Editorial

Best practice for sepsis

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The Surviving Sepsis Campaign (SSC) Guidelines recommend that "*administration of systemic antibiotics be initiated as soon as possible after recognition and within one hour for both sepsis and septic shock*" (1). In contrast, other bundles (2,3), such as those from the Institute Quality Improvement, suggested as reasonable a target within 3 hours.

Under these premises, health care systems and physicians work to reduce time to antibiotics (TTA) as short as feasible. Being sepsis defined as "clinical urgency" and septic shock as an "emergency" (like hypertension and stroke), ensure that starting antibiotic infusion was promptly administered is a measure favouring best practice for patients with sepsis (1-3). Obviously, the policy of "right first time" has been recommended by many academicians (4), but it is not exempt of the ecological potential risk of increasing emergence of resistance. As a matter of fact, excessive use of antibiotics, or unjustified prolonged use do increase the selection of resistant micro-organisms (4,5). A recent study reported that the implementation of antibiotic/sepsis bundles in patients with a sepsis code was associated with increased *Clostridium difficile* infection rates (5). Here is where diagnostic tests have an important role and a policy of antimicrobial stewardship focusing on reduced exposure to broad-spectrum antibiotic needs to be implemented (6).

In this scenario, Alam *et al.* (7) did a randomized open-label trial, after training nurses from emergency medical service staff, in ten large regional ambulance services serving 34 hospitals in the Netherlands in subjects with inclusion criteria which were suggestive of infection. The intervention group received ceftriaxone a median of 26 min before arriving to the emergency department, whereas median TTA after arriving to emergency department was 70 minutes in the control group. However, giving antibiotics in the ambulance did not lead to improved survival (92%), regardless of illness severity, with less than 10% of subjects being admitted to the ICU and a minor proportion (<5%) with shock. Additionally, the intervention was safe but they did not find any significant difference in secondary outcomes between the groups. Of note, positive cultures were less frequent in the intervention group (25% *vs.* 37%), suggesting that even one dose of ceftriaxone can negatively affect cultures. Thus, "*the authors do not advice antibiotic administration in the ambulance to patients with suspected sepsis*" (7). Several limitations should be remarked, before generalizing this conclusion, particularly in low and middle-income countries. First, the most common foci of infection in this study were the lungs and the urinary tract (7). The use of antibiotics in the ambulance might be more critical in other clinical conditions such as meningitis or sepsis in immune-compromised subjects. In addition, many patients with respiratory infection would have been treated with antibiotics regardless the most likely cause of sepsis was a respiratory virus. In these subjects, the administration of antimicrobials should be always avoided. Second, in the Netherlands, compliance with SSC and quality indicators was very high, with most patients receiving antibiotics within 1 h of presentation. This is very different from the standard of care in rural areas from other countries, with many

patients requiring a long transfer to the referring hospital and therefore receiving antibiotics hours after the onset of sepsis. In addition, 20% of these patients were already on antibiotics before presentation and all of them have short hospital arrival times. As described in demography, the intervention focused on patients with different levels of severity-of-illness (38% with infection, 57% with severe sepsis and 4% with septic shock), being patients with septic shock or organ dysfunction a small proportion (6). Moreover, time to initiation of appropriate antibiotic prescription was not reported, but due to the low rate of resistances in the Netherlands, it was expected to be small, in contrast with other geographical regions with spread rate of resistances, particularly in Enterobacteriaceae. Finally, investigators used SEPSIS-2 criteria of sepsis, whereas if using qSOFA criteria (80% average with qSOFA <2 in the ambulance), many patients would not have been eligible for inclusion to this study. Caution to generalize the authors' conclusions in other settings, where the potential benefit of quick antibiotics would be higher. As indicated by the own authors, whether including more patients with septic shock or doing the study in a pre-hospital setting with longer arrival times would have led to different outcomes remains unclear. The conclusion should be than shortening of the TTA by 26 min in Netherlands does not offer significant advantages, being consistent with prior studies. On the opposite using antibiotic in patients with potential respiratory viral infection, should be avoided. Indeed, the study reinforces that timing of antibiotic prescription is not critical when the infection is not severe (8). Source of sepsis and patient selection is recommended in the decision to start antibiotics in sepsis (9).

Sepsis code has been generalized, following the track from stroke or myocardial infarct code, with the aim of optimizing management times and response to therapy. In contrast with these other codes, where an objective event, such as an electrocardiogram would define the entity, the trigger for sepsis is based on a list of non-specific physiological variables, with difficult early identification. The idea of prescribing antibiotics in the ambulance is provocative, but it has the challenges of objective identification and the need of personalizing to subjects with bacterial infections at high risk of organ dysfunction or anticipated complicated outcomes. In our opinion, combination with a point-of-care sepsis biomarker in the ambulance to individualize prescription should be the next step in research in an era of personalized medicine.

An important observation of this study is that training nurses significantly improved sepsis recognition from 14% to 41% of cases. Indeed, this training contributed in shortening TTA from 93 to 70 min, with resultant improvement in usual care. Thus, developing educational programmes in sepsis should be a top priority. Quick diagnosis, development of sepsis biomarkers and a stewardship antimicrobial programme, adapted to the reality of low and middle-income countries are needed. The key points of early recognition, appropriate prescription and improving care need to be disseminated in educational programmes.

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Footnote

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