Identification and Management of the Patient with Sepsis
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Recall that Systemic Inflammatory Response Syndrome (SIRS) is a host response to injury (surgery, trauma), ischemia (thrombosis, shock, cellular hypoxia) or infection (virus, bacteria, fungus, toxin or foreign substance such as cancer).

Also recall that systemic coagulation is initiated whenever systemic inflammation occurs. Systemic inflammation and increased coagulation are common characteristics among many critically ill patients (e.g., shock states, multiple trauma, cancer, post surgical, sepsis). Knowledge of the inflammatory and coagulation responses helps us to recognize and manage alterations in fluid balance, blood pressure and coagulation.

Sepsis is a dysregulated host response to infection. It is characterized by excessive systemic inflammation and clotting where infection is the cause of the response.

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 and shock.

PATHOPHYSIOLOGY OF SEPSIS SYNDROME

Alterations associated with sepsis include:

1. Systemic Inflammation

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 though areas of increased permeability.

In sepsis, the inflammatory response becomes systemic. Persistent or unresolved inflammatory triggers stimulate ongoing systemic inflammation and coagulation. Both pro and anti-inflammatory cytokines are release, with a dominance of “pro” responses. 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 creates a hyperdynamic state characterized by tachycardia, tachypnea, fever, increased oxygen consumption and high caloric

demand. Increased carbon dioxide production causes minute volume requirements to rise, which can lead to respiratory muscle exhaustion with respiratory acidosis. An upward trend or high minute volume requirement may indicate that sepsis is developing.

Vasodilation produces a relative hypovolemia that causes a decrease in blood pressure. It lowers Systemic Vascular Resistance (SVR or afterload) and cardiac filling pressures. The augmented contractility (sympathetic stimulation) against a reduced SVR can create “dobutamine like” effects. Thus, patients may have a low CVP, tachycardia, warm and dilated periphery and increased cardiac output, even in the setting of hypotension. Eventually, cardiac output may become low as a result of multi organ dysfunction and myocardial depression. Elevated troponin levels and reduced ejection fraction may be identified.

Increased blood vessel permeability becomes widespread in sepsis. Edema collects in all tissue areas and likely contributes to cellular oxygen uptake impairment. Edema collections are worse in dependent areas of the body and will develop even in the setting of low intravascular and intracardiac pressures. The loss of intravascular fluid worsens the hypotension. Over correction of fluid or intravascular pressures can increase the fluid leak.

Fluid leaves the blood vessels because of enhanced permeability. The increased permeability also promotes the loss of plasma proteins which are normally too large to cross. As protein moves into the interstitial spaces, additional water is drawn out of the vasculature because of the rise in interstitial and fall in intravascular oncotic pressures. Adding to the problem of protein loss, the stress response and high metabolic demand produces a catabolic state (protein breakdown is greater than protein intake). As well, plasma proteins are utilized for the production and transport of cytokines, clotting factors, hormones and many other substances. Serum protein and albumin levels often drop quickly during sepsis, and may remain very low despite early and aggressive feeding regimens. A marked reduction in albumin levels is a common characteristic of sepsis and it often remains low until resolution of the disease, despite enteral feeding or albumin administration. The recovery of albumin levels is often a marker of sepsis recovery.

When inflammation becomes systemic, the alveolar-capillary membrane are also affected. Non-cardiac edema causes hypoxemia due to alveolar volume loss. Mild disease will require supplemental oxygen. Hypoxemia stimulates faster and deeper breathing (increased minute volume) in an effort to restore oxygen levels, which may initially be associated with respiratory alkalosis. As respiratory muscles fatigue, carbon dioxide clearance can no longer be maintained and hypercarbic respiratory failure ensues. Acute Respiratory Distress Syndrome (ARDS) develops in severe disease. Although ARDS occurs frequently among patients with Septic Shock, it can also develop as a result of many other conditions. ARDS will be discussed separately.

All patients with sepsis induced organ failure 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).

Blood sugar often increases in response to the high catecholamine and cortisol (stress hormone) output. Use of sympathetic stimulating drugs or steroids can cause a further rise. Insulin resistance can develop with prolonged cortisol output. An increased blood glucose with increasing insulin requirements is often a marker of worsening sepsis.

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 impairs 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. Antithrombin deficiency causes prolongs thrombin activity and availability (clotting enhancement). Consumption of clotting factors can lead to DIC with prolonged INR and aPTT, and decreased platelet count.

It is essential to remember that the trigger for inflammation and clotting is infection. Source control (the right antimicrobial agent and abscess drainage/surgical control) is a priority; inflammation and coagulation will persist as long as the infectious trigger is present.

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 (clots that do develop will stay around longer).

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 requires thrombin, Protein C and Protein S, to combine with a protein that is found on the surface of non-activated endothelium (thrombomodulin). Once activated, our own naturally occurring Protein C will turn off inflammation, turn off coagulation an turn on fibrinolysis (clot breakdown).

5. Multi-Organ Dysfunction Syndrome (MODS)

When infection induces systemic inflammatory responses progress to the point where organ dysfunction occurs, mortality risk increases. Microscopic coagulation and cellular dysfunction plays a critical role in the development of MODS; the cause of the organ dysfunction is 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

Multiple Organ Dysfunction (MODS):

Sepsis can affect organ function throughout the body, including:

Neurological:

- Abrupt change in mental status *this may be the only initial finding in elderly patients
  Decreased Glasgow Coma Scale (GCS)
- Abnormal electroencephalographic (EEG) findings
- Metabolic encephalopathy
- Delirium

Respiratory:

- Hypoxic and hypercarbic failure
- Acute respiratory distress syndrome (ARDS) (PaO2/FiO2 ratio $\leq$ 300 or increasing need for PEEP)

Cardiovascular:

- Hypotension (MAP <60 or MAP < 70)
- Areas of mottled skin
- Capillary refill $\geq$ 3 seconds
- Cardiac dysfunction (ie, left ventricular systolic dysfunction), as defined by echocardiography or direct measurement of the cardiac index
- Troponin rise (troponitis)

Renal:

- Urine output <0.5 mL/kg for at least one hour, or renal replacement therapy
- Prerenal failure and progression to acute tubular necrosis

Hematologic:

- Platelet count <100,000 platelets/mL due to consumptive coagulopathy
- Prolonged coagulation time due to consumption of clotting factors
- Disseminated intravascular coagulation (increased INR and PTT with low platelets)

Metabolic:

- Lactate >2 mmol/L
- Increased bilirubin

SEPSIS DIAGNOSIS

Simplified 2001 to 2016 Sepsis Definitions:

For more than 15 years, sepsis was defined along a continuum of severity by applying the criteria of SIRS, Sepsis, Severe Sepsis and Septic Shock to a clinical presentation as follows:

1. Does the patient have 2 or more criteria of **SIRS.**

   2 or more of the following due to injury
   - heart rate > 90
   - respiratory rate > 20 or $PaCO_2$ < 32
   - T > 38.3 C or < 36 C
   - WBC >12,000 or < 4,000
     or >10% immature (bands)

2. If yes, is the presumed cause of the SIRS and infectious process?

3. If a patient has SIRS due to infection, they have **SEPSIS.**

4. If a patient with SEPSIS has any organ dysfunction, they have either **SEVERE SEPSIS** or **SEPTIC SHOCK.**

   - **SEVERE SEPSIS:** Organ dysfunction including hypotension due to infection that is responsive to fluid

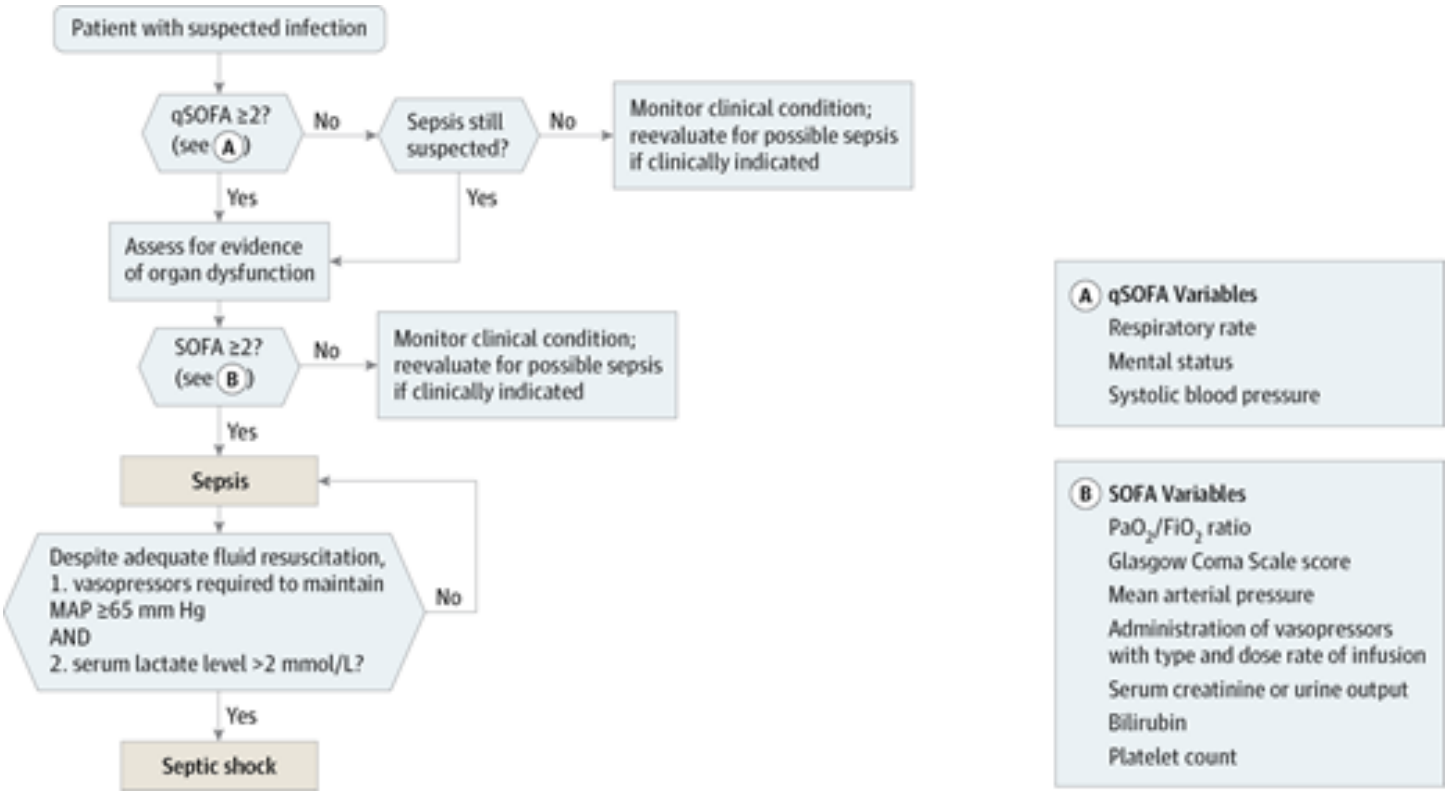
   - **SEPTIC SHOCK:** Organ dysfunction including hypotension that is not corrected by adequate fluid replacement and required vasopressor support

SEPSIS-3 DEFINITIONS 2016

The third of 3 international consensus guidelines for the definition of Sepsis was published in February 2016, modifying the long-standing definitions. The most notable changes are: 1. the removal of SIRS criteria; 2. the removal Severe Sepsis; 3. a change in the definition of "Sepsis". Only the concepts of Sepsis and Septic Shock remain.

The new recommendations **define sepsis** as life-threatening organ dysfunction due to a dysregulated host response to infection. **Septic shock** is **defined** as a subset of **sepsis** in which particularly profound circulatory, cellular, and metabolic abnormalities substantially increase mortality.

The 2016 definitions are as follows:



Singer, M et al. 2016 JAMA

<u>qSOFA > 2</u>

- RR $\geq$ 22
- SBP $\leq$ 100
- Altered Mental Status

Simplified Definition:

1. **Sepsis:** Organ failure due to an infection that is responsive to fluid

2. **Septic Shock:** Organ failure due to an infection that is not responsive to fluid, has a MAP $\leq$ 65 and lactate $\geq$ 2

Key points regarding sepsis include the following:

- Sepsis is the primary cause of death from infection especially where recognition and/or treatment is delayed
- Syndrome influenced by pathogen and host factors identified by dysregulated response and organ dysfunction
- Should be considered in any patient with infection or with unexplained organ dysfunction

Previous Guideline Limitations

- Excessive focus on inflammation
- Misleading model that sepsis follows a continuum
- Lack of sensitivity and specificity of SIRS criteria

Problems and Controversies

Over the past 15 or more years, there have been extensive international efforts to promote the early recognition and management of sepsis (based on the SIRS, Sepsis, Severe Sepsis and Septic Shock Model). Many organizations have invested heavily in education and early warning systems or checklists to increase uptake. Early warning systems that detect SIRS criteria provide a prompt to care providers to consider whether infection could be the cause. The goal is earlier recognition and intervention.

What about SIRS?

The new definitions have removed the SIRS criteria because it lacks specificity (many things can cause SIRS criteria other than infection). It shifts the focus from "hunting" for infection when SIRS criteria are identified, to identifying organ dysfunction (hypotension, mental confusion and/or tachypnea) after infection has already been diagnosed. This has an important inherent risk…identifying organ failure once a patient has been diagnosed with infection has not been our biggest problem. Delayed recognition often occurs because we didn't consider infection as one of the possible causes. While the new definitions are based on a lower risk for mortality among patients who don't present with organ dysfunction, this might change if the urgency of treating infection loses its importance and we allow more patients to progress to organ failure because of delayed recognition.

Understanding SIRS has value. While many patients who are admitted to critical care will meet SIRS criteria, knowledge of the systemic response helps us to appreciate why blood pressure often falls and fluid boluses are required after surgery. It helps us to appreciate why patients with inflammatory conditions like trauma, cancer or post surgery have increased risk for thrombosis. It provides rationale for fever or WBC elevations after traumatic injury, and provides a basis for understanding treatment requirements. More importantly, while patients admitted with a

traumatic event will surely meet the definition of SIRS, resolution and subsequent redevelopment of criteria provide important markers to begin the hunt for infection.

What is Organ Dysfunction?

Organ dysfunction scoring tools exist to provide consistency around the definition of organ dysfunction for the purpose of research or statistical analysis. These tools are not specific to sepsis or any other cause for organ dysfunction. They have limited utility in the clinical setting; the diagnosis of organ dysfunction is made at the bedside and not by entering criteria into a scoring calculator.

The 2016 definitions is based on a Sequential Organ Failure Assessment (SOFA) score. This is a tool that has been around for many years and is used most frequently in Europe. The classification of cardiovascular dysfunction includes an assessment of vasoactive drug use. This criteria alone has important error potential; the drug choice does not define the severity of the shock and the drugs listed in the SOFA score do not reflect current clinical practice (particularly for Septic Shock). Organ dysfunction scores are collected for all patients admitted to critical care units in Ontario based on the Multi Organ Dysfunction Score (MODS). Data are entered into the Critical Care Information System (CCIS) database, but this information is not used for diagnosing a clinical condition.

Sequential [Sepsis-Related] Organ Failure Assessment Score

	0	1	2	3	4
P/F ratio	≥400	<400	<300	<200 with respiratory support	<100 with respiratory support
Platelets	≥150	<150	<100	<50	<20
Bilirubin	<20	20-32	33-101	102-204	> 204
MAP	≥70	<70	Dopamine <5 or dobutamine (any dose)*	Dopamine 5.1-15 or epinephrine ≤ 0.1 or norepinephrine ≤ 0.1*	Dopamine > 15 or epinephrine > 0.1 or norepinephrine > 0.1*
GCS	15	13-14	10-12	6-9	<6
Creatinine	<110	110-170	171-299	300-440	440
Urine Volume				<500 ml/day	<200 ml/day

*Catecholamines in μ/kg/min for at least one hour

Record the worst score for each physiological variable in 24 hours

Multiple Organ Dysfunction (MODS) Score					
	0	1	2	3	4
P/F ratio	300-1000	226-300	151-225	76-150	0-75
Platelets	>120	81-120	51-80	21-50	≤20
Bilirubin	≤20	21-60	61-120	121-240	>240
Pressure adjusted HR (HR*CVP/MAP)	0-10	10.1-15	15.1-20	20.1-30	30.1-300
GCS	15	13-14	10-12	7-9	≤6
Creatinine	≤100	101-200	201-350	351-500	>500

Is it Sepsis or Sepsis?

There are two distinctly different definitions for the term “Sepsis”. The pre 2016 definition is the presence of SIRS criteria due to infection (without organ dysfunction. The post 2016 definition is organ dysfunction due to infection.

Diagnostic Limbo

The 2016 definitions have not received widespread adoption. The Canadian Critical Care Society has not officially accepted them and organizations. Centres that have well established and effective SIRS-based warning systems may be unwilling to change. Most importantly, we are no longer “talking the same language”. There is significant risk for diagnostic confusion.

Recommendation

- Continue to provide education on SIRS
- When using the term “Sepsis”, use language that makes it very clear what you mean by describing the patient as “Sepsis with organ failure” (2016) or Sepsis without organ failure (pre 2016)

Management of Sepsis and Septic Shock

Within Hour 0-1

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

By the End of the First Hour:

- ✓ **Manage Shock (ABC/CABs)**
  - 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 elevated
  - Intubate, ventilate and provide PEEP before overt failure develops
  - Give isotonic or balanced salt solutions. Give 30 ml/kg over 3 hours, and then carefully reassess to determine volume status
  - CVP target 8 to 12.

Endpoints:

- HR <100
- MAP≥65
- U/O >.5 ml/kg
- ScvO2 ≤ 70%

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.

While fluid resuscitation remains one of the first line interventions for the management of Sepsis (along with antimicrobials), there is increasing concern that too much may be equally harmful. Over resuscitation can prolong ventilation days and produce a host of edema induced problems including organ dysfunction due to compartment syndrome of the abdomen.

While early and rapid fluid replacement continues to be the priority, a less liberal and more thoughtful approach to fluid resuscitation is now recommended. This includes the prompt administration of fluid until 30 ml/kg have been given. Early use of vasopressors if needed to support blood pressure are also encouraged. Once 30 ml/kg of isotonic or balanced salt solutions (normal saline, ringers lactate or plasmolyte solutions) have been given, the patient's volume status should be carefully reassessed. Note: 30 ml/kg is the point for reassessment; some patients may still need more!

Bedside ultrasound is available in many centres and can add valuable data to the assessment (dynamic assessment). CVP (static assessment), urine output trends, pulse

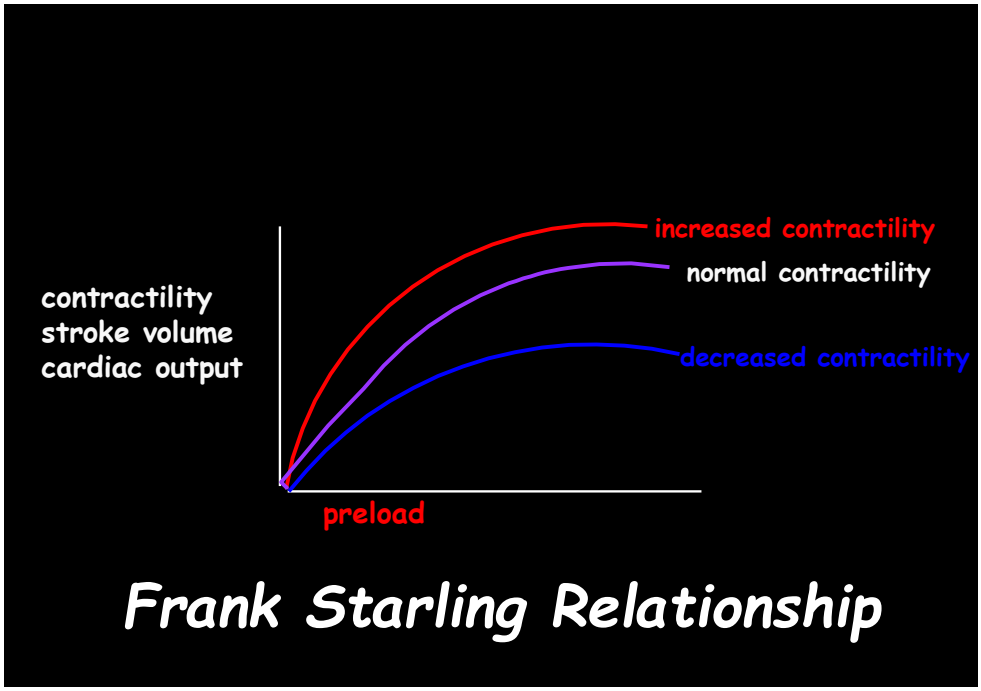
contour/arterial waveform analysis, urine sodium and fluid challenge responsiveness are strategies used to help inform practitioners.

Currently, there is no clear benefit associated with one type of resuscitation fluid versus another. Current recommendations are to begin by giving crystalloid solutions. Fluid resuscitation should never be done with dextrose containing or hyponatremic solutions. If additional fluid is required, albumin can be considered in sepsis and ARDS. Starch solutions should not be used (associated with increased renal failure and mortality).

Finally, there is some evidence that a conservative approach to fluid management may be safe and not associated with renal failure as long as urine output is maintained > 0.5 ml/hour and the patient is not hypotensive. A more restrict approach to fluid is usually introduced at ~72 hours and may include furosemide to achieve a neutral fluid balance.

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 $ScvO_2$.



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 ($ScvO_2$). $ScvO_2$ 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. Alternatively, in mechanically ventilated patients, a variance of > 10-15mmHg between inspiration and expiration in Systolic Blood Pressure may suggest hypovolemia. Variability due to irregular heart rhythm should first be ruled out.

Bedside echocardiogram is being used with increasing frequency. A quick assessment of the Inferior Vena Cava to ensure it is open (intravascular volume adequate) and not collapsed can confirm the adequacy of fluid replacement. A full heart with evidence of poor contraction on echocardiogram indicates the need for inotropic therapy.

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 and epinephrine are associated with significant tachycardia.

If shock persists despite norepinephrine, vasopressin should be considered at a maximum dose of 0.03 u/min (1.8 u/hr)

✓ **Obtain Labs**

Think of how you will assess for organ dysfunction when ordering labs. In addition to identifying current organ dysfunction, labs provide a baseline assessment to monitor future trends:

- Lytes (assess bicarb and lytes)
- CBC with platelets and differential (to look for neutrophils/L shift or bands)
- Urea, creatinine
- Bilirubin, LFTs
- Liver function tests
- Blood gases (venous can be used to determine acid base balance)
- 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).
- Ensure sufficient volume of blood for culture based on your lab recommendation
- Collect simultaneous cultures from a peripheral sample and indwelling line if venous catheter infection is considered. Arterial lines can be the source of infection.
- 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.
- TPN promotes fungal growth, a potentially lethal and difficult to irradicate infection. Ensure diligent

✓ **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.

- Consider whether broad spectrum coverage should include antifungal (e.g., cancer patients) (~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. Pipercillin or Pipercillin/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**
• Amoxicillin,/penicillin	• Can be given IV direct
• Cephalosporins	• Can be given IV direct
• Imipenem/Meropenem	• Can be given IV direct
• Pipercillin or Pip/Tazo	• Give over a minimum of 30 minutes Note: administration over 5 minutes is reported to be safe by manufacturer.
• Cipro	• Give over a minimum of 60 minutes for peripheral IV/30 minutes for central
• Levofloxacin	• Give 500 mg over a minimum of 60 minutes; 750 mg over 90 minutes
• Metronidazole	• Give over minimum of 30 minutes
• Vancomycin/aminoglycocides	• 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 $ScvO_2$.
- ✓ **Monitor Central Venous blood gases** ($S_{cv}O_2$) **q 30-60 minutes or continuously until stable**
  - $S_{cv}O_2$ 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 PaO_2 ~40 mmHg).
  - $S_{cv}O_2$ 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 u/min).
  - Doses >.03 u/min (1.8 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 catacholamines 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 may be considered for patients with Septic Shock and poor response to fluid and pressors
    - hydrocortisone 50 mg QID plus fludrocortisone .1 mg/day

    or

    - hydrocortisone 100 mg T.I.D.
  - 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.
  - During weaning/discontinuation, monitor for return of hypotension (indication that adrenal suppression is present and the need for ongoing steroids)

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✓ **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 appears that worse outcomes were due to hypoglycemia; was he protocol the issue?
  - 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 may 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 no 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).

Ongoing Management and Prevention of Complications:

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

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

- ✓ **Maintain goal-directed therapy**

- ✓ Initiate early enteral feeding

- ✓ Provide GI prophylaxis: Shock and GI hypoperfusion provides the greatest ongoing risk for GI bleeding, along with mechanical ventilation > 72 hours.

- ✓ Maintain protective lung ventilation strategies as patients with organ dysfunction typically have ARDS
  - Pulmonary manifestation of SIRS should be managed with lung protection strategies.

- ✓ VAP prevention bundle

- ✓ Central Line Infection reduction bundle

- ✓ DVT prophylaxis

- ✓ Promote patient comfort

- ✓ Support the patient and family

- ✓ Remove lines and tubes when no longer needed, early mobilization

WEBSITE:

Surviving Sepsis Campaign:
http://www.survivingsepsis.org

Watch for 2012 Surviving Sepsis Guidelines

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