

Management of Sepsis

Definitions

Infection

A host response to the presence of microorganisms or tissue invasion by microorganisms

Bacteremia

The presence of viable bacteria in circulating blood

Definitions

Systemic Inflammatory Response Syndrome (SIRS)

The systemic inflammatory response to a wide variety of **severe clinical insults**, manifested by two or more of the following conditions:

- Temperature $> 38^{\circ}\text{C}$ or $< 36^{\circ}\text{C}$
- Heart rate > 90 beats/min
- Respiratory rate > 20 breaths/min or $\text{PaCO}_2 < 32$ mm Hg
- WBC count $> 12,000/\text{mm}^3$, $< 4000/\text{mm}^3$, or $> 10\%$ immature (band) forms

Definitions

Sepsis

The systemic inflammatory response to infection

In association with infection, manifestations of sepsis are the same as those defined for SIRS

It should be determined whether they are a direct systemic response to the presence of an infectious process and represent an acute alteration from baseline in the absence of other known causes for such abnormalities

Definitions

Refractory (Septic) Shock/SIRS Shock

A subset of severe sepsis (SIRS) and defined as sepsis (SIRS) induced hypotension despite adequate fluid resuscitation along with the presence of perfusion abnormalities that may include, but are not limited to, lactic acidosis, oliguria, or an acute alteration in mental status

Patients receiving inotropic or vasopressor agents may no longer be hypotensive by the time they manifest hypoperfusion abnormalities or organ dysfunction, yet they would still be considered to have septic (SIRS) shock

Definitions

Severe Sepsis/SIRS

- Sepsis (SIRS) associated with organ dysfunction, hypoperfusion, or hypotension
- Hypoperfusion and perfusion abnormalities may include, but are not limited to, lactic acidosis, oliguria or an acute alteration in mental status

Definitions

Multiple Organ Dysfunction Syndrome (MODS)

- Presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention

Basic Problems in Sepsis

Severe sepsis is characterized by stimulation of a series of inflammatory cascades leading to:

- Uncontrolled systemic inflammatory response
- Activation of the coagulation cascades

Systemic inflammatory response

Extensive cardiovascular derangement, the most overt sign of which is hypotension due to:

- Vasoplegia and myocardial depression
- relative hypovolemia
- widespread dysfunction of the microvasculature (“capillary leak”)

Activation of the coagulation cascades

- Formation of intravascular thrombus
- Subsequent tissue injury and multi-organ dysfunction

Major priorities in management of septic patients

- To maintain delivery of oxygen to the tissues, by way of optimization of cardiac output and peripheral resistance
- To modulate the procoagulation response

Priorities in management of septic patients

- It is essential to obtain maximal results from minimal interventions
- In particular, it is *important to avoid using excessive amounts of catecholamines, in under-resuscitated patients*

History, physical, immediate investigations

- History (direct or a collateral one) is important to identify the initial event
- Chest pain on inspiration - pneumonia
- Severe abdominal pain boring through to the back: pancreatitis
- Pain during micturition: urinary tract infection
- Persistent dry cough: atypical pneumonia
- Examine the patient

Collateral history

- Any recent injuries? a car crash two days ago, but was sent home from the hospital (**many possibilities**)
- Does he take drugs? (**endocarditis**)
- Any problems recently? has been drinking heavily (**pancreatitis**)

Collateral history

- Any medical problems? gallstones (cholecystitis, cholangitis), rheumatoid arthritis (steroids /immunosuppressants)
- Recent surgery? (post operative complication)

Laboratory tests

- Hemoglobin
- TLC, DLC
- Platelet Counts
- Complete chemistry profile
- Coagulation parameters
- Serum lactate
- Urine analysis
- Arterial blood gases (metabolic acidosis and hypoxemia)
- Serum amylase and lipase
- Liver function tests
- ECG
- Chest radiograph

Cultures

- Appropriate cultures should be obtained prior to institution of antibiotics
- Cultures may confirm infection and are invaluable in guiding antibiotic selection
- Blood cultures
- Cultures and stains appropriate to any organ system that might harbor the infection causing severe sepsis
- If no localizing signs are obvious – then check: blood, urine, and sputum

- Quantify the extent of sepsis:
 - Temperature
 - white cell count
 - ABG & acid-base status
 - Cultures
- The choice of antimicrobial is determined by the source of infection and a best guess of the organism involved

Immediate Stabilization

Initial treatment priority

- Reverse life threatening physiologic abnormalities
- Begins as soon as the syndrome is recognized
- Ensure oxygenation and ventilation by maintaining patency and adequacy of the airway
- Endotracheal intubation and commencement of mechanical ventilation

Mechanical ventilation

Indications for intubation and mechanical ventilation:

- failure to protect the airway (altered mental status etc)
- failure to ventilate and failure to oxygenate
- *When in doubt, it is rarely wrong to intubate patients*

Oxygenation

- In sepsis, supplemental oxygen is almost always required
- Accelerated oxygen demand by respiratory muscles may cause oxygen debt and acidosis
- Mechanical ventilation reduces this

Hypotension

- Care must be taken when administering anesthetic agents for gaining airway control
- Many of these, propofol in particular, are potent vasodilators, and may worsen hypotension
- This situation may get worse when positive pressure ventilation is applied, as the increase in intrathoracic pressure will reduce venous return

Hypotension

Aggressive volume resuscitation

- isotonic crystalloids
- in combination with colloids

*Do not interfere with the heart rate:
tachycardia is a compensatory maneuver*

Hypotension & Tissue hypoperfusion

Volume Resuscitation

- The initial resuscitative effort is to attempt to correct the absolute and relative hypovolemia by refilling the vascular tree
- *There is good evidence that early goal directed aggressive volume resuscitation improves outcomes in sepsis*

Fluids

Crystalloids

- Normal saline or Ringer's lactate are used
- Hypo-osmolar dextrose based fluids have no role).
- Very large amounts of fluid may be required due to redistribution to extravascular "3rd" spaces (which sequester fluid), and the patient may become extremely edematous

Fluids

- Large volume saline resuscitation may be associated with acidemia, due to hyperchloremia (“dilutional acidosis”).
- Lactate cannot safely be given to patients with severely impaired liver function
- Acetate buffered fluids (such as Normisol) have not yet gained widespread use

Fluids

Colloids

- Dextrans are used rarely (due to the tendency to cause bleeding)
- Albumin not used (may worsen outcome)
- Blood and plasma are used as restorative liquids
- Gelatins are popular – but not available easily

Fluids

Which fluids to use?

- lactated Ringers is a more physiologic mix than normal saline
- Colloids will give a greater volume expansion in a shorter time
- *It doesn't really matter which isotonic is used, as long as it is adequate*

Monitoring tissue perfusion

- Few markers of end organ perfusion in sepsis:
- *Urinary output is one of them*
- *Do not give it away by administering diuretics or low dose dopamine*

Goals of Initial (0-6hrs) Resuscitation

- CVP: 8 – 12 mm Hg
- MAP: \geq 65 mm Hg
- Urine output: \geq 0.5 ml/Kg/hr
- $S_{v}O_2$ (central or mixed) \geq 70%

Initial Resuscitation

- If during the first 6 hours, CVP: 8 – 12 mm Hg is achieved but $S_{v}O_2$ (central or mixed) $\geq 70\%$ is not:
- Transfuse packed red cells to achieve PCV $\geq 30\%$
- Dobutamine infusion (max 20 ug/Kg/min)

Re-establishing the circulation

Vasoactive Drugs

- Vasoactive therapy is commenced *after other measures have failed*
- The patient *must be volume resuscitated first*
- Vasoactive medication must be aimed at restoring tissue perfusion without causing ischemia
- Vasoactive drugs may be essential, to help resuscitation, but they are also harmful

Vasoactive Drugs

- Sepsis is a complex disorder of macro- and micro-circulation
- Some tissues are overperfused, some underperfused, the ability to extract oxygen is variable
- The concept of using a pure vasoconstrictor to treat “low SVR” is no longer appropriate

Vasoactive Drugs

- Current pharmacological management of sepsis is *to maintain blood pressure and tissue perfusion*, whilst minimizing unwanted systemic/metabolic effects
- It may be necessary to combine multiple agents with differing pharmacologic profiles

Vasoactive Drugs

- The current use of vasoactive agents emphasizes organ perfusion along the continuum
- First brain, then heart, then splanchnic (gut, liver and kidneys) then all else
- Use an agent or a combination that not only maintains brain and heart perfusion, but renal, liver and gut mucosal perfusion also

Dopamine

- Dopamine has predominantly beta adrenergic effects in low to moderate dose ranges (up to 10 mic/kg/min), although there is much inter-patient variability
- Converts to norepinephrine in the myocardium, and activates adrenergic receptors
- In higher dose ranges, alpha adrenoceptor activation increases and causes vasoconstriction
- The agent is thus a mixed **inotrope and vasoconstrictor**
- At all dose ranges it is a potent **chronotrope**
- Increases CO (increased HR and SV) and MAP

Dopamine

- The so-called “renal protective” effect appears to be a misnomer
- The logic behind this concept is the theory that, at low dosage (<5mic/kg/min) dopamine stimulates dopaminergic receptors in renal, mesenteric and coronary beds, resulting in vasodilatation
- This causes an increase in urinary output, and is thought to protect the kidneys from ischemic insults

Dopamine

Thus, the effects of dopamine are due to:

- An increase in cardiac output, due to inotropy, and thus renal perfusion pressure
- A direct diuretic action

Some consider the concept of vasodilating vessels, which have constricted due to hypoxemia (acute renal “salvage”) as an unnecessary and potentially harmful interference in the body’s response to hypovolemia

There is no evidence that dopamine, at low dose, protects or harms the kidneys

Dopamine

The effects of dopamine elsewhere may be harmful:

- Dopamine increases heart rate, and may precipitate myocardial ischemia
- Effects on the splanchnic circulation are complex: While increasing overall mesenteric blood flow, it may preferentially steal blood from the mucosa, and redistribute it to the larger vessels
- Effects at distal sites in the central nervous system and gut remain to be clarified: It may interfere with pituitary and thyroid function and have an immunosuppressive effect

Dobutamine

- Dobutamine is a potent beta-1 agonist
- Increases myocardial contractility and thus stroke volume and cardiac output
- Dobutamine is associated with much less increase in heart rate than dopamine
- Dobutamine has a mild vasodilatory effect (inodilator), reducing mean arterial pressure: thus it is very effective in cardiogenic shock

Dobutamine

- Dobutamine differs from isoproteranol in that it has less beta-2 activity (bronchodilation) and has less effect on heart rate
- Isoproteranol is predominantly used as a stop-gap in patients requiring a pacemaker due to its chronotropic effect
- In sepsis, dobutamine, although a vasodilator, increases oxygen delivery and consumption

Dobutamine

- Dobutamine is particularly effective at splanchnic resuscitation, increasing pHi (gastric mucosal pH) and improving mucosal perfusion in comparison with dopamine
- Dobutamine is a useful second line agent to add in septic shock, to improve cardiac performance and to improve splanchnic perfusion
- The combination with nor-epinephrine is often advantageous and appropriate

Norepinephrine

- Norepinephrine has pharmacologic effects on both alpha-1 and beta-1 adrenoceptors.
- In low dosage ranges, the beta effect is noticeable, and there is a mild increase in cardiac output.
- Increase in SV is less than that with Dopamine
- In most dosage ranges, vasoconstriction and increased mean arterial pressure are evident.
- Norepinephrine does not increase heart rate: its effects on MAP may actually reduce heart rate as a result of baroreceptor activation.

Norepinephrine

- The main beneficial effect of norepinephrine is to increase organ perfusion by increasing vascular tone
- Studies of norepinephrine vs dopamine have favored the former in terms of overall improvements in oxygen delivery, organ perfusion and oxygen consumption
- Unlike epinephrine, norepinephrine reduces serum lactate levels
- Has a favorable influence on splanchnic perfusion

Norepinephrine

- Norepinephrine is more effective at fulfilling targeted endpoints than dopamine
- It is considerably less metabolically active than epinephrine
- It appears that norepinephrine is as effective as dopamine at improving renal perfusion, as long as the patient is adequately resuscitated
- Norepinephrine appears to be most effective at splanchnic resuscitation if used in combination with dobutamine

NE or Dopamine or Dobutamine?

- Either may be used as a first-line agent
- NE is more potent and may be more effective than Dopamine
- Dopamine is more effective when systolic function is compromised
- Dopamine is also more arrhythmogenic
- Dobutamine is first choice if CO remains low inspite of adequate fluids
- If CO measurements are not available, prefer NE plus Dopamine
- If CO can be measured and is low, prefer NE plus Dobutamine

Norepinephrine

- Combination improves oxygen delivery and consumption compared with dopamine
- The increase in splanchnic blood flow associated with dobutamine and norepinephrine appears to arise from beta adrenergic activity

Epinephrine

- Epinephrine (adrenaline) is the original inotrope/vasopressor
- It remains the agent of choice in extreme emergencies such as in anaphylactic shock or cardiac arrest
- Status: as an add on vasopressor (with norepinephrine) or when the cause of hypotension is unclear (it is a most reliable “backs to the wall” pressor)



Epinephrine

- Epinephrine has potent beta-1, beta-2 and alpha-1 adrenergic activity
- The increase in MAP in sepsis is mainly from an increase in cardiac output (stroke volume)

Three major drawbacks

- Increases myocardial oxygen
- It increases serum lactate – this may be due to either worsening of perfusion to certain tissues, or due to a calorogenic effect (increased release and anaerobic breakdown of glucose)
- Epinephrine appears to have adverse effects on splanchnic blood flow

Other Vasoactive Drugs

Vasopressin

- Vasopressin is an alternative vasoconstrictor in septic shock, in patients who have become resistant to catecholamines
- There is a quantitative deficiency of this hormone in sepsis

Vasopressin

- Pharmacological doses are much lower in vasodilated patients, as compared to normal
- Effective dose: 0.04units/minute
- Effects on splanchnic perfusion and the extremities are probably adverse as the dose increases (used to reduce splanchnic blood flow, in the treatment of bleeding esophageal varices)
- Currently, the principle use of this agent is as a physiologic replacement for depleted endogenous stores

Dopexamine

- Designed to combine the inodilatory effects of dobutamine and the dopaminergic effects of dopamine (it is a synthetic analogue of dopamine), thus improving cardiac output and splanchnic perfusion
- Studies disappointing, and it is not in common usage

Phenylephrine

- An almost pure alpha-1 agonist
- Used predominantly in anesthesia practice
 - to increase blood pressure without increasing heart rate in patients with vasoplegia, due to spinal-epidural anesthesia
 - to reverse the afterload reducing effects of propofol and volatile inhalation agents

Phenylephrine

- Used in intensive care units as a vasoconstrictor to improve SVR in patients (in whom PA catheters had been inserted) in septic shock
- May be useful as an additional vasoconstrictor in fluid loaded patients where catecholamines are causing excessive tachycardia

Phenylephrine

- Use as a single agent is probably not wise, due to its tendency to reduce cardiac output
- Patients in septic shock were treated initially with norepinephrine and subsequently crossed over to phenylephrine: a decrease in splanchnic blood flow, oxygen delivery and lactate uptake was observed
- The most likely explanation for this phenomenon is reduced beta adrenergic stimulation

Phosphodiesterase Inhibitors

- Little available data on the use of phosphodiesterase inhibitors in sepsis
- Milrinone/enoximone are potent inotropes, but also cause vasodilatation and tachycardia, which limits their use in sepsis
- Have lusitropic properties – they relax the heart in diastole, compared to inoconstrictor type drugs, which appear to impair diastolic relaxation
- These agents thus are of more value in cardiogenic shock

Empiric Therapy - Antibiotics

- The presumed site of infection
- Gram's stain results
- Suspected or known organisms
- Local resistance patterns
- Patient's immune status (especially neutropenia and immunosuppressive drugs), allergies, renal dysfunction, and hepatic dysfunction
- Antibiotic availability, hospital resistance patterns, and clinical variables of patient to be treated

Frequency of Source of Infection

- Respiratory Tract 25%
- Abdominal / Pelvic 25%
- Bacteremia 15%
- Urinary Tract 10%
- Skin 5%
- IV Catheter 5%
- Other sources 15%

Likely organisms

- In intensive care units approximately:
- 25% gram negative
- 25% gram positive
- 20% mixed gram positive/gram negative
- 3% fungal

Gram negative organisms

- E.coli (25%)
- Klebsiella/citrobacter (20%)
- Pseudomonas (15%)
- Enterobacter (10%)
- Proteus (5%)
- The remaining 25% is made up other bacteriae.

Gram positive organisms

- Staphylococcus aureus (35%)
- Enterococcus (20%)
- Coagulase negative staphylococcus (15%)
- Streptococcus pneumoniae (10%)

- The vast majority of fungal infections are candidal.

Empiric Therapy: Activated Protein C

- Activated protein C (drotrecogin alfa) is an endogenous protein that promotes fibrinolysis and inhibits thrombosis and inflammation
- It is an important modulator of the coagulation and inflammation associated with severe sepsis

Activated Protein C

- Activated protein C is converted from its inactive precursor, protein C, by thrombin coupled to thrombomodulin
- The conversion of protein C to activated protein C may be impaired during sepsis as a result of the down-regulation of thrombomodulin by inflammatory cytokines

Activated Protein C

- Reduced levels of protein C are found in the majority of patients with sepsis and are associated with an increased risk of death
- This led to interest in therapeutic administration of activated protein C (and similar agents) in early sepsis
- A large randomized controlled trial has confirmed the efficacy of Activated Protein C (drotrecogin alfa)

Activated Protein C

- In patients with severe sepsis, IV infusion of drotrecogin alfa activated is associated with a significant reduction in mortality
- **Dose:** 24 µg per kg per hour for 96 hours
- The use of this drug is indicated:
 - APACHE II \geq 25
 - Sepsis-induced MOF
 - Septic shock
 - Sepsis-induced ARDS

Activated Protein C

- Monitor for signs of bleeding
- Value in patients with multi-organ failure, or outside the first 24 hours of injury, is unknown

Corticosteroids

IV Hydrocortisone 200–300 mg/day, for 7 days (in TDS/QID or by infusion)

- If despite adequate fluid replacement, vasopressor therapy is required to maintain adequate blood pressure

DVT Prophylaxis

Patients with severe sepsis:

- Low dose heparin/low dose unfractionated heparin

Contraindications

- Thrombocytopenia
- Severe coagulopathy
- Recent active bleed (GI, CVA)

Use mechanical measures (compression devices, stockings)

Stress Ulcer Prophylaxis

- H₂ receptor blockers have proven efficacy
- PIP: not assessed
- H₂ receptor blockers are superior to sucralfate

Glycemic Control

- After initial stabilization, maintain blood glucose < 150 mg%
- Use insulin infusion
- Monitor every 30 min till goal achieved, then every 4 hourly

Bicarbonate

- Not recommended for improving hemodynamics or for reducing vasopressor requirements at a pH ≥ 7.15
- Effect of HCO_3 on hemodynamics and vasopressor requirements at lower pH not studied

Find the site and control the source

- Trace the source of infection and remove it
- Examination and initial investigations provide the answer in most cases
- Treatment of infection includes appropriate antibiotics and factors leading to or associated with infection

Control the source

- Necrotic tissue, as in necrotizing fasciitis
- Feces, as in the case of the ruptured diverticulum
- An obstructive ureteric stone
- Infected central line
- Intra-abdominal abscess
- Infection of the respiratory or urinary tract

Often source control means surgical intervention

No obvious source?

Causes of fever without an infective agent

- Myocardial infarction
 - Pulmonary embolism
 - Gastrointestinal bleeds
 - Inflammatory bowel disease
 - Hematomas
 - Thrombophlebitis
-
- These rarely cause a syndrome akin to septic shock
 - Therefore, assume a source, and try to control it

No obvious source?

- Firstly, always suspect an iatrogenic source
- Does the patient has artificial material imbedded:
 - A vascular graft
 - A tunneled intravenous catheter
 - Mechanical heart valves
 - Joint prosthesis
- All invasive devices such as IV lines, present at the time of infection, should be removed/replaced

No obvious source?

- Common things are common
- Respiratory tract infections the first place to start
- “pus somewhere, pus nowhere, pus under the diaphragm”: the abdomen is the next place to look

Respiratory infection

- Lower respiratory tract infection – there may be no evidence on chest x-ray
- Further investigations:
 - serological tests: atypical organisms (mycoplasma and legionella)
 - broncho-alveolar lavage (this tends to be low yield)

Abdominal

- A perforated viscus, pneumoperitoneum on chest x-ray

USG

- dilated bile ducts if there is biliary obstruction and ascending cholangitis
- necrotic gallbladder (acalculous cholecystitis)
- intrahepatic or subphrenic collections/abscesses
- splenic abscesses, free fluid (possible perforated bowel), and dilated renal pelvis (urinary tract obstruction)
- If free fluid is present it should be tapped and sent for culture and gram stain

Abdominal

- Ultrasound is a very poor test for imaging the pancreas and bowel
- If USG is non-contributory, CT is necessary
- Ischemic bowel: pneumatosis (air in the bowel wall)
- necrotic lesions in the pancreas
- liver, splenic lesions
- fluid collections
- Any collection viewed should be tapped and drained

Urinary tract

- Urinary cultures
- Changing or removing catheters
- Abdominal imaging (USG, CT)

Sinuses

- Patients with long term nasogastric tubes all develop occluded sinuses, with or without sinusitis
- Plain x-rays and CT are diagnostic

Conservative treatment:

- Removal of the offending tube
- Topical anti congestants
- Antibiotics and surgical drainage

Heart

- Endocarditis is one of the most malignant causes of systemic sepsis
- A murmur may be audible
- Splinter hemorrhages in the nail beds, hematuria, splenomegaly
- Transthoracic echocardiography (echo)
- Transesophageal echo

Central nervous system

- Brain abscess or meningitis
- Spreading ear infections
- A CT of the head with contrast should be performed
 - to look for infection and
 - to determine if the ventricles are normal in size (i.e. normal intracranial pressure)
- If so, lumbar puncture should be performed to obtain cerebrospinal fluid (CSF), which is sent for culture

Other sources

- Dental abscesses
- Prostatitis
- Ischeo-rectal area for evidence of infection
- All intravenous catheter sites should be carefully expected for thrombophlebitis, or subcutaneous pus collection

Enteral Nutrition

- Prevention of gut mucosal villous atrophy and bacterial translocation involves restoration of splanchnic blood flow and of gut luminal nutrition
- Effects of vasoactive drugs on intestinal blood flow are important
- The lining of the gut requires oxygen, from the blood, and nutrients, from the gut lumen, to stay intact
- The presence of this lining is important as a barrier to bacterial translocation

Enteral Nutrition

- Early enteral nutrition maintains it
- Thus an “inside-outside” gut protection strategy has emerged:
- Combine splanchnic vasodilators, such as dobutamine, with feeding
- Immunonutrition is an advanced enteral strategy that combines glutamine, omega-3 fatty acids, arginine and ribonucleotides and conventional feeding substances. There is some evidence that these formulas reduce the risk of infection

Monitoring

- Adequacy of resuscitation is evaluated by looking at endorgan perfusion – using **clinical examination** and interpretation of **monitored variables**
- There is no ideal method
- Direct measurement of blood pressure (using an arterial line) is essential to guide therapy
- Strong relationship between restoration of blood pressure and urinary output

Monitoring

- Central venous pressure is useful for monitoring volume status, but of little value in terms of organ perfusion
- pH, base deficit and serum lactate are useful guides of all body perfusion and anaerobic metabolism
- During the resuscitation process, the patient should become gradually less acidotic and the base deficit and serum lactate should reduce

Invasive measures of perfusion

- Pulmonary artery catheters are inserted to construct pressure volume relationships of the left ventricle and to measure cardiac output
- The normal mixed venous oxygen saturation is 70%.
- A very low mixed venous saturation ($S_{V}O_2$) is indicative of excessive extraction of oxygen per unit blood – “under-resuscitation”.

Invasive monitoring

- A very high S_vO_2 is difficult to interpret
 - May represent the inability of the tissues to extract oxygen, which may occur in sepsis
 - It may also be due to hyperdynamic circulation and overall increased oxygen delivery
- This is the problem with SvO_2 : it is a very blunt measurement.
- A normal SvO_2 may represent normal whole body oxygen utilization while some organs and tissue systems may have little oxygen
- Thus, the pulmonary artery catheter is of uncertain benefit, particularly in sepsis

Other methods of monitoring

- Non invasive monitors of stroke volume: the esophageal doppler
- Non invasive cardiac output monitor using CO₂ rebreathing (NICO)
- These techniques represent recent advances in monitoring volume resuscitation
- There is at present little evidence of efficacy

Other methods of monitoring

- Measurement of $S_{v}O_2$ from an adapted central venous catheter has been shown to be a good measure of adequacy of resuscitation
- Jugular venous oxygen saturation (SjO_2) which is used in head injury
- Gastric tonometry is sometimes used in sepsis

Other methods of monitoring

- A recent variant of tonometry, regional capnometry, measures gastric carbon dioxide (CO₂) production, by absorbing CO₂ from an air filled balloon attached to a modified nasogastric tube
- End tidal CO₂, from the ventilator circuit
- The presence of a very high concentration of CO₂ in the stomach or a wide gastric-end tidal CO₂ gap, is believed to be indicative of poor splanchnic blood flow
- There are, however, concerns about measurement error and interpretation, and this technique is not widely accepted

Iatrogenic injuries and complications

Critically ill patients are vulnerable

- deep venous thrombosis
- line sepsis
- pressure sores
- the presence of an endotracheal tube provides a route for bowel organisms to infect the lung
- Prolonged use of neuromuscular blocking agents and steroids predispose to critical illness polymyopathy
- the insertion of a central line can cause pneumothorax, air embolism, venous thrombosis, arterial dissection

Weigh up the potential benefits and costs of each intervention

Review management

- look at all of the ongoing therapies and interventions and question: are they still necessary?
- If a patient is hemodynamically stable and the source controlled, it is unlikely that a pulmonary artery catheter will continue to be of any benefit, it carries a risk
- The spectrum of antimicrobial therapy should be narrowed, in accordance to laboratory results
- Aggressive moves to wean vasopressor support and mechanical ventilation should be made
- If the patient is not improving clinically, re-assess if the source has been controlled

Keep Looking

- Constantly vigilant towards source control is necessary
- If the patient remains unstable or if new signs of infection appear – a new temperature, a rising white cell count, additional vasopressor therapy – the source is NOT controlled.
- Intermittent chest radiographs, urinary cultures, blood cultures when the patient “spikes” a temperature are all useful methods of looking for infection
- Common things are common – a new infection is likely to come from the chest, the urinary tract or from lines

- Abdomen should never be forgotten
- Critical illness predisposes patients to a variety of other infections – acalculous cholecystitis, perforated peptic ulcers, missed diverticular ruptures, retained surgical dressings

Metabolic and Neuroendocrine aspects

- The early response is characterized by reduced metabolism and vasoconstriction
- This is followed by a hypermetabolic phase, characterized by vasodilation, fluid sequestration, hyper-adrenergic activity, protein catabolism, hyperlactemia and dysregulation of fat and lipoprotein metabolism
- Hyperglycemia is inevitable and there is good evidence that control of blood sugar improves outcome in critical illness due to a reduction in infectious complications

Metabolic and Neuroendocrine aspects

- Prolonged critical illness is characterized by derangement of the entire neuroendocrine response
- Dysfunction of the somatrophic and the hypothalmo-pituitary axis, sick euthyroid syndrome and loss of central endocrine control

Metabolic and Neuroendocrine aspects

- A relative adrenal insufficiency frequently manifests – the patient remains pressor dependent in spite of apparent source control (cortisol is required to facilitate the activity of norepinephrine and epinephrine at sympathetic nerve terminals)
- The diagnosis is made by ACTH stimulation test (a 2 hour “bump” of less than 5mg/dl or a cortisol level of <20mg/dl is diagnostic) and the treatment is hydrocortisone
- It is controversial whether other hormones should be replaced with similar physiologic doses

Summary

Initial management involves

- protection of the airway
- delivery of oxygen into the blood (including MV)
- restoration of circulating volume, initially with fluids and, if necessary, vasoactive agents

- The splanchnic circulation appears to be a particularly important site for resuscitation, as the physiological response to hypotension causes reduction in blood flow to this area
- The result is gut ischemia, bacterial translocation, worsened sepsis and renal failure
- Gut resuscitation involves the use of beta-adrenergic agonists and early enteral nutrition, preferably with immunomodulatory supplements

Summary

- Take a history (or obtain a collateral one)
- Examine the patient
- Quantify the extent of sepsis:
temperature, white cell count, acid-base
status and cultures
- The choice of antimicrobial is determined
by the source of infection and a best
guess of the organism involved

Summary

- Vasoactive therapy is commenced after other measures have failed
- There is no simple solution. Vasoactive medication must be aimed at restoring tissue perfusion without causing ischemia.
- Persistent requirement for vasopressors requires investigation of adrenal function

Summary

- The systemic inflammatory response is driven along by persistent infection: Find the source and remove it. This may involve extensive detective work.
- The use of activated protein C at 24 μg per kilogram per hour for 96 hours is associated with a significant reduction in mortality
- Prevention of villous atrophy and bacterial translocation involves restoration of circulation and restoration of gut luminal nutrition
- Secondary sources of sepsis (lines) and organ dysfunction (pulmonary embolism) must be avoided

- Adequacy of resuscitation is evaluated by looking at endorgan perfusion – using clinical examination and interpretation of monitored variables. There is no ideal method.
- It is the second and subsequent hits that often kill patients: it is important to prevent this from arising from an iatrogenic source
- Minimize the amount of interventions involved and wean and remove therapies that are no longer beneficial

All the best..