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Strategies to Shorten Antibiotic Therapy Duration in the ICU (J. Pugin, V. Nobre)

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There is little controversy as to whether patients with severe sepsis and septic shock should receive a prompt, broad-spectrum antibiotic treatment. The Surviving Sepsis Campaign care bundles popularised this concept, and a recent Canadian study based on a large registry of septic shock patients further supports it (Kumar et al. 2006). These investigators showed that mortality rates correlated with the time delay between the onset of shock and the administration of the first dose of antibiotics. De-escalation therapy, i.e. narrowing the antibiotic spectrum and/or changing the route of administration, is also becoming popular among critical care physicians. This strategy is certainly associated with a lower risk of developing multi-resistant bacteria, and also decreases drugrelated costs. Decreasing antibiotic treatment duration should carry the same beneficial effects.

In our ICUs and elsewhere, the duration of antibiotic therapy is not governed by clear and unequivocal rules. It is mainly based on empirical recommendations, derived from expert advice. Recently we have become concerned that critically ill patients may be receiving unnecessary prolonged antibiotic treatment based on such rules. Several approaches can be taken in order to possibly decrease the duration of antibiotic therapy. One possibility is to modify the empirical rule and to test whether a shorter duration changes any aspect of patients' outcomes. This was the approach taken by Chastre et al. when they compared 8 vs. 15 days in the treatment of ventilator- associated pneumonia (Chastre et al. 2003). In this study, mortality rates were the same for patients regardless of whether they were treated for 8 or 15 days. The authors however reported an increased recurrence of pneumonia in patients treated only 8 days infected with non-fermenting Gramnegative bacteria. This may show the limit of changing an empirical rule by another one, highlighting the fact that patients and the causative microorganisms are non-homogenous, and thus may require differential treatment durations. Another strategy to shorten antibiotic therapy duration utilised by Singh and colleagues is to use a clinical score to help the clinician to stop unnecessary antibiotic treatments (Singh et al. 2000). In Pittsburgh, mechanically ventilated patients with a new infiltrate on the chest radiography or with a new fever tended to receive an indiscriminate 10 to 21-day course of ciprofloxacin. They were able to stop unnecessary antibiotics in many patients with low probability of VAP based on low clinical pulmonary infection scores measured at day 1 and day 3. The outcome was similar in patients receiving the full course and in those in whom antibiotics were stopped on day 3.

A third approach is to use a marker of the infectious process resolution as a tool to decide when to stop the antibiotic therapy. Procalcitonin (PCT) is a biomarker that has been shown to decrease rapidly in plasma from septic patients with favourable outcome, and to remain high in those patients who will eventually die (Harbarth et al. 2001). It was therefore natural to test the concept that the duration of antibiotic therapy could be customised based on the evolution of plasma PCT levels. This concept had previously been proposed and tested in patients with community-acquired pneumonia (Christ- Crain et al. 2006). The duration of antibiotic therapy was cut in half in this trial (6 vs. 12 days) without negatively impacting on patients' outcome. Based on this concept, we designed a randomised-controlled trial in patients with severe sepsis and septic shock (Nobre et al. 2008). In the test arm, when plasma PCT levels had reached < 10% of the initial value and the patient was stable, clinicians were asked to stop antibiotics (see figure). Controls were treated according to empirical rules. The group of patients in whom antibiotics were stopped based on PCT levels had a median duration of antibiotic treatment of 6 days, compared with 10 days in the empirical group. The reduction of antibiotic treatment duration was neither associated with increased recurrence of the infection nor with increased mortality, but rather with a significant shorter ICU length of stay. Importantly, only a selection of patients with uncomplicated infections was studied, and results may therefore not be generalised to the whole population of patients with septic shock. These results on a relatively small number of patients also need to be confirmed in larger multi-centre clinical trials.

In conclusion, it is our impression that critical care physicians are moving towards shorter durations of antibiotic treatment for their patients. There is no reason why the antibiotic treatment should not be adapted to the infectious response when this is possible. The evolution of plasma PCT levels brings objectivity to the clinical decision and allows customization of therapy, with no apparent harm. In any case, the clinician should not rely only on a marker to make a decision, but rather thoroughly examine his patient together with laboratory and radiologic tests, and integrate the marker in his decision. Given the relatively high price of PCT measurements, further medico-economic studies are needed to determine whether this approac h is cost-efficient.

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