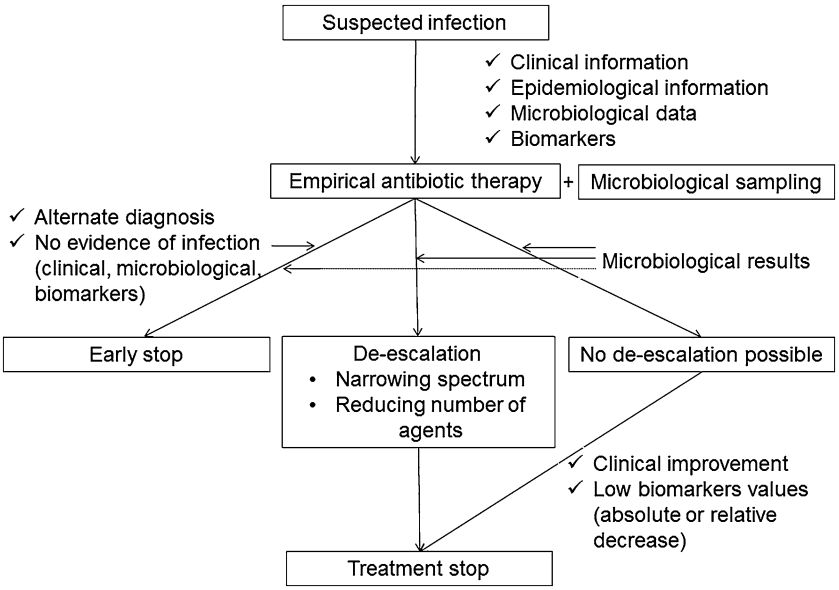

Fig. 4 Algorithm combining antibiotic de-escalation with biomarker guidance in critically ill patients with suspected infection

pneumonia (at most 7 days [59]), pyelonephritis (5–7 days [60]), and VAP (8 days except for non-fermenters [44]). For VAP, several strategies have been proposed to reduce antibiotic duration, including use of the clinical pulmonary infection score (CPIS) [61], application of routine bronchoscopy and microbiologic specimen collection [62], or a simple clinical decision rule (consisting of normalization of temperature, leukocyte count, radiology, sputum purulence, and oxygenation), which further reduced treatment duration from 8 to 6 days [63]. Interestingly, this is approximately the same mean duration of therapy as achieved with PCT guidance [40], while challenges remain for the diagnosis of VAP, which make comparisons between different studies problematic. A strength of biomarker-guided algorithms might be the individualization of therapy.

The worldwide crisis of antibiotic resistance led to the recommendation that all ICUs incorporate an antibiotic stewardship (ABS) program as a multidisciplinary approach to improve outcome and limit emergence of resistance [64]. Key elements include aggressive microbiologic testing, rapid identification of patients requiring antimicrobials, optimal selection of antimicrobial agents and dosing based on pharmacokinetics and pharmacodynamics, antibiotic de-escalation and early discontinuation together with provider education, auditing, and feedback [64]. Various tools such as computerized decision support systems, biomarkers, antibiotic restriction and availability of infectious disease experts are applied as part of ABS [65]. Utilization of rapid testing such as MALDI-TOF significantly reduced time to optimal therapy in bacteremia and candidemia from 90 to 47 h [66]. Recent reviews showed success of at least one targeted outcome in 81 % of studies evaluating ABS in ICUs [65] and a reduction in antibiotic exposure and lower antibiotic costs [67]. In a mathematical model the impact on colonization rates with resistant *Pseudomonas aeruginosa* was highest with restricting treatment indications and optimizing antibiotic choices rather than shortening antibiotic courses [68].

Recently, the safety of antibiotic de-escalation, defined as discontinuation of antibiotics or change to an antibiotic with a narrower spectrum, was prospectively confirmed in a Spanish ICU in patients with severe sepsis or septic shock using both logistic regression analysis and propensity score matching. De-escalation, which was performed in 34.9 % of patients, was protective against hospital mortality (propensity score adjusted OR 0.55, 95 % CI 0.32–0.98, $p = 0.022$) [69]. In contrast, a controversial multicenter study from nine French ICUs raised concern about potential harm of antibiotic de-escalation despite non-inferiority of the primary outcome (median ICU LOS 9 [interquartile range (IQR) 5–22] in the de-escalation group vs. 8 days [IQR 4–15] in the standard group, mean difference 3.4 days [95 % CI −1.7 to 8.5]) and similar mortality, as there were more superinfections in the de-escalation group (27 vs. 11 %, $p = 0.03$) [70]. Despite some concerns [71], the necessity of de-escalation to combat antibiotic resistance while allowing early and appropriate broad-spectrum therapy even in neutropenic patients [72] has been emphasized [73–75]. An integral but not always explicitly emphasized part of antibiotic de-escalation is to early discontinue antibiotics, either when there is no evidence of infection or once the infection has resolved clinically or according to biomarker levels (Fig. 4) [73, 75].

Conclusion

The available literature on several RCTs confirms the safety and efficacy of PCT guidance, particularly for antibiotic withdrawal decisions, but probably not for guiding treatment initiation in critically ill patients. While serial PCT values provide prognostic information, it was detrimental when used as an escalation strategy. Limitations are currently high assay costs and the still limited diagnostic accuracy with too many false-positive and false-negative results. A head-to-head comparison RCT suggested that CRP, which is less expensive and more widely available, might be similarly effective and safe for antibiotic discontinuation as PCT. Further RCTs on CRP or other biomarkers are needed but might suffer from lack of industry interest in sponsoring such complicated studies. The results of the randomized SISPCT trial (https://clinicaltrials.gov/ct2/show/NCT00832039), which evaluates both selenium supplementation and PCT guidance for antibiotic duration in severe sepsis or septic shock, are awaited with interest. Biomarkers should never be used alone but always in addition to microbiological information and clinical assessment over time, which by itself might be able to considerably reduce antibiotic duration. It is time to implement these concepts into clinical routine.

Compliance with ethical standards

Conflicts of interest WCA has received support from BRAHMS Thermo Fisher and from bioMérieux to attend meetings and fulfilled speaking engagements and served as consultants for BRAHMS Thermo Fisher. SH has received consultant and speaker honoraria from bioMérieux, Da Volterra, and Destiny Pharma. In 2007, SH received a research grant from Brahms GmbH, the initial producer of a procalcitonin assay, to do a clinical trial on procalcitonin. He also received a speaker honorarium from this company in 2009. SH has received research funds from Pfizer, B Braun, the Centre de Recherche Clinique at the Geneva University Hospitals, and the European Commission (SATURN, AIDA, R-Gnosis, Rapp-ID, DRIVE-AB, and COMBACTE network contracts).

References

1. Vincent JL, Rello J, Marshall J, Silva E, Anzueto A, Martin CD, Moreno R, Lipman J, Gomersall C, Sakr Y, Reinhart K (2009) International study of the prevalence and outcomes of infection in intensive care units. JAMA 302:2323–2329
2. Fischer JE, Harbarth S, Agthe AG, Benn A, Ringer SA, Goldmann DA, Fanconi S (2004) Quantifying uncertainty: physicians' estimates of infection in critically ill neonates and children. Clin Infect Dis 38:1383–1390
3. Gaieski DF, Mikkelsen ME, Band RA, Pines JM, Massone R, Furia FF, Shofer FS, Goyal M (2010) Impact of time to antibiotics on survival in patients with severe sepsis or septic shock in whom early goal-directed therapy was initiated in the emergency department. Crit Care Med 38:1045–1053
4. Kumar A, Roberts D, Wood KE, Light B, Parrillo JE, Sharma S, Suppes R, Feinstein D, Zanotti S, Taiberg L, Gurka D, Cheang M (2006) Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med 34:1589–1596
5. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R, Osborn TM, Nunnally ME, Townsend SR, Reinhart K, Kleinpell RM, Angus DC, Deutschman CS, Machado FR, Rubenfeld GD, Webb S, Beale RJ, Vincent JL, Moreno R (2013) Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. Intensive Care Med 39:165–228
6. Paterson DL, Rice LB (2003) Empirical antibiotic choice for the seriously ill patient: are minimization of selection of resistant organisms and maximization of individual outcome mutually exclusive? Clin Infect Dis 36:1006–1012
7. Dennesen PJW, van der Ven AJAM, Kessels AGH, Ramsay G, Bonten MJM (2001) Resolution of infectious parameters after antimicrobial therapy in patients with ventilator-associated pneumonia. Am J Respir Crit Care Med 163:1371–1375
8. Corona A, Wilson AP, Grassi M, Singer M (2004) Prospective audit of bacteraemia management in a university hospital ICU using a general strategy of short-course monotherapy. J Antimicrob Chemother 54:809–817
9. Shehabi Y, Seppelt I (2008) Pro/Con debate: is procalcitonin useful for guiding antibiotic decision making in critically ill patients? Crit Care 12:211
10. Christ-Crain M, Opal SM (2010) Clinical review: the role of biomarkers in the diagnosis and management of community-acquired pneumonia. Crit Care 14:203
11. Kofoed K, Andersen O, Kronborg G, Tvede M, Petersen J, Eugen-Olsen J, Larsen K (2007) Use of plasma C-reactive protein, procalcitonin, neutrophils, macrophage migration inhibitory factor, soluble urokinase-type plasminogen activator receptor, and soluble triggering receptor expressed on myeloid cells-1 in combination to diagnose infections: a prospective study. Crit Care 11:R38
12. Harbarth S, Holeckova K, Froidevaux C, Pittet D, Ricou B, Grau GE, Vadas L, Pugin J (2001) Diagnostic value of procalcitonin, interleukin-6, and interleukin-8 in critically ill patients admitted with suspected sepsis. Am J Respir Crit Care Med 164:396–402
13. Muller B, Becker KL, Schachinger H, Rickenbacher PR, Huber PR, Zimmerli W, Ritz R (2000) Calcitonin precursors are reliable markers of sepsis in a medical intensive care unit. Crit Care Med 28:977–983
14. Simon L, Gauvin F, Amre DK, Saint-Louis P, Lacroix J (2004) Serum procalcitonin and C-reactive protein levels as markers of bacterial infection: a systematic review and meta-analysis. Clin Infect Dis 39:206–217

15. Ingram PR, Inglis T, Moxon D, Speers D (2010) Procalcitonin and C-reactive protein in severe 2009 H1N1 influenza infection. Intensive Care Med 36:528–532
16. Cuquemelle E, Soulis F, Villers D, Roche-Campo F, Ara Somohano C, Fartoukh M, Kouatchet A, Mourvillier B, Dellamonica J, Picard W, Schmidt M, Boulain T, Brun-Buisson C (2011) Can procalcitonin help identify associated bacterial infection in patients with severe influenza pneumonia? A multicentre study. Intensive Care Med 37:796–800
17. Reinhart K, Bauer M, Riedemann NC, Hartog CS (2012) New approaches to sepsis: molecular diagnostics and biomarkers. Clin Microbiol Rev 25:609–634
18. Becker KL, Snider R, Nylen ES (2010) Procalcitonin in sepsis and systemic inflammation: a harmful biomarker and a therapeutic target. Br J Pharmacol 159:253–264
19. Reinhart K, Karzai W, Meisner M (2000) Procalcitonin as a marker of the systemic inflammatory response to infection. Intensive Care Med 26:1193–1200
20. Schuetz P, Mueller B, Trampuz A (2007) Serum procalcitonin for discrimination of blood contamination from bloodstream infection due to coagulase-negative staphylococci. Infection 35:352–355
21. Vigushin DM, Pepys MB, Hawkins PN (1993) Metabolic and scintigraphic studies of radioiodinated human C-reactive protein in health and disease. J Clin Invest 91:1351–1357
22. Christ-Crain M, Muller B (2005) Procalcitonin in bacterial infections–hype, hope, more or less? Swiss Med Wkly 135:451–460
23. Kutz A, Grolimund E, Christ-Crain M, Thomann R, Falconnier C, Hoess C, Henzen C, Zimmerli W, Mueller B, Schuetz P (2014) Pre-analytic factors and initial biomarker levels in community-acquired pneumonia patients. BMC Anesthesiol 14:102
24. Grace E, Turner RM (2014) Use of procalcitonin in patients with various degrees of chronic kidney disease including renal replacement therapy. Clin Infect Dis 59:1761–1767
25. Bouadma L, Luyt CE, Tubach F, Cracco C, Alvarez A, Schwebel C, Schortgen F, Lasocki S, Veber B, Dehoux M, Bernard M, Pasquet B, Regnier B, Brun-Buisson C, Chastre J, Wolff M (2010) Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial. Lancet 375:463–474
26. Koivula I, Hamalainen S, Jantunen E, Pulkki K, Kuittinen T, Nousiainen T, Juutilainen A (2011) Elevated procalcitonin predicts Gram-negative sepsis in haematological patients with febrile neutropenia. Scand J Infect Dis 43:471–478
27. Povoa P, Souza-Dantas VC, Soares M, Salluh JF (2011) C-reactive protein in critically ill cancer patients with sepsis: influence of neutropenia. Crit Care 15:R129
28. Pierrakos C, Vincent JL (2010) Sepsis biomarkers: a review. Crit Care 14:R15
29. Kopterides P, Siempos II, Tsangaris I, Tsantes A, Armaganidis A (2010) Procalcitonin-guided algorithms of antibiotic therapy in the intensive care unit: a systematic review and meta-analysis of randomized controlled trials. Crit Care Med 38:2229–2241
30. Wacker C, Prkno A, Brunkhorst FM, Schlattmann P (2013) Procalcitonin as a diagnostic marker for sepsis: a systematic review and meta-analysis. Lancet Infect Dis 13:426–435
31. Afshari A, Harbarth S (2013) Procalcitonin as diagnostic biomarker of sepsis. Lancet Infect Dis 13:382–384
32. Prkno A, Wacker C, Brunkhorst FM, Schlattmann P (2013) Procalcitonin-guided therapy in intensive care unit patients with severe sepsis and septic shock—a systematic review and meta-analysis. Crit Care 17:R291
33. Fischer JE, Bachmann LM, Jaeschke R (2003) A readers' guide to the interpretation of diagnostic test properties: clinical example of sepsis. Intensive Care Med 29:1043–1051
34. Muller B, Harbarth S, Stolz D, Bingisser R, Mueller C, Leuppi J, Nusbaumer C, Tamm M, Christ-Crain M (2007) Diagnostic and prognostic accuracy of clinical and laboratory parameters in community-acquired pneumonia. BMC Infect Dis 7:10
35. Kaukonen KM, Bailey M, Pilcher D, Cooper DJ, Bellomo R (2015) Systemic inflammatory response syndrome criteria in defining severe sepsis. N Engl J Med 372:1629–1638
36. Jensen JU, Hein L, Lundgren B, Bestle MH, Mohr TT, Andersen MH, Thornberg KJ, Loken J, Steensen M, Fox Z, Tousi H, Soe-Jensen P, Lauritsen AO, Strange D, Petersen PL, Reiter N, Hestad S, Thormar K, Fjeldborg P, Larsen KM, Drenck NE, Ostergaard C, Kjaer J, Grarup J, Lundgren JD (2011) Procalcitonin-guided interventions against infections to increase early appropriate antibiotics and improve survival in the intensive care unit: a randomized trial. Crit Care Med 39:2048–2058
37. Layios N, Lambermont B, Canivet JL, Morimont P, Preiser JC, Garweg C, Ledoux D, Frippiat F, Piret S, Giot JB, Wiesen P, Meuris C, Massion P, Leonard P, Nys M, Lancellotti P, Chapelle JP, Damas P (2012) Procalcitonin usefulness for the initiation of antibiotic treatment in intensive care unit patients. Crit Care Med 40:2304–2309
38. Nobre V, Harbarth S, Graf JD, Rohner P, Pugin J (2008) Use of procalcitonin to shorten antibiotic treatment duration in septic patients: a randomized trial. Am J Respir Crit Care Med 177:498–505
39. Shehabi Y, Sterba M, Garrett PM, Rachakonda KS, Stephens D, Harrigan P, Walker A, Bailey MJ, Johnson B, Millis D, Ding G, Peake S, Wong H, Thomas J, Smith K, Forbes L, Hardie M, Micallef S, Fraser JF (2014) Procalcitonin algorithm in critically ill adults with undifferentiated infection or suspected sepsis. A randomized controlled trial. Am J Respir Crit Care Med 190:1102–1110
40. Stolz D, Smyrnios N, Eggimann P, Pargger H, Thakkar N, Siegemund M, Marsch S, Azzola A, Rakic J, Mueller B, Tamm M (2009) Procalcitonin for reduced antibiotic exposure in ventilator-associated pneumonia: a randomised study. Eur Respir J 34:1364–1375
41. Hochreiter M, Kohler T, Schweiger AM, Keck FS, Bein B, von Spiegel T, Schroeder S (2009) Procalcitonin to guide duration of antibiotic therapy in intensive care patients: a randomized prospective controlled trial. Crit Care 13:R83
42. Schroeder S, Hochreiter M, Koehler T, Schweiger AM, Bein B, Keck FS, von Spiegel T (2009) Procalcitonin (PCT)-guided algorithm reduces length of antibiotic treatment in surgical intensive care patients with severe sepsis: results of a prospective randomized study. Langenbecks Arch Surg 394:221–226
43. Agarwal R, Schwartz DN (2011) Procalcitonin to guide duration of antimicrobial therapy in intensive care units: a systematic review. Clin Infect Dis 53:379–387
44. Chastre J, Wolff M, Fagon JY, Chevret S, Thomas F, Wermert D, Clementi E, Gonzalez J, Jusserand D, Asfar P, Perrin D, Fieux F, Aubas S (2003) Comparison of 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia in adults: a randomized trial. JAMA 290:2588–2598

45. Hayashi Y, Paterson DL (2011) Strategies for reduction in duration of antibiotic use in hospitalized patients. Clin Infect Dis 52:1232–1240
46. Albrich WC, Dusemund F, Bucher B, Meyer S, Thomann R, Kühn F, Bassetti S, Sprenger M, Baechli E, Sigrist T, Schwietert M, Amin D, Hausfater P, Carre E, Gaillat J, Schuetz P, Regez K, Bossart R, Schild U, Mueller B (2012) Effectiveness and safety of procalcitonin-guided antibiotic therapy in lower respiratory tract infections in "real life": an international, multicenter post-study survey (ProREAL). Arch Intern Med 172:715–722
47. Garin N, Genne D, Carballo S, Chuard C, Eich G, Hugli O, Lamy O, Nendaz M, Petignat PA, Perneger T, Rutschmann O, Seravalli L, Harbarth S, Perrier A (2014) Beta-lactam monotherapy vs beta-lactam-macrolide combination treatment in moderately severe community-acquired pneumonia: a randomized noninferiority trial. JAMA Intern Med 174:1894–1901
48. Blum CA, Nigro N, Briel M, Schuetz P, Ullmer E, Suter-Widmer I, Winzeler B, Bingisser R, Elsaesser H, Drozdov D, Arici B, Urwyler SA, Refardt J, Tarr P, Wirz S, Thomann R, Baumgartner C, Duplain H, Burki D, Zimmerli W, Rodondi N, Mueller B, Christ-Crain M (2015) Adjunct prednisone therapy for patients with community-acquired pneumonia: a multicentre, double-blind, randomised, placebo-controlled trial. Lancet 385:1511–1518
49. Luyt CE, Combes A, Reynaud C, Hekimian G, Nieszkowska A, Tonnellier M, Aubry A, Trouillet JL, Bernard M, Chastre J (2008) Usefulness of procalcitonin for the diagnosis of ventilator-associated pneumonia. Intensive Care Med 34:1434–1440
50. Jensen JU, Heslet L, Jensen TH, Espersen K, Steffensen P, Tvede M (2006) Procalcitonin increase in early identification of critically ill patients at high risk of mortality. Crit Care Med 34:2596–2602
51. Schuetz P, Briel M, Christ-Crain M, Stolz D, Bouadma L, Wolff M, Luyt CE, Chastre J, Tubach F, Kristoffersen KB, Wei L, Burkhardt O, Welte T, Schroeder S, Nobre V, Tamm M, Bhatnagar N, Bucher HC, Mueller B (2012) Procalcitonin to guide initiation and duration of antibiotic treatment in acute respiratory infections: an individual patient data meta-analysis. Clin Infect Dis 55:651–662
52. Povoa P, Salluh JI (2012) Biomarker-guided antibiotic therapy in adult critically ill patients: a critical review. Ann Intensive Care 2:32
53. Schuetz P, Balk R, Briel M, Kutz A, Christ-Crain M, Stolz D, Bouadma L, Wolff M, Kristoffersen KB, Wei L, Burkhardt O, Welte T, Schroeder S, Nobre V, Tamm M, Bhatnagar N, Bucher HC, Luyt CE, Chastre J, Tubach F, Mueller B, Lacey MJ, Ohsfeldt RL, Scheibling CM, Schneider JE (2015) Economic evaluation of procalcitonin-guided antibiotic therapy in acute respiratory infections: a US health system perspective. Clin Chem Lab Med 53:583–592
54. Oliveira CF, Botoni FA, Oliveira CR, Silva CB, Pereira HA, Serufo JC, Nobre V (2013) Procalcitonin versus C-reactive protein for guiding antibiotic therapy in sepsis: a randomized trial. Crit Care Med 41:2336–2343
55. Salluh JI, Nobre V, Povoa P (2014) Using procalcitonin to guide antimicrobial duration in sepsis: asking the same questions will not bring different answers. Crit Care 18:142
56. Havey TC, Fowler RA, Pinto R, Elligsen M, Daneman N (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
57. Havey TC, Fowler RA, Daneman N (2011) Duration of antibiotic therapy for bacteremia: a systematic review and meta-analysis. Crit Care 15:R267
58. Sawyer RG, Claridge JA, Nathens AB, Rotstein OD, Duane TM, Evans HL, Cook CH, O'Neill PJ, Mazuski JE, Askari R, Wilson MA, Napolitano LM, Namias N, Miller PR, Dellinger EP, Watson CM, Coimbra R, Dent DL, Lowry SF, Cocanour CS, West MA, Banton KL, Cheadle WG, Lipsett PA, Guidry CA, Popovsky K (2015) Trial of short-course antimicrobial therapy for intraabdominal infection. N Engl J Med 372:1996–2005
59. Woodhead M, Blasi F, Ewig S, Garau J, Huchon G, Ieven M, Ortqvist A, Schaberg T, Torres A, van der Heijden G, Read R, Verheij TJ (2011) Guidelines for the management of adult lower respiratory tract infections—full version. Clin Microbiol Infect 17(Suppl 6):E1–59
60. Gupta K, Hooton TM, Naber KG, Wullt B, Colgan R, Miller LG, Moran GJ, Nicolle LE, Raz R, Schaeffer AJ, Soper DE (2011) International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: a 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clin Infect Dis 52:e103–e120
61. Singh N, Rogers P, Atwood CW, Wagener MM, Yu VL (2000) Short-course empiric antibiotic therapy for patients with pulmonary infiltrates in the intensive care unit. A proposed solution for indiscriminate antibiotic prescription. Am J Respir Crit Care Med 162:505–511
62. Fagon JY, Chastre J, Wolff M, Gervais C, Parer-Aubas S, Stephan F, Similowski T, Mercat A, Diehl JL, Sollet JP, Tenaillon A (2000) Invasive and noninvasive strategies for management of suspected ventilator-associated pneumonia. A randomized trial. Ann Intern Med 132:621–630
63. Micek ST, Ward S, Fraser VJ, Kollef MH (2004) A randomized controlled trial of an antibiotic discontinuation policy for clinically suspected ventilator-associated pneumonia. Chest 125:1791–1799
64. Bassetti M, De Waele JJ, Eggimann P, Garnacho-Montero J, Kahlmeter G, Menichetti F, Nicolau DP, Paiva JA, Tumbarello M, Welte T, Wilcox M, Zahar JR, Poulakou G (2015) Preventive and therapeutic strategies in critically ill patients with highly resistant bacteria. Intensive Care Med 41:776–795
65. Zhang YZ, Singh S (2015) Antibiotic stewardship programmes in intensive care units: why, how, and where are they leading us. World J Crit Care Med 4:13–28
66. Huang AM, Newton D, Kunapuli A, Gandhi TN, Washer LL, Isip J, Collins CD, Nagel JL (2013) Impact of rapid organism identification via matrix-assisted laser desorption/ionization time-of-flight combined with antimicrobial stewardship team intervention in adult patients with bacteremia and candidemia. Clin Infect Dis 57:1237–1245
67. Kaki R, Elligsen M, Walker S, Simor A, Palmay L, Daneman N (2011) Impact of antimicrobial stewardship in critical care: a systematic review. J Antimicrob Chemother 66:1223–1230
68. Hurford A, Morris AM, Fisman DN, Wu J (2012) Linking antimicrobial prescribing to antimicrobial resistance in the ICU: before and after an antimicrobial stewardship program. Epidemics 4:203–210
69. Garnacho-Montero J, Gutierrez-Pizarraya A, Escoresca-Ortega A, Corcia-Palomo Y, Fernandez-Delgado E, Herrera-Melero I, Ortiz-Leyba C, Marquez-Vacaro JA (2014) De-escalation of empirical therapy is associated with lower mortality in patients with severe sepsis and septic shock. Intensive Care Med 40:32–40

70. Leone M, Bechis C, Baumstarck K, Lefrant JY, Albanese J, Jaber S, Lepape A, Constantin JM, Papazian L, Bruder N, Allaouchiche B, Bezulier K, Antonini F, Textoris J, Martin C (2014) De-escalation versus continuation of empirical antimicrobial treatment in severe sepsis: a multicenter non-blinded randomized noninferiority trial. Intensive Care Med 40:1399–1408
71. De Waele JJ, Bassetti M, Martin-Loeches I (2014) Impact of de-escalation on ICU patients' prognosis. Intensive Care Med 40:1583–1585
72. Mokart D, Slehofer G, Lambert J, Sannini A, Chow-Chine L, Brun JP, Berger P, Duran S, Faucher M, Blache JL, Saillard C, Vey N, Leone M (2014) De-escalation of antimicrobial treatment in neutropenic patients with severe sepsis: results from an observational study. Intensive Care Med 40:41–49
73. Kollef MH (2014) What can be expected from antimicrobial de-escalation in the critically ill? Intensive Care Med 40:92–95
74. Morel J, Casoetto J, Jospe R, Aubert G, Terrana R, Dumont A, Molliex S, Auboyer C (2010) De-escalation as part of a global strategy of empiric antibiotherapy management. A retrospective study in a medico-surgical intensive care unit. Crit Care 14:R225
75. Timsit JF, Harbarth S, Carlet J (2014) De-escalation as a potential way of reducing antibiotic use and antimicrobial resistance in ICU. Intensive Care Med 40:1580–1582