Smith Seminars
Online Continuing Education
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Multiple Organ Dysfunction Syndrome (MODS)

Objectives

Become familiar with the organs that can be affected by multiple organ dysfunction syndrome.
Know the mechanisms of cell injury and resulting organ dysfunction in sepsis leading to MODS.
Have a working knowledge of the staging factors and diagnostic modalities in sepsis.
Know what treatments are available to patients with sepsis and MODS.

The word "sepsis" was derived from the ancient Greek for rotten flesh and putrefaction. Sir William Osler was the first to recognize that "except on few occasions, the patient appears to die from the body's response to infection rather than from the infection."
In the late 1960s, several reports appeared describing remote organ failure (pulmonary failure, liver failure) as a complication of severe sepsis. In 1975, a classic editorial by Baue was entitled "Multiple, progressive or sequential systems failure, a syndrome of the 1970s." This concept was formulated as the basis of a new clinical syndrome. Several terms were cloned thereafter, such as multiple organ failure, multiple system organ failure, and multiple organ system failure, to describe this evolving clinical syndrome of otherwise unexplained progressive physiological failure of several interdependent organ systems. More recently, the term multiple organ dysfunction syndrome (MODS) has been proposed as a more appropriate description.

Multiorgan Failure from Sepsis

Sepsis is a clinical syndrome that complicates severe infection and is characterized by systemic inflammation and widespread tissue injury. Multiple organ dysfunction is a continuum, with incremental degrees of physiological derangements in individual organs; it is a process rather than an event. Alteration in organ function can vary widely from a mild degree of organ dysfunction to completely irreversible organ failure. The degree of organ dysfunction has a major clinical impact. The term MODS is defined as a clinical syndrome in which the development of progressive and potentially reversible physiological dysfunction in 2 or more organs or organ systems induced by a variety of acute insults, including sepsis, is characteristic. The American College of Chest Physicians/Society of Critical Care Medicine Consensus Panel developed definitions of the various stages of sepsis, which can be summarized as follows: Infection is a microbial phenomenon in which an inflammatory response to the presence of microorganisms or the invasion of normally sterile host tissue by these organisms is characteristic. Bacteremia is the presence of viable bacteria in the blood.

Systemic inflammatory response syndrome (SIRS) may follow a variety of clinical insults, including infection, pancreatitis, ischemia, multiple trauma, tissue injury, hemorrhagic shock, or immune-mediated organ injury.
Sepsis is a systemic response to infection. This is identical to SIRS, except that it must result from infection.
Septic shock is sepsis with hypotension (systolic BP < 90 mm Hg or a reduction of 40 mm Hg from baseline) despite adequate fluid resuscitation. Concomitant organ dysfunction or perfusion abnormalities (lactic acidosis, oliguria, coma) are present in the absence of other known causes.
MODS is the presence of altered organ function in a patient who is acutely ill such that homeostasis cannot be maintained without intervention. Primary MODS is the direct result of a well-defined insult in which organ dysfunction occurs early and can be directly attributable to the insult itself. Secondary MODS develops as a consequence of a host response and is identified within the context of SIRS. The inflammatory response of the body to toxins and other components of microorganisms cause the clinical manifestations of sepsis.

Pathogenesis

Sepsis has been referred to as a process of malignant intravascular inflammation. Normally, a potent, complex, immunologic cascade ensures a prompt protective response to microorganism invasion in humans. A deficient immunologic defense may allow infection to become established; however, an excessive or poorly regulated response may harm the host through maladaptive release of indigenously generated inflammatory compounds.
Lipid A and other bacterial products release cytokines and other immune modulators that mediate the clinical manifestations of sepsis. Interleukins, tumor necrosis factor-alpha (TNF-alpha), interferon gamma, and other colony-stimulating factors are produced rapidly within minutes or hours after interactions of monocytes and macrophages with lipid A. Inflammatory mediators release becomes a self-stimulating process (an autocrine), and release of other inflammatory mediators, including interleukin-1 (IL-1), platelet activating factor, IL-2, IL-6, IL-8, IL-10, INF, and nitric oxide, further increases cytokine levels. This leads to continued activation of polymorphonuclear leukocytes (PMNs), macrophages, and lymphocytes; proinflammatory mediators recruit more of these cells (a paracrine process). All of these processes create a state of destructive immunologic dissonance.
Sepsis is described as an autodestructive process that permits extension of the normal pathophysiologic response to infection to involve otherwise normal tissues and results in MODS.

Specific Organ Involvement

Organ dysfunction or organ failure may be the first clinical sign of sepsis, and no organ system is immune from the consequences of the inflammatory excesses of sepsis. Mortality rates increase with the increase of failed organs.

Circulation

Significant derangement in autoregulation of circulation is typical of sepsis. Vasoactive mediators cause vasodilatation and increase the microvascular permeability at the site of infection. Nitric oxide plays a central role in the vasodilatation of septic shock. Also, impaired secretion of vasopressin may occur, which may permit persistence of vasodilatation.

Central circulation: Changes in both systolic and diastolic ventricular performance occur in sepsis. Through the use of the Frank Starling mechanism, cardiac output often is increased to maintain the BP in the presence of systemic vasodilatation. Patients with preexisting cardiac disease are unable to increase their cardiac output appropriately.

Regional circulation: Sepsis interferes with the normal distribution of systemic blood flow to organ systems; therefore, core organs may not receive appropriate oxygen delivery leading to what is known as regional hypoperfusion.

Microcirculation is the key target organ for injury in sepsis syndrome. A decrease in the number of functional capillaries causes an inability to extract oxygen maximally, which is caused by intrinsic and extrinsic compression of capillaries and plugging of the capillary lumen by blood cells. Increased endothelial permeability leads to widespread tissue edema of protein-rich fluid. Septic shock and the systemic inflammatory response is characterized by reversible myocardial depression, which can prove resistant to catecholamine and fluid administration. Circulating "myocardial depressant factor," probably representing the synergistic effects of TNFα, IL-1β, other cytokines, and nitric oxide, is implicated in pathogenesis. Macrovascular myocardial ischemia and hypoperfusion are unlikely contributors. In severe sepsis and septic shock, microcirculatory dysfunction, and mitochondrial depression cause regional tissue distress, therefore, regional hypoxia persists. This condition is termed microcirculatory and mitochondrial distress syndrome (MMDS). Sepsis-induced inflammatory autoregulatory dysfunction persists and oxygen need is not matched by supply, leading to multiorgan system dysfunction.

Redistribution of intravascular fluid volume resulting from reduced arterial vascular tone, diminished venous return from venous dilation, and release of myocardial depressant substances causes hypotension.

Pulmonary Dysfunction

Endothelial injury in the pulmonary vasculature leads to disturbed capillary blood flow and enhanced microvascular permeability, resulting in interstitial and alveolar edema. Neutrophil entrapment within the pulmonary microcirculation initiates and amplifies the injury to alveolar capillary membranes. Acute respiratory distress syndrome (ARDS) is a frequent manifestation of these effects.

Gastrointestinal Dysfunction

The GI tract may help propagate the injury of sepsis. Overgrowth of bacteria in the upper GI tract may be aspirated into the lungs, producing nosocomial or aspiration pneumonia. The normal barrier function of the gut may be affected, allowing translocation of bacteria and endotoxins into the systemic circulation and extending the septic response. Septic shock can

cause paralytic ileus that can lead to a delay in institution of enteral feeding. The optimal level of nutritional intake is interfered with in the face of high protein and calorie requirements. Narcotics and muscle relaxants can further worsen the gastrointestinal tract motility.

Liver

By virtue of the role of the liver in host defense, the abnormal synthetic functions caused by liver dysfunction can contribute to both the initiation and progression of sepsis. The reticuloendothelial system of the liver acts as a first line of defense in clearing bacteria and their products; liver dysfunction leads to a spillover of these products into systemic circulation. Liver failure or "shock liver" can manifest by elevation of liver enzymes and bilirubins, coagulation defects, and failure to excrete toxins such as ammonia, which lead to worsening encephalopathy.

Renal Dysfunction

Acute renal failure often accompanies sepsis due to acute tubular necrosis. The mechanism is complex but involve decrease effective intravascular volume due to systemic hypotension, direct renal vasoconstriction, release of cytokines, and activation of neutrophils by endotoxins and other peptides, which contribute to renal injury.

Central Nervous System Dysfunction

Involvement of the CNS in sepsis produces encephalopathy and peripheral neuropathy. The pathogeneses is poorly defined but likely related to systemic hypotension, which can lead to brain hypoperfusion.

Coagulopathy

Subclinical coagulopathy signified by a mild elevation of the thrombin or activated partial thromboplastin time (aPTT) or a moderate reduction in platelet count is extremely common, but overt disseminated intravascular coagulation (DIC) could happen. Deficiencies of coagulation system proteins, including protein C, antithrombin III, and tissue factor inhibitors, cause coagulopathy.

Mechanisms of Organ Dysfunction and Injury

The precise mechanisms of cell injury and resulting organ dysfunction in sepsis are not understood fully. Multiorgan dysfunction syndrome is associated with widespread endothelial and parenchymal cell injury, some of which can be explained by the following proposed mechanisms:

Hypoxic hypoxia: The septic circulatory lesion disrupts tissue oxygenation, alters the metabolic regulation of tissue oxygen delivery, and contributes to organ dysfunction. Microvascular and endothelial abnormalities contribute to the septic microcirculatory defect in sepsis. The reactive oxygen sepsis, lytic enzymes, and vasoactive substances (nitric oxide, endothelial growth factors) lead to microcirculatory injury, which is compounded by the inability of the erythrocytes to navigate the septic microcirculation.

Direct cytotoxicity: The endotoxin, TNF-alpha, and nitric oxide may cause damage to mitochondrial electron transport, leading to disordered energy metabolism. This is called cytopathic or histotoxic anoxia, an inability to utilize oxygen even when it is present.
Apoptosis: Apoptosis (programmed cell death) is the principal mechanism by which dysfunctional cells are eliminated normally. The proinflammatory cytokines may delay apoptosis in activated macrophages and neutrophils, but other tissues, such as the gut epithelium, may undergo accelerated apoptosis. Therefore, derangement of apoptosis plays a critical role in tissue injury of sepsis.
Immunosuppression: The interaction between proinflammatory and anti-inflammatory mediators may lead to an imbalance. An inflammatory reaction or immunodeficiency may predominate, or both may be present.

Characteristics of Sepsis That Influence Outcomes

Clinical characteristics that relate to the severity of sepsis include an abnormal host response to infection, the site and type of infection, the timing and type of antimicrobial therapy, the offending organism, and the development of shock, underlying disease, the patients' chronic health condition, and the number of failed organs. Factors that lead to sepsis and septic shock may not be essential in determining the ultimate outcome.

Frequency in United States

Current estimates suggest that the incidence of sepsis is greater than 500,000 cases per year. Approximately 40% of patients who are septic may develop shock. Patients who are at risk include those with positive blood cultures. Prevalence rates for SIRS of sepsis vary from 20-60%.

Mortality/Morbidity

Mortality from multiorgan dysfunction syndrome remains high. Mortality rate from ARDS alone is 40-50%. Once additional organ system dysfunction occurs, the mortality rate increases as much as 90%.

History

Symptoms of sepsis are usually nonspecific and include fever, chills, and constitutional symptoms of fatigue, malaise, anxiety, or confusion. These symptoms are not pathognomonic for infection and may be observed in a wide variety of noninfectious inflammatory conditions. They may be absent in serious infections, especially in elderly individuals.
Sepsis, SIRS, septic shock, and multiorgan dysfunction syndrome represent a clinical continuum. The specific features exhibited depend on where the patient's case falls on that continuum. SIRS is defined by the presence of 2 or more of the following: Temperature greater than 38.0°C or less than 36.0°C; Heart rate greater than 90 beats per minute; Respiratory rate greater than 20 breaths per minute; WBC count greater than 12,000 cells/µL, less than 4000 cells/µL, or more than 10% bands.

Fever is a common feature of sepsis. Fever from an infectious etiology results from resetting the hypothalamus so that heat production and heat loss are balanced to maintain a higher temperature. An abrupt onset of fever usually is associated with a large infectious load.
Chills are a secondary symptom associated with fever and result from increased muscular activity in an attempt to produce heat in order to raise the body temperature to the level required to reset the hypothalamus.
Sweating occurs when the hypothalamus returns to its normal set point and senses that the body temperature is above the desired level. Perspiration is stimulated to evaporate and cool excess body heat.
Alteration in mental function often is observed. Mild disorientation or confusion especially is common in elderly individuals. More severe manifestations include apprehension, anxiety, and agitation, and it may eventually lead to coma. The mechanism of alteration in mental function is not known, but altered amino acid metabolism has been proposed as one cause of metabolic encephalopathy.
Hyperventilation with respiratory alkalosis is a common feature of sepsis. Stimulation of the medullary ventilatory center by endotoxins and other inflammatory mediators has been proposed as the cause of hyperventilation.
The following localizing symptoms are some of the most useful clues to the etiology of both fever and sepsis:
Head and neck infections - Earache, sore throat, sinus pain, or swollen lymph glands
Chest and pulmonary infections - Cough, especially if productive; pleuritic chest pain; and dyspnea
Abdominal and GI infections - Abdominal pain, nausea, vomiting, and diarrhea
Pelvic and genitourinary infections - Pelvic or flank pain, vaginal or urethral discharge, urea, frequency, urgency
Bone and soft tissue infections - Focal pain or tenderness, focal erythema, edema

Physical

Physical examination notes the general condition of the patient first. Observe the overall hemodynamic condition to search for signs of hyperperfusion. Look for signs suggestive of a focal infection. An acutely ill, toxic appearance is a common feature in serious infections.
The vital signs may suggest sepsis, even if fever is absent. As noted above, tachypnea is common; tachycardia with an increased pulse pressure also is common.
Measure the body temperature accurately. Oral temperatures often are unreliable; obtain rectal temperatures.
Investigate signs of systemic tissue perfusion. In the early stages of sepsis, cardiac output is well maintained or even increased. Along with vasodilatory mediators, this may result in warm skin, warm extremities, and normal capillary refill. As sepsis progresses, stroke volume and cardiac output fall. Patients begin to manifest signs of poor distal perfusion, including cool skin, cool extremities, and delayed capillary refill.

The following physical signs suggest focal, usually bacterial, infection:
CNS infection - Profound depression in mental status and meningismus
Head and neck infections - Inflamed or swollen tympanic membranes, sinus tenderness, pharyngeal exudates, stridor, cervical lymphadenopathy
Chest and pulmonary infections - Localized rales or evidence of consolidation
Cardiac infections - Regurgitant valvular murmur
Abdominal and GI infections - Focal tenderness, guarding or rebound, rectal tenderness, or swelling
Pelvic and genitourinary infections - Costovertebral angle tenderness, pelvic tenderness, cervical motion pain, and adnexal tenderness
Bone and soft tissue infections - Focal erythema, edema, infusion, and tenderness
Skin infections - Petechiae and purpura

Laboratory Studies

Laboratory tests are useful in suspected sepsis or septic shock to assess the general hematologic and metabolic condition of the patient. The microbiologic studies provide results, which may indicate occult bacterial infection or bacteremia, and indicate the specific microbial etiology.
CBC count with differential should be obtained to monitor a hemoglobin concentration. An adequate hemoglobin concentration is necessary to ensure oxygen delivery in shock. The hemoglobin should be maintained at a level of 8 g/dL.
Acute phase reactants, platelets usually increase at the onset of any serious stress. The platelet count will fall with persistent sepsis, and DIC may develop.
The white cell differential and the WBC count may predict the existence of a bacterial infection. In adults who are febrile, a WBC count > 15,000 cells/μL or a neutrophil band count > 1,500 cells/μL is associated with a high likelihood of bacterial infection.
Metabolic assessment with serum electrolytes, including magnesium, calcium, phosphate, and glucose should be performed at regular intervals.
Renal and hepatic function with serum creatinine, BUN, bilirubin, alkaline phosphate, and alanine aminotransferase (ALT) should be assessed.
Arterial blood gas measurement provides assessment of the respiratory system.
Measurement of serum lactate provides an assessment of tissue hypoperfusion. Elevated serum lactate indicates that significant tissue hypoperfusion exists with the shift from aerobic to anaerobic metabolism. Higher serum lactate indicates a worse degree of shock and a higher mortality.
Coagulation status can be assessed with prothrombin time (PT) and activated partial thromboplastin time (aPTT). Patients with clinical evidence of coagulopathy require additional tests to detect the presence of DIC.
Blood culture is the primary modality for aiding in the diagnosis for intravascular infections (endocarditis) and infections of indwelling intravascular devices. Two populations, people who abuse IV drugs and patients with prosthetic heart valves, are at high risk for endocarditis.

Patients at risk for bacteremia include adults who are febrile with an elevated WBC or neutrophil band counts, elderly patients who are febrile, and patients who are febrile and neutropenic. These populations have a 20-30% incidence of bacteremia. The incidence of bacteremia is at least 50% in patients with sepsis and evidence of end-organ dysfunction.

A urinalysis and urine culture should be ordered for every patient who is septic. Urinary infection is a common source for sepsis, especially in elderly individuals. Adults who are febrile without localizing symptoms or signs have a 10-15% incidence of occult urinary tract infection (UTI).

Secretions or tissue for Gram stain and culture from sites of potential infection can be collected. Generally, the Gram stain is the only available test to immediately document the presence of bacterial infection and guide the choice of initial antibiotic therapy.

Imaging Studies

A variety of imaging modalities are employed to diagnose clinically suspected focal infection, detect the presence of a clinically occult focal infection, and detect complications of sepsis and septic shock.

A chest radiograph in patients with severe sepsis should be obtained because the clinical examination is unreliable for pneumonia. Clinically occult infiltrates have been detected by routine use of chest radiography in adults who are febrile without localizing symptoms or signs and in patients who are febrile and neutropenic without pulmonary symptoms.

Supine and upright or lateral decubitus abdominal films may be useful when an intraabdominal source is suspected. Ultrasound is the imaging modality of choice when a biliary tract source is suspected to be the source of sepsis. CT scan is the imaging modality of choice for excluding intraabdominal abscess or a retroperitoneal source of infection. A CT scan of the head should be obtained in patients with evidence of increased intracranial pressure (papilledema) or suggestion of focal mass lesions (focal defects, previous sinusitis or otitis, recent intracranial surgery) or prior to lumbar puncture when meningitis is suspected.

When clinical evidence of a deep, soft tissue infection exists, such as, crepitus, bullae, hemorrhage, or foul smelling exudate, a plain radiograph should be obtain. The presence of soft tissue gas and the spread of infection beyond clinically detectable disease may require surgical exploration.

Procedures

The lumbar puncture needs to be performed urgently when meningitis or encephalitis is suspected. In patients with an acute presentation, rapid onset of septic shock, and severe impairment of mental status, bacterial meningitis should be ruled out by lumbar puncture.

Procedures, such as cardiac monitoring, noninvasive BP monitoring, and pulse oximetry, are necessary because patients often require ICU admission for invasive monitoring and support.

Supplemental oxygen is provided during initial stabilization and resuscitation.

All patients in septic shock should have adequate venous access for volume resuscitation. A central venous line also can be used to monitor central venous pressure to assess intravascular volume status.
An indwelling urinary catheter used to monitor urinary output is used as a marker for adequate renal perfusion and cardiac output.
Patients who have developed septic shock require right heart catheterization with a pulmonary artery (Swan-Ganz) catheter. This catheter provides an accurate assessment of the volume status of a patient who is septic. The cardiac output measurement can be obtained. Furthermore, determination of mixed venous oxygenation is helpful in determining the status of tissue oxygenation.
Most patients who are septic develop respiratory distress secondary to severe sepsis or as a manifestation of septic shock. Pulmonary dysfunction of sepsis (such as ARDS) also may occur. These patients need intubation and mechanical ventilation for optimum respiratory support.

Staging

Stages of sepsis are based on American College of Chest Physicians/Society of Critical Care Medicine Consensus Panel guidelines.

Stages of Sepsis

Systemic Inflammatory Response Syndrome (SIRS)

Two or more of the following:

Temperature of >36˚ C or <36˚C

Heart Rate >90

Respiratory Rate >20

WBC count >12 x 10^9/L (12,000 cells/μL) or <4 x 10^9/L (4,000 cells/μL) or 10% immature forms (bands)

Sepsis

SIRS plus a culture-documented infection

Severe Sepsis

Sepsis plus organ dysfunction, hypotension, or hypoperfusion (including but not limited to lactic acidosis, oliguria, or acute mental status changes)

Septic Shock

Hypotension (despite fluid resuscitation) plus hypoperfusion

Two well-defined forms of multiorgan dysfunction syndrome exist. In both, the development of acute lung injury or ARDS is of key importance to the natural history. ARDS is the earliest manifestation in all cases.
In the more common form of multiorgan dysfunction syndrome, the lungs are the predominant, and often the only, organ system affected until very late in the disease. These patients most often present with primary pulmonary disorder, such as pneumonia, aspiration, contusion, near drowning, exacerbation of chronic obstructive pulmonary disease (COPD), hemorrhage, or

pulmonary embolism. Lung disease progresses to meet ARDS criteria. Encephalopathy or mild coagulopathy may accompany pulmonary dysfunction, which persists for 2-3 weeks. At this time, the patient either begins to recover or progresses to develop dysfunction in another organ system. Once another major organ dysfunction occurs, these patients frequently do not survive. The second form of multiorgan dysfunction syndrome presents quite differently. These patients often have an inciting source of sepsis in organs other than the lungs, the most common being intraabdominal sepsis, extensive blood loss, pancreatitis, or vascular catastrophes. Acute lung injury or ARDS develops early, and dysfunction in other organ systems also develops much sooner than in the more common form of multiorgan dysfunction syndrome. The organ systems affected are hepatic, hematological, cardiovascular, and renal. Patients remain in a pattern of compensated dysfunction for several weeks, at which time they either recover or deteriorate further and die.

Criteria for Organ Dysfunction

Mild Criteria

Pulmonary - Hypoxia/hypercarbia requiring assisted ventilation for 3-5 days
Hepatic - Bilirubin 2-3 mg/dL or other liver function tests more than twice normal, PT elevated to twice normal
Renal - Oliguria (< 500 mL/d or increasing creatinine) 2-3 mg/dL
Gastrointestinal - Intolerance of gastric feeding for more than 5 days
Hematologic - aPTT >125% of normal, platelets < 50-80,000
Cardiovascular - Decreased ejection fraction with persistent capillary leak
CNS - Confusion
Peripheral nervous system - Mild sensory neuropathy

Severe Criteria

Pulmonary - ARDS requiring PEEP >10 cm H_2O and FiO_2 >0.5
Hepatic - Jaundice with bilirubin 8-10 mg/dL
Renal – Dialysis
Gastrointestinal - Stress ulceration with need for transfusion, acalculous cholecystitis
Hematologic - Disseminated intravascular coagulation
Cardiovascular - Hyperdynamic state not responsive to pressors
CNS - Coma
Peripheral nervous system - Combined motor and sensory deficit

Medical Care

The treatment of patients with septic shock consists of the following 3 major goals: (1) Resuscitate the patient from septic shock using supportive measures to correct hypoxia, hypotension, and impaired tissue oxygenation. (2) Identify the source of infection and treat with antimicrobial therapy, surgery, or both. (3) Maintain adequate organ system function guided by cardiovascular monitoring and interrupt the pathogenesis of multiorgan system dysfunction.

General Supportive Care

Initial treatment includes support of respiratory and circulatory function, supplemental oxygen, mechanical ventilation, and volume infusion. Treatment beyond these supportive measures includes a combination of several parenteral antibiotics, removal or drainage of infected foci, treatment of complications, and pharmacologic interventions to prevent further harmful host responses.

Supplemental oxygen should be administered to any patient who is septic with hypoxia or respiratory distress. If the patient's airway is not secure or respirations are inadequate, endotracheal intubation and mechanical ventilation should be performed.

Intravascular Volume Resuscitation

All patients with sepsis require supplemental fluids. Assessment of the patient's volume and cardiovascular status guides the amount and rate of infusion. For adult patients who are hypotensive, an isotonic crystalloid solution (sodium chloride 0.9% or Ringer lactate) in boluses of 500 mL (10 mL/kg in children) should be administered, with repeat clinical assessments after each bolus. Repeat boluses should be administered until signs of adequate perfusion are restored. A total of 4-6 L may be required. Patients should be monitor for signs of volume overload, such as dyspnea, pulmonary crackles, and pulmonary edema, on chest radiograph. Improvement, stabilization, and normalization of the patient's mental status, heart rate, BP, capillary refill, and urine output indicate adequate volume resuscitation.

In some patients, clinically assessing the response to volume infusion may be difficult. By monitoring the response of central venous pressure or pulmonary artery occlusion pressure (PAOP) to fluid boluses, the physician can assess these patients. A control venous pressure of 10-15 mm Hg, a PAOP greater than 18 mm Hg, or a rise in the PAOP by 5 mm Hg or more following fluid bolus indicates adequate volume resuscitation. Such patients are susceptible to volume overload; therefore, further fluid should be administered carefully. Colloid resuscitation (with albumin or pentastarch) has no proven benefit over isotonic crystalloid resuscitation (normal saline or Ringer lactate).

Empirical Antimicrobial Therapy

Selection of particular antimicrobial agents is empirical and is based on an assessment of the patient's underlying host defenses, the potential sources of infection, and the most likely responsible organisms. Antibiotics must be broad spectrum and cover gram-positive, gram-negative, and anaerobic bacteria because all classes of these organisms produce identical clinical pictures. Antibiotics can be administered parenterally in doses adequate to achieve bactericidal serum levels. Many studies have found that clinical improvement correlates with the achievement of serum bactericidal levels rather than the number of antibiotics administered. coverage directed against anaerobes in the therapy of patients with intraabdominal or perineal infections should be included. Antipseudomonal coverage is indicated in patients with

neutropenia or burns. Patients who are immunocompetent usually can be treated with a single drug with broad-spectrum coverage, such as a third-generation cephalosporin. Patients who are immune-compromised usually require dual antibiotic coverage with broad-spectrum antibiotics with overlapping coverage. Within these general guidelines, no single combination of antibiotics is clearly superior to others.

Vasopressor Supportive Therapy

When proper fluid resuscitation fails to restore hemodynamic stability and tissue perfusion, therapy with vasopressor agents should be initiated. These agents are dopamine, norepinephrine, epinephrine, and phenylephrine. These vasoconstricting drugs maintain adequate BP during life-threatening hypotension and preserve perfusion pressure for optimizing flow in various organs. The mean BP required for adequate splanchnic and renal perfusion (mean arterial pressure [MAP] of 60 or 65 mm Hg) based on clinical indices for organ perfusion need to be maintained. If the patient remains hypotensive despite volume infusion and moderate dose dopamine, a direct vasoconstrictor (norepinephrine) at a dose of 0.5 mcg/kg/min in should be started and titrated to support a systolic BP of 90 mm Hg. Although potent vasoconstrictors (such as norepinephrine) traditionally have been avoided because of their adverse events on cardiac output and renal perfusion, human data has shown that norepinephrine can reverse septic shock in patients unresponsive to volume and dopamine. These patients require invasive hemodynamic monitoring with arterial lines and pulmonary artery catheters.

Recombinant Human-Activated Protein C

The inflammatory mediators are known to cause activation of coagulation inhibitors of fibrinolysis, thereby causing diffuse endovascular injury, multiorgan dysfunction, and death. Activated protein C is an endogenous protein that not only promotes fibrinolysis and inhibits thrombosis and inflammation but also may modulate the coagulation and inflammation of severe sepsis. Sepsis reduces the level of protein C and inhibits conversion of protein C to activated protein C. Administration of recombinant activated protein C inhibits thrombosis and inflammation, promotes fibrinolysis, and modulates coagulation and inflammation.

Corticosteroids

While evidence exists for the use of large doses of corticosteroids in those with severe sepsis and septic shock, randomized human studies found that corticosteroids did not prevent the development of shock, reverse the shock state, or improve the 14-day mortality rate. Therefore, no support exists in the medical literature for the routine use of high doses of corticosteroids in patients with sepsis or septic shock. A meta-analysis of 10 prospective, randomized, controlled trials of glucocorticoid use did not report any benefit from corticosteroids. Therefore, high-dose corticosteroids should not be used in patients with severe sepsis or septic shock.

Inpatient Care

The major focus of resuscitation from septic shock is supporting cardiac and respiratory functions. To prevent multi-organ failure, these patients require a very close monitoring and institution of appropriate therapy for major organ function. Some of the problems encountered in these patients are the following:

Temperature control - Fever generally requires no treatment, except in patients with limited cardiovascular reserve, because of increased metabolic requirements. Antipyretic drugs and physical cooling methods, such as sponging or cooling blankets, may be used to lower the temperature.

Metabolic support - Patients with septic shock develop hyperglycemia and electrolyte abnormalities.

Serum glucose should be kept in normal range with insulin infusion. Regular measurement and correction of electrolyte deficiency including hypokalemia, hypomagnesemia, hypocalcemia and hypophosphatemia is recommended.

Anemia and coagulopathy - Hemoglobin as low as 80 mg/dL is well tolerated and does not require transfusion unless the patient has poor cardiac reserve or demonstrates evidence of myocardial ischemia. Thrombocytopenia and coagulopathy are common in sepsis and do not require replacement with platelets or fresh frozen plasma, unless the patient develops active clinical bleeding.

Renal dysfunction - Closely monitor urine output and renal function in all patients who are septic.

Any abnormalities of renal function should prompt attention to adequacy of circulating blood volume, cardiac output, and BP; correct these if they are inadequate.

Nutritional support - Early nutritional support is of critical importance in patients with septic shock. The enteral route is preferred unless the patient has an ileus or other abnormality. Gastroparesis is observed commonly and can be treated with motility agents or placement of a small bowel feeding tube.

Prevention

Patients with impaired host defense mechanisms are at a greatly increased risk for developing sepsis and multiorgan failure. The main causes are: chemotherapeutic drugs, malignancy, severe trauma, burns, diabetes mellitus, renal or hepatic failure, old age, ventilatory support, and invasive catheters.

The development of severe sepsis may be prevented by avoidance of invasive catheters or removing them as soon as possible. Prophylactic antibiotics in the perioperative phase, particularly following GI surgery, may be beneficial. Use of topical antibiotics around invasive catheters and as part of a dressing for patients with burns is helpful. Maintenance of adequate nutrition, pneumococcal vaccine in patients who have had a splenectomy, and early enteral feeding are other preventive measures.

To prevent sepsis and multiorgan failure with topical or systemic antibiotics in patients who are at high risk, such as the use of nonabsorbable antibiotics in the stomach to prevent translocation

of bacteria and occurrence of bacteremia has been a controversial issue. Numerous trials have been performed over the years using either the topical antibiotics alone or a combination of topical and systemic antibiotics. A systemic review of data presented no benefit in medical patients but a reduced mortality in surgical trauma patients. The beneficial effect was from a combination of systemic and topical antibiotics, predominantly by reducing lower respiratory tract infections in patients who were treated.

Prognosis

Several clinical trials have demonstrated a mortality ranging from 40-75% in patients with multiorgan failure of sepsis. The poor prognostic factors are advanced age, infection with a resistant organism, impaired host immune status, and poor prior functional status. Development of sequential organ failure, despite adequate supportive measures and antimicrobial therapy is a precursor of a poor outcome. In one study, mortality rates were 7% with SIRS, 16% with sepsis, 20% with severe sepsis, and 46% with septic shock. A multicenter prospective study published in JAMA reported a mortality of 56% during ICU stay. Of all deaths, 27% occurred within 2 days of the onset of severe sepsis, and 77% of all deaths occurred within the first 14 days. The risk factors for early mortality in this study were a higher severity of illness score, presence of 2 or more acute organ failures at the time of sepsis, shock, and a low blood pH (< 7.3).

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