The organization of timely care in septic patients

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Intensive care clinicians are often exposed to patients with severe sepsis or septic shock. They know, by virtue of their experience, the need for action and the advantage that is created when they use the 'golden hour of sepsis'. We know that septic patients can show fast deterioration and ultimately die due to progressive organ failure. Organ failure that is caused by circulatory and mitochondrial dysfunction following the inflammatory response to infection. The inflammation cascade leads to inappropriate oxygen delivery and metabolism which is recognized by clinicians as an increase in serum lactate. Endothelial dysfunction and vasodilatation cause hypotension which, by itself, enhances organ failure. The interventions that are usually performed in septic patients aim to stop this self-enhancing circle of events. Fluids and vasopressors are the cornerstone of the treatment of circulatory failure. In the meantime, the infection should be determined and treated. Infection, usually of bacterial origin, is the primary reason for the inflammation that precedes the clinical syndrome of sepsis. As a consequence, it is logical to start antimicrobial therapy as soon as possible next to source control. When appropriate antimicrobial therapy has been initiated, other interventions have two goals. First, to bridge the time till the infection is overcome and second to limit organ dysfunction and its sequelae. In the last 30 years, no new interventions for patients with severe sepsis or septic shock have been developed. We still use fluids, vasopressors and antimicrobial agents. In contrast, the organization of care has changed dramatically. More dedicated intensivists, concentration of complex care, improved recognition of septic patients (with the use of early warning scores and emergency medical teams), the use of protocols and other organizational innovations have been implemented in hospital and intensive care. The surviving sepsis campaign and the sepsis bundles aim to standardize and prioritize medical interventions globally (1,2). These guidelines have helped to develop an organizational structure in hospitals to implement the sepsis campaign recommendations. A gradual decrease in sepsis related mortality is the result (3). Over time, the sepsis recommendations and bundles have been adapted several times to match with the latest level of evidence and knowledge. The time windows for interventions have, over time, been shortened to 3- and 6-hour bundles. Some of these time frames are, however, arbitrarily chosen and, although logical, not based on solid evidence. It is known from several studies that any delay in antimicrobial treatment enhances mortality rates (4). The relevance of timely lactate measurement is more complex. It is known that a faster lactate clearance is associated with lower mortality but it is scarcely studied how lactate clearance can be promoted and whether such interventions do reduce mortality (5). In one multicenter study the use of vasodilators and inotropes was associated with greater lactate clearance and better outcomes (6). The 3-hour sepsis bundle asks for early blood culture drawings and lactate measurement. These diagnostic interventions are inevitably important but diagnostic tests can, by definition, not lead to better outcome unless followed by appropriate therapeutic intervention. The registration of the 3-hour sepsis bundle does not mention the actions that followed, for instance,

lactate measurement. For treatment interventions in the 3-hour bundle, antimicrobial treatment and fluid therapy, a timely intervention might be beneficial. Pruinelli and co-workers recently studied the timeliness of the 3-hour sepsis bundle and the association with outcome measured as hospital mortality (7). This study shed some light on the issue of time in relation to outcome in patients with severe sepsis and septic shock but also raises several new questions. All four 3-hour sepsis bundle interventions—blood cultures, lactate measurement, initiation of broad-spectrum antimicrobials and infusion of crystalloids—did show an improved outcome when given early compared to later. They performed a complex statistical procedure which combined retrospective data from the electronic health records of 6 hospitals and 45 clinics. This study, of course, suffers from the standard flaws of retrospective cohort studies such as unmeasured confounders and bias. The researchers, however, tried to mimic a randomized controlled design by applying propensity score matching. Basically, this is an elegant and potent way to reduce bias but it is limited by the choice and availability of the matching variables. One of the factors that is difficult to measure and to include in the analysis is frailty. It is increasingly clear, as more and more older patients enter the intensive care, that frailty is an independent factor for outcome (8). Frailty scores are now being developed and validated for clinical use in intensive care. Pruinelli and co-workers tried to avoid bias as much as possible but factors like frailty, type of sepsis (abdominal, respiratory, urinary, etcetera), additional treatment (e.g., mechanical ventilation, vasoactive medication, steroids, source control) and treatment limitation orders were not considered. It cannot be excluded that their propensity score matching is in fact an inappropriate matching due to the absence of these factors. In addition, severity of disease is not considered although co-morbidity is. The severity of disease is relevant as the baseline characteristics of included patients show a relatively low burden of disease with a median lactate of 1.8 mmol/L and a median mean blood pressure of 81 mmHg. It is shown that the average treatment effect over time declines for all four bundle items, which in itself is a paradoxical finding. Probably, the most severely ill patients received the interventions earlier, leading to a diminished effect for the less ill patients despite their delay. It is not reported which part of the patients were treated and admitted to the intensive care as all hospitalized patients were included. It may be true that patients in the intensive care receive more interventions and more often timely interventions. When the individual sepsis bundle interventions are studied in relation to each other, the late moment for antimicrobial treatment initiation to become significant in Pruinelli's study is remarkable. This is in contrast with previous findings that every hour earlier initiation of treatment with antibiotics reduces mortality (4). Finally, the time of onset of the sepsis syndrome is unclear from these data. Patients with sepsis might have been septic for days at home but they may also present at the hospital early.

The recent decades have taught us that timely recognition of severe sepsis and septic shock attributes to a better outcome. The 3- and 6-hour sepsis bundles helps us to initiate appropriate diagnostic tests and treatment. However, Pruinelli and co-workers provide deeper insight in the influence of time and the importance of the interventions. It is clear from their study that organizing the care for septic patients in a way that it leads to early recognition and early initiation of diagnostic tests and treatment is a cornerstone of successful sepsis management. Doctors should therefore focus on the organization of their care as much as on the medical reasoning of their interventions. The main lesson that can be drawn from this study is that doctors should (re)organize the care for patients with severe sepsis and septic shock in a way that timely interventions will occur.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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