SYSTEMATIC REVIEW

Mortality and Other Outcomes in Relation to First Hour Fluid Resuscitation Rate: *A Systematic Review*

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Received; April 04, 2015; Initial review: May 29, 2015; Accepted: July 29, 2015.

Objective: To determine the effect of different regimen of first hour fluid administration rates on mortality and severe consequences of impaired circulation in 2 to 60 months old children with impaired circulation.

Design: Systematic review of randomized controlled trials.

Data sources: Various databases including PubMed, Cochrane Library and EMBASE were searched.

Results: We found only two relevant trials; one was excluded as there was no comparator arm. Only one study (The FEAST Trial) compared boluses with maintenance fluid alone in children with severe febrile illness and one or more signs of impaired perfusion. The 48-hour mortality was more in the bolus group (RR 1.45, 95% CI 1.13,1.86). The quality of evidence is rated as 'moderate'. For the children who met the WHO criteria for shock (severely impaired circulation) (*n*=65 children), those receiving boluses had higher mortality (RR 2.40, 95% CI 0.84, 6.88); the quality of evidence was rated as 'very low'.

Conclusions: A single large randomized controlled trial conducted in low-resource settings indicates that administration of fluid bolus is associated with higher mortality in comparison to the maintenance fluids alone in children with severe febrile illness and one or more signs of impaired perfusion. The findings are not generalizable to contexts with different severity of and different causes of shock and in centers with better facilities. There is urgent need for research in different settings to determine the optimal rate of fluid resuscitation in the first hour in children presenting with impaired circulation, particularly with severely impaired circulation.

Keywords: *Infection, Intravenous fluids, Septic shock.*

Sepsis and septic shock are important causes of morbidity and mortality in children in developing countries [1]. The mortality rate in children with septic shock may be as high as 50% [2]. The outcome is worse when shock is associated with co-morbidities and organ dysfunction [3]. The major physiological abnormality in shock is hypovolemia, and early repletion by appropriate fluid infusion should improve the physiology and survival. Fluid boluses include rapid administration of crystalloids or colloids. The outcome may be largely dependent on the quantity of fluids used in the first hour [4]. Pediatric life support training program recommends administration of up to 60 ml/kg of fluids in the first hour, preferably within the first 15 minutes of diagnosing shock [5]. World Health Organization (WHO) advocates exercising caution in liberal fluid administration policy, especially in children with advanced shock in resource-limited conditions [6]. There may be differences in response in children with severe malnutrition, age <60 months, severe anemia, severe dehydration and varying severity of impaired circulation.

Evidence from randomized controlled trials (RCTs) is lacking to support all components of fluid resuscitation guidelines [5,7]. Moreover, these guidelines have been developed in high-resource countries with well-developed intensive care services where malnutrition, particularly the severe form, is uncommon. A large trial (The FEAST trial) [8] in a resource-limited setting has questioned the use of boluses in children with severe febrile illness and impaired perfusion. It is, therefore, important to systematically evaluate the available evidence to determine the appropriate fluid adminis-tration strategy in children with impaired circulation. The aim of this systematic review was to evaluate the effect of first hour fluid-administration rates on mortality and other outcomes in 2-to 60-month old children with impaired circulation. The primary objective was to determine the effect of first hour fluid administration rates on mortality and severe consequences of impaired circulation in children. Secondary objective was to determine the effect of first hour fluid-administration rates on improved circulation.

METHODS

Criteria for Selecting Studies

We restricted our review to controlled clinical trials (randomized or quasi-randomized) in 2- to 60-month old

children that compared the different rates of isotonic fluid administration in the first hour of shock/impaired circulation (defined as the presence of one or more of the following signs: systolic blood pressure less than the age appropriate cut-off, cold peripheries, capillary refill time >2 s). There was no language restriction. Studies on children suffering from burns, hemorrhage, anaphylaxis and cardiac disorders were excluded. We categorized fluid regimens as follows:

- *Standard care:* Isotonic fluid intravenous (IV) boluses or rapid continuous infusions of 20-60 ml/kg in addition to maintenance rates within the first hour of resuscitation (control group).
- *Maintenance fluids only:* Isotonic fluid IV at maintenance rates only in the first hour of resuscitation.
- *Small bolus plus maintenance:* Isotonic fluid boluses or rapid continuous infusions of a maximum of 20 mL/kg in addition to maintenance rates within the first hour of resuscitation.

Outcome Measures

Primary outcome measures were mortality in first week and severe consequences of impaired circulation in the form of cardiac failure, renal failure or neurological deterioration as defined by the author. Secondary outcome measures were improvement in circulation (responders) based on blood pressure (BP), pulse rate (PR) and capillary refill at or before 6 hours, improvement in circulation based on BP, PR and capillary refill at 24 hours and requirement of endotracheal intubation and mechanical ventilation (indications as defined by the investigators).

Data Sources and Search Strategy

We searched the Cochrane Central Register of Controlled Trials, Pub Med (1966 to September 2014), EMBASE (1980 to September 2014) by using appropriate terms. The search strategy is shown in ***Web Appendix* 1**. Abstracts of all articles were read by two authors independently and the relevant articles were selected. Full text articles of selected studies were obtained. The references of the selected articles were screened to identify any further eligible studies. Disagreements were resolved by discussion.

Data Syntheses

We developed a structured data extraction form to collect the relevant information from the selected papers. Data of baseline characteristics, and primary and secondary outcome measures were extracted in the pretested form by two authors independently. Differences in the data were resolved by discussion. Co-interventions were also documented. We had planned to perform statistical analysis using the Review Manager software but due to paucity of relevant studies, we provided the narrative synthesis instead of meta-analysis in this review. The data were also synthesised using a 'Summary of findings' table. Risk ratio (RR) estimations with 95% confidence intervals (CI) were used for binary outcomes [9].

Assessment of Risk of Bias

Two authors independently assessed the risk of bias for each controlled trial using the criteria outlined in the 'Cochrane Handbook for Systematic Reviews of Interventions' and those recommended by Effective Practice and Organisation of Care (EPOC) [10-14]. The judgment for each entry involved assessing the risk of bias as 'low risk', 'high risk' or 'unclear risk'. Any disagreements were resolved by mutual discussion.

Assessment of Quality of Evidence

The quality of evidence for each of the efficacy and safety outcomes was assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach. Key quality elements assessed by GRADE included: risk of bias, precision, consistency, directness of evidence and publication bias.

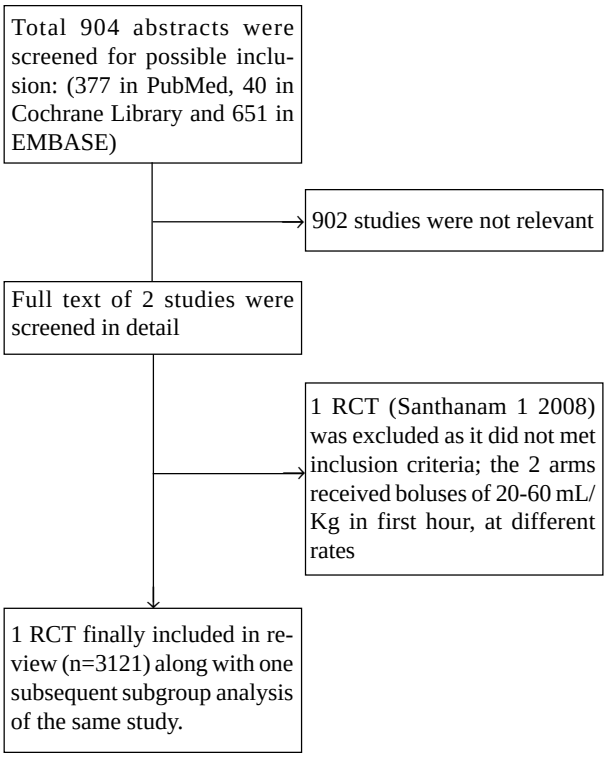

FIG.1 *The PRISMA flow chart.*

The grade evidence profiles were prepared by one reviewer and verified independently by two reviewers.

RESULTS

We could identify only two relevant RCTs, which compared different rates of fluid administration in the first hour in children presenting with impaired circulation (***Fig.*** **1**). One trial had to be excluded as there was no comparator arm of 'no maintenance fluids' [15]. Only one study - Fluid Expansion as Supportive Therapy (FEAST Trial) [8] compared bolus with maintenance fluid alone. We also identified articles reporting the subgroup analysis of the data from the FEAST trial [16,17].

Characteristics of Excluded Study

One trial was excluded as there was no comparator arm [15]. They compared two rates of boluses (20-60 mL/kg within one hour of admission).

Characteristics of Included Study

The summary of the selected study is shown in ***Table*** **I**. In this RCT from Africa, in Stratum A, 3141 children were randomized to a fluid bolus (20-40 mL/kg 5% albumin or normal saline over 1 h) or maintenance fluids (2.5-4.0 mL/kg/h) [8]. The median (IQR) age of participants was 24 (13,38) months; 62% had prostration, 15% were

TABLE I SUMMARY OF THE INCLUDED STUDY (FEAST TRIAL)

Study	Maitland, *et al*., 2011 [8]
Study group	Children were eligible for inclusion in the study if they were between 60 d and 12 y of age and presented with a severe febrile illness and with impaired perfusion. Major exclusion criteria included: • Severe acute malnutrition • Gastroenteritis • Conditions where intravascular volume expansion is contraindicated, *viz.,* chronic renal failure, pulmonary edema • Non-infectious causes of severe illness: trauma; burns; intoxication • Children who have already received volume expansion using an isotonic volume expander during the current illness.
Study setting	Resource-limited settings in Sub Saharan countries— Kenya, Tanzania and Uganda.
Study type	Two-strata (Stratum A and Stratum B), multicenter, open, randomized, controlled study in six clinical sub-centers in Kenya (one center), Tanzania (one center), and Uganda (four centers).
Selection criteria	Children with severe febrile illness and clinical evidence of impaired perfusion, Severe illness and impaired perfusion were defined as follows: *Severe febrile illness: one or more of the following:* • Impaired consciousness: prostration or coma • Respiratory distress *Impaired perfusion: one or more of the following:* • Capillary refill > 2s • Lower limb temperature gradient • Weak radial pulse volume • Severe tachycardia *Hypotensive shock *(Allocated to Stratum B only)*: Systolic BP <50, <60, <70 mm Hg for ages < 1y, 1-4y, >=5 y.
Intervention	*Maintenance fluids only:* Isotonic fluid IV at maintenance rates in the first hour of resuscitation, with no additional IV boluses or rapid continuous infusions. *Standard care:* Isotonic fluid IV boluses or rapid continuous infusions of 20-60 ml/kg, in addition to maintenance rates, within the first hour of resuscitation. An equal number of children were randomized to receive one of the 2 types of fluids as boluses: normal saline or 5% albumin.
Outcomes	*Primary Endpoint:* In-hospital mortality at 48 hours after randomization. *Secondary Endpoints:* Mortality at 4 weeks, neurological sequelae at 4 weeks and 24 weeks, episodes of hypotensive shock within 48 hours of randomization, adverse events related to fluid resuscitation (pulmonary edema, intracranial hypertension or severe allergic reaction to those receiving albumin).

TABLE II SUMMARY OF OUTCOME MEASURES IN THE INCLUDED STUDY

End Point	*Albumin Bolus (N=1050)*	*Saline Bolus (N=1047)*	*No Bolus (N=1044)*	*Saline Bolus vs. No Bolus*	*Albumin Bolus vs. No Bolus*	*Albumin Bolus vs. Saline Bolus*	*Albumin and Saline Boluses vs. No Bolus*
				Relative Risk (95% CI)	*Relative Risk (95% CI)*	*Relative Risk (95% CI)*	*Relative Risk (95% CI)*
48 Hours							
Death, no. (%)	111 (10.6)	110 (10.5)	76 (7.3)	1.44 (1.09-1.90)	1.45 (1.10-1.92)	1.00 (0.78-1.29)	1.45 (1.13-1.86)
Pulmonary edema, no. (%)	14 (1.3)	6 (0.6)	6 (0.6)				
Increased intracranial pressure, no. (%)	16 (1.5)	18 (1.7)	11 (1.1)				
Severe hypotension, no. (%)	1 (0.1)	2 (0.2)	3 (0.3)				
Allergic reaction, no. (%)	3 (0.3)	4 (0.4)	2 (0.2)				
Pulmonary edema, increased intracranial pressure, or both, no. (%)	27 (2.6)	23 (2.2)	17 (1.6)	1.34 (0.72-2.51)	1.57 (0.87-2.88)	1.17 (0.68-2.03)	1.46 (0.85-2.53)
4 Weeks							
Death, no. (%)	128 (12.2)	126 (12.0)	91 (8.7)	1.38 (1.07-1.78)	1.40 (1.08-1.80)	1.01 (0.80-1.28)	1.39 (1.11-1.74)
Neurologic sequelae, no. /total no. (%)	22/990 (2.2)	19/996 (1.9)	20/997	0.95 (0.51-1.77)	1.10 (0.61-2.01)	1.16 (0.63-2.14)	1.03 (0.61-1.75)
Neurologic sequelae or death, no. /total no. (%)	150/990 (15.2)	145/996 (14.6)	111/997 (11.1)	1.31 (1.04-1.65)	1.36 (1.08-1.71)	1.04 (0.84-1.28)	1.33 (1.09-1.64)

comatose and 83% had respiratory distress. The majority (52%) of children had more than one feature of impaired perfusion, most commonly severe tachycardia and cold extremities. Moderate to severe acidosis was present in 51% of the children and severe lactic acidosis (lactate ≥5 mmol/L) in 39% of the children. The mean (SD) hemoglobin level was 7.1(3.2) g/dL and the glucose was 6.9 (3.9) mmol/l. Malaria was confirmed in 57% of the children and 4% were positive for HIV infection. Only 17 (0.5%) children were lost to follow-up for the primary end point. The median volume of fluid administered was 20 mL/kg in the first hour and 40 mL/kg in the first 8 h for both bolus-fluid groups, compared to 1.2 mL/kg and 10 mL/kg at 1 and 8 h, respectively, in the no-bolus group [8,16].

Risk of Bias in the Included Study

In the included study, the overall risk for bias was assessed as 'Low Risk based on the criteria of allocation sequence concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias), comparability of baseline outcome and characteristics, protection from contamination and other potential sources of bias [8]. The details of risk of bias assessment are mentioned in ***Web Appendix* 2**.

Effects of Intervention on Outcomes

Summary of outcome measures in the included study is shown in ***Table* II**. Compared to the maintenance fluids, the fluid bolus was associated with increased 48 h mortality (RR 1.45; 95% CI 1.13,1.86) and increased mortality at 4 weeks (RR 1.39; 95% CI 1.11,1.74). There was no evidence that albumin performed in a different manner than saline (albumin vs. saline bolus (RR; 1.0; 95% CI, 0.78,1.29) [8,16]. There was no evidence of difference between the two groups in the risk of neurological sequelae at 4 weeks (RR 1.03; 95% CI 0.61,1.75) or the combined outcome of pulmonary edema

TABLE III SUMMARY OF FINDINGS (FLUID BOLUS COMPARED TO MAINTENANCE FLUID ALONE FOR CHILDREN 2 MONTHS TO 60 MONTHS WITH SIGNS OF IMPAIRED CIRCULATION)

Patient or population: children 2 months to 60 months with signs of impaired circulation
Settings: Low resource African countries[1]; Intervention: Fluid bolus[2]; Comparison: Maintenance fluid alone[3]

Outcomes	*Illustrative comparative risks* (95% CI)*		*Relative effect (95% CI)*	*No of Participants (studies)*	*Quality of the evidence (GRADE)*
	Assumed risk Maintenance fluid alone	*Corresponding risk Fluid bolus*			
Mortality at 48 hours Assessed clinically[4]	73 per 1000	106 per 1000 (82 to 135)	RR 1.45 (1.13 to 1.86)	3141 (1 study)	⊕⊕⊕⊖ moderate[5]
Mortality at 4 weeks Assessed clinically[4]	87 per 1000	121 per 1000 (97 to 152)	RR 1.39 (1.11 to 1.74)	3141 (1 study)	⊕⊕⊕⊖ moderate[5]
Neurological sequelae at 4 weeks Assessed clinically[6]	19 per 1000	20 per 1000 (12 to 34)	RR 1.03 (0.61 to 1.75)	2983 (1 study)	⊕⊕⊕⊖ moderate[5]
Improvement in circulation in less than 6 hours (Responders)	315 per 1000	426 per 1000 (385- 473)	RR 1.35 (1.22 to 1.5)	3080 (1 study)	⊕⊕⊕⊖ Moderate[5]

**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*
GRADE Working Group grades of evidence–High quality: Further research is very unlikely to change our confidence in the estimate of effect; Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; Very low quality: We are very uncertain about the estimate.
[1] Study was two strata, multicentric RCT in Sub Saharan countries - Kenya, Tanzania and Uganda. [2] Maintenance fluid alone or small bolus up to a maximum of 20 ml/kg within the first hour served as intervention group for our review purpose. [3] Isotonic fluid bolus 20-60 ml/kg within the first hour served as control group for our review purpose. [4] Mortality is a terminal event assessed clinically. [5] Generalizability is limited as study was carried out in a resource limited setting where facilities for respiratory support were not available; majority of children had malaria. Therefore, there is a concern regarding applicability of study findings in all settings and in all causes of shock. [6] Assessed clinically. [7] We intended to measure this outcome which was not done in the included study.

or increased intracranial pressure (RR 1.46; 95% CI 0.85, 2.53) [9,17]. In a subsequent analysis, the effect of boluses on 48-hour all-cause mortality was assessed in different sub-groups created by clinical presentation at enrolment, hemodynamic changes over the first hour and on different modes of death according to terminal clinical events (TCE) [16].

By one hour, shock had resolved (responders) more frequently in bolus *vs.* control groups (43% *vs*.32%, *P*<0.001) but excess mortality with boluses was evident in responders (RR 1.98; 95% CI 0.94,4.17; *P*=0.06) and 'non-responders' (RR 1.67; 95% CI 1.23, 2.28; *P*=0.001) [8]. The adverse effect of fluid boluses on mortality was reported to be similar across various subgroups reported. The difference was not found to be significant while comparing albumin *vs*. saline bolus groups.

We graded the overall quality of evidence as 'moderate' as we downgraded the quality one notch in view of indirectness (generalizability is limited as study was carried out in a resource-limited setting where facilities for respiratory support were not available; and majority of children had malaria. (***Table* III**).

The authors presented the data for the main outcome (mortality at 48 hours) in the subgroup of 65 children fulilling the WHO definition of severely impaired circulation [8, 16, 17]. The mortality was 48% and 20% in the two arms, respectively (RR 2.40; 95% CI 0.84, 6.88). The quality of evidence was downgraded as 'very low' based on concerns of indirectness (as above), bias (as children were not randomized based on the presence of severely impaired circulation; the analysis is post-hoc; the numbers in the bolus and no-bolus arms are not balanced — the ratio is >3:1 against an expected ratio of 2:1), and imprecision (the confidence interval for the relative risk is wide and includes 1) (***Table* IV**).

DISCUSSION

This systematic review could identify only one RCT that met the inclusion criteria. This highlights the paucity of evidence for formulation of guidelines for management of children with shock. Data from this single study enrolling more than 3000 children with severe febrile illness and impaired perfusion suggested significantly higher mortality in bolus group compared to control arm in children having one or more signs of impaired

TABLE IV SUMMARY OF FINDINGS (MAINTENANCE FLUID ALONE COMPARED TO FLUID BOLUS FOR SIGNS OF SEVERELY IMPAIRED CIRCULATION IN CHILDREN 2 MONTHS TO 60 MONTHS)

Patient or population: patients with signs of severely impaired circulation in children 2 months to 60 months
Settings: children 2 months to 60 months; Intervention: fluid bolus; Comparison: Maintenance fluid alone

Outcomes	*Illustrative comparative risks* (95% CI)*		*Relative effect (95% CI)*	*No of Participants (studies)*	*Quality of the evidence (GRADE)*
	Assumed risk Maintenance fluid alone	*Corresponding risk Fluid bolus*			
Mortality Assessed clinically[1]	200 per 1000[2]	480 per 1000[2] (168 to 1000)[2]	RR 2.40 (0.84 to 6.88)	65 (1 study)	⊕⊕⊕⊖ very low[1,4,5]

**The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*
[1] Mortality is a terminal event assessed clinically. [2] Maintenance fluid alone or small bolus up to a maximum of 20 ml/kg within the first hour served as intervention group for our review purpose. Isotonic fluid bolus 20-60 ml/kg within the first hour served as control group for our review purpose. [3] The children were not randomised based on the WHO criteria; this is post hoc analysis [4] Generalizability is limited as study was carried out in a resource limited setting where facilities for respiratory support were not available; majority of children had malaria. Therefore, there is a concern regarding applicability of study findings in all settings and in all causes of shock. [5] The confidence interval is wide.

circulation. The higher mortality rate in the bolus arm was consistent across all subgroups.

These findings are contrary to the current practice recommendations for the management of shock [5,18-20]. The use of intravenous fluids in management of shock has evolved over last two centuries. Most of the information on fluid resuscitation in children has been from observational studies **(*Web Appendix* 3)**. Various professional bodies have recommended use of rapid fluid boluses in children with shock [18-20]. Oliveira, *et al*. [21] in 2008 highlighted the role of early goal-directed-therapy in pediatric septic shock. In the 2012 Surviving Sepsis Campaign guidelines, the recommendations for fluid resuscitation were restricted to the industrialized world [20].

Though our findings are comparable to two earlier reviews [22,23], there are concerns regarding the definition of impaired circulation/ shock in the included study. The inclusion criteria were broader than most shock-classification systems [24], and these results refer to impaired perfusion rather than decompensated shock. While using any one of the signs of shock increases the sensitivity, specificity will be reduced significantly [24], and this may have led to inclusion of children who did not have shock. There is lack of studies evaluating different definitions of shock so as to determine the optimal definition. The FEAST investigators had previously shown poor-to-moderate inter-observer agreement for these signs used to identify impaired perfusion [25]. It is important to note that the cause of excess deaths in the FEAST trial was primarily refractory shock and not fluid overload [16]. This indicates potential role of reperfusion injury [16]. However, the current standard of care in intensive care setting for management of impaired circulation is use of fluid boluses. In these settings, the availability of invasive monitoring, mechanical ventilation and vasoactive drug infusions may contribute to improved outcomes.

Several concerns have been raised regarding applicability or results of FEAST trial [26-30]. There is also concern about impaired free-water excretion during severe infections [31]. It is likely that the many of conditions that the FEAST study subjects had may be adversely affected by extra intravenous volume infusion because of high circulating levels of anti-diuretic hormone [24,32,33]. There is also some concern regarding the discrepancy in the inclusion criteria in the study protocol and the published paper. The original study protocol does not mention severe febrile illness as an inclusion criterion but the amended protocol (June 2011) mentions severe febrile illnesses as the inclusion criterion.

While the FEAST trial was conducted in a resource-limited setting, further trials to determine the optimal fluid infusion rate in children with shock should collect information on baseline severity of illness using the PRISM or PIM scores, etiology of shock and regarding the cardiac function as these were not available in the FEAST study.

A single high-quality randomized controlled trial, conducted in Africa in low-resource settings with no facilities for mechanical ventilation, indicates that administration of fluid bolus increases mortality in comparison to only maintenance fluids in 2- to 60-months old children with severe febrile illness and one or more signs of impaired circulation. The overall quality of evidence was assessed as 'moderate'. For the subgroup of

children fulfilling the WHO-ETAT criteria for severely impaired circulation, there was a trend towards increased mortality in the bolus arm; however, the quality of evidence was rated as 'very low'. There is need for research in formulating uniform diagnostic criteria for shock, identifying determinants of fluid responsiveness, and further studies in different settings to determine the optimal rate of fluid resuscitation in the first hour in children presenting with signs of impaired circulation, particularly in intensive care settings with optimal resources.

Acknowledgements: Dr Bipin Jose for assisting the development of protocol and literature search. The experts participating in the WHO Guideline Meeting — Paediatric Emergency Triage, Assessment and Treatment at Geneva, Switzerland, 30 September - 2 October 2014 for their comments.
Contributors: RL, SKK, HPS: conceptualized the review, developed search strategy, developed the protocol, analyzed the data and wrote the review, AT performed literature search, wrote the manuscript. All authors approved the final version.
Funding: None; *Competing interests*; None stated.

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