EDITORIAL

Polymyxin B hemoperfusion in sepsis: perseverance is the key

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Sepsis is a major healthcare problem, with millions of patients affected each year around the world. The incidence of sepsis is currently increasing,[1] while the mortality is still dramatically high:[2] its most severe forms (*i.e.*, severe sepsis and septic shock) resulted to have a mortality between 50-80% in a survey conducted in Italian Intensive Care Units.[3] Septicemia is currently ranked as the tenth cause of death in the United States, but many experts consider this an underestimation and believe that sepsis may actually caused as many deaths each year as those from acute myocardial infarction.[4]

In the recent years major improvements have been made in our knowledge of pathophysiologic mechanisms of sepsis. This syndrome is the result of a very complex interaction between an infectious stimulus and the host immune system. The driving force of the inflammatory response is usually an infectious agent (*i.e.*, viruses, bacteria or parasites), that causes an intricate cascade characterized by a "chaotic" activation/deactivation of several factors of the inflammatory and coagulatory systems.[5] The endotoxin, that is a component of the outer membrane of gram-negative bacteria, have a major role in causing initial cytokines release during acute severe infection. In the past, great efforts were devoted to find therapeutic options able to block the inflammatory response precociously, avoiding the uncontrolled evolution of inflammatory cascade. Polymyxin B was initially evaluated for its endotoxin-binding properties, but its relevant nephrotoxic and neurotoxic effects have always limited the intravenous administration of this drug. Therefore, some researchers from Japan conducted pioneering studies on extracorporeal blood purification by using a cartridge with polymyxin B immobilized to polystyrene fibers. This technique has been demonstrated to be effective in removing the circulating endotoxin, preventing the inflammatory cascade of sepsis, with limited side effects.[6] Polymyxin B hemoperfusion has been widely accepted and applied in Japan [7] (this treatment has been reimbursed by the National Healthcare System of this country since 1994), but the lack of clear evidences of survival benefits [8, 9] have limited its application in other countries.

In this issue of the Minerva Anestesiologica, Zagli *et al.*[10] reported their experience in the use of polymyxin B hemoperfusion in 12 patients with severe sepsis or septic shock due to intra-abdominal cavity infection. Patients enrolled in this study were characterized by a high severity of the disease (average SAPSII score was 61), severe multi-organ failure and full resuscitative treatment (in fact all of them were treated with continuous reno-venous hemofiltration and significant levels of vasoactive agents). In these subjects, the application of two cycles of polymyxin B hemoperfusion markedly reduced plasmatic concentration of cytokines. These biohumoral effects were associated to significant clinical benefits, with improvement in cardiovascular and respiratory dysfunctions, and with an observed mortality surprisingly low considering the severity of the illness (50%). Furthermore, an interesting correlation was found between reduction of cytokines level and clinical outcome, confirming that polymyxin B hemoperfusion is effective in increase survival by reducing the proinflammatory state. Finally, the authors observed that different pattern of baseline cytokines expression

might help to predict the response to polymyxin B hemoperfusion. Overall, the findings of this study encourages the use of this treatment, and they stimulate further research on biohumoral monitoring during sepsis.

However, as clinicians, the most relevant question to ask is: nowadays, are the evidences available strong enough to support clinical application of this treatment to our septic patients? Of note, the largest randomized controlled trial on polymyxin B hemoperfusion in abdominal septic patients has been very recently released on a leading medical journal.[11] This study, carried out by a group of talented Italian researchers, convincingly demonstrated that polymyxin B hemoperfusion reduced organ dysfunction and markedly improve survival (one death prevented every five patients treated). Despite these remarkable results, relevant issues remain currently unresolved, mainly the timing and length of treatment and the generalizability of the benefits in sepsis caused by non-abdominal foci. Further studies are needed for definitive guidelines. However, we can give some recommendations for a reasonable clinical application of this treatment: first, polymyxin B hemoperfusion should not be limited to patients with severe abdominal infection, but should be used in any severely-septic patient with known or highly suspected gram-negative infection (*e.g.*, ventilator-associated pneumonia, urinary-tract infection, etc.). Accordingly, considering the high cost of the polymyxine-B cartridge (around 4 000 Euros), this treatment should be avoided in less severe patients, in patients with uncontrolled source of infection, or in patients with gram-positive infection (as proposed by some authors [6]). Second, polymyxin B hemoperfusion has shown a greater efficacy in patients with higher endotoxin and cytokines level, but until the assessment of biohumoral profile is not available at the bedside, patient selection should be based primarily on the illness severity. Third, polymyxin B hemoperfusion should be used as earlier as possible, *i.e.*, when the "inflammatory storm" is more likely to occur. Finally, as clinical studies [9] that applied one cycles of polymyxin B hemoperfusion were less effective in endotoxin clearance and mortality reduction, a treatment protocol with at least two-cycles of hemoperfusion should be adopted.

In conclusion, after several years of conflicting results, basic and clinical studies finally proved that polymyxin B hemoperfusion is an effective therapeutic option for severe septic patient. We should be grateful to all the researchers and clinicians involved in this outstanding achievement, for their hard work and tireless perseverance. As a Japanese proverb goes "stumbling seven times, but recovering eight", *i.e.*, perseverance is the key. This is particularly truthful for researching in critical care medicine.

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