First-line Vasopressor in Septic Shock
Dopamine vs Epinephrine

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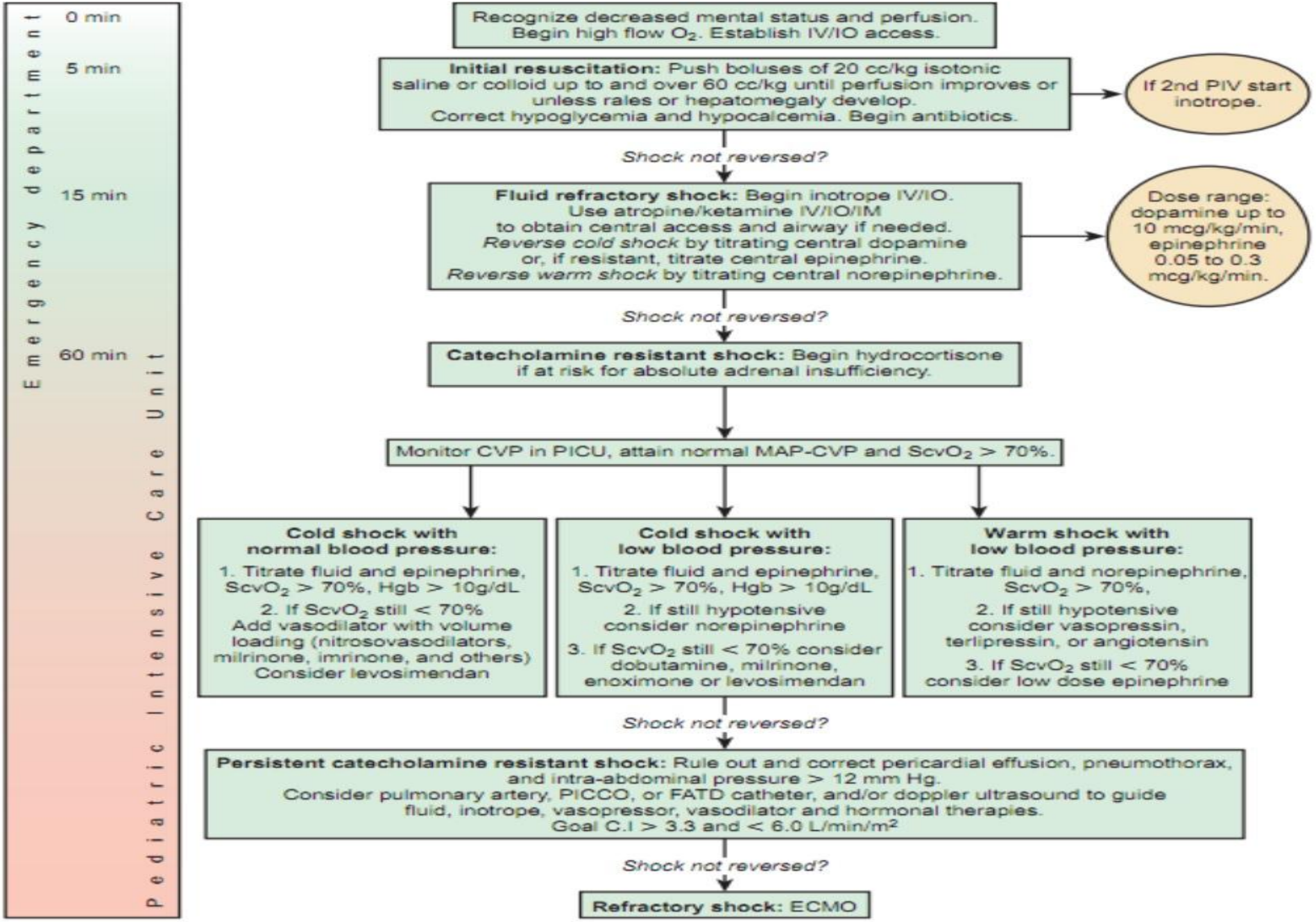
Reviews

- Septic shock : Sepsis plus cardiovascular organ dysfunction

- Mortality: 20-60%*

*WHO-2009



*2007 the American College of Critical Care Medicine

Which Vasopressor is the 1st- choice?

Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2012

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Objective: To provide an update to the "Surviving Sepsis Campaign Guidelines for Management of Severe Sepsis and Septic Shock," last published in 2008.

Design: A consensus committee of 68 international experts representing 30 international organizations was convened. Nominal groups were assembled at key international meetings (for those committee members attending the conference). A formal conflict of interest policy was developed at the onset of the process and enforced throughout. The entire guidelines process was conducted independent of any industry funding. A stand-alone meeting was held for all subgroup heads, co- and vice-chairs, and selected individuals. Teleconferences and electronic-based discussion among subgroups and among the entire committee served as an integral part of the development.

Methods: The authors were advised to follow the principles of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to guide assessment of quality of evidence from high (A) to very low (D) and to determine the strength of recommendations as strong (1) or weak (2). The potential drawbacks of making strong recommendations in the presence of low-quality evidence were emphasized. Some recommendations were ungraded (UG). Recommendations were classified into three groups: 1) those directly targeting severe sepsis; 2) those targeting general care of the critically ill patient and considered high priority in severe sepsis; and 3) pediatric considerations.

Results: Key recommendations and suggestions, listed by category, include: early quantitative resuscitation of the septic patient during the first 6 hrs after recognition (1C); blood cultures

TABLE 7. Norepinephrine Compared With Dopamine in Severe Sepsis Summary of Evidence

Norepinephrine compared with dopamine in severe sepsis

Patient or population: Patients with severe sepsis
Settings: Intensive care unit
Intervention: Norepinephrine
Comparison: Dopamine
Sources: Analysis performed by Djillali Annane for Surviving Sepsis Campaign using following publications: De Backer D. *N Engl J Med* 2010; 362:779–789; Marik PE. *JAMA* 1994; 272:1354–1357; Mathur RDAC. *Indian J Crit Care Med* 2007; 11:186–191; Martin C. Chest 1993; 103:1826–1831; Patel GP. *Shock* 2010; 33:375–380; Ruokonen E. *Crit Care Med* 1993; 21:1296–1303

Outcomes	Illustrative Comparative Risks[a] (95% CI)		Relative Effect (95% CI)	No. of Participants (Studies)	Quality of the Evidence (GRADE)	Comments
	Assumed Risk	Corresponding Risk				
	Dopamine	Norepinephrine				
Short-term mortality	530 per 1000	Study population 482 per 1000 (440 to 524)	RR 0.91 (0.83 to 0.99)	2043 (6 studies)	⊕⊕⊕⊖ moderate[b,c]	
Serious adverse events —Supraventricular arrhythmias	229 per 1000	Study population 82 per 1000 (34 to 195)	RR 0.47 (0.38 to 0.58)	1931 (2 studies)	⊕⊕⊕⊖ moderate[b,c]	
Serious adverse events —Ventricular arrhythmias	39 per 1000	Study population 15 per 1000 (8 to 27)	RR 0.35 (0.19 to 0.66)	1931 (2 studies)	⊕⊕⊕⊖ moderate[b,c]	

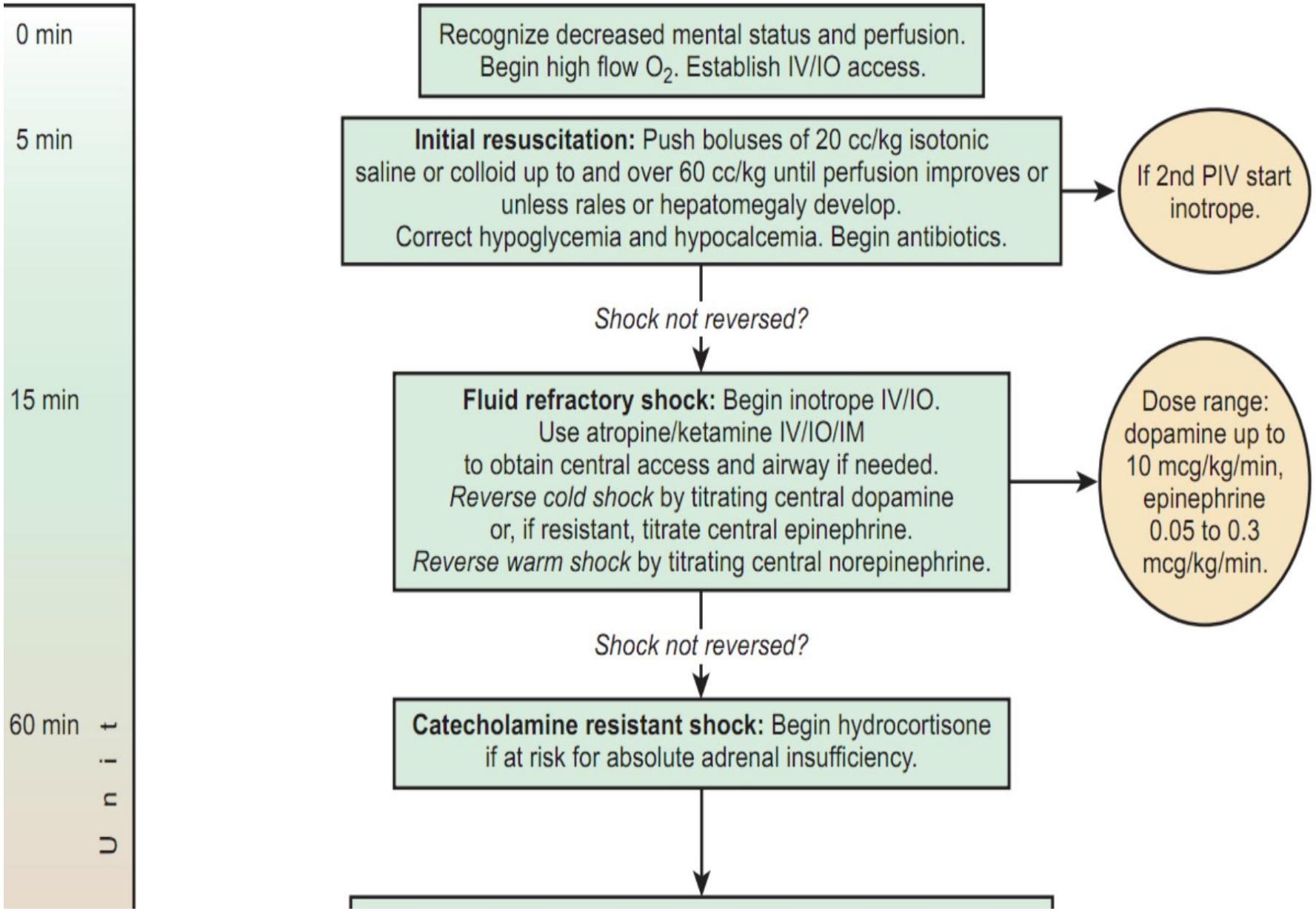
[a]The assumed risk is the control group risk across studies. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI = confidence interval, RR = risk ratio.

[b]Strong heterogeneity in the results ($I^2 = 85\%$), however this reflects degree of effect, not direction of effect. We have decided not to lower the evidence quality.

[c]Effect results in part from hypovolemic and cardiogenic shock patients in De Backer, *N Engl J Med* 2010. We have lowered the quality of evidence one level for indirectness.

H. Vasopressors

1. Vasopressor therapy initially to target a mean arterial pressure (MAP) of 65 mm Hg (grade 1C).
2. Norepinephrine as the first choice vasopressor (grade 1B).
3. Epinephrine (added to and potentially substituted for norepinephrine) when an additional agent is needed to maintain adequate blood pressure (grade 2B).
4. Vasopressin 0.03 units/minute can be added to norepinephrine (NE) with intent of either raising MAP or decreasing NE dosage (UG).
5. Low dose vasopressin is not recommended as the single initial vasopressor for treatment of sepsis-induced hypotension and vasopressin doses higher than 0.03-0.04 units/minute should be reserved for salvage therapy (failure to achieve adequate MAP with other vasopressor agents) (UG).
6. Dopamine as an alternative vasopressor agent to norepinephrine only in highly selected patients (eg, patients with low risk of tachyarrhythmias and absolute or relative bradycardia) (grade 2C).
7. Phenylephrine is not recommended in the treatment of septic shock except in circumstances where (a) norepinephrine is associated with serious arrhythmias, (b) cardiac output is known to be high and blood pressure persistently low or (c) as salvage therapy when combined inotrope/vasopressor drugs and low dose vasopressin have failed to achieve MAP target (grade 1C).
8. Low-dose dopamine should not be used for renal protection (grade 1A).
9. All patients requiring vasopressors have an arterial catheter placed as soon as practical if resources are available (UG).


0 min
5 min
15 min
60 min
Unit
Recognize decreased mental status and perfusion.
Begin high flow O_2. Establish IV/IO access.
Initial resuscitation: Push boluses of 20 cc/kg isotonic saline or colloid up to and over 60 cc/kg until perfusion improves or unless rales or hepatomegaly develop.
Correct hypoglycemia and hypocalcemia. Begin antibiotics.
If 2nd PIV start inotrope.
Shock not reversed?
Fluid refractory shock: Begin inotrope IV/IO.
Use atropine/ketamine IV/IO/IM to obtain central access and airway if needed.
Reverse cold shock by titrating central dopamine or, if resistant, titrate central epinephrine.
Reverse warm shock by titrating central norepinephrine.
Dose range: dopamine up to 10 mcg/kg/min, epinephrine 0.05 to 0.3 mcg/kg/min.
Shock not reversed?
Catecholamine resistant shock: Begin hydrocortisone if at risk for absolute adrenal insufficiency.

?

Dopamine Vs Epinephrine

Crit Care Med. 2015 Nov;43(11):2292-302. doi: 10.1097/CCM.0000000000001260.

Double-Blind Prospective Randomized Controlled Trial of Dopamine Versus Epinephrine as First-Line Vasoactive Drugs in Pediatric Septic Shock.

Ventura AM[1], Shieh HH, Bousso A, Góes PF, Fernandes Ide C, de Souza DC, Paulo RL, Chagas F, Gilio AE.

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Abstract

OBJECTIVES: The primary outcome was to compare the effects of dopamine or epinephrine in severe sepsis on 28-day mortality; secondary outcomes were the rate of healthcare-associated infection, the need for other vasoactive drugs, and the multiple organ dysfunction score.

DESIGN: Double-blind, prospective, randomized controlled trial from February 1, 2009, to July 31, 2013.

SETTING: PICU, Hospital Universitário da Universidade de São Paulo, Brazil.

PATIENTS: Consecutive children who are 1 month to 15 years old and met the clinical criteria for fluid-refractory septic shock. Exclusions were receiving vasoactive drug(s) prior to hospital admission, having known cardiac disease, having already participated in the trial during the same hospital stay, refusing to participate, or having do-not-resuscitate orders.

INTERVENTIONS: Patients were randomly assigned to receive either dopamine (5-10 μg/kg/min) or epinephrine (0.1-0.3 μg/kg/min) through a peripheral or intraosseous line. Patients not reaching predefined stabilization criteria after the maximum dose were classified as treatment failure, at which point the attending physician gradually stopped the study drug and started another catecholamine.

MEASUREMENTS AND MAIN RESULTS: Physiologic and laboratory data were recorded. Baseline characteristics were described as proportions and mean (± SD) and compared using appropriate statistical tests. Multiple regression analysis was performed, and statistical significance was defined as a p value of less than 0.05. Baseline characteristics and therapeutic interventions for the 120 children enrolled (63, dopamine; 57, epinephrine) were similar. There were 17 deaths (14.2%): 13 (20.6%) in the dopamine group and four (7%) in the epinephrine group (p = 0.033). Dopamine was associated with death (odds ratio, 6.5; 95% CI, 1.1-37.8; p = 0.037) and healthcare-associated infection (odds ratio, 67.7; 95% CI, 5.0-910.8; p = 0.001). The use of epinephrine was associated with a survival odds ratio of 6.49.

CONCLUSIONS: Dopamine was associated with an increased risk of death and healthcare-associated infection. Early administration of peripheral or intraosseous epinephrine was associated with increased survival in this population. Limitations should be observed while interpreting these results.

Dopamine vs Epinephrine

- Design: prospective RCT, 01/02/2009 - 31/07/2013
- Setting: PICU, Universidade de São Paulo, Brazil
- Patients: children 1m-15y fluid-refractory septic shock
- Interventions:

  Dopamine (5-10) - Epinephrine (0.1-0.3 µg/kg/min)
- Outcomes: 28-day mortality

  Healthcare-associated infections

Dopamin vs Epinephrine

Figure 1. Study protocol. *Response to treatment include all of the following: Normal heart rate/age, normal mental status, systolic blood pressure > 5th percentile for age, capillary refill time < 2 s, palpable peripheral pulses with no difference between central and peripheral, urine output > 1 mL/kg/hr; •Observe signs of fluid overload: hepatomegaly, crackles, increased work of breathing or gallop rhythm; §Consider endotracheal intubation/nasal continuous positive airway pressure (CPAP), +**X** dose: dopamine = 5 μg/kg/min and epinephrine = 0.1 μg/kg/min, **Y** dose: dopamine = 7.5 μg/kg/min and epinephrine = 0.2 μg/kg/min, **Z** dose: dopamine = 10 μg/kg/min and epinephrine = 0.3 μg/kg/min.

TABLE 1. Characteristics of 120 Children With Septic Shock at Baseline

Characteristic	Dopamine ($n = 63$)	Epinephrine ($n = 57$)	p
Age, mo (± SD)	39.6 (46.3)	56.9 (58.2)	0.145[a]
Male gender, *n* (%)	35.0 (55.6)	35.0 (61.4)	0.516[b]
Body mass index/age *z* score (± SD)	0.16 (1.5)	−0.08 (1.9)	0.142[a]
Pediatric Risk of Mortality (± SD)	15.7 (10.4)	14.4 (9.9)	0.527[a]
Pediatric Logistic Organ Dysfunction (1st day) (± SD)	15.5 (6.5)	14.7 (6.3)	0.582[a]
Underlying disease, yes, *n* (%)	13 (20.6)	12 (21.1)	0.955[b]
Cold shock during use of study drug, yes, *n* (%)	43 (88.3)	40 (70.2)	0.818[b]
Community-acquired infection, yes, *n* (%)	59 (93.6)	51 (89.4)	0.563[b]
Source of infection, *n* (%)			
Respiratory	41	36	0.788[c]
Intra-abdominal	12	7	
Skin/soft tissue	3	3	
CNS	7	5	
Urinary tract	1	2	
Others	19	10	
Etiology, *n* (%)	40 (63.4)	40 (70)	0.735[c]
Streptococcus pneumoniae	9 (22.5)	8 (20)	
Methicillin-sensitive *Staphylococcus aureus*	7 (17.5)	5 (12.5)	
Neisseria meningitidis	4 (10)	7 (17.5)	
Streptococcus pyogenes	4 (10)	3 (7.5)	
Haemophilus influenzae	4 (10)	3 (7.5)	
Methicillin-resistant *S. aureus*	1 (2.5)	4 (10)	
Others	15 (37.5)	13 (32.5)	

TABLE 2. Treatment Administered

Interventions	Dopamine ($n = 63$)	Epinephrine ($n = 57$)	p
Time to fluids, hr[a]	0.4 (0.6)	0.4 (0.8)	0.344[b]
Fluids 1st hr, mL/kg[a]	49.7 (18.1)	50.7 (10.9)	0.114[b]
Fluids 1st 6 hr, mL/kg[a]	90.3 (33.9)	86.9 (23.4)	0.787[b]
Antibiotics 1st hr, yes, *n* (%)	53 (84)	47 (82.5)	0.167[c]
Time to study drug, hr[a]	3.2 (3.1)	2.4 (1.9)	0.441[b]
Duration of resuscitation, hr[a]	33.6 (57)	16.1 (23.6)	0.024[b]
MV, yes, *n* (%)	62 (98.4)	51 (89.5)	0.052[c]
MV-free days[a]	16.3 (10.6)	18.6 (10.3)	0.174[b]
Hydrocortisone for shock, yes, *n* (%)	21 (33.3)	17 (29.8)	0.680[c]
Renal replacement therapy, yes, *n* (%)	11 (17.4)	6 (10.5)	0.001[c]

MV = mechanical ventilation.

[a]Values are expressed as mean ± SD.

[b]Mann-Whitney test.

[c]Chi-square test.

TABLE 3. Profile of Use of Vasoactive Drugs According to Study Group

Interventions	Dopamine ($n = 63$)	Epinephrine ($n = 57$)	p
Duration of the use of study drug, hr, mean (± SD)	20.4 (21.4)	36.5 (46.3)	0.003[a]
Need for other drugs, yes, *n* (%)	33 (52.4)	22 (38.6)	0.130[b]
VIS category 1st day, *n* (%)			
< 10	30 (47.6)	1 (1.8)	0.078[a]
10–14	1 (1.6)	21 (36.8)	
15–19	1 (1.6)	9 (15.8)	
20–24	0 (0)	4 (7)	
≥ 25	31 (49.2)	22 (38.6)	
VIS category 2nd day, *n* (%)			
< 5	13 (21.7)	21 (37.5)	0.769[a]
5–9	21 (35)	1 (1.8)	
10–14	5 (8.3)	14 (25)	
15–19	2 (3.3)	5 (8.9)	
≥ 20	19 (31.7)	15 (26.8)	
Other vasoactive drugs used, yes, *n* (%)			
Dopamine	0 (0)	0 (0)	NA
Epinephrine	23 (36.5)	19 (33.3)	0.08[b]
Dobutamine	14 (22.2)	8 (14)	0.247[b]
Milrinone	3 (4.8)	3 (5.3)	> 0.999[c]
Vasopressin	2 (3.2)	2 (3.5)	> 0.999[c]
Norepinephrine	19 (30.2)	13 (22.8)	0.363[c]
Vasoactive drug–free days	18.9 (11.3)	23.7 (9)	0.028[a]

VIS = vasoactive inotropic score, NA = not applicable.

TABLE 4. Vital Signs According to Group

Variable	Baseline	Before Randomization	6 Hr After Randomization	At the End of Resuscitation
Heart rate (beats/min)				
Dopamine	159 ± 25 (108–204)	154 ± 23 (96–206)	145 ± 27 (98–207)	142 ± 26 (81–201)
Epinephrine	149 ± 31 (76–205)	143 ± 28 (74–190)	142 ± 25 (81–188)	140 ± 23 (86–185)
p	0.047[a]	0.02[a]	0.50[a]	0.67[a]
Systolic blood pressure (mm Hg)				
Dopamine	85 ± 22 (40–135)	85 ± 18 (43–144)	92 ± 19 (55–161)	96 ± 18 (53–143)
Epinephrine	87 ± 19 (56–143)	80 ± 15 (52–120)	99 ± 17 (52–150)	104 ± 19 (53–169)
p	0.59[a]	0.13[a]	0.03b	0.01[b]
Shock index				
Dopamine	1.9 ± 0.6 (1–4.3)	1.9 ± 0.6 (0.9–3.6)	1.7 ± 0.6 (0.9–3.4)	1.5 ± 0.4 (0.7–2.6)
Epinephrine	1.7 ± 0.5 (0.7–3)	1.8 ± 0.6 (0.7–4.t5)	1.5 ± 0.4 (0.6–2.4)	1.3 ± 0.4 (0.6–2.9)
p	0.12[b]	0.87[b]	0.02[a]	0.07[a]
Mean arterial pressure and central venous pressure (cm H_2O)				
Dopamine	47 ± 10 (33–56)	54 ± 13 (35–75)	55 ± 14 (25–87)	57 ± 11 (26–76)
Epinephrine	49 ± 19 (35–77)	53 ± 10 (35–77)	66 ± 10 (46–88)	68 ± 13 (41–93)
p	0.99[b]	0.86[a]	0.003[a]	0.007[a]
$Svco_2$ (%)				
Dopamine	72 ± 8 (59–81)	67 ± 8 (54–80)	74 ± 10 (38–91)	76 ± 8 (42–89)
Epinephrine	67 ± 3 (64–74)	66 ± 8 (50–80)	77 ± 5 (64–89)	79 ± 5 (69–89)
p	0.24[a]	0.70[a]	0.31[b]	0.18[b]

$Scvo_2$ = central venous oxygen saturation.
[a]Student *t* test.
[b]Mann-Whitney test.
Values are expressed as mean ± SD (limits).

TABLE 6. Multiple Logistic Regression Analyses: Outcomes Odds Ratios or Relative Risk With 95% CI

	OR (95% CI); *p*			Relative Risk (95% CI); *p*
Variable	Death at 28 D	Healthcare-Associated Infection	Need for Other Vasoactive Drugs	Multiple Organ Dysfunction Score (PELOD)
Dopamine	6.51 (1.12–37.80); 0.037	67.74 (5.04–910.87); 0.001	–	–
PELOD	1.22 (1.09–1.36); < 0.001	–	–	–
Renal replacement therapy	38.89 (7.39–204.80); < 0.001	12.57 (2.28–69.40); 0.004	–	
Hydrocortisone for shock	–	–	42.85 (7.86–233.78); < 0.001	2.31 (1.23–1.55); < 0.001
Duration of resuscitation	–	–	1.10 (1.03–1.17); 0.004	1.002 (1.0–1.01); < 0.001
ICU length of stay	–	1.13 (1.06–1.21); 0.001	–	–
Pediatric Risk of Mortality (risk)	–	–	–	1.006 (1.001–1.003); < 0.001
Need for other vasoactive drugs	–	–	–	1.60 (1.25–1.30); 0.037

OR = odds ratio, PELOD = Pediatric Logistic Organ Dysfunction.

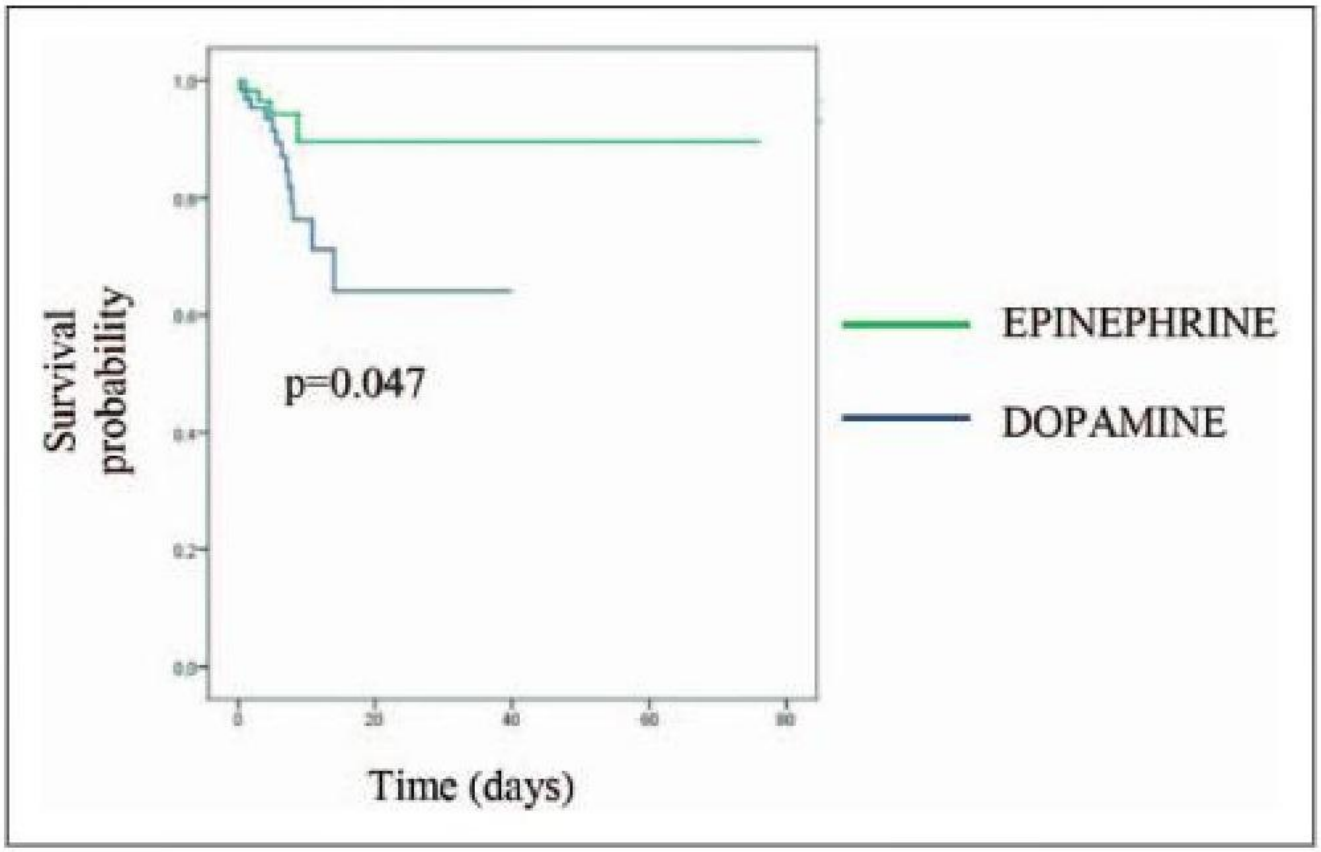

Figure 3. Kaplan-Meyer survival function according to group.

Conclusions

0.05. Baseline characteristics and therapeutic interventions for the 120 children enrolled (63, dopamine; 57, epinephrine) were similar. There were 17 deaths (14.2%): 13 (20.6%) in the dopamine group and four (7%) in the epinephrine group ($p = 0.033$). Dopamine was associated with death (odds ratio, 6.5; 95% CI, 1.1–37.8; $p = 0.037$) and healthcare–associated infection (odds ratio, 67.7; 95% CI, 5.0–910.8; $p = 0.001$). The use of epinephrine was associated with a survival odds ratio of 6.49.

Conclusions

1st-choice Vasopressor in Septic shock:

Epinephrine > Dopamine

(Survival and Healthcare-associated infection)

Thank for Yours Attention!