**Controversies in Surgery** 



# **POSTOPERATIVE SEPSIS?**

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### We are not studying exactly the same thing

Jonathan Cohen

Comment: Sepsis studies need new direction

Lancet Inf Dis 2012

#### Table 1-Definitions

Infection = microbial phenomenon characterized by an inflamma-

tory response to the presence of microorganisms or the invasion of normally sterile host tissue by those organisms.

Bacteremia = the presence of viable bacteria in the blood.

- Systemic inflammatory response syndrome (SIRS) = the systemic inflammatory response to a variety of severe clinical insults. The response is manifested by two or more of the following conditions:
  (1) temperature >38°C or <36°C; (2) heart rate >90 beats per minute; (3) respiratory rate >20 breaths per minute or PaCO<sub>2</sub>
  <32 mm Hg; and (4) white blood cell count >12,000/cu mm, <4,000/cu mm, or >10% immature (band) forms
- Sepsis = the systemic response to infection, manifested by two or more of the following conditions as a result of infection: (1) temperature >38°C or <36°C; (2) heart rate >90 beats per minute; (3) respiratory rate >20 breaths per minute or PaCO<sub>2</sub>
  <32 mm Hg; and white blood cell count >12,000/cu mm, <4,000/cu mm, or >10% immature (band) forms.
- Severe sepsis = sepsis associated with organ dysfunction, hypoperfusion, or hypotension. Hypoperfusion and perfusion abnormalities may include, but are not limited to lactic acidosis, oliguria, or an acute alteration in mental status.
- Septic shock = sepsis-induced with hypotension despite adequate fluid resuscitation along with the presence of perfusion abnormalities that may include, but are not limited to, lactic acidosis, oliguria, or an acute alteration in mental status. Patients who are receiving inotropic or vasopressor agents may not be hypotensive at the time that perfusion abnormalities are measured.
- Sepsis-induced hypotension = a systolic blood pressure <90 mm Hg or a reduction of  $\geq 40 \text{ mm Hg}$  from baseline in the absence of other causes for hypotension.
- Multiple organ dysfunction syndrome (MODS) = presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention.

### Terminology



#### accp/sccm consensus conference

Definitions for Sepsis and Organ Failure and Guidelines for the Use of Innovative Therapies in Sepsis





### Sepsis definitions: time for change

Jean-Louis Vincent, Steven M Opal, John C Marshall, Kevin J Tracey

Lancet 2013

- SIRS approach has 3 major problems
  - If SIRS + infection = sepsis, and up to 90% of patients in ICU meet SIRS criteria, then sepsis = infection. But not all patients with infection have sepsis
  - Some degree of host response inherent to infection
  - Deciphering the role of infection in the pathogenesis of SIRS is difficult

### **Clinical definitions**



Phenotype of SIRS clinically indistinguishable in patients with severe infection and those with major tissue injury.

Lancet 2013

*Figure:* Infectious and non-infectious stimuli that activate innate immunity and cytokine release and can cause sepsis

LPS=lipopolysaccharide. HMGB1=high mobility group box 1. mDNA=mitochondrial DNA. TLR=toll-like receptor. NOD=nucleotide-binding oligomerisation domain protein. NLR=NOD-like receptor. RIG=retinoic-acid-inducible gene. TNF=tumour necrosis factor.

- "Sepsis is not simply the host response to infection, nor is it the same as sterile inflammation. Rather, sepsis is the host's deleterious, non-resolving inflammatory response to infection that leads to organ dysfunction."
- Priority therefore to identify any focus of infection, then rapid treatment (AB & source control) and maintenance of perfusion

### **Clinical definitions**

- Postoperative bacteremia causing sepsis
  - Referred to in studies on cardiac, paediatric cardiac, urogenital, dental and plastic (flap) surgery
  - Colonizing agent determines choice of antibiotic prophylaxis
- Postoperative blood stream infections
  - Referred to as central line associated BSI in most instances
- Postoperative sepsis
  - Agency for Healthcare Research & Quality (AHRG): focus on preventable causes of complications & iatrogenic events
  - Clinical definition: includes all types of postoperative patients with an infection leading to sepsis, severe sepsis and septic shock
     Fried et al Curr Opin Crit Care 2011

### Postoperative Definitions

- Epidemiology of Sepsis in Surgical Patients
  - Incidence continues to rise
  - Mortality >40%
  - NSQIP database: Sepsis 10x more common than peri-operative MI & PE, and mortality rate higher than both MI & PE
  - Risk factors
    - Age >60 yrs
    - Emergency surgery
    - Co-morbid disease
  - Intra-abdominal infections most common (2/3s): specifically colon perforation
  - Modified definition of surgical sepsis by authors:

SIRS plus an infection requiring surgical intervention for source control or SIRS plus an infection within 14 days of a major surgical procedure

Moore & Moore Surg Clin N Am 2012

## Epidemiological Definitions

NCCEMD Report: Confidential Enquiry into Maternal Deaths in SA 2008-2010

#### health Department: Health REPUBLIC OF SOUTH AFRICA

### Epidemiology

Direct causes of maternal death	EC	FS	Gau	KZN	Lim	Мри	NW	NC	wc	SA	
Ectopic pregnancy	1.6	1.4	4.4	3.5	3.3	3.0	3.7	9.7	3.4	3.3	
Miscarriage	3.1	6.2	9.5	16.5	7.9	5.9	4.8	6.5	4.3	8.3	
Hyperemesis gravidarum	0.0	0.5	0.0	0.5	0.0	0.0	0.5	0.0	0.0	0.2	
Pregnancy-related sepsis	12.6	10.0	13.7	12.3	7.2	11.4	12.3	6.5	12.0	11.5	
Obstetric haemorrhage	32.1	29.2	28.7	24.8	35.1	38.1	41.7	21.0	17.9	30.6	
Hypertension	34.0	39.7	29.1	27.3	27.5	24.8	28.9	29.0	35.0	30.2	
Anaesthetic complications	4.1	1.4	3.1	7.0	11.5	7.4	4.3	3.2	2.6	5.4	
Embolism	5.3	2.9	3.3	0.8	4.3	6.9	1.1	14.5	12.0	4.1	
Acute collapse - cause unknown	7.2	8.6	8.2	7.3	3.3	2.5	2.7	9.7	12.8	6.6	

#### Table1.10. Distribution of direct causes of maternal death within Provinces



Second priority Third priority



## is coming to a center near you

- South African Surgical Outcomes Study 2014
  - Multi-center 7 day cohort study
- "Performance improvement requires evaluation of process change with consistent education, protocol development and implementation, data collection, measurement of indicators, and feedback."

### Epidemiology

1990's: '..many patients could die ..(and) that the host's intertwined inflammatory and physiologic responses were at least as much to blame as the pathogen itself..'

2000's: 'Multidimensional state: ...dynamic, complex process .. acute inflammation a central mechanism that helps connect these processes across time and space.. Feedback mechanisms.. Series of interlinked and overlapping networks.. Lead to a immunosuppressed state.'

## Biochemical/Molecular definitions: Understanding Sepsis

R Namas et al Journal of Crit Care 2012



Figure 1. Onset of sepsis beginning either as bacterial pneumonia or as peritonitis associated with extramural leaking of intestinal contents. A: Subsequent events include apoptotic deletion of T and B cells, defective DCs, and onset of immunosuppression, together with defective innate immunity. These events lead to loss of the ability to clear bacteria, resulting in development of multiorgan failure (MOF) and death. B: Development of sepsis can also lead to redox imbalance in a variety of cells (leukocytes) and organs due to buildup of reactive oxygen species (ROS). This is followed by an inflammatory response (SIRS), including a sustained immune response and other immune activation states in endothelial cells and leukocytes, ultimately associated with MOF and death.

Am J Pathol 2012



Systems-Based Drug Design and In Silico Clinical Trials

Fig. 3 Toward multidimensional, individualized description of patient state. The future of sepsis diagnosis and therapy will depend on a growing understanding of the cellular and molecular mechanisms of inflammation by which pathogens are sensed and eliminated along with the effects of inflammation on physiology and vice versa. These interactions will form the basis of computational models used for rational design of drugs and the clinical trials by which those drugs are tested. Multidimensional analysis of inflammation biomarkers and physiologic waveforms along with mechanistic mathematical modeling may aid in discerning individual patient states for the purposes of diagnosis and therapy.

#### R Namas et al Journal of Crit Care 2012

- Early identification & screening
  - <40% of nurses are able to recognize sepsis, and only 27% of physicians
  - Thus: mandatory sepsis screening tool for nurses and for physicians
- Early resuscitation: fluids & vasopressors
- Steroids in shock
- Identifying the source
  - 2 Blood cultures, one from vascular access device and one from peripheral site, >10 ml (differential time to positivity at least 120 min)
  - Additional site cultures
  - Radiography
  - Do not delay antibiotics

Management issues for Postoperative sepsis

Moore & Moore Surg Clin N Am 2012

- Empiric antimicrobial therapy
  - Within 1 hour of recognizing sepsis
  - Delayed antifungal therapy is independent risk factor for mortality
  - Vigilant monitoring of culture data
- Source control
  - Concept and process of damage-control laparotomy and what follows
  - Deliberate decision by the surgeon with the peri-operative team following the clinical pathway
  - Crucial question is timing: Source identified, resuscitation initiated, preoperative optimization, abbreviated operative intervention
  - Communication essential
- Computerized clinical decision support (CCDS)
  - Only 1/3 of patients receive appropriate care
  - Bedside application of technology with CCDS improves compliance with guidelines

Management issues for Postoperative sepsis

Moore & Moore Surg Clin N Am 2012

### Controversies

In Postoperative Sepsis





#### Stop sepsis, Save lives

The burden of sepsis: A call for action and support of world sepsis day

Clean care is safer care: priority for the WHO and worldwide perspectives

Update on the Surviving Sepsis Campaign Guidelines General strategies to fight sepsis in resource poor settings

Central line-associated infection prevention: State-ofthe art and innovative approaches

Prevention of sepsis in the ICU

Prevention and early recognition and diagnosis of sepsis

Role of vaccination in patients at risk Early clinical and laboratory signs of sepsis

Role of blood cultures and PCR microbiology Diagnosis of sepsis in neonates and children

#### Sepsis: Is there evidence or just enthusiasm?

Oxygenation: Get the balance right Vasopressor therapy in septic shock Role of lactate Steroids - Who, when and how? Resource limitations: What is the game plan?

#### Sepsis: Will we ever get it right?

Immune failure in sepsis Adrenocortical dysfunction in septic shock Role of statins in sepsis Role of steroids

#### Treating the cause of sepsis

Antibiotic therapy Treating tropical sepsis Surgical source control Management of viral sepsis Achieving reliable implementation of guidelines

#### Sepsis: Micro mayhem

The microcirculation in sepsis Mitochondrial dysfunction Quantitative resuscitation of sepsis induced tissue hypoperfusion

#### Sepsis: The first 24 hours

Avoiding ventilator induced lung injury Antibiotics: An update Targets of haemodynamic resuscitation Role of bundled care

What really makes the difference to outcomes of severe sepsis?

#### It's in the implementation of the guidelines

The focus should be in the ER: Well before the PICU Is it respiratory failure that needs to be addressed? What are the goals of cardiovascular support for sepsis in the PICU?

Blood Transfusions in the intensive care unit following paediatric cardiac surgery: a North American multicenter prospective study (free communication)

#### **Challenges for the future**

Theragnostics and monitoring of immune function Of mice and men: The flaws of animal models Lessons learned from failed sepsis trials

#### **Management of Sepsis**

The role of bundled care Extracorporeal blood detoxification Choice of Fluids The role of nursing in the management of sepsis: Setting goals of care



Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis & Septic Shock: 2012

To bundle or not to bundle: is it all or nothing?

Within 3 hrs		
	Measure lactate	
	Blood cultures before AB	
	Broad spectrum AB	
	30 ml/kg crystalloid	
Within 6 hrs		
	Vasopressors for unresponsive hypotension	
	Persistent hypotension	
		Measure CVP
		Measure ScvO2
	Remeasure lactate	

### Controversies



Dellinger vs Marik. Chest Aug 2013

### Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis & Septic Shock: 2012

### Controversies

Results: Key recommendations and suggestions, listed by category, include: early quantitative resuscitation of the septic patient during the first 6 hrs after recognition (1C); blood cultures before antibiotic therapy (1C); imaging studies performed promptly to confirm a potential source of infection (UG); administration of broad-spectrum antimicrobials therapy within 1 hr of recognition of septic shock (1B) and severe sepsis without septic shock (1C) as the goal of therapy; reassessment of antimicrobial therapy daily for de-escalation, when appropriate (1B); infection source control with attention to the balance of risks and benefits of the chosen method within 12 hrs of diagnosis (1C); initial fluid resuscitation with crystalloid (1B) and consideration of the addition of albumin in patients who continue to require substantial amounts of crystalloid to maintain adequate mean arterial pressure (2C) and the avoidance of hetastarch formulations (1C); initial fluid challenge in patients with sepsis-induced tissue hypoperfusion and suspicion of hypovolemia to achieve a minimum of 30 mL/kg of crystalloids (more rapid administration and greater amounts of fluid may be needed in some patients) (1C); fluid challenge technique continued as long as hemodynamic improvement, as based on either dynamic or static variables (UG); norepinephrine as the first-choice vasopressor to maintain mean arterial pressure  $\geq$  65 mm Hg (1B); epinephrine when an additional agent is needed to maintain adequate blood pressure (2B); vasopressin (0.03 U/min) can be added to norepinephrine to either raise mean arterial pressure to target or to decrease norepinephrine dose but should not be used as the initial vasopressor (UG); dopamine is not recommended except in highly selected circumstances (2C); dobutamine infusion administered or added to vasopressor in the presence of a) myocardial dysfunction as suggested by elevated cardiac filling pressures and low cardiac output, or b) ongoing signs of hypoperfusion despite achieving adequate intravascular volume and adequate mean arterial pressure (1C); avoiding use of intravenous hydrocortisone in adult septic shock patients if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability (2C); hemoglobin target of 7–9 g/dL in the absence of tissue hypoperfusion, ischemic coronary artery disease, or acute hemorrhage (1B); low tidal volume (1A) and limitation of inspiratory plateau pressure (1B) for acute respiratory distress syndrome (ARDS); application of at least a minimal amount of positive end-expiratory pressure (PEEP) in ARDS (1B); higher rather than lower level of PEEP for patients with sepsis-induced moderate or severe ARDS (2C); recruitment maneuvers in sepsis patients with severe refractory hypoxemia due to ARDS (2C); prone positioning in sepsis-induced ARDS patients with a Pao2/Fio2 ratio of ≤ 100 mm Hg in facilities that have experience with such practices (2C); head-of-bed elevation in mechanically ventilated patients unless contraindicated (1B); a conservative fluid strategy for patients with established ARDS who do not have evidence of tissue hypoperfusion (1C); protocols for weaning and sedation (1A); minimizing use of either intermittent bolus sedation or continuous infusion sedation targeting specific titration endpoints (1B); avoidance of neuromuscular blockers if possible in the septic patient without ARDS (1C); a short course of neuromuscular blocker (no longer than 48 hrs) for patients with early ARDS and a Pao2/Fio2 < 150 mm Hg (2C); a protocolized approach to blood glucose management commencing insulin dosing when two consecutive blood glucose levels are > 180 mg/dL, targeting an upper blood glucose  $\leq$  180 mg/dL (1A); equivalency of continuous venovenous hemofiltration or intermittent hemodialysis (2B); prophylaxis for deep vein thrombosis (1B); use of stress ulcer prophylaxis to prevent upper gastrointestinal bleeding in patients with bleeding risk factors (1B); oral or enteral (if necessary) feedings, as tolerated, rather than either complete fasting or provision of only intravenous glucose within the first 48 hrs after a diagnosis of severe sepsis/septic shock (2C); and addressing goals of care, including treatment plans and end-of-life planning (as appropriate) (1B), as early as feasible, but within 72 hrs of intensive care unit admission (2C). Recommendations specific to pediatric severe sepsis include: therapy with face mask oxygen, high flow nasal cannula oxygen, or nasopharyngeal continuous PEEP in the presence of respiratory distress and hypoxemia (2C), use of physical examination therapeutic endpoints such as capillary refill (2C); for septic shock associated with hypovolemia, the use of crystalloids or albumin to deliver a bolus of 20 mL/kg of crystalloids (or albumin equivalent) over 5 to 10 mins (2C); more common use of inotropes and vasodilators for low cardiac output septic shock associated with elevated systemic vascular resistance (2C); and use of hydrocortisone only in children with suspected or proven "absolute"' adrenal insufficiency (2C).

- Resuscitation targets
  - Guidelines within 6 hrs:
    - CVP 8-12 mmHg
    - MAP>= 65 mmHg
    - Urine output >= 0.5 ml/kg/hr
    - ScvO2 70% or SvO2 65% 1C
    - Normalize lactate
       2C
  - Adherence to CVP and ScvO2 targets are low
  - Technologies to monitor flow at the bedside need to universally tested &accepted, and possible to implement in all settings before being introduced in guidelines and protocols

### Controversies



Fluid resuscitation in sepsis: the starches

#### Summary of the main points

- 1. The three recent studies used as a basis for condemning the use of colloids are seriously flawed and do not apply to the perioperative and acute resuscitation period.
- 2. The context of fluid administration appears to be increasingly important. There is no real conflict. The liberal use of colloids in the intensive care unit (ICU) after the initial resuscitation appears to be problematic.
- 3. However, there is significant evidence that perioperative and post-trauma outcomes, e.g. the incidence of multiple organ dysfunction and ICU stay, and better acute resuscitation is accomplished early and follows established, well-recognised haemodynamic goals. A balanced approach (the combined use of crystalloids and colloids) is important, and the inclusion of modern hydroxyethyl starch products derived from maize is associated with improved outcomes.
- 4. The current maize-based hydroxyethyl starches must be viewed as drugs with their own indications, contraindication and complications. As such, they do not have significant organ toxicity and the associated renal dysfunction is not attributable to the fluid alone, but rather to the context in which they are used. Alternative strategies, such as the use of albumin, gelatins, hypertonic saline, crystalloids alone, and blood and blood products, all have serious potential complications.

### Controversies

South Afr J Anaesth Analg 190 2013;19(4)



### Steroids

- Guidelines:
  - IV hydrocortisone 200 mg per day only if fluids and vasopressors do not restore hemodynamic stability 2C
  - CORTICUS failed to show benefit but patients did not have sustained shock, in contrast to French study showing reversal of unresponsive shock

### Controversies





### Source Control

... is what the rest of today's symposium is about!