Neonatal Sepsis and Hemodynamic Support: Evolving Toward Phenotype-Driven Protocols for Superior Outcomes

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18th Hot Topics in Perinatal Medicine, Jeddah 2024

Disclosure & Conflict of Interest

- I have nothing to disclose

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Objective

- Review the new criteria for sepsis and septic shock in children
- Describe the hemodynamic phenotypes of sepsis shock
- Review the management of septic shock in neonates

Neonatal Sepsis

- Global Burden of disease
  - ~ 1.3 million cases of neonatal sepsis annually
  - ~ 203,000 deaths per year

- Third most common cause of mortality in neonate

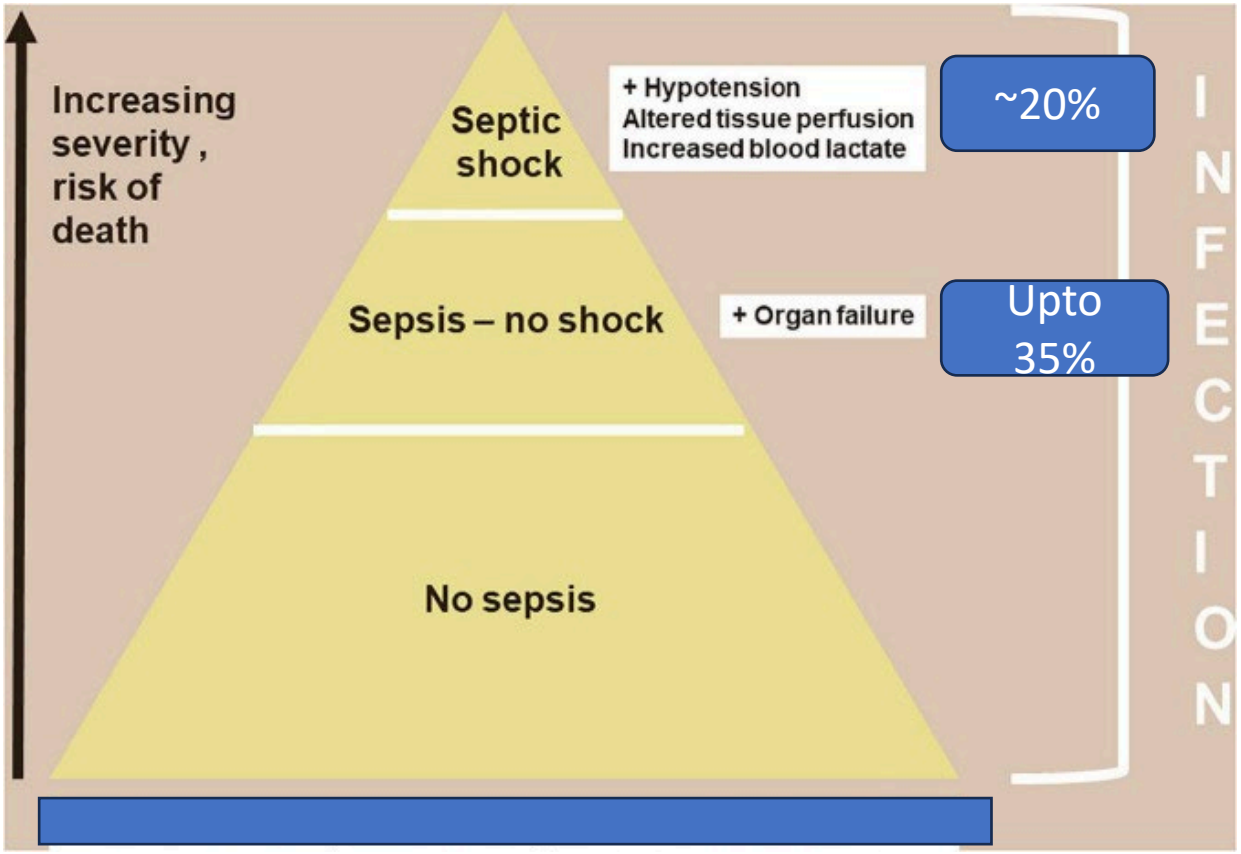
GBD 2017 ;A systematic analysis for the global burden of disease study 2017. *Lancet* 2018;392:1789–858

World Health Organization: Global report on the epidemiology and burden of sepsis: current evidence, identifying gaps and future directions.

PYRAMIDS OF INFECTION SEVERITY

25-50%

20-25%



Vincent JL. Sepsis and infection: Two words that should not be confused. Front Med 2023: 10;1156732

Incidence of Sepsis in Canada

- Late-onset sepsis (LOS) < 32 weeks
- Incidence in Canada: ~ 15%; **~20-25% need cardiotropic drugs**

Year	Affected population	Mortality n (%)
2016	246	77 (31%)
2017	266	93 (35%)
2018	269	92 (34%)
2019	232	95 (41%)
Average per year	**253**	**35.4%**

*Source: Canadian Neonatal Network

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New Pediatrics Sepsis Criteria(incl term neonates)

Table. Comparison of Phoenix Pediatric Sepsis Criteria With International Pediatric Sepsis Consensus Conference Criteria

	International Pediatric Sepsis Consensus Conference criteria	Phoenix pediatric sepsis criteria
Sepsis	2005	2024
Definition	SIRS in the setting of a suspected or confirmed infection: ≥2 SIRS criteria, of which 1 must be temperature or white blood cell count	Life-threatening organ dysfunction in the setting of suspected or confirmed infection, defined as ≥2 points on the Phoenix Sepsis Score
Criteria	Pediatric SIRS Criteria • Core temperature • White blood cell count • Heart rate • Respiratory rate	Organ dysfunction may include • Respiratory (Pao_2:FIo_2 or Spo_2:FIo_2) • Cardiovascular (vasoactive medications, lactate, age-specific MAP • Coagulation (platelets, INR, D-dimer, fibrinogen) • Neurologic systems (Glasgow Coma Scale)
Severe sepsis		
Definition	Sepsis with at least 1 of the following: cardiovascular organ dysfunction, acute respiratory distress syndrome, or ≥2 other organ dysfunctions.	Term no longer used now that sepsis definition requires organ dysfunction
Criteria	Organ dysfunctions include • Respiratory (Pao_2:FIo_2 ratio, $Paco_2$, FIo_2, mechanical ventilation) • Neurological (Glasgow Coma Scale) • Hematologic (platelet count, INR) • Kidney (serum creatinine) • Hepatic (bilirubin, alanine aminotransferase)	
Septic shock		
Definition	Sepsis and cardiovascular organ dysfunction[a]	Sepsis with ≥1 point in the cardiovascular system[b]

Carlton FE. Context and implication of the new pediatric sepsis criteria JAMA January 21,2014

International Consensus Criteria for Pediatric Sepsis and Septic Shock

Table. The Phoenix Sepsis Score[a]

Variables	0 Points	1 Point	2 Points	3 Points
Respiratory, 0-3 points				
	Pao_2:FIo_2 ≥400 or Spo_2:FIo_2 ≥292[b]	Pao_2:FIo_2 <400 on any respiratory support or Spo_2:FIo_2 <292 on any respiratory support[b,c]	Pao_2:FIo_2 100-200 and IMV or Spo_2:FIo_2 148-220 and IMV[b]	Pao_2:FIo_2<100 and IMV or Spo_2:FIo_2 <148 and IMV[b]
Cardiovascular, 0-6 points				
		1 Point each (up to 3)	2 Points each (up to 6)	
	No vasoactive medications[d]	1 Vasoactive medication[d]	≥2 Vasoactive medications[d]	
	Lactate <5 mmol/L[e]	Lactate 5-10.9 mmol/L[e]	Lactate ≥11 mmol/L[e]	
Age based[f]				
	Mean arterial pressure, mm Hg[g]			
<1 mo	>30	17-30	<17	
1 to 11 mo	>38	25-38	<25	
1 to <2 y	>43	31-43	<31	
2 to <5 y	>44	32-44	<32	
5 to <12 y	>48	36-48	<36	
12 to 17 y	>51	38-51	<38	
Coagulation (0-2 points)[h]				
		1 Point each (maximum 2 points)		
	Platelets ≥100 × 10^3/μL	Platelets <100 × 10^3/μL		
	International normalized ratio ≤1.3	International normalized ratio >1.3		
	D-dimer ≤2 mg/L FEU	D-dimer >2 mg/L FEU		
	Fibrinogen ≥100 mg/dL	Fibrinogen <100 mg/dL		
Neurological (0-2 points)[i]				
	Glasgow Coma Scale score >10; pupils reactive[j]	Glasgow Coma Scale score ≤10[j]	Fixed pupils bilaterally	
Phoenix sepsis criteria				
Sepsis	Suspected infection and Phoenix Sepsis Score ≥2 points			
Septic shock	Sepsis with ≥1 cardiovascular point(s)			

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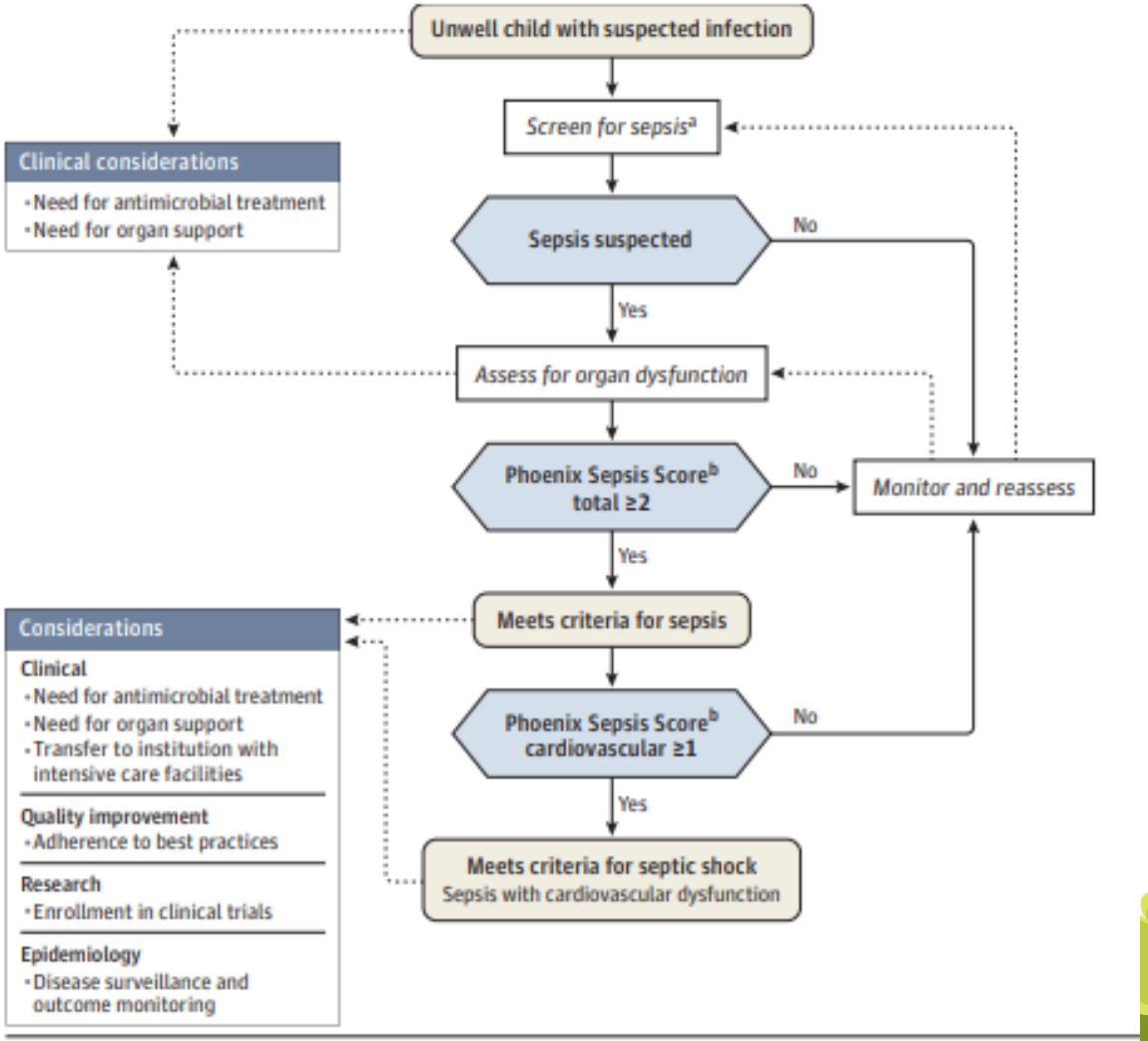
Figure. Proposed Diagnostic Flow to Characterize Patients Using the New Criteria for Sepsis and Septic Shock in Children



Pathophysiology of Sepsis and septic shock

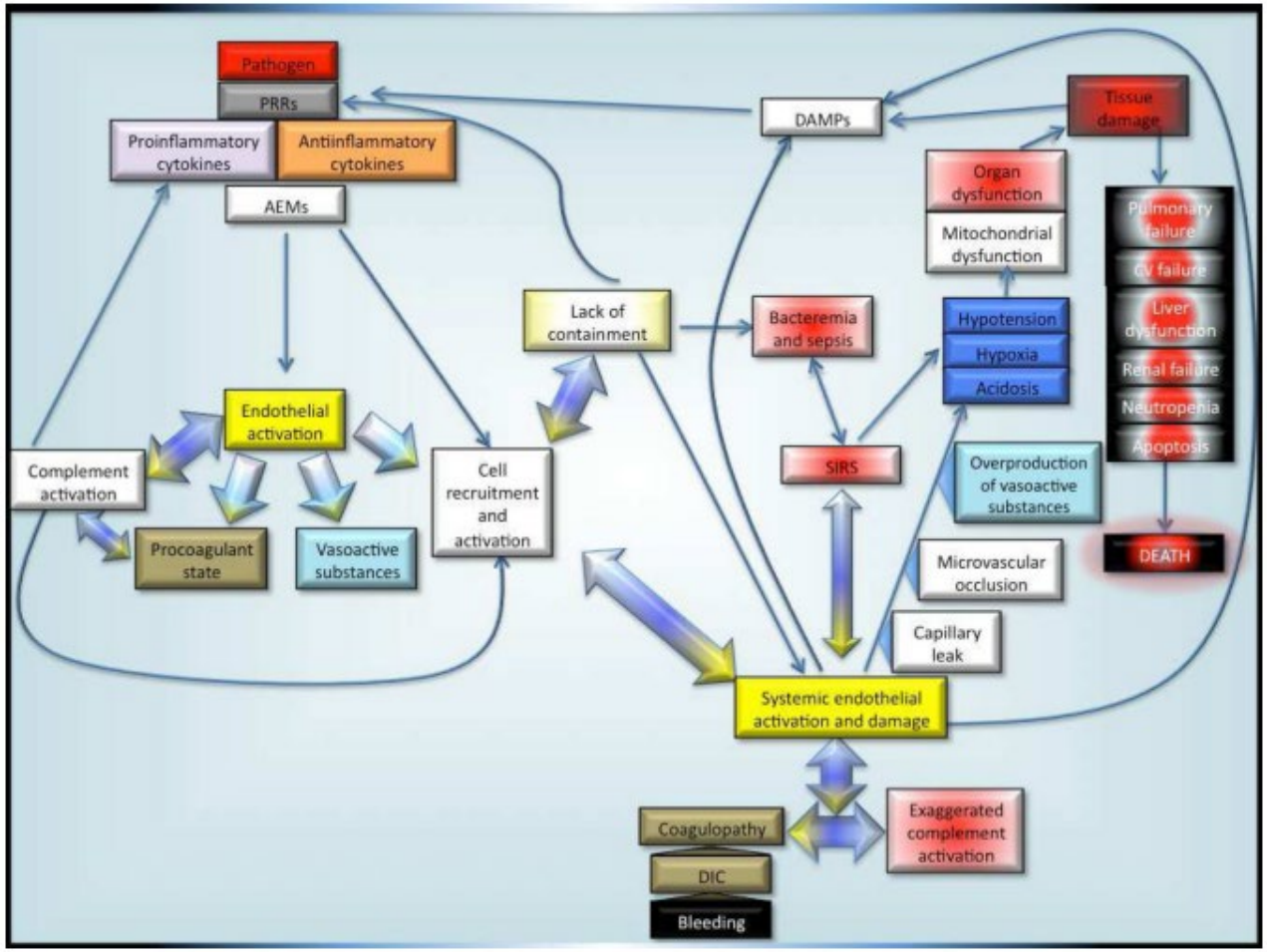
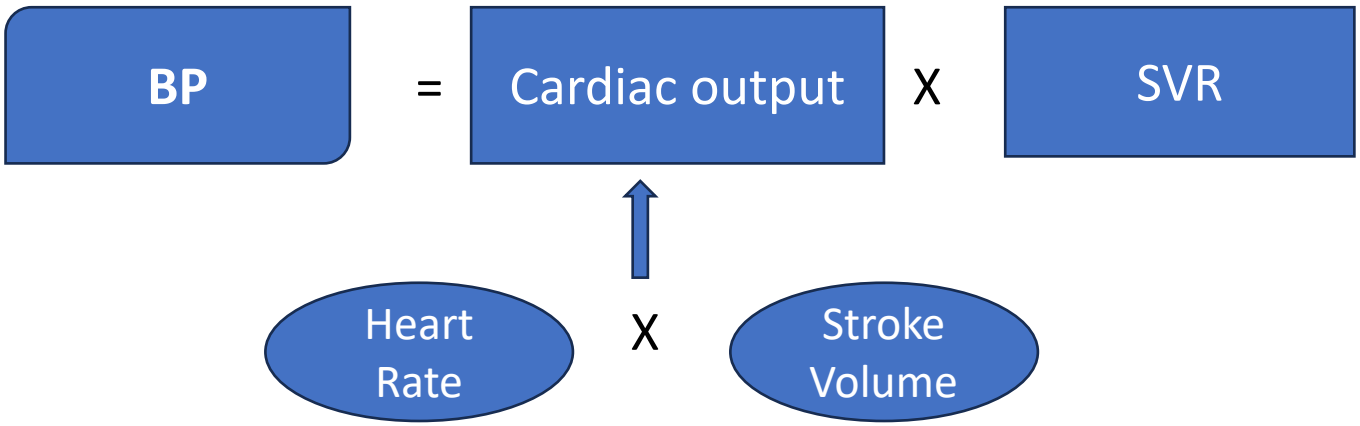
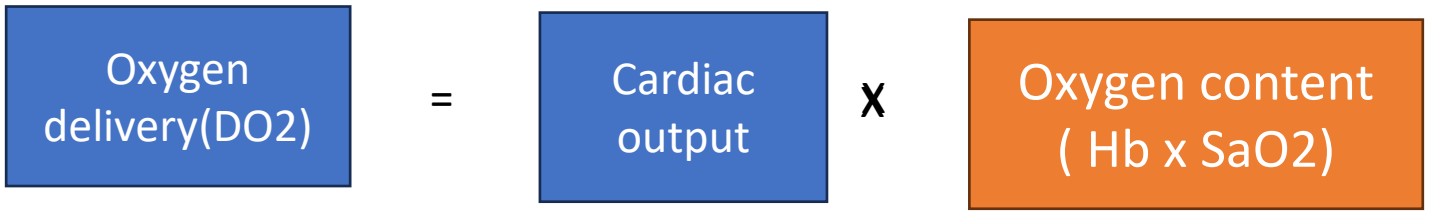


Figure 3. Pathophysiology of neonatal sepsis and septic shock

Wynn JL. Clin Perinatol 2010: 37: 439-79


BP
=
Cardiac output
X
SVR
Heart Rate
X
Stroke Volume


Oxygen delivery(DO2)
=
Cardiac output
X
Oxygen content (Hb x SaO2)

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BP= CO X SVR

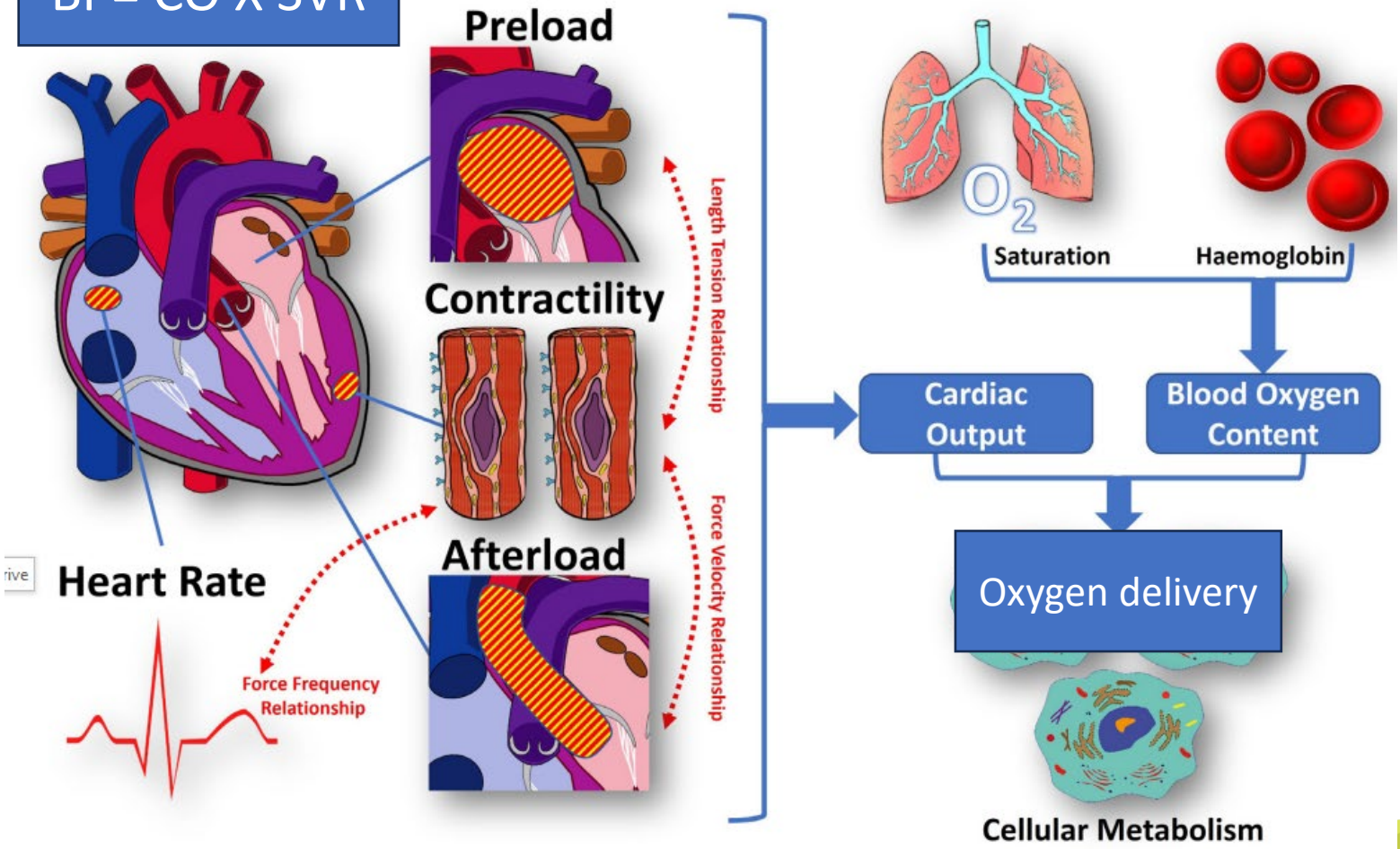

Figure 1 Cellular metabolism is the goal. CO is determined by preload, afterload, contractility and heart rate. CO and adequate blood oxygen concentration determine cellular metabolism. CO, cardiac output.

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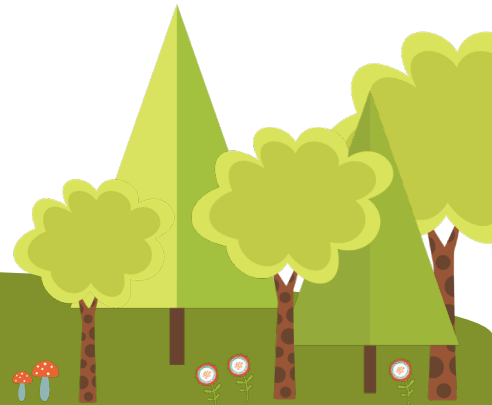
Two phenotypes of septic shock

WARM SHOCK

- **Hemodynamics**
  - Vasodilation
  - ↓ SVR, ↑ CO
- **Clinical:**
  - Warm extremities,
  - Tachycardia
  - Bounding pulses
  - Flushed CRT

COLD SHOCK

- **Hemodynamic changes**
  - Peripheral vasoconstriction
  - ↑ SVR
- **Clinical:**
  - Cold, mottled skin
  - Weak pulses
  - Delayed CRT
  - Oliguria



Warm shock

↓ SVR

↓ SV return
↓Right heart preload

Compensatory tachycardia

TNE: Hyperdynamic profile
BP= CO x SVR

↓ Left heart preload

↓LV systolic performance

Ventricular interdependence

↓ RV filling

↓CO and shock

Kharrat A Pediatric Res 2022

Cold shock

↑ SVR

↓ LV systolic performance

Compensatory tachycardia and increased contractile force

↓ Stroke volume

↑ end-diastolic pressure

↓ Cardiac filling

Ventricular dysfunction

↓CO and shock

Kharrat A Pediatric Res 2022

Hemodynamic phenotype of sepsis differs with age

- Adults: Decreased SVR and increased CO (warm shock)
- Children: Non-hyperdynamic state with reduced CO and increased SVR (cold shock)
- Neonates: variable presentation, most commonly low SVR state

Hemodynamics of sepsis in preterm

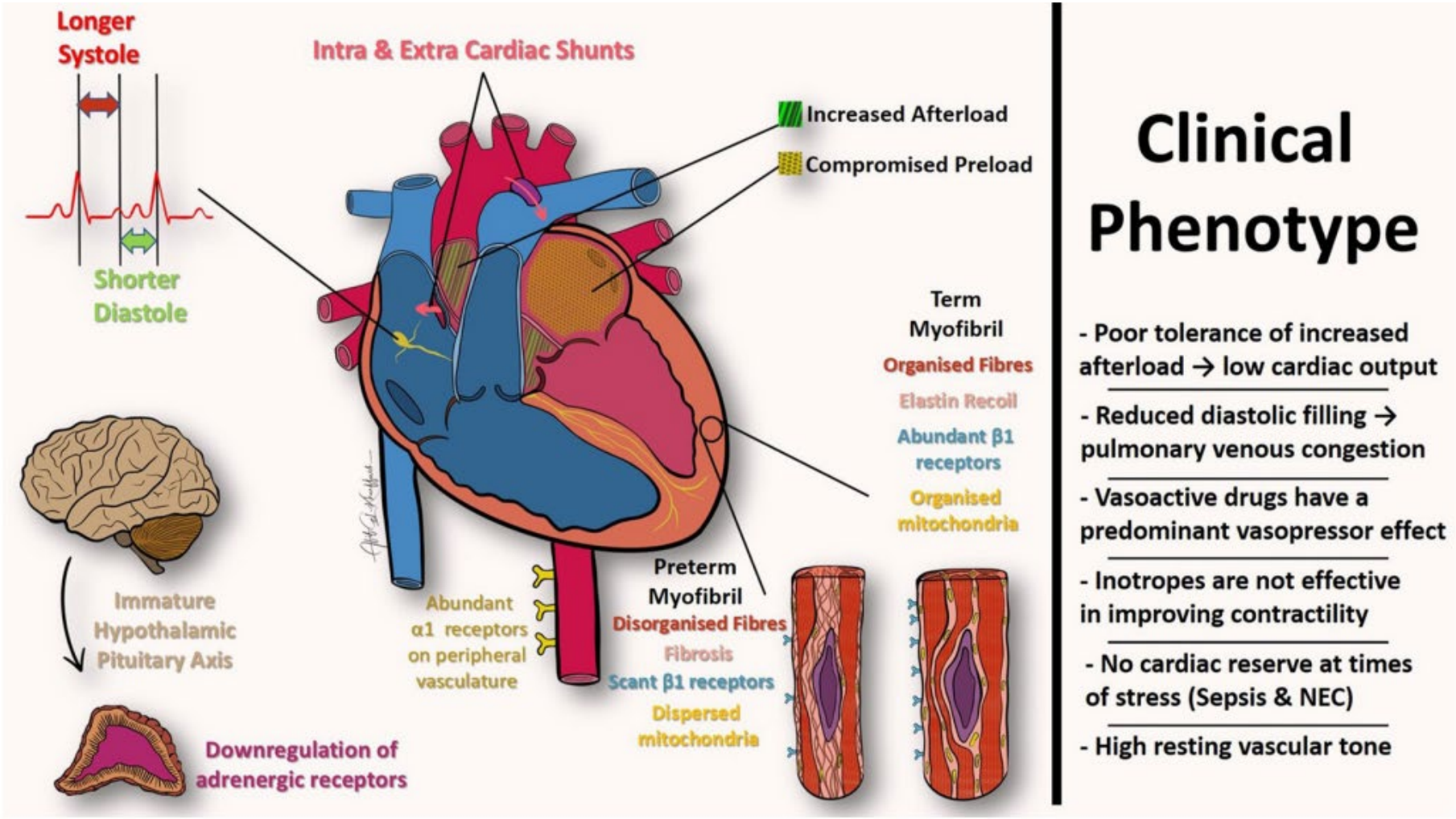
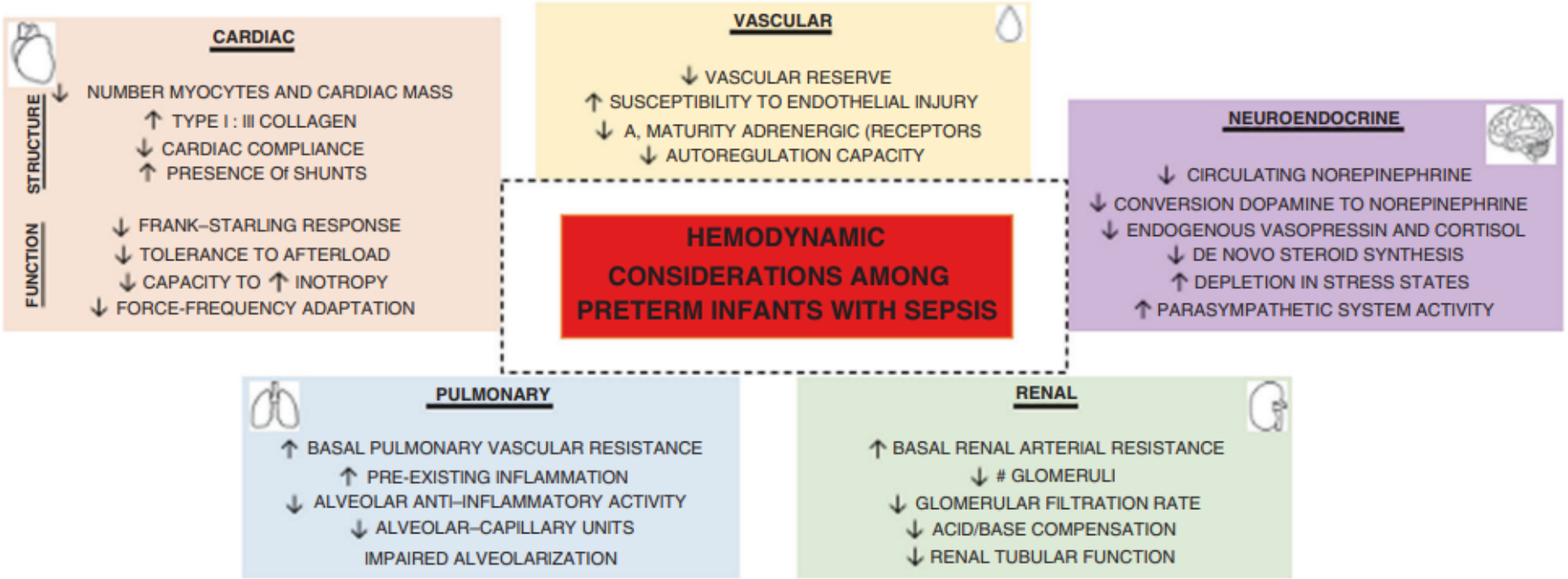


Figure 2 Premature pathophysiology is unique. Differences in the preterm and term myocardia and underlying pathophysiological processes lead to a unique clinical phenotype in the preterm neonate when the cardiovascular system becomes compromised. NEC, necrotising enterocolitis.

Mullaly R, El-Khuffash AF. Arch Dis Child Fetal Neonatal Ed 2023;0:F1–F8.

Hemodynamic of sepsis in preterm

A. Kharrat and A. Jain



Kharrat A. Pediatr Res 2023

Role of pathogens

GBS tend to present cold shock with marked decrease in CO and BP maintained by vasoconstriction

E. coli or Gram-negative sepsis tends to present as a warm shock

Hemodynamic monitoring of sepsis

- Basic
  - HR
  - BP – systolic, diastolic , MAP
  - Central venous pressure (CVP)
  - Central venous oxygen saturation (ScvO2),
  - Perfusion pressure (MAP-CVP)
  - Lactate

- Advanced
  - Cardiac output
  - Contractility, preload and afterload
  - NIRS

Lee E. Biomed J. 2022 Feb; 45(1): 63–73.

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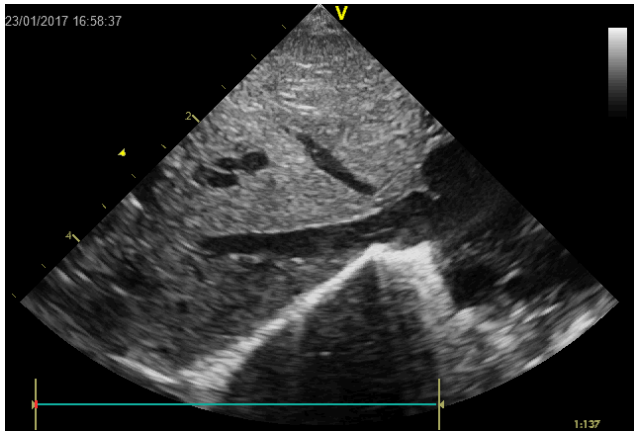
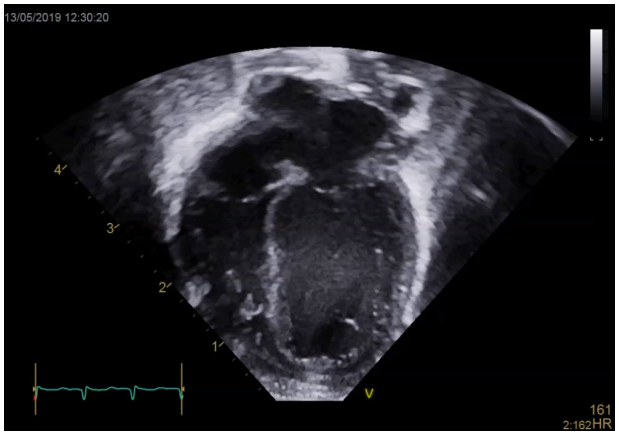
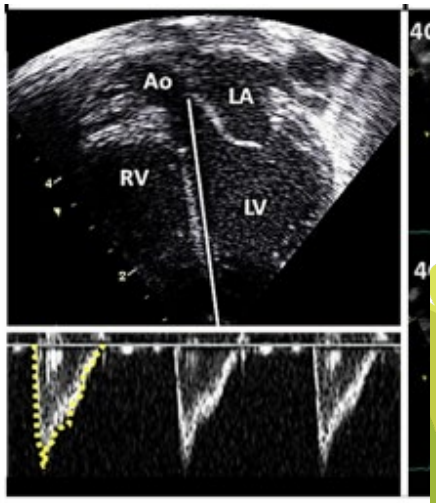
Table 1 Measurement of hemodynamic parameters using different non-invasive tools

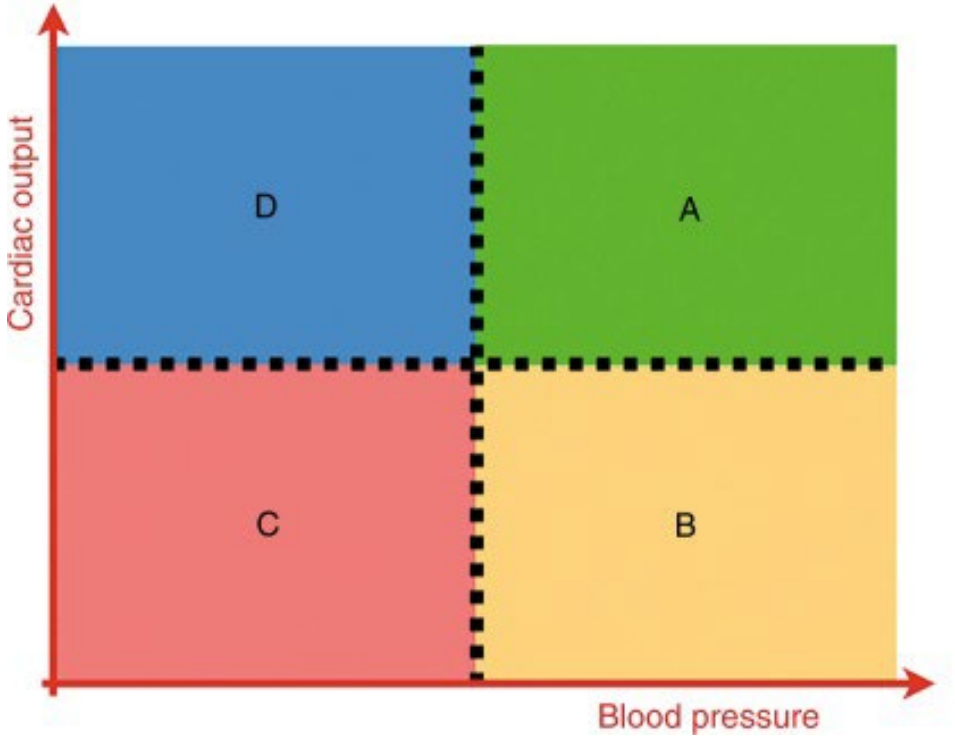
Hemodynamic parameter	Echo	Trans-thoracic Trans-esophageal Doppler	Electrical cardiometry	NIRS
Preload (fluid responsiveness)				
IVCDI	+	-	-	-
CI before and after fluid bolus	+	+	+	-
Afterload				
SVRI	+	+	+	-
Contractility				
CI	+	+	+	-
End-organ perfusion				
rSO_2	-	-	-	+

IVCDI: Inferior vena cava distensibility index; CI: Cardiac index; SVRI: Systemic vascular resistance index; rSO_2: Regional tissue oxygen saturation; NIRS: Near infra-red spectroscopy.









	Cardiac output	Blood pressure	Situation
A	Normal/ High	Normal/ High	Normal
B	Low	Normal/ High	Compensated shock
C	Low	Low	Uncompensated shock
D	Normal/ High	Low	Hyperdynamic circulation

Identification of the stage of shock by simultaneous measurement of cardiac output and blood pressure

De Boot WP. Pediatr Res. 2018; 84(Suppl 1): 57–67

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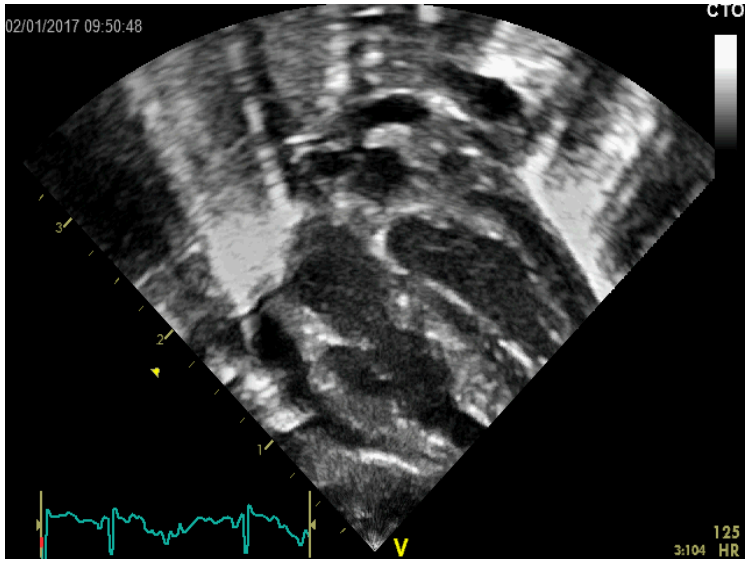
The ventricular walls collapse and touch each other during systole (Kissing ventricles)



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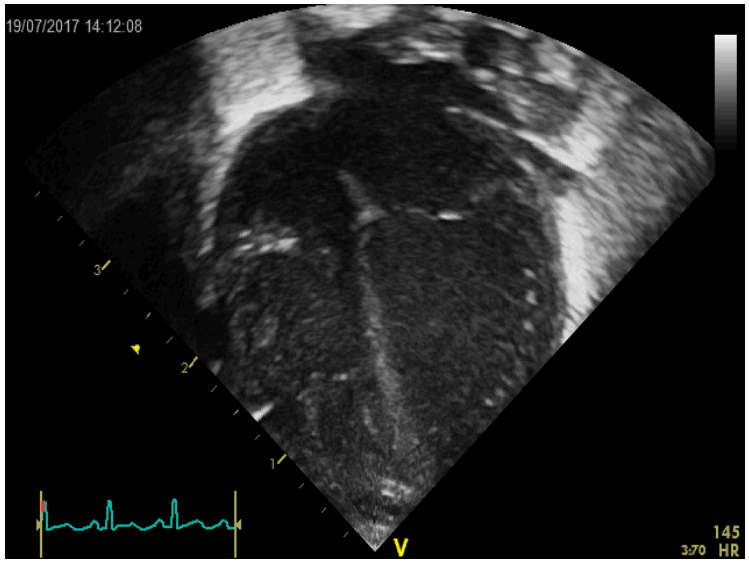
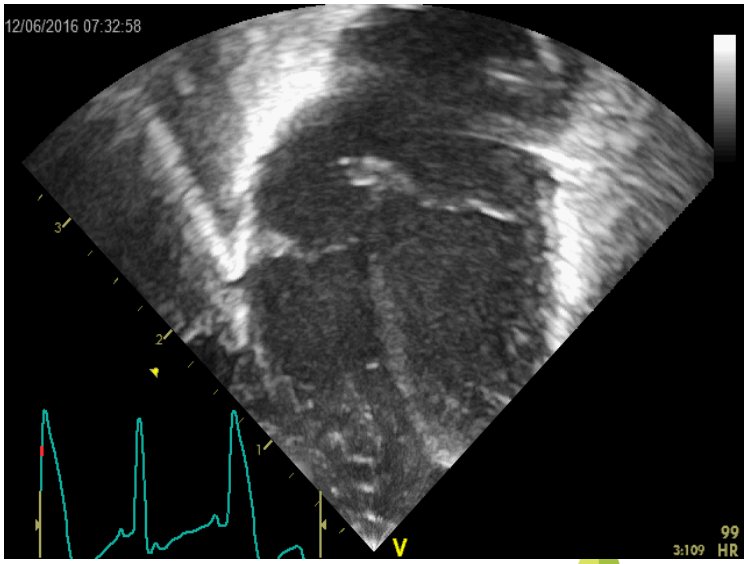
Cardiac contractility





THE JOURNAL OF MATERNAL-FETAL & NEONATAL MEDICINE
2022, VOL. 35, NO. 25, 6815–6822
https://doi.org/10.1080/14767058.2021.1926447

ORIGINAL ARTICLE

Functional echocardiographic preload markers in neonatal septic shock

Shiv Sajan Saini[a], Venkataseshan Sundaram[a], Praveen Kumar[a] and Manoj Kumar Rohit[b]

[a]Division of Neonatology, Department of Paediatrics, Post Graduate Institute of Medical Education & Research, Chandigarh, India;
[b]Department of Cardiology, Post Graduate Institute of Medical Education & Research, Chandigarh, India

Table 2. Preload markers before and after fluids resuscitation.

Variable	Baseline ($n = 16$)	After 10 mL/kg ($n = 16$)	After 20 mL/kg ($n = 8$)	p-Value
Inferior Vena Cava Collapsibility Index (%)	74 (33, 100)	48 (13, 93)	50 (40, 69)	.05
Left ventricle end diastolic volume (mL)	1.3 (1.1, 1.7)	1.4 (1.0, 1.8)	1.4 (1.0, 2.0)	.42
Left ventricle end diastolic volume index (mL/m^2)	2.9 (2.4, 3.6)	2.2 (1.8, 3.4)	3.6 (2.4, 3.9)	.42
Left ventricle end systolic volume (mL)	12 (10, 15)	13 (9, 15)	11 (10, 16)	.31
Left Ventricle End Systolic Volume Index (mL/m^2)	25 ± 5	24 ± 6	28 ± 6	.32

Among five preload markers, only IVC-CI was significantly elevated in neonates with septic shock as compared to hemodynamically stable controls

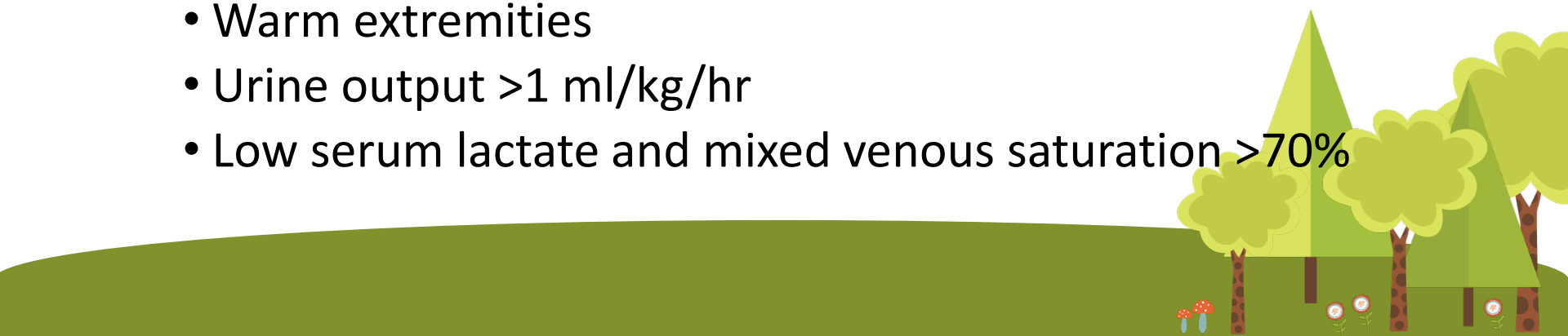
Basic principles of sepsis management

- Early recognition
- Prompt antibiotic treatment
- Frequent assessment and reevaluation of vitals
- In septic shock: fluid +/- vasoactive medication

Therapeutic goals

- Aim: to restore blood flow and oxygen delivery to tissues so that perfusion and aerobic cellular metabolism are restored and preserved

- Clinical goals:
  - Normal pulses with no difference in peripheral and central pulses,
  - CRT < 2 sec,
  - Warm extremities
  - Urine output >1 ml/kg/hr
  - Low serum lactate and mixed venous saturation >70%



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What is initial vasoactive agents for septic shock in neonate ?

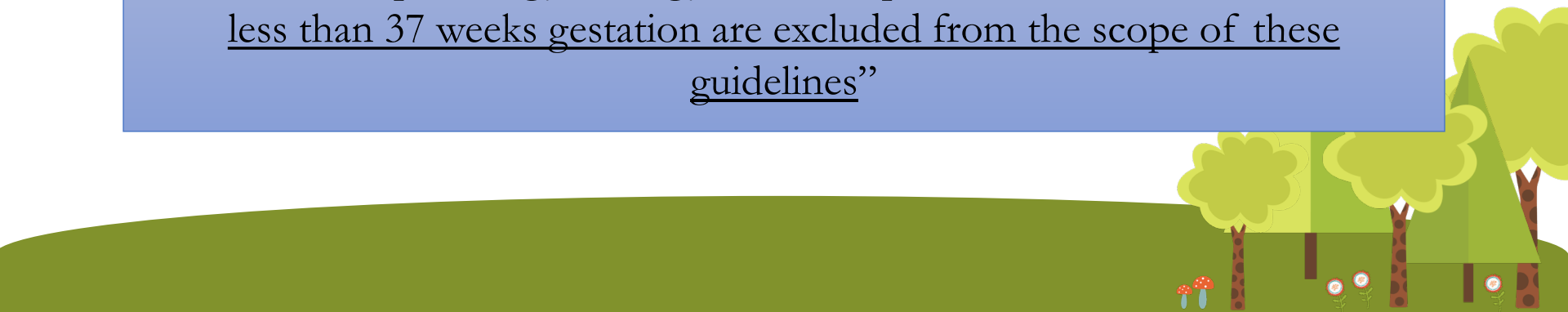
Surviving Sepsis Campaign Guidelines

- ***Adult patients with septic shock***: "**Norepinephrine** as the first-line vasopressor, over Dopamine" [strong recommendation, moderate level of evidence]

  12% RR in mortality (95% CI 4% - 20%)] and fewer complications

- ***Pediatric patients with septic shock:*** "using epinephrine or norepinephrine, rather than dopamine" [weak recommendation, low quality of evidence]
- Near complete absence of evidence for neonates with septic shock

"acknowledging that neonatal sepsis, especially in premature neonates, may have a distinct pathology, biology, and therapeutic considerations, newborns less than 37 weeks gestation are excluded from the scope of these guidelines"



Epinephrine vs Dopamine for neonatal septic shock

- A double-blind RCT of 40 neonates with fluid refractory septic shock.
- No difference in shock reversal (25% versus 30%)after 45 min of therapy or mortality (70% vs 80%)
- Subgroup analysis, Epinephrine was more effective than dopamine in reversing shock and hemodynamic instability in premature neonates under ≤ 30 weeks' gestation.

Baske K, Saini SS, Dutta S, et al. Epinephrine versus dopamine in neonatal septic shock: a double-blind randomized controlled trial. *Eur J Pediatr.* 2018;177:1335–1342.

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Dopamine versus epinephrine for pediatric or neonatal septic shock: a meta-analysis of randomized controlled studies

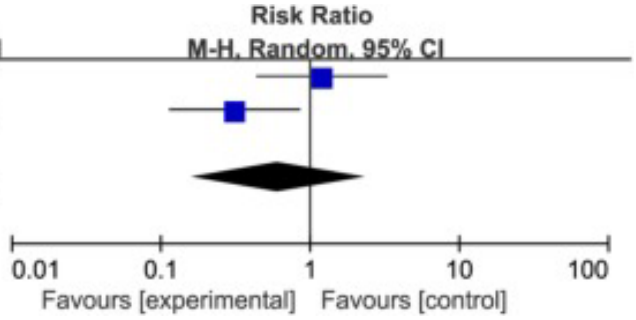
Wen L. Italian J Pediatr 2020

Shock reversal within 1 hours

Study or Subgroup	Dopamine group Events	Total	Epinephrine group Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Baske 2018	6	20	5	20	50.0%	1.20 [0.44, 3.30]
Ramaswamy 2016	4	31	12	29	50.0%	0.31 [0.11, 0.86]
Total (95% CI)		51		49	100.0%	**0.61 [0.16, 2.31]**
Total events	10		17			

Heterogeneity: Tau² = 0.65; Chi² = 3.45, df = 1 (P = 0.06); I² = 71%

Test for overall effect: Z = 0.72 (P = 0.47)

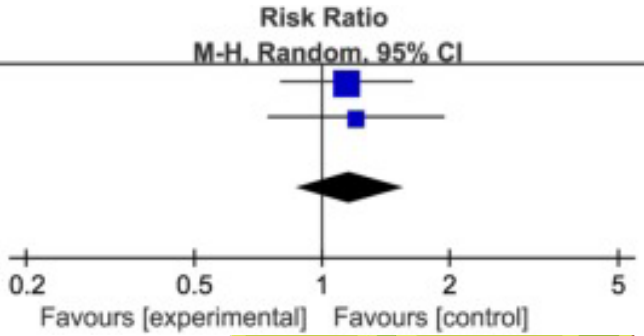


Mortality

Study or Subgroup	Dopamine group Events	Total	Epinephrine group Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Baske 2018	16	20	14	20	64.0%	1.14 [0.80, 1.64]
Ramaswamy 2016	18	31	14	29	36.0%	1.20 [0.74, 1.95]
Total (95% CI)		51		49	100.0%	**1.16 [0.87, 1.55]**
Total events	34		28			

Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 1 (P = 0.86); I² = 0%

Test for overall effect: Z = 1.03 (P = 0.30)



- N= 3 studies
- Shock reversal after 1 hour

ARTICLE

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

Henry P. Foote[1], Daniel K. Benjamin[2], Rachel G. Greenberg[1,3], Reese H. Clark[4] and Christoph P. Hornik[1,3]✉

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- Multicentre cohort study in 175 NICUs in US
- N= 1592 (Median GA; 25 wk BW: 760g
- Mortality rate 50%

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]

Foote HP et al . J Perinatol 2023: 43(10)1274-1280

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Norepinephrine in neonates

Norepinephrine infusion improves haemodynamics in the preterm infants during septic shock. M Y Rizk , et al Acta Pedaitrica2018 March: 107(3):408-413

The effect of norepinephrine on clinical and hemodynamic parameters in neonates with shock: a retrospective cohort study. Gupta S, et al. Eur J Pediatr. 2022 Jun;181(6):2379-2387

Use of **norepinephrine** in preterm **neonates** with **dopamine**-resistant **shock**: a retrospective single-centre cross-sectional study. Pei Lu, et al. BMJ Paediatr Open. 2023; 7(1): e001804.

•. 2023 Mar;182(3):1029-1038

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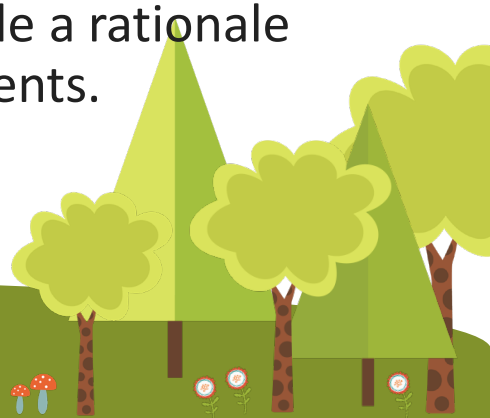
Norepinephrine versus Dopamine in NICU

- Retrospective study in 2 centres in Toronto
- N= 156 over 10 years
- Dopamine=113 Norepinephrine= 43
- After PS adjustment, NE was associated with lower episode-related mortality [aOR 95% CI) 0.55 (0.33, 0.92)], pre-discharge mortality [0.60 (0.37, 0.97)], post-illness new diagnosis of significant neurologic injury [0.32 (0.13, 0.82)], and subsequent occurrence of NEC/sepsis among the survivors [0.34, (0.18, 0.65)].
- NE may be more effective than DA for management of sepsis-related hypotension among preterm infants. These data provide a rationale for prospective evaluation of these commonly used agents.



Sagee Nissimov Eur J Pediatr 2023 March 182:1029-38

Currently limited information of choice of vasoactive medication

- Cold shock phenotype: Inotrope (Dopamine or epinephrine)

- Warm shock: Vasopressor (Norepinephrine or high dose dopamine, vasopressin)

Cold shock

↑ SVR

↓ LV systolic performance

Compensatory tachycardia and increased contractile force

↓ Stroke volume

Ventricular dysfunction

↑ end-diastolic pressure

Inotropes (Dopamine or epinephrine

↓ Cardiac filling

↓CO and shock

Kharrat A Pediatric Res 2022

Warm shock

↓ SVR

Vasopressor (NE, Dopamine, Vasopressin

↓ SV return
↓Right heart preload

↓ Left heart preload

↓LV systolic performance

↓ RV filling

↓CO and shock

Kharrat A Pediatric Res 2022

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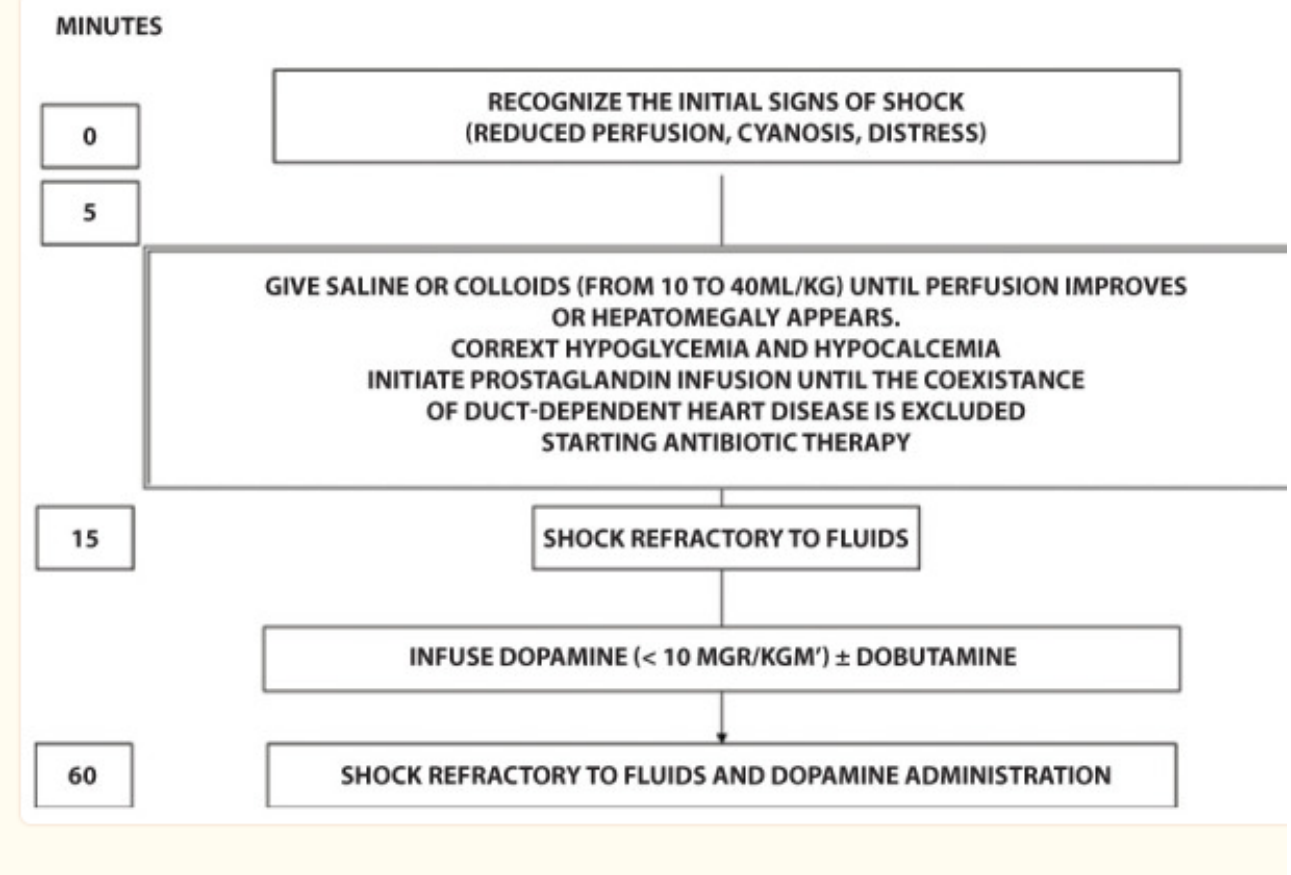
Vasoactive Drugs Mode of Action

	SV	SVR	PVR
Adrenaline	↑↑↑	↑↑↑	↑↑
Noradrenaline	↑/≈	↑↑↑	↓/≈
Vasopressin	≈	↑↑↑	↓/≈
Dobutamine	↑↑	↓/≈	≈
Milrinone	↑↑	↓↓	↓↓
Dopamine	↑	↑↑	↑↑↑

SV = stroke volume; SVR = systemic vascular resistance; PVR = pulmonary vascular resistance

↑ = increase; ↓ = decrease; ≈ = no effect

Treatment of septic shock



•Davis AL,et all. American College of Critical Care Medicine Clinical Practice Parameters for Hemodynamic Support of Pediatric and Neonatal Septic Shock. *Crit Care Med.* 2017;45:1061–1093.]

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Fluid refractory-dopamine resistant shock?

Titrate Epinephrine 0.05 -0.3 µg/kg/min

60 min

Catecholamine-resistant shock?

Goals

Normal MAP-CVP.$ScvO_2$ >70 %, SVC flow>40 mL/kg/min or CI > 3.3 L/m^2/min

Cold Shock
Normal Blood Pressure
Poor LV function
$ScvO_2$ < 70, Hgb ≥ 12 g/dL
SVC flow < 40 mL/kg/min
or CI < 3.3 L/m^2/min?

Add Nitrosovasodilator,
Milrinone
with volume loading

Cold Shock
Poor RV function PPHN
$ScvO_2$ < 70%
SVC flow < 40 mL/min
or CI < 3.3 L/m^2/min?

Inhaled Nitric Oxide
Inhaled Iloprost/ IV Adenosine
IV Milrinone, ? Levosimendan

Warm Shock
Low Blood Pressure?

Titrate Volume
Add Norepinephrine
? Vaso/Terlipressin/
Angiotensin
Keep $ScvO_2$ >70%,
SVC flow > 40 mL/kg/min,
or CI > 3.3 L/m^2/min
with Inotropic Support

Refractory Shock?

Evacuate pneumothoraces and pericardial effusion. Give Hydrocortisone if Absolute Adrenal Insufficiency and T_3 if Hypothyroid. Begin Pentoxifylline if VLBW newborn. Consider Closing PDA if hemodynamically significant.

ECMO
(110 mL/kg/min)

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Vasopressin	≈	↑↑↑	↓/≈
Dobutamine	↑↑	↓/≈	≈
Milrinone	↑↑	↓↓	↓↓
Dopamine	↑	↑↑	↑↑↑

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Summary

- The phenotypic presentation of septic shock in neonate vary with type of infection and can change during course of illness.
- Comprehensive hemodynamic monitoring is important for an individualized pathophysiology-based hemodynamic management
- Treatment should be based on underlying mechanisms and need frequent **reevaluation,** and **readjustment** of management strategies is important to improve outcome.

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THANK YOU