

Corticosteroids in septic shock: What should the decision in pediatrics be?

CORTICOSTEROIDES NO CHOQUE SÉPTICO: QUE DECISÃO TOMAR NA PEDIATRIA?

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Severe sepsis and septic shock are major global causes of morbidity and mortality in children. In this context, consensus and guidelines were created for early and effective identification and therapeutic approach. As with adults, the guidelines for septic shock in pediatrics suggest the use of corticosteroids in cases that are refractory to vasoactive drugs.¹ However, there are no pediatric clinical studies supporting the recommendation satisfactorily, and it is important to remember the fact that children are not small adults and that the steroid metabolism in both differs.²

The use of corticosteroids in septic shock has a long history in medicine and continues to generate great controversy. Its history began in the 1950s, in an attempt to treat adrenal insufficiency allegedly caused by meningococemia in pediatric patients.³ In 1963, a study involving adults and children showed no benefit from the use of hydrocortisone in severe infections.⁴ However, supported by studies by Schumer⁵ in the 1970s, the use of corticosteroids in high doses and for short periods of time became widespread in the treatment of sepsis until the 1980s. In 1987, in turn, two large randomized controlled studies failed to confirm its effect on mortality reduction.^{6,7} In 1995, two meta-analyses (Lefering et al. and Cronin et al.) concluded there was no impact on mortality and the results could even be adverse.^{8,9} In the late 1990s, it was speculated that lower doses (stress-dose) could reduce vasopressor doses in critically ill patients.¹⁰⁻¹² The article that reinforced this thesis and made an immediate impact on clinical practice was published

by Annane et al.¹³ and proposed the use of low doses over a longer period of time. This approach produced very inconsistent results in many randomized trials, which ended up concluding that this conduct not only did not reduce mortality but also could be associated with increased morbidity.^{14,15} The PROGRESS trial (n=8,960)¹⁵ revealed the widespread adoption of steroids in sepsis worldwide (Brazil was the country with greater use) and significant variations as to its use. In 2012, Casserly et al.¹⁶ examined the use of low doses of corticosteroids in septic shock based on data from the Surviving Sepsis Campaign and concluded that these drugs were used indiscriminately and were associated with increased mortality. Their study had the advantage of deriving from a multicenter database, and of having examined a very large population (n=17,847). Recent meta-analyses have concluded that corticosteroids appear to improve the hemodynamics of patients in shock, but without significant results on mortality.¹⁷ Currently, several studies stand out on the subject in various areas, such as the suppression of adaptive immunity¹⁸ and the resistance of tissues to stimulation by corticosteroids.¹⁹

The studies on corticosteroids in pediatric sepsis are not as scarce as before; however, there are no large controlled clinical trials on its use. Since 2005, based on a study by Markowitz et al.,²⁰ it has been discussed whether pediatric patients with septic shock would benefit from treatment with corticosteroids. Markowitz's work used data from the Pediatric Health Information System (n=6,693) and showed there is no evidence to indicate bet-

ter results in children. But the assessment was limited by lack of data related to the severity of the analyzed population. In that same year, Pizarro et al.²¹ concluded that absolute and relative adrenal insufficiency was common in children with catecholamine-resistant shock, and with shock not responsive to fluid resuscitation. Menon et al. conducted a very comprehensive work of relative adrenal insufficiency in critically ill children (n=381), not necessarily in shock, in seven pediatric tertiary intensive care units in Canada, supporting the concept of relative adrenal insufficiency in critical conditions.²² In 2011, the RESOLVE trial²³ examined children with severe sepsis who received corticosteroids and showed that disease progression was similar to those who did not receive them. The results (mortality, time using inotropes, mechanical ventilation time, organ failure resolution, changes in mortality score, and hospitalization) were similar in children who were treated with and without steroids. Recent studies, including those conducted in developing countries and involving specific pathologies, emphasize the reduction of inotropic agents, without impact on mortality.^{24,25} In 2013, a meta-analysis of trials with a small number of patients showed no benefit attributable to corticosteroids.²⁶ Atkins et al.²⁷ proposed the lack of evidence of improvement could be due to the fact that children who received corticosteroids had a higher initial mortality risk than those who did not receive them. But in this exact multicentric and retrospective study (n=496), based on severity stratifications (PERSEVERE and PRISM), no benefits were observed from its use.

Since the first guidelines for the diagnosis and treatment of severe sepsis and septic shock in the 1990s, one of the most controversial issues is the use of corticosteroids as a treatment option, especially in cases of catecholamines resistance. This subject has produced multiple randomized controlled trials in adults, but results are conflicting and a consensus has not been reached. In pediatrics, studies are less abundant, but hydrocortisone is currently recommended for children with septic shock, although there is no clear evidence of its effectiveness. The guidelines of the Surviving Sepsis Campaign 2012¹ stipulated that the use of hydrocortisone should be considered for adult and pediatric septic shock when hypotension does not respond to adequate fluid resuscitation and vasopressors (level 2C of evidence in adults and 1A in pediatrics). The recommendation is also suggested by the American College of Critical Care Medicine.²⁸ We must bear in mind that, despite the absence of large randomized controlled trials in children, some information is available from several small studies in the literature, al-

though the results are still very unsatisfactory. Thus, in addition to children receiving chronic steroids and children with "classic" adrenal insufficiency, the accumulated evidence does not support a routine use of corticosteroids in children with septic shock.

Guidelines have emerged to standardize the treatment of sepsis and septic shock around the world, also in countries with few resources, reducing costs, morbidity, and mortality. Considering the results of current pediatric studies on the subject, we believe there is a pressing need to update the guidelines, based on the most consistent clinical results. This point-of-view article shows the very limited evidence that is the basis for current guidelines, and thus the need for well-designed studies on the use of corticosteroids in pediatric shock to update future guidance.

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