Evidence-based medicine

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Restrictive versus liberal fluid bolus therapy in septic shock children: An evidence-based case report

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Abstract

Fluid bolus therapy (FBT) is one of prime management in *early goal-directed therapy* (EGDT) to achieve adequate cardiac output. The Fluid Expansion as Supportive Therapy (FEAST) trial, a randomized-clinical trial that was used as an evidence to support fluid resuscitation recommendation in Surviving Sepsis Campaign (SSC) 2020, must be discontinued because of increasing mortality in the group that received higher volume of FBT. We present a case of a 9-year-old girl, 15 kg, came to emergency ward with refractory septic shock and became fluid overload after the second FBT. This proceeding aimed to deliver evidence-based case practice if the comparison between liberal versus restrictive FBT in children with septic shock.

Key words: Pediatric, shock, fluid, resuscitation, restrictive, liberal.

Introduction

Sepsis is defined as life-threatening, multiple organ dysfunction resulting from immune dysregulation due to severe infection. (1) Mortality ranges between 4-50%, with more than one million new cases in children per year. (2) Survivors are threatened with an increased risk of morbidity, re-admission, and mortality until the next month or even years. (3)

In 2004, Surviving Sepsis Campaign (SSC) was established for the sole purpose of delivering evidence-based recommendations to manage septic patients. The campaign prompts immediate and accurate hemodynamic resuscitation during the first six hours to reduce 28-day mortality, a feat that was dubbed early goal-directed therapy (EGDT). (4) Although proven to decrease septic shock mortality (54% to 16,2% in three years), (5) in 2019 its case fatality rate (CFR) was still 25%, especially in developing countries. Limited resources or inability to refer to intensive care unit contributed to those numbers. (6) Those handicaps cause not all centers to adhere to SSC, which caused many questions and even controversies regarding the protocol's application. (7,8)

Fluid bolus therapy (FBT) is one of the prime management in EGDT to achieve adequate preload by filling the blood vessels and thereby increasing cardiac output. A retrospective study reported that children with septic shock that received less than 40 ml/kgBW in the first 30 minutes have higher mortality. (9) Even though its quality of evidence is low, this practice is still adapted in SSC 2020 and the fluid resuscitation can be continued until fluid overload signs emerge. (2) Concerns regarding the danger of FBT developed with increasing observational studies that correlate positive fluid balance with poorer clinical outcomes. (10,11) The Fluid Expansion as Supportive Therapy (FEAST) trial, a randomized clinical trial that was used as an evidence to support fluid resuscitation recommendation in SSC 2020, must be discontinued because of increased mortality in the group that received a

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higher volume of FBT. (12) Those reports make clinicians questioned whether higher volume FBT (liberal) is superior to a lesser dose of FBT ('conservative' or 'restrictive'), with the possibility to start vasoactive agents earlier. (3)
This proceeding aimed to deliver evidence-based case practice of the comparison between liberal versus restrictive FBT in children with septic shock.

Case presentation
A 9-year-old girl, 15 kg, came to the emergency ward with cardiorespiratory failure. The primary survey suggests Kussmaul breathing without any oxygen desaturation from peripheral oximetry, with tachycardia (150-160 beats per minute [bpm]) with regular rhythm but weak pulse. She was hypotensive according to her age group percentile (73/24 mmHg), with prolonged capillary refill time (CRT). She was oliguric for at least six hours. Initial physical examination did not find any increased jugular vein pressure, lung crackles, gallop rhythm, or hepatosplenomegaly. Both of her eyelids were swollen.
We assessed her as a hypovolemic shock with the possibility of septic shock. Initial management included administration of 2 liters per minute oxygen by nasal cannula, intravenous access insertion, and rapid FBT of lactated Ringer (RL) 20 ml/kgBW (300 ml) over 15 minutes. Hemodynamic was closely monitored and an initial laboratory assessment was performed.
After administration of 20 ml/kgBW FBT, her consciousness recovered, with the improvement of hemodynamic: normotensive, responsive tachycardia (120 bpm) with good quality pulse and normal respiratory rate with normal breathing pattern. Oxygen enrichment was maintained at 2 liters per minute. Initial urine came out after FBT. Her initial lab showed anemia (hemoglobin [Hb] 5.6 g/dl), hematocrit [Ht] 17.6% with leukocytosis (7170/µl), and thrombocyte 153,000/µl. An increased procalcitonin (5.26 ng/ml) was noted. Later microbial culture from the blood, urine, or feces did not yield any specific pathogen. The Ultrasound Cardiac Output Monitor (USCOM) reported low cardiac output, with low pre-load, low contractility, and normal afterload, but we deemed initial fluid resuscitation was achieved.
One hour after initial FBT, tachycardia ensued (150 bpm), with poor quality of pulse but regular rhythm. She was hypotensive (64/26 mmHg) despite no marked fluid loss. We assessed her shock had not completely resolved and administered the second FBT of RL 20 ml/kgBW over 15 minutes. We administered cefotaxime (25 mg/kgBW/8 hours) intravenously and paracetamol. One hour after the second FBT was given, improvement of hemodynamic was noted, and diuresis in the first hour was 2.3 ml/kgBW/hour. We continued the fluid administration in maintenance rate.
At the sixth hour, she was oliguric (0.3 ml/kgBW/hour). Hemodynamic suggested re-shock with tachycardia (140 bpm) with weak pulse, hypotensive (60/40 mmHg), but no desaturation was noted. Extremities were cold, pallor and there was a prolongation of CRT. There were signs of fluid overload: crackles in both lungs and 4 cm below rib hepatomegaly. We withheld FBT and performed USCOM, which showed low cardiac output, with low contractility and high afterload. Dobutamine 5 µg/kgBW/minute was titrated with maintenance fluid rate. We diagnosed her has refractory septic shock and she was transferred to the pediatric intensive care unit (PICU). She continued to receive vasoactive agent for 24 hours and her condition improved until the third day, which she suffered from pericardial effusion. At that point, she already had fluid from enteral nutrition only. We administered furosemide and her condition improved. On the fifth day in PICU, she was transferred to the ward for further diagnostic. After ten days in the ward, she suffered from re-sepsis, with increased procalcitonin and sudden onset of dyspnea. On the 14th day since her hospital administered, she died with her cause of death was suspected to be sepsis.

Clinical question
Based on the case, we proposed a clinical question: in septic shock children, does conservative fluid bolus therapy compared to liberal fluid bolus therapy have better mortality (**Table 1**)?

Literature finding method
We searched evidence to answer the above clinical question by looking up three search engines: PubMed, Cochrane, and Google Scholar. The literature searching was performed in February 2020. The keywords we used were 'children with septic shock', 'conservative or restrictive fluid bolus therapy', 'liberal fluid bolus therapy or current practice', and 'clinical outcome' (**Table 2**). We considered liberal fluid therapy as the current practice, as recommended by SSC 2020. We did not limit the keywords to only 'mortality' to widen our search and changed the keywords to be 'clinical outcome' instead.
We included randomized-controlled trials (RCT), including quasi-RCTs or cluster-RCTs, as well as

systematic reviews and/or meta-analyses. The population is limited to children. We only included English articles within the last ten years. The exclusion criteria were: 1) post-operative articles; 2) research protocols; and 3) duplicate articles (**Figure 1**). After the selection process, we found two relevant articles to which we critically appraised. The level of evidence was assessed based on Oxford for Evidence-based Medicine for therapeutic trials.

Results

Two articles were discovered based on the above search methods. The relevant articles were reported by Inwald, et al, 2019 (13) and Li, et al, 2018. (14)

The first article was reported in 2019 (level of evidence 1c) by Inwald, et al. (13) This was a pilot RCT performed in three regions of the United Kingdom. The study included patients from 37 weeks of gestational age until 16 years old with clinical suspicion of infection and came with signs of shock, and had received 20 ml/kgBW FBT initially before allocated into respective arms. Patients then were allocated into two groups: 1) fluid bolus therapy 10 ml/kgBW FBT each bolus; and 2) 20 ml/kgBW FBT. Both groups were observed within four hours of resuscitation. Within those first four hours, should shock persisted, supplemental FBT according to the regimen prescribed in each arm can be repeated until shock resolved or overload signs emerged or total bolus dose had reached 120 ml/kgBW. This study, being a pilot study, did not specifically aim for certain goals, and rather performed the study to assess its feasibility and potential outcomes. Among the potential outcomes measured were mortality, length of PICU and hospital stay, and any adverse effects. (13)

The pilot study was conducted successfully. There were 73 subjects in the final analysis, with 39 subjects were in the conservative group (10 ml/kgBW FBT) and 34 subjects in the liberal or current practice group (20 ml/kgBW FBT). Besides the significant differences between age and thus body weight between the two groups, the two groups were equal. The 10 ml/kgBW FBT group received less total resuscitative volume than the 20 ml/kgBW group (mean difference 14.5 vs 27.5 ml/kgBW, respectively). There were no deaths during the first 24 hours or after 30 days post-randomized. The conservative group had quicker PICU hours (-65 hours, 95% confidence intervals [CI] -171 to 41 hours) and hospital overall days of stay (-6.7 days, 95% CI -27.6 to 14.1 days) than the liberal group. Adverse effects assessed were subject with mechanical ventilator use (-13.9 subjects; 95% CI -32.1 to 4.3) and inotropic agents use (-12.8 subjects; 95% CI -26.5 to 0.8). All of them were deemed insignificant. (13)

The second article was a systematic review in 2018 by Li, et all. (14) The review combined results from RCTs, including quasi- or cluster-RCTs. The review aimed to answer the clinical question of whether conservative FBT has some benefits compared to liberal FBT in severe sepsis or septic shock. The populations were children and/or adults with severe sepsis or septic shock. The intervention group was conservative fluid, which was defined (for children population) as without FBT, titrated according to heart rate, diuresis, CRT, and level of consciousness, or total fluid volume was less than that of the liberal group. The comparison group was liberal FBT, which was defined as children with 20 ml/kgBW crystalloid over five to ten minutes prior titration according to the hemodynamic, or greater volume than the conservative group. The primary outcome was overall mortality. Secondary outcomes were: 1) vasoactive agent-free days; 2) pulmonary edema; 3) adverse effects (organ dysfunction); 4) organ dysfunction duration; 5) length of stay in Intensive Care Unit (ICU); and 6) ventilator-free days that survived until 28 days. (14)

The systematic review found three RCTs, all of them had children as participants. The studies that were discovered were by Santhanam, et al, 2008, (15) Maitland, et al, 2011, (12), and Benakatti, et al, 2012. (16) Total sample was 3402 children. Benakatti, et al, 2012 (16) measured conservative FBT against liberal FBT. Maitland, et al, 2011 (12) reported results from three different arms, including 1.2 ml/kgBW no bolus control. Santhanam, et al, 2008 (15) compared liberal FBT as many as 40 ml/kgBW over 15 minutes with conservative FBT 20 ml/kgBW over 20 minutes. The three studies measured mortality, pulmonary edema, organ dysfunction, and adverse effect. One study assessed the intervention group with ICU length of stay. Due to specific numbers of participants were unavailable, results from Benakatti, et al, 2012 (16) could not be analyzed for meta-analysis.

Pooled estimates of overall mortality in PICU and hospital from two studies reported relative risk (RR) 1.38 for liberal FBT group (95% CI 1.07 to 1.77). The number needed to harm (NNH) was 34. We deemed the evidence was of moderate level because analysis of estimates was considered weak. Benakatti, et al, 2012 (16) reported a similar result, which favored conservative FBT over liber-

al, but the overall data was unavailable to be calculated in the final result. Mortality after 28-day follow-up reported RR 1.39 with 95% CI 1.11 to 1.74, with NNH 29 subjects. That would mean for every 29 children receiving liberal FBT, we would expect one more death.

Only Benakatti, et al, 2012 (16) analyzed the length of stay in PICU comparison between the liberal and conservative groups. The study reported fewer PICU-free days in the liberal group compared to the conservative group (mean±standard deviation [SD] 12.7±9.5 days vs 17.2±9 days, p=0.015). No further analysis can be extracted since participant numbers were unavailable. (14)

Two studies took their samples from India and Africa and could cause racial and geographical differences with the case study. Maitland, et al, 2011 (12) also included malaria patients and thus can contribute to clinical heterogeneity. The three above studies have a moderate risk of bias, with a low risk of selection bias, but a high risk of attrition bias. The level of evidence was deemed to be weak due to the wide confidence of interval. (14)

Critical appraisal

Both relevant articles have been appraised as shown in **Table 3** and **Table 4**. Inwald, et al, 2019 (13) showed a valid result, with no significant importance but nevertheless applicable results. Li, et al, 2018 (14) have a valid method, with importance despite only two included studies that can be meta-analyzed and applicable.

Discussion

Sepsis is a clinical syndrome that involves multiple organ dysfunction, caused by immune dysregulation, and has the potential to be life-threatening. (1,17) Sepsis can manifest as shock, as a result of decreasing vascular resistance due to vasodilation. The process results in fluid loss to the third space, causing a decrease in end-diastolic volume, practically impairing cardiac contractility and causes cardiac output to fall. (18-20) Failure to maintain adequate cardiac output leads to refractory shock, which is the most frequent cause of death in sepsis. (21)

Fluid bolus therapy (FBT) is a vital management to replenish volume depletion. (17) Fluid administration improves cardiac index and cardiac output as measured by echocardiography. (22) This benefit prompts SSC to recommend administration of FBT 20-60 ml/kgBW to improve hemodynamic. (4) Until 2020, the amount of FBT did not change drastically and was further stratified into the availability of intensive monitoring in the respective facilities. Unfortunately, evidence supporting the recommendation was graded low, especially in the child population. (2)

Maitland, et al, 2012 (12) conducted a trial for fluid bolus therapy in African children with sepsis in a limited setting. The research found increased mortality within the first 48 hours (RR 1.45; 95% CI 1.13-1.86, p=0.003) for the fluid bolus therapy group. The causes of death were severe metabolic acidosis, accompanied by cardiogenic or uncompensated shock. The report questioned the benefits of fluid bolus therapy, especially bolus in huge amounts. (23) Wong, et al, 2019 (10) reported 2.3 to 14.6% of cumulative positive fluid balance had an odds ratio (OR) of mortality 5.81; 95% CI 1.29-26.25; p=0.022, compared to the patients with cumulative balance did not exceed 2.3%. Similar result was also reviewed by Tigabu, et al, 2018 (19) which reported 70% increment of mortality risk in patients with positive fluid balance (RR 1.70; 95% CI 1.20-2.41, p=0.003). The review was deemed homogenous (p=0.389, I2=0.5%), although the review involved adult participants. Positive fluid balance is associated with tissue edema, metabolite and oxygen diffusion impairment, tissue necrosis, and drainage abnormalities in lymphatic and capillary systems. (10) Excessive fluid administration increases atrial and ventricle elongation, which further prompts natriuretic peptides, and impairs glycocalyx endothelia, thereby causes acute kidney injury. (19) These unfavorable outcomes prompt suspicion of inappropriate liberal fluid bolus therapy. (22)

This evidence-based case report compared restrictive against liberal fluid bolus therapy, based on SSC 2020's recommendation. There was never any specific definition about how 'restrictive' or 'conservative' a fluid bolus therapy can be. Total resuscitation volume, total fluid intake, and fluid administration rate are aspects that being studied so far. This review focused on total fluid volume and will not review fluid administration rate. This report reviewed one clinical trial and one systematic review.

The first study by Inwald, et al, 2019 (13) is a pilot clinical trial. They found no significant difference in mortality between groups who received restrictive fluid bolus therapy and liberal fluid bolus therapy. The study was valid from its methodology. The sample was randomized but blinding of the groups was unavailable since the total volume administered would be known by the clinician, suggesting detection bias potential. While the mortality outcome was similar, this result suggests no additional harm administering fewer bolus volumes.

The restrictive fluid bolus group also had a quicker length of overall and PICU stay.

This study's limitation was the small sample size. A wide confidence interval reduces this study's quality of evidence (level of evidence 1c). However, similar results between the two groups proposed an idea of redundancy of administering 20 ml/kgBW bolus.

The second study was a systematic review of three articles by Li, et al, 2018. (14) All of them were randomized clinical trials, with moderate level of evidence. The review was deemed valid, with extensive literature searching throughout every trial and language. Inclusion criteria in the restrictive group were considered too unrestrictive since the definition of restrictive fluid can be as loose as any fluid lesser than the liberal group. However, we value such criteria were defined in order to include as much evidence as it can be. Thirteen studies were excluded with a valid reason, resulting in three studies that answered the clinical question. Two of them had low risk of bias, with unclear risk of bias in Benakatti, et al, 2012. (16) Two other studies have the risk of attrition bias due to the drop-out samples. (12,15)

The review noted homogeneity between the two studies. The result from Benakatti, et al, 2012 (16) could not be included in the further meta-analysis, because access to the total sample was unavailable. Based on pooled mortality, both of the studies reported the liberal fluid group had 1.38 times of mortality risk compared to the restrictive group. The total number needed to harm was 34, which means for every 34 liberal bolus therapy administered, one death is expected. Since the mortality of sepsis itself is already high, the NNH was considered big. Both studies have homogeneity (I2=3.7%). That, and the narrow confidence interval, suggests significant harm in the liberal fluid group (level of evidence 1a). Mortality during follow-up was only analyzed by Maitland, et al, 2012. (12) Liberal group had RR 1.39; 95% CI 1.11 to 1.74 after four weeks of follow-up. Length of stay comparison was only done by Benakatti, et al, 2012 (16) which resulted in a shorter length of stay in the restrictive fluid group. The study did not provide numbers between the two groups, thereby disabling further analysis.

The review only involved few trials in the pooled analysis. Considering how extensive Li, et al, 2018 (14) searched the evidence, it is presumed the practice of restrictive fluid bolus was still rare. Despite only two trials involved, the review had a strong level of evidence. The review also did not find any evidence in the adult population, even though it can still answer the clinical question by applying it to the children population. An involved study had an unclear risk of bias, although the evidence compared the length of stay. Considering all of the strengths and limitations, this review has applicable results nonetheless.

The patient is a 9-year-old girl with clinical signs of sepsis. She was assessed as septic shock because of signs of impaired perfusion and received FBT of lactated Ringer (RL) 20 ml/kgBW two times within 24 hours. Before bolus reached 60 ml/kgBW, overload signs such as hepatomegaly became apparent. We withheld the fluid bolus and started vasoactive agent. Our hospital is considered to have adequate intensive care and based on SSC, the above fluid administration was still in accordance with the said recommendation. Based on our review, the patient had received a liberal fluid bolus and was not evidently recommended. Fluid bolus therapy has the potential to increase mortality, by organ dysfunction due to glycocalyces impairment. Here, we found 10 ml/kgBW would not have a significant change than administering 20 ml/kgBW of fluid. Specific volume was uncertain but evidence showed the upper limit was at 10 ml/kgBW, but further research was required. This review's clinical question does not appraise comparison in regards to fluid administration rate, fluid types, or timing to start vasoactive agents.

The scarcity of clinical evidence prompts us to improve our clinical practice. Close hemodynamic monitoring is compelled, especially in a sufficient facility. Regardless of resuscitation volume, FBT is contraindicated in patients with apparent overload signs due to increased mortality. (19) Resuscitation strategy must achieve the optimum hemodynamic target by specific parameters, including cardiac output, systemic vascular resistance, or central venous oxygen saturation. (2) Accurate preload, cardiac output, and afterload analysis, like by echocardiography, can assist clinical practice. (24) Indonesian Pediatric Society (IPS) recommended fluid adequacy by hemodynamic parameters such as fluid challenge and passive leg raising (PLR) test to increase cardiac index ≥10% or stroke volume variation (SVV) ≥30% by USCOM, arterial waveform, or pulse contour analysis. No other specific parameter to quantify fluid overload status as of yet, making clinical signs like hepatomegaly and gallop remain as an essential guide. (1) In this patient, intensive monitoring was necessary to ensure fluid bolus therapy precisely. Improper monitoring has a risk of hypoperfusion or fluid overload. Further research is needed with an accurate parameter to decide safe fluid bolus volume administration.

Conclusion

In patients with clinical signs of septic shock, liberal fluid administration worsens mortality risk up to 1.39 times that of the restrictive group. The restrictive fluid volume still has no definite volume, but from the evidence we found, the volume must not exceed 10 ml/kgBW. Until now, the level of evidence of this review was considered

Recommendation

In patients with clinical signs of sepsis, fluid bolus administration of 20 ml/kgBW is not recommended, unless intensive monitoring is available. Further inquiries for finding the best evidence are required especially in the children population with septic shock.

Table 1. Patient, Intervention, Comparison, Outcome (PICO) in clinical question

Patient (P)	Intervention (I)	Comparison (C)	Outcome (O)
Children with septic shock	Conservative fluid bolus therapy	Liberal fluid bolus therapy	Mortality

Table 2. Terminology and searching

Search engines	Keywords	Articles
PubMed	((((((Children with septic shock[MeSH Terms]) AND conservative) OR restrictive) AND liberal) OR current practice) AND fluid bolus therapy[MeSH Terms]) AND clinical outcome Filter: articles within 10 years, children population	5
Cochrane	(“children with septic shock”) AND “conservative fluid therapy” AND “liberal fluid therapy” AND “clinical outcome”	3
Google Scholar	"children with septic shock" and "conservative fluid therapy" and "liberal fluid therapy"	2

Table 3. Critical appraisal of Inwald, et al, 2019 (13)

Article	Inwald, et al (13)
Design	Randomized-controlled trial
Level of evidence	1c
Patient Intervention Comparison Outcome	Children with septic shock Conservative FBT 10 ml/kgBW Liberal FBT 20 ml/kgBW Clinical outcome
Validity	Randomization Stratified randomized Subject characteristic Significant difference from age median and bodyweight Intervention Similar Analysis Intention-to-treat analysis Blinding Blinding is not available (total volume FBT is recognized by attending clinician) Follow-up Adequate follow-up 30 days after post-randomization Conclusion: valid
Importance	1. Overall mortality: no significant difference between the two groups; no death during resuscitation or 30 days post-randomization 2. Length of stay in PICU: lesser length of stay (-6.7 hours, 95% CI -27.6 to 14.1 hours). Not significant result. 3. Hospital length of stay: conservative group 10 ml/kgBW faster (mean difference -1 day, 95% CI -2.5 to 0.5 days). The result was insignificant Conclusion: no significant difference; important nonetheless
Applicability	1 Similarity to patient The age criteria was similar, but the case patient does not belong to the age group. Our center has the same facility as the research facility 2 Feasibility of the interventions • Yes, it was feasible 3 Benefit outweighs effect • Yes Conclusion: applicable

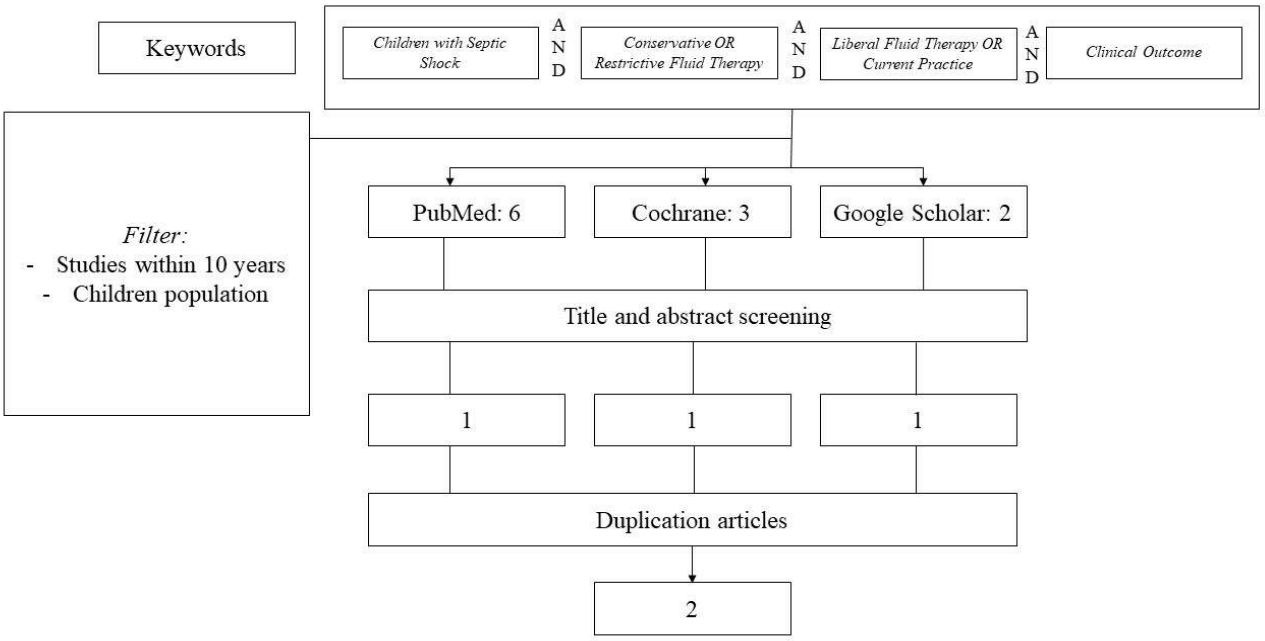
Legend: FBT=fluid bolus therapy; PICU=pediatric intensive care unit; CI=confidence intervals.

Table 4. Critical appraisal of Li, et al, 2018 (14)

Article	Li, et al (14)
Design	Systematic review and meta-analysis
Level of evidence	1a
Patient Intervention Comparison Outcome	Adult or children with severe sepsis or septic shock Any conservative FBT Liberal FBT or current practice or higher volume than conservative Mortality and other clinical outcomes
Validity	Searching method The search was extensive and included many RCTs, as well as the unpublished ones, not limited to English. The search did not limit conference proceedings or ongoing trials. Search inclusion criteria Inclusion criteria matched the clinical question Validity of studies Each trials were assessed for their validities and only those who correlate with the clinical question were assessed Homogeneity Two of three studies reviewed showed homogeneity (one study could not be measured since data were unavailable) Conclusion: valid
Importance	Mortality Liberal FBT group had RR 1.38 (95% CI 1.07 to 1.77), with I2=3.17% (homogen), and NNH=34. Conclusion: important
Applicability	1. Feasibility to apply the treatment Conservative FBT is feasible 2. Consideration of every possible result Low risk of selection bias 3. Benefit outweighs harm Similar to insignificant difference adverse effects between two groups Conclusion: applicable

Legend: FBT=fluid bolus therapy; RCT=randomized controlled trial; RR=relative risk; CI=confidence intervals; NNH=number needed to harm.

Figure 1. Schematic searching methods for evidence



References

1. Hadinegoro SRS, Chariulfatah A, Latief A, Pudjiadi AH, Malisie RF, Alam A. Konsensus diagnosis dan tata laksana sepsis pada anak. Jakarta: Badan Penerbit Ikatan Dokter Anak Indonesia; 2016.
2. Weiss SL, Peters MJ, Alhazzani W, Agus MSD, Flori HR, Inwald DP, et al. Surviving sepsis campaign international guidelines for the management of septic shock and sepsis-associated organ dysfunction in children. Intensive Care Med 2020;46:10-67.
3. Moss SR, Prescott HC. Current controversies in sepsis management. Semin Respir Crit Care Med 2019;40:594-603.
4. Dellinger RP, Carlet JM, Masur H, Gerlach H, Calandra T, Cohen J, et al. Surviving sepsis campaign guidelines for management of severe sepsis and septic shock. Intensive Care Med 2004;30:536-55.
5. Shiramizo SCPL, Marra AR, Durao MS, Paes AT, Edmond MB, dos Santos OFP. Decreasing mortality in severe sepsis and septic shock patients by implementing a sepsis bundle in a hospital setting. PLoS One 2011;6:1-6.
6. Tan B, Wong JJ-M, Sultana R, Koh JCJW, Jit M, Mok YH, et al. Global case-fatality rates in pediatric severe sepsis and septic shock: a systematic review and meta-analysis. JAMA Pediatr 2019;173:352-62.
7. Yuliarto S, Kadafi KT, Nugrahani ITL, Aminingrum R, Asariati H. Hambatan Implementasi Surviving Sepsis Campaign Guidelines 2012 pada Pasien Anak di Rumah Sakit Rujukan Tersier. Jurnal Kedokteran Brawijaya 2014;28:49-52.
8. Saetae T, Pongpirul K, Samransamruajkit R. Assessment of early goal-directed therapy guideline adherence: balancing clinical importance and feasibility. PLoS ONE 2019;14: 1-10.
9. de Oliveira CF. Early goal-directed therapy in treatment of pediatric septic shock. Shock 2010;34:44-7.
10. Wong JJ, Ho SX, Lee AOC, Sultana R, Chong SL, Mok YH, et al. Positive fluid balance is associated with poor clinical outcome in paediatric severe sepsis and septic shock. Ann Acad Med Singap 2019;48:290-7.
11. Marquez-Gonzalez H, Casanova-Bracamontes L, Munoz-Ramirez CM, Peregrino-Bejarano L, Bolanos-Tellez B, Yanez-Gutierrez L. Relation between fluid overload and mortality in chil children with septic shock. Arch Argent Pediatr 2019;117:105-13.
12. Maitland K, Kiguli S, Opoka RO, Engoru C, Olupot-Olupot P, Akech SO, et al. Mortality after fluid bolus in African children with severe infection. N Engl J Med 2011;364:2483-95.
13. Inwald DP, Canter R, Woolfall K, Mouncey P, Zenasni Z, O'Hara C, et al. Restricted fluid bolus volume in early septic shock: results of the fluids in shock pilot trial. Arch Dis Child 2019;104: 426-31.
14. Li D, Li X, Cui W, Shen H, Zhu H, Xia Y. Liberal versus conservative fluid therapy in adults and children with sepsis or septic shock. Cochrane Database Syst Rev 2018;2018:1-40.
15. Santhanam I, Sangareddi S, Venkataraman S, Kissoon N, Thiruvengadamudayan V, Kasthuri RK. A prospective randomized controlled study of two fluid regimens in the initial management of septic shock in the emergency department. Pediatr Emerg Care 2008;24:647-55.
16. Benakatti G, Singhi SC, Jayashree M, Bansal A. 15 conventional versus restrictive maintenance fluid regime in children with septic shock after initial resuscitation: a randomized open label controlled trial. Arch Dis Child 2012;97:A5.
17. Garcia PCR, Tonial CT, Piva JP. Septic shock in pediatrics: the state-of-the-art. J Pediatr (Rio J) 2019. [Epub ahead of print]
18. Thijs LG, Schneider AJ, Groeneveld AB. The haemodynamics of septic shock. Intensive Care Med 1990;16:182-6.
19. Tigabu BM, Davari M, Kebriaeezadeh A, Mojtahedzadeh M. Fluid volume, fluid balance and patient outcome in severe sepsis and septic shock: a systematic review. J Crit Care 2018;48: 153-9.
20. Berlin DA, Bakker J. Starling curves and central venous pressure. Crit Care 2015;19:55.
21. de Souza DC, Machado FR. Epidemiology of pediatric septic shock. J Pediatr Intensive Care 2019;8:3-10.
22. Gelbart B. Fluid bolus therapy in pediatric sepsis: current knowledge and future direction. Front Pediatr 2018;6:1-8.
23. Maitland K, George EC, Evans JA, Kiguli S, Olupot-Olupot P, Akech SO, et al. Exploring mechanisms of excess mortality with early fluid resuscitation: insights from the FEAST trial. BMC Med 2013;11:68.
24. Fathi EM, Narchi H, Chedid F. Noninvasive hemodynamic monitoring of septic shock in children. World J Methodol 2018;8:1-8.