Australasian Journal of Paramedicine

Review

State of the evidence for emergency medical services care of adult patients with sepsis: an analysis of research from the Prehospital Evidence-based Practice program

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https://doi.org/10.33151/ajp.18.851

Abstract

Introduction
The Prehospital Evidence-based Practice (PEP) program is an online, freely accessible, continuously updated emergency medical services evidence repository. This PEP summary describes the research evidence for the identification and management of adult patients with sepsis or septic shock.

Methods
A systematic search of the literature on sepsis or septic shock was conducted. Studies were scored by trained appraisers on a three-point level of evidence scale (based on study design and quality) and a three-point direction of evidence scale (supportive, neutral or opposing findings based on the studies' primary outcome for each intervention).

Results
One hundred forty-three studies (80 existing and 63 new) were included for 16 interventions listed in PEP for adult patients with sepsis. The evidence matrix rank for supported interventions (n=16) were supportive-high quality (n=2, 12.5%) for crystalloid infusion and vasopressors, supportive-moderate quality (n=8, 50%) for identification tools, pre-notification, point-of-care lactate, titrated oxygen, temperature monitoring and balanced crystalloids. The benefit of pre-hospital antibiotics, colloids, Trendelenburg position and early goal-directed therapy remain inconclusive with a neutral direction of evidence. There is moderate level evidence opposing the use of high flow oxygen.

Conclusion
Several standard treatments are well supported by the evidence including fluid resuscitation, using balanced crystalloids, vasopressors and titrating oxygen. Tools for identifying and guiding treatment are also supported (eg. pre-notification, temperature monitoring and lactate). The evidence for antibiotic use is inconclusive. This PEP state of the evidence analysis can be used to guide selection of appropriate pre-hospital therapies during the development of pre-hospital protocols or clinical practice guidelines.

Keywords:
emergency medical services; knowledge translation; evidence-based practice; paramedic; evidence appraisal; clinical recommendation

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Introduction

A major barrier to evidence-based practice in emergency medical services (EMS) is the lack of high-quality evidence. Discovering the existing literature and applying it to practice can be a challenge for paramedics. This is due, in part, to few university library affiliations (particularly in countries lacking a degree-based educational pathway) and limited focus on evidence-based practice fundamentals in paramedic education. The Prehospital Evidence-based Practice (PEP) program seeks to bridge this gap by identifying and critically appraising EMS research. The PEP platform is a web-based, open access, continuously updated EMS evidence synthesis repository (1,2). The PEP program's primary objective is to systematically identify, critically appraise and collate studies on EMS clinical interventions. Recommendations are provided for clinical interventions used in specific clinical conditions. The evidence-based recommendations can guide EMS practice via integration into clinical practice guidelines or protocols (1,3,4). Critically appraising and summarising the pre-hospital evidence on sepsis identification and management is an important first step towards developing an evidence informed approach to care.

Sepsis is defined as life-threatening organ dysfunction caused by a pro-inflammatory and anti-inflammatory dysregulated host response (5). Septic shock is a subset of sepsis characterised by persistent hypotension, among other cellular and metabolic abnormalities (5). Mortality from sepsis is high at about 19 to 35%; seven to 11 times the risk compared to myocardial infarction (6-8). Paramedics often care for patients with sepsis – 1 to 8% of calls with 40 to 60% of these patients admitted to hospital. However, consistent strategies to identify and manage these patients in the pre-hospital setting are seldom adopted (9). Reducing mortality is dependent on timely access to definitive treatment (6,10-13). Paramedics are often the first point of medical contact for these patients and have an opportunity to impact their clinical trajectory with early identification of sepsis and medical intervention (6,10-13). We report on the current evidence for these pre-hospital inteventions.

In addition to the regular productivity of the PEP program; the PEP team annually selects relevant clinical presentations on which to focus a current state of the evidence report. The objective of this PEP state of the evidence report is to describe and critically appraise the published evidence for the identification and management of adult patients with sepsis or septic shock. Research gaps are identified, and EMS intervention recommendations provided.

Methods

Design

We conducted a PEP state of the evidence review of the literature using aspects of systematic review methods described previously (2,14).

The PEP database and website are structured with clinical conditions and EMS interventions (eg. pre-hospital antibiotics) by which a paramedic may treat that condition. For this review, the clinical conditions are separated into sepsis (referred to as sepsis syndrome on the PEP website) and septic shock. Clinical interventions include assessments (eg. quick Sepsis related Organ Failure Assessment (qSOFA)), and treatments (eg. oxygen – high flow). The studies informing the application of each intervention are listed underneath each intervention with the related appraisal information provided.

Search strategy

Systematic searches are conducted in PubMed annually. The most up-to-date sepsis search was conducted on 30 November 2019 and was date-limited to the previous year. Search strings were established using MeSH and title/abstract keywords. Search strategies are developed broadly employing a Population, Intervention, Comparison, Outcome (PICO) format. The population component of the search includes selected EMS terms (2). Search hedges, also known as filters, developed specifically to capture only the study designs meeting PEP's inclusion criteria, are applied. An EMS sepsis search was created in consultation with a health sciences librarian (Table 1).

Table 1. PubMed EMS search strategy

EMS search string:

1. emergency medical services [mh] OR "emergency medical technicians"[mh]
2. paramedic* [tiab]
3. emergency medical technician* [tiab]
4. prehospital[tiab] or pre-hospital [tiab]
5. out of hospital [tiab]
6. technician*[tiab] OR responder*[tiab] OR service*[tiab])
7. ambulance [tiab]
8. 6 AND 7
9. 1 OR 2 OR 3 OR 4 OR 5 OR 8

Filters: case reports, review, meta-analysis, systematic reviews, multicenter study, observational study, randomized controlled trial, clinical trial, controlled clinical trial, comparative study

Search results were imported to Covidence review software for screening and then into reference management software to remove duplicates (15,16).

Inclusion/exclusion criteria

One author reviewed title and abstracts for relevance (JG). Studies were included if they involved sepsis and investigated an intervention currently existing in the PEP database or an intervention recently adopted in the pre-hospital setting. In the latter case, identified studies may prompt a review by the senior editorial team to add new interventions to the database. Studies conducted in the pre-hospital setting are included. If the setting is generalisable to the pre-hospital setting, such as the emergency department, studies may still be reviewed at full text stage to be assessed for relevance to inform pre-hospital clinical care. Included studies must be primary studies, including

observational and experimental designs, or be systematic reviews on an intervention available for use in the pre-hospital context. The studies must have reported results from measures related to clinical patient outcomes (eg. mortality) or process-related outcomes (eg. time to antibiotic).

Studies were excluded if the intervention investigated is not currently practised in the pre-hospital setting and not expected to be part of paramedic scope of practice. Protocols, narrative reviews, reports with no results, epidemiological reports or economic evaluations were excluded.

Evidence appraisal
The PEP appraisers include primarily paramedics and physicians trained in critical appraisal. The primary appraiser team is currently represented by seven countries. Team members bring with them varying clinical backgrounds, including critical care transport. Appraisals are completed online, using fillable forms and a methods reference sheet for consistent application. The primary appraisal is the first stage of critical appraisal. The appraisers are asked to extract data on the study setting, the population, limitations and assign a level and direction of evidence for the intervention(s) studied. The Level of Evidence (LOE) scale is three-level, based on study design and quality. The Direction of Evidence (DOE) scale is a three-point colour-coded scale which indicates if the study's results are supportive, neutral or opposing for the application of the relevant intervention in EMS clinical practice (2). The DOE is appointed specifically according to the results of the primary outcome.

Primary outcomes of included studies
Appraisers identify each study's primary outcome. If the primary outcome is not clearly listed by the authors, the first reported outcome result is used. The LOE, DOE, primary outcome, whether the outcome measure is process or patient related, setting and citation are displayed on the PEP website (14).

Level of evidence
The PEP critical appraisal process has been published previously (2). The PEP appraisal process has been adapted from other established methodologies including the Centre for Evidence Based Medicine (16) and Canadian Task Force Guidelines. The PEP LOE scale is based on other grading schemes such as the Oxford Scale, as described previously (2,17). The unique LOE scale used by PEP was developed by the PEP team based on fundamental critical appraisal ideologies strictly for the purposes of this program. Level I evidence includes adequately powered randomised controlled trials (RCTs) and systematic reviews that include only RCTs. Level II evidence includes prospective and retrospective cohort or registry studies with comparison groups. Human studies in which comparisons are made with statistical techniques are LOE II. Level III evidence includes simulation studies, cohort studies without comparison groups, and underpowered/pilot RCTs. The LOE relies on the study design and quality and is consistent throughout the PEP database, regardless of the intervention(s) under which the study is listed.

Direction of evidence
The DOE is applied to a study based on whether the results for the study's primary outcome are supportive (green), neutral direction (yellow) or opposing (red) of the use of that intervention in the pre-hospital/paramedic setting. Studies are designated an opposing direction if the results demonstrate harm for the primary outcome. When assigning DOE, the appraiser considers the study's settings and practitioners and that potential impact on generalisability to EMS. If the article could inform pre-hospital practice, a setting is considerably different from EMS, the appraiser will assign a neutral DOE to reflect the limited generalisability.

Second party appraisal
Second party review is performed by a select team of senior appraisers. If there is disagreement between primary and senior appraisal (primary outcome, LOE, DOE) it is resolved by team consensus at a monthly senior appraiser meeting.

Evidence recommendation
Once all studies are assigned a final LOE and DOE, the senior appraiser/editorial team summarises the overall level and direction. The interventions are then plotted for each clinical condition on a 3x3 evidence summary matrix (LOE x DOE). The team decision on 3x3 evidence matrix placement considers the number of studies, LOEs, DOEs, outcomes investigated and current practice, and applicability. Highest level of evidence and important patient outcomes (eg. mortality) as well as studies reporting harms are considered.

Results

The search retrieved 327 studies of which 101 full text articles were reviewed (Figure 1). Sixty-three studies were ultimately included and critically appraised in addition to 80 studies already existing within the PEP database (n=143). The 80 existing studies had been included in previous years using earlier searches. The included studies reported on a total of 16 interventions in the context of septic shock or sepsis (Tables 2 and 3).

The evidence matrix rank for supported interventions were supportive-high quality (n=2, 12.5%) for crystalloid infusion and vasopressors; supportive-moderate quality (n=8, 50%) for identification tools, pre-notification, point-of-care lactate, titrated oxygen, temperature monitoring and balanced crystalloids. The benefit of pre-hospital antibiotics, colloids, Trendelenburg position and early goal-directed therapy remain inconclusive with a neutral DOE. There is moderate level evidence opposing the use of high flow oxygen. No evidence was found for the use of hypertonic saline.

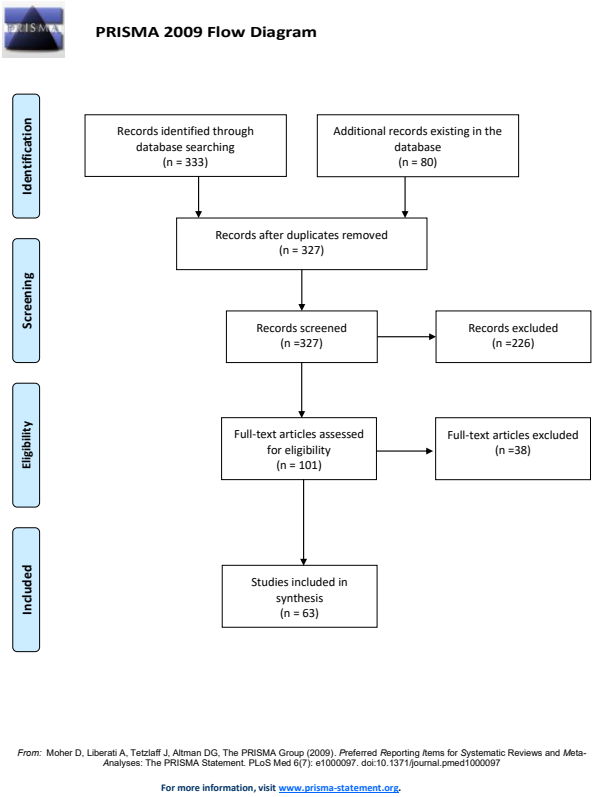

Figure 1. PRISMA flow diagram (22)

Table 2. Direction of recommendation matrix for septic shock

Recommendation		**Recommendation for intervention**			
		Supportive (Green)	Neutral (Yellow)	Against (Red)	Not yet graded (White)
Strength of evidence for intervention	1. (Strong evidence exists)	• Crystalloid infusion • Pressors	• Colloid infusion		• Hypertonic saline
	2. (Fair evidence exists)	• Balanced cystalloids			
	3. (Weak evidence exists)		• Trendelenburg		

Table 3. Direction of recommendation matrix for sepsis

Recommendation		**Recommendation for intervention**			
		Supportive (Green)	Neutral (Yellow)	Against (Red)	Not yet graded (White)
Strength of evidence for intervention	1. (Strong evidence exists)		• Early goal directed therapy • Pre-hospital antibiotics		
	2. (Fair evidence exists)	• Identification tools - (other) • Identification tools - qSOFA • Identification tools - SIRS • Oxygen titrated • Point-of-care lactate • Pre-notification • Temperature monitoring		• Oxygen-high flow	
	3. (Weak evidence exists)				

The interventions with the most pre-hospital studies were related to identification tools (n=67, 46%), early goal-directed therapy (n=23, 16%) and crystalloid infusion (n=16, 11%). Identification tools included Systematic Inflammatory Response Syndrome (SIRS), qSOFA and other unique sepsis identification tools. These unique strategies typically involved the addition of other measures such as ETCO2, modification of an existing formal tool or a computerised screening algorithm. Other formal tools listed in this section include the GYM score (Glasgow <15; tachypnoea >20 bpm; Morbidity-Charlson index ≥3), MEWS (Modified Early Warning Score), MRST (Robson Screening Tool), PRESEP score (Pre-hospital Early Sepsis Detection score) and Sepsis-3 score. The primary outcomes were related to diagnosis (n=63, 44%), mortality (n=53, 37%), treatment goals (eg. time to antibiotic) (n=26, 18%) and adverse event (n=1, 0.6%).

Discussion

To our knowledge, PEP is the only open access evidence synthesis repository of appraised literature tailored to EMS care. This report describes the state of the evidence for adult patients with sepsis and septic shock. There is moderate level evidence to support the use of many EMS interventions used in practice for the treatment of sepsis and septic shock. Unfortunately, much of this evidence is derived from emergency department and intensive care unit settings.

Due to challenges generalising hospital in-patient data to the pre-hospital setting, some international guideline recommendations may not reflect the unique early stage of pre-hospital care. The 2016 Surviving Sepsis Campaign Guidelines published by the Society of Critical Care Medicine strongly recommend empiric treatment with broad-spectrum antimicrobials as early as possible (6). Early paramedic recognition of sepsis is desirable, however, higher quality and innovative pre-hospital research is required to develop and validate paramedic screening methods (18). There are several tools identified by our search that may be useful for sepsis screening. So far, SIRS and qSOFA have the most literature and have been separated as specific interventions within PEP; as literature mounts for other tools the PEP team will identify those separately as well. The current guidelines state that trending lactate can aide in guiding resuscitation goals; a pre-hospital measure can be part of this data trend. The PEP program summarises the evidence for point-of-care lactate as supportive with moderate quality evidence (6). There has been recent investigation into capillary refill as a resuscitation guide and this may be considered for addition to the PEP intervention list (19). Both PEP and current guidelines support the administration of vasoactive agents and crystalloids in patients exhibiting signs of hypoperfusion (6). While PEP recommendations align with current clinical practice guidelines, it is evident that there is a paucity of research conducted in the pre-hospital setting on interventions used to treat sepsis and septic shock.

The PEP program is a living systematised review and knowledge translation initiative, providing evidence summaries for EMS interventions. These summaries can be utilised in EMS guideline development and informing local clinical practice guidelines and EMS protocols for sepsis (20).

Limitations

There are a few limitations that should be acknowledged. One database (PubMed) is searched so we may be missing studies. PubMed was selected because it captures the majority of medical literature that would inform EMS systems. A strength is that PEP is subject to ongoing peer-review by end-users so if discrepancies are noted, they can be addressed. Only English studies are included. We also identified that our evidence matrix is simple; making it easily applied, understood and presented, however, it may be too basic to account for the risk of bias and other notable methodological components of each study (21). The three-point LOE scale poses challenges when the quality of evidence is lower. For example, underpowered RCTs are scored in the same category as studies with no comparison group or simulation research; LOE III. The modern paramedic-based EMS setting is the reference setting for PEP and, as such, some of the recommendations may not be completely generalisable to all EMS (eg. interventions used by EMS physicians providing on scene treatment in a Franco-German service). While the PEP program website is continuously updated with new studies from regular searches, publications such as this one may not reflect the most up-to-date iteration of the evidence because of delays to publication.

Conclusion

The PEP evidence supports the use of identification tools and other aids for early treatment/diagnosis such as point-of-care lactate, temperature monitoring and emergency department pre-alerts in the pre-hospital setting. Pre-hospital antibiotic delivery is neither supported nor opposed by the evidence. Oxygen is found to be harmful by moderate quality evidence in patients with sepsis and should be titrated. There is a need for further prospective research on sepsis in the pre-hospital setting, especially with regards to vasopressors and the utility of paramedic-initiated antibiotics. This PEP state of the evidence on sepsis and septic shock identified, critically appraised and categorised the research evidence to inform EMS clinicians at the point-of-care, potentially narrowing the research to practice gap.

Competing interests

The authors delare no competing interests. Each author of this paper has completed the ICMJE conflict of interest statement. The authors are primary and senior appraisers for the PEP program. They receive no financial gain from their

association with PEP. Author JG is the paramedic knowledge translation coordinator for the program and is responsible for the maintenance of the website and functioning of the PEP program.

Funding

The PEP program is supported by Emergency Health Services Nova Scotia, and housed within the Dalhousie Department of Emergency Medicine, Division of Emergency Medical Services. The appraisers' time is volunteered to this academic venture.

Author contributions

Authors AJEC, JG, JPG, YL, DF, JS, JLJ, RB developed the idea of the report. JG and JPG drafted the first version of the manuscript. Author JG is the PEP coordinator. Authors DL and MS are PEP primary appraisers and provided content expertise on sepsis. Authors JLJ, AJEC, JG, JPG, DF, JS, RB are PEP senior appraisers. All authors have contributed to the design of this methodology and to writing the manuscript. All authors have read and approved the final manuscript.

Acknowledgements

The authors would like to acknowledge the contributions of Melissa MacDougall (Dalhousie Division of EMS), David Urquhart (Dalhousie University Department of Medicine) and Katie McLean (Nova Scotia Health Authority Health Sciences Librarian). The authors would also like to acknowledge the PEP primary appraisers' contributions.

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