Development and Implementation of a Multidisciplinary Sepsis Protocol

Kathy M. Picard, RN, MS, CCRN
Sharon C. O'Donoghue, RN, MS
Duane A. Young-Kershaw, RN, BSN
Kristin J. Russell, RN, BSN

Sepsis is a complex condition that is often life threatening. It is characterized by hematological derangements and a profound inflammatory response to an infection or injury. Despite recent advances in critical care, sepsis affects more than 750 000 patients and accounts for 215 000 deaths in the United States each year, at a cost of more than $16 billion.[1] Mortality in septic shock has decreased only slightly between 1970 and the late 1990s; it remains the most frequent cause of death in noncardiac intensive care units (ICUs). Septicemia is currently ranked by the Centers for Disease Control and Prevention as the 10th leading cause of death in the United States.[2(p27)] Incredibly, and perhaps more disturbing, severe sepsis is responsible for the deaths of more Americans than are colon, breast, prostate, and pancreatic cancers combined, and the mortality rate for sepsis is virtually equal to the rate for acute myocardial infarction (Figure 1).

Sepsis consists of a series of inflammatory and hemostatic alterations presumably caused by invasion of the bloodstream by micro organisms. However, a subset of critically ill patients have features characteristic of sepsis despite blood cultures that are repeatedly negative for microorganisms and no identified source of bacterial, fungal, or viral infection.[5] Trauma, surgery, burns, and illnesses such as cancer and pneumonia can trigger the onset of sepsis. In 1991, the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference[6] outlined definitions for systemic inflammatory response syndrome, sepsis, severe sepsis, septic shock, and multiple organ dysfunction syndrome (Table 1). These definitions have been widely adopted. They have allowed greater consistency in diagnosis and treatment and in tracking statistics on the incidence and occurrence of sepsis.

Patients vulnerable to sepsis may have a number of risk factors[7,8] (Table 2). Despite the wide variety of patients who initially have systemic inflammatory response syndrome, if

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Authors

Kathy Picard is the clinical nurse specialist, Sharon O'Donoghue is a clinical nurse educator, and Kristin Russell is a nurse manager in the medical intensive care units and Duane Young-Kershaw is the clinical nurse educator in the emergency department at Beth Israel Deaconess Medical Center, Boston, Mass.

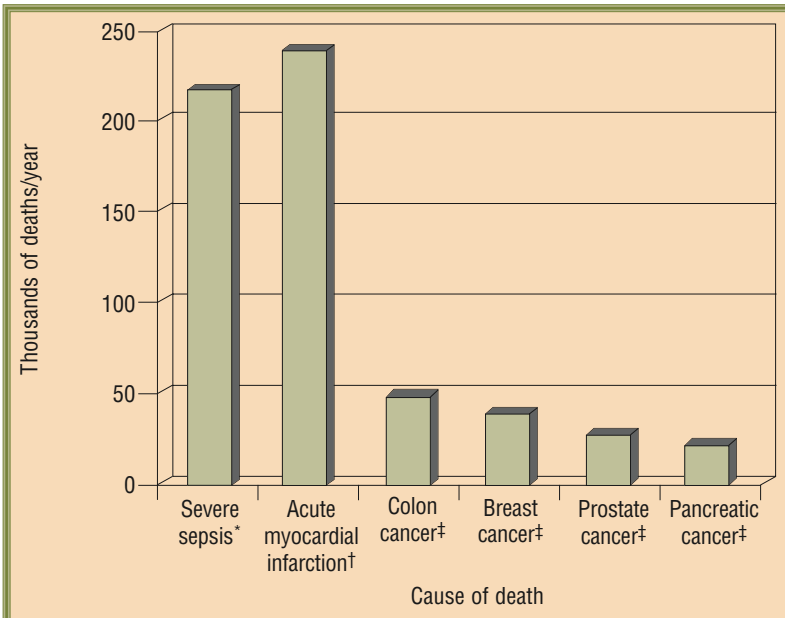

Figure 1 Comparison of mortality in the United States, by cause.

*Data from Angus et al.[1]
†Data from the Centers for Disease Control and Prevention, 2003.[3]
‡Data from the American Cancer Society, 2001.[4]

the syndrome is not self-limiting and progresses to sepsis, the disease progression is fairly homogeneous. Cellular mediators are produced early in the onset of sepsis and initiate a cascade of events, including activation of the coagulation and complement pathways, vasodilation leading to hypotension, endothelial dysfunction and fluid transudation, and generalized inflammation. A triad of events occurs, consisting of a profound inflammatory response, processes that promote coagulation, and impaired fibrinolysis. In healthy persons, homeostasis is maintained because these 3 mechanisms balance one another (see Sidebar 1).

Background of the Protocol

Treatment of sepsis is largely focused on supporting failing organ systems. Interventions include fluid replacement, airway management, antibiotic therapy, use of vasoactive medications, and hemodialysis. Various treatments used to improve patients' outcomes can paradoxically contribute to organ dysfunction. Examples of these treatments include the use of high-tidal-volume ventilation to improve oxygenation, which may cause barotrauma or damage of the lung parenchyma; use of antimicrobial agents that cause nephrotoxic effects; and hemodialysis in renal dysfunction, which may worsen a preexisting coagulopathy.

Recent studies have shown that early goal-directed therapy is beneficial to patients with sepsis.[10] Advances in the management of severe sepsis and septic shock have resulted in improved survival for these critically ill patients. Current management includes early goal-directed therapy,[10] activated protein C for severe sepsis,[11] intensive insulin therapy,[12] steroids for patients with adrenal suppression,[13] and protective lung ventilation.[14] Rivers et al[10] reported the use of early goal-directed therapy in patients entering the emergency department with sepsis or septic shock. The therapy, which included manipulating preload by using fluids and blood transfusions and manipulating oxygen delivery by using vasopressors, inotropic agents, and blood

Table 1 American College of Chest Physicians/Society of Critical Care Medicine consensus panel definitions[6]

Systemic inflammatory response syndrome (SIRS): SIRS is a widespread inflammatory response to a variety of severe clinical injuries. This syndrome is clinically indicated by the presence of 2 or more of the following:
- Temperature >38°C or <36°C
- Heart rate >90/min
- Respiratory rate >20/min or $Paco_2$ <32 mm Hg
- White blood cell count >12 x 10^9/L or <4 x 10^9/L, or with >10% immature (band) forms

Sepsis: In sepsis, the clinical signs of SIRS are present together with definitive evidence of infection.

Severe sepsis: Sepsis is considered severe when it is associated with organ dysfunction, hypoperfusion, or hypotension. The manifestations of hypoperfusion may include, but are not limited to, lactic acidosis, oliguria, and an acute alteration in mental status.

Septic shock: Septic shock is sepsis with hypotension despite adequate fluid replacement combined with perfusion abnormalities that may include, but are not limited to, lactic acidosis, oliguria, and an acute alteration in mental status. Patients who require inotropic or vasopressor support despite adequate fluid replacement are in septic shock.

Multiple organ dysfunction syndrome: Multiple organ failure refers to the presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention.

Table 2 Risk factors for the development of sepsis[7,8]

Extremes of age (<1 year and >65 years)
Malnutrition
Hypothermia
Use of central venous catheters
Endotracheal intubation/mechanical ventilation
Aspiration
Chronic illness
Diabetes
Renal failure
Hepatic failure
Immunodeficiency
AIDS
Alcoholism
Use of chemotherapeutic agents
Use of surgery or invasive procedures

transfusions, resulted a significant improvement in mortality. Mortality rates were 46.5% in the control group and 30.5% in the treatment group, for an absolute reduction in death of 16%.

At Beth Israel Deaconess Medical Center (BIDMC) in Boston, Mass, caregivers identified an opportunity to improve patients' care by initiating an aggressive treatment protocol early in the hospital course of patients who have sepsis. The BIDMC protocol incorporates early goal-directed therapy based on the study by Rivers et al[10] and includes use of antibiotics early on, activated protein C, steroids, insulin therapy, and protective lung ventilation. This comprehensive protocol was titled the Multiple Urgent Sepsis Therapies (MUST) Protocol. We chose MUST as a title for our protocol because the argument that these therapies must be delivered to patients with sepsis is compelling and because the approach incorporates several different therapies. A description of each of the therapies is provided in Sidebar 2. Table 3 summarizes nursing actions and expected outcomes for each of these

Sidebar 1: Pathophysiology of Sepsis

In patients with sepsis, inflammation, coagulation, and fibrinolysis are closely related, and the balance among them must be restored to improve outcomes.

Inflammation

Proinflammatory mediators, including interleukin-1 (IL-1), IL-8, and tumor necrosis factor (TNF), are activated to mount a normal immune response. These mediators act directly or indirectly through secondary mediators such as platelet-activating factor to attract leukocytes and circulating cytokines. Cytokines result in endothelial cell adhesion, activation of clotting, and generation of numerous secondary mediators that participate in the generation of fever, tachycardia, tachypnea, ventilation-perfusion abnormalities, and lactic acidosis.[5] Simultaneously, anti-inflammatory mediators, most notably IL-6 and IL-10, inhibit the generation of TNF in an attempt to balance the inflammatory response.[5] IL-4 is produced by activated T cells to suppress TNF and IL-1. IL-10 is synthesized by monocytes to inhibit inflammatory mediators and suppress procoagulant activity. This normal balance is lost in sepsis and the overwhelming proinflammatory response is left unchecked.

Endothelial cell damage and dysfunction increase vascular permeability. This increase leads to the expression of vasoconstrictors such as endothelin and vasopressin and vasodilators such as nitric oxide, bradykinin, and histamines. In addition, myocardial depressant factor is released from injured cells. These substances result in a maldistribution of blood flow and potential ischemia to end organs. Decreased perfusion at the tissue level causes further cellular injury, localized edema, and capillary leakage. Even if tissue perfusion is adequate, cellular uptake of oxygen is often inadequate because of dysfunctional mitochondria and other cellular disturbances caused by the effect of endotoxins.

Coagulation

The coagulation cascade can be initiated by a number of different mechanisms. In sepsis, as circulating cytokines, IL-1, and TNF damage the surface of endothelial cells, tissue factor is released, which can initiate the coagulation cascade.[7] Tissue factor stimulates the production of thrombin, which in turn facilitates the conversion of plasma fibrinogen to fibrin, leading to the formation of a stable fibrin clot.[7] Platelet activity is enhanced by circulating thrombin, which contributes to the prothrombotic state, compromising blood flow to organs. Thrombin and other factors of coagulation can also mediate systemic inflammation by releasing cytokines and by directly activating monocytes and macrophages. Clinical laboratory findings include increases in platelets, fibrin degradation products, and D-dimer, a marker of fibrin breakdown products, and decreases in the serum levels of fibrin and plasminogen.

Microaggregates of platelets, red blood cells, white cells, fibrin, and other cellular debris contribute to microcirculatory thrombosis, further impairing normal blood flow. Oxygen delivery to tissues is impaired despite adequate fluid replacement. As ischemic tissues are reperfused, oxygen metabolites are released that cause apoptosis, or programmed cell death, compounding the initial endothelial injury. Oxygen-free radicals may interfere with the contractile function of the heart, resulting in further decreased myocardial performance.

Impaired Fibrinolysis

The expected response to coagulation is activation of the fibrinolytic system to remove thrombi and preserve microcirculation. Tissue plasminogen activator is the primary enzyme responsible for fibrinolysis; it achieves its effect by converting plasminogen to plasmin. Plasmin is primarily responsible for degradation of fibrin clots. Plasminogen activator inhibitor-1 and thrombin-activatable fibrinolysis inhibitor are naturally occurring substances that guard against excess fibrinolysis.[7] With an infection, an excess of plasminogen activator inhibitor-1 impairs the normal fibrinolytic response.[9] Suppression of fibrinolysis coupled with activation of coagulation creates an excess deposition of fibrin in the microvasculature, leading to thrombus formation and organ dysfunction.

Table 3 Nursing actions and expected treatment outcomes

Treatment	Nursing action	Expected outcomes	Rationale
Fluid replacement	Assess fluid status, monitor CVP Administer 500-mL fluid challenge every 20-30 minutes	CVP is maintained at 8-12 mm Hg Urine output is >20 mL/h Lungs are clear	EGDT with fluid replacement can improve cardiac output, tissue perfusion, oxygen delivery and survivability in patients with sepsis[10]
Control of blood pressure	Monitor MAP Adjust dosage of norepinephrine if MAP <65 mm Hg after fluid replacement	MAP is maintained at >65 mm Hg	In EGDT, MAP >65 mm Hg improved outcomes in patients with sepsis[10] Use of norepinephrine may improve outcomes in patients with sepsis[17]
Tissue perfusion	Assess for evidence of adequate tissue perfusion (eg, heart rate, respirations, urine output, mentation) Monitor $Scvo_2$ Begin dobutamine infusion if $Scvo_2$ <70% after CVP and MAP corrected Monitor hematocrit	$Scvo_2$ is maintained at >70% Tissue perfusion is adequate as evidenced by urine output >20 mL/h, skin warm/dry, pulses palpable, normal mentation Give blood transfusion if hematocrit <0.30	EGDT guided by $Scvo_2$ monitoring can reduce mortality in patients with sepsis[10] Improving cardiac output and oxygen delivery to tissues improves outcomes in patients with sepsis[23]
Early treatment with antibiotics	Ensure that administration of anti biotics begins within 1 hour of patient's entry into the protocol Begin after samples sent for culturing	Therapy with broad-spectrum antibiotics begins early, and treatment is refined according to the results of cultures	Early antibiotic therapy can improve mortality rates in patients with sepsis[5]
Administration of steroids for adrenal insufficiency	Obtain a random blood sample for assay of serum cortisol level and then do a corticotropin stimulation test	Hydrocortisone therapy is started and maintained for patients who do not respond to the cortico-tropin test	Treatment with low-dose steroids significantly reduces the risk of death in patients with septic shock and adrenal insufficiency[13]
Control of blood glucose levels	Monitor blood glucose levels every hour Adjust dosage of insulin as needed	Blood glucose level is maintained at 4.4-6.7 mmol/L (80-120 mg/dL)	Tight glycemic control can improve outcomes in critically ill patients[12]
Protective lung ventilation	Monitor and assess patient for evidence of acute organ dysfunction Identify patients with ALI or ARDS	Patients with evidence of ALI will receive lower tidal volume ventilation Plateau pressures will be <30 cm H_2O	Lower tidal volume ventilation results in decreased mortality in patients with ALI or ARDS[14]
Administration of activated protein C	Begin administration of activated protein C in eligible patients Assess patients for signs and symptoms of bleeding Monitor indicators of coagulation	All eligible patients will receive activated protein C	Treatment with activated protein C improves outcomes in patients with sepsis who have scores >25 on the Acute Physiology and Chronic Health Evaluation II[7,11]

Abbreviations: ALI, acute lung injury; ARDS, acute respiratory distress syndrome; CVP, central venous pressure; EGDT, early goal-directed therapy; MAP, mean arterial pressure; $Scvo_2$, central venous oxygen saturation.

therapies. Supportive therapy also includes proper handwashing, enforcing infection control measures, use of semirecumbent positioning during mechanical ventilation, stress ulcer prophylaxis, prevention of deep vein thrombosis, turning, and skin care.[5,7] A complete summary of the MUST Protocol can be viewed online at www.mustprotocol.org.

BIDMC Protocol

Members of the BIDMC emergency department and surgical and medical ICUs formed a multidisciplinary team made up of physicians and nurses to design ways to implement this quality improvement pathway. The purpose of the protocol is early recognition of sepsis and treatment of patients with sepsis with proven therapies. The team's goals were to develop a multidisciplinary, evidence-based protocol

that would allow for rapid identification and early triage of patients and to educate and empower nurses to use the protocol to manage patients with sepsis.

Physician and nursing leaders from the BIDMC emergency department and ICUs convened a series of bimonthly meetings to develop the content of the protocol, to identify team members, and to determine the resources required to develop and implement the protocol. A literature review was completed, and a time line was established. Key clinical nurses representing the ICUs, emergency department, and admission facilitation (nursing capacity managers) were asked to join the team to assist with planning and implementation. The goals were to have representation and acceptance of the protocol by members from all disciplines and staff who would be involved in use of the protocol and to have input from these team members about how the protocol would affect all areas of practice. Meeting attendance was mandatory; members who were unable to attend appointed a proxy. Communication among members was necessary to ensure collaboration and to coordinate activities. Each member was held accountable for the information to keep the project on track. Minutes were drafted for each meeting and were distributed via e-mail.

Eligibility of Patients

Patients were eligible for the protocol if they were 18 years or older and had signs and symptoms suggestive of infection, met 2 or more criteria for systemic inflammatory response syndrome, and had evi-

Sidebar 2: Procedures Used to Treat Sepsis

Volume Replacement

With any infection or injury of the body, an immune response is triggered, which stimulates the release of soluble protein molecules called cytokines. In patients with sepsis, cytokines are responsible for vasodilatation, increased capillary permeability through damage of the vascular endothelium, fever, and decreased myocardial contractility.[15] Most patients with sepsis have intravascular volume depletion related to the vasodilatory effects of cytokine release. Therefore, fluid replacement is the best initial therapy for treatment of hypotension in patients with sepsis.[16]

Effective fluid replacement can improve cardiac output, tissue perfusion, oxygen delivery, and survivability in patients with septic shock.[14] Isotonic sodium chloride solution is often used for volume replacement because colloids are not more beneficial than crystalloids.[5] If monitoring via a central venous or pulmonary artery catheter indicates that a patient is still hypovolemic after adequate volume replacement, vasopressor therapy should be started.[16,17] Patients with anemia may require blood transfusion to increase oxygen delivery.[16] Patients with sepsis may be at increased risk for adverse consequences of anemia because of the cardiovascular, respiratory, and metabolic compromise associated with this abnormality.[18]

In the study by Rivers et al,[10] aggressive treatment with fluids, vasoactive agents, and blood transfusions was used in the first 6 hours to improve oxygen delivery in patients with sepsis or septic shock. End points of replacement included blood lactate levels, mixed venous oxygen saturation, base deficit, and pH. Patients receiving the early goal-directed therapy had higher mean mixed venous oxygen saturation, lower mean blood lactate levels, lower mean base deficit, and higher mean pH than did the control group. In-hospital mortality rates, as well as 28-day and 60-day mortality rates, were significantly lower in the group receiving early goal-directed therapy than in the group receiving standard treatment. The authors[10] concluded that early interventions to restore balance between oxygen supply and demand improve survivability in patients with sepsis.

Antibiotics

Bacterial endotoxins cause the accelerated release of cytokines, which may directly injure the endothelium or cause the release of lysosomal enzymes that induce microvascular damage. Prompt, appropriate treatment with antibiotics can lower the mortality rate in sepsis by as much as 10%.[5] Broad-spectrum antibiotic therapy should be initiated soon after the diagnosis of sepsis is made and samples have been sent for culturing. The choice of empiric therapy is based on the suspected site of infection, means of acquisition (community or nosocomial), causative organism, and host factors (eg, degree of immunodeficiency).[19] Antimicrobial therapy should be modified to an agent with a narrow spectrum as soon as cultures indicate the presence of a specific microorganism. Causes for lack of response to antibiotics are a resistant strain of bacteria or an unknown abscess. Patients should be evaluated daily for signs of a surgically removable source of infection.

Activated Protein C

Endogenous protein C, a protein present on the surface of endothelial cells, contributes to homeostasis in sepsis. Before the protein can be effective, it must be converted to its active form by thrombomodulin. Activated protein C prevents the generation of thrombin by interfering with clotting factors. Inhibition of thrombin generation decreases inflammation by inhibiting activation of platelets and recruitment of neutrophils. Activated protein C has direct anti-inflammatory properties; it suppresses monocyte activation and interferes with proinflammatory cytokines.[7] Additionally, activated protein C has profibrinolytic properties; it neutralizes substances that guard against excess fibrinolysis, thereby facilitating clot breakdown.[7] The protein is normally generated in amounts proportional to the formation of thrombin. During sepsis, thrombomodulin on the surface of endothelial cells is downregulated, reducing the ability to generate activated protein C.[20]

Clinical trials are under way to determine the efficacy of using cogins such as recombinant activated protein C and antithrombotics such as tissue factor pathway inhibitor to

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Sidebar 2: Procedures Used to Treat Sepsis (continued)

treat severe sepsis. Currently, only treatment with drotrecogin alfa (recombinant activated protein C) has improved all-cause mortality in patients at 28 days, and thus it is the only agent approved for treatment of severe sepsis.

In patients with sepsis, the administration of activated protein C resulted in a 19.4% reduction in the relative risk of death and an absolute risk reduction of 6.1%.[11] Patients who were more acutely ill, that is, those who had a score greater than 25 on the Acute Physiology and Chronic Health Evaluation II, had the most dramatic improvement after administration of drotrecogin alfa. A major risk associated with the use of activated protein C is bleeding; serious hemorrhage occurs in 3.5% of patients. Caution is advised in patients with an international normalized ratio greater than 3 or a platelet count less than 30×10^9/L.

Steroid Therapy

Historically, use of steroid anti-inflammatory agents in the treatment of sepsis was not effective. However, the results of recent trials with low-dose corticosteroid therapy in patients with adrenal insufficiency have been promising. Annane et al[13] reported a significant reduction in mortality in a group of patients with septic shock who received a 7-day regimen of hydrocortisone and fludrocortisone. These patients had a relative adrenal insufficiency as indicated by a corticotropin stimulation test. In a study by Yildiz et al,[21] mortality rates were 40% in patients with sepsis who received prednisolone and 55.6% in the nontreatment group. A recently published meta-analysis[22] confirms that a long course (5-11 days) of low-dose corticosteroid therapy improves mortality in patients with sepsis and septic shock.

Intensive Insulin Therapy

Van den Berghe et al[12] found that intensive insulin therapy resulted in lower morbidity and mortality among critically ill patients. Patients whose blood glucose level was maintained between 4.4 and 6.2 mmol/L (80-110 mg/dL) had better outcomes than did those who received conventional treatment that maintained blood glucose levels between 10.0 and 11.1 mmol/L (180-200 mg/dL). In this study,[12] intensive insulin therapy reduced the frequency of episodes of bloodstream infections by 46%. Patients with bacteremia who were treated with intensive insulin therapy had a 12.5% mortality rate; the mortality rate in the group receiving conventional treatment was 29.5%. Tight glycemic control reduced morbidity and mortality among critically ill patients in the surgical intensive care unit, regardless of whether or not they had a history of diabetes.

Protective Lung Ventilation

The lungs are a frequent and early target organ for mediator-induced injury and are often the first organ affected in severe sepsis.[5] Acute pulmonary dysfunction in sepsis is manifested as acute respiratory distress syndrome and occurs in 30% to 60% of patients with septic shock.[16] Acute respiratory distress syndrome typically occurs 24 to 72 hours after the initial injury. Clinical outcomes are improved by using lower tidal volume ventilation (6 mL/kg ideal body weight) and by using strategies to keep the plateau pressure less than 30 cm H_2O. In an article published in 2000, the Acute Respiratory Distress Syndrome Network[14] reported that patients who received protective lung ventilation had an absolute reduction in risk for mortality of 9%.

dence of hypoperfusion (Table 4). Hypoperfusion was defined as systolic blood pressure less than 90 mm Hg after a administration of a bolus of fluid of 20 to 30 mL/kg and/or a serum lactate level greater than 4 mmol/L. Suspected infections included pneumonia, meningitis, intra-abdominal infection, urinary tract infection, and catheter infections; a fever (body temperature >38.0°C [>100.4°F]) was considered a sign of a suspected infection.

To practically implement the lactate screening, emergency department nurses initiated a standing policy that they would obtain measurements of serum lactate in all patients who had blood samples obtained for cultures or who had signs and symptoms suggestive of infection. Samples of venous blood were used for assays of lactate because these samples are easily obtained and the results are roughly equivalent to those of assays of arterial samples.[24] Thus, the serum level of lactate was used as a screening tool. Lactate was chosen because it is used as a prognostic marker of global tissue hypoxia and because the clearance of circulating lactate is prolonged in patients with sepsis. Our group has recently published data[25] indicating that patients with a suspected infection had a higher hospital mortality rate when their venous serum level of lactate was elevated at the time of admission to the emergency department. The 28-day in-hospital mortality rate for patients with a venous serum lactate level of 4 mmol/L or greater was 28% (38 deaths of 134 patients), versus a mortality rate of 5.9% (67 deaths of 1144 patients) for patients with a venous lactate level less than 4 mmol/L (Figure 2). We endorse the measurement of serum lactate as a promising and effective screening tool because the assay is relatively easy to obtain, is inexpensive, and has a rapid laboratory turnaround time.

The Sepsis Team

Patients are triaged and the BIDMC protocol is initiated in the emergency department. Emergency department nurses assess patients by using the previously described criteria and activate a "code sepsis."

Table 4 Criteria for admission to the Mutliple Urgent Sepsis Therapies Protocol

Patients eligible for admission must meet the following criteria:
1. Suspected infection
2. Two of the following 4 criteria for systemic inflammatory response syndrome:
   - Temperature >38.0°C (>100.4°F) or <36°C (<96.8°F)
   - Heart rate >90/min
   - Respirations >32/min or $Paco_2$ <32 mm Hg
   - White blood cell count >12 x 10^9/L or <4 x 10^9/L or with >10% immature neutrophils

and
3. Hypoperfusion, as evidenced by
   - Lactate level >4 mmol/L or
   - Hypotension (systolic blood pressure <90 mm Hg) after initial fluid challenges

Once nurses determine that a patient meets the eligibility criteria for the protocol, members of the sepsis pathway team are paged. The team includes, but is not limited to, the ICU attending physician and resident, emergency department attending physician and resident, the ICU clinical nurse specialist, and the nursing admission facilitator. The rationale is that by alerting the right clinicians quickly, we can mobilize an early resuscitation effort and prepare the ICU to assume care of the patient.

Entry Documentation

An intake and tracking form (Figure 3) for patients with sepsis was designed by the team to guide nurses in implementing the MUST protocol. This form was modeled on the current emergency department trauma flow sheet so that nurses would be familiar with most of its content and layout. The vision of the group was that the protocol would be used by nurses and that the intake and tracking form would guide nurses at the bedside in a checklist fashion.

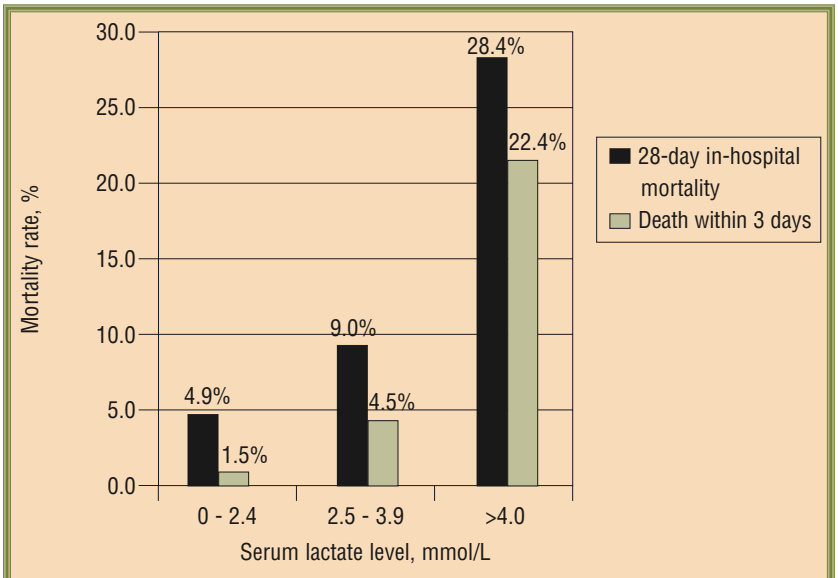

Figure 2 Serum lactate level as a predictor of mortality in patients with sepsis (n = 1278). The 28-day in-hospital mortality was 8.2% (105 patients); death occurred within 3 days in 4.3% (55 patients).

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All interventions, collections of blood samples, and treatments are included on the form so that no part of the pathway is missed.

Components of the MUST Protocol

Early goal-directed therapy, as described by Rivers et al,[10] is the heart of the resuscitation interventions in the MUST protocol (Figure 4). All patients receive supplemental oxygen or mechanical ventilation as needed to maintain adequate oxygenation and ventilation. A central venous catheter is placed in the emergency department to monitor the need for fluid replacement. The goal is a central venous pressure (CVP) of 8 to 12 mm Hg.[10] If the CVP is less than 8 mm Hg, 500 mL of isotonic sodium chloride solution is given. Lung sounds are evaluated for tolerance of the fluid bolus and, if the lung sounds are stable, the bolus is repeated every 20 to 30 minutes until the CVP reaches 8 mm Hg. The target mean arterial pressure (MAP) is 65 to 90 mm Hg.[10] If MAP remains low after the CVP is greater than 8 mm Hg, vasopressor therapy, preferentially with norepinephrine, is started. Studies have shown that the use of norepinephrine can improve outcomes in patients with septic shock.[17] Fluid replacement and vasopressor therapy are managed by the nurse caring for the patient. The nurse has the protocol as ordered by the physician; this arrangement enables the nurse to monitor and assess the patient's response to the protocol interventions and quickly respond without the need to obtain further orders from the physician.

At BIDMC, a catheter (PreSep Catheter, Edwards Lifesciences, Irvine, Calif) that measures CVP as well as

Figure 3 Nurses' intake and tracking form for patients with sepsis.

Abbreviations: ABG, arterial blood gases; AP, anteroposterior; BIDMC, Beth Israel Deaconess Medical Center; BP, blood pressure; CL, chloride; CO2, carbon dioxide; cont, continued; CPK, creatine kinase; CVP, central venous pressure; CXR, chest radiograph; DNR/DNI, do not resuscitate/do not intubate; ECG, electrocardiogram; ED, emergency department; EM, emergency medicine; ETT, endotracheal tube; Glu, glucose; gm, gram; Hct, hematocrit; HR, heart rate; Init, initials; INR, international normalized ratio; IV, intravenous; IVF, intravenous fluids; K, potassium; Lab, laboratory; LR, lactated Ringer's solution; M/F, male/female; MAP, mean arterial pressure; MB, creatine kinase–MB; mcg, microgram; MD, physician; MEDS or med, medications; MICU, medical intensive care unit; NA, sodium; NC, nasal cannula; NRB, non-rebreather mask; NS, isotonic sodium chloride solution; O2%, oxygen saturation; PA posteroanterior; PMH, past medical history; PRBC, packed red blood cells; q, every; RN, registered nurse; RR, respiratory rate; ScvO2, central venous oxygen saturation; T, temperature; UO, urine output; Vent, ventilation; Vol, volume; Wt, weight.

central venous oxygen saturation ($Scvo_2$) is inserted to evaluate end-organ perfusion. Mixed venous oxyhemoglobin levels provide an indication of the balance between oxygen delivery and consumption. Normal tissue oxygen extraction is approximately 25%; therefore normal $Scvo_2$ is 70% to 80%. With the early goal-directed therapy protocol, after the CVP and MAP have been normalized, the $Scvo_2$ is assessed. If the $Scvo_2$ is less than 70% and the hematocrit is less than 0.30, a blood transfusion is given to improve oxygen delivery to the tissues. If, after the blood transfusion, the hematocrit is greater than 0.30 and the $Scvo_2$ remains less than 70%, dobutamine is given as a continuous infusion to increase cardiac output.

Because the main objective of the MUST Protocol is to decrease the time between identification of patients with sepsis and the start of interventions, the team set a target time limit of 5 hours from a patient's enrollment in the protocol to

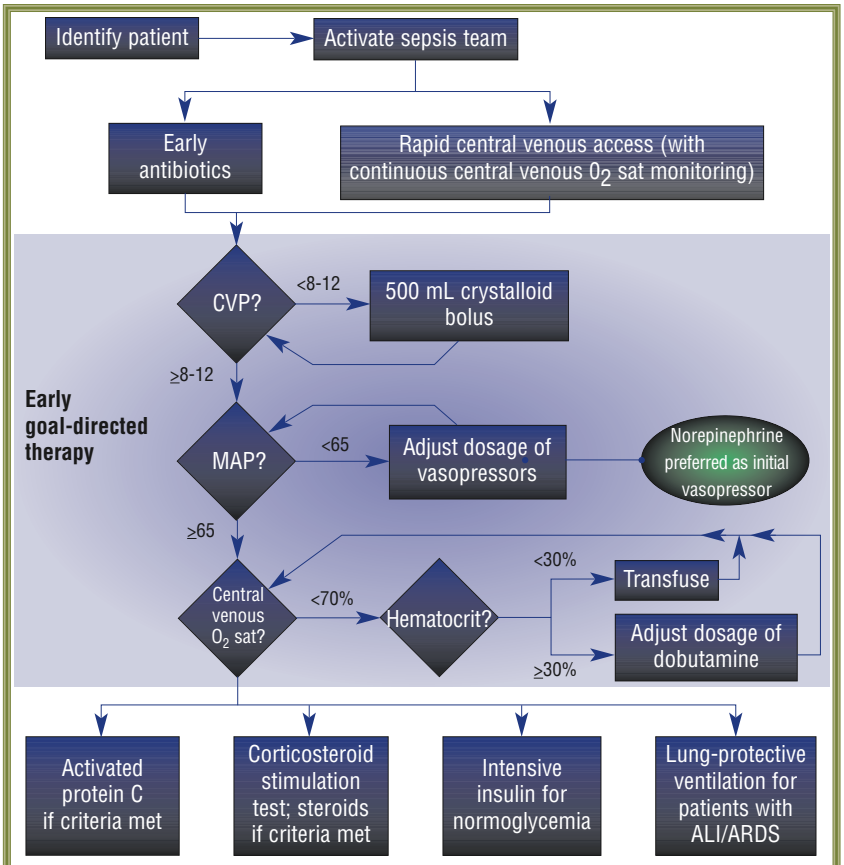

Figure 4 Summary of the Multiple Urgent Sepsis Therapies Protocol.

Abbreviations: ALI/ARDS, acute lung injury or acute respiratory distress syndrome; MAP, mean arterial pressure; O_2 sat, oxygen saturation.

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placement in an ICU bed. Once the patient is transferred to the ICU, treatments and interventions continue according to the protocol. Broad-spectrum antimicrobial therapy is started as soon as possible in the emergency department and is directed at the suspected cause of infection. A random blood sample for determination of serum cortisol level is obtained, and then a corticotropin stimulation test is done. Patients who do not have an increase in cortisol greater than 248 nmol/L (>9 µg/dL) receive steroid replacement for 7 days.

Glucose levels are monitored at least every 6 hours. Insulin therapy is initiated to maintain blood glucose levels between 4.4 and 6.7 mmol/L (80-120 mg/dL). The Acute Respiratory Distress Syndrome Network 2000 guidelines[14] are used to manage patients with acute lung injury or acute respiratory distress syndrome; low-tidal-volume ventilation is used to decrease airway pressures. Finally, patients are evaluated for the need for activated protein C, and, if appropriate, therapy with the protein is initiated according to BIDMC guidelines.

Data Collection

Initial and serial blood samples for laboratory tests are collected for all patients (Table 5). Blood samples for serum lactate levels are collected hourly until the value is normalized. Numerous studies have established the use of lactate as a marker of tissue hypoxia in shock. Lactate clearance early in the course of therapy is associated with decreased mortality.[26] Vital signs are assessed and documented at least every hour and more often as needed at the nurse's discretion. Vital signs include, but are not limited to, body temperature, respiratory rate, blood pressure including MAP, heart rate, urine output, oxygen saturation, $ScvO_2$, CVP, and neurological checks. Blood samples for assays of arterial blood gases and additional laboratory studies are collected at the discretion of the emergency department and ICU teams.

Implementation of the MUST Protocol

Members of the sepsis treatment team obtained approval of the MUST

Table 5 Routine laboratory studies

Initial studies
Complete blood cell count with differential
Chemistry panel
Serum level of lactate
Serum level of cortisol (random blood sample)
Serum level of C reactive protein
Blood cultures
International normalized ratio, prothrombin time, and partial thromboplastin time
ABO and Rh typing and antibody screen
Urinalysis with culture
Liver function tests
Serial studies
Serum level of lactate every hour for 4 times
Complete blood cell count and chemistry panel every 6 hours

Protocol from the BIDMC critical care executive committee. The executive committee is the governing board for BIDMC's critical care units. Once approval was received, the team enlisted the support of multiple hospital services to put the protocol into action. The BIDMC equipment and distribution departments procured the $Scvo_2$ catheters required to assess tissue perfusion in the patients to be studied. Hospital Information Systems was enlisted to modify the patient data entry system to allow relevant information to be entered in a single field, thus simplifying data extraction. Team members also worked with personnel from Hospital Information Systems to build a sepsis "order set" (a list of required protocol treatments) to streamline entry of physicians' orders. The order set was instrumental in guiding the ICU physicians to quickly prescribe all treatments outlined in the protocol with the ease of a single computer mouse click. More importantly, the order set enabled nurses to rapidly acknowledge the orders, expedite all communication with clinicians, and prevent order errors and omissions.

The sepsis team worked with the hospital's telecommunications specialists to obtain pagers for a core group of caregivers responsible for responding to sepsis-related codes. A system of "virtual pagers" was designed to enable on-call ICU and emergency department physicians to sign into the sepsis emergency response system, thus ensuring they are paged in a timely manner to respond to any sepsis-related code.

Despite the level of complexity and collaboration required to successfully implement the MUST Protocol at BIDMC, the team set aggressive time lines for the project. Total time from initial planning meetings to the official roll out of the protocol was targeted at less than 7 months. While acknowledging the challenges that such a short time frame might represent, all clinicians involved were committed to meeting the projected timetables. Table 6 describes the brief time line for the MUST Protocol.

Staff Education for the Protocol

The education efforts required to implement the protocol were 2-fold: all emergency department and ICU personnel required education on the actual treatment protocol, and ICU and emergency department nursing staff required education on the equipment to be used. This task was daunting, because the sepsis team needed to educate a critical number of the nurses and physicians staffing 46 emergency department and 60 ICU beds. The team used several methods in the education campaign, including the following:

- In-service programs were developed and presented in the units by the clinical nurse specialists in the ICUs and emergency department; included was training on new equipment to be used such as the central venous catheter to measure $Scvo_2$.
- MUST Protocol binders containing copies of the user guide and reference articles were distributed to all units.
- Copies of the protocol were posted on the BIDMC intranet.
- Poster-sized color copies of the sepsis clinical pathway were posted in the emergency department and ICUs.

The education needs of the ICU nurses differed markedly from those of the emergency department nurses. For this reason, the clinical nurse specialists for the 2 groups worked independently to develop and teach required classes. We used 2 models for the education rollout: the emergency department nurses attended a 3-hour in-service program divided into 3 sections consisting of (1) material on pathophysiology and early detection of sepsis; (2) presentation of the study by Rivers et al[10] (early goal-directed therapy) and principles behind the protocol; and (3) information on new equipment, monitoring procedures, and documentation. The program was presented "off shift" as part of a continuing education unit initiative. In addition, approximately 75 prehospital providers were also educated within the first 6 months of initiation of the protocol to promote general knowledge of sepsis and the availability of the MUST Protocol at BIDMC.

Table 6 Timetable for implementation of the Multiple Urgent Sepsis Therapies Protocol

May 2003	Initial planning meeting
August 2003	Rollout of protocol for obtaining blood samples in the emergency department for assays of serum lactate
September 2003	Forms committee submission
October 2003	Physicians' and nurses' educational campaign
November 2003	Rollout of protocol, first patient November 10, 2003
November 2003	Computer documentation system modified
April 2004	Protocol order set developed for physicians' system for entry of orders

The ICU nurses received "on-shift training." The nurse educator developed a short program that was presented on a small-group basis; the program covered the nuances of the protocol, the new catheter, and $Scvo_2$. ICU in-service training was provided during regularly scheduled work hours. Individual support was provided as needed by members of the sepsis team to ensure that the protocol became a part of practice at BIDMC. Nursing competency with the protocol will be verified with a mandatory annual competency test.

Education of physicians was accomplished through grand rounds, in-service training during morning rounds, and continual online training. The sepsis order set in the system for entering physicians' orders also introduced the physicians to the nuances of the protocol. All treatments, including fluid therapy, medications and dosing, and antimicrobial therapy, are contained in a template that is tailored to individual patients.

Challenges During Implementation

Some of the difficulties encountered during the implementation of the MUST Protocol included educating the large number of staff working various shifts, transferring patients treated by using the MUST Protocol from the emergency department to the ICU in a timely fashion, expediting placement of the $Scvo_2$ catheter; and dealing with problems with equipment.

The team also discovered that the healthcare staff had not been educated on exactly how long a patient was expected to be treated by using the protocol. The team regrouped and decided that for each patient, termination of treatment based on the protocol would be explored daily during rounds. Now, if treatment is still required, the patient remains in the protocol. An order from a physician is required to terminate the protocol. This information was quickly disseminated to the staff.

The education rollout was complicated by the large number of nurses and physicians typically involved in the care of a patient with sepsis. The team planned to initiate the in-service programs 2 weeks before the first anticipated use of the protocol so that caregivers would be able to quickly use the knowledge gained. As in most healthcare education, the requirement for staffing 7 days a week, 24 hours a day presented the challenge of trying to reach personnel on all shifts within the short 2-week time frame. During the first months of implementation of the protocol, nurses caring for patients being treated according to the protocol had questions. Members of the sepsis team made themselves available via pager to provide the support needed. This support was considered imperative for successful implementation of the protocol within the specified time line. Support provided included fielding telephone calls, directing staff to online resources or MUST protocol binders, and working side-by-side with nurses at the bedside as patients were admitted.

Currently, team members are exploring possible solutions to improve the time to initiation of treatment. For example, shifting the responsibility for the placement of catheters (currently the responsibility of the emergency department team) to whoever can get it done quickly is being considered. BIDMC opened an additional 7-bed ICU to increase the total number of critical care beds in an attempt to have "sepsis code beds" readily available. Emergency department nurses have continued to administer antibiotics and the initial fluid bolus immediately by using a peripheral intravenous catheter rather than delay treatment until the central catheter is placed.

Equipment challenges centered on tracking cables and monitors used for assessment of $Scvo_2$ as patients were transferred from the emergency department to multiple ICUs. For each patient, the central venous catheter is connected to the patient's monitor via a fiber-optic cable that enables continuous display of $Scvo_2$ values. This cable travels with the patient to the ICUs because calibration data is stored in the cable. Some difficulties have been experienced with returning cables to the emergency department for use on subsequent patients. This problem is complicated by the fact that BIDMC has ICUs on 2 separate campuses, requiring that some patients be transported via ambulance. To fix this problem, we adopted a system in which an extra cable is swapped out by the emergency department and ICU teams during transfer to the ICU. Additional cables were purchased to help alleviate this problem.

Conclusion

Sepsis continues to be common in patients and is associated with a high mortality rate despite advances in critical care in the past 2 decades. According to predictions, the incidence of sepsis and septic shock will increase dramatically in the years to come because of the so-called graying of America and the increased occurrence of chronic disease and HIV

infection.[1] These factors, coupled with the improved ability to diagnose and identify sepsis, will lead to an even greater challenge for caregivers.

The multidisciplinary sepsis team at BIDMC has taken proven therapies for the treatment of sepsis and incorporated them into an evidence-based clinical pathway that is used by nurses. The team's goals were to expedite detection of patients at risk for sepsis and to initiate early goal-directed therapy for these patients. Collaborative efforts and institutional acceptance of the MUST protocol led to the successful development and implementation of the protocol. The multidisciplinary sepsis team met bimonthly to implement the protocol and now meets on a periodic basis. The agenda includes an update on the number of patients treated by using the protocol and any issues or challenges, for example, the need to provide education on the protocol as the ICUs and emergency department acquire new staff members. The team also discusses future directions. Team members are currently looking at the feasibility of early recognition of sepsis in patients in the medical-surgical inpatient units.

As advances occur in the treatment of patients with severe sepsis and new interventions are proved effective, members of the sepsis team at BIDMC expect to modify the MUST Protocol accordingly. We hope that this new protocol, as it exists today and as it evolves, will improve survivability for patients with sepsis and decrease related healthcare costs.

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