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Evolution of haemodynamics and outcome of fluid-refractory septic shock in children

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Abstract *Background:* Maintaining threshold values of cardiac output (CO) and systemic vascular resistance (SVR) when used as part of the American College of Critical Care Medicine (ACCM) haemodynamic protocol improves the outcomes in paediatric septic shock. *Objective:* We observed the evolution of CO and SVR during the intensive care admission of children with fluid-refractory septic shock and report this together with the eventual outcomes. *Design:* Prospective observational study. *Setting:* Tertiary care Paediatric Intensive Care Unit (PICU) in London. *Methods:* Children admitted in fluid refractory septic shock to the Intensive Care Unit over a period of 36 months were studied. Post liver retransplant children and delayed septic shock admissions were excluded. A non-invasive ultrasound cardiac output monitor device (USCOM) was used to measure serial haemodynamics. Children were allocated at presentation into one of two categories: (1) hospital-acquired infection and (2) community-acquired infection. Vasopressor, inotrope or inodilator therapies were titrated to maintain threshold cardiovascular parameters as per the ACCM guidelines. *Results:* Thirty-six children [19 male, mean age (SD) 6.78 (5.86) years] were admitted with fluid-refractory septic shock and studied. At presentation, all 18 children with hospital-acquired (HA) sepsis and 3 from among the community-acquired (CA) sepsis group were in 'warm shock' (SVRI < 800 dyne s/cm^5/m^2) whereas 15 of the 18 children with community-acquired sepsis and none in the hospital-acquired group were in 'cold shock' [cardiac index (CI) < 3.3 l/min/m^2]. All 21 children in 'warm shock' were initially commenced on a vasopressor (noradrenaline). Despite an initial good response, four patients developed low CI and needed adrenaline. Similarly, all 15 children in cold shock were initially commenced on adrenaline. However, two of them subsequently required noradrenaline. Five others needed milrinone as an inodilator. In general, both groups of children had normalised SVRI and CI within 42 h of therapy but required variable doses of vasopressors, inotropes or inodilators in a heterogeneous manner. The overall 28-day survival rate was 88.9 % in both groups. Central venous oxygen saturation (ScvO2) was significantly ($p = 0.003$) lower in the community-acquired group (mean 51.72 % ± 4.26) when compared to the hospital-acquired group (mean 58.72 % ± 1.36) at presentation but showed steady improvement during therapy. Gram-positive organisms were predominant in blood cultures, 61 % in HA and 56 % in CA groups. *Conclusions:* In general, we found children with community-acquired septic shock

presented in cold shock whereas hospital-acquired septic shock children manifested warm shock. Both types evolved in a heterogeneous manner needing frequent revision of cardiovascular support therapy. However the 28-day survival in both groups was the same at 89 %. Frequent measurements of haemodynamics using non-invasive ultrasound helped in fine tuning cardiovascular therapies.

Keywords Paediatrics · Intensive care · Septic shock · Haemodynamics · Cardiac output · Systemic vascular resistance

Introduction

Early aggressive fluid resuscitation, antibiotics and vasoactive therapies are recommended by the American College of Critical Care Medicine (ACCM) clinical practice parameters for haemodynamic support of paediatric and neonatal septic shock (ACCM-CPP) [1, 2]. These guidelines suggest that when decreased systemic vascular resistance (SVR) contributes to continuing shock, vasopressor therapy should be used whereas with decreased cardiac output (CO) inotropes should be added [1]. Associated high SVR is treated with a vasodilator to facilitate CO. It is known that persisting abnormal haemodynamic values predict mortality in shock states [3] and that the longer a child remains in shock the higher the mortality risk [4].

Septic shock in children is traditionally classified as either cold shock (low CI, often high SVRI) or warm shock (low SVRI, high CI). There is an association with whether the infection originates outside the hospital, termed community-acquired infections (CA), or within the hospital, termed hospital-acquired infections (HA) [5, 6]. At present, aggressive fluid resuscitation of children with septic shock is strongly recommended by the ACCM-CPP [1, 2]. If these guidelines are followed, children admitted to ICUs will have received adequate fluid resuscitation and if still shocked are mostly in need of appropriate cardiovascular or vasoactive therapies: vasopressors and inotropes depending upon whether the child is in warm or cold shock. One previous study has suggested that the paediatric shock states might evolve over time, unlike the adult manifestation of shock in critical care [6]. We sought to clarify the following question in a contemporary setting following the introduction of the latest ACCM-CPP [2]: "Do the haemodynamics in fluid-refractory septic shock at presentation remain in a steady state throughout the course or do they change with time?" This will have implications in the choice of cardiovascular therapies used depending upon the shock state. If the shock state varies then it could become important to measure the haemodynamic parameters regularly to optimise these therapies.

Traditionally, clinical and biochemical parameters have been taken as endpoints of resuscitation, e.g., the heart rate, capillary refill time, and base deficit. In shock states, when the oxygen supply is insufficient to meet the metabolic requirements, increased tissue oxygen extraction results in a decrease in the oxygen content of effluent venous blood [7]. Thus, central venous saturation (ScvO2) is a marker of peripheral oxygen extraction and indirectly of the global haemodynamic state. ScvO2 has been used as a marker of the haemodynamic response to resuscitation as elucidated by Rivers in adults and de Oliveira in paediatric patients [8, 9].

With the introduction of minimally invasive methods, paediatric cardiac output monitoring to optimise haemodynamics has been simplified and the risk of large-bore catheters largely negated. Ceneviva et al. [6] showed that optimisation of CO and SVR was associated with improved outcomes in fluid-refractory septic shock in children. Similar observations have been made in adults too, using goal-directed therapy [10]. We incorporate a cardiovascular therapeutic regimen that also takes into account the serially measured haemodynamics of children including $ScvO_2$ in fluid-refractory septic shock patients presenting to paediatric intensive care.

Although haemodynamic parameters are recommended as resuscitation endpoints, there is limited literature on their quantification and evolution during the admission of critically unwell children with fluid-refractory septic shock [11]. In the present study we report the haemodynamic state at presentation, subsequent evolution of haemodynamics and the outcome of 36 children with fluid-refractory septic shock who were admitted to the Paediatric Intensive Care Unit (PICU).

Methods

The evolution of CI and SVRI in children in fluid-refractory septic shock admitted to King's College Hospital PICU was studied over a period of 36 months (January 2009–December 2011) and treatment with cardiovascular threshold directed therapies and response recorded.

The inclusion criterion was children admitted in fluid-refractory septic shock. Exclusion criteria included re-admissions, neonates and re-liver transplant patients, and those who had been in septic shock for more than 6 h. Post-liver re-transplant children have particular problems with adhesions, excessive bleeding in the dissection

phase, a more pronounced post-reperfusion phase and an exaggerated systemic inflammatory response; hence, these patients were excluded from the study group.

Shock was classified as 'fluid refractory' when the total fluid requirement during resuscitation exceeded 60 ml/kg, fulfilling international consensus conference criteria [12]. The severity of illness was assessed using the Paediatric Index of Mortality score (PIM2) [13].

We classified these patients into two groups. Children developing septic shock whilst receiving treatment in hospital for another ailment were allocated to the HA group and children who presented from home to the CA group. Children in the CA group presented to the Emergency Department of either King's College Hospital (KCH) or the local hospital. Children in HA group had resuscitation therapy initiated in the paediatric wards whereas children admitted from home were resuscitated either in the Emergency Department (local hospital or at KCH) and/or during transfer by retrieval teams.

All children had systemic haemodynamic trends observed using a non-invasive ultrasonic cardiac output monitor (USCOM) upon referral and subsequently pre- and post-therapeutic interventions every 4–6 h. The cardiac index (CI), systemic vascular resistance index (SVRI) and central venous oxygen saturation (ScvO2) were measured.

The USCOM device (USCOM model 1-A, USCOM, Ltd., Australia http://www.uscom.com.au/) uses a 3.3-MHz Doppler through a transcutaneous probe placed at the suprasternal notch directed at the aortic valve that analyses the reflected signal and calculates the haemodynamic variables. This device has been validated in children [14, 15]. In order to minimise the interobserver variability, USCOM operators were certified as competent by the author (AD) [16, 17]. In addition, all children had standard continuous PICU haemodynamic monitoring including invasive arterial blood pressure and central venous pressure (internal jugular). As defined in the literature, warm shock was classified as SVRI $<$ 800 dyne s/cm^5/m^2 and cold shock as CI $<$ 3.3 l/min/m^2 [3].

The threshold haemodynamic indices were (1) CI 3.3–5.5 l/min/m^2 and (2) SVRI 800–1,600 dyne s/cm^5/m^2 [18]. Simultaneously, central venous oxygen saturations (ScvO2) were measured as an indicator of recovery [7, 8, 19]. As per the ACCM-CPP, the initial vasoactive agents before our assessment were dopamine or adrenaline—commenced during fluid resuscitation if peripheral intravenous access was available. Thereafter, children with low SVRI were commenced on a vasopressor (noradrenaline) whereas a low CI was treated with an inotrope (adrenaline). If shock persisted despite this, it was classified as catecholamine-resistant fluid refractory shock and, after thorough clinical and biochemical re-assessment, further therapy was titrated, consistent with the ACCM-CPP. This included the addition of milrinone for cold shock to lower SVRI and improve cardiac output and for detrimentally low SVRI further vasopressors and i-notropy from adrenaline as required [2].

Statistics

The primary analysis was carried out based on the patient referral pattern to the PICU. A secondary analysis was performed based on their haemodynamic status at presentation, i.e. low CI state (cold shock) or low SVRI/high CI state (warm shock).

Continuous variables were summarised as mean (SD) and categorical data as count (percentage). Student's t test and Wilcoxon signed-rank test were used to test differences in continuous variables where appropriate and the χ^2 test and Fisher's exact test used for proportions where appropriate. The changes in physiological parameters over time were analysed by means of the analysis of variance (ANOVA). All statistical analyses were performed with statistical software SPSS version 17 (SPSS Inc., Chicago, USA). All tests were two tailed, and $p < 0.05$ was considered statistically significant.

Ethics

This study was registered as a service evaluation project at King's College Hospital (Clinical Audit Support System (CASS) project no. 2902).

Results

During this 3-year study period, 36 children satisfying the inclusion criterion were admitted with fluid-resistant septic shock from a total of 1,775 PICU admissions, and all were studied.

All 36 children had received more than 60 ml/kg of fluid resuscitation within 6 h of presentation.

Of these 36 children 18 (9 male, age mean ± SD 5.9 ± 6.4) had HA infection, and 18 (10 male, age mean ± SD 7.6 ± 5.3) had CA infection. The baseline data of both groups were compared, as shown in supplementary files Table 1.

All patients were found to have a microbiologically proven septic focus subsequently and 34 of the 36 children (94.5 %) had a positive blood culture (supplementary files—demographic data table).

All 18 children with HA infection were in warm shock at presentation (SVRI $<$ 800 dyne s/cm^5/m^2), whereas 15 of the 18 children with CA infection (88.9 %) were in cold shock (CI $<$ 3.3 l/min/m^2). The remaining three children in the CA group were in warm shock (Fig 1). CVS therapy regimes were based on haemodynamic indices. Children with low CI were treated with infusions of adrenaline and those with low SVRI with noradrenaline.

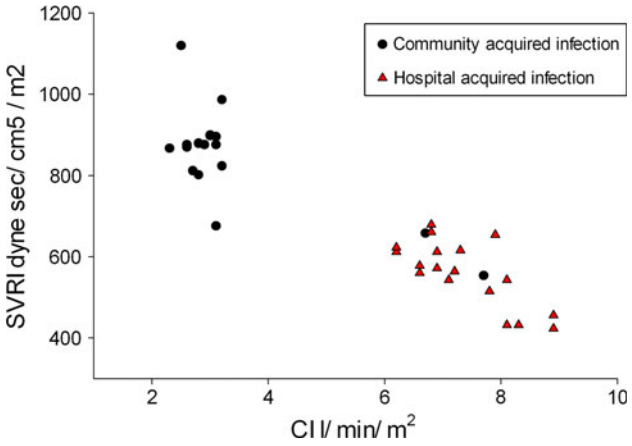

Fig. 1 The cardiac index (CI) vs. systemic vascular resistance index (SVRI) of septic children in fluid refractory shock at presentation in a scatter plot showing clustering, i.e. a majority of the community-acquired group having low CI and hospital-acquired group low SVRI

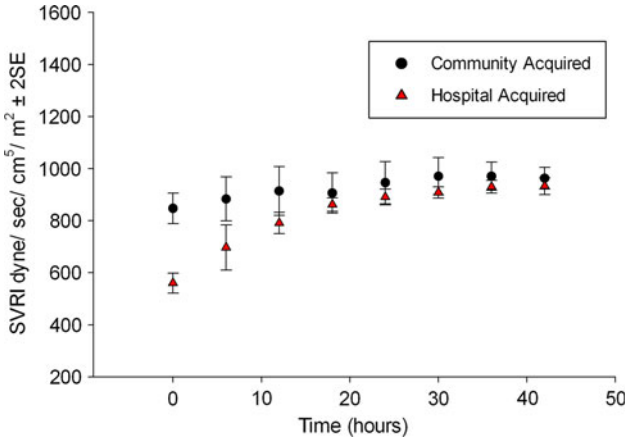

Fig. 3 The systemic vascular resistance index (SVRI) during intensive care shown at 6-h intervals between the CA and HA groups plotted with 2 SE *bars* to display statistically significant differences (one-way ANOVA, $p = 0.004$)

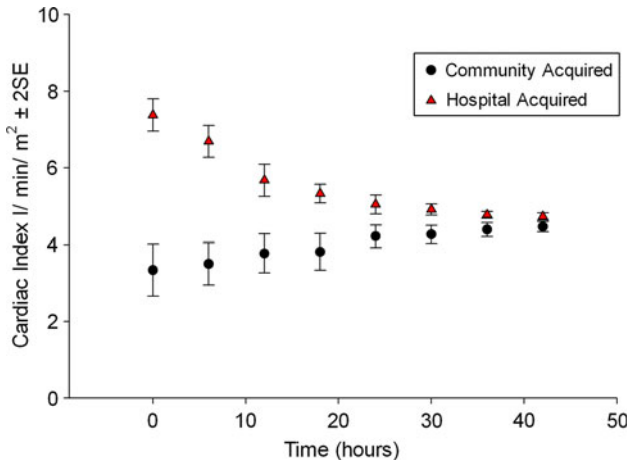

Fig. 2 The cardiac index (CI) during intensive care at 6-h intervals between the CA and HA groups serially plotted with its variance (mean ± 2SE *bars*) at each time point to display statistically significant differences (one-way ANOVA, $p < 0.001$)

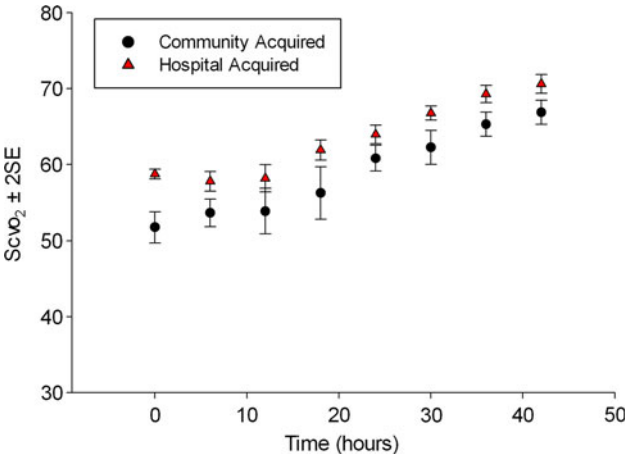

Fig. 4 A scatter plot of the mean ScvO2 (±2 SE) of CA and HA groups of children recorded at 6-h intervals during the first 42 h of intensive therapy displaying differences in its normalisation (one-way ANOVA, $p < 0.001$)

Two-thirds of the 21 children in warm shock in fact required adrenaline in addition to noradrenaline during the course of therapy at 12 h because of falling CI. One other required both adrenaline and milrinone. Despite an initial good response, four patients with warm shock became refractory to noradrenaline therapy and required substitution of noradrenaline with adrenaline. The haemodynamics of these children had changed to low CI state.

Similarly, of the 15 children in cold shock treated with adrenaline, two required substitution of adrenaline with noradrenaline after 8 h because of falling blood pressure, high CI and low SVRI. Another six needed a vasopressor in addition at 12 h. Five others needed an inodilator (milrinone). This variable requirement of inotropes, vasopressors and inodilators at different time scales in both HA and CA groups is illustrated in the supplementary files.

Both groups of children showed normalisation of CI (Fig. 2) and SVRI (Fig. 3) over the 42-h study period whilst some children were still receiving inotropes, vasopressors and inodilator therapies at variable doses as continuous infusions (see supplementary files).

The ScvO2 was significantly ($p = 0.003$) lower in the CA group [mean (SD) 51.72 (4.26) %] when compared to the HA group [mean (SD) 58.72 (1.36) %] on admission. Both groups showed a steady improvement in ScvO2 during therapy but the community-acquired group lagged behind by 5–8 % (Fig. 4). During therapy, the ScvO2 significantly correlated with CI and the relationship

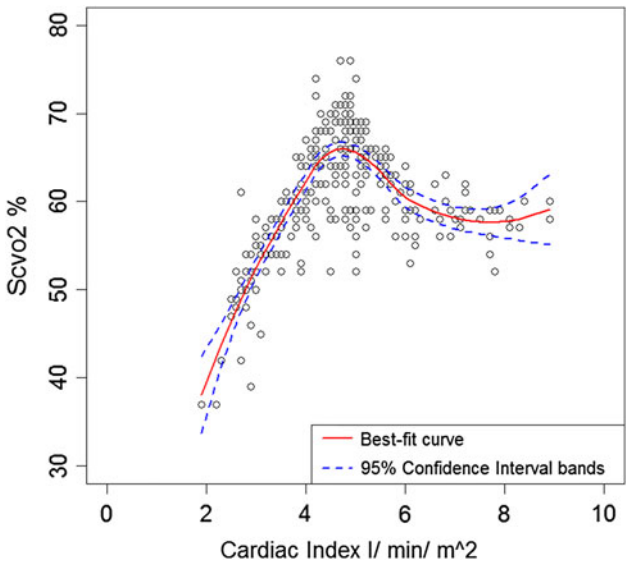

Fig. 5 The ScvO2 values at 0, 6, 12, 18, 24, 30, 36 and 42 h of intensive care of all 36 children plotted against concurrent CI values shown with a best-fit curve and 95 % confidence interval bands (Statistical software R version 2.15)

appeared to be non-linear as shown in Fig. 5. However, ScvO2 had no significant association with SVRI.

In both groups, gram-positive organisms were more frequent in blood cultures, i.e. 11/18 (61 %) in the hospital-acquired group and 10/18 (56 %) in the community-acquired group. Of the four children who died, two were in warm shock and two in cold shock at presentation. Three children had gram-positive organisms in the blood culture and one had Candida albicans (Supplementary files). It is noteworthy that two deceased children who presented in cold shock had much lower CI and ScvO2 at presentation compared to other children with cold shock that survived. The increment in CI and ScvO2 was much slower with maximal therapies and the patients died within a median duration of 26 h of admission. Two children with warm shock who died also had very low SVRI at admission and showed a delayed response to therapies instituted for both SVRI and ScvO2.

Discussion

We described the evolution and management of fluid-refractory septic shock within one PICU. This is a prelude to a multicentre study to assess the impact of targeted haemodynamic optimisation in children with septic shock.

The main observation in this study was the initial, and continuing, haemodynamic variability found in children with septic shock.

There are fundamental pathophysiological differences between warm and cold shock. In cold shock low cardiac output associated with myocardial depression predominates with a variable systemic vascular resistance state [6]. In warm shock, the pattern frequently seen in adults with sepsis, vascular failure is the primary derangement, often in association with an (possibly compensatory) increased cardiac output.

Septic myocardial dysfunction is well described [20] and four of our cases initially presenting in high CI warm shock demonstrated covert myocardial dysfunction during initial vasopressor therapy. In children with cold shock progressive reduction of initial high SVRI was seen, which could be ascribed to fluid and vasodilator therapy, although cytokine release and reperfusion have also been suggested [21].

The clinical practice parameters for haemodynamic support of paediatric and neonatal septic shock (ACCM-CPP) suggest titration of vasoactive therapy to normal haemodynamic ranges for persistent catecholamine-resistant shock in the PICU [2].

We observed that the haemodynamic status of shocked children does not remain static after initial resuscitation, but changes over time. This evolution of the shock state seems rather unpredictable, supporting frequent re-evaluation of haemodynamics and of the effects of vasoactive therapies if ACCM-CPP [2] or similar recommendations [22] are to be followed.

In essence, this provides a strong argument for quantification and consideration of all three circulatory components when treating septic shock: flow, pressure and resistance [23].

Interestingly, we also found a novel relationship between the cardiac index and ScvO2 in children with septic shock. Low CI is clearly associated with lower ScvO2, though there is also a suggestion of tail off at higher CI, arguably supporting an optimal CI range of between 4 and 6 l/min/m^2 (Fig. 5).

Early aggressive shock reversal in paediatric sepsis confers a mortality benefit [4]. Randomised trials in septic adults and children support the efficacy of structured, early goal-directed resuscitation algorithms, which target the indirect markers of global perfusion: lactate clearance or ScvO2 [9, 10, 24].

Inotropes in the context of goal-directed bundle therapies have also been shown to improve outcomes in severe sepsis [25] with many bundles including titration of vasoactive medication to maintain threshold haemodynamic values [26]. However, contemporary evidence that such late haemodynamic optimisation is of benefit in isolation is lacking, although Pollack and colleagues did report increased survival in septic children by maintaining CI between CO 3.3–6.0 l/min/m^2 [18].

Carcillo et al., have suggested that maintenance of threshold values of CO and SVR might be associated with an improved paediatric septic shock outcome compared to historical controls [6]. Although this concept is included in the ACCM-CPP, to date there has been no randomised

trial evidence to support either early or continuing haemodynamic targeting in paediatric septic shock. Furthermore, it is unknown whether other haemodynamic targets, such as the stroke volume variability index (SVVI), may prove superior targets. Given the changes in outcomes alluded too, and the non-invasive techniques now available, a trial to delineate optimal haemodynamic management of the child with septic shock seems both feasible, and warranted.

Half of the children in the study were suffering from HA sepsis and half CA sepsis. The finding that high CI warm shock was initially present in all HA patients but only in three CA children is consistent with the results of a previous study [5]. That study, however, had later haemodynamic assessment of CA children as they were all brought back to the PICU. The reason for this distinction in shock pattern is unclear—possibilities include: different bacterial aetiology (supplementary files), direct bacterial load from the central line affecting the vasculature [5] and earlier recognition/resuscitation of shock in hospitalised children. The last is interesting as it suggests that initial CA shock might have a high CI pattern, but by the time of presentation haemodynamics might have changed in some cases. Arguably these children have a worse PIM2 score because they have been in shock longer because of the lack of early fluid resuscitation, inotrope therapy [2] and antibiotics [27]. It is known that the longer a child remains in shock, the greater their mortality risk [4, 25].

However, overall survival from infant and neonatal sepsis had improved to 90 % by the late 1990s [28]. Inwald and colleagues have recently shown a 17 % mortality for children with severe sepsis referred to the PICU in the UK; non-adherence to the ACCM-CPP was suggested to be an important factor in those who died [25].

Both that study and previous work [4] have demonstrated a striking mortality benefit in getting septic children out of the shock state rapidly. After a child has been admitted to the PICU, persisting shock has been shown to be a poor prognostic sign [29].

We observed an overall survival rate of 89 % in children presenting to one tertiary PICU with fluid-resistant septic shock. This lower mortality could be ascribed to adherence to ACCM-CPP, with titrated haemodynamic threshold therapy arguably an important component [2].

All four children who died had haemodynamic parameters and ScvO2 refractory to resuscitation: Two children had persisting low CI, a known predictor of mortality [6]; the others had an extremely low SVRI, which is consistent with adult data demonstrating decreased survival with low SVR [4] regardless of CO [30]. In the latter group an energy-demanding persistent hyper-dynamic state may lead to a state of intractable myocardial failure due to low coronary perfusion associated with low diastolic pressures.

We found no real difference in infective aetiology between the CA and HA groups, with gram-positive organisms being more frequent in both than gram negatives. The evolving haemodynamics of paediatric septic shock can be readily studied using newer non-invasive cardiac output devices [6]. USCOM, one such device, has been validated against Pulse Contour Cardiac Output (PiCCO®) [31, 32] and pulmonary artery catheter-based cardiac output measuring techniques [33].

Limitations

Whilst CI and SVRI returned to normal during haemodynamic-guided titration of vasoactive therapy, we cannot claim an effect without a control group.

Recruitment was based on local practice whereas in other settings the HA and CA septic shock division may be less relevant.

The study population was heterogeneous—as is our case mix—ranging from previously healthy children to those with complex pre-morbid host characteristics such as immunosuppression.

This study used CI and SVRI threshold targets suggested by the parameter guidelines. However, the truly optimal CI and SVRI to target in paediatric septic shock are yet to be elucidated. Larger multicentre studies are needed to determine optimal vasoactive agent use in the various subgroups.

Only a small number of patients was investigated and any suggestion that individual titration of haemodynamic therapy might affect outcome is made with this caveat.

This study confirms that the haemodynamic pattern of paediatric septic shock evolves over time supporting the regular re-assessment of haemodynamics in critically ill shocked children. This enables bespoke, individualised, vasoactive therapy—an approach supported by observational studies of shock bundles. However, we recognise that no randomised controlled trial evidence supports this approach to haemodynamic optimisation in isolation.

Further studies are needed to clarify the optimal CI and SVRI thresholds to directed vasoactive agent therapy in children in septic shock and even whether other haemodynamic targets (SVVI) might be superior.

However, a multi-centre large-scale randomised trial of haemodynamic directed vasoactive therapy to ACCM-CPP ranges is now both warranted and feasible.

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Conflicts of interest The authors declare that they have no conflict of interest.

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