# Early Goal-Directed Therapy of Pediatric Septic Shock in the Emergency Department

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**Abstract**

Cumulative evidence from studies of severe sepsis and septic shock has confirmed the importance to patient survival of timely oxygen augmentation targeted at specific goals related to oxygen delivery to the tissues. This work describes the evolution of our understanding of the pathophysiology of septic shock and the integration at our center of the guidelines of the American College of Critical Care Medicine and the Surviving Sepsis Campaign into a step-by-step protocol for early recognition and resuscitation of children with severe sepsis and septic shock in the emergency department. This work is intended to alert emergency room physicians of the critical need for early screening and aggressive efforts to reverse tissue hypoperfusion in pediatric patients with septic shock, even in the presence of normal mental status and blood pressure.

**MeSH Words**: Sepsis, shock, pediatric, emergency, resuscitation

## Introduction

*Illustrative Case: A previously healthy 13 month old boy weighing 11 Kg is brought to the Emergency Department (ED) with a 2-day history of flu-like symptoms, decreased oral intake and fever of $40^0$C. Upon admission, he seems irritable and his extremities are cold to touch and his capillary filling time is 6 seconds; his blood pressure is 89/40, heart rate 160, respiratory rate 42, and his arterial oxygen saturation in room air is 94% by pulse oximetry. There is no apparent source for the fever. Because of the cool extremities, obtaining I.V. access is challenging, but after several attempts over 30 minutes, an antecubital venous catheter is inserted and blood work is drawn. He is given a bolus of 220 cc of normal saline over an hour, I.V. ceftriaxone and oral acetaminophen. Laboratory results show a white blood cell count of 18,000 with 11% bands, serum bicarbonate of 18 mEq/L and base deficit of 6 mEq/L. Electrolytes, BUN and creatinine are normal. Another bolus of 220cc of fluid is given over an hour. At 3 hours after admission to the ED, his temperature improves to 38.9C, and his heart rate is decreased to 150/minute. His capillary*

*refill time remains prolonged and he seems lethargic. He is admitted to the pediatric ICU with the diagnosis of "rule out sepsis" for observation and close monitoring.*

The child described in the illustrative case suffered from septic shock with evidence of organ hypoperfusion. The fever, tachycardia, tachypnea and leukocytosis indicate that this child presented with signs and symptoms of Systemic Inflammatory Response Syndrome (SIRS) [1]. SIRS in the presence of proven or suspected infection indicates *sepsis*. The presence of prolonged capillary refill and metabolic acidosis after fluid resuscitation indicates fluid-refractory cardiovascular dysfunction. The co-existence of sepsis and organ dysfunction indicates that the patient suffered from *severe sepsis*. When the dysfunctional organ in a patient with severe sepsis is the cardiovascular system, the diagnosis of fluid-refractory *septic shock* is made [2]. In adults, hypotension is a required criterion for the definition of cardiovascular failure in septic shock. Since hypotension is a late manifestation of cardiovascular dysfunction in children, additional criteria for cardiovascular dysfunction have been added; a combination of two of the following in the presence of sepsis leads to the diagnosis of septic shock: unexplained metabolic acidosis, increased serum lactate, oliguria, prolonged capillary refill and increased core to peripheral temperature gap [2]. One can determine the presence of t*issue hypoperfusion* during sepsis when the patient has very high serum lactate levels (>4 mmol/L), resulting from shift of the hypoperfused tissue to anaerobic metabolism, or by the presence of cardiovascular dysfunction and septic shock. The determination that the patient suffers from tissue hypoperfusion is critical, since this condition requires early aggressive reversal in order to prevent organ damage.

Although the course of treatment described in the illustrative case is commonly applied in pediatric emergency departments (EDs), it does not meet the current recommended treatment guidelines for septic shock, and could place the child at risk of organ injury and death. Some septic shock patients maintain reasonable mental status and blood pressure despite significant tissue hypoperfusion, which has led many of us in the past to be less aggressive in our resuscitative efforts than we should have been.

Our goal is to review recent changes in our understanding of the pathophysiology of septic shock and the new goal-directed management strategies aimed at preventing organ failure in order to improve survival.

**Review of the literature**

Sepsis is the most common cause of death in children worldwide. Using World Health Organization criteria (severe sepsis defined as sepsis with acidosis, hypotension or both), it was determined that in 1995 there were more than 42,000 cases of severe sepsis in children in the United States [3]. Mortality rates from severe sepsis and septic shock in pediatric patients are lower than the rates in adults. Hospital mortality among U.S. children with severe sepsis in 1995 was 10.3% (7.8% in previously healthy children and 12.8% in children with underlying disease) [4].

During sepsis, tissue oxygen demand is high. Organ function depends on oxygen delivery to meet that demand. When oxygen delivery does not meet oxygen demand, oxygen debt and tissue hypoxia develop [5]. The development of tissue hypoxia was predictive of the development of multiorgan failure and death in adults [6], and studies in children with meningococcal shock have shown that delay in diagnosis and treatment was associated with higher mortality [7]. It is apparently the development of organ failure in the context of septic shock that is the major determinant of outcome. In one study of 96 episodes of pediatric septic shock, 13 of 70 episodes of septic shock and multiple organ system failure resulted in death, as opposed to none of the other 26 episodes with septic shock without organ failure [8].

Therefore, augmentation of oxygen delivery during severe sepsis and septic shock is the key strategy available to us to prevent organ dysfunction. As shown in Figure 1, oxygen delivery to the tissues can be improved by increasing cardiac output, plasma hemoglobin concentration, and arterial oxygen saturation. Interventions to increase cardiac output include fluid resuscitation for preload optimization, administration of inotropes to improve contractility, and administration of vasopressors (and sometimes vasodilators) to optimize afterload. However, aggressive "flagging" of the heart during sepsis is not without risk, and the

major challenge facing clinicians is how to determine how much augmentation of oxygen delivery is adequate for the individual patient.

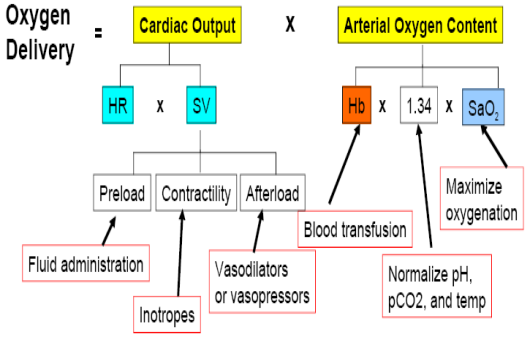



*Figure 1: Determinants of oxygen delivery and therapeutic interventions for their optimization. HR = heart rate; SV = stroke volume; Hb = hemoglobin; $SaO_2$ = arterial oxygen saturation. The value of 1.34 is the number of milliliters of oxygen bound to each gram of hemoglobin. The contribution of oxygen dissolved in plasma to oxygen delivery is very small in this setting and is therefore not displayed in the figure.*

As far back as 1988, Shoemaker et al have shown that the development of oxygen debt in critically ill high-risk surgical patients results in organ failure and increased mortality [9]. Using data obtained from pulmonary artery catheters, they applied aggressive early resuscitation prior to and during surgery by targeting specific goals linked to oxygen delivery to the tissues (cardiac index, oxygen delivery and oxygen consumption). Their protocol resulted in remarkable decrease in mortality rate from 38% to 4% [9]. The value of such goal-directed therapy was confirmed by others in the surgical setting [10] but could not be demonstrated in ED patients and medical ICU patients with septic shock [11-13]. The discrepancy can be explained by differences in timing. Since insertion of a pulmonary artery catheter is impractical in the ED setting, most centers transferred patients identified as having severe sepsis or septic shock to the ICU and only there a pulmonary artery catheter was inserted and resuscitation efforts began. In this "Late Goal-Directed Therapy" strategy, the hemodynamic and oxygen-derived variables used to target therapy were available only after tissue hypoxia has been present for a while, which may explain the failure of these protocols to improve survival in patients with septic shock.

These findings prompted a search for alternative measures to quickly assess the adequacy of tissue perfusion. It has long been known that inadequate oxygen delivery to the tissues results in compensatory increase in tissue oxygen extraction, leading to low mixed venous oxygen saturation ($SmvO_2$) in the pulmonary artery [13]. However, central venous oxygen saturation obtained from the vena cava ($ScvO_2$) has also been shown to correlate well with oxygen delivery and may serve as a reliable proxy for the adequacy of tissue oxygen delivery during resuscitation [14].

Since the insertion of a catheter into the superior vena cava can be accomplished quite quickly in the ED, Rivers et al used $ScvO_2$ as a substitute for Shoemaker's oxygen-derived goals in the ED setting [15]. They demonstrated in a randomized controlled study that the key to successful implementation in the ED of goal-directed therapy of septic shock and severe sepsis with hypoperfusion was aggressive *early* intervention (dubbed Early Goal Directed Therapy or EGDT). Early identification of adult patients with severe sepsis and hypoperfusion (diagnosed by a serum lactate level $\geq$ 4 mmol/L or septic shock), and targeting a superior vena cava oxygen saturation of $\geq$70% within 6 hours of diagnosis, in addition to standard goals (mean arterial pressure, CVP, urine output), resulted in successful reversal of cardiovascular failure, prevented the development of multiple organ failure and improved 28-day survival by 34% compared to a protocol that was using only the standard goals. Stepwise augmentation of oxygen delivery was accomplished as follows: a central venous catheter was inserted, fluid boluses were used to achieve a CVP goal of 8-12 mmHg, and vasopressors were used to normalize blood pressure. The next goal was to achieve a $ScvO_2$ of 70%. If $ScvO_2$ was <70% and the hematocrit < 30%, packed red blood cells were transfused; if the $ScvO_2$ was <70% despite adequate filling pressures and hematocrit, inotropes were added. To accomplish this demanding regimen within 6 hours, the authors established a "sepsis resuscitation unit" in their ED at Henry Ford Hospital in Detroit and staffed it with a well-trained team that included an emergency physician, 2 residents and 3 nurses. Since its publication in 2001, this Early Goal-Directed Therapy (EGDT) protocol has been implemented in many hospitals around the world. It was shown to be feasible in both the ED and the ICU setting, and it was associated with a substantial decrease in morbidity and mortality of patients

with severe sepsis and septic shock [16-20]. Some institutions established the Henry Ford model in their ED; in others, the ED setup was modified to whisk the patients quickly to the ICU so that the 6-hour resuscitation protocol could be completed there.

The critical importance of timely aggressive restoration of oxygen delivery serves as the basis for a new set of recommendations published by a group of experts that established the Surviving Sepsis Campaign [21]. This is an international effort to educate health care professionals and patients on recent evidence-based therapeutic interventions that can improve outcomes in severe sepsis and septic shock. The Campaign uses 2 sets of "bundles" of evidence-based interventions: a "6-hour Resuscitation Bundle" and a "24-hour Management Bundle." Among the key strategies included in the Campaign are

Rivers' EGDT, early use of broad-spectrum antibiotics, use (in adults only) of recombinant human activated protein C (drotrecogin alpha), tight control of serum glucose levels in the 80-110 mg/dL range, low dose steroids in catecholamine-dependent shock, and protective lung ventilation. Special pediatric considerations are also included in the report.

**Early augmentation of oxygen delivery in children**

The EGDT protocol of Rivers et al did not include specific guidelines for the timing to initiation of IV access, since this is rarely an issue in adults. For children with septic shock, the Pediatric Advanced Life Support (PALS) program of the American Heart Association as well as the Task Force for Clinical Practice Parameters for Hemodynamic Support of Pediatric and Neonatal Patients in Septic Shock of the American College of Critical Care Medicine (ACCM) recommend that intravenous access in shock be established within 5 minutes of diagnosis [22]. Several studies have shown that this limit is achievable in the ED setting provided that when peripheral access is not attainable, intraosseous and/or central venous access is included early in the algorithm [23,24]. The ACCM Task Force also recommends completing the 20-60cc/Kg fluid boluses within the next 10 minutes of resuscitation and, if there is no response to fluid administration, starting dopamine within the first hour of resuscitation.

In a retrospective study, pediatric survivors of septic shock were found to have received an average of 42 cc/Kg over the first hour of resuscitation, whereas non-survivors had received only an average of 23 cc/Kg over the first hour. By the end of the first 6 hours, both survivors and non survivors ended up receiving similar volumes [25]. Thus, it was apparently the rapid replenishment of intravascular volume that prevented the development of organ hypoperfusion and organ failure. There was no evidence that rapid replenishment was associated with an increased risk of pulmonary edema or acute respiratory distress syndrome (ARDS) [25].

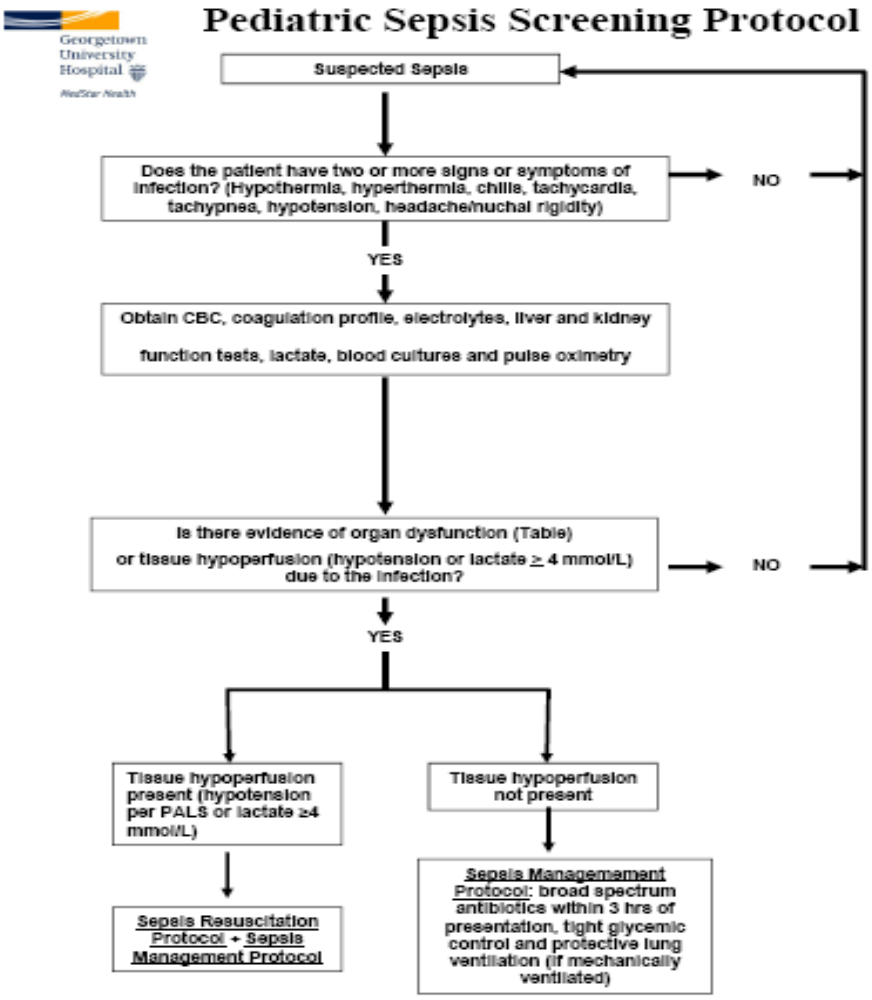
Further support for the importance of early shock reversal in young patients by aggressive fluid resuscitation and vasopressors was provided by a more recent retrospective study of 91 infants and children with septic shock who were transported from community hospitals to a tertiary facility.

Results showed that compliance with ACCM and PALS guidelines was associated with early shock reversal and improved survival. The mortality rate was 8% for patients who were treated in compliance with the guidelines compared to 38% for patients who were not [26].

**Pediatric sepsis management protocols**

Timely management of sepsis is impossible without proper screening. Our center has formulated a pediatric S*epsis Screening Protocol* which incorporates the ACCM guidelines [22] into the Surviving Sepsis Campaign [27] (Figure 2). The protocol emphasizes the evaluation of all children with suspected sepsis for signs and symptoms of infection. A finding of two or more signs is an indication for further laboratory tests to assess organ function. Patients with evidence of tissue hypoperfusion undergo both the 6-hour sepsis resuscitation and the 24-hour sepsis management protocols; patients with organ dysfunction but no evidence of tissue hypoperfusion undergo the sepsis management protocol only.

Figure 3 presents a *Sepsis Resuscitation protocol* used in our center, integrating the ACCM principles for pediatric patients into the Surviving Sepsis Resuscitation protocol [22,27]. The rationale for the integration of these two regimens, even though the EGDT has not been




| Are any of the following organ dysfunction criteria present and not due to other direct infection involvement or considered to be chronic conditions? |
|---|
| Cardiovascular dysfunction:<br>Hypotension or need for vasopressors OR 2 of the following:<br>- Unexplained metabolic acidosis (base deficit > 5 mEq/L<br>- Arterial lactate > 2 times upper limit of normal<br>- Urine output <0.5mL/kg/hr<br>- Capillary refill > 5 secs<br>- Core to peripheral temperature gap >3°C |
| Acutely altered mental status |
| Hypotension (per PALS criteria) |
| $SpO_2$ <90% on room air or on supplemental $O_2$, hypercarbia or need for mechanical ventilation |
| Creatinine >2 times upper limit for age or urine output <0.5 ml/kg/hour for > 2 hours |
| Bilirubin >2 mg/dl (34.2 mmol/L) |
| Platelet count <80,000 or 50% decline in platelet count or INR ≥ 2 |
| Lactate >2 mmol/L (18.0 mg/dl) |

*Figure 2: Pediatric Sepsis Screening Protocol. Modified from Townsend et al. [27] with permission.*

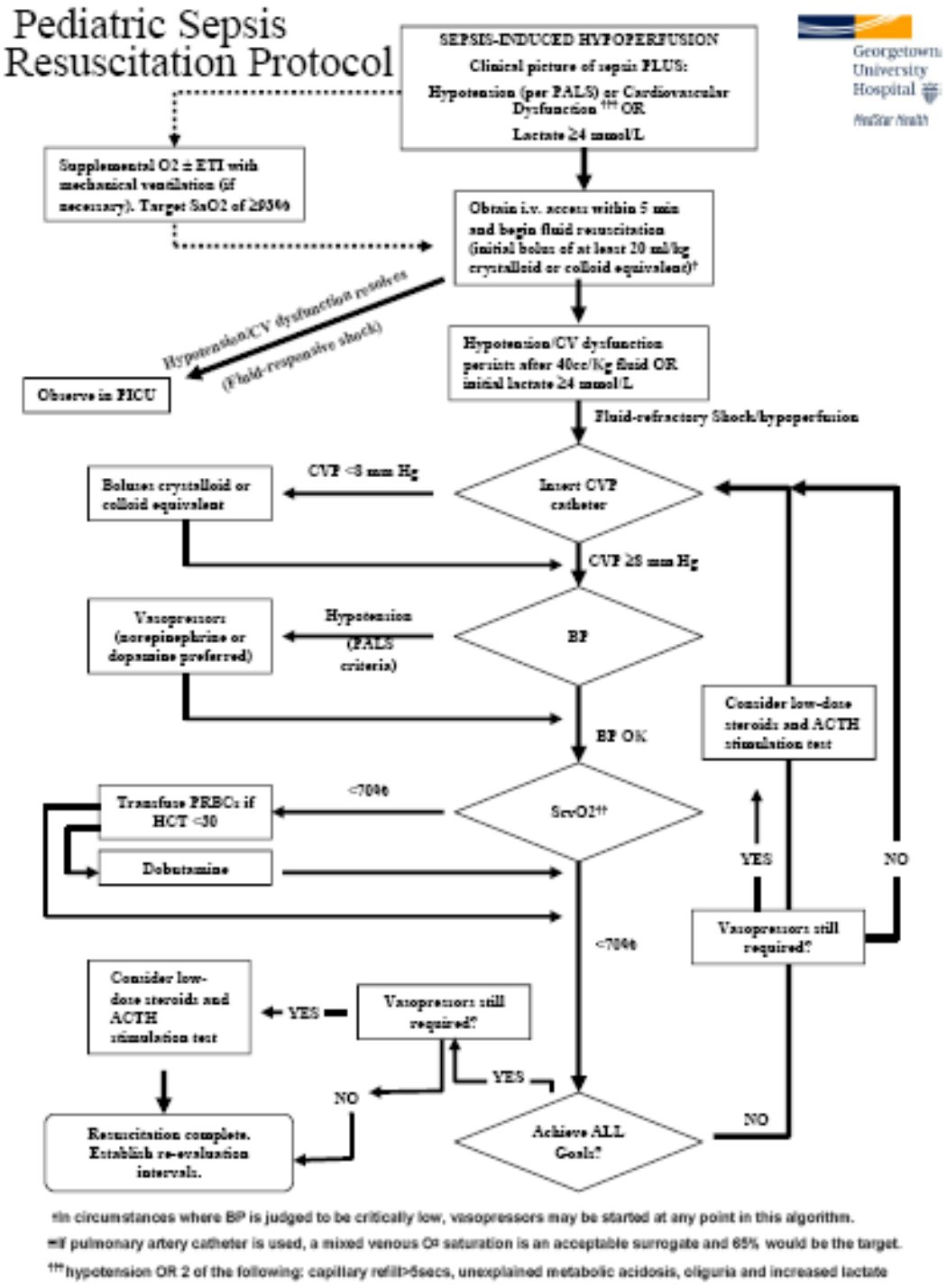



*Figure 3: Pediatric Sepsis Resuscitation Protocol. Modified from Townsend et al. [27] with permission.*

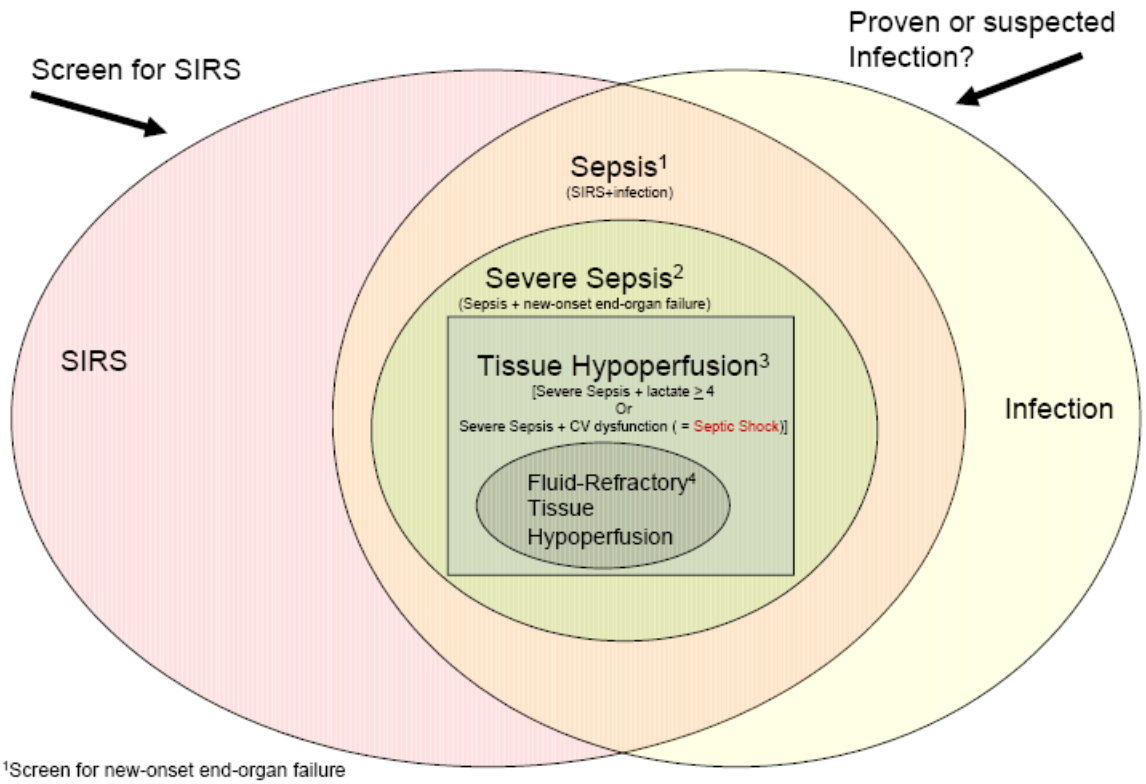



*Figure 4: Stages of the sepsis spectrum and recommended interventions at each level based on the Surviving Sepsis Campaign principles.*

validated in children, was based on the EGDT's sound physiological reasoning, successful implementation in adults, and emphasis on early aggressive resuscitation, in agreement with the ACCM guidelines .

The first step in the sepsis resuscitation protocol is the rapid establishment of IV access with administration of a fluid bolus of 20 cc/Kg as quickly as feasible, followed by additional boluses up to 60 cc/Kg or until signs of cardiovascular failure or hypoperfusion are reversed. The persistence of these signs after 40 cc/Kg of resuscitation suggests the presence of fluid-refractory shock, warranting EGDT. The protocol attempts to achieve its goal by 6 hours from diagnosis. Figure 4 shows the different stages of the sepsis spectrum and the recommended interventions at each level. Appendices I and II to this article contain the standard order sets from Georgetown University Hospital for the screening and resuscitation of pediatric patients with severe sepsis and septic shock.

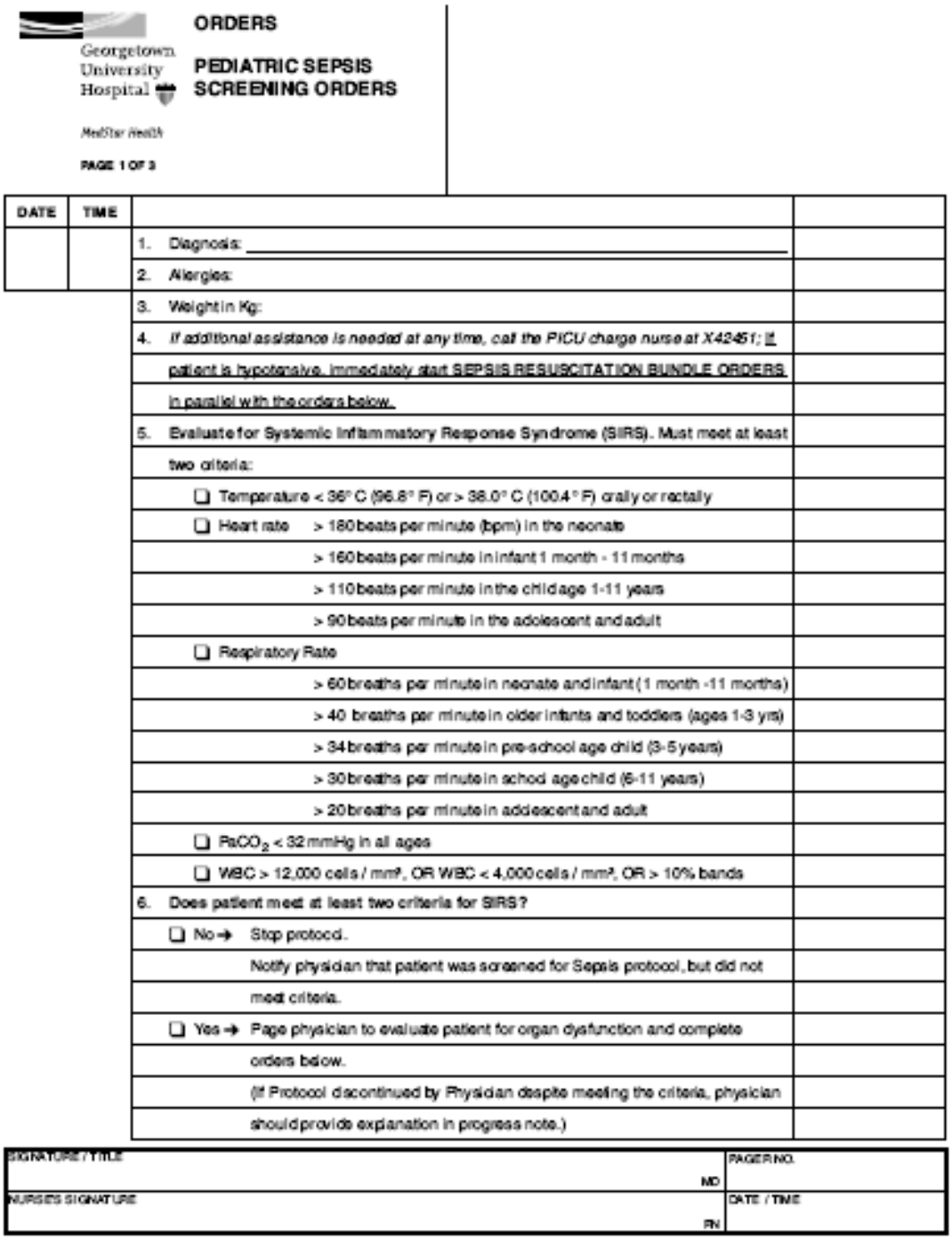
The *Sepsis Management protocol* applies the results of several landmark studies that have led to a change in the management of septic shock. One of these showed that early, adequate empirical antibiotic therapy is crucial to outcome [28]. The antibiotic must be tailored to cover the prevalent organisms in the community. Thus, obtaining two blood cultures prior to the initiation of antibiotic therapy helps to adjust therapy on the basis of subsequent cultures. In patients with chronic indwelling central venous catheters, one of the culture samples should be taken from a peripheral vein.

Adrenal insufficiency is a common manifestation of organ failure in pediatric patients with septic shock [29]. Studies in adults have shown that hydrocortisone replacement therapy leads to early shock reversal and improved survival [30-32]. The current dose recommendation is 2 mg/Kg/day in 4 divided doses or by drip, 0.18 mg/kg/hr, for 7 days. The diagnosis may be confirmed by an increase of $\leq$9 mcg/ml in serum cortisol at 30 and 60 minutes after

adrenocorticotropic hormone (ACTH) stimulation test with 250 mcg of intravenous cosyntropin; however, this measure is optional. We use dexamethasone for the first steroid dose because it does not interfere with the results of the ACTH stimulation test, and then continue with hydrocortisone once adrenal insufficiency is confirmed. In certain adult subpopulations, activated protein C (drotrecogin alpha) is recommended [21], although this practice has received some recent criticism [33]. It is not included in pediatric protocols because it has not been shown to be effective in pediatric septic shock and may increase the risk of bleeding [34].

Attempts to identify and control the source of the infection are important components of the protocol as well. Patients who require mechanical ventilation may benefit from lung protective strategies. The large randomized multicenter ARDSnet group study [35] showed that the use of low tidal volumes of 6ml/Kg (*vs* 12 ml/Kg) while aiming for a plateau pressure less than 30 $cmH_2O$ resulted in a 9% reduction in all-cause mortality in patients with ARDS. Additional recommendations made by the Surviving Sepsis Campaign (most relevant to patients transferred to the ICU) include keeping serum glucose levels between 80 and 110 mg/dL [36], prophylaxis of deep vein thrombosis, maintaining hemoglobin in the 7-9 g/L range once hypoperfusion has resolved [37], and stress ulcer prophylaxis. Information on the Campaign is available on its website as well as on the website of the Institute for Healthcare Improvement [38, 39], which also include the detailed protocols and educational material.

The recommendations of the Surviving Sepsis Campaign are currently undergoing scrutiny and are likely to be modified in the near future, with the release of the results of several large multinational studies. However, the principle of early aggressive augmentation of oxygen delivery to reverse tissue hypoperfusion and organ damage will remain at the heart of sepsis resuscitation.



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**ORDERS**

**PEDIATRIC SEPSIS SCREENING ORDERS**

| DATE | TIME | | |
|---|---|---|---|
| | | 1. Diagnosis: _____ | |
| | | 2. Allergies: | |
| | | 3. Weight in Kg: | |
| | | 4. *If additional assistance is needed at any time, call the PICU charge nurse at X42451; If* | |
| | | patient is hypotensive, immediately start SEPSIS RESUSCITATION BUNDLE ORDERS | |
| | | in parallel with the orders below. | |
| | | 5. Evaluate for Systemic Inflammatory Response Syndrome (SIRS). Must meet at least | |
| | | two criteria: | |
| | | ❑ Temperature < 36° C (96.8° F) or > 38.0° C (100.4° F) orally or rectally | |
| | | ❑ Heart rate > 180 beats per minute (bpm) in the neonate | |
| | | > 160 beats per minute in infant 1 month - 11 months | |
| | | > 110 beats per minute in the child age 1-11 years | |
| | | > 90 beats per minute in the adolescent and adult | |
| | | ❑ Respiratory Rate | |
| | | > 60 breaths per minute in neonate and infant (1 month -11 months) | |
| | | > 40 breaths per minute in older infants and toddlers (ages 1-3 yrs) | |
| | | > 34 breaths per minute in pre-school age child (3-5 years) | |
| | | > 30 breaths per minute in school age child (6-11 years) | |
| | | > 20 breaths per minute in adolescent and adult | |
| | | ❑ $PaCO_2$ < 32 mmHg in all ages | |
| | | ❑ WBC > 12,000 cells / mm³, OR WBC < 4,000 cells / mm³, OR > 10% bands | |
| | | 6. Does patient meet at least two criteria for SIRS? | |
| | | ❑ No → Stop protocol. | |
| | | Notify physician that patient was screened for Sepsis protocol, but did not | |
| | | meet criteria. | |
| | | ❑ Yes → Page physician to evaluate patient for organ dysfunction and complete | |
| | | orders below. | |
| | | (If Protocol discontinued by Physician despite meeting the criteria, physician | |
| | | should provide explanation in progress note.) | |

| SIGNATURE / TITLE | PAGER NO. |
|---|---|
| MD | |
| NURSES SIGNATURE | DATE / TIME |
| RN | |

*Appendix I: Sample Pediatric Sepsis Screening Order Set*

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**PEDIATRIC SEPSIS TREATMENT ORDERS**

**SEPSIS RESUSCITATION BUNDLE ORDERS**

☐ **STAT** PAGE 1 OF 6

PATIENT IDENTIFICATION

| DATE | TIME | DRUG ALLERGIES | |
|---|---|---|---|
| | | 1. Is the patient hypotensive? | |
| | | ☐ Yes → Administer 0.9 NS 20 ml /kg = ____ ml IV over 15 - 30 minutes. If unable | |
| | | to administer entire ordered amount by IV pump within 30 minutes, deliver | |
| | | bolus IVP manually. Time started: _____ | |
| | | ☐ No → Continue to monitor BP and move to #2 - 4 | |
| | | | |
| | | Is the patient hypotensive after the bolus? | |
| | | ☐ Yes → Repeat the bolus and start orders #2 - 4 below. | |
| | | ☐ No → Continue to monitor BP and move to #2 - 4 | |
| | | | |
| | | 2. ☐ Obtain STAT Labs: Time labs drawn: _____ | |
| | | • CBC with manual differential • Random serum cortisol level | |
| | | • Comprehensive metabolic panel • ABG (if patient has an a-line) | |
| | | • Urine Analysis / Urine Culture • Lactate (from VBG or ABG) | |
| | | • Urine pregnancy test (adolescent female) | |
| | | • Blood Culture from a peripheral stick (except Hemeonc / transplant patients with | |
| | | central line where culture from line only) | |
| | | 3. ☐ Obtain microbiological studies: | |
| | | • Urine analysis for gram stain, culture and sensitivity | |
| | | • Sputum for gram stain, culture and sensitivity (if available) | |
| | | • Blood cultures x 1 (in patients who are <u>not</u> Gold or Blue service, add a second | |
| | | culture by peripheral stick). | |
| | | Time cultures obtained: _____ | |
| | | | |
| | | *Note: Cultures should be obtained prior to antibiotics. Antibiotics should be given within 1* | |
| | | *HOUR of diagnosis of sepsis on the floor / ICU and within 3 HOURS of diagnosis in* | |
| | | *the ED.* | |

| SIGNATURE / TITLE MD | PAGER NO. |
|---|---|
| NURSES SIGNATURE RN | DATE / TIME |

*Appendix II: Sample Pediatric Sepsis Treatment Order Set*

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