ARTICLE

Use of vasopressors for septic shock in the neonatal intensive care unit

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OBJECTIVE: To describe outcomes for infants in the neonatal intensive care unit with septic shock based on the vasopressor administered.
METHODS: This is a multicenter cohort study of infants with an episode of septic shock. We evaluated the primary outcomes of mortality and pressor-free days alive in the first week after shock using multivariable logistic and Poisson regressions.
RESULTS: We identified 1592 infants. Mortality was 50%. Dopamine was the most used vasopressor (92% of episodes) and hydrocortisone was co-administered with a vasopressor in 38% of episodes. Compared to infants treated with dopamine alone, adjusted odds of mortality were significantly higher for those treated with epinephrine alone (aOR 4.7 [95% CI: 2.3–9.2]). Adjuvant hydrocortisone was associated with significantly lower adjusted odds of mortality (aOR 0.60 [0.42–0.86])
CONCLUSIONS: The use of epinephrine as either a solo agent or in combination therapy was associated with significantly worse outcomes, while adjuvant hydrocortisone was associated with decreased mortality.

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INTRODUCTION

Infants in the neonatal intensive care unit (NICU) are at high risk for sepsis, which occurs in up to 20% of premature and low birth weight infants [1, 2]. Sepsis may progress to septic shock with associated end-organ injury and cardiovascular dysfunction, requiring treatment with a combination of fluid resuscitation and inotropic therapy [3, 4]. Sepsis remains a leading cause of neonatal mortality, with mortality rate estimates of 10–20% [5–8]. For neonates with septic shock, mortality may increase to 40–80% [9, 10].

The recent Surviving Sepsis Campaign guidelines recommend epinephrine or norepinephrine as first-line therapy, rather than dopamine, for children with septic shock [11]. Two single-center randomized trials of children with septic shock older than 1 month suggested treatment with epinephrine compared with dopamine was associated with improved organ function and decreased mortality [12, 13]; however, the optimal treatment for neonates is unknown. The Surviving Sepsis Campaign explicitly excluded premature infants from their recommendations and acknowledged that neonatal sepsis might require tailored management compared to older children. Premature infants have unique physiology, including decreased and immature cardiac mass with less adrenergic innervation and less vascular reserve that may require distinct vasopressor support strategies in septic shock [14].

Dopamine is the most used inotrope in the neonatal population [4, 15]. A recent small single-center randomized trial of 40 neonates with septic shock did not find an overall difference in mortality between those treated with epinephrine or dopamine, but infants less than 31 weeks gestational age treated with epinephrine had improved hemodynamics [9]. Together, these trials demonstrate a need for further investigation of therapies for septic shock in premature and very low birth weight infants. In this study, we describe the use of vasopressors for septic shock across a large multicenter cohort of NICUs and assess outcomes for infants with septic shock based on the type of vasopressor they receive.

METHODS

Study cohort

We performed a cohort study of inborn infants less than 120 days old with an episode of septic shock who were discharged from NICUs managed by the Pediatrix Medical group from 2010 to 2018. This database prospectively captures deidentified information from the Electronic Health Record, including patient demographics, medical history, diagnoses, medications, and laboratory results [16]. Infants were excluded if admission day or discharge day was absent or if the episode extended beyond 120 days of life. We obtained institutional review board approval from the Duke University Health System IRB with a waiver of informed consent for our study, protocol Pro00112607. The study was performed in accordance with the Declaration of Helsinki.

Septic shock definition

We defined an episode of septic shock as a positive blood culture with an organism not typically considered a contaminant and concomitant new vasopressor requirement, with use starting between 1 day prior and 2 days after positive culture. Included vasopressors were dobutamine, dopamine, epinephrine, norepinephrine, and phenylephrine. We did not include vasopressin as this shares the same label as desmopressin in the database. Episodes started on the first day of qualifying vasopressor exposure and

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ended on the final day of continuous vasopressor exposure or if death occurred. Only the first episode was included for each infant.

Outcomes

Our primary outcomes were mortality and pressor-free days alive. We defined mortality as a discharge disposition of died. We defined pressor-free days alive as the total number of days in the first 7 days following shock onset that an infant did not receive any vasopressor and remained alive. For the pressor-free day alive analysis, we included only infants who either remained inpatient or died during the first 7 days after an episode. Those who were discharged with another disposition (e.g., transfer to another facility) were excluded as we could not determine their final mortality status.

We evaluated outcomes based on the combination of vasopressor therapy received during an episode. We analyzed systemic hydrocortisone only when it was co-administered with other vasopressors. Systemic hydrocortisone included both intravenous (IV) and oral (PO) administration. For infants with available dosing documentation for epinephrine, we described each administration as either an infusion or a bolus dose.

We included the following covariates for adjusted analyses for each outcome: gestational age by group (<26, 26–28, 29–32, 33–36, or ≥37 weeks gestational age at birth), small for gestational age, sex, race, history of congenital heart disease (CHD), history of persistent pulmonary hypertension of the newborn (PPHN), recent use of antibiotics, recent use of vasopressor, recent use of systemic steroid, current use of diuretic, current use of inhaled nitric oxide, age at shock onset by group (0–2, 3–7, 8–28, and >28 days), and modified neonatal sequential organ failure assessment (nSOFA) score at the start of shock. We defined CHD and PPHN by clinician diagnosis in the medical record. Systemic steroids included dexamethasone, prednisolone, and prednisone, in addition to hydrocortisone. We defined recent medication use as usage between 7 and 3 days prior to the start of shock, inclusive. We defined current medication use as any usage from 2 days prior up to the start day of shock, inclusive. We created a modified nSOFA score similar to that previously described by Wynn and Polin [17] with higher scores for progressive physiologic derangement across three domains (respiratory, cardiovascular, and hematologic) and total scores ranging from 0 to 15 (Supplementary Table 1). Our modified nSOFA score uses a fraction of inspired oxygen (FiO_2) rather than the ratio of oxygen saturation to FiO_2 (SpO_2/FiO_2), as we did not have SpO_2 available in our dataset. We used the highest score for each domain on the start day of shock. We performed two secondary sensitivity analyses. The first included epinephrine only if the epinephrine was documented explicitly as an infusion dose. We excluded bolus dose epinephrine or epinephrine without dosing information. We did not change the criteria for other vasopressors. The second sensitivity analysis used the original vasopressor definitions, but included the additional covariate of organism type (gram-positive, gram-negative, fungus, or other). We excluded sepsis episodes with polymicrobial cultures.

Statistical methods

The unit of observation for this analysis is an infant's first episode of septic shock. We used summary statistics to define baseline characteristics, using median (interquartile values (IQV)) for continuous variables and frequencies (percentages) for continuous variables. We used non-parametric tests for trends to compare medication usage by gestational age group and by discharge year. We describe mortality with adjusted odds ratios (ORs) and 95% confidence intervals (CIs) using pooled multivariable logistic regression, because a χ^2 test ($p = 0.49$) revealed that site-level effects contributed negligibly to overall variance. We describe pressor-free days alive with mean predicted days and 95% CIs using Poisson regression adjusted for fixed site effects. In this case, χ^2 tests showed that site-level effects contributed importantly to overall variance ($p < 0.001$), and that fixed site effects were preferred to random effects ($p < 0.001$). P values <0.05 were considered statistically significant. All analyses were conducted using Stata version 16.1 (College Station, TX).

RESULTS

Patients and septic shock episode characteristics

We identified 1592 infants across 175 NICUs (Table 1); of these, 58% were male and 38% were white. The median (IQV) gestational age was 25 weeks (24, 28) and the median birth weight was 760 g (605 g, 1174 g). Episodes began on median postnatal day 8 (1, 15) and lasted for a median of 3 days (1, 5). Five hundred infants (31%) had early onset sepsis, defined as onset on postnatal days 0–2. Overall mortality was 50%. Vasopressor was most commonly started on the same day that positive blood culture was drawn (55% of cases). Gram-negative organisms (52% of cases) were most commonly identified, and *Escherichia coli* was the most common organism (22% of cases) (Supplementary Table 2).

Table 1. Demographics and overall outcomes for infants with septic shock.

	***N* = 1592**
Demographics	
Male	919 (58)
Race	
White	583 (38)
Black	521 (34)
Hispanic	328 (21)
Other	107 (7)
GA (weeks)	25 (24, 28)
GA group (weeks)	
≤25	832 (52)
26–28	369 (23)
29–32	176 (11)
33–36	87 (5)
≥37	127 (8)
BW (g)	760 (605, 1174)
BW group (g)	
<1000	1095 (69)
1000–1499	206 (13)
1500–2499	148 (9)
2500–3499	104 (7)
≥3500	39 (2)
Outcomes	
Postnatal age at diagnosis (days)	8 (1, 15)
Duration of shock (days)	3 (1, 5)
Length of stay (days)	38 (14, 103)
Mortality	675 (50)
Days from positive culture to vasopressor initiation	
−1	114 (7)
0	869 (55)
1	495 (31)
2	114 (7)
Organism identified	
Gram-negative	837 (52)
Gram-positive	663 (41)
Fungus	69 (4)
Other	39 (2)

Continuous variables described using median (interquartile values) and categorical variables described as frequencies (percentage).
BW birth weight, *GA* gestational age.

Vasopressor usage

Dopamine was the most used vasopressor (92% of episodes) with epinephrine (28%) and dobutamine (24%) also frequently used (Table 2). Neither norepinephrine (1%) nor phenylephrine (1%) was commonly used. Hydrocortisone was co-administered with a

Table 2. Overall usage of vasopressors and hydrocortisone for septic shock.

Medication	Overall usage	Duration of use (days)	Postnatal age at treatment initiation (days)	Day of septic shock therapy started
Dopamine	1459 (92)	3 (1, 5)	8 (1, 15)	1 (1, 1)
Dobutamine	387 (24)	1 (1, 3)	8 (1, 15)	1 (1, 2)
Epinephrine	452 (28)	1 (1, 2)	8 (1, 16)	1 (1, 2)
Norepinephrine	11 (1)	1 (1, 4)	12 (1, 34)	2 (1, 2)
Phenylephrine	15 (1)	3 (2, 4)	36 (15, 46)	1 (1, 1)
Hydrocortisone	606 (38)	2 (1, 4)	9 (3, 17)	1 (1, 2)

Hydrocortisone assessed only when it was co-administered with other vasopressors. Continuous variables described using median (interquartile values) and categorical variables described as frequencies (percentage).

vasopressor in 38% of episodes. All treatments other than norepinephrine had median initiation on the first day of shock. Medication usage did not vary significantly across gestational age groups (Fig. 1a). Use of dopamine (95% of patients in 2010, 90% in 2018; $p = 0.014$) and dobutamine (25% in 2010, 16% in 2018; $p = 0.034$) both decreased over time while the use of epinephrine increased (25% in 2010, 34% in 2018; $p = 0.016$) (Fig. 1b). Use of phenylephrine increased ($p = 0.049$), although interpretation is limited given only 15 total infants received phenylephrine. The three most common vasopressors and their combinations comprised 98% of total episodes. Therefore, we evaluated outcomes using dopamine, epinephrine, and dobutamine as mono or combination therapy during a shock episode.

Adjusted outcomes

Compared to infants who were treated with dopamine alone, adjusted odds of mortality were higher for those who received epinephrine alone (aOR 4.7 [95% CI: 2.3–9.2]) or the combinations of dobutamine and dopamine (aOR 2.3 [1.5–3.6]); epinephrine and dopamine (aOR 6.2 [3.8–10.2]); or epinephrine, dobutamine, and dopamine together (aOR 15.6 [7.6–32.2]) (Table 3). Compared to infants who received the combination of dopamine and dobutamine, adjusted odds for mortality were higher for those who received a combination of dopamine and epinephrine ($p = 0.001$). No difference in adjusted odds for mortality was seen between infants who received epinephrine alone and those who received the combination of epinephrine and dopamine ($p = 0.48$). Adjuvant hydrocortisone was associated with lower adjusted odds of mortality (aOR 0.60 [0.42–0.86]) compared to infants to did not receive hydrocortisone.

Compared to infants who were treated with dopamine alone (adjusted mean 3.4 days [3.2–3.6]), adjusted mean pressor-free days were lower for those who received the combinations of dobutamine and dopamine (2.1 days [1.8–2.5]); epinephrine and dopamine (1.2 days [0.9–1.6]); or epinephrine, dobutamine, and dopamine together (0.5 days [0.3–0.8]). Infants who received the combination of dopamine and epinephrine had lower adjusted pressor-free days alive than those who received epinephrine alone ($p < 0.001$) or the combination of dopamine and dobutamine ($p = 0.001$). Adjuvant hydrocortisone was not associated with a significant change in pressor-free days ($p = 0.16$). Sensitivity analysis restricting the cohort to only premature infants demonstrated similar adjusted outcomes based on vasopressor combinations for both mortality and pressor-free days (Supplementary Table 3).

Among the covariates, higher modified nSOFA scores were associated with both increased mortality (aOR 1.2 [1.1–1.2] for each 1-point score increase) and decreased pressor-free days (marginal change of –0.10 days [–0.15 to –0.05] for each 1-point score increase).

Recent antibiotic usage was associated with lower adjusted odds of mortality (OR 0.52 [0.34–0.78]) with no significant change in pressor-free days. Recent vasopressor or systemic steroid usage had no significant effect on either outcome. Sensitivity analysis including organism type as a covariate showed no difference in mortality based on organism, but shock episodes with fungal infection had higher pressor-free days compared to those with either gram-negative or gram-positive organisms (3.53 days [2.77–4.30] for fungus vs. 2.55 days [2.35–2.74] for gram-negative vs. 2.59 days [2.38–2.80] for gram-positive) (Supplementary Table 4).

Unadjusted mortality was high for all infants who received epinephrine, regardless of dosing type (Table 4). Sensitivity analysis including epinephrine only when explicitly documented as an infusion dose demonstrated similar outcomes based on vasopressor combinations compared to the overall cohort (Supplementary Table 5).

DISCUSSION

Septic shock for infants in the NICU carries severe morbidity, reflected by the 50% mortality in our study cohort, although there is limited clinical trial evidence to guide therapy. Our study demonstrates a significant difference in outcomes based on vasopressor therapy, adjusting for both demographic and clinical factors. Infants who received epinephrine as either solo or combination therapy had significantly higher adjusted odds of mortality. Furthermore, unadjusted mortality was high for infants who received epinephrine as either infusion or bolus dosing. This finding represents the first study in the neonatal population to demonstrate a significant mortality difference based on vasopressor therapy.

Premature infants with sepsis are at risk for cardiovascular dysfunction and poor vascular tone from systemic inflammation, neurohormonal changes, and premature cardiac tissue that may be less responsive to dynamic loading conditions [14]. Dopamine may have a greater benefit than dobutamine or hydrocortisone alone at improving blood pressure in hypotensive premature infants, and it remains the most commonly used vasopressor in neonates, reflected by the 92% usage seen in our study [18]. However, epinephrine is recommended as the preferred first-line therapy for septic shock in older children, and there was a steady increase in epinephrine usage over time in our cohort [11].

In a previous trial of forty premature infants (mean gestational age 30 weeks) with fluid refractory septic shock prospectively randomized to either dopamine or epinephrine, no difference in the primary outcome of shock reversal after 45 min of therapy or the secondary outcome of mortality was seen [9]. Of the subcohort of infants less than 31 weeks, five of nine who received epinephrine, compared to none of nine who received dopamine, had improved hemodynamic stability, pointing to a potential benefit to epinephrine therapy. While a separate single trial of children (mean age 4 years) with septic shock demonstrated improved survival in infants randomized to epinephrine rather

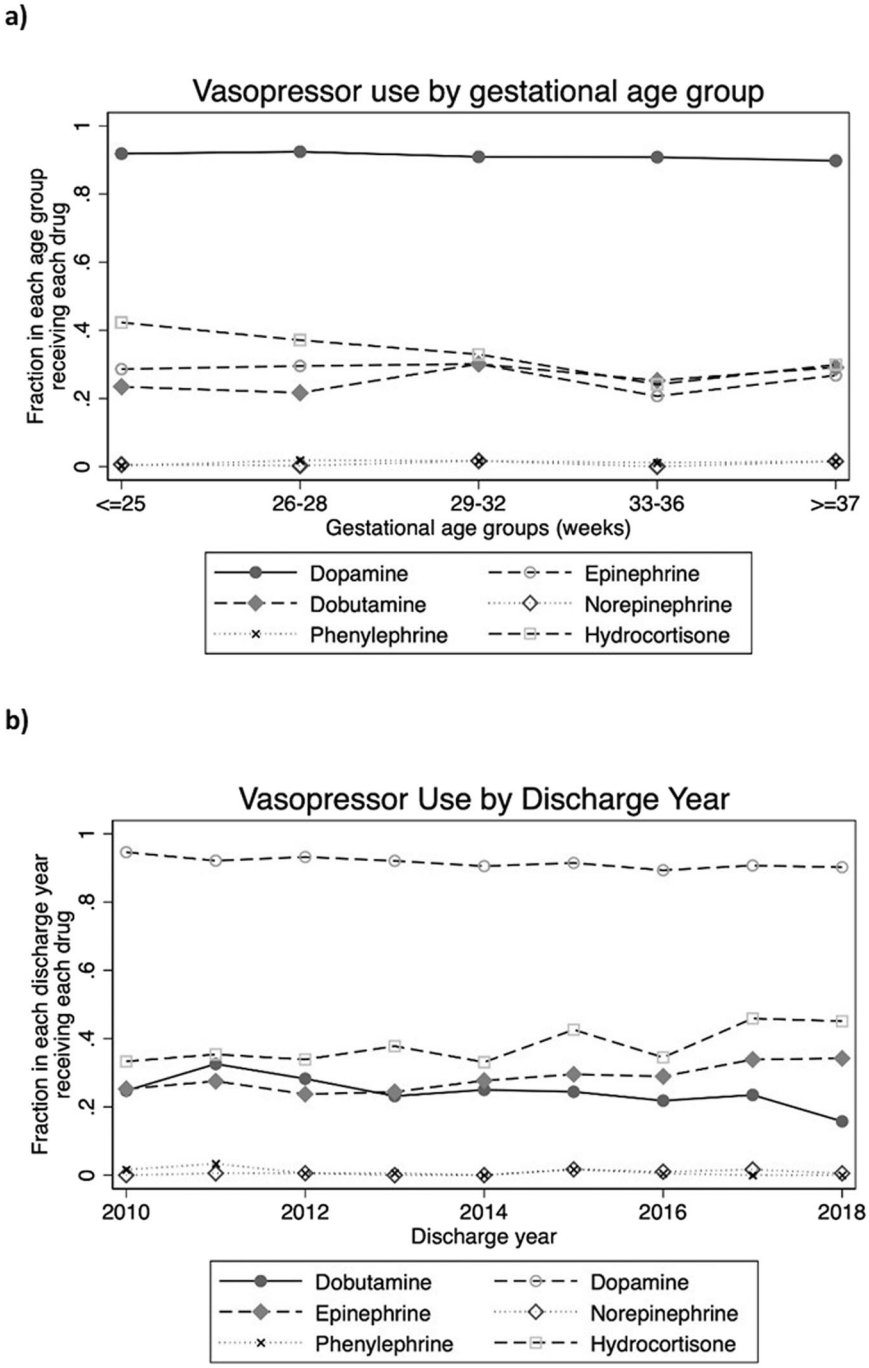

Fig. 1 Vasopressor use. Vasopressor use by **a** gestational age group and **b** discharge year. Between-group difference in usage for each mediation assessed by non-parametric test for trend. No medication class demonstrated significant variation across age groups. Variation by discharge year for each mediation assessed by non-parametric test for trend. Use of dopamine ($p = 0.014$), dobutamine ($p = 0.034$), epinephrine ($p = 0.016$), and phenylephrine ($p = 0.049$) varied significantly by discharge year.

than dopamine, multiple other trials in the neonatal population have failed to demonstrate a mortality difference between therapies, but all have been small, single-center studies [12, 19–21]. Our study included almost 1600 infants across 175 sites, representing a substantially larger cohort than previously published. This cohort likely reflects generalizable treatment practices, as well as outcomes for septic shock and minimizes site-specific effects on treatment outcomes to which single-center studies may be prone [16]. Prospective multicenter trials will be required to define optimal treatment; however, traditional prospective trials have been challenging to conduct in the vulnerable neonatal population, especially those with septic shock who require rapid initiation of therapy [9, 22].

In our study, infants who received adjuvant hydrocortisone for treatment of septic shock had reduced odds of mortality even when adjusting for recent hydrocortisone use as a covariate. Premature infants are at high risk for adrenal insufficiency with a blunted cortisol response to stress suggesting an increased hemodynamic benefit from hydrocortisone use [23]. An ongoing multicenter, randomized, controlled trial seeks to evaluate the role of stress hydrocortisone in pediatric patients with septic shock, but notably excludes infants with corrected gestational age less

Table 3. Adjusted outcomes for septic shock episodes based on treatment combination, from multivariable logistic (mortality) and Poisson (pressor-free days) regression.

	Mortality OR	95% CI	Pressor-free days	95% CI
Treatment group				
Solo dopamine ($n = 883$)	Ref.		3.40	[3.19, 3.62]
Solo epinephrine (81)	**4.66**	**[2.35, 9.23]**	2.73	[1.92, 3.54]
Solo dobutamine (25)	2.12	[0.67, 6.68]	3.56	[2.03, 5.09]
Dopamine + dobutamine (211)	**2.31**	**[1.47, 3.64]**	**2.14**	**[1.75, 2.53]**
Dopamine + epinephrine (218)	**6.18**	**[3.75, 10.2]**	**1.24**	**[0.90, 1.57]**
Dopamine + dobutamine + epinephrine (136)	**15.6**	**[7.59, 32.2]**	**0.53**	**[0.25, 0.81]**
No hydrocortisone (986)	Ref.		2.70	[2.53, 2.88]
Hydrocortisone (606)	**0.60**	**[0.42, 0.86]**	2.45	[2.19, 2.71]
Covariates				
GA group				
<26 weeks	**5.78**	**[2.45, 13.7]**	2.60	[2.39, 2.80]
26–28 weeks	**3.70**	**[1.54, 8.92]**	2.69	[2.40, 2.99]
29–32 weeks	**6.18**	**[2.46, 15.6]**	2.58	[2.13, 3.03]
33–36 weeks	1.91	[0.64, 5.71]	2.64	[2.15, 3.14]
≥37 weeks	Ref.		2.56	[2.00, 3.12]
Not SGA	Ref.		2.54	[2.39, 2.68]
SGA	1.12	[0.73, 1.74]	**3.06**	**[2.66, 3.47]**
No recent antibiotics	Ref.		2.61	[2.41, 2.82]
Recent antibiotics	**0.52**	**[0.34, 0.78]**	2.63	[2.33, 2.92]
Modified nSOFA score	**1.17**	**[1.12, 1.23]**	**-0.10**	**[–0.15, –0.05]**
Age at shock				
<3 days	Ref.		2.98	[2.64, 3.33]
3–7 days	**4.24**	**[2.36, 7.62]**	**2.29**	**[1.95, 2.64]**
8–28 days	**2.84**	**[1.77, 4.55]**	**2.44**	**[2.21, 2.66]**
>28 days	**2.85**	**[1.51, 5.38]**	2.87	[2.36, 3.39]
Female	Ref.		2.49	[2.28, 2.69]
Male	1.00	[0.73, 1.37]	2.71	[2.53, 2.89]
White	Ref.		2.74	[2.49, 2.99]
Black	0.91	[0.63, 1.31]	2.39	[2.15, 2.62]
Hispanic	0.95	[0.61, 1.48]	2.71	[2.31, 3.12]
Other	0.75	[0.37, 1.52]	3.00	[2.43, 3.56]
No CHD	Ref.		2.65	[2.51, 2.78]
CHD	1.30	[0.58, 2.93]	2.15	[1.56, 2.75]
No PPHN	Ref.		2.58	[2.42, 2.73]
PPHN	0.76	[0.48, 1.19]	2.77	[2.41, 3.13]
No recent vasopressor	Ref.		2.61	[2.46, 2.75]
Recent vasopressor	1.00	[0.60, 1.67]	2.68	[2.24, 3.12]
No recent steroid	Ref.		2.60	[2.46, 2.74]
Recent steroid	0.81	[0.46, 1.42]	2.81	[2.30, 3.31]
No current diuretic	Ref.		2.61	[2.47, 2.76]
Current diuretic	1.39	[0.88, 2.22]	2.66	[2.24, 3.08]
No current iNO	Ref.		2.61	[2.47, 2.75]
Current iNO	0.76	[0.42, 1.35]	2.68	[2.16, 3.19]

Bold values indicate a significant difference from the baseline with $p < 0.05$. Therapy with dopamine alone is used as the baseline for comparison between vasopressor treatment groups. Values for modified nSOFA score reflect the marginal effect of a 1-point increase (score can range from 0 to 15).
CHD congenital heart disease, *CI* confidence interval, *iNO* inhaled nitric oxide, *nSOFA* modified sequential organ failure assessment, *OR* odds ratio, *PPHN* persistent pulmonary hypertension of the newborn.

Table 4. Unadjusted outcome of mortality based on epinephrine dosing for 197 of 452 infants with dosing data available (described as frequency [percentage]).

	Infusion epinephrine	Bolus epinephrine	Infusion and bolus combined	Total
Survived	17 (15)	16 (22)	1 (8)	34 (17)
Died	96 (85)	56 (78)	11 (92)	163 (83)
Total	113	72	12	197

than 42 weeks (Stress Hydrocortisone In Pediatric Septic Shock; ClinicalTrials.gov Identifier: NCT03401398). Further study with prospective trials will be required to demonstrate the benefit of adjuvant steroid usage in the NICU population.

An nSOFA score developed by Wynn and Polin correlated well with increased mortality for preterm infants (median gestational age 25.5 weeks) with late-onset sepsis [8]; however, this score requires oxygen saturation data that were not available in our cohort. Our modified score with only FiO_2 data still correlated well with both mortality and pressor-free days alive. This allows for the potential use of our modified score in future cohort studies that may not have full saturation data available.

The most significant limitation of our study arises from the observational design of the cohort. Although our inclusion criteria ensure all infants have new bacteremia with associated new use of vasopressor, the specific indication for vasopressor use, as well as the severity of illness at therapy initiation, is not known. Dopamine is commonly used to augment renal perfusion for low birth weight neonates in addition to its role in hypotension and cardiac output augmentation [24]. Perhaps the divergent observed outcomes between infants that received dopamine compared to epinephrine are due to the cohort of infants who received epinephrine representing a baseline sicker population. While the use of our modified nSOFA score as a covariate allowed for adjustment for illness severity at the time of shock, there is likely some clinical variability that was not accounted for with our included covariates. In addition, the time interval of the included data is the day. More granular timing of interventions, such as the minutes between concern for clinical sepsis and antibiotic initiation, are not captured in our data and may have a large effect on clinical outcomes [25, 26]. Other interventions, such as fluid administration, as well as hemodynamic responses, such as blood pressure, urine output, and capillary refill assessment, are also not captured. Our cohort included data through 2018. Future studies will be needed to assess patient outcomes as clinical practices and vasopressor use evolve over time.

CONCLUSION

Overall, we have described vasopressor use and outcomes for septic shock for a large multicenter cohort of infants in the NICU. Those who received epinephrine as either solo or combination therapy had significantly increased odds of mortality. Adjuvant hydrocortisone use was associated with decreased odds of mortality. Prospective randomized trials will be required to clarify optimal therapy for this vulnerable population.

DATA AVAILABILITY

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

CODE AVAILABILITY

The computer code and Stata do-files used to generate the results of the manuscript are available from the corresponding author on reasonable request.

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AUTHOR CONTRIBUTIONS

All authors made substantial contributions to the conception or design of the work, or the acquisition, analysis, or interpretation of data. HPF drafted the work, all authors revised it critically for important intellectual content. All authors approved the final version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

We obtained institutional review board approval from the Duke University Health System IRB with a waiver of informed consent for our study, protocol Pro00112607. The study was performed in accordance with the Declaration of Helsinki.

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