Editorial

Septic shock in the era of precision medicine

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Septic shock is a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality. Patients with septic shock can be identified with a clinical construct of sepsis with persistent hypotension requiring vasopressors to maintain MAP >65 mmHg and having a serum lactate level >2 mmol/L (18 mg/dL) despite adequate volume resuscitation (1). The treatment include combined regimens of antibiotics, source control and hemodynamic resuscitation.

Although recent studies described decreasing mortality rates in critically ill patients with septic shock, the overall hospital mortality remains high. Five subsets of septic shock have been identified, being the combination of refractory hypotension with hyperlactacidemia associated with poor survival, in spite of aggressive management. It should be denoted that hypotension should be defined as a mean arterial pressure less than 65 mmHg according to the pragmatic decision that this was most often recorded in datasets derived from patients with sepsis (2).

Lamontagne *et al.* (3) conducted a pilot trial to inform the design of a larger trial examining the effect of lower versus higher mean arterial pressure (MAP) targets for vasopressor therapy in shock. The authors randomized assigned critically ill patients who were presumed to suffer from vasodilatory shock regardless of admission diagnosis to a standard (60–65 mmHg) versus a higher (75–80 mmHg) MAP target. Other aspects of management, such as sedation and volume status assessment, are also potential confounders in the hypotension-vasopressor relationship, but were not assessed. A total of 118 patients were enrolled from 11 Canadian centers. Overall mortality risk was not different between standard and "intensificated" reanimation intervention. Whereas it was not documented in younger patients, among patients aged 75 years or older, an "intensificated" management to get a higher MAP target was associated with increased hospital mortality (60% *vs.* 13%, P=0.03). Moreover, risk of cardiac arrhythmias increased near two-fold (36% *vs.* 20%, P=0.07) when vasoactive agents were prescribed to get "supranormal" values. A trend of higher ischemic events in elderly with supranormal resuscitation is also reported. No information was provided in the effect of age in arrhythmias.

The study has some imbalances and peculiarities, for instance 48% use of vasopressine. A difference in 13% in septic shock, different infectious sites [double prevalence (12% *vs.* 23% for pneumonia] and differences in acute pancreatitis (additional 5%). Differences in chronic hypertension (33% *vs.* 57%), in albumin infusion (49% *vs.* 64%) and significant differences in red cells packed transfusion needs (49% *vs.* 71%, P=0.024) should be noted.

Their findings underscores the concept that optimal MAP targets may vary across specific patient subgroups (4). Indeed, at the bedside, it is a common practice titrate the need of volume resuscitation and norepinephrine to the urine output. This is indeed, an approach based on the more modern concept of "Precision" or "Personalized" medicine (5). Other variables, including other tissue perfusion markers (e.g., base deficit, acute alteration in mentation, venous-arterial PCO_2 gap), resuscitation end points (central venous saturation, lactate clearance) or blood pressure characteristics (e.g., diastolic pressure) could potentially improve on the proposed targets to optimize outcomes.

In septic shock patients, beyond the selection of a suitable antibiotic, the administration of an appropriate antimicrobial dosing regimen (dose and schedule) influences

the probability of success. Patients with more energetic resuscitation present higher positive volume infusion balance and this is associated with an increase in the volume of distribution (6,7). This condition might be associated with therapeutic underdosing, delaying to get recommended plasma concentrations of antibiotics above the minimal inhibitory concentration of the responsible pathogen, requiring therapeutic drug monitoring and higher doses of antimicrobials.

Identification of a critically ill patient with shock would benefit from obtaining serum lactate measurements, both to stratify and to monitor the response to therapy (8). However, serum lactate measurements are not universally available, especially outside the ICU or in low and medium income countries (LMIC). And it time to move forward from lactate measurement to proteomics and genomics, because the core problem is a mitochondrial dysfunction.

It is cornerstone to acknowledge that current therapies are likely effective only in some subgroups during specific phases of diseases. Advanced age, like in the OVATION trial (3), is an example. Incorporating theranostics, to individualize different therapeutic approaches depending of the host is an urgent need. The concept of "Precision Medicine"—prevention and treatment strategies that take individual variability into account—has been well developed in chronic diseases, such as diabetes mellitus. The prospect to apply this concept has been dramatically improved. It is urgently needed the development of large-scale biological databases, newer methods for characterizing patients (proteomics, metabolomics, genomics, cellular assays), and recent computational tools to assess large data sets. Advances in basic research, including molecular biology, genomics and bioinformatics are largely applied to cancer (9). Next steps should be to translate this experience to sepsis and septic shock, being crucial to incorporate the inherent concept of diversity to patients requiring vasopressors.

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Footnote

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