Academy of Emergency Medicine and Care-Society of Clinical Biochemistry and Clinical Molecular Biology consensus recommendations for clinical use of sepsis biomarkers in the emergency department

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Abstract

Increasing evidence is emerging that the measurement of circulating biomarkers may be clinically useful for diagnosing and monitoring sepsis. Eight members of AcEMC (Academy of Emergency Medicine and Care) and eight members of SIBioC (Italian Society of Clinical Biochemistry and Laboratory Medicine) were identified by the two scientific societies for producing a consensus document aimed to define practical recommendations about the use of biomarkers for diagnosing of sepsis and managing antibiotic therapy in the emergency department (ED). The cumulative opinions allowed defining three grade A recommendations (*i.e.*, highly recommended indications), entailing ordering modality (biomarkers always available on prescription), practical use (results should be interpreted according to clinical information) and test ordering defined according to biomarker kinetics. Additional grade B recommendations (*i.e.*, potentially valuable indications) entailed general agreement that biomarkers assessment may be of clinical value in the diagnostic approach of ED patients with suspected sepsis, suggestion for combined assessment of procalcitonin (PCT) and C-reactive protein (CRP), free availability of the selected biomarker(s) on prescription, adoption of diagnostic threshold prioritizing high negative predictive value, preference for more analytically sensitive techniques, along with potential clinical usefulness of measuring PCT for monitoring antibiotic treatment, with serial testing defined according to biomarker kinetics. PCT and CRP were the two biomarkers that received the largest consensus as sepsis biomarkers (grade B recommendation), and a grade B recommendation was also reached for routine assessment of blood lactate. The assessment of biomarkers other than PCT and CRP was discouraged, with exception of presepsin for which substantial uncertainty in favor or against remained.

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Introduction

Around the 700 BC the ancient Greeks identified with the term σηψίζ (*i.e.*, sepsis), intended as *decomposition* or *putrefaction*, a severe medical condition carrying a high risk of infection-related mortality.[1] Despite this rather long history, clinicians felt the need for a more precise definition of the syndrome only in the last decades of the past century, and three essential - though not fully concordant - milestones were set in 1992, 2003 and 2016.[2] After the third international conference on sepsis and septic shock, sepsis was hence defined as a life-threatening organic dysfunction caused by a disordered response of the host to an infection.[3] Notably, this definition brings back to the illuminating intuition of Sir William Osler, who had already written at the beginning of the 1900s that *with rare exceptions, the patient seems to die because of the body's reaction to infection rather than because of the infection itself*.[4] The term septic shock refers instead to a particular type of sepsis, whose deep circulatory, cellular and metabolic abnormalities are associated with a greater risk of mortality than sepsis alone.

As regards the epidemiology, recent data shows that the frequency of sepsis is approximately 2% in the general hospital population, but can increase up to 6-30% in patients admitted to the intensive care unit (ICU).[5] Nevertheless, these estimates are influenced by considerable heterogeneity depending on geographical setting, type of facility and hospital department, since more than 50% of patients with severe sepsis are admitted to the ICU with a considerably high mortality rate (*i.e.*, between 28-50%).[6] The recent findings of an observational study in the United States attest that the frequency of sepsis in hospitalized patients will approximately increase by 9% per year.[7] In the emergency room setting, an Australian prospective study has recently shown that most (*i.e.*, over 97%) of patients admitted with severe sepsis in the ICU had been earlier triaged in the emergency department (ED).[8] Notably, sepsis could be identified in only 53% of these patients while in the ED, thus emphasizing the need to further refine the diagnostic tools available to the emergency physicians.

The recent conclusions of the Sepsis-3 group substantially simplified the classification, eliminating the subgroups of SIRS (Systemic Inflammatory Response Syndrome) and severe sepsis, thus maintaining only the two categories of sepsis and septic shock.[3] The SIRS has hence disappeared as an autonomous condition, since it is now considered an appropriate physiological response to a large number of infectious and non-infectious conditions and remains as a set of signs and symptoms characterizing sepsis only with the concomitant presence of

organ damage identified by attributing at least two points to the SOFA (Sequential [Sepsis-Related] Organ Failure Assessment) score.[3] Since the parameters of both SIRS and SOFA scores also include laboratory tests, the authors have searched for, and have identified, a simplified clinical system which allows a high degree of suspicion and attention from the triage. This simplified system involves the assessment of three simple parameters, *i.e.*, respiratory rate, altered mental status and arterial pressure. The combination of these three parameters was included in a simplified and fast score, called qSOFA (quick-SOFA) score. The task force suggests that the qSOFA criteria, when positive, should allow to early detecting organ damage and infection sources, as well as initiating, or early reinforcing, the therapy.[3] According to the conclusions of the task force, the qSOFA is not intended as a diagnostic criterion, but rather a sort of *red flag* for triage.

Interestingly, the definition of sepsis ironically resembles that of *time*; the closer we get, the farther we are. The conclusions of the Sepsis-3 task force have already raised criticisms and demands for revision and/or further validation. One of the main criticisms is that the validation of qSOFA criteria has been obtained retrospectively in ICU patients, thus lacking reliable data on large populations of patients evaluated in the ED and then hospitalized. Therefore, prospective validation is needed in these care settings.[9] A first observational study conducted outside the ICU does not seemingly support the usefulness of qSOFA, which has a significantly lower diagnostic performance than the MEWS (Modified Early Warning Score) and NEWS (National Early Warning Score), which are already widely used in many emergency rooms.[10] According to the new definitions, sepsis and septic shock are treated as syndromes and not as specific diseases. The challenges to establishing whether sepsis may actually be secondary to an infection, and which is the etiology and the site of the infection, still represent important limitations for clinical use in the individual patient.

Some clinical conditions mimicking sepsis may be due to non-infectious conditions, such as acute pancreatitis, major trauma, burns and venous thromboembolism.[9] The search for the septic source, when not immediately apparent, is a priority, which can be somehow supported by bedside ultrasound.[11] Therefore, there is ongoing research for identifying other tools which may support clinicians not only for identifying patients presenting with sepsis, but also for defining the potential etiology and stratifying the risk earlier and more accurately, since the outcome is strongly influenced by early diagnosis and appropriate and timely treatment.[12,13] The

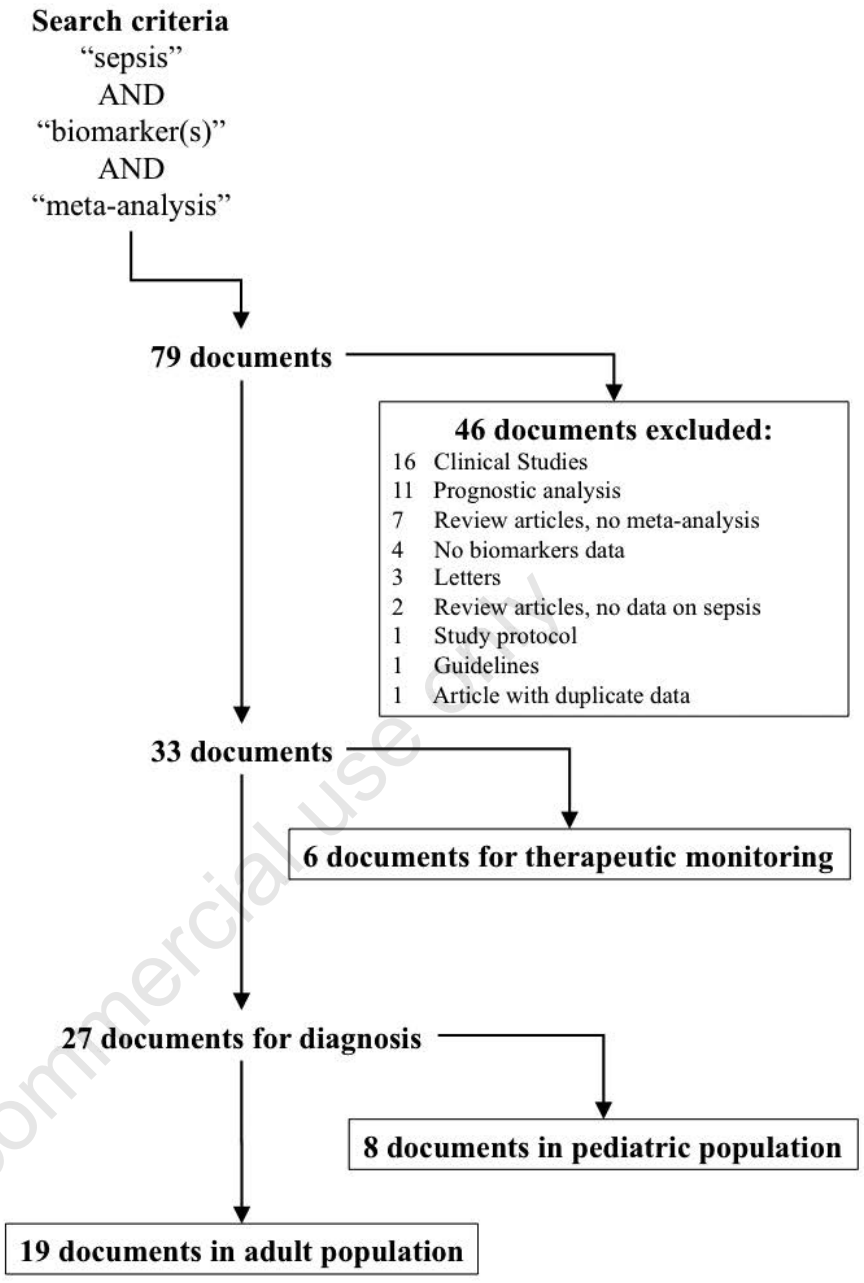

Figure 1. Electronic search strategy conducted on the three major scientific databases (Medline with PubMed interface, Scopus and Web of Science), using the keywords sepsis AND biomarker (s) AND meta-analysis, without language and/or date restrictions.

Table 1. Definition of the strength of recommendations, in accordance with the National Guidelines Program.

A	Highly recommended indication: Indicates a specific recommendation supported by good-quality scientific evidence
B	Doubts remain that a specific indication may always be recommended, but there is general consensus that it should be carefully considered
C	There is substantial uncertainty in favor of or against this recommendation
D	The indication is discouraged
E	Highly discouraged indication

Table 2. Meta-analyses about biomarkers for the diagnosis of sepsis.

Authors	Biomarkers	Cut-off	Study and populations	Setting	Heterogeneity	Results
Adults						
Uzzan *et al.*, 2006[17]	PCT, CRP	PCT: 0.6-5.0 ng/mL; CRP: 39-180 mg/L	33 studies, 3943 patients (prospective/case- control studies)	Patients in intensive care for trauma/surgery	Significant	PCT: AUC, 0.78 (95% CI, 0.71-0.84); sensitivity, 0.42-1.00; specificity, 0.48-1.00 CRP: AUC, 0.71 (95% CI, 0.64-0.76); sensitivity, 0.35-1.00; specificity, 0.18-0.85
Tang *et al.*, 2007[18]	PCT	0.50-20 ng/mL	18 studies, 2097 patients (prospective/case- control studies)	Patients in intensive care (14 studies) and/or emergency department (4 studies)	Significant	PCT: AUC, 0.78; sensitivity, 0.71 (95% CI, 67-76); specificity, 0.71 (95% CI, 67-76)
Wu *et al.*, 2012[19]	sTREM-1	40-3500 pg/mL	11 studies, 1795 patients (prospective/case- control studies)	Patients with systemic inflammation	Significant	sTREM-1: AUC, 0.87 (95% CI, 0.84 to 0.89); sensitivity, 0.79; specificity, 0.80 (sensitivity, 0.83 e specificity, 0.68 in emergency department)
Wacker et al., 2013[20]	PCT	0.10-15.75 ng/mL	30 studies, 3244 patients (prospective/case- control studies)	Patients with systemic inflammation	Significant	PCT: AUC, 0.85 (95% CI, 0.81-0.88); sensitivity, 0.77; specificity, 0.79
Lee *et al.*, 2013[21]	PCT	PCT: 0.20-0.51 ng/mL; CRP: 30-175 mg/L	4 studies, 760 patients (only prospective studies)	Elderly population (≥65 years)	Significant	PCT: AUC, 0.89 (95% CI, 0.86-0.92); sensitivity, 0.83; specificity, 0.83 (sensitivity, 0.97 e specificity, 0.61 in emergency department) CRP: AUC, non-calculated; sensitivity, 0.91; specificity, 0.36
Hoeboer *et al.*, 2015[22]	PCT	0.15-17 ng/mL (optimal: 0.5 ng/mL)	58 studies, 16514 patients (prospective/case- control studies)	Unselected population	Significant	PCT: AUC, 0.79; sensitivity, 0.76; specificity, 0.80 (AUC 0.78, sensitivity, 0.76 e specificity, 0.68 in emergency department)
Ren *et al.*, 2015[23]	PCT	0.5-30 ng/mL	8 studies, 566 patients (non-specified types of studies)	Burn patients	Significant	PCT: AUC, 0.92 (95% CI, 0.81-0.88); sensitivity, 0.74; specificity, 0.88
Wang *et al.*, 2015[24]	nCD64	Arbitrary	8 studies, 1986 patients (non-specified types of studies)	Unselected population	Significant	nCD64: AUC, 0.95 (±0.02); sensitivity, 0.76; specificity, 0.85
Wu *et al.*, 2015[25]	Presepsin	317-700 pg/mL	9 studies, 2159 patients (only prospective studies)	Unselected population	Significant	Presepsin: AUC, 0.89 (95% CI, 0.84-0.94); sensitivity, 0.78; specificity, 0.83
Tong *et al.*, 2015[26]	Presepsin	317-864 pg/mL	11 studies, 3106 patients (10 prospective studies, 1 case-control study)	Unselected population	Significant	Presepsin: AUC, 0.89 (95% CI, 0.86-0.92); sensitivity, 0.83; specificity, 0.81
Chengfen *et al.*, 2015[27]	PCT	0.1-15.75 ng/mL	24 studies, 3107 patients (prospective/case- control studies)	Unselected population	Significant	PCT: AUC in non-surgical patients, 0.80 (95% CI, 0.75-0.85); AUC in surgical patients, 0.71 (95% CI, 0.65-0.81); sensitivity, 0.74; specificity, 0.70
Zhang *et al.*, 2015[28]	Presepsin	317-729 pg/mL	8 studies, 1815 patients (only prospective studies)	Patients with systemic inflammation	Significant	Presepsin: AUC, 0.89 (95% CI, 0.86-0.92); sensitivity, 0.86; specificity, 0.78 (sensitivity, 0.85 e specificity, 0.79 in emergency department)
Zhang *et al.*, 2015[29]	Presepsin	317-729 pg/mL	11 studies, 3052 patients (prospective/case- control studies)	Unselected population	Significant	Presepsin: AUC, 0.88 (95% CI, 0.84-0.90); sensitivity, 0.83; specificity, 0.78 (slightly lower in emergency department)
Zheng *et al.*, 2015[30]	Presepsin	317-729 pg/mL	8 studies, 1757 patients (only prospective studies)	Patients with systemic inflammation	Significant	Presepsin: AUC, 0.86 (±0.02); sensitivity, 0.77; specificity, 0.73
Chen *et al.*, 2016[31]	LBP	27.3-64.4 µg/mL	8 studies, 1684 patients (prospective studies)	Unselected population	Significant	LBP; AUC, 0.68 (95% CI, 0.64-0.72); sensitivity, 0.64; specificity, 0.63 (sensitivity, 0.70 e specificity, 0.56 in emergency department or general medicine)
Ma *et al.*, 2016[32]	IL-6, PCT, CRP	IL-6, 0.02-1000 pg/mL; PCT, 0.1-6.0 ng/mL: CRP, 11-400 mg/L	22 studies, 2680 patients (prospective/case- control studies)	Patients with systemic inflammation	Significant	IL-6: AUC, 0.80 (±0.03); sensitivity, 0.68; specificity, 0.73 PCT: AUC, 0.83 (±0.03); sensitivity, 0.78; specificity, 0.67 CRP: AUC; 0.71 (±0.02); sensitivity, 0.78; specificity, 0.67

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Authors	Biomarkers	Cut-off	Study and populations	Setting	Heterogeneity	Results
Adults						
Liu *et al*., 2016[33]	PCT, CRP, IL-6, sTREM-1, presepsin, LBP, nCD64	IQR: PCT, 0.5-1.7 g/mL; CRP, 38-140 mg/L; IL-6, 75-220 pg/mL; sTREM-1, 35-594 pg/mL; presepsin, 415-647 pg/mL; LBP, 24.3-32 µg/mL; nCD64, non-specified	86 studies, 10438 patients (non-specified types of studies)	Patients with systemic inflammation	Significant	PCT: AUC, 0.85 (0.82-0.88); sensitivity, 0.79; specificity, 0.78 CRP: AUC, 0.77 (0.73-0.81); sensitivity, 0.75; specificity, 0.67 IL-6: AUC, 0.79 (0.75-0.82); sensitivity, 0.72; specificity, 0.73 sTREM-1: AUC, 0.85 (0.82-0.88); sensitivity, 0.78; specificity, 0.78 Presepsin: AUC, 0.88 (0.85-0.90); sensitivity, 0.84; specificity, 0.77 LBP: AUC, 0.71 (0.67-0.75); sensitivity, 0.62; specificity, 0.70 nCD64: AUC, 0.96 (0.94-0.97); sensitivity, 0.87; specificity, 0.93
Ni *et al*., 2016[34]	suPAR	2.7-9.5 ng/mL	7 studies, 1062 patients (4 studies and 4812 patients with systemic inflammation; 6 prospective studies and 1 case-control study)	Patients with and without systemic inflammation	Significant	suPAR: AUC, 0.82 (95% CI, 0.78-0.85); sensitivity, 0.67; specificity, 0.80 (for diagnosing sepsis in patients with systemic inflammation: AUC, 0.68 e 95% CI, 0.64-0.72; sensitivity, 0.61; specificity, 0.82)
Cabral *et al*., 2016[35]	PCT	0.5-5.0 ng/mL	14 studies, 830 patients (prospective/case- control studies)	Burn patients	Significant	PCT: AUC, 0.87 (±0.04); sensitivity, 0.77; specificity, 0.65
Neonates						
Yu *et al.*, 2010[36]	PCT, CRP	Non-specified	22 studies, 2836 patients	Neonates	Significant	PCT for neonatal sepsis: AUC, 0.77; sensitivity, 0.72; specificity, 0.77. CRP for probable neonatal sepsis: AUC, 0.88; sensitivity, 0.81; specificity, 0.92 CRP for neonatal sepsis: AUC, 0.75; sensitivity, 0.55, specificity, 0.85. CRP for probable neonatal sepsis: AUC, 0.81; sensitivity, 0.77, specificity, 0.79
Vouloumanou *et al.*, 2011[37]	PCT	0.50-5.75 ng/mL	16 studies, 1959 patients	Neonates	Significant	PCT: AUC, 0.87 (95% CI, 0.84-0.90); sensitivity, 0.81; specificity, 0.79
Yuan *et al.*, 2013[38]	SAA, CRP	Non-specified	9 studies, 823 patients	Neonates	Significant	SAA: AUC, 0.90 (95% CI, 0.87-0.93); sensitivity, 0.84; specificity, 0.89 CRP: AUC, 0.92 (0.87-0.93); (95% CI, to); sensitivity, 0.67; specificity, 0.92
Lv *et al*., 2014[39]	TNF-α	0.18-20000 pg/mL	15 articoli e 23 trials	Neonates	Significant	TNF-α in articles: AUC, 0.74 (95% CI, 0.70-0.78); sensitivity, 0.66; specificity, 0.76 TNF-α in trials: AUC, 0.87 (95% CI, 0.85-0.89); sensitivity, 0.68; specificity, 0.73
Zhou *et al*., 2015[40]	IL-8	0.6-300 pg/mL	8 studies, 548 patients	Neonates	Significant	IL-8: AUC, 0.89 (±0.05); sensitivity, 0.78; specificity, 0.83
Xu *et al*., 2016[41]	CRP	2.5-21.0 mg/L	31 studies, 5698 patients	Neonates	Significant	CRP: AUC, 0.85 (±0.05); sensitivity, 0.69; specificity, 0.77
Shi *et al*., 2016[42]	nCD64	1.63-6136 (arbitrary measure unit)	17 studies, 3478 patients	Neonates	Significant	CRP: AUC, 0.87 (±0.02); sensitivity, 0.77; specificity, 0.74
Pontrelli *et al*., 2017[43]	PCT	0.28-14.0 ng/mL	17 studies, 1408 patients	Pediatric population	Non-significant	PCT: AUC, non-calculated; sensitivity, 0.85; specificity, 0.54

AUC, Area Under the Curve; IL-6, interleukin 6; IL-8, interleukin 8; IQR, interquartile range; LBP, lipopolysaccharide-binding protein; nCD64, neutrophil CD64; PCT, procalcitonin; CRP, C reactive protein; SAA, Serum Amyloid A; suPAR, serum soluble urokinase-type plasminogen activator receptor; sTREM-1, soluble triggering receptor expressed on myeloid cells-1; TNF-α , tumor necrosis factor-α.

measurement of circulating infective biomarkers is one of the most promising tools that have recently emerged. The term biomarker is conventionally used to define a measurable analyte, which can improve diagnostic accuracy, simplify complex clinical algorithms and improve the clinical decision-making.[14] In the specific area of sepsis, an ideal marker should allow early diagnosis (*i.e.*, be measurable before or at the appearance of clinical signs), be very sensitive and specific also for the differential diagnosis of infectious and non-infectious forms of systemic dysfunction, permit to obtain valid clinical information about the course and prognosis of sepsis and, last but not least, provide reliable indications for guiding antibiotic therapy.

Search strategy

An electronic search strategy was conducted on the three major scientific databases (Medline with PubMed interface, Scopus and Web of Science),[15] using the keywords *sepsis* AND *biomarker (s)* AND *meta-analysis*, without language and/or date restrictions (Figure 1). The existence of additional meta-analyses published in scientific journals was then verified by accurately checking the list of bibliographic references. The title, summary and, when necessary, the full text of the documents identified with the search criteria were independently evaluated by two authors (GL and MM), with exclusion of all meta-analyses in which the diagnostic performance of biomarkers for diagnosing sepsis and managing antibiotic therapy was unavailable. The following information was reported, when available, for all selected documents: (A) clinical setting; (B) number of studies included in the meta-analysis; (C) total number of patients included in the meta-analysis and characteristics of the studies (*i.e.*, prospective and/or case-control); (D) heterogeneity of studies (significant, >50%); (E) diagnostic performance expressed in terms of area under the curve (AUC), sensitivity and specificity, or clinical efficacy in case of biomarker-guided antibiotic therapy; (F) diagnostic cut-offs.

The consensus document was drafted after identification by both scientific societies SIBioC (Italian Society of Clinical Biochemistry and Laboratory Medicine) and AcEMC (Academy of Emergency Medicine and Care) of eight members each, to whom a questionnaire was administered. The consensus members were asked to rate some recommendations about the use of biomarkers for diagnosing sepsis and managing antibiotic therapy in the ED. In accordance with the National Guidelines Program (PNLG) (16), the recommendations were then formulated with a *grading* system based on the *strength of the recommendation* expressed in letters (from A to E), as summarized in Table 1. The questionnaire containing the recommendations was sent by e-mail to all participants, who were asked to rate each recommendation from A to E, as in Table 1. The final grade of recommendation was expressed as the average (and standard deviation; SD) of individual opinions after rating was converted in numeric data (A = 1; B = 2; C = 3; D = 4; E = 5). A mean score of <1.5 was rated as grade A, between 1.5 and <2.5 as grade B, between 2.5 and <3.5 as grade C, between 3.5 and <4.5 as grade D and ≥4.5 as grade E.

Results and Discussion

The systematic search, carried out according to the above-mentioned criteria, allowed identifying 79 documents after duplicates elimination. Forty-six items were excluded since they were not relevant for the purpose of this document (Figure 1). Six out of the 33 remaining documents contained data about the use of biomarkers for monitoring antibiotic therapy in sepsis patients (all about procalcitonin, PCT), whereas 27 dealt with the use of biomarkers for diagnosing sepsis. Eight of these documents were carried out in pediatric populations, the remaining 19 in adult populations. The agreement between the two authors who analyzed the search products was 100%. Documents about the use of biomarkers for diagnosing sepsis in the adult[17-35] and pediatric populations (added for comprehensiveness)[36-43] are summarized in Table 2.[17-43] The documents containing data about biomarker-guided antibiotic therapy is summarized in Table 3.[44-49] The heterogeneity of the studies was found to be significant in almost all meta-analyses. In particular, only 4 of the 6 meta-analyses about biomarker-guided antibiotic therapy were not characterized by significant heterogene-

Table 3. Meta-analyses about the biomarker-guided antibiotic therapy.

Authors	Biomarkers	Studies and population	Setting	Heterogeneity	Results
Kopterides *et al*., 2010[44]	PCT	7 studies, 1131 patients	Intensive care	Significant	Reduction of 4.2 days (95% CI, 3.4-5.0) duration of antibiotic therapy; reduction of 18% antibiotic therapy expenditure
Heyland *et al.*, 2011[45]	PCT	5 studies, 947 patients	Intensive care	Non-significant	Reduction of 2.1 days (95% CI, 1.8-2.5) duration of antibiotic therapy; likely economic benefit
Schuetz *et al*., 2011[46]	PCT	14 studies, 4467 patients	Primary care, emergency department, intensive care	Non-significant	Reduction of 29% (95% CI, 15-37%) duration of antibiotic therapy (34%; 95% CI, 15-53 for emergency department)
Soni *et al*., 2013[47]	PCT	18 studies, number of patients unavailable	Intensive care	Non-significant	Reduction of 2.0 days (95% CI, 1.5-2.6) duration of antibiotic therapy
Prkno *et al*., 2013[48]	PCT	7 studies, 1075 patients	Intensive care	Non-significant	Reduction of 27% (95% CI, 5-53%) duration of antibiotic therapy
Andriolo *et al*., 2017[49]	PCT	10 studies, 1215 patients	Unselected population	Significant	Reduction of 1.3 days (95% CI, 0.6-2.0) duration of antibiotic therapy

PCT, procalcitonin; CI, confidence interval.

ity. The main source of heterogeneity in studies included in the different meta-analyses was attributable to the use of different diagnostic cut-offs (Table 2). In most cases, the meta-analyses included a large number of prospective studies (Table 2).

The largest number of meta-analyses on the use of biomarkers for diagnosing sepsis in adults contained data about PCT (10 overall) (Table 4). Six meta-analyses contained information about presepsin and three meta-analyses contained data about C reactive protein (CRP). Information about interleukin 6 (IL-6), lipopolysaccharide-binding protein (LBP), neutrophil CD64 (nCD64) and soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) was available in two meta-analyses for each of these markers, whereas only one meta-analysis contained data about soluble urokinase-type plasminogen activator receptor (suPAR). The most favorable diagnostic performance, expressed as area under the curve (AUC), was observed for nCD64, PCT, sTREM-1, suPAR and presepsin, although none of these biomarkers reached a diagnostic efficiency close to 100% (Table 4). The AUC of IL-6, LBP and CRP in the adult population were overall lower than

Table 4. Summary of individual biomarker performance research for diagnosing sepsis in adult populations.

Biomarker	Meta-analyses (n)	Range AUC	Range sensitivity	Range specificity
IL-6	2	0.79-0.80	0.68-0.72	0.73-0.73
LBP	2	0.68-0.71	0.62-0.70	0.56-0.70
nCD64	2	0.95-0.96	0.76-0.87	0.85-0.93
PCT	10	0.78-1.00	0.71-1.00	0.61-0.88
CRP	3	0.71-0.77	0.75-0.91	0.36-0.67
Presepsin	6	0.86-0.89	0.77-0.85	0.73-0.88
sTREM-1	2	0.85-0.87	0.78-0.83	0.68-0.78
suPAR	1	0.82	0.80	0.80

AUC, area under the curve; IL-6, interleukin 6; LBP, lipopolysaccharide-binding protein; nCD64, neutrophil CD64; PCT, procalcitonin; CRP, C reactive protein; sTREM-1, soluble triggering receptor expressed on myeloid cells-1; suPAR, serum soluble urokinase-type plasminogen activator receptor.

Table 5. Kinetics of C reactive protein, procalcitonin, presepsin, and suggested cut-off for ruling out sepsis.

	Increase (h)	Peak (h)	Half-life (h)	Cut-off for ruling out sepsis
CRP	12-24	48-72	20	<10 mg/L
PCT	2-4	6-8	20-24	<2.0 mg/L
Presepsin	2	3	4-5	<500-600 pg/mL

CRP, C reactive protein; PCT, procalcitonin.

Table 6. Cumulative recommendations according to the available literature data, and to the opinions of the consensus group.

Recommendation	Score	Strenght
The measurement of biomarkers may be of clinical significance in the diagnostic approach of patients with suspect sepsis	1.56±1.06	B
In the diagnostic approach of patients with suspect sepsis, biomarker assessment should be:		
Always available on prescription (24/365)	1.36±1.04	A
Free on prescription (*i.e.*, no need to contact the laboratory to agree on the request)	1.63±0.78	B
In the diagnostic approach of patients with suspect sepsis, it is advisable to measure		
IL-6	3.88±0.99	D
LBP	4.06±0.83	D
nCD64	3.69±0.92	D
PCT	1.56±0.79	B
CRP	2.00±0.94	B
Presepsin	2.50±1.06	C
sTREM-1	3.81±0.88	D
suPAR	3.50±0.79	D
The biomarker cut-off should be selected:		
Favoring a high negative predictive value, for ruling out a diagnosis of sepsis	1.75±0.83	B
Favoring a high positive predictive value, for enabling a diagnosis of sepsis	2.75±0.90	C
Test results should always be interpreted according to clinical data	1.00±0.00	A
For PCT assessment immunoassays with better functional sensitivity (*i.e.*, ≤0.05 ng/mL) should be preferred	1.63±0.60	B
The assessment of a second biomarker may be useful when the result of the first biomarker is negative in patients with a strong clinical suspect of sepsis	2.38±1.11	B
Due to availability of multiple assays, short turnaround time and low costs, CRP should be the second sepsis biomarker	2.31±1.31	B
Serial testing in patients with sepsis should be defined according to biomarker kinetics (repeated testing not early that 18-24 hours for PCT and CRP, not earlier than 5 hours for presepsin)	1.38±0.99	A
Serial PCT testing can be used for monitoring antibiotic therapy in patients with sepsis	1.50±1.00	B
Serial testing for monitoring antibiotic therapy should be defined according to biomarker kinetics (*i.e.*, repeated testing not early that 18-24 hours for PCT)	1.63±1.05	B
The test panel in patients with sepsis should also include the assessment of lactic acid	1.50±0.79	B

IL-6, interleukin 6; LBP, lipopolysaccharide-binding protein; nCD64, neutrophil CD64; PCT, procalcitonin; CRP, C reactive protein; sTREM-1, soluble triggering receptor expressed on myeloid cells-1; suPAR, serum soluble urokinase-type plasminogen activator receptor.

those of the other biomarkers. The values of sensitivity and specificity were globally aligned with those of the AUCs (Table 4).

As regards the five biomarkers displaying the better diagnostic performance (*i.e.*, nCD64, PCT, presepsin, sTREM-1 and suPAR), some additional considerations may be necessary about the analytical technology used for their assessment. Only for PCT and presepsin automatic or semi-automatic immunoassays are currently available for urgent measurement, whereas only manual enzyme-linked immunosorbent assay (ELISA) are available for sTREM-1 and suPAR, thus making their assessment rather impractical for rapid diagnosis of sepsis.[50] A similar consideration can be made for nCD64. This biomarker can only be assessed with flow-cytometry and specific kits, so that the measurement of nCD64 is currently incompatible with an urgent diagnosis of sepsis in most clinical laboratories.[50] Although PCT can now be measured with a wide range of commercial methods based on different analytical techniques (immunochemiluminescence, immunofluorescence, immunoturbidimetry), and so potentially adaptable to the vast majority of clinical and immunochemical analyzers available in clinical laboratories,[51] the quantification of presepsin is now only possible using a single point-of-care (POC) analyzer. It is also noteworthy that the analytical performance of the PCT immunoassays currently commercially available may substantially differ. The techniques with better sensitivity are usually characterized by a functional sensitivity ≤0.05 ng/mL (51) and are hence more suited for monitoring of antibiotic therapy. The *in vivo* kinetics of PCT, presepsin and CRP in patients with sepsis are described in Table 5.[52]

A single meta-analysis could be identified in pediatric populations for each of serum amyloid A (SAA), tumor necrosis factor (TNF)-α and interleukin 8 (IL-8) (Table 3), so that translation of diagnostic performance in adults is unadvisable according to the search criteria defined in this consensus document.

As regards monitoring of antibiotic therapy, all the six meta-analyzes identified by our literature search dealt with PCT. In all cases the serial assessment of this biomarker allowed to significantly reducing the duration of antibiotic therapy (Table 3). In the two meta-analyses also evaluating economic issues, PCT-guided antibiotic therapy allowed to reduce the overall cost of patient management. Unfortunately, little evidence is currently available about the effectiveness of PCT-guided antibiotic therapy to narrow the spectrum of antibiotic therapy. Notably, a retrospective study including more than 20000 patients hospitalized in 107 UTI failed to show significant benefits (in terms of outcome or duration of therapy) in patients with serial PCT testing.[53]

Recommendations

According to the available literature data, and to the opinions of the consensus group, the following cumulative recommendations can be made (the score reflects the mean and SD of individual opinions) as in Table 6.

Conclusions

The World Health Organization (WHO) has recently published a firm resolution mandating that sepsis should be considered a global health priority.[54-57] Among the various recommended actions for reducing the global burden of this time-critical medical emergency, the WHO urges member states to develop evidence-based strategies for early diagnosis and appropriate treatment in order to avert deterioration, improve outcomes and ensure patient safety. Our consensus document should hence be seen as a timely reaction to the WHO resolution.

The cumulative opinions of the members of this consensus document allowed to define three grade A recommendations (*i.e.*, highly recommended indications), substantially in line with those previously published in our country and complementing the indications about blood culture (55-57), but are now supported by a more systematic and recent collection of evidence analyzed by means of an interdisciplinary consensus between two scientific societies of Emergency (AcEMC) and Laboratory (SIBioC) Medicine.

The three grade A recommendations entailed the ordering modality (biomarkers always available on prescription), the practical use (results should be interpreted according to clinical information) and test ordering defined according to biomarker kinetics. Additional grade B recommendations (*i.e.*, potentially valuable indications) entailed general agreement that biomarkers assessment may be of clinical value in the diagnostic approach of ED patients with suspect sepsis, suggestion for combined assessment of PCT and CRP, free availability of the selected biomarker(s) on prescription, adoption of diagnostic threshold prioritizing a high negative predictive value giving preference to more analytically sensitive techniques, along with the potential clinical usefulness of measuring PCT for monitoring antibiotic treatment, with serial testing defined according to biomarker kinetics. PCT and CRP were the two biomarkers, which received the largest consensus as biomarkers of sepsis (grade B recommendation), and a grade B recommendation was also reached for routine assessment of blood lactate. The assessment of biomarkers other than PCT and CRP was discouraged, with the exception of presepsin for which substantial uncertainty in favor or against remained.

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