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Living FRIendly Summaries of the Body of Evidence using Epistemonikos (FRISBEE)
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Are steroids effective in toxic epidermal necrolysis and Stevens-Johnson syndrome?

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Abstract

Toxic epidermal necrolysis and Stevens-Johnson syndrome are severe adverse skin reactions to medications and infections. Steroids are described as a therapeutic alternative, but their use is still controversial. To answer this question, we searched in Epistemonikos database, which is maintained by screening multiple information sources. We identified four systematic reviews including 11 primary studies answering the question of interest. We extracted data, conducted a meta-analysis and generated a summary of findings table using the GRADE approach. We concluded it is not clear whether steroids reduce mortality or hospital stay in toxic epidermal necrolysis and Stevens-Johnson syndrome because the certainty of the evidence is very low.

Problem

Toxic epidermal necrolysis and Stevens-Johnson syndrome are severe, idiosyncratic skin reactions, mainly caused by drug exposure, or secondary to bacterial and viral infections. They are both considered part of the spectrum of the same disease characterized by generalized epidermal necrosis secondary to keratinocytes apoptosis, and differentiated according to the extent of cutaneous involvement. The main pathway leading to apoptosis is the binding of FAS, a membrane receptor present in keratinocytes, with its ligand.

The therapeutic management includes general measures of support, prevention of complications and the use of different immunosuppressive drugs such as systemic steroids. However, their effectiveness in the treatment of toxic epidermal necrolysis and Stevens-Johnson syndrome is controversial and its use is associated with significant adverse effects.

Methods

We used Epistemonikos database, which is maintained by screening multiple information sources, 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

- It is not clear whether steroids reduce mortality or hospital stay in toxic epidermal necrolysis and Stevens-Johnson syndrome compared to support measures, because the certainty of the evidence is very low.

About the body of evidence for this question

What is the evidence. See evidence matrix in Epistemonikos later	We found four systematic reviews [1],[2],[3],[4] including 11 primary studies [5],[6],[7],[8],[9],[10],[11],[12],[13],[14],[15]. None is a randomized controlled trial.
What types of patients were included	All of the studies included patients diagnosed with Stevens-Johnson syndrome (<10% of cutaneous involvement), Stevens-Johnson syndrome/toxic epidermal necrolysis overlap (10% to 30% of cutaneous involvement) and/or toxic epidermal necrolysis (>30% of cutaneous involvement). Seven studies [5],[6],[7],[8],[9],[10],[11] included patients older than 18 years, and four studies [12],[13],[14],[15] only included children. Only three studies [7],[9],[11] reported the percentage of cutaneous involvement. Six studies [6],[7],[8],[9],[10],[11] reported the etiology, with drugs being the leading cause.
What types of interventions were included	The included studies used different types of steroids, doses, route of administration, and duration. The use of oral prednisone, intravenous dexamethasone and intravenous methylprednisolone (with or without an initial bolus) was reported. Three of the studies [6],[8],[9] also incorporated intravenous immunoglobulin.
What types of outcomes were measured	The studies measured multiple outcomes. However, those that were grouped in the identified reviews were: • Mortality • Hospital stay • Fever duration • Evolution of lesions • Complications • Superinfection • Need of intravenous fluids

Summary of findings

The information about the effects of steroids on toxic epidermal necrolysis and Stevens-Johnson syndrome is based on 11 observational studies [5],[6],[7],[8],[9],[10],[11],[12],[13],[14],[15]. It was not possible to extract the information of the primary studies from the systematic reviews, in order to rebuild the meta-analysis. So, the information is presented here such as presented in the systematic reviews [1],[2],[3],[4]. The summary of findings is as follows:

- It is not clear whether steroids reduce mortality in toxic epidermal necrolysis and Stevens-Johnson syndrome compared to support measures, because the certainty of the evidence is very low.
- It is not clear whether steroids reduce hospital stay in toxic epidermal necrolysis and Stevens-Johnson syndrome compared to support measures, because the certainty of the evidence is very low.
- The use of systemic steroids is associated to several adverse effects, probably frequent when treating toxic epidermal necrolysis and Stevens-Johnson syndrome. The certainty of the evidence is moderate.

Steroids for toxic epidermal necrolysis and Stevens-Johnson syndrome		
Patients	Toxic epidermal necrolysis, Stevens-Johnson syndrome and Stevens-Johnson syndrome/toxic epidermal necrolysis overlap	
Intervention	Systemic steroids	
Comparison	Support management	
Outcomes	**Impact**	**Certainty of the evidence (GRADE)**
Mortality	None of the systematic reviews found benefits with the use of systemic steroids. One of them provides a pooled measure based on three studies; *mortality ratio** of 0.92 (95% CI: 0.53 to 1.48) [2]. The other reviews present the results of each study separately, concluding they have limitations and reach to discordant results [1], [3], [4].	⨁◯◯◯[1,2,3] Very low
Hospital Stay	All of the reviews present the results of each study separately, agreeing on their limitations and their discordant results.	⨁◯◯◯[1,2] Very low
Adverse effects	None of the systematic reviews assessed adverse effects within their outcomes. However, in similar populations, frequent and severe adverse effects have been reported with high doses of steroids [1], [12].	⨁⨁⨁◯[4] Moderate

Margin of error = 95% confidence interval
CI = confidence interval
GRADE: evidence grades of the GRADE Working Group (see later in this article)

* Mortality ratio: calculated based on the frequency of observed and expected deaths (according to SCORTEN prognostic score).

[1] Evidence comes from observational studies.
[2] The certainty of the evidence was downgraded because the studies have a high risk of bias. All of the studies are retrospective, among other limitations.
[3] The certainty of the evidence was downgraded for imprecision, due to the wide confidence interval of the results.
[4] Evidence comes from studies in different populations.

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 evidence presented in this summary is broadly applicable to patients of any age with toxic epidermal necrolysis, Stevens-Johnson syndrome and Stevens-Johnson syndrome/toxic epidermal necrolysis overlap.
- The systemic steroids used in the included studies were methylprednisolone, dexamethasone and prednisone, which correspond to drugs usually administered in clinical practice.

About the outcomes included in this summary

- This summary considers as critical outcomes for decision-making those that are relevant from the perspective of the authors. These coincide with those presented in the systematic reviews analyzed and in the main clinical guidelines, except the outcome adverse effects that was not evaluated in the systematic reviews.

Balance between benefits and risks, and certainty of the evidence

- It is not possible to balance risks and benefits, because the certainty about the benefits is very low.

What would patients and their doctors think about this intervention

- In view of the evidence presented in this summary, most clinicians should lean against the use of this intervention.
- However, taking into account the lack of effective alternatives in the management of this condition, and the existence of contradictory recommendations in the current guidelines, some physicians could decide to use a therapeutic measure whose effects have not been proven.
- In this setting, it is essential to emphasize the limitations of the existing evidence to all those involved in the decision.

Resource considerations

- It is not possible to provide a cost/benefit estimation due to the uncertainty about the benefits.
- In general, systemic steroids are drugs of low-cost and widely available.This factor should probably not be determinant in the decision-making process.

Differences between this summary and other sources

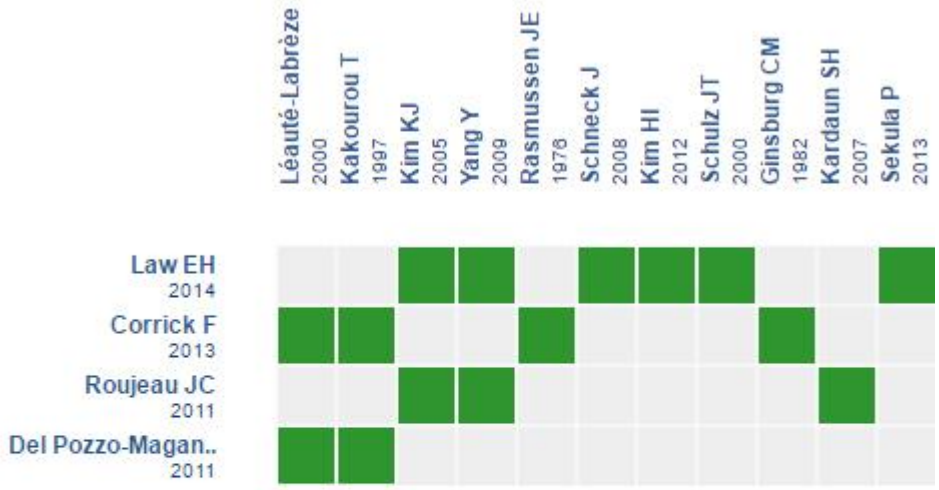
- The conclusions of this summary are consistent with the findings of the analyzed systematic reviews.
- There is variability in the recommendations of the main clinical guidelines regarding the management of toxic epidermal necrolysis and Stevens-Johnson syndrome, but they agree in general with the conclusions of this summary. The American Burn Association [16] and the UK guidelines for the management of Stevens-Johnson syndrome/toxic epidermal necrolysis in adults [17] do not mention the use of systemic steroids within their recommendations.

Could this evidence change in the future?

- The possibility that future evidence lead to changes in the conclusions of this summary is very high due to the existing uncertainty, especially if it comes from randomized trials.
- According to the International Registry Platform for Controlled Trials of the World Health Organization, there are no ongoing trials regarding the use of systemic steroids compared to placebo or no treatment. We identified at least one trial evaluating the use of topical steroids [18].

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.

Follow the link to access the **interactive version:** Steroids for Stevens-Johnson syndrome and toxic epidermal necrolysis

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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