Sepsis

Matthew Cassar

Introduction

- In-dwelling catheters
- Prosthetic heart valves
- Chemotherapy and steroids
- Intensive care
- Progressive ageing population
- Ability to treat patients with major chronic illness

The mortality of major sepsis and septic shock is 50 %

Pathophysiology

- Release of endogenous mediators
- Triggered by presence of bacteria and/or toxins associated with bacteria
- Vasoactive agents
  - Nitric oxide
  - Bradykinin
  - Histamine
  - Prostaglandins
  - Cytokines (IL-1, TNF, IL-6)

Pathophysiology

- Some mediators are necessary to combat infection but an excessive or prolonged activation leads to septic shock and MOF
- Vasoactive agents produce a state of
  - Vasodilation
  - Enhanced capillary leak
  - Subsequent myocardial depression

Definitions of Sepsis

- Spectrum: localised infection to bacteraemia associated with shock and ensuing organ failure

Systemic Inflammatory Response Syndrome (SIRS)

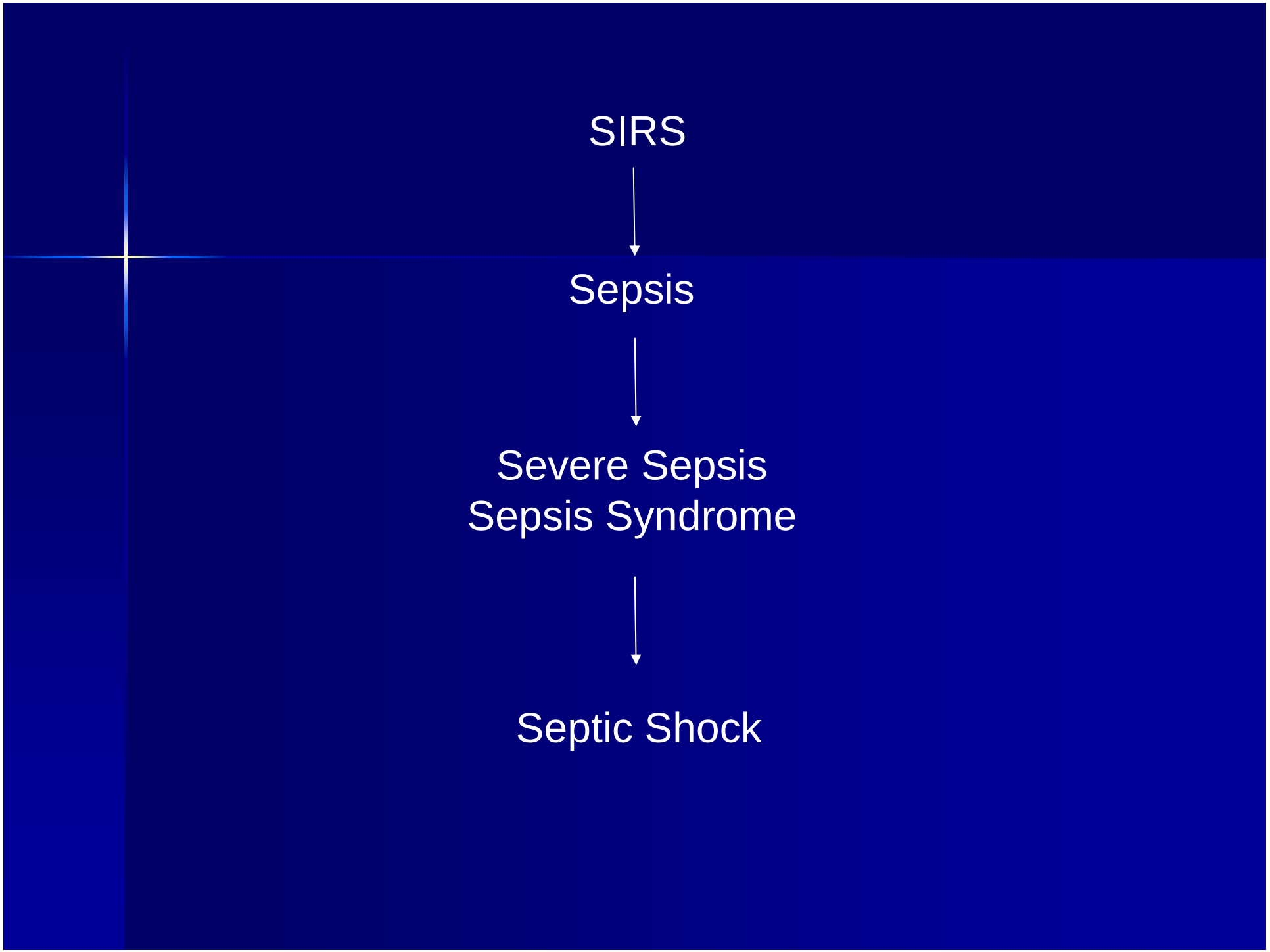
- May result from an infective process or a severe inflammatory disorder
- Two of
  - Pyrexia (>38˚C) or hypothermia (<36˚C)
  - Tachycardia (>90bpm in the absence of beta blocker)
  - Tachypnoea (>20/min) or $PaCO_2$ <32mmHg PCO_2
  - WCC >12,000/mm^3 or <4,000/mm^3 or with >10% immature forms

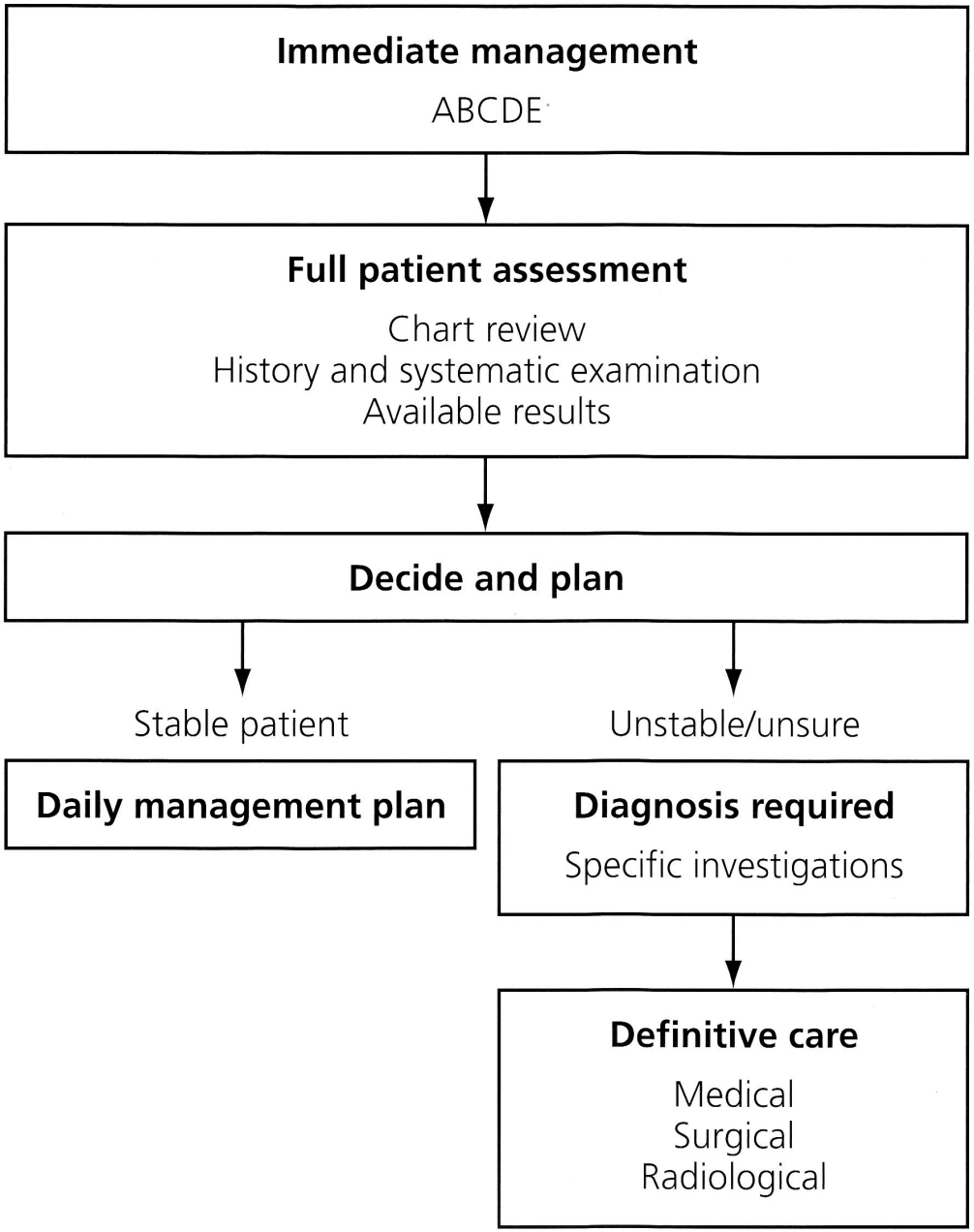
Causes of the septic process

	Infective	Non-Infective
Non-Surgical	Pulmonary	Acute pancreatitis
	Urinary & catheter related	Reperfusion injury
	Intravenous lines esp CVP	
	Soft tissue infection	
Surgical	Anastomotic leak	Ischaemic gut
	Biliary especially if obstructed	Ruptured aorta
	Urinary with obstruction	Major haemorrhage
	Collection / abscess	
	Infected prosthesis	
	Necrotic tissue	

- Sepsis = SIRS + documented source of infection
- Severe sepsis or sepsis syndrome = SIRS + altered organ perfusion or evidence of dysfunction of one or more organs
- Any organ can be involved:
  - CVS: lactate >1.2mmol/L or SVR <800dyne/s/cm^3
  - Respiratory: $Pa0_2/FiO_2$ <30 or PaO_2 <70mmHg
  - Renal: urine output <120mL over 4 hours
  - CNS: GCS <15 in the absence of sedation/neuro deficit
  - Haematology: Abnormal coagulation

- Septic shock = SIRS + organ dysfunction + refractory hypotension (despite adequate fluid resuscitation or blood lactate concentration of >4mmol/L)
- Sepsis induced hypotension is defined as
  - Systolic Blood Pressure (SBP) <90mmHg
  - Mean Arterial Pressure (MAP) <70mmHg
  - SBP decrease >40mmHg or <2SD below normal for age in the absence of other causes of hypotension


SIRS
Sepsis
Severe Sepsis
Sepsis Syndrome
Septic Shock



CCrISP system of patient assessment

Immediate Management

- ABCDE
- High flow oxygen via facemask
- Intravenous access and volume expansion by appropriate fluid boluses

Full Patient Assessment

- Chart Review
  - Vital signs (tachypnoea, hypo- hyperthermia, tachycardia)
  - Central Venous Pressure (5-10cmH20)
  - Urine output

Full Patient Assessment

- History and Systemic Examination
  - Chronic health problems and current medication
  - Warm / pink peripheries, bounding pulse which progresses to hypovolaemia and myocardial depression
  - Establish the likely source of sepsis (Resp, GI, GU, CNS)
  - Timing: Pneumonia >D1; Anastomotic leak D4-10; Central line >D5-7

Full Patient Assessment

- Available Results
  - Abnormally high or low WCC
  - Decrease platelets
  - Abnormal coagulation screen
  - Urea, electrolytes and creatinine (!ARF; adequate volume loading)
  - Liver function tests: primary source of sepsis or liver dysfunction; progressively rising bilirubin indicates poor prognosis

Full Patient Assessment

- Anaerobic / Aerobic blood cultures (+ve in ~20%)
- Arterial blood gases (hypoxaemia, metabolic acidosis)
- Electrocardiogram (ischaemia or arrythmia)
- Culture primary source of sepsis (±Gram stain, ±fungal cultures)
- CXR, US, CT,
- Laparotomy

Surviving Sepsis Campaign

International guidelines for management of severe sepsis and septic shock 2008

Initial resuscitation (first 6 hours)

- Begin resuscitation immediately if hypotension or elevated lactate >4mm/L; do not delay pending ITU admission
- Resuscitation goals should include all of the following
  - CVP 8-12mmHg (12-15mmHg in mechanically ventilated, decr vent compliance; inc IAP; PAHT)
  - MAP >65mmHg
  - Urine output >0.5mL/kg/hr
  - Central venous (SVC) O_2 sat >70% or mixed venous >65%

Initial resuscitation (First 6 hours)

- If venous oxygen saturation target is not achieved
  - Consider further fluid
  - Transfuse PRBC to hematocrit >30%
  - Start dobutamine infusion, max 20μg/kg/min
- Resuscitation directed toward the above goals was able to reduce 28 day mortality rate

Diagnosis

- Obtain appropriate cultures before starting abts provided no delay in abt administration
  - 2 or more BCs
  - 1 or more BCs should be percutaneous
  - 1 BC from each vascular access >48hrs
  - Culture other sites as clinically indicated
- Essential to
  - Confirm infection
  - Responsible pathogens
  - Allow de-escalation of antibiotic therapy

Diagnosis

- Imaging studies promptly to confirm and sample any source of infection, if safe
- Transport of patients can be dangerous therefore balancing risk and benefit is therefore mandatory

Antibiotic therapy

- Begin IV antibiotics as early as possible and always within the 1st hour of recognizing severe sepsis and septic shock
- In the presence of septic shock each hour delay in achieving administration of effective antibiotics is associated with a measurable increase in mortality
- Bolus administration versus infusion if vascular access is limited

Antibiotic therapy

- Broad spectrum: 1 or more agents active against likely bacterial / fungal pathogens and with good penetration into the presumed tissue
- Choice depends on drug intolerances, underlying disease, clinical syndrome, susceptibility patterns in community and hospital

Antibiotic therapy

- Especially wide range of potential pathogens for neutropenic patients
- Recently used antibiotics should generally be avoided
- Consider candidaemia (Rx with fluconazole, amphotericin B or echinocandin)
- Failure to initiate appropriate therapy correlates with increased morbidity and mortality

Antibiotic therapy

- Patients with sepsis and septic shock often have deranged renal and hepatic function, and abnormal volumes of distribution
- Drug concentration monitoring
- Consultation with clinical pharmacist or experienced physician

Antibiotic therapy

- Reassess antimicrobial therapy daily to optimize efficacy, prevent resistance, avoid toxicity and minimise costs
- Narrowing spectrum and reducing duration of therapy will reduce superinfection with pathogenic or resistant organisms (Eg *Candida* species, *C. difficile*, vancomycin resistant *Enterococcus faecium*

Antibiotic therapy

Name of Medication / Dosage Regimen	Cost Per Vial	Total Daily Cost
Cefuroxime 750mg tds	€ 1.01	€ 3.03
Metronidazole 500mg tds	€ 0.91	€ 2.73
Ciprofloxacin 200mg bd	€ 2.11	€ 4.22
Meropenem 1g tds	€ 34.72	€ 104.16
Piperacillin with Tazobactam 4.5g tds	€ 16.66	€ 49.98
Ceftriaxone 2g od (available as Rocephin®)	€ 38.01	€ 38.01
Ceftriaxone 1g od (available as generic product)	€ 3.51	€ 3.51

Antibiotic therapy

- Consider combination therapy in *Pseudomonas* infections
- Consider combination empiric therapy in neutropenic patients
- Combination therapy <3-5 days and de-escalation following susceptibilities

Antibiotic therapy

- Duration limited to 7-10 days; longer if slow response or undrainable foci of infection or immunological deficiencies
- Stop antimicrobial therapy if cause is found to be non-infectious

Source identification and control

- Specific anatomic site of infection should be established rapidly and within 1st 6 hours of presentation
- Evaluate patient for a focus of infection amenable to source control measures (abscess drainage, tissue debridement, removal of potentially infected devices)

Source identification and control

- Implement source control measures ASAP following successful initial resuscitation
- Exception: infected pancreatic necrosis, where surgical intervention is best delayed until adequate demarcation of viable / nonviable tissue

Source identification and control

- Choose source control measure with maximum efficacy and minimal physiological upset
- Percutaneous versus surgical drainage; endoscopic versus surgical drainage of biliary tree
- Source control interventions may cause further complications
- Remove intravascular access devices if potentially infected

Fluid therapy

- Fluid resuscitation using crystalloids or colloids
- Target CVP >8mmHg (>12mmHg if mechanically ventilated)
- Use a fluid challenge technique while associated with a hemodynamic improvement (UO, HR, BP)
- Fluid challenges of 1000mL crystalloids and 300-500mL colloids over 30 mins; more rapid and larger volumes may be required in sepsis-induced tissue hypoperfusion

Fluid therapy

- Rate of fluid administration should be reduced if cardiac filling pressures increase without concurrent hemodynamic improvement
- Fluid challenge must be separated from simple fluid administration
- Input >> output and input/output ratio is of no use to judge fluid resuscitation needs

Vasopressors

- Maintain MAP >65mmHg
- Below a certain MAP autoregulation in various vascular beds can be lost and perfusion can become linearly dependent on pressure
- Preexisting comorbidities should be considered as to most appropriate MAP target (Eg. Uncontrolled HT)
- Supplementing end points (eg. BP) with assessment of regional and global perfusion (eg. lactate and UO) is important
- Norepinephrine and dopamine centrally administered are the initial vasopressors of choice

Vasopressors

- Epinephrine, phenylephrine or vasopressin should not be administered as the initial vasopressor in septic shock. Vasopressin 0.03 units/min may be subsequently added to norepinephrine with anticipation of an effect equivalent to norepinephrine alone

Vasopressors

- Use epinephrine as the first alternative agent in septic shock when blood pressure is poorly responsive to norepinephrine and dopamine
- Do not use low-dose dopamine for renal protection
- In patients requiring vasopressors, insert an arterial catheter as soon as possible

Inotropic therapy

- Use dobutamine in patients with myocardial dysfunction as supported by elevated cardiac filling pressures and low cardiac output
- Do not increase cardiac index to predetermined supranormal levels

Steroids

- Consider IV hydrocortisone only for adult septic shock when hypotension responds poorly to adequate fluid resuscitation and vasopressors – Vaspressor unresponsive septic shock
- Significant shock reversal and reduction of mortality rate in patients with relative adrenal insufficiency*

Steroids

- ACTH stimulation test is not recommended to identify the subset of adults with septic shock who should receive hydrocortisone
- Hydrocortisone is preferred to dexamethasone
- Dexamethasone can lead to immediate and prolonged suppression of the HPA axis

Steroids

- Fludrocortisone may be included if an alternative to hydrocortisone is being used that lacks MC activity
- Steroid therapy may be weaned once vasopressors are no longer required
- Hydrocortisone dose should be <300mg/day

Steroids

- Do not use corticosteroids to treat sepsis in the absence of shock unless the patient's endocrine or corticosteroid history warrants it
- Eg. History of steroid therapy or adrenal dysfunction

Recombinant human Activated Protein C

- Consider rhAPC in adult patients with sepsis induced organ dysfunction with clinical assessment of high risk of death if there are no contraindications
- Adult patients with severe sepsis and low risk of death should not receive rhAPC

Blood Product Administration

- RBC transfusion when Hb <7 g/dL to target Hb 7-9g/dL in adults
- Higher Hb level may be required in special circumstances (Eg. MI, acute hemorrhage, severe hypoxaemia, lactic acidosis)
- Do not use EPO to treat sepsis-related anaemia
- EPO may be used in renal failure induced compromise of RBC production

Blood Product Administration

- Do not use FFP to correct lab clotting abnormalities unless bleeding or planned surgical procedure
- Do not use antithrombin therapy
- Administer platelets when
  - Counts $<5x10^9/L$ regardless of bleeding
  - $5\text{-}30x10^9/L$ and there is significant bleeding
  - $<50x10^9/L$ if planned surgery or invasive procedures

Mechanical Ventilation of Sepsis-Induced ALI/ARDS

- Tidal volume 6mL/kg body weight
- Upper limit plateau pressure <30cmH_20
- Permissive hypercapnia to minimize volume and pressure
- PEEP
- Consider prone position
- Maintain mechanically ventilated patients in semirecumbent position (30-45˚)

Mechanical Ventilation of Sepsis-Induced ALI/ARDS

- Consider non-invasive ventilation if mild to moderate hypoxaemic respiratory failure
- Use a weaning protocol and an SBT regularly to evaluate discontinuation of mechanical ventilation
- Do not use pulmonary artery catheter for the routine monitoring of patients with ALI/ARDS
- Conservative fluid strategy if no evidence of tissue hypoperfusion

Sedation, Analgesia and Neuromuscular Blockade in Sepsis

- Use sedation protocols
- Intermittent bolus sedation or continuous infusion with daily interruption/lightening for awakening
- Avoid neuromuscular blockades where possible

Glucose control

- Following initial stabilization, patients with severe sepsis and hyperglycaemia who are admitted to the ITU receive IV insulin to reduce glucose levels
- Suggest use of validated protocol for insulin dose adjustment
- Aim glucose levels at <8.3mmol/L

Glucose control

- Provide glucose calorie source and monitor blood glucose values every 1-2hours in patients receiving IV insulin
- Interpret with caution low glucose levels obtained with point of care testing as these techniques may overestimate arterial blood or plasma glucose values

Renal Replacement

- Intermittent hemodialysis and CVVH are considered equivalent
- CVVH offers easier management in hemodynamically unstable patients

Bicarbonate Therapy

- Do not use bicarbonate therapy for the purpose of improving hemodynamics or reducing vasopressor requirements when treating hypoperfusion-induced lactic acidaemia with pH>7.15

DVT prophylaxis

- Use either low-dose UFH or LMWH, unless contraindicated
- Use a mechanical prophylactic device, such as compression stockings or an intermittent compression device, when heparin is contraindicated
- Combination of pharmacological and mechanical therapy for patients at very high risk for DVT
- In patients at very high risk LMWH>UFH

DVT Prophylaxis

- UFH tds produced more efficacy and UFH bd produced less bleeding
- UFH is preferred to LMWH in moderate to severe renal dysfunction
- Patients receiving heparin should be monitored for the development of HIT

Stress Ulcer Prophylaxis

- Provide stress ulcer prophylaxis using H2 blocker or PPI. Benefits of prevention of upper GI bleed must be weighed against the potential for development of ventilator-acquired pneumonia
- Reduction in clinically significant upper GI bleed
- Potential effect of increased stomach pH on greater incidence of ventilator-associated pneumonia
- H2 antagonists = PPIs

Consideration for Limitation of Support

- Discuss advance care planning with patients and families. Describe likely outcomes and set realistic expectations
- Early and frequent caregiver discussions with patients who face death in the ITU and with their relatives may facilitate appropriate application and withdrawal of life-sustaining therapies
- Recent RCT showed reduction of anxiety and depression in family members

Thank you

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