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Review Article

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Implementation of Procalcitonin in Antibiotic Stewardship: Derivation of a Consensus Algorithm for Procalcitonin Use in Clinical Practice

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ABSTRACT

Reducing antibiotics overuse is essential to minimize antibiotics related side effects and to prevent the emergence of multidrug-resistant bacteria. Procalcitonin (PCT) guided antibiotics therapy has been reported to be safe in patients with acute respiratory infections and sepsis, improving clinical outcomes as well as reducing the duration of antibiotics use. However, there is still no universal agreement on clinical guidelines in Korea for optimal PCT applications. Through this expert consensus meeting, clinical research findings in the PCT-guided antibiotics treatment interventions and real-world clinical applications were discussed. From the perspective of antibiotic stewardship, PCT application target groups, cut-offs, and testing cycles were discussed to reach a consensus on the PCT-guided antibiotics treatment algorithm for application in Korea. Combining clinical assessment for patients with an appropriate PCT-guided antibiotics treatment algorithm could improve the diagnosis and treatment of acute respiratory infections and sepsis. In addition, continuous education and regular feedback would improve the effectiveness of antibiotic stewardship.

Keywords: Procalcitonin; Antibiotics; Antimicrobial Stewardship

INTRODUCTION

The increasing emergence of multidrug-resistant bacteria is a global public health crisis which is directly correlated to the overuse of antibiotics [1]. An optimal antibiotics treatment should protect the patient not only from the side effects caused by unnecessary long-
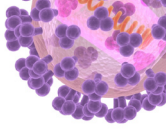
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term antibiotics treatment without additional benefits, but also from the development of antibiotics resistance without compromising the treatment outcome or prognosis of the patient receiving the treatment [2]. Excessive use of antibiotics can lead to increased risk of opportunistic infections, acquisition of multidrug resistance, and drug toxicity, which could increase mortality as well as healthcare costs [1].

Personalized antibiotics treatment including the duration of the treatment remains controversial. Ultimately, due to the lack of clinical parameters that can identify the resolution of the infection, doctors often resort to long-term antibiotics treatment. This unnecessarily longer treatment period tends to be reinforced by the antibiotics regimen, currently recommended in the national or international guidelines [3].

Recently, biomarkers have been shown to be helpful in improving infection diagnosis, early risk classification, and optimal treatment, especially antibiotic stewardship [4, 5]. In this regard, since a correlation between Procalcitonin (PCT) levels and bacterial infection has been reported in 1993, PCT is extensively evaluated by applying it in antimicrobial stewardship [6]. PCT is a precursor of the calcitonin hormone, which is normally produced in the thyroid gland and is detected at <0.1 µg/L in healthy individuals [7]. In case of bacterial endotoxins or invasive bacterial infections, PCT is secreted from tissues other than the thyroid gland and increases to a detectable level in the plasma within 2-6 hours. When the infection is appropriately controlled, the level peaks at 24 hours, and decreases daily by 50% onwards, but impaired renal elimination prolong the half-life of PCT [8-10]. Regarding the application to antibiotic stewardship, recent studies have reported that PCT-guided antibiotics treatment can reduce antibiotics exposure and antibiotics-related side effects, while reducing the risk of treatment failure, thereby reducing mortality [11, 12]. Based on these evidences, the US Food and Drug Administration (FDA) approved the use of PCT as a guide for antibiotics treatment of acute respiratory infections and sepsis [13]. However, there is no universal consensus on the optimal use of PCT of sepsis and respiratory tract infections in clinical practices [3].

The purpose of this expert consensus meeting is to review the results of PCT-guided antibiotics treatment intervention research and its application in real-world practice, and to discuss the optimal application of PCT from antibiotic stewardship perspective.

IMPLEMENTATION OF PCT USE IN CLINICAL PRACTICE

Use of PCT in real-world practice

Dong-Gun Lee (Division of Infectious Diseases, The Catholic University of Korea): When treating patients in clinical practice, PCT is utilized to consider antibiotics discontinuation for hospitalized patients in the infectious diseases department. In case of consultation requested by other clinical departments, it is recommended to be used to determine whether the disease is infectious or non-infectious, or to determine whether it is bacterial or non-bacterial.

Dae Won Park (Division of Infectious Diseases, Korea University College of Medicine): PCT test is widely used in emergency room (ER) and intensive care unit (ICU), and it is tested twice a week for infectious diseases as a sequential test together with C-reactive protein (CRP). A comparative study on several biomarkers such as interleukin-6 (IL-6) and PCT was conducted in patients with sepsis in the ER to identify the biomarkers helpful in diagnosing sepsis [14-16]. Thereafter, interests and implementation of PCT-guided diagnostics and

treatment has increased. In the ER, if the PCT level is high upon the test, there is a tendency to be assigned to an infectious disease department. In the ICU, it is measured together with CRP to evaluate the prognosis of the disease or the efficacy of the treatment as a reference, along with the clinical signs. Fortunately, there is no issue of insurance reimbursement cuts due to the increase in PCT tests. If it is difficult to make a differential diagnosis such as pneumonia and pulmonary edema in interdepartmental consultations, it is recommended to proceed the additional PCT tests by the relevant department.

Jun Yong Choi (Division of Infectious Diseases, Yonsei University College of Medicine): PCT is more useful in determining whether to discontinue antibiotics therapy than whether to initiate it. The decision to start antibiotics takes account of the evidence that a high PCT level is more likely to be associated with bacterial infection. However, it is not easy to decide not to use the antibiotics because the PCT level is low. Although the approval is applied to patients with sepsis and pneumonia, it is also used to differentiate infection from procedure-related fever such as Trans-arterial chemoembolization (TACE) in real-world practice. If the PCT level is low when fever occurs after TACE, fever can be considered as procedure-related rather than infectious complications.

Hong Bin Kim (Division of Infectious Diseases, Seoul National University College of Medicine): For the use of antibiotics, I rely more on clinical judgment than PCT level. I do not rely solely on test results to make decisions about starting or stopping antibiotics. Clinical judgment is important in the decision-making process, and biomarkers such as PCT or CRP should be used as supplementary tools. The use of PCT or CRP tests has increased significantly in recent years in ICU and ER. If the PCT level is low and the clinically determined probability of bacterial infection is low, PCT level can be used as a reference of withhold using antibiotics, and it can be used to stop antibiotics if the infection is not obvious. PCT can also be used when discontinuation of antibiotics therapy is considered with low level of PCT and no signs of infections after antibiotics have already been used for an appropriate period of treatment. In recent clinical settings, it seems that PCT tests are being conducted not only in ER and ICU, but also in general wards. In the real-world clinical setting, PCT seems to be used as a part of the basis for clinical judgment, rather than as a guideline for antibiotics treatment decisions.

Jong Hun Kim (Division of Infectious Diseases, CHA University College of Medicine): PCT is mainly used to differentiate pulmonary edema, viral pneumonia, and bacterial pneumonia. In other cases, it is not used often.

Chung-Jong Kim (Division of Infectious Diseases, Ewha Womans University College of Medicine): PCT tests are recommended to determine the cause of fever when consulting on patients with fever after a neurosurgery. The problem with using PCT tests in clinical practice is that many tests are being conducted, but the interpretation of the results is limited and appropriate interpretation for actual use is not given. Another problem is that if the use of PCT test is recommended when providing a consultation, there is a concern that the PCT test is indiscriminately conducted and interpreted to suit the taste.

Dong-Gun Lee: The patients I usually see with leukemia and lymphoma can develop fever by the disease itself, and it is very important to determine whether their fever is caused by an infectious disease or an underlying disease. If an infectious disease is accompanied, anti-cancer chemotherapy should be put on hold, and reconsidered after controlling the infectious disease to some extent. In case of fever associated with underlying disease, PCT can be used

to distinguish the timing of treatment decision, because it is important for the patient's prognosis to start the chemotherapy as soon as possible.

Usefulness of PCT vs CRP as biomarker in antibiotic stewardship

Jun Yong Choi: PCT can reflect conditions of a patient more quickly because it rises rapidly within 2 - 6 hours and decreases after reaching a peak at 24 hours [9, 10]. The advantage of PCT over CRP in clinical settings seems that the rapid rise and decrease in PCT levels in bacterial infection more immediately reflects the patient's condition [17]. PCT specifically increases in bacterial infections and does not tend to increase significantly in viral infections such as COVID-19 or severe fever with thrombocytopenia syndrome (SFTS) [18-20].

Chung-Jong Kim: CRP starts to increase 12 - 24 hours after infection or inflammatory stimulus and reaches a peak 2 - 3 days later, responding later than the actual course of the disease, and can still remain high even when the infection is improving [21]. CRP tends to be fluctuating before decreasing. For example, there is a case of a request for consult on the appropriateness of antibiotics use, when there is clinical improvement but CRP is not decreasing. In that case, waiting a few more days may reduce the fluctuating CRP. However, PCT tends to consistently decrease without such fluctuation [10]. Clinically, it is common for PCT and CRP to show differences in kinetics of decreasing levels.

Dong-Gun Lee: CRP is a protein mainly synthesized in the liver. If there is a disease or factor affecting liver function or liver failure, the CRP level may be different than the rise and fall of CRP in normal cases [22]. In this case, an increased CRP level may not fall easily, or the level may rise slowly. Since liver cirrhosis conditions affect changes in the concentration of CRP, a consult is requested asking which biomarker to use. However, in general, patients with low CRP are not recommended to take the PCT test again. This is because if CRP is low, the possibility of infection is determined to be low, so PCT is not additionally performed even if there is a fever [22]. However, a PCT test is recommended if the CRP level is high and the possibility of infection is low. If PCT level is low, antibiotics may be stopped and may start treating the patients' underlying diseases such as chemotherapy. This is because if the initiation of critical treatments such as chemotherapy is decided immediately without sufficient verification, there would be further loss such as worsening of infection or delayed chemotherapy.

Dae Won Park: CRP is known as a low-cost, widely used marker, which is highly sensitive to inflammatory responses [23, 24]. However, it is not specific to the presence of infection, and may increase in rheumatic diseases or some certain cancers, trauma, or surgery [25]. It is also difficult to differentiate between bacterial infection, viral infection, or non-infectious inflammatory response only with CRP levels. Therefore, there is no suggested cut-offs to distinguish them. However, in chronic infections such as osteomyelitis, the CRP level decreases in response to treatment and normalizes, which can be used to judge the treatment effects [25]. On the other hand, PCT has been reported in several studies where cut-offs have been established in the initiation and discontinuation of antibiotics [12, 26-29]. Setting the cut-off high can increase the specificity and help the diagnosis, and setting it low can lessen the risk of early discontinuation of antibiotics. Therefore, it would be helpful to set the cut-off range of PCT and make a clinical judgment.

Hong Bin Kim: PCT may also increase in systemic inflammations such as severe burns, cardiogenic shock, and trauma, which are not infectious diseases [30-32]. PCTs may increase

in autoimmune diseases or after surgery, but they do not increase more than 2 µg/L. On the other hand, in the case of 0.2 µg/L or less, the negative prediction of bacteremia exceeds 90% [33]. Therefore, PCT can be helpful when the possibility of infection is low, but the cause is not clear. If the blood PCT concentration is lower than the cut-off, it is useful to proceed the treatment for the underlying diseases as planned without administering the antibiotics. This is actually used commonly in such cases.

Jun Yong Choi: As limitation of PCT, considerable data have been reported mainly related to sepsis and lower respiratory tract infection (LRTI), and few studies are reported on other diseases for this biomarker [11-13]. Therefore, as of now, PCT is thought to be used in a narrower range of infectious diseases than CRP.

Jong Hun Kim: PCT is widely used as a differential diagnosis of bacterial and viral infections, but studies are insufficient in infections other than LRTI or sepsis such as chronic infectious diseases, infections in immunocompromised, and urinary tract infections [34]. CRP is considered a universal screening marker for inflammatory responses, and the specificity for bacterial infection is low. When determining treatment based on the CRP levels, antibiotics prescriptions for acute viral diseases may increase [35]. CRP levels may also be affected by steroid use [36].

Hong Bin Kim: Clinical trials on PCT have mostly been conducted in Europe such as France and Switzerland [26, 27]. Studies were mainly conducted on upper respiratory tract infections or respiratory infections, and the purpose was to reduce the duration of antibiotics use, especially in ICU patients with pneumonia, ventilator-associated pneumonia, and sepsis [29]. In the United States, the PCT test has not been used much before, but recently various studies are being conducted [28, 37]. While CRP has been used for various purposes and studied for a long time, PCT has a shorter history since it was developed and studied than CRP, and PCT related studies have only been conducted on some infectious diseases, limiting the PCT test due to its difficulty to apply extensively in the clinical settings.

Implementation of PCT into antibiotic stewardship in clinical practice

Chung-Jong Kim: Applying antibiotic stewardship within a complicated hospital system with insufficient staffing is the biggest challenge, and providing a clear guidance in various situations based on a solid supporting data could overcome the challenges. PCT is not tested routinely. The antibiotics use is discontinued when clinical improvement is observed, and it is not considered only with biomarker test results. If the blood test results are consistent with the patient's condition, it is recommended to use it as a support for clinical judgment, and if they are inconsistent, using a blood diagnostic test is recommended to find the cause.

Jun Yong Choi: Even for infectious diseases specialists, PCT does not seem to be a supporting biomarker that provides a strong confidence in the decision to start and stop antibiotics. PCT is just used as a reference for clinical judgment, because there is high level of concern and risks in reducing the duration of antibiotics use in patients with pneumonia and sepsis. Therefore, it is hoped that more convincing evidence-based data on PCT testing will be reported in the future.

Dong-Gun Lee: Interpreting the meaning and results of objective markers can be considered a scientific evidence-based approach, but real-world practices may sometimes require a slightly different approach from the evidence-based practice. In other words, antibiotics

may sometimes be maintained even if the PCT level is low, or it may be stopped even if the PCT level is high. It is not easy to control all such cases. In addition, it is a general rule that judging whether a pneumonia patient shows improvement involves identifying first if the patient's symptoms (*e.g.*, fever) have improved, rather than the findings on blood tests and imaging diagnostics. Therefore, in the real-world settings, it may be difficult to make a decision only by test results, without clinical data such as patient symptoms. Not only establishing a clear evidence-based cut-offs and guidelines for determining the start and end of antibiotics treatment is difficult, but it can also be challenging to apply them in the real-world, where patient symptoms must be prioritized. I think that's the hurdle of the PCT test.

Hong Bin Kim: The findings from various studies should be considered to determine the application of PCT to antibiotic stewardship. It is difficult not to use broad-spectrum antibiotics in patients at a time when prevalence of multidrug-resistant bacteria are increasing. Therefore, the recent trend of antibiotic stewardship is that numerous studies are being published related to attempts to shorten the duration of antibiotics use while not reducing the therapeutic effect, rather than suppressing the use of broad-spectrum antibiotics [38, 39]. It is believed that the PCT test plays a significant role only by being used in the same context as these recent findings.

Chung-Jong Kim: PCT is being tested frequently on outpatients. It is mainly prescribed to patients with a fever. Most of the outpatients are cases where their fever has not been resolved even after treatment at primary and secondary medical institutions for more than 10 days. Since most of them visit at an improving status, the PCT level would also be low. A low PCT level can be an explanation for patients that the infection is improving. It would be good for primary and secondary medical institutions to utilize PCT values to evaluate the improvement of patient's condition in this way.

Dae Won Park: Taking into account of systematic review, the use of antibiotics used for acute respiratory infection was effectively reduced by using PCT tests in the outpatient clinics [11]. Therefore, it is considered useful to utilize the PCT test in outpatient settings.

Dong-Gun Lee: It would be helpful to use PCT tests in the ER. A policy of reducing the length of stay in the ER has been implemented recently in Korea, allowing patients who need hospitalization to be hospitalized and those who do not to be discharged as soon as possible. As a result, there are cases where situations require discharge from the hospital even though there is a fever which is not resolved. In that case, oral antibiotics are prescribed most of the time because the culture test results are not yet reported. In addition, when a decision is to be made on whether to discontinue antibiotics after using them for the first 4 - 5 days and is hospitalized again, and is told that antibiotics should be used for a certain period of time from ER doctor, the patient may question whether antibiotics can be stopped. In such cases, PCT testing may be appropriately utilized. If the PCT test is utilized properly in ER, the antibiotics prescription may be induced appropriately. (Appropriate use of PCT tests in ER can lead to appropriate antibiotics prescriptions.)

Jong Hun Kim: When I personally asked Dr. David Huang of the University of Pittsburgh Medical Center (UPMC), who led the ProACT trial, his answer was that PCT was not frequently used in ICU after the ProACT trial. The first reason was that, in the study results, there was only 1 day difference in the duration of antibiotics use between the group with and without PCT [28]. The second reason was that the recent guideline itself has developed as

short-duration therapy, so it is considered appropriate to use it for a short time, and then make a clinical judgment. In addition, there was no PCT protocol in UPMC.

At the University of Michigan, a PCT protocol was developed in 2018 and updated during the COVID-19 pandemic. According to the protocol, it is recommended to use a PCT test for differential diagnosis in COVID-19 infection and to hold the use of antibiotics if below the cut-off of 0.25 µg/L because it is likely to be viral. This PCT protocol is said to be more widely used by hospitalists, nurse practitioners (NPs), and physician assistants (PA) etc. than infectious disease specialists. Since patients treated in infectious disease department are often complicated cases, it is difficult to make a judgment by PCT results alone, and it is made based on clinical features.

Based on the previous opinions and my personal opinions, the effect of reducing the duration of antibiotics use seems to be quite attenuated as the recent pneumonia guideline has shifted to short-duration therapy. However, there are clinical areas in Korea where short-duration therapy is not yet available or difficult to try. Therefore, it is expected that the PCT test can be used to introduce short-duration therapy in such situations.

Dae Won Park: Most of the positive PCT results were generated in Europe [26, 27, 29], and studies with negative results were published in the United States [28]. Europe and the United States differ in the antibiotics prescription system, where short-duration therapy is possible in the U.S. due to abundant human resources related to antibiotic stewardship, prior authorization for selected antibiotics, daily monitoring, and high guideline compliance rates. In Dr. Huang's ProACT study, short-term antibiotics treatment according to usual treatment guidelines was well followed, with an average duration of 4 days for both PCT group and usual treatment group [28]. There are many hospitals in Europe that apply the audit and feedback system like Korea, in which the antibiotics is used first, and then the infectious diseases specialist reviews the approval. In this case, the average period of use in the usual treatment group is 10 days [27]. Since hospitals in Korea has insufficient staff, various tools will be needed to review the use of antibiotics in many patients with a small number of staff. In the United States, there was also an opinion that PCT was more utilized in small and medium-sized hospitals or community hospitals with only hospitalists, rather than large hospitals [37]. Tertiary general hospitals in Korea also lack human resources for antibiotics management, and it will be beneficial if PCT is used with an intention to reduce the period of antibiotics use.

Hong Bin Kim: I personally consulted with some researchers at the PRODA Trial [40] in Korea and heard that PCT does not tend to be used often, considering the recently published findings [41, 42]. When a new biomarker is introduced, it tends to be prescribed more to identify its benefits, and for this reason, there was a shift from a previously commonly used CRP to PCT, which is now shifting to more diverse biomarkers. The benefits of PCT are considered to be limited in ICUs, and it is considered more appropriate to use it to reduce the duration of antibiotics treatment in Korea.

DERIVATION OF A CONSENSUS ON PCT-GUIDED ALGORITHM

Target population

Jun Yong Choi: Whether to start or discontinue antibiotics is not judged by PCT tests alone, but by considering clinical features and several other factors together. For that reason, it is

difficult to apply the PCT to patients in ICU since the algorithm is rather simple for complex clinical situations.

Hong Bin Kim: PCT tests are done very often regardless of the algorithm in the field. Even if conditions of a patient improve, antibiotics are often maintained while continuing to perform tests such as CRP and PCT. In particular, since the ICU accommodates patients from various medical departments, it is questionable whether the algorithm can be easily applied. As others mentioned earlier, if there are many cases where unnecessary antibiotics are used for fevers derived from non-infectious causes such as central nervous system complications, the algorithm could be applied. In a situation where an infection is uncertain and there is a strong possibility that it is not an infection, it seems highly applicable in real-world practice to develop an algorithm to maintain or discontinue antibiotics based on the PCT test.

Jun Yong Choi: Making a decision by PCT test when deciding to start antibiotics treatment is difficult to apply to ICU patients in critical conditions. When deciding to stop using antibiotics, it seems that a PCT-based algorithm should be applied to induce short-duration therapy.

Dong-Gun Lee: When applying the PCT algorithm in ICU, it seems that two things should be considered. First, it will be important which group is the user of this algorithm. The perspective of accepting algorithms may also differ depending on which clinical department is in charge of patients of the ICU. For example, the hospital where I work has a special ICU where only hematologic diseases patients are admitted, and compliance with the cooperating infectious disease department is good. However, the clinical department in charge of ICU patients of the surgical and internal medicine differs in the acceptance of the cooperating infectious diseases department. When selecting antibiotics, there are cases in which the recommendations by the department of infectious diseases are not followed and each clinical department has its own right to decide on antibiotics treatment in real-world practice in Korea.

Secondly, Korea is currently in the initiating stage of antibiotic stewardship, and there are many obstacles in the process. One of them is the shortage of staff [38]. From the hospital's point of view, antibiotics use is not considered to be controlled for overuse because the more expensive antibiotics are used, the better it is for economic benefits of hospitals. However, in the United States, there are infectious diseases pharmacists or physicians to manage antibiotics, who have authorities for two activities. The first authority is to determine the maintenance and discontinuation of antibiotics, and the second authority is for ICUs, where antibiotics is used first, and then the maintenance/disruption of antibiotics is determined through culture test results 1 or 2 days later [38, 39].

One of the most frequently asked questions when being evaluated for Joint Commission International (JCI) accreditation is how medical collaboration requests are being carried out in ICUs. There is a practical challenge of staff shortage in deciding whether to stop or maintain antibiotics by following up with patients received antibiotics. PCT-based algorithms would not even be necessary if there are enough staff to implement all such decisions. However, such algorithms will be needed in situations where there is insufficient staff. The decisions to use or stop antibiotics in Korea is currently up to the clinical department, and it is difficult for the infectious diseases department to take the lead on advising and induce decisions on the use or discontinuation of antibiotics, due to shortage of staff [38]. In current situations, PCT is evaluated to be helpful if antibiotic stewardship is introduced under 'medical practice' in which medical insurance charges are established for 'antibiotics management'.

Chung-Jong Kim: The difficulty of applying the PCT algorithm can be explained in two ways. First, in the clinical practice setting, there will be a tendency to continue to maintain antibiotics even if it is recommended to stop antibiotics based on algorithms. In the PRORATA study, the PCT guide adherence was low at 47%. Although some recommended discontinuation of antibiotics, the medical staff continued to use it because they were insecure [29]. Second, it is the selection of subjects to whom the algorithm is applied. Among patients with systemic inflammatory response syndrome (SIRS) admitted to ICUs, there may be patients who must receive antibiotics. For example, in patients with urinary tract infection, cholecystitis, and pancreatico-biliary sepsis, antibiotics must be administered regardless of PCT levels. Therefore, it is appropriate to apply the algorithm by narrowing down the applicable subjects to 'those whose heart failure and pneumonia are difficult to distinguish'. Otherwise, if the algorithm is applied to all SIRS patients entering the ICU, patients who need antibiotics may also be wrongfully classified by the algorithm of a low PCT level.

Jong Hun Kim: When applying the PCT algorithm to ICU patients, it is considered that including patients who belonged to the exclusion criteria in previous studies [12, 27, 29] should be approached with caution. As a key example, patients with severe immunodeficiency and need long-term antibiotics use were excluded from the study [12, 27, 29]. It is difficult to apply the algorithm to immunocompromised patients or patients whose cause of infection has not been identified.

Cut-off of PCT

Jong Hun Kim: 0.25 μg/L as a basis for starting and discontinuation of antibiotics was presented in 2004 in a study of LRTI s [26], and 0.5 μg/L in a 2010 study of sepsis, PRORATA trial [29]. The reason for applying a cut-off of 0.5 μg/L was described in the discussion part of the paper. The cut-off of LRTIs was 0.25 μg/L, which was suggested in previous studies, but the range of bacterial infection threshold was determined to be 0.5 - 1.0 μg/L in critically ill conditions. However, it was determined that a reference value which is too low or too high would not be appropriate, so a intermediate value cut-off of 0.5 μg/L was determined [29]. Subsequent studies were also conducted by applying a cut-off of 0.5 μg/L for sepsis. Ultimately, a cut-off of 0.5 μg/L is set as an intermediate value of the threshold.

Hong Bin Kim: The cutoff presented as <0.25, 0.25 - 0.5, 0.5 - 1.0, and >1.0 in protocol [29] of the PRORATA study may be ambiguous to interpret. It is described that the use of antibiotics is strongly discouraged at a cut-off of <0.25, and discouraged at a cut-off of >0.25 - 0.5, which can be interpreted as having little cut-off difference between 0.25 and 0.5. The cut-off classification should be simpler than the algorithm cut-off above. For example, it would be more practical to classify <0.25 as antibiotics discontinuation, ≥1.0 as antibiotics use, and 0.25 - 1.0 as a decision to be made based on the doctor's own clinical judgment. The more complex the algorithm, the lower the adherence will be.

It seems that the cut-off should be vary depending on the aim of using the algorithm. If you focus more on discontinuing the antibiotics, you should raise the cut-off, and if you focus more on starting the antibiotics, you will put the cut-off at 0.25 μg/L. Personally, even if the cut-off is set to 0.5 μg/L, I am not sure whether it is necessary to lower the cut-off to 0.25 μg/L when deciding to discontinue the antibiotics.

Dae Won Park: Pneumonia is usually accompanied by sepsis, so it would be appropriate to differentiate the cut-off according to the purpose of application of the PCT algorithm, rather

than differentiating the cut-off by respiratory infectious diseases and sepsis. If the focus is on discontinuing the antibiotics, setting the cut-off high can help early discontinuation of the antibiotics. However, as there is no one-size-fits-all approaches, it is difficult to determine initiation and discontinuation of antibiotics with only a single cut-off, and clinical judgment should also be included in the algorithm.

Regarding antibiotics discontinuation, if the peak PCT value was high, it may take a long time to fall to 0.5 μg/L, even if clinically improved, and a decrease of more than 80% of the peak [12, 27, 29] should be included, as previous studies have shown.

Jong Hun Kim: The reason for the cut-off setting in the previous study [29], as mentioned above, was that the cut-off of 0.25 μg/L increases unnecessary antibiotics prescriptions, and the cut-off of 1.0 μg/L can adversely affect the patient, so the median value of 0.5 μg/L was selected.

One more important disease in clinical practice in relation to protocol application is renal failure. PCT tests may be false positive when renal failure is present, and there is still debate over the cut-off to be applied for patients with renal failure [43]. When literatures were reviewed on this topic, cut-off values such as 0.75 μg/L and 1.5 μg/L were suggested, but it was not established clearly. In particular, patients in ICUs often undergo continuous renal replacement therapy (CRRT), and PCT can also be filtered out in such cases. More information on PCT kinetics is needed to apply the algorithms in ICUs where CRRT is frequently performed.

Interval of PCT test

Hong Bin Kim: If a PCT-based algorithm is developed, the test can be performed almost daily. The decision on antibiotics treatment is based on a comprehensive judgment of the clinical situations. Since tests such as PCT are supplementary, it is unnecessary to be performed every day, and it will be appropriate to use about twice a week.

Dong-Gun Lee: In general, the test is followed up after 3 - 4 times the half-life. If the half-life of PCT is 24 hours, the test would be performed after 3 - 4 days, so it is twice a week. It is recommendable to be tested twice a week or every 3 - 4 days.

Chung-Jong Kim: It is thought that the test interval should be different between ICU and general ward patients. If a patient's conditions worsen, the test needs to be done more often. If the patient's conditions deteriorate, it is recommended to follow up again 48 hours after the initial test.

The prerequisite of the short test cycle is that the PCT kinetics decreases immediately when appropriate antibiotics are selected and used. If the response is favourable with appropriate or optimal antibiotics, it is expected to decrease within 48 hours, but it may not occur. Even if the test is planned twice a week, it would be acceptable to test 48 hours after the initial test and maintain test twice a week the following week.

Jong Hun Kim: If the condition of a patient's is improving, it would be appropriate to test once every three days. If the condition worsens again after improvement, it is necessary to retest at that point to identify if there is a change in the trends of the test results.

Consensus algorithm for PCT use

In some infectious diseases, the practice guidelines clearly suggest on the timing of treatment initiation and duration of it (*e.g.*, infectious endocarditis, *Staphylococcus aureus* bacteremia, etc.). However, it is often difficult to decide whether to use antibiotics in the early stages of suspected sepsis when the causative microorganism or infection site is not clearly identified. It is also difficult to determine when to discontinue after a certain period of using the antibiotics. In this case, as a way to utilize the PCT results for patient care, the following algorithmic flow chart can be used (**Fig. 1**). However, it should be reminded that PCT measurement is supplementary means of diagnosis, and the most important part in the process of applying the algorithm is to evaluate whether the patient is suspected of having an infectious disease through history taking and physical examination. Antibiotics therapy is not necessary if the clinical evaluation determines that there is no sepsis. If sepsis is clinically suspected, PCT can be tested as the next step to evaluate the need for antibiotics
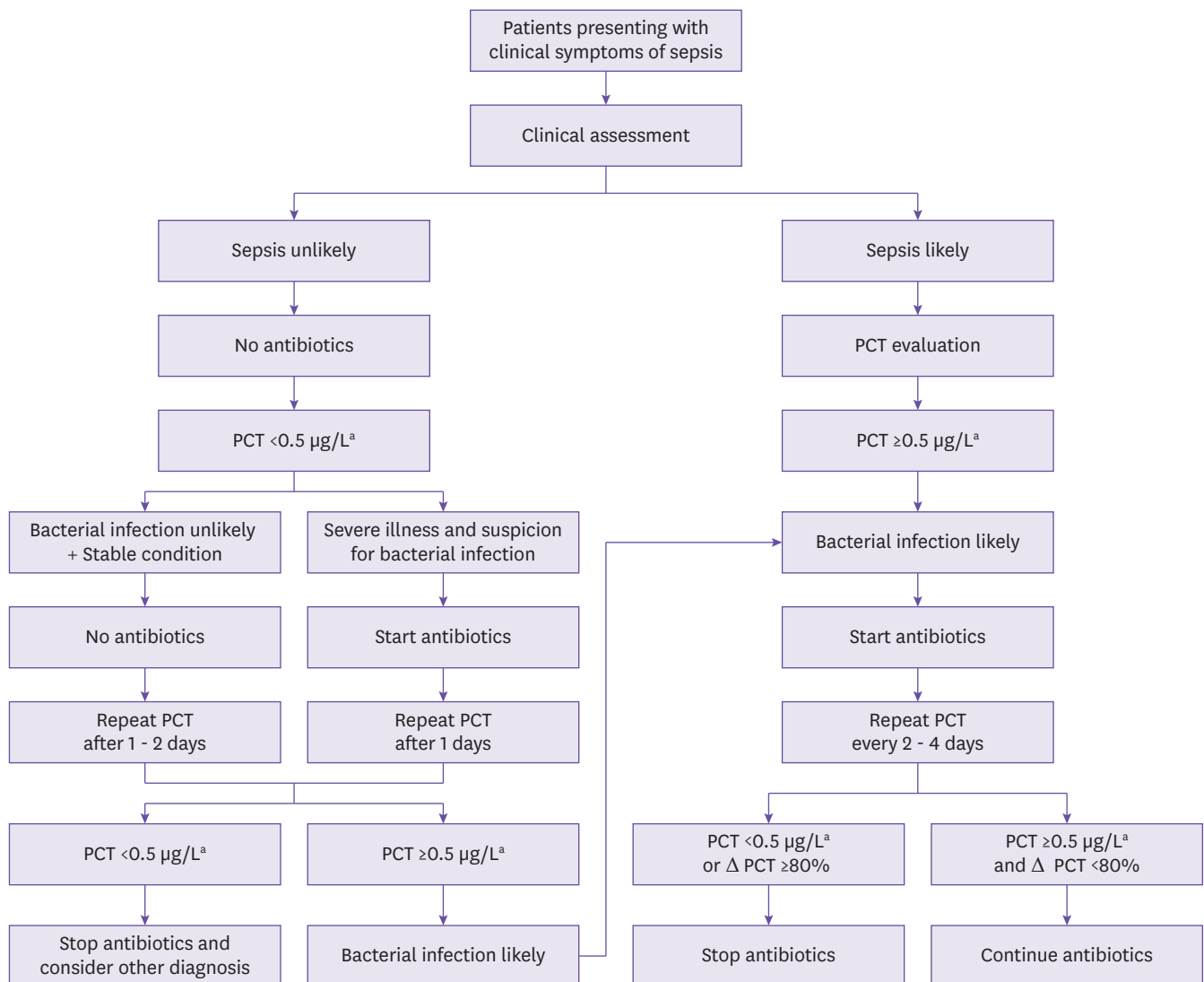

Figure 1. Procalcitonin algorithm for optimal use of antibiotics. This consensus algorithm may not be applicable to chronic infections (*e.g.*, osteomyelitis, endocarditis) or infections in immunocompromised patients.
[a]For LRTI patients, Cut off can be considered "0.25ug/L".
PCT, procalcitonin; Δ PCT, reduction of peak PCT.

use. Numerous studies evaluating whether PCT is useful in sepsis establish the cutoff for PCT to be 0.5 µg/L [44], so 0.5 µg/L was also suggested as a reference point in Korea. However, since there were studies on lower respiratory infections and pneumonia that suggested this reference point as 0.25 µg/L [26], a treatment plan based on 0.25 µg/L was suggested for LRTI. If the PCT is lower than 0.5 µg/L (0.25 µg/L in LRTI), the progress of the patient can be monitored without using antibiotics. However, even in case of a bacterial infection, PCT level may not yet rise if tested at a very early stage, so it is recommended to test the PCT again 1 - 2 days later if a bacterial infection is suspected. In addition, if the medical staff considers the patient as unstable although the PCT is less than 0.5 µg/L, it is necessary to use antibiotics regardless of the result and to test the PCT again 1 days later.

If the PCT is higher than 0.5 µg/L (0.25 µg/L in LRTIs) in the initial evaluation, antibiotics use is recommended. 2 - 4 days later after starting antibiotics, PCT can be tested again, and based on this result, whether to continue using antibiotics or to discontinue can be determined. At this time, if it decreases to 80% or less compared to the previous measurement (*e.g.*, 3 µg/L to ≤0.6 µg/L) or if the absolute value of PCT decreases to ≤0.5 µg/L or less, discontinuation of antibiotics treatment can be considered. On the other hand, if the absolute value of PCT is ≥ 0.5 µg/L and the degree of decrease compared to the previous measurement is not 80% (*e.g.*, 3 µg/L to >0.6 µg/L), antibiotics are maintained. After 2 - 4 days, the PCT can be retested again to determine the antibiotics use according to the algorithm.

CONCLUSION AND OUTLOOK

As a diagnostic and prognostic biomarker, PCT has been demonstrated to be safe and to improve clinical outcomes, while reducing antibiotics exposure by personalized antibiotics treatment for patients with acute respiratory infections and sepsis [12, 26, 27, 29]. However, PCT should not be considered to replace appropriate clinical practices but be used as a tool to complement the treatment based on clinical symptoms and other examination findings. In critical situations, the use of PCT should not day or impede the initiation of empirical antibiotics therapy, but rather should be used to discontinue antibiotics therapy when the PCT level is <0.5 µg/L or reduced by more than 80% from the peak level.

Although this PCT algorithm consensus is based on the evidence from national and international clinical trials and the effectiveness and safety of the cut-off and algorithm have been proven, the algorithm is based on the opinions of participating experts, and its benefits should be proven in the clinical practices. In addition, experience and education on the proper use of PCT should be a prerequisite for enhancing the effectiveness of PCT-based treatment. On the other hand, PCT studies have not yet provided substantial evidence for infections other than respiratory infections and sepsis, and there have been few studies involving immunosuppressed patients. Therefore, the application of the PCT consensus algorithm to these patients should be limited [45].

It is expected to find an effective way to reduce diagnostic uncertainty and antibiotics overuse based on both clinical judgments on patients and PCT, a diagnostic and prognostic biomarker. In addition, further research on the optimal use of PCT is necessary for the best infection treatment.

SUPPLEMENTARY MATERIAL

Review article Korean version

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