Editorial

Giuseppe Lippi

Sepsis biomarkers: past, present and future

https://doi.org/10.1515/cclm-2018-1347

According to the Third International Consensus Definitions for Sepsis and Septic Shock [1], sepsis is currently defined as severe organ dysfunction caused by a dysregulated host response to infection associated with severe injuries to tissues and organs, up to septic shock, multiorgan failure (MOF) and death. Sepsis is a major public healthcare issue, being now considered as the leading cause of mortality from infections, accounting for more than 20 billion US $ hospital costs each year in the US [1].

Recent statistics shows that the actual prevalence of sepsis is as high as 6% in hospitalized adults [2], whilst reliable predictions suggest that its future incidence may nearly double in the next 30 years [3]. The cumulative in-hospital mortality is approximately 15% [2], whereas a much higher death rate is observed in intensive care units (ICUs), typically comprised between 20% and 45% [4]. Although both Gram-positive and -negative bacteria may trigger sepsis, the most frequent of which are *Staphylococcus aureus* (20.5% of cases), *Pseudomonas* species (19.9%), *Escherichia coli* (16.0%), *Klebsiella* species (12.7%), *Enterococcus* (10.9%) and *Staphylococcus epidermidis* (10.8%), sepsis can also be frequently develop in patients infected by *Candida* (17.0%) and other microorganisms [5]. The lungs (36%–42%) are the more frequent infection sites in patients with severe sepsis, followed by genitourinary tract (10%–18%), abdomen (8%–9%) and wounds or soft tissues (7%–9%), whilst no precise source of bacteremia can be identified is as many as 20% of patients [5].

Irrespective of the fact that a timely and accurate diagnosis of sepsis is essential to reverse its otherwise unfavorable clinical course, the diagnostic approach remains challenging. Some scoring systems have been developed in recent years, including the host systemic inflammatory response syndrome (SIRS) criteria, the sequential [sepsis-related] organ failure assessment (SOFA) and the quick SOFA (qSOFA) scores [6]. Nevertheless, all these tools are primarily intended for predicting outcomes, especially death, whilst their early diagnostic efficiency remains unsatisfactory [7]. Even if the Sepsis-3 Task Force reiterates the concept that sepsis shall be identified using clinical criteria for life-threatening organ dysfunction and blood culture [1], both these approaches would only be efficient for delayed diagnosis and thus partially unable to substantially ameliorate an unfavorable prognosis.

For a long time, standard blood culture techniques have represented the only reliable means for diagnosing sepsis, and are still regarded as the gold standard reference methods for detecting and isolating pathogenic organisms from sterile body fluid specimens [8]. Unfortunately, however, blood culture has many drawbacks such as a long turnaround time (TAT) (i.e. 6 h to 5 days are needed for microorganisms to grow to detectable levels, with an additional 24–48 h needed for testing antibiotic susceptibility), low sensitivity, large sample volume, frequent need for repeated testing, risk of false negative test results after initiation of antibiotic therapy (between 30% and 63% of cases) and preanalytical variables (e.g. 2%–4% sample contamination due to non-observance of standard antiseptic procedures during blood drawing) (Figure 1). Finally, albeit that automated approaches have been developed [9], blood culture remains a labor-intensive and time-consuming procedure in many clinical laboratories.

Due to these inherent limitations, a large armamentarium of serum (or plasma) sepsis biomarkers has been commercialized over the past decades. These typically include C-reactive protein (CRP), procalcitonin, presepsin, interleukin 6 (IL-6), lipopolysaccharide-binding protein (LBP), neutrophil CD64 (nCD64), soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) and the serum soluble urokinase-type plasminogen activator receptor (suPAR), among others. Although none of these biomarkers would thoughtfully fulfil all the ideal features of a sepsis biomarker, as briefly summarized in Table 1, stronger clinical evidence of clinical usefulness has emerged for procalcitonin, presepsin and CRP from many published studies and meta-analyses. Both procalcitonin and presepsin now appear to be the most promising tests, not only for early diagnosis of sepsis, but also for garnering valuable prognostic information and for guiding therapeutic decision-making (i.e. antibiotic stewardship) [7, 10–11]. Nonetheless, their measurement is also plagued by some important drawbacks, such as insufficient standardization [12], the inability to provide information on causative microorganism and suboptimal diagnostic accuracy. Regarding this last aspect, a recent study published by Brodska et al. showed that the diagnostic

Diagnostic features	Blood culture	Serum biomarkers	Molecular biology
Etiological diagnosis	Yes	No	Yes
Standardization	Acceptable	Limited	Limited
Rapidity	Limited	High	Limited
Accuracy	Partial	Partial	Partial
Predictiveness	No	Yes	No
Antibiotic resistance	Yes	No	No
Preanalytical issues	Yes	Limited	Yes

Figure 1: Diagnostic features of past, present and future sepsis biomarkers.

Table 1: Ideal features of sepsis biomarkers.

- Being present at symptoms onset (or even earlier), to allow for an early diagnosis
- Being highly sensitive and specific for infections, to allow for an accurate differential diagnosis between infectious and non-infectious diseases
- Being capable of identifying the causative microorganism
- Being informative on the clinical course
- Providing valuable information on the prognosis
- Guiding therapeutic decisions (e.g. antibiotic stewardship)

accuracy of some of the currently available biomarkers remains limited (i.e. <80%), and that presepsin even failed to outstrip more conventional sepsis biomarkers such as procalcitonin and CRP for both diagnosing sepsis and prognosticating death in critically ill patients [13].

Nucleic acid amplification is one of the most promising perspectives in sepsis diagnostics. The current techniques are essentially based on rapid amplification of DNA or RNA of pathogen origin, up to obtaining detectable levels which can then be assayed using mass spectrometry (MS), high-resolution melting or sequencing. Several commercial methods have been commercialized and cleared by many regulatory agencies worldwide, as is thoughtfully reviewed elsewhere [8]. Albeit recent evidence suggests that the diagnostic performance of these assays is comprised between 70% and 90%, the ability to accurately detect pathogens is still limited by some preanalytical issues, the need for effective lysis across a broad range of bacteria, interference from host DNA or other inhibitory substances, off-target interactions and amplification bias [8]. Moreover, antimicrobial stewardship may remain virtually unchanged even after molecular biology detection, so that clinical efficiency and cost-effectiveness of these techniques remain largely untested [14]. Hence, further refinements of molecular assays would be needed to overcome the current limitations in their diagnostic performance.

Early diagnosis of sepsis remains crucial for the managed care of patients with severe infections, who need timely treatment much earlier than after any signs and symptoms of organ failure have appeared. Prompt pathogen identification would also be highly effective for limiting inappropriate antibiotics usage, thus lowering the risk of antimicrobial resistance, which is one of the biggest threats to global health according to the World Health Organization (WHO). As previous work suggested, neither the past, present or future tests would fulfil all the features of an ideal sepsis biomarker and thus being considered the panacea that clinicians are expecting (Table 1). On the other hand, the integration of these existing technologies would probably be effective for counterweighing individual drawbacks but will exponentially increase the healthcare expenditure. Future cost-effectiveness studies aimed at comparing and validating their diagnostic usage, alone or in combination, will thus be necessary.

The most reliable strategy for early diagnosis of sepsis appears to be that suggested by Schuetz et al. in this issue of the journal [15], relying on diagnostic algorithms integrating the pretest probability of infection, clinical features and results of *in vitro* diagnostic testing (e.g. procalcitonin). This approach, entailing close collaboration and cooperation between laboratory professionals and clinicians, reflects the current value of the

so-called "clinical laboratory stewardship" [16], which must be seen as an essential step forward for improving the appropriateness of laboratory test ordering and the accuracy of interpretation of test results. Nonetheless, additional practical issues should be addressed, such as the current lack of standardization of procalcitonin immunoassays, as is also highlighted in another interesting article published by Chambliss et al. in this issue of the journal [17].

Author contributions: The author has accepted responsibility for the entire content of this submitted manuscript and approved submission.
Research funding: None declared.
Employment or leadership: None declared.
Honorarium: None declared.

References

1. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). J Am Med Assoc 2016;315:801–10.
2. Rhee C, Dantes R, Epstein L, Murphy D, Seymour CW, Iwashyna TJ, et al. Incidence and trends of sepsis in US hospitals using clinical vs claims data, 2009–2014. J Am Med Assoc 2017;318:1241–9.
3. Angus DC, Kelley MA, Schmitz RJ, White A, Popovich J Jr. Caring for the critically ill patient. Current and projected workforce requirements for care of the critically ill and patients with pulmonary disease: can we meet the requirements of an aging population? J Am Med Assoc 2000;284:2762–70.
4. Melville J, Ranjan S, Morgan P. ICU mortality rates in patients with sepsis compared with patients without sepsis. Crit Care 2015;19(Suppl 1):14.
5. Mayr FB, Yende S, Angus DC. Epidemiology of severe sepsis. Virulence 2014;5:4–11.
6. Marik PE, Taeb AM. SIRS, qSOFA and new sepsis definition. J Thorac Dis 2017;9:943–5.
7. Lippi G, Montagnana M, Balboni F, Bellone A, Casagranda I, Cavazza M, et al. 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. Emerg Care J 2017;13:6877.
8. Sinha M, Jupe J, Mack H, Coleman TP, Lawrence SM, Fraley SI. Emerging technologies for molecular diagnosis of sepsis. Clin Microbiol Rev 2018;31. doi: 10.1128/CMR.00089-17. Print 2018 Apr.
9. Da Rin G, Zoppelletto M, Lippi G. Integration of diagnostic microbiology in a model of total laboratory automation. Lab Med 2016;47:73–82.
10. Yang HS, Hur M, Yi A, Kim H, Lee S, Kim SN. Prognostic value of presepsin in adult patients with sepsis: systematic review and meta-analysis. PLoS One 2018;13:e0191486.
11. Bartoletti M, Antonelli M, Bruno Blasi FA, Casagranda I, Chieregato A, Fumagalli R, et al. Procalcitonin-guided antibiotic therapy: an expert consensus. Clin Chem Lab Med 2018;56:1223–9.
12. Eidizadeh A, Asif AR, von Ahsen N, Binder L, Schnelle M. Differences in procalcitonin measurements between three BRAHMS-partnered immunoassays (Liaison, Elecsys and Architect). Clin Chem Lab Med 2019;57:e207–10.
13. Brodska H, Valenta J, Pelinkova K, Stach Z, Sachl R, Balik M, et al. Diagnostic and prognostic value of presepsin vs. established biomarkers in critically ill patients with sepsis or systemic inflammatory response syndrome. Clin Chem Lab Med 2018;56:658–68.
14. Karrasch M, Geraci J, Sachse S, Rödel J, Löffler B, Bauer M, et al. Early adjustment of antimicrobial therapy after PCR/electrospray ionization mass spectrometry-based pathogen detection in critically ill patients with suspected sepsis. Clin Chem Lab Med 2018;56:e207–9.
15. Schuetz P, Beishuizen A, Broyles M, Ferrer R, Gavazzi G, Gluck EH, et al. Procalcitonin (PCT)-guided antibiotic stewardship: an international experts consensus on optimized clinical use. Clin Chem Lab Med 2019;57:1308–18.
16. Plebani M, Laposata M, Lippi G. A manifesto for the future of laboratory medicine professionals. Clin Chim Acta 2019;489:49–52.
17. Chambliss AB, Hayden J, Colby JM. Evaluation of procalcitonin immunoassay concordance near clinical decision points. Clin Chem Lab Med 2019;57:1414–21.

Prof. Giuseppe Lippi, Section of Clinical Biochemistry, University Hospital of Verona, Piazzale LA Scuro, 37134 Verona, Italy,
E-mail: giuseppe.lippi@univr.it.
https://orcid.org/0000-0001-9523-9054

Opinion Paper

Philipp Schuetz*, Albertus Beishuizen, Michael Broyles, Ricard Ferrer, Gaetan Gavazzi, Eric Howard Gluck, Juan González del Castillo, Jens-Ulrik Jensen, Peter Laszlo Kanizsai, Andrea Lay Hoon Kwa, Stefan Krueger, Charles-Edouard Luyt, Michael Oppert, Mario Plebani, Sergey A. Shlyapnikov, Giulio Toccafondi, Jennifer Townsend, Tobias Welte and Kordo Saeed

Procalcitonin (PCT)-guided antibiotic stewardship: an international experts consensus on optimized clinical use

https://doi.org/10.1515/cclm-2018-1181
Received November 3, 2018; accepted December 16, 2018; previously published online February 6, 2019

Abstract

Background: Procalcitonin (PCT)-guided antibiotic stewardship (ABS) has been shown to reduce antibiotics (ABxs), with lower side-effects and an improvement in clinical outcomes. The aim of this experts workshop was to derive a PCT algorithm ABS for easier implementation into clinical routine across different clinical settings.
Methods: Clinical evidence and practical experience with PCT-guided ABS was analyzed and discussed, with a focus on optimal PCT use in the clinical context and increased adherence to PCT protocols. Using a Delphi process, the experts group reached consensus on different PCT algorithms based on clinical severity of the patient and probability of bacterial infection.
Results: The group agreed that there is strong evidence that PCT-guided ABS supports individual decisions on initiation and duration of ABx treatment in patients with acute respiratory infections and sepsis from any source, thereby reducing overall ABx exposure and associated side effects, and improving clinical outcomes. To simplify practical application, the expert group refined the established PCT algorithms by incorporating severity of illness

***Corresponding author: Philipp Schuetz,** MD, MPH, Department of Internal Medicine, Kantonsspital Aarau, Aarau, Switzerland; and University of Basel, Basel, Switzerland, Phone: +41 (0) 79 365 10 06, Fax: 41 (0) 62 838 9524, E-mail: Philipp.Schuetz@unibas.ch
Albertus Beishuizen: Medisch Spectrum Twente, Enschede, The Netherlands
Michael Broyles: Five Rivers Medical Center, Pocahontas, AR, USA
Ricard Ferrer: Department of Intensive Care. Shock, Organ Dysfunction and Resuscitation Research Group, Vall d'Hebron University Hospital, Barcelona, Spain
Gaetan Gavazzi: University Clinics of Geriatrics, University Hospital of Grenoble-Alpes, GREPI EA7408 University of Grenoble Alpes, Grenoble, France
Eric Howard Gluck: Swedish Covenant Hospital, Chicago, IL, USA
Juan González del Castillo: Emergency Department, Hospital Clinico San Carlos, Madrid, Spain
Jens-Ulrik Jensen: Respiratory Medicine Section, Department of Internal Medicine, Herlev-Gentofte Hospital, Hellerup, Denmark; and CHIP & PERSIMUNE, Rigshospitalet and University of Copenhagen, Copenhagen, Denmark
Peter Laszlo Kanizsai: University of Pécs, Clinical Centre, Pécs, Hungary. https://orcid.org/0000-0001-7896-2857
Andrea Lay Hoon Kwa: Singapore General Hospital, Singapore, Singapore; Emerging Infectious Diseases Program, Duke-National University of Singapore Medical School, Singapore, Singapore
Stefan Krueger: Florence-Nightingale-Krankenhaus, Kaiserswerther Diakonie, Düsseldorf, Germany; and Clinic for Cardiology, Pneumology and Angiology, University Hospital Düsseldorf, Düsseldorf, Germany
Charles-Edouard Luyt: Service de Médecine Intensive Réanimation, Institut de Cardiologie, Groupe Hospitalier Pitié-Salpêtrière, Assistance Publique-Hôpitaux de Paris, Paris, France
Michael Oppert: Klinik für Notfall- und Internistische Intensivmedizin, Klinikum Ernst von Bergmann, Potsdam, Germany
Mario Plebani: Azienda Ospedaliera-Universitata di Padova, Padua, Italy. https://orcid.org/0000-0002-0270-1711
Sergey A. Shlyapnikov: Severe Sepsis Center, Scientific Research Institute of Emergency, St. Petersburg, Russian Federation; and North-West University-Mechnikov, St. Petersburg, Russian Federation
Giulio Toccafondi: Department for Health of the Tuscany Region, Clinical Risk Management and Patient Safety Centre of Tuscany Region, Florence, Italy
Jennifer Townsend: The Johns Hopkins University School of Medicine, Baltimore, MD, USA
Tobias Welte: University of Hannover, Hannover Medical School, Hannover, Germany; and Member of the German Center of Lung Research
Kordo Saeed: Department of Microbiology, Hampshire Hospitals NHS Foundation Trust, Winchester and Basingstoke, UK; and University of Southampton, School of Medicine, Southampton, UK

and probability of bacterial infection and reducing the fixed cut-offs to only one for mild to moderate and one for severe disease (0.25 µg/L and 0.5 µg/L, respectively). Further, guidance on interpretation of PCT results to initiate, withhold or discontinue ABx treatment was included. **Conclusions:** A combination of clinical patient assessment with PCT levels in well-defined ABS algorithms, in context with continuous education and regular feedback to all ABS stakeholders, has the potential to improve the diagnostic and therapeutic management of patients suspected of bacterial infection, thereby improving ABS effectiveness.

Keywords: ABx stewardship; bacterial infection; biomarker; procalcitonin; respiratory tract infections; sepsis.

Introduction

Increasing emergence of multi-drug resistant pathogens is considered to be one of the most urgent threats to global health and is directly linked to antibiotic overuse [1]. Patients presenting with symptoms of acute respiratory tract illnesses and systemic inflammatory response syndrome (SIRS) or suspected sepsis are often prescribed antibiotics by default, although more than 40% of respiratory infections are due to viruses [2, 3]. For example, in recent a large Center for Disease Control (CDC) study, 86% of patients presenting with pneumonia had a viral or no pathogen identified [3]. Despite the wider availability of rapid molecular viral diagnostics [4], antibiotics are frequently over-prescribed in patients with acute respiratory illnesses on a "just in case" basis, primarily due to physician concerns about bacterial coinfections and thus about the safety of withholding antibiotics. In addition, physicians often use prolonged antibiotic courses because there is a lack of clinical parameters ultimately proving resolution of illness. Unnecessarily long treatment durations may further result from the use of fixed antibiotic regimens as advocated by current International and local guidelines, although patients may show variable treatment responses.

A diagnostic marker providing information about the probability of bacterial infection and the resolution of disease therefore has high potential to improve the clinical assessment of patients, aid clinicians to improved antibiotic decision-making and potentially improve clinical outcomes. In this context, the use of the host-response marker procalcitonin (PCT) has gained much attention lately as adjunct to clinical judgement. Levels of PCT can help to discriminate bacterial from viral disease and have been shown to lead to decreased rates of antibiotic prescriptions safely and early discontinuation of therapy [5–7]. PCT expression is upregulated in epithelial cells which encounter bacterial pathogens and thus provides information about the risk for bacterial infection upon initial patient assessment [8]. Conversely, PCT expression is down-regulated in patients with viral infections [9]. PCT also decreases once the bacterial infection is controlled and thus provides information about the resolution of illness. Integration of PCT into the overall assessment may complement traditional clinical parameters and information from other diagnostic and microbiological tests and inform treatment decisions in patients with suspicion of bacterial infection [10].

Using a biomarker, such as PCT, may help to personalize treatment decisions. Such a strategy reduces antibiotic exposure and may also lower mortality by decreasing antibiotic associated side effects and by reducing the risk for treatment failure, as shown in recent trials [6, 7]. Moreover, several reports have found positive effects of antibiotic stewardship (ABS) protocols on outcomes in patients with sepsis, with current sepsis guidelines recommending to implement strategies to reduce antibiotic exposure [11–13]. Knowledge of PCT kinetics also provides prognostic information which may influence decisions to obtain further samples for diagnostic testing or pursue other therapeutic strategies and the timing of patient discharge [14]. Based on the current body of evidence, the US Food and Drug Administration (FDA) recently approved the use of PCT testing to guide antibiotic use in the context of acute respiratory illnesses and sepsis in the US.

Still, one barrier to the more wide-spread routine use of PCT is the lack of clarity regarding the clinical algorithm because previous trials all used somewhat different PCT protocols depending on clinical setting (primary care settings, emergency departments [ED] and intensive care units [ICU]) and type of infection e.g. community-acquired pneumonia (CAP), bronchitis, chronic obstructive pulmonary disease (COPD) or asthma exacerbation, sepsis and post-operative sepsis [8]. Algorithm recommendations differed in regard to timing of follow-up PCT measurement and specific treatment recommendation. The several PCT cut-off points used for the recommendation to discontinue antibiotics further contributed to complexity of PCT algorithm adherence (range of cut-offs for antibiotic discontinuation as ≤0.25/≤0.1 µg/L in ED and medical ward patients; ≤0.5/≤0.25 µg/L in ICU patients; reduction by ≥80% from peak levels in sepsis patients). Additionally, there is a lack of guidance on how to best integrate PCT test results into the clinical management of patients and decision-making for antibiotic therapy. Thus, deriving a consensus algorithm for use in patients with suspicion of bacterial infection which considers these aspects may improve the effective and safe use of PCT in routine clinical settings.

The objective of the international experts consensus meeting was therefore to close this gap, discuss the optimal use of PCT in clinical routine, including prerequisites for implementation into clinical protocols and work flow and to find a consensus on these aspects.

Materials and methods

The consensus process took place during a 1-day workshop in Berlin in late September 2018. The consensus was developed by a multidisciplinary team of 19 experts on PCT use in clinical practice, from 12 countries mirroring the different functional stakeholders in hospital ABS programs, such as critical care medicine (both medical and surgical intensive care), emergency medicine, respiratory medicine, clinical microbiology and infectious diseases, pharmacy, patient safety and laboratory medicine (see Table 1).

Consensus process

The expert group reviewed the current evidence from interventional trials on PCT-guided ABS and discussed the different approaches and algorithms that were used, including those that did not lead to reduced antibiotic exposure. The experts also discussed the clinical evidence for different patient populations such as primary care [15], ED [16], ICU [7, 17] or geriatrics and exchanged practical experience from own experience in routine clinical practice. In addition, experience on the process and the impact of clinical implementation was shared and discussed. Based on the discussions, three modified PCT algorithms were proposed for patients with mild, moderate and severe illness.

The controversial issues were openly discussed, debated and the algorithms were further edited during several feedback rounds by incorporating adjustments until consensus was found. All delegates who attended the meeting then voted to: 1) agree, 2) disagree or 3) abstain, on each algorithm on the same day. For the voting a modified Delphi process was used [18].

Results

The experts voted on algorithms 1, 2, 3 with unanimous agreement during voting on all three final algorithms (Figures 1–3).

PCT algorithms used in clinical trials on ABS in respiratory infections

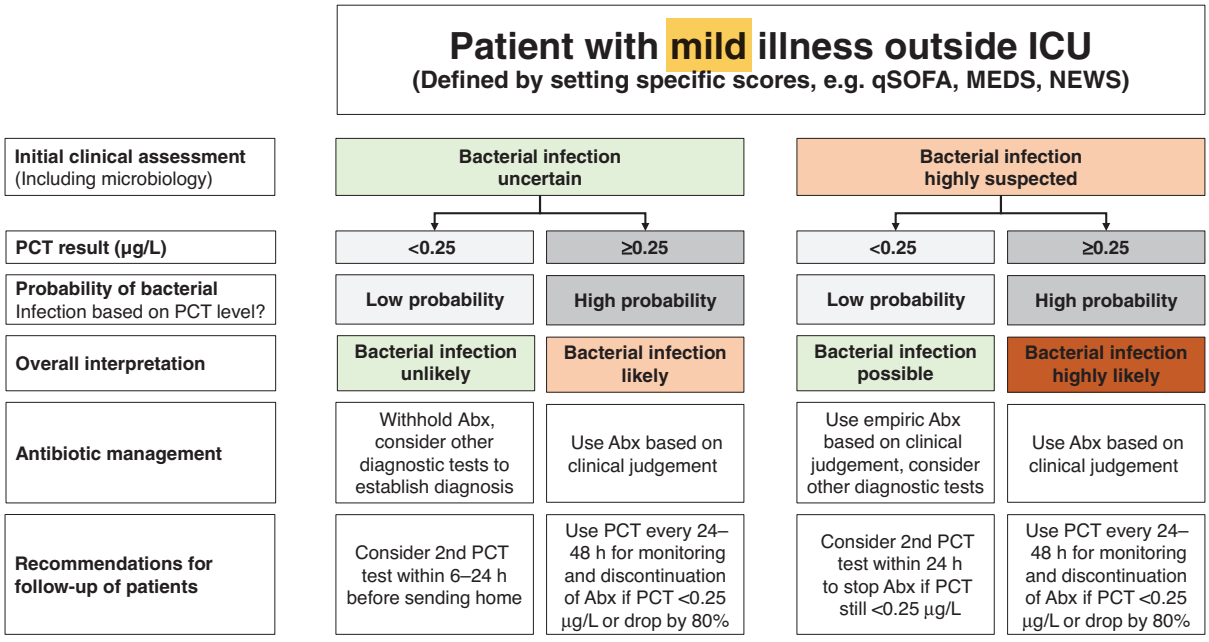
The concept of PCT-guided ABS was first tested in ED patients with infection of the lower respiratory tract [19]. Considering that PCT remains low (undetected) in viral infection and increases in bacterial infection, the study algorithm recommended very strongly or strongly against the use of antibiotics if PCT levels were <0.1 µg/L or <0.25 µg/L, respectively. The algorithm also included some overruling criteria, so patients at very high risk would still be treated empirically despite low PCT levels. Accordingly, a two-level recommendation was given also for the initiation of antibiotic treatment for patients with PCT higher than 0.25 µg/L (antibiotic recommended) and PCT higher than 0.5 µg/L (antibiotic strongly recommended). The study demonstrated significant reduction in antibiotic prescription rates, particularly in patients with bronchitis and COPD exacerbation.

Later studies not only investigated PCT for the initiation of empirical antibiotic therapy, but also used PCT to monitor the response to therapy and to decide on discontinuation of antibiotic therapy on an individual basis [19, 20]. The drop of PCT below 0.25 µg/L or by at least >80%–90% from the peak was used as stopping rule thresholds. This approach further decreased antibiotic exposure by shortening the duration of therapy, particularly in patients with CAP. Subsequently a large Swiss-wide, randomized, non-inferiority trial found this approach to be highly effective in reducing antibiotic exposure by more than 3 days with no increase in the risk for adverse outcome [16, 21].

Today, several similar trials have been conducted in different countries and different clinical settings (i.e. from primary care to emergency departments and medical wards, to intensive care). A recent meta-analysis including individual patient data from 6708 patients with different types and severities of respiratory infections from 26 randomized-controlled trials performed in 12 different countries investigated the effects of PCT-guided antibiotic decision making in the context of respiratory infections [22, 23] compared to aggregate data meta-analysis, patient-level data meta-analysis permitted standardization of outcome definitions and subgroup analyses by type of infection and clinical setting. The study showed that PCT use in the setting of respiratory infection reduces antibiotic exposure (initiation of antibiotics from 86% to 72% and a reduction in overall exposure from 8.1 days to 5.7 days), side effects from antibiotics (decreased from 22.1% to 16.3%) and significantly reduced mortality by 14% (from 10% to 8.6%). Results were consistent for the different clinical settings

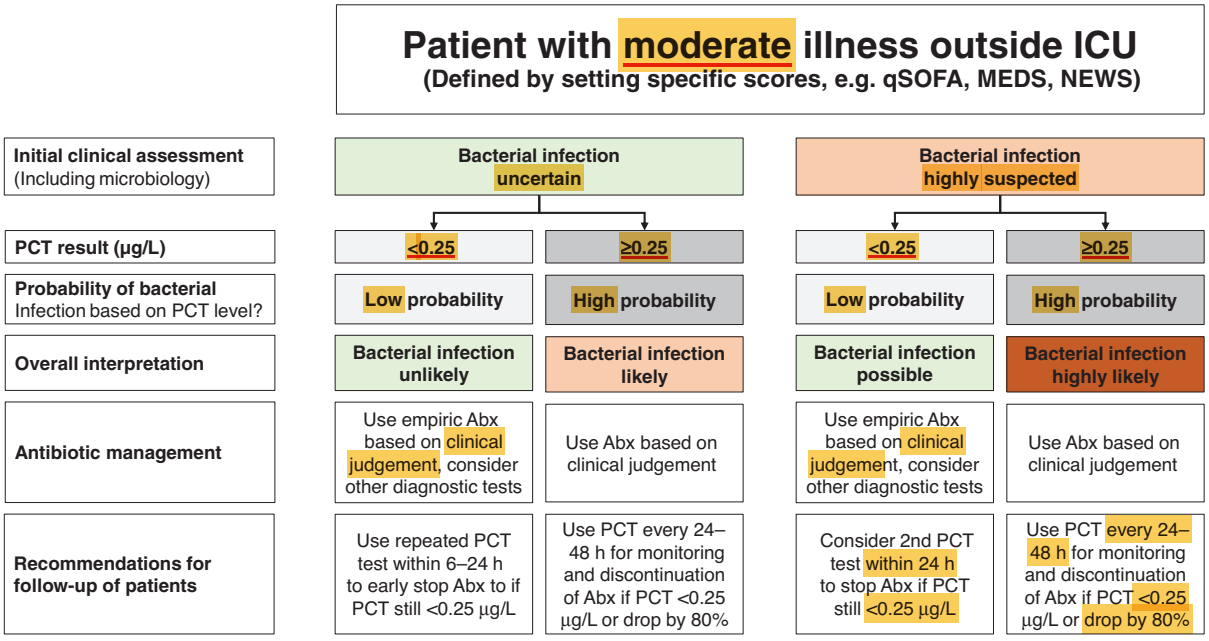
Table 1: List of participating experts.

Name	Affiliation	Field of expertise
Albertus Beishuizen	Intensive Care Center, Medisch Spectrum Twente, Enschede, The Netherlands	Intensive Care Medicine
Michael Richard Broyles	Clinical Pharmacy and Laboratory Services, Five Rivers Medical Center, Pocahontas, AZ, USA	Clinical Pharmacy and Laboratory Medicine
Ricard Ferrer	Intensive Care Department, Hospital Universitari Vall d'Hebron, Barcelona, Spain	Intensive Care Medicine, Severe Infections and Sepsis
Gaetan Gavazzi	Centre Hospitalier Universitaire Grenoble Aples (CHUGA), Grenoble, France	Geriatrics, Internal Medicine
Eric Howard Gluck	Critical Care Services, Swedish Covenant Hospital, Chicago, IL, USA	Intensive Care Medicine
Juan González del Castillo	Emergency Department, Hospital Clinico San Carlos, Madrid, Spain	Emergency Medicine, Infectious Diseases
Jens-Ulrik Jensen	Respiratoy Medicine Section, Herlev-Gentofte Hospital, Herlev, Denmark CHIP & PERSIMUNE, Rigshospitalet and University of Copenhagen, Copenhagen, Denmark	Pneumology, Microbiology
Peter Lazslo Kaniszai	Emergency Department, Semmelweis University Clinical Center, Budapest, Hungary	Emergency Medicine
Andrea Lay Hoon Kwa	Department of Pharmacy, Singapore General Hospital, Singapore; Department of Pharmacy, Faculty of Science, National University of Singapore; Department of Emerging Infectious Diseases, Duke-NUS Graduate Medical School	Pharmacotherapy, Infectious Diseases, Antimicrobial Stewardship
Stefan Krüger	Pneumology Department, Florence-Nightingale-Krankenhaus, Kaiserswerther Diakonie, Düsseldorf, Germany; Clinic for Cardiology, Pneumology and Angiology, University Hospital Düsseldorf, Germany	Pneumology
Charles-Edouard Luyt	Service de Médecine Intensive Réanimation, Institut de Cardiologie, Groupe Hospitalier Pitié–Salpêtrière, Assistance Publique–Hôpitaux de Paris, Paris, France; and Sorbonne Universités, UPMC Université Paris 06, INSERM, UMRS_1166-ICAN Institute of Cardiometabolism and Nutrition, Paris, France	Intensive Care Medicine, Infectious Diseases
Michael Oppert	Emergency and Intensive Care Department, Klinikum Ernst von Bergmann, Potsdam, Germany	Emergency and Intensive Care Medicine
Mario Plebani	Laboratory Medicine Department, Azienda Ospedaliera-Università di Padova, Padua, Italy	Laboratory Medicine
Kordo Saeed	Department of Microbiology, Hampshire Hospitals NHS Foundation Trust, Winchester and Basingstoke, UK; University of Southampton, School of Medicine, Southampton, UK	Clinical Microbiology and Infection
Philipp Schuetz	Department of Internal Medicine, Kantonsspital Aarau, Switzerland; University of Basel, Switzerland	Internal Medicine, Emergency Medicine Clinical trials
Sergey Alekseyevich. Shlyapnikov	Severe Sepsis Center, Scientific Research Institute of Emergency, St. Petersburg, Russian Federation; Surgical Infections Department of North-West Medical University-Mechnikov, St. Petersburg, Russian Federation	Intensive Care Medicine, Surgical Infections
Giulio Toccafondi	Clinical Risk Management and Patient Safety Centre of Tuscany Region, Florence, Italy	Patient Safety, Quality Improvement Sepsis
Jennifer Townsend	Infectious Disease Department, The Johns Hopkins University School of Medicine, Baltimore, MD, USA	Infectious Diseases, Antibiotic Stewardship
Tobias Welte	Department of Respiratory Medicine, Hannover Medical School, Hannover, Germany	Pneumology, Infectious Diseases, Intensive Care Medicine



* Caution in patients with immuno-suppression (including HIV), CF, pancreatitis, trauma, pregnancy, high volume transfusion, malaria; PCT-guided stewardship should not be applied to patients with chronic infections (e.g. abscess, osteomyelitis, endocarditis)

Figure 1: PCT use in patients with mild illness outside the ICU.

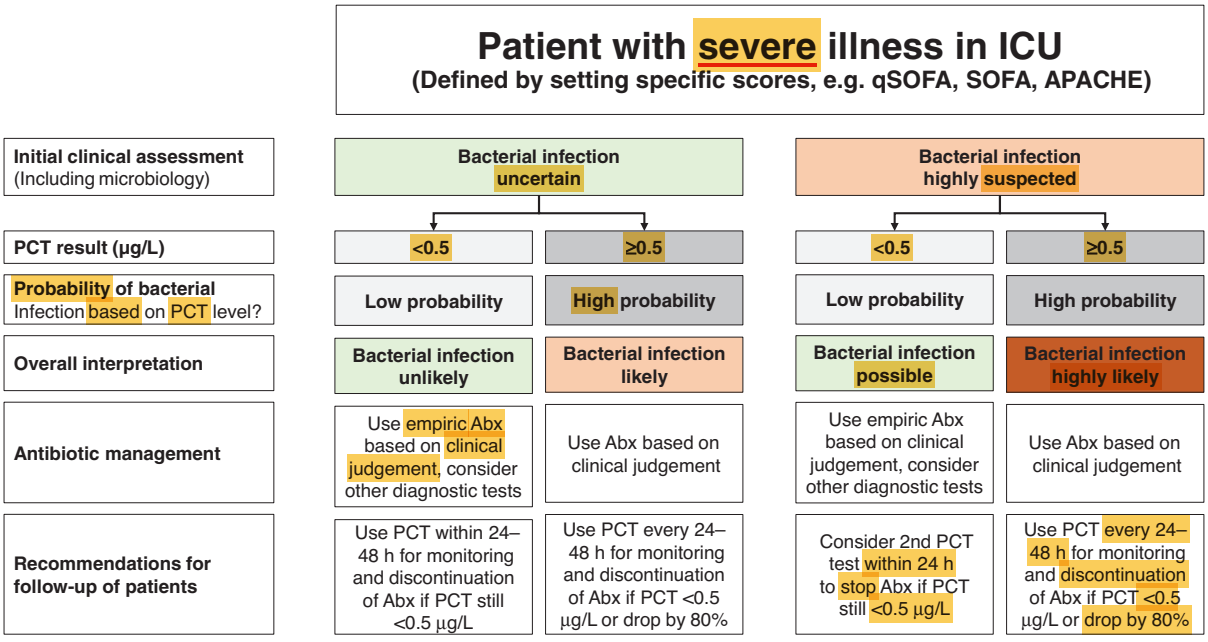


* Caution in patients with immuno-suppression (including HIV), CF, pancreatitis, trauma, pregnancy, high volume transfusion, malaria; PCT-guided stewardship should not be applied to patients with chronic infections (e.g. abscess, osteomyelitis, endocarditis)

Figure 2: PCT use in patients with moderate illness outside the ICU.

(i.e. primary care, ED or critical care) and types of infections (pneumonia, bronchitis, COPD exacerbation).

The secondary analysis of PCT cut-offs used in the trials revealed that the main cut-offs used for initiation of antibiotics were adapted to the severity of the patient. Thus, for patients with mild or moderate disease treated in primary care or the ED, a PCT cut-off of 0.25 µg/L was used, whereas for patients with severe disease (e.g. those



* Caution in patients with immuno-suppression (including HIV), CF, pancreatitis, trauma, pregnancy, high volume transfusion, malaria; PCT-guided stewardship should not be applied to patients with chronic infections (e.g. abscess, osteomyelitis, endocarditis)

Figure 3: PCT use in patients with severe illness in the ICU.

requiring ICU admission) cut-offs of 0.5 µg/L were mainly used [24]. Similarly, for antibiotic discontinuation a PCT decrease below 0.25 µg/L or 0.5 µg/L were used for mild/moderate or severe illness, respectively, or when PCT showed a drop by ≥80% from the peak [8].

Trials and algorithms for PCT-guided ABS in sepsis

The mentioned concept of using PCT to individualize antibiotic therapy is also appealing in patients with sepsis in the ICU. Yet, initially, there were concerns about safety of this approach in the sickest patients as too short courses of antibiotics could possibly result in the recurrence of infection and higher mortality. The first proof-of-concept study looking at ICU patients with sepsis [14] found a reduction of antibiotics exposure without obvious negative impact on outcome. The trial used the higher PCT cut-offs for sepsis patients (0.5–1 µg/L) and also used the PCT kinetics (decline by >90% from the peak level) to recommend cessation of antibiotic. This concept was later validated in the multicenter, non-inferiority PRORATA trial [17], where PCT use was efficient and safe when used in sepsis patients. Because sepsis patients in ICU have an *a priori* high risk and time to treatment is crucial, PCT was used mainly for early discontinuation of treatment, but not for guiding empiric treatment [25]. This concept was later also tested in the Stop Antibiotics on guidance of Procalcitonin (SAPS) study where antibiotics were started in all patients with clinical suspicion of sepsis, but were recommended to be discontinued when either the PCT level declined by at least 80% from the peak level and/or when the PCT fell below 0.5 µg/L. Compared to standard of care, the use of PCT resulted in lower antibiotic exposure (antibiotic duration reduced from 7 days to 5 days) and in improved survival (6.1% better survival at 1 year) [7].

A recent patient-level meta-analysis of 11 trials on PCT-guided ABS in critically ill patients with sepsis [26] also found that mortality was significantly lower in the 2252 PCT-guided patients compared with the 2230 control group patients (21.1% vs. 23.7%). This finding was consistent in subgroup analyses stratified by type of infection (respiratory, urinary tract, abdominal, skin or central nervous system), sepsis-3 definition or severity of sepsis (defined by either the sequential organ failure assessment [SOFA] score, the presence of septic shock or renal failure, or the need for vasopressor or ventilatory support). The study also revealed that in sepsis patients, PCT use results in earlier discontinuation of antibiotics with a reduction in treatment duration from 10.4 to 9.3 days, with stronger effects seen in patients with less severe sepsis and those with respiratory infections. A further meta-analysis also revealed, that survival benefit was associated with a PCT algorithm for cessation of antibiotics only, whereas for ICU patients a PCT algorithm for antibiotic initiation or a

mixed approach did not reduce mortality [27]. Finally, a meta-analysis focusing on bacteremic patients with positive cultures also found a significant effect of PCT use on antibiotic usage with no evidence for adverse clinical outcomes despite shorter antibiotic durations [28].

Learnings from 'negative' studies

Beside the studies mentioned already which showed efficacy and safety of PCT guided ABS, there have also been some studies with negative results.

First, the PASS trial was an interventional study with the rational to improve survival by early antibiotic intervention and escalation any time when PCT is rising. However, although diagnostic and therapeutic measures were escalated in the PCT-guided intervention group, there was no outcome benefit. The lack of effect may be explained by an outbalance of the benefits of earlier treatment with side effects due to escalated antibiotic treatment [29, 30].

Second, the recently published multicenter ProACT trial, which studied the effects of PCT in lower respiratory tract infection (LRTI) in US hospitals, [31] failed to demonstrate any benefit of PCT guidance despite the fact that a similar algorithm was applied as already successfully used in European studies [24]. Several factors may have contributed to this result. Inclusion of patients with very low severity of disease and low likelihood of bacterial infection (extremely low median PCT values, primarily mild CAP, high number of asthma and bronchitis patients), poor adherence to algorithms and study protocols, both for patients admitted and those discharged to primary care, lack of physician inexperience with PCT, and very short overall antibiotic use in both the control and PCT arms [24]. The low experience to PCT use of investigators and a low inclusion rate for the intervention arm (26–111 patients in 2.5 year/center) provided the clinicians with little opportunity to get practical experience with the PCT concept and develop trust in the approach.

Third, the recently published HiTEMP study, investigated the value of PCT to guide antibiotic therapy in ED patients with fever in regard to rates of antibiotic prescription, clinical outcomes and costs [32]. Investigators did not find any added benefit of PCT, demonstrating that while PCT-guided therapy was non-inferior in terms of safety, it did not reduce the prescription of antibiotics. There are several important lessons learned also from this study, which may help to better understand the use of PCT in clinical practice and should be considered when designing future trials [33]. The trial included unselected patients with fever including patients with no diagnostic uncertainty (e.g. patients with skin and soft tissue, intra-abdominal and urinary tract infections). In such patients, PCT has little potential to add value to clinical judgement, as the decision to initiate antibiotics has already been made. The investigators used only a single PCT measurement upon ED admission with a high PCT cut-off (>0.5 µg/L). As the default position in patients with a high pre-test probability for bacterial infection is generally to prescribe antibiotics, a high negative predictive value is mandatory, and thus lower PCT levels <0.25 µg/L or <0.1 µg/L may have been preferable to allow safe withholding of antibiotics. While most previous trials relied on repeated PCT measurements for early discontinuation of therapy, this trial only used one single measurement [24]. Adherence to the study PCT protocol was low with half of patients receiving antibiotics despite low PCT levels illustrating again the need for provider education and feedback when implementing PCT-guided care.

Fourth, the BPCTrea study investigated a PCT algorithm to guide antibiotic treatment for COPD patients admitted to the ICU for ventilator support [34]. Although the 28-day mortality was similar for both the PCT and standard of care group, a higher 3-month mortality was observed for the PCT group. The increase in mortality was most prominent in patients who did not immediately get antibiotic treatment based on the protocol. For patients who received antibiotics immediately the outcome of the PCT group was non-inferior to the standard of care group. These data support the recommendations that in high-risk patients with suspected bacterial infection antibiotic treatment should be started immediately to improve safety of PCT use.

Real world data on clinical integration into ABS programs

It has been shown that the successful implementation of ABS programs requires a holistic approach across the hospital, with education of all stakeholders as a key element. This educational process ideally includes regular auditing, measuring of the success based on clear outcome parameters and feedback to all involved parties to increase trust, confidence and eventually adherence, and achieve the desired effect to reduce antibiotic use and thus antibiotic resistance [35].

This holds true also for an integration of PCT to guide the judicious use of antibiotics in patients suspected of bacterial infection. The low adherence rates observed in some interventional studies such as proACT [31], reflect missing experience with PCT and its interpretation in

the clinical context as well as lack of trust in the efficacy and safety of this approach. In contrast, successful, education-based clinical integration of PCT-guided ABS led to reduced use of antibiotics and reduced resistance rates and was associated with improved clinical outcomes like lower re-admission rates, less *Clostridium difficile* infections and shorter length of stay, without any negative impact on survival [35]. Thus, education may result in increased physician confidence and, when combined with better communication with patients on the risks associated with inappropriate antibiotic therapy, lead to improved algorithm adherence and decreased antibiotic overuse [10, 36].

The results of both, the clinical trials as well as the implementation studies, support the view that the PCT cut-offs and algorithm need to be adapted by the severity and clinical risk of the patient to secure effective and safe use and that education, auditing and continuous feedback are required to develop trust and increase adherence to PCT algorithms.

Discussion

Derivation of a consensus algorithm for PCT use

Based on the analysis of trials, the group agreed that for optimal use, the PCT levels should be put into the context of the clinical assessment in regard to severity of illness and probability of bacterial infection to make reasonable recommendations. We thus derived three different algorithms based on severity of illness (i.e. mild, moderate and severe illness) and stratified patients according to the probability of bacterial infection (uncertainty vs. bacterial infection highly suspected) (Figures 1–3). PCT should then be added to the assessment of patients with PCT cut-offs of <0.25 µg/L in non-ICU patients and <0.5 µg/L in ICU patients indicating a low likelihood of bacterial infection. While in patients with mild disease and low probability of bacterial infection a low PCT level should advise physicians against the use of antibiotic, for patients with moderate or high severity, empiric therapy may still be used with retesting of PCT after 6–24 h to re-evaluate the need for antibiotic therapy. Further, for patients where empiric antibiotic therapy was started, serial testing of PCT levels is recommended to monitor the response to antibiotic therapy and control of infection. A drop in PCT from the peak by >80% and/or fall below the cut-off was taken as a strong indicator for resolution of illness and earlier discontinuation of antibiotics is recommended when a patient is clinically stable.

Figure 1 shows the proposed algorithm for patients with mild disease (e.g. patients seen in primary care or patients in the ED with bronchitis). The initial step is to evaluate the pre-test probability for a bacterial infection based on the clinical assessment, radiographic assessment and, if indicated, microbiological work-up. In patients with mild disease and diagnostic uncertainty regarding bacterial infection, a low PCT level <0.25 µg/L effectively rules out bacterial infection and there is no benefit from antibiotic treatment. Yet, additional diagnostic tests may be warranted to establish the final (non-infectious) diagnosis. If there is concern that the initial value was negative due to early stages of infection, a second PCT test can be considered within 6–24 h before discharging the patient. If PCT is elevated >0.25 µg/L, the presence of bacterial infection becomes more likely and, if appropriate in the overall clinical context, antibiotic treatment should be initiated. PCT should be re-measured every 24–48 h to discontinue antibiotics when the level falls below 0.25 µg/L or declines by at least 80% versus peak.

In patients with mild disease and highly suspected bacterial infection based on the clinical, radiological and microbiological assessment, a PCT <0.25 µg/L still argues against bacterial infection, but antibiotics may be started based on clinical judgement. Again, the indication for antibiotic use should be re-evaluated when after 24 h with a second PCT test and results of additional microbiological tests. If PCT >0.25 µg/L a bacterial infection is very likely and empiric antibiotics should be started immediately. The PCT level should be re-tested every 24–48 h to assess response to therapy and control of infectious focus. With PCT decline by >80% vs. peak value or fall <0.25 µg/L, the antibiotics can be discontinued if the patient is clinically stable.

Figure 2 shows the proposed algorithm for moderate severity of disease as assessed by clinical scores. The use of PCT in this situation is similar as for mild disease, yet empiric antibiotic treatment in patients with diagnostic uncertainty may still be advised despite low PCT levels to increase safety and adherence of physicians.

Figure 3 shows the proposed algorithm for high severity patients in the ICU with a recommendation for antibiotic treatment in all patients including those with low PCT. Yet, for patients with PCT <0.5 µg/L, further diagnostic testing should be initiated to look for non-bacterial causes of the clinical symptoms or fungal infections. Repeated testing every 24–48 h is recommended to decide on antibiotic discontinuation when PCT levels drop to <0.5 µg/L or by at least 80% from the peak.

For all proposed algorithms, caution was recommended for patients with immuno-suppression (including HIV), autoimmune diseases, cystic fibrosis (CF), pancreatitis, trauma, pregnancy, high volume transfusion and malaria. Also, the algorithm should be used in acute infections, but not in patients with chronic infections (e.g. abscess, osteomyelitis, endocarditis). If patients are pretreated with antibiotics [37], PCT levels may also be low leading to a potential underestimation of infectious complications. For measurements of PCT it should be secured that only high-sensitive PCT assays with sufficient precision in the relevant cut-off ranges are used for optimal safety. Most trials today have used the highly sensitive KRYPTOR immunoassay (BRAHMS, Hennigsdorf, Germany) which has a functional sensitivity of 0.06 µg/L [38, 39]. Thus, the analytical sensitivity, as expressed by the functional sensitivity should be in this range to assure the accuracy of measurement at low PCT levels. In addition, the validation of the assay should assure that the accuracy (bias and imprecision) should be appropriate [34, 35].

Conclusions and outlook

As a marker with both diagnostic and prognostic impact, PCT has demonstrated promising results to tailor antibiotic treatment to the individual patient, thereby reducing antibiotic exposure and improving clinical outcomes for patients with acute respiratory infections and sepsis [6, 23, 40, 41]. Respective clinical algorithms have been validated in interventional trials demonstrating the efficacy and safety of PCT-guided ABS. Adherence to the PCT algorithm was frequently shown to be a challenging issue both in trials and in real life, which is due to low experience and thus insecurity about interpretation and follow-up measures. Furthermore, the evidence for infections other than LRTI or sepsis is still sparse, and few trials have included patients with immunosuppression, therefore limiting the generalization of the findings for these patients [42]. These aspects were considered in the refinement of the algorithms, which is now based on clinical assessment of disease severity and probability of bacterial infection and using only one severity-specific PCT cut-off to rerate the infection probability.

Consensus on clinical algorithms are often developed by the respective specialist groups of scientific societies for specific indications. A strength of our approach is that this international expert group consisted of specialists that represent the different functions involved in ABS programs in a hospital and that all have profound scientific, clinical and practical experience with PCT (Table 1). Consensus on the refined algorithms were developed based on a thorough analysis and discussion of the currently available clinical evidence and the different PCT algorithms used, including critical appraisal of studies with 'negative' outcome as well as own practical experience from different specialists' points of view involved in ABS. Based on this, the challenges of the practical use of PCT in clinical routine and adherence to current protocols were identified and discussed to adjust the algorithms for ABS and provide a clear guidance on the process, interpretation of PCT result and follow-up measures. The resulting modified algorithms provide a more unified approach, providing guidance for use in patients with mild-to-moderate or severe disease, independently of indication or department which should facilitate adoption across departments. Our recommendation was to use PCT for initiation of antibiotics mainly in low risk patients with uncertain bacterial infection, and for other patients to monitor PCT to stop antibiotic treatment early. In higher risk patients, the algorithm focuses on early stop of treatment in the case of low PCT and no evidence for bacterial infection. The specification of one cut-off for mild-to-moderately severe and severe patients (0.25 µg/L and 0.5 µg/L, respectively) facilitates the ease of practical implementation.

Still, there are residual limitations to our approach. Although the consensus algorithms are based on the clinical evidence and cut-offs and algorithms principally have been proven for efficacy and safety in interventional trials, the proposed algorithm modification is based on expert opinion of this group and the postulated advantage for practical implementation should still be demonstrated in clinical practice.

The herein proposed modified algorithm should enable easier clinical adoption across departments as it includes also recommendation for the follow-up measures. Still, experience with PCT and education about its correct use remain essential prerequisites to leverage the benefits of PCT-guided treatment [35]. A broader knowledge of real world data, e.g. from registries, would be of interest to assess clinical and health economic impact in the different countries. Additional research should consider both less understood indications or patient groups as well as patients in primary care and/or nursing homes where a major proportions of antibiotics are prescribed.

In conclusion, integration of PCT into ABS algorithms has the potential to improve the diagnostic and therapeutic management of patients presenting with respiratory

illnesses and sepsis, and holds great promise to mitigate the global bacterial resistance crisis and move from a default position of standardized care to more personalized treatment decisions.

Author contributions: All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.
Research funding: The entire project received an unrestricted grant by Thermo Fisher Scientific. P. Schuetz reported receiving support from BRAHMS GmbH and Biomérieux to attend meetings and fulfilling speaking engagements. C.E. Luyt reported receiving support from Bayer, Biomérieux and MSD for lecture fees. K. Saeed reported receiving research and educational grants and support from Thermo Fisher Scientific.
Employment or leadership: None declared.
Honorarium: None declared.
Competing interests: The funding organization(s) played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the report for publication.

References

1. Jee Y, Carlson J, Rafai E, Musonda K, Huong TT, Daza P, et al. Antimicrobial resistance: a threat to global health. Lancet Infect Dis 2018;18:939–40.
2. Musher DM, Thorner AR. Community-acquired pneumonia. N Engl J Med 2014;371:1619–28.
3. Jain S, Self WH, Wunderink RG, Fakhran S, Balk R, Bramley AM, et al. Community-acquired pneumonia requiring hospitalization among U.S. adults. N Engl J Med 2015;373:415–27.
4. Mitsuma SF, Mansour MK, Dekker JP, Kim J, Rahman MZ, Tweed-Kent A, et al. Promising new assays and technologies for the diagnosis and management of infectious diseases. Clin Infect Dis 2013;56:996–1002.
5. Schuetz P, Raad I, Amin DN. Using procalcitonin-guided algorithms to improve antimicrobial therapy in ICU patients with respiratory infections and sepsis. Curr Opin Crit Care 2013;19:453–60.
6. Schuetz P, Wirz Y, Sager R, Christ-Crain M, Stolz D, Tamm M, et al. Effect of procalcitonin-guided antibiotic treatment on mortality in acute respiratory infections: a patient level meta-analysis. Lancet Infect Dis 2018;18:95–107.
7. de Jong E, van Oers JA, Beishuizen A, Vos P, Vermeijden WJ, Haas LE, et al. Efficacy and safety of procalcitonin guidance in reducing the duration of antibiotic treatment in critically ill patients: a randomised, controlled, open-label trial. Lancet Infect Dis 2016;16:819–27.
8. Schuetz P, Bolliger R, Merker M, Christ-Crain M, Stolz D, Tamm M, et al. Procalcitonin-guided antibiotic therapy algorithms for different types of acute respiratory infections based on previous trials. Expert Rev Anti Infect Ther 2018;16:555–64.
9. Linscheid P, Seboek D, Nylen ES, Langer I, Schlatter M, Becker KL, et al. In vitro and in vivo calcitonin I gene expression in parenchymal cells: a novel product of human adipose tissue. Endocrinology 2003;144:5578–84.
10. Sager R, Kutz A, Mueller B, Schuetz P. Procalcitonin-guided diagnosis and antibiotic stewardship revisited. BMC Med 2017;15:15.
11. Garnacho-Montero J, Gutierrez-Pizarraya A, Escoresca-Ortega A, Corcia-Palomo Y, Fernandez-Delgado E, Herrera-Melero I, et al. De-escalation of empirical therapy is associated with lower mortality in patients with severe sepsis and septic shock. Intensive Care Med 2014;40:32–40.
12. Schuetz P, Mueller B. Biomarker-guided de-escalation of empirical therapy is associated with lower risk for adverse outcomes. Intensive Care Med 2014;40:141.
13. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving sepsis campaign: International guidelines for management of sepsis and septic shock: 2016. Intensive Care Med 2017;43:304–77.
14. Nobre V, Harbarth S, Graf JD, Rohner P, Pugin J. Use of procalcitonin to shorten antibiotic treatment duration in septic patients: a randomized trial. Am J Respir Crit Care Med 2008;177:498–505.
15. Briel M, Schuetz P, Mueller B, Young J, Schild U, Nusbaumer C, et al. Procalcitonin-guided antibiotic use vs a standard approach for acute respiratory tract infections in primary care. Arch Intern Med 2008;168:2000–7; discussion 7–8.
16. Schuetz P, Christ-Crain M, Thomann R, Falconnier C, Wolbers M, Widmer I, et al. Effect of procalcitonin-based guidelines vs standard guidelines on antibiotic use in lower respiratory tract infections: the ProHOSP randomized controlled trial. J Am Med Assoc 2009;302:1059–66.
17. Bouadma L, Luyt CE, Tubach F, Cracco C, Alvarez A, Schwebel C, et al. Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial. Lancet 2010;375:463–74.
18. Memtsoudis SG, Hargett M, Russell LA, Parvizi J, Cats-Baril WL, Stundner O, et al. Consensus statement from the consensus conference on bilateral total knee arthroplasty group. Clin Orthop Relat Res 2013;471:2649–57.
19. Christ-Crain M, Jaccard-Stolz D, Bingisser R, Gencay MM, Huber PR, Tamm M, et al. Effect of procalcitonin-guided treatment on antibiotic use and outcome in lower respiratory tract infections: cluster-randomised, single-blinded intervention trial. Lancet 2004;363:600–7.
20. Stolz D, Christ-Crain M, Bingisser R, Leuppi J, Miedinger D, Muller C, et al. Antibiotic treatment of exacerbations of COPD: a randomized, controlled trial comparing procalcitonin-guidance with standard therapy. Chest 2007;131:9–19.
21. Schuetz P, Christ-Crain M, Albrich W, Zimmerli W, Mueller B, Pro HS. Guidance of antibiotic therapy with procalcitonin in lower respiratory tract infections: insights into the ProHOSP study. Virulence 2010;1:88–92.
22. Schuetz P, Wirz Y, Mueller B. Reassessment of a meta-analysis of procalcitonin-guided antibiotic therapy for lower respiratory tract infections – authors' reply. Lancet Infect Dis 2018;18:141.
23. Schuetz P, Wirz Y, Sager R, Christ-Crain M, Stolz D, Tamm M, et al. Procalcitonin to initiate or discontinue antibiotics in acute respiratory tract infections. Cochrane Database Syst Rev 2017;10:CD007498.
24. Schuetz P, Chiappa V, Briel M, Greenwald JL. Procalcitonin algorithms for antibiotic therapy decisions: a systematic review of

randomized controlled trials and recommendations for clinical algorithms. Arch Intern Med 2011;171:1322–31.
25. Ferrer R, Martin-Loeches I, Phillips G, Osborn TM, Townsend S, Dellinger RP, et al. Empiric antibiotic treatment reduces mortality in severe sepsis and septic shock from the first hour: results from a guideline-based performance improvement program. Crit Care Med 2014;42:1749–55.
26. Wirz Y, Meier MA, Bouadma L, Luyt CE, Wolff M, Chastre J, et al. Effect of procalcitonin-guided antibiotic treatment on clinical outcomes in intensive care unit patients with infection and sepsis patients: a patient-level meta-analysis of randomized trials. Crit Care 2018;22:191.
27. Lam SW, Bauer SR, Fowler R, Duggal A. Systematic review and meta-analysis of procalcitonin-guidance versus usual care for antimicrobial management in critically Ill patients: focus on subgroups based on antibiotic initiation, cessation, or mixed strategies. Crit Care Med 2018;46:684–90.
28. Meier MA, Branche A, Neeser OL, Wirz Y, Haubitz S, Bouadma L, et al. Procalcitonin-guided antibiotic treatment in patients with positive blood cultures: a patient-level meta-analysis of randomized trials. Clin Infect Dis 2018.
29. Jensen JU, Hein L, Lundgren B, Bestle MH, Mohr TT, Andersen MH, et al. Procalcitonin-guided interventions against infections to increase early appropriate antibiotics and improve survival in the intensive care unit: a randomized trial. Crit Care Med 2011;39:2048–58.
30. Jensen JU, Lundgren B, Hein L, Mohr T, Petersen PL, Andersen LH, et al. The procalcitonin and survival study (PASS) – a randomised multi-center investigator-initiated trial to investigate whether daily measurements biomarker procalcitonin and pro-active diagnostic and therapeutic responses to abnormal procalcitonin levels, can improve survival in intensive care unit patients. Calculated sample size (target population): 1000 patients. BMC Infect Dis 2008;8:91.
31. Huang DT, Yealy DM, Filbin MR, Brown AM, Chang CH, Doi Y, et al. Procalcitonin-guided use of antibiotics for lower respiratory tract infection. N Engl J Med 2018;379:236–49.
32. van der Does Y, Limper M, Jie KE, Schuit SCE, Jansen H, Pernot N, et al. Procalcitonin-guided antibiotic therapy in patients with fever in a general emergency department population: a multicentre non-inferiority randomized clinical trial (HiTEMP study). Clin Microbiol Infect 2018;24:1282–9.
33. Schuetz P, Falsey AR. Procalcitonin in patients with fever: one approach does not fit all. Clin Microbiol Infect 2018;24:1229–30.
34. Daubin C, Valette X, Thiolliere F, Mira JP, Hazera P, Annane D, et al. Procalcitonin algorithm to guide initial antibiotic therapy in acute exacerbations of COPD admitted to the ICU: a randomized multicenter study. Intensive Care Med 2018;44:428–37.
35. Broyles MR. Impact of procalcitonin-guided antibiotic management on antibiotic exposure and outcomes: real-world evidence. Open Forum Infect Dis 2017;4:ofx213.
36. Schuetz P, Aujesky D, Muller C, Muller B. Biomarker-guided personalised emergency medicine for all – hope for another hype? Swiss Med Wkly 2015;145:w14079.
37. Tessmer A, Welte T, Martus P, Schnoor M, Marre R, Suttorp N. Impact of intravenous {beta}-lactam/macrolide versus {beta}-lactam monotherapy on mortality in hospitalized patients with community-acquired pneumonia. J Antimicrob Chemother 2009;63:1025–33.
38. Schuetz P, Christ-Crain M, Wolbers M, Schild U, Thomann R, Falconnier C, et al. Procalcitonin guided antibiotic therapy and hospitalization in patients with lower respiratory tract infections: a prospective, multicenter, randomized controlled trial. BMC Health Serv Res 2007;7:102.
39. Schuetz P, Albrich W, Christ-Crain M, Chastre J, Mueller B. Procalcitonin for guidance of antibiotic therapy. Expert Rev Anti Infect Ther 2010;8:575–87.
40. Schuetz P, Balk R, Briel M, Kutz A, Christ-Crain M, Stolz D, et al. Economic evaluation of procalcitonin-guided antibiotic therapy in acute respiratory infections: a US health system perspective. Clin Chem Lab Med 2015;53:583–92.
41. Stojanovic I, Schneider JE, Wei L, Hong Z, Keane C, Schuetz P. Economic evaluation of procalcitonin-guided antibiotic therapy in acute respiratory infections: a Chinese hospital system perspective. Clin Chem Lab Med 2017;55:561–70.
42. Lima SS, Nobre V, de Castro Romanelli RM, Clemente WT, da Silva Bittencourt HN, Melo AC, et al. Procalcitonin-guided protocol is not useful to manage antibiotic therapy in febrile neutropenia: a randomized controlled trial. Ann Hematol 2016;95:1169–76.