

Supplemental Digital Content

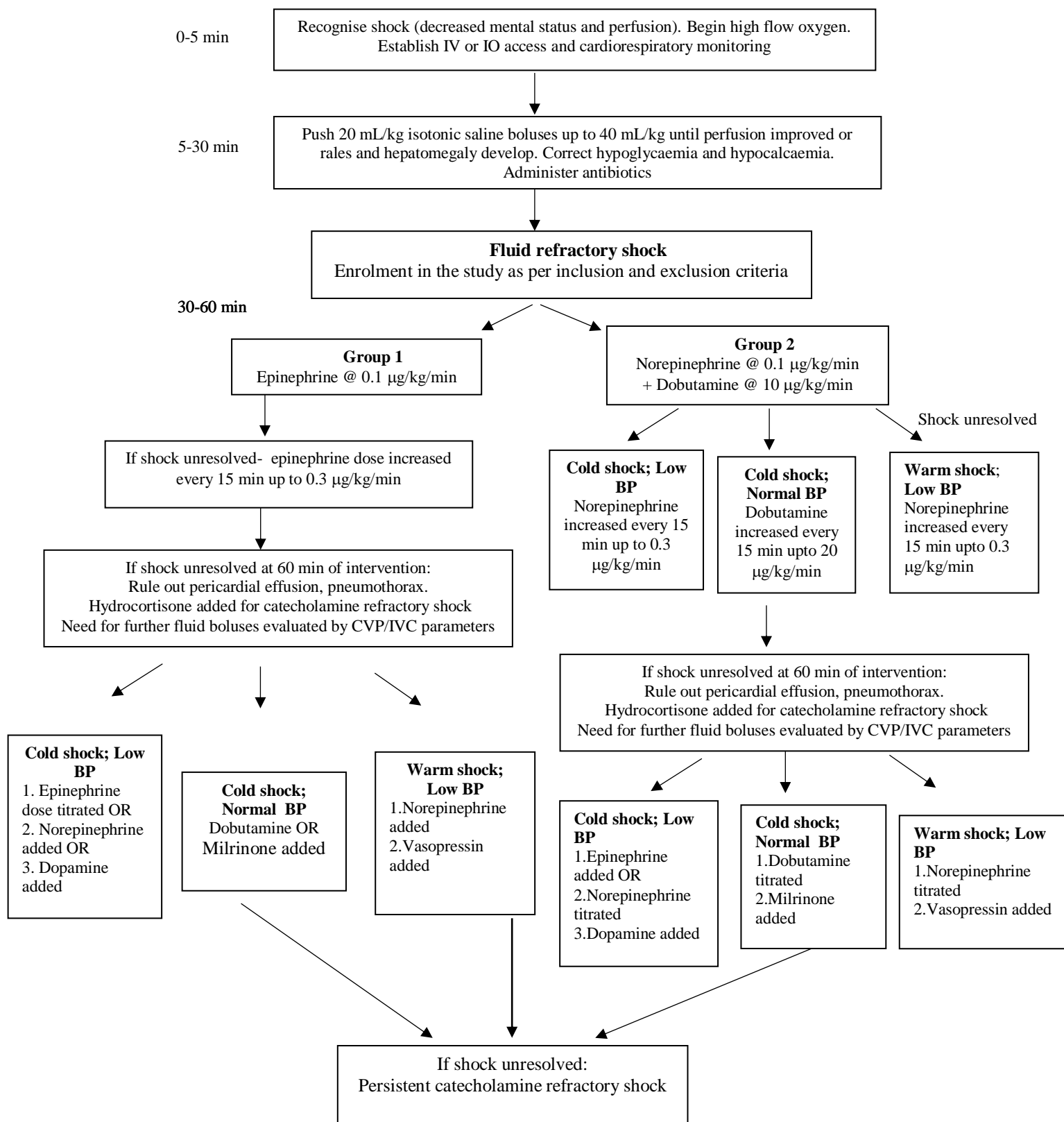
Norepinephrine plus Dobutamine versus Epinephrine as First line Vasoactive agents for Children with Fluid Refractory Cold Septic Shock – A Randomized Controlled Trial

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Figure 1. Study protocol



IV=Intravenous, IO=Intraosseous, BP=Blood pressure, CVP=Central venous pressure, IVC=Inferior vena cava.

Table 1. Study definitions

Definitions used for the study purpose						
Systemic inflammatory response syndrome (SIRS) (1)	<p>Systemic inflammatory response syndrome is defined by two of the following, one of which must be abnormal temperature or leucocyte count:</p> <ul style="list-style-type: none"> • Temperature >38.4°C or <36°C • Heart rate >160/min in infants and >150/min in children • Respiratory rate >60/min in infants and >50/min in older children • Peripheral white blood cell count <4000/mm³ or > 12,000/mm³ or >10% band forms. 					
Sepsis (1)	<p>SIRS due to infection</p> <p>Infection is defined as - A suspected or proven (by positive culture, tissue stain, or polymerase chain reaction test) infection caused by any pathogen OR a clinical syndrome associated with a high probability of infection. Evidence of infection includes positive findings on clinical exam, imaging, or laboratory tests (e.g., white blood cells in a normally sterile body fluid, perforated viscus, chest radiograph consistent with pneumonia, petechial or purpuric rash, or purpura fulminans)</p>					
Septic shock (1, 2)	<p>Children who had a suspected infection and had at least 2 of the following clinical signs of decreased perfusion with or without hypotension, including decreased mental status, prolonged capillary refill of >2 seconds (cold shock), diminished (cold shock) or peripheral pulses, mottled cool extremities (cold shock), or parents gave history of decreased urine output.</p>					
Mean arterial pressure	<p>Mean arterial pressure was calculated using definition suggested by Haque <i>et al</i> in 2007 and subsequently endorsed by the ACCM guidelines for hemodynamic support in children with septic shock in 2017 (3, 4).</p>					
Central and peripheral pulses	<ol style="list-style-type: none"> 1. Central pulses are palpated in brachial artery and peripheral pulses in radial artery. 2. For palpating the pulse, after following hand hygiene and positioning the hand for palpation, the artery is compressed lightly against the radius, obliterating the pulse initially. After this, the pressure is released so that it became easily palpable. 3. The strength of the pulse is palpated based on thrust of the vessel against the fingertips and characterized as absent, thready, bounding or normal. To make this as less subjective as possible, we use a score as suggested in Siedel's guide to physical examination (5) <table border="1" style="margin-left: auto; margin-right: auto;"> <thead> <tr> <th>Amplitude of the pulse on a scale of 0 to 3</th> </tr> </thead> <tbody> <tr> <td>0- absent, not palpable</td> </tr> <tr> <td>1- diminished, difficult to palpate, thready</td> </tr> <tr> <td>2- expected, easy to palpate</td> </tr> <tr> <td>3- bounding, strong</td> </tr> </tbody> </table> <p>The pulse character is cross checked by another physician/ nurse present at the time to confirm the same.</p>	Amplitude of the pulse on a scale of 0 to 3	0- absent, not palpable	1- diminished, difficult to palpate, thready	2- expected, easy to palpate	3- bounding, strong
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0- absent, not palpable						
1- diminished, difficult to palpate, thready						
2- expected, easy to palpate						
3- bounding, strong						

Peripheral temperature (peripheries were warm or cool)	Peripheral temperature (peripheries are warm or cool) This is measured by palpating the dorsal aspect of index finger with the dorsal aspect of examiners hand and comparing it with the forearm temperature (adapted from van Genderen ME <i>et al</i> methods of assessing peripheral perfusion in critically ill patients) (5). The finding is recorded as warm or cool. For each patient the finding is cross checked by another physician/nurse present at the time.
Capillary refill time	For measuring capillary refill the method suggested by Tibby <i>et al</i> (6) is followed and adapted to measure central capillary refill time. At the sternum or forehead, pressure is applied by the index finger for five seconds. The finger is then released and the time taken for the area compressed to return to its previous colour is recorded. Wristwatch is used to measure the accurate time. All measurements are made under adequate lighting conditions. Two measurements are taken for each patient each time. Measurements are only taken after a time interval of at least one hour and after a treatment that might alter the hemodynamic profile, such as a fluid bolus or the addition of an inotrope. Normal capillary refill is defined as ≤ 2 seconds, and prolonged refill as > 2 seconds.
Improving mental status	Improvement in mental status from baseline is assessed using modified Glasgow Coma Scale for infants and children (7).
Definitions used for study purposes	
Shock resolution	Defined as attainment of at least 4 of the following therapeutic end points (2-4, 8) <ul style="list-style-type: none"> • Appropriate-for-age mean arterial pressure (MAP) • Normal pulses with no difference between peripheral and central pulses • Warm extremities • Capillary refill time < 2 seconds • Improving mental status • Urine output > 1 mL/kg/hr For the purpose of the study, shock resolution was defined as normal MAP for age AND any FOUR of the above (if not hypotensive shock) without need for fluid bolus or vasoactive dose escalation for 4 hours.
Refractory to treatment	Epinephrine group: Children not attaining shock resolution on epinephrine at 0.3 μg/kg/min. Norepinephrine plus dobutamine group: Children not attaining shock resolution on norepinephrine at 0.3 μg/kg/min or dobutamine at 20 μg/kg/min.
Time to achieving shock resolution	Time taken to achieve all the end points as defined above.
p-SOFA score	Simultaneous occurrence of two or more organ dysfunctions. Organ systems typically included in the diagnostic criteria of pediatric MODS are cardiovascular, pulmonary, neurologic, hematologic, renal, hepatic, and gastrointestinal (9) The range for pSOFA score is 0 – 24 points (a higher score indicates a worse outcome), and the minimal clinically important difference is 3.
Pediatric Index of mortality score (PIM-3)	Ten variables of PIM-3 include pupillary reaction to light, systolic blood pressure, need for mechanical ventilation, base excess, PaO ₂ /FiO ₂ ratio, elective admission and specified diagnosis calculated within 1 hour of admission, high risk, low risk and very high risk diagnosis (10).

Vasoactive inotrope score	The score is based on the dose, type and duration of inotropic medications. The score is obtained by summing the dose of inotrope while corrected for potency multiplied by the number of hours delivered. For example if a patient received dobutamine and epinephrine at different infusion rates and for different time periods, inotrope score will be calculated as follows: [(dobutamine dose $\mu\text{g}/\text{kg}$ per min x 1) x number of hours delivered] + [(epinephrine dose $\mu\text{g}/\text{kg}$ per min x 100) x number of hours delivered] (11).
Pediatric Logistic Organ Dysfunction (PELOD-2)	PELOD -2 score includes 9 variables for six key organ dysfunctions (cardiovascular, respiratory, hematologic, neurologic and renal) (12).

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Table 2. Timing of administration of various interventions during initial resuscitation

Variable	Norepinephrine plus dobutamine group (n=34)	Epinephrine group (n=33)	p value
• Time to administration of first dose of antibiotics (minutes), median (IQR)	90 (50-160)	80 (20-40)	0.67
• Time to administration of first fluid bolus (minutes), median (IQR)	10 (5-20)	8 (6-20)	0.56
• Time to initiation of inotropes (minutes), median (IQR)	45 (30-50)	40 (25-45)	0.72

Table 3. Comparison of hemodynamic variables and biochemical parameters between the two groups

Variable	Norepinephrine plus dobutamine group (n=34)	Epinephrine group (n=33)	Mean difference / Risk ratio (95% CI)	p value
Heart rate (/min)				
1 hour	143.2 (25.8)	146 (24.6)	-2.7 (-15, 9.6)	0.66
6 hours	144.2 (27.1)	150.7 (23.6)	-6.5 (-18.9, 5.9)	0.29
24 hours	132.9 (30.3)	144.4 (24.6)	-11.4 (-25.1, 2.1)	0.09
48 hours	123.7 (27.6)	138.1 (27.7)	-14.3 (-28.2, -0.5)	0.04
72 hours	118.6 (24.7)	128.9 (26.9)	-10.2 (-23.3, 2.7)	0.12
At any time between 1 hr and 72 hours	NA	NA	-9.03 (-19, 1.0)	0.07
Mean blood pressure (mm Hg)				
1 hour	74 (12)	65.8 (14)	8.1 (1.7, 14.6)	0.01
6 hours	76.3 (15.6)	68.7 (10.7)	7.5 (0.9, 14.1)	0.02
24 hours	78.4 (12)	68.3 (9.4)	10 (4.6, 15.4)	0.004
48 hours	73.7 (13)	70.1 (10.7)	3.5 (-2.4, 9.6)	0.24
72 hours	75.7 (13.1)	74.3 (11.2)	1.3 (-4.8, 7.5)	0.67
At any time between 1 hr and 72 hours	NA	NA	6.4 (2.3, 10.5)	0.002
Capillary refill time (sec)				
1 hour	2.8 (0.6)	3 (0.6)	-0.1 (-0.5, 0.1)	0.28
6 hours	2 (0.2)	2.3 (0.5)	-0.2 (-0.4, -0.06)	0.01
24 hours	2 (0)	2.1 (0.4)	-0.1 (-0.2, 0.01)	0.08
48 hours	2 (0.3)	2 (0.2)	0.02 (-0.1, 0.1)	0.79
72 hours	2 (0.1)	2 (0.1)	-0.005 (-0.09, 0.08)	0.91
At any time between 1 hr and 72 hours	NA	NA	-0.1 (-0.2, -0.01)	0.02

Lactate (mmol/L), median (IQR)				
1 hour	2.6 (2.4, 3.6)	3.6 (2.5, 5.5)	NA	0.02
6 hours	1.5 (0.9, 1.9)	2 (1.4, 4.1)	NA	0.01
24 hours	1.05 (0.75, 1.95)	1.4 (1, 2.6)	NA	0.11
48 hours	1.2 (0.8, 1.7)	1.3 (0.7, 1.6)	NA	0.86
72 hours	1.4 (1, 1.6)	1.25 (0.85, 2)	NA	0.68
Blood bicarbonate (mEq/L)				
1 hour	18.6 (6.7)	19.6 (9.2)	-0.9 (-4.9, 2.9)	0.62
6 hours	19.7 (7.3)	19.9 (8.3)	0.02 (-3.8, 3.9)	0.93
24 hours	21.3 (5.2)	20.2 (7.7)	1.1 (-2.1, 4.4)	0.48
48 hours	27.7 (9.7)	23.5 (7.2)	4.1 (-6.9, 15.2)	0.62
72 hours	23.1 (5)	23.2 (5.7)	-0.08 (-2.9, 2.7)	0.95
At any time between 1 hr. and 72 hours	NA	NA	1.08 (-2.2, 4.4)	0.52
Base deficit(mEq/L), median (IQR)				
1 hour	-7.9 (-10.1, -2.6)	-8.15 (-13.85, -3.05)	NA	0.68
6 hours	-4.75 (-10.4, 0.25)	-6.7 (-11.9, -3.2)	NA	0.25
24 hours	-4.1 (-8, 0.1)	-5.8 (-10, -1.6)	NA	0.17
48 hours	-1.85 (-5.3, 2.2)	-2.05 (-5.4, 0.7)	NA	0.71
72 hours	0.75 (-5.5, 1.45)	-0.5 (-4, 2.9)	NA	0.84
Cardiac index (L/min/m²)				
1 hour	3.8 (1.1) (n=26)	3.3 (1.3) (n=20)	0.5 (-0.2, 1.3)	0.15
6 hours	4 (1) (n=24)	3.1 (1.2) (n=17)	0.8 (0.1, 1.5)	0.01
24 hours	4.2 (1.1) (n=25)	3.5 (1.2) (n=16)	0.7 (-0.01, 1.5)	0.05
48 hours	3.5 (1) (n=14)	3.4 (1.1) (n=11)	0.04 (-0.9, 0.9)	0.9
At any time between 1 hr and 72 hours	NA	NA	0.51 (-0.01, 1.04)	0.05
Central pulses (normal), n (%)				
1 hour	34 (100)	33 (100)	NA	NA
6 hours	34 (100)	33 (100)	NA	NA
24 hours	34 (100)	32 (100)	NA	NA
48 hours	34 (100)	30 (100)	NA	NA
72 hours	34 (100)	29 (100)	NA	NA
Peripheral pulses (normal), n (%)				
1 hour	31 (91.1)	28 (84.8)	1.07 (0.8, 1.2)	0.42
6 hours	34 (100)	31 (93.9)	1.06 (0.9, 1.1)	0.14
24 hours	34 (100)	31 (96.8)	1.03 (0.9, 1.09)	0.29
48 hours	33 (97)	30 (100)	0.9 (0.9, 1.02)	0.34
72 hours	34 (100)	29 (100)	NA	NA
Peripheries (warm), n (%)				
1 hour	7 (20.6)	5 (15.1)	1.3 (0.4, 3.8)	0.56
6 hours	29 (85.2)	22 (66.6)	1.2 (0.9, 1.6)	0.07
24 hours	34 (100)	29 (90.6)	1.1 (0.9, 1.2)	0.06
48 hours	31 (91.1)	30 (100)	0.9 (0.8, 1.01)	0.09
72 hours	33 (97)	28 (96.5)	1.0 (0.9, 1.1)	0.90

Urine output (mL/kg/hr)				
6 hours	2 (1.3)	2.4 (1.4)	-0.3 (-1.02, 0.3)	0.27
24 hours	2 (1.4)	2.5 (1.8)	-0.5 (-1.3, 0.2)	0.22
48 hours	1.8 (1.0)	2.3 (1.6)	-0.4 (-1.1, 0.2)	0.26
72 hours	2.1 (1.3)	2.1 (1.3)	-0.005 (-0.6, 0.6)	0.88

Data presented as mean (SD) unless otherwise specified
NA = not applicable.