Shock Index Values and Trends in Pediatric Sepsis: Predictors or Therapeutic Targets? A retrospective observational study.

Samiran Ray[1,5], Mirjana Cvetkovic[2], Joe Brierley[1], Daniel H. Lutman[1], Nazima Pathan[3], Padmanabhan Ramnarayan[1,4], David P. Inwald[4], Mark J. Peters[1,5]

Author affiliations:

[1] Children's Acute Transport Service, Great Ormond Street Hospital NHS Trust, London

[2] University Hospitals of Leicester NHS Trusts, Leicester

[3] Addenbrookes Hospital NHS Trust, Cambridge

[4] Imperial College Healthcare NHS Trust, London

[5] University College London Institute of Child Health, 30 Guildford Street, London WC1N

Corresponding author:

Dr Samiran Ray MBBChir, MA

Children's Acute Transport Service,

Great Ormond Street Hospital,

London WC1N 3JH

Tel: (044) 2074059200

Fax: (044) 2078297830

e-mail: Samiran.ray@gosh.nhs.uk

Conflict of Interest: No conflicts of interest to declare.

Running head: Shock index in pediatric sepsis prior to PICU

Word count: 3751

Abstract

Background: Shock index (SI) (heart rate/systolic blood pressure) has been used to predict outcome in both adult and pediatric sepsis within the intensive care unit (ICU). We aimed to evaluate the utility of SI prior to pediatric ICU (PICU) admission.

Methods: We conducted a retrospective observational study of children referred to a pediatric intensive care transport service (PICTS) between 2005 and 2011. The predictive value of SI, heart rate and blood pressure at three pre-specified time points (at referral to PICTS, at PICTS arrival at the referring hospital, and at PICU admission), and changes in SI between the time points, were evaluated. Death within the first 48 hours of ICU admission (early death) was the primary outcome variable.

Results: Over the seven-year period, 572 children with sepsis were referred to the PICTS. Thirty-nine children died prior to transport to a PICU, while 474 were transported alive. Adjusting for age, time-points and time duration in a multi-level regression analysis, SI was significantly higher in those who died early. There was a significant improvement in SI with the transport team in survivors but not in non-survivors. However, the predictive value of a change in SI for mortality was no better than either a change in heart rate or blood pressure.

Conclusions: The absolute or change in SI does not predict early death any more than heart rate and systolic blood pressure individually in children with sepsis.

Keywords: shock; sepsis; children; transport; predictors; physiology

Introduction

Shock index (SI), the ratio of heart rate (HR) and systolic blood pressure (SBP), is used as a composite marker to describe myocardial and vascular dysfunction. Unlike heart rate and blood pressure alone, SI may distinguish shock from states of over/under sedation, sympathetic suppression and anti-cholinergic use, all of which can confound assessments during critical illness.

Shock index predicts clinical outcomes and the required level of care in adults (1-5). However, the normal values for SI are not easy to define in childhood. Age-standardised heart rate data are available for children (6). Blood pressure data across the age spectrum of pediatric care are either only available based on height centiles, or not available for the entire age spectrum (7-9). Height measurements are not routinely undertaken in emergency departments, and may not be easy to estimate, especially in the context of chronic illness. Age-standardised SI values have been described (10), but only in children above 8 years of age. Given that infants constitute the majority of critically ill children, the use of shock index in younger children has not been adopted widely (11).

Nevertheless, SI has found use in pediatric critical illness. The current American College of Critical Care Medicine haemodynamic support guidelines recommend SI as a therapeutic target (12). Carcillo et al (13) demonstrated that SI improves in response to therapeutic interventions such as fluid resuscitation and use of vaso-active drugs. The potential utility of SI in risk stratification in trauma has been demonstrated (14-16). In pediatric sepsis, two studies (17-18) support the predictive value of an 'abnormal' SI, using age-stratified cut-offs, for early death after pediatric intensive care unit (PICU) admission.

Deaths from pediatric sepsis predominantly occur early in the course of a PICU admission (19) and are affected by treatment prior to admission (20-21). Therefore the utility of a

mortality predictor in PICU may be limited. Furthermore, the value of SI as a therapeutic target is limited following admission to PICU, where a greater amount of data become available with time (end-organ function) and resources (investigation results, haemodynamic monitoring). However SI may have a role to play as both an outcome predictor and a therapeutic target *prior* to PICU admission. In particular there is potential utility in the transport environment where monitoring data may be relatively limited.

We hypothesised that the SI prior to PICU admission is a better predictor of outcome in children with sepsis compared to heart rate and blood pressure individually. Furthermore, we hypothesised that a change in SI has greater predictive value rather than absolute SI values. This is likely given that a change in physiology will reflect both severity of disease and treatment given. Change in SI has the advantage of not requiring age standardisation, with each patient being their own control subject. In addition, we explore the effect of vas-active drugs on the SI in this setting.

Materials and Methods

Patients

We conducted a retrospective review of transport case notes for all children referred to the Children's Acute Transport Service (CATS), London, with a diagnosis of sepsis, between 1st January 2005 and 31st December 2011. The case note review was initially conducted to characterise the timing of death in children with sepsis (the data collection methods have been previously reported) (19). The dataset was then augmented with further data extraction and case note review for this study.

CATS is a centralised, specialist pediatric intensive care transport service (PICTS) serving a population of approximately 2 million children in North London and East Anglia. Referrals are made for both advice and transport to intensive care. Local hospital teams will start the process of stabilisation in majority of cases as previously described (22). CATS will provide ongoing remote advice, until a team is on-site.

Search terms '*sepsis'*, '*severe sepsis'*, '*meningococcal sepsis'* or '*septic shock'* were used to interrogate an electronic database of all cases referred to the service. The diagnosis of sepsis was made by the referrer. Notes were screened by two intensive care physicians (SR, MJP) for diagnostic accuracy, and children who did not fulfil the International Pediatric Sepsis Consensus Conference definition of sepsis at referral (24) were not included.

All patients transported to PICU, and those who died in the local hospital prior to transport, were included for analysis.

Data

Demographic and operational data were collected from case notes of each patient. Physiological data were noted at three pre-specified time points: at referral to the PICTS (**R**), at transport team arrival to the local hospital (**A**) and at PICU admission (**P**). Data included heart rate; systolic, diastolic and mean blood pressure; central capillary refill time; pH; lactate; and base excess (blood gas data was approximated to the closest available prior time point). Data were collected for interventions undertaken by the local hospital and transport team, from the acute deterioration till PICU admission. Outcome data were collected from routine follow-up undertaken by the transport service, and hospital records, up to a year post referral.

Data definitions

SI was calculated as the heart rate divided by systolic blood pressure. Mode of blood pressure measurement (invasive versus non-invasive) was not regarded. For unrecordable blood pressure a systolic of 30 mmHg was used (as used for the Paediatric Index of Mortality Score) (24). For an absent heart rate (i.e. during cardiac arrest), a heart rate of 0 was used. Therefore during an arrest the shock index was 0. Patients who died with the transport team prior to PICU admission had 'P' values as those at time of death i.e. heart rate of 0, and shock index as 0. Values of 0 were removed for trend or multivariate analyses (used only for description of absolute values). An improvement in SI was defined as a decrease in SI between PICTS referral and PICU admission (both values had to be available – therefore children who died prior to PICU admission were omitted in analysis exploring change in SI). An improvement in heart rate was defined as a decrease between PICTS referral and PICU admission; an improvement in systolic blood pressure as an increase.

Death was categorised as early death (within the first 2 days of referral) or late death (after 2 days post referral, up to 1 year post admission). Late death in this cohort occurred mainly in children with co-morbidities as previously described (19). In these children life sustaining treatment was often withdrawn due to the burden of disease, therefore the pre-existing co-morbidity contributes to outcome. Since SI in the pre-PICU care was most likely to influence early death, this was used as the primary outcome measure.

Statistical analysis

The distribution, sensitivity, specificity, predictive values, likelihood ratios and the area under the receiver operator characteristic (ROC) curve for early death were calculated for (a)

absolute values for SI, heart rate and systolic blood pressure, and (b) changes in SI, heart rate and systolic blood pressure. A multi- level regression model was used to analyse the association between SI, heart rate and systolic blood pressure and early death. Transport time-points, time interval between time-points (as a linear variable with referral being time=0), age categories (<1 year, 1-2 years, 2-5 years, 5-12 years, >12 years) and outcome were used as fixed effects variables, while a unique patient identifier was used as the random effect variable. The dose of dopamine, epinephrine and norepinephrine at each of the three time-points were included in the model to explore the effects of vaso-active drugs. Results are expressed as SI standardised to the age category of <1 year and unit time (decimalised unit of 1 day).

The study was registered with the Institutional Audit Department (Project ref 1014) as a wider service evaluation of the management of sepsis. It was discussed with the Bloomsbury Research Ethics Committee who waived a requirement for formal review.

Results

Six hundred and thirty three children were referred to PICU with a referral diagnosis of sepsis in the 7 year period. Hospital outcome data were not available for 61/633 children (9.6%): these children were not included in further analysis. Of the remainder, 132/572 (23.1%) children died in hospital, with 82/132 (62.1%) occurring within the first two days of referral. Data on deaths beyond hospital discharge were not available.

Four hundred and seventy four children were transported to PICU, while 39 children died in their local hospital (figure 1). Three hundred and sixty four children were started on a vaso-active drug prior to admission to PICU. The characteristics of patients are described in table

1. This cohort has previously been presented to characterise the timing to death in pediatric sepsis (18).

1) Absolute shock index, heart rate and blood pressure values as a predictor of early mortality

The distribution of absolute values of shock index, heart rate and systolic blood pressure according to (a) transport time points, and (b) outcomes, are shown in figure 2. The distribution of heart rate shifts to the right between referral (R) and transport team arrival (A), and to the left between team arrival (A) and patient admission to PICU (P). This suggests that the heart rate increases between R and A, and decreases between A and P. Systolic blood pressure is similar between R and A, but then increases from A to P. The distribution of SI shifts to the left between R and A, and moves further to the left at P. Therefore SI improves from referral to intensive care to patient admission to PICU. However some of this shift is due to selection effects of deaths prior to PICU admission: SI was calculated as 0 during cardiac arrest. This would have been the case for those children who died before PICU admission (if a child had a cardiac arrest with the transport team and died, this was considered the time of 'PICU admission').

Heart rate and SI are both higher in children who died early compared to survivors (this difference is mitigated by the heart rate and SI being 0 for those who died before PICU admission). Systolic blood pressure distribution seems to be similar, apart from the expected peak around 30 mm Hg in those who died early (where blood pressure was not recordable a value of 30mm Hg was assigned) (figure 2).

The distribution of SI values suggests that a higher absolute SI may predict early mortality. However when directly tested unadjusted absolute values of SI are a poor predictor of early mortality at all time-points: R, A and P. The area under the ROC curve was 0.60 at R, 0.59 at A and 0.63 at P. In comparison, the area under ROC curve for heart rate was 0.54 at R, 0.50 at A and 0.59 at P, and for systolic blood pressure was 0.60 at R, 0.61 at A and 0.73 at P. The systolic blood pressure at patient admission to PICU therefore had the best predictive value for early death compared to both heart rate and shock index (Table 2).

However unadjusted absolute values do not account for age differences, time intervals between the time points, or the effect of vaso-active drugs. Using a multi-level regression model with age, time, transport time-points, dopamine, epinephrine and norepinephrine doses and outcome as fixed effect variables and individual patient identifiers as the random effect variable, SI was significantly higher in those who died early compared with those who survived or died after 48 hours post-admission. This was not the case for heart rate but the systolic blood pressure was lower in those who died early compared the those who survived or died late.

2) Change in shock index, heart rate and blood pressure as a predictor of early mortality:

We hypothesised that the change in SI would perform better as a predictor of early mortality compared to absolute values. Figure 3 shows the distribution of change in SI between time-points and for outcomes. SI improves (more negative) with the transport team, more so than with the local team. However there is very little difference in the distribution of overall change in SI (i.e. between R and P) according to outcome. This would suggest that change in SI may not predict early mortality. However as suggested, the change in SI is different prior to the transport team arrival and with the transport team. This needs to be taken into account:

it is possible that those children that deteriorate first before improving may fare worse than those who consistently improve. Similarly, age and time intervals between the time-points may have an effect on change.

Using a multi- level regression model for each outcome using transport time-points, dopamine, epinephrine and norepinephrine doses, time and age as fixed effect variables and patient identifiers as the random effect variable, we were able to characterise the changes in SI between transport time points (Figure 4). Survivors showed a significant decrease in SI between A and P and no change between R and A (a significant decrease in SI between R and P). Children who died after 48 hours had a similar profile to survivors. SI decreased with time as linear variable, as patients stabilised with resuscitation and intensive care (the variable coefficients with confidence intervals are listed in the supplementary appendix). Both heart rate and blood pressure show similar significant improvement between A and P, with no change between R and A in survivors. Again, there is no such improvement seen in those who died, within 48 hours or beyond.

While the multi-level regression analysis suggests that improvement in physiology between the time-points A and P predicts survival, we wanted to test if this had practical utility for individual patients. The negative predictive value of non-improvement (i.e. predicting survival at 48 hours when the SI improves) is high: 91.3% (95% confidence interval 84.1-95.9%). However the positive and negative likelihood ratios were not significant. The area under the receiver operating curve (ROC) was poor: 0.48 for non-improvement between R and A, 0.60 between A and P and 0.51 between R and P. The values for non-improvement in heart rate and blood pressure were similar (Table 3).

Effect of vaso-active drugs: As some vaso-active drugs are both chronotropic, inotropic and have vasoconstrictor and vasodilatory properties, the effect on SI may be variable. Dopamine,

10

norepinephrine and epinephrine doses at the three transport time-points were used in the logistic regression analyses to explore the effect of these three drugs. Dopamine and epinephrine significantly increased SI. A 1 microgram/kg/min increase in the dopamine infusion increased the SI by 0.01 (95% CI 0.004-0.02), while a 1 microgram/kg/min increase in epinephrine increased the SI by 0.44 (95% CI 0.18-0.70). Norepinephrine did not have a significant effect on SI in this cohort.

Discussion

This study describes the utility of SI as a predictive marker in pediatric sepsis prior to admission to PICU: during referral and subsequent transport. Following multivariate analysis adjusting for age and time, those who die early have higher values of SI at all time-points compared to survivors or those who die late. There is also a significant decrease in SI between referral and drop-off in survivors. However the same pattern of change is seen for both heart rate and blood pressure values individually. When changes in the parameters are compared for predictive value, they all perform similarly: improvement predicts survival, but the areas under the receiver operating curves are poor. Change in physiology performs no better than the absolute values at any of the time points.

Our multivariate analysis is consistent with previous reports that unresolved shock prior to PICU admission is associated with death (19): those who died early had high SI values compared to those who survived or died after 48 hours. Improvement is associated with survival. However on an individual patient basis, the change in SI performs no better than change in heart rate or blood pressure. While improvement predicts survival, with a predictive value of 91.3% for SI, this may not add much utility given that the overall early

survival rate of those children admitted to PICU is 89.7% (425/474). Non-improvement on the other hand does not predict death.

These data open to question the relentless pursuit of 'normal' physiological parameters in sepsis. This is consistent with recent trial evidence in adults, suggesting no improvement in outcome when a higher blood pressure is targeted (26). We speculate that where improvement can be achieved easily, benefits are seen; where they are not, the treatments may not add more value, and may cause harm from multi-organ failure secondary to treatment: as suggested by the results of the FEAST trial and subsequent studies (27-30). Therefore our results suggest the need for refinement in our therapeutic targets. Shock index is unlikely to provide this. What may be necessary is a better description of what is 'normal' in critical illness: what amounts to physiological compensation and what can be tolerated.

For absolute values, only the systolic blood pressure at PICU admission has moderate predictive value for early death. This is consistent with the greater predictive value of blood pressure rather than heart rate, as evident from the use of blood pressure in the pediatric index of mortality score. Absolute values of SI are significantly higher in those who die early once adjusted for age and time in the multi-variate model, unlike heart rate and blood pressure. Age standardised values for shock index may have some value in identifying children who are at risk of death prior to PICU admission. However this needs to be evaluated further and described for a critically ill population. Interestingly, when we used age standardised z-scores for heart rate, as described by Fleming et al (6), the area under the ROC curve performed no better than non-standardised heart rate (0.50, 0.52 and 0.51 at R, A and P respectively). Similarly, when stratified by age categories, neither absolute SI nor change in SI had better areas under the ROC curve, apart from in older children where the numbers were small (therefore confidence intervals were wide).

Some commentators have questioned the effect of vaso-active drugs on SI (22). Vaso-active drugs such as dopamine and epinephrine are chronotropic as well as inotropic. Therefore, it is possible that any predictive value of SI is blunted by the use of vaso-active drugs. Our regression analysis data suggest dopamine and epinephrine increase SI. The effect size is small in both cases. Both drugs are chronotropic, unlike norepinephrine, which does not significantly affect SI. However, when the effect on heart rate and blood pressure of the drugs are similarly analysed the results are less intuitive. None of the agents have a significant effect of the heart rate. Norepinephrine significantly increased the systolic blood pressure – a 1 microgram/kg/min increase in norepinephrine dose increased it the systolic blood pressure by 13.3 mmHg (95% CI 5.5-20.9 mmHg). However dopamine and epinephrine paradoxically decreased the systolic blood pressure. This may suggest a methodological flaw in using single time point infusion rates rather than plasma levels of the drugs, or in using a linear regression model. Examining the effects of the drugs according to the outcomes however suggest that the negative pressor effect of epinephrine is only significant in the children who die early. It is possible that this reflects a practice of using epinephrine late, only once the myocardium is failing irreversibly. On the other hand the negative pressor effect of dopamine is significant in survivors. This may reflect a practice of switching dopamine to norepinephrine (or epinephrine), with a subsequent increase in blood pressure, in children who survive. Further work is needed to explore this hypothesis further.

One observation that is evident from the multi-level regression analysis is that intensive care is able to change the course of shock. With the centralisation of pediatric intensive care in the U.K., intensive care is considered to start with the specialised transport team arrival. In survivors, shock index starts to improve from this point. Even in those who die early the trajectory of shock index is changed. The implication would be to minimise the time to intensive care delivery. However this is a resource limited solution. As we have previously

reported, the local teams are able to undertake most technical intensive care interventions - including over 90% of all endotracheal intubations, and 67% of all central venous catheter insertions (23). The transport team continues to give guidance on resuscitation and stabilisation to the local teams remotely until arrival on-site. Nevertheless the response to treatment appears to be different. This phase of management therefore needs more attention in order to improve outcomes.

Limitations

There are limitations to our study. We used data from a single pediatric intensive care transport service, although patients were transported to several centres. This is a retrospective case note review, and therefore is limited by missing data and the level of detail documented. In particular we do not account for treatment given at each stage of the transport process beyond infusion rates of vaso-active drugs at the three transport time points. Using infusion rates at single time-points does not take into account the plasma levels of these drugs, or assess drug delivery. Other drugs such as sedative agents or analgesics were not taken into account. Pragmatic time-points were chosen to maximise data availability and integrity. Although it would have been useful to compare the performance of SI against other more established variables such as lactate and central venous saturations, these data were largely missing, especially at referral. We also did not have good quality data on temperature. Similarly high temperatures may increase the heart rate, but may be associated with vasoconstriction (in fever), or vasodilation (if heating is external). This will need further evaluation in the future. Finally early death was used as the primary outcome as the effect of SI improvement was most likely to be seen within the first 48 hour in our cohort, where early mortality was high. It may be possible that the use of SI may have more benefit in reducing

ICU length of stay or length of ventilation (for example, by reducing the urge to give fluid in states of over-sedation).

Conclusion

Where does this leave SI in pediatric sepsis? Given that change in SI performs no better than change in heart rate and blood pressure in predicting early death, the use of a change in shock index is unlikely to improve outcomes as a therapeutic target. If adjusted appropriately for age, it may have some benefit in predicting outcome at different time points. In order to be useful in the context of critical illness, standardised values of shock index for children in the ICU need to be described and then tested as predictors of outcome.

Conflict of Interest: No conflicts of interest to declare.

	Referrals (n=633)	Transports/Died in local hospital (n=513)	Children on vaso-active drugs (n=364)
Median age in months (IQR)	14.75 (3.3-49.9)	13.9 (2.4-47.9)	15.4 (2.4-51.7)
Median weight in kg (IQR)	10 (4.6-16.0)	10 (4-16)	10 (4.5-17.7)
Sex male:female	355:278	293:220	211:153
Co-morbidities[a] (%)	166 (26.2)	141 (27.4)	91 (25.0)
Immunosuppression[b] (%)	26	20	14
Ventilated (%)	459 (72.5)	451 (87.9)	335 (92.0)
invasive ventilation	446	442	334
non-invasive ventilation	13	9	1
Vaso-active drugs[c] (%)	364 (57.5)	356 (69.4)	364 (100)
Median fluid administered in ml (IQR)	70 (40-100)	80 (50-110)	90 (60-120)
Cardiac arrest prior to PICU admission	64 (10.1)	64 (12.5)	46 (12.6)
Death (%)			
early (<=2 days post admission)	82 (14.3)	81 (17.2)	57 (12.1)
late (>2 days after admission)	49 (8.6)	46 (9.7)	34 (7.2)
unknown status	61 (9.6)	41 (8.0)	20 (5.5)

Table 1: Baseline characteristics of children referred to CATS (n=633); retrieved to PICU or died prior to retrieval in local hospital following referral (n=513) and those started on vaso-active drugs (n=364). Continuous values are expressed as medians with interquartile ranges (IQR). Categorical variables are expressed as frequencies with percentages.

[a]Co-morbidty defined as acute or chronic conditions unrelated to the principle diagnosis that had required hospital admission/investigation

[b]Immunosuppression included children with acquired immunodeficiency (e.g. due to chemotherapy or high dose steroid treatment) or congenital immunodeficiency syndromes

[c]Vaso-active drugs included dopamine, dobutamine, epinephrine, norepinephrine, vasopressin and milrinone

	Referral	Transport team arrival	PICU admission
Shock index	0.60 (0.51-0.69)	0.59 (0.50-0.69)	0.63 (0.53-0.73)
Heart rate	0.55 (0.48-0.63)	0.53 (0.48-0.62)	0.56 (0.47-0.66)
Systolic blood pressure	0.60 (0.52-0.69)	0.61 (0.52-0.70)	0.73 (0.65-0.82)

Table 2: Areas under the receiver operating characteristic curve for shock index, heart rate and systolic blood pressure at the three operational time points: referral, transport team arrival, and PICU admission. Early death was the outcome measure used. 95% confidence intervals are in brackets.

	Referral-Team arrival	Team arrival-PICU admission	Referral-PICU admission
Shock index	0.48 (0.37-0.59)	0.60 (0.50-0.71)	0.51 (0.39-0.62)
Heart rate	0.55 (0.44-0.64)	0.59 (0.49-0.69)	0.56 (0.45-0.66)
Systolic blood pressure	0.52 (0.41-0.62)	0.61 (0.53-0.69)	0.63 (0.53-0.73)

Table 3: Areas under the receiver operating characteristic curve for *change* in shock index, heart rate and systolic blood pressure, during operation time intervals: between referral and transport team arrival, transport team arrival and PICU admission, and overall change between referral to PICU admission.

Figure 1: Flow diagram showing outcomes of patients referred over the 7 year study period (2005-2011).

Figure 2: Density distribution of heart rate (top panel), systolic blood pressure (middle panel) and shock index (bottom panel), according to transport time-points (left) and outcomes (right).

Figure 3: Density distribution of change in shock index, expressed as a fraction. A negative value suggests improvement, a positive value suggests worsening. Top panel: change in shock index between R-A (pink line) and A-P (grey line). There is a shift towards improvement in shock index between A-P compared to R-A. Bottom panel: overall change in shock index(R-P) according to outcome (survivors – blue line, early deaths – red line, late deaths – green line). The distribution is similar for all outcomes, with a slight shift towards worsening in those who die late.

Figure 4a: Changes in shock index at the three retrieval time points in (a) all retrieved children (R=referral, A=retrieval team arrival to referral hospital, P=patient admission to PICU) following multi-variate analysis with age, time-points and time. Age of less than 1 year is used as the reference age category; *this pattern is consistent across the age categories*. Shock index is significantly lower at P compared to R in children who survived, but not those who died (p<0.05) (Although the profile for those who died late is similar to survivors, the change between R and P is non-significant, given the smaller number of children in the late death group). Shock index is significantly higher at all 3 time-points in children who died early compared to those who survived, or died after 48 hours. The coefficients and confidence intervals are included in the Supplementary Appendix. **Figure 4b (page below)**: Changes in heart rate (top panel) and systolic blood pressure (bottom panel) at the three retrieval time points in all retrieved children drugs (R=referral, A=retrieval team arrival to referral hospital, P= PICU admission). Age of less than 1 year is used as the reference age category. Heart rate is significantly lower at P compared to R in children who survived, but

not those who died (p<0.05). Systolic blood pressure is significantly higher at P compared to

R in children who survived and those who died late, but not those who died early (p<0.05).

References:

1. Keller AS, Kirkland LL, Rajasekaran SY, Cha S, Rady MY, Huddleston JM: Unplanned transfers to the intensive care unit: the role of the SI. *J Hosp Med*. 5(8):460-5, 2010

2. Zarzaur BL, Croce MA, Fischer PE, Magnotti LJ, Fabian TC: New vitals after injury: SI for the young and age x SI for the old. *J Surg Res*. 147(2):229-36, 2008

3. Birkhahn RH, Gaeta TJ, Terry D, Bove JJ, Tloczkowski J: SI in diagnosing early acute hypovolemia. *Am J Emerg Med*. 23(3):323-6, 2005

4. Jaimes F, Farbiarz J, Alvarez D, Martínez C: Comparison between logistic regression and neural networks to predict death in patients with suspected sepsis in the emergency room. *Crit Care*. 9(2):R150-6, 2005

5. Sohn CH, Kim WY, Kim SR, Seo DW, Ryoo SM, Lee YS, Lee JH, Oh BJ, Won HS, Shim JY, Lim KS: An increase in initial shock index is associated with the requirement for massive transfusion in emergency department patients with primary postpartum hemorrhage. *Shock*. 40(2):101-5, 2013

6. Fleming S, Thompson M, Stevens R, Heneghan C, Plüddemann A, Maconochie I, Tarassenko L, Mant D: Normal ranges of heart rate and respiratory rate in children from birth to 18 years of age: a systematic review of observational studies. *Lancet*. 377(9770):1011-8, 2011

7. Jackson LV, Thalange NK, Cole TJ: Blood pressure centiles for Great Britain. *Arch Dis Child.* 92(4):298-303, 2007

8. National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents: The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. *Pediatrics.* 114(2 Suppl 4th Report):555-76, 2004

9. Haque IU, Zaritsky AL: Analysis of the evidence for the lower limit of systolic and mean arterial pressure in children. *Pediatr Crit Care Med.* 8(2):138-44, 2007

10. Rappaport LD, Deakyne S, Carcillo JA, McFann K, Sills MR: Age- and sex-specific normal values for SI in National Health and Nutrition Examination Survey 1999-2008 for ages 8 years and older. *Am J Emerg Med.* 31(5):838-42, 2013

11. Pediatric Intensive Care Audit Network: A decade of data. Universities of Leeds and Leceister. http://www.picanet.org.uk/Audit/Annual-Reporting/PICANet_A_Decade_of_Data_2014_Annual_Report_Summary.pdf. Last accesed January 2016.

12. Brierley 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, immerman 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*. 37(2):666-88, 2009

13. Carcillo JA, Kuch BA, Han YY, Day S, Greenwald BM, McCloskey KA, Pearson-Shaver AL, Orr RA: Mortality and functional morbidity after use of PALS/APLS by community physicians. *Pediatrics*. 124(2):500-8, 2009

14. Acker SN, Ross JT, Partrick DA, Tong S, Bensard DD: Pediatric specific SI accurately identifies severely injured children. *J Pediatr Surg*. 50(2):331-4, 2015

15. Acker SN, Ross JT, Partrick DA, Bensard DD: A pediatric specific SI in combination with GMS identifies children with life threatening or severe traumatic brain injury. *Pediatr Surg Int*. 31(11):1041-6. 2015

16. Newgard CD, Cudnik M, Warden CR, Hedges JR: The predictive value and appropriate ranges of prehospital physiological parameters for high-risk injured children. *Pediatr Emerg Care*. 23(7):450-6, 2007

17. Rousseaux J, Grandbastien B, Dorkenoo A, Lampin ME, Leteurtre S, Leclerc F: Prognostic value of SI in children with septic shock. *Pediatr Emerg Care*. 29(10):1055-9, 2013

18. Yasaka Y, Khemani RG, Markovitz BP: Is SI associated with outcome in children with sepsis/septic shock?. *Pediatr Crit Care Med*. 14(8):e372-9, 2013

19. Cvetkovic M, Lutman D, Ramnarayan P, Pathan N, Inwald DP, Peters MJ: Timing of death in children referred for intensive care with severe sepsis: implications for interventional studies. *Pediatr Crit Care Med*. 16(5):410-7, 2015

20. Weiss SL, Fitzgerald JC, Balamuth F, Alpern ER, Lavelle J, Chilutti M, Grundmeier R, Nadkarni VM, Thomas NJ: Delayed antimicrobial therapy increases mortality and organ dysfunction duration in pediatric sepsis. *Crit Care Med*. 42(11):2409-17, 2014

21. Inwald DP, Tasker RC, Peters MJ, Nadel S; Pediatric Intensive Care Society Study Group (PICS-SG): Emergency management of children with severe sepsis in the United Kingdom: the results of the Pediatric Intensive Care Society sepsis audit. *Arch Dis Child*. 94(5):348-53, 2009

22. Zaritsky A: Is the shock index useful in children? *Pediatr Crit Care Med*. 14(8):830-1, 2013

23. Lampariello S, Clement M, Aralihond AP, Lutman D, Montgomery MA, Petros AJ, Ramnarayan P: Stabilisation of critically ill children at the district general hospital prior to intensive care retrieval: a snapshot of current practice. *Arch Dis Child*. 95(9):681-5, 2010

24. 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*. 6(1):2-8, 2005

25. Slater A, Shann F, Pearson G; Paediatric Index of Mortality (PIM) Study Group: PIM2: a revised version of the Paediatric Index of Mortality. Intensive Care Med. 29(2):278-85, 2003

26. Asfar P, Meziani F, Hamel JF, Grelon F, Megarbane B, Anguel N, Mira JP, Dequin PF, Gergaud S, Weiss N, Legay F, Le Tulzo Y, Conrad M, Robert R, Gonzalez F, Guitton C, Tamion F, Tonnelier JM, Guezennec P, Van Der Linden T, Vieillard-Baron A, Mariotte E, Pradel G, Lesieur O, Ricard JD, Hervé F, du Cheyron D, Guerin C, Mercat A, Teboul JL, Radermacher P; SEPSISPAM Investigators: High versus low blood-pressure target in patients with septic shock. *N Engl J Med*. 370(17):1583-93, 2014

27. Maitland K, Kiguli S, Opoka RO, Engoru C, Olupot-Olupot P, Akech SO, 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*. 364(26):2483-95, 2011

28. van Paridon BM, Sheppard C, G GG, Joffe AR; Alberta Sepsis Network: Timing of antibiotics, volume, and vasoactive infusions in children with sepsis admitted to intensive care. *Crit Care*. 19:293, 2015

29. Bhaskar P, Dhar AV, Thompson M, Quigley R, Modem V: Early fluid accumulation in children with shock and ICU mortality: a matched case-control study. *Intensive Care Med.* 41(8):1445-53, 2015

30. Sinitsky L, Walls D, Nadel S, Inwald DP: Fluid overload at 48 hours is associated with respiratory morbidity but not mortality in a general PICU: retrospective cohort study. *Pediatr Crit Care Med.* 16(3):205-9, 2015