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NARRATIVE REVIEW

How to use biomarkers of infection or sepsis at the bedside: guide to clinicians

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Abstract

Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection. In this context, biomarkers could be considered as indicators of either infection or dysregulated host response or response to treatment and/or aid clinicians to prognosticate patient risk. More than 250 biomarkers have been identified and evaluated over the last few decades, but no biomarker accurately differentiates between sepsis and sepsis-like syndrome. Published data support the use of biomarkers for pathogen identification, clinical diagnosis, and optimization of antibiotic treatment. In this narrative review, we highlight how clinicians could improve the use of pathogen-specific and of the most used host-response biomarkers, procalcitonin and C-reactive protein, to improve the clinical care of patients with sepsis. Biomarker kinetics are more useful than single values in predicting sepsis, when making the diagnosis and assessing the response to antibiotic therapy. Finally, integrated biomarker-guided algorithms may hold promise to improve both the diagnosis and prognosis of sepsis. Herein, we provide current data on the clinical utility of pathogen-specific and host-response biomarkers, offer guidance on how to optimize their use, and propose the needs for future research.

Keywords: Sepsis, Intensive care unit, Biomarkers, Diagnosis, Antibiotic stewardship

Introduction

Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection [1]. In this context, biomarkers could be considered as indicators of either infection or dysregulated host response or response to treatment and/or help clinicians to prognosticate patient risk. In daily bedside practice, for the diagnosis and management of sepsis as well as for antibiotic stewardship, clinicians combine data from different sources that results from the intersection of three vectors (Fig. 1): systemic manifestations, organ dysfunction and microbiological documentation. Biomarkers could provide additional information in the vector systemic manifestations (host-response biomarkers e.g., C-reactive protein–CRP, and procalcitonin–PCT), organ dysfunction (e.g., kidney injury biomarkers) and microbiological documentation (pathogen-specific biomarkers—see Table 1). The first two vectors are neither specific nor sensitive to sepsis. The microbiological documentation often takes at least 2–3 days to finalize and is not particularly sensitive especially when cultures are collected while patients are receiving antimicrobial therapy. Thus, approximately 40–50% of cases of sepsis are deemed to be culture-negative [2, 3]. Biomarkers have been studied in the context of prediction of sepsis [4], diagnosis of sepsis [5], assessment of sepsis response to therapy [6–8] and biomarker-guided antibiotic therapy [9] (for examples of clinical scenarios of sepsis with biomarker use see—ESM). In addition, biomarkers of sepsis can be

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divided into prognostic, predictive and theranostic, i.e., to guide choice, dose, and duration of therapy (Fig. 1).

More than 250 biomarkers have been studied and evaluated over the last decades, which were reviewed in detail recently elsewhere [10]. The aim of this review is to inform clinicians about biomarkers of infection or sepsis and guidance as to their use, namely pathogen-specific biomarkers, and two host-response biomarkers, PCT and CRP.

How to use biomarkers?

Faced with a suspicion of sepsis the clinician has several questions to address. As well recognized by the Surviving Sepsis Campaign guidelines [11] the first questions are:

1) What is the likelihood of infection?
2) What is the severity of illness and the risk to develop septic shock?
3) What is/are the most likely pathogen(s)?
4) What is the most appropriate antimicrobial treatment?
5) Is the patient improving or not, and if not, why?
6) When can antimicrobials be stopped?

Clinicians frequently try to answer these questions with the aid of biomarkers, but it is important to acknowledge that biomarker performance in sepsis management is suboptimal [12].

Pathogen-specific and host-response biomarkers

Biomarkers are described as a biological characteristic, objectively measured, and used as a surrogate marker for a physiological or pathologic process, or as an indicator of the activity of a drug [13]. In the present context, biomarkers of infection and sepsis could be considered as indicators of either infection or dysregulated host response or response to treatment.

Pathogen-specific biomarkers

Although the detection of microbial nucleic acids is becoming more common, their place in the management of infections in general, and in bacterial infections specifically, remains uncertain and it is not yet well standardized [14]. Pathogen-specific biomarkers, like direct antigen tests, are already widely used in the critically ill. The pooled diagnostic performance of the major tests is shown in Table 1.

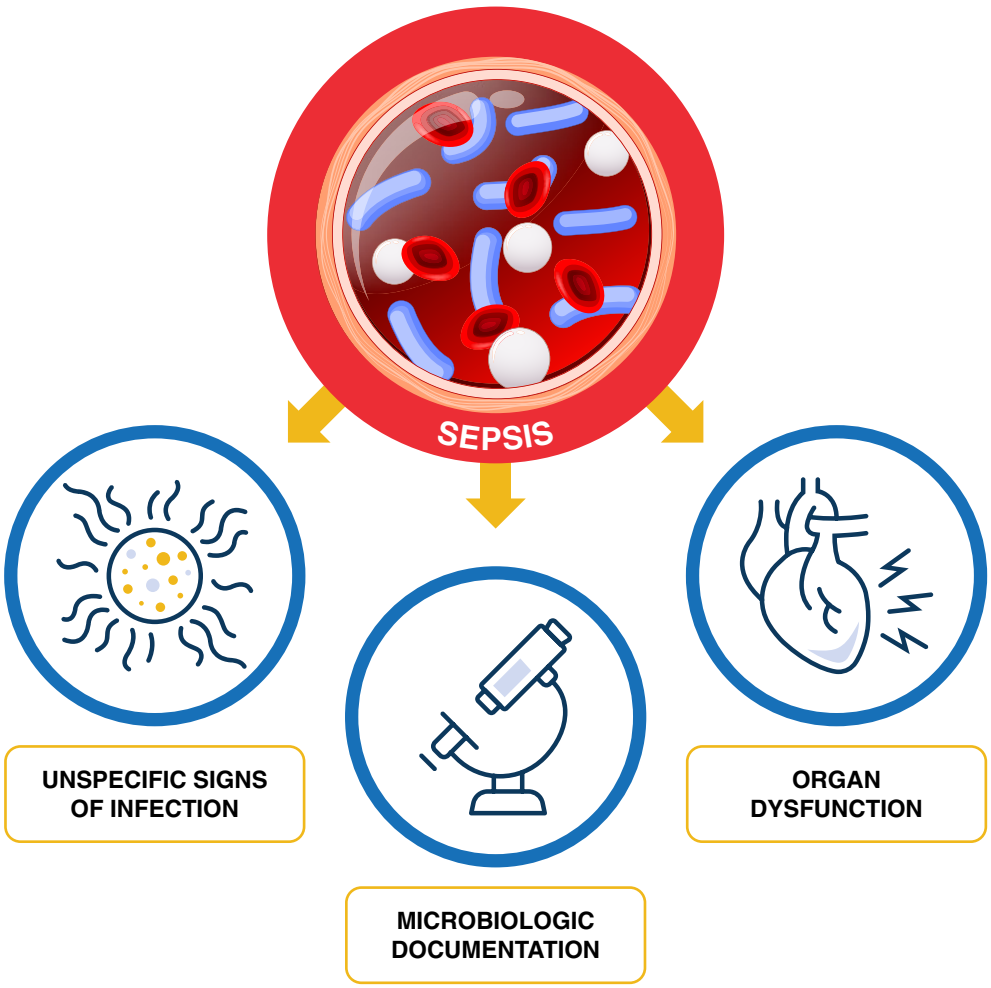
Most rapid antigen-based tests are based on immunochromatographic assays and have the potential for bedside use. Influenza and SARS-CoV-2 respiratory antigen tests, and *Streptococcus pneumoniae* and Legionella spp. urinary antigen tests are used in community-acquired pneumonia (CAP). They exhibit a high specificity, but low to moderate sensitivity. Notwithstanding improvements through automated reading, a negative test cannot be reliably considered to be a rule-out result [15]. Legionella antigen tests detect *Legionella pneumophila* serogroup 1. While this is the predominant cause of legionellosis, false negatives occur with other serogroups or species [15]. The diagnostic accuracy of pneumococcal antigen tests is also highly dependent on serotype; lower sensitivity has been noted due to antigenic shift following the introduction of the 13-valent polysaccharide conjugate vaccine. Currently, few rapid diagnostic tests, such as the mariPOC® test, utilize multiplex testing for several pathogens in a single sample. But none of the antigenic tests give information about antibiotic sensitivity.

Clostridioides difficile infection (CDI) can be diagnosed in symptomatic patients, using a two-step algorithm with rapid enzyme immunoassays to test stool samples for both glutamate dehydrogenase (GDH) and free toxins A and B. Low positive predictive values at low CDI prevalence should prevent either test from being used alone [16]. The GDH test is highly sensitive, and if positive, is combined with the more specific toxin A/B detection test. Careful evaluation of patients with positive GDH but a negative toxin A/B detection is needed, as it may indicate CDI with toxin levels below the detection threshold in patients with diarrhea or non-toxigenic *Clostridioides difficile* carriage.

Fungal antigen assays target structural polysaccharides derived from fungal cell walls. (1,3)-β-D-glucan (BDG) is a panfungal serum biomarker commonly used to detect invasive candidiasis. With high sensitivity, but poor specificity, BDG is a valuable tool to rule-out invasive candidiasis in low-prevalence intensive care unit (ICU) [17]. However, a recent randomized clinical trial (RCT) failed to demonstrate survival benefits from BDG-guided early initiation of antifungal therapy in critically ill septic patients with a low to intermediate risk for invasive candidiasis, and at the cost of a substantial overuse of antifungals [18]. Similarly, BDG has a high negative predictive value for the diagnosis of *Pneumocystis jirovecii* pneumonia in non-HIV patients and a low/intermediate likelihood of the disease [19]. Specificity and positive

Take-home message

This narrative review shows that pathogen-specific and host-response biomarkers can be useful tools for clinicians since they provide additional information to optimize patient care at the bedside. Serial determinations are more informative than a single value. Biomarkers should never be used as a stand-alone test, but always in conjunction with a thorough clinical evaluation and comprehensive knowledge of the biomarkers' biology, interferences, strengths, and limitations.



Biomarkers	Comments
Prognostic	Assess the likelihood of an event or outcome during the course of sepsis; limited clinical usefulness; useful for trial enrichment
Predictive	Add valuable information (post-test probability) to the initial clinical suspicion of sepsis (pre-test probability); can be useful in sepsis diagnosis and monitoring response to therapy
Theranostic	Ability to identify a particular patient that could benefit from a specific therapy (precision medicine)

Fig. 1 The three vectors of the sepsis approach: systemic manifestations, organ dysfunction and microbiological documentation (see text). Biomarkers could provide additional information in the vector systemic manifestations (host-response biomarkers e.g., C-reactive protein–CRP, and procalcitonin–PCT), organ dysfunction (e.g., kidney injury biomarkers) and microbiological documentation (pathogen-specific biomarkers—see Table 1). Biomarkers can be classified as prognostic, predictive and theranostic. Prediction refers also to the ability of a biomarker to predict the occurrence of sepsis before its clinical suspicion (presymptomatic) as well as identify the response to therapy. For this purpose, biomarkers kinetics are more informative than a single value. A useful biomarker for the assessment of response to therapy should decline or return to baseline levels with successful therapy or remain elevated or increase if sepsis is treatment-refractory. To evaluate the clinical course, the biomarker should exhibit a large amplitude of variation, and neither 'exhaustion' nor 'fatigue' behavior with prolonged sepsis episodes

Table 1 Main pathogen-specific biomarkers used in routine practice in critically ill patients

Biomarker	Methods	Infection diagnosis	Sample (Cut-off)	Diagnostic accuracy		Comments
				Sensitivity (95% CI)	Specificity (95% CI)	
Influenza A/B Ag test	EIA ICT FIA	Influenza pneumonia	Nasal swab Other respiratory samples	0.69 (0.64–0.74)	0.97 (0.96–0.98)	Sensitivity varies according to test method (higher sensibility with FIA > ICT—EIA) and population Rapid results with ICT
SARS-CoV-2 Ag test	ICT FIA	SARS-CoV-2 pneumonia	Nasal swab Other respiratory samples	0.70 (0.69–0.71)	0.98 (0.98–0.98)	Higher sensitivity with nasal swab (*versus* other respiratory samples), among symptomatic patients (*versus* asymptomatic) and with higher viral load (RT-PCR cycle threshold ≤ 25) Rapid results
Streptococcus pneumoniae urinary Ag test	ICT FIA	Pneumococcal pneumonia	urine	0.72 (0.62–0.80)	0.83 (0.65–0.93)	Sensitivity varies depending on the pneumococcal serotype Higher sensitivity with FIA > ICT, and in pneumonia with positive blood or pleural fluid cultures No impact of antibiotic exposure on sensitivity False positives: *Streptococcus pneumoniae* colonisation in children, vaccination (48 h), prior infection (several months) Rapid results (15 min) Can also be used on CSF in suspected pneumococcal meningitis
Legionella urinary Ag test	EIA ICT FIA	Legionellosis caused by *Legionella* spp.	urine	0.79 (0.71–0.85)	1.00 (0.99–1.00)	Mainly detect *Legionella pneumophila* serogroup 1 (LP1), resulting in higher sensitivity for legionellosis cause by LP1 0.84 (0.75–0.90) Higher sensitivity with FIA > ICT > EIA, and in severe legionellosis No impact of antibiotic exposure on sensitivity Rapid results (ICT/FIA 15 min, EIA 90 min)
Glutamate dehydrogenase (GDH)	EIA	*Clostridioides difficile* infection	unformed stool	0.94 (0.89–0.97)	0.90 (0.88–0.92)	At low CDI prevalence (5%), PPV 34–38% and NPV 100% Rapid results
Clostridium difficile toxins A/B	EIA	*Clostridioides difficile* infection	unformed stool	0.83 (0.76–0.88)	0.99 (0.98–0.99)	At low CDI prevalence (5%), PPV 69–81% and NPV 99% Rapid results (30 min) Several tests include both detections of GDH and toxins A/B A positive GDH result but negative toxins A/B detection may indicate a false positive GDH, a false negative toxins A/B result, CDI with toxin levels below the threshold of detection, or toxigenic *Clostridioides difficile* carriage
(1,3)-β-D-glucan (BDG) (Fungitell® assay)	Protease zymogen-based colorimetric assay	Invasive Candida infection	Serum (> 80 pg/mL)	0.81 (0.74–0.86)	0.60 (0.49–0.71)	Early positivity (24-72 h before blood culture), slow decreasing kinetics (up to 7 weeks persistence after positive blood culture) Sensitivity depends on fungal species (lower sensibility for *C. parapsilosis*) At a low prevalence of invasive Candida infection (< 5%), PPV 10–15% and NPV > 95% Specificity and PPV can be increased by two consecutive positive samples, increased cut-off value, or combination with other specific biomarker for Candida such as mannan or *Candida albicans* germ tube-specific antibody BDG test requires glucan-free laboratory equipment Numerous causes of false-positive results, but less frequent in current clinical practice than in theory: fungal colonization, severe mucositis, disruption of gastrointestinal tract integrity, blood transfusions, albumin, immunoglobulin, hemodialysis/hemofiltration, surgical gauze, β-lactam antibiotics, enteral nutrition, Gram-positive bacteremia, sample contamination

Table 1 (continued)

Biomarker	Methods	Infection diagnosis	Sample (Cut-off)	Diagnostic accuracy		Comments
				Sensitivity (95% CI)	Specificity (95% CI)	
		Pneumocystis jirovecii pneumonia	Serum (> 80 pg/mL)	0.91 (0.87–0.94)	0.79 (0.72–0.84)	Increased sensitivity in HIV patients 0.94 (0.91–0.96) *versus* non-HIV patients 0.86 (0.78–0.91) At low/intermediate pre-test probability (≤ 20% in non-HIV and ≤ 50% in HIV), NPV ≥ 95% A negative BDG cannot rule out the diagnosis among patients with a higher likelihood of *Pneumocystis jirovecii* pneumonia
Galactomannan (GM)	EIA	Invasive pulmonary aspergillosis	Serum (ODI ≥ 0.5) Serum (ODI ≥ 1)	0.74 (0.64–0.82) 0.79 (0.60–0.91)	0.85 (0.77–0.90) 0.88 (0.78–0.94)	Increasing cut-off (ODI ≥ 1) increased both sensitivity and specificity False negatives are frequent in non-neutropenic critically ill patients, except for Influenza-associated pulmonary aspergillosis Causes of false-positive results: intestinal mucositis, β-lactams antibiotics
			BAL (ODI ≥ 0.5) BAL (ODI ≥ 1.0)	0.79 (0.65–0.88) 0.90 (0.77–0.96)	0.84 (0.74–0.91) 0.94 (0.88–0.97)	Increasing cut-off (ODI ≥ 1) increased both sensitivity and specificity More useful for the diagnosis of invasive pulmonary aspergillosis in non-neutropenic critically ill patients than that serum GM
Cryptococcal Ag test	EIA ICT	Cryptococcal meningitis	Serum Cerebrospinal fluid	0.99 (0.88–100) 0.99 (0.96–100)	0.95 (0.88–0.98) 0.99 (0.97–100)	Detects all cryptococcal serotypes In HIV adults with cryptococcal meningitis symptoms, a negative serum cryptococcal Ag test may rule out cryptococcal meningitis Rapid results (10 min) with point of care lateral flow ICT

For the Influenza A/B Ag test, pooled sensitivity and specificity are presented for ICT only. For legionellosis diagnostic, reference test = positive culture and/or PCR and/or serology. For CDI diagnosis, reference test = cell cytotoxicity neutralization assay. BDG diagnostic accuracy for invasive *Candida* infection was assessed in an ICU population at risk for ICI, reference standard = European Organization for Research and Treatment of Cancer (EORTC) and the Mycoses Study Group (MSG) criteria for proven invasive candidiasis. For *Pneumocystis jirovecii* pneumonia diagnostic, reference test = cytological sputum staining, except for 2 studies with PCR. GM diagnostic accuracy for invasive pulmonary aspergillosis was assessed in patients with impaired immunity suspected of having invasive aspergillosis, reference standard = EORTC/MSG criteria for proven/probable aspergillosis. Cryptococcal antigen diagnostic accuracy for cryptococcal meningitis was assessed in HIV-positive patients with central nervous system symptoms, reference test = cerebrospinal fluid fungal culture

Ag antigen, *BAL* bronchoalveolar lavage, *BDG* (1,3)-β-D-glucan, *CDI Clostridium difficile* infection, *CI* confidence interval, EIA enzyme immunoassay, *FIA* fluorescence immunoassay, *GM* galactomannan, *GDH* glutamate dehydrogenase, *HIV* human immunodeficiency virus, *ICT* immunochromatographic test, *NPV* negative predictive value, *ODI* optical density index, *PPV* positive predictive value

predictive value can be increased by repeating the test and/or increasing the cut-off value.

Galactomannan (GM) can be measured in serum and broncho-alveolar lavage (BAL) samples and shows high specificity for the diagnosis of invasive pulmonary aspergillosis (IPA). Of note, GM testing of BAL fluid is more sensitive than serum testing for diagnosing IPA in non-neutropenic patients, and this test plays a central role in the diagnostic criteria for IPA amongst the critically ill [20]. Rapid, bedside Aspergillus lateral-flow device tests for BAL samples have been developed and research is ongoing (Trial ISRCTN 43895480). Cryptococcal antigen detection in serum is highly predictive of cryptococcal meningitis in HIV patients with central nervous system symptoms [21].

Pathogen-specific biomarker-guided algorithms have also been tested. Two RCT assessed a BDG-guided strategy on discontinuation of empirical antifungal therapy in critically ill patients with suspected invasive candidiasis showing that it was safe and associated with a reduction of the duration of antifungal therapy [22, 23].

Host-response biomarkers

In the following section, we discuss two host-response biomarkers, PCT and CRP.

Procalcitonin

Procalcitonin is a prohormone that is the precursor of calcitonin; PCT is produced by almost all organs and macrophages, and its levels start to increase at 3–4 h after an inflammatory stimulus, peaking at about 24 h, and with a half-life of 22–35 h [24] (Table 2). However, PCT levels are influenced by glomerular filtration rate as well as renal replacement therapy [25, 26].

Table 2 Main host-response biomarkers used in routine practice in critically ill patients

	C-reactive protein	Procalcitonin
Properties	Acute phase protein (pentraxin)	Hormokine
Normal values	0.08 mg/dL (median)	< 1 ng/mL
Maximum peak	> 50 mg/dL (> 1000 × reference value)	> 100 ng/mL (> 10.000 × reference value)
Source	Liver	Virtually all cells and macrophages
Time to increase after insult	4–6 h	3–4 h
Time to peak concentration	36–50 h	Around 24 h
Half-life	19 h	22–35 h
Possible confounders		
Steroids	No effect	frequent false negatives
Immunosuppression	No effect	frequent false negatives
Neutropenia	No effect	frequent false negatives
Renal failure	No effect	⬆⬆
Renal replacement therapy	No effect	⬇⬇
Chronic liver failure	⬇ (70% of the normal)	No effect
Acute liver failure	No CRP increase	No effect
Secondary infection (2nd hit)	⬇ (70% of 1st episode)	⬇⬇⬇ (10% of 1st episode)
Bacterial vs viral infections	Poor	Poor

CRP C-reactive protein, *PCT* Procalcitonin

Prediction of sepsis

PCT is the most studied biomarker in the setting of ventilator-associated pneumonia (VAP). The lack of utility of PCT measurements, either singly or serial, in VAP prediction and diagnosis has been shown in several observational studies [4, 27].

Studies of PCT kinetics in critically ill patients showed poor diagnostic accuracy and a low impact regarding guidance for the initiation of therapy [28]. Thus, although associated with decreased antibiotic use in selected settings, the utility of PCT to predict sepsis in the ICU is limited.

Diagnosis of sepsis

There is no agreed PCT cutoff value for sepsis diagnosis; published studies have either not reported the cutoff value, or used values ranging from 0.5 to 2 μg/L [29]. Numerous noninfectious inflammatory states are also associated with elevated PCT serum levels [30]. Three separate meta-analyses of PCT for the diagnosis of sepsis revealed a sensitivity and specificity range of 77–85% and 75–83%, respectively [31–33]. While PCT may be superior to CRP in patients with suspicion of sepsis, PCT should not be used to guide antimicrobial prescription [11, 34]. Similarly, both the 2016 IDSA/ATS guidelines [35] and the 2017 ERS/ESICM/ESCMID/ALAT guidelines [36] do not recommend the use of PCT for the diagnosis of VAP.

In patients with severe CAP, PCT have been evaluated to assess the presence of bacterial co-infection in influenza. Preliminary studies in documented influenza cases suggest PCT levels may offer a higher negative predictive value to rule out bacterial co-infection [37]. However, these findings have not been replicated by others [38, 39]. More studies are needed before a wider use of this strategy, especially in other viral (non-Influenza) infections, can be recommended. In addition, a recent meta-analysis showed that PCT lacks sensitivity early during CAP and cannot reliably distinguish viral from bacterial infections at that point [40].

Assessment of sepsis response to therapy

Approximately 48–72 h after the diagnosis of sepsis is made and antibiotic therapy is initiated, it is important to assess the clinical course of the patient and ask: (1) Is the patient clinically improving? (2) If the patient is not improving, is it due to an undetected septic complication (e.g., empyema, pulmonary abscess), a secondary infection (at the same or another site), inadequate or inappropriate antibiotic therapy? (3) Or is it due to a noninfectious cause?

In VAP patients, PCT measured at onset and on D4 of treatment could predict survival, differentiating patients with good and bad outcome [41, 42]. Persistent high levels of PCT at D4 of antibiotic therapy were indicative of a failure of infection control [43, 44].

In clinical practice, patients who present persistently elevated levels of biomarkers by D3/D4 of antibiotic therapy should raise suspicion of treatment failure and should prompt an aggressive diagnostic and therapeutic

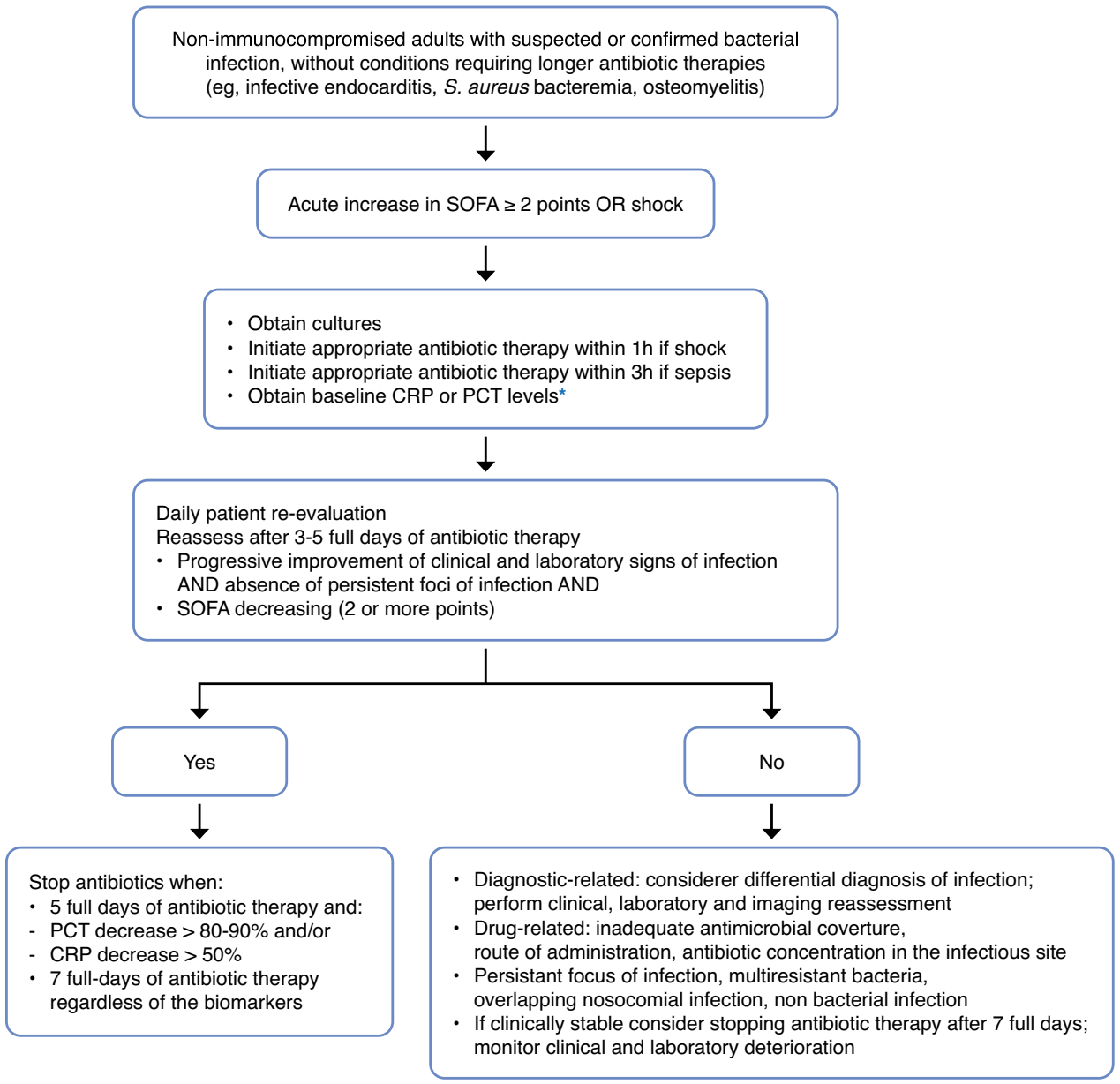


Fig. 2 User's guide for biomarker-guided antibiotic therapy. Starting antibiotics in critically ill patients with suspicion of sepsis should be done irrespective of any biomarker level. But this should be reassessed daily. Use the clinical course, the organ dysfunction course (with SOFA score), the kinetics of biomarkers and the duration of antibiotic therapy to ascertain the optimal duration of therapy. PCT, procalcitonin; CRP, C-reactive protein; SOFA, sequential organ failure assessment, NOTE–CRP and PCT thresholds should be used only as indicative and orientation; These recommendations do not apply to immune-compromised patients nor to patients with infections requiring long-term antibiotic therapy, like endocarditis or osteomyelitis. Adapted from Salluh Crit Care 2014; 18:142 [74]. *Do not use CRP or PCT levels to guide decision to initiate antibiotic therapy

approach. However, caution should be exercised in using biomarkers as a stand-alone criterion to decide when to escalate the diagnostic. A clinical approach algorithm based on the concept of "alert PCT" (PCT ≥ 1 ng/mL and not decreasing > 10%/day) was evaluated in an RCT showing no mortality benefit at the expense of higher large-spectrum antibiotic consumption, more days on antibiotics, prolonged length of mechanical ventilation and ICU stay [45].

PCT-guided antibiotic therapy

While one strategy of antibiotic stewardship is simply to convert fixed long antibiotic durations to fixed short ones, an increasingly popular approach is to use biomarkers to personalize antibiotic treatment duration. This approach includes the individual patient's response to therapy, matching the antibiotic discontinuation to the patient's actual clinical course. While it was initially unknown whether such an approach would be antibiotic sparing, increasing evidence confirms a reduction in overall antibiotic use with PCT [33, 46]. So far there are at least 18 RCT evaluating PCT-guided antibiotic therapy in critically ill patients with strong evidence that this strategy is safe, is associated with a shorter duration of therapy and, in some RCT, decrease mortality. However, the major criticisms were that, in the controls of the early RCT, the duration of antibiotic therapy was longer than recommended [13].

A recent systematic review and meta-analysis assessed the impact of PCT-guided strategy on mortality and duration of antibiotic therapy in critically ill patients, as well as other factors like industry sponsorship, algorithm adherence and simultaneous availability of CRP [47]. Overall, PCT-guided strategy decreased antibiotic duration by 1 day and improved survival, particularly in RCT without high protocol adherence and when PCT was combined with CRP.

C-reactive protein

Serum CRP is an acute-phase protein exclusively synthesized in the liver in response to cytokines, in particular interleukin 6. Its levels start to increase 4–6 h after an inflammatory stimulus, doubling every 8 h, peaking at 36–50 h, and with a half-life of 19 h [48] (Table 2). Its level is not influenced by immunosuppression (steroids or neutropenia) nor influenced by renal failure or renal replacement therapy, and does not significantly differ between individuals with or without cirrhosis [49–52].

Prediction of sepsis

C-reactive protein kinetics in the days before ICU-acquired sepsis accurately predicted its diagnosis with a maximum daily CRP increase > 4.1 mg/dL (in particular if associated with an absolute concentration > 8.7 mg/dL) [53]. A similar finding was observed in a large study of community-acquired bloodstream infections (BSI) wherein CRP concentration start to increase over the three days preceding a definitive diagnosis of BSI [54].

The BioVAP multicenter study investigated biomarker kinetics in patients under invasive mechanical ventilation for non-infectious reasons in the days before VAP diagnosis and found that CRP and the CRP slope over time were good predictors of VAP occurrence. This finding was not seen with PCT kinetics [4]. However, both the 2016 IDSA/ATS guidelines [35] and the 2017 ERS/ESICM/ESCMID/ALAT guidelines [36] do not recommend the use of any biomarker for the diagnosis of VAP, neither PCT nor CRP.

Diagnosis of sepsis

The value of a single CRP determination in patients with suspicion of sepsis has not been consistently demonstrated by two meta-analyses (one analysis was of adult-only trials) noting a sensitivity and specificity range from 78–80% to 60–61%, respectively [31, 55]. The variable accuracy of CRP in clinical studies is also impacted by the use of different cutoff points typically ranging between 2 and 10 mg/dL [48, 56]. However, in a recent prospective observational study, CAPTAIN study, assessing the performance of 53 biomarkers in the discrimination between sepsis and non-septic systemic inflammatory response syndrome (SIRS) it was found that no biomarker or combination performed better than CRP alone, and better than PCT [5].

The diagnosis of CAP is frequently difficult because chest X-ray may not present infiltrates in the first 24–72 h. In a study performed on patients with a clinical diagnosis of CAP, a CT scan was performed to confirm the presence or absence of pneumonia. It was found that a very high CRP level was a good predictor of CAP in a patient with a false-negative chest X-ray and, conversely, low CRP was useful to exclude CAP in a patient with a false-positive chest X-ray [57]. However, PCT showed to be a poor discriminator of both false-positive and false-negative chest X-rays.

Assessment of sepsis response to therapy

C-reactive protein has been extensively studied in the assessment of response to therapy for several severe infections, namely VAP, BSI and CAP; the trajectory after the prescription of antibiotics correlates with clinical course and prognosis [6–8]. The use of relative CRP variations (CRP-ratio)—the ratio of each day's CRP concentration in relation to the day 0 (D0) level—was more informative than absolute CRP changes. A sharp decrease in CRP-ratio is a surrogate marker of sepsis resolution whereas a persistently elevated or an increasing CRP-ratio suggests sepsis is refractory to therapy. In patients with microbiologically documented VAP, a CRP > 0.6 of the initial value at D4 was a marker of poor outcome [8]. Similar results were observed in BSI, severe CAP, nosocomial pneumonia and sepsis [7, 58–60].

Using the concept of CRP-ratio, four individual patterns of response to antibiotic therapy have been defined [8]: (1) fast response pattern, consists of a rapid decline of CRP-ratio to < 0.4 by D4; (2) slow response pattern, is a

continuous decline of CRP-ratio, with a value by D4 > 0.4 but < 0.8; (3) nonresponse pattern, is defined by a CRP-ratio persistently > 0.8 (and sometimes even increasing); (4) biphasic response pattern, is characterized by an initial drop in CRP-ratio < 0.8, followed by a secondary rise to a value above that threshold. In severe CAP, VAP and BSI, patients with fast and slow response patterns had significantly lower mortality than patients with either nonresponse or biphasic patterns [6–8, 61].

Although there are no RCT, the 2017 ERS/ESICM/ESCMID/ALAT guidelines recognize the added value of biomarkers in the assessment of response to therapy namely CRP-ratio and the identification of patterns of CRP-ration response [36].

CRP-guided antibiotic therapy

The number of RCT assessing CRP-guided strategy are scarce, namely in ICU patients [12]. The first RCT was a head-to-head comparison between PCT vs CRP-guided strategy and found that CRP was non-inferior to PCT for duration guidance and with no difference in morbidity or mortality [62]. But very important, in this single-center RCT the maximum duration of antibiotic therapy was 7 days regardless of biomarker levels. So far this is the only RCT comparing the performance of both biomarkers in antibiotic duration. Subsequently, observational and randomized studies have found that CRP-guided strategy compared to PCT-guided or fixed duration (short course) presented no substantial differences in the ability to reflect improvement (or worsening) in the clinical course of sepsis and septic shock as well as in reducing antibiotic exposure [46, 62–65].

Early trials investigating biomarker-guided strategies to guide antibiotic duration had control group patients treated according to standard practices [46, 66, 67]. Given the lack of evidence for treatment durations for most primary foci, these control groups received what would today be considered excessively prolonged therapy, resulting in a potentially biased conclusion that a biomarker-based strategy was associated with reduced antibiotic exposure [68, 69]. To overcome these limitations, more recent trials have used shorter, fixed control durations [70–73]. The individualize therapy would be to combine the fixed duration with biomarker guidance, using a "double trigger" strategy [74]. After some days of therapy, antibiotics could be stopped according to the clinical course and either decreases in biomarker levels (CRP or PCT), according to a predefined algorithm, or the completion of 5–7 days of full days of antibiotic therapy, whichever came first (Fig. 2). This individualized strategy has been assessed in several RCT showing that biomarker guidance can safely decrease the duration of therapy in comparison with fixed duration [9, 64, 65, 75, 76].

Future perspectives

The combination of various biomarkers to construct a diagnostic panel has not been shown to be consistently superior to any individual biomarker in diagnosing sepsis [5]. This arises from the fact that sepsis biomarkers are usually highly correlated, and thus diagnostic accuracy has not improved when these assays have been combined. Diagnostic accuracy of a biomarker panel is further dependent upon how the results of the individual assays are weighted and how many individual assays need to be positive for the overall panel to indicate the presence of sepsis. For example, a biomarker panel can be relatively sensitive (requiring only one individual assay to be "positive") or relatively specific (requiring all the individual assays to be positive) dependent upon how the panel is interpreted. However, algorithms that combine biomarkers with clinical data have shown promise for identifying patients with sepsis in the emergency department [77]. One such algorithm combining clinical variables and a panel of biomarkers claimed a negative predictive value of 100% and a positive predictive value of 93% in a cohort of 158 patients [78]. Two limitations of this study should be noted. Firstly, all study participants had at least two SIRS criteria so how this algorithm would perform in SIRS-negative sepsis is not known. Secondly, the speed with which the results of this algorithm was delivered was not described.

Conclusion

In summary, moving forward from where we currently are with biomarkers of sepsis to a point where we have clinically useful markers driving patient treatment pathways to improve outcomes will require a significant change in approach. Single center, unidimensional studies will unlikely bring much progress. Large multi-center cohort studies, utilizing state-of-the-art omics, bioinformatics, and machine learning algorithms to identify biomarkers that predict differential responses to interventions in specific clinical endotypes are what is needed. The combination of existing tools in multicenter and multidisciplinary collaborations will be the most effective way of discovering new biomarkers that can be implemented into clinical practice to optimize patient care. Until then, biomarkers of sepsis can be useful adjunctive tools when clinicians need additional information to optimize patient care at the bedside. Serial determinations are more informative than a single value and biomarkers should never be used as a stand-alone test, but always in conjunction with a thorough clinical evaluation

and a comprehensive knowledge of biomarkers' biology, interferences, strengths, and limitations.

Supplementary Information
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Data availability
Not applicable.

Declarations

Conflict of interest
PP received fees for a lecture from Gilead, Pfizer and Mundipharma, consulting from MSD and Sanofi, and an unrestricted research grant from Abionic. AR received fess for lectures from MSD. ACM received fees for lectures from Boston Scientific and consulting from Cambridge Infection Diagnostics, is supported by a Clinician Scientist Fellowship from the Medical Research Council (MR/V006118/1). MS received fees for lectures at educational meetings for Biomerieux and Radiometer, consulting from Abbott, Biomerieux, deePull, Roche Diagnostics, Safeguard Biosystems and Spiden and performed preclinical and clinical research studies with Biomerieux, Cornel Scientific, DSTL (UK Ministry of Defence), Gentian. RF received fees for lectures, speakers' bureaus or advisory boards from Grifols, MSD, Pfizer, Gilead, Shionogi, Thermofisher, Hill Rom, AOP Health and BD. LC, FD-P, AH, AK, VN, JS, PR, DS, GW, AT declare no conflict of interest.

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