American Journal of Medical Sciences and Medicine, 2017, Vol. 5, No. 4, 79-90
Available online at http://pubs.sciepub.com/ajmsm/5/4/3

DOI:10.12691/ajmsm-5-4-3

The Effect of Dopamine versus Norepinephrine on the Outcome of Pediatric Septic Shock

Miriam Magdy Aziz[1,*], Hala Mohammed Amin Fouad[1], Taher H[1], Abdel Rahman Emam Sayed Amin[2]

[1]Pediatrics, Faculty of Medicine, Cairo University
[2]MSc Pediatrics, Cairo University
*Corresponding author: miriammagdyaziz@gmail.com

Received October 09, 2017; Revised November 23, 2017; Accepted December 15, 2017

Abstract **Background:** Septic shock is a leading cause of mortality and morbidity among children all over the world. Vasoactive therapy must be initiated in patients who have not improved after fluid resuscitation. **Aim of work:** The aim of this study was to compare the effect of dopamine versus norepinephrine on the outcome of pediatric septic shock. **Patients and methods:** The study was a prospective observational study that was conducted on 40 children aged from 1 month to 12 years who were admitted to the emergency department. They were assigned by the treating physicians to two groups: 1) Group A: 20 patients who received dopamine (5-20 mcg/kg/min). 2) Group B: 20 patients who received norepinephrine (1-1.5 mcg/kg/min). Clinical, hemodynamic, and laboratory data were recorded and compared using appropriate statistical tests. **Results:** Baseline characteristics for the 40 children enrolled were nearly similar. There was a significantly higher mortality rate in the dopamine group compared with the norepinephrine one ($P < 0.05$). As in the dopamine group, 15 patients died out of 20 patients, while in the norepinephrine group 8 patients died out of 20 patients, (75% vs. 40%, p=0.025). Stepwise logistic regression analysis revealed that PRISM-24 (p=0.001), drug (p=0.019), and MODS (p=0.003) could independently predict the mortality in septic shock patients. **Conclusions:** Norepinephrine was associated with an increased response to treatment and decreased risk of death in children with septic shock as compared to dopamine. Dopamine, PRISM-24, and MODS could independently predict the mortality in children with septic shock.

Keywords: *children, septic shock, mortality, dopamine, norepinephrine, outcome*

Cite This Article: Miriam Magdy Aziz, Hala Mohammed Amin Fouad, Taher H, and Abdel Rahman Emam Sayed Amin, "The Effect of Dopamine versus Norepinephrine on the Outcome of Pediatric Septic Shock." *American Journal of Medical Sciences and Medicine*, vol. 5, no. 4 (2017): 79-90. doi: 10.12691/ajmsm-5-4-3.

1. Introduction

Adequate fluid resuscitation is an essential aspect of the hemodynamic management of patients with septic shock and should be achieved before vasopressors and inotropes are used, but early use of vasopressors in patients with severe shock is frequently necessary [1].

Dopamine increases mean arterial pressure and cardiac output, primarily due to an increase in stroke volume and heart rate. Norepinephrine increases mean arterial pressure due to its vasoconstrictive effects, with little change in heart rate and less increase in stroke volume compared with dopamine. Either may be used as a first-line agent to correct hypotension in sepsis. Norepinephrine is more potent than dopamine and may be more effective at reversing hypotension in patients with septic shock. Dopamine may be particularly useful in patients with compromised systolic function but causes more tachycardia and may be more arrhythmogenic [1].

When fluid administration fails to restore an adequate arterial pressure and organ perfusion in patients with septic shock, vasopressor agents should be initiated. The goal is to restore effective tissue perfusion and to normalize cellular metabolism [2].

There has been longstanding debate about whether one catecholamine vasopressor agent is superior to another, but different agents have different effects on pressure and flow. The argument about which catecholamine is best in a given situation is best transformed into a discussion about which agent is best suited to implement the therapeutic strategy chosen. The efficacy of hemodynamic therapy in sepsis should be assessed by monitoring a combination of clinical and hemodynamic parameters. End points for therapy are debatable. Clinicians should define specific goals and end points, titrate therapies to those end points, and evaluate the results of their interventions on an ongoing basis [2].

2. Patients and Methods

This was a prospective observational study which was designed to compare the effect of dopamine versus norepinephrine on the outcome of septic shock. It was conducted on 40 patients with septic shock who were admitted to the emergency department in Cairo University

Children Hospital during six months interval from January 2012 to June 2012. The number of patients who were admitted with septic shock or developed septic shock was 53 patients, but we included only 40 patients, as 13 patients were dropped out, because of death in the early hours on diagnosis of septic shock. The included 40 patients were assigned by treating physician to two groups: Group A: 20 patients who received dopamine and Group B: 20 patients who received norepinephrine.

Patients were included if they were admitted with septic shock or developed septic shock. Patients were excluded if total length of stay in the emergency department after diagnosis of septic shock was < 24hrs, or if they were presenting with cardiogenic shock.

All patients were monitored by automated monitoring equipments for arterial pressure (systolic, diastolic, and MAP), heart rate, oxygen saturation, respiratory rate and ECG tracing. Urine was collected via a urethral catheter and bag. Variables were collected at study entry during the first 24-48 hrs.

Data included the following variables: age, sex, cause of admission, number and type of organ failure, heart rate, blood pressure, and respiratory rate according to age specific vital signs [3], core temperature using rectal thermometer, mean arterial pressure (MAP) using the 2007 American College of Critical care Medicine (ACCM) age-specific MAP indicating adequate resuscitation [5], capillary refilling time, urine output, mental status, need for mechanical ventilation, weaning from mechanical ventilation, length of stay, pediatric risk of mortality (PRISM) scoring, use of dopamine or norepinephrine (24 hrs). Complete laboratory assessments including; sepsis profile, blood gases, blood chemistry, cultures were recorded.

Patients with variable sepsis syndromes (SIRS, sepsis, severe sepsis, septic shock and MODS) were defined according to the International Pediatric Sepsis Consensus Conference (IPSCC) [3].

Pediatric Risk of mortality (PRISM) III score [4] was applied in the first 24 hrs of ED admission to predict outcome and severity of illness.

All patients in the study received broad-spectrum antibiotic coverage upon diagnosis of septic shock till culture results were obtained then the antibiotic regimen was adjusted accordingly. Also all patients needed respiratory support either by oxygenation or mechanical ventilation. Hemoglobin concentration was maintained at normal range for age. Glycemic control as blood glucose was kept within the normal range (70-110 mg / dl) to avoid both hypoglycemia and hyperglycemia with targets of <180 mg/dl. Once diagnosis of septic shock was established, and before addition of any inotrope, all children were exposed to rapid and regular evaluation, assessment, and recording of clinical examination especially blood pressure (systolic, diastolic, and MAP), capillary refilling time (CRT), HR, UOP, conscious level and also results of laboratory and radiological investigations. A hemodynamic management was used in which all patients were given fluid resuscitation mainly crystalloids (normal saline in all patients) up to 60 mL/kg to raise MAP to normal range for age. After hypotension persisted in all 40 patients despite this fluid challenge, then patients were assigned by treating physician to one of two treatment groups 1) those who received dopamine (5-20 mcg/kg/min), (n = 20), dopamine was initiated at a dose of 5 mcg/kg/min followed by 5 mcg/kg/min increments every 10 – 20 minutes up to a dose of 20 mcg/kg/min and the dose was titrated until the desirable effect was reached, or 2) those who received norepinephrine(1 mg / 1ml) (started at 0.1 mcg/kg/min) with 0.3 mcg/kg/min increments every 10 – 20 minutes up to a maximal dose of 1.5 mcg/kg/min,(n = 20), and the dose was titrated until the desirable effect was reached. The treating physician calculated the dose of each drug by the equation:

$$\text{The desired amount} = \frac{\left[\begin{array}{l}\text{desired dose}\times\text{body weight}\\ \times 60\left(\text{to convert min to hrs}\right)\times 24\text{hr}\end{array}\right]}{\left[\begin{array}{l}1000\left(\text{to convert mcg to mg}\right)\\ \times\left(40\text{for DA or1for NE}\right)\end{array}\right]}.$$

Compatible solution (glucose 5%) added by the nurse to the measured amount for each drug in a 50 ml syringe to reach to 24 ml. The infusion was started at the rate of 1 mL/hr via infusion pump through a separate peripheral line and usually a central line. This vasoactive and inotropic support was titrated to keep MAP ≥ normal for age, urine output ≥ 1ml/kg/hr, improve of oxygenation and ventilation, and normalization of mental status. When the hemodynamic status of patients was stable for at least 24 hours, progressive weaning of the drugs was begun by treating physicians. The daily evaluation and follow up were done until death or discharge from emergency department.

Table 1. ACCM Age-specific MAP Indicating Adequate Resuscitation [5]

Age	Goal Mean Arterial Pressure
Term newborn	55
Up to 1 year	60
1-2 years	65
2-7 years	65
7-15 years	65

Laboratory investigations were recorded from files of patients including: Complete blood count (CBC): White blood cell count (WBC) was assessed according to age specific laboratory value for sepsis definition [3] and hemoglobin for age [6], Platelet count: 150,000-450,000, C- reactive protein (CRP): Normal level (< 6 mg / ml) [6]. Erythrocyte sedimentation rate (ESR): Normal value (0-20 mm / hr) [6] and Cultures (blood, sputum, broncho-alveolar lavage, CSF, urine, stool, and wound). Chemistry including: Serum blood urea nitrogen (BUN), Creatinine, Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), bilirubin age specific values [6], Glucose 70-110 mg / dl, electrolytes (Na, K, Ca), and arterial blood gases (ABG).

3. Statistical Analysis

Data were coded and entered using the statistical package SPSS (Statistical Package for the Social Sciences)

version 24. Data was summarized using mean, standard deviation, median, minimum and maximum in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. Comparisons between quantitative variables were done using the non-parametric Kruskal-Wallis and Mann-Whitney tests. For comparison of serial measurements (before and after) within each patient the non-parametric Wilcoxon signed rank test was used [7]. For comparing categorical data, Chi square ($\chi 2$) test was performed. Exact test was used instead when the expected frequency is less than 5 [8]. Logistic regression was done to detect independent predictors of outcome [9]. P-values less than 0.05 were considered as statistically significant.

4. Results

The age of all 40 patients ranged from 1 month to 143 months (mean 22.675 months)

Table 2. Comparison of age variation between the study groups

Age (months)	**dopamine**					**P value**
	Mean	**SD**	**Median**	**Minimum**	**Maximum**	
	17.60	31.59	8.50	1.00	143.00	**0.017**
	norepinephrine					
	27.75	21.58	20.00	2.00	72.00	

The age of patients in the dopamine group was significantly lower ($P < 0.05$) than that in the norepinephrine group.

Out of 40 patients included; 23 (57%) were males and 17 (43%) were females.

Table 3. Comparison of sex distribution between the study groups

Sex		**dopamine**		**norepinephrine**		**P value**
		Count n=20	**%**	**Count n=20**	**%**	
	male	10	50.0%	13	65.0%	**0.337**
	female	10	50.0%	7	35.0%	

There was no statistically significant difference in the sex distribution between the two groups ($P > 0.05$).

Out of 40 patients, 22 (55%) patients admitted to ER with septic shock and 18 patients admitted with another cause other than septic shock which were neurological (25%), respiratory (17.5%), and renal (2.5%). In all 40 patients, pneumonia was the cause of septic shock in 31/40 patients (77.5%).

All 40 patients had MODS ranging from 2 systems up to 6 systems.

Table 4. Comparison of MODS between the study groups

		dopamine		norepinephrine		P value
		Count n=20	**%**	**Count n=20**	**%**	
MODS	2	6	30.0%	7	35.0%	**1**
	3	4	20.0%	4	20.0%	
	4	6	30.0%	6	30.0%	
	5	2	10.0%	2	10.0%	
	6	2	10.0%	1	5.0%	
respiratory	yes	16	80.0%	18	90.0%	**0.661**
	no	4	20.0%	2	10.0%	
neurologic	yes	11	55.0%	5	25.0%	**0.053**
	no	9	45.0%	15	75.0%	
hematologic	yes	10	50.0%	6	30.0%	**0.197**
	no	10	50.0%	14	70.0%	
hepatic	yes	5	25.0%	8	40.0%	**0.311**
	no	15	75.0%	12	60.0%	
cardiovascular	yes	20	100.0%	20	100.0%	---
renal	yes	8	40.0%	9	45.0%	**0.749**
	no	12	60.0%	11	55.0%	

Table 5. Comparison of MAP, CRT, HR, and UOP, before and after addition of dopamine and norepinephrine

	dopamine					P value
	Mean	SD	Median	Minimum	Maximum	
MAP before inotrope (mmHg)	43.67	3.56	44.50	38.00	47.00	**0.028**
MAP after inotrope (mmHg)	65.40	7.06	65.00	52.00	78.00	
CRT before inotrope (seconds)	5.75	2.51	6.00	2.00	10.00	**< 0.001**
CRT after inotrope (seconds)	3.05	1.28	3.00	2.00	7.00	
HR before inotrope (b/m)	178.35	15.28	180.00	155.00	210.00	**< 0.001**
HR after inotrope (b/m)	137.50	21.93	135.00	110.00	193.00	
UOP before inotrope (cc/Kg/h)	.68	.21	.70	.30	1.00	**0.002**
UOP after inotrope (cc/Kg/h)	1.00	.41	1.00	.40	1.80	
	norepinephrine					**P value**
	Mean	**SD**	**Median**	**Minimum**	**Maximum**	
MAP before inotrope (mmHg)	32.38	9.75	32.50	16.00	47.00	**0.012**
MAP after inotrope (mmHg)	65.75	14.12	66.00	24.00	91.00	
CRT before inotrope (seconds)	6.00	1.86	6.00	2.00	10.00	**< 0.001**
CRT after inotrope (seconds)	2.25	1.21	2.00	1.00	6.00	
HR before inotrope (b/m)	175.15	16.59	174.50	150.00	210.00	**< 0.001**
HR after inotrope (b/m)	122.85	19.02	118.00	100.00	170.00	
UOP before inotrope (cc/Kg/h)	.68	.24	.70	.10	1.00	**< 0.001**
UOP after inotrope (cc/Kg/h)	1.13	.38	1.10	.50	2.00	

Table 6. Comparison of mental status before and after addition of dopamine

	dopamine						P value
	normal		altered due to pre-existing neurological cause		altered due to septic shock		
	Count n=20	%	Count n=20	%	Count n=20	%	
Mental status before inotrope	0	.0%	8	40.0%	12	60.0%	0.015
Mental status after inotrope	6	30.0%	8	40.0%	6	30.0%	
	norepinephrine						P value
	normal		**altered due to pre-existing neurological cause**		**altered due to septic shock**		
	Count n=20	**%**	**Count n=20**	**%**	**Count n=20**	**%**	
Mental status before inotrope	0	.0%	5	25.0%	15	75.0%	<0.001
Mental status after inotrope	12	60.0%	5	25.0%	3	15.0%	

There was a statistically significant improvement in all parameters after addition of dopamine or norepinephrine.

Table 7. Comparison of MAP, CRT, HR, and UOP between two groups before and after addition of inotrope:

	dopamine					norepinephrine					P value
	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	
MAP before inotrope (mmHg)	43.67	3.56	44.50	38.00	47.00	32.38	9.75	32.50	16.00	47.00	**0.029**
MAP after inotrope (mmHg)	65.40	7.06	65.00	52.00	78.00	65.75	14.12	66.00	24.00	91.00	**0.478**
CRT before inotrope (seconds)	5.75	2.51	6.00	2.00	10.00	6.00	1.86	6.00	2.00	10.00	**0.883**
CRT after inotrope (seconds)	3.05	1.28	3.00	2.00	7.00	2.25	1.21	2.00	1.00	6.00	**0.028**
HR before inotrope (b/m)	178.35	15.28	180.00	155.00	210.00	175.15	16.59	174.50	150.00	210.00	**0.512**
HR after inotrope (b/m)	137.50	21.93	135.00	110.00	193.00	122.85	19.02	118.00	100.00	170.00	**0.015**
UOP before inotrope (CC/Kg/h)	.68	.21	.70	.30	1.00	.68	.24	.70	.10	1.00	**0.968**
UOP after inotrope (CC/Kg/h)	1.00	.41	1.00	.40	1.80	1.13	.38	1.10	.50	2.00	**0.461**

Comparison of all variables before addition of inotrope showed no statistically significant difference between the two groups except for MAP, where MAP in the norepinephrine group was significantly lower ($P < 0.05$) than that in the dopamine group.

CRT after addition of inotrope in the norepinephrine group was significantly decreased ($P < 0.05$) more than that in the dopamine group. HR after addition of inotrope in the dopamine group was significantly higher ($P < 0.05$) than that in the norepinephrine group.

Out of 40 patients, 30 patients needed mechanical ventilation and 10 patients needed only nasal oxygen supply. In the two groups; comparison was done between the number of patients who did not need mechanical ventilation, the number of patients who needed mechanical ventilation and weaned after improvement of shock, and the number of patients who needed mechanical ventilation and not weaned due to worsening of the condition.

Table 8. Comparison of ventilatory support between the two groups

		dopamine		norepinephrine		P value
		Count n=20	%	Count n=20	%	
Mechanical ventilation	not need for mechanical ventilation (nasal oxygen)	5	25.0%	5	25.0%	**0.030**
	need for mechanical ventilation and weaned	2	10.0%	9	45.0%	
	need for mechanical ventilation and not weaned	13	65.0%	6	30.0%	

Weaning from mechanical ventilation in the norepinephrine group was significantly higher ($P < 0.05$) than that in the dopamine group.

Table 9a. Comparison of laboratory values between the two groups

	dopamine					norepinephrine					P value
	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	
TLC(X1000/microlt)	15.30	10.25	15.30	1.80	36.00	14.50	8.50	13.15	1.40	37.00	**0.841**
Hb (gm/dl)	9.78	1.84	9.70	6.00	13.60	10.31	2.89	10.60	3.80	16.50	**0.461**
platelets(X1000/microlt)	130.90	101.30	107.50	16.00	370.00	209.50	136.89	181.50	17.00	453.00	**0.06**
CRP (mg/ml)	78.34	63.59	72.00	.10	198.00	58.95	49.83	48.00	12.00	192.00	**0.398**
Creatinine (mg/dl)	1.06	1.03	.60	.10	3.70	1.17	1.32	.65	.10	5.90	**0.883**
ALT (IU/L)	156.85	296.60	53.00	18.00	1238.00	253.35	352.48	60.00	28.00	1214.00	**0.253**
Glucose (mg/dl)	192.10	109.11	164.50	32.00	555.00	153.75	72.36	139.50	21.00	333.00	**0.201**

Table 9b. Comparison of laboratory values between the two groups

		dopamine		norepinephrine		P value
		Count n=20	%	Count n=20	%	
TLC	normal count for age	6	30.0%	9	45.0%	0.327
	abnormal count for age either increased or decreased	14	70.0%	11	55.0%	
shift to left	no shift to left	1	5.0%	1	5.0%	1
	presence of shift to left	19	95.0%	19	95.0%	
Hb	normal	9	45.0%	12	60.0%	0.342
	low (anaemia) and need blood transfusion	11	55.0%	8	40.0%	
platelets	normal count	5	25.0%	12	60.0%	0.025
	low count < 150,000/microlt	15	75.0%	8	40.0%	
CRP	normal value < 6mg /ml (negative)	2	10.0%	0	.0%	0.487
	abnormal value >= 6mg /ml (positive)	18	90.0%	20	100.0%	
cultures	not done	8	40.0%	6	35.0%	0.071
	no growth or inhibited growth	5	25.0%	5	25%	
	positive growth	7	35.0%	9	45.0%	
ABG	normal	1	5.0%	7	35.0%	0.044
	metabolic acidosis	19	95.0%	13	65.0%	
Creatinine	normal	6	30.0%	10	50.0%	0.197
	more than normal value for age	14	70.0%	10	50.0%	
ALT	normal	11	55.0%	5	25.0%	0.053
	more than normal value for age	9	45.0%	15	75.0%	
Na	normal	14	70.0%	13	65.0%	0.736
	abnormal either high or low	6	30.0%	7	35.0%	
K	normal	13	65.0%	12	60.0%	0.744
	abnormal either high or low	7	35.0%	8	40.0%	
Glucose	normal	2	10.0%	7	35.0%	0.127
	hyperglycemia	11	55.5%	8	40%	
	hypoglycemia	7	35.0%	5	25%	

Platelets count in the dopamine group was significantly lower (P < 0.05) than that in the norepinephrine group. The patients who recorded metabolic acidosis at the worst values in the 1st 24 hrs after diagnosis of septic shock were significantly higher (P < 0.05) in the dopamine group as compared to the norepinephrine group. Otherwise, there was no statistically significant difference in the other laboratory variables between the two groups (P > 0.05).

Also the serum total calcium was measured in all patients in the two groups where only 5 patients (3 in the dopamine group and 2 in the norepinephrine group) had mild hypocalcemia (7.5 -9mg / dl) and was corrected properly. According to the cultures with positive growth, the majority of cultures were blood cultures, the isolated organisms were staphylococcus aureus (4 patients), streptococcus pneumonia (3 patients), klebsiella (3 patients), pseudomonas aeruginosa (2 patients), enterococci (2 patients), acinobacter (1 patient), and E- coli (1 patient).

Table 10. Comparison of PRISM III score, length of stay (LOS) in ED in days and duration of the use of study drug in days between the two groups

PRISM-24	**dopamine**					**P value**
	Mean	**SD**	**Median**	**Minimum**	**Maximum**	
	16.45	7.14	18.00	5.00	29.00	**0.081**
	norepinephrine					
	12.30	6.43	10.00	3.00	24.00	
Length of Stay in ICU in days	**dopamine**					**P value**
	Mean	**SD**	**Median**	**Minimum**	**Maximum**	
	7.85	6.01	6.50	1.00	24.00	**0.414**
	norepinephrine					
	5.90	3.67	5.00	1.00	17.00	
Length of stay on inotrope in days (days)	**dopamine**					**P value**
	Mean	**SD**	**Median**	**Minimum**	**Maximum**	
	4.20	3.19	3.50	1.00	14.00	**0.114**
	norepinephrine					
	2.55	1.19	2.50	1.00	5.00	

There was no statistically significant difference in PRISM III score in the 1st 24 hours, length of stay in emergency department in days or duration of the use of inotrope between the two groups (P > 0.05).

Out of 40 studied patients, 23 patients died with mortality rate (57.5%).

Table 11. Comparison of final outcome between the two groups

		dopamine		**norepinephrine**		**P value**
		Count n=20	**%**	**Count n=20**	**%**	
Final Outcome	discharged	5	25.0%	12	60.0%	**0.025**
	died	15	75.0%	8	40.0%	

Mortality rate in the norepinephrine group was significantly lower (P < 0.05) than that in the dopamine group.

5. Predictors of Outcome

A multivariate logistic regression analysis was used for identifying independent predicators of outcome in both groups

Table 12. Logistic regression with outcome as dependent variable and Age and drug as independent predicators

		P value	**OR**	**95% C.I**	
				Lower	**Upper**
Outcome	Age (months)	**.295**	.987	.962	1.012
	Drug	**.046**	4.079	1.024	16.248

CI, Confidence interval.

By entering age and drug in a multivariate model we found that drug acts as a predictor of outcome (P <0.05) rather than the age. Norepinephrine was predictor for survival while dopamine was predictor for mortality.

Table 13. Logistic regression with outcome as dependent variable and prism and drug as independent predicators

		P value	**OR**	**95% C.I**	
				Lower	**Upper**
Outcome	Drug	**.142**	4.790	.592	38.765
	PRISM-24	**.001**	1.469	1.175	1.836

By entering drug and PRISM-24 in a multivariate model we found that PRISM-24 acts as a predictor of outcome (P <0.05) rather than the choice of the drug.

Table 14. Logistic regression with outcome as dependent variable and MODS and drug as independent predicators

		P value	**OR**	**95% C.I**	
				Lower	**Upper**
Outcome	Drug	**.019**	10.635	1.486	76.086
	MODS	**.003**	4.987	1.704	14.591

By entering drug and MODS in a multivariate model we found that both drug and MODS act as predictors of outcome (P <0.05).

Table 15. Logistic regression with outcome as dependent variable and mechanical ventilation and drug as independent predicators

		P value	OR	95% C.I	
				Lower	Upper
Outcome	Drug	.027	4.898	1.199	20.000
	Mechanical ventilation	.176	3.021	.609	14.980

By entering drug and MV in a multivariate model we found that MV was not predictor for outcome (P <0.05).

6. Discussion

Dopamine and norepinephrine are probably the most widely studied vasoactive drugs in the treatment of septic shock. In adults with septic shock, there were many studies comparing between dopamine and norepinephrine, but in pediatric patients no such studies were done. The majority of these studies, in adults, found superiority of norepinephrine over dopamine. Recently two studies comparing between dopamine and epinephrine in children with septic shock were done [10,11].

Although the ACCM guidelines in 2002 and updated 2007 chose and classified the use of vasoactive drug upon the type of shock whether cold or warm, we did not follow this classification on the basis that septic shock is a hemodynamic changing process that may move from one type to another, so it requires frequent assessment and therapeutic adjustments [12]. Luckily and recently, this classification also has been demonstrated to be fraught with errors. Indeed, as many as 66% of children judged by experienced clinicians to be in “cold shock” were noted to be vasodilated “warm shock” on invasive monitoring by arterial catheter placement [13]. As septic shock represents a dynamic process so that the agents selected and their infusion dose may need to be changed over time based on the need to maintain adequate organ perfusion. It is also important to recognize that the vasoactive agents are characterized by varying pharmacologic effects. These effects are determined by the pharmacokinetics of the agent and the pharmacodynamics of the patient’s response to the agent. In critically ill septic children, perfusion of the liver and kidney is often altered leading to changes in the pharmacokinetics of these drugs. So, recently the 2014 ACCM guidelines recommended frequent reevaluation of hemodynamic parameters when a patient requires the use of vasopressors, especially in relation to cardiac output, systemic venous return, and peripheral perfusion so as to choose the appropriate combination with inotropic or vasodilator drugs ± fluids [14].

The overall mortality in our study was 57.5%. This was similar to Ramaswamy et al study where the mortality was nearly 53.3%, in spite of adherence to the 2007 ACCM guidelines [11]. Also, this study was close Sankar et al study which observed a mortality of 42% in fluid-refractory pediatric septic shock in spite of more than 90% adherence to the 2007 ACCM guidelines [15]. Our finding was compatible with Weiss et al study which observed mortality from septic shock in children in developed countries ranging from 10% to 50% and up to 80% in developing countries [16].

In our study, there was a significantly higher mortality rate in the dopamine group compared with the norepinephrine one (P < 0.05). As in the dopamine group, 15 patients died out of 20 patients, while in the norepinephrine group 8 patients died out of 20 patients, (75% vs.40%, p=0.025). This study was similar to Ramaswamy et al study where the mortality rate in the dopamine group was 58.1% [11]. Also, this study was similar to Ventura et al study where they found a significant increase in mortality in children who received dopamine [10].

In adults with septic shock, there was strong evidence that dopamine was associated with increased mortality. Many studies [17,18,19,20,21] found that norepinephrine is associated with a lower mortality rate than dopamine in the management of septic shock.

All these studies were done on adult patients. We know that kids aren’t little adults. For example, pediatric sepsis and septic shock usually present as ‘cold shock’ whereas adult septic shock usually presents as ‘warm shock’, in addition to the main presentation of septic shock in adult patients is myocardial dysfunction, while in children, peripheral vasodilation is more occurred. In pediatric patients with septic shock, dopamine use may be associated with doubled mortality rate as compared with norepinephrine [10]. Also, epidemiological surveys showed that norepinephrine was the most favored vasopressor in the treatment of septic shock followed by dopamine [22].

In contrast to our study, the study made by De Backer in adults where they found that mortality rate did not differ significantly between the group of patients treated with dopamine and the group treated with norepinephrine **[23]**. Also, the Havel’s review failed to identify beneficial effect of norepinephrine on mortality reduction over dopamine in adult patients with septic shock [24].

The age of all 40 patients ranged from 1 month to 143 months (mean 22.675 months). This was in contrast to the study of Ventura et al where the mean age was 48.25 months [10]. In our study, this lower age could be explained by the study of Singhal et al where they found that most cases of severe sepsis occurred in infant ages 31 days–1 year [25]. This was in consistence with Hartman et al study who found a highest mortality rates in infants less than 1 year-old [26]. Also, susceptibility to severe viral infection was most prominent in children less than 2 y old due in part to unchecked viral replication caused by lower production of IFNγ and diminished cytotoxic lymphocyte responses [27]. Another important factor in our study could also explain this overall younger age, was the presence of a specific room in the emergency department in Cairo University Children Hospital containing more beds specified for younger infants.

The median age of patients in the dopamine group was 8.5 months which was significantly (P = 0.017) lower than the median age in the norepinephrine group (20 months). This younger age in the dopamine group signified that they were the more vulnerable group to sepsis and this may explain the increased mortality rate in the dopamine

group. Also infants < 1 year old may be less responsive to dopamine, due to incompletely developed sympathetic innervation via which dopamine initiates the release of endogenic norepinephrine [28].

With regard to sex distribution, cause of admission, cause of septic shock, MODS, temperature, and PRISM III score, there were no statistically significant difference between the two groups, and this was in consistence with Ventura study [10].

According to sex distribution, a higher mortality among male patients, suggested by studies in adult patients, appeared less prominent in children [29] and this was in consistence with our study.

In our study, septic shock was the major cause of admission (55%). This was similar to study done by Ventura et al where they found that septic shock was the major cause of admission (69%) [10]. Similarly, Jaramillo-Bustamante et al reported that in their study nearly 50% of the children presented with septic shock on PICU admission [30]. While other causes of admission were neurological (25%), respiratory (17.5%), and renal (2.5%), this was similar to a study done by Qureshi et al where they found that causes of admission were; 28.7% neurological diseases, 18.8% respiratory diseases [31].

Pneumonia was the major cause of septic shock in both groups (77.5 %), and this was similar to the study of Agrawal et al who found that pneumonia was one of the major causes of sepsis in adult patients with septic shock [17]. Also, this was similar to a study done by Ventura et al where they found that pneumonia was the major cause of septic shock (64%) [10]. Rudan et al found that childhood pneumonia had an estimated incidence of 0.29 episodes per child-year in developing countries and 0.05 episodes per child-year in developed countries, making it the most common cause of pediatric sepsis and it was also the leading cause of mortality in children less than 5 y of age (19%) [32]. There was a slight reduction in child mortality related to pneumonia in the last few years, however, pneumonia is still the leading cause of child mortality globally [33]. Although streptococcus pneumoniae is still the leading cause of hospitalization for pneumonia in childhood, conjugate 7-valent and 13-valent S. pneumoniae vaccine use has decreased the incidence of invasive bacterial infection by as much as 76% [34]. So, it is important to add these vaccines to our Egyptian vaccination schedule as early as possible to decrease the incidence of pneumonia and hence the decrease in incidence of septic shock. Although influenza virus is a common cause of viral pneumonia in infants, influenza vaccines are not approved for children less than 6 mo old and are poorly immunogenic in children <2 y old compared with older children and adults [35]. Also viral–bacterial co-infection occurs in up to 23% of cases of severe pneumonia, resulting in a higher likelihood of respiratory failure and septic shock [36].

Septic shock was defined by Goldstein et al as sepsis plus cardiovascular organ dysfunction. So, all included patients had cardiovascular failure (100%). MODS in our study included the cardiovascular failure as it was the essential system failure (100%), then respiratory failure (85%), renal failure (42%), neurological failure (40%), hematologic failure (40%), and hepatic failure (32.5%). We found that there was no significant difference between the two groups with regard to the number of dysfunctional organ systems. In our study patients who had 2 system failure were 32.5%, 3 system failure were 20%, 4 system failure were 30%, 5 system failure were 10%, and 6 system failure were 7.5%. The extent of systemic involvement in septic shock is also very important, as children who develop multiple organ system failure from sepsis have the lowest likelihood of surviving [37]. Typpo et al found that mortality rate varies directly with the number of dysfunctional organ systems, where they found that mortality from failure of two, three, and four or more organ systems at PICU admission was 6.8%, 16.2%, and 43.5%, respectively [38].

PRISM III score in the 1st 24 hours was used for predicting mortality and assessment of severity of illness in both groups. In our study, there was no statistically significant difference in PRISM III score in the 1st 24 hours between the two groups ($P > 0.05$), where PRISM was (16.45 ± 7.14) in dopamine group while it was (12.30 ± 6.43) in norepinephrine group. This was similar to Ventura et al study where PRISM was (15.7 ± 10.4) in dopamine group [10]. The non-significant difference in PRISM scoring between the two groups could be explained by the large similarity in the baseline characteristics between the two groups, and also the significant improvement in all hemodynamic and clinical parameters after addition of inotrope for each group alone.

Before and after addition of inotrope, comparative analysis of MAP, CRT, HR, UOP, and mental status for each group alone was done and we found a significant improvement in all parameters after addition of either inotrope. This was similar to the study of Agrawal et al who found significant improvement in post-treatment hemodynamic and metabolic parameters in the two studied groups for each group alone [17].

In our study, before addition of inotrope, comparative analysis of MAP, CRT, HR, UOP, and mental status between the two groups was done and we found that there was no statistically significant difference between the two groups except for MAP, where MAP before treatment in the norepinephrine group (mean 32.38 ± SD 9.75) was significantly lower ($P = 0.029$) than that in the dopamine group (43.67 ± 3.56). This was in contrast to the study of Agrawal et al who found no significant difference in MAP between the two groups before addition of inotrope [17].

After addition of inotrope, the comparative analysis of MAP, HR, CRT, UOP, and mental status between the two groups was done and we found that there was no statistically significant difference between the two groups except for HR and CRT.

HR after addition of inotrope in the dopamine group (mean 137.50 ± SD 21.93) was significantly higher ($P = 0.015$) than that in the norepinephrine group (mean 122.85 ± SD 19.02). This was similar to Agrawal et al study, who found a significant increase in HR in the dopamine group than norepinephrine group after addition of inotrope [17]. Herget-Rosenthal et al study found that norepinephrine exerts a minimal increase of heart rate or stroke volume [39]. On the other hand the significant tachycardia in the dopamine group may explain to some extent the increased mortality in this group as the 2014 ACCM guidelines considered threshold heart rates associated with increased mortality in critically ill infants

are a HR less than 90 or greater than 160 beats/min, and in children are a HR less than 70 or greater than 150 beats/min [14].

The significant tachycardia in the dopamine group was attributed to the β-adrenergic properties of dopamine which predominate in patients with sepsis [39]. Also this significant tachycardia together with vasoconstriction may be harmful as it can lead to increased cardiac oxygen demand and decreased oxygen delivery and may trigger myocardial ischemia and arrhythmias. The major side effects of dopamine are tachycardia and arrhythmogenesis. Both of which are more prominent in dopamine than with other vasopressor agents [40]. Although the use of dopamine in adults with septic shock was associated with occurrence of arrhythmias when compared with norepinephrine [23], no patient in our study developed any type of arrhythmia.

CRT after addition of inotrope in the norepinephrine group was achieved <3 sec (mean 2.25 ± SD 1.21) significantly (P = 0.028) more than that in the dopamine group (mean 3.05 ± SD 1.28). Also this was attributed to the more potent peripheral vasoconstrictive action of norepinephrine as compared to dopamine. Norepinephrine is considered the first-line vasopressor in vasodilatory shock because of its marked vasoconstrictive characteristics, increasing mean arterial pressure (MAP), effective circulating blood volume, and venous return and preload [39].

In our study, there was no statistically significant difference in the MAP after addition of inotrope between the two groups (P > 0.05). This was in contrast to the studies of Mathur et al and Agrawal et al who found a significant increase in the MAP in the norepinephrine group after addition of inotrope as compared to dopamine group [17,41]. Although norepinephrine has marked vasoconstrictive effect more than dopamine, this non-significant difference in MAP between the two groups in our study after addition of inotrope could be explained by the pre-existing significant lower MAP in the norepinephrine group. So, norepinephrine still has the superiority in increasing MAP better than dopamine.

In our study, there was no statistically significant difference in UOP after addition of inotrope between the two groups (P > 0.05). This was in contrast to the study of Agrawal et al who found significant increase in UOP in the norepinephrine group after addition of inotrope as compared to dopamine group [17]. Contrary to what was expected from its marked vasoconstrictive effects, norepinephrine could improve parameters of visceral and renal microperfusion when hypotension was reversed, compared with dopamine [42]. Also maintenance of MAP with norepinephrine has been shown to improve urine output and creatinine clearance in hyperdynamic sepsis [43]. Since low-dose dopamine is ineffective and potentially harmful in the prevention and treatment of acute kidney injury (AKI) [39], we used both inotropic and vasoconstrictive dose of dopamine in our study.

In our study, patients who needed mechanical ventilation were the same in both groups, 15 patients out of 20 for each group (75%) with no significant difference and this was nearly similar to a study done by Ventura et al, where patients who needed for mechanical ventilation were 62 patients out of 63 (98.4%) [10]. In our study, the patients who were weaned from mechanical ventilation in the norepinephrine group (45%) after improvement of shock was significantly more (P = 0.030) than that in the dopamine group (10%). This was near from Teixeira et al study where they did not find that the use of noradrenaline at the time of weaning was associated with extubation failure [44]. Also Ranjit et al study found that early norepinephrine with fluid restriction may be of benefit in resolving pediatric vasodilatory septic shock with less need for further fluid and ventilatory support [45].

With regard to laboratory variables, there was no statistically significant difference between the two groups except for; 1) Platelets count in the dopamine group (75%) was significantly lower (P = 0.025) than that in the norepinephrine group (40%). This significant thrombocytopenia in the dopamine group could explain the increased mortality in this group and this was in consistence to Thiery-Antier et al study where they found that thrombocytopenia within the first 24 hours of septic shock is associated with an increased risk of death and this could be explained by increased serious thrombotic complications and platelet consumption reflected by thrombocytopenia or an increased bleeding frequency and severity [46]. 2) Also, the patients who recorded metabolic acidosis at the worst values in the 1st 24 hrs after diagnosis of septic shock were significantly higher (P = 0.044) in the dopamine group (95%) as compared to the norepinephrine group (65%). This finding could be explained by the significant lower age in the dopamine group, as newborns and infants are more vulnerable than older children and adults to develop acidosis because, the maximum net acid excretion by the distal nephron is limited in infants [47]. Also, the acid load is higher in preterm infants and growing children as the endogenous acid production per kilogram in preterm infants and growing children is 50 to 100 percent higher than that of adults [48]. As dopamine group was associated significantly with both increased mortality and metabolic acidosis, this was in consistence with Maciel et al study where they found that the severity of metabolic acidosis is associated with poor clinical outcomes [49].

In general, the patients who recorded metabolic acidosis in both groups were 80% and this was nearly similar to the study of Maitland et al where the patients who recorded metabolic acidosis were 51% [50].

Length of stay (LOS) in PICU reflects degree of severity and health status, also the quality and performance of PICU [51]. In our study, there was no significant difference in length of stay in emergency department in days between the two groups (P > 0.05), where LOS in the dopamine group was 6.5 days (median), and in the norepinephrine group was 5 days (median). This was similar to Ramaswamy et al study where LOS in the dopamine group was 7 days (median) [11]. This could be explained by the non-significant difference in MODS, PRISM-24hrs, and most of the baseline characteristics between the two groups.

With regard to the duration of the use of inotrope, there was no significant difference between the two groups (P > 0.05). This could be explained by the significance improvement in all parameters (MAP, CRT, HR, UOP, and mental status) in each group alone after addition of inotrope.

Although septic shock is one of the most important causes of mortality in patients admitted to EDs, there is lack in studies regarding predictive factors for mortality and morbidity, especially in developing countries [52]. So, in our study, a multivariate logistic regression analysis was used for identifying independent predicators of outcome in both groups.

Stepwise logistic regression analysis was done by using outcome as a dependent variable and (PRISM-24 and drug, MODS and drug) as independent predicators revealed that PRISM-24 (p=0.001), drug (p=0.019), and MODS (p=0.003) could independently predict the mortality in septic shock patients. This was inconsistence with El Hamshary et al study where they found that PRISM-24 and MODS were accurate predictors of mortality [53]. The explanation was that PRISM-24 and MODS were associated with the severity of illness. This was in contrast to Kaur et al study where PRISM-24, drug, and MODS failed to independently predict the overall mortality in septic children [54].

Stepwise logistic regression analysis was done by using outcome as a dependent variable and (age and drug, MV and drug) as independent predicators revealed that age and MV failed to predict the mortality in septic shock patients (p= 0.295), (p= 0.176), respectively. This was similar to Kaur et al study where age and MV failed to independently predict the overall mortality in septic children [54]. This was in contrast to El Hamshary et al study where they found that mechanical ventilation (MV) was an independent risk factor for death [53].

The limitations of our study were; 1) It was an observational study, as selection of the patients was done by the treating physicians according to their experience. 2) Single-center study where it was conducted on patients with septic shock who were admitted to the emergency department unit in Cairo University Children Hospital, so the results from single-center studies are infrequently reproduced and may not be suitable to all ICU patients. 3) A small sample size which hindered doing some statistical methods where the multivariable analyses could not take all possible confounding factors into account. 4) The initial assessment of the patient and decision to start, stop, or increase the dose of the study drug were based only on clinical variables, which are highly sensitive but lack specificity. 5) As central venous catheter was not routinely inserted into the patients, we were unable to measure CVP, SvO_2, and the effect of test drugs on cardiac index and systemic vascular resistance using cardiac output monitors. Also, lactate was not routinely measured to be used as a laboratory monitor and predictor for septic shock outcome [55].

7. Conclusion

- Septic shock is a major childhood disease and it represents a common cause of mortality and morbidity in children all over the world.
- The mortality due to septic shock can be as high as 50% and may reach up to 80% in developing countries.
- Pneumonia is the major cause of septic shock.
- The most recent studies and guidelines regarding the use of inotropes and vasopressor drugs in the management of pediatric septic shock recommend epinephrine in low dose for cold shock and if it is unavailable, dopamine could be used instead. Also, they recommend norepinephrine for the warm shock and if it is unavailable, dopamine could be used instead.
- Both dopamine and norepinephrine improve the hemodynamic and clinical parameters more than the baselines.
- Norepinephrine increases MAP efficiently despite of the pre-existing lower MAP.
- Dopamine is associated with tachycardia and higher mortality.
- Dopamine, PRISM-24, and MODS are predictors of mortality while norepinephrine is predictor of survival.

8. Recommendations

- Further evaluation by prospective, randomized, and controlled studies using larger sample size in multi-centers will be of benefit and more accurate.
- Early recognition and management of patients presented with septic shock through adherence to the most recent guidelines especially ACCM guidelines can reduce morbidity and mortality.
- Introduction of central venous catheter as a routine in patients with septic shock and provide bedside echocardiography with well-trained persons to calculate accurately cardiac output and to detect any change in hemodynamics.
- Further isolated prospective, randomized, and controlled studies are needed for assessment of the predictors of mortality among patients with septic shock.
- Future studies are needed to compare between the effects of single vasoactive agent alone versus combination of more than one agent guided by strict hemodynamic monitoring.

References

[1] Dellinger RP, Levy MM, Carlet JM, Bion J, Parker MM, Jaeschke R, Reinhart K, Angus DC, Brun-Buisson C, Beale R, Calandra T, Dhainaut JF, Gerlach H, Harvey M, Marini JJ, Marshall J, Ranieri M, Ramsay G, Sevransky J, Thompson BT, Townsend S, Vender JS, Zimmerman JL, Vincent JL ; International Surviving Sepsis Campaign Guidelines Committee; American Association of Critical-Care Nurses; American College of Chest Physicians; American College of Emergency Physicians; Canadian Critical Care Society; European Society of Clinical Microbiology and Infectious Diseases; European Society of Intensive Care Medicine; European Respiratory Society; International Sepsis Forum; Japanese Association for Acute Medicine; Japanese Society of Intensive Care Medicine; Society of Critical Care Medicine; Society of Hospital Medicine; Surgical Infection Society; World Federation of Societies of Intensive and Critical Care Medicine. Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2008. Crit Care Med 2008; 36: 296-327.

[2] Hollenberg SM. Vasopressor support in septic shock. Chest 2007; 132: 1678-87.

[3] Goldstein B, Giroir B, Randolph A; International Consensus Conference on Pediatric Sepsis. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. Pediatr Crit Care Med 2005; 6: 2-8.

[4] Pollack MM, Patel KM, Ruttimann UE. PRISM III: an updated Pediatric Risk of Mortality score. Crit Care Med. 1996; 24: 743-52

[5] Carcillo JA. A synopsis of 2007 ACCM clinical practice parameters for hemodynamic support of term newborn and infant septic shock. Early Human Development 2014; 90: S45-7.

[6] Andropoulos DB. Pediatric Normal Laboratory Values. In: Gregory GA, Andropoulos DB (Eds.), Gregory's Pediatric Anesthesia (5th Ed.).New York, NY, USA, Blackwell Publishing Ltd 2012:1301-14.

[7] Chan YH (a). Biostatistics102: quantitative data – parametric & non-parametric tests. Singapore Med J 2003; 44: 391-6.

[8] Chan YH (b). Biostatistics 103: Qualitative Data –Tests of Independence. Singapore Med J 2003; 44: 498-503.

[9] Chan YH. Biostatistics 202: logistic regression analysis. Singapore Med J 2004; 45: 149-53.

[10] Ventura AM, Shieh HH, Bousso A, Góes PF, de Cássia FO Fernandes I, de Souza DC, Paulo RL, Chagas F, Gillio AE. Double-blind prospective randomized controlled trial of dopamine versus epinephrine as First-line vasoactive drugs in pediatric septic shock. Crit Care Med 2015; 43: 2292-302.

[11] Ramaswamy KN, Singhi S, Jayashree M, Bansal A, Nallasamy K. Double-Blind Randomized Clinical Trial Comparing Dopamine and Epinephrine in Pediatric Fluid-Refractory Hypotensive Septic Shock. Pediatr Crit Care Med 2016; 17:e502-12.

[12] Irazuzta J, Sullivan KJ, Garcia PC, Piva JP. Pharmacologic support of infants and children in septic shock. J pediatr (Rio J) 2007; 83: 36-45.

[13] Ranjit S, Aram G, Kissoon N, Ali MK, Natraj R, Shresti S, Jayakumar I, Gandhi D. Multimodal monitoring for hemodynamic categorization and management of pediatric septic shock: a pilot observational study*. Pediatr Crit Care Med 2014; 15: e17-26.

[14] Davis AL, Carcillo JA, Aneja RK, Deymann AJ, Lin JC, Nguyen TC, Okhuysen-Cawley RS, Relvas MS, Rozenfeld RA, Skippen PW, Stojadinovic BJ, Williams EA, Yeh TS, Balamuth F, Brierley J, de Caen AR, Cheifetz IM, Choong K, Conway E Jr, Cornell T, Doctor A, Dugas MA, Feldman JD, Fitzgerald JC, Flori HR, Fortenberry JD, Graciano AL, Greenwald BM, Hall MW, Han YY, Hernan LJ, Irazuzta JE, Iselin E, van der Jagt EW, Jeffries HE, Kache S, Katyal C, Kissoon NT, Kon AA, Kutko MC, MacLaren G, Maul T, Mehta R, Odetola F, Parbuoni K, Paul R, Peters MJ, Ranjit S, Reuter-Rice KE, Schnitzler EJ, Scott HF, Torres A Jr, Weingarten-Abrams J, Weiss SL, Zimmerman JJ, Zuckerberg AL. American College of Critical Care Medicine Clinical Practice Parameters for Hemodynamic Support of Pediatric and Neonatal Septic Shock. Crit Care Med 2017; 45: 1061-93.

[15] Sankar J, Sankar MJ, Suresh CP, Dubey NK, Singh A. Early goal-directed therapy in pediatric septic shock: comparison of outcomes "with" and "without" intermittent superior venacaval oxygen saturation monitoring: a prospective cohort study. Pediatr Crit Care Med 2014; 15: 157-67.

[16] Weiss SL, Fitzgerald JC, Pappachan J, Wheeler D, Jaramillo-Bustamante JC, Salloo A, Singhi SC, Erickson S, Roy JA, Bush JL, Nadkarni VM, Thomas NJ; Sepsis Prevalence, Outcomes, and Therapies (SPROUT) Study Investigators and Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network. Global epidemiology of pediatric severe sepsis: The sepsis prevalence, outcomes, and therapies study. Am J Respir Crit Care Med 2015; 191:1147-57.

[17] Agrawal A, Gupta A, Consul S, Shastri P. Comparative study of dopamine and norepinephrine in the management of septic shock. Saudi J Anaesth 2011; 5: 162-6.

[18] De Backer D, Aldecoa C, Nijmi H, Vincent JL. Dopamine versus norepinephrine in the treatment of septic shock: a meta- analysis. Crit Care Med. 2012; 40: 725-30.

[19] Oba Y, Lone NA. Mortality benefit of vasopressor and inotropic agents in septic shock: a Bayesian network meta-analysis of randomized controlled trials. J Crit Care 2014; 29: 706-10.

[20] Avni T, Lador A, Lev S, Leibovici L, Paul M, Grossman A. Vasopressors for the Treatment of Septic Shock: Systemic Review and Meta-Analysis. PLoS ONE: 2015; 10: e1209305.

[21] Zhang Z, Chen K. Vasoactive agents for the treatment of sepsis. Ann Transl Med 2016; 4: 333.

[22] Pei XB, Ma PL, Li JG, Du ZH, Zhou Q, Lu ZH, Yun L, Hu B. Extensive variability in vasoactive agent therapy: a nationwide survey in Chinese intensive care units. Chin Med J (Engl) 2015; 128: 1014-20.

[23] De Backer D, Biston P, Devriendt J, Madl C, Chochrad D, Aldecoa C, Brasseur A, Defrance P, Gottignies P, Vincent JL; SOAP II Investigators. Comparison of dopamine and norepinephrine in the treatment of shock. N Engl J Med 2010; 362: 779-89.

[24] Havel C, Arrich J, Losert H, Gamper G, Mullner M, Herkner H. Vasopressors for hypotensive shock. Cochrane Database syst Rev 2011; (5): CD 003709.

[25] Singhal S, Allen MW, McAnnally JR, Smith KS, Donnelly JP, Wang HE. National estimates of emergency department visits for pediatric severe sepsis in the United States. PeerJ 2013; 1: e79.

[26] Hartman ME, Linde-Zwirble WT, Angus DC, Watson RS. Trends in the epidemiology of pediatric severe sepsis. Pediatr Crit Care Med 2013; 14: 686-93.

[27] Ygberg S, Nilsson A. The developing immune system - from foetus to toddler. Acta Paediatr 2012; 101: 120-7.

[28] Brierly J, Carcillo JA, Choong k, Cornell T, Decaen A, Deymann A, Doctor A, Davis A, Duff J, Dugas MA, Duncan A, Evans B, Feldman J, Felmet K, Fisher G, Frankel L, Jeffries H, Greenwald B, Gutierrez J, Hall M, Han YY, Hanson J, Hazelzet J, Hernan L. Kiff J, Kissoon N, Kon A, Irazuzta J, Lin J, Lorts A, Mariscalco M, Mehta R, Nadel S, Nguyen T, Nicholson C, Peters M, Okhuysen-Cawley R, Poulton T, Relves M, Rodriguez A, Rozenfeld R, Schnitzler E, Shanley T, Kache S, Skippen P, Torres A, von Dessauer B, Weingarten J, Yeh T, Zaritsky A, Stojadinovic B, Zimmerman J, Zuckerberg A. Clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock: 2007 update from the American College of Critical Care Medicine. Crit Care Med 2009; 37: 666-88.

[29] García-Gómez E, González-Pedrajo B, Camacho-Arroyo I. Role of sex steroid hormones in bacterial-host interactions. Biomed Res Int 2013; 2013: 928290.

[30] Jaramillo-Bustamante JC, Martin-Agudelo A, Fernández-Laverde M, Bareno-Silva J. Epidemiology of sepsis in pediatric intensive care units. Pediatr Crit Care Med 2012; 13: 501-8.

[31] Qureshi AU, Ali AS, Ahmad TM. Comparison of three prognostic scores (PRISM, PELOD and PIM2) at pediatric intensive care unit under Pakistani circumstances. J Ayub Med Coll Abbottabad 2007; 19:49-53.

[32] Rudan I, Boschi-Pinto C, Biloglav Z, Mulholland K, Campbell H. Epidemiology and etiology of childhood pneumonia. Bull World Health Organ 2008; 86: 408-16.

[33] Rudan I, O'Brien KL, Nair H, Liu L, Theodoratou E, Qazi S, Lukšić I, Walker CL, Black RE, Campbell H; Child Health Epidemiology Reference Group (CHERG). Epidemiology and etiology of childhood pneumonia in 2010: estimates of incidence, severe morbidity, mortality, underlying risk factors and causative pathogens for 192 countries. J Glob Health 2013; 3: 10401.

[34] Myint TT, Madhava H, Balmer P, Christopoulou D, Attal S, Menegas D, Sprenger R, Bonnet E. The impact of 7-valent pneumococcal conjugate vaccine on invasive pneumococcal disease: a literature review. Adv Ther 2013; 30: 127-51.

[35] Beeler JA, Eichelberger MC. Influenza and respiratory syncytial virus (RSV) vaccines for infants: safety, immunogenicity, and efficacy. Microb Pathog 2013; 55: 9-15.

[36] Michelow IC, Olsen K, Lozano J, Rollins NK, Duffy LB, Ziegler T, Kauppila J, Leinonen M, McCracken GH. Epidemiology and clinical characteristics of community-acquired pneumonia in hospitalized children. Pediatrics 2004; 113: 701-7.

[37] Leclerc F, Leteurtre S, Duhamel A, Grandbastien B, Proulx F, Martinot A, Gauvin F, Hubert P, Lacroix J. Cumulative influence of organ dysfunctions and septic state on mortality of critically ill children. Am J Respir Crit Care Med 2005; 171: 348-53.

[38] Typpo KV, Petersen NJ, Hallman DM, Markovitz BP, Mariscalco MM. Day 1 multiple organ dysfunction syndrome is associated with poor functional outcome and mortality in the pediatric intensive care unit. Pediatr Crit Care Med 2009; 10: 562-70.

[39] Herget-Rosenthal S, Saner F, Chawla LS. Approach to hemodynamic shock and vasopressors. Clin J Am Soc Nephrol 2008; 3: 546-53.

[40] Oberbeck R, Schmitz D, Wilsenack K, Schuler M, Husain B, Schedlowski M, Exton MS. Dopamine affects cellular immune

functions during polymicrobial sepsis. Intensive Care Med 2006; 32: 731-9.

[41] Mathur SK, Dhunna R, Chakraborty A. Comparison of norepinephrine and dopamine in the management of septic shock using impedance cardiography. Indian J Crit Care Med 2007; 11: 186-91.

[42] Guerin JP, Levraut J, Samat-Long C, Leverve X, Grimaud D, Ichai C. Effects of dopamine and norepinephrine on systemic and hepatosplanchnic hemodynamics, oxygen exchange, and energy balance in vasoplegic septic patients. Shock 2005, 23: 18-24.

[43] LeDoux D, Astiz ME, Carpati CM, Rackow EC. Effects of perfusion pressure on tissue perfusion in septic shock. Crit Care Med 2000; 28:2729-32.

[44] Teixeira C, Frederico Tonietto T, Cadaval Gonçalves S, Viegas Cremonese R, Pinheiro de Oliveira R, Savi A, Silvestre Oliveira E, André Cardona Alves F, Fernando Monteiro Brodt S, Hervê Diel Barth J, Santana Machado A, de Campos Balzano P, Gasparetto Maccari J, Brandão Da Silva N. Noradrenaline use is not associated with extubation failure in septic patients. Anaesth Intensive Care 2008; 36: 385-90.

[45] Ranjit S, Natraj R, Kandath SK, Kissoon N, Ramakrishnan B, Marik PE. Early norepinephrine decreases fluid and ventilatory requirements in pediatric vasodilatory septic shock. Indian J Crit Care Med 2016; 20: 561-9.

[46] Thiery-Antier N, Binquet C, Vinault S, Meziani F, Boisramé-Helms J, Quenot JP; EPIdemiology of Septic Shock Group. Is Thrombocytopenia an Early Prognostic Marker in Septic Shock? Crit Care Med 2016; 44: 764-72.

[47] Jones DP, Chesney RW. Tubular Function Potassium and Acid-Base. In: Pediatric Nephrology, Avner ED, Harmon WE, Niaudet P (Eds). Lippincott Williams & Williams, Philadelphia; 2004: 59.

[48] Chan JC, Mak RH. Acid-base homeostasis. In: Avner ED, Harmon WE, Niaudet P : Pediatric Nephrology, 5th ed. Lippincott Williams & Williams, Philadelphia; 2004: 189-208.

[49] Maciel AT, Noritomi DT, Park M. Metabolic acidosis in sepsis. Endocr Metab Immune Disord Drug Targets 2010; 10: 252-7.

[50] Maitland K, Kiguli S, Opoka RO, Engoru C, Olupot-Olupot P, Akech S, Nyeko R, Mtove G, Reyburn H, Lang T, Brent B, Evans JA, Tibenderana JK, Crawley J, Russell EC, Levin M, Babiker AG, Gibb DM; FEAST Trial Group. Mortality after fluid bolus in African children with severe infection. N Engl J Med 2011; 364: 2483-95.

[51] Marcin JP, Slonim AD, Pollack MM, Ruttimann UE. Long-stay patients in the pediatric intensive care unit. Crit Care Med 2001; 29: 652-7.

[52] Shrestha P, Mohan A, Sharma S, Guleria R, Vikram N, Wig N et al. To Determine the Predictors of Mortality and Morbidity of Sepsis in Medical ICU of All India Institute of Medical Sciences (AIIMS) New Delhi, India: 2012. Chest 2012; 142: 407.

[53] El Hamshary AA, El Sherbini SA, Elgebaly HF, Amin SA. Prevalence of multiple organ dysfunction in the pediatric intensive care unit: Pediatric Risk of Mortality III versus Pediatric Logistic Organ Dysfunction scores for mortality prediction. Rev Bras Ter Intensiva 2017; 29: 206-12.

[54] Kaur G, Vinayak N, Mittal K, Kaushik JS, Aamir M. Clinical outcome and predictors of mortality in children with sepsis, severe sepsis, and septic shock from Rohtak, Haryana: A prospective observational study. Indian J Crit Care Med 2014; 18: 437-41.

[55] Kim YA, Ha EJ, Jhang WK, Park SJ. Early blood lactate area as a prognostic marker in pediatric septic shock. Intensive Care Med 2013; 39: 1818-23.