

Identification and Management of the Patient with Sepsis Brenda Lynn Morgan RN BScN MSc CNCC(C)

SIRS (SYSTEMIC INFLAMMATORY RESPONSE SYNDROME)

Inflammation is an immediate response to any cellular injury. It is triggered in response to a variety of causes, including ischemia, infection, trauma, foreign substances or malignancies. When the response is localized to a specific area (e.g. a sprained ankle), the response is referred to as localized inflammation. When a large or persistent number of inflammatory mediators are released, the response can become generalized and systemic. This is referred to as "SIRS" or Systemic Inflammatory Response Syndrome. Common causes for **SIRS** include massive trauma, burns, pancreatitis, major surgery, Acute Coronary Syndrome or infection. Exposure of blood to extracorporeal circuits (e.g. hemodialysis filters, cardiopulmonary bypass membranes) can also trigger SIRS.

SIRS is defined by 2 or more of the following clinical findings that occur *as a result of tissue injury*:

- Temperature $\geq 38^{\circ}\text{C}$ or $\leq 36^{\circ}\text{C}$
 - Heart rate ≥ 90
 - Respiratory rate ≥ 20 or respiratory alkalosis
 - WBC $\geq 12,000$ or $\leq 4,000$ or $>10\%$ bands (or a left shift)
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- An increased metabolic rate is stimulated by proinflammatory cytokines (tachycardia, tachypnea, fever).
 - Patients on beta or calcium channel blockers, or who have conduction disturbances, may have an inappropriately normal heart rate.
 - Systemic inflammation causes widespread edema. As pulmonary edema fluid accumulates, alveolar volume decreases, causing hypoxemia. Hypoxemia stimulates increased breathing, which can produce a respiratory alkalosis.
 - Bands are immature neutrophils. They are released into the circulation in increased numbers when the demand for neutrophils exceeds the ability to produce a sufficient number of mature cells.
 - Some guidelines for defining sepsis for the purpose of administering activated Protein C may require the presence of 3 or more signs of SIRS to reduce the risk for diagnostic error.

SEPSIS

When an individual has signs of SIRS (2 or more of the signs listed above), and the **SIRS** is likely **due to infection**, the condition is called **SEPSIS**. Or, sepsis is a widespread inflammatory response that is *caused by* infection.

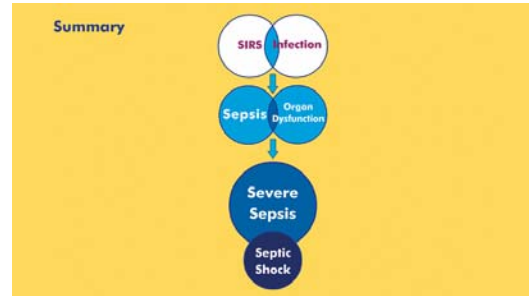
SEVERE SEPSIS

Systemic inflammation is characterized by vasodilation of blood vessels, increased blood vessel permeability, increased metabolic rate and increased microscopic clotting. The dilation of blood vessels associated with SIRS can cause hypotension. Fluid that leaks into tissues causes a further reduction in circulating volume, worsening the hypotension. The procoagulant state can obstruct the microcirculation, reducing blood flow to the organs. Persistence of these responses can quickly lead to organ dysfunction. When the patient develops evidence of organ dysfunction, the sepsis has moved along the continuum to a more serious phase of the disease. If the **shock** or organ failure can be **reversed by fluid** resuscitation, the condition is called **SEVERE SEPSIS**.

SEPTIC SHOCK

When the organ failure described in severe sepsis fails to respond to fluid administration, drugs that constrict the blood vessels are required. When the **shock** requires **vasoactive drugs**, the disease is called **SEPTIC SHOCK**.

CONTINUUM OF SEPTIC SHOCK



PATHOPHYSIOLOGY OF SEPSIS SYNDROME

Refer to the overview of inflammation and coagulation at:

<http://www.lhsc.on.ca/critcare/icu/edubriefs/>

Alterations associated with sepsis include:

1. Systemic Versus Local Response

When inflammatory responses are localized to an area of injured tissue, local inflammation is present. The affected area appears red, warm, swollen and tender (pain is triggered by the production of proinflammatory prostaglandins). Neutrophils collect locally, as they begin to roll along the surface of activated endothelium and migrate toward injured tissue through areas of increased permeability.

In sepsis, persistent or unresolved inflammatory triggers stimulate ongoing inflammation. Although some anti-inflammatory cytokines are also generally present, they are insufficient to overcome the proinflammatory cytokines. Consequently, proinflammatory characteristics are the dominant response in sepsis.

When the inflammatory response is large or persistent, the inflammatory response can become widespread and systemic. This can lead to excessive systemic vasodilation, increased metabolic rate, increased neutrophil count and widespread vessel permeability. Shock can develop from the intravascular volume deficit that occurs when blood vessels dilate and fluid shifts into interstitial fluid compartments. Vasodilation can produce a periphery that is warm and flushed, even in the setting of hypotensive shock.

The increased metabolic rate can cause a rise in the respiratory and heart rates, fever and increased caloric requirements. Blood sugar may rise and insulin resistance may develop in response to catecholamine and cortisol release. Cardiac contractility may initially be enhanced as the heart begins to pump more forcefully against a vasodilated periphery. The net effect can be an increased cardiac output and low Systemic Vascular Resistance (SVR). Eventually, the cardiac output may become too low, as organ dysfunction develops and the myocardium begins to fail.

Increased blood vessel permeability and increased protein requirements (e.g., to produce acute phase inflammatory mediators, coagulation factors, repair injured tissue), lead to a rapid fall in serum albumin. Widespread edema develops.

When inflammation becomes systemic, the alveolar-capillary membrane is also affected. Non-cardiac edema can cause hypoxemia due to alveolar volume loss, producing Acute Lung Injury (ALI) or Acute Respiratory Distress Syndrome (ARDS). ALI can be defined as non-cardiac pulmonary edema with a $\text{PaO}_2:\text{FiO}_2$ ratio < 300 , whereas, ARDS is a $\text{PaO}_2:\text{FiO}_2 < 200$ (Bernard, 1994). Hypoxemia stimulates faster and deeper breathing (increased minute volume) in an effort to restore normal oxygen levels. This may cause the over removal of carbon dioxide with respiratory alkalosis (one of the signs

of SIRS). All patients with severe sepsis or septic shock will have some degree of non-cardiac edema. If ventilation becomes necessary, Protective Lung Ventilation Strategies (PLVS) should be used to reduce further lung harm. PLVS goals include efforts to limit the peak or distending airway pressures (by using lower tidal volumes and/or using pressure control ventilation), prevent over-distention of the alveoli (by using lower tidal volume ventilation of 4-8 cc/kg), reduce the risk for oxygen toxicity (keeping $FiO_2 < .6$) and maintain a “lung open technique” by the liberal application of PEEP (increased PEEP may also improve the distribution of the tidal volume and facilitate the use of lower FiO_2 levels) (American Thoracic Society, 1999; ARDSnet, 2000).

2. Altered Coagulation

Activated endothelial cells generate Tissue Factor (TF) and trigger platelet adherence and aggregation. TF is also generated on monocytes. TF activates the coagulation cascade to stimulate thrombin and fibrin production. Unresolved inflammatory triggers lead to persistent coagulation and microscopic thrombosis. Continued coagulation leads to impaired blood flow to body tissues, causing or contributing to, organ dysfunction. It is important to note that organ dysfunction can develop very quickly and involves organs that are distant from the site of injury or source of infection (referred to as “remote organs”).

Sepsis is characterized by persistent coagulation. If coagulation continues for a prolonged period of time, clotting factors can become depleted. Antithrombin, an important homeostatic protein, has been shown to decrease in septic shock. Consumption of clotting factors can lead to DIC with prolonged INR and aPTT, and decreased platelet count.

3. Altered Fibrinolysis

To ensure that adequate coagulation occurs when it is needed, both thrombin and tissue factor stimulates the production of factors that temporarily block normal fibrinolysis (clot breakdown). The continued production of thrombin causes Thrombin Activatable Fibrinolysis Inhibitor (TAFI) to be produced. Persistent TF generation stimulates the production of Plasminogen Activator Inhibitor (PAI-1), which inhibits endogenous Tissue Plasminogen Activator (tPA). Thus, in addition to persistent coagulation, continued inflammation causes ongoing blockade of fibrinolysis.

4. Alteration in Activated Protein C

Activated Protein C is an important homeostatic protein. Protein C levels have been shown to be reduced (possibly due to increased consumption of clotting factors) in septic shock. In addition, the ability to convert Protein C to activated protein C is reduced in severe sepsis and septic shock. This is because activation of protein C occurs when thrombin, Protein C and Protein S, combine with a protein that is found on non-activated endothelium, called thrombomodulin. In severe sepsis and septic shock, widespread activation of endothelium reduces the availability of thrombomodulin.

Activated Protein C reduces inflammatory cytokines, deactivates factors VIII and V, and inhibits both TAFI and PAI-1. Thus activated Protein C is an important endogenous protein that has anti-inflammatory, anticoagulant and profibrinolytic properties.

Activated Protein C deficiency during severe sepsis and septic shock contributes to the persistent inflammation and coagulation, worsening the organ dysfunction. The administration of activated Protein C in severe sepsis and septic shock reduces mortality.

5. Multi-Organ Dysfunction Syndrome (MODS)

When sepsis progresses to the point where organ dysfunction occurs, severe sepsis or septic shock is present. Microscopic coagulation plays a role in the development of MODS, however, the cause of the organ dysfunction is likely multi-factorial. Although individually, organ dysfunction may be reversible upon resolution of the septic shock, morbidity and mortality increases as the number of affected organs increase, with

increased duration of organ dysfunction and when co-morbidities exist (Vincent, 2003; 2005).

Organ dysfunction includes:

- Hypoxia, hypercarbia, increased ventilation requirements
- Hypotension, decreased cardiac output
- Oliguria, increasing creatinine
- Decreased level of consciousness
- Metabolic derangements, including lactic acidosis
- Rising hepatic enzymes
- Coagulopathies

Activated Protein C administration is indicated when *2 or more of the following* organ dysfunction exists. These are the organs that were included in the definitions for inclusion to the PROWESS trial and should be used to determine suitability for Xigris (Bernard, 2001):

Cardiovascular: The use of vasopressors or SBP \leq 90mm Hg or MAP \leq 70mm Hg for at least 1 hour, despite adequate fluid resuscitation

Renal: Urine output $<$ 0.5mL/kg/hr for one hour, despite adequate fluid resuscitation

Respiratory: Mechanical ventilation (invasive or non-invasive) with PaO₂ / FiO₂ \leq 250

Hematologic: Platelet count $<$ 80 x 10⁹/L in the last 3 days or platelet count decreased by 50% in the last 3 days

Arterial Lactic Acidosis: Plasma lactate $>$ 3.3 mmol/L

OR

One of the above sepsis-induced organ failures AND APACHE II Score \geq 25

6. **Myocardial Dysfunction**

Myocardial depression can develop during sepsis. Although sepsis is often characterized by an increased cardiac output, contractility can become impaired as septic shock worsens. Troponin levels can rise during septic shock, and ejection fractions can become low. Myocardial dysfunction may resolve if the septic shock is reversed early.

During a study that compared an early goal directed therapy protocol versus usual care for the treatment of severe sepsis and septic shock, low ScvO₂ levels (indicative of inadequate cardiac output) were identified among patients with adequate mean BPs. Administration of dobutamine to provide inotropic support was associated with improvement in ScvO₂ (Rivers, 2001).

**OVERVIEW OF BEST PRACTICE FOR SEVERE SEPSIS AND SEPTIC SHOCK:
APPLICATION OF EARLY GOAL DIRECTED THERAPY**
(Hotchkiss, 2003; Dellinger, 2008).

Within Hour 0-1...

Make the Diagnosis! Early recognition is essential..the clock is ticking!

- ✓ Does the patient have “SIRS”
- ✓ Is infection the likely cause of the SIRS
If yes: Sepsis is diagnosed
- ✓ Does the patient have organ dysfunction that is due to the sepsis?
If yes: *Severe Sepsis* is present if hypotension resolves with adequate fluid resuscitation;
Septic Shock is present if hypotension persists despite adequate fluid resuscitation.

By the End of the First Hour...

- ✓ **Manage Shock (ABCs)**
 - Oxygen
 - IV access (2 large bore peripheral lines)
 - Foley catheter to hourly output monitoring
 - Arterial and central venous line if shock does not resolve immediately or screening lactate is increased
 - PEEP, intubate and ventilate before overt failure develops
 - Fluid, fluid, fluid!
Goal: HR,100, MAP \geq 65, U/O >.5 ml/kg
CVP 8-12 mmHg(12-15 if ventilated)

Fluid:

It is important to remember that one of the most common errors made during resuscitation of the patient with sepsis is the inadequate replacement of fluid. Following initial resuscitation, intravascular fluid requirements may continue to be high as a result of third space losses. Patients in ED with severe sepsis/septic shock who were managed with an early goal directed therapy protocol had increased survival and received more fluid during the first 6 hours of admission than patients managed with standard care. Both groups received similar total fluid volumes over the study period (Rivers, 2001).

Currently, there is no clear benefit associated with one type of resuscitation fluid versus another. In a large RCT of patients with shock who were randomized to receive 0.4% albumin versus 0.9% saline (SAFE trial), no difference in survival was found (Finfer, 2004). Subgroup analysis (determined a priori) suggested a trend toward lower mortality among patients with sepsis who received albumin versus saline, however, the difference did not meet statistical significance. This finding is non conclusive, but supports the need to conduct further research to explore fluid options among different subsets of patients.

A recent comparison of Hespan (not available in Canada) and ringers lactate demonstrated more renal failure among patients randomized to receive starch solution (Brunkhorst 2008). Concern has been raised over the significance of this study and association with other starches such as pentaspan, and the potential risk for the development of renal failure. Evidence to date is inconclusive and needs further study.

Resuscitation fluid should be at least isotonic (0.9 % saline or lactated ringers), or a colloid (pentaspan, albumin). Large volume infusions of normal saline can produce hyperchloremic acidosis that might be avoided by ringers lactate resuscitation. Potassium

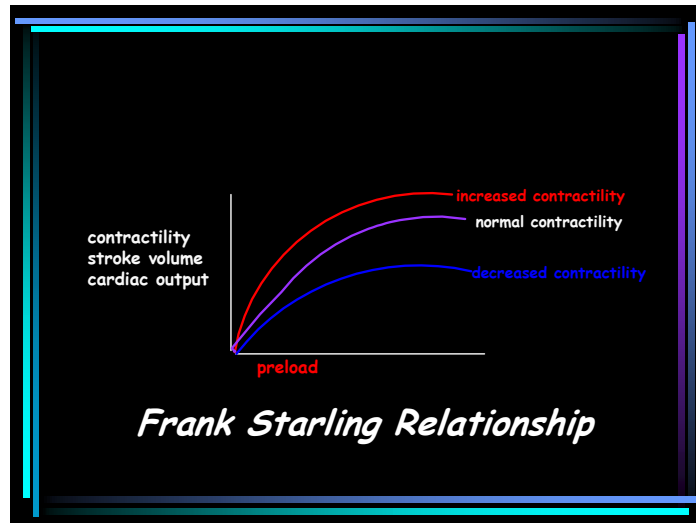
should be monitored as ringers lactate contains potassium chloride, however, hyperkalemia has not been demonstrated during clinical trials. Ringers lactate can cause a transient rise in serum lactate. Hypertonic saline is currently being studied to examine its potential role as a resuscitation fluid in trauma and/or head injury, where potential benefits include anti-inflammatory properties. More research is needed to determine the optimal resuscitation fluid for different patient populations.

Finally, in a study of patients with ARDS (Weidemann, 2006), a restrictive approach to fluid management was associated with earlier liberation from the ventilator (but no decrease in mortality), with no increase in renal failure. It should be noted that this study was implemented at ~72 hours; aggressive fluid resuscitation is still recommended in early sepsis, severe sepsis and septic shock.

Conduct a Fluid Challenge:

The only way to know whether more fluid is needed is to conduct a fluid challenge. Recall the relationship between preload and contractility described by Starling's Law. When preload increases, contractility improves. If fluid is the correct intervention, administration of fluid should be associated with evidence of increased blood pressure, cardiac output, urine output, mentation, decreased heart rate or increased ScvO₂.

Administer fluid in increments of rapid 500 ml boluses q 15 minutes (consider 250 ml increments in a small or elderly patient with cardiac disease). To assess for benefit, monitor for evidence of increased contractility or cardiac output following each bolus. Increased cardiac output may be identified by increased urine output, mentation, blood pressure, ScvO₂/SvO₂ or decreased heart rate.



If hypotension does not show signs of immediate response to fluid, a foley catheter, arterial line and central line should be considered. A central line can be used to measure both CVP and central venous oxygen saturation (ScvO₂). ScvO₂ can be measured by drawing a blood gas sample from a central venous line. Mean arterial pressure provides the best blood pressure parameter.

Monitor CVP before and after each bolus. Be sure to use a consistent technique for measurement (ideally through waveform assessment). Before each measurement, confirm correct placement of the transducer (in relation to the mid axillary line). Once the CVP has reached 8-12 mmHg, improvement should be identified in the cardiac output if the CVP is pushed up another 3-4 mmHg during fluid administration. If CVP increases with no improvement in cardiac output indicators, it is unlikely that the patient will benefit from further fluid administration.

Stroke Volume Variability (SVV) is an emerging technology that is being used in some centres to assist in the evaluation of fluid status. It is available with minimally invasive cardiac output technologies that analyze the arterial pressure waveform to determine stroke volume. The degree of variability in the stroke volume with breathing (SVV) is expressed as a percentage. A high % SVV (> 8-12%) may indicate volume deficit. Widespread experience and understanding of the role of this technology during low tidal volume ventilation, heart rate variability (e.g. stroke volume variability due to arrhythmia) or poor lung compliance has not been clearly established.

Vasopressors:

If blood pressure does not respond to fluid resuscitation, initiate vasopressors. Vasopressors are indicated if hypotension persists despite adequate intravascular volume (septic shock). Vasopressors should also be considered if hypotension does not respond quickly to fluid administration; initiate vasopressors and continue fluid administration until adequate intravascular volume has been restored. It may be possible to wean the vasopressors off as the intravascular volume increases.

Alpha stimulants are the first line pharmacological agents for the treatment of septic shock. Evidence to recommend one vasopressor over another is limited, however, most physicians today use norepinephrine as the first line agent based on clinical experience. Dopamine may also be considered, however, use is often associated with significant tachycardia. Epinephrine may be useful in non-responsive shock. Vasopressin may improve blood pressure by restoring vasopressin deficiency, however, vasopressin is not recommended at vasoconstricting doses (> 2.4 units per hour).

✓ Obtain Labs

- Think of how you will assess for organ failure when ordering labs:
Minimum blood work
 - CBC with differential and platelets
 - Lytes, glucose
 - Urea, creatinine
 - Liver function tests
 - Blood gases
 - Lactate
 - Central venous oxygen saturation if central venous line established

✓ Collect Cultures

- Culture all available sources
- Do not delay starting antibiotics to obtain cultures
- Label culture specimens carefully (i.e. identify date and time lines or catheters were inserted if drawing blood cultures from indwelling lines).
- Draw at least 2 sets of blood cultures. Attempt to get at least one culture from a peripheral stab. Culture all indwelling lines (with duration >48 hours).
- At least 10 ml blood volume is required per bottle.
- Collect simultaneous cultures from a peripheral sample and indwelling line. If possible, request assessment for Catheter Associated Bacteremia. If the lab will perform this test, they will report a “time-to-positivity” for each culture (report the time that each line became positive).
- If an indwelling line becomes positive by > 2 hours before the peripheral culture (and both grow the same organism), a catheter associated bacteremia has been identified (meaning the line is the likely source of the infection).
- If a “suspect” line is being removed, draw cultures prior to removal and send the catheter tip for semi-quantitative culture (if available). If the catheter tip has a colony count > 15 with the same organism growing in the blood culture, catheter associated bacteremia has been identified.
- Determination of line infection can help to avoid unnecessary line removal; if the patient has a bacteremia from a non-line source, antibiotics should be started for 24-48 hour before placement of a new line.

✓ Start Broad Spectrum Antibiotics STAT

- Administer as soon as possible; start **while** treating shock.
- Antibiotics should be administered within 30-60 minutes of admission. For every hour of delay in starting an **appropriate antibiotic** (one that covers the actual organism), mortality increases ~7.6% (Kumar, 2006).
- Early recognition is essential; if sepsis is one of the differential diagnoses for a patient in shock, empiric broad spectrum antibiotics are essential.
- Evidence is emerging to suggest that antifungal therapy should be considered when providing empiric therapy (~7-8% of patients with severe sepsis/septic shock had yeast/fungi suspected as the primary microbiological pathogen) (Kumar, 2006).
- To avoid delays:
 - Early recognition is mandatory; physicians must order antibiotics as soon as sepsis is suspected.
 - Have one nurse collect cultures and start antibiotics while primary nurse manages shock.
 - Antibiotic administration should be considered as important as vasopressors.

- Identify barriers to timely administration within your own ICU, for example, are first line broad spectrum antibiotics readily available at night?
- Antibiotics must be given STAT; do not delay administration while awaiting “regular dosing times”.
- Do not delay antibiotics if cultures cannot be obtained; culture all available fluids, however, if cultures cannot be obtained, start antibiotics without the culture
- Always send two sets of blood cultures to aid in correct interpretation.
- Do not delay blood culture collection while awaiting line insertion; send peripheral cultures ASAP
- Administer beta lactam antibiotics first and give them in 50 ml over 5 minutes. This will ensure the first antibiotic is administered quickly; hang antibiotics that require longer administration time second. Beta lactams include penicillins, cephalosporins and mero/imipenem. Piperacillin or Piperacillin/tazocin are also beta lactams, but they should be given over 30 minutes.
- Multiple antibiotics can be administered at the same time if each antibiotic is administered via a different site.

| Antibiotic | Maximum Speed of Administration |
|---|---|
| <ul style="list-style-type: none"> • Amoxicillin,/penicillin • Cephalosporins • Imipenem/Meropenem • Piperacillin or Pip/Tazo | <ul style="list-style-type: none"> • Can be given IV direct • Can be given IV direct • Can be given IV direct • Give over a minimum of 30 minutes Note: administration over 5 minutes is reported to be safe by manufacturer. |
| <ul style="list-style-type: none"> • Cipro | <ul style="list-style-type: none"> • Give over a minimum of 60 minutes for peripheral IV/30 minutes for central |
| <ul style="list-style-type: none"> • Levofloxacin | <ul style="list-style-type: none"> • Give 500 mg over a minimum of 60 minutes; 750 mg over 90 minutes |
| <ul style="list-style-type: none"> • Metronidazole • Vancomycin/aminoglycosides | <ul style="list-style-type: none"> • Give over minimum of 30 minutes • Give over minimum of 60 minutes |

Table I

Hours 1-8...

- ✓ If organ dysfunction is present (including persistent hypotension or elevated lactate), **arterial line is recommended**
- ✓ If organ dysfunction is present (including persistent hypotension or elevated lactate), **central venous line is recommended** (or PA catheter)
- ✓ **Continue fluid resuscitation until CVP >8-12 (12-15 if ventilated)** or additional fluid causes CVP to rise with no improvement in MAP or ScvO₂.
- ✓ **Monitor Central Venous blood gases (S_{cv}O₂) q 30-60 minutes or continuously until stable**
 - S_{cv}O₂ is a measurement of the amount of oxygen returning to the right side of the heart.
 - Normally, the oxygen saturation in the superior vena cava is >70% (with a PaO₂ ~40 mmHg).
 - S_{cv}O₂ reflects the amount of oxygen that is “leftover” after tissue oxygenation has occurred.
 - A decrease in the right atrial oxygen saturation to <70% (i.e., there is less oxygen “leftover”) indicates that tissue oxygen extraction has increased (the tissues are extracting a greater percentage of the oxygen from circulating hemoglobin molecules).

- An increase in oxygen extraction indicates that the Oxygen Delivery is inadequate (Oxygen Delivery = Cardiac Output X Arterial Oxygen Content).
- Assuming that the arterial oxygen saturation and hemoglobin are adequate (components of arterial oxygen content), an $S_{cv}O_2 < 70\%$ suggests that the cardiac output is too low.
- A decrease in the $S_{cv}O_2$ indicates a need to increase the cardiac output.
- If increased extraction fails to meet tissue oxygen need, the third and final compensation is anaerobic metabolism (increased lactate).
- Treatment for a low $S_{cv}O_2$
 - Ensure the patient has received adequate fluid resuscitation.
 - If the MBP remains low despite adequate fluid resuscitation, vasopressors should be added to increase the BP.
 - Treat low hemoglobin.
 - If the $S_{cv}O_2$ remains low, consider adding an inotrope such as dobutamine (does not usually cause tachycardia, has a short-half life and is inexpensive). Other inotropes may be considered (e.g., dopamine, epinephrine or milrinone).
 - Caution: Dobutamine is a vasodilator; ensure the patient has received adequate fluid resuscitation and initiate a vasopressor if required. Anticipate the need for additional fluid following dobutamine administration.
- If the patient has a pulmonary artery catheter, an S_vO_2 (mixed venous) can be measured from the tip of the pulmonary artery catheter. Normal S_vO_2 is $>65\%$.

✓ **Titrate fluid, vasopressor/inotropes and blood products to a goal directed algorithm**

Continue to monitor and intervene to keep CVP > 12, MAP > 65, SVO₂>70%, HCT \geq 30%. Early goal-directed therapy has been shown to improve patient outcomes.

✓ **Consider hormone replacement.**

- **Vasopressin:**
 - Deficiency of vasopressin has been demonstrated in septic shock.
 - The VASST trial failed to show a mortality benefit when norepinephrine was compared to norepinephrine plus low dose vasopressin (.03 units/min) for the treatment of septic shock (Russell 2008). In an a priori subgroup analysis, patients randomized to receive vasopressin while receiving low doses of norepinephrine (<15 ug/min) demonstrated a mortality reduction. Early intervention with vasopressin may be optimal, however, further research is needed to confirm this hypothesis.
 - Administer at hormone replacement doses (maximum doses .03 - .04 u/min or 2 - 2.4 u/h). Doses >.04 u/min (2.4 u/hr) are associated with coronary, GI and digit ischemia.
 - The goal for vasopressin therapy is to replace the hormone deficiency; it should not be titrated to BP or used as a specific vasopressor.
 - Suggested weaning strategy is to wean vasopressors (e.g., norepinephrine) off first, followed by vasopressin once vasopressors are off for 8 hours.
- **Cortisol:**
 - In shock, endogenous levels rise; in septic shock endogenous cortisol levels are depressed or inappropriately normal.
 - Vasopressin (also known to be deficient) stimulates ACTH production. The role that vasopressin may play on cortisol is unclear.
 - Cortisol is a stress hormone; it is a catabolic hormone that makes fuel available during times of stress by breaking down glycogen, fats and proteins (raises blood glucose).

- Cortisol also makes blood vessels respond to catecholamines and increases the available supply of catecholamines.
- Cortisol deficiency can cause profound hypotension.
- Only indicated in septic shock (vasopressor dependent despite adequate fluid resuscitation).
- Administration of steroids to patients with septic shock who were vasopressor dependent > 48 hours facilitated weaning of vasopressor therapy (Bollaert, 1998).
- Cortisol replacement improved survival among patients with septic shock that was refractory to vasopressors, and who failed to respond to an adrenal stimulation test (Annane, 2002). Fludrocortisone was added by Annane to cover the potential for other corticosteroid deficiency (e.g., aldosterone). Aldosterone causes sodium and water reabsorption from the kidney. Some centers administer cortisone and fludrocortisone according to the original trial, whereas, other centers use a higher dose of hydrocortisone (which provides sufficient aldosterone replacement). Dosing regimes include:
 - hydrocortisone 50 mg QID plus fludrocortisone .1 mg/day

or

 - hydrocortisone 100 mg T.I.D.
- The most recent cortisol in septic shock trial called CORTICUS (Sprung, 2008) showed faster resolution of shock when steroids were used, however, it did not show a mortality reduction in the steroid group. There was more superimposed infection in the steroid group.
- Two important points should be considered for the CORTICUS trial:
 - Investigators had significant difficulty with recruitment, due to the "common practice" of using steroids in septic shock. Consequently, many physicians refused to enroll subjects because of a perceived risk associated with potential randomization to the placebo group. Consequently, patients were less sick in the CORTICUS trial.
 - The study was stopped before the desired sample size was achieved, creating the potential to miss a true difference between groups (potential Type II error).
- CORTICUS also demonstrated the lack of reliability/usefulness of routine
- ACTH stimulation testing.
- Steroids increase blood glucose levels and insulin resistance; concurrent insulin therapy is usually required. Blood glucose levels may transiently rise immediately following steroid administration. Careful blood glucose monitoring is required.
- Steroids can also cause an increase in the WBC.
- The CORTICUS trial has added to the ongoing controversy. A consensus statements from an international task force by the American College of Critical Care Medicine that included both Annane and Sprung, provide the following recommendations:
 - The task force coined the term critical illness-related corticosteroid insufficiency, described as dysfunction of the hypothalamic-pituitary-adrenal axis during critical illness. It is caused by a combination of adrenal insufficiency and tissue corticosteroid resistance, and is exaggerated by a protracted proinflammatory response.
 - It should be suspected in hypotension that is not responsive to fluid and vasopressors, especially if induced by sepsis.
 - It is best defined as a delta serum cortisol of < 9 ug/dL after a 250 microgram bolus of cosyntropin, or random total cortisol of < 10 ug/dL.
 - Glucocorticoids should be limited to patients with vasopressor-dependent septic shock and early severe acute respiratory distress syndrome.
 - Hydrocortisone 50 mg IV QID is recommended for septic shock X 7 days, whereas, methylprednisolone at 1 mg/kg/day for \geq 14 days is recommended for severe ARDS.
 - .

- Although tapering doses of steroids are not routinely ordered following a 5-7 day course of steroids, there is evidence to suggest that adrenal suppression may persist following steroid discontinuation. Following withdrawal of steroids, patients should be monitored closely for return of hypotension. Steroids may need to be restarted and/or ACTH stimulation testing considered.

ACTH Stimulation Test using cosyntropin (not routinely recommended):

- A synthetic polypeptide identical to corticotropin (ACTH)
 - Normal physiology:
 - Low levels of cortisol or an increased stress response causes the hypothalamus to release Corticotrophic Releasing Hormone (CRH). CRH stimulates the release of Adrenocorticotrophic Hormone (ACTH) by the pituitary.
 - ACTH stimulates the adrenal gland to make more cortisol.
 - If ACTH (or a synthetic form of the hormone such as cosyntropin) is given, the adrenal gland should be stimulated to increase cortisol production.
 - Vasopressin also stimulates ACTH production; the relationship between these two hormones in septic shock is unclear.
- **Test:**
 - Obtain a baseline cortisol level.
 - Administer cosyntropin 250 ug in 50 ml IV fluid over 5 minutes (may also be given IM). Some physicians will use a 1 ug dose.
 - Obtain a repeat cortisol level at 30 and 60 minutes post infusion of cosyntropin.
- **Response**
 - Normal response is a stimulated cortisol level of >500 nmol/L (>18 ug/dL) and a minimal stimulated increment of >200 nmol/L (>7 ug/dL) above baseline.
 - Baseline serum levels will be higher in the morning than in the evening due to diurnal variation.
 - Baseline levels may be higher in patients receiving hydrocortisone, oral contraceptives, or who are pregnant or severely ill patients.
 - The standard dose of cosyntropin 250 ug is very high; this may cause a rise in cortisol level in patients with marginal adrenal function, producing a false negative (rise in cortisol in the presence of adrenal insufficiency). Some endocrinologists suggest that a dose of 1 ug is sufficient and would reduce false negatives. There is also wide lab variability in test results, raising concerns over reliability.
 - Septic shock may provide a sufficient enough stressor to stimulate an increase in the cortisol level. Marik (2003) suggests that a random cortisol level <25 microg/dL (<700 nmol/L) in any stressed patient suggests adrenal insufficiency.
 - CORTICUS founded wide variation among lab results and reference samples.
 - Etomidate should be used with caution in severe sepsis/septic shock as it causes acute adrenal suppression.

✓ **Maintain normoglycemia**

- Intensive Insulin Therapy (keeping blood glucose 4.4 – 6.1) was found to reduce 28 day mortality, days on ventilator, dialysis requirements, bacteremia and polyneuropathy of critical illness. The greatest benefit was identified among patients in ICU > 5 days (van den Berge, 2001, 2006).
- Two European trials of Intensive Insulin Therapy were stopped early due to high hypoglycemia rates.

- Large multicentre trial (NICE-SUGAR) (2009) found an increase in 90 day mortality with high incidence of hypoglycemia among patients receiving Intensive Insulin Therapy. No difference in weaning, incidence of dialysis or ICU LOS.
 - There were more patients in the Intensive Insulin group who received steroids.
 - It is not clear whether worse outcomes are due to insulin or hypoglycemia.
 - A computerized protocol was used for adjustment of infusions; not clear whether protocol contributed to hypoglycemia.
- Current recommendations:
 - Hyperglycemia is associated with adverse outcomes in conjunction with a variety of disorders (trauma, brain injury, stroke, myocardial infarction, hematological malignancies and sepsis and critical illness).
 - The ideal glucose is not clear. Intensive blood sugar control is still considered best practice, however, a more conservative target glucose should be considered (e.g., 7-10 versus 4.4-6.1) should be considered.
 - Judicious blood sugar monitor is required, especially with history of DM or neurological injury.
 - Monitor your incidence of hypoglycemia and consider revisions to your protocol if high rates of hypoglycemia occur.
 - Allow flexibility in the protocol and avoid “overshooting” your goal; allow nurses to “not respond” to minor blips in the blood sugar (e.g., following steroids or changes in enteral feeding).
 - Monitor trends and decrease infusion rate more quickly when downward trend detected.
 - Do not increase insulin more frequently than q2h to avoid delayed drop in blood glucose. Avoid use of insulin bolus (increase drip rate only).
 - Use a dedicated line with no fluid flushes or boluses via insulin lumen. Monitor site carefully.
 - Do not use Intensive Insulin Therapy without a source of nutrition; adjust insulin and monitor sugar carefully for changes in feeding rates/feeding tolerance or when feeding tubes become blocked.
 - Err on the higher side of the glucose range.
 - Monitoring carefully for signs of hypoglycemia.
- Monitor potassium carefully (insulin and/or catecholamines can decrease serum K by shifting potassium into cells).
- Increased monitoring is needed when glucose requirements increase (e.g. shock, sympathomimetic use, change in feeding, use of steroids).

Within First 24 Hours..

✓ **Consider drotrecogin-alfa activated (Xigris)**

Xigris administration replaces endogenous activated Protein C deficiency. Activated Protein C produces the following effects:

- Anti-inflammatory: turns off inflammation and decreases adhesion and rolling of leukocytes.
- Anticoagulant: deactivates cofactors VIIIa and Va to decrease thrombin production
- Profibrinolytic: deactivates inhibitors of fibrinolysis (PAI-1 and TAFI) to promote clot lysis.
- Indicated for severe sepsis or septic shock where 2 or more organ failure is present despite adequate fluid resuscitation. Organ failure must be due to sepsis. Risk for death increases with increased number of organ dysfunction (Vincent, 2003).
- Xigris reduced relative risk of death by 19.4% among patients with organ dysfunction with severe sepsis and/or septic shock (Protein C World Wide Evaluation in Severe Sepsis [PROWESS trial]). NNT is 16. (Bernard, 2001).
- It is recommended that Xigris be started within 48 hours of organ failure onset. Subgroup analysis of subjects who received Xigris within 24 versus 48 hours suggests that outcomes are better when given in the first 24 hours versus hours 25-48 (Vincent, 2003).
- ADDRESS trial compared Xigris to placebo among patients with single system failure or low predicted risk of death (APACHE < 25). This study was stopped early for futility. Subgroup analysis of surgical patients with single system failure in both the PROWESS and ADDRESS trial showed increased mortality. Xigris is not recommended for post op patients with single system organ failure who receive Xigris.
- Controversy around the use of Xigris continues. The high cost associated with drug use contributed to the controversy, as clinicians look for strong evidence of cost/benefit. Two additional RCTs comparing Xigris to placebo and adjusted dose Xigris are in their completion stages.
- Xigris use should be limited to patients with 2 or more organ failure and high risk of death. Early administration versus late is likely best. Strict adherence to the inclusion criteria of the PROWESS trial is recommended to avoid adverse events and ensure therapy is restricted to those patients shown to benefit.
- Contraindications include any important and unmanageable bleeding risk, particularly if risks for bleeding within the brain or GI tract exist. Patients should not receive it if they have an epidural catheter in place, however, it can be started after the catheter is removed.
- Xigris has a 13 minute half-life; if bleeding occurs or invasive procedures are required, stop the infusion as soon as possible to reduce bleeding risk:
 - Ideally, stop 2 hours prior to invasive procedure including OR
 - Resume drug 1-hour post minor procedure (line, chest tube insertion) and 12 hours post major procedures (e.g. surgery).
- Xigris is administered 24 ug/kg/hr X 96 hours; if therapy is stopped during treatment (e.g. for line insertion), the infusion time should be adjusted to ensure that a full 96 hours of therapy has been received.
- Activated Protein C produces anticoagulation as a result of deactivation of VIIIa and Xa. This may prolong the PTT but should have minimal effect on INR. Significant prolongation of the INR *and* PTT may indicate sepsis induced coagulopathy versus effect from Xigris. INR and PTT prolongation can be treated by FFP administration. One or two doses of Vitamin K may be considered in the INR is prolonged.
- Xigris can be administered 12 hours post surgery, with the following precaution: mortality rate is increased among post-operative patients with SINGLE organ failure, who received Xigris versus placebo within 30 days of surgery (Abraham, 2004).

Administration precautions include:

- INR >3.0 (treat with FFP; consider administration after INR is decreased)
- Platelets <30,000
 - If platelets are low, consider platelet transfusion.
 - Bleeding risk is increased with low platelets, therefore, clinical judgment is needed to evaluate the risk-benefit. If activated protein C successfully corrects the coagulopathy, platelets should begin to recover.
- Indwelling epidural catheter is a contraindication (may be administered 12-hours post removal)
- Patient may receive heparin or LMWH provided that the dose is no greater than 15,000 units per day (subcutaneously).
 - In a study of patients receiving Xigris plus placebo (XPRESS), subcutaneous unfractionated heparin (UH) or subcutaneous low molecular heparin (LMWH), there was a trend toward lower mortality (not significant) among patients who received low dose UH or LMWH versus placebo (p=.04). No difference in the secondary outcome of veno-thrombo embolic events was identified (secondary outcome) when aPC was combined with or without low dose UH/LMWH. There was more bleeding among patients receiving UH/LMWH and aPC but less thrombotic stroke (secondary outcomes).

Subgroup analysis identified a significant difference in mortality among patients who were on UH/LMWH prior to randomization and were randomized to placebo (i.e. the heparin was stopped). Patient's whose UH/LMWH was stopped had a statistically higher mortality rate. Consequently, it is recommended that low dose UH/LMWH be continued after starting aPC (unless otherwise contraindicated).

✓ **Repeat labs q6h and prn X 24 hrs**

✓ **Maintain goal-directed therapy**

✓ **Consider need for hemodialysis**

Hemofiltration

- One study reported that high hemofiltration (at rates of 35 ml/kg/hr) is associated with increased survival among septic patients. Theoretically due to increased removal of cytokines, however, cytokines removal via the effluent has not been demonstrated. Some methodological limitations exist with this study and findings remain controversial. In addition, post dilution replacement was used in this study; Canadian practice prior to 2005 was exclusively predilution (Ronco, 2001).
- Filters used in Continuous Renal Replacement Therapies (continuous hemodialysis) have been shown to have good adsorption properties; proteins (e.g. inflammatory cytokines) "stick" to the filter and may be removed during filter change. It is not known how frequently filters should be changed to obtain optimal benefit.

✓ **Initiate early enteral feeding**

✓ **Provide GI prophylaxis**

Critically ill patients are at risk for GI bleeding. Risk may increase with the use of anticoagulants.

✓ **Maintain protective lung ventilation strategies**

Pulmonary manifestation of SIRS should be managed with lung protection strategies.

✓ **Consider DVT prophylaxis**

✓ **Prevent complications (institute Ventilator Associated Pneumonia [VAP] prevention; remove lines and tubes when no longer needed)**

✓ **Promote patient comfort**

- ✓ Support the patient and family

>24 Hours...

- ✓ Narrow antimicrobials
- ✓ Reassess necessity for/efficacy of source control
- ✓ Reassess all monitoring and treatment on an ongoing basis

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