EDITORIAL

Procalcitonin: "To Follow or Not to Follow" That's the Question

Subhash K Todi

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Sepsis has been recognized as an important cause of mortality globally, more so in resource-limited regions.[1] It accounts for 19.7% of all global deaths. Timely antibiotic therapy in patients with septic shock is associated with a significant decrease in mortality in observational studies.[2] Though this has not been uniformly noted in patients with sepsis without shock. Moreover, empirical use of appropriate antibiotic therapy has also been associated with a significant decrease in infection-related and all-cause mortality in critically ill patients.[3] This has led to a widespread use of early broad-spectrum antibiotics in patients with septic shock. Unfortunately, despite the lack of robust evidence, similar practice is usually followed in patients with infection without organ dysfunction or shock. This has resulted in the emergence of multidrug-resistant (MDR) bacterial infections not only in hospitals but also in the community, which leads to a vicious cycle of prescribing further empirical broad-spectrum antibiotics for a new infection especially hospital-acquired. In the absence of a reliable method to "rule in" or "rule out" infection, it will be difficult to curb the upfront use of antibiotics. Decreasing antibiotic burden in the intensive care unit (ICU) and in the individual patient will be possible by sending appropriate microbiological cultures and deescalating antibiotics wherever possible and to decrease the duration of antibiotic therapy. As cultures are often negative and may only yield colonizing organisms, the scope of de-escalation may be limited especially in settings with MDR infection with limited options for de-escalation. Shortening the duration of antibiotics without compromising the efficacy may be the only way to achieve the goal of decreasing antibiotic exposure. Assessment of clinical improvement is the current prevalent practice of deciding on the duration of antibiotic therapy. This practice is based predominantly on a subjective assessment, which has led to a widely variable practice of antibiotic duration, which on an average is longer than what is probably desirable. Utilizing biomarkers like Procalcitonin has been recommended for decreasing the duration of antibiotic therapy.[4]

To discuss the impact of a biomarker on the duration of antibiotic therapy, one needs to ascertain what should be an "ideal" duration of therapy. This will depend on multiple factors, with some situations requiring "prolonged" therapy like immunosuppressed state, the severity of infection (debatable), sites of infection like endocarditis, and microbiological factors like staphylococcal bacteremia and MDR gram-negative infection. Even in these situations exact duration of therapy is arbitrary and is dependent on the clinical response of the patient. On the other hand, in most other situations duration of antibiotic therapy may be "shorter". The current practice of prescribing antibiotics for a certain minimum number of days, usually seven days is not based on sound evidence.

Department of Critical Care Medicine, AMRI Hospitals, Kolkata, West Bengal, India

Corresponding Author: Subhash K Todi, Department of Critical Care Medicine, AMRI Hospitals, Kolkata, West Bengal, India, Phone: +91 9830202040, e-mail: drsubhashtodi@gmail.com

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There is a growing literature of evidence that the duration of antibiotic therapy can be shortened even further in most infections including severe infection. Recent trials in intra-abdominal infections requiring surgery have compared four days of antibiotics with seven days and have found equivalent results.[5] The generalizability of these results is not possible in many situations and also clinical trials on the duration of antibiotic therapy are not available for many infections encountered in clinical practice in ICU. It is evident that the duration of antibiotic therapy requires individualization and is a field where personalized medicine can be readily practiced. Procalcitonin is the biomarker most commonly studied in this regard. Earlier studies on procalcitonin use in various infectious diseases had shown a decrease in duration of antibiotic therapy without any harmful effect with the use of this biomarker. This was achieved by serially measuring procalcitonin values and stopping the antibiotic when the level came below a certain percentage of baseline (usually 80%) or below a certain cutoff value usually less than 0.5 μg/mL. Relapse of infection was not noticed in these trials, with some trials even showing a decrease in mortality.[6] Thus, the use of procalcitonin was recommended in sepsis guidelines to decrease the duration of antibiotic therapy.

In a study published this issue, the author randomized 90 patients (45 in each arm) admitted with sepsis/septic shock to a procalcitonin-guided duration of antibiotic therapy or institutional protocol-based therapy. Procalcitonin value of <0.1 μg/mL was taken as the cut-off for stopping antibiotic therapy. Clinical response was also considered in both arms while considering the duration of antibiotic therapy. Patients requiring a short course of therapy like elective surgery or prolonged course of therapy like endocarditis, immunocompromised patients were excluded from the study. Duration of antibiotic therapy was significantly shorter in the procalcitonin group of 5 days vs 8 days in the control group. ICU length of stay, duration of mechanical ventilation, and duration of inotrope requirement were also significantly higher in

the control group. Secondary infection defined as the occurrence of a new infection at another site was significantly higher in the control group, probably due to longer ICU stay and longer duration of mechanical ventilation. Reinfection rate which was defined as recurrence of infection at the same site was similar in both the group and also there were no significant differences in mortality between the groups. There were baseline differences in the groups, with septic shock patients being significantly higher in the control group, though the severity of score markers like SOFA and APACHE II and lactate levels were surprisingly similar between the two groups and bacteremia was more common in the procalcitonin group, which could be due to less robust randomization due to small sample size. Historically, clinicians are reluctant to shorten the duration of therapy in patients with sepsis and septic shock, which leads to prolonged antibiotic therapy and the authors should be commended to undertake this study in the septic shock population. Despite limitations, this study emphasizes the scope of safely decreasing the duration of antibiotic therapy in these groups of patients.

Similar to the present study most of the studies on duration of antibiotic therapy have used clinical response along with procalcitonin levels to adjudicate duration of antibiotic justifying shortening the duration only in patients with positive clinical response. In practice, "positive clinical response" is an not all-or-none phenomenon with various parameters like fever, leukocytosis showing favorable or unfavorable trends that might be concordant or discordant and the composite response assessment remains a subjective impression. Moreover, the duration of antibiotic therapy in the control arm in many studies on procalcitonin has been of more than seven days duration which is contrary to the present evidence of shorter duration even in a sicker group of patients. Studies comparing the use of procalcitonin where the control arm had a shorter duration of antibiotic have not yielded significant results. The use of the procalcitonin strategy in infections with MDR organisms or immunosuppressed patients has also not been well studied as these were excluded from many procalcitonin studies. Despite these limitations, the current trend of prescribing a longer duration of antibiotics can only be curbed by judicious use of biomarkers like procalcitonin along with antibiotic stewardship practices. In the absence of a willingness to shorten the duration of antibiotics based on the procalcitonin result, the utility of this biomarker will not be realized. Moreover, the need for serial measurement of this expensive test also adds to the cost of care in ICU. Future research agenda on the utility of procalcitonin would be to compare this molecule with a relatively inexpensive biomarker like C-reactive protein on decreasing duration of therapy and total antibiotic burden in a critically ill patient with sepsis and septic shock and its effect on other important clinical and economic parameters like resource utilization, secondary bacterial and fungal infection, incidence of MDR bacterial infection and *Clostridium difficle* infection. This should be achieved without increasing the incidence of relapse or reinfection. The utility of the use of this biomarker in patients infected with MDR infection or immunosuppressed patients also needs to be studied. It might even be prudent to study the negative impact of the use of this molecule which may lead to unnecessary prolongation of antibiotic duration in patients who have clinically responded but not yet reached the procalcitonin cutoff. The control arm duration of antibiotic therapy in procalcitonin should be shorter in accordance with the recent guidelines. Approach to the duration of antibiotic therapy in patients with initial norma procalcitonin values and what should be the ideal frequency of repeating this marker need also be studied. Last but not the least, compliance with antibiotic stewardship practices of deescalating or stopping antibiotic based on a protocolized algorithm of procalcitonin value need to be studied in critically ill patient population.[7]

Orcid

*Subhash K Tod*i https://orcid.org/0000-0003-2306-6080

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