Introduction

Sepsis is a leading cause of multiple organ dysfunction (MODS) and death in critically ill children [1, 2, 3]. It is characterized by the systemic inflammatory response syndrome (SIRS) [4], an abnormal redistribution of circulatory blood flow and a modified substrate utilization associated with hypermetabolism [5].

Early detection of physiologic abnormalities is the basis for monitoring in the intensive care unit (ICU) [6]. Various markers have been proposed in order to modify therapy with the underlying assumption that inadequate oxygenation and tissue hypoperfusion are central to the pathogenesis of MODS. Pulmonary artery catheters provide information on systemic hemodynamics at the global level. Nevertheless, increased oxygen-
Table 1  Diagnostic criteria for the systemic inflammatory response syndrome SIRS, sepsis, severe sepsis, and septic shock [2] (PaCO₂ arterial carbon dioxide tension)

| SIRS (at least two of the following criteria): |  |
|---------------------------------------------|---|
| (a) Temperature > 38 °C or < 36 °C rectal  |  |
| (b) Heart rate > 90th percentile for age  |  |
| (c) Tachypnea with a respiratory rate > 90th percentile for age or PaCO₂ < 4.3 kPa (< 32 torr) |  |
| (d) White blood cell count > 12 × 10⁹/l (> 12000 cells/mm³) or < 4 × 10⁹/l (< 4000 cells/mm³) or > 10% immature (band) forms |  |

Sepsis
SIRS caused by an infection (positive culture from any site, clinical evidence of infection)

Severe sepsis: sepsis plus one of the following criteria

(a) decreased consciousness (Glasgow Coma Score < 15 without disease of the central nervous system)
(b) arterial blood lactate > 1.6 mmol/l (> 1.6 mEq/l)
(c) urine output < 1 ml/kg per h for 2 consecutive h with a urinary catheter

Septic shock
Presence of hypotension with two distinct measurements of blood pressure < 3rd percentile for age after administration of ≥ 20 ml/kg of crystalloids or colloids plus (a) the requirement for inotropic or vasopressor support (excluding dopamine ≤ 5 µg/kg per min) or (b) any of the previously defined diagnostic criteria for severe sepsis

Patients and methods

Population characteristics

The study was approved by the ethics committee of Sainte-Justine Hospital. Informed consent was obtained from the parents for inclusion in the study. This study was conducted prospectively in a 22-bed, multidisciplinary pediatric ICU of a university hospital. All children aged between 1 and 18 years old, who had been admitted to the pediatric ICU at Sainte-Justine Hospital from 15 February 1995 to 15 March 1997 were screened for the study. Patients were eligible only if they required mechanical ventilation for septic shock. Those children who developed septic shock after ICU admission were not eligible. Children under 1 year of age and those with the following comorbid states were also excluded: inborn errors of metabolism, Reye-like syndrome, use of valproic acid, prior renal or hepatic dysfunction, diabetes mellitus, and malnutrition defined as weight [18] or tricipital skinfold thickness < 10th percentile for age and sex [19].

Clinical data

Age, sex, physiologic variables, therapeutic interventions. Pediatric Risk of Mortality (PRISM) score [20], length of ICU stay, and ICU mortality were noted. The expected rate of mortality for our study population was calculated according to the following formula: p (ICU death) = exp(r)/[1 + exp(R)], where r = 0.207 × PRISM–0.005 × age (months)–0.433 × operative status (postoperative = 1, nonoperative = 0)–4.782. Operational diagnostic criteria for SIRS, sepsis, severe sepsis, and septic shock are presented in Table 1. Diagnostic criteria for MODS used in this study have been previously defined [2]. Weight was obtained on a metabolic balance (Scale-Tronix 2001, White Plains, N.Y., USA). Tricipital skinfold thickness was measured with a skinfold caliper (Lange HB 859-1-2, Cambridge Scientific Industries, Cambridge, Md., USA). The mean of three consecutive measurements was compared to normal values [19]. Oxygen consumption and delivery (VO₂, DO₂), gastric intramucosal pH (pHi), gastro-arterial PCO₂ gradient (APCO₂-PaCO₂), serum lactate, pyruvate, 3-hydroxybutyrate, acetoacetate, and plasma free fatty acids (FFA), total carnitine, and esterified carnitine were measured on study entry and then 6, 12, 24, 36, and...
48 h later. The data collection was stopped before 48 h if the patient could be weaned from mechanical ventilation and extubated.

**Oxygenation indices**

A 5 or 7 French pulmonary artery catheter (Arrow International, Reading, Penna., USA) was inserted by the attending physician. An arterial line was placed in all patients. Pressure transducers (Baxter, Irvine, Calif., USA) were calibrated before each set of measurements. Cardiac output was measured randomly throughout the respiratory cycle [21] by rapid injection of 5 or 10 ml of saline at room temperature. All patients received continuous infusions of fentanyl and midazolam, and five children were given continuous vecuronium. The mean of three consecutive measurements was used for calculation of cardiac index; oxygenation parameters were then calculated using simultaneously drawn mixed venous and arterial blood gases according to the following formula: arterial O2 content = (hemoglobin g/dl × systemic arterial O2 saturation × 1.34) + (arterial O2 tension × 0.003); DO2 = (cardiac index l/min per m2 × systemic arterial O2 content); VO2 = mixed venous content–systemic arterial O2 content, using mixed venous and systemic arterial saturation [22]. Systemic arterial O2 saturation was measured using a blood gas analyser (Nova Stat Profile 5, Nova Biomedical, Watham, Mass., USA).

**L/P ratio**

Blood samples were immediately deproteinized by precipitation of 200 μl titrated whole blood with 400 μl of trichloric acid 2%. These were transported on ice and centrifuged at 2200 rpm, 4°C for 10 min. Supernatants were then neutralized with bicarbonate and frozen at -80°C. Lactate and pyruvate were determined by an enzymatic method as previously reported [23].

**Marker of splanchnic hypoperfusion**

A 16 French gastric tonometer (TRIP-NGS catheter, Tonometrics, Worcester, Mass., USA) was introduced orally; adequate positioning into the stomach was verified by radiography. No patients were fed enterally, but all children received ranitidine, 0.5 mg/kg per dose intravenously every 6 h. The silicone balloon was flushed many times with phosphate buffer solution (Omega, Montreal, Canada) and then filled with 2.5 ml of this solution. It was allowed to equilibrate for 240 min. Then, the first 1 ml was discarded and 1.5 ml was put on ice. Measurement of CO2 was done using a blood gas analyser (Nova Stat Profile 5, Nova Biomedical, Watham, Mass., USA). The pHi was calculated according to the modified Henderson-Hasselbach equation: pHi = 6.1 + log10[bicarbonate arterial / (F × PCO2)], where F is a constant accounting for both the solubility of CO2 and the equilibration time. Using this method, Takala et al. have reported a bias ranging from –1.4 to 2.0 torr for high and low control values of CO2, respectively [24].

**Other markers of intermediary metabolism**

For 3-hydroxybutyrate and acetoacetate measurements, samples were deproteinized by adding 500 μl of perchloric acid (0.9 mmol/l) to 500 μl of whole blood. These measurements were done in duplicate. They are based on a fully enzymatic endpoint spectrophotometric method. The concentrations of ketone bodies are calculated from the amount of nicotinamide-adenine dinucleotide to the reduced form (NADH) converted during the time required to complete the reaction using the absorption coefficient of NADH at 340 nm [25, 26]. Quantification of FFA was performed in duplicate by an vitro enzymatic colorimetric method (Wako Chemicals, Dallas, Tex., USA). Plasma total and free carnitine concentrations were determined in duplicate by radioenzymatic assay as previously reported by us [27].

**Table 2 Characteristics of patients (ARDS adult respiratory distress syndrome, CSF cerebrospinal fluid, TTP thrombotic thrombocytopenic purpura)**

| Patientsa | Age (months) | Sex | PRISM | Diagnosis | Culture (sites) |
|----------|-------------|-----|-------|-----------|----------------|
| 1        | 19          | M   | 7     | Severe chickenpox | Negative |
| 2        | 174         | F   | 3     | Peritonitis/Meckel Pancreatitis/ARDS | Negative |
| 3        | 187         | F   | 33    | Chorioamniotis/ARDS | Escherichia coli (blood + vagina) |
| 4        | 67          | F   | 20    | Meningococcemia/ARDS | Nesseria meningitidis (blood) |
| 5        | 48          | F   | 20    | Sepsis-associated hemophagocytosis | Respiratory syncytial virus (nasopharyngeal) |
| 6        | 145         | F   | 24    | Toxic shock | Streptococcus A (pus) |
| 7        | 25          | F   | 5     | Meningitis | Streptococcus pneumoniae (blood and CSF) |
| 8        | 29          | F   | 7     | Meningococcemia | Nesseria meningitidis (blood and CSF) |
| 9        | 39          | F   | 19    | Meningococcemia | Nesseria meningitidis (blood) |
| 10       | 188         | F   | 17    | Community-acquired pneumonia | Negative |
| 11       | 75          | M   | 46    | TTP/ARDS | Negative |

a The symbols refer to individual patients identified in Figs. 1 to 4
Fig. 1 Global markers of tissue hypoperfusion. Oxygen consumption (\(VO_2\)), oxygen delivery (\(DO_2\)), arterial pH (\(pHa\)), and serum bicarbonate in children with septic shock (individual measurements are shown on left, mean ± 95% confidence interval is presented on right).

\(VO_2\) and \(DO_2\) were measured in 7 children only, who required a pulmonary artery catheter. Levels of serum bicarbonate normalized over time in all patients recovering from sepsis, while those of \(VO_2\), \(DO_2\) and \(pHa\) displayed large variances. Three children (closed circle, closed triangle, open diamond) showed decreasing \(VO_2\) values to less than 100 ml/min per m\(^2\) at the end of the study. Another patient (open triangle) survived without ever reaching supranormal \(DO_2\) (> 570 ml/min per m\(^2\)) [8]
Statistical analysis

Descriptive statistics are presented as mean ± 95% confidence interval. Coefficients matrix of correlation between measurements of the different markers under study were established using the values obtained upon admission. Statistical significance was established at 0.05.

Results

Eleven previously healthy children were admitted to the pediatric ICU for septic shock. Characteristics of these patients are presented in Table 2. All patients required mechanical ventilation and met criteria for septic shock. Nine children (80%) also developed MODS [2]. The mean age was 91 ± 69 months, the PRISM score was 17 ± 11 (expected mortality of 50%), and the length of
ICU stay was 8 ± 7 days. The use of dopamine or dobutamine alone (15 µg/kg per min) was required in 3 children, dopamine and dobutamine (15–20 µg/kg per min, 10–15 µg/kg per min, respectively) were required in 2 patients, and 6 children were treated with three vaso-pressors (dopamine 15–25 µg/kg per min, dobutamine 10–43 µg/kg per min, and epinephrine 0.2–0.7 µg/kg per min). All patients were survivors from pediatric ICU.

VO₂, DO₂, arterial pH (pHa), and levels of serum bicarbonate are presented in Fig. 1. The figure shows that large variations were observed for both VO₂ and DO₂. We noted unexpected values of VO₂ < 100 ml/min per m² at the end of the study in 3 patients. However, supranormal values of DO₂ (> 570 ml/min per m²) [8] were observed in 7 of 8 patients, accounting for 56% (18/32) of DO₂ measurements. Only 23% (13/57) of pHa measurements were lower than 7.35; this was secondary to high minute ventilation induced by mechanical ventilation (data not shown). Overall, the steadily increasing values of serum bicarbonate reflected well patients’ recovery from septic shock. Levels of serum lactate and pyruvate and the L/P ratio are presented in Fig. 2. The figure shows that serum lactate levels rapidly normalized over time in all individuals. We noted abnormal levels of lactate in 29% (15/53) of samples and of L/P in 27% (14/53) (normal lactate < 1.8 mmol/l, L/P 16 ± 5 [28]). Increasingly abnormal values for the L/P ratio were noted at normal lactate levels in 1 patient who was recovering, suggesting increased pyruvate utilization. Nevertheless, upon admission, the L/P ratio was significantly inversely correlated with VO₂ (r² = –0.8; p = 0.02) and with pHi (r² = –0.5; p = 0.03). Regional markers of splanchnic hypoperfusion are presented in Fig. 3. The figure shows that both ΔPtCO₂-PaCO₂ and gastric pHi displayed significant variability over time with unpredictable trends in individual measurements within the first 24 h. We noted abnormal levels of pHi in 72% (38/53) of samples and of ΔPtCO₂-PaCO₂ in 78% (41/53) of samples (normal pHi < 7.35 [14, 15], ΔPtCO₂-PaCO₂ < 7 mmHg [29]). Moreover, 58% (31/53) of pHi measurements were less than 7.32 and 43% (23/53) were lower than 7.30 [17]. Five patients (45%) presented a gastric pHi < 7.30 on admission and 7 children (63%) had two or more pHi values of < 7.30 during the study period. Markers of intermediary metabolism are presented in Fig. 4. The figure shows that most values for the ketone body ratio remained within the normal range (3.5 ± 1.2 mmol/l) [28]. The total production of ketone bodies and FFA also appeared appropriate. There was no evidence of carnitine deficiency in
this population [30]. The esterified carnitine (EC/FC) ratio was also within the normal range (0.4 ± 0.2) and thus gave little information [30].

**Discussion**

The patients included in this study were severely ill as reflected by their high PRISM score and their requirement for significant cardiopulmonary support. We estimated that the expected survival rate was lower than 50%. The lack of any death among our study population...
Calculation of VO\textsubscript{2}, and to a lesser extent DO\textsubscript{2}, be associated with patients' recovery from septic shock. Over time of serum bicarbonate and lactate seemed to were frequently noted. However, only the normalization pHa, serum bicarbonate, lactate, L/P ratio, and pHi levels in 1 child who survived sepsis. This may question the biological significance of the L/P ratio as being only a marker of the cytosolic redox potential in vivo. As reported among adults with sepsis [33] and children with extensive burns [34], this may rather reflect the occurrence of an increased rate of glycolysis and pyruvate utilization in order to meet increased metabolic needs as reflected by high VO\textsubscript{2} upon initial presentation.

We observed appropriate FFA, ketone bodies, and plasma carnitine levels. As 3-hydroxybutyrate and acetocetate freely penetrate the cell membrane, it has been suggested that the arterial ketone body ratio may adequately reflect the redox potential within hepatic mitochondria during liver transplantation [35]. The value and the biological significance of this marker during pediatric septic shock remains unclear. Our data do not suggest an inhibition of carnitine palmitoyl transferase [36, 37, 38]. Indeed, although no carnitine deficiency was observed in this study, slightly increased plasma concentrations of EC may have been related to the net synthesis of ketone bodies, an increased production of toxic acyl-CoA esters [39], or an increased production of malonyl-CoA due to an increased rate of pyruvate oxidation. Circulating concentrations of these metabolic markers may simply not reflect intracellular conditions [27].

In this study, we showed that the normalization of serum bicarbonate and lactate has a timely association with patients recovery during pediatric septic shock. The unpredictable trends noted within the serial measurements of individual patients for VO\textsubscript{2}, DO\textsubscript{2}, pH\textsubscript{i}, or PtCO\textsubscript{2}-PaCO\textsubscript{2} raise questions on how these markers may have been rationally used to modify therapy in this population.

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