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Review Article

OUTCOMES OF PEDIATRIC FLUID-REFRACTORY SEPTIC SHOCK ACCORDING TO DIFFERENT VASOACTIVE STRATEGIES: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT—**Background:** Hemodynamic support using vasoactive agents is a mainstay in the management of patients with pediatric fluid-refractory septic shock (FRSS). However, evidence supporting the appropriate choice of vasoactive agent is limited. This study aimed to perform a systematic review and meta-analysis on the effect of different first-line vasoactive strategies on mortality in pediatric FRSS. **Methods:** MEDLINE, Embase, Scopus, CINAHL, Web of Science, the Cochrane Library, ClinicalTrials.gov, and the ISRCTN registry were searched up until December 2023. Randomized controlled trials and observational cohort studies reporting vasoactive agent-specific outcomes of children with FRSS were included. Mortality was assessed as primary outcome in studies on patients receiving dopamine, epinephrine, or norepinephrine as first-line. Random-effects meta-analyses were conducted. Prevalence ratio (PR) estimates were calculated between two drugs when was available in the same study. **Findings:** Of the 26,284 identified articles, 13 were included, for a total of 997 children. Twelve studies included 748 patients receiving a single vasoactive agent. Of these, 361 received dopamine, 271 epinephrine, and 116 norepinephrine. Overall pooled mortality for patients receiving a single vasoactive was 12% (95% CI 6%–21%) of which 11% (95% CI 3%–36%) for patients receiving dopamine, 17% (95% CI 6%–37%) for epinephrine, and 7% (95% CI 1%–48%) for norepinephrine. Four first-line dopamine (176 patients) and first-line epinephrine (142 patients): dopamine showed a tendency toward higher mortality (PR 1.38, 95% CI 0.81–2.38) and a significant higher need for mechanical ventilation (PR 1.12, 95% CI 1.02–1.22). **Interpretation:** Among children with FRSS receiving a single vasoactive agent, norepinephrine was associated with the lowest mortality rate. Comparing dopamine and epinephrine, patients receiving epinephrine needed less mechanical ventilation and showed a trend for lower mortality rate. Further research is needed to better delineate the first-line vasoactive agent in this population.

KEYWORDS—Children; fluid refractory septic shock; vasoactive agent; mortality; PICU

ABBREVIATIONS—ACCM—American College of Critical Care Medicine; CI—confidence interval; CRSS—catecholamine-refractory septic shock; FRSS—fluid-refractory septic shock; HICs—high-income countries; ECMO—extracorporeal membrane oxygenation; LICs—low-income countries; LOS—length-of-stay; LMICs—lower-middle income countries; MV—mechanical ventilation; PICU—pediatric intensive care unit; RCTs—randomized controlled trials; RRT—renal replacement therapy; SSC—Surviving Sepsis Campaign; UMICs—upper-middle income countries

INTRODUCTION

Septic shock is a leading cause of mortality and morbidity among children globally (1–3), especially in lower-middle (LMIC) or low-income countries (LIC), accounting for 80% of cases and deaths occurring worldwide (4). Early treatments usually employ fluid resuscitation to maintain adequate organ perfusion (5). Hemodynamic support using vasoactive agents is a mainstay in the management of patients with fluid-refractory septic shock (FRSS), but high quality, consistent evidence supporting the appropriate choice of vasoactive agent is limited.

The American College of Critical Care Medicine (ACCM) 2017 guidelines (6) recommend initiation of epinephrine *via* peripheral access, followed by titration of either central epinephrine or norepinephrine in patients with clinical findings suggestive of cold or warm shock, respectively. The Surviving Sepsis Campaign (SSC) 2020 guidelines (7) recommend either epinephrine or norepinephrine and suggest the use of advanced hemodynamic monitoring in the face of recent evidence highlighting discordance between clinical assessment and hemodynamic variables measured invasively (8,9).

Both guidelines present a change from their previous versions (10,11), where dopamine was recommended as a potential first-line-agent. Dopamine is now suggested as a second-line agent if both epinephrine and norepinephrine are not available.

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Despite those recommendations (6,7) and new data recently published on a combination of agents (12), the best choice of vasoactive agent(s) in pediatric patients with FRSS remains unclear.

We therefore conducted a systematic review and meta-analysis in children with FRSS to examine the effect of specific vasoactive agents on all-cause mortality and other clinically important outcomes.

METHODS

Study design

The research question has been illustrated in Population Intervention Comparison Outcomes format (Table S1, Supplemental Digital Content, http://links.lww.com/SHK/C36).

We conducted this systematic review following Cochrane methodology (13) and reported the results according to the Meta-analysis of Observational Studies in Epidemiology (14) guideline and Preferred Reporting Items for Systematic Reviews and Meta-analyses guideline (15). We registered the protocol for this systematic review on the International Prospective Register of Systematic Reviews (www.crd.york.ac.uk). This systematic review did not require Institutional Review Board approval.

Inclusion and exclusion criteria

In the absence of a standard definition, we defined FRSS as the persistence of septic shock and poor perfusion despite fluid resuscitation. The inclusion criteria were a) studies on patients less than or equal to 18 years of age receiving one or two vasoactive agents for FRSS and b) RCTs and observational cohort studies, both prospective and retrospective.

The exclusion criteria were as follows: a) studies on patients receiving three or more vasoactive agents as a first-line therapy or those receiving extracorporeal membrane oxygenation (ECMO) for septic shock, as we considered those cases to be catecholamine-refractory septic shock (CRSS) (16) and not the target for this study; b) non-English language; c) nonpeer-reviewed publications, meta-analyses and reviews, editorials, commentaries, abstracts, book chapters, letters, editorials, and conference abstracts; d) studies involving only adults or premature neonates; e) studies with less than five patients per vasoactive drug arm to ensure consistency of the treatment provided to the selected cohort of patients; f) studies where neither vasoactive agent specific mortality nor secondary outcomes could not be extracted.

Search strategy

Three key concepts informed our search strategy: (i) pediatric population, (ii) septic shock, (iii) patients undergoing vasoactive agent treatment. Seven electronic databases (MEDLINE, Embase, Scopus, CINAHL, Web of Science, the Cochrane Library, ClinicalTrials.gov, and the ISRCTN registry) were extracted from inception to December 3, 2023. We included all studies regardless of publication date. Details of the search strategy are reported in Table S2, http://links.lww.com/SHK/C36 (Supplemental Digital Content).

Data management and study selection

Studies identified from the literature were imported into Rayyan (http://rayyan.qcri.org) online software (17) for abstract screening, full-text review, and data extraction. The study selection was conducted independently by two investigators both at abstract and full-text level. Relevant papers cited in the reference list of the included articles were evaluated and included in the selection if they fulfilled the eligibility criteria. Any disagreement regarding inclusion criteria was resolved by the senior author.

Data collection

Data extraction included study characteristics, patient demographics, definition of septic shock and FRSS used, indications for vasoactive treatment, characteristics of vasoactive agents administered (i.e., type of drug, timing of infusion, dosage range, and duration if available), indications for escalation of treatment, adjunctive treatments (mechanical ventilation [MV], steroids, renal replacement therapy [RRT], ECMO), and information about primary and secondary outcomes (see next section). When the required data were not clearly presented in the study, we contacted the corresponding author. If we could not retrieve the necessary information after this correspondence, we either excluded the article or only used the data presented for clearly specified outcomes.

Outcomes

Our primary outcome was PICU all-cause mortality. Secondary outcomes, if available, included: proportion of patients with shock resolution at a defined time, time to shock resolution, duration of vasoactive support (or vasoactive-free days), need for MV, duration of MV (or ventilation-free days), PICU and hospital length of stay (LOS), organ dysfunction scores at a defined time (or organ failure-free days).

Quality assessment

Observational cohort studies were analyzed for quality using the Newcastle-Ottawa Quality Assessment scale (18). RCTs were evaluated using the Revised Cochrane Risk-of-Bias (RoB) tool for randomized trials (13). Two investigators independently rated each study. Any disagreement between investigators about overall quality assessment was resolved *via* consensus with a third investigator.

Statistical analysis

Random effects meta-analysis using generalized linear mixed model was performed to pool outcome proportions for each vasoactive drug considered (19). Both 95% confidence intervals (CIs), with Clopper-Pearson method to stabilize the variance, and 95% prediction intervals were estimated (20). For studies that compared outcome rates between two vasoactive drugs we computed prevalence ratios (PRs). Pooled PRs were calculated using the inverse variance method. The heterogeneity between study-specific estimates was measured with the I^2 statistics (21).

We performed subgroup analyses (when at least two studies per subgroup were available) according to study design (RCTs or observational cohort studies), income level of the country where the studies were conducted (high-income countries [HIC]/upper-middle income countries [UMIC]/LMIC/LIC), based on The World Bank classification (22) and year of study publication (in particular, pre- and post-2017, when dopamine was shifted as second-line agent by the ACCM guidelines (6)). We assessed the publication bias using both the visual inspection of the funnel plot and the Egger test (23). Sensitivity analyses were performed using the leave-one-out technique to control the between-study heterogeneity (24) and excluding low-quality studies.

Statistical significance was established for outcomes with a P value <0.05. Data were collected in an Excel database (Microsoft Office 365; Microsoft Corporation, Redmond, WA) and all analyses were performed using the statistical program R (version 4.2.2) (25) with metafor and meta packages (26). A systematic narrative synthesis was performed to present available data for all studies that could not be included in the meta-analyses.

RESULTS

Study selection and characteristics

We identified 26,284 eligible studies through the online database search strategy of which we excluded 10,009 duplicates. Through a manual review of abstract and title, 200 articles were selected for full-text review. Based on the predefined inclusion criteria, eight studies were initially included. Data on five more studies were retrieved by direct correspondence with authors. Finally, 13 studies reporting outcomes of different vasoactive agents for FRSS were included, five (38.5%) RCTs, and eight (61.5%) observational cohort studies. The study selection is detailed in Figure 1. Among the observational cohort studies, seven (87.5%) were conducted retrospectively, and 11 (84.6%) were single-center. Four (30.8%) studies were performed in HICs, while five (38.4%) and four (30.8%) were performed, in UMICs and LMICs, respectively. Septic shock definition was specified in 10 (76.9%) studies, with the ACCM guidelines (6) reported as the most frequently used document for classification and management (four studies, 30.8%).

Study population

A total of 997 patients with FRSS, aged under 18 years, were included in the pooled study population, of which 748 received a

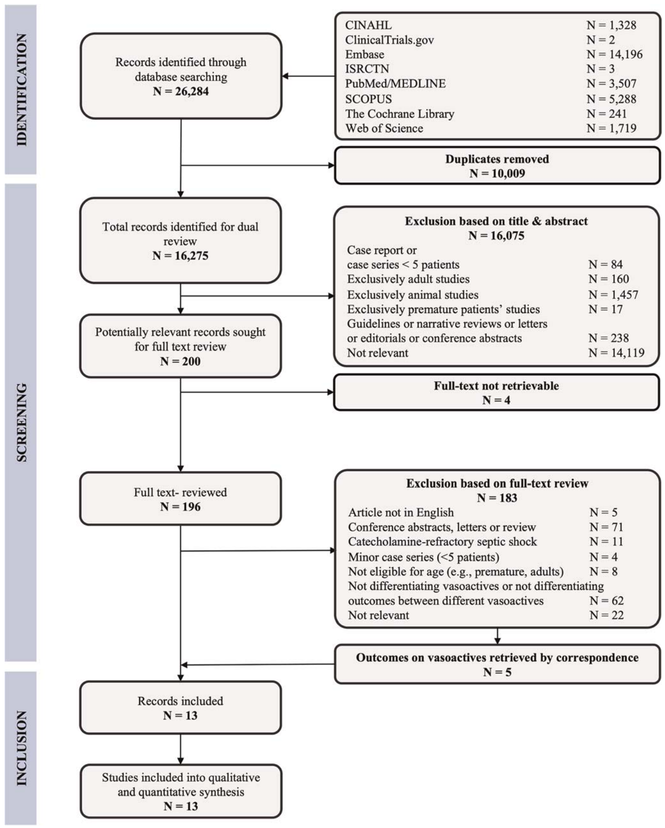

FIG. 1. Flow-diagram of the studies selection process.

single vasoactive agent (12 studies) and 249 two vasoactive agents (nine studies). Dopamine was the most frequently administered single vasoactive agent (361 patients, 55% of total pooled population), followed by epinephrine (271 patients, 36.2%) and norepinephrine (116 patients, 15.5%). No other agents were used as first-line vasoactive drugs. Among patients who received two vasoactive agents, the combination of dopamine and norepinephrine was the most frequent (74 patients, 29.7% of total pooled population). Drug dosing was reported in 10 studies (76.9%). The specific amount of fluid resuscitation required to define "fluid-refractory" and to trigger the initiation of a vasoactive agent was specified in eight studies (61.5%). Reason for allocation of patients to specific vasoactive strategies was specified in four studies (38.4%). Reason for escalation to a new vasoactive or to more advanced therapies for presumptive CRSS was specified in seven studies (53.8%). A comprehensive description of all the studies reporting outcomes on patients undergoing one or two vasoactive agents is available, in Table 1 and Table S3, http://links.lww.com/SHK/C36 (Supplemental Digital Content), respectively.

Primary outcome

Among patients who were treated with a single vasoactive agent (748 patients, 11 studies), the overall pooled mortality was 12% (95% CI 6%–21%). Seven studies explored mortality outcome in patients using dopamine alone (27–33) and epinephrine alone (12,27,28,31,32,34,35), and five studies consider the use of norepinephrine alone (30,31,34,36,37). Those who received norepinephrine (116 patients) showed the lowest pooled estimate of mortality (7%, 95% CI 1%–48%), with dopamine (361 patients, 11% pooled mortality, 95% CI 3%–36%) and epinephrine (271 patients, 17% pooled mortality, 95% CI 6%–37%) showing higher pooled mortality (Fig. 2). For both dopamine and epinephrine pooled mortality estimates, the heterogeneity among studies was high (80%–86%).

The comparison of the mortality estimates between patients treated (within the same study) with epinephrine (142 patients) and dopamine (176 patients) (27,28,31,32) showed a tendency toward a higher mortality in the dopamine group (PR 1.38, 95% CI 0.81–2.38), with low level of heterogeneity (Fig. 3).

Among patients who were administered a two-agent vasoactive strategy (249 patients, nine studies (12,29–31,33,34,36–38)), the overall pooled estimate of mortality was 4% (95% CI 0%–29%). Meta-analysis of studies on patients receiving different combination of vasoactive drugs was not performed because of the low number of studies for each drug combination.

Secondary outcomes

Secondary outcomes were reported inconsistently throughout the studies. The most retrieved secondary outcomes were need for MV (12,27,28,31,32) and hospital LOS (12,28,30,32,34), reported in five studies (38.4%), while duration of MV (12,28,30,32), ICU LOS (12,28,32,34), and duration of vasoactive treatments (12,29,30,34) were reported in four studies each (30.8%) (Table S4, Supplemental Digital Content, http://links.lww.com/SHK/C36).

Regarding the need for MV, the overall pooled estimate was 73% (95% CI 47%–89%) on 420 patients. Patients treated with epinephrine (244 patients) (27,28,31,32) showed the lowest rate of need for MV (64%, 95% CI 32%–87%), while those treated with dopamine (176 patients) (12,27,28,31,32,35) reported the highest one (83%, 95% CI 22%–99%) (Fig. 4). No data were available regarding need for MV in those treated with norepinephrine alone.

The comparison of the need for MV between patients treated (within the same study) with epinephrine (142 patients) and dopamine (176 patients) (27,28,31,32) showed a significantly higher pooled prevalence in the dopamine group (PR 1.12, 95% CI 1.02–1.22), without heterogeneity among studies (Fig. 5).

Meta-analyses on other secondary outcomes were not performed because of low number of studies for each outcome available.

Quality assessment

As for RCTs, we judged three out of five trials (12,27,28) to be at low RoB (https://sites.google.com/site/riskofbiastool/ welcome/rob-2-0-tool?authuser=0) according to the Revised Cochrane RoB tool (13) (Table S5A, Supplemental Digital Content, http://links.lww.com/SHK/C36). All but one (29) of the observational cohort studies showed fair or high quality (score >5/9) on each assessment area (selection, comparability, outcome) according to the Newcastle-Ottawa Scale (18) (Table S5B, Supplemental Digital Content, http://links.lww.com/SHK/C36).

Subgroup analyses

Subgroup analyses (Fig. S6.1–S6.6, Supplemental Digital Content, http://links.lww.com/SHK/C36) were performed on those studies reporting outcomes related to the exposure to a single vasoactive agent.

Table 1. **Studies reporting outcomes on patients undergoing one vasoactive agent for FRSS**

First author, year	Study design	Single vs. multicenter, Study period, Country	Inclusion criteria	Definitions of Sepsis, septic shock & FRSS ("trigger to vasoactive")	Trigger-to-vasoactive	No. of patients On 1 vasoactive agent	Vasoactive received (drug, dosage, duration)	Reason for change/ escalation to more vasoactives	Age (cohort)	Adjunctive therapies	Mortality rate (primary outcome)	Secondary outcomes
Ventura, 2015 (27)	RCT	Single-center, 2009–2013, Brazil (UMIC)	1 mo–15 yrs with FRSS	• **Severe sepsis:** ACCM/PALS guidelines definition • **FRSS:** persistence of signs of hypoperfusion after 40 mL/kg of crystalloids	After randomization —3.2 ± 3.1 h mean ± SD	63 pts	**Dopamine** (range 5–10 mcg/kg/min) until shock resolution or maximum dose	After 60 min and three further increases of selected drug with no clinical response	39.6 mo ± 46.3, mean ± SD	*Other vasoactive:* 33 pts (52.4%) *Hydrocortisone:* 21 pts (33.3%) *MV* 62 pts (98.4%) *RRT:* 11 pts (17.5%)	*28-Day mortality* 13 pts (20.6%)	*Duration of resuscitation:* 33.6 h ±57, mean ± SD *Vasoactive drug-free days*: 18.9 days ±11.3, mean ± SD *MV-free days:* *16.3* days ±10.6, mean ± SD
					After randomization —2.4 ± 1.9 h mean ± SD	57 pts	**Epinephrine** (range 0.1–0.3 mcg/kg/min) until shock resolution or maximum dose	After 60 min and three further increases of selected drug with no clinical response	56.9 mo ± 58.2, mean ± SD	*Other vasoactive:* 22% (38.6%) *Hydrocortisone:* 17 pts (29.8%) *MV:* 51 pts (89.5%) *RRT:* 6 pts (10.5%)	*28-Day mortality* 4 pts (7.0%)	*Duration of resuscitation:* 16.1 h ±23.6, mean ± SD *Vasoactive drug-free days:* 23.7 days ±9, mean ± SD *MV-free days:* *18.6* days ±10.3, mean ± SD
Fernandez, 2016 (36)	Retrospective cohort study	Single-center, 2008–2013, Colombia (UMIC)	1 mo–18 yrs with crystalloid-RSS	• Not reported	Not reported	70 pts	**Norepinephrine** (range 0.01–1 mcg/kg/min) Until maximum dose of 1 mcg/kg/min, followed by vasopressin	Not responding to 1 mcg/kg/min of norepinephrine, followed by vasopressin	50 mo ± 60, mean ± SD	/	*28-Day mortality:* 12 pts (17.1%)	/

Ramaswamy, 2016 (28)	RCT	Single-center, 2013–2014, India (LMIC)	3 mo–12 yrs with cold FRSS	• **Septic shock:** sepsis including cardiovascular dysfunction (hypotension according to PALS vitals or 2 signs of poor perfusion) • **FRSS:** hypotension and poor perfusion after 40 mL/kg crystalloids	After randomization —not reported timing	31 pts	**Dopamine** (range 10–20 mcg/kg/min) Until shock resolution or maximum dose, followed by open-label epinephrine	After 30 min and three further increases of selected drug with no clinical response	4 (0.8–8) yrs, median (IQR)	*Steroids*: 24 pts (77.4%) *MV*: 28 pts (90.3%)	*28-Day mortality:* 18 pts (58.1%)	*Resolution of shock:* 4 pts (12.9%) *Organ failure-free days:* 20 (18.5–24) days, median (IQR) *Duration MV:* 7.0 (3.0–11.5) days, median (IQR) *SOFA day 3:* 12 (6–14), median (IQR) *ICU LOS:* 7 (5–12) days, median (IQR) *Hospital LOS:* 11 (9–13) days, median (IQR)
					After randomization —not reported timing	29 pts	**Epinephrine** (range 0.1–0.3 mcg/kg/min) Until shock resolution or maximum dose, followed by open-label epinephrine	After 30 min and three further increases of selected drug with no clinical response	7 (1–11) yrs, median (IQR)	*Steroids:* 20 pts (69.0%) *MV:* 19 (65.5%)	*28-Day mortality:* 14 pts (48.3%)	*Resolution of shock:* 12 pts (41.4%) *Organ failure-free days:* 24 (23–26) days, median (IQR) *Duration MV:* 7.9 (3.7–7.9) days, median (IQR) *SOFA day 3*: 8 (2–13), median (IQR) *ICU LOS:* 8 (4–12) days, median (IQR) *Hospital LOS:* 9 (8–17) days, median (IQR)
Ranjit, 2016 (37)	Retrospective cohort study	Single-center, 2014–2015, India (LMIC)	1 mo–16 yrs with vasodilatory FRSS	• **Shock:** ACCM/PALS guidelines definition • **FRSS:** after 30 mL/kg crystalloids	Not reported	12 pts	**Norepinephrine** (range 0.05–0.3 mcg/kg/min)	Not reported	Range 2 mo–16 yrs	/	*Mortality:* 2 pts (15.4%)	

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TABLE 1. (Continued)

First author, year	Study design	Single vs. multicenter, Study period, Country	Inclusion criteria	Definitions of Sepsis, septic shock & FRSS ("trigger to vasoactive")	Trigger-to-vasoactive	No. of patients On 1 vasoactive agent	Vasoactive received (drug, dosage, duration)	Reason for change/ escalation to more vasoactives	Age (cohort)	Adjunctive therapies	Mortality rate (primary outcome)	Secondary outcomes
Rivero-Calle, 2016 (29)	Retrospective cohort study	Single-center, 2008–2013, Spain (HIC)	<15 yrs with confirmed or probable invasive meningococcal disease diagnosis	• Not reported	Not reported	93 pts	**Dopamine** (range not reported)	Not reported	/	/	*Mortality*: 1 pt (1.1%)	*Time requiring vasoactive:* 2 (1–2) days, median IQR
Mc-Intosh, 2017 (30)	Retrospective cohort study	Single-center, 2012–2015, USA (HIC)	>2 mo, <18 yrs patients with sepsis identified in the ED	• Not reported	Within 48 h after arrival to the ED or ICU (not reported specifically)	70 pts	**Dopamine** (range 2–18 mcg/kg/min)	Not specified	8.8 (4.7–13.4) yrs, median (IQR)	*ECMO:* 1 patient (1.4%)	*30-day mortality* 4 pts (5.7%)	*Vasopressor days:* 2 (1–3) days, median (IQR) *Ventilator days:* 0 (0–3) median (IQR) *Hospital LOS:* 7 (4–12) days, median (IQR)
						22 pts	**Norepinephrine** (range 0.03–0.2 mcg/kg/min)	Not specified	6.7 (12.8–16.2) yrs, median (IQR)	/	*30-Day mortality* 0 pts (0%)	*Vasopressor days:* 2 (1–3) days, median (IQR) *Ventilator days:* 0 (0–1) days, median (IQR) *Hospital LOS:* 6 (5–12) days, median (IQR)
Menon, 2017 (31)	RCT	Multicenter, 2014–2016, Canada (HIC)	Newborn (>38 GA), <18 yrs patients with septic shock	• **Septic shock:** cardiovascular instability, requiring the administration of at least one vasoactive medication, which was not attributable to a hemorrhagic, hypovolemic, cardiogenic, or neurogenic/spinal pathology	Not reported	13 pts	**Dopamine** (range 2–15 mcg/kg/min)	Not specifically reported, suggested management as per SSC guidelines	/	*MV:* 8 pts (62%)	*Mortality:* 0 pts (0%)	/
						7 pts	**Epinephrine** (range 0.01–0.1 mcg/kg/min)			*MV:* 5 pts (71%)	*Mortality:* 1 pts (14%)	/
						6 pts	**Norepinephrine** (range 0.02–0.2 mcg/kg/min)			*MV:* 4 pts (66%)	*Mortality:* 0 pts (0%)	/

Kohn-Loncarica, 2020 (32)	Retrospective cohort study	Single-center, 2009–2017, Argentina (UMIC)	Children with FRSS admitted to the PED	• **Septic shock:** children admitted to PED with fever, tachycardia, and suspicion of infection associated with hypoperfusion. • **FRSS:** infusion of 60 mL/kg of fluids or clinical signs of fluid overload or poor general status	Not reported	69 pts	**Dopamine** (range not reported)	According to ACCM guidelines	81 (31–144) mo, median (IQR)	*MV:* 28 pts (40.6%)	*Mortality:* 9 pts (13.0%)	*Duration of MV:* 5.5 days, IQR not reported *ICU LOS:* 4 days, IQR not reported *Hospital LOS:* 13 days, IQR not reported
						49 pts	**Epinephrine** (range not reported)		63 (19–92) mo, median (IQR)	*MV:* 19 pts (38.8%)	*Mortality:* 5 pts (10.2%)	*Duration of MV:* 4 days, IQR not reported *ICU LOS:* 4 days, IQR not reported *Hospital LOS:* 11 days, IQR not reported
Chowdhury, 2022	Retrospective cohort study	Single-center, 2013–2017, Bangladesh (LMIC)	2–59 mo malnourished patients with FRSS admitted to the PICU that received a blood transfusion	• **FRSS:** tachycardia, with hypo or hyperthermia, or abnormal WBC count, along with presumed presence of infection, with age-specific hypotension that did not resolve with 20 mL/kg–max 40 mL/kg	Not reported	25 pts	**Dopamine** (range not reported)	No clinical improvement, followed by epinephrine initiation	Range 2–59 mo	/	*Mortality:* 6 pts (24.0%)	*Shock resolution:* 19 pts (76%)
Iramain, 2022 (35)	RCT	Multicenter, 2015–2020 Colombia (UMIC)	<18 yrs patients with hypotensive septic shock at PED admission	• **Septic shock:** ACCM and SSC guidelines definition • **FRSS:** patients with minimal or no signs of improvement or patients with signs of fluid overload after 40 mL/kg (up to 60 mL/kg in one arm of the study)	After 40 mL/kg of fluid (first arm), after 60 mL/kg (second arm)	63 pts	**Epinephrine** (0.1 mcg/kg/min—upper range not reported)	Not reported	Not reported for the whole cohort	*MV:* 15 pts (23.8%)	*Mortality:* 14 pts (22.2%)	/

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TABLE 1. *(Continued)*

First author, year	Study design	Single vs. multicenter, Study period, Country	Inclusion criteria	Definitions of Sepsis, septic shock & FRSS ("trigger to vasoactive")	Trigger-to-vasoactive	No. of patients On 1 vasoactive agent	Vasoactive received (drug, dosage, duration)	Reason for change/ escalation to more vasoactives	Age (cohort)	Adjunctive therapies	Mortality rate (primary outcome)	Secondary outcomes
Kohn-Loncarica, 2022 (34)	Prospective cohort study	Single-center, 2015–2018, Argentina (UMIC)	1 mo—16 yrs patients with septic shock admitted to the PED and requiring PVL administration of inotropic drug	• **Septic shock:** ACCM guidelines. • **FRSS:** infusion of 40 to 60 mL/kg of fluids or more; or appearance of fluid overload; or presence of "critical condition"	After 30 min of resuscitation according to ACCM guidelines and not achieving clinical goals	33 pts	**Epinephrine** (range 0.05–0.3 mcg/kg/min)	Not reported	6 (2–11.8) yrs, median (IQR)	/	*Mortality:* 1 pt (3.0%)	*Time requiring vasopressors:* 24 (0–48) hours, median (IQR) *ICU LOS:* 4.5 (3–7) days, median (IQR) *Hospital LOS:* 8 (7–14.5) days, median (IQR)
						6 pts	**Norepinephrine** (range 0.05–1.0 mcg/kg/min)	Not reported		/	*Mortality:* 0 pts (0.0%)	*Time requiring vasopressors:* 36 (24–72) hours, median (IQR) *ICU LOS:* 4 (1.75–9.5) days, median (IQR) *Hospital LOS:* 17.5 (9.25–32.75) days, median (IQR)

Banothu, 2023 (12)	RCT	Single-center, India (LMIC)	>2 mo, <18 yrs patients with cold FRSS	• **Septic shock:** children with suspected infection and at least two signs of decreased perfusion with or without hypotension • **FRSS (vasoconstricted "cold" shock):** signs of cold shock and poor perfusion despite 40 mL/kg of fluid bolus or if there was worsening after fluid therapy	After randomization—not reported timing	33 pts	**Epinephrine** (0.1–0.3 mcg/kg/min, as >0.3 were labeled as treatment refractory)	In children who failed to attain therapeutic end-points, epinephrine dose was titrated every 15 min, up until 0.3 mcg/kg/min (treatment refractory), following management as per ACCM guidelines	5 (1.5–10) yrs, median (IQR)	*Other vasoactive:* 27 pts (82%) *MV:* 28 pts (85%) *Hydrocortisone:* 15 pts (44%) *RRT:* 9 pts (27.2%)	*28-Day Mortality:* 13 pts (39.3%)	*Shock resolution (at 1 h):* 3 pts (9%) *Shock resolution (at 6 h):* 18 pts (54.5%) *Shock resolution (at 24 h):* 28 pts (84.8%) *Time to shock resolution:* 6 (3–10) hours, median (IQR) *Duration of vasoactive therapy:* 65 (40–124) hours, median (IQR) *Duration of MV:* 6.5 (3.2–19) days, median (IQR) *Duration of PICU stay:* 6 (5–13) days, median (IQR) *Duration of hospital stay:* 15 (9–28) days, median (IQR) *SOFA day 3*: 8 (5–10), median (IQR)

ACCM, American College of Critical Care Medicine; ECMO, extracorporeal-membrane oxygenation; FRSS, fluid-refractory septic shock; GA, gestational age; HIC, high-income country; IQR, interquartile range; LMIC, lower-middle income country; MV, mechanical ventilation; PALS, Pediatric Advanced Life Support; PED, Pediatric emergency department; PICU, pediatric intensive care unit; PVL, peripheral venous line; pts, patients; RCT, randomized clinical trial; RRT, renal replacement therapy; SD, standard deviation; SOFA, Sequential Organ Failure Assessment; UMIC, upper-middle income country; WBC, white blood cell.

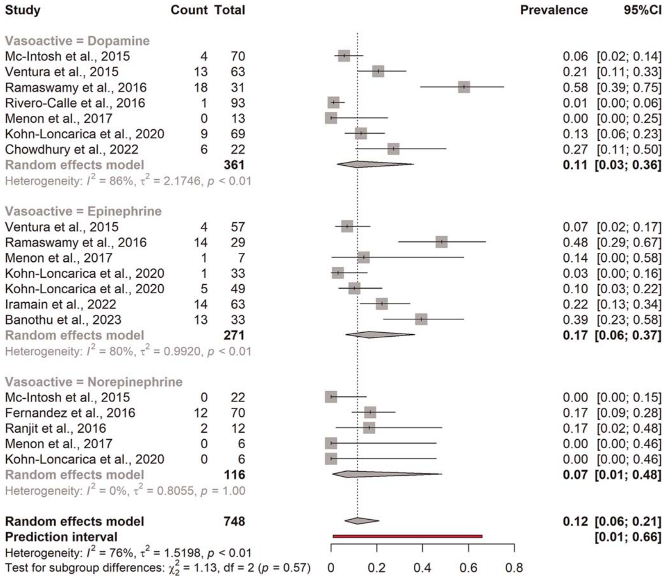

Fig. 2. Forest-plot of pooled-estimate for mortality in patients undergoing a single vasoactive as first-line agent.

Subgroup analysis for HIC versus UMIC/LMIC was performed only on those studies reporting outcomes for patient undergoing dopamine as a single vasoactive agent. Pooled-mortality among UMIC/LMIC (27,28,32,33) (27%, 95% CI 9%–59%) was higher compared to studies from HIC (29–31) (3%, 95% CI 0%–28%) (Fig. S6.1, Supplemental Digital Content, http://links.lww.com/SHK/C36).

Subgroup analysis according to the design of the study (RCTs vs. observational cohort studies) was performed on mortality prevalence rate according to single vasoactive agent exposure. Both epinephrine and dopamine showed higher pooled-mortality in RCTs compared to observational cohort studies and the overall sample. Dopamine pooled-mortality in RCTs (27,28,31) was 19% (95% CI 0%–96%) compared to 8% (95% CI 1%–36%) in observational cohort studies (29,30,32,33) and 11% (95% CI 3%–36%) in the overall sample. Epinephrine pooled-mortality in RCTs (12,27,28,31,35) was 24% (95% CI 9%–51%), compared to 7% (95% CI 0%–95%) in observational cohort studies (32,34) and 17% (95% CI 6%–37%) in the overall sample (Fig. S6.2–S6.4, Supplemental Digital Content, http://links.lww.com/SHK/C36).

Subgroup analysis for studies published pre- and post-2017 was performed on mortality prevalence rate according to dopamine or epinephrine exposure (Fig. S6.5–S6.6, Supplemental Digital Content, http://links.lww.com/SHK/C36). Epinephrine pooled-mortality in pre-2017 studies (27,28,31) was 19% (95% CI 1%–84%), compared to 15% (95% CI 3%–49%) in post-2017 studies (12,32,34,35). Dopamine pooled-mortality in pre-2017 studies (27–31) was 8% (95% CI 1%–53%), compared to 16% (95% CI 1%–88%) in post-2017 studies (32,33). Both comparisons were not statistically significant.

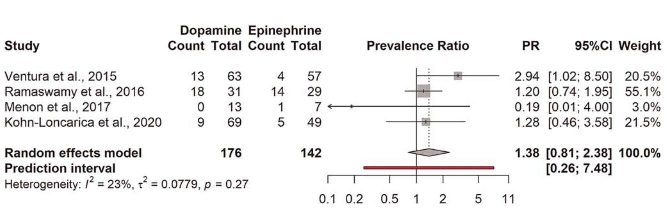

Fig. 3. Forest-plot of pooled-estimate for mortality comparing patients undergoing dopamine versus epinephrine as first-line vasoactive agent.

Publication bias assessment and sensitivity analyses

No publication bias was seen after inspection of the funnel plot and the Egger test (Fig. S7.1–S7.5, Supplemental Digital Content, http://links.lww.com/SHK/C36).

We performed leave-one-out sensitivity analysis for both outcomes (mortality and need for MV), which overall confirmed our main results (Fig. S7.6–S7.12, Supplemental Digital Content, http://links.lww.com/SHK/C36). Furthermore, a second sensitivity analysis was performed by excluding low-quality studies (29,31,35) (Fig. S7.13–S7.16 Supplemental Digital Content, http://links.lww.com/SHK/C36). The exclusion of low-quality studies led to a higher prevalence of mortality in patients who received only dopamine (20%, 95% CI 7%–49% vs. 11%, 9533 3%–36%) and an overall slightly higher prevalence of need for MV (80%, 95% CI 50%–94% vs. 73%, 95% CI 47%–89%).

DISCUSSION

This systematic review and meta-analysis of 13 studies including 997 patients compared first-line vasoactive agent strategies for the treatment of FRSS in children. Among single vasoactive strategies, norepinephrine was associated with the lowest mortality rate, followed by dopamine and epinephrine. The mortality rate was lower in patients treated with two vasoactive agents when compared to those receiving only one vasoactive agent. The comparison between epinephrine and dopamine, available in four studies, showed a tendency toward higher mortality and a significantly higher need for MV in patients treated with dopamine.

Our review revealed a significant heterogeneity in the definition, management, and treatment of FRSS. Additionally, we observed differences in measures used across studies to assess the improvement of FRSS. These variations ranged from overall shock resolution to time-to-shock resolution, organ dysfunction scores, liberation from organ support, leading to high levels of statistical heterogeneity among studies.

Recent guidelines by the ACCM (6) and SSC (7) have reshaped the approach to the selection of the first vasoactive agent to be used. Dopamine is now considered a second-line choice, with the decision between epinephrine and norepinephrine guided by the patient's clinical condition and advanced hemodynamic monitoring. Despite those recent recommendations, the optimal choice of vasoactive agent(s) for pediatric patients with FRSS continues to be a subject of debate in the pediatric critical care community (7).

Two randomized controlled trials (RCTs) investigating the efficacy of dopamine versus epinephrine for the treatment of septic shock in children showed conflicting results (27,28). A 2020 meta-analysis on three RCTs (27,28,39) compared dopamine and epinephrine in neonatal and pediatric septic shock and concluded similar efficacy between the two agents (40).

The ACCM/SSC recommendations (6,7) partially align with the findings of our study where patients treated with norepinephrine as first-line demonstrated the highest survival. Dopamine as first-line vasoactive showed lower pooled mortality compared

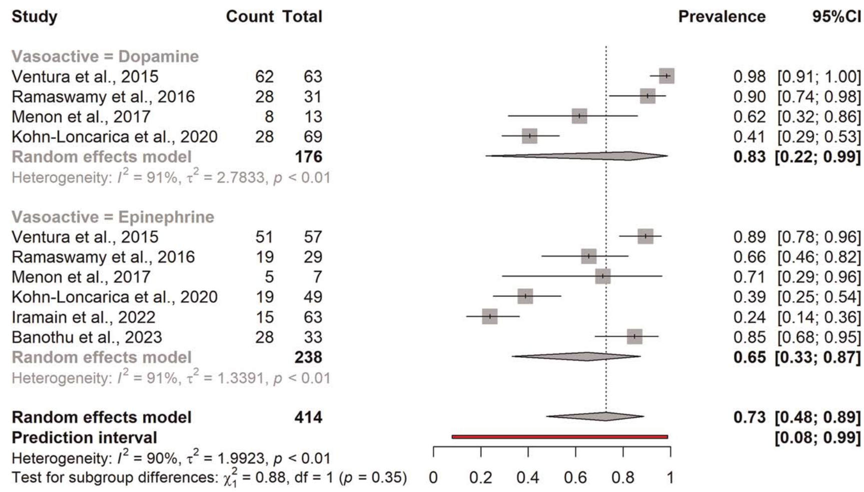

FIG. 4. Forest-plot of pooled-need for MV in patients undergoing a single vasoactive as first-line agent. MV, mechanical ventilation.

to epinephrine as an individual agent. This was not confirmed by the sensitivity analysis excluding low-quality studies, where dopamine showed higher mortality compared to epinephrine. The direct comparison between the two vasoactives, performed in four studies, showed a tendency to higher mortality and a significant higher need for MV in patients receiving dopamine compared to epinephrine.

Historically, the choice of vasoactive agents in pediatric FRSS has leaned toward those with inotropic properties (e.g., dopamine and epinephrine), primarily due to the relatively higher incidence of septic myocardial dysfunction in the pediatric population as compared to adults (41,42). Epinephrine is a potent inotropic and peripheral vasoconstrictor agent at high doses, while dopamine, in contrast, has a lower inotropic effect. Both agents are known for exacerbating tachycardia, arrhythmias, and increasing myocardial oxygen consumption (43,44). Among known dopamine's side effects, the unpredictable response to drug dosing is also reported, especially in infants and young children: in those subjects, dopamine's insensitivity and depletion of body catecholamines during shock have been described (45,46). This last factor and the lower overall inotropism may explain why epinephrine appears to be a more consistent and favorable choice than dopamine in the management of pediatric FRSS.

Conversely, norepinephrine is known for increased vasoconstriction, mild chronotropy, and modest inotropic effect. Norepinephrine is the vasoactive agent of first choice in septic shock in adults (47), especially because of its properties of improved ventriculo-arterial coupling, increased coronary artery perfusion and modest inotropy (48). In children it is recommended only for patients with "warm" shock at presentation, according to the current ACCM guidelines (6). However, it is used as first-line agent by many pediatric intensivists in Europe (49). In our study, use of norepinephrine was associated with the lowest mortality rate, although the majority of the data was derived from nonrandomized studies.

We observed that the pooled mortality of patients receiving two vasoactive agents was lower compared to those receiving only one drug. Some authors have advocated combination therapy to allow use of lower doses of medications and mitigation of dose-related side effects. A recent systematic review and network meta-analysis of studies conducted on adult patients (50) investigated the efficacy and safety of multiple vasoactives in reducing 28-days mortality, with the combination of norepinephrine and dobutamine being the most effective. A recent pediatric RCT by Banothu *et al.* (12) compared the combination of norepinephrine and dobutamine with epinephrine alone as first-line treatment for children presenting with "cold" shock. This study yielded promising results, significantly favoring the combination of vasoactive drugs in time to shock resolution.

Our study has several limitations. We observed considerable heterogeneity among the included studies, which could lead to reduced representativeness of the pooled estimates. In addition, the incidence and mortality rates for septic shock vary considerably by setting (2) with higher rates reported in LMICs and LICs (4). Therefore, the absence of randomized data from HICs, and lack of information regarding the severity of patients' conditions at baseline, may limit the generalizability of our results. Finally, our search strategy included all studies regardless of publication

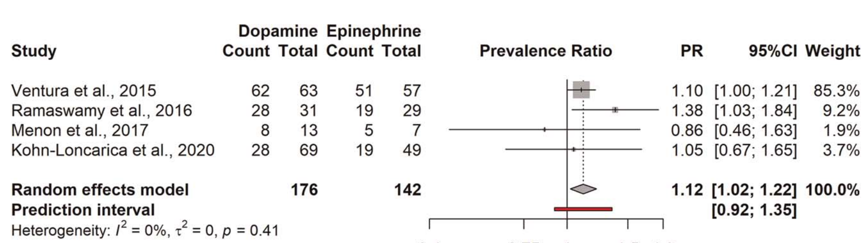

FIG. 5. Forest-plot of pooled-estimate for need for MV comparing patients undergoing dopamine versus epinephrine as first-line vasoactive agent. MV, mechanical ventilation.

date. This could be considered a potential limitation of the study, considering potential time-dependent differences in mortality. To address this issue, we performed a subgroup analysis comparing studies pre- and post-2017, which resulted not statistically significant.

Despite these limitations, to the best of our knowledge, this is the first systematic review evaluating the efficacy of all the possible first-line vasoactive agents for pediatric patients with FRSS. Our review significantly contributes to the existing literature by offering a more extensive body of evidence, adding important considerations in the management of vasoactive agents for pediatric FRSS.

CONCLUSIONS

In children with FRSS norepinephrine used as first-line vasoactive agent showed the lowest mortality rate, although the majority of the data was derived from nonrandomized studies. Epinephrine significantly reduced the need for MV and showed a trend for lower mortality when compared to dopamine. The use of two vasoactive agents resulted in lower mortality than the use of a single agent.

The significant heterogeneity in the definition, management, and treatment approaches for FRSS emphasizes the need for more cohesive efforts to enhance definitions and standardize FRSS management practices globally.

Further RCTs and high-quality data are required to evaluate efficacy and safety of first-line vasoactive agent(s) in pediatric FRSS and to investigate the potential use for a combination of agents compared to a single vasoactive drug.

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