Opinion Paper

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Procalcitonin (PCT)-guided antibiotic stewardship in Asia-Pacific countries: adaptation based on an expert consensus meeting

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Abstract

Introduction: Recently, an expert consensus on optimal use of procalcitonin (PCT)-guided antibiotic stewardship was published focusing mainly on Europe and the United States. However, for Asia-Pacific countries, recommendations may need adaptation due to differences in types of infections, available resources and standard of clinical care.

Methods: Practical experience with PCT-guided antibiotic stewardship was discussed among experts from different countries, reflecting on the applicability of the proposed Berlin consensus algorithms for Asia-Pacific. Using a Delphi process, the group reached consensus on two PCT algorithms for the critically ill and the non-critically ill patient populations.

Results: The group agreed that the existing evidence for PCT-guided antibiotic stewardship in patients with acute respiratory infections and sepsis is generally valid also for Asia-Pacific countries, in regard to proposed PCT cut-offs, emphasis on diagnosis, prognosis and antibiotic stewardship, overruling criteria and inevitable adaptations to clinical settings. However, the group noted an insufficient database on patients with tropical diseases currently limiting the clinical utility in these patients. Also, due to lower resource availabilities, biomarker levels may be measured less frequently and only when changes in treatment are highly likely.

Conclusions: Use of PCT to guide antibiotic stewardship in conjunction with continuous education and regular feedback to all stakeholders has high potential to improve the utilization of antibiotic treatment also in Asia-Pacific countries. However, there is need for adaptations of

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existing algorithms due to differences in types of infections and routine clinical care. Further research is needed to understand the optimal use of PCT in patients with tropical diseases.

Keywords: antibiotic stewardship; Asia-Pacific; bacterial infection; biomarker; procalcitonin; respiratory tract infections; sepsis.

Introduction

Individualizing the antibiotic treatment approach to patients by use of procalcitonin (PCT), a blood biomarker of bacterial infection, is an increasingly accepted concept particularly in the setting of respiratory infections and sepsis [1, 2]. As a marker with both diagnostic and prognostic properties, several trials found that PCT-guided antibiotic stewardship leads to a reduction in antibiotic consumption and better clinical patient outcomes [3–6].

However, PCT protocols used in previous trials had some differences in regard to PCT cut-off, frequency of PCT measurement and overruling criteria limiting the clinical implementation of this marker in routine care [7]. For the purpose of harmonization of the use of PCT across different clinical settings and diagnoses, a consensus conference took place in Berlin in 2018, where, based on the analysis of available trials and studies, experts agreed on three different PCT algorithms for antibiotic stewardship in patients with mild, moderate and severe disease [8].

In brief, these algorithms proposed that for optimal use, PCT levels should be put into the context of the clinical assessment in regard to severity of illness and probability of bacterial infection (uncertainty vs. bacterial infection highly suspected) to make reasonable and safe recommendations. The group also agreed on PCT cut-offs indicating low likelihood of bacterial infection of $<0.25 \mu\text{g/L}$ in non-intensive care unit (non-ICU) patients and $<0.5 \mu\text{g/L}$ in ICU patients. Emphasis was laid on serial testing of PCT levels to monitor the response to antibiotic therapy, and control of infection with a decrease in PCT from the peak by $\geq 80\%$ and/or fall below the cut-off indicates resolution of illness and earlier discontinuation of antibiotics is recommended. However, most trials were done in European and US health care settings and also most experts participating in the meeting came from these countries. Due to differences in types of infections, patient populations, available resources and standard of clinical care, however, these recommendations and algorithms may need adaptations before they can be broadly

implemented in other geographic regions such as Asia-Pacific countries [9].

Herein, our aim was to discuss within a group of experts from different Asia-Pacific countries, the necessary modifications of the Berlin consensus algorithm and to derive adapted algorithms on optimal use of PCT for the purpose of antibiotic stewardship in the Asia-Pacific region.

Materials and methods

The consensus process took place during a 1-day workshop in Bangkok on September 21, 2019. The consensus was developed by a multidisciplinary team of 16 experts on clinical use of PCT from 12 Asia-Pacific countries each representing different functional stakeholders in antibiotic stewardship, including physicians from medical and surgical critical care medicine, emergency medicine, respiratory medicine, clinical microbiology, infectious diseases, pharmacy and laboratory medicine. Table 1 gives an overview of the participants and their clinical and geographic background.

Consensus process

In the first step, the expert group reviewed the current evidence from previous trials on PCT-guided stewardship discussing the different algorithms that were previously used and the differences in PCT across clinical settings in regard to PCT cut-offs and emphasis on initiation or early stopping of antibiotics [10–13]. There was particular emphasis on the Berlin algorithms and how these could be applied to Asia-Pacific countries considering the differences in patient populations, types of infections and differences in resources available for diagnostic tests [8, 14].

Experts also exchanged experiences in routine clinical practice where PCT use for differential diagnosis and prognostication still prevails over its use for antibiotic stewardship in most hospitals of the region. Also, the limitations of these approaches as well as the barriers for broader PCT implementation for antibiotic stewardship in these health care systems were discussed. All controversial issues were openly 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 the adaptations to

Table 1: List of participating experts.

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Apisarnthanarak		Antibiotic Stewardship
Jia-Yih Feng	Taipei Veterans General Hospital, Department of Chest Medicine, Taipei, Taiwan	Pneumology
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Akihiro Ito	Ohara Healthcare Foundation, Kurashiki Central Hospital, Department of Respiratory Medicine, Okayama, Japan	Pneumology
Anis Karuniawati	Department of Microbiology, Faculty of Medicine, Universitas Indonesia; Cipto Mangunkusumo Hospital, Jakarta, Indonesia	Clinical Microbiology
Andrea Lay Hoon Kwa	Singapore General Hospital, Singapore, Singapore; Emerging Infectious Diseases Program, Duke-National University of Singapore Medical School, Singapore, Singapore	Pharmacotherapy Infectious Diseases Antibiotic Stewardship
Chien-Chang Lee	National Taiwan University Hospital, Emergency Medicine Department and Health Data Science Research Group, Taipei, Taiwan	Emergency Medicine
Petrick	PPUKM (HCTM), Hospital Canselor Tuanku Muhriz UKM (HCTM), Universiti Kebangsaan Malaysia Medical Centre (UKMMC), Kuala Lumpur, Malaysia	Infectious Disease
Periyasamy		
Busadee	Mahidol University, Faculty of Medicine Siriraj Hospital, Department of Clinical Pathology, Bangkok, Thailand	Laboratory Medicine
Pratumvinit		
Jeetendra Sharma	Artemis Hospital Critical Care Medicine, Gurgaon, India	Critical Care Medicine
Rontgene Solante	San Lazaro Hospital, Adult Infectious Diseases and Tropical Medicine, Manila, Philippines	Infectious Diseases
Subramanian Swaminathan	Gleneagles Global Hospitals, Infectious Diseases, Chennai and Bengaluru, India	Infectious Diseases
Niraj Tyagi	Sir Ganga Ram Hospital, Institute of Critical Care & Emergency Medicine, Delhi, India	Critical Care Medicine
Dien Minh Vu	National Hospital of Tropical Diseases, Critical Care Dept., Hanoi, Vietnam	Critical Care Medicine
Kapil Zirpe	Ruby Hall Clinic, Dept. of Neuro Critical Care, Grant Medical Foundation, Pune, India	Critical Care Medicine
Philipp Schuetz	Department of Internal Medicine, Kantonsspital Aarau, Aarau, Switzerland; and University of Basel, Basel, Switzerland	Internal Medicine

the algorithm on the same day using a modified Delphi process [15].

Results

Overall, the expert group agreed that the existing evidence for PCT-guided antibiotic stewardship in patients with acute respiratory infections and sepsis is valid also for Asia-Pacific countries in regard to proposed PCT cut-offs, emphasis on diagnosis, prognosis and antibiotic stewardship, overruling criteria and adaptations to clinical settings (outpatients, emergency department, clinical wards and intensive care). The trial data have shown most promising results for PCT to guide the initiation of antibiotics in patients with bronchitis and COPD exacerbation, and to guide duration in patients with CAP [4, 8].

The group also noted an important lack of trials focusing on some specific patient populations important to Asia-Pacific countries, such as tropical diseases [16–26]. Because of the lack of strong trial data currently limiting the clinical utility in these patients, there is need for

adaptation of the proposed algorithms. Also, due to lower resource availabilities, not all critically ill patients may be treated in an ICU, and biomarker levels may be measured less frequently and particularly for the purpose of stopping the antibiotic treatment. The experts decided that two adapted algorithms, one for the critically ill and one for the non-critically ill patient population would be best to reduce complexity in clinical routine for optimal PCT use in Asia-Pacific countries (Figures 1 and 2).

Use of PCT-guided stewardship in critically ill and non-critically ill patients

Similar to the proposed algorithms from the Berlin conference, the group agreed that 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 safe and efficient recommendations. To reduce complexity, however, we decided on only two algorithms, for non-critically ill (mild to moderate severity of disease) and critically ill (severe disease) patients. Again,

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

** Tropical diseases include, but are not limited to, malaria, dengue fever, hemorrhagic fever, typhus and others

Figure 1: PCT use in non-critically ill patients in Asia-Pacific countries.

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

** Tropical diseases include, but are not limited to, malaria, dengue fever, hemorrhagic fever, typhus and others

Figure 2: PCT use in critically ill patients in Asia-Pacific countries.

in a first step, patients need to be stratified according to clinical criteria and based on the probability of bacterial infection (uncertainty vs. bacterial infection highly suspected). PCT should then be added to the assessment of patients with PCT cut-offs of <0.25 µg/L in non-critically ill patients, and <0.5 µg/L in critically ill patients indicating low likelihood of bacterial infection. While in non-critically ill patients and low probability of bacterial infection a low PCT level should advise physicians against the use of antibiotic, for critically ill patients empiric therapy is mandatory with retesting of PCT after

6–24 h to re-evaluate the need for antibiotic therapy. Thus, for critically ill patients, the main purpose of PCT is to discontinue antibiotics but not for decision regarding initiation. 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 the patient is clinically stable.

Discussing the application of the algorithms in the context of the Asia-Pacific patient population, it was emphasized that for patients with clinical suspicion of tropical diseases such as malaria, Dengue fever or hemorrhagic fever, and other diseases with high prevalence in the region, such as tuberculosis or typhus, there is a lack of systematic PCT studies in general and of antibiotic stewardship studies in particular [16–22]. There are some studies suggesting that PCT may help to risk-stratify these patients and provide prognostic information, but more research is needed to understand the role of PCT in these clinical conditions before applying PCT-guided antibiotic stewardship to them. The group thus decided that,

at this time point, these PCT algorithms cannot be used to guide any antibiotic decisions in these patients and management should be based on clinical grounds and international recommendations. This was reflected in the proposed modified algorithms.

For the outpatient and emergency department settings, an initial PCT value was found to be helpful in estimating the likelihood for bacterial infection and thus the need for antibiotic treatment – particularly for the low-risk and low-probability patient population (e.g. a patient with a bronchitis-type infection). A high-sensitive point-of-care device with a fast turn-around time would be helpful to enable rapid decision-making. Clinical trials

Table 2: Barriers to the implementation of PCT in Asia-Pacific countries.

Topic	Comment	References
Lack of evidence for some patient populations		
Tropical disease	Few studies have looked at tropical diseases (e.g. malaria, dengue fever, rickettsia, typhoid); current data have been inconclusive on whether PCT improves stewardship, PCT may provide prognostic information	[16–26]
Tuberculosis	Few studies on tuberculosis, PCT remains low in patients with tuberculosis limited to the lung but increases in severe cases with systemic infection	[27, 28]
Hemorrhagic fever syndrome	Few studies have looked at hemorrhagic fever syndromes, PCT has been reported to be increased in severe cases despite lack of bacterial infection, PCT seems to provide prognostic information	[16, 17]
Lack of research in Asia-Pacific countries	There has been little research done in Asia-Pacific countries, particularly regarding interventional research; thus unclear how PCT impacts antibiotic use in clinical routine in the very different countries and health care environments in this region	[29, 30]
Resources		
Cost to the hospital	Added costs for PCT testing are often only compared to the very low antibiotic costs in some countries, without considering other potential cost savings like from shorter LOS, reduced adverse effects like <i>C. diff.</i> etc. Also, fixed budget for the lab in some hospitals limit broader PCT implementation as costs and savings occur in different departments. PCT testing often limited to —one to three tests per patient	[5, 6]
Limitation for measurement by government	Some countries restrict PCT reimbursement to certain indications and time points	[31]
Lack of high-quality (sensitive) POC technology	For primary care and smaller emergency care institutions, POC devices may help to implement a PCT strategy Currently available POC tests often have insufficient technical performance and are not validated to be used for antibiotic stewardship	[32]
Educational support		
Educational material on PCT	Many physicians have no formal education for the use of PCT and educational material is scarce	[33]
General ASP education and resources	Lack of well-established infectious disease clinical training for hospital pharmacists, and the paucity of infectious disease specialists to oversee ASPs	[34]
Cultural differences		
Self-medication of patients with antibiotics	In some countries, over-the-counter use of antibiotics may overrule physicians	[26]
Patient expectation for antibiotics	Patients are demanding antibiotics for some conditions even if no bacterial infection is evident. Education of patients and relatives may be needed to make them understand the problems of antibiotic overuse	

have shown that for inpatient treatment in the ward and the ICU, measuring a baseline level within the first 24 h is helpful with repeated levels within 24–72 h depending on the clinical situation. Importantly, however, experts felt that – in case of resource limitations – measurement of PCT may be prioritized for patient populations and time points where antibiotic decision-making is directly influenced, thus at a time point where either a physician considers stopping antibiotic treatment (but needs reassurance) or where a patient is clinically deteriorating (and physicians need additional information about resolution of infection).

Barriers to the use of PCT in Asia-Pacific countries

During the meeting, we also discussed major barriers for the more widespread use of PCT in Asia-Pacific countries. It was discussed that in Asia-Pacific countries, both cultural and health care-related aspects play a role, but also some medical aspects are important. Culturally, many patients expect antibiotic treatment and a doctor's decision to withhold antibiotic in a case with low probability of bacterial infection may be not accepted, particularly as patients may buy the drugs over the counter. Changing this mindset requires national educational programs addressed to the entire population. A lack of education and deeper understanding regarding PCT use for antibiotic stewardship also plays a role at the level of healthcare providers. Importantly, several studies have proven overall cost-savings of PCT-guided stewardship at the hospital level when considering expenses in the laboratory but lower costs for antibiotics at the pharmacy [5, 6]. This overall cost saving potential is often not understood at the level of hospital administration or health care authorities leading to hospitals and health insurances limiting the use in PCT to seemingly reduce costs for diagnostic tests. When local data on the clinical and health economic impact of PCT are available and are communicated to the respective functions, PCT can often better be implemented as part of the antibiotic stewardship program. Another implementation barrier relates to the fact that a majority of antimicrobial prescribing and PCT result interpretation are done by individuals who are not infection specialists. As the laboratory reports usually provide a reference cut-off value of 0.5 ng/mL for PCT test results, misinterpretation with resulting inappropriate antibiotics use is likely. From the medical standpoint, the biggest hurdle for wider implementation in Asia-Pacific countries is a lack of scientific data for tropical diseases (Table 2), which are highly prevalent in the region

and require additional consideration when interpreting the PCT results in the clinical context.

Discussion

Recently, it has been recognized that one of the biggest risks to human health comes in the form of antibiotic-resistant bacteria. Increasing emergence of multidrug-resistant pathogens is considered to be one of the most urgent threats to global health [35, 36]. This is particularly true for Asia-Pacific countries where antibiotic overuse has been a major problem, with multidrug-resistant pathogens on the rise [31, 37]. While several factors contribute to the problem of multidrug resistance including antibiotic usage in animals, self-medication of patients and poor hygiene standards, overuse of antibiotics in the in-hospital settings has been recognized as a main driver [36]. Accordingly, with support of the WHO, national antibiotic stewardship programs have been initiated over the last decade to facilitate a judicious use of antibiotics and reduction of antibiotic resistance rates in the Asian countries [34, 38, 39].

Herein, the use of a biomarker-guided treatment protocol aiming to provide the shortest possible duration of antibiotics only to patients truly in need of these drugs is one promising approach [29, 30]. Therefore, some of these antibiotic stewardship programs also included the integration of PCT to support clinical decision-making on the initiation or stop of antibiotic treatment in the individual patient [40]. Where consequently applied over a longer time period, the more judicious use of antibiotics led not only to reduced antibiotic exposure of patients, but was also accompanied by lower side effects, shorter length of stay and cost savings [4, 6, 41].

This, however, is currently still limited to certain segments in the hospital sector in Asia-Pacific countries. Besides health care system-related hurdles, there are also acceptance barriers to overcome. Thus, despite solid evidence from interventional trials including more than 10,000 patients [3, 4], there is still much heterogeneity regarding the optimal integration of PCT into clinical workflow. To improve PCT use in clinical practice, three algorithms for PCT use in mild, moderate and severe infections have been proposed during the Berlin conference [8]. These algorithms, however, may not unconditionally be transposed to other health care settings, such as Asia-Pacific countries due to differences in patient populations, types of infections, health care structure, resource use and cultural differences. To close this gap, we have now – during an Asia-Pacific experts meeting – modified the algorithms of the Berlin consensus and propose two

algorithms for clinical practice that consider the specific regional situation and needs (Figures 1 and 2).

Importantly, patients presenting with fever in Asia-Pacific countries may have tropical diseases, tuberculosis, hemorrhagic fever syndrome and other conditions where we currently have insufficient data on optimal use of PCT [16–22, 27, 28]. In our adapted algorithm, we therefore excluded such patients based on clinical suspicion from the PCT stewardship algorithm. Although it may be difficult to understand if a patient has tropical or non-tropical illness, after in-depth examination and history taking a physician may come up with a probability which directs him to further treat the patient. It is important that future studies also look at this important and large patient population regarding optimal use of PCT.

Importantly, also for the Asia-Pacific population, the proposed algorithms need to be used only in conjunction with a thorough clinical examination and caution should be used in patients with immunosuppression, autoimmune diseases, cystic fibrosis, pancreatitis, trauma, pregnancy and high-volume transfusion [42–45]. As there are higher prevalence of chronic liver disease and chronic kidney disease in Asia-Pacific countries, interpretation of PCT results in these patient populations may warrant caution [46]. Evidence shows that PCT tests are sufficiently accurate in differentiating bacterial infection from other causes of febrile illness in patients with liver cirrhosis [47]. However, PCT in patients with chronic kidney disease may lack sensitivity [48]. In Asia-Pacific countries, patients often receive hemodialysis rather than peritoneal dialysis. There is a lack of data on the accuracy of PCT in patients undergoing hemodialysis [48]. Thus, the results of PCT in this patient population needs to be interpreted in the context of clinical findings. Also, the algorithm should be used in acute infections, but not in patients with chronic infections (e.g. abscess, osteomyelitis, endocarditis), and pretreatment with antibiotics may effect PCT levels [49, 50]. PCT measurements should be done with high-sensitive PCT assays with sufficient precision in the relevant cut-off levels [51, 52]. We recommend against the use of off-label assays with low quality because false-negative and false-positive PCT levels may affect treatment safety of patients [32].

Conclusions and outlook

Using a biomarker, such as PCT, may help to personalize treatment decisions, which translates into lower antibiotic exposure and better clinical outcomes through the decrease in antibiotic-associated side effects [4, 13]. PCT should always be implemented in antibiotic stewardship

protocols which have shown to also have favorable effects on outcomes in patients with sepsis, and current sepsis guidelines recommend to implement strategies to reduce antibiotic exposure [53–55]. 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 [56]. The herein proposed modified algorithm should enable easier clinical adoption in Asia-Pacific countries where differences exist. Yet, experience with PCT and education about its correct use remain essential prerequisites to optimize PCT-guided treatment [57]. A clinical decision support system or including several decision cut-offs of PCT in the laboratory reports may lower the barrier of PCT-guided treatment for non-experts [58]. More clinical trials and a broader knowledge of real-world data in these countries 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 proportion of antibiotics are prescribed. Also, PCT cut-offs may need to be adapted to specific diseases and differences in patient populations seen in Asia-Pacific countries. Thus, we encourage further research efforts for this specific region for optimal patient care and use of PCT.

In conclusion, integration of PCT into algorithms for antibiotic stewardship 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. There is need for adaptation of existing PCT algorithms for Asia-Pacific countries and for further research.

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