Acta Clin Croat 2023; 62:36-44
doi: 10.20471/acc.2023.62.01.05

Original Scientific Paper

PROCALCITONIN GUIDED ANTIBIOTIC STEWARDSHIP: A BALKAN EXPERT CONSENSUS STATEMENT

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SUMMARY – Sepsis as a consequence of infection is a frequent cause of death among critically ill patients. The most common sites of infection are lover respiratory tract, abdominal, urinary tract and catheter-associated blood stream infections. Early empiric, broad-spectrum therapy in those with severe sepsis and/or shock with the aim of reducing mortality may lead to antibiotic overuse, resistance and increased costs. Among numerous serum biomarkers, procalcitonin (PCT) has proved to be one of the most reliable ones in the diagnosis of sepsis. An important means of limiting antibiotic resistance is the antibiotic stewardship program, especially in intensive care units with critically ill patients and prevalence of multiple drug-resistant pathogens. The PCT-guided antibiotic stewardship was first started in Western Europe and Asia-Pacific countries, as well as in the United States. Considering that this method has proven to be effective in reducing antibiotic consumption while improving clinical outcome, a group of experts from the Balkan region decided to make their own recommendations and PCT protocol. When creating this protocol for initiation and duration of antibiotic treatment, they especially reviewed the literature for lower respiratory tract infection and sepsis. In the protocol, they have included the severity of illness, clinical assessment, and PCT levels. Developing a consensus on the clinical algorithm by eminent experts/specialists in various fields of medicine should enable clinicians to use PCT for initiation of antibiotic therapy and monitoring PCT to stop antibiotics earlier. It is crucial that the PCT-guided algorithm becomes an integral part of institutional stewardship program.

Key words: *Antibiotic stewardship; Procalcitonin; Respiratory tract infections; Sepsis*

Introduction

Today, a significant problem around the world is the burden of infectious disease, as well as unjustified prescribing of antibiotics that lead to antibiotic resistance[1,2], especially in moderately developed countries[3]. It is generally accepted that antibiotics are often prescribed empirically and without confirmation of bacterial infection, when the cause most often are other pathogens[4]. Overusing and misusing of antibiotics also may have a significant negative impact on the economic aspect of the healthcare system[5-8]. When there is a suspicion of infection, the key is to decide when to include or withhold antimicrobial medications[9].

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Received September 2, 2022, accepted February 22, 2023

One of the standard approaches to assess the possible presence of bacterial infection is monitoring clinical signs and symptoms, but the additional approach is to measure serum markers of infection[9,10]. Since the laboratory parameters such as white blood cell (WBC) count, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and clinical signs and symptoms are insufficient for treatment and decision on antibiotic initiation in febrile patients, there was a need to identify markers with greater specificity and sensitivity. One of the promising markers is procalcitonin (PCT) synthesized in different tissues in response to invasion of bacteria, fungi and some parasites[11]. In viral infection, interferon gamma blocks upregulation of PCT, thus indicating that PCT, unlike CRP, can be used to differentiate bacterial from viral infections[9]. Its plasma concentration increases within 6-12 h, in contrast to CRP and ESR rise after 24 h[12], and decreases approximately at a 50% day rate in patients adequately responding to therapy[13]. Although certain markers such as CRP, leukocyte count and PCT may be used to guide the initiation of antibiotic treatment, PCT can also serve as a marker for reducing antibiotic treatment, shorten intensive care unit (ICU) length of stay and decrease costs[14]. Some of the advantages in relation to CRP and WBC are specificity for bacterial infection, the rapidity of rise, a rapid decline with control of infection, and correlation with the severity of disease.

Since 2016, the World Health Organization (WHO) has advocated setting up a surveillance system that would include data on antibiotic consumption globally, and guidelines for establishing a system for antibiotic consumption at the national level. In generally, each country should have its own surveillance system which can be used nationally and internationally.

Materials and Methods

The consensus on the clinical use of PCT took place during 1-day workshop in Belgrade on July 3, 2021. It was developed by a multidisciplinary team of 8 experts from 8 Balkan countries, including anesthesiologists particularly involved in ICU work and organization in adults, with one of them being pediatric anesthesiologist (Table 1).

First, the expert group reviewed current evidence from previous trials on PCT-guided stewardship and discussed different approaches and algorithms, those which did and did not lead to reduce antibiotic use[15-17]. A systematic review of the available literature using PubMed/MEDLINE was performed during the first half of 2021. Key words (English) used in researching were "procalcitonin, infection, sepsis, lower respiratory tract infection, bacterial infection, antimicrobial stewardship". Only available literature with recommendations in adult patients was used. The cut-off values are proposed as in Berlin algorithms, considering that it

Table 1. List of participating experts

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has been proved to be effective in reducing antibiotic consumption, while improving clinical outcome, and appeared to be most appropriate for application in Balkan countries[14]. Considering that the largest number of patients in our ICUs are those with sepsis, septic shock and lower respiratory tract infections (LRTI), a special review of the literature addressed these fields of interest. They also represent the groups of patients who are given antibiotics by default and for unjustifiably long time.

As the leader of the group, Prof. Radmilo Janković gathered eminent experts with whom he had previously cooperated, who have experience in ICU protocols. They exchanged their experience in everyday clinical practice and at the end voted to 1) agree, 2) disagree, or 3) abstain on each algorithm. For this purpose, the modified Delphi process was used[18].

Results

In patients with mild illness outside the ICU, before determining PCT levels, the initial test based on clinical assessment is crucial. If a mild disease is present, along with diagnostic uncertainty about bacterial infection and PCT <0.25 μg/L, there is a low probability of bacterial infection, with the recommendation to withhold antibiotics and repeat PCT test within 6-12 h. If the value is >0.25 μg/L, the presence of bacterial infection is more likely, so the recommendation is to initiate antibiotics. Also, there is need to re-evaluate PCT every 24-48 h for monitoring and discontinuation of antibiotics if PCT is <0.25 μg/L or there is a drop by 80%. In patients with mild disease and highly suspected bacterial infection, if PCT is <0.25 μg/L antibiotics can be started based on clinical judgment. Also, repeat PCT should be considered within 24 h

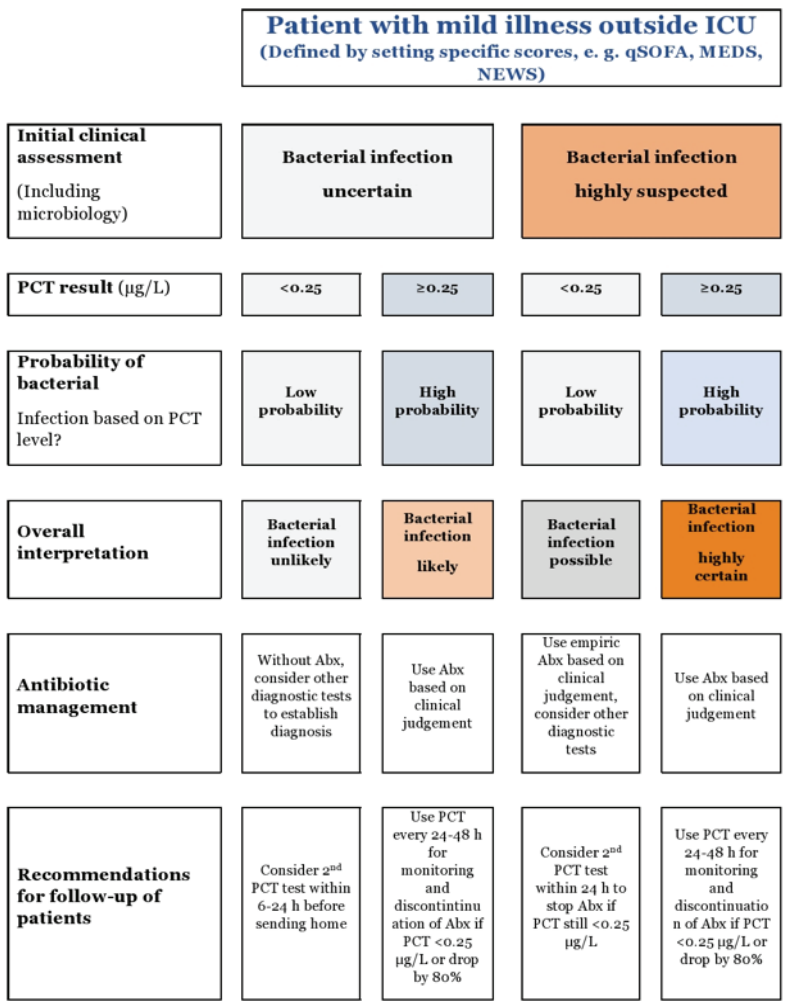

Fig. 1. Patient with mild illness outside the intensive care unit.

to stop antibiotics if PCT is still <0.25 μg/L. If the value is >0.25 μg/L, bacterial infection is highly likely, so antibiotics should be initiated, with the recommendation to use PCT every 24-48 h for monitoring and discontinuation of antibiotics if PCT is <0.25 μg/L or there is a drop by 80% (Fig. 1).

In patients with moderate disease outside the ICU, if initial clinical assessment indicates that bacterial infection is uncertain and PCT is <0.25 μg/L, the probability of bacterial infection is low. Antibiotic initiation could be considered based on clinical judgment or other diagnostic tests. Repeat PCT test within 6-24 h to early stop antibiotics if PCT is still <0.25 μg/L. If PCT is >0.25 μg/L and bacterial infection is uncertain, there is high probability of bacterial infection, so antibiotic treatment should be started. Re-evaluate PCT every 24-48 h for monitoring and discontinuation of antibiotic therapy if <0.25 μg/L or there is a drop by 80%.

If bacterial infection is highly suspected based on clinical assessment and PCT is <0.25 μg/L, the presence of bacterial infection is possible. The recommendation is to use antibiotics based on clinical judgment or use another diagnostic test and consider repeat PCT test within 24 h to stop antibiotics if PCT is still <0.25 μg/L. If initial clinical assessment suggests that bacterial infection is highly suspected and PCT level is >0.25 μg/L, the overall interpretation is that bacterial infection is highly likely. Antibiotics should be initiated. Consider PCT every 24-48 h for monitoring and discontinuation of antibiotics if PCT is <0.25 μg/L or there is a drop by 80% (Fig. 2).

In patients with severe disease in ICU if initial clinical assessment suggests that bacterial infection

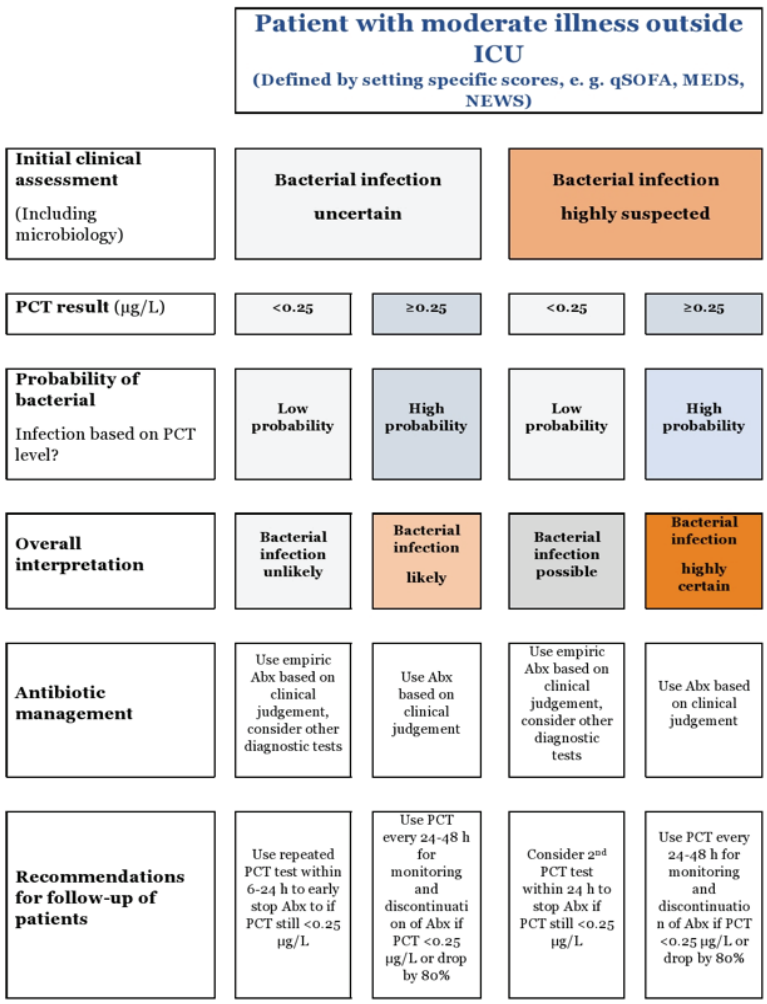

Fig. 2. Patient with moderate illness outside the intensive care unit.

is uncertain and PCT is <0.5 μg/L, the probability of bacterial infection is low. The recommendation is that antibiotic therapy should be initiated based on clinical judgment or other diagnostic tests. Use PCT within 24-48 h for monitoring or discontinuation of antibiotics if PCT is still <0.5 μg/L. If clinical judgment is that bacterial infection is uncertain and PCT is >0.5 μg/L, bacterial infection is likely. Use PCT every 24-48 h for discontinuation of antibiotic treatment if PCT is <0.5 μg/L or there is a drop by 80%. If based on clinical assessment bacterial infection is highly suspected and PCT is <0.5 μg/L there is still low probability of bacterial infection. The recommendation is to use antibiotic therapy based on clinical judgment or use another diagnostic test. Consider repeat PCT test within 24 h to stop antibiotics if PCT is still <0.5 μg/L. If bacterial infection is highly suspected and PCT is >0.5 μg/L, bacterial infection is highly likely. Use antibiotics based on clinical judgment. Consider PCT every 24-48 h for monitoring and discontinuation of antibiotics if PCT is <0.25 μg/L or there is a drop by 80% (Fig. 3).

Discussion

In the Balkan study group perspective, one of the reasons and the need for implementation of the already existing algorithms was the increase of bacterial resistance and antibiotic consumption, and their toxic effects. Therefore, some Balkan countries participated in the Central Asian and European Surveillance of Antimicrobial Resistance (CAESAR) network with the aim to set up national antimicrobial resistance surveillance system and in the future PCT-guided antibiotic therapy algorithms for Balkan countries[19].

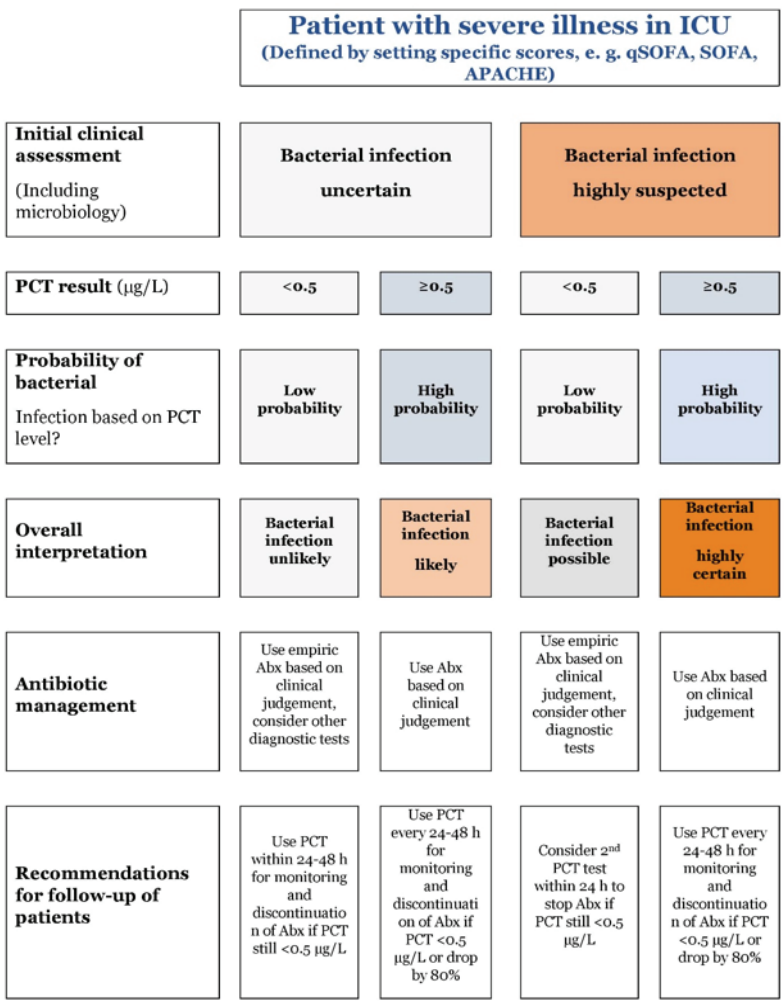

Fig. 3. Patient with severe illness in the intensive care unit.

Considering the widespread and often unjustified use/overuse of antibiotics accompanied by the high cost and development of resistance, there is no doubt that with the WHO support, the national guide for antibiotic use, or antibiotic stewardship, should be an integral part of treatment of patients with suspected infection[20,21]. One study from Serbia once more showed that the increase of antimicrobial resistance and hospital acquired infections can be particularly worrying in ICUs. Compared to European Union countries, study data showed an increase in resistance of the most common pathogens responsible for hospital acquired infections. This could be due to the lack of antimicrobial stewardship[22].

There are PCT algorithms for LRTI and sepsis. For primary care and emergency department, in patients with LRTI it can be summarized as follows: PCT <0.25 ng/mL bacterial infection is unlikely or very unlikely and without recommendations for antibiotic initiation/continuation. If PCT value is >0.25 ng/mL, bacterial infection is likely or highly likely with recommendation to consider antibiotic usage or to continue[23]. For sepsis and critically ill patients in ICU, the cut-off values are a little higher. Antibiotic therapy should be encouraged if the value is >0.5 ng/mL and discouraged if it is <0.5 ng/mL[24].

It may be most difficult to decide if antibiotic therapy is justified in patients with low respiratory tract infection. It is because most signs and symptoms of bacterial and viral infections overlap. Even when bacteria are isolated from sputum, it cannot be known for sure whether it is colonization or infection. Based on several trials, in 2017, the Food and Drug Administration allowed using PCT-based guidance on making decision to start or stop antibiotic treatment in patients with suspected lower respiratory tract infection[25,26]. Considering that the diagnosis is most often made on the basis of clinical signs and symptoms, as well as radiographic findings without identifying the bacterial cause, it is reasonable that the use of PCT may be beneficial in these patients[27,28].

The study by Christ-Crain *et al.* unequivocally demonstrated the advantage of PCT guidance for safe reduction of antibiotic overuse in patients with respiratory tract infection. Second, withholding antibiotics was safe in patients included in the study[29]. Also, the Stop Antibiotics on Procalcitonin Guidance Study was performed in the Netherlands in 15 ICUs and showed that adherence to the PCT algorithm resulted in less antibiotic use and reduction in 1-year mortality[30]. Townsend *et al.*[12] compared the PCT-guided antibiotic therapy group and the usual standard of care group. They came to a conclusion that median antibiotic duration in PCT group was shorter (5 *vs*. 6 days) and overall time of antibiotic therapy was significantly lower. Also, significantly fewer patients were discharged on antibiotics (37.4% *vs*. 55.5%). There was no statistically significant difference in terms of side effects. Physicians often do not follow the protocol even when the institution has one, which makes implementation of the process of protocolization and PCT-guided algorithm more difficult.

Huang *et al*. and Van der Does *et al.* show that use of PCT-guided therapy in suspected lower respiratory tract infection in patients with fever did not show any additional benefit in Emergency Medicine patients and that it was not non-inferior to standard care in terms of safety[31,32].

It is known that the sepsis treatment guidelines change over time because sepsis is one of the most common causes of death in the intensive care unit. One of the ways of treatment is to start adequate antibiotic therapy as early as possible[33]. In terms of sepsis, it is considered that antibiotics are not necessary in 30%-50% of cases because patients do not have proven bacterial infection. Blood cultures have some limitations; they are rarely positive and are negative in 40%-90% of patients with suspected systemic infection. Early empiric therapy in septic patients reduces morbidity and mortality, but too long exposure to antibiotics can lead to adverse drug reaction without therapeutic benefit[34,35].

The study by Nobre *et al.* showed a significant reduction in antibiotic use, without harm in patients with severe sepsis and septic shock based on serial PCT measurements. These patients also had a significantly shorter length of ICU stay. This study supports the concept that PCT guidance may reduce antibiotic exposure, and that it is related to reduced costs and not to worse outcome[36].

In ICU patients with sepsis or septic shock, studies have found that monitoring of PCT kinetics over time can optimize therapeutic approach, while stopping antibiotics once the PCT level has dropped to <0.5 ng/mL or by at least 80%-90% of the peak[27].

A meta-analysis by Tang *et al.* in 2007 (2097 patients) showed that median sensitivity of PCT was 74%, thus indicating that PCT cannot make a differ-

ence between infectious and non-infectious systemic inflammatory response syndrome (SIRS)[37]. Conversely, a more recent meta-analysis (3244 patients) showed that PCT may with high certainty differentiate between sepsis and SIRS of non-infectious origin[38].

A study by Hohn *et al.* showed that in postsurgical patients with sepsis, the length of antibiotic treatment was shorter by 1 day *per* year after implementation of the PCT-guided algorithm in 2005. A significant reduction was also recorded in ventilation hours, ICU re-infection rate, ICU length of stay, nonsignificant reduction of 28-day mortality and mean costs *per* patient[39].

With the aim to release some recommendations, the decision to use PCT and its management during further therapy must be considered taking account the clinical status and severity of illness. The algorithm recommends that determining the severity of illness (mild, moderate or severe) and with initial clinical assessment, the presence of a bacterial infection can be assumed. Based on the value of PCT, a decision can be made to start or withhold antibiotic therapy.

Conclusion

It is important to note that for middle-income countries, introducing the PCT-algorithm in everyday clinical practice may have cost-saving effects reducing the antibiotic exposure. Determination and monitoring of PCT values are an integral part of decision making for initiation and duration of antibiotic therapy and may help personalize the treatment. Also, it can be useful to differentiate infective from non-infective cause of severe inflammation, and the severity of systemic inflammation caused by bacteria and infection. It should not be forgotten that the interpretation of biomarkers, as in other settings[40], should be carried out in the context with clinical presentation, medical history, physical examination, and microbiological assessment.

Adoption of PCT monitoring and institution of PCT-driven antibiotic therapies are challenging due to the lack of PCT algorithm at the national level, as well as antibiotic consumption surveillance policies.

In addition to clinical assessment, the introduction of PCT algorithm along with effective education of clinicians may improve antibiotic management and reduce the occurrence of their side effects. Developing a consensus on clinical algorithm by eminent experts/specialists in various fields of medicine should enable clinicians to use PCT for initiation of antibiotic therapy and monitoring PCT to stop antibiotics earlier. It is crucial that PCT-guided algorithm becomes an integral part of institutional stewardship program.

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Sažetak

UPRAVLJANJE ANTIBIOTICIMA VOĐENO PROKALCITONINOM: KONSENZUS EKSPERATA IZ BALKANSKIH ZEMALJA

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Sepsa kao posljedica infekcije jedan je od čestih uzroka smrti među kritično oboljelim pacijentima. Najčešća mjesta infekcije su donji respiracijski putovi, abdomen, mokraćni sustav i infekcije krvi povezane s centralnim vesnkim kateterima. Rana empirijska upotreba antibiotika širokog spektra kod onih s teškom sepsom/septičnim šokom radi smanjivanja smrtnosti može voditi prekomjernoj upotrebi antibiotika, bakterijskoj rezistenciji i povećanju troškova. Među mnogobrojnim serumskim biološkim biljezima prokalcitonin se pokazao kao jedan od najpouzdanijih u dijagnosticiranju sepse. Jedan od bitnih načina za smanjenje bakterijske rezistencije predstavlja uvođenje protokola o upotrebi antibiotika, naročito među kritično oboljelima u jedinicama intezivnog liječenja gdje su prisutni multirezistentni patogeni. Prokalcitoninom vođeni protokoli za upotrebu antibiotika prvo su uvedeni u Zapadnoj Europi i Azijsko-pacifičkim zemljama, kao i u Americi. S obzirom na to da se ovakav program pokazao učinkovitim u pogledu potrošnje antibiotika, a ujedno i u poboljšanju ishoda liječenja, grupa eksperata s Balkana odlučila je napraviti svoje vlastite preporuke. Tijekom izrade ovog protokola za uvođenje i dužinu trajanja antibiotskog liječenja autori su se uglavnom usredotočili na pretragu literature koja se tiče donjeg respiracijskog sustava i sepse. Protokol uključuje težinu bolesti, kliničku procjenu i razine prokalcitonina. Razvijanje konsenzusa o kliničkom algoritmu od strane eminentnih stručnjaka iz različitih područja medicine trebalo bi omogućiti kliničarima da prokalcitonin koriste pri donošenju odluke o započinjanju i ranijem prestanku terapije antibioticima. Neophodno je da prokalcitoninom vođen algoritam postane sastavni dio institucionalnog protokola o upotrebi antibiotika.

Ključne riječi: *Upravljanje antibioticima; Prokalcitonin; Infekcije dišnog sustava; Sepsa*