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Surviving Septic Shock in the Operating Room and Beyond: What Do the Guidelines Say?

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Stem Case and Key Questions Content

A 58 year-old woman is brought to the Emergency Department (ED) because of changes in mental status and severe abdominal pain. The patient has a history of paroxysmal atrial fibrillation, hypertension and COPD. She is confused and unable to give a coherent medical history. She has no gross neurological deficits. BP 70/45, HR 110, irregular, RR 26, SpO_2 94%. Abdominal exam is positive for signs of peritoneal irritation. Lactate level is 6 mmol/dL. A surgical team has scheduled this patient for emergency exploratory laparotomy.

1. How would you determine the cause of hypotension in this patient?

2. Assuming the patient has an arterial line, would it be helpful in the assessment of volume status?

3. How can you assess fluid status with bedside transthoracic echocardiography?

4. What anesthetic induction agent would you select for this patient? Discuss controversy surrounding the use of etomidate in these circumstances.

5. What type of intraoperative monitoring would you use for this case?

6. What are the hemodynamic end-points of resuscitation? Are there specific guidelines regarding MAP, CVP, Hct? How much and what kind of fluid would you administer prior to induction of anesthesia?

7. The nurse notifies you that the patient did not receive any antibiotic in the ED. What would be your approach to perioperative antibiotic administration? How does it affect prognosis and outcome?

8. After induction of anesthesia the MAP remains below 50 mmHg despite fluid resuscitation. How and when will you administer vasoactive medications? Would you use a pressor or an inotrope as the initial choice? Which one and why?

9. Amiodarone has been administered for treatment of atrial fibrillation with rapid ventricular response and patient has converted to normal sinus rhythm. How can we use goal directed fluid therapy and dynamic markers of resuscitation for this patient?

10. Are there any long-term effects related to the choice of fluid for resuscitation in this patient? Is there a role for the new generation starches? What about albumin?

11. Peak airway pressures are increasing up to 40 cmH_2O. What is your ventilation strategy for this patient? What are the goals of ventilation in the septic patient?

12. Infusions of norepinephrine and vasopressin are started; CVP is now 18, Hct 27, MAP still below 60mmHg. How would you interpret? Is there a role for TEE in this setting? If yes, what are you looking for?

13. You decide to proceed with a TEE exam. Posterior and posterior-lateral wall motion abnormalities are noted. What is the most likely etiology for this finding? How would it alter your therapy?

14. Dobutamine is added for sepsis induced myocardial dysfunction.
The patient remains hypotensive. In addition to pressors and inotropes which other pharmacological interventions you would consider in sepsis?

Model Discussion Content
Sepsis and septic shock are major healthcare problems with high morbidity, mortality and enormous socio-economic cost. Frequently patients with sepsis or septic shock are taken to the operating room for “source control.” According to the 2012 International Surviving Sepsis Campaign Guidelines source control should be achieved within 12 hours of *initial* presentation. This frequently entails surgical intervention. Therefore anesthesiologists should be intimately familiar with the management of these conditions. Most of the Sepsis Campaign recommendations have supportive evidence and significantly improve outcomes. Nowadays we see constant focus on care outcome and cost. The importance of adhering to this well-established, evidence-based approach in management of septic patients in the operating room cannot be overemphasized.(1)

Hemodynamic changes in sepsis.
Sepsis and septic shock result in profound hemodynamic changes that anesthesiologists need to recognize and promptly treat. In the early stages of septic shock, also called warm shock, there is significant decrease in systemic vascular resistance (SVR) and an increase in cardiac output (CO). These changes usually lead to a decrease in systemic blood pressure. Intravascular fluid volume is frequently depleted due to increases in capillary permeability, diminished oral intake or vomiting.

In late sepsis the clinical picture may be reverse. There is peripheral vasoconstriction and decreased CO. It is important do distinguish the stage of sepsis because treatment options would vary accordingly. In the early stage vasoconstrictors, such as norepinephrine, would be preferable. In the late stages inotropes, like dobutamine, may be a better choice. Inflammatory mediators and toxins may lead to myocardial depression with further decreases in cardiac output.

The degree f sepsis induced myocardial depression is frequently underestimated. In some studies patients who had normal baseline cardiac function had a decrease in ejection fraction of

up to 30%. In elderly patient with coronary artery disease wall motion abnormalities can be due to ischemia or the depressant effects of inflammatory mediators. In such cases, a transthoracic (TTE) or transesophageal echocardiogram (TEE) may reveal a decrease in ejection fraction and an increases in left ventricular end-diastolic volume and left ventricular end-systolic volume. The use of bedside TTE to determine preload and contractility in septic patients prior to induction of general anesthesia may prove to be the most valuable tool of preoperative assessment. Perioperative use of Focus Assessed Transthoracic Echocardiography (FATE) is gaining popularity in perioperative arena, especially in Europe and Australia. This protocol is based on 5 transthoracic views, which can be obtained easily after limited training or some expertise in transesophageal echocardiography and may rapidly provide valuable information. With the ubiquitous availability of portable ultrasound machines due to rapid expansion of ultrasound guided regional anesthesia and vascular access, perioperative physicians should utilize this technology for hemodynamic assessment, especially in the settings of emergent surgery. The size of the inferior vena cava on bedside TTE and its collapsibility with respirations in a spontaneously breathing patient are well-established and sensitive predictors of intravascular fluid volume and preload. Size and contractility of cardiac chambers in subcostal or apical 4-chamber view may provide a rough estimate of intravascular fluid status and, more importantly, aid in assessment of contractility and ejection fraction. This may be crucial information prior to induction of general anesthesia and would help to make decision regarding fluid expansion, placement of pre-induction central access, initiation inotropes or vasopressors. According to recent study of patients admitted for emergency non-cardiac surgery FATE TTE performed by anesthesiologist has changed management plan in 44% of the patients.

Induction of general anesthesia in a patient with septic shock.
All induction agents may produce profound hemodynamic effects in septic patients. There is an increased risk of cardiovascular toxicity due to decreased circulating volume, depressed myocardial function, and sepsis induced adrenal suppression. Use of conventional doses of ANY induction agent may lead to cardiovascular collapse on induction.
Propofol has the most profound effects on hemodynamics in septic patients. Even when reduced doses are used this agent may lead to myocardial depression, vasodilation, and abolished baroreceptor response leading to hemodynamic collapse during induction.
Ketamine may produce more stable conditions because of its sympathomimetic properties. Unfortunately, it also has direct depressant effects on the myocardium. Patients in septic shock have depressed myocardial function and increased circulating catecholamines. There is a prevalent opinion that in this group ketamine may lead to a profound hypotension and even hemodynamic collapse on induction due to predominance of its depressant effects. Cardiodepressant effects of ketamine have been demonstrated in canine studies with doses, which were 10-fold higher comparing to conventional induction dose. There are few studies to show either superiority on non-inferiority of ketamine vs etomidate in humans. Some case reports described hemodynamic collapse after induction with ketamine. It is difficult to ascertain if it was because of ketamine itself or initiation of positive pressure ventilation, exacerbation of acidosis etc.

Etomidate is frequently selected as the induction agent of choice in unstable patients. However, there is ongoing debate regarding clinical significance of etomidate's adrenal suppression. Studies in patients that received etomidate demonstrated higher vasopressor requirements, higher mortality rate, and increased incidence of adrenal insufficiently demonstrated by cosyntropin stimulation test Use of supplemental corticosteroids in this setting makes intuitive

sense. Although currently there is insufficient evidence, some experts suggest low-dose steroid supplementation after intubation with etomidate in the ICU or ED. Resent double blinded randomized controlled trial showed that prophylactic use of steroids in patients without septic shock in this setting failed to produce any improvement in outcomes, although norepinephrine requirements were reduced.(7)The American Heart Association no longer recommends etomidate for endotracheal intubation of pediatric patients in septic shock. Most recent retrospective data base analysis compared induction with propofol vs etomidate and showed significantly increased 30-day mortality in etomidate group. Because of the nature of retrospective studies it is difficult to ascertain if etomidate causes above-mentioned effects or serves as a marker of illness severity.

Without prospective studies this debate is unlikely to be resolved. Clinicians should be aware of long-term effects of etomidate and minimize its use if possible.

Fluid resuscitation

Fluid resuscitation is a mainstay of early goal-directed therapy in septic shock.(5) There is no outcome benefit of colloids over crystalloids in this setting. Normal saline, which is frequently used in ED settings, may lead to hyperchloremic metabolic acidosis. This may cause confusion in the interpretation of arterial blood gases and acid-base status. Newly published prospective study compared used chloride liberal (normal saline) vs chloride restricted solutions in ICU has demonstrated increased incidence of renal failure in chloride liberal group. While additional studies are pending it is prudent to select resuscitative solutions with lower chloride concentrations such as Lactated Ringer or Isolyte.

Initial fluid bolus of 30ml/kg has been suggested to begin resuscitation of septic patient. If it fails to restore adequate mean arterial pressure (MAP) >65mmHg practitioner should strongly consider initiation of vasopressors in addition to ongoing fluid resuscitation.
There is concern regarding the use of low molecular weight starches for resuscitation in septic patients. Several recent studies showed an increased incidence of acute renal failure and use of renal-replacement therapy if low molecular starches are used instead of crystalloids for resuscitation in septic patients. Therefore, at this time low molecular weight starches have no role in goal-directed therapy in sepsis. Despite unproven outcome benefit, some authors have advocated albumin as a colloid of choice due to its safety record in the setting of septic shock and it mentioned as an alternative to crystalloid in latest addition of the guidelines.

Transfusion strategy

If resuscitative goals cannot be achieved with fluid and vasopressors, pack red cells should be administered to achieve a central venous oxygen saturation ($ScvO_2$) >70% or hemoglobin (Hb) of 7-9 g/dL. It's important to notice that Hb of 10 (hematocrit 30) is no longer recommended as transfusion goal for a patient in septic shock.

Monitoring septic patient in the OR

Specific hemodynamic goals have been suggested as part of the comprehensive treatment of sepsis. They include the following (should be achieved within 6 hrs of presentation):

- Central venous pressure(CVP):
    - 8-12 mm Hg in a spontaneously breathing patient
    - 12-15 mm Hg in a patient receiving positive pressure ventilation or with decreased left ventricular compliance

- Mean arterial pressure greater than 65 mm Hg
- Central venous saturation grater than 70%
- Urine output greater than 0.5ml/kg/hr

Use of CVP, which is a static parameter of resuscitation, is one of the most controversial points in the guidelines. There are numerous studies demonstrating poor or no correlation between CVP and intravascular volume status. It seems that because of international status of the guidelines, familiarity with CVP monitoring worldwide and lack of universally accepted alternatives this modality was included.

It is important to point out that central venous, not mixed venous saturation is used. Mixed central venous oxygen saturation, Scv02, has been used for early goal directed therapy of septic patient over the last 2 decades, since land-mark study of Rivers et all. Interpretation of Scv02 values requires thorough understanding of sepsis physiology and normal hemodynamics. Scv02 used as a surrogated of SvO2 (mixed venous oxygen saturation) to assess global oxygen delivery and consumption. In the healthy patient there is minimal or no difference between values of Sv02 and ScvO2 (normal ScvO2 around 75%). It's important to remember that actual position of the tip of CVP catheter (right atrium vs SVC) significantly influences these differences. If the tip of CVP is in the right atrium difference of ScvO2 and SvO2 in healthy patient is minimal. If the tip is located in SVC - ScvO2 will be slightly less than right atrial Scv02 or SvO2 due to lower oxygen extraction ratios from kidneys and gut in healthy patients. For patient in shock reversal of this ratio is observed, with ScvO2 being 5-18% higher than SvO2. Higher contributing fraction of desaturated blood from coronary sinus as well as redistribution of blood flow from splachnic to cerebral and renal circulation explains these findings. Therefore in shock states ScvO2 consistently overestimates true SvO2. In Surviving Sepsis Campaign guidelines Scvo2 of >70% is used as one of the targets for goal-directed therapy.

Pulmonary artery catheters are no longer recommended for routine use in septic patients but may have a role in patients with multisystem organ failure.

The parameters listed above have been chosen because of availability and international familiarity. Although in the operating room more advanced monitoring techniques are available (e.g., systolic or pulse pressure variation, transesophageal Doppler, transesophageal echocardiogram, etc.) these devices are not universally available and often require some expertise for interpretation. Use of above described dynamic parameters if available is encouraged in newest version of the guidelines.

Intraoperative TEE remains a gold standard for assessment of hemodynamic instability unresponsive to conventional interventions. When equipment and expertise are available TEE should used if patient fails to improve after initial conventional approach. In addition to assessing volume status TEE may provide valuable information regarding ejection fraction and contractility. When sepsis induced myocardial depression is present, dobutamine infusion may be used to increase oxygen delivery.

Role of Vasopressors
Norepinephrine is recommended as a first-line agent for treatment of septic shock, which is defined as hypotension (MAP<65mmHg) unresponsive to fluid resuscitation. Vasopressin is not recommended as initial therapy. Low-dose vasopressin infusion (0.04Units/min) can be added

to norepinephrine and has been shown to decrease overall dose of norepinephrine but did not affect clinical outcomes. Epinephrine now listed as an alternative to norepinephrine and can be added or substitute epinephrine if hemodynamic goals cannot be achieved. Dopamine is recommended only for patients who have septic shock and symptomatic bradycardia.(3)
In late stages of sepsis inotropic support with dobutamine is recommended to increase CO and oxygen delivery. This therapy should be guided by monitoring CO via dynamic markers of resuscitation (commercial CO monitors based no arterial waveform analysis) or intraoperative TEE.

Ventilation strategies
Patients with septic shock are at high risk to develop acute respiratory distress syndrome (ARDS) or acute lung injury (ALI). ALI defined as a ratio of arterial oxygen concentration to fraction of inspired oxygen (PaO_2/FiO_2) less than 300, and ARDS less than 200. This nomenclature was changed recently and acute lung injury named mild ARDS. There is no evidence of superiority of one mode of ventilatory support over another in ARDS. Low tidal volume mechanical ventilation (4-6ml/kg of ideal body weight) with target plateau pressures <30 cm H_2O and increased levels of positive end-expiratory pressure (PEEP) are the cornerstones of a lung protective strategy. Even a few hours of non-adherence to this strategy may unfavorably affect long-term outcome. Recent prospective randomized trial of intraoperative lung-protective strategy ventilation in moderate and high-risk surgical patients has demonstrated decreased incidence of pulmonary complication and shorter hospital stay. Transmural pressure, which is intra-alveolar pressure minus pleural pressure, is a determinant factor of barotrauma. If a patient has decreased chest wall compliance due to obesity or increased intra-abdominal pressure, the target plateau pressure that exceed 30 cmH_2O may be needed to maintain adequate minute ventilation, assuming tidal volumes of 4-6ml/kg are used.(4)

Minimizing FiO_2 to avoid oxygen toxicity and absorption atelectasis is another important maneuver that is frequently overlooked in the operating room. There is a growing body of evidence to suggest that arterial hyperoxia, even for relatively short period of time (defined in one of the studies as 2hrs) may increase long-term mortality comparing to normoxia or even hypoxia. Patient who had in-hosptial cardiac arrest and patients who had cancer related abdominal surgery have been shown to be particularly vulnerable to the toxic effects of high FIO2, which was linked to increased odds ratio of death. It seems that supraphysiologic arterial concentration of pO_2 (defined in one study as >300mmHg) is the major detrimental factor. Therefore patient who have no or minimal damage to the lungs and have normal gas exchange and high P/F ratio would be at greater risk that patients with severe ARDS and significant impairment of gas exchange. Arterial saturation should usually be maintained between 94-99%. A saturation of 100% is unnecessary and should be avoided. In severe ARDS saturations above 88% are adequate. There are at least 3 positive randomized controlled trials that showed decreased incidence of postoperative wound infections with high perioperative FiO2 (80%). However, the largest and the most recent trial on patients undergoing elective or emergent exploratory laparotomy showed no reduction in surgical site infection and statistically significant increase in mortality in cancer patients.

Occasionally septic patients will develop ARDS so severe that adequate oxygenation might be difficult to achieve. In these circumstances liberal application of PEEP up to the levels of 15-20cmH_2O may be necessary, with monitoring of P_{plt}. Other methods such as recruitment maneuvers, increasing I:E ratio, changing to pressure controlled ventilation all lead to

improvement in oxygenation by increase in mean airway pressure. If proper lung protective strategy is applied, patients may develop hypercapnea. This approach is described as "permissive hypercapnea" in ARDS literature and is usually well tolerated, not requiring treatment unless pH decreases below 7.15.

Rarely conventional lung protective strategies may not be feasible postoperatively due to either high FiO_2 requirements or high mean airway pressure. Less conventional modes of mechanical ventilation should be considered as a rescue therapy. Choice of specific mode would depend on institutional availability and familiarity.

APRV (Airway Pressure Release Ventilation) has been shown to improve oxygenation, but not clinical outcome of severe ARDS. It is a time-triggered, pressure-limited and time-cycled mode of ventilation that allows the patient to breath spontaneously throughout the ventilator cycle. The bulk of the ventilator cycle is spent in high-pressure (P_{high}) with a release period at the low-pressure (P_{low}). The time in each phase is controlled with the T_{high} and T_{low} duration setting. Spontaneous breathing must occur throughout this entire ventilatory cycle. If the patient does not breathe spontaneously, APRV mode will become essentially inverse ratio ventilation, negating the beneficial effects. Therefore, it has limited utility in the immediate postoperative period in the presence of decreased/absent respiratory effort. As respiratory effort is regained, this mode may be initiated in the ICU.

HFOV is a subtype of High Frequency Ventilation (HFV) and functions by using a piston pump to oscillate at very high frequency (180-600 breaths per minute or 3-10 Hertz) with fresh gas flow delivered at 30-60L/min. This functionally results in a rapid delivery of very small tidal volumes with application of high mean airway pressures. Two recent randomized prospective clinical trials comparing HFOV to conventional lung-protective strategy ventilation failed to show any clinical improvement. One trial showed no improvement in morbidity or 28 day mortality in the HFOV group; another one had to be terminated prematurely due to higher mortality in the HFOV group. This recent data questions routine use of HFOV in the adult population, although it still may have a role as a rescue modality in the settings of refractory hypoxemia.

Antibiotic administration

Timely initiation of appropriate antimicrobial therapy is essential for improved outcomes. Mortality from sepsis increases in direct proportion to every hour of delay of appropriate antibiotic administration.(6) Sometimes antibiotics are not administered in the emergency room due to insufficient vascular accesses. If antibiotics have been administered, time for re-dosing should be noted and medications ordered from pharmacy. Empiric broad-spectrum coverage should be initiated immediately after cultures are obtained. However absence of cultures should not delay initiation of therapy. Antibiotic regimen usually consists of a combination of vancomycin and a carbapenem or antipseudomonal penicillin. Consultation with the intensivist or surgeon should be sought regarding appropriate empiric antimicrobial therapy.

Role of steroids in the operating room

Hydrocortisone is recommended for use in septic shock unresponsive to fluid resuscitation or vasopressors. In a recent trial steroid supplementation hastened shock resolution, but did not improve overall survival rate. In the operating room setting rapid reversal of shock is paramount. Hence if a septic patient is unresponsive to vasopressors and fluid resuscitation, hydrocortisone supplementation should be initiated. There is no evidence to support use of ACTH stimulation

test to differentiate who will benefit from steroids. The total dose of hydrocortisone should not exceed 200 mg over 24 hrs. Higher doses have no additional benefit and may be harmful.

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