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 ^oC or <36 ^oC
    - 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 (S_pO_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 regular 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 maintain 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 heptatobiliary 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_pO_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_pO_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_aCO_2 <4.3 kPa
        - Heart rate (HR) >90
        - Temperature >38.3 ^oC or <36 ^oC
        - 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)
- 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
    - Sepsis + persistent hypoperfusion despite adequate fluid resuscitation (20 ml/kg bolus of crystalloid)
- List three broad categories of risk factors for sepsis
    - Immunocompromised
    - In-dwelling devices
    - Recurrent antibiotic therapy
- What six steps should be taken on recognition of sepsis?
    - Oxygen titrated to achieve S_pO_2 94-98% or 88-92% if known to have COPD
    - Check lactate
    - Take blood cultures
    - Give IV antibiotics
    - Commence IV fluid resuscitation
    - Monitor urine output
- What is the purpose of checking lactate levels?
    - Hyperlactataemia acts as a marker of tissue hypoperfusion suggesting severe sepsis (>2 mM) or septic shock (>4 mM)
    - 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?
    - 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
- In addition to antibiotics, what action may also be required to target the underlying infection
    - Source control
- What approach should be taken to fluid resuscitation in sepsis?
    - 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
- What medication can be given to control fever in sepsis?
    - Anti-pyretics e.g. paracetamol 1 g PO +/- ibuprofen 400 mg PO if no contraindications
- List the three aims of EGDT in sepsis
    - 1: CVP >8 mmHg
    - 2: MAP >65 mmHg or SBP >90 mmHg
    - 3: $S_{cv}O_2$ >70%
- Outline the possible complications of sepsis
    - Respiratory failure
    - Cardiac failure
    - Renal failure
    - Hepatic failure
    - Shock
    - DIC
    - Death