MEDwave

Living FRIendly Summaries Of The Body Of Evidence Using Epistemonikos (FRISBEE)
Medwave 2016;16(Suppl3):e6522 doi: 10.5867/medwave.2016.6522

What is the role of corticosteroids in the management of sepsis?

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Citation: Jerez J, Castro R . What is the role of corticosteroids in the management of sepsis?. *Medwave* 2016;16(Suppl3):e6522 doi: 10.5867/medwave.2016.6522
Publication date: 30/8/2016

Abstract

During an episode of sepsis, the systemic inflammatory response phenomenon triggers a deficit in the action and/or secretion of cortisol. It has been suggested that the use of corticosteroids may have a role in the management of sepsis, but there is no consensus. Searching in Epistemonikos database, which is maintained by screening 30 databases, we identified 16 systematic reviews including 64 randomized trials addressing the question of this article. We combined the evidence using meta-analysis and generated a summary of findings following the GRADE approach. We concluded the use of corticosteroids during a sepsis episode probably favors reversal of shock, briefly shortens the stay in intensive care unit and might reduce mortality, with few clinically relevant adverse effects.

Problem

Sepsis remains the leading cause of morbidity and mortality in intensive care units worldwide. Its incidence has been increasing, with more complications and more resistant infectious agents. While there has been a tendency to a decrease in mortality due to some interventions, effective therapeutic tools remain limited.

During an episode of sepsis, systemic inflammatory response phenomenon triggers a deficit in action and/or cortisol secretion secondary to proinflammatory cytokines. For this reason, it has been postulated the use of steroids may play a role in the management of sepsis. However, evidence has been mixed regarding its actual effect, and there is still no consensus on the role played by this treatment in sepsis.

Methods

We used Epistemonikos database, which is maintained by screening more than 30 databases, to identify systematic reviews and their included primary studies. With this information we generated a structured summary using a pre-established format, which includes key messages, a summary of the body of evidence (presented as an evidence matrix in Epistemonikos), meta-analysis of the total of studies, a summary of findings table following the GRADE approach and a table of other considerations for decision-making.

Key messages
- The use of corticosteroids in patients with sepsis might reduce mortality.
- The use of corticosteroids in patients with sepsis probably favors the reversal of shock and decreases stay in intensive care units.
- Use of corticosteroids in patients with sepsis is a low-cost therapy with minimal adverse effects, so risk/benefit and cost/benefit balance are probably favorable.

About the body of evidence for this question

What is the evidence. See evidence matrix in Epistemonikos later	We found sixteen systematic reviews [1],[2],[3],[4],[5],[6],[7], [8],[9],[10],[11],[12],[13],[14],[15],[16], including 66 primary studies (64 randomized controlled trials). Two systematic reviews were excluded from the analysis. One was exclusively focused on pediatric population (whose protocols and evolution differs regarding adult population) [9] and the other was restricted to patients with dengue [6]. The remaining reviews include fifty-three randomized controlled trials [17],[18],[19],[20],[21],[22],[23],[24],[25],[26],[27],[28],[29],[30],[31], [32],[33],[34],[36],[37],[38],[39],[40],[41],[42],[43],[44],[45],[46],[47], [48],[49],[50],[51],[52],[53],[54],[55],[56],[57],[58],[59],[60],[61],[62], [63],[64],[65],[66],[67],[68],[69].
What types of patients were included	Nineteen studies included were conducted prior to 1991, when the first Consensus Definitions for Sepsis and Septic Shock [70] was released. So, the definition and classification of the severity of sepsis was heterogeneous among studies, added to the fact the third Consensus Definitions for Sepsis and Septic Shock has been published recently [71].
What types of interventions were included	The most commonly used steroid was hydrocortisone (53.8%), then dexamethasone (21.1%), methylprednisolone (17.3%) and others (e.g. betamethasone, prednisolone; 7.8%). The route of administration was intravenous in all of the studies. Regarding the dose (equivalent to hydrocortisone), doses ranged from 30 mg to 4200 mg per day. The different systematic reviews used different definitions to consider low-dose corticosteroids. Some used a dose equivalent <300 mg hydrocortisone per day, another 400 mg and even 500 mg. 50% of the studies used less than or equal to 300 mg daily dose. Only two studies added mineralocorticoids [18],[28]. All of the studies compared against placebo or standard treatment.
What types of outcomes were measured	The different systematic reviews pooled the following outcomes: - Mortality at 28 days - Reversal of shock at 7 days - Reversal of shock at 28 days - Stay in intensive care unit - Sequential Organ Failure Assessment (SOFA) score at 7 days - Gastrointestinal bleeding - Superinfection - Hyperglycemia - Critical illness myoneuropathy - Hypernatremia

Summary of findings

Information on the effects of using steroids in sepsis is based on 44 randomized trials that provided information usable for meta-analysis involving 5618 patients. Forty-four trials reported mortality [17],[18],[19],[20],[21],[22],[23],[24],[25],[26],[27],[29],[30],[32],[33],[34],[39],[40],[41],[42],[43],[44],[45],[46],[47],[48],[51],[52],[53],[55],[56],[57],[58],[59],[60],[61],[62],[63],[64],[65],[66],[67],[68],[69], 12 trials reported reversal of shock [18],[19],[22],[23],[24],[25],[32],[34],[55],[57],[60],[61], 12 trials reported stay in intensive care [18],[19],[22],[24],[25],[29],[32],[34],[44],[59],[61],[66], 20 trials reported gastrointestinal bleeding [18],[19],[20],[22],[24],[25],[27],[29],[32],[42],[44],[46],[55],[57],[59],[61],[63],[67],[68],[69], 21 trials reported superinfection [17],[18],[19],[20],[22],[23],[24],[25],[27],[29],[32],[39],[42],[46],[57],[59],[60],[61],[63],[68],[69], 13 trials reported hyperglycemia [18],[19],[22],[42],[44],[46],[57],[59],[60],[61],[63],[68],[69] and three trials reported myoneuropathy of critically ill patients [18],[19],[61]. The summary of findings is the following:

- The use of corticosteroids in patients with sepsis might decrease mortality. The certainty of the evidence is low.
- The use of corticosteroids in patients with sepsis probably increases the chance of shock reversal at 7 days. The certainty of the evidence is moderate.
- The use of corticosteroids probably produces a slight increase in the risk of upper gastrointestinal bleeding. The certainty of the evidence is moderate.
- The use of corticosteroids in patients with sepsis increases the risk of hyperglycemia. The certainty of the evidence is high
- The use of corticosteroids in patients with sepsis has little or no effect on the risk of superinfection. The certainty of the evidence is high.
- It is unclear whether the use of corticosteroids in patients with sepsis increases the risk of critical illness myoneuropathy. The certainty of the evidence is very low.
- The use of corticosteroids probably decreases slightly the time spent in intensive care units. The certainty of the evidence is moderate.

Corticosteroids for sepsis				
Patients	Sepsis			
Intervention	Corticosteroids			
Comparison	Placebo or standard therapy			
Outcomes	Absolute effect*		Relative effect (95% CI)	Certainty of the evidence (GRADE)
	WITHOUT Corticosteroids	**WITH** Corticosteroids		
	Difference: patients per 1000			
Mortality at 28 days	339 per 1000	298 per 1000	RR 0.88 (0.79 to 0.98)	⊕⊕◯◯[1,2] Low
	Difference: 41 patients less per 1000 (Margin of error: 7 to 71 less)			
Shock reversal at 7 days	536 per 1000	692 per 1000	RR 1.29 (1.13 to 1.47)	⊕⊕⊕◯[2] Moderate
	Difference: 156 patients more per 1000 (Margin of error: 70 to 252 more)			
Gastrointestinal bleeding	48 per 1000	59 per 1000	RR 1.24 (0.93 to 1.67)	⊕⊕⊕◯[3] Moderate
	Difference: 11 patients more per 1000 (Margin of error: 3 less to 32 more)			
Superinfection	145 per 1000	150 per 1000	RR 1.03 (0.85 to 1.25)	⊕⊕⊕⊕ High
	Difference: 5 patients more per 1000 (Margin of error: 22 less to 36 more)			
Hyperglycaemia	351 per 1000	425 per 1000	RR 1.21 (1.10 to 1.33)	⊕⊕⊕⊕ High
	Difference: 74 patients more per 1000 (Margin of error: 35 to 116 more)			
Critical illness myoneuropathy	17 per 1000	11 per 1000	RR 0.63 (0.12 to 3.35)	⊕◯◯◯[2,3] Very low
	Difference: 6 patients less per 1000 (Margin of error: 15 less to 41 more)			
Length of stay in intensive care unit	20 days **	18.32 days		⊕⊕⊕◯[2] Moderate
	Margin of error: 1.68 days less (MD) (0.09 to 3.27 days less)			

RR= Risk ratio.
MD= Mean difference.
Margin of error = 95% confidence interval (CI).
GRADE: evidence grades of the GRADE Working Group (see later in this article).

* The risk **WITHOUT CORTICOSTEROIDS** is based on the risk in the control group of the trials. The risk **WITH CORTICOSTEROIDS** (and its margin of error) is calculated from relative effect (and its margin of error)
** The risk **WITHOUT CORTICOSTEROIDS** is based on the risk on the risk of the more representative trials (and with larger sample size) [18], [61]. The risk **WITH CORTICOSTEROIDS** (and its margin of error) is calculated from the mean difference (and its margin of error).

[1] The certainty of the evidence was downgraded in one level because of indirect evidence, due to variability in the definition of septic patients
[2] The certainty of the evidence was downgraded in one level because of inconsistency.
[3] The certainty of the evidence was downgraded in two levels for imprecision as the confidence interval includes both a benefit and a clinically significant risk.

About the certainty of the evidence (GRADE)*

⊕⊕⊕⊕
High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.

⊕⊕⊕◯
Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate

⊕⊕◯◯
Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.

⊕◯◯◯
Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.

*This concept is also called 'quality of the evidence' or 'confidence in effect estimates'.
† Substantially different = a large enough difference that it might affect a decision.

Other considerations for decision-making

To whom this evidence does and does not apply

- The first Consensus Definitions for Sepsis and Septic Shock in 1991 included the concepts of severe sepsis and septic shock. The latest revision of this consensus held in 2016 gave rise to a new definition of sepsis (as a condition involving organ dysfunction) and removed the concept of severe sepsis. Considering the above, according to latest consensus, most patients in the studies would fall into the category of sepsis (formerly severe sepsis) and septic shock. So the use of steroids could be applied in patients with sepsis and septic shock according to the latest consensus, and not in patients in whom organ dysfunction can not be substantiated.

About the outcomes included in this summary

- Seven relevant outcomes were included in this summary as key when deciding whether or not to implement the therapy, according to the opinion of the authors of this summary. They are also the outcomes more frequentely selected by the identified systematic reviews.
- Some outcomes as Sequential Organ Failure Assessment (SOFA) Score at seven days, shock reversal at 28 days and hypernatremia were considered less relevant for decision making.

Balance between benefits and risks, and certainty of the evidence

- The use of steroids in sepsis probably leads to benefits in patients with septic shock: it increases the reversal of shock, decreases length of stay in intensive care units, and may reduce mortality, with the only adverse effect of hyperglycemia (which in turn would decrease with use of low-dose steroids). The benefit/risk is probably favorable to the use of corticosteroids.
- The main systematic review conducted a subgroup analysis [1] suggesting the population who benefit most are patients with septic shock receiving low doses (<400 mg/day) for prolonged periods (> 5 days), which has been corroborated by other systematic reviews [2],[3],[10],[11].

What would patients and their doctors think about this intervention

- This is a clinical decision where variation in preferences by physicians can be expected, due to the low certainty of the evidence about mortality.
- It is reasonable to think the decision for the majority of clinicians will range from treating all patients to selecting those with the highest expected benefit, such as those suggested by the subgroup analysis mentioned above.

Resource considerations

- Corticosteroids probably constitute a cost/effective intervention because of their low-cost, and some benefits that lead to savings such as shorting length of stay in intensive care units, reversion of shock with consequent reduction in the use of other supportive therapies (e.g. vasoactive drugs), apart from the possibility of reduction in mortality.

Differences between this summary and other sources

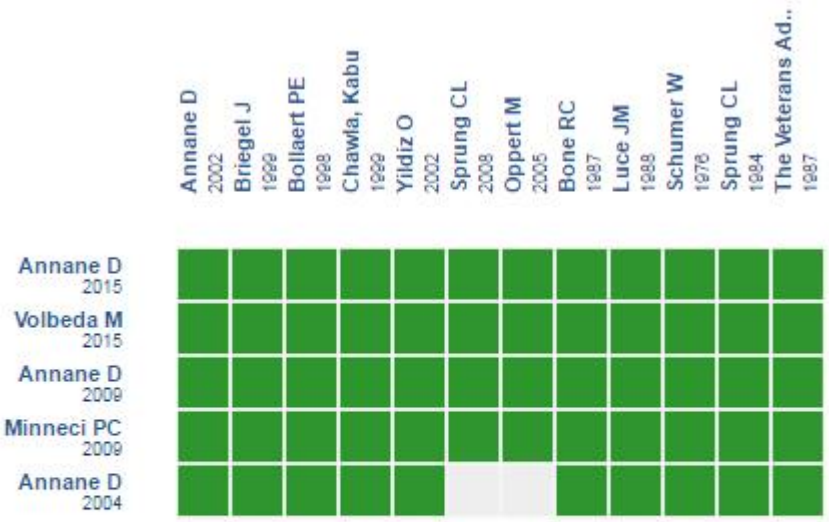
- Our summary is partially consistent with the systematic reviews identified, although they are preferentially focused on the effect of corticosteroids on mortality.
- Our summary is partially consistent with the Surviving Sepsis Campaign, the main guideline in the management of sepsis [72] which stipulates steroids use should be restricted to the group of patients with septic shock who do not respond favorably to fluid resuscitation and vasoactive drugs, in doses equivalent to hydrocortisone 200 mg per day in continuous intravenous infusion (it would decrease the risk of hyperglycemia and hypernatremia) until reversal of shock. Our summary extends the benefit of low-dose corticosteroids to a wider group of patients. A significant proportion of the evidence collected in this summary was not available when this guideline was developed.

Could this evidence change in the future?

- The probability that the evidence presented in this summary change in the future is low due to the certainty of the evidence for most outcomes.
- New systematic reviews could provide relevant information. On one hand there are different methodological approaches to the synthesis of existing studies, and on the other hand none of the identified reviews considered a substantial proportion of the trials included in this summary.
- There are no ongoing trials regarding this question, at least according to the records of the International Clinical Trials Registry Platform of the World Health Organization.

How we conducted this summary

Using automated and collaborative means, we compiled all the relevant evidence for the question of interest and we present it as a matrix of evidence.



Starting from any systematic review, Epistemonikos builds a matrix based on existing connections in the database.
The author of the matrix can select relevant information for a specific health question (typically in PICO format) in order to display the information set for the question.
The *rows* represent systematic reviews that share at least one primary study, and *columns* display the studies.
The boxes in green correspond to studies included in the respective reviews.

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Notes

The upper portion of the matrix of evidence will display a warning of "new evidence" if new systematic reviews are published after the publication of this summary. Even though the project considers the periodical update of these summaries, users are invited to comment in *Medwave* or to contact the authors through email if they find new evidence and the summary should be updated earlier. After creating an account in Epistemonikos, users will be able to save the matrixes and to receive automated notifications any time new evidence potentially relevant for the question appears.

The details about the methods used to produce these summaries are described here: http://dx.doi.org/10.5867/medwave.2014.06.5997.

Epistemonikos foundation is a non-for-profit organization aiming to bring information closer to health decision-makers with technology. Its main development is Epistemonikos database (www.epistemonikos.org).

These summaries follow a rigorous process of internal peer review.

Conflicts of interest
The authors do not have relevant interests to declare.

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