MANAGEMENT OF SEPSIS

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SUBSPECIALIST IN INFECTIOUS DISEASE

MOFID CHILDREN HOSPITAL

SEPSIS

- is one of the main causes of mortality in children worldwide; therefore, it is a top priority for the public health system.
- It is caused by an inadequate immune response to an infection and is characterized by organ system failure, which is highly life-threatening

Sepsis:
Defining a Disease Continuum

Infection/ Trauma → SIRS → Sepsis → **Severe Sepsis**

Sepsis with ≥2 sign of organ failure

- **Cardiovascular (refractory hypotension)** → **Shock**
- **Renal**
- **Respiratory**
- **Hepatic**
- **Hematologic**
- **CNS**
- **Metabolic acidosis**

- Severe sepsis : dysfunction of ≥2 organ systems

Organ dysfunction (normal physiology cannot be maintained without support)

- septic shock : cardiovascular dysfunction

SEPTIC SHOCK

- refers to sepsis with cardiovascular dysfunction: hypotension, reliance on vasoactive drug administration to maintain a normal blood pressure
- or two of the following: prolonged capillary refill, oliguria, metabolic acidosis, or elevated arterial lactate that persists despite the administration of ≥40 mL/kg of isotonic saline in one hour.

- Septic shock is associated with high morbidity and mortality.
- delayed recognition of septic shock has repeatedly been associated with worse clinical outcomes in adults and children.
- The mortality rates associated with severe sepsis and septic shock are 25 to 30% and 40 to 70%, respectively.

PATHOPHYSIOLOGY

Sepsis is the culmination of complex interactions between the:

- Infecting microorganism
- The host immune
- Inflammatory
- Coagulation responses

SEPS

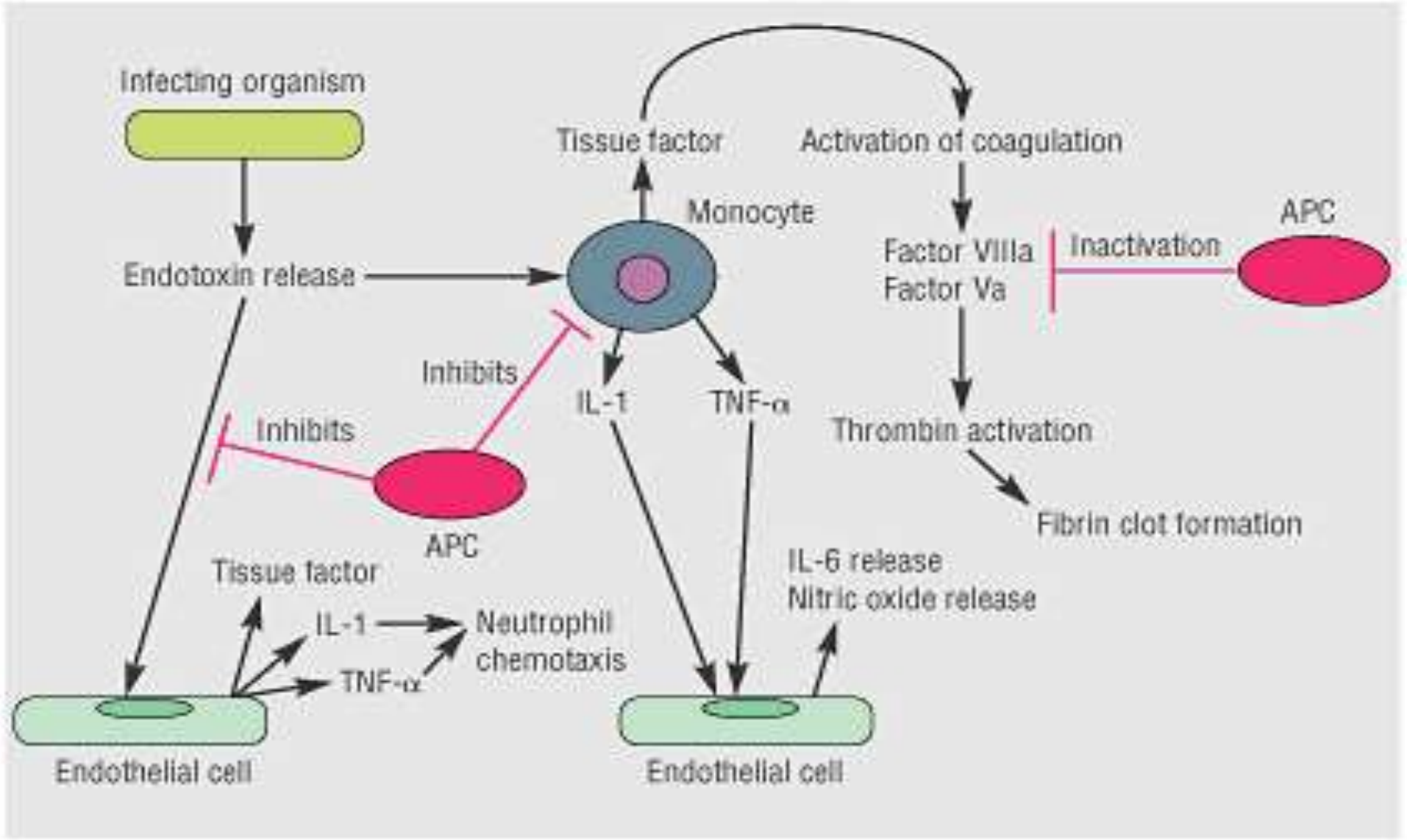


Figure 1. Events associated with major mediators of cytokine cascade in septic shock. Endotoxin and other antigenic components of infecting organism stimulate monocytes and local endothelial cells, resulting in elaboration of IL-1, tumor necrosis factor-α (TNF-α), and tissue factor (primary stimulant for coagulation cascade). Activated protein C (APC) is shown to inhibit several areas of pathway.

For diagnosis we should triage patients based on:

- high-risk patient conditions
- vital signs, and/or physical findings

Suspected patients should undergo rapid clinical assessment within 15 minutes

Resuscitation should be initiated within 15 minutes

RED FLAG FINDINGS

clinical assessment :

- Presence of fever (core temperature >38.3°C for patients 3 months of age and older or >38°C for infants <3 months of age)
- Hypothermia (core temperature <36°C)

- Tachycardia
- Tachypnea
- Abnormal pulse (diminished, weak, or bounding)
- Abnormal capillary refill (central refill ≥3 seconds or flash refill [<1 second])
- Hypotensive

- Abnormal mental status:

Irritability

Inappropriate crying

Inappropriate drowsiness (eg, excessive per caregiver)

Not interacting with caregiver

Difficult to arouse (lethargic or obtunded)

Confused (not oriented to person, place, or time)

- Purpura anywhere on the body or petechiae below the nipple line
- Macular erythema with mucosal changes (eg, strawberry tongue and conjunctival injection) suggestive of toxic shock syndrome

MANAGEMENT

Initially resuscitate :

- Airway
- Breathing
- Circulation

Seek a brief history and perform a limited examination of the relevant body systems.

A,B,C

- Give oxygen
  depressed conscious level is the most common cause of airway compromise

- Patients who do not localize to a painful stimulus have inadequate airway protection reflexes. Intubation and mechanical ventilation are indicated
- Prepare appropriate iv access for patient

GOAL-TARGETED THERAPY

- refers to an aggressive systematic approach to resuscitation aimed at improving physiologic indicators of perfusion and vital organ function **within the first six hours of care**.

EARLY, GOAL-DIRECTED THERAPY

- decreased mortality at 28 and 60 days and duration of hospitalization
- The mechanisms of the benefit of EGDT are unknown but may include reversal of tissue hypoxia and a decrease in inflammation and coagulation defects

EARLY, GOAL-DIRECTED THERAPY

the key is to look at three things:

- volume
- Pressure
- oxygen delivery (arterial oxygen saturation, hemoglobin and cardiac output)

MANAGEMENT

- Obtain vascular access (IV or intraosseous [IO]) **within 5 minutes**
- Start appropriate fluid resuscitation **within 30 minutes**
- Begin broad-spectrum antibiotics **within 60 minutes**
- For patients with fluid-refractory shock, initiate peripheral or central inotropic infusion **within 60 minutes**

EXAMINATION

- Respiratory system
- Central nervous system
- Gastrointestinal tract
- Genital tract
- Skin
- Consider ***non-infective causes*** ,such as myocardial infarction, pulmonary embolism, diabetic ketoacidosis, poisoning or drug overdose, cerebrovascular event

HEMODYNAMIC RESUSCITATION

FLUID RESUSCITATION

- patient will be hypovolemic due to fever, reduced oral intake, vascular vasodilatation, and increased losses (bleeding, vomiting, sweating, and tachypnea)
- Fluid resuscitation is initiated with boluses of crystalloid or colloid, ***titrated by HR, BP, urine output, and mental status***
- SysBP of 90mmHg or a MAP of 60mmHg

RAPID IV ACCESS

- IV access (preferably two sites and of the largest caliber that can be reliably inserted) should be established within 5 minutes.
- If a peripheral IV cannot be obtained in this time, guidelines advise placement of an IO needle.

FLUID RESUSCITATION

- in a child with tachycardia and impaired perfusion, a rapid fluid bolus of 20 mL/kg normal saline or lactated Ringer solution is recommended

unless

there is evidence for cardiac dysfunction (eg, hepatomegaly, jugular venous distention, S3 gallop, and/or cardiomegaly)

or

impending respiratory failure from pulmonary edema for which fluid should be carefully titrated.

FLUID RESUSCITATION

- After the initial infusion, the child should be quickly reassessed for signs of inadequate end-organ perfusion to determine if additional fluid is needed and to identify any signs of fluid overload (eg, pulmonary rales or gallop rhythm)

FLUID RESUSCITATION

- Experience suggests that patients with septic shock often require volumes of up to 60 mL/kg in the first hour and some receive 120 mL/kg or more during the first several hours of fluid administration
- Use of a time clock has facilitated the timely administration of fluids in at least one setting.

FLUID RESUSCITATION

- Fluid resuscitation should continue until tissue perfusion, oxygen delivery, and blood pressure are adequate, or signs of fluid overload (rales, gallop rhythm, enlarged liver) develop.
- Ideally within the first hour of treatment, the physician should determine if the patient is responding to timely fluid administration or not.

ANSWER TO FLUID THERAPY

- Restoration of tissue perfusion and reversal of shock is identified by the following therapeutic endpoints
- Quality of central and peripheral pulses (strong, distal pulses equal to central pulses)
- Skin perfusion (warm, with capillary refill <2 seconds)
- Mental status (normal mental status)
- Urine output (≥1 mL/kg/hour)

ANSWER TO FLUID THERAPY

- Blood pressure (systolic pressure at least fifth percentile for age):

<1 month of age – 60 mmHg

1 month to 10 years– 70 mmHg + [2 x age in years]

10 years of age and older – 90 mmHg

- However, blood pressure by itself is not a reliable end point for assessing the adequacy of resuscitation

ANSWER TO FLUID THERAPY

- Hypotension is a late sign of cardiovascular dysfunction and shock and is **not** necessary to diagnose septic shock.
- Infants and children with sepsis often maintain blood pressure despite the presence of septic shock through an increase in heart rate, systemic vascular resistance, and venous tone but have a limited capacity to augment myocardial stroke volume.

MONITORING

- As a rule , the trend of lactate concentrations is a better indicator of resuscitation than a single value
- Normal serum lactate (eg, <2 mmol/L)
- therapeutic lactate target is <2 mmol/L

- Measure urine output hourly and aim to achieve > 0.5 ml/kg/hour.

OXYGEN SUPPORT

- Patients with septic shock should initially receive 100 % supplemental oxygen to optimize blood oxygen content and, thus, oxygen delivery to tissues.

- Oxygenation should be monitored using continuous pulse oximetry (SpO_2) .

- Once adequate perfusion has been restored, supplemental oxygen should be titrated to avoid SpO_2 >97 % to prevent the adverse effects (eg, lung injury and microcirculatory vasoconstriction) associated with hyperoxia and free radical generation

OXYGEN SUPPORT

- Central venous oxygen saturation ($ScvO_2$) (≥70 percent), if available and appropriate
- This target is **not** applicable to children with congenital heart disease characterized by mixing lesions.
- However, a $ScvO_2$ ≥70 percent can be falsely reassuring in sepsis due to hyperdynamic cardiac function, microcirculatory shunting, or mitochondrial dysfunction

- Patients who are fluid-refractory (ie, no improvement or worsening despite appropriate fluid resuscitation) should begin inotropic therapy tailored to blood pressure and whether cold or warm shock is present
- Children with persistently elevated heart rate unresponsive to repeated fluid boluses should be evaluated for cardiac dysfunction.

OBTAIN LABORATORY STUDIES

- Rapid blood glucose
- ABG,VBG
- CBC with differential
- Blood lactate
- Serum electrolytes
- BUN ,Cr, BS,Ca
- Ionized blood calcium
- PT and PTT ,INR
- Fibrinogen and D-dimer
- total bilirubin and ALT
- Blood culture
- U/A,U/C
- Diagnostic serologic testing as indicated to identify suspected sources of infection
- Inflammatory biomarkers (eg, C-reactive protein, procalcitonin) in selected cases

LAB

- **ECG**: exclude cardiac causes of hypotension
- **Chest X-ray**
- Deeper infection may be clinically or radiologically evident.
- Samples may be amenable to percutaneous aspiration or sent after surgical drainage or debridement.

ABNORMAL LAB FINDING

- Lactic acidosis (metabolic acidosis on ABG and arterial blood lactate >2 mmol/L)
- leukocytosis or leukopenia
- Platelet <80,000/microL or a decline of 50 % from highest value recorded over the past three days
- DIC (decreased fibrinogen with increased D-dimer, INR, PT, or PTT)
- Renal insufficiency (Cr ≥2 times upper limit of normal for age or twofold increase in baseline creatinine)
- Liver dysfunction (a total BIL ≥4 mg/dL or ALT >2 times upper limit of normal for age)
- Pyuria indicating an urinary tract infection

TREAT HYPOGLYCEMIA

- rapid IV infusion of dextrose ,then continuous infusion of dextrose to maintain blood glucose in a safe range (70 to 150 mg/dL)
- Hypoglycemia may also be an indicator of adrenal insufficiency in predisposed children and those with refractory septic shock
- In normoglycemic young children, acontinue maintenance infusion of dextrose 10 %
- Hyperglycemia should be avoided

CORRECT HYPOCALCEMIA

- Children with persistent shock and ionized calcium <4.8 mg/dL or symptomatic hypocalcemia (eg, positive Chvostek or Trousseau signs, seizures, prolonged QT interval on electrocardiogram, or cardiac arrhythmias) use calcium gluconate 10 % solution in a dose of 0.5 to 1 mL/kg, up to 2 g (20 mL) by slow IV or IO infusion over 5 minutes.
- Sodium bicarbonate should **not** be introduced into an IV or IO cannula without flushing before and after administration

AFTRER ONE HOUR

- Vasoactive agents are frequently necessary in the initial resuscitation of children with septic shock to sustain perfusion pressure while hypovolemia is corrected and are indicated in patients with fluid-refractory septic shock

COLD SHOCK

- manifested by weak peripheral pulses, cold distal extremities, and prolonged capillary refill time
- epinephrine infusions (initial starting dose 0.05 to 0.1 mcg/kg/minute, titrate to response up to 1.5 mcg/kg/minute)
- second vasopressor if patients have not responded to an epinephrine dose of 1.5 mcg/kg/minute.

- patients with persistent signs of cold shock but normal blood pressure after initial fluid resuscitation receive low-dose epinephrine infusions (eg, 0.03 to 0.05 mcg/kg/minute)
- These patients should also continue to receive fluid resuscitation unless signs of volume overload are present.
- If patients do not respond to fluid resuscitation AND low-dose epinephrine , then vasodilatory agents (eg, dobutamine or milrinone) are typically employed.
- Close monitoring of clinical and laboratory parameters (ie, lactate, urine output, and heart rate) with frequent patient reassessment are needed to guide the need for escalation of therapies

WARM SHOCK

- For patients with warm shock (eg, bounding pulses, pink extremities, and "flash" capillary refill)
- norepinephrine infusion starting at 0.03 to 0.05 mcg/kg/minute as the first-line drug

STEROIDS

- IV hydrocortisone 200-300 mg/day in 3-4 divided doses or by continuous infusion or patients with septic shock who require vasopressors despite adequate fluid therapy

SOURCE CONTROL

- drainage of abscess
  - percutaneous
  - surgical
- debridement of infected necrotic tissue
- removal of potentially infected device(cvp)

source control should be instituted as soon as possible after initial resuscitation

ANTIBIOTIC THERAPY

- The choice of antimicrobials can be complex and should consider the child's age, history, comorbidities, clinical syndrome, Gram stain data, and local resistance patterns.
- Whenever possible, broad spectrum IV antibiotic therapy should begin within one hour of presentation, preferably after obtaining appropriate cultures

- Each hour delay in antibiotic administration has been associated with an approximately 8 percent increase in mortality in adults.

ANTIBIOTIC THERAPY

- If a causative organism is identified (20% of patients with sepsis have negative culture), then the antibiotic regimen should be narrowed to decrease the likelihood of the emergence of resistant organisms.

ANTIBIOTIC THERAPY

- Most children with septic shock should receive coverage for MRSA
- Coverage for enteric organisms should be added whenever clinical features suggest GU and/or GI sources
- Treatment for Pseudomonas species should be included for children who are immunosuppressed or at risk for infection with these organisms (ie, neutropenic patient).
- Listeria monocytogenes and HSV are important pathogens in infants ≤28 days of age.

EARLY GOAL-DIRECTED RESUSCITATION

targets include :

- CVP 8 - 12 mm Hg
- mean arterial pressure ≥ 65 mm Hg
- central or mixed venous O2sat ≥ 70%
- urine output ≥ 0.5 ml/kg/hr

The cornerstone of emergency management of sepsis is:

- early, goal-directed therapy
- lung-protective ventilation
- broad-spectrum antibiotics
- possibly activated protein C

MONITORING

- Patients with severe SIRS should have observations recorded *hourly*
- Record ***Temp, PR, BP, RR , CVP, SaO2***

  and urine output
- *Accurate fluid balance is essential*

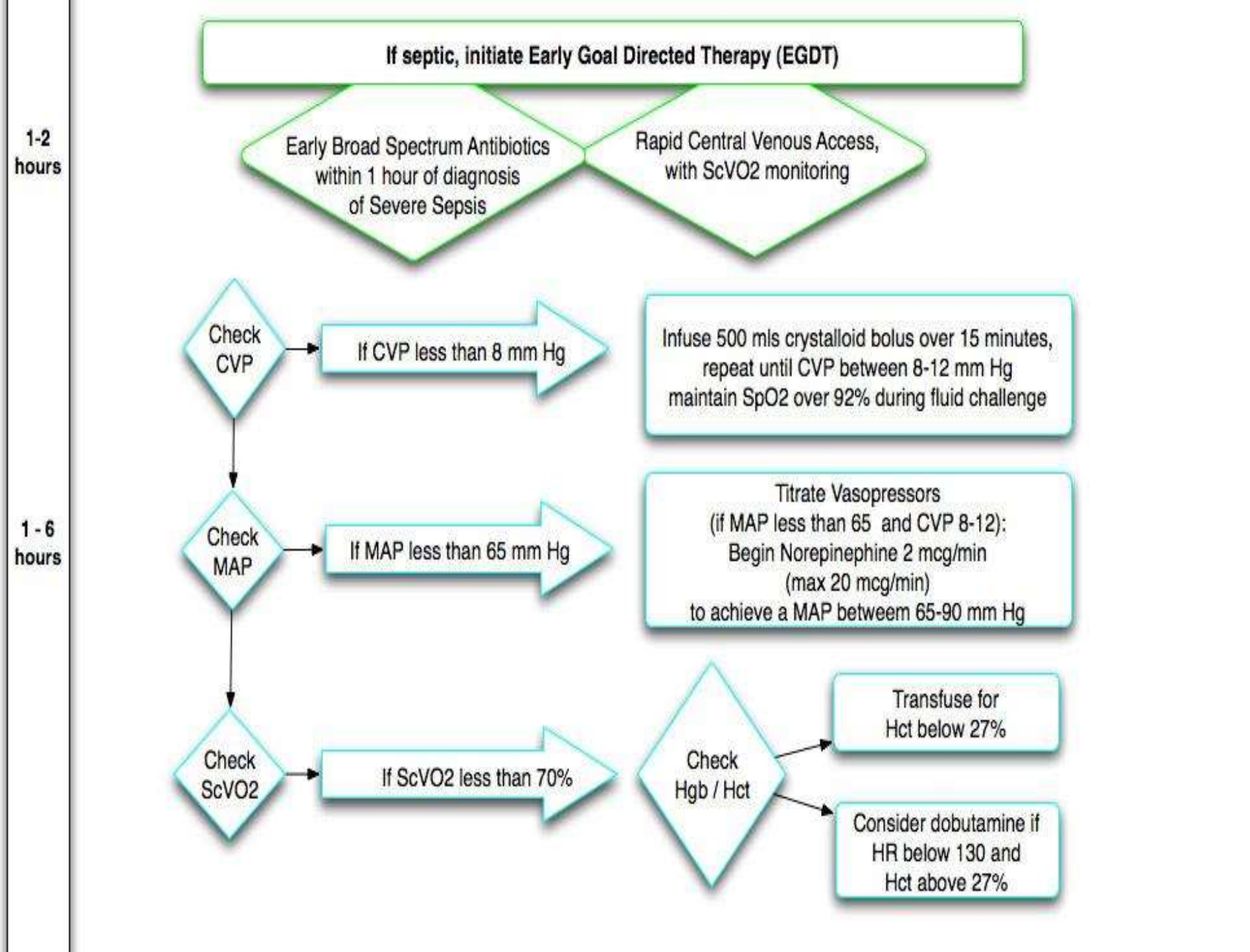
INTRAVENOUS ACCESS AND INVASIVE MONITORING I

- ***In patients who do not respond quickly to fluid resuscitation***, CVP is recommended

- patients with pneumonia may have a spuriously high CVP secondary to high pulmonary vascular resistance , (recommended cvp is 8-14mmHg)

- Rivers et al used a *HCT of 30%* as a threshold for transfusion in early sepsis as part of a *6-hour protocol*
- Hebert et al suggest maintaining *Hb levels at 70 to 90 g /L after the first 6 hours*

- N Engl J Med 2001;345:1368-1377
- N Engl J Med 1999;340:409-417

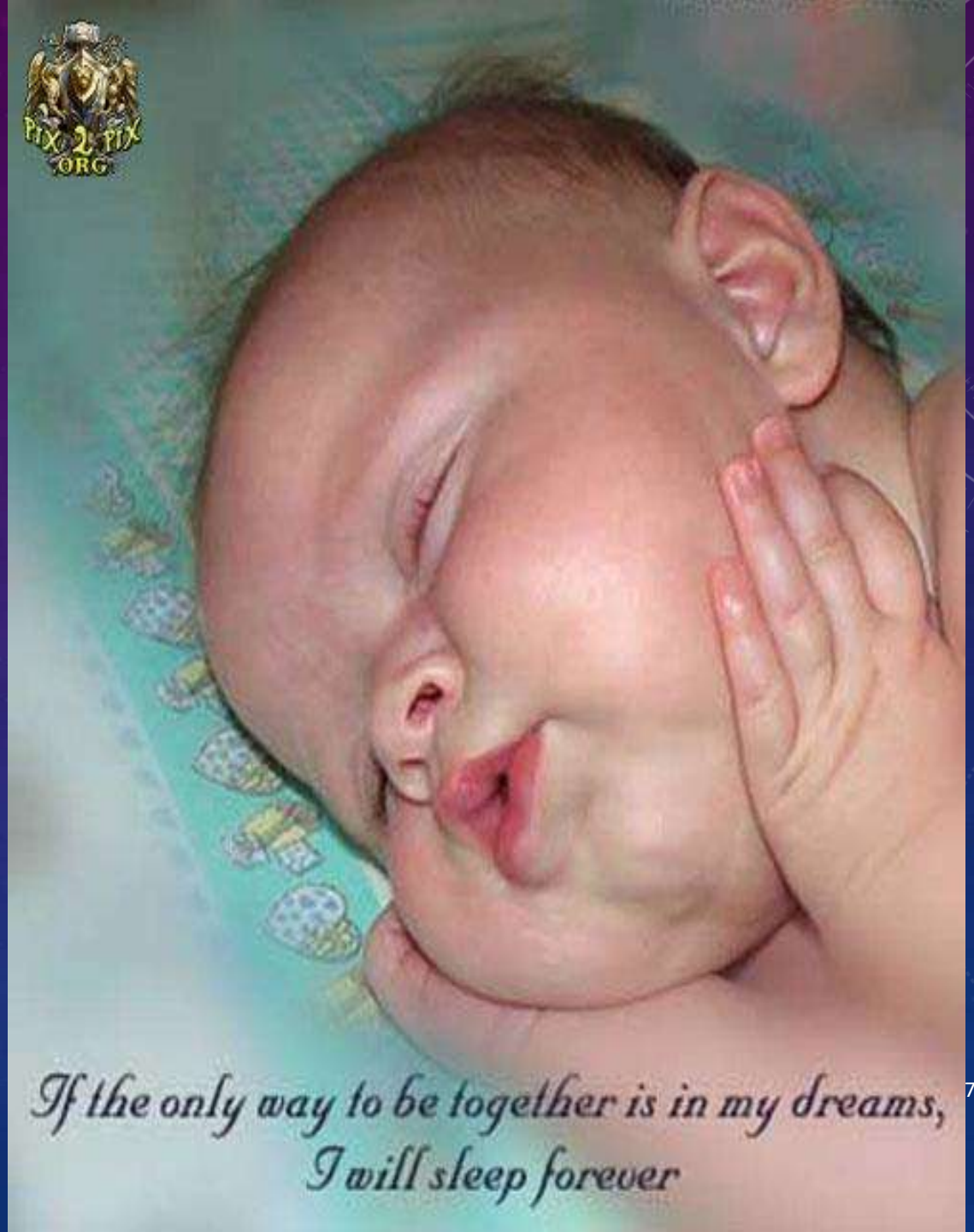

If septic, initiate Early Goal Directed Therapy (EGDT)
1-2 hours
Early Broad Spectrum Antibiotics within 1 hour of diagnosis of Severe Sepsis
Rapid Central Venous Access, with ScVO2 monitoring
Check CVP
If CVP less than 8 mm Hg
Infuse 500 mls crystalloid bolus over 15 minutes, repeat until CVP between 8-12 mm Hg maintain SpO2 over 92% during fluid challenge
1 - 6 hours
Check MAP
If MAP less than 65 mm Hg
Titrate Vasopressors (if MAP less than 65 and CVP 8-12): Begin Norepinephine 2 mcg/min (max 20 mcg/min) to achieve a MAP betweem 65-90 mm Hg
Check ScVO2
If ScVO2 less than 70%
Check Hgb / Hct
Transfuse for Hct below 27%
Consider dobutamine if HR below 130 and Hct above 27%

TRANSFUSION

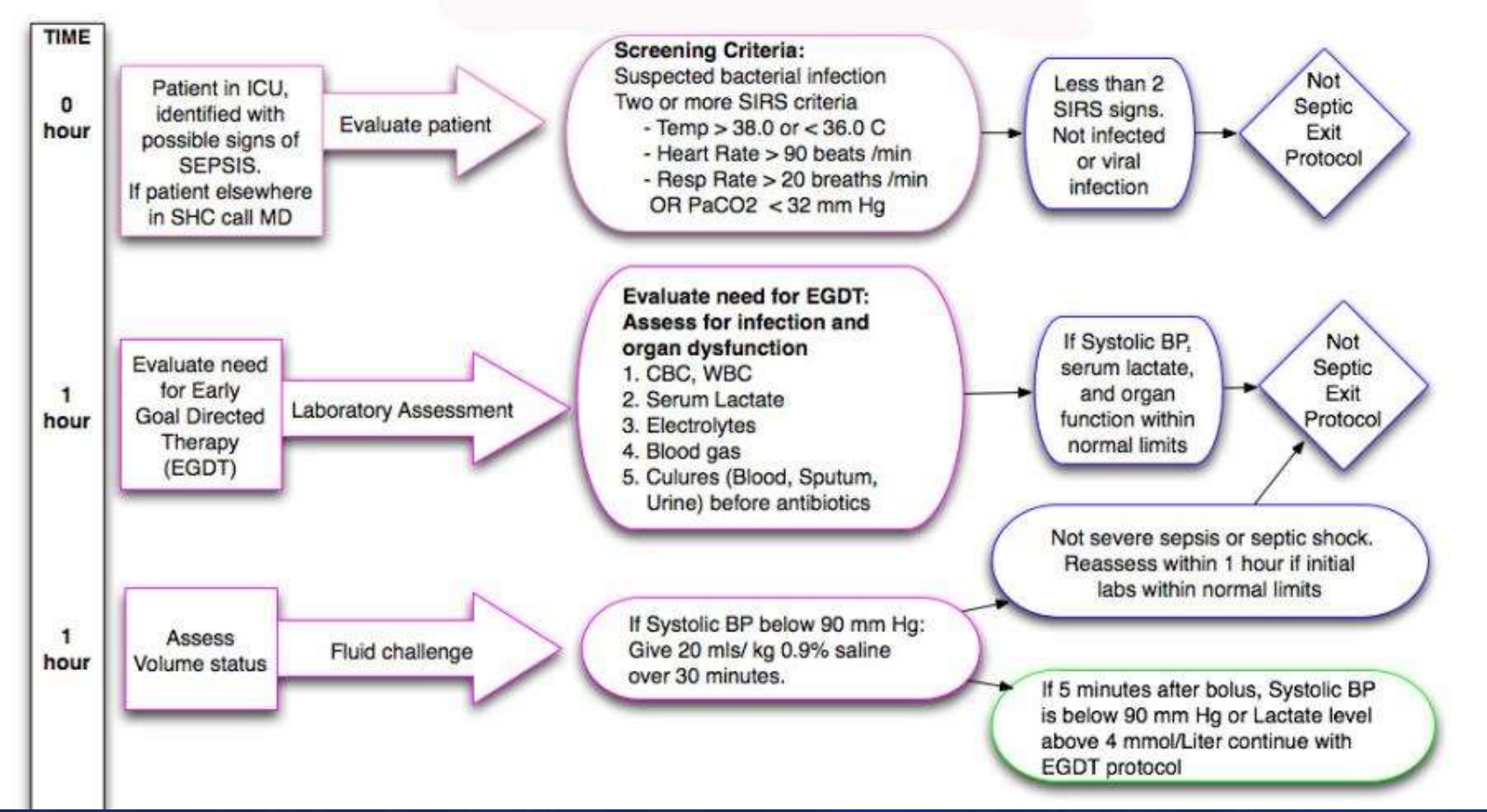
- If ScvO2 fell below 70% after early goal-directed therapy , transfuse RBC to achieve a HCT of at least 30%

- If ScvO2 remained below 70% after these measures were instituted, dobutamine (2.5–20 µg/kg/min) was administered to bring ScvO2 to 70%

Thanks for your attention



ASSESSMENT OF SEPSIS AND POTENTIAL ORGAN FAILURE



ANTIBIOTIC SELECTION & ADMINISTRATION