WORKSHEET for Evidence-Based Review of Science for Emergency Cardiac Care

Worksheet author(s)

Sharon Kinney

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Clinical question.

In infants and children with shock (P), does the use of specific diagnostic tests [mixed venous oxygen saturation, pH, lactate] plus clinical assessment to guide management (I), as opposed to clinical assessment alone to guide management (C), improve outcome (survival) (O)?

Is this question addressing an intervention/therapy, prognosis or diagnosis? Intervention/therapy

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

Conflict of interest specific to this question

Do any of the authors listed above have conflict of interest disclosures relevant to this worksheet? No

Search strategy (including electronic databases searched).

Medline (ISI web of knowledge)
“Shock” as MeSH AND “goal directed” or “goal-directed” as Topic (textword) AND limited age to “all child-0-18 years” (15 hits)
“Shock” as MeSH AND “central venous oxygen saturation” or “mixed venous oxygen saturation” as Topic AND limited age to “all child-0-18 years” (11 hits)
“Shock” as MeSH AND “blood gas analysis” as MeSH AND limited age to “all child-0-18 years” (48 hits)
“Shock” as MeSH AND “pH” as Topic AND limited age to “all child-0-18 years” (54 hits)
“Shock” as MeSH AND “lactate” Topic AND limited age to “all child-0-18 years” (124 hits)
“Shock” as MeSH AND “cardiac output” as MeSH or “cardiac index” AND limited age to “all child-0-18 years” (110 hits)
Similar strategies as above repeated and limited to adult age group and randomized controlled trials (64 hits)

“Heart disease” as MeSH AND “central venous oxygen saturation” or “mixed venous oxygen saturation” as Topic AND limited age to “all child-0-18 years” and MeSH heading refined by (Heart Defects, congenital) (44 hits).

EMBASE repeated similar strategies used above – revealed no new articles

AHA Endnote Master Library, Cochrane database, review of references from articles and forward search using SCOPUS from relevant articles revealed no new articles

State inclusion and exclusion criteria

Included interventional and observational (prognostic) studies in children “all child-0 to 18 years” and adult RCT’s

Excluded single case studies in all age groups and observational studies in adults except for 1 very relevant cohort study

Number of articles/sources meeting criteria for further review:

23 articles met criteria for review. Of these one was LOE1, one LOE4 and twenty-one LOE5.
## Summary of evidence

### Evidence Supporting Clinical Question

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Rivers, 2001, CE
Nguyen, 2007, C
Duke, 1997, C
Hatherill, 2003,E
Tweedell, 2007, CE
Bradley, 2005, E
Krafte-Jacobs, 1995,C
Hatherill, 1998, C
Pollock, 1985, E,

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

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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  
E = Other endpoint

*Italics = Animal studies*

### Evidence Opposing Clinical Question

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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  
E = Other endpoint

*Italics = Animal studies*
There is only one interventional study that has evaluated the use of specific diagnostic tests and clinical assessment, compared with clinical assessment alone for infants and children with shock. A randomized controlled trial examining the effect of using a goal-directed protocol to achieve a central venous oxygen saturation (ScvO₂) ≥ 70% demonstrated a significant reduction in 28 day mortality amongst children with severe sepsis or fluid refractory septic shock (De Oliveira et al., 2008). In the control group, the protocols (crystalloid, red blood cells & inotrope regime) targeted normal perfusion pressure for age, urine output > 1ml/kg/hr, CRT < 2 seconds and normal pulses. The study was conducted in two university affiliated hospitals in Brazil, therefore the findings may be more applicable to developing countries. Of note, was the high baseline mortality (57%) prior to the study which reduced during the study period to 39% for the control group (12% for the intervention group) suggesting a treatment effect of implementing goal-directed protocols without any ScvO₂ monitoring. Limitations of the study included the inability to blind the clinicians to the intervention, and stopping the trial early after an interim analysis showed that the intervention group had improved survival. Stopping the trial early is likely to overestimate the treatment effect.

There were some paediatric prognostic studies (cohort or case series) that indicated lactate (Duke et al., 1997; Hatherill et al., 2003) and gastric tonometry (Hatherill et al., 1998; Krafte-Jacobs et al., 1995) were beneficial in discriminating high risk patients, however, there have been no prospective controlled trials targeting these parameters in children with shock. Similarly, mixed venous oxygen saturation has identified infants at risk of early mortality and has been beneficial in guiding postoperative management following 1st stage repair of Hypoplastic Left Heart Syndrome (Bradley et al., 2005; Tweedell et al., 2007). Because all of these studies were not testing an intervention or were conducted within a different population, they have been regarded as level 5 evidence.

There were a number of adult studies that were also related to the worksheet question and apart from one cohort study (Nguyen, 2007) only randomized controlled trials were included in the review. These studies were also regarded as Level 5 evidence and the findings were varied. The majority of the adult studies found no difference in mortality and/or other outcomes with therapies targeting a range of haemodynamic parameters, such as oxygen delivery index, cardiac index, ScvO₂, SvO₂ (mixed venous) and intrathoracic blood volume (Alia et al., 1999; Csontos et al., 2008; Gattinoni et al., 1995; Holm et al., 2004; Tuchschmidt et al; 1992; Yu et al., 1993). The main limitation of these studies was the small sample size, except for the larger multicentre trial involving 56 ICU’s in Italy (Gattinoni et al., 1995), although the sample was a heterogeneous group (N=762) including patients not necessarily in shock. Some of these adult studies were targeting supranormal haemodynamic parameters and it was evident that the treatment goal was not always achieved for the intervention group and likewise, the control group often attained supranormal values (Alia et al., 1999; Gattinoni et al., 1995; Tuchschmidt et al; 1992; Yu et al., 1993). One adult randomized controlled trial found that therapies targeting higher than normal cardiac index, oxygen delivery and consumption was detrimental, resulting in increased mortality (Hayes et al., 1994). Another adult randomized controlled trial found increased mortality amongst a group that were treated to SvO₂ and Do₂ goals compared to the group that were treated to a measure of peripheral perfusion as determined by transcutaneous monitoring of oxygen pressure (Yu et al., 2007). However, for both of these latter trials the treatment effect may have been overestimated as the trials were stopped early after an interim analysis indicated that the outcome was worse for the intervention groups.

The two adult studies that support the use of goal-directed therapy, were both conducted in the emergency department setting, suggesting that early goal-directed therapy, which includes normalization of ScvO₂, maybe the key to improving outcomes. Rivers et al., (2001) in a good quality randomized controlled trial, found that in-hospital mortality was significantly lower (30.5% versus 46.4%) for the intervention group that used a protocol guided by continuous ScvO₂ monitoring for at least 6 hours in the ED (RR=0.58; 95% CI: 0.38, 0.87, p=0.009). Nguyen, et al. (2007) in a cohort study, evaluated compliance and outcomes associated with implementing a sepsis bundle. Monitoring ScvO₂ and lactate were two of the five quality indicators that comprised the bundle. Multivariable analysis identified the completion of early goal-directed therapy at six hours as the only quality indicator associated with decreased mortality (OR=0.36; 95% CI: 0.17, 0.79, p=0.01). No individual quality indicator was associated with decreased mortality.

In summary, early resuscitation with goal-directed therapy that includes targeting of ScvO₂ appears to improve outcomes for patients with septic shock. The cost of the technology to continuously monitor central venous oxygen saturation may prohibit its use in some countries, but it is possible that intermittent measurements via blood gas analysis from a central venous line may also be beneficial.

Acknowledgements:
Nil
Citation List


LOE5 fair, adult RCT neutral evidence for ICU mortality and organ dysfunction in tertiary hospital in Spain. All patients treated with conventional therapies, and the control group targeted Do$_2$I of >330 mL/min/m$^2$ and the intervention group Do$_2$I of >600 mL/min/m$^2$. Although the mean CI was significantly higher in the intervention group it did not significantly affect oxygen delivery. No significant differences in mortality but trending towards higher mortality in intervention group. Post hoc power analysis demonstrated sample size underpowered to detect difference. Suggested explanations for failure of intervention were treatment starting too late & failure to achieve treatment goals with many patients not capable of achieving supranormal values.


LOE5, case series, poor, supportive evidence for identifying 30 day mortality using (MvO$_2$) in postop cyanotic infants with HLHS. No difference in mean systemic saturation between survivors and non-survivors, but MvO$_2$ significantly lower during first 48 hours for non-survivors (p<0.01).


LOE 5 fair, observational cohort study, neutral evidence. No interventions but used ScvO$_2$ as part of observations that helped distinguish different patterns of shock for the 2 groups- community acquired infection or CVC infection.


LOE 4, fair, supportive evidence for decreased 28 day mortality. PA catheters placed within 6 hours of children with fluid refractory shock and measures of CI & SVR were used to direct inotrope, vasopresor & vasodilator therapy. Three haemodynamic states identified and patterns noted to change over time.


LOE5, poor adult RCT, neutral evidence for mortality, supporting evidence for targeting ITBVI amongst burns patients in critical care unit in Hungary University hospital. Small sample size (N=24) calculated for 4.5% difference in ScvO$_2$. Control group targeted hourly urine output. Intervention group targeted lower/normal intrathoracic blood volume index between 800 and 830mL/m$^2$ to avoid IV fluid overload. Lactate Ringers fluid used for both groups and noradrenaline used to maintain MAP > 70 mm/Hg. ScvO$_2$ was significantly higher for intervention group at 24 hours, but not at 48 or 72 hours. MODS was significantly decreased for intervention group at 48 and 72 hours but not at 24 hours. No significant differences in ICU mortality, 4/12 intervention group & 5/12 control group, but not powered to detect change in mortality


LOE1 fair, supporting evidence for decreased 28 day mortality, & less organ dysfunction

Initial power analysis determined sample size 268 patients but study stopped after interim analysis by Safety & Monitoring committee of 102 patients- stopping trial early at risk of overestimating treatment effect. Clinicians not blinded to intervention. Trial conducted at 2 university affiliated hospitals in Brazil with high baseline mortality high (57%) prior to study. Control group younger 4.5 years v 6.5 yrs, otherwise groups similar. Intervention group – continuous ScvO$_2$ monitoring targeting ScvO$_2$ ≥ 70% with specified crystalloid, RBC & inotrope regimen. Control group – ACCM/PALS protocols targeted normal perfusion pressure for age, urine output > 1mL/kg/hr, CRT < 2 secs, and normal pulses. ScvO$_2$ was calculated at intermittent intervals via blood gas analysis and values recorded but not used to guide treatment. Primary outcome 28 day mortality significantly lower in intervention group -Hazard ratio 3.78; 95% CI:1.58, 7.52, p=0.002, NNT = 3.6. Goal directed resuscitation for ScvO$_2$ independently associated with decreased mortality - Odds ratio 0.18; 95% CI:0.05, 0.69, p=0.01. pH not independently associated with 28 day mortality.

**LOE5, small prognostic case series, poor, neutral evidence. All patients survived.**


**LOE5, prognostic, cohort study, fair, supportive evidence for identifying hospital mortality. A blood lactate level > 3 mmol/L, discriminated survivors earlier in illness than heart rate, BP and pH. At 12 hours if lactate > 3, Odds ratio for death =7.5; 95% CI:1.4-40.2, wide CI, small sample size (N=31). Gastric tonometry tube not tolerated in children who were not heavily sedated.**


**LOE5 E – adult, fair multicentred RCT, neutral evidence for ICU mortality, 6 month mortality & organ dysfunction. Heterogeneous sample from 56 ICU’s in Italy including those with massive blood loss, septic shock or sepsis syndrome, acute resp failure ± COPD or multiple trauma. 3 arms -normal CI (control), supranormal CI & normal SvO2 ≥ 70% (mixed venous). 4 units didn’t randomly assign pts to supranormal CI group, but results unchanged when accounting for this. Interruptions to protocol similar for each group for technical problems with PA catheter. The % who reached targeted parameters was lower in normal SvO2 ≥ 70% group compared with control group (p<0.001). No difference in ICU death when comparing SvO2 ≥ 70% group and control group, RR=1.16; 95% CI:0.82, 1.64.**


**LOE5 small prognostic case series, poor, supportive evidence for gastric tonometry as predictor of mortality. Found to be better predictor than standard arterial pH or lactate levels.**


**LOE5 prognostic study, poor, supporting evidence for lactate as a marker of 24 hour mortality amongst children with shock in PICU in South Africa.**


**LOE5, adult RCT, fair opposing evidence for hospital and ICU mortality. Examining effects of targeting increased cardiac index, oxygen delivery and consumption in heterogeneous group of ICU patients (most had sepsis syndrome, septic shock and ARDS). Intervention group received dobutamine 5-200 mcg/kg/min targeting Do2 600ml/min/m2, Vo2 170ml/min/m2 & CI 4.5 L/min /m2. Control group received dobutamine if CI < 2.8 L/min /m2. Power analysis determined sample size 130 patients in each group but study stopped early after 2nd interim analysis of 100 patients (50 in each group). Therefore, there is a risk of over estimating treatment effect. ICU and hospital mortality higher in the treatment group: ICU mortality was 50% versus 30% (95% CI:1.2, 38.8) and hospital mortality 54% versus 34% (93% CI:0.9, 39.1).**


**LOE5 good adult RCT, neutral evidence for hospital mortality. Conducted in Burns ICU in Germany. Intervention group – targeted invasive haemodynamic goals including intrathoracic blood volume > 800mL/m2 & CI > 3.5 L/min/m2 with crystalloids & colloids after 24 hours, and adrenaline for low CI & noradrenaline for low SVR. Control group resuscitated according to usual Baxter formula targeting some haemodynamics eg. CVP, MAP. Other invasive haemodynamic measurements made for control group but stored in software and clinicians blinded to data. No difference in hospital mortality - treatment group 32% versus 40% for control group (p=0.556). Treatment group received significantly more fluids.**

LOE5 small prognostic case series, poor, supportive evidence for gastric tonometry as predictor of mortality. Only 8 patients in series. pH$i$ correlated with lactate levels, but not with other haemodynamic variables.


LOE5 prognostic study, case series, neutral evidence for hospital survival. Described cardiovascular variables in 12 survivors and 6 nonsurvivors of meningococcal shock in French PICU. No significant difference in HR, CI, SI & echo shortening fraction between groups. Significant difference in wedge pressures, MAP, & SVR.


LOE5 adult cohort study, good, supportive evidence for hospital mortality. Trial evaluating compliance and outcomes associated with implementing sepsis bundle in ED setting in large tertiary hospital in USA. Monitoring lactate clearance and ScvO$_2$ were two of the five quality indicators for bundle. Multivariable analysis identified completed early goal directed therapy at 6 hours as the only quality indicator associated with decreased hospital mortality (OR = 0.36; 95% CI: 0.17, 0.79, p=0.01)


LOE5 poor, case series, prognostic study supportive evidence for identifying variables associated with improved ICU survival. Expansion of a previous 1984 study. Determined 8 therapeutic goals for managing pediatric shock based on the distribution of a number of either normal variables or median values of survivors.


LOE 5, good RCT in adult population, supportive evidence for decreased hospital mortality & multiorgan dysfunction. Trial partially blinded – clinicians involved in treatment after patients leaving ED were unaware of treatment group. Setting large tertiary ED in USA, Excluded those < 18 years. Control group – treated according to defined standard protocol targeting CVP, MAP and urine output. Intervention group – continuous ScvO$_2$ monitoring for 6 hours in ED targeting ScvO$_2$ ≥ 70% with specified interventions as well as standard protocol. Monitoring of ScvO$_2$ discontinued prior to transfer to ICU or inpatient bed. In-hospital mortality significantly lower in intervention group (30.5 % vs 46.5%), RR = 0.58; 95% CI: 0.38, 0.87, p=0.009.


LOE5 case series, poor, neutral evidence. Investigating relationship CRT & temperature gap and various haemodynamic parameters. Weak relationship of CRT to lactate and SVI amongst the group of general PICU patients (most had septic shock).


LOE5 adult RCT, poor, neutral evidence for hospital mortality. No power calculation to determine sample size. Both groups followed same shock protocol except the targeted CI was higher for the Intervention group. Mortality data in abstract (likely error) opposite to what was reported in main paper – should read ‘Seventy-two percent of the NT patients (control) died vs 50 percent of the OT patients (intervention group) (p=0.14). Targets not reached for some in intervention group & some in control group had generated higher CI.'

LOE5, fair, prognostic cohort study, supportive evidence for decreased hospital and 30 day mortality & other complications, amongst infants with cyanotic CHD following stage 1 repair HLHS. Evaluating range of haemodynamic variables, including Svo₂ (SVC, mixed venous) during the first 48 postoperative hours that could identify three groups - uncomplicated survival, survival with complications (eg. ECMO or CPR) and early death. Usual post-op management target Svo₂ >50%. Lower Svo₂ only independent predictor of death. Svo₂ was higher in uncomplicated survivors compared with survivors with complications, and also survivors with complications had higher Svo₂ than those that died (p=0.03).


LOE5, poor adult RCT neutral for 30 day mortality, organ dysfunction, hospital stay & hospital costs. Small sample size (N=67, no power calculation), 5 removed from study & not included in intention-to-treat analysis, unknown concealment of randomisation and unlikely blinding of clinicians. Subgroup analysis indicated that patients with supranormal Do₂I values (>600mL/min/m²) from either intervention or control group had significantly lower mortality (p=0.001) than those with normal Do₂I values.


LOE5, fair adult RCT, opposing evidence for hospital mortality and mortality from MSOF. The intervention was targeting a measure of adequate tissue perfusion as calculated from continuous transcutaneous pressure (PtcO₂) monitoring and a test that involved the administration of 100% oxygen. The comparison group targeted mixed venous saturation (≥70%) and DO₂ goals. As PtcO₂ monitoring is non-invasive and relatively easy to implement it could be considered as “clinical assessment”. The average time to study enrollment was 11 and 12 hours for each group therefore may not reflect the early resuscitation period. Partial blinding of investigators. No intention-to-treat analysis (1 protocol violation & removed from PtcO₂ group). Trial stopped early after interim analysis and therefore at risk of overestimating treatment effect.