Clinical question.
In infants and children with distributive shock, with or without myocardial dysfunction (P), does the use of any specific inotropic agent (I), when compared to standard care (C), improve patient outcome (O)?

P = full term neonates, infants and children < 18 years
I = positive inotropy
C = none / standard care / inotropic and or vasoactive agent(s)
O = patient outcome (reduced mortality, hemodynamic effects, therapeutic goals)

Is this question addressing an intervention/therapy, prognosis or diagnosis? This is an intervention / therapy question: a proposed new topic. The comparator (or control) is ‘usual management’ or inotropic agent or any substance with positive inotropic effects.

State if this is a proposed new topic or revision of existing worksheet: New topic

Conflict of interest specific to this question
Do any of the authors listed above have conflict of interest disclosures relevant to this worksheet? Nil

Search strategy (including electronic databases searched).

The following electronic databases were systematically searched with no restriction to years:
- PubMed MEDLINE
- Embase.com integrating MEDLINE & EMBASE records
- OvidSP’s EBMR
- ISI Web of Science
- http://clinicaltrials.gov/
- Cochrane Central Register of Controlled Trials

EMBASE MEDLINE search

#31
#16 AND #28 AND #29 AND ([article]/lim OR [article in press]/lim OR [letter]/lim) AND ([internal medicine]/lim OR [pediatrics]/lim OR [pharmacology and pharmacy]/lim OR [physiology and endocrinology]/lim)

#30
#16 AND #28 AND #29

#29
'child'/de OR child OR 'children'/de OR children OR 'infant'/de OR infant OR 'newborn'/de OR newborn OR 'neonate'/de OR neonate OR pediatric OR paediatric OR teenage* OR adolescen*

#28
#17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27

#27
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'phosphodiesterase inhibitor'/exp/mj OR 'phosphodiesterase inhibitor'
#19
'adrenergic receptor stimulating agent'/exp/mj OR 'adrenergic receptor stimulating agent'
#18
'catecholamine'/exp/mj OR 'catecholamine'
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'inotropic agent'/exp/mj OR 'inotropic agent'
#16
#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15
#15
(injury NEAR/5 shock):ab
#14
('drug intoxication' NEAR/5 shock):ab
#13
'spinal shock'
#12
(vasogenic NEAR/5 shock):ab
#11
('acute adrenal insufficiency' NEAR/5 shock):ab
#10
((vasodilation OR vasodilatory) NEAR/5 shock):ab
#9
(refractory NEAR/5 shock):ab
#8
(neurogenic NEAR/5 shock):ab
Other strategies to complete the search

Searches were also done in www.medscape.com, Google Scholar and Paediatric Advanced Life Support texts. References of articles of relevance were reviewed and full-text obtained as far as possible.

EndNote Database
1,715 records were exported into EndNote Library [ENX3] for review.

• State inclusion and exclusion criteria

Inclusion criteria
1. Distributive shock or shock caused by
   a. Sepsis /SIRS
   b. Anaphylaxis
   c. Acute adrenal insufficiency
   d. Injuries to central nervous system
   e. Drug intoxication
2. RCTs, observational studies, case reports, case series in children
3. Vasodilatory shock

Exclusion criteria
1. Adult RCTs, case studies and experimental models
2. Premature population
3. Other forms of shock (e.g. haemorrhagic, cardiogenic, hypovolaemic)
4. Letters, editorials, review articles, updates, consensus statements

Search Strategy

Concept 1: “distributive shock” is not indexed in any of the abovementioned databases. Using free text searching pulled up few records; hence search was done using phrases taken from the etiology of “distributive shock,” namely:
- Sepsis or septicemia or endotoxemia
- Anaphylaxis or “anaphylactic shock”
- Systemic inflammatory response syndrome (SIRS) due to burns, pancreatitis, trauma, fulminant hepatic failure, surgery
- Neurogenic shock due to brain or spinal cord injury
- Acute adrenal insufficiency
- Vasodilatory or vasodilated shock

Concept 2: “inotropic agent” is mapped to
- ‘inotropic agent’ in Embase.com
- ‘cardiotonic agents’ in PubMed MEDLINE

Indexed terms as well as free text searching and synonyms were used.

Concept 1: all search strings ORed together relevant to “distributive shock.”

Concept 2: all search strings ORed together relevant to “inotropic agent.”

Concept 1 ANDed Concept 2 limited to children population.

In OvidSP’s All EBM Reviews: Concept 1 AND Concept 2 AND children population limited to “evidence based medicine” study types.

1. Since ‘usual / standard care’ primarily consists of volume resuscitation, early antibiotic administration, rapid source identification and control, and support of major organ dysfunction; it is not effective to include ‘usual / standard care’ as Concept 3 in the search strategy. The focus of search is on positive inotropic agents that increase the strength of muscular contraction as well as to compare use of inotropes to ‘standard’ treatment. We felt it was appropriate to search for other cardiovascular acting drugs that may be studied as treatments for distributive shock. Therefore, drugs like vasopressin, terlipressin were included even though they are traditionally not viewed as inotropes.

2. Population with mixed population i.e. not true ‘distributive shock’ cases but hybrid of say, septic shock and cardiogenic shock were excluded unless patients with distributive/vasodilatory shock were separately analyzed. Studies on patients with hypovolemia were also excluded.

3. Studies on other forms of shock e.g. cardiogenic shock were excluded unless the investigators studied distributive / vasodilatory shock in context of patient with these shock states.

4. Consensus statements, reviews, updates, editorials, letters and comments were excluded. Only clinical trials, observational studies, comparative studies and case reports were included.

5. In cases of mixed population, for example – aged, adult, adolescent and children, the number of pediatric patients out of the total number was taken into consideration. All papers on exclusively adult population were excluded.

6. Papers on premature infants / newborns of <1501 g birth weight or <32 weeks of gestational age were excluded as this population is at risk for intraventricular hemorrhage after rapid shifts in blood pressure and also because the immature muscle is less able to constrict. However references from review articles on term neonatal septic shock were searched and reviewed.
7. Very old papers and papers with no abstracts were excluded. There was no restriction to language; and attempts on document delivery for non-English papers, if significantly relevant – for example Zhonghua Yi Xue Za Zhi, 1983 on “The use of isoproterenol in treating infectious shock” were made.

8. Animal studies were included although evaluation of evidence is on children and infants.

<table>
<thead>
<tr>
<th>Number of articles/sources meeting criteria for further review:</th>
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<tbody>
<tr>
<td><strong>English articles</strong></td>
</tr>
<tr>
<td>LOE 1: 4</td>
</tr>
<tr>
<td>LOE 2: 0</td>
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<tr>
<td>LOE 3: 0</td>
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<tr>
<td>LOE 4: 25</td>
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<td>LOE 5: 0</td>
</tr>
<tr>
<td><strong>Non English articles LOE 1-5: 0</strong></td>
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# Summary of evidence

## Evidence Supporting Clinical Question

<table>
<thead>
<tr>
<th>Good</th>
<th>Barton ‘96 (C E1)</th>
<th>Tourneux ‘08 (E1-3)</th>
</tr>
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<tbody>
<tr>
<td><strong>Fair</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lindsay ‘98 (E1)</td>
<td></td>
<td>Irazuza ‘01 (E1)</td>
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<tr>
<td>Yildizdas ‘08 (B E1)</td>
<td></td>
<td>Ceneviva ‘98 (B E1)</td>
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<td></td>
<td></td>
<td>Jerath ‘08 (E1 E3)</td>
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<td></td>
<td></td>
<td>Lechner ‘07 (E1 E3)</td>
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<td></td>
<td></td>
<td>Masutani ‘05 (E1 E2)</td>
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<tr>
<td></td>
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<td>Matok ‘05 (E1-3)</td>
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<tr>
<td></td>
<td></td>
<td>Perkin ‘02 (E1-3)</td>
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<td></td>
<td></td>
<td>Rodriguez ‘06 (E1 E3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rosenzweig ‘99 (E1 E3)</td>
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<tr>
<td><strong>Poor</strong></td>
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<td></td>
<td></td>
<td>Tourneux ‘08 (E1 E2)</td>
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<td></td>
<td></td>
<td>Perkin’82 (E1-3)</td>
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<td></td>
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<td>Di Chiara ‘08 (E1)</td>
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<td>Liedel ‘02 (E1)</td>
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<td>Moffett ‘06 (E2)</td>
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<td>Yunge ‘00 (E1 E3)</td>
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<table>
<thead>
<tr>
<th>Level of evidence</th>
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<tbody>
<tr>
<td>A = Return of spontaneous circulation</td>
</tr>
<tr>
<td>B = Survival to PICU discharge</td>
</tr>
<tr>
<td>C = Survival to hospital discharge</td>
</tr>
<tr>
<td>D = Intact neurological survival</td>
</tr>
<tr>
<td>E = Other endpoint (hemodynamics)</td>
</tr>
<tr>
<td>Italic = Animal studies</td>
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</tbody>
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E1 = Acute changes (<24hrs) in haemodynamics
E2 = End organ function (renal, cerebral)
E3 = Reduction in inotropes score, doses of inotropes/vasopressors or cessation
E4 = Mortality/Morbidity benefit or harm
# Evidence Neutral to Clinical question

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<tr>
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<td>NIL</td>
<td>Peters ’04 (E1)</td>
<td>Zeballos ‘06 (E1 E3)</td>
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</table>

**Level of evidence**

A = Return of spontaneous circulation  
B = Survival of event  
C = Survival to hospital discharge  
D = Intact neurological survival  
E = Other endpoint  
Italics = Animal studies

E1 = Acute changes (<24hrs) in haemodynamics  
E2 = End organ function (renal, cerebral)  
E3 = Reduction in inotropes score, doses of inotropes/vasopressors or cessation  
E4 = Mortality/Morbidity benefit or harm
**Evidence Opposing Clinical Question**

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<td>NIL</td>
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<td>NIL</td>
<td>NIL</td>
<td>NIL</td>
</tr>
<tr>
<td>Poor</td>
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**Level of evidence**
- A = Return of spontaneous circulation
- B = Survival of event
- C = Survival to hospital discharge
- D = Intact neurological survival
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- E1 = Acute changes (<24hrs) in haemodynamics
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- E4 = Mortality/Morbidity benefit or harm

Italic = Animal studies
REVIEWER’S FINAL COMMENTS AND ASSESSMENT OF BENEFIT / RISK:

This is a re-submission of the worksheet after review and comments from the ILCOR review committee and discussions with co-author. Literature on this subject remains limited in paediatric literature with few high level trials and mostly observational studies or case reports.

**Paediatric RCTs**

There are 2 LOE 1 studies in this category that looked at use of milrinone in context of catecholamine resistant nonhyperdynamic septic shock (Barton ’96 and Lindsay ’98). Both had similar design and results. Lindsay study was designed to also have a pharmacodynamic assessment of milrinone. Haemodynamic parameters (stroke volume index, cardiac indices, oxygen delivery, systemic vascular resistance and pulmonary arterial pressures) were significantly improved with milrinone. However, results were available for the first 24 hours of therapy.

The other 2 LOE 1 studies looked at use of terlipressin (Yildizdas D ’08) and vasopressin (Choong K ’09) in context of septic shock resistant to fluid and catecholamine therapy. Yildizdas showed that terlipressin improved clinical haemodynamic measures of cardiac output (mean arterial pressures, heart rate), oxygen indices (P/F rations) and length of ICU stay. However, no measureable difference was noted in mortality between 2 groups. Choong study was a multicenter, prospective randomized, blinded study that looked at vasodilatory septic shock patients on high doses of catecholamines. She found no difference in primary outcomes measures (time to haemodynamic stability, inotropes scores, urine output and mean arterial pressures) or secondary outcomes (LOS, mortality, ventilator free days or organ injury scores). In addition, there was a trend to increased mortality to treatment group.

**Paediatric observational studies**

Majority of the paediatric data in observational studies or case reports concerns use of vasopressin or terlipressin in population of catecholamine resistant vasodilatory shock. Terlipressin has been shown to achieve haemodynamic benefits and/or improved clinical state (e.g. urine output, cerebral perfusion pressures) that allows physicians to decrease or cease concurrent inotropes support. No mortality benefit was shown (Matok ’05; Fillipi ’08; Michel ’07; Papoff ’07; Salluh ’07; Zeballos ’06). Vasopressin infusion has also been studied in the same population with similar results (Di Chiara ’08; Jerath ’08; Lechner ’07; Liedel ’02; Masutani ’05; Rodignex-Nunez ’04 & ’06; Rosenzweig ’99; Tobias ’02; Vasudevan ’05). Therefore, there are limited data to suggest transient beneficial effects of vasopressin or terlipressin in paediatric vasodilatory shock.

There are also many small case reports that suggest various drugs may have short term haemodynamic effects in various causes of vasodilatory shock resistant to catecholamine: septic shock (Moffet ’06 [fenoldopam]; Perkin ’82 [dobutamine]; Ringe ’03 [enoximone]; Tounenx ’08 [noradrenaline]; Yunge ’00 [angiotensin II]), anaphylactic shock (Momeni ’07 [isoproterenol]).

An observational study by Ceneviva ’98 suggests that paediatric sepsis physiology runs a dynamic course during the stay in PICU and regular serial assessments is needed to titrate the type of inotropes or vasopressor therapy to achieve optimal haemodynamics.

**Acknowledgements:**

Ms Peggy Fong (Medical Librarian)
KK Women’s and Children’s Hospital
Citation List


   LOE 1: Designed as prospective, randomized, placebo controlled interventional and double blinded study on septic patients with non-hyperhemodynamic shock with placebo and interventional drug (milrinone). Thus the patients were not analyzed in the assigned randomized group. The patients were fluid resuscitated and remained in shock despite catecholamine (dopamine, dobutamine and epinephrine) before initiation of trial. The study showed the inodilator, milrinone, to improve hemodynamic indices (cardiac index, stroke volume index, and both ventricular stroke volume and oxygen delivery) in patients fluid resuscitated and in shock despite administration of catecholamine. There were statistical significant changes in CI, Left ventricular stroke work index (LVSWI) and oxygen delivery. SVRI was reduced. Mortality was 33% in the study population where the Pediatric risk of mortality score (PRISM) predicted a mortality of 75%. The patients were followed up for the duration of the infusion of milrinone. No data on mechanical ventilation was available but the authors did comment that there were no adjustments made. Fluid resuscitation was standardized.


   LOE 4: Authors reported case series of fluid refractory septic shock and documented 3 distinct groups of septic patients. Group I had low cardiac index which responded to inotrope support. Group II had high cardiac index and low SVRI requiring vasopressor instead of inotropes. Group III had both decreased CI and SVRI that needed both inotrope and vasopressor. Subsequently, Group I needed vasodilators to improve shock and Group II needed inotrope to support cardiac output. 58% of patient belonged to Group I with lowest mortality of 72% whilst the remaining 2 groups accounted for 20% and 22% of population with mortality at 90% and 91% respectively. Overall, 78% survived to PICU discharge but no data on historical controls were made available. Improvements in CI were seen in Group I and III after 48 hours of therapy. Group II with hyper hemodynamic shock had CI reduced to target level. This is the only paper that suggested septic shock maybe heterogeneous in hemodynamic disturbances and therefore there is a need to tailor and adjust inotropic, vasopressor and vasodilator support with time. This requires advanced hemodynamic monitoring to be made available to all septic patients. Fluid resuscitation details were provided but no data on mechanical ventilation was given.


   LOE 1: Well conducted MCT on vasopressor agents with highest number of paediatrics patient recruited (n=65) to date. No benefit was seen in terms of primary outcome measures (time to haemodynamic stability, MAP improvements, urine output and vasoactive scores) and secondary outcomes (mortality, LOS, organ-free days and ventilator-free days). Authors comment there was a statistically non-significant trend to higher mortality in vasopressin treated group.

LOE 4: Case report of a child with epinephrine-refractory anaphylactic shock (heparin) responding to vasopressin infusion.


LOE 4: Case report of a neonate with catecholamine resistant shock after neuroblastoma surgery but responded well to terlipressin infusion.


LOE 4: This paper reported use a phosphodiesterase III inhibitor, amrinone in an open label pharmacodynamics study of the drug in single centre with septic shock refractory to fluid resuscitation and catecholamines. They showed an increase (42%) in cardiac index and oxygen delivery at 15mcg/kg/min of amrinone infusion. Decreased in SVRI (31%) were observed in these patients treated with amrinone infusions up to dose of 15mcg/kg/min. These changes were statistically significant compared to preinfusion values. The follow up was for the duration of drug administration. No data on mechanical ventilation was available and the extent of fluid resuscitation in all patients were not compared or standardised.


LOE 4: Retrospective review of 117 children (cardiac and noncardiac origin) with vasodilatory shock diagnosed on 2D echocardiography. Vasopressin decreased inotropic requirements in children with advanced vasodilatory shock of non cardiac origin but had reduced urine output and abnormal liver function tests with prolonged or higher doses of vasopressin infusion. Platelet counts were also reduced.


LOE 4: 17 neonates with vasodilatory shock on multiple inotropes and vasopressors after cardiac surgery had improved blood pressure and reduction of concurrent vasopressors doses. No peripheral ischaemia or vasoconstriction noted.


LOE 4: Case reports of 5 children with good response to vasopressin for catecholamine resistant vasodilatroy shock.

LOE 1: Designed as prospective, randomised, placebo controlled interventional and double blinded study on septic patients with non-hyperhaemodynamic shock with placebo and interventional drug (milrinone). Thus the patients were not analysed in the assigned randomised group. Whether fluid resuscitation was standardised was not commented in the second paper. The patients were fluid resuscitated and remained in shock despite catecholamines (dopamine, dobutamine and epinephrine) before initiation of trial. The study published showed the inodilator, milrinone, to increase, by 20%, CI and 20% reduction in SVRI. However, the aim of the paper was also to profile the dosing of milrinone to give achieve positive haemodynamic effects. The patients were followed up for the duration of the infusion of milrinone. No data on mechanical ventilation was available.


LOE 4: 12 Children with catecholamine resistant vasodilatory shock from diverse etiology was shown to have low plasma vasopressin levels which increased during vasopressin infusion. Vasopressin infusion was generally associated with increased blood pressure and urine output in some patients. No side effects were noted.


LOE 4: Terlipressin improves hemodynamics (increase MAP, reduction in HR, reduction or stoppage of eprinephrine infusion, respiratory function (reduction in oxygenation index) and renal function (urine output) in 14 children with catecholamine resistant septic shock.


LOE 4: Case report of 1 child with septic shock on multiple inotropes and furosemide infusion for oliguria. Fenoldopam increased increased urine output.


LOE 4: Case report of successful use of isoproterenol on a child for bradycardiac due to anaphylactic shock resistant to epinephrine and fluid resuscitation.

LOE 4: Case report of 2 children with catecholamine resistant vasodilatory sepsis shock with good response to terlipressin.


LOE 4: This paper analysed the effect of dobutamine in shock in a single center study of 33 patients with both septic and cardiogenic shock. The authors in this study did report their results for septic patients separately and were able to analyse the responses independently. They found improvement in cardiac index, LVSWI and stroke index (SI) of up to 22% at dose of 7.5 mcg/kg/min of dobutamine infusion. There were no changes in SVRI. Mortality was 67% but the authors did not report any historical control data or disease acuity score e.g. PRISM for comparison. There was no mention of other clinical outcomes. The treatment pre-intervention that the study population received was not detailed and follow up was taken until the time of completion of dobutamine. Researchers found an incremental response to dobutamine up till 7.5 mcg/kg/min. Mechanical ventilation data and the amount fluid resuscitation each patient received was not detailed.


LOE 4: Case report of 1 child treated with terlipressin boluses for septic shock with decreased SVRI despite norepinephrine infusion. Treatment resulted in temporary increase in systemic vascular resistance for several hours.


LOE 4: In two children with refractory septic shock resulting in cardiovascular collapse from meningococcemia sepsis, enoximone boluses and drip were associated with improved hemodynamics (blood pressure and shorten fraction) and immediate reduction in concurrent catecholamines needs.


LOE 4: Case study of 4 children with catecholamine-resistant septic shock that had improved haemodynamics after terlipressin infusions.


LOE 4: In 16 children with refractory septic shock, terlipressin increased blood pressure and decreased vasopressor requirement. 4 survivors had major amputation whilst 1 needed minor amputations.

LOE 4: Case report of 11 children with vasodilatory shock after cardiac surgery on multiple inotropic support. 9 of the patients had normal heart function on 2D echocardiography. Vasopressin infusion was associated with increased mean arterial pressure, decreased inotrope score and improved mixed venous oxygenation. No change in urine output and serum bicarbonate noted.


LOE 4: Case report of catecholamine resistant shock from trauma with severe traumatic head injury. Terlipressin infusion was associated with improved mean arterial pressure, reduction in concurrent epinephrine infusion, improved cerebral perfusion pressure and mixed jugular venous saturation.


LOE 4: Case report of 2 children with catecholamine vasodilatory shock from poisoning and sepsis. Vasopressin infusion improved haemodynamics.


LOE 4: This paper investigated 22 term newborns with septic shock despite fluid resuscitation and use of dopamine/dobutamine and showed that nor adrenaline infusion increase cardiac index, improve blood pressures, reduce serum lactate levels and increase urine output. Overall mortality in this group was 15% with no historical controls suggested nor any neonatal severity disease score mentioned for the study population. Fluid resuscitation was detailed and although mechanical ventilation data was recorded for the study period, none were described in the paper. Haemodynamic data was limited to clinical indices including blood gas and lactate reports with no measures of direct cardiac index or other variables e.g. SVRI made.


LOE 4: Three children with refractory septic shock had increased blood pressure and decreased need for concurrent inotropes after starting vasopressin.


LOE 1: Single centre randomised controlled non blinded trial to study effect of terlipressin on patients with catecholamine refractory septic shock. 58 patients were enrolled and both intervention and control group were comparable. Confounders were accounted for and follow up was adequate. Terlipressin infusion was associated with improved mean arterial pressure, reduced heart rate, \( \text{PaO}_2/\text{FiO}_2 \), length of PICU stay. No mortality differences noted.

LOE 4: Angiotensin infusion improved hemodynamics and decreased other inotropes in 2 children with severe septic shock.


LOE 4: Terlipressin infusion temporarily improved hemodynamics and decreased inotropes in a child with refractory septic shock. Intense vasoconstriction was reported.