

Opinion Paper

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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

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 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).

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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 $\leq 0.25/\leq 0.1$ $\mu\text{g/L}$ in ED and medical ward patients; $\leq 0.5/\leq 0.25$ $\mu\text{g/L}$ in ICU patients; reduction by $\geq 80\%$ 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 workflow 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

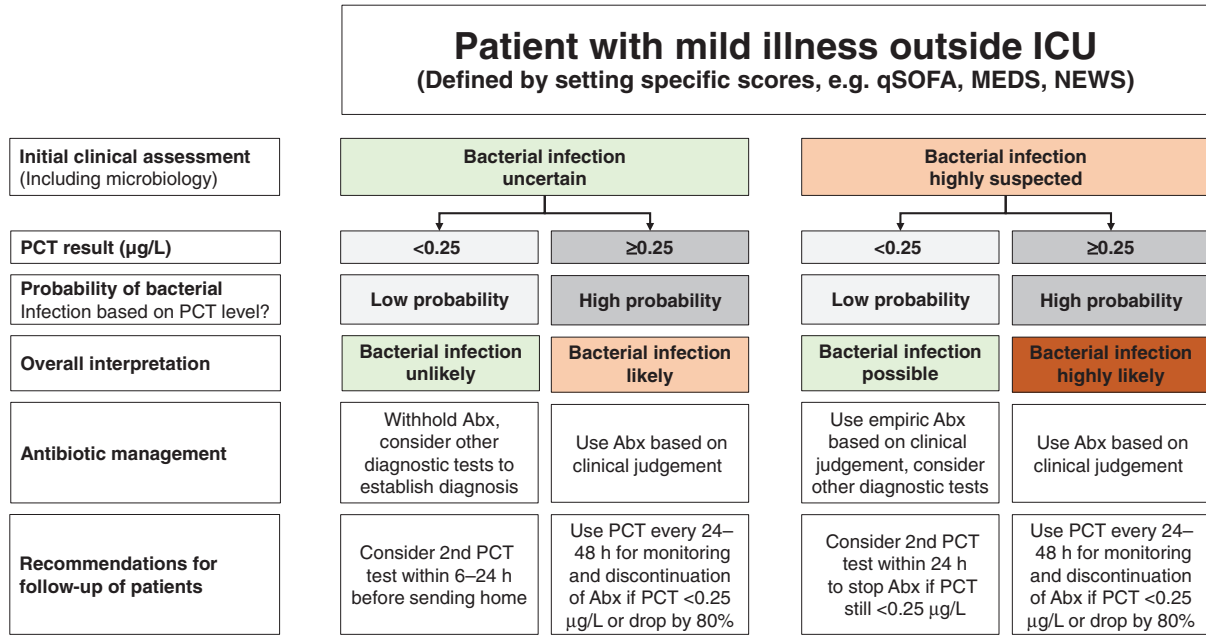
The concept of PCT-guided ABS was first tested in ED patients with infection of the lower respiratory tract [19]. Considering that PCT remains low (undetected) in viral infection and increases in bacterial infection, the study algorithm recommended very strongly or strongly against the use of antibiotics if PCT levels were $<0.1 \mu\text{g/L}$ or $<0.25 \mu\text{g/L}$, 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 $0.25 \mu\text{g/L}$ (antibiotic recommended) and PCT higher than $0.5 \mu\text{g/L}$ (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 $0.25 \mu\text{g/L}$ 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

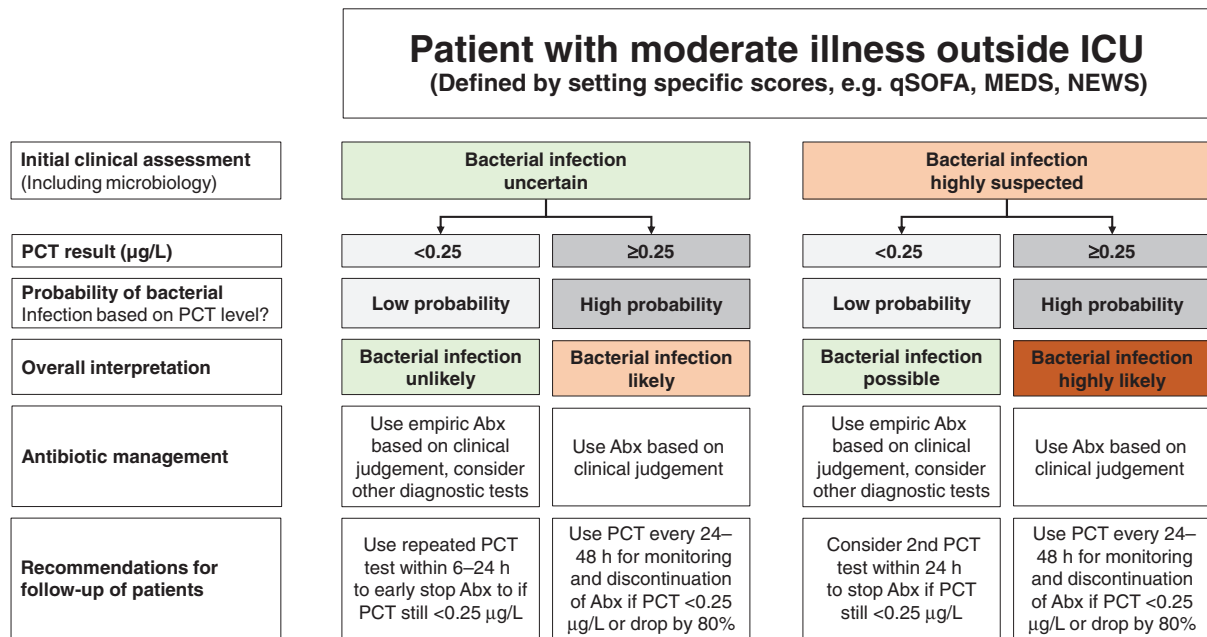
Table 1: List of participating experts.

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Albertus Beishuizen	Intensive Care Center, Medisch Spectrum Twente, Enschede, The Netherlands	Intensive Care Medicine
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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
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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.



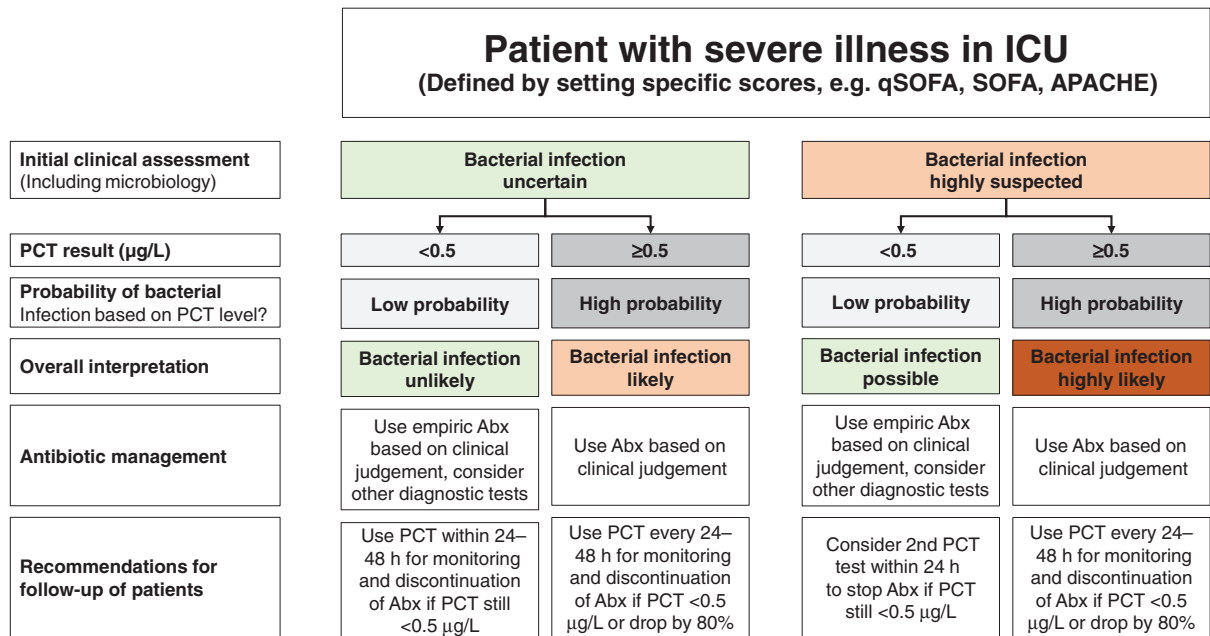
* Caution in patients with immuno-suppression (including HIV), CF, pancreatitis, trauma, pregnancy, high volume transfusion, malaria; PCT-guided stewardship should not be applied to patients with chronic infections (e.g. abscess, osteomyelitis, endocarditis)

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



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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 rationale 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 $\mu\text{g/L}$). 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 $\mu\text{g/L}$ or <0.1 $\mu\text{g/L}$ 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 $\mu\text{g/L}$ in non-ICU patients and <0.5 $\mu\text{g/L}$ 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 $\mu\text{g/L}$ 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 $\mu\text{g/L}$, 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 $\mu\text{g/L}$ 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 $\mu\text{g/L}$ 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 $\mu\text{g/L}$ 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 $\mu\text{g/L}$, 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 $\mu\text{g/L}$, 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 $\mu\text{g/L}$ 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.

Contributions and conflict of interest statement

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

- 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.
- Musher DM, Thorner AR. Community-acquired pneumonia. *N Engl J Med* 2014;371:1619–28.
- 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.
- 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.
- 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.
- 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.
- 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.
- 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.
- 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.
- Sager R, Kutz A, Mueller B, Schuetz P. Procalcitonin-guided diagnosis and antibiotic stewardship revisited. *BMC Med* 2017;15:15.
- Garnacho-Montero J, Gutierrez-Pizarraya A, Escosca-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.
- 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.
- 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.
- 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.
- 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.
- 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.
- 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.
- 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.
- 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.
- 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.
- 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.
- 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.
- 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.
- 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, Pernet 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, Suttrop 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.