

REVIEW

Early and innovative interventions for severe sepsis and septic shock: taking advantage of a window of opportunity

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ABSTRACT

The pathogenic, diagnostic and therapeutic landscape of sepsis is no longer confined to the intensive care unit: many patients from other portals of entry to care, both outside and within the hospital, progress to severe disease. Approaches that have led to improved outcomes with other diseases (e.g., acute myocardial infarction, stroke and trauma) can now be similarly applied to sepsis. Improved understanding of the pathogenesis of severe sepsis and septic shock has led to the development of new therapies that place importance on early identification and aggressive management. This review emphasizes approaches to the early recognition, diagnosis and therapeutic management of sepsis, giving the clinician the most contemporary and practical approaches with which to treat these patients.

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Severe sepsis and septic shock are common, accounting for about 2.9% of hospital admissions and 10% of admissions into the intensive care unit (ICU). The mortality rates for these 2 conditions exceed 30%.¹ A report from an attempt to quantify the incidence of sepsis upon initial arrival at hospital² estimated that half of such cases come to the emergency department (ED), which would mean some 387 600 cases in US EDs annually. A retrospective observational study³ of 496 patients with severe sepsis and septic shock who were admitted to several Canadian ICUs found that 32% had been admitted through their respective EDs.

The importance of the first 6 hours

Patients admitted and treated for sepsis in the ICU are often transferred from general medical–surgical practice units (GPUs), operating rooms (ORs), EDs, long-term care facilities and other hospitals. The diagnosis and treatment of these patients may be suboptimal, even among those who were admitted to GPUs⁴ or the ICU.⁵ Delays in the identification, transfer and management of critically ill patients during the first 6 hours after ICU admission have been associated with higher mortality rates⁴ and increased utilization of

hospital resources.⁶ Within the last 5 years, advances in the treatment of severe sepsis and septic shock have provided new therapies to treat this disease. Although these studies were ICU-based, the timeliness of treatment became a more important issue when Rivers and colleagues⁷ were able to show a significant mortality benefit when hemodynamic optimization was provided within the first few hours of disease presentation. This “golden hour” and “silver day”⁸ perspective of early resuscitation, which traditionally has been applied to trauma, can now be applied to severe sepsis and septic shock. Early diagnosis and rapid intervention became synonymous with improved outcomes for trauma patients, which inspired the concept of the “golden hour.”⁹ In turn, the “silver day” represented the first day’s remaining hours, during which aggressive correction of shock and organ dysfunction was found to decrease health-care resource utilization¹⁰ and improve outcomes.⁸ These ideals have been incorporated into the Surviving Sepsis Campaign, a multinational initiative, which recommends a 24-hour sepsis pathway that includes a critical 6-hour course of action.¹¹

The transition from sepsis to severe sepsis

The initial presentation of severe sepsis and septic shock is often nonspecific, and its severity, cryptic. Patients who arrive with a relatively benign or clinically unapparent infection can progress within hours to a more devastating form of disease.

Abnormalities in temperature, heart and respiratory rates and leukocyte count are manifestations of the systemic inflammatory response syndrome (SIRS).^{12,13} Because SIRS is a host response and can also arise from noninfectious causes, as a disease stage it is nonspecific. Sepsis is defined by the presence of 2 or more SIRS criteria in the setting of a documented or presumed infection. Severe sepsis is hallmarked by concomitant organ hypoperfusion or organ dysfunction (Box 1).^{7,14} Septic shock results when blood pressures fall and patients become hypotensive (i.e., < 90 mm Hg systolic blood pressure or < 65 mm Hg mean arterial pressure) despite adequate fluid resuscitation, and the patient requires vasopressor support.

The transition from sepsis to septic shock occurs most often during the first 24 hours of hospitalization. It carries with it an increase not only in morbidity¹⁰ but also in mortality: 20%–46%.^{7,15–17} The decreases in tissue oxygen delivery and

the cardiovascular insufficiency that accompany this transition may not be detected by vital signs nor SIRS criteria.¹⁸ It is at this critical juncture that outcomes can be much improved.

The science

Host response to infection

Numerous and complex pathogenic mechanisms are responsible for the transition from sepsis to severe sepsis and septic shock. The initial host response to infection is a humoral, cellular and neuroendocrine reaction to the infectious insult. Cells such as neutrophils, monocytes, macrophages, basophils and platelets interact with endothelial cells by means of adhesion molecules, receptors, selectins, immunoglobulins, oligosaccharides and integrin families.¹⁹ Endothelial interaction involving these mediators and products of inflammation is further amplified when the coagulation and complement systems are activated. In the most exaggerated scenario, vasoregulatory dysfunction and microaggregation impair microvascular flow, creating local ischemia and hypoxia, which may impair cellular respiration.^{20–27} Structural decreases in the permeability of the endothelium permit inflammatory cells and products to leave the circulation (Fig. 1),²⁸ leading to generalized edema.

Since endothelium is ubiquitous throughout the body, this “pan-endothelial cell disruption” is central to the development of multisystem organ failure. In recent years, components of this host response have been the target of outcome trials for many therapies.

Oxygen transport and utilization

Impairment in oxygen delivery and utilization at the tissue level parallels the host response to infection; this pathogenic mechanism leads to global tissue hypoxia. Tissue hypoxia not only results from host inflammatory response, it can also stimulate further inflammation.²² Fundamental to the recognition and treatment of global tissue hypoxia is an understanding of the principles of oxygen transport and utilization.

Oxygen is delivered to the tissues as a product of cardiac output (heart rate \times stroke volume) and oxygen content: (hemoglobin oxygen saturation \times hemoglobin \times 1.34) + (partial pressure of oxygen \times 0.003). The tissues extract a percentage of the delivered oxygen for cellular respiration: oxygen consumption. The blood, with its remaining oxygenation, returns to the venous circulation (Fig. 2); its remaining oxygenation can be measured with a blood sample from the pulmonary artery (mixed venous oxygen saturation, SvO₂) or from the central venous circulation (central venous oxygen saturation, ScvO₂).

SvO₂ is not readily measurable without a Swan–Ganz catheter. However, ScvO₂ is measurable through central venous cannulation of the superior vena cava or right atrium (Fig. 2). SvO₂ measurement indicates the level of venous oxygenation throughout the body; in nonshock states, it generally reflects venous oxygenation from the head and upper extremities. When the patient is in shock and SvO₂ testing yields low val-

ues, ScvO₂ measurements will consistently read (5–6%) higher but still correlate well with SvO₂.^{29–31}

Global tissue hypoxia develops when systemic oxygen delivery is insufficient to meet the oxygen demands of the tissues. When this critical delivery threshold is not reached, increased lactate production ensues as a by-product of anaerobic cellular respiration. A low SvO₂ (< 65%) or ScvO₂ (< 70%) result and an increased serum lactate concentration suggest the presence of global tissue hypoxia because a

Box 1: Sepsis definitions

Systemic inflammatory response syndrome (SIRS) – includes 2 or more of:

- Temperature > 38° or < 36°C
- Heart rate > 90 beats/min unless the patient is taking medications to reduce the rate (a beta-blocker or calcium-channel blocker) or the heart is paced
- Respiratory rate > 20 breaths/min (or PaCO₂ < 32 torr) or mechanically ventilated
- Leukocyte count > 12 000/ μ L or < 4 000/ μ L, or > 10% immature band forms

Sepsis

- Presence or presumed presence of an infection accompanied by evidence of SIRS

Severe sepsis – presence of sepsis, plus organ hypoperfusion or dysfunction

- Organ hypoperfusion; for example:
 - Increased blood lactate levels
 - Oliguria
 - Abnormal peripheral circulation, such as poor capillary refill, mottled skin
 - Acute alteration in mental status
- Dysfunction* of 1 or more organs, such as abnormalities of:
 - The hematologic system; e.g., thrombocytopenia, disseminated intravascular coagulation
 - The pulmonary system; e.g., acute respiratory distress syndrome
 - The renal system; e.g., acute renal failure
 - The gastrointestinal system with hepatic dysfunction; e.g., hyperbilirubinemia
 - The central nervous system; e.g., delirium

Septic shock†

- Presence of sepsis
- Refractory hypotension:
 - A systolic blood pressure < 90 mm Hg
 - A mean arterial pressure < 65 mm Hg, or a 40 mm Hg drop in systolic blood pressure compared to baseline
 - Unresponsive to a fluid challenge of 20–40 mL/kg
- Vasopressor dependency after adequate volume resuscitation

*Organs are considered to have failed when the organ dysfunction becomes most severe.

†Note that this is a standard definition. It is important to recognize that a patient may be in septic shock with a normal blood pressure if the baseline blood pressure is elevated (e.g., someone with a history of hypertension, diabetes or vascular disease) or there is concomitant myocardial dysfunction.

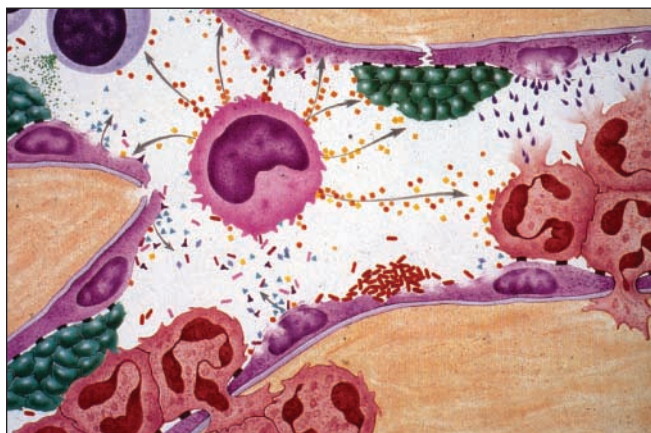


Fig. 1: Endothelial disruption and the inflammatory response. The platelets (green bodies), endothelial cells (purple), macrophages (light blue cell with dark centres), polymorphonuclear cells (pink with 3 inner lobes) and cytokines (small pellets) are inflammatory mediators. Adapted with permission from Matuschak GM. Continuous central venous and pulmonary artery oxygen saturation monitoring in the critically ill. *Crit Care Med* 1996;24:1769-71.²⁸

greater percentage of delivered oxygen is being extracted by the tissues, resulting in less venous oxygen to be measured distal to this extraction. This is considered to be early-stage or hypodynamic sepsis.³² A normal SvO₂ or ScvO₂ and serum lactate level suggest that oxygen supply meets demand (Fig. 3 and Fig. 4). Correction of these hemodynamic perturbations with prompt resuscitation, or in the presence of adequate compensatory mechanisms in the host, may result in a hyperdynamic state with high cardiac output. Although the origin of lactate generation in sepsis has been debated,³³ its presence and clearance over time are strongly associated with morbidity and mortality.^{34,35}

A normal or increased SvO₂ or ScvO₂ value in isolation does not always equate with normal or adequate tissue oxygenation: these measurements reflect global oxygen kinetics rather than those at the tissue level. In cases of severe sepsis or septic shock, abnormalities of hypoperfusion can still exist even in the presence of normal or high cardiac output and blood pressure. This “distributive shock” refers to a state of either regional or systemic hypoperfusion secondary to derangements in blood flow or the loss of vasoregulatory control in microcirculatory vascular beds.^{16,36,37} In particular, a normal or high SvO₂ or ScvO₂ reading accompanied by an increased blood lactate concentration (in other words, increasing metabolic acidosis) indicates that despite adequate global systemic oxygen delivery, the tissues are unable to extract the oxygen, perhaps because of microvascular shunting, microcirculatory failure³⁸ or mitochondrial dysfunction. This clinical syndrome has been termed cytopathic tissue hypoxia,³⁹ an oxygen delivery-independent state that is associated with increased morbidity and mortality (Fig. 4).^{40,41}

Global tissue hypoxia has pathogenic implications. In vitro, there is a significant correlation between SvO₂ and impairment of mitochondrial oxygen utilization.⁴² The resultant tissue hypoxia can serve to further activate endothelial media-

tors,²² causing loss of vascular integrity,⁴³ increased release of inflammatory cytokines⁴⁴ and procoagulants,⁴⁵ and reduced fibrinolysis.⁴⁶

The microcirculation

Much of the pathophysiology of sepsis involves disordered microcirculation. Considerable research has been conducted to enable clinicians to assess metabolic by-products and be able at bedside to envision the patient’s microcirculation.^{38,47} Intestinal and sublingual capnography devices, which measure partial carbon dioxide pressures (Pco₂) in the stomach and under the tongue, respectively, may reflect local cellular respiration in those tissues, suggesting regional hypoperfusion.⁴⁸⁻⁵⁰

A difference in mixed venous-arterial Pco₂ measurements between sampling locations correlates inversely with the patient’s cardiac index. In a prospective cohort study, the venous-arterial Pco₂ differences obtained from the pulmonary artery and central venous circulations were equal and inversely correlated with the cardiac index. A venous-arterial Pco₂ difference of more than 5 mm Hg suggests that cardiac output to tissue is inadequate and a supply-dependent state of severe sepsis exists. Hence, in the absence of a Swan-Ganz catheter, this value may be used as an additional surrogate marker that may reflect adequacy or inadequacy of cardiac output.⁵¹

Direct methods to evaluate microcirculatory flow are intravital microscopy (IVM) or orthogonal polarization spectral (OPS) imaging.³⁸ These tools are not yet available for widespread clinical use, but are currently undergoing evaluation; future research should help determine their role in sepsis treatment.

The clinical link

Identification of the high-risk patient

Early identification of the high-risk patient begins with a marker of illness severity. The systemic inflammatory response syndrome (SIRS) can be invoked by infection, trauma, ischemic or reperfusion injury, or sterile inflammation.⁵² Although the components of SIRS are nonspecific (Table 1), the combination of a suspected infection and the presence of SIRS may help alert the clinician to a possible diagnosis of sepsis. Although hypotension is another clinical sign that may signal the onset of septic shock, patients may present with severe sepsis and clinically significant global tissue hypoxia in its absence. Hence, signs of organ hypoperfusion and organ dysfunction (Table 1) must be sought by the treating clinician to evaluate severity of illness.

Because significant global tissue hypoxia in patients with sepsis can coexist with vital signs within normal ranges,⁵³ metabolic markers may help to identify high-risk patients. A single lactate measurement of 4 mmol/L or more at initial presentation is associated with an increased rate of mortality.^{54,55} Failure to clear lactate levels during as little as the first 6 hours after presentation is also associated with higher morbidity and mortality.³⁵ Serum bicarbonate measure-

ments and arterial base deficits correlate and remain indicators of tissue hypoperfusion.⁵⁶ However, serum bicarbonate may be depressed and the base deficit persist when large volumes of chloride-rich crystalloid resuscitation fluids are administered.⁵⁷

Serologic tests and biomarker assays may one day be critical in the assessment and treatment of the patient with sepsis.⁵⁸ Likely candidates include C-reactive protein (CRP),^{59–63} endotoxin (a component of Gram-negative cell walls),^{58,64} brain natriuretic peptide (an indicator of myocardial dysfunction),^{65–67} procalcitonin,^{68–75} interleukin-6 and endogenous protein C.^{76–81} At present their use is limited because these assay results as yet lack diagnostic accuracy, prognostic capability and timeliness; but one day, these markers may provide bedside tests to help diagnose and treat the entire spectrum of sepsis disease.

Several scoring systems have been developed to determine severity of illness in the ICU and predict the risk of death in populations of critically ill patients. These include the Acute Physiology and Chronic Health Score (APACHE) II and III,⁸² Simplified Acute Physiology Score (SAPS),⁸³ Sepsis-related Organ Failure Assessment Score,⁸⁴ Multiple Organ Dysfunction Score,⁸⁵ Logistic Organ Dysfunction System⁸⁶ and Mortality Probability Models.⁸⁷ APACHE II and SAPS II scores can readily be calculated with use of the Internet; at www.sfar.org/scores2/apache22.html and www.sfar.org/scores2/saps2.html a clinician can use these tools to compare illness severity and, moreover, access guidelines for diagnostic prognostication and therapeutic interventions, such as the use of recombinant human activated protein C (r-APC). The MEDS score, developed specifically for sepsis patients in the ED, correlates with sepsis outcomes.⁸⁸ In this scoring system, independent predictors of mortality upon arrival at the ED include terminal illness, tachypnea, hypoxia, septic shock, thrombocytopenia, a band proportion above 5%, infection of the lower respiratory tract, residence in a nursing home and altered mental status.⁸⁸ Current Canadian guidelines are evolving for triage and the use of acuity scales; future adjustments will be required to better detect sepsis in its early stages.⁸⁹

From a therapeutic perspective,⁹⁰ Hillman⁹¹ and others^{92–102} examined the effects of an in-hospital medical emergency team using early identifiers of the high-risk patient. These teams of intensive-care nurses and physicians were mobilized when specified alterations in airway, breathing, circulation and neurologic status were met.

Whether patient outcomes improve with this approach remains inconclusive.

Appendix 1 lists several useful Web resources related to sepsis care.

Treatment

Early antimicrobial therapy

The association of timely and appropriate antibiotic therapy with improved morbidity and mortality has been established in the ICU setting.^{103,104} Observational studies^{105,106} suggest a significant reduction in mortality when antibiotics are ad-

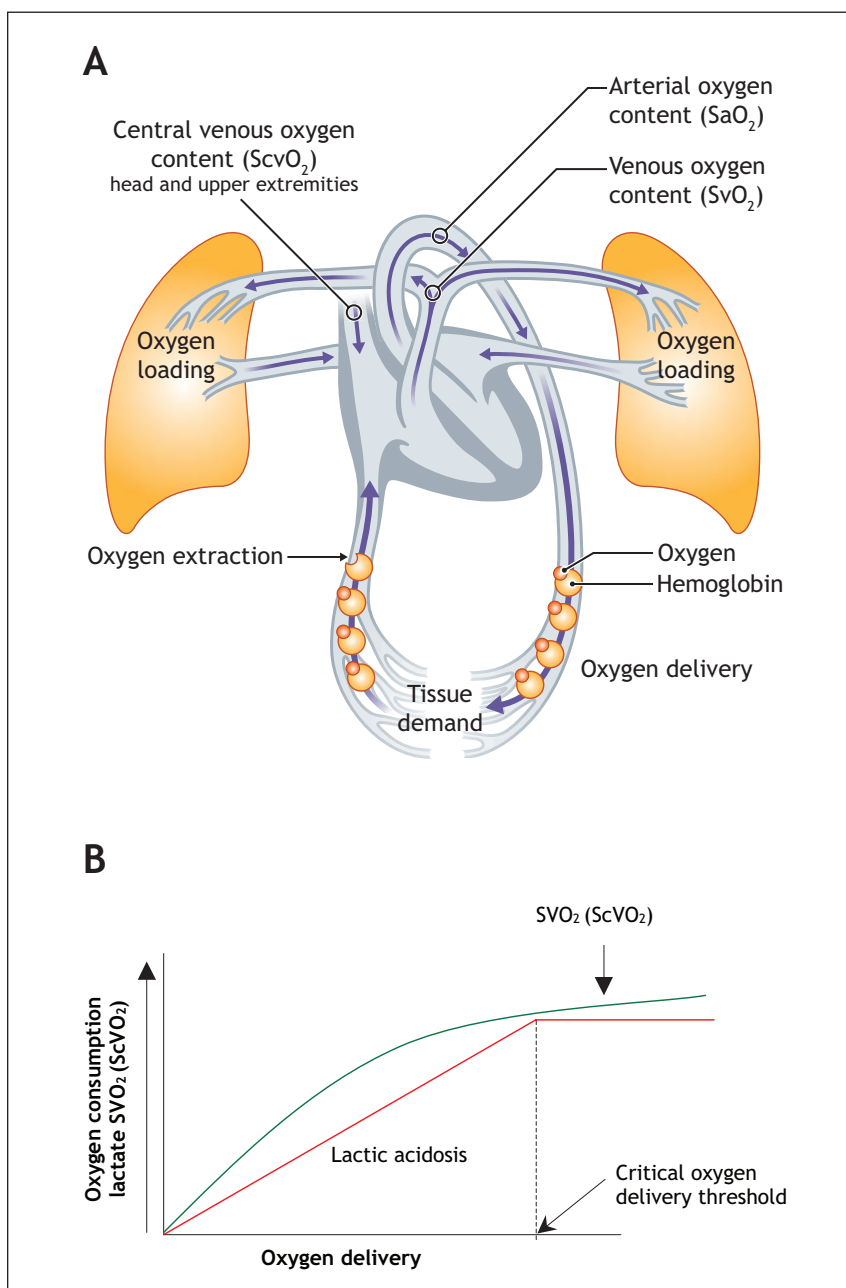


Fig. 2: Oxygen transport and utilization.

ministered within 4¹⁰⁵ and 8 hours¹⁰⁶ of hospital presentation ($p < 0.01$). Current Surviving Sepsis Campaign recommendations¹¹ are to administer antibiotics within 1 hour of a sepsis diagnosis.

Specific antibiotic strategies are beyond the scope of this paper, and reviews on antibiotic strategies may be found elsewhere.¹⁰⁷ However, we recommend broad coverage initially that is tailored to the potential source of infection and according to local hospital sensitivity and resistance patterns.

Surgical consultation for source control is appropriate when a patient has an undrainable abscess or an intra-abdominal source of sepsis. Consideration should also be given to the possibility of resistant organisms when patients live in nursing home or are users of intravenous drugs.

Early hemodynamic optimization

Resuscitation strategies for cases of severe sepsis or septic shock have been studied intensely and debated for years.¹⁰⁸ Investigations¹⁰⁹ involving strategies aimed at obtaining supranormal physiologic endpoints in ICU patients up to 72 hours into their hospitalization have led to negative and even deleterious results. Meta-analyses of sepsis resuscitation trials have indicated that early interventions¹¹⁰ that take place before organ dysfunction¹¹¹ provide better outcomes. A recent trial⁷ involving ED patients with severe sepsis or septic shock to examine hemodynamic resuscitation to normal physiologic parameters or early goal-directed therapy (EGDT) revealed a statistically significant mortality reduction of 16.5%.

EGDT is an algorithmic approach of hemodynamic optimization (Fig. 5) that aims to restore the balance between oxygen supply and demand in cases of severe sepsis or septic shock within the first 6 hours of ED care. The strategy targets the attainment of adequate oxygen delivery by optimization of intravascular volume (preload) with the use of central venous pressure (CVP) monitoring, blood pressure (afterload) with mean arterial pressure monitoring, contractility with use of monitoring to avoid tachycardia, and restoration of the balance between systemic oxygen delivery and oxygen demand (guided by ScvO₂ measurements) to resolve global tissue hy-

poxia. The components of EGDT were derived from the recommendations by the Society of Critical Care Medicine for hemodynamic support in sepsis.^{112,113}

Hemodynamic monitoring

Early hemodynamic optimization requires the monitoring of CVP, arterial blood pressure and ScvO₂. Intra-arterial pressure monitoring is recommended — especially for patients who are prescribed vasopressor medications,^{11,113} but with the caveat that vasopressor agents may cause central arterial pressure to be underestimated when measured from the radial artery.¹¹⁴ ScvO₂ can be measured intermittently from venous gas samples taken from the distal port of a standard central venous catheter or continuously by use of a fibre-optic central venous catheter and monitor (Edwards Lifesciences, Irvine, Calif.). Although in expert hands the pulmonary artery remains effective as a measurement site, proof of outcome benefit from its use remains to be demonstrated.¹¹⁵⁻¹¹⁷

Volume therapy

The first goal of EGDT in cases of sepsis is repletion of the patient's intravascular volume. Intravenous fluid therapy should begin with rapid and repeated 500-mL boluses of either crystalloid or colloid fluid up to an initial resuscitation volume of 20–40 mL/kg body weight, to attain a CVP of 8–12 mm Hg.

Until last year no randomized controlled trial or systematic review has definitively shown a benefit in the critically ill for the use of colloid or crystalloid fluid.¹¹⁸⁻¹²⁰ However, a large randomized controlled trial¹¹⁹ that compared 4% albumin with normal saline in the treatment of 6997 heterogeneous critically ill patients in need of volume resuscitation found no significant difference in mortality between the groups. Although a subgroup analysis of patients with severe sepsis suggested a trend for mortality benefit for the group receiving albumin, these findings should be considered only for the generation of hypotheses: they require confirmation with a randomized controlled trial involving patients with sepsis.

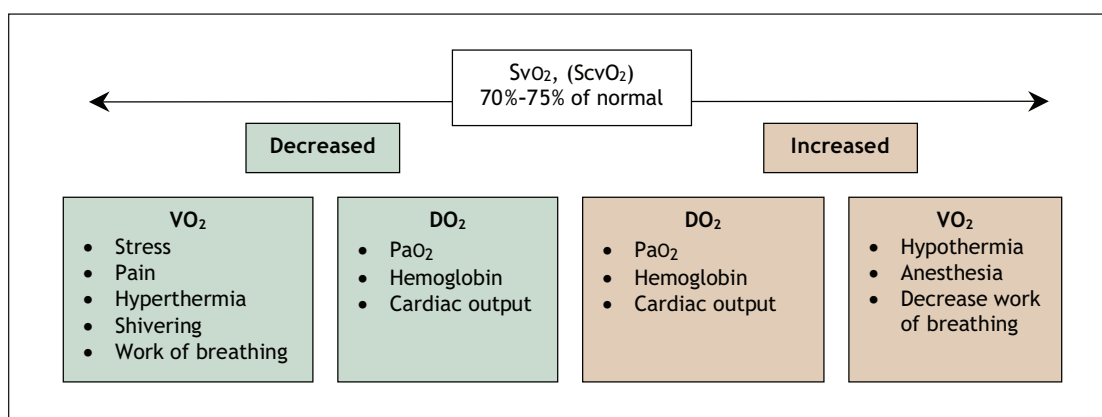


Fig. 3: The clinical utility of venous oxygen saturation (SvO₂ or ScvO₂).

Vasoactive agents

After the CVP goal is met, a vasopressor drug is given if the patient remains hypotensive (mean arterial blood pressure < 65 mm Hg). The target goal of a mean arterial pressure of 65 mm Hg has been shown to be physiologically equivalent to higher pressures.^{121,122}

Vasopressor agents include dopamine (5–20 µg/kg/min intravenously), norepinephrine (2–20 µg/min), phenylephrine (40–300 µg/min) and vasopressin (0.01–0.04 units/min). Both norepinephrine and dopamine have been advocated as first-line vasopressor agents in cases of sepsis.¹¹³ Because tachycardia may be exacerbated by β-agonist vasopressors, agents with more α-agonist effects (i.e., norepinephrine and phenylephrine) may be preferable for patients with pre-existing tachycardia or coronary disease.

When hypotension persists in a patient already taking a vasopressor medication, vasopressin deficiency may be considered;^{123,124} vasopressin is an endogenously produced hormone that is deficient in many patients with septic shock. Exogenously administered vasopressin in physiologic replacement doses (0.01–0.04 units/min) may act synergistically with other vasopressor agents, and has been associated with early withdrawal of other catecholamines.^{125–127} Current treatment doses of 0.01–0.04 units/min are meant to reflect

physiologic replacement doses. High doses of 0.06–1.8 units/min (as traditionally used)^{128,129} are not recommended in the context of septic shock because of reported adverse events.^{130,131}

Epinephrine (1–10 µg/min) may be considered for patients unresponsive to other vasopressors. It increases mean arterial pressure by increasing cardiac output and stroke volume.¹³²

Deleterious effects associated with vasopressor agents include the development of splanchnic hypoperfusion, excess tachycardia and coronary ischemia.¹³³ Existing evidence has not definitively proven one vasopressor agent superior to another in the setting of severe sepsis or septic shock.¹³³ Some definitive evidence on the current role of vasopressin and its effect on outcome is expected from the Canadian multicentre Vasopressin and Septic Shock Trial, VASST.

Administration of erythrocytes

If the ScvO₂ remains below 70% after optimization of preload, afterload and arterial oxygen saturation, the patient's oxygen-carrying capacity may be augmented by the administration of packed erythrocytes to achieve a hematocrit above 30%. Although recent studies^{134,135} have suggested that more conservative transfusion thresholds may be tolerated in a heterogeneous and clinically stable group of critically ill patients, these

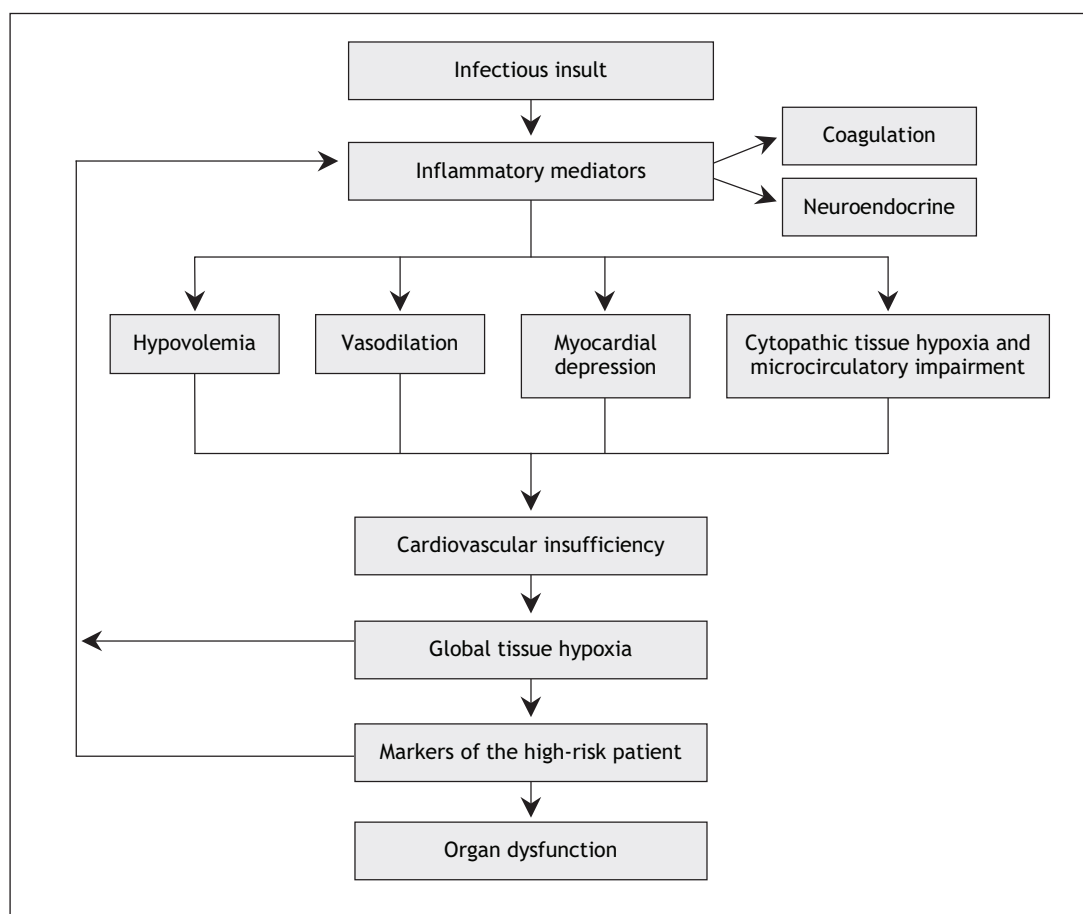


Fig. 4: The pathogenesis of cardiovascular insufficiency.⁴¹

results should not be extrapolated to acutely septic patients with an oxygen supply–demand mismatch. In the acute phase of resuscitation a hematocrit target of 30% appears reasonable, with a more restrictive transfusion strategy in the convalescent phase of the disease. Resuscitation trials that specifically address questions such as optimal erythrocyte transfusion triggers and the value of fresh versus old blood should help to further define the optimal role of red blood cells for patients with early septic shock.

Inotropic therapy

Sepsis may be accompanied by myocardial suppression in 10%–15% of patients, irrespective of age.^{7,136} In the EGDT study,⁷ these patients had persistently low readings of ScvO₂ after meeting the goals of CVP, mean arterial pressure and hematocrit. Some of them presented with an initially elevated CVP as a result of decreased ventricular compliance rather than volume overload. Inotropic support with dobutamine may improve myocardial depression, but may also unmask underlying hypovolemia because it acts to increase contractility and reduce peripheral vascular resistance. As ventricular compliance and contractility respond, CVP will decrease as the stroke volume improves.^{137,138} Further fluid replacement may be required to maintain CVP at 8–12 mm Hg. Dobutamine is then titrated at increments of 2.5 µg/kg/min every 20–30 minutes to a ScvO₂ measurement of 70%.

Clinicians must take care to avoid tachycardia (by keeping the heart rate < 100 beats/min) to optimize stroke volume and minimize myocardial oxygen consumption. Milrinone, a phosphodiesterase inhibitor, may be considered as an alternative agent to augment cardiac output. Like dobutamine, it is an inotropic agent that also reduces peripheral vascular resistance. However, its half-life (2.4 hours) is much longer than that of dobutamine, and it accumulates in renal failure. Future resuscitation research aimed specifically at optimal inotropic support is required to further define the role of these agents.

Decreasing oxygen consumption

In the severely septic patient, maximized oxygen delivery may be inadequate to restore the balance between oxygen supply and demand. Strategies to minimize oxygen demand should

therefore also be considered. Intubation, sedation and analgesia with mechanical ventilation will reduce both the work of breathing and oxygen consumption by the respiratory muscles.¹³⁹ Control of fever with antipyretics such as acetaminophen will also decrease oxygen consumption.

Adjunctive therapies

Several additional therapies initiated within the first 24 hours after identification of severe sepsis and septic shock have recently demonstrated a mortality benefit. Early implementation of these therapies may improve patients' survival, since they may wait several hours or even days before transfer to an ICU.

Steroid therapy

In the neurohumoral response to septic shock, many patients have manifestly inadequate adrenal reserve, or relative adrenal insufficiency (RAI).^{140–143} The mechanism for RAI is complex and incompletely understood, but is likely caused in part by the inflammatory cascade leading to an inadequate release or response to adrenocorticotropin, in combination with peripheral steroid resistance at the receptor level.^{144,145} RAI should be considered clinically distinct from absolute adrenal insufficiency because RAI usually clears up when the septic shock resolves. Patients with RAI therefore do not require corticosteroid replacement after resolution of shock.

Compared with placebo, the administration of low doses of hydrocortisone to patients with septic shock decreased their requirements for vasopressors^{146,147} and lowered their mortality rate.¹⁴⁸ In the one multicentre, randomized controlled trial that demonstrated a mortality benefit,¹¹⁷ corticosteroids (hydrocortisone 50 mg intravenously every 6 hours and fludrocortisone 50 µg by mouth once daily) were started within 8 hours after the diagnosis of septic shock and continued for 7 days. There was a 10% absolute reduction in 28-day mortality in the group that received hydrocortisone and fludrocortisone and who were diagnosed with RAI at randomization. In this study,¹¹⁷ RAI was diagnosed if the patient's increase in serum cortisol 1 hour after he or she received 250 µg of adrenocorticotropin was 250 nmol/L (9 µg/dL) or less. However, the study was unable to determine if the administration of corticosteroids was safe and effective for the group of patients who did not have RAI according to the definition

Table 1: The stages of sepsis and appropriate therapies

Stage	Mean arterial pressure	Central venous pressure	ScvO ₂	Serum lactate	Cardiac Index	Systemic vascular resistance	Treatment
1 Hypovolemia	Variable	↓	↓	↑	↓	↑	Volume
2 Compensated and vasodilatory	↓	Normal	↑	Variable	↑	↓	Vasopressors, corticosteroids
3 Myocardial suppression	Variable	↑	↓	↑	Normal or ↓	Normal or ↓	Inotropic therapy
4 Impairment of tissue O ₂ utilization	↓ or normal	Normal	↓	↑	Variable	↓, normal or ↑	Vasodilators, recombinant human activated protein C

Note: ScvO₂ = central venous oxygen saturation, ↓ = decreased, ↑ = increased. Sources: *N Engl J Med* 2001;345:1368-77 and 149. *Crit Care Med* 1987;15:26-8.

used in the study by Annane and associates.¹⁴⁸ Since the cut-off values for benefit are still in question, it should be left to the treating clinician to decide whether to order an adrenocorticotropin stimulation test to aid clinical decision-making. Because dexamethasone does not interfere with adrenocorticotropin test results, immediate empiric treatment with 2 mg of this steroid may be given and the test performed at a more convenient time.

Although the study by Annane and associates¹⁴⁸ has helped to establish the use of low-dose corticosteroids to treat septic shock, several questions remain. These include better consensus definitions for RAI with regard to baseline and stimulated cortisol concentrations in septic shock, and

whether the measurement of free cortisol may increase the accuracy of adrenocortical function tests.^{149,150} Much debate has ensued on the correct definition of RAI; it is still unclear whether patients who were deemed to not have RAI in the Annane study would have benefited from hydrocortisone.¹⁵⁰ Future research in this area will help to answer these questions more definitively.

Activated protein C

Protein C is an endogenous anticoagulant that also possesses profibrinolytic, anti-inflammatory anti-apoptotic effects and may improve microcirculatory flow.^{76,151} The Recombinant

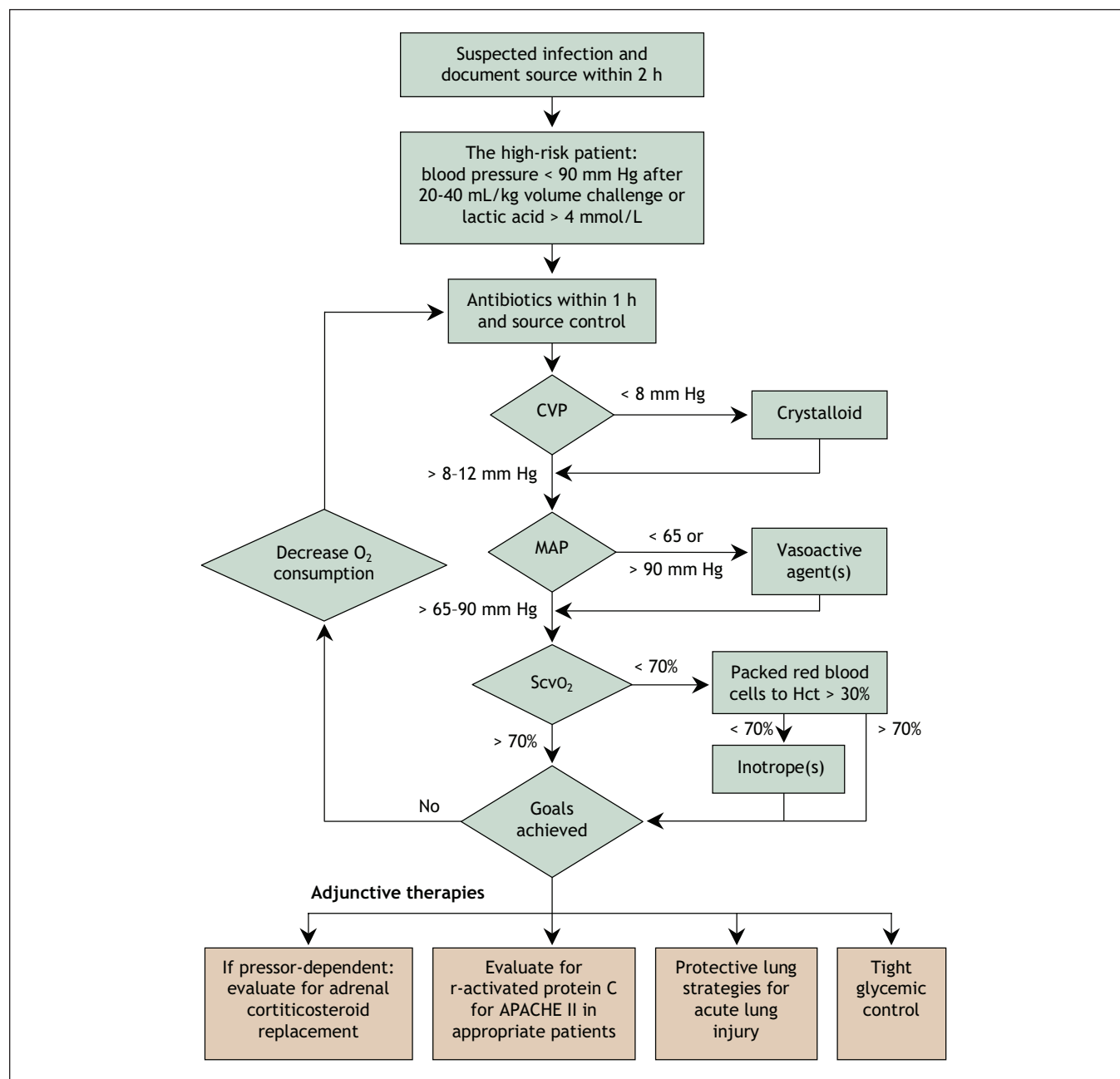


Fig. 5: Treatment options in sepsis. CVP = central venous pressure, MAP = mean arterial pressure, ScvO₂ = central venous oxygen saturation, Hct = hematocrit.

Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) study,⁷⁶ a multicentre randomized controlled trial, showed that the administration of r-APC (also known as drotrecogin alfa [activated] or Xigris) reduced mortality from severe sepsis or septic shock by 6% compared with placebo.^{76,152-154} Subgroup analyses suggested that survival with r-APC was improved in patients whose APACHE II scores were 25 or greater and also had dysfunction of 2 or more organs. Receiving r-APC was also associated with a trend toward an increased risk of bleeding (3.5% v. 2.0%, $p = 0.06$). In the PROWESS trial, r-APC was started within 24 hours after the criteria for severe sepsis were met.

Our understanding of the role of r-APC in earlier phases of disease presentation, such as those seen in the ED, is evolving.¹⁵⁵ Post-hoc studies conducted on subsets of patients participating in r-APC trials suggest that earlier administration of r-APC may improve morbidity and mortality and moreover reduce health care resource consumption.¹⁵⁵ A second large randomized controlled trial¹⁵⁶ that compared the efficacy of r-APC with that of placebo in patients with less severe sepsis (defined as zero or one organ dysfunction) was terminated early, when there appeared to be no mortality benefit for this patient population. This study did not address the timing of administration. Future research efforts, exploring the optimal timing for administration of r-APC and other anticoagulants will help determine its role in the earlier stages of severe sepsis and septic shock.

Protective lung strategies

Experimental data have revealed that mechanical ventilation with large tidal volumes can stretch lung tissue to excess (volume trauma), exacerbating the inflammatory response and leading to acute lung injury.¹⁵⁷ A multicentre randomized controlled trial¹²⁵ involving patients with acute lung injury and adult respiratory distress syndrome (ARDS) evaluated the effect of a low tidal volume (6 mL/kg of estimated body weight) versus a conservative volume strategy (12 mL/kg) with plateau pressures maintained at < 30 cm H₂O and demonstrated a 9.9% absolute reduction in 28-day mortality in the low tidal volume group for patients with acute lung injury or ARDS. Since sepsis is the most common cause of ARDS, it is prudent to institute ventilation with low tidal volumes when lung injury or ARDS is present. Prophylactic strategies to prevent the development of ARDS have not yet been researched, although a Canadian trial, the Lung Open Ventilation Study (LOVS), is currently evaluating the efficacy of recruitment maneuvers to keep the lungs open in cases of ARDS. LOVS will provide further information on optimal mechanical-ventilation methods for patients who have septic shock and ARDS.

Tight glycemic control

Another therapeutic strategy that has been found to confer a mortality benefit to critically ill and predominantly postsurgical cardiothoracic patients is tight glycemic control.¹²⁶ When conservative (10.0–11.1 mmol/L) glycemic control was com-

pared with tight control (4.4–6.1 mmol/L) in a multicentre, randomized controlled trial,¹²⁶ tight control led to a significant reduction in mortality (8.0% v. 4.6%, $p < 0.04$) and improved morbidity at 12 months.¹⁵⁸ This included a significant reduction in organ failure ($p = 0.04$) with a proven septic focus. Studies are underway in Australia, New Zealand, Britain and Canada that should help to determine whether tight glycemic control affords a mortality benefit for the more severely ill among critically ill patients.

Future directions

Resuscitation research is required to further elucidate the role of established resuscitation treatments for septic shock, such as fluid therapy, vasopressors, inodilating agents and erythrocyte transfusion triggers. New research on the diagnostic and prognostic roles of monitoring microcirculation, sepsis biomarkers and scoring tools for severity of illness is underway that may help in the rapid identification, diagnosis and management of these patients.

Other innovative therapies may eventually play a role in the treatment of sepsis. Examples include the administration of vasodilators, high-volume hemofiltration and corticosteroids for severe community-acquired pneumonia. In an early stage of severe sepsis, a patient may have normal or increased blood pressure after volume resuscitation despite signs of tissue hypoperfusion.¹⁸ Low-dose nitroglycerin (5–50 µg/min) may improve ScvO₂ by decreasing afterload when the mean arterial pressure is elevated, especially after volume resuscitation. Preliminary data also suggest that nitroglycerin may improve microcirculatory blood flow by allowing for capillary recruitment and increased perfusion.¹⁵⁹ High-volume hemofiltration with removal of inflammatory cytokines is another therapeutic strategy that may afford a mortality benefit for patients with early severe sepsis or septic shock.¹⁶⁰

In a recent preliminary multicentre trial, patients admitted to ICU with severe community-acquired pneumonia received protocol-guided antibiotic treatment and were randomly assigned to hydrocortisone infusion or placebo groups. Hydrocortisone was given as an intravenous 200-mg bolus followed by infusion at a rate of 10 mg/h for 7 days. The hydrocortisone group had significant improved chest radiograph scores ($p < 0.001$), C-reactive protein levels ($p = 0.01$), Multiple Organ Dysfunction Scores ($p = 0.003$) and delayed septic shock ($p = 0.001$). Hydrocortisone treatment was associated with shorter hospital stays ($p = 0.03$) and reduced mortality ($p = 0.009$).¹⁶¹ Future research shall help to determine if there may be roles for these therapies in the clinical arena.

Conclusion

Early recognition and prompt resuscitation during the first several hours of severe sepsis and septic shock optimizes outcome. Other therapies that can afford a mortality benefit for patients with severe sepsis and septic shock include the administration of corticosteroids, activated protein C, mechanical ventilation with low tidal volumes, and tight glycemic control. Specific emphasis on appropriate triage to ensure

prompt diagnosis of the high-risk patient is vital to the launch of a coordinated and cooperative effort by the primary treating clinician and the intensivist. Because the reversibility of this disease and the resultant mortality may be greatest during the earliest stages of presentation, proper sepsis management should not be confined within the walls of an ICU.

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Appendix 1: Internet resources

- ARDS Support Centre: www.ards.org
- American Sepsis Alliance: www.sepsisalliance.org
- ICU-USA: www.icu-usa.com
- Institute for Health Improvement: www.ihl.org
- International Sepsis Forum: www.sepsisforum.org
- Mayo Clinic: www.mayoclinic.com
- Society of Critical Care Medicine: www.sccm.org
- Volunteer Hospital Association: www.vha.com

Note: ARDS = adult respiratory distress syndrome.