Severe Sepsis: Pathophysiology, Diagnosis, and Treatment

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Severe sepsis (acute organ dysfunction secondary to infection) and septic shock (severe sepsis plus hypotension not reversed with fluid resuscitation) are major healthcare problems, affecting millions around the world each year, killing 1-2 in 4, and increasing in incidence.

Angus, *Crit Care Med* 2001

Dellinger, *Crit Care Med* 2003


Epidemiology

- Every year, severe sepsis strikes about 750,000 Americans.
- Between 28-50% will die—far more than the number of US deaths from prostate cancer, breast cancer, and AIDS combined.
- The number of sepsis cases per year has been on the rise in the US.
- An estimated $17 Billion is spent annually to treat sepsis in the US.

Sepsis Fact Sheet www.nigms.nih.gov/education/factsheet_sepsis.htm
Epidemiology

One of the main challenges in sepsis treatment is diagnosis.

Often the diagnosis is made late with significant effects on patient outcomes.

Current research focuses on:

- Improving earlier diagnosis
- Improved understanding of the inflammatory response
- How best to treat the syndrome and at what points treatments are most effective.
Surviving Sepsis Campaign: International Guidelines

In 2004, and again in 2008 an international group of experts representing 11 organizations, published the 1st and 2nd internationally accepted guidelines to improve outcomes in severe sepsis and septic shock.

Dellinger, *Crit Care Med* 2004

Dellinger, *Crit Care Med* 2008

In February, the 2012 guidelines will be jointly published in *Intensive Care Medicine* and *Critical Care Medicine*.

www.survivingsepsis.org
How did we get here? An early influential study

Early Goal Directed Therapy (EGDT): Rivers, *NEJM* 2001

- Randomly assigned 263 pts who presented to an urban ED with severe sepsis or septic shock to receive either 6 hrs of EGDT or SC before ICU.
- In-hospital mortality was 30.5% in EGDT and 46.5% w/ SC.
- At 7-72 hrs, EDGT pts had a significantly higher mean ScVO2 (70.4 vs. 65.3%), lower lactate (3.0 vs. 3.9mmol/L), lower BD (2.0 vs. 5.1mmol/L), and a higher pH (7.40 vs. 7.36).
- APACHE II scores were lower over the same period, indicating less severe organ dysfunction (13.0 vs. 15.9)
Efforts to improve outcomes: Do guidelines and bundles improve outcome?

- Multiple studies have shown that EGDT and guidelines can improve mortality in severe sepsis and septic shock.
  - Micek, *Crit Care Med* 2006; Castellano-Ortega, *Crit Care Med* 2010

- BUT, achieving improvements in mortality requires energy, physician buy-in, monitoring, feedback, and QI efforts.

- Unfortunately many studies demonstrate that bundle compliance is often low (6%) and simply applying a sepsis bundle did not significantly improve compliance (21.1% to 13.7% at 24 and 36 months).
Pathophysiology of Sepsis

NORMAL BLOOD

Cytokines (G-CSF, GM-CSF)
β2 integrins
Chemotactic receptors

SEPSIS BLOOD

Cytokines (G-CSF, GM-CSF)

Inflammatory/bacterial factors (e.g., TNFα, IL6, IL8, C5a, LPS)

CD64

Endothelium

Chemokines (IL8, LTB4, fMLP, C5a)

TLR-2

TLR-4

TREM-1

Gram-positive bacteria

Gram-negative bacteria
Pathophysiology of sepsis associated coagulopathy (SAC)

- Sepsis is associated with hemostatic changes that range from hypercoagulability to systemic clotting activation with massive thrombin and fibrin formation, eventually leading to consumption of platelets and acute disseminated intravascular coagulation (DIC).

- DIC following sepsis is considered to be a condition where advanced hypercoagulability and suppressed fibrinolysis cause a decompensated failure of the coagulation system.

- Widespread thrombosis in the microcirculation can contribute to acute organ dysfunction or MODS.


Semeraro, *Mediterr J Hematol Infect Dis* 2010
Pathophysiology of sepsis associated coagulopathy (SAC)

Fibrin deposition in small and midsize vessels of various organs has resulted in ischemia and necrosis.


Experimental bacteremia or endotoxemia causes intra and extravascular fibrin deposition in kidneys, lungs, liver, brain, and other organs.


Why sepsis associated coagulopathy matters

DIC is an independent predictor of organ failure and mortality in patients with sepsis.

- Fourrier, *Chest* 1992
- Dhainaut, *J Thromb Haemost* 2004

Thrombocytopenia is an independent predictor of ICU mortality and has been shown to be a stronger predictor of ICU mortality than APACHE II or MODS score.

- Vanderschueren, *Crit Care Med* 2000
- Strauss, *Crit Care Med* 2002
Pathophysiology of sepsis associated coagulopathy (SAC)

- The pathophysiology of sepsis-associated DIC is extremely complex and extensively studied.

- The Key event is the systemic inflammatory response to the infectious agent.

- Extensive cross talk exists between the coagulation system and the inflammatory response.
Pathophysiology of sepsis associated thrombus formation

The causative agent and the associated inflammatory response drive fibrin formation and deposition by several simultaneously acting mechanisms:

- Up-regulation of procoagulant pathways
- Down-regulation of physiologic anticoagulants
- Suppression of fibrinolysis


Semeraro, *Mediterr J Hematol Infect Dis* 2010

The role of Tissue Factor (TF)

In the 1990s it became apparent that the principal initiator of thrombin generation in sepsis is tissue factor.

- Van Deventer, *Blood* 1990
- Van der Poll, *NEJM* 1990

Nullification of the TF-factor VIIa pathway by monoclonal antibodies directed against TF resulted in a complete inhibition of thrombin generation in endotoxin challenged chimpanzees and prevented DIC and mortality in baboons infused with *E. coli*.

The role of Tissue Factor (TF)

- While endothelial cells and mononuclear phagocytes synthesize TF in response to a wide variety of conditions, TF expression has been shown in neutrophils, eosinophils, and activated platelets.

- Some studies suggest these cells acquire TF rather than synthesize it, by binding TF-expressing microparticles (MP).
So which cell is the main trigger for coagulation?

- While all mentioned cells might contribute to the aberrant expression of TF, most studies point to activated monocytes-macrophages as the main triggers of blood coagulation during sepsis.

- Further support for the prominent role of monocytes-macrophages comes from studies investigating the role of MP.

- MP are small phospholipid vesicles released from cells that carry surface proteins and are associated with thrombosis and inflammation.
Is there a potential benefit to inhibition of TF?

- Selective inhibition of TF expressed by non-hematopoietic cells substantially reduces the clotting activation in endotoxemic mice.
  - Pawlinski, *Thromb Res* 2010
  - Pawlinski, *Blood* 2010

- As the role of ECs and vascular smooth muscle cells remains uncertain, it is likely that TF up-regulation in parenchymal cells of target organs contributes to clotting coagulation during sepsis.

- Additionally, TF is cleaved from the EC surface and higher elevated blood levels are reported in pts with severe sepsis with organ dysfunction than those without organ dysfunction.
Impairment of anticoagulant pathways in sepsis

Three main anticoagulant pathways regulate activation of coagulation:

- Antithrombin (AT)
- The Protein C system
- Tissue Factor Pathway Inhibitor (TFPI)
Impairment of anticoagulant pathways in sepsis: Antithrombin

During severe inflammation AT levels are markedly decreased due to consumption, impaired synthesis, and degradation by elastase from activated neutrophils.


Prospective clinical trials have shown a marked decrease in AT precedes the clinical manifestations of infection, indicating that AT may be involved in the early stages of coagulation activation during sepsis.


Similarly, elevated levels of TAT have been found in early sepsis.

Impairment of anticoagulant pathways in sepsis: Protein C

Endothelial dysfunction is even more important in impairment of the Protein C system.

Under physiologic conditions, Protein C is activated by thrombin bound to the EC membrane-associated thrombomodulin (TM).

During severe inflammation, Protein C levels are decreased from impaired synthesis and degradation by neutrophil elastase, and the system is defective due to down-regulation of TM at the endothelial surface, mediated by proinflammatory cytokines (TNF-α and IL-1β).

- Vary, Am J Physiol 1992
- Eckle, Biol Chem Hoppe Seyler 1991
- Nawroth, J Exp Med 1986
Impairment of anticoagulant pathways in sepsis: Protein C: Thrombomodulin

In sepsis, both the synthesis and recycling of TM are inhibited, therefore its expression on the endothelial cell surface is suppressed by 40-80%.


TM is cleaved from the EC and TM levels found in blood have been significantly elevated in septic patients with MODS.

Activation of Protein C and degradation of thrombomodulin (TM)
Changes in endothelial cell after stimulation of thrombin receptor by thrombin
The significance of PC deficiency

- Acquired severe PC deficiency has been associated with early death.
  - Macias, *Crit Care Med* 2004

- APC plasma levels vary markedly in patients with severe sepsis and are significantly higher in survivors, suggesting that endogenous APC serves protective functions.
  - Liaw, *Blood* 2004

- APC has inflammation modulating effects, including down-regulation of cytokines and TF in activated leukocytes, antioxidant properties, anti-apoptotic activity and prevention of loss of endothelial barrier function.
Impairment of anticoagulant pathways in sepsis: TFPI

- TFPI is the third inhibitory mechanism of thrombin generation and is the main inhibitor of the TF-factor VIIa complex, binding to the TF-factor VIIa complex and factor Xa.
  - Broze, *Biochemistry* 1990

- Animal models have shown decreased TFPI expression in ECs of several organs.

- Anti-TFPI antibodies increase fibrin accumulation.

- TFPI under expression coupled with TF up-regulation, might augment local procoagulant potential, promoting fibrin deposition in tissues.
Impairment of anticoagulant pathways in sepsis: TFPI: a potential treatment?

- Administration of recombinant TFPI has been shown to block inflammation-induced thrombin generation in humans.

- High concentrations of TFPI may be capable of significantly modulating TF-mediated coagulation.

  Creasey, *J Clin Invest* 1993

Plasminogen activator inhibitor-1 (PAI-1) mediated inhibition of fibrinolysis in sepsis

- At the time of maximal activation of coagulation in sepsis, the fibrinolytic system is largely shut off.

- The acute fibrinolytic response to inflammation is the release of plasminogen activators, particularly tissue plasminogen activator (t-PA), however, this increase in plasminogen activation and subsequent plasmin generation is counteracted by a delayed but sustained increase in PAI-1.


- This results in a complete inhibition of fibrinolysis, inadequate fibrin removal, and microvascular thrombosis.
Suppression of fibrinolysis (hypofibrinolysis)

- A sustained increase in plasma PAI-1 has been consistently reported in human sepsis. 
  
  - Elevated PAI-1 levels have been found to correlate with lactate as well as incidence and severity of organ dysfunction, and persisted in non-survivors in small studies of pts in septic shock.

  - Thus a coagulation/fibrinolysis imbalance may contribute to tissue hypoxygenation.

  - Further evidence of this imbalance: Thrombin causes resistance to fibrinolysis by forming more compact and less permeable clot and by activating thrombin-activatable fibrinolysis inhibitor (TAFI).
  
  - Semeraro, Mediterr J Hematol Infect Dis 2010
  
  - Hartemink, J Clin Pathol 2010
  
  - Iba, J Jpn Assoc Acute Med 1994
Changes in endothelial function in sepsis

Anti-thrombotic endothelium
- RBC
- Platelet
- WBC

Prothrombotic endothelium
- t-P
- PAI-1
- Selectins

Plasminogen → Plasmin → Fibrin → Fibrinogen → Thrombin
Potential to reverse hypofibrinolysis through thrombin-activatable fibrinolysis inhibitor (TAFI)?

- Evidence is accumulating that TAFI may be involved in sepsis-associated hypofibrinolysis.

- Additionally, TAFI activation markers have been increased in patients with DIC and non-survivors: showing strong correlation with severity of illness scores.

- Encouragingly, blocking TAFIa with synthetic inhibitors or inhibiting thrombin-TM-dependent TAFI activation enhances the rate of fibrin degradation and reduces fibrin deposition in target tissues.

Semeraro, *Mediterr J Hematol Infect Dis* 2010
The role of cytokines in sepsis and the development of MODS

Emphasis has been placed on the role of polymorphonuclear leukocytes in the development of MODS.

Particularly, in the role of neutrophil-endothelial cell interaction.


The role of cytokines in coagulation/fibrinolysis

- While TNF, IL-1, and IL-6 can activate coagulation in humans and primates, most likely via the TF pathway, neutralization studies with specific antibodies suggest a major role of endogenous IL-6 and to a lesser extent IL-1.

- TNF and IL-1 are involved in TM and PC down regulation and PAI-1 mediated suppression of fibrinolysis.

- Excess proinflammatory cytokines (eg. TNF-α and IL-1B) and other mediators increase vascular permeability, shunt flow, and vasospasm, leading to an increase in tissue hypoxia and cellular insufficiency in the organ.
Inflammation and coagulation cross-talk is not limited to Pro-inflammatory cytokines.

Anti-inflammatory cytokines, such as IL-10, may modulate the activation of coagulation as well, however, the relevance of this role of anti-inflammatory cytokines in the pathogenesis of sepsis-associated coagulopathy remains to be established.

Coagulation/inflammation “cross talk” and the role of PARs

The most important mechanism in which coagulation proteases influence inflammation is by binding to protease-activated receptors (PARs).

- Binding of TF-factor VIIa to PAR-2 results in up-regulation of inflammatory responses in macrophages, affecting neutrophil infiltration and proinflammatory cytokine expression (TNF-α, IL-1β).
  - Cunningham, *Blood* 1999

- Additionally, fibrinogen and fibrin can directly stimulate expression of proinflammatory cytokines on mononuclear cells and induce chemokine production (IL-8 and MCP-1).
  - Szaba, *Blood* 2002
Inter-relationships between inflammation/coagulation and the pathogenesis of MODS

MODS is the hallmark of severe sepsis and septic shock and is the main cause for the high associated mortality.

DIC plays an important role in MODS.
Pathophysiology of MODS

Additional widely recognized mechanisms contributing to MODS include:

- Release of reactive oxygen and nitrogen species and proteolytic enzymes by neutrophils recruited at the tissue level.
- High concentrations of cytokines in the interstitial space that may be directly toxic to vulnerable parenchyma, especially in sepsis with severe leukopenia.
- Extracellular nuclear proteins originating from dying cells may be late mediators of MODS.
- Extracellular histones (esp. H3 and H4) are also major mediators of injury in sepsis and likely come from activated inflammatory cells and dying cells.
Cell death perpetuates inflammation, coagulation, and organ failure

Inflammation can also result in cell apoptosis or necrosis and products released from dead cells, such as nuclear proteins, are able to propagate further inflammation, coagulation, cell death and organ failure.

- Cinel, *Crit Care Med* 2009
- Xu, *Nat Med* 2009
- Semeraro, *Thromb Res* 2012
Pathophysiology of sepsis associated coagulopathy (SAC): Autophagy

- The activation of autophagy in human neutrophils has been linked with phagocytosis and activation of Toll-like receptors.

- Additionally, Neutrophil extracellular traps (NETs) constitute an antimicrobial mechanism that has been implicated in thrombosis via platelet entrapment and aggregation and localization of thrombogenic TF in NETs released by neutrophils has been identified in sepsis.

So how do we modulate the altered inflammation/coagulation of sepsis?
Novel approaches that have failed to gain traction

- Considerable progress has been made in our understanding of the mechanisms underlying sepsis-associated DIC and MODS; however, efforts to modulate these mechanisms have proven challenging.
  
  - Use of TF inhibitors, which would seem logical, remains debated.
  
  - Recombinant TFPI did not show a survival benefit in septic patients.
    
  
  - Treatment with antithrombin concentrates failed to reduce mortality in a large clinical trial.
    
    Warren, JAMA 2001 (KyberSept Trial)
Novel approaches that have failed to gain traction

Recombinant human APC has shown the most promising results, with benefits attributed to the restoration of the protein C anticoagulant pathway and its anti-inflammatory action and degradation of histones.
Xigris (recombinant human APC)

- PROWESS Trial: Randomized, double-blinded, MCT in 164 medical centers. 1271 patients with a 75.2% incidence of MODS at study entry.
  - Xigris was given for 96 hours to 634 patients
  - 28 day mortality was significantly lower (26.5% vs. 33.9%)
  - Cardiovascular and respiratory dysfunction resolved more rapidly
  - Incidence of serious bleeding events (2.4% vs. 1.3%)


- Post-hoc analysis demonstrated greater benefit in pts with DIC.

  - Dhainant, *J Thromb Haemost* 2004
Xigris (recombinant human APC)

- ENHANCE Trial: Randomized, double-blinded, MCT in 361 centers across 25 countries. 2,434 patients enrolled with 2,375 completing.
  - Xigris was given for 96 hours
  - 28 day mortality was similar to that seen in PROWESS (25.3% vs. 24.7%)
  - Incidence of serious bleeding events was increased compared to PROWESS (3.6% vs. 2.4%)
  - Patients treated w/in 24 hours had improved mortality (22.9% vs. 27.4%)

  Vincent, *Crit Care Med* 2005
Xigris (recombinant human APC)

ENHANCE US Trial: Randomized, double-blinded, MCT in 85 centers across the US and Puerto Rico. 273 patients enrolled severe sepsis.

- Xigris was given for 96 hours
- 28 day mortality was significantly lower (26.4% vs. 32.9%)
- Provided confirmatory efficacy and safety documented in the PROWESS trial.

- Bernard, *Chest* 2004
Xigris (recombinant human APC)

October 25, 2011:

Eli Lilly announced withdrawal of Xigris in all markets following results of the PROWESS-SHOCK study, which demonstrated the study did not meet the primary endpoint of statistically significant reduction in 28-day all-cause mortality in patients with septic shock.
Recombinant Thrombomodulin, ART-123

We are currently investigating whether ART-123 has the same potential benefit that generated so much excitement for APC.

This is based upon favorable results in Japan where 41 pts treated with rhTM had improved mortality over 45 who were treated with SOC. While pts treated with rhTM had higher SOFA scores at baseline the 90-day mortality was significantly lower at 37% vs 58%, p=0.038.

Ogawa, J Trauma Acute Care Surg 2012
ART-123 Primary Mechanism of Action

ART-123 binds to thrombin and activates protein C

TF / VIIa

Prothrombinase complex

Prothrombin

Xa

Va

Thrombin

ART-123

Protein S

Protein C

APC

Fibrinogen

Platelet

Thrombin
ART-123 Placebo

N = 370 N = 371

28 Day Mortality (%) 66 (17.8%) 80 (21.6%)

P = 0.273

Meets pre-specified statistical test of P < 0.3
Recombinant Thrombomodulin, ART-123

- The current study will be a randomized, double-blinded, placebo-controlled, phase 3 study to assess the safety and efficacy of ART-123 in subjects with severe sepsis and coagulopathy.

- Enrollment goals: up to 240 centers globally and 800 randomized subjects.
So what do we do with all of this pathophysiology? Back to the guidelines

- Surviving Sepsis Campaign Guidelines
- Current Guidelines for Diagnosis and Treatment
Treatment: Initial resuscitation and infections

_initial Resuscitation (1st 6 hours):

- Begin IVFs immediately in pts with hypotension or lactate > 4mmol/L
- Resuscitation goals: CVP 8-12 mmHg, MAP ≥ 65mmHg,
  - Uop ≥ 0.5cc/kg/hr, ScVO2 ≥ 70% or SaVO2 ≥ 75%
  - If not met, consider further IVF, transfuse PRBC if Hgb < 10, or start dobutamine
Treatment: Initial resuscitation and infections

Diagnosis:

- Obtain appropriate cultures before antibiotics
- 2 Blood cultures, site specific cultures
- Perform imaging studies promptly
Treatment: Initial resuscitation and infections

Antibiotics:
- Begin antibiotics as soon as possible and always within 1 hour of recognizing severe sepsis or septic shock
- Broad spectrum coverage
- Reassess regimen daily to optimize
- Consider combination therapy in Pseudomonas infections
- Consider combination therapy in neutropenic pts
- De-escalate as able, limit to 7-10 days
- Stop antibiotics if cause is found to be non-infectious
Treatment: Initial resuscitation and infections

- Source Identification and Control:
  - Specific anatomic site should be identified ASAP
  - Implement source control measures ASAP following initial resuscitation
  - Choose source control measure with max efficacy and least physiologic cost
  - Remove IV access devices if potentially infected
Treatment: Hemodynamic support & adjuncts

Fluid Therapy:

- Use crystalloids or colloids
- Albumin should be used in patients who require significant amounts of crystalloids
- Target CVP of 8 to 12 (12-15 if MV)
- Use fluid challenge to assess fluid responsiveness (initial bolus of 30ml/kg)
- Rate of fluids should be reduced if cardiac filling pressures increase without improvement in hemodynamics
Treatment: Hemodynamic support & adjuncts

☞ Vasopressors:
- Maintain MAP ≥ 65mmHg
- Norepinephrine is the 1st choice agent
- Epinephrine, phenylephrine, or vasopressin should not be given as initial choice. Vasopressin may be added to Norepinephrine.
- Use Epinephrine as 1st alternative when BP is poorly responsive.
- Do not use low-dose dopamine for renal protection
- A trial of dobutamine (up to 20mcg/kgmin) can be administered in the presence of myocardial dysfunction or ongoing hypoperfusion
- Insert an arterial line as soon as practical
Steroids:

- Consider IV hydrocortisone when hypotension responds poorly to adequate fluids and vasopressors
- ACTH stimulation test is not recommended
- Hydrocortisone is preferred to dexamethasone
- Fludrocortisone may be included if an alternative to hydrocortisone is used
- Steroids may be weaned when vasopressors are not needed
- Hydrocortisone dose should be 200 mg/day
Treatment: Hemodynamic support & adjuncts

- Additional ICU adjuncts:
  - Blood transfusion
  - Mechanical ventilation management
  - Sedation and neuromuscular blockade
  - Glucose control
  - Renal replacement therapy
  - DVT prophylaxis
  - Stress ulcer prophylaxis