

## PEER REVIEW HISTORY

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### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Identification of adults with sepsis in the prehospital environment: a systematic review.
<b>AUTHORS</b>	Smyth, Michael; Brace-McDonnell, Samantha; Perkins, Gavin

### VERSION 1 - REVIEW

<b>REVIEWER</b>	Nai Ming Lai School of Medicine, Taylor's University, Malaysia.
<b>REVIEW RETURNED</b>	05-Feb-2016

<b>GENERAL COMMENTS</b>	<p>Statistical review</p> <p>Thank you for giving the opportunity to review the methods of this manuscript. Overall this systematic review is well-conducted and reported as the authors have clearly followed established standards. The data collection and analyses sections are particularly robust and should be commended.</p> <p>There are a few observations that I have made which I hope the authors will address to improve the manuscript. Among them, the search strategy and the use of GRADE are key areas of concerns that should be revised.</p> <p>1. Objectives The objectives need to be more specific. I believe the research question is about the diagnostic accuracy and/or utility of pre-hospital sepsis screening tools, and this should be clearly stated. One useful framework when undertaking a systematic review is to frame the research question in a format that allows for clear directions in the subsequent steps of the review. A common framework to use is the PICO framework, which in this case, when the review covers a screening or diagnostic question, should stand for P (population), I (Index test), C (compared test/reference standard) and O (target disorder).</p> <p>2. Study selection: electronic search Medline is a search engine that are hosted by different platforms, including the PubMed, which is a free platform hosted by the US National Library of Medicine, So, searches in PubMed and any other Medline platform should retrieve the same set of studies. I would think searching either one would be sufficient. Please include the date of search so the readers would know when the evidence was current to.</p> <p>Conference proceedings/meeting abstracts: please state the name of the conference proceedings and meetings searched.</p>
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	<p><b>3. Inclusion criteria</b>  Publication type: conference proceedings are included under “peer-reviewed publication”– they authors may wish to check this as not many conference proceedings are fully peer-reviewed.</p> <p>Study design: retrospective analyses is too broad a term as it denotes several possible study designs, including case control studies which have been mentioned. Was it “retrospective cohort study” that the authors had in mind? Conference proceedings is not a study design, but rather a publication type.</p> <p>Study population: if the population is limited to adults, it should be stated in the title, as sepsis is common in children.</p> <p>Exclusion criteria: the authors excluded “non-systematic reviews”. How did the authors identify non-systematic review and differentiate between systematic and non-systematic reviews? Please clarify.</p> <p><b>4. Appendix 1: Medline search strategy</b>  It is surprising to me that the authors did not include terms related to screening or diagnosis in their search strategy. If such terms as “diagnos*”, “screen*”, “detect*”, “identif*” and the like were included and combined with the settings using the Boolean operator ‘OR’, there might have been more relevant articles retrieved.</p> <p><b>5. Supplementary material: GRADE rating</b>  I am not sure whether the authors used GRADE in the most appropriate way. GRADE is used to rate the quality of a body of evidence for each major outcome in a systematic review. It is not usually used to rate the quality of evidence for each included study, as done by the authors. The authors might have felt awkward rating inconsistency on every single study here, as this only applies for evidence gathered from a group of studies.</p> <p>The authors should rework this section by taking the major outcome and rate the quality of evidence from all the studies gathered based on the five criteria for downgrading of evidence and three criteria for upgrading of evidence (download the gradepro software or go to GDT Guideline development site for an online free version). In this case, choosing an outcome should be straightforward, as there is only one major outcome, namely, detection of sepsis. However, the authors should bear in mind that the best form of study to assess the usefulness of pre-hospital sepsis screening tool is a randomized controlled trial that assess sepsis-related mortality and morbidities with pre-hospital screening in one arm and no screening in the other arm. In this case, there might be more than one outcome. The authors might wish to rerun their searches taking into account of my suggestions in point 4 to see if there is any relevant RCT retrieved (although I doubt so).</p>
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<b>REVIEWER</b>	Ole Bayer, MD Department of Anesthesiology and Intensive Care Jena University Hospital Erlanger Allee 101 07747 Jena Germany
<b>REVIEW RETURNED</b>	22-Feb-2016

<b>GENERAL COMMENTS</b>	<p>This is a well done systematic review that collates summary measures of effectiveness for prehospital sepsis screening tools. The methods are detailed and targets predefined. Strength and weaknesses are discussed adequately by the authors. I would only describe more details of the statistical methods of the included studies. For example: To develop the PRESEP score, Loess curves were used for empirical identification of cutoffs for potential predictors for prehospital sepsis. To summarize, I score this work highly, think it will be of interest to EMS providers, emergency physicians, paramedics and clinicians as well because sepsis is a relevant disease in emergency medicine, and recommend approval with minor changes.</p> <p>Page 8, Line 5: BAS 90-30-90, not 30-90-90 Page 21, Reference 29 and 33 are the same</p>
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### VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Thank you for giving the opportunity to review the methods of this manuscript.

Overall this systematic review is well-conducted and reported as the authors have clearly followed established standards. The data collection and analyses sections are particularly robust and should be commended. There are a few observations that I have made which I hope the authors will address to improve the manuscript. Among them, the search strategy and the use of GRADE are key areas of concerns that should be revised.

#### 1. Objectives

The objectives need to be more specific. I believe the research question is about the diagnostic accuracy and/or utility of pre-hospital sepsis screening tools, and this should be clearly stated. One useful framework when undertaking a systematic review is to frame the research question in a format that allows for clear directions in the subsequent steps of the review. A common framework to use is the PICO framework, which in this case, when the review covers a screening or diagnostic question, should stand for P (population), I (Index test), C (compared test/reference standard) and O (target disorder).

- We have rewritten the objective utilising a PICO structure

#### 2. Study selection: electronic search

Medline is a search engine that are hosted by different platforms, including the PubMed, which is a free platform hosted by the US National Library of Medicine, So, searches in PubMed and any other Medline platform should retrieve the same set of studies. I would think searching either one would be sufficient. Please include the date of search so the readers would know when the evidence was current to.

- We acknowledge that searching PubMed will include the Medline platform and creates additional work without any guarantee of a greater yield, however Pubmed seaches include additional journals submitted to PMC, which may return results not identified searching Medline alone. In turn, Medline offers convenient searching utilising MeSH terms. We hope this outlines why we chose to search both platforms.

Conference proceedings/meeting abstracts: please state the name of the conference proceedings and meetings searched.

- We did not expressly search conference/meeting databases. Embase includes conference/meeting abstract in its results. Such abstract publications were retained if no full publication could be found.

### 3. Inclusion criteria

Publication type: conference proceedings are included under “peer-reviewed publication”– they authors may wish to check this as not many conference proceedings are fully peer-reviewed.

- We have amended the publication type to state ‘original research published in peer-reviewed journals, conference proceedings’

Study design: retrospective analyses is too broad a term as it denotes several possible study designs, including case control studies which have been mentioned. Was it “retrospective cohort study” that the authors had in mind? Conference proceedings is not a study design, but rather a publication type.

- We have deleted retrospective analyses and moved conference proceedings to publication type

Study population: if the population is limited to adults, it should be stated in the title, as sepsis is common in children.

- Title amended to reflect adult population

Exclusion criteria: the authors excluded “non-systematic reviews”. How did the authors identify non-systematic review and differentiate between systematic and non-systematic reviews? Please clarify.

- Non-systematic reviews was intended to imply literature reviews without adequate description of method to ensure there was no bias in the inclusion of evidence. Non-systematic reviews has been deleted and publication type amended to state narrative/literature reviews

### 4. Appendix 1: Medline search strategy

It is surprising to me that the authors did not include terms related to screening or diagnosis in their search strategy. If such terms as “diagnos\*”, “screen\*”, “detect\*”, “identif\*” and the like were included and combined with the settings using the Boolean operator ‘OR’, there might have been more relevant articles retrieved.

- A key challenge identified by this review was the poor / inconsistency of index terms for studies in this are. As an illustration inclusion of the above terms makes the search more specific and results in 0 articles identified

### 5. Supplementary material: GRADE rating

I am not sure whether the authors used GRADE in the most appropriate way. GRADE is used to rate the quality of a body of evidence for each major outcome in a systematic review. It is not usually used to rate the quality of evidence for each included study, as done by the authors. The authors might have felt awkward rating inconsistency on every single study here, as this only applies for evidence gathered from a group of studies.

- The supplementary material has been amended to better reflect a traditional evidence table. We have reported each critical appraisal consistent with the 5 GRADE domains to enable readers not familiar with GRADE to readily see how the level of evidence within the summary of findings table has been reached.

The authors should rework this section by taking the major outcome and rate the quality of evidence from all the studies gathered based on the five criteria for downgrading of evidence and three criteria for upgrading of evidence (download the gradepro software or go to GDT Guideline development site for an online free version). In this case, choosing an outcome should be straightforward, as there is only one major outcome, namely, detection of sepsis. However, the authors should bear in mind that the best form of study to assess the usefulness of pre-hospital sepsis screening tool is a randomized controlled trial that assess sepsis-related mortality and morbidities with pre-hospital screening in one arm and no screening in the other arm. In this case, there might be more than one outcome. The authors might wish to rerun their searches taking into account of my suggestions in point 4 to see if there is any relevant RCT retrieved (although I doubt so).

- The supplementary material was never intended to present a summary of findings table as this is included within the manuscript itself. We acknowledge that the manuscript summary of findings table does not present a summary estimate of effect across all included studies as might normally be expected with GRADE. There was significant heterogeneity between studies that precluded the metaanalysis that would be required to present a single summary statistic across the included studies. The approach we have adopted to present the estimates of effect for each of the included studies is the same as was adopted by the International Liaison Committee on Resuscitation (ILCOR) Consensus of Science and Treatment Recommendations, the largest GRADE style project completed thus far.

All the best.

Reviewer: 2

Please leave your comments for the authors below

This is a well done systematic review that collates summary measures of effectiveness for prehospital sepsis screening tools. The methods are detailed and targets predefined. Strength and weaknesses are discussed adequately by the authors. I would only describe more details of the statistical methods of the included studies. For example: To develop the PRESEP score, Loess curves were used for empirical identification of cutoffs for potential predictors for prehospital sepsis. To summarize, I score this work highly, think it will be of interest to EMS providers, emergency physicians, paramedics and clinicians as well because sepsis is a relevant disease in emergency medicine, and recommend approval with minor changes.

- We have expanded our description of statistical approach used to develop the screening tools, however we have not been detailed in doing so. The purpose of the review was to determine the effectiveness of the various tools. What matters to clinicians is how effective the screening tool is, not how complex model development was. We have included detail on numbers of participants to enable readers to make their own decisions as to precision and confidence in estimate of effect.

Page 8, Line 5: BAS 90-30-90, not 30-90-90  
Page 21, Reference 29 and 33 are the same

- Above points amended in manuscript.

**VERSION 2 – REVIEW**

<b>REVIEWER</b>	<p>Ole Bayer, MD, consultant Department of Anesthesiology and Intensive Care Medicine Jena University Hospital Erlanger Allee 101 07747 Jena Germany</p> <p>Dr. Bayer was supported, in part, by an unrestricted grant of the Thuringian Ministry of Cultural Affairs (Landesprogramm Pro-Exzellenz; PE 108-2); the Foundation of Technology, Innovation, and Research Thuringia (STIFT); and the German Sepsis Society and received speaker's fees from CSL Behring, Germany.</p>
<b>REVIEW RETURNED</b>	10-May-2016

<b>GENERAL COMMENTS</b>	<p>The manuscript "Identification of adults with sepsis in the prehospital environment: a systematic review" is now a very good review with a very relevant topic. The authors did all the suggested corrections. In my opinion no more changes are necessary. I suggest to publish this manuscript in BMJ.</p>
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