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Role of biomarkers in the management of antibiotic therapy: an expert panel review: I – currently available biomarkers for clinical use in acute infections

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Abstract

In the context of worldwide increasing antimicrobial resistance, good antimicrobial prescribing in more needed than ever; unfortunately, information available to clinicians often are insufficient to rely on. Biomarkers might provide help for decision-making and improve antibiotic management. The purpose of this expert panel review was to examine currently available literature on the potential role of biomarkers to improve antimicrobial prescribing, by answering three questions: 1) Which are the biomarkers available for this purpose?; 2) What is their potential role in the initiation of antibiotic therapy?; and 3) What is their role in the decision to stop antibiotic therapy? To answer these questions, studies reviewed were limited to recent clinical studies (<15 years), involving a substantial number of patients (>50) and restricted to controlled trials and meta-analyses for answering questions 2 and 3. With regard to the first question concerning routinely available biomarkers, which might be useful for antibiotic management of acute infections, these are currently limited to C-reactive protein (CRP) and procalcitonin (PCT). Other promising biomarkers that may prove useful in the near future but need to undergo more extensive clinical testing include sTREM-1, suPAR, ProADM, and Presepsin. New approaches to biomarkers of infections include point-of-care testing and genomics.

Keywords: Infection; Sepsis; Emergency medicine; Biomarkers; Procalcitonin; C-reactive protein; sTREM-1; suPAR; proADM; Presepsin

Review

Introduction

Good antibiotic prescribing-which often means less prescribing-is of major concern to physicians nowadays, both because of high levels of antibiotic consumption in hospitals, and of the increasing prevalence of antimicrobial resistance, even if rates of methicillin-resistant *Staphylococcus aureus* have decreased recently in many European countries since the early 2000s. The principal objective of antibiotic prescribing is to ensure appropriate therapy when needed, while avoiding unnecessary or unduly prolonged therapy. Within this framework, obtaining adequate microbiological information is of paramount importance; unfortunately, such information is lacking in more than 50% of clinical situations where antibiotic therapy is prescribed, even in hospitalized patients. Whereas clinical information is usually sufficient to initiate empiric therapy, they lack accuracy to tailor subsequent therapy and decide on its duration. Physicians' decisions would be strengthened if they could get help from results of accurate biomarkers reflecting the diagnosis or evolution of the infectious processes. The

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field of infection-associated biomarkers has grown rapidly within the past few years and is still expanding; few of them, however, have gone through the hurdles of rigorous testing in the clinical arena to allow specifying their role in clinical practice.

An 18-member expert panel convened under the auspices of the Maurice Rapin Institute, a not-for-profit independent physicians' association (http://www.institutmauricerapin.org), to provide a state-of-the-art assessment of the currently available biomarkers and their potential role as an aid to the management of antibiotic therapy for acute infections. This report is a summary of their work and conclusions.

To frame the appraisal of the potential clinical role of biomarkers, the panel was asked to answer three formatted questions, as follows:

1. Which are the currently available biomarkers of the host's response, those that are routinely available and which may contribute to the management of antibiotics in acute infections, and what are the limitations to the interpretation of their results in this context?
2. What is the potential contribution of such biomarkers to the initial decision of antibiotic prescription, and does this vary according to the characteristics of infection (i.e., site of infection, comorbidities, mode of acquisition, severity of presentation)?
3. When can biomarkers help make decisions to stop antibiotic therapy, and which factors mitigate their clinical use in this process?

The panel discussion was based on an analysis of the available literature through December 2012, after making the a priori decision to limit publications considered for answering questions 2 and 3 to clinical studies fulfilling the following criteria:

- Having enrolled a minimum of a substantial number of patients (i.e., >50 patients);
- Performed within less than 15 years (i.e., published since 2000);
- Pertaining to biomarkers available for routine testing in hospitals' laboratories.

The first part of this paper deals with the first question asked to the panel, and the second part deals with questions 2 and 3.

Currently available biomarkers of the host

Definition and role of a host's biomarker

Biomarkers from the host can be anatomical, physiological, biochemical (either circulating or membrane-bound), or molecular markers. The latter two categories are detected within a tissue or biological fluid (e.g., blood, cerebrospinal fluid, or urine) and their presence or absence, or over- vs. under-expression is the judgment criteria. Of note, more than 90% currently available biomarkers are used only within research program and have not been introduced within the field of clinical biology.

Definitions

Currently accepted definitions for biomarkers have emerged from an expert panel driven by the U.S. National Institute of Health [1] and from regulatory definitions issued by the European Medicines Agency. A biomarker is "a biological characteristic, objectively measured (i.e., with acceptable accuracy and reproducibility) and used as an indicator for a physiological or pathological process, or of the activity of a medicine." According to the NIH panel [1,2], biomarkers can be stratified in two categories (Table 1): *prognostic markers*, allowing to stratify patients according to their individual risk of having a specified outcome, independently of therapy (or of the lack of therapy), and *predictive markers*, which allow to predict the potential benefit (efficacy) and/or the risks (toxicity) of a therapy according to the biomarker status (absent/present).

In clinical practice, two types of biomarkers can be identified, which follow different development and validation pathways:

- Those used independently from a specific therapy, as a diagnostic test, or for follow-up or prognosis, which will only be discussed in this paper from the viewpoint of infectious processes;
- Those used as a companion to treatment, to select patients who may benefit from a specific therapy or used during follow-up of therapy as early predictors of efficacy or of treatment toxicity.

The ideal biomarker in infectious diseases

Within the field of infectious diseases, a biomarker may be used for identifying a high risk group or predisposing

Table 1 Definition of biomarkers and subtypes according to the national institute of health [1]

Denomination	Definition
Biomarker	Biological characteristics objectively measured, and used as a marker either of a normal or pathological biological pathway, or of a pharmacological response to a specific intervention
Biomarker type 0	Biological maker of the disease course, linked to a recognised clinical variable
Biomarker type I	Biological marker reflecting the effects of a therapy, and linked to its mechanism of action
Biomarker type II	Biological marker used as a surrogate endpoint, where changes in the biomarker levels are associated to a clinical benefit or to an increased risk.

condition, as an aid to identification of the disease, or to direct therapy and stratify patients according to their specific risk factors, and/or as an aid to therapeutic management in order to avoid relapse of infection. An ideal biomarker for infection would combine diagnostic, prognostic, and follow-up of therapy characteristics and should be easily and rapidly available for routine clinical use (Table 2).

Potential role of biomarkers in acute infections: performance measurements

Biomarkers are expected to provide an assessment of the severity of infection or predict a complicated course to help making a decision on the best therapeutic approach and appropriate site of care (i.e., hospital or ambulatory care, intensive or ward care). Foremost, they should help the physician to decide about introducing or maintaining antibiotic therapy.

Within the recent years, dozens of potential biomarkers of infection have been described, and their analysis is a complex task. Current trends are to use a combination of biomarkers—notably cytokines—with multiplex tests providing simultaneous measurements of several biomarkers from a single biological sample. The major point is to examine whether their clinical performance and utility can be transposed to acute care situations.

Table 2 Important characteristics of biomarkers for clinical use in acute infections (from [3])

Criteria for use	Characteristics
Diagnostic test	General: known preanalytic and analytic (accuracy, reproducibility) as well as physiological (intra and interindividual) variability, integrated in the interpretation of assay results
	High predictive values
	Ability to differentiate sepsis and noninfectious SIRS (specificity)
	Ability to differentiate acute viral from bacterial infection
Prognostic test	Early detection of patients at risk of a complicated course
	Levels associated with the inflammatory response (i.e., correlated to the severity of presentation and/or to organ dysfunctions)
	Predictor of mortality
Therapeutic test	Follow-up of the efficacy of a therapy (e.g., rapid kinetics, independent of organ dysfunction)
Accessibility	Routinely available
	Good acceptability to patients (i.e., noninvasive)
	Rapid turnaround time
	Easily interpreted
	Low cost

The diagnostic performance of biomarkers is usually measured in terms of sensitivity (probability of a positive test among affected patients), specificity (probability of a negative test in unaffected patients), and by likelihood ratios and area under the ROC (*Receiver Operating Characteristics*) curves. Ideally, a biomarker would be both highly sensitive and specific; however, very sensitive tests provide few false-negative results, whereas highly specific ones provide few false-positive results. In emergency medicine practice, more emphasis is usually put on sensitivity (and negative predictive value, NPV), as the primary objective is to rule out the disease, whereas specificity (or positive predictive value, PPV) is emphasized when the objective is to confirm a clinical diagnosis. For quantitative tests, establishing ROC curves allows to select the best compromise between sensitivity and specificity of the test, according to which approach is emphasized. When a low threshold for positivity of the test is selected, its sensitivity increases but its specificity is lowered.

Sensitivity and specificity are however defined within a population where the patients' status ("infected" or "noninfected") is known, which does not corresponds to the population seen by the physician in his routine clinical practice. The clinical utility of a biomarker is therefore best assessed by measuring its predictive values (both positive and negative, PPV and NPV) and changes between pre- and post-test likelihood ratios in a given clinical context.

Two important points, often overlooked in the literature, should be considered when assessing the operating characteristics of biomarkers:

- The characteristics of the population studied and of the "control group" (i.e., noninfected). For example, it is quite different to analyse a group of patients with a systemic inflammatory response (SIRS) following cardiac surgery (where the severity and prevalence of infection is low) or patients with SIRS within the context of pancreatitis evolving since >1 week, and both the severity and prevalence of infection are higher, with a high clinical impact of diagnosing infected pancreatitis necrosis.
- Criteria used as the "gold standard" for defining infection (or lack thereof) [4,5].

Limitations to the interpretation of biomarker levels

Improved measurement methods have largely enhanced the potential for biomarkers to identify patients at high risk of death or a complicated course, whether individual patients or the general population. Nevertheless, persisting difficulties arise when interpreting measurements of biomarker levels, a problem that is compounded by the dissemination of multiplex tests [6], thus increasing the volume of information generated. For some biomarkers, a

threshold value can be determined, which allows a simple binary interpretation, but inevitably results in loss of precision; however, this approach cannot be generalised.

Interpreting biomarker levels can be problematic because of the variability of measurements resulting from several factors:

- A lack of standardisation between different methods,
- Biological factors, including preanalytical variables (tubes and transport media, time from sampling to analysis, etc.), analytical (precision, reproducibility, threshold of measurement, etc.), and intra- or interindividual variations; such factors must be assessed and controlled for before providing an interpretation of assays results.

In addition, prudent interpretation is mandatory when the known sensitivity or specificity of the biomarker measured is <90% or when the number of subjects studied is small. Moreover, in many studies, a single point in time has been obtained for biomarker measurement, and the lack of repeated measurements does not allow the use of such marker for adapting the duration of therapy.

We conclude that standardisation of measurement methods and guideline for the interpretation of biomarker levels in acute infections is mandatory before introducing their measurements into clinical practice. This development phase, including the determination of associated quality criteria (i.e., reproducibility and variation coefficient, threshold for detection), identification of confounding factors and corrective factors must be investigated. Finally, medico-economic evaluation is usually lacking and should be performed before proposing their introduction into routine clinical use.

Biomarkers currently available for optimising antibiotic therapy

More than a hundred biomarkers have been studied in the serum of septic patients [7-9]. Few of them however are eligible for entering the clinical arena (see Additional file 1: Table S1) and being used for optimising antibiotic therapy because of limitations to the interpretation of results from these studies. Assays used often are not standardised (especially for ELISA and "multiplex" tests), making it difficult to compare results from different studies. Some techniques are difficult to adapt to the emergency context (multiplex tests, ELISA or high-flux cytometry). Some biomarkers cannot be presently retained because of a poor performance, of studies limited to a small population (e.g., <50 patients) or too scarce to allow conclusions on their potential utility. A limited number of biomarkers are currently of established or potential clinical interest within the field of acute infection.

Routinely available biomarkers

Two biomarkers fulfill the selection criteria mentioned above and are routinely available: C-Reactive protein (CRP) and procalcitonin (PCT). CRP has been tested in various conditions, but only a few of these studies have focused on its use for optimising antibiotic therapy. A single, prospective, randomized, controlled trial performed in the 1990s in children is available [10]; other studies have compared an intervention group to historical controls [11,12]. Despite the few available studies confirming its usefulness, CRP measurements are widely used in children to adjust the duration of therapy. Several studies are ongoing, testing the usefulness of CRP measurements as an aid to shorten the duration of therapy in adult patients having sepsis, community-acquired pneumonia or exacerbation of chronic obstructive pulmonary disease (COPD). Pending results from these studies, the use of CRP cannot be recommended at present as an aid to the initiation or discontinuation of antibiotics in adults; in children, however, CRP can probably be used to help discontinuing therapy, although the evidence is limited.

Procalcitonin has been more widely tested for optimising antibiotic therapy in both children and adults. In adults presenting with community-acquired lower respiratory tract infections (LRTI), several randomized, controlled trials (RCTs) have tested the use of PCT as an aid to the initiation and/or discontinuation of antibiotics and have been summarised in a recent individual patient meta-analysis [13-17]. Four of these studies enrolled more than 900 patients hospitalised in intensive care or high-dependency units [18-21]. Two well-designed studies have been performed in children: one study included 121 neonates having early sepsis [22] and another studied 384 children aged 1 to 36 months with acute fever of undetermined origin (Manzano, Bailey et al. 2010; Esposito, Tagliabue et al. 2011).

In view of these studies, the inclusion of PCT measurements within decision algorithms of antibiotic management for specific infections is likely appropriate (refer to Part II). However, further studies are needed in infections which have been insufficiently examined so far (i.e., most infections other than LRTI) to better define the role of PCT in the antibiotic strategy.

Recent biomarkers of potential interest in the near future

Intensive efforts are being made in the search of new diagnostic and prognostic biomarkers, which may be helpful for the management of antibiotic therapy in acute infections. In adults, four of these, the soluble Triggering Receptor Expressed on Myeloid cells-1 (sTREM-1), Soluble urokinase-type Plasminogen receptor (suPAR), proadrenomedullin (ProADM), and Presepsin appear promising. These four biomarkers are of reasonably easy access, have demonstrated acceptable sensitivity and/or

Table 3 Clinical experience with the use of sTREM-1 in acute infections

sTREM-1	References	Syndrome/ disease studied	Sampling
Diagnostic value	[23]	Pneumonia	Plasma
	[24]	Pneumonia	BAL
	[25]	Meningitis	CSF
	[26]	Meningitis	CSF
Prognostic value	[27]	SIRS, sepsis, severe sepsis, septic shock	Plasma
	[28]	Sepsis, severe sepsis, septic shock	Plasma
	[29]	Sepsis, septic shock	Plasma

specificity, and have been studied in a substantial number of patients to merit further consideration in adults. In children or neonates, too few and heterogeneous studies have been conducted with these new biomarkers to allow recommending any of these for potential introduction in the clinical arena at the present time; further studies are needed in these age groups.

sTREM-1 A member of the immunoglobulin superfamily, TREM-1 is a surface receptor of mature polymorphonuclear and monocytes cells contributing to innate immunity. Its expression is up-regulated when phagocytic cells are exposed to bacterial and fungal pathogens, but not during other non-septic inflammatory processes. TREM-1 amplifies the inflammatory response by increasing the production of pro-inflammatory cytokines while inhibiting IL-10 synthesis. During up-regulation of the surface receptor TREM-1, the soluble form sTREM-1 increases in biological fluids (blood, broncho-alveolar lavage fluid, CSF), where it can be assayed by ELISA using commercial immunoassay kits.

Several clinical studies [23-29] have tested the diagnostic and prognostic value of sTREM-1 (Table 3). Measurements in samples taken at the site of infection (CSF, BAL, pleural fluid) appear of higher clinical significance than plasma measurements.

suPAR suPAR (soluble urokinase-type plasminogen activator receptor) or CD87 is a widespread receptor for inflammatory response. Its constitutive expression is limited to some cell types, such as endothelium and leucocytes (polymorphonuclear, monocytes/macrophages). Its gene expression is under control of immune and inflammatory effectors, such as bacterial products (LPS), cytokines (IFN-gamma, TNF-alpha, IL-1-beta), and growth factors (FGF-2, VEGF, TGF-beta, EGF). During the inflammatory and immune response, the expression of suPAR is up-regulated on epithelial cells, leucocytes (lymphocytes), smooth muscle cells and fibroblasts; it also is up-regulated during tumour growth and metastatic tumour dissemination. Measurements can be obtained from commercial ELISA kits; suPAR measurements also are included in multiplex assays together with cytokines.

Table 4 Clinical experience with the use of suPAR in acute infections

suPAR			
Clinical value	**References**	**Syndrome/disease**	**Sampling**
Diagnostic value	[33,34]	Sepsis	Plasma
Pronostic value	[33-35]	Sepsis	Plasma

suPAR is of limited value as a diagnostic test. Its clinical value appears associated with its ability to identify patients at risk (Table 4) and might be of interest for the management of HIV patients receiving antiretroviral therapy [30], during the follow-up of patients who have nonpulmonary mycobacterial infection [31] and in children who have *Plasmodium falciparum* malaria [32]. suPAR also might be useful for the management of antibiotics in patients with sepsis [33-35], but this approach needs more extensive evaluation.

Pro-ADM Adrenomedullin (ADM) is a 52-amino acids peptide, and a marker of the *CALC* gene family, acting as a mediator of cell proliferation, hormone regulation and embryogenesis. ADM is produced by endothelial cells, where it induces vasodilatation and maintains homeostasis. Pro-hormone fragments (pro-ADM) are more stable than the complete peptide and their levels can be measured in biological fluids by automated methods using the TRACE (Time-Resolved Amplified Cryptate Emission) method after immuno-capture. ProADM secretion increases during the immune response to viral or bacterial products in relation to the importance of the stimulation.

Table 5 Clinical experience with the use of pro-ADM in acute infections

proADM			
Clinical value	**References**	**Syndrome/disease**	**Sampling**
Diagnostic value	-	-	
Prognostic value	[38-40]	Pneumonia	Plasma

Pro-ADM is a biomarker of prognostic value (Table 5). Added to a clinical pneumonia severity score [36], pro-

Table 6 Clinical experience with the use of Presepsin in acute infections

Presepsin			
Clinical value	**References**	**Syndrome/disease**	**Sampling**
Diagnostic value	[41,42]	SIRS, Sepsis	plasma
Pronostic value	[43]	SIRS, Sepsis, Severe sepsis	plasma

ADM could be used to identify the more severe patients for close monitoring and/or needing ICU care [37-40].

Presepsin Presepsin (formerly CD14), is a glycoprotein receptor occurring at the surface of monocytes/macrophages. CD14 binds to lipopolysaccharide (LPS) complexes and LPS binding protein (LPB), which triggers the activation of toll-like receptor 4 (TLR4), resulting in the production of numerous pro-inflammatory cytokines. Following Presepsin activation by bacterial products, the CD14 complex is released in the circulation as its soluble form (sCD14), which in turn is cleaved by a plasma protease to generate a sCD14 fragment called sCD14-subtype (sCD14-ST). Plasma levels of sCD14 can be measured using an automated chemo-luminescent assay (PATHFAST®, Ingen®, France).

The most recent of the 4 biomarkers analysed, presepsin is both sensitive and specific and might be helpful to differentiate SIRS from sepsis associated with a bacterial infection [41-43] (Table 6).

We conclude that information gathered so far on these four biomarkers— sTREM-1, suPAR, proADM, and presepsin—suggest that they may have a role in future clinical developments, whether as diagnostic tests, or for stratification of patients by type of insult or severity, or to assess the therapeutic activity and efficacy and during follow-up of patients. To date, there are too few studies of the impact of these new biomarkers on the antibiotic management of patients and larger studies are required in this field.

Future developments

Micro-RNAs (miR) are recently discovered potential candidate biomarkers. miR are small molecules (about 20 nucleotides) present in eucaryotic cells, which act as biologic regulators by modulating posttranscriptional regulation. They are ubiquitous and abound in the lung, liver, and kidney. After binding the corresponding smRNA sequence, they regulate gene expression by a repressor effect or by altering its target. A mi-RNA can bind to several smRNA. Their expression can be measured by RT-PCR and quantitative PCR.

Their multiple potential roles in positive or negative regulation of gene expression have been uncovered since the early 2000s, and dysfunctions of miR expression have been implicated in numerous human diseases (http://www.miR2Disease.org/), such as various types of cancers ("oncomir"), cardiomyopathy, or central nervous system diseases. miR also have been implicated in defense mechanisms against viral infections, where they may contribute to controlling viral infections. Integrated in the viral genome, a number of miR can regulate viral mRNA such as Epstein-Barr, cytomegalovirus, herpes, hepatitis C virus as well as the host's RNA. Among bacterial infections, a role for miR has been suggested in *M. tuberculosis* infections by modulating the monocytes/macrophages interactions with the bacterium or regulating the expression of resistance gene or virulence factors. Modulation of the inflammatory response to infection with *H. pylori* also has been attributed to miR [44], notably miR-155 [45].

The spectrum of miRNAs initially released in blood and leucocytes of patients with septic shock differs from that of control patients. The three most dysregulated miR are miR-150, miR-182, miR-342-5p; miR-150 interferes with the development of an immune response by lymphocytes and thus might be a potential candidate as an early diagnostic and/or prognostic marker [46].

Other miRNAs have been associated with a high probability of a poor outcome in patients with septic shock: miR-223, miR-15a, miR-16, miR-122, miR-193*, and miR-483-5p. Based on individual AUROC for each miR, prediction of death varied between 0.61 (95% confidence interval (CI) 0.523-0.697) and 0.79 (95% CI 0.719-0.861) but reached 0.953 (95% CI 0.923-0.983) when combining the seven parameters [47].

Thus, miR might be potential candidates as early diagnostic and/or prognostic markers in sepsis. Numerous studies are needed with these new markers to better understand their role in biochemical and immunobiology processes in humans before their use for diagnostic and stratification of patients, prognostication, or therapeutic decision can be considered.

Two main technological advances are in progress, including 1) the development of point-of-care testing, with the availability of miniaturised and portable machines, allowing rapid testing at the bedside, even for sophisticated measurements (e.g., flux cytometry), which have been confined to specialised laboratories up to recently; and 2) the development of new methods, including the analysis of gene expression (genomics), of ARN activation (transcriptome), of production of proteins (proteomics), of lipids (lipidomics), or of metabolites (metabolomics). It is likely that these progresses will allow identifying new markers for better identification of patients, stratification of prognosis, and targeting therapy.

Additional file

Additional file 1: Table S1. List of biomarkers tested in the field of infectious diseases.

Abbreviations

ADM and pro-ADM: Adrenomedullin and pro-adrenomedullin; aPTT: Activated partial thromboplastin time; AUROC: Area under the receiver operating curve; BAL: Broncho-alveolar lavage; BM: Bacterial meningitis; CAP: Community-acquired pneumonia; CCR3: Chemokine (C-C motif) receptor 3; CRP: C-Reactive protein; CRTH2: Chemoattractant receptor-homologous molecule expressed on Th2; CSF: Cerebrospinal fluid; DNI: Differential count of immature PMN; ELISA: Enzyme-linked immuno-

sorbent assay; G-CSF: Granulocyte colony-stimulating factor; HLA: Human leukocyte antigens; HMGB1: High mobility group protein B1; ICAM 1: Intercellular adhesion molecule 1; ICU: Intensive care unit; IFN-γ: Interferon-gamma; IL: Interleukin; IP-10: Interferon gamma-induced protein 10; LBP: Lipopolysaccharide binding protein; LPS: Lipopolysaccharide; LRTI: Lower respiratory tract infection; MC: Monocytes; MCP-1: Monocyte chemotactic protein-1; MIF: Macrophage migration inhibitory factor; MR-proADM: Mid-regional proadrenomedullin; NIH: U.S. National institute of health; NPV: Negative predictive value; PAI 1: Plasminogen activator inhibitor 1; PCT: Procalcitonin; PMN: Polymorphonuclear neutrophil; PPV: Positive predictive value; ProADM: Proadrenomedullin; ProANP: Proatrial natriuretic peptide; ROC: Receiver operating characteristic curve; ROS: Reactive oxygen species; SAA: Serum amyloid A protein; sCD14-ST: Soluble CD14 subtype; sELAM: Soluble endothelial leucocyte adhesion molecule-1; sFlt-1: Soluble fms-like tyrosine kinase-1 or sVEGFR1; sPLA2: Soluble phospholipase A2; sTREM-1: Soluble triggering receptor expressed on myeloid cells-1; suPAR: Soluble urokinase-type plasminogen activator receptor; sVEGFR1: Vascular endothelial growth factor receptor 1 soluble; TNF: Tumor necrosis factor; TLR-2 or 4: Toll-like receptor 2 or 4; TRACE: Time-resolved amplified cryptate emission; uMIF: Urinary macrophage migration inhibitory factor; uMIF/cr: uMIF/Creatinine; VCAM-1: Vascular cell adhesion molecule 1; VEGF: Vascular endothelial growth factor.

Competing interests
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A-MD declared participation as an investigator to the UTAPE study, sponsored by Thermo-Fisher, and her institution received funding for analytic studies of CT-proAVP using Kryptor.
CB-B was an investigator in the Prorata trial.
MC holds a patent for the MENINGITEST in Europe (European patent EP1977244), USA and Canada, and has a patent pending for the REFLUTEST (WO2010/109089).
C-EL was an investigator for the Prorata trial, and received lectures honoraria from Thermo-Fisher and Biomérieux.
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JP received speaking fees for giving lectures within symposia organized by ThermoFischer.
J-PB, P-EC, RG, SL, BM, J-PQ, FP, YP, and J-PS have declared no competing interest in relation to the subject of this manuscript.

Authors' contributions
All panel members contributed to the panel discussions and analyses. Each panel members contributed to drafting different sections of the manuscript: A-MD, YP, FP, SR, and BM drafted part I; J-PQ, SL, Y-EC, J-PS, CG-L, MC, and RG drafted part II; and C-EL, NR, J-PB, JP, and CB-B drafted part III. A-MD, J-PQ, C-EL, RG, BM, MC, and CB-B extensively reviewed the consolidated manuscript and all authors approved its final version.

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REVIEW Open Access

Role of biomarkers in the management of antibiotic therapy: an expert panel review II: clinical use of biomarkers for initiation or discontinuation of antibiotic therapy

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Abstract

Biomarker-guided initiation of antibiotic therapy has been studied in four conditions: acute pancreatitis, lower respiratory tract infection (LRTI), meningitis, and sepsis in the ICU. In pancreatitis with suspected infected necrosis, initiating antibiotics best relies on fine-needle aspiration and demonstration of infected material. We suggest that PCT be measured to help predict infection; however, available data are insufficient to decide on initiating antibiotics based on PCT levels. In adult patients suspected of community-acquired LRTI, we suggest withholding antibiotic therapy when the serum PCT level is low (<0.25 ng/mL); in patients having nosocomial LRTI, data are insufficient to recommend initiating therapy based on a single PCT level or even repeated measurements. For children with suspected bacterial meningitis, we recommend using a decision rule as an aid to therapeutic decisions, such as the Bacterial Meningitis Score or the Meningitest®; a single PCT level ≥0.5 ng/mL also may be used, but false-negatives may occur. In adults with suspected bacterial meningitis, we suggest integrating serum PCT measurements in a clinical decision rule to help distinguish between viral and bacterial meningitis, using a 0.5 ng/mL threshold. For ICU patients suspected of community-acquired infection, we do not recommend using a threshold serum PCT value to help the decision to initiate antibiotic therapy; data are insufficient to recommend using PCT serum kinetics for the decision to initiate antibiotic therapy in patients suspected of ICU-acquired infection. In children, CRP can probably be used to help discontinue therapy, although the evidence is limited. In adults, antibiotic discontinuation can be based on an algorithm using repeated PCT measurements. In non-immunocompromised out- or in- patients treated for RTI, antibiotics can be discontinued if the PCT level at day 3 is < 0.25 ng/mL or has decreased by >80-90%, whether or not microbiological documentation has been obtained. For ICU patients who have nonbacteremic sepsis from a known site of infection, antibiotics can be stopped if the PCT level at day 3 is < 0.5 ng/mL or has decreased by >80% relative to the highest level recorded, irrespective of the severity of the infectious episode; in bacteremic patients, a minimal duration of therapy of 5 days is recommended.

Keywords: Infection; Sepsis; Emergency medicine; Biomarkers; Procalcitonin; C-reactive protein; Pancreatitis; Meningitis; Pneumonia

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Biomarkers and initiation of antibiotic therapy

According to the preset selection criteria (see part I), the panel reviewed four conditions in which the potential clinical role of biomarkers has been studied: acute pancreatitis, respiratory tract infections, meningitis, and sepsis in the ICU.

Acute pancreatitis in adults

The clinical presentation and severity of patients having acute pancreatitis varies considerably, from a mild abdominal discomfort to multiple organ failure and death. The potential role of biomarkers in this condition should thus be twofold: 1) a prognostic value, to help define the most appropriate therapeutic approach, by predicting the severity of the disease and accurately select those patients needing close monitoring in the ICU; and 2) a diagnostic value, to help identify those patients having infected pancreatic necrosis, who might need drainage or surgery. Mofidi et al. [1] have recently reviewed the potential role of PCT in answering these two questions, by analysing 12 observational studies [2-9] totalling 956 patients. The threshold PCT value used in these studies to predict the severity of pancreatitis varied from 0.25 to 1.8 mg/L, with an associated combined sensitivity of 0.72 (0.65-0.78), a specificity of 0.86 (0.83-0.89), and an area under the receiver operating curve (AUROC) of 0.87. In the seven studies (n = 264 patients) examining the value of PCT for predicting the presence of infected necrosis [2-5,7-9], the threshold value varied across studies between 0.48 and 3.5 mg/L, with an associated sensitivity of 0.8 (0.71-0.88), a specificity of 0.91 (0.87-0.94), and an AUROC of 0.91 (Table 1). In these seven studies, PCT levels were confronted to microbiological results obtained from fine-needle biopsy and culture of intra-abdominal collections, taken as the "gold standard."

Other less commonly measured biomarkers (IL-6, IL-8 , sTREM-1, TNF-α) also have been compared to PCT for their ability to help answer the two questions above. These biomarkers provided AUROC comparable to those of PCT, both in terms of prognostic value and of diagnosis of infected necrosis [2,4-6,9,10]. Conversely, CRP levels appear less discriminatory for the prediction of infected necrosis [2]. No study has evaluated the value of repeated PCT measurements to predict infection, and no study has evaluated the impact on patients' outcome of the initiation of antibiotic therapy guided by a biomarker level in patients suspected of infected necrosis.

In summary, we suggest that PCT be measured to help predict infection in patients suspected of infected necrosis during acute pancreatitis; it is however difficult from the available literature to define a precise threshold value (0.5-1.0 mg/L). A PCT value above the threshold might reinforce the clinician's judgment that a fine-needle aspiration and culture is needed to confirm infection, while a value below this threshold might help deferring this intervention and proceed with watchful waiting. There is insufficient data to recommend initiating antibiotic therapy based on biomarker levels: this decision is based on a careful repeated evaluation of the patient and on the results of fine-needle aspiration material, which currently remains the cornerstone for the decision to initiate or maintain antibiotic therapy.

Lower respiratory tract infection in adults

Antibiotics often are prescribed in excess to patients having a clinical syndrome of community-acquired lower respiratory tract infection (LRTI). Despite the usually viral aetiology of their illness, an estimated 75% of patients with acute bronchitis receive antibiotics [11]; indeed, clinical presentation does not allow the distinction between bacterial and viral infection, which encourages physicians to err on the "safe side" and prescribe antibiotics. Communication campaigns inciting primary physicians to limit unnecessary prescriptions for LRTI have a moderate impact, which is difficult to maintain over time [12,13]. In this context, the addition of biomarker measurements to the clinical evaluation of such patients may have two main potential effects: improve the diagnostic accuracy, and reassure the patient and the physician that antibiotic therapy is unnecessary.

An abundant literature is available on PCT-guided initiation of antibiotic therapy in patients suspected clinically of having LRTI, providing a high-level of evidence. To date, 11 randomised, controlled studies using a similar approach have been published and provide consistent results [14-25]. All these studies have used a similar algorithm [26-29] to help decide on the initiation and continuation of antibiotic therapy, with a lower PCT threshold of ≤0.25 ng/mL to encourage physicians to withhold antibiotic prescription. The absolute risk reduction of antibiotic administration varies between 11% and 72% across these studies compared with "usual care" based on local recommendations and physicians' judgment and preferences (Table 2). In one study, however, antibiotic prescriptions increased by 6% with PCT-guided therapy [19]. It also should be noted that the 0.25 ng/mL threshold may be less reliable in the elderly, where an 8% false-positive rate has been reported [30].

Among the 14 studies of PCT-guided therapy for LRTI reviewed by the Cochrane Collaboration [31,32], only 3 enrolled patients with a nosocomial infection (hospital-acquired or ventilator-associated) [33-35], 2 of which evaluated the impact of PCT-guided therapy on the initiation of treatment [33,34]. However, nosocomial acquisition of infection is identifiable only in the study by Bouadma et al. [33], and only 5% (n = 141) of all patients enrolled fulfilled this criteria; nearly all patients in this

Table 1 Use of biomarkers for the diagnosis of infected necrosis secondary to acute pancreatitis

Marker	Study *1st author, [Ref]*	Study design	Nb of patients, *n*	Level of evidence	Biomarker tested and groups compared	Main results
PCT/CRP	Rau B, [2]	Observational	61	Low	Comparison of PCT and CRP levels between 3 groups:	AUROC for the diagnosis of infected necrosis:
					Oedematous pancreatitis (n = 22)	PCT (>1.8 mg/L) = 0.95 (Se: 95%, Sp: 88%),
					Sterile necrosis (n = 18)	CRP (>300 mg/L) = 0.86 (Se:86%, Sp: 75%); $p < 0.02$
					Infected necrosis (n = 21) according to imaging/surgery/microbiological data	
PCT/CRP/GCSF	Muller CA, [3]	Observational	64	Low	Comparison of PCT, G-CSF, and CRP between patients having oedematous pancreatitis (n = 29)	AUROC for diagnosing infected necrosis:
					Noninfected necrosis (n = 23)	CRP (>250) = 0.79 (Se: 83, Sp: 70%), PCT (0.45) = 0.77 (Se: 92%, Sp: 65%), AUC G-CSF (101) = 0.72 (Se: 92%, Sp: 48%)
					Infected necrosis (n = 12) according to imaging/surgery/microbiological data	
PCT/CRP/IL8	Rau B, [4]	Observational	50	Low	Comparison of PCT, IL8, and CRP levels between patients with:	AUROC for diagnosing infected necrosis:
					Oedematous pancreatitis (n = 18)	CRP (>300) = 0.84 (Se: 83, Sp: 78%),
					Non-infected necrosis (n = 14)	PCT (>1.8) = 0.97 (Se: 94%, Sp: 90%)
					Infected necrosis (n = 18) according to imaging/surgery/microbiological data	IL-8 (112) = 0.78 (Se: 72%, Sp: 75%)
PCT/CRP/IL6/TNF	Riche F, [5]	Observational	48	Low	Comparison of PCT, IL-6, TNF-α, and CRP between patients having	AUROC for diagnosing infected necrosis:
					- Noninfected necrosis (n = 33)	CRP = 0.76,
					- Infected necrosis (n = 15), according to imaging/surgery/microbiological data	PCT = 0.78,
						IL 6 = 0.77,
						TNF α = 0.5
PCT	Purkayastha S, [6]	Literature review (5 studies)	206	Low	Assessing the value of PCT for diagnosing infected pancreatic necrosis	Threshold values for PCT vary from 0.48 to 2;
						Sensitivity: 0.73 to 0.94
						Specificity: 0.65 to 1
PCT/IL6/TNF/sTREM1	Lu Z, [7]	Observational	30	Low	Comparison of PCT, IL-6, TNF-α, and sTREM-1 levels in serum and drainage fluid between patients having:	Biomarker levels in drainage fluid: No difference between the two groups for CRP, TNF-α, and IL-6 levels
					- Noninfected necrosis (n = 12), or	- sTREM1 (287), AUC = 0.97 (Se = 94, Sp = 92)
					- Infected necrosis (n = 18), according to imaging/surgery/microbiological data	- PCT (2.1): AUC = 0.9 (Se = 86, Sp = 91).
						Lower AUCs for serum levels:
						PCT: 0.79; sTREM1: 0.73

Table 1 Use of biomarkers for the diagnosis of infected necrosis secondary to acute pancreatitis *(Continued)*

PCT	Olah A, [8]	Observational	24	Low	Comparison of PCT levels in patients having	Serum PCT level >0.5 predicts infected necrosis with Se = 75% and Sp = 83%.
					- Noninfected necrosis (n = 12)	Fine-needle aspiration predicts infection with Se = 92% and Sp = 100%.
					- Infected necrosis (n = 12)	
					According to results of fine-needle aspiration and culture and surgery	
PCT/IL6/sICAM1	Mandi Y, [9]	Observational	30	Low	Comparison of PCT, IL-6, and sICAM-1 between patients with	Only PCT (threshold >1 mg/L) allowed to distinguish patients with or without infected necrosis (Se = 90%; Sp = 100%).
					Noninfected necrosis (n = 10)	
					Infected necrosis (n = 10), according to results of biopsy and culture.	
PCT	Mofidi R, [1]	Literature review (7 studies)	264	Low	Assessment of PCT serum levels for the diagnosis of infected pancreatic necrosis	Threshold values vary from 0.48 to 3.5 mg/L, with a sensitivity of 0.63 to 0.92 and specificity of 0.71 to 0.97.

Summary table: infected necrosis in acute pancreatitis

Number of studies, n	Total number of patients, n	Highest level of evidence	Directness*	Consistency of results**	Overall strength of evidence
7	264[a]	Low	Yes	Yes	Moderate

[a]Number of patients included in diagnostic studies of infected pancreatic necrosis.
*Directness: studies provide evidence of a direct association between a treatment or a given risk factor and a judgment criterion.
**Consistency: results from studies of similar level of evidence are not contradictory.

Table 2 Role of biomarkers in the initiation of antibiotic therapy for lower respiratory tract infection

Biomarker	Study (ref) *1st author, [Ref]*	Study design	Nb patients, *n (setting)*	Level of evidence	End-point	Main results, absolute risk reduction (ARR) or odds ratio (OR; 95% CI)
PCT	Stolz D, [20]	Single-centre, randomised, controlled open study	208 (AECB)	High	Antibiotic exposure and rate of initiation of antibiotic therapy, based on PCT level > 0.25 μg/L	ARR = 32% (40% vs. 72%) of antibiotic prescriptions in the PCT-guided group. Ab exposure OR = 0.56 [0.43-0.73]
PCT	Schuetz P, [25]	Multicentre, open RCT Noninferiority study	1359 (ED)	High	Antibiotic exposure Based on a PCT level > 0.25 μg/L for initiating prescription.	ARR = 12% (75.4% vs. 87.7%) in PCT group, Overall antibiotic exposure = - 35% (5.7 vs. 8.7 days).
PCT	Christ-Crain M, [18]	Single-centre open RCT	302 (ED, ward)	High	Antibiotic initiation rate Antibiotic exposure Based on a PCT level > 0.25 μg/L to initiate therapy	ARR = 14% (85% vs. 99%) in initial antibiotic prescription in PCT group Overall ab exposure: OR = 0.52 [0.48–0.55]
PCT	Kristoffersen KB, [19]	Single-centre, open, RCT	210 (ED, ward)	High	Antibiotic prescription rate, based on a PCT level > 0.25 μg/L to initiate therapy in PCT group	3% increase in antibiotic prescription (88% vs. 85%) in the PCT group
PCT	Long W, [23]	Single-centre, open RCT	127 (ED)	High	Antibiotic prescription rate, based on a PCT level > 0.25 μg/L in the PCT group	ARR = 11% of antibiotic prescriptions in the PCT group
PCT	Long W, [22]	Single-centre, open RCT	156 (ED)	High	Antibiotic prescription rate, based on a PCT level > 0.25 μg/L in the PCT group	ARR = 13% of antibiotic prescriptions in the PCT group
PCT	Burkhardt O, [16]	Single-centre, open RCT, noninferiority	550 (PC)	High	Antibiotic prescription rate, based on a PCT level > 0.25 μg/L in the PCT group	ARR = 15% (21.5% vs. 36.7%) for antibiotic prescription rate in the PCT group
PCT	Briel M, [15]	Multicentre, open RCT, noninferiority	458 (PC)	High	Antibiotic prescription rate, based on a PCT level > 0.25 μg/L in the PCT group	ARR = 72% [95% CI 66-78] for antibiotic prescription rate in the PCT group
PCT	Schuetz P, [30]	Meta-analysis of 14 RCTs	3 119	High		Risk reduction of initial antibiotic therapy: OR = 0.24 (95% CI, 0.2-0.29) Overall antibiotic exposure: OR = 0.1 (95% CI = 0.07-0.14), without difference in mortality rates
PCT	Van der Meer V, [28]	Literature review on the use of CRP (13 studies)	13	High	Prediction of LRTI	Bacterial LRTI predicted with a sensitivity varying from 8% to 99% and a specificity varying from 27% to 95%
PCT	Schuetz P, [29]	Review of 8 RCTs using an PCT-based algorithm for the initiation of antibiotic therapy	3 457	High	Antibiotic prescription rate	ARR varying from 6% to 72%

Table 2 Role of biomarkers in the initiation of antibiotic therapy for lower respiratory tract infection *(Continued)*

CRP	Cals JW, [24]	Multicentre, open cluster-RCT, testing a CRP-based algorithm	431	High	Antibiotic prescription rate and antibiotic exposure, based on a CRP value < 20 : no antibiotic; CRP >100 : atb recommended, and 20<CRP<99 : reassess for possible therapy	ARR = 22% (31% vs. 53%) of initial antibiotic prescriptions in the CRP group Overall antibiotic exposure: - 13% (45% vs. 58%)
PCT	Christ-Crain M, [17]	Multicentre, open, cluster-RCT	243 (ED)	High	Antibiotic prescription rate, based on a PCT level > 0.25 μg/L in the PCT group	ARR = 39% for antibiotic prescription rate in the PCT group

Summary of evidence table: Lower respiratory tract infection

Number of studies, n	Total number of patients, n	Highest level of evidence	Directness*	Consistency**	Overall strength of evidence
12	4 412	High	Yes	Yes	Strong

*Directness: studies provide evidence of a direct association between a treatment or a given risk factor and a judgment criterion.
**Consistency: results from studies of similar level of evidence are not contradictory.

subgroup were administered antibiotics (99% in the PCT-guided therapy group and 100% in controls). Repeated measurements might be helpful for initiating antibiotics in this subgroup; however, the few data available on a limited number of patients (n = 89 patients) [36] do not allow making a recommendation in this regard.

In summary, we suggest withholding antibiotic therapy in adult patients suspected of community-acquired LRTI and having a serum PCT level <0.25 ng/mL; if clinical suspicion is high, it is however recommended to repeat the PCT measurement at a 6-h interval and reassess the therapeutic approach, accounting for new clinical findings. In patients having nosocomial LRTI, data are insufficient to recommend tailoring the therapeutic approach based on a single PCT level or even repeated measurements.

Meningitis

Childhood meningitis

Most acute meningitis in children is of viral aetiology and evolves favourably [37,38]. Despite their relatively low prevalence, acute bacterial meningitis are severe infections, often resulting in debilitating sequels or even death [39]; thus, antibiotic therapy is recommended in children presenting with acute meningitis, at least until cerebrospinal fluid (CSF) cultures are available, i.e., within the first 48–72 h [40]. The risk-benefit ratio and costs associated with this prudent approach is likely unfavourable, because it involves numerous unnecessary hospitalisations, increased costs, and side effects of treatments, including selection of resistant organisms [41]. Biomarkers might help to reduce these unwanted effects [42,43]. Ideally, a good biomarker would have 100% sensitivity for the diagnosis of bacterial meningitis, together with an acceptable specificity [38]; however, when used alone, available biomarkers (PCT, CRP, IFN-ϒ, etc.) have sensitivities and specificities that do not appear high enough to base a therapeutic decision on their results given the risks incurred in case of a false-negative test [44,45].

To overcome this problem, several groups have proposed decision rules combining clinical criteria and biomarker results [46-50]. The Bacterial Meningitis Score (BMS) [46] has been reported to have 100% sensitivity and 67% specificity for the detection of bacterial meningitis and is easily applicable at the bedside. This decision rule encourages ambulatory treatment of children having meningitis (i.e., a CSF leucocytes count ≥7/mm^3) if none of the following five criteria is present: seizures, blood polymorphonuclear (PMN) cells count ≥10,000/mm^3, direct examination of CSF positive, CSF protein level ≥0.8 g/L, or CSF PMN ≥1000/mm^3. The BMS has undergone external validation on the large database of the French national registry for childhood bacterial meningitis (ACTIV-GPIP) [51]. Of 889 children with confirmed bacterial meningitis, 884 were correctly identified by the BMS rule (sensitivity = 99.6%; 95% confidence interval (CI) 98.9-99.8) with a specificity >60%. Thus, despite these near-perfect results, a few patients with bacterial meningitis (n = 5) were not detected by the BMS [52]; that the BMS can have a few false-negatives also was confirmed by a recent meta-analysis [53]. The Meningitest® (European patent EP1977244) has been subsequently proposed to refine the BMS and avoid these false-negatives, by omitting some variables of poor discriminatory power and introducing the serum PCT level [45,54]. The Meningitest® rule suggests initiating antibiotic therapy if at least one of the following criteria is present: seizures, toxic appearance, purpura, PCT level ≥0.5 ng/mL, positive CSF Gram stain, or CSF protein level ≥0.5 g/L. External validation of the Meningitest® has been performed on an European database of 198 patients (including 96 with bacterial meningitis), where its sensitivity and specificity were respectively of 100% (95% CI 96–100) and 36% (95% CI 27–46) for the diagnosis of bacterial meningitis, whereas corresponding values for the BMS were 100% (95% CI 96–100) and 52% (95% CI 42–62) [55]. A single serum PCT level ≥0.5 ng/mL has similar sensitivity and specificity as the BMS, whereas combining CRP with CSF protein levels provided lower performances.

In summary, for children with suspected bacterial meningitis, we recommend using a decision rule as an aid to triage decisions and antibiotic prescribing, such as the BMS (more specific, but with a few false-negatives) or the Meningitest® (less specific, but no false-negative described to date). A single PCT level ≥0.5 ng/mL also may be used, but false-negatives may occur.

Adult meningitis

The potential role of biomarkers in the management of meningitis has been much less studied in adults than in children. Similarly to children, the use of a clinical decision rule to distinguish between viral and bacterial meningitis is recommended in adults [56]. For example, the French 2008 consensus conference on meningitis recommended using one of three decision rules: the rule developed by Hoen et al. [57], the BMS, or the Meningitest® [56]. It should be noted that the former rule has insufficient sensitivity in children (94%), with a risk of false-negatives [45].

Knudsen et al. have examined the impact of various biomarkers in the diagnostic workup of 55 adult patients with meningitis [58]. These authors found an AUROC of 0.91, 0.87, and 0.72 for CRP, PCT, and sCD 163, respectively, and concluded that CRP and PCT levels could be useful when combined with results of CSF examination to help diagnose bacterial meningitis. One recent study [59] included 151 patients admitted to an adult emergency

department with suspected of bacterial meningitis and a negative direct examination of CSF, to assess the diagnostic value of CRP, PCT, and CSF leucocytes count. The AUROC of PCT and CRP were 0.98 (95% CI, 0.83-1.0) and 0.81 (95% CI, 0.58-0.92), respectively; however, the small number of patients with confirmed bacterial meningitis (n = 18) limits the inferences from this study. Of note, the CSF leucocytes count appeared to have little discriminatory value (AUC = 0.59) in that study. In another study of 30 patients (including 16 having bacterial meningitis), Schwarz et al. [60] found that PCT had a sensitivity of 69% and a specificity of 100% for diagnosing bacterial meningitis. In another larger prospective study that included 112 adult patients admitted to the hospital for meningitis (90 viral and 22 bacterial), Viallon et al. [61] found that a serum PCT value >0.93 ng/ml was 100% sensitive for the diagnosis of bacterial meningitis; conversely, a CSF lactate level <3.2 mmoles/L had a 100% NPV (Table 3). Low CRP levels have high NPV, but have not been shown to contribute markedly to the diagnostic approach [62]. The 2008 French consensus conference on management of acute bacterial meningitis [56] concluded that these biomarkers could be helpful for diagnosing bacterial meningitis in adults, pointing out that a threshold value for serum PCT of 0.5 ng/mL had a high sensitivity (99%; 95% CI, 97–100) and specificity (83%; 95% CI, 76–90), and that bacterial meningitis could be considered very unlikely when PCT was ≤0.5 ng/mL or CSF lactate was below 3 mmoles/L.

In summary, we suggest integrating serum PCT measurements in a clinical decision rule for meningitis in adults to help distinguish between viral and bacterial meningitis, using a threshold of 0.5 ng/mL.

Adult intensive care patients

Most controlled studies performed in intensive care patients have examined the value of biomarkers to limit the duration of antibiotic therapy, and few have concentrated on its initiation. Although a recent meta-analysis suggests that PCT is helpful for differentiating sepsis from SIRS [63], the initiation of antibiotic therapy in ICU patients has been assessed in only two randomised open studies testing a PCT-based algorithm (Table 4) [33,34]. In the study by Layios et al. [34], there was no difference in the rate of initiation of therapy between the control group and the PCT-based group (where antibiotics were strongly discouraged if PCT was lower than 0.25 ng/mL, and strongly encouraged if PCT was higher than 1 ng/mL). In the multicentre study performed by Bouadma et al. [33] and using a similar algorithm, the risk reduction of initiating antibiotic therapy varied between 5% and 13% across centres. However, the small number of patients having CAP (n = 69) and the very low observance of the algorithm for withholding antibiotics when PCT levels were low (6%) in this study do not allow concluding on this point.

Relying on changes in PCT levels might be helpful for the initiation of antibiotic therapy in intensive care patients suspected of ICU-acquired infection; however, currently available data (on a total of 207 patients) are insufficient to base a recommendation on these [36,64]. One randomized, controlled study that enrolled 604 ICU patients has tested the diagnostic value of daily measurements of serum PCT levels (using a threshold of 1 ng/mL to rapidly initiate a diagnostic workup and protocolised therapy) [65]. The length of ICU stay and of mechanical ventilation were actually higher in the PCT arm (without difference in 28-day mortality), and time to adequate therapy was not lower (except for patients with bacteremia). Of note, antibiotic consumption was significantly higher in the PCT arm, as well as the total number of days spent in the ICU with three or more antibiotics.

In summary, we do not recommend using a threshold serum PCT value to help in the decision to initiate antibiotic therapy in ICU patients suspected of community-acquired pneumonia. There are insufficient data available to recommend using repeated PCT measurements and serum kinetics for the decision to initiate antibiotic therapy in ICU patients suspected of ICU-acquired infection.

When can biomarkers help the decision to stop antibiotic therapy?

Given the number of studies examining this question and the high level of evidence generated, investigating this question was limited to examining randomized, controlled studies having tested a strategy based on biomarker measurement(s), to the exclusion of all other study designs. All studies in hospitalised patients used serum PCT level measurements, as there is no study testing the impact of using another biomarker in this specific indication; whereas several studies have tested the value of CRP for initiating antibiotics in pre-hospital care [24,66-68], none examined its potential impact on discontinuation of antibiotics, although several studies are ongoing (see http://www.clinicaltrials.gov/ct2/results?term=c+reactive+protein+and+duration&recr=&rslt=&type=&cond=&intr=&outc=&spons=&lead=&id=&state1=&cntry1=&state2=&cntry2=&state3=&cntry3=&locn=&gndr=&rcv_s=&rcv_e=&lup_s=&lup_e=). Accordingly, only studies using PCT levels are considered below.

How can biomarkers be used to help decide on discontinuing antibiotic treatment?

To date, 14 trials have examined the clinical impact of PCT-guided antibiotic therapy and its discontinuation [15-20,22,23,33,35,69,70,72,73]. Nine of these focused on the latter objective; four were conducted in prehospital care or emergency room, whereas the remaining five

Table 3 Studies of biomarkers in the diagnosis of bacterial meningitis (BM) and its distinction from viral meningitis (VM)

Marker	Study *1st author, [ref]*	Study design	Number of patients, *n*	Level of evidence	End-point	Main result Absolute risk reduction (RR)
PCT	Gendrel D, [42]	Single-centre observational study	59 children (18 BM, 41 VM)	Very low	Comparison of PCT and CRP level in patients with bacterial or viral meningitis	A serum PCT level >0.5 μg/L is associated with bacterial meningitis (Se = 94%; Sp = 100%). Large overlap for CRP values
PCT/CRP/ INF-ϒ	Marc E, [43]	Single-centre observational study	58 viral (enterovirus outbreak) Children (2 mo – 14 yr)	Very low	Antibiotic initiation and hospital days, based on a serum PCT < 0.5 to not initiate or stop antibiotics. If PCT >0.5, antibiotics stopped if negative cultures and/or INF or PCR (+) in CSF	41 patients did not receive antibiotics; antibiotics stopped in 15/17 pts treated by day 1 or 2, because of a PCT < 0.5. Hospital days reduced to 2 days.
PCT/CRP/ sCD 163	Knudsen T, [58]	Single-centre observational study (ID department)	55 adult patients suspected of BM	Very low	Comparison of PCT, CRP and sCD163 levels in patients with bacterial or viral meningitis, or other infection	Diagnostic value of CRP (AUC = 0.91) and PCT (AUC = 0.87) superior ($p < 0.02$ and $p < 0.06$) to sCD163 (AUC = 0.72); sCD163 most specific for systemic bacterial infection (Sp = 0.91).
PCT/CRP	Viallon A [61]	Single-centre observational study	254 adults (183 VM, 97 BM)	Low	Predictive value of serum PCT and CRP for the diagnosis of BM	AUROC PCT = 0.86; threshold 0.28 μg/mL (Se = 0.97; Sp = 1, VPP = 0.97, VPN = 1) AUROC CRP = 0.92; threshold 37 mg/L (Se = 0.86, Sp = 0.84, VPP = 0.46, VPN = 0.97)
CRP	Gerdes L, [62]	Meta analysis of 10 studies	Children and adults	low	Predictive value of serum CRP for bacterial meningitis	Threshold value for CRP varies across studies from 19 to 100 mg/l. Se varies from 92% to 94% and NPV is >97%.

Summary table

	Total number of patients	Highest level of evidence	Directness*	Consistency of results**	Overall strength of evidence	Number of studies
	371	Low	Yes	Yes	Low	3 (PCT)

*Directness: studies provide evidence of a direct association between a treatment or a given risk factor and a judgment criterion.
**Consistency: results from studies of similar level of evidence are not contradictory.

Table 4 Biomarkers and initiation or discontinuation of antibiotic therapy in adult ICU patients with sepsis

Biomarker	Study *1st author, year [ref]*	Study design, patient selection (objective)	Nb of patients *n*	Level of evidence	Primary endpoint and protocol	Main results PCT-guided vs. controls (ARR, absolute risk reduction)
PCT	Layios N, [34]	Open, randomised controlled trial, 5 ICUs	509	High	Total antibiotic use in ICU patients when using a PCT-based algorithm for initiating antibiotics (lower PCT threshold for not initiating therapy: 0.25 ng/mL)	Percent days on antibiotics or overall DDD did not differ between the two groups. Withholding or withdrawing antibiotics similar overall (ARR = 3%) and with low PCT levels (PCT: 46.3%; controls: 32.7%; p = NS), or higher levels.
		Patients suspected of infection on admission or during the ICU stay (initiation of therapy)	PCT: 353			
			Ctr: 314			
PCT	Nobre V, [35]	Single-centre, open RCT;	79	Moderate	Total antibiotic days.	ARR antibiotic days: 3.5 (6 vs. 9.5 days; p = 0.15),
		PCT-guided withdrawing antibiotics vs. "standard care" (duration)ICU patients with severe sepsis/shock on admission or during ICU stay (excl. immunosuppressed patient or requiring prolonged therapy)	PCT: 39 (31 assessed)*		Recommend stopping antibiotics if PCT levels ≤ 90% of initial value but not before Day 3 (if baseline PCT level <1 ng/mL) or Day 5 (if baseline level ≥ 1 ng/mL).	Less overall ab exposure (504 vs. 655 ab days; p = 0.28); days alive without antibiotics at 28 days (15.3 vs. 13.3 days; p = 0.28). 28-d mortality: 20.5% vs. 20%
			Ctr: 40 (37 assessed)*			
			70% CA infections			*4 and 2 secondary exclusions for complicated infections (empyema, mastoiditis, abscess)
PCT	Bouadma L, [33]	Multicenter randomised open trial, 7 ICUs	630	High	Number of days alive and without antibiotics; noninferiority in terms of mortality by using a PCT-based algorithm for initiating or withdrawing antibiotics in those suspected of infection on admission or during the ICU stay (lower PCT threshold for not initiating or stopping therapy: 0.25 ng/mL)	ARR: 5% for initiating antibiotics (PCT: 91% vs. 96% in Ctr group).
		Sepsis in ICU patients, on admission or ICU-acquired (Initiation and duration)	PCT: 311			
			Ctr: 319			ARR for nb of antibiotic days: 2.7 days [1.4–4.1]
						Ab-free days by 28 d: 11.6 vs. 14.3 days
						28-d mortality : 21.2% vs. 20.4%; ARR = 0.8% [-4.6 to 6.2]
PCT	Stolz D, [69]	Multicentre open randomised trial, 7 ICUs (duration of therapy for VAP)	101	Moderate	Ab-free days alive at 28 days	Ab-free days at 28 d: 13 vs. 9.5 days
			PCT: 51		Discontinue ab if PCT <0.25 or <0.5 ng/ml and decrease by >80% from initial level	Ab duration: 10 vs. 15 days
			Ctr: 50			28-d mortality: 20% vs. 28%
PCT	Hochreiter M, [70]	Single-centre open randomised trial	110	Moderate	Reduction in ab duration	Mean Ab duration: 5.9 vs. 7.9 d
		Postoperative sepsis (duration)	PCT: 57		Discontinue ab if PCT <1.0 and clinical improvement, or sustained decrease to 25-35% initial value for 3 days	Mean ICU LOS:
			Ctr: 53			28-dMortality: 26.3% vs. 26.4%
PCT	Kopterides P, [71]	Meta-analysis of RCT in ICU patients (7 studies)	1131 patients	High	Various algorithms for discontinuation of Ab therapy	Duration ab : -2.1 [-2.5 to – 1.8] d
						Total Ab exposure: -4.2 [-5 to -3.4] days
						Ab free-days: 2.9 [1.9–3.9] days
						28-d mortality: OR = 0.93 [0.69-1.26]

Table 4 Biomarkers and initiation or discontinuation of antibiotic therapy in adult ICU patients with sepsis *(Continued)*

Summary table: Sepsis in ICU patients						
	Total number of patients, n	**Highest level of evidence**	**Directness***	**Consistency****	**Overall strength of evidence**	**Number of studies, n**
	1010	High	Yes	Yes	**Initiation of therapy: low** **Discontinuation of therapy: high**	7

*Directness: studies provide evidence of a direct association between a treatment or a given risk factor and a judgment criterion.
**Consistency: results from studies of similar level of evidence are not contradictory.

were conducted in ICU patients. Although specific stopping rules may vary across trials and population enrolled, all studies used a PCT-based algorithm to help decide on stopping antibiotics (Table 5).

In outpatients and emergency room patients (excluding ICU patients), a serum PCT level below 0.25 ng/mL obtained 3 days or more after initiation of antibiotics, or a more than 80% decrease from the peak PCT level, allows stopping therapy.

Five studies have enrolled ICU patients with community- or hospital-acquired infection; four used a similar algorithm and the fifth used a different algorithm. It seems reasonable to recommend using the algorithm tested on the largest number of patients, i.e., as in the ProVAP et Prorata studies [33,69], where stopping therapy was strongly encouraged when the serum PCT level was ≤0.5 ng/mL at 3 days or more after initiating antibiotics, or an ≥80% decrease from the maximal serum PCT value was recorded.

Table 5 PCT-based algorithms used for discontinuing antibiotic therapy in randomized, clinical trials

Author [ref], acronym	Setting	Population	Number of patients	Algorithm used
Emergency department and ambulatory care				
Christ-Crain [18], ProCAP trial	Emergency room	CAP	302	PCT measured d4, d6, d8
			- 151 PCT-guided arm	Stopping antibiotics encouraged if PCT < 0.25μg/L; strongly encouraged if PCT < 0.1 μg/L
			- 151 control arm	If initial PCT >10μg/L, stop when decreased by ≥90%
Briel [15]	Ambulatory care	Lower RTI	458	PCT at d3
			- 232 PCT-guided arm	Encourage stopping if PCT d3 ≤ 0.25 μg/L
			- 226 control arm	
Schuetz [25]	Emergency room	Upper & lower RTI	1359	PCT at d3, d5, d7 if patient still hospitalised
			- 671 PCT-guided arm	Stop antibiotics when PCT ≤ 0.25 μg/L
			- 688 control arm	If initial PCT >10 μg/L, stop when decreased by ≥80%
Long W [22]	Emergency room	CAP	172	PCT at d1, d3, d6, & d8
			- 86 PCT-guided arm	Stop when PCT ≤ 0.25 μg/L
			- 86 control arm	
Intensive care unit				
Nobre [35]	ICU	Severe sepsis & septic shock	79	PCT d1 > 1 μg/l :
			- 39 PCT-guided arm	• Stop if PCT d5 decreased by > 90% or PCT < 0.25 μg/L
			- 40 control arm	PCT d1 < 1μg/l :
				• Stop if PCT d3 < 0.1 μg/l (but not before d5 if bacteremia)
Hochreiter [70]	ICU	Sepsis	110	Stop if clinical symptoms resolved and PCT < 1 μg/L (or dropped by 25% - 35% over 3 days if initial PCT > 1 μg/L)
		(Infection + 2 SIRS criteria)	- 57 PCT-guided arm	
			- 53 control arm	
Schroeder [73]	ICU	Severe sepsis after abdominal surgery	27	Stop if clinical symptoms resolved and PCT < 1 μg/L (or dropped by 25% - 35% over 3 days if initial PCT > 1 μg/L)
			- 14 PCT-guided arm	
			- 13 control arm	
Stolz [69], ProVAP trial	ICU	VAP	101	Daily PCT measurements PCT from d3 on
			- 51 PCT-guided arm	Stop when PCT < 0.5 μg/L or dropped by ≥ 80% from initial value but stopping discouraged if PCT >1 μg/L
			- 50 control arm	
Bouadma [33], PRORATA trial	ICU	Sepsis, severe sepsis	621	Daily PCT measurements from d3 on
			- 307 PCT-guided arm	Stop when PCT < 0.5 μg/L or dropped by ≥ 80% from initial value
			- 314 control arm	

CAP community-acquired pneumonia, *ICU* intensive care unit, *PCT* procalcitonin, *RTI* respiratory tract infection, *SIRS* systemic inflammatory response syndrome, *VAP* ventilator-associated pneumonia.

Does the site of infection (known, presumed, unknown) influence the utility of biomarkers to help withdrawing antibiotics?

In all studies examining the prognostic and follow-up value of PCT, the site of infection was known, to the exception of a few patients (n = 18) in the PRORATA study (10 and 8 in the PCT arm and control group, respectively). This small number does not allow any conclusion for this subgroup. It should be noted that patients having infective endocarditis, bone and joint infection, acute mediastinitis, intracerebral or intra-abdominal abscess were excluded from the above studies. Therefore, PCT-based algorithms cannot be used in these patients for discontinuing antibiotics.

Therefore, PCT-guided interruption of therapy can be used as indicated above in patients having a clinically documented site of infection to the exception of those sites listed above, which were excluded from clinical trials. When the site of infection is unknown, insufficient data are available to make a recommendation.

Does microbiological documentation influences the clinical utility of biomarkers to help withdrawing antibiotics?

Microbiologically documented infection

In the PRORATA study, most patients enrolled (70%) had microbiologically documented infection (222 and 213 in the PCT and control group, respectively) [33]. In the subgroup of 108 patients having positive blood cultures (55 and 53 in the PCT and control group, respectively), those randomised to the PCT-guided algorithm received 3 days less antibiotics than those enrolled in the control group (IC95%, -6 to 0.1 day, $p = 0.06$), without difference in mortality rate.

In the ProHosp trial, 72 patients had positive blood cultures [25]; patients enrolled in the PCT-guided therapy group received 5 days less antibiotics (10.3 vs. 15.1 days). Among 237 patients with bacteremic LRTI included in a recent meta-analysis [32], those treated with the aid of a PCT-based algorithm had 3.5 less antibiotic days (95% CI 1.55-5.54, $p < 0.001$), without significant difference in mortality rate (OR 1.09; 95% CI 0.51-2.31).

Lack of microbiological documentation

Most studies conducted outside of the ICU have enrolled patients in whom microbiological documentation was lacking. Although this specific subgroup has not been examined separately in individual studies or meta-analyses, it seems reasonable to recommend using a PCT algorithm in the non-ICU population to help decide stopping antibiotic therapy.

Most ICU patients enrolled in the above mentioned studies had documented infection. However, in the PRORATA study [33], 186 episodes were nondocumented and those treated in the PCT-guided therapy arm had a nonsignificant reduction in antibiotic days (2.4 less days), with no difference in mortality rate. Therefore, the documentation of infection does not appear to influence the impact of PCT-guided withdrawal of therapy, whether in ICU or non-ICU populations.

Does an immunocompromised status of patients influence the use of biomarkers for stopping antibiotic therapy?

Among the nine trials testing the impact of PCT-guided discontinuation of therapy, only the PRORATA trial [33] enrolled immunocompromised patients in the ICU. This trial enrolled patients having HIV infection or AIDS, organ transplant recipients, patients having haematological malignancy or receiving chemotherapy or radiation therapy, immunosuppressive agents or long-term steroids, to the notable exception of bone marrow transplant recipients or those having severe neutropenia (<500 leucocytes/mm^3). About a hundred such immunocompromised patients were included (47 and 51 in the PCT-guided therapy group and control group, respectively). In this subgroup, PCT-guided discontinuation of therapy was associated with a significantly reduced duration of therapy (3.6 days; 95% CI, 0.2-7 days), without apparent effect on morbidity or mortality (control vs. PCT, -7.1%; 95% CI −18.7 to 4.5%).

Therefore, PCT-guided algorithms to reduce the duration of antibiotic therapy can be used safely in immunocompromised patients, to the exception of neutropenic patients (<500 neutrophils/mm^3) or bone marrow transplant recipients, which were excluded from trials and in whom PCT-guided therapy cannot be recommended.

Does the impact of PCT-guided therapy vary according to the severity of acute illness?

Systematic reviews and meta-analyses

Six studies were reviewed in the meta-analysis by Tang et al. [74], totalling 1,548 patients. Four of these trials enrolled patients with suspected LRTI, two studies enrolled patients with sepsis, and one focused on severe infections in surgical ICU patients. Algorithms used varied across studies, using 2, 3, or 4 PCT levels for decision-making. There was a nonsignificant trend to a reduced duration of antibiotic therapy among LRTI studies ($p = 0.067$), which showed significant heterogeneity between trials. Conversely, in the other three studies of sepsis and surgical patients that enrolled more severe patients, no substantial heterogeneity was observed, and PCT-based algorithm for discontinuation of antibiotics were associated with a significant reduction in antibiotic duration, without apparent deleterious effect. This meta-analysis did not, however, stratify trials according to the severity of illness. In the

subgroup of four studies having the strongest design (including 3 of the 4 studies on LRTI), there was a significant reduction in the duration of antibiotic therapy, but a significant heterogeneity persisted.

Significant heterogeneity also was evidenced in a recent meta-analysis including eight studies of LRTI [75]. There was one trial in patients with acute exacerbation of COPD, one on patients with CAP, two on patients with upper and lower RTI [16], and three on LRTI. A significant reduction of antibiotic duration was noted in all but one study [16], where a PCT-based algorithm was not used. Similarly to the previous analysis, this meta-analysis did not stratify patients according to their severity.

In the more recent systematic review by Schuetz et al. focusing on LRTI [32], 14 trials totalling 4,221 patients were analysed. A reduced rate of treatment initiation was confirmed in studies performed in primary care and patients having upper or lower RTI or acute bronchitis. Trials performed in the emergency department or the ICU and enrolling patients with LRTI, whether CAP or VAP, also found a reduction in the duration of antibiotic therapy. A sensitivity analysis showed no significant difference in the reduction of antibiotic duration according to the type of LRTI and site of care. It was however noted that the observance of clinical algorithms was lower in the ICU setting than at other sites.

Individual studies

Christ-Crain et al. [18] reported that PCT levels increased with the severity of illness, as assessed by the pneumonia severity index (PSI). However, the duration of antibiotic prescription decreased similarly with PCT-guided therapy in the low-risk (PSI I-III) or high-risk (PSI IV-V) group. In another study in patients with LRTI from the same group [17], only admission PCT levels were recorded but not duration of therapy. In the PROHOSP study [25], the reduction of antibiotic duration with PCT-guided therapy was more marked among patients having acute bronchitis (–65%) than among patients with acute exacerbation of COPD (–50%), and lowest (–32%), but still strongly significant, among those with CAP.

In the trial conducted by Stolz et al. in patients with acute exacerbation of COPD [20], the impact of PCT-guided therapy was not analysed according to the severity of the episode or of the underlying COPD, which included all severity stages.

Briel et al. enrolled patients with RTI from various causes, including upper respiratory tract infection or acute bronchitis, CAP, or acute exacerbation of COPD [15]. The reduction in antibiotic duration was more marked in the former group than in those with CAP or acute exacerbation of COPD.

The proREAL trial also enrolled patients (n = 1,759) with acute bronchitis, exacerbation of COPD, and CAP [27]. The observance of the algorithm was 81%, 70%, and 64% respectively, confirming other observations [32,33] that the observance decreases with increasing severity of illness. Of note, the algorithm used in that study included both the clinical context and PCT levels (Table 3).

Long et al. also found a reduction in antibiotic duration of patients with CAP [22]. However, this study enrolled only patients with nonsevere pneumonia and cannot inform this assessment according to severity of illness. In trials dealing with the more severe infections (VAP, sepsis) [33,35,65,66], analyses have not been stratified according to the level of severity.

Summary and conclusions

In view of currently available data, PCT is the only biomarker that has been extensively studied so far to help decision-making in discontinuing antibiotic therapy in adults. In clinical practice, an algorithm should be used, based on PCT levels on day 1 (reference value), then at day 2–3, and every 48 h until antibiotic therapy is stopped.

In nonimmunocompromised patients treated for RTI as outpatients or hospitalised in regular wards, the following stopping rule can be used: discontinuation of antibiotic therapy if the PCT level at day 3 is lower than 0.25 ng/mL or has decreased by >80-90% relative to the maximal value initially recorded, whether or not microbiological documentation has been obtained.

For patients hospitalised in ICU, including immunocompromised patients (but not neutropenic patients or bone marrow transplant recipients), the following decision rule can be suggested for nonbacteremic patients with a known site of infection (whether or not microbiological documentation is obtained): stopping antibiotics if the PCT level at day 3 is <0.5 ng/ml or has decreased by >80% relative to the highest level recorded during this episode. In bacteremic patients, a minimal duration of therapy of 5 days is recommended.

Overall, the severity of the infectious episode does not appear to alter substantially the impact of PCT measurements on the reduction of antibiotic duration; however, the magnitude of the reduction is more marked in infections of lesser severity, which likely reflects at least two factors: 1) the less common indications for antibiotic therapy in such conditions, which is in contrast to the high tendency among physicians to initiate therapy when in doubt on the aetiology; 2) the better observance of decision algorithms by physicians, likely related to their greater confidence in the lack of serious risk associated with withholding or withdrawing antibiotics in these low-severity patients.

Abbreviations
AIDS: Acquired immunodeficiency syndrome; AUC: Area under the curve; AUROC: Area under the receiver operating curve; BM: Bacterial meningitis; BMS: Bacterial meningitis score; CAP: Community-acquired pneumonia; COPD: Chronic obstructive pulmonary disease; CRP: C-Reactive protein; CSF: Cerebrospinal fluid; HIV: Human immunodeficiency virus; ICU: Intensive care unit; IFN-Y: Interferon-gamma; IL: Interleukin; LRTI: Lower respiratory tract infection; PCT: Procalcitonin; PMN: Polymorphonuclear neutrophil; PPV: Positive predictive value; PSI: Pneumonia severity index; ROC: Receiver Operating Characteristic curve; RTI: Respiratory tract infection; SIRS: systemic inflammatory response syndrome; sTREM-1: soluble Triggering Receptor Expressed on Myeloid cells-1; TNF: Tumor necrosis factor; VAP: ventilator-associated pneumonia.

Competing interests
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Authors' contributions
All panel members contributed to the panel discussions and analyses. Each panel members contributed to drafting different sections of the manuscript: A-MD, YP, FP, SR, and BM drafted part I; J-PQ, SL, Y-EC, J-PS, CG-L, MC, and RG drafted part II; and C-EL, NR, J-PB, JP, and CB-B drafted part III. A-MD, J-PQ , C-EL, RG, BM, MC, and CB-B extensively reviewed the consolidated manuscript and all authors approved its final version.

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