Sepsis

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Rather than climb inside macrophage cells, the bacteria hover outside and, like a molecular syringe, shoot six so-called *Yersinia* outer proteins (Yops) into the cells, each of which plays a distinct role in killing the cell. Science 1992
Infections: Plagues and Epidemics

- Spartan Wars 430-427.
- An epidemic breaks out and half the population of Athens died.
- Thucydides vivid description of the upheaval and death.
- Langmuir hypothesizes combined influenza/Staph toxin.
- Morrens and Chu ----Rift Valley Fever.
- Holladay believes the agent no longer exists.
In his treatise *airs water and places* Hippocrates coins the terms epidemics and endemic.

"sepsis" was first introduced by Hippocrates (ca. 460-370 BC) and is derived from the Greek word *sipsi* ("make rotten").

Some diseases were thought to be contagious.

Once we discovered the microbe the focus became the contagion.

John Snow epidemiology of Cholera 1813-1850

In the last twenty years we have been moving from that to the body’s response.
Disruptive

- Ignaz Semmelweis (1818-1865) was the first researcher who developed a modern view of sepsis.
- Obstetrician at the Vienna General Hospital
- His department had an especially high mortality rate. Semmelweis discovered that it was common for medical students to examine pregnant women directly after pathology lessons.
- Hygenic measures such as handwashing or surgical gloves were not customary practice.
- That Semmelweis made some brilliant observations in 1847 on the manner in which puerperal fever is transmitted is beyond doubt. But he was his own worst enemy.
Sepsis is an inflammatory response to an infection that may lead to severe organ dysfunction. Annually, it affects approximately 750,000 people in the United States and is responsible for more than 215,000 deaths.

The estimated cost of sepsis is more than $17 billion each year. The term severe sepsis describes sepsis with acute organ dysfunction, and the term septic shock describes sepsis with organ dysfunction and hypotension refractory to fluid resuscitation.
Etiology

- Spectrum of responsible microorganisms appears to have shifted from predominantly Gram-negative bacteria in the late 1970s and 1980s.
- The rate of fungal infections is reported to have increased more than 200% during the same period.
Definitions

- **Infection**: A suspected or proven (by positive culture, tissue stain, or PCR test) infection caused by any pathogen or a clinical syndrome associated with a high probability of infection, or as a result of, suspected or proven infection.

- **Severe Sepsis**: Sepsis plus one of the following: cardiovascular organ dysfunction: ARDS OR 2 or more other organ dysfunctions.

- **Septic Shock**: Sepsis and cardiovascular organ dysfunction.

DEFINITIONS OF SYSTEMIC INFLAMMATORY RESPONSE SYNDROME, INFECTION, SEPSIS, SEVERE SEPSIS, AND SEPTIC SHOCK

**SIRS**

- The presence of at least 2 of the following 4 criteria, one of which must be abnormal temperature or leukocyte count:
- Core temperature of >38.5°C or <36°C.
- Tachycardia, defined as a mean heart rate >2 SD above normal for age.
- Children <1 yr old: bradycardia, defined as a mean heart rate <10th percentile for age.
- Mean respiratory rate >2 SD above normal for age or mechanical ventilation.
- Leukocyte count elevated or depressed for age (not secondary to chemotherapy-induced leucopenia) or >10% immature neutrophils.
- Non-specificity is a challenge
Overlap

- Bacteria
- Sepsis
- Viruses
- Parasites
- Fungi
- Infection
- SIRS
- Burns
- Trauma
- Other
- Blood Born Infection

Helen DeVos Children's Hospital
Sepsis is associated with both pro- and anti-inflammatory cytokines, which are detectable within the bloodstream. Their 'half-angel, half-devil' properties are fully illustrated in sepsis. While they are a prerequisite to fight infection, their overzealous production is deleterious.

The highest levels are found in plasma of non-surviving patients: they are markers and causative agents of poor outcome.

Process needs to be stabilized.
The link, interplay and network of cytokines taking place during sepsis are illustrated by the correlations between the levels of most pro- and anti-inflammatory cytokines.

However, despite the presence of huge amounts of anti-inflammatory cytokines and molecules targeting specifically interleukin-1 (IL-1) (i.e. IL-1 receptor antagonist) and tumour necrosis factor (TNF) (i.e. soluble TNF receptors), there is no indication that their levels are sufficient to counteract fully these pro-inflammatory cytokines.
Fire Blitz on Bath, 1942, by Wilfred Haines
Fire-fighting 101

Guiding principle “Speedy response”
Fire Extinguishment Theory

1. Fuel removal (Antibiotics, source control)
   a. Accomplished by removal of fuel or by stopping flow of fuel
   b. Also accomplished by allowing fuel to be consumed
2. Oxygen exclusion
3. Chemical reaction inhibition
   a. Effective on gas and liquid fuels
Concept of PIRO

- Recognition that sepsis was a heterogeneous condition.
- P stands for predisposition to infection.
- I for the characteristics of the infection.
- R for the inflammatory response.
- O for organ dysfunction.
- The goal of the PIRO concept was to better understand the differences and similarities among septic patients. The four components exerted independent effects on the likelihood of survival. Moreno Intensive Care Med 2008
Early Vs On time

Outcomes in acute myocardial infarction, trauma, and stroke have seen improvements by the application of early diagnosis and time-sensitive therapies at the most proximal stage of hospital presentation.

The study, using early goal-directed therapy (EGDT) in the treatment of patients with severe sepsis and septic shock, began as a quality initiative that challenged the paradigm of sepsis management at a large urban tertiary care hospital. Rivers et al
Start early

- A study looking at early fluid resuscitation by community physicians showed when shock reversal was accomplished by a median time of 75 minutes there was 96% survival and >9-fold increased odds of survival (9.49 [1.07–83.89]).

- Each additional hour of persistent shock was associated with >2-fold increased odds of mortality {2.29 [1.19–4.44] Pediatrics. 2003 Oct.}
Shock reversal from resuscitative efforts by community hospital physicians resulted in 96% survival versus 63% survival among patients who remained in persistent shock state. B, Resuscitation consistent with the ACCM-PALS Guidelines resulted in a significant increase in survival compared to shock reversal; *P < .001 versus shock reversed; †P < .001 versus resuscitation consistent with ACCM-PALS Guidelines. Pediatrics 2003
EGDT is essentially a comprehensive strategy for evaluating septic patients that includes the following:

1) Assessment of the sepsis prevalence and mortality at the hospital.
2) Identification of high-risk patients based on early pathogenesis.
3) Mobilization of resources for intervention.
4) Performance of a consensus-derived protocol to reverse early hemodynamic perturbations.
5) Appraisal of the quality indicators to assess compliance.
6) Quantification of health-care resource consumption.
7) Assessment of outcomes.
Elements of EGDT

- Treat hypoperfusion aggressively to prevent or limit multiple organ dysfunction, as well as reduce mortality.
- Hypoperfusion results from loss of plasma volume into the interstitial space, decreased vascular tone, and myocardial depression.
- The increase in the cardiac output that is necessary to compensate for the diminished vascular tone may be limited by the myocardial depression.
Goals of therapy

- Goals during the first six hours of fluid resuscitation
- Central venous pressure 8 to 12 mmHg
- Central venous (superior vena cava) or mixed venous oxygen saturation 70 or 65 percent, respectively
- Mean arterial pressure ≥65 mmHg
- Urine output ≥0.5 mL/kg/hour
- The best evidence favors targeting central venous oxygen saturation (ScVO$_2$) ≥70 percent.

Rivers et al 2001 NEJM
Recognize decreased mental status and perfusion. Begin high flow O₂. Establish IV/IO access.

**Initial resuscitation:** Push boluses of 20 cc/kg isotonic saline or colloid up to & over 60 cc/kg until perfusion improves or unless rales or hepatomegaly develop. Correct hypoglycemia & hypocalcemia. Begin antibiotics.

**shock not reversed?**

**Fluid refractory shock:** Begin inotrope IV/IO. use atropine/ketamine IV/IO/IM to obtain central access & airway if needed. Use dopamine up to 10 mcg/kg/min, epinephrine 0.05 to 0.3 mcg/kg/min. 
*Reverse cold shock* by titrating central dopamine or, if resistant, titrate central epinephrine. 
*Reverse warm shock* by titrating central norepinephrine.

**shock not reversed?**

**Catecholamine resistant shock:** Begin hydrocortisone if at risk for absolute adrenal insufficiency

Monitor CVP in PICU, attain normal MAP-CVP & ScvO₂ > 70%

**Cold shock with normal blood pressure:**
1. Titrate fluid & epinephrine, ScvO₂ > 70%, Hgb > 10 g/dL
2. If ScvO₂ still < 70%
   - Add vasodilator with volume loading (nitroprusside, milrinone, iminorine, & others)
   - Consider levsimendan

**Cold shock with low blood pressure:**
1. Titrate fluid & epinephrine, ScvO₂ > 70%, Hgb > 10 g/dL
2. If still hypotensive consider norepinephrine
3. If ScvO₂ still < 70%
   - Consider dobutamine, milrinone, enoximine or levosimendan

**Warm shock with low blood pressure:**
1. Titrate fluid & norepinephrine, ScvO₂ > 70%
2. If still hypotensive consider vasopressin, terlipressin or angiotensin
3. If ScvO₂ still < 70%
   - Consider low dose epinephrine

**shock not reversed?**

**Persistent catecholamine resistant shock:** Rule out and correct pericardial effusion, pneumothorax, & intra-abdominal pressure >12 mm/Hg. Consider pulmonary artery, PICCO, or FATD catheter, &/or doppler ultrasound to guide fluid, inotrope, vasopressor, vasodilator and hormonal therapies. Goal C.I. > 3.3 & < 6.0 L/min/m²

**shock not reversed?**

**Refractory shock:** ECMO
Randomized trials have found no difference between using albumin solution and a crystalloid solution (e.g., normal saline, Ringer’s lactate) in the treatment of severe sepsis or septic shock, but they have identified potential harm from using pentastarch or hydroxyethyl starch rather than a crystalloid versus albumin: In the saline versus albumin fluid evaluation (SAFE) trial, 6997 critically ill patients were randomly assigned to receive 4 percent albumin solution or normal saline for up to 28 days.

Crystalloid versus hydroxyethyl starch:
Crystalloid versus pentastarch: The Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP) trial compared pentastarch to modified Ringer's lactate in patients with severe sepsis and found no difference in 28-day mortality [31].

The trial was stopped early because there was a trend toward increased 90-day mortality among patients who received pentastarch.
A Randomized clinical trial of early goal-directed therapy for pediatric septic shock showed that the group in which Svco₂ saturation was maintained at 70% for the first 72 h of pediatric ICU admission had improved survival (28-day mortality 11.8% vs. 39.2%, p=0.002), and fewer new organ dysfunctions (p=0.03). Oliviera, CF Intensive Care Med. 2008
When Pressor

- When the ScvO$_2$ remains $<$70 percent after optimization of intravenous fluid and vasopressor therapy, it is reasonable to consider additional therapies, such as inotropic therapy or red blood cell transfusion.

- Inotropic therapy – For patients who have diminished cardiac output, a trial of inotropic therapy is warranted if ScvO$_2$ remains $<$70 percent after all of the interventions.

- Inotropic therapy should not be used to increase the cardiac index to supranormal levels.

- However, other data support a more cautious approach to transfusion in critically ill patients.
To Transfuse or Not

- Red blood cell transfusions – The ideal threshold for red blood cell transfusion in patients with sepsis is not known.
- Early goal-directed therapy, as described above, aggressively utilized red blood cell transfusions to raise the ScvO$_2$ Rivers et al 2001 NEJM.
- Nearly 70 percent of patients in the early goal-directed therapy group received transfusions, compared to 45 percent in the conventional therapy group, suggesting a beneficial effect of transfusions.
- In a separate observational study of 1054 patients with severe sepsis or septic shock, transfused patients had a lower risk of 7 and 28-day mortality (hazard ratio [HR] 0.42, 95% CI 0.19-0.50 and HR 0.43, 95% CI 0.29-0.62, respectively) Critical Care 2012.
A subgroup analysis of the TRIPICU study in which patients with sepsis were separately analyzed. In the restrictive group, the transfusion threshold was hemoglobin of 7.0 g/dL and in the liberal group, the threshold was 9.5 g/dL. There was no differences in primary outcome such as incidence of MODS and secondary outcomes such as duration of mechanical ventilation, oxygenation indices and ICU days. Karam, O. Volume 12(5), September 2011, pp 512-518
Transfusion

- This suggests there may be no therapeutic advantage to transfusing septic patients.
- Transfusion may not provide the purported cardiovascular support and it has been shown in acyanotic pediatric patients undergoing cardiac surgery tolerated a hemoglobin level of 8 mg/dl. de Gast-Bakker DH. *Intensive Care Med.* 2013 Aug 31
CONTROL OF THE SEPTIC FOCUS — Prompt identification and treatment of the primary site or sites of infection are essential. This is the primary therapeutic intervention, with most other interventions being purely supportive.

A careful history and physical examination may yield clues to the source of sepsis and help guide microbiologic evaluation. As an example, sepsis arising after trauma or surgery is often due to infection at the site.

The presence of a urinary or vascular catheter.
Initiatives

- Appreciate the problem.
- Conceive / Pediatric study ???/ Need
- Buy in.
- Invest.
- Implement.
- Please publish or at least maybe.