Sepsis

Introduction

- Common ED presentation.
- 2% of hospitalisations
- Significant hospital mortality if shock: 23-46%.

Role of Emergency Physicians

- ~33% patients with sepsis admitted through the ED.
- "Golden hour" may be critical concept
- ED Sepsis Education Program and Strategies to Improve Survival (ED-SEPSIS) Working Group 2004 EBM guidelines (updated in January 2008)

Definition of Sepsis Syndromes and Organ Failure

Sepsis = Systemic inflammatory response syndrome (SIRS) during an infection. Need ≥2 from:

- Temperature > 38°C or < 36°C
- HR >90bpm (>160 infants, >150 children)
- Respiratory Rate (RR) > 20 breaths/min or P_aCO_2<32mmHg
- WBC>$12x10^9$/L or <$4x10^9$/L (or >10% immature bands)

Infection without SIRS = Suspected infection without SIRS criteria.

Severe sepsis = Sepsis and organ dysfunction or hypoperfusion:

- **Neurologic:** New altered mental status;
- **Hematologic:** plt<$100x10^6$/L; Coagulopathies i.e INR >1.5; APTT >60 secs
- **Renal:** Cr>44.2μmol/L w/o CRF; or ↑11.1μmol/L; acute oliguria (<0.5mL/kg/hr) for ≥2hr despite fluid resuscitation
- **Pulmonary:** RR>20; SaO_2<90% or <94%+O_2/mech vent; PaO_2/FIO_2<300
- **GI:** Ileus; absent bowel sounds; hyperbilirubinemia (total bilirubin >70mmol/L)
- **Cardiovascular:** Septic shock

Septic shock. Sepsis and refractory hypotension - BP_{sys}<90 mmHg (<75mmHg child, <65mmHg infants), MAP<65mmHg, or BP_{sys} ↓40mmHg from baseline; unresponsive to fluid (20-40ml/kg)

Assessment

History – risk factors (age, M>F, immune status, EtOH dependence, malignancy, indwelling catheter, prosthetics), contacts, likely source. Premorbid state/medical history.

Examination – Vitals, signs of SIRS/sepsis as above, focal signs of infection

Investigations

Beside: Urinalysis (& send for MC&S), BSL, ABG + serial lactate (for 2h clearance)

Blood: FBC (↓Hb, ↓Hct, ↑↓WCC+diff, ↓plt), UEC (↑Cr, ↓HCO_3^-), ↑LFT, gluc, ↑coags, ± D-dimers & FDPs, Procalcitonin, CRP, CK, cultures

Imaging: CXR, ±AXR, CT as indicated. USS (dynamic change in IVC diameter may be useful).

Other: Other culture sites e.g. wounds, in-dwelling lines, CSF

Targets for therapy

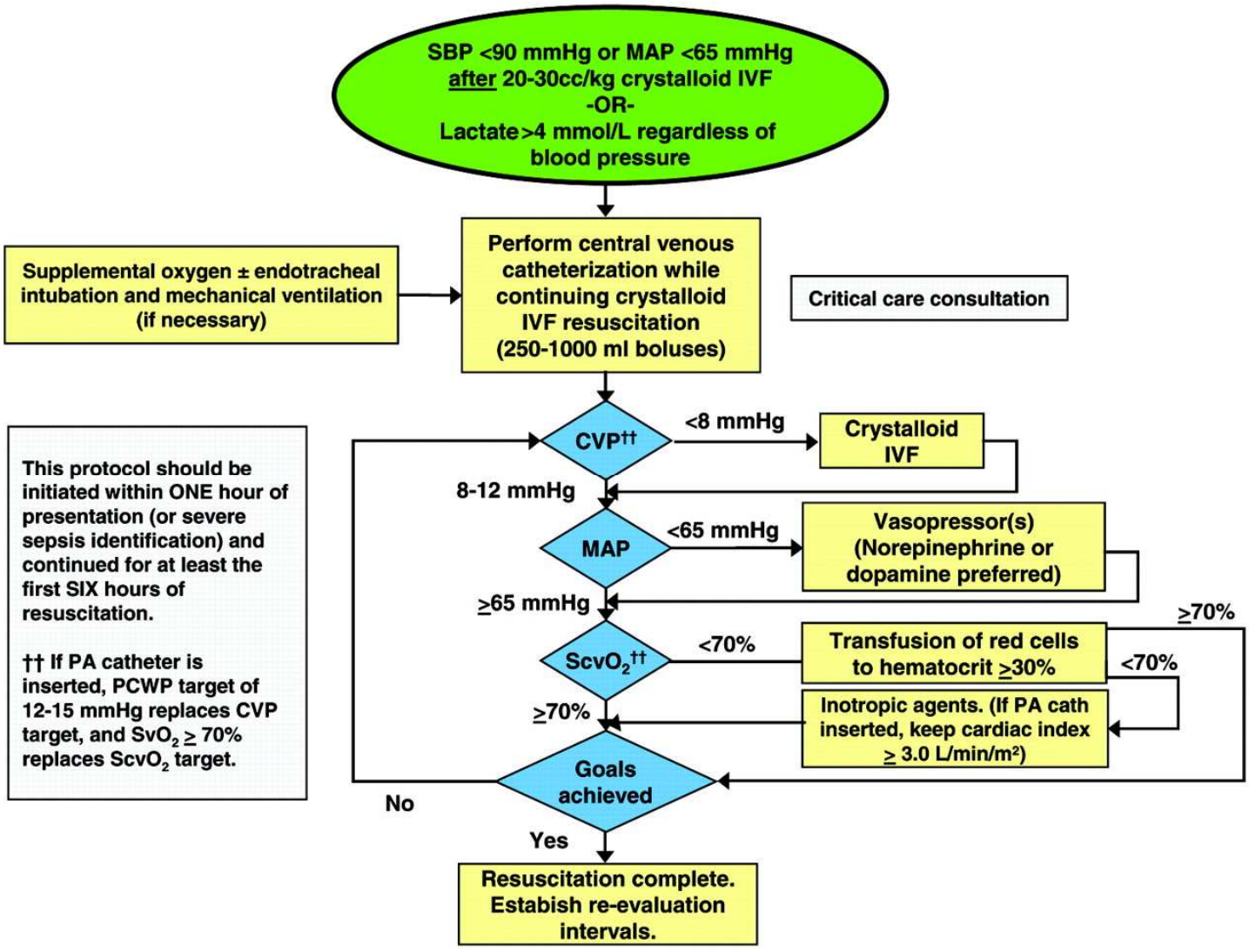
- Immune suppression cellular mechanisms
- Early goal-directed therapy (EGDT®)
- The Surviving Sepsis Campaign guidelines.

General Management Overview

- Triage to resus
- Team approach, early involvement – ED, ICU, appropriate to septic source
- Establish monitoring, HR, BP, RR, sats, BSL, urinary catheter for output monitoring
- **HypoBP** (MAP <65mmHg) after initial fluid challenge, **lactate >4mmol/L**, clinical evidence of **hypoperfusion**, or **organ failure** strongly suggests severe sepsis / septic shock.
- In severe sepsis arterial line for IABP and CVL for CVP/$ScvO_2$ should be inserted
- Seek and treat immediate resuscitation needs (Airway & Breathing, Circulation - EGDT)
    - O_2 + if inadequate ventilation/airway intubate – **ketamine** may be best induction
        - IPPV - ARDS strategy: TV 6ml/kg, P_{plat}<30cmH_2O, min PEEP & wean FiO2 prn
    - Fluids – 20ml/kg NS over 30min – rpt if BPsys<90 or MAP<65 while CVP<8mmHg
    - Vasopressors – **noradrenaline** if hypotensive despite adequate filling (CVP≥8)
        - Consider steroids (**hydrocortisone**) if requiring high doses of vasopressors
    - Blood Transfusion – if ScvO2<70% and Hb<70g/L or Hct<30%
    - Inotropes – Add **dobutamine** if ScvO2<70% or still oligo/anuric
- Remove any ongoing infection source & give appropriate empiric antibiotics
- Consider activated Protein C (if no abs CI and severe sepsis/multi-organ failure)
- Supportive / symptomatic care as per Surviving Sepsis Guidelines
    - Maintain normoglycaemia, skin care, DVT/stress ulcer prophylaxis, PRN dialysis
- Disposition (usually ICU)

Surviving Sepsis Guidelines (Pub. 2004 and updated in 2008)

Initial fluid resuscitation (EGDT)



EGDT (cont)

- Colloid=crystalloid [meta-analyses & also the Saline vs Albumin Fluid Evaluation (SAFE)]
- Use fluid challenges of at least 500-1L crystalloid (child 10-20ml/kg) q15-30min
- EGDT - Maintain:
    - CVP 8-12mmHg (12-15mmHg if ventilated) with crystalloid or colloid infusions
    - MAP ≥ 65 (and ≤90mmHg)
    - $ScvO_2$ or SvO_2 ≥ 70%
    - UO ≥ 0.5mL/kg/hour
- If venous oxygen saturation ≥ 70% is not achieved, consider:
    - Transfusion of red blood cells (RBCs) as needed to Hb ≥ 10 & hematocrit ≥ 30%
    - If $ScvO_2$ still < 70% then try inotropic agents (**dobutamine** 2.5-20mcg/kg/min)
    - Dobutamine may need vasopressors too if hypotensive.

Diagnosis

- Obtain cultures prior to broad-spectrum antibiotic administration.
- ≥2 blood cultures and other samples (urine, CSF, sputum, wounds, pus) should be taken.
- Bacteraemia found in only ~50% severe sepsis/ septic shock. 20-30% have no cause.

Antibiotic therapy

- Start empiric IV antibiotics within 1hr. Likely sources: Lung (35%), Abdo (21%), Urinary tract (13%) (Esp elderly, very young), Skin and soft tissue (7%), Other site (8%) and Unknown (16%). Likely pathogens: E coli (25%), Pneumococcus (16%), S. aureus (14%)
    - Possible choice in adults:
        - Empiric: **flucloxacillin** + **gentamicin**
        - Respiratory tract: **ceftriaxone** (or **moxifloxacin**) + **azithromycin**
        - GIT: **metronidazole** + **ampicillin** (or **ceftriaxone**) + **gentamicin**
        - Urinary tract: **ampicillin** (or **ceftriaxone**) + **gentamicin**
        - Female genital tract: **ceftriaxone** + **azithromycin** + **metronidazole**
        - Skin: **flucloxacillin**
        - Neurological: **ceftriaxone** + **benzylpenicillin**
        - IV line related: **vancomycin** + **gentamicin**
        - Febrile neutropaenia: **piperacillin/tazobactam** (or **cefepime**) + **gentamicin**
        - Penicillin-allergic: replace penicillin drug with **vancomycin**
- Reassess antibiotics with culture results (~48-72hr)
- Duration guided by clinical response (usually 7-10d)
- If determined to be non-infectious, cease antibiotics to minimize resistance.
- Combination therapy for
    - Pseudomonas sp coverage regardless of sensitivities and
    - Neutropenia and severe sepsis or septic shock

Source Control

- Early surgical intervention if indicated
- Drainage of an abscess or focus of infection
- Debridement of necrotic tissue or
- Removal of infected device/catheter/FB.

Vasopressors

- If MAP<65mmHg after a crystalloid challenge of 20-40ml/kg
- 1st choices: **Noradrenaline** 0.5-20mcg/min, 2nd line:**dopamine** 5-20mcg/kg/min, **adrenaline**
- Low-dose dopamine is not renal protective and shouldn't be used as such
- If still hypotensive on max NA, consider **vasopressin** 0.01-0.04units/min IV

Steroids

- Only if vasopressors rqd to maintain BP, otherwise ↑superinfection mort
  - **Hydrocortisone** 50mg IV q6h x 7d
- [Metanalysis of trials since 1998 published in JAMA 2009 suggested a small short term reduction in 28d mortality with low dose (≤300mg/d) ≥5d course in severe, vasopressor-dependent sepsis, however the evidence is not particularly robust.]

Recombinant human activated protein C (rAPC)

Potent anticoagulant, pro-fibrinolytic, anti-inflammatory, and anti-apoptotic in septic patients. No proven mort in Paeds (RESOLVE 2007), but up to 6.1% in adults (PROWESS, ENHANCE & ADDRESS). Debated benefit. D/W intensivist if:

- APACHE II score ≥ 25, Sepsis-induced multiple (≥2) organ failure, and no abs CI.

Blood Product Administration

- If reqd in EGDT protocol to maintain hematocrit of 30%
- Otherwise RBC transfusions if adult Hb<70g/L (to achieve Hb70-90g/L) [TRICC]
- FFP not recommended as routine in absence of bleeding
- Platelets if count<$5x10^9$/L or high risk of bleeding and count<$30\text{-}50x10^9$/L

Mechanical Ventilation of Sepsis-induced Acute Lung Injury (ALI/ARDS)

- ARDS:
  - Bilateral infiltrates consistent with pulmonary oedema on chest x-ray
  - PaO_2:FiO_2 ratio <300, and
  - No left atrial hypertension; i.e. PCWP < 18mmHg.
- Recommendations:
  - Tidal volume of 6ml/kg with permissive hypercarbia
  - End inspiratory pressure<30cmH_2O
  - Use minimal PEEP
  - Bed tilted up 45°

Sedation, Analgesia, and Neuromuscular Blockade in Sepsis

- Protocol guided, sedation scales
- Daily interruption or lightening with awakening and re-titration
- Neuromuscular blockers should be avoided

Other:

- Glucose Control – strict control unnecessary & ?harmful. Aim for BSL 4-10mmol/L
- Renal Replacement - If have ARF, daily dialysis or CVVH beneficial
- Bicarbonate Therapy - Not recommended esp if pH>7.15.
- Deep Vein Thrombosis (DVT) Prophylaxis - heparin (LMWH or UFH) or TEDS if CI.
- Stress Ulcer Prophylaxis - H2 receptor blockers or PPI

Future of Sepsis Research and Management

- Immunotherapy
  - Immunoglobulin – 'promising' according to Cochrane
  - IL-12, an immune stimulant and Th1 inducer reduces mortality from burns sepsis
  - Antibodies against C5a
- Increasing use of IVC USS to recognise hypovolaemia

Disposition

- ICU/HDU
- May be controversy if premorbid state poor, advance directives.
- Counselling

Addenda

Risk Stratification and Prognostic Models

- Shift Mx to Early Goal-Directed Therapy (EGDT) in ED rather than ICU.
- Older risk stratifications such as Acute Physiology And Chronic Health Evaluation (APACHE) II score and Simplified Acute Physiology Score (SAPS) were done in ICU.
- ED organ dysfunction assessment (see above) promoted. ↑Mort rate with ↑no. organs:
    - 1.0% (0 organs), 5.9% (1), 12.5% (2), 25.9% (3), 53.3% (4).
- ↑Mortality also with ↑lactate (>2.5mmol/L→4.3% mort, >4mmol/L→28%), and lactate clearance of >10% at 2h favours a positive outcome.

APACHE II score. 0-71. Criteria include T, HR, MAP, RR, oxygenation, serum Na, serum K, serum Cr, arterial pH/venous HCO3, WBC, Hct, and GCS. This acute physiology score is combined with age and chronic health score comprise the APACHE II score.
SAPS II. The SAPS II score includes 17 variables: 12 physiology variables, age, type of admission (scheduled surgical, unscheduled surgical, or medical), and 3 underlying disease variables (AIDS, metastatic cancer, and hematologic malignancy).
MEDS: Mortality in Emergency Department Sepsis. Criteria: terminal illness, shock, plt, WBC diff, age, LRTI, nursing home, mental status. 28d Mortality for score >15 = ~45%

Rivers Trial

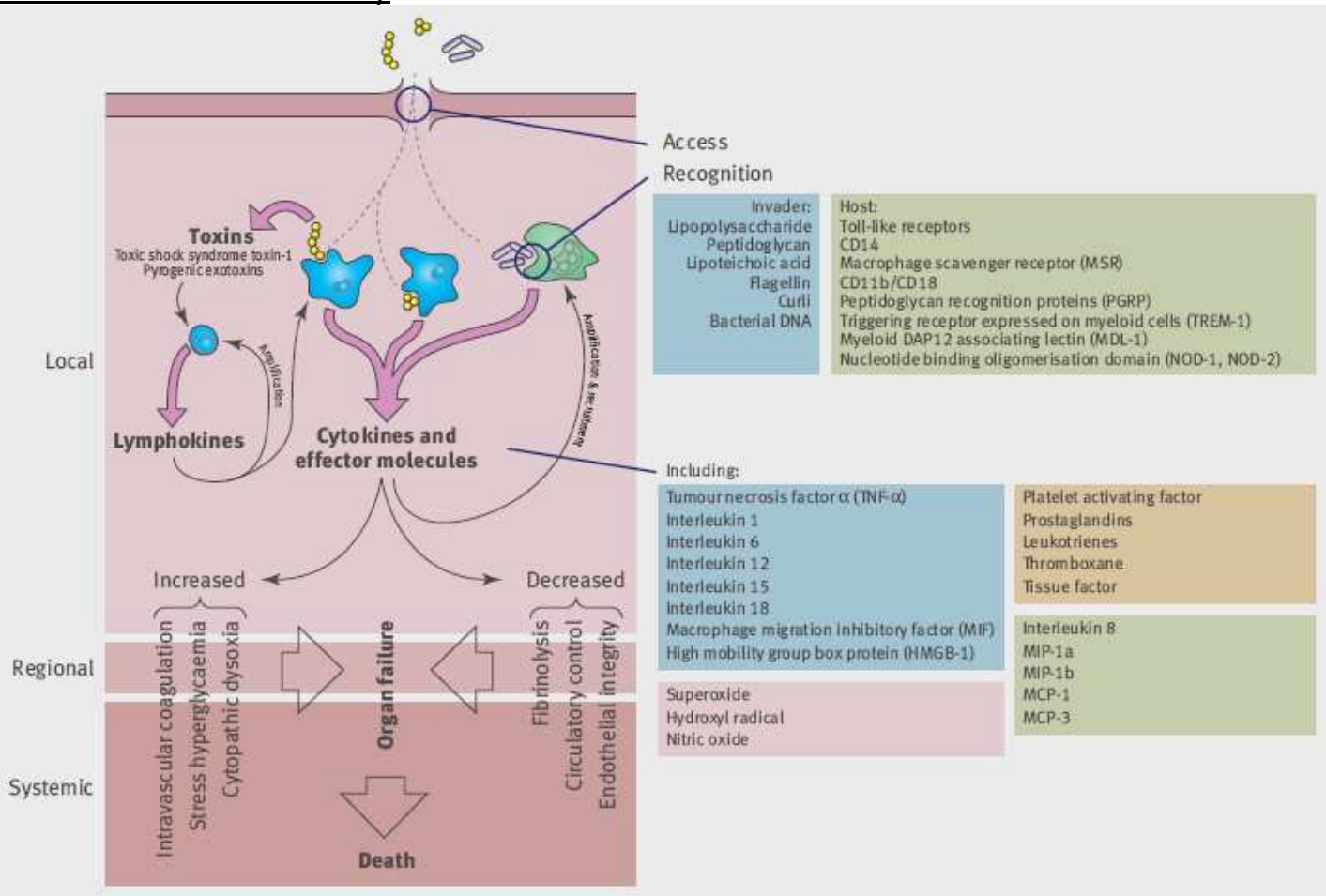
In the trial by Rivers and co-workers (NEJM 2001), 263 patients with infection associated with hypotension after a fluid bolus or with serum lactate levels ≥ 4 mmol/L were randomized to standard care vs EGDT in the ED prior to ICU transfer. Those in the EGDT group had received more fluid resuscitation (5L vs 3.5L), RBC transfusions (64.1% vs 18.5%), and inotrope administration (13.7% vs 0.8%) compared with the control group within the first 6 hours. In the subsequent 7 to 72 hours, patients that had been in the EGDT group had:

- Higher mean $ScvO_2$;
- Lower mean lactate concentration;
- Lower mean base deficit; and
- Higher mean pH
- Less fluid therapy
- Fewer RBC transfusions
- Less vasopressor therapy
- Less mechanical ventilation
- Also improved were:
    - Organ dysfunction scores
    - Earlier survivor hospital d/c
    - Incidence of cardiopulmonary Cx (halved)
    - Lower mortality 30.5% vs 46.5% in the control group.

EGDT is a systematic approach to restoration of systemic oxygen delivery by aggressively optimizing cardiac preload, afterload, and contractility in patients with severe sepsis and septic shock, while avoiding excessive increases in myocardial oxygen consumption and maintaining coronary perfusion pressure, all leading to reduced mortality.
Some criticisms of the Rivers trial: Single centre trial, unusually high mortality in control arm, unclear which of Rx was the cause of improvement, (or if early specialist involvement in study arm lead to bias), use of specialised equipment not available in most EDs, use of transfusion for HCT<30% w/o anaemia.

Pathophysiology

Cardiovascular Insufficiency



Early stages of sepsis - hypodynamic cardiac state → cardiovascular insufficiency → global tissue hypoxia (via ↓preload (from left ventricular dysfunction and hypovolaemia), vasoregulatory dysfunction, myocardial depression, ↑metabolic demands and ↓tissue oxygen delivery).

Later - a hyperdynamic cardiac state (distributive shock) may occur after fluid resuscitation manifested by increased cardiac output because of compensatory mechanisms of ventricular dilatation and tachycardia. The imbalance between systemic oxygen delivery and consumption is reflected by the mixed venous oxygen saturation (SvO2) which is used as an objective measure in sepsis care. Central venous oxygen saturation (ScvO2, typically 5-7% >SvO2), and arterial lactate can also be helpful.