Sepsis and Goal directed Therapy- the first few hours

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Origins from language

- **Pepsis**: good, maturation + fermentation
- **Sepsis**: bad, putrefaction + smell
- **Shock**: “choquer” – to collide with
Definitions

- **Sepsis** - The host systemic response to infection characterised by ≥ 2 of:
  - Tachycardia
  - Elevated respiratory rate
  - Abnormal temperature (high or low)
  - Abnormal WCC (high or low)
  - **Shock** - when demand for oxygen outstrips supply
Definitions cont...

- **Septic shock**- The systemic response to infection + hypotension after adequate fluid resuscitation
- **Severe sepsis**- The systemic response to infection + evidence of end organ dysfunction
- **Sepsis-induced multiple organ failure**- The systemic response to infection + evidence of dysfunction of two or more organ systems
P.I.R.O.

- Predisposition
- Infection
- Response, and
- Organ dysfunction
- E.g.
  - 3 year old neutropenic child with a hickman line infection,
  - Tachycardia and pyrexia,
  - Hypotensive, acidotic and oliguric, needing oxygen
What kills in Sepsis?

- Bacteria very sensitive to antibiotics
- Early myocardial depression
- Neurology - poor perfusion/ bleed into brain
- Mitochondria unable to use oxygen
- Endotoxin - starts up immune response
- Anti-endotoxin - no difference
- Redundancy in system
Cell death in sepsis

- Previously thought cells die by necrosis
- Recently discovered cells die by apoptosis
- Genetically programmed cell death
- Stress induced endogenous release glucocorticoids
- Necrotic cells - immune stimulation + microbial defences
- Apoptotic cells - anti-inflammatory cytokines that impair response to pathogens
Inflammatory response

- Evolutionary advantage
  - Bleeding clot well
  - Infection clear quickly

Pro-inflammatory

Normal response

Anti-inflammatory immunosuppressive state

Immune modulation- increased risk infection
Genetic differences?

- Low levels TNF
- High levels IL10
- Low monocyte surface HLA-DR expression
- Reduced ability to produce pro-inflammatory cytokine response
- 60 times more likely to get infection
- Mannose binding lectin deficiency
- Increased risk resp/meningococcal infection
- Increased risk SIRS
Single cells obtain oxygen through diffusion
Body plans more complex - time distance constraints of diffusion
Cardiovascular system - bulk flow to various tissues
Oxygen poorly soluble in water - respiratory pigment that binds and carries oxygen in the blood (haemoglobin in vertebrates)
Useful framework for considering Oxygen delivery to tissues

1. Increase oxygen levels environment-
   Increase oxygen saturation

2. Increase diffusion (lungs-blood)
   Increase arterial haemoglobin concentration

3. Increase cardiac output
   Pre-load, After-load, contractility, diastolic function

4. Increase diffusion (blood-tissue)
Why do cells need Oxygen?

- Activities essential for survival - membrane transport, growth, cellular repair
- Facultative functions - contractility, electrolyte transport, motility
- If oxygen availability falls, consumption will become supply dependant
- Facultative functions lost first - organ dysfunction
- Obligatory functions lost - cell death
Relationship between oxygen delivery and consumption

- Oxygen consumption is independent of delivery over a wide range of values.
- Oxygen extraction can readily adapt to changes in supply.
- When oxygen delivery acutely reduced (↓CO, ↓Hb or ↓O2 sats) oxygen extraction increases and oxygen consumption remains stable.
- When oxygen delivery falls below a critical value that oxygen consumption starts to fall.
- Anaerobic metabolism - increase lactate.
Septic shock

- Hypovolemic
- Capillary leak
- Venodilation
- Loss of cardiac filling
- Decrease in cardiac contractility
- Increased pulmonary vascular resistance
- Altered blood distribution
- Shunting
- Cellular inability to use oxygen
“Last ditch stand”- hypovolemic shock

- Cerebral ischemia- profound sympathetic stimulation
- Angiotensin + vasopressin
- Redistribution of fluid from extravascular to intravascular space
- Cardiac output maintained (↑HR +↑pre-load) vasoconstriction
- Systemic arterial constriction
- Impairment of flow to most tissues
- Autoregulation- cerebral + coronary circulation preserved
- Compensatory mechanisms overwhelmed- blood flow to all tissues impaired leading to widespread cellular dysfunction
History of Resuscitation

- WW1: None
- Early death
- WW2: Colloids, Blood
  - ↑Early survival, ↑acute renal failure
- Vietnam: Crystalloids
  - ↑Early survival, ↑respiratory distress syndrome
- 1970-80s: Resuscitation to end points
  - ↑Early survival, ↑multi organ failure
Haemodynamic states in paediatric septic shock

- Flow = pressure ÷ resistance
- CO = (MAP - CVP) ÷ SVR
- 58% low CO high SVR (high mortality)
- 20% high CO low SVR
- 22% low CO low SVR
- Children often change between states

Treatment- Fluid

- ABC
- No more than 90 secs attempting first venous access
- Use interosseus route!
- > 40ml/kg 1st hour reduces mortality
- Fluid boluses 20ml/kg over 5-10mins
  - (Titrate to HR, urine, CRT + consciousness level)
- Hepatomegaly?
- Hepatic compression- judge adequate filling
  - Dellinger et al Crit care Med 2004
Safe Study

- 7000 adults randomised to either albumin or saline for fluid resuscitation on ICU
- Diagnosed with trauma, sepsis or ARDS
- Albumin group ↓HR ↑CVP days 1-4
- Saline group greater volumes days 1-4
- Albumin group more blood days 1-2
- No difference 28 day mortality, days in ICU, days on ventilator, days of CVVH
- Not powered for subgroup analysis but clear trend to increased mortality with saline in the septic shock subgroup
- (N Engl J Med; May 2004)
Airway- take time to get ready

- All children in septic shock require high flow oxygen via reservoir mask
- NBM
- Prompt anaesthetic/ intensivist review
- Intubate > 60ml/kg fluid
- If NG tube present aspirate it!
- Can drop Bp on induction high SVR → vasodilate → Arrest
Airway

- Pre-oxygenate (Parents can help)
- Fentanyl 2mcg/kg + ketamine 1mg/kg
- Don’t use Etomidate
- Rocuronium 1mg/kg or Vecuronium 100mcg/kg
- Modified RSI- cricoid pressure- may need to bag to maintain sats
- ? Cuffed tube
- Will require PEEP once intubated (pulmonary oedema)
Airway

- Monitor BP every 1-2 minutes
- Push fluid in slowly during induction
- Atropine bolus to hand (10-20mcg/kg)
- NGT to decompress stomach
- Will require high pressures 25/10 initially
- Find ventilator
- CXR
- Don’t forget sedation!
Access

- Insert arterial and Central lines
- Femoral is first choice for CVL
- These children are coagulopathic - neck lines increase risk of complications
  - Don’t let lack of central line stop you from using inotropes
Inotropes

- If still low Bp after 15mins aggressive fluid resuscitation → inotropes
- Anticipate- ask for help (lots of people) + start drawing up early
- Dopamine @ 5-10mcg/kg/min is the first choice vasoactive drug for children presenting in septic shock
- Don’t use dobutamine (vasodilation + tachycardia)
- If still low Bp: Cold shock- Adrenaline
  Warm shock- Nor adrenaline

- Vasodilators/ Inodilators should not be used early in resuscitation
Clinical Parameters

- Sats > 93%
- pH, CO₂, Base excess
- Mean Bp ≥40 neonate ≥50 child ≥70 adult
- HR appropriate
- CVP (8-14)
- CRT
- Core-toe temperature gap
- Lactate trend
Central Venous Oxygen Saturation

- Clinically useful approx Mixed Venous sats
- Mixed venous sats measured with pulmonary artery catheter
- Dependent on CO, Oxygen demand, haemoglobin, arterial oxygen saturation
- Normal SVO2 70%
- Low SVO2 inadequate cardiac output
- High SVO2 Cells unable to use oxygen
Goal directed therapy

- Balance oxygen supply to demand
- Optimise cardiac output
  - (manipulate Preload, Afterload and Contractility)
- 263 patients A+E with severe sepsis or septic shock
- Randomised to GDT or standard therapy for 72 hours
- GDT higher Bp, higher MVO2, lower lactate
- GDT lower mean APACHE11 scores
- In hospital mortality 30.5% GDT Vs 46.5% standard therapy group (p=0.009)

Protocol for Goal Directed Therapy

Oxygen, Fluid + Intubate

Arterial + central line

CVP

CVP < 8
- Crystalloid

CVP 8-12
- Colloid

MAP

Low Bp
- Vasoactive agents

Normal Bp

MVO2

< 70
- Transfuse and Inotropes

> 70

Goals achieved
Blood products

- Well child ~ Hb of 7
- Transfuse to achieve MVO2 ~ 70
- Transfusion related immunosuppression
- Cytokines TNF, IL1, IL6, IL8
- Shape changes + impaired deformability
- Impaired tissue access + entrapment
- Microvascular obstruction
- Elevated clotting times- FFP
- Low fibrinogen- cryoprecipitate
- Do not correct plts unless bleeding
Steroids

- Use when catecholamine resistance
- Or proven adrenal insufficiency
- ACTH stimulation test
- Hydrocortisone 1mg/kg qds IV

- RCT 7 days treatment low dose hydrocortisone + fludrocortisone reduced risk of death in 300 adult patients with septic shock and relative adrenal insufficiency
- Annane et al; JAMA 2002