SEPSIS
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OVERVIEW
Sepsis is a common, life-threatening condition in the pediatric ICU. Severe sepsis and septic shock occur in all settings and age groups though these children often have associated co-morbidities such as prematurity or malignancy. Though in the community at large recent epidemiologic data indicate that more than half the cases of severe sepsis occur in children without a predisposing condition. Early recognition and aggressive early intervention for severe sepsis and septic shock, however, are essential in preventing a poor outcome.

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tbody>
<tr>
<td>SIRS: Systemic Inflammatory Response Syndrome</td>
<td>Presence of two or more of the following symptoms (see Table 1): temperature instability (core temp &gt; 38.5 / &lt;36), tachycardia / bradycardia, tachypnea or mechanical ventilation, leukocytosis/leucopenia.</td>
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<tr>
<td>Sepsis</td>
<td>SIRS with infection</td>
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<tr>
<td>Severe Sepsis</td>
<td>Sepsis with one other organ dysfunction (see Table 2): cardiovascular dysfunction, ARDS/ALI, mechanical ventilation, change in mental status, rising creatinine, rising hepatic enzymes TBili or ALT</td>
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<tr>
<td>Septic Shock</td>
<td>Fluid refractory hypotension: hypotension or hypoperfusion despite fluid resuscitation</td>
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<tr>
<td>MODS / MOFS</td>
<td>Multi-organ dysfunction syndrome / multi-organ failure syndrome – at least two organ system failures – see table below</td>
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SEPSIS EPIDEMIOLOGY
In children the vast majority (? millions of cases per year) with a SIRS type picture will have minor infectious disease and be treated as outpatients. The second and third tears of the pyramid will be much smaller.

- Estimates of the incidence of severe sepsis in children suggest that there are about 40,000 cases per year, some 10 – 15% of who develop septic shock (4,000 – 6,000). Half of these cases occur in children with co-morbidities.
- Co-morbidities conditions include prematurity, therapeutic immunosuppression (e.g. transplant or cancer patients) along with patients with neurological, cardiac, respiratory, GI, etc. diseases.
- Neonates (under 30 days) account for about 1/3 of cases and infants under 1 year account for half.
- The mortality rate for severe sepsis in children is estimated to be between 5 – 10% regardless of age group. Patients with co-morbidities, in particular, those with...
neoplasms, immunodeficiency or severe cardiac disease have significantly higher mortality rates (15%).

**BACTERIOLOGY**
The bacteriology varies by age, co-morbidity, and geography.

- Coagulase negative staphylococcus, non – group A or B strep, and fungus now predominate in all age groups.
- In neonates Group B strep and gram negative species including pseudomonas account for about 10% of cases.
- H. Flu and pneumococcus have become uncommon due to immunization but still account for 2 – 7% of all severe sepsis cases in the US.
- Meningococcus, the other classic pathogen, is also uncommon in the US accounting for less than 2% of severe sepsis cases overall and for less than 10% in the 1 – 10 year old group.
- In previously healthy children the predominance of the classic bacterial pathogens is approximately twice what it is overall. S. aureus and gram-negative enterics are also significant contributors.

**PATHOPHYSIOLOGY** (See Figure 1)

- The basic pathophysiology of severe sepsis and septic shock includes:
  - **Vasodilation**
  - **Third spacing** due to capillary leak
  - **Myocardial dysfunction**.
- Vascular endothelium is both a source and target of injury in SIRS / sepsis. Injury may be due to toxins such as LPS (endotoxin) or from ischemia itself. Tissue factor release leads to amplification of the inflammatory response and to DIC via the thrombin pathway. Thrombin not only catalyzes fibrin formation but also causes leukocyte adhesion which leads to further endothelial damage. As DIC progresses, clotting factors are consumed and bleeding occurs.
- Clotting factors, pro-fibrinolytic, and anti-thrombin factors are consumed leading to loss of fibrinolysis & normal down-regulation of thrombin pathway. This phenomenon is both pro-inflammatory and pro-thrombotic.
- Protein C depletion has been associated with increased mortality. In meningococcemia protein C depletion can be profound and is associated with large vessel thromboses (purpura fulminans) as well as mortality. This has led to a series of clinical trials utilizing protein C, activated protein C (APC), antithrombin III (AT-III), and tissue factor pathway inhibitor to try and disrupt this cycle. Activated protein C has in fact been shown to reduce mortality in severe sepsis in adults. Bleeding problems seems to outweigh the benefits in children.

**CLINICAL PRESENTATION / EVALUATION**
The recognition of sepsis may be straightforward in the hospital setting where it is common. In the office setting, identifying which of the many febrile children is actually
septic may be much more difficult. *Severe sepsis should be suspected when there is lethargy and flash capillary perfusion.* The additional presence of a rash should alert one to the possibility of meningococcemia.

- **Cardiovascular** changes (see Table 1) are most significant physical findings in patients with septic shock; changes of heart rate – tachycardia / bradycardia, and changes in perfusion are seen. Hypotension, when noted is a late finding and suggests decompensated shock.
  - **Warm / Early shock:** presentation is a febrile, warm, pink, well-perfused child with tachycardia and tachypnea. The initial release of inflammatory cytokines causes a drop in systemic vascular resistance (SVR) which leads to low diastolic blood pressures. On physical exam, this causes a widened pulse pressure and bounding pulses.
  - **Cold shock:** describes a condition that resembles cardiogenic or severe hypovolemic shock. Pulses are poor, extremities are cool, and perfusion is severely diminished. The septic patient progresses to this state once the compensatory mechanisms are exhausted. Myocardial function is depressed and catecholamine response may be diminished due to relative cortisol and vasopressin deficiency.

- **Respiratory:** (see Table 1) Tachypnea is primarily due either to an inciting respiratory process or metabolic acidosis. Patients often have a primary respiratory alkalosis on presentation and develop hypoxemia and respiratory acidosis as the sepsis progresses.

- **Neurologic:** Patients may present with agitation, which often progresses, to decreased mentation due to poor end organ perfusion.

- **Renal:** Decreased urine output is noted for inpatients and elicited on history for outpatients.

- **Skin:** Palpable petechiae and purpura may be present if the patient presents in DIC. Poor skin turgor and perfusion can also be noted.

- **Pediatric ICU patients** often have significant co-morbidities leading to unusual presentations:
  - Patients with pulmonary hypertension may develop a pulmonary hypertensive crisis and severe RV failure
  - Single ventricle patients may develop profound hypoxemia from a decreased Qp:Qs as blood is “shunted” into the vasodilated peripheral vascular bed
  - Transplant patients may manifest failure of the transplanted organ.

Table 1 – Age Specific Vital and WBC
Table 2 – Organ dysfunction criteria

From: “International pediatric sepsis consensus conference: Definitions for sepsis and organ dysfunction in pediatrics”. Goldstein, Brahman MD; Girir, Brett MD; Randolph, Adrienne MD; Members of the International Consensus Conference on Pediatric Sepsis. Pediatric Critical Care Medicine: Volume 6(1) January 2005 pp 2-8

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Tachycardia</th>
<th>Bradycardia</th>
<th>Respiratory rate</th>
<th>WBC X10^3/mm</th>
<th>Systolic BP mm Hg</th>
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<tbody>
<tr>
<td>0 days – 1 wk</td>
<td>&gt; 180</td>
<td>&lt; 100</td>
<td>&gt; 50</td>
<td>&gt; 34</td>
<td>&lt; 65</td>
</tr>
<tr>
<td>1 wk – 1 mo</td>
<td>&gt; 180</td>
<td>&lt; 100</td>
<td>&gt; 40</td>
<td>&gt; 19.5 or &lt; 5</td>
<td>&lt; 75</td>
</tr>
<tr>
<td>1 mo – 1 yr</td>
<td>&gt; 180</td>
<td>&lt; 90</td>
<td>&gt; 34</td>
<td>&gt; 17.5 or &lt; 5</td>
<td>&lt; 100</td>
</tr>
<tr>
<td>2-5 yrs</td>
<td>&gt; 140</td>
<td>NA</td>
<td>&gt; 22</td>
<td>&gt; 15.5 or &lt; 6</td>
<td>&lt; 94</td>
</tr>
<tr>
<td>6-12 yrs</td>
<td>&gt; 130</td>
<td>NA</td>
<td>&gt; 18</td>
<td>&gt; 13.5 or &lt; 4.5</td>
<td>&lt; 105</td>
</tr>
<tr>
<td>13 - &lt;18 yrs</td>
<td>&gt; 110</td>
<td>NA</td>
<td>&gt; 14</td>
<td>&gt; 11 or &lt; 4.5</td>
<td>&lt; 117</td>
</tr>
</tbody>
</table>

Cardiovascular dysfunction
- Decrease in BP (hypotension) < 5th percentile for age or systolic BP < 2 standard deviation below normal for age
- Need for vasopressor drug to maintain BP in normal range (dopamine > 5 µg/kg/min or dobutamine, epinephrine, or norepinephrine at any dose)
- Two of the following:
  - Unexplained metabolic acidosis: base deficit > 5.0 mEq/L
  - Increased arterial lactate > 2 times upper limit of normal
  - Oliguria: urine output < 0.5 mL/kg/hr
  - Prolonged capillary refill: > 5 secs
  - Core to peripheral temperature gap > 3°C

Respiratory
- PaO2/FIO2 < 300 in absence of cyanotic heart disease or preexisting lung disease
- PaCO2 > 65 torr or 20 mm Hg over baseline PaCO2
- Proven need or > 50% PaO2 to maintain saturation > 92%
- Need for noninvasive or noninvasive mechanical ventilation

Neurologic
- Glasgow Coma Score < 11 (57)
- Acute change in mental status with a decrease in Glasgow Coma Score ≥ 3 points from abnormal baseline

Hematologic
- Platelet count < 30,000/mm³ or a decline of 50% in platelet count from highest value recorded over the past 3 days (for chronic hematologic/oncology patients)
- International normalized ratio > 2

Renal
- Serum creatinine ≥ 2 times upper limit of normal for age or 2-fold increase in baseline creatinine

Hepatic
- Total bilirubin ≥ 4 mg/dL (not applicable for newborn)
- ALT 2 times upper limit of normal for age

BP, blood pressure; ALT, alanine transaminase.

*See Table 2; acute respiratory distress syndrome must include a PaO2/FIO2 ratio ≤ 200 mm Hg, bilateral infiltrates, acute onset, and no evidence of left heart failure (Refs. 58 and 59). Acute lung injury is defined identically except the PaO2/FIO2 ratio must be ≤ 300 mm Hg; proven need assumes oxygen requirement was tested by decreasing flow with subsequent increase in flow if required; in postoperative patients, this requirement can be met if the patient has developed an acute inflammatory or infectious process in the lungs that prevents him or her from being extubated.
**TREATMENT**

Between 1963 and 1993, with the advent of neonatal and pediatric intensive care units, mortality from sepsis decreased from >95% to 10%. The basic tenets of treatment developed over those three decades are: recognition, appropriate antibiotics, fluid resuscitation and to a lesser extent other intensive care interventions such as inotropes and mechanical ventilation. Despite a large number of clinical trials trying to identify the “magic bullet” for the treatment of sepsis these interventions remain the cornerstones of management.

An algorithm published by the society of critical care medicine for the treatment of pediatric and adult severe sepsis follows. Essential elements in this algorithm are,

- Recognition
- Initial resuscitation
- Diagnosis
- Appropriate antibiotics
- Source identification and control
- Early access to critical care. *Delays in access to a critical care bed should not delay these interventions.*
- Institution of inotropic and vasopressor support
- Management of metabolic derangements
- Frequent, repeated assessment of the response to therapy

Institution of this type of protocol has been the basis for current reductions in mortality in pediatric septic shock. Each of these topics is discussed in detail below.

- **Recognition:** Flash capillary refill and altered mental status with a febrile illness are the hallmarks. Rash in this setting should signal possible meningococcemia. Increased suspicion is warranted in children with co-morbidities.

- **Resuscitation:** the ABCDs of sepsis

  A – Airway
  B – Breathing
  C – crystalloids, crystalloids, crystalloids, crystalloids, calcium
  D – Dextrose, Drugs = antibiotics, inotropes
  s – Steroids

- **Airway:**
  - Septic patients often have depressed mental status and may require airway protection.

- **Breathing** – consider intubation in the following circumstances. Assure lung protective strategies are instituted if the patient requires intubation (see chapter 13 – ARDS).
- Hypoxemia: ALI / ARDS, pneumonia
- Metabolic acidosis
- Work of breathing accounts for up to 40% of cardiac output in children; intubation may therefore improve end organ perfusion
- After 40ml/kg of fluid resuscitation
- Induction meds: Ketamine minimizes hypotension by maintaining systemic vascular resistance + atropine to decrease secretions and a short acting neuromuscular blocking agent

- **Circulation:** **Rapid fluid administration is the key.**
  - The first 20 ml/kg should be given in **5 – 10 minutes**. Adequate IV access should be established quickly to allow for rapid fluid administration. If IV access cannot be rapidly accomplished, an IO should be placed (a minimum of 4 potential IO sites exist).
  - Fluids should be given in 20 ml/kg boluses and patients may require up to 200 ml/kg. Fluid resuscitation should occur until resolution of tachycardia, improvement of end organ perfusion or the patient develops hepatomegaly or rales. Note frequent patient reassessment is required.
  - Those patients requiring > 40-60 ml/kg of volume should have a central venous catheter placed and the CVP should be continuously measured. Note however that continued fluid resuscitation should not be delayed for a CVC placement.
  - Adult studies have demonstrated that targeting a CVP of 8-12 (slightly higher in mechanically ventilated patients to account for increased intrathoracic pressure) and a MVO2 Sat > 70% increases survival.
  - Concerns about worsening respiratory distress should not limit fluid resuscitation unless the CVP is higher than the target range.
  - Crystalloids are the choice of fluids for patients in septic shock since no data exists to demonstrate improved outcomes with colloid solution. Patients with severe malaria are the only group of patients in whom decreased mortality has been noted with 5% albumin resuscitation. There is a growing body of evidence for the use of hypertonic saline (3% to 7% or more) as a resuscitation fluid.
  - Data shows that early rapid fluid resuscitation in referring clinics / emergency rooms without delay of initiation of treatment improves mortality in pediatric septic patients. The most common cause of delay in treatment is inability to establish vascular access. Therefore, an IO should be considered if vascular access cannot be rapidly established in a patient with septic shock.

- **Fluid refractory shock:** Hypotension despite 40 – 60 ml/kg of fluid
o Dopamine is initiated through a central venous catheter. If a CVC is not available, inotropic support should not be delayed and should be initiated through a PIV / IO as the CVC is being placed.

o Note that in adult sepsis guidelines, either norepinephrine or dopamine can be the initial inotrope (and many pediatric intensivists may also choose to start with norepinephrine.)

o An arterial line for continuous blood pressure monitoring is recommended if prolonged or increasing doses of inotropes are required.

- **Dopamine refractory shock**: Hypotension on 10 mcgs/kg/min of dopamine.
  o Warm shock – norepinephrine – flash capillary refill, bounding pulses
  o Cold shock – epinephrine – prolonged cap refill, thready pulses
  o Once the blood pressure has normalized, if signs of poor perfusion persist, dobutamine, milrinone, and/or vasodilators like nitroprusside may also be considered.
  o Other vasoconstrictors to be considered include vasopressin and phenylephrine if hypotension persists despite optimal inotropic support.

- **Catecholamine refractory shock – consider Steroid replacement**:
  o Consider if patient on steroids within last year or at high risk for being steroid deficient
    ▪ Oncology
    ▪ Organ transplant
    ▪ Asthma
    ▪ Meningococcemia (Waterhouse-Friderichsen syndrome)
    ▪ Congenital adrenal hyperplasia
  o Send spot cortisol level prior to administering steroids
  o Hydrocortisone: 1 – 50 mg/kg/day can be administered until the reversal of shock symptoms are noted.

- Correct hypocalcemia and hypoglycemia

Note from the diagram below that the initial resuscitation of sepsis, ABCDs, all occur within 60 minutes of diagnosing a patient with septic shock.
**Diagnosis: Lab studies:**
- **Chemistries:**
  - Evaluate the degree of acidosis
  - Evaluate for possible end organ dysfunction – liver, kidney
- **CBC:**
  - Often an elevated WBC count is noted, but a low WBC with immature neutrophils is a strong indicator of severe sepsis as well.
  - Low Hct and platelet count can be seen in patients with DIC
- **Coag panel:**
  - Elevated Pt, PTT, INR, d-dimer and decreased fibrinogen levels can be seen in patients with DIC
- **Appropriate cultures**
  - Blood & urine culture in all patients prior to antibiotics if feasible.
  - An LP should be considered in patients with signs of meningitis.
  - Indwelling catheters, drains, etc. should be cultured
  - ETT culture and gram stain in intubated patients.
- **Acute phase reactants:** CRP, fibrinogen, platelets, ESR, will be elevated
- **Lactate:** Multiple studies in adults and children have shown that elevated lactate levels are predictive of early mortality in sepsis.
  - May be elevated in warm shock due to poor oxygen extraction and micro shunts in the capillary beds that may be the cause of flash capillary filling.
  - Elevated in cold shock due to poor tissue perfusion.
- **Consider further radiologic studies based on patient's presenting symptoms – e.g. CXR if respiratory symptoms, abdominal CT if abdominal pain, etc.**

**Antibiotic selection:**
- Data shows that incorrect empiric antibiotic coverage increases morbidity and mortality. Therefore, broad-spectrum coverage is initiated and then narrowed as the organism and resistance pattern are identified.
- Empiric antibiotic therapy should be based on the clinical scenario. Table 3 below provides guidelines for empiric antibiotic selection.
- For nosocomial infections, institutional antibiotic resistance patterns and prior antibiotic exposure in the child become important factors.
- When Staphylococcus aureus is suspected vancomycin should be used because of the rising incidence of MRSA.
- If a source of infection is identified (i.e. positive blood culture or urine culture), antimicrobials should be tailored appropriately.
Table 3 – Empiric antibiotic coverage

<table>
<thead>
<tr>
<th>CLINICAL SCENARIO</th>
<th>ANTIMICROBIAL</th>
<th>RATIONALE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meningitis – GPC on gram stain</td>
<td>Vanco + 3&lt;sup&gt;rd&lt;/sup&gt; gen cephalosporin</td>
<td>Cover for resistant S. pneumo</td>
</tr>
<tr>
<td>Meningitis – gram neg diplococci</td>
<td>3&lt;sup&gt;rd&lt;/sup&gt; gen cephalosporin</td>
<td>Likely N. meningitides</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>Vanco + Double-coverage for GNR</td>
<td>Pts are susceptible to Pseudomonas and other SPACE organisms</td>
</tr>
<tr>
<td>Toxic shock</td>
<td>Clinda + Vanco</td>
<td>Cover for MRSA/Strep</td>
</tr>
<tr>
<td>Indwelling central venous catheters</td>
<td>Vanco + 3&lt;sup&gt;rd&lt;/sup&gt; gen cephalosporin</td>
<td>Vanco is needed for Gram + organisms, most notably S. epi.</td>
</tr>
<tr>
<td>Deterioration despite broad-spectrum antibiotics</td>
<td>Antifungals; also consider what possible resistant organisms may be involved</td>
<td>Loss of normal bacterial flora increases susceptibility to fungus, particularly in patients on steroids, with hyperglycemia, or who are immunosuppressed.</td>
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</tbody>
</table>

❖ **Source Control:**
- Consider if a specific anatomic site of infection can be identified – e.g. necrotizing fasciitis, diffuse peritonitis
- If focus of infection can be treated by surgical intervention, e.g. abscess drainage, it should implemented as quickly as possible

❖ **Supportive Therapy:**

- **Glucose control:** Much recent ICU literature has been devoted to the association noted between high blood sugar levels and short term increases in morbidity and mortality. RCTs in adults have demonstrated that maintaining euglycemia (blood sugars 80-110) with insulin significantly improves morbidity and mortality in critically ill surgical patients. In medical patients, improvements are noted in patients that have a 3-day or longer ICU stay. Though data in children is lacking, consensus supports treatment of hyperglycemia in critically ill children. Given that children are more susceptible to hypoglycemia, the targeted range is usually higher than in adults, 100-150 mg/dL. The risk of hypoglycemia was highlighted in a recent adult trial (Brunkhorst et al, NEJM, 2008) where severe hypoglycemia was 4x higher in the intensive insulin group. Mortality outcomes did not differ between groups in this study.
• **Nutrition and gastric acid suppression:** Sepsis is not a contraindication to enteral nutrition. TPN should be avoided if possible as risk of secondary infections increases. Patients may have poor gastric motility and benefit from trans-pyloric feeding. Shock and intestinal hypoperfusion, however, require more caution, especially in patients with even moderate vasoconstrictor requirements. These patients are generally kept NPO. Nutrition, whether enteral or parenteral, should not be neglected given the high metabolic demands of the septic patient. Stress ulceration and GI bleed is a serious concern and although no hard evidence exists for the use of acid-blockade, most septic ICU patients are placed on an H2-blocker or proton pump inhibitor, especially when NPO.

• **Transfusion:** Blood products have risks and therefore should be used with caution and appropriate justification. PRBC transfusion to a Hct > 30% should be considered in the following circumstances:
  - Signs of shock – hypotension, acidosis, mixed venous O2 saturation < 70% – despite adequate fluid resuscitation and inotropic support
  - Ongoing blood loss – exsanguination or DIC
  - Cyanotic heart disease
  - Myocardial ischemia

**NOVEL THERAPIES**

- **ECMO** is an important though infrequent tool. It should be considered in patients with refractory shock despite maximal medical treatment, multi-system organ dysfunction and patients with severe respiratory failure.

- **CVVH** has become an important tool for patients developing renal failure and fluid overload. The cytokine removal properties of CVVH are discussed extensively and remain investigational.

- **Plasma exchange** will remove cytokines, large von Willebrand multimers and other toxic substances. It is used increasingly to manage patients with severe shock though this indication is also still investigational.

- **Vasopressin** is being increasingly used for sepsis but pediatric studies are limited. It should be considered for cases of catecholamine-refractory vasodilatory shock. Patients with sepsis have a relative vasopressin deficiency state and it may therefore be very effective in increasing SVR. Vasopressin stimulates vascular smooth muscle V1 receptors (i.e. not alpha receptors) and increases MAP. Pediatric dosing begins at 0.01 unit/kg/hr and can be titrated up to 0.04 units/min.
**NEONATAL SEPTIC SHOCK**
The management of neonatal septic shock deserves some special comments.

- **Traditional view:** Historically, the regulation of cardiac output in neonates was thought to be insensitive to both fluid loading and inotropes. Recent studies have however documented that both these strategies can be effective and should be used.

- **Intracranial hemorrhage:** Concerns over precipitation of an intracranial hemorrhage with rapid swings in intravascular volume, particularly in premature infants, has led to a tempered use of volume resuscitation. New evidence, however, implicates persistent under perfusion as perhaps a more significant cause of injury than ICH alone. Therefore, overly cautious resuscitation in premature infants may be more of a problem than vigorous resuscitation.

- **Pulmonary hypertension in the newborn (PHN):** Neonates with acidosis, hypercarbia, and temperature instability are at risk for the development of PHN. This will lead to RV decompensation and can be addressed with a number of strategies including alkalinization, ventilation, intravenous drug therapy with inodilators (drugs that are both inotropes and vasodilators such as dobutamine and milrinone), inhaled nitric oxide, and ultimately ECMO.

- **Metabolic considerations:** deficiencies in glycogen, thyroid hormone, parathyroid hormone, the adrenocortical axis may exist and need to be addressed with appropriate replacement therapy.
FIGURE 1

Initial Insult / Infection

Local inflammatory cytokine release

Systemic inflammatory cytokine release

Vascular Endothelial Injury

Tissue Factor Release

- Increased microvascular permeability
- Vasodilation

Third Spacing

- Decreased preload

Sludging & Micro-thrombi

WBC & Platelet adhesion

Thrombin pathway

DIC

Consumption of Coagulation Factors

Bleeding / Red cell hemolysis

Decreased O$_2$ carrying capacity

Poor end-organ perfusion

Septic Shock

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