Education Seeping Through Sepsis

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Sepsis is an infection-induced syndrome defined as the presence of two or more of the signs of the systemic inflammation response syndrome (SIRS):[1] fever or hypothermia; leukocytosis or leukopenia; tachycardia, tachypnea, or supra-normal minute ventilation; and the development of at least one organ failure (Figure 1). Each year, sepsis develops in more than 750,000 patients in the U.S., and approximately 60% of these patients survive.[2,3] Fortunately, the death rates in some subgroups of patients with sepsis have decreased, even before there were specific therapies.[3,4] This initial reduced mortality may have resulted from better detection and treatment of the underlying infection, or from improved supportive care. Many pharmacologic agents tested in large trials have not reduced overall mortality, however, they have dramatically expanded our knowledge of sepsis.[1,5]

In short, the development of inflammatory signals contributes to formation of diffuse micro-thrombi, and to subsequent end-organ hypoperfusion, and, finally, organ failure as an etiology for the poor outcome from sepsis.

The usual patient diagnosed with sepsis is elderly, on immunosuppressive medications, or with an immunocompromised condition (such as human immunodeficiency virus, underlying malignancy, or diabetes). This profile does not mean, however, that only these individuals are at risk. We do not fully understand the factors or genetic risks to allow for such an excessive inflammatory response to propagate. Sepsis can affect and cause death in the young, and in the previously healthy.

Rachel's dilemma

Rachel, 24, returned from India due to a recurrent episode of fever and rash. She is evaluated in the outpatient clinic. Radiologic evaluation of her abdomen demonstrated an enlarged, thick-walled gallbladder. Liver enzymes at this time were only non-specifically elevated. See box for lab results.

She was scheduled for elective laparoscopic evaluation of her hepatobiliary structures. The surgeon noted a hydropic gallbladder with exudative inflammation, which he wanted to remove. The organ was friable, however, and could not be removed. The procedure was converted to an open cholecystectomy to complete the removal. Before the surgery, Rachel was beginning to develop intermittent hypotension; her post-op was characterized by profound hypotension to 70/30 mmHg. She also had fever, tachycardia to a heart rate of 135 beats per minute (bpm), and hypoxemia with a respiratory rate > 40 bpm. Antibiotics were initiated, a chest X-ray was obtained, and ongoing fluid challenges were administered.

Within 5 hours she remained in shock. The hypoxemic respiratory failure then required intubation and mechanical ventilation, and her shock worsened.

Her physician requested a transfer to a tertiary care centre.

For a followup on Rachel, go to page 96.

Rachel's lab results:

Sodium: 132	Potassium: 3.9
Creatinine: 219	Urine output: < 0.5 mL/kg/hour
White blood count: 4.9	Hematocrit: 0.31

Blood gas pH 6.9 P_{CO2} 72 and P_{O2} 42 on FiO_2 0.9 and positive end-expiratory pressure 5 cm H_2O

What can you do for the septic patient?

There are therapeutic interventions which have produced dramatic reductions in septic mortality. These treatments may be different from previous standards of care, but should be considered a part of the care for all patients with severe sepsis.

Early, goal-directed therapy

The patient with sepsis often develops shock as a progression of the condition. The longer the shock persists, the more organ failures accumulate (due to organ hypo-perfusion) and contribute to mortality. Rivers et al. studied usual care compared to therapy directed by measures of tissue perfusion and oxygenation.[6] Usual care for septic shock would be the addition of vasoactive medications, such as norepinephrine or dopamine, with the infusion of intravenous crystalloid. These agents increase cardiac contractility and blood pressure by vasoconstriction. It is unclear if achieving a set blood pressure corresponds to improved organ perfusion. A mixed venous oxygenation (MvO_2) > 70% was the target for resuscitation, once adequate circulating volume (mean arterial pressure of 8 mmHg to 12 mmHg) and hemoglobin levels (> 30g) were attained. In this randomized trial, the use of MvO_2 as target demonstrated a 15% absolute reduction in mortality relative to usual care. This survival benefit corresponded to significantly more crystalloid being administered in the initial six hours of the hospital stay (even with the same volume in the first 72 hours), with dobutamine being administered instead of norepinephrine or dopamine. Early aggressive volume resuscitation in combination with dobutamine preserved organ function and reduced mortality.

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Activated protein C (APC) in severe sepsis

The detection of disseminated intravascular coagulation (DIC) in sepsis has been recognized as a predictor of poor outcome. The pro-inflammatory environment and cytokines, which characterize sepsis, predispose to the development of intravascular microthrombus, even prior to the clinical identification of DIC. APC is an anticoagulant protease involved in the regulation and balance of the coagulation cascade. APC levels have been identified as low in sepsis. In a study of subjects diagnosed with septic shock, 96 hours of APC infusion reduced absolute mortality by 6.4%, when compared to placebo infusion.[7] Most of the survival benefit was in the group of patients whose Acute Physiology and Chronic Health Evaluation (APACHE) II score was > 24, or with severe septic shock. The APACHE II is a score of physiology and acute illness, and predicts the mortality associated with a variety of conditions, including sepsis. Because of bleeding risks associated with thrombocytopenia occurring in some cases of sepsis, the use of APC should be restricted to patients with severe sepsis as defined by APACHE.

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Low tidal volume ventilation in acute respiratory distress syndrome (ARDS)

Ventilation was once thought to be only supportive of the respiratory failure common in sepsis. Information gathered clinically led some to believe that mechanical ventilation could also cause injury to the lung.[8] Radiographically, the injured lung in

Frequently Asked Questions

1. Who is at risk for developing sepsis and septic shock?

The elderly, persons with immunocompromised conditions, such as HIV disease, underlying malignancy, or diabetes, and people on immunosuppressive medications are at the highest risk of developing sepsis.

2. What is the burden of this condition on our population, and what is the associated mortality?

In Canada, there are 40,000 to 60,000 cases of sepsis each year, with a mortality of 40% to 80%.

3. What is the mechanism of the disease process?

After infection, the resulting development of inflammatory signals contributes to the formation of diffuse microthrombi, to subsequent end-organ hypoperfusion, and to organ failure.

4. What is the usual care for a patient with sepsis?

- Supportive care, including adequate nutrition
- Maintainance of the ABCs of acute illness including intubation, mechanical ventilation, fluid challenges, and vasoactive medications
- Antibiotics for documented or presumed infection.

5. Are there any new therapies that have been developed to improve the outcome of sepsis?

The roles for low tidal volume mechanical ventilation, activated protein C infusions, goal-directed resuscitation (to achieve an aggressive and early organ perfusion), steroids for shock, and tight glucose control have all recently been demonstrated to provide mortality benefit in sepsis.

sepsis looks like ARDS; it is composed of both injured and normal segments of airspace and parenchyma. The ARDSNet group of investigators developed a study protocol to identify whether or not lung "protective" strategies (*i.e.*, mechanical ventilation), and their subsequent prevention of organ failure, would improve sepsis-related mortality. This randomized, clinical study identified that using tidal volume ventilation of 6 mL/kg of ideal body weight/breath (when compared to 12 mL/kg/breath) produced an absolute reduction in mortality of approximately 9%. At the time of this study, 12 mL/kg tidal volumes were the usual care and the excess mortality caused by this procedure is thought to be due to over-expansion of the normal lung segments.

Steroids in septic shock[9] and tight glycemic control in sepsis[10] are two additional, adjuvant therapies that have demonstrated significant benefits in mortality. The addition of low-dose hydrocortisone combined with fludrocortisone, in patients that had an inappropriate adrenocorticotropic hormone response, produced an absolute reduction in mortality of 10%. Previously, hypoglycemia in intensive care unit (ICU) patients was a concern, and blood glucose was allowed to persist at a range higher than normal. However, a European study of surgical ICU patients demonstrated that "tight" control of serum glucose within the normal range provides an absolute reduction in mortality of approximately 10%.

The studies listed above have generated profound reductions in sepsis-associated mortality rates. It is unclear if the benefits of these studies are additive when used in combination. However, given the large risk of mortality with sepsis and septic shock, it is recommended to introduce protocols and care plans to incorporate these new clinical findings into the usual care of ICU patients. CME

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How to treat Rachel

What do you do?

Provide supportive care; check the ABCs (airway, breathing, circulation) of any acute illness, and look for the source of the inflammation, which is usually an infection.

Initiate antibiotics within the first 24 hours of sepsis. This early intervention has been demonstrated to reduce mortality. If the source of infection is identified it must be excised.

What happened with Rachel?

Rachel had another computed tomography scan upon arrival at the medical centre, which identified a possible leak from the common bile duct. Be cautious in tapering the antibiotic coverage too soon, as these patients can demonstrate multiple, positive microbiologic specimens and pathologic organisms.

As Rachel remained in shock, she was resuscitated according to the Rivers protocol, with 11 L of crystalloid being administered in the first 24 hours.

Dobutamine and norepinephrine in combination were used as vasoactive medications to maintain the mean arterial pressure > 60 mmHg and measuring mixed venous PO_2 > 70%.

Steroids were added to the antibiotics, until it was definite that Rachel was not adrenal deficient.

She was ventilated with positive end-expiratory pressure 12 cm H_2O and tidal volume of 6 mL/kg. She was fed enteral nutrition, and blood sugars were maintained by an insulin infusion protocol within the normal range.

Upon calculation of her APACHE II score, she received APC for 96 hours after she was 12 hours from the repair of her bile duct.

These interventions all occurred within her first day post-op. After 6 days of aggressive care in the ICU, she was no longer in shock, was liberated from mechanical ventilation, and was well into recovery.

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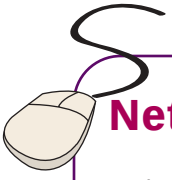

Net Reading

National Initiative in Sepsis Education
http://www.nise.cc/

www.stacommunications.com

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