Sepsis

Definition of sepsis
- Infection: the inflammatory response to micro-organisms or the presence of micro-organisms in normally sterile sites
- Systemic inflammatory response syndrome (SIRS): systemic response to various insults including infection, trauma, surgery, burns; includes two or more of the following:
  - Respiratory rate (RR) >20 or $P_aCO_2 <4.3$ kPa
  - Heart rate (HR) >90
  - Temperature >38.3 °C or <36 °C
  - White cell count (WCC) >12 or <4 $x 10^9$/L
  - Acutely altered mental state
  - Glucose >8.3 mM (in the absence of diabetes mellitus)
- Sepsis: systemic response to infection i.e. SIRS + source of infection e.g.
  - Focal crackles/bronchial breathing on chest auscultation
  - Consolidation on chest radiograph (CXR)
  - Positive urine dipstick and/or culture
- Severe sepsis: sepsis + organ dysfunction or tissue hypoperfusion
  - Organ dysfunction
    - Respiratory: new/increased oxygen requirements to maintain oxygen saturations ($SpO_2$) >90%
    - Renal: creatinine >177 µM or urine output <0.5 ml/kg/hour for 2 hours
    - Hepatic: bilirubin >34 µM
    - Coagulation: platelets <100 $x 10^9$/L, INR >1.5 or APTT >60 s
  - Tissue hypoperfusion
    - Systolic blood pressure (SBP) <90 mmHg or mean arterial pressure (MAP) <65 mmHg
    - SBP >40 mmHg below normal
    - Lactate >2 mM
- Septic shock: sepsis + persistent hypoperfusion despite adequate fluid resuscitation (20 ml/kg bolus of crystalloid)
  - SBP <90 mmHg or MAP <65 mmHg despite adequate fluid resuscitation
  - SBP >40 mmHg below normal despite adequate fluid resuscitation
  - Lactate >4 mM

Aetiology of sepsis
- Sepsis can occur due to infection at any site in the body; bacteria are the usual culprit although viruses, fungi and parasites can all cause sepsis
- Respiratory
  - Pneumonia
  - Lung abscess
- Cardiac
  - Endocarditis
  - Myocarditis
  - Pericarditis
- Genito-urinary
  - Cystitis
  - Pyelonephritis
  - Sexually-transmitted infections (STIs)
- Gastrointestinal
  - Gastroenteritis
- Cholecystitis
- Ascending cholangitis
- Appendicitis
- Diverticulitis
- Bowel perforation
- **Neurological**
  - Meningitis
  - Encephalitis
  - Cerebral abscess
- **Dermatological**
  - Cellulitis
  - Ulcers
  - Wound infection
  - Necrotising fasciitis
- **Orthopaedic**
  - Osteomyelitis
  - Septic arthritis

### Risk factors for sepsis
- **Immunocompromise**
  - Extremes of age
  - Acquired immunodeficiency syndrome (AIDS)
  - Chemotherapy or underlying malignancy (especially haematological)
  - Steroids
  - Alcohol misuse
  - Malnutrition
  - Pregnancy
  - Genetic immune deficiencies — can present in adulthood (e.g. CVID)
- **In-dwelling devices**
  - Vascular lines
    - Peripheral venous cannula (PVC)
    - Central venous catheter (CVC)
    - Arterial line (ART)
  - Urinary catheters
    - Urethral catheter
    - Suprapubic catheter
  - Drains
- **Recurrent antibiotic therapy**

### Pathophysiology of sepsis
- **Increased vascular permeability**
  - Pro-inflammatory cytokines released as part of the systemic response to infection damage the vascular endothelium resulting in an inability to regulate vascular permeability
  - As a result, the vascular endothelium becomes leaky, resulting in the migration of fluid and protein from the intravascular to extravascular space and a ‘capillary leak syndrome’
  - This leads to hypovolaemia, reduced preload, stroke volume (SV) and cardiac output (CO) via the Frank-Starling mechanism, as well as pulmonary oedema and hypoxia in the lungs
- **Myocardial dysfunction**
  - The reduction in SV due to increased vascular permeability reduces CO via the Frank-Starling mechanism
- In the early stages of sepsis, CO is maintained via an increase in HR and myocardial contractility and a ‘hyperdynamic circulation’ is seen.
- However, further increases in HR reduce cardiac filling and coronary perfusion time, resulting in reduced CO and myocardial ischaemia, respectively.
- In the later stages of sepsis, pro-inflammatory cytokines, in addition to hypoxia and acidosis, directly impair myocardial contractility, reducing CO further.
- **Disseminated intra-vascular coagulation (DIC)**
  - Pro-inflammatory cytokines damage the vascular endothelium leading to widespread activation of the coagulation system and clot formation.
  - This leads to thrombosis and multi-organ failure, but also thrombocytopenia and prolonged coagulation times from the consumption of platelets and clotting factors.

### History in sepsis

- **General symptoms**
  - Fever
  - Chills
  - Malaise
  - Myalgia
  - Confusion
  - Constitutional symptoms indicative of underlying systemic disease (weight loss, fever, night sweats, lumps and bumps [nodes]).
- **Symptoms of the source**
  - Respiratory
    - Productive cough
    - Dyspnoea
    - Pleuritic chest pain
  - Cardiac
    - Chest pain
    - Valvular heart disease
    - Prosthetic valve replacement
  - Genito-urinary
    - Dysuria
    - Urinary frequency
    - Urinary urgency
    - Strangury
    - Cloudy, foul-smelling urine
    - Loin pain
  - Gastrointestinal
    - Abdominal pain
    - Nausea and vomiting
    - Diarrhoea
    - Jaundice
  - Neurological
    - Headache
    - Neck stiffness
    - Photophobia
    - Confusion
    - Drowsiness
    - Seizures
  - Dermatological
    - Hot, swollen, red, painful areas of skin
  - Orthopaedic
- Hot, swollen, red, painful joints

- Other considerations
  - Contacts, including non-human
  - Travel history
    - Dates and destinations
    - Vaccinations
    - Chemoprophylaxis
  - Sexual history
    - Sexual partners in last three months (women, men, hetero/homosexual)
    - Last sexual intercourse
    - Use of protective contraception
    - Previous STIs
    - Current partner and their sexual history
  - Vaccination history

### Examination in sepsis

- General signs
  - Pyrexia
  - Rigors
  - Tachypnoea
  - Tachycardia
  - Acutely altered mental state

- Signs of the source
  - Respiratory
    - Ipsilateral reduced air entry
    - Ipsilateral dullness to percussion
    - Ipsilateral crackles/bronchial breathing
  - Cardiac
    - Splinter haemorrhages
    - Osler nodes
    - Janeway lesions
    - New regurgitant murmur
    - Roth spots
  - Genito-urinary
    - Suprapubic tenderness
    - Loin tenderness
  - Gastrointestinal
    - Abdominal distension
    - Abdominal tenderness
    - Guarding
    - Rigidity
    - Jaundice
  - Neurological
    - Nuchal rigidity
    - Kernig’s sign positive
    - Brudzinski’s sign positive
    - Photophobia
    - Confusion
    - Reduced/fluctuating consciousness level
    - Focal neurological signs
    - Papilloedema
  - Dermatological
- Warm, erythematous, tender, oedematous areas of skin
- Pupuric rash
  - Orthopaedic
    - Warm, erythematous, tender, oedematous joints
  - Other
    - Nodes
- Signs of septic shock
  - Airway
    - May be compromised by reduced consciousness level
  - Breathing
    - Hypoxia
    - Tachypnoea
  - Circulation
    - Warm, flushed peripheries
      - In early stages of sepsis
    - Cold, pale peripheries
      - In later stages of sepsis
    - Tachycardia
    - Hypotension
  - Disability
    - Confusion
    - Reduced consciousness level

**Initial investigation of sepsis**
- Venous blood gas (VBG) looking for lactic acidosis suggestive of severe sepsis (>2 mM) or septic shock (>4 mM)
- Full blood count (FBC) looking for raised WCC, neutrophilia or neutropenia, as well as haemoglobin (Hb) level for its oxygen-carrying capacity
- Urea & electrolytes (U&Es) looking for impaired renal function
- Liver function tests (LFTs) looking for derangement that may suggest a hepatobiliary source or hepatic failure as a complication
- Clotting and fibrinogen looking for DIC
- C-reactive protein (CRP)
- Blood cultures
  - Peripheral cultures
  - Lines cultures if vascular lines present
- Urine dipstick +/- culture looking for leucocytes, nitrites and bacteria that would suggest a genito-urinary source
- Electrocardiogram (ECG)
- CXR looking for focal consolidation that would suggest a respiratory source or pulmonary oedema that would suggest acute respiratory distress syndrome (ARDS)
- Sputum culture if productive cough present
- Stool culture if diarrhoea present

**Further investigation of sepsis**
- Echocardiography (echo) if endocarditis suspected
- Lumbar puncture (LP) if meningitis suspected
- CT chest and/or abdomen if source remains occult
Initial management of sepsis

- Assess the patient from an ABCDE perspective
- Maintain a patent airway: use manoeuvres, adjuncts, supraglottic or definitive airways as indicated and suction any sputum or secretions
- Deliver high flow oxygen 15L/min via reservoir mask and titrate to achieve $S_{p}O_{2}$ 94-98% or 88-92% if known to have chronic obstructive pulmonary disease (COPD)
- Attach monitoring
  - Pulse oximetry
  - Non-invasive blood pressure
  - Three-lead cardiac monitoring
- Request 12 lead ECG and portable CXR
- Obtain intravenous (IV) access and take bloods
- Anti-pyretics
  - Give paracetamol 1 g orally (PO) +/- ibuprofen 400 mg PO if no contraindications
  - If temperature remains high consider removal of excess clothing +/- bathing with tepid water
- Sepsis six
  - Oxygen titrated to achieve $S_{p}O_{2}$ 94-98% or 88-92% if known to have COPD
  - Check lactate
  - Take blood cultures
  - Give IV antibiotics
    - Should be given as soon as possible and within an hour of recognising severe sepsis or septic shock
    - If the source is known, give the appropriate empirical IV antibiotic(s) as per local guidelines
    - For sepsis of unknown origin, give the appropriate broad-spectrum IV antibiotic(s) as per local guidelines e.g. piperacillin + tazobactam (tazocin) + gentamicin; once the source has been identified, switch to the appropriate empirical IV antibiotic(s) as per local guidelines
    - Give dexamethasone 10 mg IV if bacterial meningitis suspected
  - Commence IV fluid resuscitation
    - Guided by clinical context
    - Give boluses of crystalloid 500-1000 ml IV and re-assess after each
    - Patients with severe sepsis should receive a minimum of 20 ml/kg
    - Patients with septic shock often require up to 60 ml/kg
  - Monitor urine output, aiming for >0.5 ml/kg/hour; this may require urinary catheter insertion
- Source control
  - Removal of infected line eg urinary catheter, arterial line, central line
  - Abscess drainage
  - Tissue debridement
- Early goal-directed therapy (EGDT)
  - 1: Central venous pressure (CVP) >8 mmHg
    - Patients who remain hypotensive (SBP <90 mmHg) despite 20 ml/kg of crystalloid IV by definition have septic shock
    - These patients should ideally have a CVC inserted and their CVP monitored; fluid resuscitation should continue with boluses of crystalloid 500-1000 ml IV, aiming to maintain CVP >8 mmHg
  - 2: Mean arterial pressure (MAP) >65 mmHg or SBP >90 mmHg
    - Once CVP >8 mmHg, patients can be considered to have adequate preload to maintain CO
If they remain hypotensive (MAP <65 mmHg and/or SBP <90 mmHg) in spite of this, a vasopressor should be commenced to maintain these target BPs

First line vasopressor is noradrenaline

- 3: Central venous oxygen saturations ($S_{cv}O_{2}$) >70%
  - $S_{cv}O_{2}$ can be considered a marker of the balance between oxygen supply and demand; if low (<70%), there is a relative deficiency ie inadequate supply and/or excessive demand
  - If $S_{cv}O_{2}$ is low, it may be improved by increasing oxygen content and myocardial contractility
    - Oxygen content can be improved with high-flow oxygen and transfusion to a target Hb of 70-90 g/L
    - Myocardial contractility can be improved by commencing an inotrope such as dobutamine

Further management of sepsis

- Ensure tight glycaemic control with a sliding scale if necessary to maintain glucose <8.3 mM
- If mechanically ventilated, avoid excessive inspiratory pressures and aim for tidal volume 5-7 ml/kg
- Treat any complications
- Consider low dose steroids for septic shock refractory to fluid resuscitation and vasopressor therapy
- Consider activated protein C for severe sepsis and high risk of death
- Once a specific culprit organism has been identified from culture growth, switch to narrower-spectrum antibiotic(s) to which the organism is sensitive
- As sepsis resolves and patient improves, consider switching antibiotics from IV to oral

Complications of sepsis

- Respiratory failure
  - Acute lung injury (ALI)
  - Acute respiratory distress syndrome (ARDS)
- Cardiac failure
- Renal failure
- Hepatic failure
- Shock
- DIC
- Death

Common questions concerning sepsis

- Define the term 'systemic inflammatory response syndrome' (SIRS)
  - Systemic response to various insults including infection, trauma, surgery, burns; includes two or more of the following:
    - Respiratory rate (RR) >20 or $P_{a}CO_{2}$ <4.3 kPa
    - Heart rate (HR) >90
    - Temperature >38.3 °C or <36 °C
    - White cell count (WCC) >12 or <4 x 10⁹/L
    - Acutely altered mental state
    - Glucose >8.3 mM (in the absence of diabetes mellitus)
- Define the term sepsis
  - Systemic response to infection ie SIRS + source of infection
- Define the term severe sepsis
  - Sepsis + organ dysfunction or tissue hypoperfusion
• Define the term septic shock
  o Sepsis + persistent hypoperfusion despite adequate fluid resuscitation (20 ml/kg bolus of crystalloid)

• List three broad categories of risk factors for sepsis
  o Immunocompromised
  o In-dwelling devices
  o Recurrent antibiotic therapy

• What six steps should be taken on recognition of sepsis?
  o Oxygen titrated to achieve $S_pO_2$ 94-98% or 88-92% if known to have COPD
  o Check lactate
  o Take blood cultures
  o Give IV antibiotics
  o Commence IV fluid resuscitation
  o Monitor urine output

• What is the purpose of checking lactate levels?
  o Hyperlactataemia acts as a marker of tissue hypoperfusion suggesting severe sepsis (>2 mM) or septic shock (>4 mM)
  o In addition, the resulting high anion gap metabolic acidosis has negative effects on cellular and organ function

• What antibiotics should be commenced on recognition of sepsis?
  o If the source is known, give the appropriate empirical IV antibiotic(s) as per local guidelines
  o For sepsis of unknown origin, give the appropriate broad-spectrum IV antibiotic(s) as per local guidelines e.g. piperacillin + tazobactam (tazocin) + gentamicin; once the source has been identified, switch to the appropriate empirical IV antibiotic(s) as per local guidelines

• In addition to antibiotics, what action may also be required to target the underlying infection
  o Source control

• What approach should be taken to fluid resuscitation in sepsis?
  o Guided by clinical context
  o Give boluses of crystalloid 500-1000 ml IV and re-assess after each
  o Patients with severe sepsis should receive a minimum of 20 ml/kg
  o Patients with septic shock often require up to 60 ml/kg

• What medication can be given to control fever in sepsis?
  o Anti-pyretics e.g. paracetamol 1 g PO +/- ibuprofen 400 mg PO if no contraindications

• List the three aims of EGDT in sepsis
  o 1: CVP >8 mmHg
  o 2: MAP >65 mmHg or SBP >90 mmHg
  o 3: $S_cvO_2$ >70%

• Outline the possible complications of sepsis
  o Respiratory failure
  o Cardiac failure
  o Renal failure
  o Hepatic failure
  o Shock
  o DIC
  o Death