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Review Article

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Current Status of Antibiotic Stewardship and the Role of Biomarkers in Antibiotic Stewardship Programs

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ABSTRACT

The importance of antibiotic stewardship is increasingly emphasized in accordance with the increasing incidences of multidrug-resistant organisms and accompanying increases in disease burden. This review describes the obstacles in operating an antibiotic stewardship program (ASP), and whether the use of biomarkers within currently available resources can help. Surveys conducted around the world have shown that major obstacles to ASPs are shortages of time and personnel, lack of appropriate compensation for ASP operation, and lack of guidelines or appropriate manuals. Sufficient investment, such as the provision of full-time equivalent ASP practitioners, and adoption of computerized clinical decision systems are useful measures to improve ASP within an institution. However, these methods are not easy in terms of both time commitments and cost. Some biomarkers, such as C-reactive protein, procalcitonin, and presepsin are promising tools in ASP due to their utility in diagnosis and forecasting the prognosis of sepsis. Recent studies have demonstrated the usefulness of algorithmic approaches based on procalcitonin level to determine the initiation or discontinuation of antibiotics, which would be helpful in decreasing antibiotics use, resulting in more appropriate antibiotics use.

Keywords: Antibiotic stewardship; Biomarker; C-reactive protein; Procalcitonin

INTRODUCTION

Antibiotics are considered one of the greatest discoveries of the 20th century [1, 2]. However, there is a risk that we may return to a period without antibiotics in the near future [2]. With the emergence of antibiotic-resistant bacteria, it is becoming increasingly difficult to use older antibiotics, a problem that has already been encountered in many fields of healthcare. Just 20 years ago, the most problematic antibiotic-resistant bacteria in the healthcare field was methicillin-resistant *Staphylococcus aureus* (MRSA) and extended-spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae*, while 10 years ago, the extensive spread of carbapenem-resistant *Acinetobacter baumannii* (CRAB) became a major problem. While these are still an issue, carbapenemase-producing *Enterobacterales* (CPE) are now a major public health problem [3]. It has been a long time since multidrug-resistant bacteria started to appear even in

local community-acquired infections without healthcare-associated risk factors [4-6]. The burden of disease caused by resistant organisms is also very large, with confirmed cases in Korea derived from MRSA bacteremia in 2011 reaching a cost of $67,192,559 [7]. In addition, the disease burdens of bacteremia caused by major multidrug resistant strains, *i.e.*, MRSA, vancomycin-resistant Enterococci, CRAB, multidrug-resistant *Pseudomonas aeruginosa* (MRPA), and CPE, were reported to have cost $84,707,359, $79,215,694, $74,387,364, $10,344,370, $45,850,215, respectively, in 2017 [8]. The disease burdens of pneumonia caused by CRAB and MRPA were reported to have cost $64,549,723 and $15,241,883, respectively, in 2017 [9].

Antibiotics are different from other drugs in clinical use in that the antibiotics we use today may affect patients in the future. In other fields of medicine, such as the treatment of cancer or dementia, the most recent or newly developed drugs are used first for the treatment of patients, but in perspective of antibiotics, efforts are made to reduce antibiotic exposure by reducing the use of new drugs as much as possible. An emerging concept to address these concerns is antibiotic stewardship, the most important goal of which is to ensure that the antibiotics we are currently using can still be used for a long time [10, 11]. For this purpose, a number of efforts are being made, and the so-called "One Health" concept that considers not only medicine but also veterinary medicine and the impact on the environment has been introduced to extend the shelf-life of antibiotics [12-14].

No medical practitioner will object to the proper use of antibiotics, without their abuse or misuse. Nevertheless, there are still many obstacles to antibiotic stewardship. In cases of severe infection, such as sepsis, it is difficult to choose an appropriate antibiotics in tension between antibiotic stewardship and concerns about the failure of antibiotic treatment [15]. This review examined the obstacles in operating antibiotic stewardship programs (ASPs), and whether the use of biomarkers within currently available resources can be useful for ASPs.

1. Antibiotic Stewardship in Korea

The definition of stewardship is an embodiment of responsible planning and organization for efficient management of resources. Therefore, antibiotic stewardship is a coherent set of actions that promote the responsible use of antimicrobials to leave antibiotics available for ourselves and future generations, at the individual level as well as the national and global levels, and across human health, animal health, and the environment [13]. Various activities for the proper and responsible use of antibiotics can be grouped and defined as ASPs.

The Infectious Diseases Society of America (IDSA)/Society for Healthcare Epidemiology of America (SHEA) presented major ASP activities categorized according to the recommendation level [16, 17]. Here, interventions, such as pre-authorization and/or prospective audit and feedback interventions, and application of computerized clinical decision support systems in electronic health records at the time of prescription were recommended. In addition, advice to convert to oral antibiotics as early as possible and implementing interventions to reduce antibiotic therapy to the shortest effective duration are suggested as major interventions. In Korea, Yoon et al. published guidelines for ASP interventions that are customized for local conditions [18]. These guidelines set pre-authorization, prospective audit, and feedback as the core strategies of ASPs, and also emphasize the necessity to support appropriate antibiotics duration and dose.

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2. Obstacles in ASP

There is general agreement regarding the need for and usefulness of ASPs, and that current antibiotics will remain useful for longer through such programs. However, there are still many obstacles to the effective operation of an ASP, including irregular work processes, such as excessive workload, time constraints, and decision fatigue; diagnostic barriers, social and ethical barriers; hospital hierarchies; lack of training and knowledge; communication between microbiology laboratories and clinical units; interprofessional and interspecialty conflict; and lack of resources [19].

The challenges to overcome for active ASP operation may differ between countries and between hospitals. There may also be differences between large and small to medium hospitals. A study regarding the current status of ASP among doctors who participated in such programs in hospitals with more than 500 beds in Korea [20] indicated that challenges to ASP were (in descending order of importance) shortages of time and personnel, lack of appropriate compensation for ASP operation, and difficulty of cooperation with other departments. A similar study conducted in smaller hospitals yielded similar results, also showing that staffing shortages were the most important challenge followed by lack of guidelines or appropriate manuals and the lack of compensation according to ASP operation [21].

As each country has a different healthcare system, resources, and level of interest, some studies conducted in other countries have yielded different results. In a survey on the status of ASP among healthcare professionals in the USA, Doron et al. reported that most common challenges to ASP operation were staffing constraints (69.4%), funding (50.6%), insufficient healthcare staff buy-in (32.8%), ASP was not high on the list of priorities (22.2%), and there were too many other more pressing issues (42.8%) [22]. In nonteaching hospitals, staffing constraints represented the main problem. Pakyz et al. also conducted a survey among healthcare professionals participating in ASP to identify the facilitators and barriers to ASP. In their study, the supply of appropriate resources, particularly staff, the provision of accurate information, including data interpretation, and the need for a clinical decision support system were suggested to be necessary for a successful ASP operation [23]. A similar study conducted among pharmacists also emphasized the importance of sufficient personnel and a clinical decision support system [24]. Wolf et al. conducted a questionnaire survey on the obstacles and goals of ASP among healthcare professionals working in pediatric oncology and in a bone marrow transplant unit in the USA and Australia. Healthcare professionals participating in ASP reported the most important challenges as (in decreasing order) lack of resources to analyze data, insufficient time to devote to ASP, insufficient data analysis resources, insufficient clinician time assigned to ASP, and ASP not having enough power or authority. Oncology clinicians, on the other hand, presented concerns about side effects due to the restriction of antibiotics use, lack of knowledge about antibiotics or usage strategies as major problems, and 25.0% of respondents reported lack of trust in ASP/infectious diseases (ASP/ID) clinicians as challenges [25].

In a study conducted in relatively medical resource-poor underdeveloped countries, inappropriate use of antibiotics was attributed to a lack of resources for proper diagnosis and follow-up, and lack of education on antibiotics use. Assignment of a dedicated team and the introduction of resources to evaluate and monitor the appropriate use of antibiotics were suggested as solutions [26]. Hwang et al. also summarized the core elements for domestic ASP activities [27].

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Commonly mentioned obstacles to ASPs include staffing shortages to perform relevant work, lack of adequate compensation, and lack of a clinical decision support system to support the justification of ASP. Lack of time is another issue. In a recent study that examined the working conditions of doctors in infection control in Korea, one ID physician worked 60.5 h (53.5 – 71.0 h) per week, of which 4 h were spent on infection control and 3 h on ASP [28].

A study conducted in 2015 among members of the European Society of Clinical Microbiology and Infectious Diseases to estimate the number of personnel required for infection control and ASP reported that 1.16 doctors were in charge of infectious disease, clinical microbiology, and infection control per 100 beds, which included 0.18 infection control doctors per 100 beds [29]. In a survey conducted in the Middle East where invested resources are relatively abundant, 21.4% of hospitals had 1 infection control medical personnel per 50 beds, 39.5% had 1 in 100 beds, and 24.6% had 1 in 150 beds, suggesting that about 86% of hospitals have one infection prevention and control personnel per 150 beds or less [30]. The appropriate staff level required to operate an ASP depends on the healthcare system and may vary from country to country. A study conducted in the USA suggested having 0.08 - 0.25 full-time equivalent (FTE) people per 100 beds, while studies conducted in Australia, France, and Canada suggested the need for 0.1, 0.36, and 0.1 workers per 100 beds, respectively [31]. A study to calculate the FTE required for effective operation of an ASP in Korea indicated the need for 1.04 (0.85 - 1.22) workers with ASP as their main task per 100 beds or 1.20 with ASP as their main task but with additional tasks [32].

Several studies have suggested that a clinical decision support system is useful to improve ASP operation by compensating for the shortage of staff. Developments in modern healthcare information technology systems provide the opportunity to expand the breadth and depth of these programs. Expert clinical decision support systems are the most promising tools making use of these information technology advances. In the field of infectious diseases, clinical decision support systems can be used in various areas, including parenteral to oral switch alerts; automated formulary checking systems; automated recommendations for defined infections; evidence-based knowledge bases; automated antibiograms; automated empirical antibiotics recommendations; target drug alerts; and duration of therapy alerts in terms of appropriate use of antibiotics [33]. Hermsen et al. reported that the use of a clinical decision support system could reduce the use of vancomycin against coagulase-negative *Staphylococcus* strains or methicillin-sensitive *S. aureus*, and accelerate the termination of antibiotics in culture-negative cases [34].

3. Use of biomarkers in ASP

An appropriate level of medical staff, ensuring sufficient work time, and introduction of a clinical decision support system are necessary for effective operation of an ASP. However, these factors are difficult for individuals to overcome. ASP activities that can be done easily by an individual can be of great help. As biomarkers can be very useful in this regard, their use is reviewed below.

A biomarker is a surrogate marker indicating the body's response to an infectious disease, and can be used for diagnostic evaluation of whether the infection requires the use of antibiotics, prognostic assessment of the infectious disease, and evaluation of the discontinuation of antibiotics use [35]. To be useful for clinical practice, a biomarker must satisfy various conditions and be easy to use in terms of analytical validation, qualification, and utilization [36]. With regard to analytical power, the test should be accessible, accurate,

and cost-effective. In addition, the test should have good reproducibility and yield results rapidly. Sensitivity, specificity, predictability, and accurate reflection of the actual patient's condition are required. In addition, indicators related to infectious diseases should be helpful in evaluating prognosis, such as mortality risk. The test should be easy to interpret in terms of utilization, and an index with predictable kinetics regardless of organ dysfunction is required. It should also be able to be assessed in a minimally invasive manner.

Biomarkers that can be used in infectious diseases are very diverse, and each biomarker has different characteristics and can be utilized accordingly [37]. Taking the abovementioned analytical requirements and level of utilization into consideration, C-reactive protein (CRP), procalcitonin (PCT), presepsin, and interleukin (IL)-6 are widely used biomarkers in clinical practice.

CRP was first discovered in the 1930s as a component that reacts with complex polysaccharides, mainly present in the capsule of *Streptococcus pneumoniae*, for which it was named [38]. CRP is produced in the liver [39], and its key stimulating components are IL-6 and IL-1 [40, 41]. When a stimulus for upregulation occurs, it shows an increase of more than 1000 times, and so can be monitored easily compared to other acute phase reactants. However, CRP levels are elevated under a variety of conditions other than infectious diseases, including inflammatory diseases, such as rheumatoid arthritis, systemic vasculitis, polymyalgia rheumatica, and necrotic diseases, such as myocardial infarction or acute pancreatitis [42]. However, the levels of elevation in these other conditions are generally lower than in cases of infectious disease [43]. In an experiment investigating CRP level after administration of an inflammatory substance in healthy volunteers, CRP level increased about 6 h after stimulation and reached a maximum concentration at 24–48 h, showing a half-life of about 19 h [44, 45].

PCT is a protein composed of 116 amino acid residues and is a precursor of calcitonin, which is produced in the neuroendocrine C-cells of the thyroid gland and is involved in calcium metabolism [46]. In sepsis, PCT is produced in various parts of the body, including the liver, lungs, kidneys, adipocytes, and muscle, and the level of circulating PCT rises [46]. Proinflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and IL-6, are the main factors involved in this process. PCT is mainly elevated in sepsis caused by bacterial infection, but not by viral infection or inflammatory responses associated with conditions other than infectious disease. However, PCT level increases in malaria, invasive fungal infection, lung damage, certain tumors, such as medullary thyroid cancer, and small cell lung cancer [46]. PCT is detected 3 - 4 h after the trigger of inflammation, reaches the maximum concentration at 14 h, and lasts for about 24 h, so has a plasma half-life of about 22 - 35 h [47].

Presepsin is a soluble CD14 subtype and has been used as a biomarker for infectious diseases. CD14 plays a role in activating toll-like receptor (TLR) after binding to lipopolysaccharide through lipoprotein-binding protein (LBP), a plasma protein. When TLR is activated, monocyte-macrophages begin to engulf bound microorganisms, and CD14 coordinates the endocytosis process of the TLR in this process. CD14 is cleaved into several fragments through proteolysis, and a soluble CD14 subtype is produced, which is released into the blood [48-50]. In a rabbit peritonitis model, presepsin level started to increase 2 h after induction of inflammation, reached the highest concentration at 3 h, and continued for about 5 h.

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1) Diagnostic value of biomarkers

There have been a number of studies regarding the usefulness of biomarkers in relation to the diagnosis of infectious diseases, particularly sepsis, and numerous meta-analyses combining the results of these studies have been published. The results related to three biomarkers commonly used in clinical settings, *i.e.*, CRP, PCT, and presepsin, are summarized below (**Table 1**) [51-61].

Among the three biomarkers, CRP has been used for the longest time and is still widely used for diagnosis and assessment of progress in patients with infectious diseases. A literature review of the usefulness of CRP in diagnosis of infectious diseases was published in 1991, and the results of CRP in pneumonia, central nervous system infection, bacteremia, urinary tract infection, intraperitoneal infection, and postoperative sepsis were summarized [62]. However, the usefulness of CRP was confirmed only in some cases, such as central nervous system infection or postoperative sepsis, and it was reported that CRP was not useful for distinguishing viral and bacterial infections in pneumonia and otitis media. Most recent studies were comparative assessments of CRP with other biomarkers, such as PCT, erythrocyte sedimentation rate (ESR), or presepsin. In meta-analysis, Ivana-Lapić et al. analyzed a total of 29 studies, and showed that the pooled sensitivity of CRP for musculoskeletal bacterial infections was 79% (95% confidence interval [CI]: 69 - 87%) with pooled specificity of 70% (95% CI: 59 - 79%) [53]. The appropriate cutoff suggested in their study was 10.8 mg/L. Lan et al. conducted a meta-analysis of the diagnostic usefulness of CRP and PCT for detecting bacterial infection in patients with fever of unknown origin [52]. A total of six studies were included in the analysis of CRP, and the difference in the mean CRP level between the cases with and without bacterial infection was 1.80 mg/dL (95% CI: 1.40 - 2.19) [63, 64]. The analysis included 10 studies regarding PCT, and showed that the standard mean difference in PCT level between cases with and without bacterial infection was 3.77 (95% CI: 2.67 - 4.86) ng/mL [52, 65-67]. Meichun et al. conducted a meta-analysis of the diagnostic accuracy of CRP and PCT in sepsis patients including a total of nine articles, and the pooled sensitivity of CRP for diagnosis of sepsis was 80% (95% CI: 63 - 90%) with pooled specificity of 61% (95% CI: 50 - 72%) [54]. The cutoff of CRP for sepsis diagnosis in the included studies was distributed over the range of 12.00 to 90.00 mg/L. The pooled sensitivity of PCT for the same analysis was 80% (95% CI: 69 - 87%) with pooled specificity of 77% (95% CI: 60 - 88%). The cutoff of PCT for sepsis diagnosis varied from 0.76 to 6.03 ng/mL. The areas under the curves (AUCs) of the summary receiver-operating characteristic (ROC) curves for the tests were 0.73 (95% CI: 0.69 - 0.77) for CRP studies and 0.85 (95% CI: 0.82 - 0.88) for PCT studies, with PCT showing better results [54].

Hoeboer et al. analyzed 58 reports regarding whether PCT is useful for diagnosing bacteremia [55]. Numerous studies evaluated PCT using a cutoff of 0.5 ng/mL, and the pooled sensitivity was 76% (95% CI: 72 - 80%) with pooled specificity of 69% (95% CI: 64 - 72%) [55]. The sensitivity was low 66%, (95% CI: 54 - 76%) in studies performed in populations of immunocompromised or neutropenic patients, and was highest in studies in patients in the intensive care unit (ICU) 89%, (95% CI: 79 - 94%) [68-75]. In a meta-analysis of studies conducted in patients in the emergency room, the pooled sensitivity was 76% (95% CI: 69 - 82%) with pooled specificity of 68% (95% CI: 61 - 75%) [72, 73, 76-90].

Kondo et al. performed a meta-analysis of PCT and presepsin assessments for diagnosis of sepsis in patients in the ICU, and showed a pooled sensitivity of PCT in sepsis diagnosis of 80% (95% CI: 75 - 84%) with pooled specificity of 75% (95% CI: 67 - 81%) based on 18 studies that diagnosed sepsis using PCT [56]. Studies by Ali et al. and Godnic et al. showed relatively

Table 1. Systematic review and meta-analysis of diagnostic value of biomarker in various infectious diseases

Markers	Authors	Published year	Number of included study	Diseases	Main results	Pooled results of diagnostic accuracy
C-reactive protein	Wu et al [51]	2017	7	SIRS	The AUC of presepsin was similar with CRP (0.85 *vs.* 0.85) in 7 studies comprising 1,204 patients.	Pooled SE: 77% (95% CI: 53 - 91%) Pooled SP: 79% (95% CI: 62 - 89%)
	Lan Hu et al [52]	2017	6	Fever of unknown origin	The concentration of CRP was higher in the serious bacterial infection group than in the non-bacterial infection group (SMD, 1.80; 95% CI: 1.40 - 2.19; *P* <0.01).The AUC of SROC curve was 0.82 (95% CI: 0.78 - 0.86) for PCT and 0.78 (95% CI: 0.70 - 0.78) for CRP. The AUC was significantly higher for PCT than for CRP (*P* <0.05).	Pooled SE: 69% (95% CI: 49 - 83%) Pooled SP: 75% (95% CI: 63 - 84%)
	Ivana Lapić et al [53]	2020	Orthopedic infection: 16 Others: 10	Acute location-confined or systemic inflammation of mild or moderate degree	Pooled SE and SP were 79% (95% CI: 69 - 87%) and 70% (95% CI: 59 - 79%) in orthopedic infections. Pooled PLR and NLR for CRP were 2.7 (95% CI: 2.0 - 3.6) and 0.29 (95% CI: 0.20 - 0.43). The median cutoff value in this group was 10.8 mg/L for CRP. For the diagnosis of other various inflammatory conditions, pooled SE and SP for CRP were 86% (95% CI: 67 - 95%) and 67% (95% CI: 34 - 89%), Pooled PLR and NLR were 2.6 (95% CI: 1.1 - 6.4) and 0.20 (95% CI: 0.08 - 0.51), respectively.	Orthopedic infections Pooled SE : 79% (95% CI: 69 - 87%) Pooled SP: 70% (95% CI: 59 - 79%) Others: Pooled SE : 86% (95% CI: 67 - 95%) Pooled SP: 67% (95% CI: 34 - 89%)
	Meichun et al [54]	2018	9	Sepsis, severe sepsis, or septic shock	The pooled SE and SP of CRP were 80% (95% CI: 63 - 90%) and 61% (95% CI: 50 - 72%). The overall AUC of SROC of CRP was 0.73 (95% CI: 0.69 - 0.77)	Pooled SE: 80% (95% CI: 63 - 90%) Pooled SP: 61% (95% CI: 50 - 72%)
Procalcitonin	Hoeboer et al [55]	2015	58	Hospitalized patients suspected of infection or sepsis, in which bacteremia was confirmed by blood culture	The optimal and most widely used PCT cut-off value was 0.5 ng/mL with a corresponding SE of 76% and SP of 69%. Overall analysis the AUC of SROC curve was 0.79.In subgroup analyses the lowest AUC of SROC was found in immunocompromised / neutropenic patients (0.71), the highest AUC of SROC was found in ICU patients (0.88), SE ranging from 66 (immunocompromised / neutropenic patients, 54 - 76%) to 89% (ICU patients, 79 - 94%) and SP from 55 (local infection, 47 - 63%), to 78% (ICU patients, 71 - 83%).	Pooled SE: 76% (95% CI: 72 - 80%) Pooled SP: 69% (95% CI: 64 - 72%)
	Wu et al [51]	2017	13	SIRS	The pooled SE of presepsin was found to be higher than PCT in 5 studies conducted in ICU comprising 452 patients (0.88, 95% CI: 0.82 – 0.92 *vs.* 0.75, 95% CI: 0.68 – 0.81), while the pooled SP of presepsin was lower than PCT (0.58, 95% CI: 0.42 – 0.73 *vs.* 0.75, 95% CI: 0.65 – 0.83).	Pooled SE: 78% (95% CI: 72 - 83%) Pooled SP: 79% (95% CI: 73 - 85%)
	Kondo et al [56]	2018	19	SIRS	The pooled SE and SP were 0.80 (95% CI: 0.75 - 0.84) and 0.75 (95% CI: 0.67 - 0.81) for PCT. There were no statistically significant differences in both pooled SE (*P* = 0.48) and pooled SP (*P* = 0.57) between PCT and presepsin in 9 studies which directly compared PCT and presepsin in the same population. The overall diagnostic performance of PCT and presepsin for infection were comparable (AUC of ROC 0.84 [95% CI: 0.81 - 0.87), and 0.87 [95% CI: 0.84 - 0.90], respectively)	Pooled SE: 80% (95% CI: 75 - 84%) Pooled SP: 75% (95% CI: 67 - 81%)
	Lan Hu et al [52]	2017	10	Fever of unknown origin	Concentration of PCT is higher in the serious bacterial infection group than in the non-bacterial infection group. The overall meta-analysis showed a statistical difference between the serious bacterial infection and non-bacterial infection groups (SMD: 3.77; 95% CI: 2.67 - 4.86; *P* <0.001). PCT has higher SE than CRP [0.85 (95% CI: 0.78 - 0.91) *vs.* 0.69 (95% CI: 0.49 - 0.83)], whereas SP was roughly comparable with the 2 markers [0.80 (0.65 - 0.90) *vs.* 0.75 (0.63 - 0.84)]. The AUC of SROC was 0.82 (95% CI: 0.78 - 0.86) for PCT and 0.78 (95% CI: 0.70 - 0.78) for CRP. The AUC was significantly higher for PCT than for CRP (*P* <0.05).	Pooled SE: 85% (95% CI: 78 - 91%) Pooled SP: 80% (95% CI: 65 - 90%)
	Meichun et al [54]	2018	9	Sepsis, severe sepsis, or septic shock	The pooled SE and SP of PCT were 0.80 (95% CI: 0.69 - 0.87) and 0.77 (95% CI: 0.60 - 0.88). The overall AUC of SROC of PCT was 0.85 (95% CI: 0.82 - 0.88).	Pooled SE: 80% (95% CI: 69 - 87%) Pooled SP: 77% (95% CI: 60 - 88%)

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Table 1. (Continued) Systematic review and meta-analysis of diagnostic value of biomarker in various infectious diseases

Markers	Authors	Published year	Number of included study	Diseases	Main results	Pooled results of diagnostic accuracy
Presepsin	Wu et al [51]	2017	18	SIRS	The pooled diagnosis SE and SP of presepsin for sepsis were 0.84 (95% CI: 0.80 – 0.87) and 0.76 (95% CI: 0.67 – 0.82), respectively.The pooled DOR, PLR, and NLR of presepsin were 16 (95% CI: 10 – 25), 3.4 (95% CI: 2.5 – 4.6), and 0.22 (95% CI: 0.17 – 0.27), respectively. The median cut-off for presepsin in the included studies was 600 pg/ml (IQR: 439 – 664).	Pooled SE: 84% (95% CI: 80 - 87%) Pooled SP: 76% (95% CI: 67 - 82%)
	Tong et al [57]	2015	12	Sepsis, severe sepsis, or septic shock	The pooled SE, SP, PLR, NLR, and DOR were 0.83 (95% CI: 0.77 – 0.88), 0.81 (95% CI: 0.74 – 0.87), 4.43 (95% CI: 3.05 – 6.43), 0.21 (95% CI: 0.14 – 0.30), and 21.56 (95% CI: 10.59 – 43.88), respectively.The AUC of SROC for the included studies was 0.89 (95% CI: 0.86 - 0.92), indicating a good discriminatory ability.	Pooled SE: 83% (95% CI: 77 - 88%) Pooled SP: 81% (95% CI: 74 - 87%)
	Kondo et al [56]	2018	10	SIRS	The pooled SE and SP were 0.84 (95% CI: 0.80 - 0.88) and 0.73 (95% CI: 0.61 - 0.82) for presepsin. There were no statistically significant differences in both pooled SE (P = 0.48) and pooled SP (P = 0.57) between PCT and presepsin in 9 studies which directly compared PCT and presepsin in the same population. The overall diagnostic performance of PCT and presepsin for infection were comparable (AUC of ROC 0.84 [95% CI: 0.81 - 0.87], and 0.87 [95% CI: 0.84 - 0.90], respectively).	Pooled SE: 84% (95% CI: 80 - 88%) Pooled SP: 73% (95% CI: 61 - 82%)
	Zhongjun et al [58]	2015	8	SIRS	The pooled SE, SP, and DOR were 0.77 (95 % CI: 0.75 – 0.80), 0.73 (95 % CI: 0.69 – 0.77), and 14.25 (95 % CI: 8.66 – 23.42), respectively. The pooled PLR and pooled NLR were 3.11 (95 % CI: 2.16 – 4.50) and 0.22 (95 % CI: 0.16 – 0.32), respectively.	Pooled SE: 77% (95% CI: 75 - 80%) Pooled SP: 73% (95% CI: 69 - 77%)
	Zhang et al [59]	2015	8	SIRS	The pooled SE, SP, DOR, PLR and NLR were 0.86 (95 % CI: 0.79 - 0.91), 0.78 (95 % CI: 0.68 - 0.85), 22 (95 % CI: 10 - 48), 3.8 (95 % CI: 2.6 - 5.7), and 0.18 (95 % CI: 0.11 - 0.28), respectively. The subgroup analysis restricted to emergency department patients revealed that the pooled SE and SP were 0.85 (95 % CI: 0.77 - 0.92) and 0.78 (95 % CI: 0.69 - 0.88), respectively.	Pooled SE: 86% (95% CI: 79 - 91%) Pooled SP: 78% (95% CI: 68 - 85%)
	Zhang et al [60]	2015	11	Sepsis	The overall diagnostic SE of presepsin for sepsis was 0.83 (95% CI: 0.77 – 0.88), and SP was 0.78 (95% CI: 0.72 – 0.83). The SUC of SROC was 0.88 (95% CI: 0.84 – 0.90), and the DOR was 18 (95% CI: 11 – 30).	Pooled SE: 83% (95% CI: 77 - 88%) Pooled SP: 78% (95% CI: 72 - 83%)
	Wu et al [61]	2015	9	Sepsis	The pooled SE of presepsin for sepsis was 0.78 (0.76 – 0.80), pooled SP was 0.83 (0.80 – 0.85), pooled PLR was 4.63 (3.27 – 6.55), pooled NLR was 0.22 (0.16 – 0.30), and pooled DOR was 21.73 (12.81 – 36.86). The AUC of SROC curve was 0.89 (95% CI: 0.84 - 0.94).	Pooled SE: 78% (95% CI: 76 - 80%) Pooled SP: 83% (95% CI: 80 - 85%)

Note. SIRS; systemic inflammatory response syndrome; AUC, area under curve; CRP, C-reactive protein; SE, sensitivity SP, specificity; CI, confidence interval; PCT, procalcitonin; PLR, positive likelihood ratio; NLR, negative likelihood ratio, ICU, intensive care unit; SMD, standard mean differences; SROC, summary receiver operating characteristic; DOR, diagnostic odds ratio.

low sensitivity [91, 92]. A meta-analysis of the use of presepsin including 10 reports showed a pooled sensitivity of 84% (95% CI: 80 - 88%) with pooled specificity of 73% (95% CI: 61 - 82%) [56, 87, 91-99]. Nine studies have shown no significant difference in diagnostic accuracy between PCT and presepsin, with AUCs of 0.84 (95% CI: 0.81 - 0.87) and 0.87 (95% CI: 0.84 - 0.90), respectively [87, 91, 92, 94-99].

Wu et al. conducted a meta-analysis to compare the accuracy of each biomarker for sepsis diagnosis [51]. The accuracy of presepsin and CRP or PCT in diagnosis of sepsis

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was evaluated. A total of eighteen studies were included with analysis of data from 3,470 patients. The pooled sensitivity and specificity of presepsin were 84% (95% CI: 80 - 87%) and 76% (95% CI: 67 - 82%), respectively [87, 91, 93-95, 97, 99-109]. There were no significant differences in the AUCs between presepsin and CRP or PCT, but in a study conducted with patients in the ICU, presepsin showed higher pooled sensitivity than PCT (88%, 95% CI: 82 - 92% *vs.* 75%, 95% CI: 68 - 81%, respectively) and lower pooled specificity (58%, 95% CI: 42 - 73% *vs.* 75%, 95% CI: 65 - 83%, respectively) [91, 93-95, 97, 99-101, 106, 107].

2) Prognostic value of biomarkers

A number of studies have evaluated the prognosis of infectious diseases using biomarkers. Prognostic evaluation is divided into studies of whether tests performed at an early stage of an infectious disease can predict prognosis, such as death, and studies of whether the level of biomarker improvement is related to prognosis by continuously measuring biomarkers (**Table 2**).

Zhang et al. performed a systematic literature review and meta-analysis focusing on studies of whether CRP can predict prognosis in patients with severe conditions, such as sepsis or ventilator-associated pneumonia (VAP) [111]. Their analysis including 14 studies have shown an average difference in CRP of 9.15 mg/L (95% CI: –16.50 - 24.81) between those who survived the infectious disease and those who did not, which was lower in survivors but was not statistically significant [115-128]. Analysis of 12 studies comparing CRP at the early stage of the outbreak of an infectious disease showed little difference in CRP between survivors and nonsurvivors at 1.11 mg/L (95% CI: –14.35 - 16.57) [115-118, 120, 122-128]. However, CRP measured more than 48 h after infection was significantly higher in nonsurvivors (63.80 mg/L, 95% CI: 35.67 - 91.93). Three of the reports suggested cutoff levels of CRP that can distinguish between survival and nonsurvival [117, 120, 124], but considering the AUC of the test results, with regard to sensitivity and specificity, it could not be utilized effectively.

Diego et al. conducted a systematic review to search for useful biomarkers for predicting short-term mortality in patients with community-acquired pneumonia [110]. Proadrenomedullin (AUC 0.80), atrial natriuretic peptide (AUC 0.79), and PCT (AUC 0.75) showed useful results, in contrast to CRP, which had an AUC of 0.62.

Shubhangi et al. performed a systematic review and meta-analysis based on studies of whether PCT differs between surviving and nonsurviving patients with sepsis [113]. A total of 25 reports were analyzed, and the average difference in PCT of –6.02 ng/mL (95% CI: –10.01 - –2.03) between the two groups was significant. In particular, the average difference between the two groups on day 3 was –5.96 ng/mL (95% CI: –9.78 - –2.15), suggesting that the result on day 3 after infection can be used as a marker [113].

Liu et al. performed a meta-analysis to determine whether measurement of PCT would be informative regarding prognosis in sepsis patients [112]. The analysis included a total of 23 studies, and an elevated PCT level was associated with a higher risk of death, with relative risk (RR) 2.65 (95% CI: 2.05 - 3.30). However, the timing of PCT measurement varied markedly between the studies, and a high PCT in the early stage had limited ability to predict prognosis, and PCT nonclearance was a prognostic factor for mortality in patients with sepsis.

Dan et al. performed a meta-analysis to elucidate whether measuring PCT in sepsis patients is helpful in predicting prognosis [112]. They examined whether PCT measured at the early stage of an infectious disease could predict prognosis and whether PCT clearance could

Table 2. Systematic review and meta-analysis of prognostic value of biomarker in various infectious diseases

Markers	Authors	Published year	Number of included study	Diseases	Results	Differences
C-reactive protein	Diego et al [110]	2016	7	Community acquired pneumonia	In predicting short term (28 - 30 days) mortality of pneumonia, pooled SE and SP of CRP was 60% (95% CI: 53 - 67%) and 56% (95% CI: 53 - 58%).	Pooled SE: 60% (95% CI: 53 - 67%) pooled SP: 56% (95% CI: 53 - 58%)
	Zhang et al [111]	2011	14	Critical ill patients in ICU	The WMD in the CRP levels between survivors and non-survivors was 9.15 mg/L (95% CI: -6.50 - 24.81). The WMD in CRP levels in early stage (<48 hours of diseases onset or admission) between survivors and non-survivors was 1.11 mg/L (95% CI: -14.35 - 16.57). The CRP level was significantly greater in non-survivors with a WMD of 63.80 mg/L (95% CI: 35.67 - 91.93) in late CRP levels. CRP levels between survivors and non-survivors was not significantly different, in contrast to the late (beyond 48 hours) CRP level. This was significantly greater in non-survivors with a WMD of 63.80 mg/l (95% CI: 35.67 - 91.93).	The WMD in early CRP levels between survivors and non-survivors was not significantly different, in contrast to the late CRP level. This was significantly greater in non-survivors with a WMD of 63.80 mg/L.
Procalcitonin	Liu et al [112]	2015	23	Sepsis	An elevated PCT level was associated with a higher risk of death. The pooled RR was 2.60 (95% CI, 2.05 – 3.30). The overall AUC of SROC was 0.77 (95% CI, 0.73 - 0.80), with a SE and SP of 0.76 (95% CI, 0.67 – 0.82) and 0.64 (95% CI, 0.52 – 0.74), respectively. PCT non-clearance was a prognostic factor of death in patients with sepsis. The pooled RR was 3.05 (95% CI, 2.35 – 3.95). The overall AUC of SROC was 0.79 (95% CI, 0.75 - 0.83), with a SE and SP of 0.72 (95% CI, 0.58 – 0.82) and 0.77 (95% CI, 0.55 – 0.90), respectively.	Elevated PCT Pooled RR : 2.6 (95% CI: 2.05 - 3.30) Pooled SE: 72% (95% CI: 63 - 79%) Pooled SP: 62% (95% CI: 49 - 73%) PCT non-clearance Pooled RR : 3.05 (95% CI: 2.35 - 3.95) Pooled SE: 72% (95% CI: 58 - 82%) Pooled SP: 77% (95% CI: 55 - 90%)
	Shubhangi et al [113]	2015	25	Sepsis	The pooled mean difference between PCT levels in survivors and nonsurvivors was significant (p = 0.003). The WMD of PCT between the two groups was -6.02 ng/mL (95% CI: -10.01 ~ -2.03). The day 3 PCT levels in the survivors were significantly lower as compared with the nonsurvivors, with a WMD of -5.96 ng/mL (95% CI, -2.15 ~ -9.78 ng/mL) (p = 0.002) (8 studies).	Mean difference of PCT between survivor and non-survivor was -6.02 ng/mL
	Diego et al [110]	2016	8	Community acquired pneumonia	In predicting short term (28 - 30 days) mortality of pneumonia, pooled SE was 0.71 (95% CI, 0.63 - 0.77) and pooled SP was 0.59 (95% CI, 0.56 - 0.61)	Pooled SE: 71% (95% CI: 63 - 77%) pooled SP: 59% (95% CI: 56 - 61%)
Presepsin	Yang et al [114]	2017	10	Sepsis, septic shock	Presepsin levels in the first sampling (within 24 hours) were significantly lower among survivors as compared with non-survivors. The pooled SMD between survivors and non-survivors was 0.92 (95% CI: 0.62 - 1.22). The pooled SMD between the non-survivors (n = 246) and survivors (n = 327) was 0.81 (95% CI 0.36 - 1.27) in studies exclusively contain severe sepsis or septic shock.	Pooled SMD between survivors and non-survivors: 0.92 (95% CI: 0.62 - 1.22)

SE, sensitivity; SP, specificity; PCT, procalcitonin; CI, confidence interval; ICU, intensive care unit; CRP, C-reactive protein; WMD, weighted mean difference; RR, relative risk; AUC, area under curve; SROC, summary receiver operating characteristic; SMD, standard mean differences.

be used to assess prognosis [112]. In 13 studies that have analyzed the relations between and PCT outcome and mortality in the early stage of infection, a high initial PCT level was associated with a high mortality risk, with a pooled RR of 2.60 (95% CI: 2.05 - 3.30) [124, 129-140]. The accuracy of mortality prediction varied between studies, with pooled sensitivity of 72% (95% CI: 63 - 79%) and pooled specificity of 62% (95% CI: 49 - 73%). In nine studies evaluating whether a lack of decrease in PCT during follow-up was associated with mortality, PCT nonclearance was associated with mortality risk (pooled RR = 3.05, 95% CI: 2.35 - 3.95) [141-147]. Most of the studies used a 30 - 60% decrease in PCT within 2 - 3 days as the criterion for PCT clearance, which had sensitivity for predicting mortality of 72% (95% CI: 58 - 82%) and specificity of 77% (95% CI: 55 - 90%).

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A meta-analysis including a total of 10 studies conducted in Korea showed that presepsin test performed within the first 24 h showed an average difference of 0.92 (95% CI: 0.62 - 1.22) between survivors and nonsurvivors [114].

3) Algorithmic approach using biomarkers

As described above, biomarkers widely used in clinical practice can play a supplementary role in diagnosis or prognostic assessment of infectious diseases, such as sepsis. Attempts have been made to develop plans for antibiotics use based on assessment of biomarkers, and a number of studies using various biomarkers have been reported (**Table 3**, **Supplementary Table 1**). Studies using algorithms based on biomarkers to aid antibiotics use have mainly focused on determine whether to initiate or discontinue antibiotics use.

(1) C-reactive protein

In a systematic review, Dara et al. evaluated the appropriateness of an algorithm for determining the initiation and duration of antibiotic therapy using CRP [148]. They found

Table 3. Systematic review and meta-analysis of algorithmic approach using biomarker in decision of antibiotic use

Markers	Authors	Published year	Number of included study	Diseases	Results	Differences
C-reactive protein	Petel et al [148]	2018	6	Various infections	CRP cut-offs used to guide treatment were similar across adult studies, with most studies withholding antibiotics when CRP was <20 mg/L, using discretion when CRP was between 20 mg/L and 100 mg/L, and initiating treatment when CRP >100 mg/L. CRP guided initiation of antibiotics The pooled risk difference for initiation of antibiotics in adult population was -7% (95% CI -10 – -4%). Use CRP to guide duration of antibiotics RCT-SMD for duration of antibiotic use was -1.45 days (95% CI: -2.61 - -0.28) Cohort study-pooled SMD for duration of antibiotic use was -1.15 days (95% CI: -2.06 - -0.24) Mortality: No deaths were observed in adult studies where CRP was used to guide antibiotic initiation	Neonatal study -1.15 days (95% CI: -0.26 - -0.24) adult study -0.25 days (95% CI: -0.66 - 0.16)
Procalcitonin Huang et al [149]		2017	13	Critically ill patients	**PCT-guided initiation of antibiotics (3 studies):** There was no statistically significant difference between groups in the risk of short-term mortality (RR = 1.01; 95% CI: 0.84 – 1.23) or ICU LOS (MD: 1.22 days; 95% CI: −4.34 - 1.90). **PCT-guided discontinuation of antibiotics (8 studies):** The duration of antibiotic treatment was 1.67 days shorter in PCT-guided group (MD: −1.66 days; 95% CI: −2.36 - −0.96, *P* <0.01), while antibiotic-free days were 2.26 days longer (MD: 2.26 days; 95% CI: 1.40 – 3.12) when compared with that of standard care group. Results showed patients in PCT-guided group had lower short-term mortality than standard care group (RR: 0.86; 95% CI: 0.76 – 0.98), while no differences were found in ICU LOS (MD: −0.00 days; 95% CI: −0.58 - 0.58) and hospital LOS (MD 0.43 days; 95% CI: −0.83 - 1.70) **PCT-guided antibiotic initiation and discontinuation (2 studies):** No differences were observed between the PCT and standard care group in total days with antibiotics (MD: −1.90 days, 95% CI: −5.62 - 1.83), antibiotic-free days (MD 1.31 days; 95% CI: −1.34 - 3.95), short-term mortality (RR = 1.10; 95% CI: 0.8 - 1.39), the ICU LOS (MD: −1.45 days; 95% CI: −0.91 - 3.80), and hospital LOS (MD: -0.43 days; 95% CI : -3.36 - 2.49)	PCT-guided initiation of antibiotics: Short term mortality: RR 1.01 PCT-guided discontinuation of antibiotics: duration of antibiotic treatment -1.67 days PCT-guided antibiotic initiation and discontinuation: duration of antibiotic treatment -1.90 days

(continued to the next page)

Table 3. (Continued) Systematic review and meta-analysis of algorithmic approach using biomarker in decision of antibiotic use

Markers	Authors	Published year	Number of included study	Diseases	Results	Differences
	Yannick et al [150]	2018	11	ICU patients with any type of infection	PCT guidance facilitated earlier discontinuation of antibiotics, with a reduction in treatment duration (9.3 *vs.* 10.4 days; adjusted coefficient -1.19 days, 95% CI: -1.73 - -0.66; P <0.001). There were 529 deaths among 2,230 control group patients (23.7%) compared with 475 deaths among 2,252 PCT-guided patients (21.1%), resulting in significantly lower mortality in the PCT group (adjusted OR: 0.89, 95% CI: 0.80 - 0.99; P = 0.03).	MD of total antibiotic treatment duration: -1.19 days (95% CI: -1.73 - -0.66)
	Antonio et al [151]	2021	12	Sepsis, septic shock	The combined relative risk for 28-day mortality was 0.89 (95% CI: 0.79 - 0.99), for the duration of antimicrobial therapy was -1.98 days (95% CI: -2.76 - -1.21) and for ICU-LOS was -1.21 days (95% CI: -4.16 - -1.74).	Mean differences of antibiotic duration: -1.98 days (95% CI: -2.76 - -1.21) Mortality: RR 0.89 (95% CI: 0.79 - 0.99)
	Meier et al [152]	2019	13	Clinical infection involving any organ system who also had positive blood cultures	Mean duration of antibiotic therapy was significantly shorter for 253 patients who received PCT-guided treatment than for 270 control patients (−2.86 days [95% CI: -4.88 - -0.84]; P = 0.006). Mortality was similar in both arms (16.6% *vs.* 20.0%; P = 0.263).	Mean differences of duration of antibiotic therapy: -2.86 days (95% CI: -4.88 - 0.84)
	Dominique et al [153]	2019	16	Critically ill patients	**PCT-guided antibiotic discontinuation** PCT guided therapy was associated with decreased mortality (16 RCTs; RR, 0.89; 95% CI: 0.83 - -0.97), and decreased antibiotic duration (mean difference, 1.31 days; 95% CI: -2.27 - -0.35)	Mean difference of antibiotic duration, 1.31 days; (95% CI: -2.27 - -0.35)
	Tao et al [154]	2017	15	Intensive care unit	There was no difference in 28-day mortality between two compared groups (P = 0.626), but significant decreases were observed in the duration of antibiotic therapy for the first episode of infection (P <0.001) and LOS (P = 0.049). No significant difference was found in secondary endpoints except total duration of antibiotic therapy (P <0.001).An approximate 2-day shorter was observed in patients assigned to the PCT-guided group (WMD -1.83, 95% CI: 2.51 - -1.15, P <0.001)	Duration of antibiotic therapy for the first episode of infection: -1.83 days (95% CI: 2.51 - -1.15) 28-day mortality: OR 0.96 (95% CI: 0.82 - 1.13).

Procalcitonin.

that using a CRP-based algorithm allowed the duration of antibiotics use to be shortened by 1.45 days (95% CI: 2.61 - –0.28) in randomized controlled trials (RCTs) [155-157] and 1.15 days (95% CI: –2.06 - –0.24) in cohort studies [158-162]. There were no differences in rates of mortality or recurrence of infection according to CRP level. However, in this analysis, 5 of 7 studies that used CRP to decide whether to discontinue antibiotics use were on patients with neonatal sepsis with one study on pyogenic liver abscess. Only Oliveira et al. conducted an RCT comparing the utility of PCT and CRP in the decision to discontinue antibiotics among adult sepsis patients (**Supplementary Table 1**); the average durations of antibiotics use for CRP and PCT were 7.2 and 8.1 days, respectively, which were not significantly different [156].

(2) Procalcitonin

Many studies have initiated or discontinued antibiotics use based on the PCT results. Based on these reports, there have been a number of studies using algorithm-based approaches. This review summarizes meta-analyses based on these results.

Huang et al. performed a meta-analysis of whether antibiotics intervention using PCT is useful for patients in the ICU [149]. A total of 13 studies were included. Eight evaluated whether to discontinue antibiotics using the PCT algorithm [163-170]. The PCT-based

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algorithm for determining the discontinuation of antibiotics allowed the duration of antibiotics use to be reduced by 1.66 days (95% CI: –2.36 - –0.96). The short-term mortality rate was also reduced (RR = 0.87, 95% CI: 0.76 - 0.98).

Three studies applied a PCT-based algorithm to determine whether to use antibiotics [171-173], and found no differences in short-term mortality rate (RR 1.01, 95% CI: 0.84 - 1.23) or length of ICU stay (–1.22 days, 95% CI: –4.34 - 1.90) with and without use of the algorithm. Two studies used PCT-based algorithms for both use and discontinuation of antibiotics [174, 175], and showed no differences in duration of antibiotics use (–1.90 days, 95% CI: –5.62 - 1.83), short-term mortality rate (RR = 1.10, 95% CI: 0.86 - 1.39), length of ICU stay (–1.45 days, 95% CI: –0.91 - 3.80), or total length of hospital stay (–0.43 days, 95% CI: –3.36 - 2.49) according to algorithm use.

Wirz et al. performed a meta-analysis similar to that of Huang et al. using only randomized trials [176]. In total, 11 randomized trials were included. In most studies, antibiotics were discontinued when PCT decreased to <0.5 μg/L or <80% [163-165, 167, 172, 174, 175]. In a pooled analysis, antibiotics were discontinued 1.19 days earlier when PCT was used compared to without use of PCT (9.3 days *vs.* 10.4 days, respectively, 95% CI: –1.73 - –0.66). The mortality rate was significantly lower in the PCT-guided group than the control group (21.1% *vs.* 23.7%, respectively; adjusted odds ratio 0.89, 95% CI: 0.80 - 0.99) [156, 163-169, 172, 174-176].

In 2021, Antoni et al. compiled additional studies published in 2017 and 2018 to evaluate the effect of using the PCT algorithm in determining the duration of antibiotics use in adult patients with sepsis [151]. They included 12 articles. When the PCT algorithm was used, the duration of antibiotics use was reduced by 1.98 days (95% CI: –2.76 - –1.21), the length of stay in the ICU was decreased by 1.21 days (95% CI: –4.16 - 1.74), and the relative risk for mortality also decreased to 0.89 (95% CI: 0.79 - 0.99).

(3) Presepsin

There have been studies on whether analysis of presepsin is useful for determining when to initiate or discontinue antibiotics therapy [177], but a comprehensive meta-analysis has not yet been performed. In a multicenter prospective study that analyzed whether analysis of presepsin level was helpful in shortening the duration of antibiotics use, the duration of antibiotics use decreased in the presepsin-guided group compared to the group that followed the general treatment guidelines (11.01 days *vs.* 14.54 days, respectively, $P<0.001$). There were no differences in mortality between the two groups, so it was expected that the use of presepsin would help to decrease the duration of antibiotics use [177].

4. Future of Biomarkers

In addition to the biomarkers mentioned in this review, many other biomarkers are being actively studied, as discussed in a recent review by Kim et al. [37].

CONCLUSION

As in other countries, the most difficult challenges in operating an ASP in Korea are shortages of staff and time, and the lack of appropriate supporting data. As the problem of insufficient staff or time is an organizational issue of the healthcare system and hospital, it is not easy to find a solution. Appropriate use of biomarkers in diagnosing infectious diseases

and in determining whether to start antibiotic treatment and when it should be discontinued will be helpful in terms of the appropriate use of antibiotics. Although CRP has been used for a long time, its levels are often elevated in conditions other than infectious diseases, and it has the disadvantage that it showed a slow response compared to other recently reported biomarkers. Various lines of evidence for PCT are available, and a number of algorithms using PCT have been proposed, so it is expected to be useful for regulating antibiotics use. Presepsin is a promising biomarker that has been used in recent years, but it is necessary to accumulate more data to determine its utility.

SUPPLEMENTARY MATERIAL

Guideline Korean version

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Supplementary Table 1

Individual studies on algorithms approach using biomarker in decision of antibiotic initiation or discontinuation

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