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## ACCM/PALS haemodynamic support guidelines for paediatric septic shock: an outcomes comparison with and without monitoring central venous oxygen saturation

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**Abstract Introduction:** The ACCM/PALS guidelines address early correction of paediatric septic shock using conventional measures. In the evolution of these recommendations, indirect measures of the balance between systemic oxygen delivery and demands using central venous or superior vena cava oxygen saturation (ScvO<sub>2</sub> ≥ 70%) in a goal-directed approach have been added. However, while these additional goal-directed endpoints are based on evidence-based adult studies, the extrapolation to the paediatric patient remains unvalidated. **Objective:** The purpose of this study was to compare treatment according to ACCM/PALS guidelines, performed with and with-

out ScvO<sub>2</sub> goal-directed therapy, on the morbidity and mortality rate of children with severe sepsis and septic shock. **Design, participants and interventions:** Children and adolescents with severe sepsis or fluid-refractory septic shock were randomly assigned to ACCM/PALS with or without ScvO<sub>2</sub> goal-directed resuscitation. **Measurements:** Twenty-eight-day mortality was the primary endpoint. **Results:** Of the 102 enrolled patients, 51 received ACCM/PALS with ScvO<sub>2</sub> goal-directed therapy and 51 received ACCM/PALS without ScvO<sub>2</sub> goal-directed therapy. ScvO<sub>2</sub> goal-directed therapy resulted in less mortality (28-day mortality 11.8% vs. 39.2%,  $p = 0.002$ ), and fewer new organ dysfunctions ( $p = 0.03$ ). ScvO<sub>2</sub> goal-directed therapy resulted in more crystalloid (28 (20–40) vs. 5 (0–20) ml/kg,  $p < 0.0001$ ), blood transfusion (45.1% vs. 15.7%,  $p = 0.002$ ) and inotropic (29.4% vs. 7.8%,  $p = 0.01$ ) support in the first 6 h. **Conclusions:** This study supports the current ACCM/PALS guidelines. Goal-directed therapy using the endpoint of a ScvO<sub>2</sub> ≥ 70% has a significant and additive impact on the outcome of children and adolescents with septic shock.

**Keywords** Child · Sepsis · Resuscitation · Central venous oxygen saturation · Cardiac output · Goal-directed therapy

## Introduction

Severe sepsis and septic shock are major causes of morbidity, mortality and resource consumption. Although outcomes have improved over the last few decades [1–4], mortality rates of children with severe sepsis reach 20% in developed nations [5–8], are higher than 50% in developing countries [8–11], and even higher among patients with underlying comorbidities and organ dysfunction [7, 12–15].

Early recognition and aggressive fluid resuscitation have a crucial role in the treatment of paediatric septic shock [3, 16]. The American College of Critical Care Medicine – Paediatric Advanced Life Support (ACCM/PALS) guidelines recommend rapid, stepwise interventions with the following therapeutic endpoints in the first hour: capillary refill of < 2 s, normal pulses with no differential between peripheral and central pulses, warm extremities, urine output > 1 ml/kg/h and normal mental status. Further haemodynamic optimisation using metabolic endpoints to treat global tissue hypoxia include a superior vena cava oxygen saturation ( $ScvO_2$ )  $\geq$  70% and cardiac index > 3.3 and < 6.0 l/min/m<sup>2</sup> with normal perfusion pressure for age [17]. The evidence which has resulted in these current guidelines has been derived from limited prospective and retrospective studies or case series [3, 18, 19]. More specifically, the outcome benefit of further optimising metabolic parameters, namely  $ScvO_2$ , in goal-directed therapy remains unknown.

Although current ACCM/PALS guidelines represent best practice, prospective randomised trials are lacking to confirm all components of these recommendations. The purpose of this study was to examine whether treatment according to ACCM/PALS guidelines performed with and without goal-directed therapy to achieve a  $ScvO_2 \geq 70\%$  reduces the morbidity and mortality rate of children with severe sepsis and septic shock [20].

## Materials and methods

The ethics committees of both hospitals involved approved this prospective, randomised controlled trial, as well as the written informed consent. Interim analysis was conducted by a Safety and Monitoring Review Committee under the direction of the ethics committees.

### Participants

Patients were recruited from the emergency department, the inpatient unit and the paediatric intensive care unit (PICU) of two hospitals affiliated to the University of São Paulo, Brazil, from January 2004 to August 2005. The first is a 245-bed tertiary-care paediatric hospital, with 13 beds in the PICU; the second is a 308-bed secondary-care general hospital, with 10 beds in the PICU. We included

patients with severe sepsis or fluid-refractory septic shock that had not responded after 40 ml/kg of any resuscitation fluid or that required cardiovascular agents at any time during resuscitation. Severe sepsis was defined as sepsis (evidence of infection and two of the following: 1, hypothermia or hyperthermia; 2, tachycardia or bradycardia if < 1 year old; 3, tachypnoea; 4, white blood cell count > 12,000 or < 4,000 cells/ml<sup>3</sup> or > 10% immature form) and at least one of the following indications of altered organ function or hypoperfusion: altered mental status, hypoxaemia, increased serum lactate level, bounding pulses, oliguria (< 1 ml/kg/h) or hypotension [17, 21]. The criteria for exclusion from the study were refusal to sign the written informed consent, age less than 1 month or more than 19 years, uncorrected cyanotic heart disease, exclusive palliative care, and arrival from another hospital more than 6 h after the diagnosis of severe sepsis or septic shock.

### Randomisation

After written informed consent had been obtained from a next of kin or legal guardian, patients were randomly assigned to either the intervention or the control group. A computer-generated random sequence was placed in sealed, opaque envelopes, kept at the first hospital. For each included patient, in any of the two hospitals, the next envelope was opened, assigning that patient to intervention or control group.

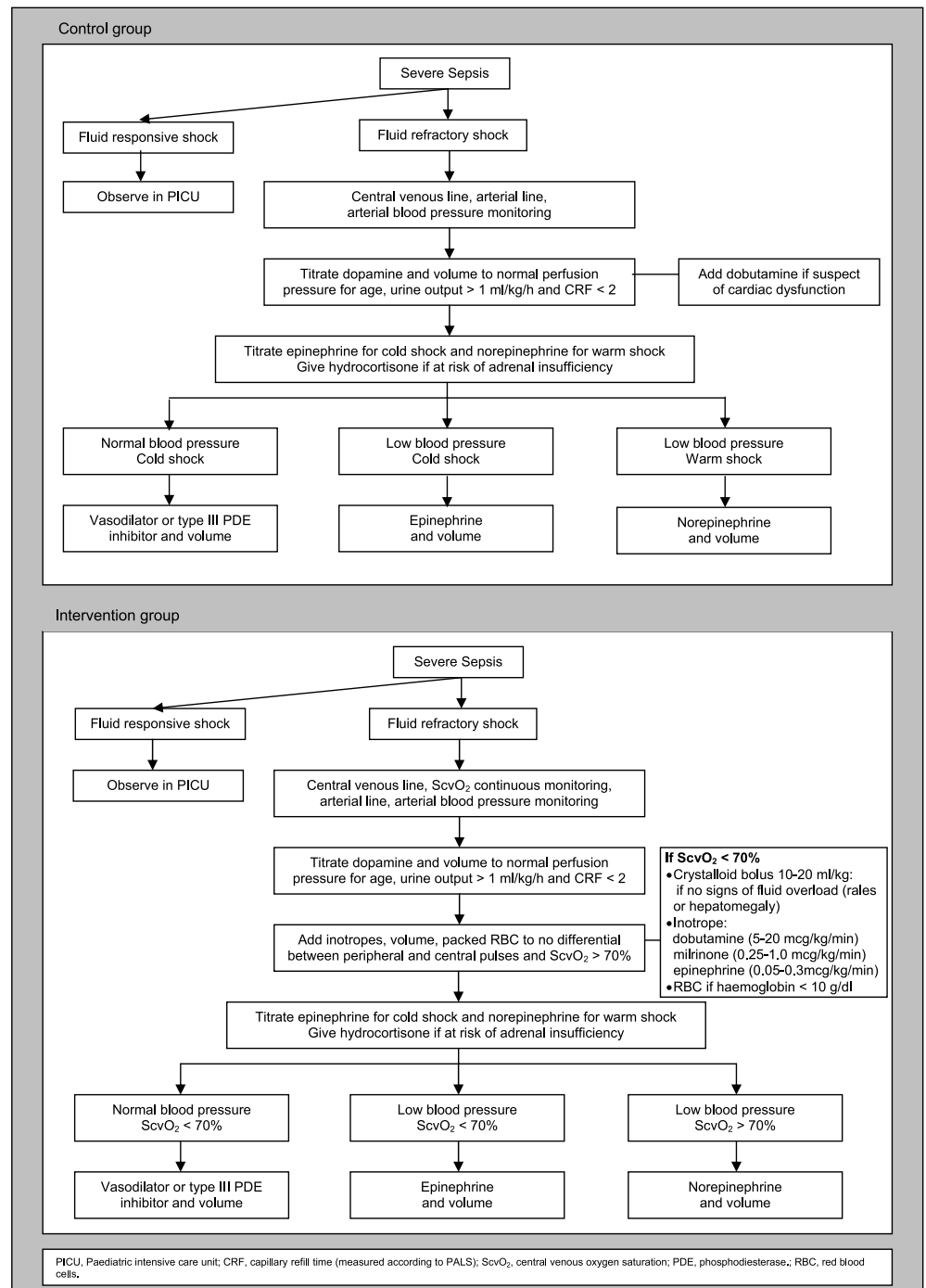
### Procedures

The patients assigned to intervention received a catheter capable of measuring  $ScvO_2$  (Edwards Lifesciences, Irvine, CA), which was connected to a monitor exclusively for continuous  $ScvO_2$  monitoring. The catheter used is 4 Fr, 40 cm long, with one infusion lumen and one optic fibre, and was inserted through a percutaneous sheath introducer (5 Fr for infants and 6 Fr for children and adolescents), that has another infusion lumen [22]. The  $ScvO_2$  monitor was calibrated after catheter placement and once daily after that.  $ScvO_2$  was continuously displayed and values were confirmed by venous blood analysis at 0, 6 and 72 h. The patients assigned to control received a double-lumen central venous catheter (5 Fr for infants and children and 7 Fr for adolescents), and  $ScvO_2$  was measured by venous blood analysis (values were recorded, but not used to guide treatment). In both groups, the catheter was placed with its tip inside the right atrium or at the superior or inferior cava junction, close to the right atrium. Catheter position was confirmed by chest radiography. In both groups, central lines were placed by the fellow or attending physician responsible for the patient's care.

The medical team was usually composed of two residents, one fellow and one attending physician. The patients assigned to the control group received ACCM/PALS therapies without continuous ScvO<sub>2</sub> monitoring, with fluid resuscitation (crystalloid or colloid), red blood cells and cardiovascular agents directed to maintain normal perfusion pressure for age, urine output > 1 ml/kg/h, capillary refill of < 2 s and normal pulses (Fig. 1).

The patients assigned to the intervention group received ACCM/PALS therapies directed toward the endpoint of ScvO<sub>2</sub> ≥ 70% using continuous monitoring. If the ScvO<sub>2</sub> was < 70%, even with normalisation of perfusion pressure, urine output and peripheral perfusion, then more fluid, red blood cells (if haemoglobin < 10 g/dl) or inotropes were given (Fig. 1). The treatment was considered to be successful if the patient showed normal

**Fig. 1** Treatment protocols following initial ACCM/PALS-recommended resuscitation



blood pressure for age, normal pulses, warm extremities, urine output  $> 1$  ml/kg/h and  $ScvO_2 \geq 70\%$ .

In both groups, other supportive therapies, such as mechanical ventilation, nutrition, antibiotics, and renal replacement therapy, were decided by the medical team, according to the routine practice. The duration of the protocol resuscitation was 72 h in each group.

Baseline characteristics of the patients were recorded including age, gender, underlying comorbidity, site of infection, time elapsed between hospital admission and the diagnosis of severe sepsis or septic shock, and the amount of resuscitation fluid and cardiovascular agent received prior to the study entry. The patients' heart rate, respiratory rate, arterial blood pressure, arterial oximetry, central venous pressure and oxygen saturation, urine output, PRISM score (PRISM) and Multiple Organ Dysfunction Score (MODS) [23, 24] (with the laboratory tests required to calculate the score) were obtained at base line (0 h) and after 6 and 72 h. The amount of resuscitation fluid (crystalloid and colloid) and red blood cells administered, and the use of cardiovascular agents and steroids, were registered during the intervals from 0 to 6 h and from 6 to 72 h after the beginning of the treatment. Patients were followed for 60 days or until hospital discharge or death.

#### Statistical analysis

Twenty-eight-day mortality was the primary endpoint. Secondary endpoints were number of organ dysfunctions, administered treatments, duration of therapy with cardio-

vascular agents, duration of mechanical ventilation, length of PICU stay, days free of cardiovascular agents and days free of mechanical ventilation.

Categorical variables are presented as percentages. Normally distributed continuous variables are presented as means with standard deviations; and skewed data are presented as median and interquartile range (25–75%). Categorical variables were compared using Fisher's exact test. Normally distributed continuous variables were analysed with Student's t-test, and non-normally distributed variables with the Mann–Whitney rank-sum test. All tests were two-sided, and a  $p$ -value of less than 0.05 was considered to indicate a statistically significant difference. Kaplan–Meier estimates of mortality, along with hazard ratios and 95% confidence intervals, were used to describe the relative risk of death.

A multivariate logistic regression model was developed to examine the odds ratios (OR) and 95% confidence intervals of variables associated with 28-day mortality. Variables with a univariate association ( $p < 0.10$ ) and variables with clinical plausibility were introduced into a backward stepwise multiple linear regression. Variables were retained in the regression model if they were significant at a level of 0.05. Renal failure (0 or 1), neurological failure (0 or 1), group (0 or 1), age, pH at baseline and PRISM score were included as co-variants.

Assuming an alpha value of 0.05 and a power of 80%, we calculated that a sample size of 268 patients was necessary to permit the detection of a 35% relative reduction or 20% absolute reduction in mortality from 57.3%, which

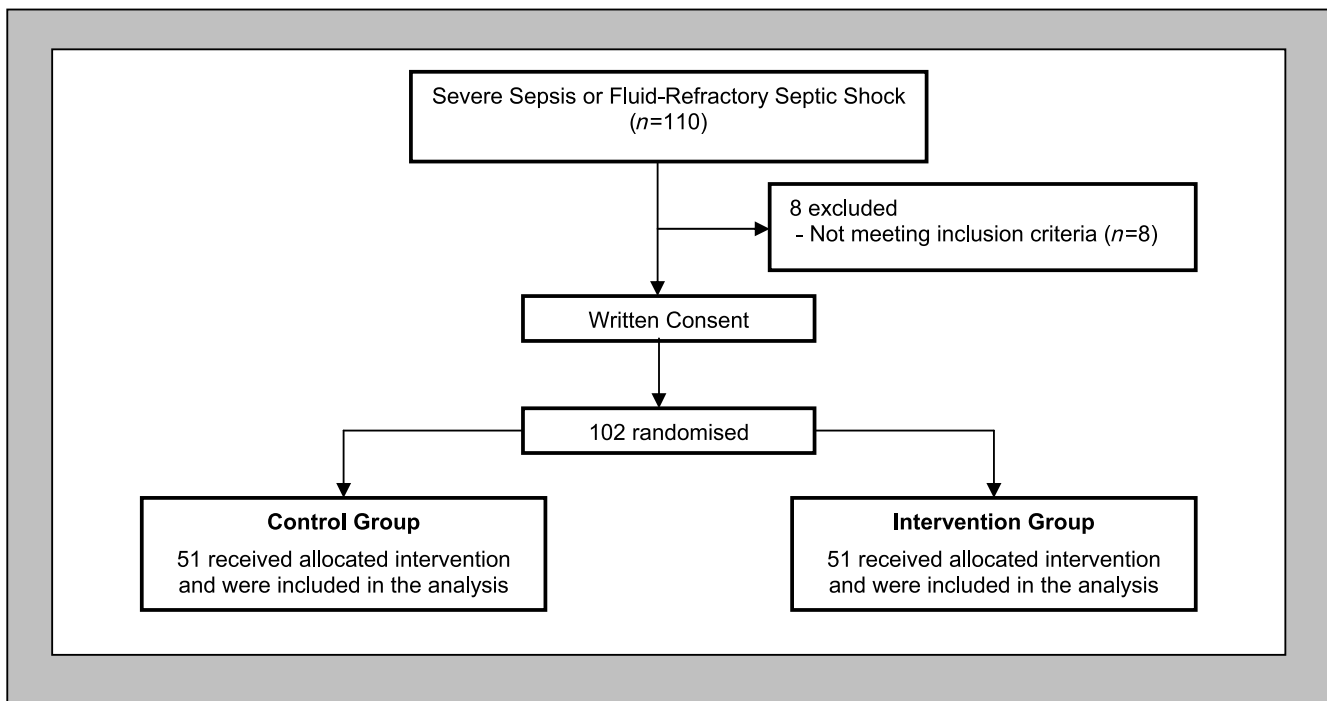
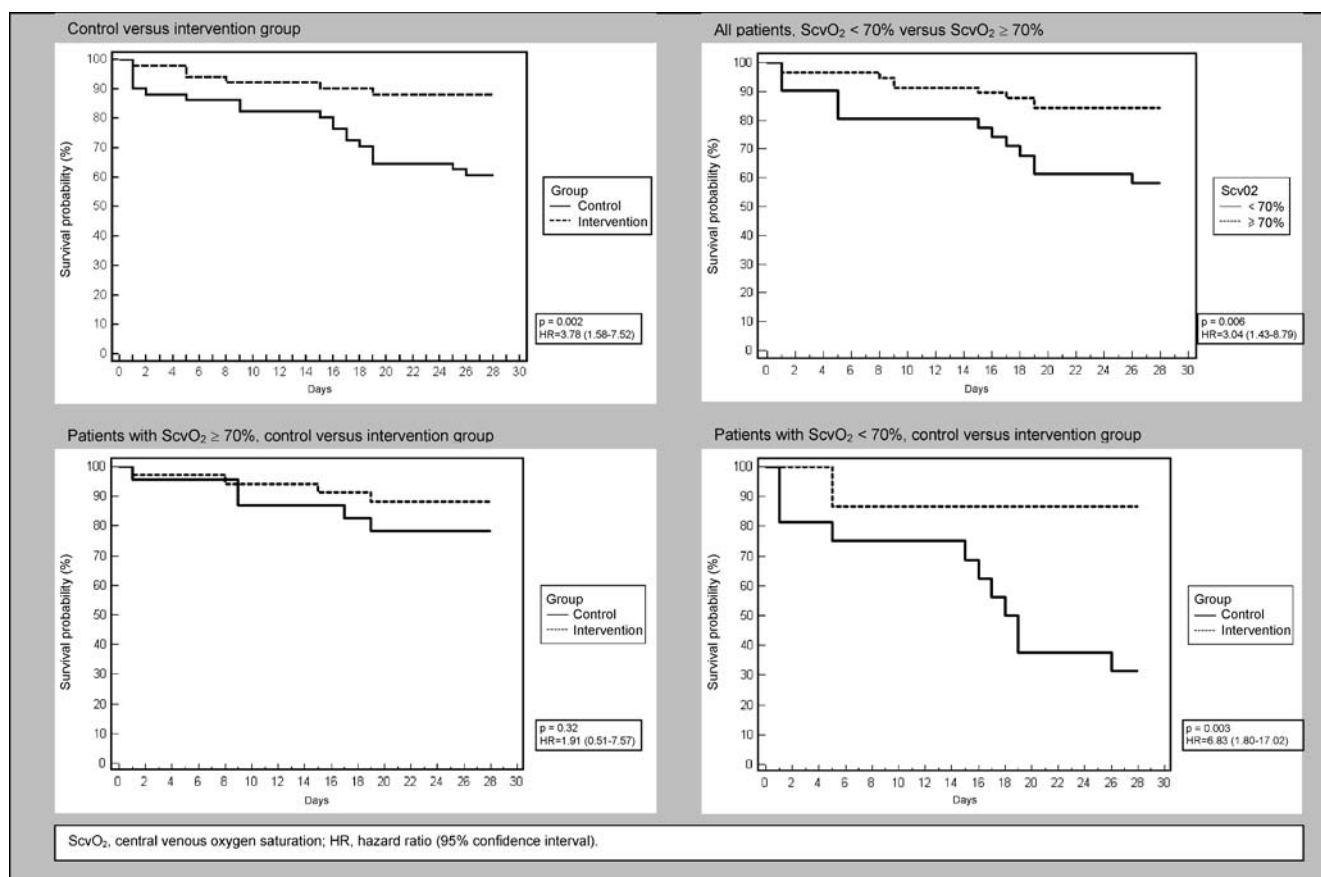


Fig. 2 Trial profile

**Table 1** Baseline characteristics

Characteristic	Control (n = 51)	Intervention (n = 51)	p-value
Age (years)	4.5 ± 4.9	6.5 ± 5.8	0.03 <sup>b</sup>
Gender (%)			
Female	43.1	45.1	1.00 <sup>a</sup>
Male	56.9	54.9	
Septic shock (%)	92.2	94.1	1.00 <sup>a</sup>
Severe sepsis (%)	7.8	5.9	
Underlying disease (%)			
Onco-haematological	31.4	39.2	0.53 <sup>a</sup>
Neurological	19.6	7.8	0.15 <sup>a</sup>
Hepatological	9.8	3.9	0.44 <sup>a</sup>
Rheumatological	3.9	7.8	0.68 <sup>a</sup>
Immunological	3.9	9.8	0.44 <sup>a</sup>
Gastrointestinal	3.9	0	0.49 <sup>a</sup>
Pulmonary	3.9	5.9	1.00 <sup>a</sup>
Other	3.9	2.0	1.00 <sup>a</sup>
None	19.6	23.5	0.81 <sup>a</sup>
Hospital infection (%)	37.3	41.2	0.84 <sup>a</sup>
Infection site (%)			
Lungs	52.9	51.0	1.00 <sup>a</sup>
Central nervous system	13.7	7.8	0.53 <sup>a</sup>
Abdomen	9.8	3.9	0.44 <sup>a</sup>
Systemic	7.8	19.6	0.15 <sup>a</sup>
Urinary tract	2.0	3.9	1.00 <sup>a</sup>
Skin	2.0	7.8	0.36 <sup>a</sup>
Not identified	11.8	5.9	0.49 <sup>a</sup>
PRISM score	8.0 (5–11.5)	7.0 (5–12)	0.96 <sup>c</sup>

<sup>a</sup> Fisher's exact test; <sup>b</sup> Student's t-test; <sup>c</sup> Mann–Whitney rank-sum test

**Fig. 3** Kaplan–Meier estimates of mortality (28 days)

was our baseline mortality. The protocol included interim analysis after the enrolment of 100 patients, which was independently conducted by the ethics committee.

## Results

During the study period, 110 patients were eligible and 8 patients (7.3%) were excluded (seven arrived from other hospitals more than 6 h after severe sepsis diagnosis and one had uncorrected cyanotic heart disease). The 102 patients enrolled were randomly assigned to either the intervention or the control group and were included in the intention-to-treat analyses (Fig. 2). The study was terminated after the interim analysis, following the recommendation of the ethics committee of our hospital.

Baseline characteristics were similar between the two groups, with the exception that the intervention group was older (Table 1). The primary endpoint, 28-day mortality rate, was significantly lower in the intervention group (hazard ratio (HR) = 3.78 (1.58–7.52);  $p = 0.002$ ), with a number needed to treat of 3.6 (Table 3). Multivariate logistic regression analysis showed that PRISM score (OR = 1.20 (1.06–1.36);  $p = 0.006$ ), and renal dysfunction (OR = 7.76 (1.86–32.33);  $p = 0.005$ ) were independently associated with increased 28-day mortality, whereas a goal-directed resuscitation using  $ScvO_2 \geq 70\%$  as an endpoint was independently associated with decreased 28-day mortality (OR = 0.18 (0.05–0.69);  $p = 0.01$ ). Age, pH at baseline and neurological dysfunction were not independently associated with 28-day mortality.

**Table 2** Laboratory tests and vital signs

Variable and treatment group	Baseline	6 h	72 h
Heart rate (beats/min)			
Control group	144 ± 27	134 ± 32	125 ± 25
Intervention group	139 ± 22	137 ± 31	120 ± 26
<i>p</i> -value	0.33 <sup>b</sup>	0.66 <sup>b</sup>	0.39 <sup>b</sup>
MAP (mmHg)			
Control group	66 ± 15	69 ± 20	77 ± 16
Intervention group	66 ± 19	73 ± 17	80 ± 17
<i>p</i> -value	0.35 <sup>b</sup>	0.32 <sup>b</sup>	0.42 <sup>b</sup>
CVP (cmH <sub>2</sub> O)			
Control group	6.0 (4–12)	8.6 ± 6	8.5 ± 6.5
Intervention group	7.5 (1.3–10)	8.6 ± 6.1	8.5 ± 6.7
<i>p</i> -value	0.45 <sup>c</sup>	0.99 <sup>b</sup>	0.99 <sup>b</sup>
ScvO <sub>2</sub> (%)			
Control group	74 (64.7–81.9)	75.4 (69.2–84.6)	74.8 ± 12.3
Intervention group	78 (67.5–82.3)	79.1 (72.3–83.6)	79.1 ± 9.4
<i>p</i> -value	0.41 <sup>c</sup>	0.54 <sup>c</sup>	0.11 <sup>b</sup>
Patients with ScvO <sub>2</sub> < 70% (%)			
Control group	41.0	30.8	37.9
Intervention group	30.6	20.8	12.5
<i>p</i> -value	0.37 <sup>a</sup>	0.33 <sup>a</sup>	0.02 <sup>a</sup>
Arterial pH			
Control group	7.32 (7.25–7.36)	7.34 (7.27–7.42)	7.39 (7.34–7.44)
Intervention group	7.36 (7.29–7.40)	7.38 (7.33–7.43)	7.42 (7.37–7.45)
<i>p</i> -value	0.05 <sup>c</sup>	0.33 <sup>c</sup>	0.14 <sup>c</sup>
Base excess (mEq/l)			
Control group	-7.9 ± 6.4	-6.0 ± 6.9	-2.0 (-6.7–3.1)
Intervention group	-6.0 ± 4.8	-5.2 ± 5.5	0.3 (-2.6–3.6)
<i>p</i> -value	0.12 <sup>b</sup>	0.55 <sup>b</sup>	0.16 <sup>c</sup>
Lactate (mmol/l)			
Control group	1.2 (0.8–2.3)	1.3 (0.9–2.3)	1.2 (0.8–1.7)
Intervention group	1.1 (0.7–2.5)	1.2 (0.8–1.6)	1.1 (0.8–1.7)
<i>p</i> -value	0.61 <sup>c</sup>	0.35 <sup>c</sup>	0.56 <sup>c</sup>
Haematocrit (%)			
Control group	27.9 ± 5.1	30.2 ± 6.1	31.3 ± 5.1
Intervention group	28.5 ± 6.3	30.8 ± 5.9	31.7 ± 5.2
<i>p</i> -value	0.67 <sup>b</sup>	0.66 <sup>b</sup>	0.76 <sup>b</sup>
INR			
Control group	1.5 (1.2–2.1)	1.5 (1.3–2.3)	1.3 (1.2–1.6)
Intervention group	1.5 (1.2–1.8)	1.5 (1.3–1.7)	1.2 (1.1–1.4)
<i>p</i> -value	0.46 <sup>c</sup>	0.43 <sup>c</sup>	0.03 <sup>c</sup>

MAP, mean arterial pressure; CVP, central venous pressure; ScvO<sub>2</sub>, central venous oxygen saturation.

<sup>a</sup> Fisher's exact test; <sup>b</sup> Student's *t*-test; <sup>c</sup> Mann–Whitney rank-sum test

**Table 3** Organ dysfunction, morbidity and mortality

	Control (n = 51)	Intervention (n = 51)	p-value
Number of organ dysfunctions at admission	2.0 (1.0–2.0)	2.0 (1.0–2.0)	0.97 <sup>c</sup>
Organ (%)			
Respiratory	47.1	43.1	0.84 <sup>a</sup>
Cardiovascular	51.0	62.7	0.32 <sup>a</sup>
Renal	11.8	11.8	1.00 <sup>a</sup>
Neurological	5.9	3.9	1.00 <sup>a</sup>
Gastrointestinal	0	0	1.00 <sup>a</sup>
Haematological	25.5	25.5	1.00 <sup>a</sup>
Hepatological	27.4	25.5	1.00 <sup>a</sup>
Number of new organ dysfunction during ICU stay	1.0 (1.0–2.0)	1.0 (0.0–2.0)	0.03 <sup>c</sup>
Development of new organ dysfunction (%)			
Respiratory	59.3	48.3	0.44 <sup>a</sup>
Cardiovascular	92.0	89.5	1.00 <sup>a</sup>
Renal	26.7	6.7	0.02 <sup>a</sup>
Neurological	10.4	0	0.03 <sup>a</sup>
Gastrointestinal	9.8	7.8	1.00 <sup>a</sup>
Haematological	31.6	15.8	0.18 <sup>a</sup>
Hepatological	13.5	15.8	1.00 <sup>a</sup>
Days			
On mechanical ventilation	4.0 (1–13)	3.0 (0–6.5)	0.41 <sup>c</sup>
On cardiovascular agent	3.0 (1–7)	3.0 (2–5)	0.69 <sup>c</sup>
Free of mechanical ventilation	2.0 (0–5)	4.0 (2–7)	0.02 <sup>c</sup>
Free of cardiovascular agent	2.0 (0–8.5)	3.0 (2–10)	0.11 <sup>c</sup>
Length of PICU stay (day)	9 (5–17)	7 (5–17.5)	0.92 <sup>c</sup>
28-day Mortality (%)	39.2	11.8	0.002 <sup>d</sup>
60-day Mortality (%)	41.2	15.7	0.002 <sup>d</sup>

PICU, paediatric intensive care unit; <sup>a</sup> Fisher's exact test; <sup>c</sup> Mann–Whitney rank-sum test; <sup>d</sup> Kaplan–Meier estimates of mortality

**Table 4** Treatments administered

	Fluids		
		Hours after study entry	
Resuscitation fluids (ml/kg)	0–6	6–72	0–72
Crystalloid			
Control group	5 (0–20)	10 (0–28)	80 (45–100)
Intervention group	28 (20–40)	0 (0–20)	90 (65–114)
p-value	< 0.0001 <sup>c</sup>	0.53 <sup>c</sup>	0.10 <sup>c</sup>
Colloid			
Control group	0 (0–0)	0 (0–15)	0 (0–15)
Intervention group	0 (0–0)	0 (0–0)	0 (0–15)
p-value	0.73 <sup>c</sup>	0.15 <sup>c</sup>	0.18 <sup>c</sup>
Red-cell transfusion (% of patients)			
Control group	15.7	43.1	58.8
Intervention group	45.1	31.4	68.6
p-value	0.002 <sup>a</sup>	0.31 <sup>a</sup>	0.41 <sup>a</sup>
Cardiovascular agents			
Addition of vasopressor (% of patients)			
Control group	56.9	18.4	74.6
Intervention group	49.0	23.5	72.5
p-value	0.55 <sup>a</sup>	0.70 <sup>a</sup>	1.00 <sup>a</sup>
Addition of inotrope (% of patients)			
Control group	7.8	22.4	29.4
Intervention group	29.4	19.6	49.0
p-value	0.01 <sup>a</sup>	0.92 <sup>a</sup>	0.07 <sup>a</sup>
Addition of vasodilator (% of patients)			
Control group	0.0	2.0	2.0
Intervention group	2.0	7.8	9.8
p-value	1.00 <sup>a</sup>	0.39 <sup>a</sup>	0.20 <sup>a</sup>
Any CVA change (% of patients)			
Control group	56.9	32.7	72.5
Intervention group	72.5	37.3	78.4
p-value	0.15 <sup>a</sup>	0.79 <sup>a</sup>	0.65 <sup>a</sup>

**Table 4** Continued

<i>Other therapies</i>	
Hydrocortisone	
Bolus dose (% of patients)	
Control group	17.6
Intervention group	19.6
<i>p</i> -value	1.00 <sup>a</sup>
24-h continuous infusion (% of patients)	
Control group	15.7
Intervention group	15.7
<i>p</i> -value	1.00 <sup>a</sup>
Mechanical ventilation (% of patients)	
Control group	80.4
Intervention group	70.6
<i>p</i> -value	0.36 <sup>a</sup>

\* Same patient may have had CVA change between 0–6 h and 0–72 h; *Colloid*, human albumin or fresh frozen plasma; *CVA*, cardiovascular agent; Vasopressor included dopamine, norepinephrine, epinephrine (> 0.3 mcg/kg/min); inotrope included dobutamine, epinephrine (< 0.3 µg/kg/min), milrinone; vasodilator included nitroprusside, milrinone.

<sup>a</sup> Fisher's exact test; <sup>c</sup> Mann–Whitney rank-sum test

Considering all patients, 28-day mortality was higher for patients who presented with  $ScvO_2 < 70\%$  (41.9% vs. 24.3%; HR = 3.04 (1.43–8.79);  $p = 0.006$ ). Comparing the control versus the intervention group, mortality was similar in the two groups for patients with  $ScvO_2 \geq 70\%$  (21.7% vs. 11.8%; HR = 1.91 (0.51–7.57);  $p = 0.32$ ), but significantly different for patients who presented with  $ScvO_2 < 70\%$  (68.8% vs. 13.3%; HR = 6.83 (1.80–17.02);  $p = 0.003$ ) (Fig. 3).

The number of organ dysfunctions at enrolment was similar in the two groups. The intervention group developed fewer new organ dysfunctions, due to reduced incidence of renal and neurological dysfunction (Table 3). Before study entry, the initial resuscitation was similar in the two groups: the control group received 40 ml/kg (interquartile range 30–70 ml/kg) of crystalloid, no colloid, and 5.9% of the patients received packed red blood cells (PRBC), while the intervention group received 40 ml/kg (interquartile range 30–70 ml/kg) crystalloid ( $p = 0.89$ ), no colloid ( $p = 1.00$ ), and 3.9% received PRBC ( $p = 1.00$ ). Between 0 and 6 h after study entry, the intervention group received significantly more crystalloids ( $p < 0.0001$ ) and more frequently received red-cell transfusion ( $p = 0.002$ ) and inotropic support ( $p = 0.01$ ) (Table 4).

Other supportive therapies were similar between the two groups (Table 4). Pulmonary artery catheters and activated protein C were not used in any patient, and extracorporeal membrane oxygenation was not available in either of the two centres involved in the trial. All patients enrolled in the study received a central line for at least 72 h and there was no complication related to line placement.

## Discussion

In this randomised controlled trial, there was a significant difference in mortality rate with use of ACCM/PALS

haemodynamic support guidelines for septic shock between patients with or without  $ScvO_2$  guided therapy. Patients who received therapies directed to the goal of  $ScvO_2 > 70\%$  were given more fluid, red blood cells and inotropic support after the initial resuscitation, with a resulting 3.3-fold reduction in mortality. This study supports the current ACCM/PALS guidelines. Goal-directed therapy using the endpoint of a  $ScvO_2 \geq 70\%$  provided a significant and additive impact on the outcome of children and adolescents with septic shock in our centres.

In 2002, consensus guidelines on haemodynamic support of paediatric and neonatal patients with septic shock recommended that early recognition, adequate fluid resuscitation, appropriate cardiovascular therapies, and timely and appropriate antibiotic therapy and source control are all crucial to optimal outcome [17]. Studies in children have shown that early aggressive volume repletion, even without addressing myocardial dysfunction, significantly improves outcome [16, 25, 26]. Similar findings have been shown when conventional ACCM/PALS guidelines are applied in the emergency department setting before PICU admission. More importantly, when the lack of shock reversal secondary to inadequate resuscitation was present, the odds of mortality doubled with each hour of persistent shock [25]. Recent adult studies have shown that goal-directed resuscitation using  $SvO_2/ScvO_2$  has pathogenic, prognostic, therapeutic and outcome benefits in the management of severe sepsis and septic shock [27, 28]. However, prior to this study, the addition of  $ScvO_2$  as an endpoint in PALS, while making physiological sense, had not been validated in an outcome study.

Goal-directed haemodynamic optimisation represents an organised approach to volume repletion, attainment of a target blood pressure (vascular tone) and a more definitive resolution of a pathologic oxygen supply dependency or global tissue hypoxia through a normalisation of  $ScvO_2$  as a surrogate endpoint. A study in adult patients



with severe sepsis and septic shock confirmed that global tissue hypoxia, defined by an  $\text{ScvO}_2 < 70\%$ , can still be present even if physical examination, vital signs, central venous pressure and urinary output are considered adequate. In addressing this global tissue hypoxia using an early goal-directed approach, further reductions in the inflammatory response, morbidity and mortality were achieved compared with conventional therapy [27]. While the early goal-directed therapy patients received more fluids, red blood cell transfusions and inotropes over the first 6 h for a higher rate of attaining a  $\text{ScvO}_2 \geq 70\%$ ; there was essentially no difference in these therapies after the first 72 h. Because of this early haemodynamic optimisation, significant reductions in vasopressors, mechanical ventilation and pulmonary artery catheter use were also realised [27].

Similar to this previous study, the mortality reduction observed in our study is most likely the result of multiple interventions. Patients who had failed initial attempts at volume resuscitation based on ACCM/PALS recommendations was equally distributed between the two treatment groups and provided a high degree of illness severity. In spite of considerable initial volume resuscitation, the intervention group received more fluid (crystalloid), more red blood cell transfusion and more inotropic support in the first 6 h of treatment than the control group. After 72 h, the amount of crystalloid administered and the percentage of red blood cells transfusion were not different between the two groups. These observations were similar to those found in adults. Together, these two studies support the concept that early resuscitation rather than later resuscitation is beneficial [17, 18, 25, 26]. In addition, there was a statistically significant reduction in the number of children with  $\text{ScvO}_2 < 70\%$  at 72 h in the intervention group. This supports the concept that goal-directed therapy can reduce global oxygen debt over the long term as well as the short term in patients with septic shock.

The issue of whether an  $\text{ScvO}_2$  of 70% is an adequate therapeutic endpoint for the resolution of global tissue hypoxia has been heavily debated in adult, paediatric and neonatal models [29–37]. Studies in this regard are lacking in children, which makes the recommended value of 70% as target value in ACCM/PALS guidelines empirical [17]. Furthermore, the evaluation of the technology of continuous venous oximetry is particularly important in developing countries because of the potential added cost to health care. Our group previously has examined the clinical utility of this technology in the paediatric patient [22].

$\text{ScvO}_2$  proved to be beneficial in discriminating high-risk patients. Kaplan–Meier estimates showed a higher mortality rate for patients with  $\text{ScvO}_2 < 70\%$  at presentation. The similarity between the curves for  $\text{ScvO}_2 \geq 70\%$  in both groups and the significant difference between the curves for  $\text{ScvO}_2 < 70\%$  in the two groups supported the hypothesis that the intervention rescued patients from cryptic shock, and provided validation of the true

independence of the treatment protocol from assignment groups.

Although a considerable proportion of children presented with  $\text{ScvO}_2$  below 70%, the average values were not as low as those reported in adults. Since very few data derived in similar circumstances are available in the literature, we can only speculate that children with severe sepsis were diagnosed earlier than adults or that unspecified age-dependent factors explain the observation. The observed absence of increased lactate values was consistent with less dramatic reductions in  $\text{ScvO}_2$  in our children than those reported in adults.

In addition to the favourable reduction in mortality, a decrease in pulmonary (increased number of ventilator-free days), neurological and renal dysfunction was also seen. These findings support previous studies showing that early haemodynamic optimisation is associated with decreased health care resource consumption [38, 39]. Because of these salutary findings, the intervention group protocol has now become a standard of care at both participating hospitals.

#### Limitations

Several limitations are important to consider when evaluating this study. First, this was not a blinded study as the catheter and spectrophotometry unit used to monitor  $\text{ScvO}_2$  was not present in the control group. To minimise this influence, all treatment decisions were based on ACCM/PALS guidelines and were decided by the medical team responsible for the patient. Second, although  $\text{ScvO}_2$  monitoring may provide an early warning signal that may prompt earlier interventions before haemodynamic deterioration [28], this study is not an endorsement of continuous venous oximetry technology. In the absence of continuous monitoring, intermittent sampling may provide benefit. Third, the mortality rate observed in the control group is similar to or even lower than those reported in studies from developing countries, especially when patients with underlying diseases and multiple organ failure were included, and it was also lower than the mortality rate reported by our group two years before the study (39.2% vs. 57.3%), possibly reflecting a treatment effect of ACCM/PALS guidelines even without  $\text{ScvO}_2$  monitoring. Fourth, baseline characteristics of the two groups were similar, except for age, with the control group population being younger. Even though the multivariate logistic regression analysis showed there was no difference in outcome attributable to age, and previous studies from our centres reported that increased age was associated with increased mortality, this baseline difference should still be kept in mind [19]. Fifth, we studied a population which had a mortality rate of 40%. A recent survey of the KIDS database in the United States showed an 8% mortality rate for children with severe

sepsis and chronic illness, and a 2% mortality rate for those with severe sepsis who were previously healthy [40]. Although validation of the presented data would be desirable for different populations, we believe it is crucial to have a resuscitation target in any environment, as we observed that the benefit arose from rescuing patients from cryptic shock, rather than offering a stimulus to more aggressive treatment. At this moment, the presented results are valid only for this sample of patients. Sixth, the trial was conducted in two centres in Brazil, indicating that the findings are specifically valid for our country and possibly other developing nations, where health care resources are limited and more sophisticated technologies are not widely available. It remains unknown whether this technology will be beneficial in technology-rich environments.

## Conclusion

We conclude that goal-oriented resuscitation with the current ACCM/PALS guidelines can improve morbidity and mortality when supplemented by ScvO<sub>2</sub> monitoring. These findings may have a significant impact on the outcome of children and adolescents with septic shock.

**Author contributions.** C.F. de Oliveira had full access to all the data in the study and had final responsibility for the decision to submit for publication. He participated in study concept and design, acquisition of data, analysis of data, drafting of the manuscript, revision of the manuscript, statistical analysis, and obtaining funding. D.S.F. de Oliveira participated in acquisition of data, revision of the manuscript, and technical and administrative support. A.F.C. Gottschald participated in acquisition of data, revision of the manuscript, and technical and administrative support. J.D.G. Moura participated in acquisition of data, revision of the manuscript, and technical and administrative support. G.A. Costa participated in acquisition of data, revision of the manuscript, and technical and administrative support. A.C. Ventura participated in study concept and design, acquisition of data, analysis of data, drafting of the manuscript, revision of the manuscript, and statistical analysis. J.C. Fernandes participated in study concept and design, acquisition of data, and revision of the manuscript. F.A.C. Vaz participated in study concept and design, analysis of data, and revision of the manuscript. J.A. Carcillo participated in study concept and design, analysis of data, drafting of the manuscript, and revision of the manuscript. E.P. Rivers participated in analysis of data, drafting of the manuscript, and revision of the manuscript. E.J. Troster participated in study concept and design, analysis of data, drafting of the manuscript, revision of the manuscript, statistical analysis, and obtaining funding.

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## References

- DuPont HL, Spink WW (1968) Infectious due to gram negative organisms: an analysis of 860 patients with bacteremia at University of Minnesota Medical Center, 1958–1966. *Medicine (Baltimore)* 48:307–311
- Pollack MM, Fields AI, Ruttimann UE (1985) Distributions of cardiopulmonary variables in paediatric survivors and nonsurvivors of septic shock. *Crit Care Med* 13:454–459
- Carcillo JA, Davis AL, Zaritsky A (1991) Role of early fluid resuscitation in paediatric septic shock. *JAMA* 266:1242–1245
- Watson RS, Carcillo JA, Linde-Zwirble WT, Clermont G, Lidicker J, Angus DC (2003) The epidemiology of severe sepsis in the United States. *Am J Respir Crit Care Med* 167:695–703
- Pollard AJ, Britto J, Nadel S, DeMunter C, Habibi P, Levin M (1999) Emergency management of meningococcal disease. *Arch Dis Child* 80:290–296
- Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR (2001) Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Crit Care Med* 29:1303–1310
- Kutko MC, Calarco MP, Flaherty MB, Helmrich RF, Ushay HM, Pon S, Greenwald BM (2003) Mortality rates in paediatric septic shock with and without multiple organ system failure. *Pediatr Crit Care Med* 4:333–337
- Khilnani P, Sarma D, Zimmerman J (2006) Epidemiology and peculiarities of pediatric multiple organ dysfunction syndrome in New Delhi, India. *Intensive Care Med* 32:1856–1862
- Sarathi M, Lodha R, Vivekanandhan S, Arora NK (2007) Adrenal status in children with septic shock using low-dose stimulation test. *Pediatr Crit Care Med* 8:23–28
- Chang P, Hsu HY, Chang MH, Lin FY (1999) Shock in the paediatric emergency service: five years' experience. *Acta Paediatr Taiwan* 40:9–12
- Branco RG, Garcia PC, Piva JP, Casartelli CH, Seibel V, Tasker RC (2005) Glucose level and risk of mortality in paediatric septic shock. *Pediatr Crit Care Med* 6:470–472
- Wilkinson JD, Pollack M, Glass NL, Kanter RK, Katz RW, Steinhart CM (1987) Mortality associated with multiple organ system failure and sepsis in paediatric intensive care unit. *J Pediatr* 111:324–328
- Proulx F, Fayon M, Farrell CA, Lacroix J, Gauthier M (1996) Epidemiology of sepsis and multiple organ dysfunction syndrome in children. *Chest* 109:1033–1037
- Plotz FB, Hulst HE, Twisk JW, Bökenkamp A, Markhorst DG, van Wijk JA (2005) Effect of acute renal failure on outcome in children with severe septic shock. *Pediatr Nephrol* 20:1177–1181
- Pancera CF, Costa CM, Hayashi M, Lamelas RG, Camargo B (2004) Severe sepsis and septic shock in children with cancer. *Rev Assoc Med Bras* 50:439–443
- Booy R, Habibi P, Nadel S, de Munter C, Britto J, Morrison A, Levin M, Meningococcal Research Group (2001) Reduction in case fatality rate from meningococcal disease associated with improved healthcare delivery. *Arch Dis Child* 85:386–390
- Carcillo JA, Fields AI, American College of Critical Care Medicine Task Force Committee Members (2002) Clinical practice parameters for hemodynamic support of paediatric and neonatal patients in septic shock. *Crit Care Med* 30:1365–1378

18. Ceneviva G, Paschall JA, Maffei F, Carcillo JA (1998) Hemodynamic support in fluid-refractory paediatric septic shock. *Paediatrics* 102:1–6
19. Pizarro CF, Troster EJ, Damiani D, Carcillo JA (2005) Absolute and relative adrenal insufficiency in children with septic shock. *Crit Care Med* 33:855–859
20. Oliveira CF, Troster E, Oliveira DSF, Gottschald A, Moura J, Costa G, Vaz F, Carcillo JA, Rivers E (2007) An outcomes comparison of ACCM/PALS guidelines for paediatric septic shock with and without central venous oxygen saturation monitoring. *Pediatr Crit Care Med* 8:A237–A238
21. Carcillo JA, Hazelzet JA (2005) Sepsis and multiple organ system failure in children. In: Fink MP, Abraham E, Vincent JL, Kochanek PM (eds) *Textbook of critical care*. Elsevier Saunders, Philadelphia, pp 1267–1273
22. Oliveira CF, Troster EJ, Vaz FAC (2005) Description of technique for continuous monitoring of central venous oxygen saturation in infants and children with septic shock. Case reports. *Revista Brasileira Terapia Intensiva* 17:305–308
23. Wilkinson JD, Pollack MM, Ruttimann UE, Glass NL, Yeh TS (1986) Outcome of paediatric patients with multiple organ system failure. *Crit Care Med* 14:271–274
24. Wilkinson JD, Pollack MM, Glass NL, Kanter RK, Katz RW, Steinhart CM (1987) Mortality associated with multiple organ system failure and sepsis in paediatric intensive care unit. *J Pediatr* 111:324–328
25. Han YY, Carcillo JA, Dragotta MA, Bills DM, Watson RS, Westerman ME, Orr RA (2003) Early reversal of paediatric-neonatal septic shock by community physicians is associated with improved outcome. *Paediatrics* 112:793–799
26. Ninis N, Phillips C, Bailey L, Pollock JI, Nadel S, Britto J, Maconochie I, Winrow A, Coen PG, Booy R, Levin M (2005) The role of healthcare delivery in the outcome of meningococcal disease in children: case-control study of fatal and non-fatal cases. *BMJ* 330:1475
27. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Peterson E, Tomlanovich M, Early Goal-Directed Therapy Collaborative Group (2001) Early goal-directed therapy in the treatment of severe sepsis and septic shock. *NEJM* 345:1368–1377
28. Krafft P, Steltzer H, Hiesmayr M, Klimscha W, Hammerle AF (1993) Mixed venous oxygen saturation in critically ill septic shock patients. The role of defined events. *Chest* 103:900–906
29. Gattinoni L, Brazzi L, Pelosi P, Latini R, Tognoni G, Pesenti A, Fumagalli R (1995) A trial of goal-oriented hemodynamic therapy on critically ill patients. *NEJM* 333:1025–1032
30. Pearse RM, Rhodes A (2005) Mixed and central venous oxygen saturation. In: Vincent JL (ed) *Yearbook of intensive care and emergency medicine*. Springer, Berlin Heidelberg New York, pp 592–602
31. Scheinman MM, Brown MA, Rapaport E (1969) Critical assessment of use of central venous oxygen saturation as a mirror of mixed venous oxygen in severely ill cardiac patients. *Circulation* 40:165–172
32. Varpula M, Karlsson S, Ruokonen E, Pettilä V (2006) Mixed venous oxygen saturation cannot be estimated by central venous oxygen saturation in septic shock. *Intensive Care Med* 32:1336–1343
33. Dueck MH, Klimek M, Appenrodt S, Weigand C, Boerner U (2005) Trends but not individual values of central venous oxygen saturation agree with mixed venous oxygen saturation during varying hemodynamic conditions. *Anesthesiology* 103:249–257
34. Chawla LS, Zia H, Gutierrez G, Katz NM, Seneff MG, Shah M (2004) Lack of equivalence between central and mixed venous oxygen saturation. *Chest* 126:1891–1896
35. Varpula M, Tallgren M, Saukkonen K, Voipio-Pulkki L-M, Pettilä V (2005) Hemodynamic variables related to outcome in septic shock. *Intensive Care Med* 31:1066–1071
36. Schranz D, Schmitt S, Oelert H, Schmid F, Huth R, Zimmer B, Schuind A, Vogel K, Stopfkuchen H, Jüngst BK (1989) Continuous monitoring of mixed venous oxygen saturation in infants after cardiac surgery. *Intensive Care Med* 15:228–232
37. Hirschl RB (1994) Oxygen delivery in the paediatric surgical patient. *Curr Opin Pediatr* 6:341–347
38. Estenssoro E, Gonzalez F, Laffaire E, Canales H, Sáenz G, Reina R, Dubin A (2005) Shock on admission day is the best predictor of prolonged mechanical ventilation in the ICU. *Chest* 127:598–603
39. Rossi C, Simini B, Brazzi L, Rossi G, Radrizzani D, Iapichino G, Bertolini G, Gruppo Italiano per la Valutazione degli Interventi in Terapia Intensiva (2006) Variable costs of ICU patients: a multicenter prospective study. *Intensive Care Med* 32:545–552
40. Odetola FO, Gebremariam A, Freed GL (2007) Patient and hospital correlates of clinical outcomes and resource utilization in severe pediatric sepsis. *Pediatrics* 119:487–494