

# New Strategies in the Management of Patients with Severe Sepsis

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# Factors of increases in the dx. of severe sepsis

- An increase in the number of immunocompromised and elderly patients
- The continued use of invasive medical procedures
- The emergence of antibiotic resistant micro-organisms



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- Appropriate management of the sepsis patient relies on awareness and sensitivity for the diagnosis as well as early treatment intervention.



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# Incidence and Cost of Sepsis

The average length-of-stay and cost-percase of sepsis is 19.6 days and \$22,100.

Costs are higher in infants, nonsurvivors, ICU patients, surgical patients, and patients with multiple organ failure. Annually, it is estimated that the United States spends \$16.7 billion for the treatment of sepsis.



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# Incidence and Cost of Sepsis

- Sepsis is responsible for over 200,000 deaths annually in the United States.
- Each year in the United States there are:
  - 200,000 cases of septic shock
  - 300,000 cases of severe sepsis
  - 400,000 cases of sepsis



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# Understanding and Defining Sepsis

TABLE 1. ACCP/SCCM CONSENSUS CONFERENCE DEFINITIONS<sup>6</sup>

## INFECTION

A microbial phenomenon characterized by an inflammatory response to the micro-organisms or the invasion of normally sterile host tissue by those organisms

## SYSTEMIC INFLAMMATORY RESPONSE SYNDROME (SIRS)

A systemic response that can result from a wide variety of clinical insults, including both infectious and non-infectious (e.g., trauma, burns, or pancreatitis) etiologies manifested by two or more of the following conditions:

- Temperature  $>38^{\circ}\text{C}$  or  $<36^{\circ}\text{C}$
- Heart rate  $>90$  beats/min
- Respiratory rate  $>20$  breaths/min or  $\text{PaCO}_2 <32$  mm Hg
- White blood cell count  $>12,000/\mu\text{L}$  or  $<4000/\mu\text{L}$  or  $>10\%$  immature (band) forms

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# Understanding and Defining Sepsis

## SEPSIS

Infection with concomitant SIRS ( $\geq 2$  more clinical symptoms)

## SEVERE SEPSIS

Sepsis associated with organ dysfunction, hypoperfusion, or hypotension

## SEPTIC SHOCK

A subset of severe sepsis with hypotension despite adequate fluid resuscitation along with the presence of perfusion abnormalities that may include, but are not limited to, lactic acidosis, oliguria, or an acute alteration in mental status

## MULTIPLE ORGAN DYSFUNCTION SYNDROME (MODS)

Presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention



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# Understanding Pathophysiology

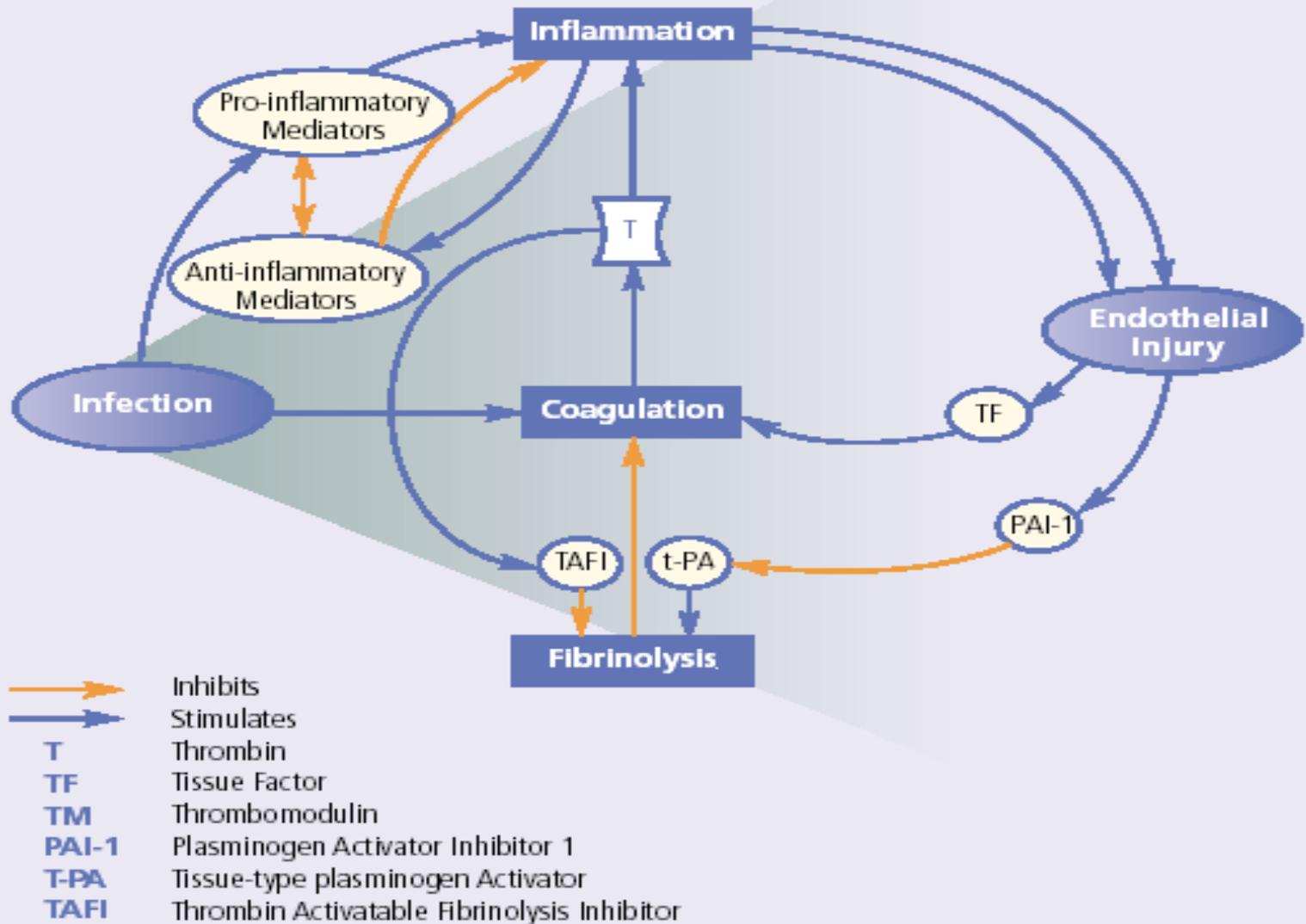
- Sepsis is a vicious cycle of inflammation and coagulopathy that spirals out of control farther and farther away from homeostasis.
- An overlapping triad of overactive systemic inflammation coupled with overactive coagulation and impaired fibrinolysis (see Figure 1).



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**FIGURE 1. SEPSIS: A NETWORK OF CASCADING EVENTS**



Bone and colleagues divided inflammatory and immunological features of sepsis into

- the infectious insult;
- the preliminary systemic response;
- the overwhelming systemic response;
- the compensatory anti-inflammatory reaction;
- the immunomodulatory failure.



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# PIRO: A New Way of Thinking

- Predisposition,
- Infection,
- Response,
- Organ dysfunction



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# Predisposition:

- Several genetic alterations have been found to lead to overexpression or over-responsiveness to infection.
- Premorbid illness, age, gender, and lifestyle habits



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# Infection:

- The type of infection, site of infection, and the extent of the infection are important variables in how the clinician will respond to and treat the infection.
- Other variables include how quickly the infection was treated and with what antibiotic.



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# Response:

- Response to infection involves a host of pro- and antiinflammatory mediators, such as IL-1, IL-6, IL-8, TNF, platelet activating factor (PAF), and heat shock proteins.



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# Organ dysfunction:

- A major component in the staging of sepsis is determining organ involvement.
- Whether a patient is mildly hypotensive, or hypotensive and in renal failure with poor cardiac function requiring multiple vassopressors.



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# Clinical Management of Sepsis

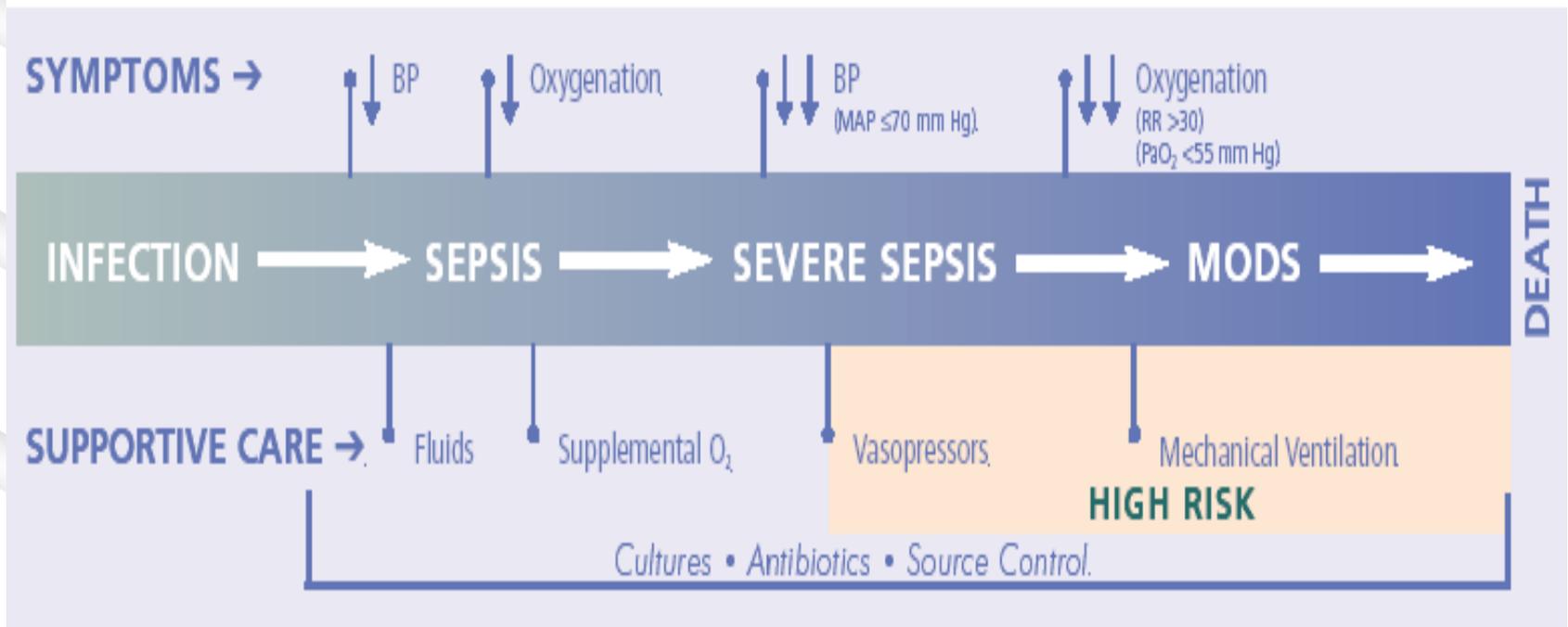
- Diagnosing and treating infection
- Maintaining adequate tissue oxygen delivery
- Preventing new and/or worsening organ dysfunction



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FIGURE 2. IDENTIFYING HIGH-RISK SEVERE SEPSIS



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# Prescribing Antibiotic Therapy

- The diagnosis and treatment of infection begins first with the identification of the source of infection and initiation of antibiotic therapy.



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# Prescribing Antibiotic Therapy

- Patient location (i.e., community acquired or nosocomial)
- Site of infection
- Likely infecting pathogenic organisms
- Local antimicrobial resistance patterns



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# Maintaining Oxygen Delivery

- Adequate oxygen to minimize the risk of developing organ dysfunction.
- Ventilation and hemodynamic support → if the patient is unable to maintain adequate gas exchange and perfusion.
- Early prompt resuscitation



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# Maintaining Oxygen Delivery

- Severe sepsis is the leading cause of ALI and an estimated 25% to 42% of septic patients progress to ARDS. Acute lung injury (ALI; bilateral chest infiltrates and a  $\text{PaO}_2/\text{FiO}_2$  ratio of less than or equal to 300 mm Hg) or acute respiratory distress syndrome (ARDS;  $\text{PaO}_2/\text{FiO}_2$  ratio of less than or equal to 200 mm Hg)



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# The Current Goals for Ventilatory Support in Sepsis Patients

- Maintenance of adequate oxygenation and acid-base status while avoiding alveolar overdistention.
- $\text{FiO}_2$  is reduced to 0.4–0.6.
- When ARDS is present, tidal volumes of 6 mL/kg of predicted body weight (to avoid alveolar overdistention and end-inspiratory plateau pressures from exceeding 30–35 cm H<sub>2</sub>O) are used.



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# The Current Goals for Ventilatory Support in Sepsis Patients

- Cardiac preload, afterload, and contractility to achieve a balance between systemic oxygen delivery and oxygen demand was reported.
- Rapid and targeted administration of IV fluids, correction of anemia, and use of vasoactive and inotropic agents.



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# The Current Goals for Ventilatory Support in Sepsis Patients

- Currently, in severe septic patients, transfusion can be considered as a part of volume resuscitation in patients with hemoglobin levels less than or equal to 7-8 Gm/L.
- transfused thresholds of 7 Gm/L seem just fine - and further transfusion is not necessary



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# Preventing Organ Dysfunction

- In general, organ dysfunction is managed using general supportive measures in addition to organ-specific management strategies.



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# Gastrointestinal Tract

- Maintain mucosal integrity and prevent translocation of microbial flora to prevent further microbial infection
- Initiating stress ulcer prophylaxis (H<sub>2</sub>-receptor antagonists, proton pump inhibitors, ..), especially in patients with prolonged mechanical ventilation, hypotension, and coagulopathy.



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# Renal system

- Maintenance of perfusion pressure and avoidance of nephrotoxins is recommended.
- The benefits of dopamine, diuretics, and/or fluid loading have not consistently been proven. In fact, a recent multicenter clinical trial showed that low-dose dopamine, which has been used to provide renal protection, is no more effective than placebo



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# The Current Goals for Ventilatory Support in Sepsis Patients

- more aggressive dialysis in chronic renal failure improves outcome.
- There are now some small studies suggesting that aggressive dialysis may also improve outcome in acute renal failure.



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- Traditional management of coagulation can include the supplementation of:
- Clotting factors (fresh frozen plasma can be considered when a patient is bleeding or requires an invasive procedure, or when prothrombin and/or activated thromboplastin times are prolonged)
- Platelets (when platelet counts are  $<20,000/\text{mm}^3$  or  $<50,000/\text{mm}^3$  with active bleeding)
- Vitamin K (in patients with prolonged prothrombin time, particularly if elderly or malnourished)



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- Currently, there are no clear guidelines on the use of clotting factors in sepsis.
- Use of clotting factors should be reserved for those patients who were at high risk of serious, life-threatening bleeding or were actively bleeding.
- While the coagulation system is adversely affected in virtually all severe septic patients, the vast majority probably do not need active treatment with replacement therapy.



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# Thromboprophylaxis

- Prevention of the development of deep venous thrombosis (DVT) and pulmonary embolism (PE) should be undertaken through prophylactic administration of a fixed-dose **unfractionated heparin, low-molecular-weight heparin**, or intermittent **venous compression devices**



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# Provide adequate oxygen delivery to tissues and organs

- maintaining a mean arterial pressure of at least 60 to 65 mm Hg
- cardiac index in the high-normal range.
- urine output of at least 0.75 mL/kg/h and minimizing
- lactic acidosis.
- Monitoring of electrolytes and pH is important;
- normalization of pH with sodium bicarbonate administration is no longer standard practice.



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# Provide adequate oxygen delivery to tissues and organs

- In a single center, prospective, randomized clinical trial of 1548 patients,
- blood glucose between 80 and 110 mg/dL (intensive insulin treatment) versus conventional treatment (insulin treatment only if blood glucose exceeds 215 mg/dL).

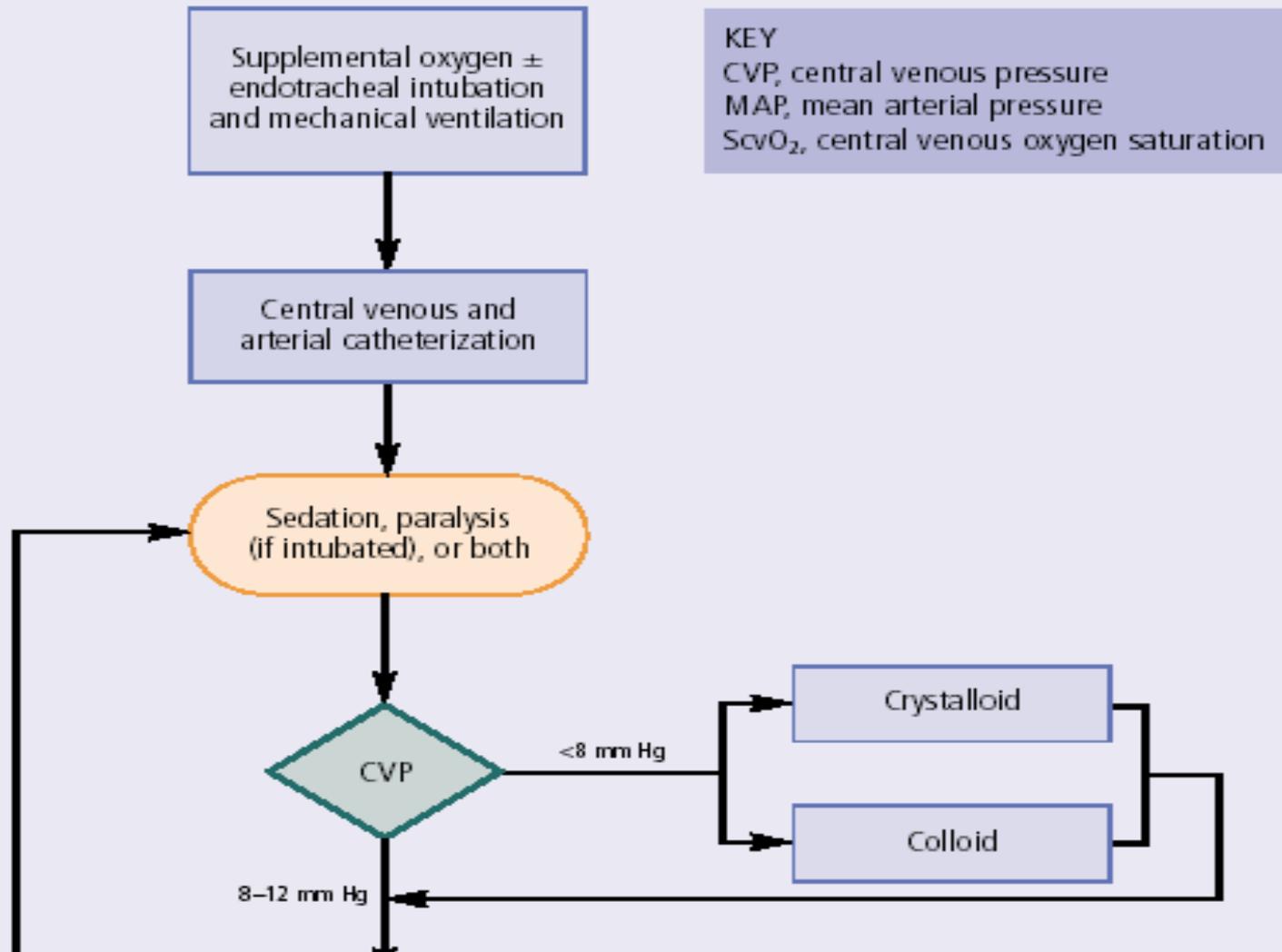
Reduced mortality from 8.0% to 4.6%  
( $P < 0.04$ )



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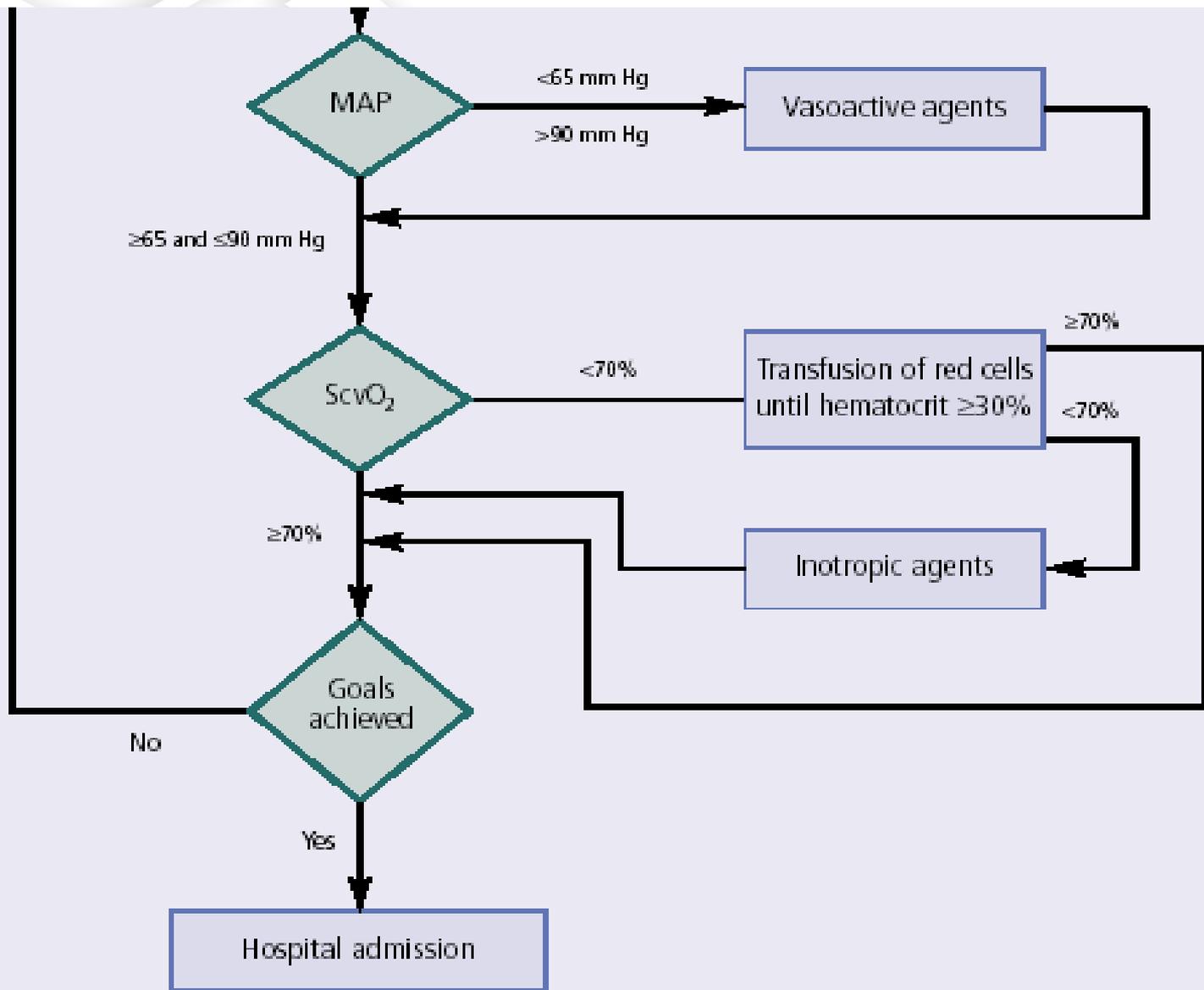
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FIGURE 3. PROTOCOL FOR EARLY GOAL-DIRECTED THERAPY<sup>18</sup>



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# Benefits of intensive insulin therapy

- reduced overall in-hospital mortality (34%),
- bloodstream infections (46%),
- acute renal failure requiring dialysis or hemofiltration (41%),
- median number of red-cell transfusions (50%),
- critical illness polyneuropathy (44%).



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# Adrenocortical Support

- Received hydrocortisone (50 mg IV q6h) and fludrocortisone (50 µg PO once daily for 7 days) versus placebo.
- Benefit to patients who had relative adrenal insufficiency, defined as an increase in serum cortisol of less than 9 µg/dL after receiving cosyntropin.
- Patients who had relative adrenal insufficiency also were weaned off vasopressor more rapidly if they received corticosteroids.



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# Activated Protein C

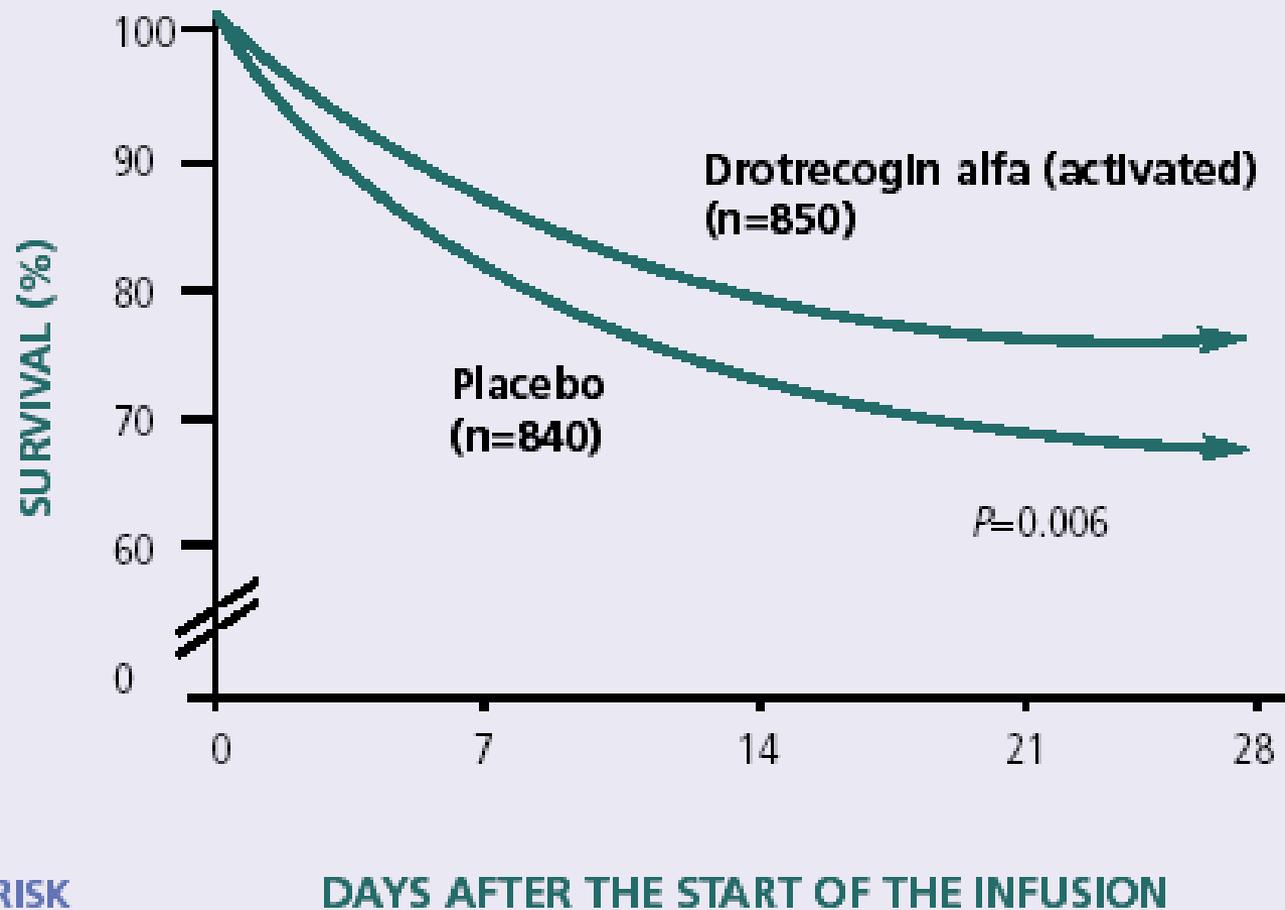
- The phase III trial conducted by Bernard and colleagues looked at the effect of activated protein C (drotrecogin alfa [activated]) on patients with severe sepsis.
- This trial, called PROWESS (Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis) prospective, randomized, doubleblind, placebo-controlled, phase III, multicenter trial to examine the efficacy of this treatment to reduce 28- day mortality (see Figure 4).



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FIGURE 4. RESULTS OF PROWESS TRIAL<sup>27</sup>



NO. AT RISK

DAYS AFTER THE START OF THE INFUSION

**Drotrecogin alfa  
(activated)**

850

737

684

657

640

**Placebo**

840

705

639

602

581

# Investigational Treatments

- Experimental exogenous modulators of coagulation include thromboxane inhibitors, antithrombin, and tissue factor pathway inhibitors.



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# Conclusion

- Recently, new advances in the management of severe sepsis and septic shock have demonstrated improved survival for these critically ill patients.
- maintaining normal blood glucose levels,
- early goal-directed therapy,
- steroids for septic shock,
- activated protein C for severe sepsis.



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