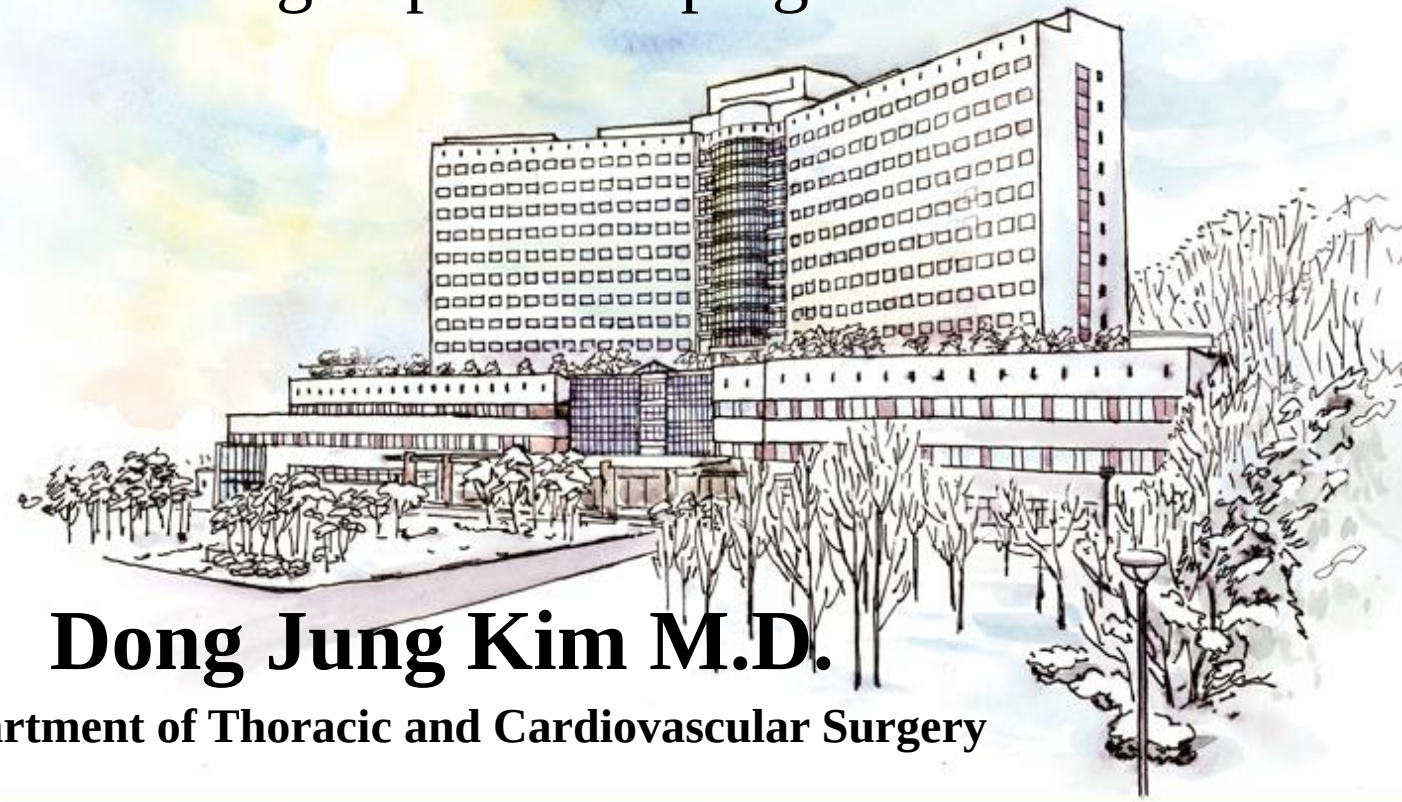
흉부외과 전공의 연수강좌

# Management of Sepsis

## Surviving Sepsis Campaign



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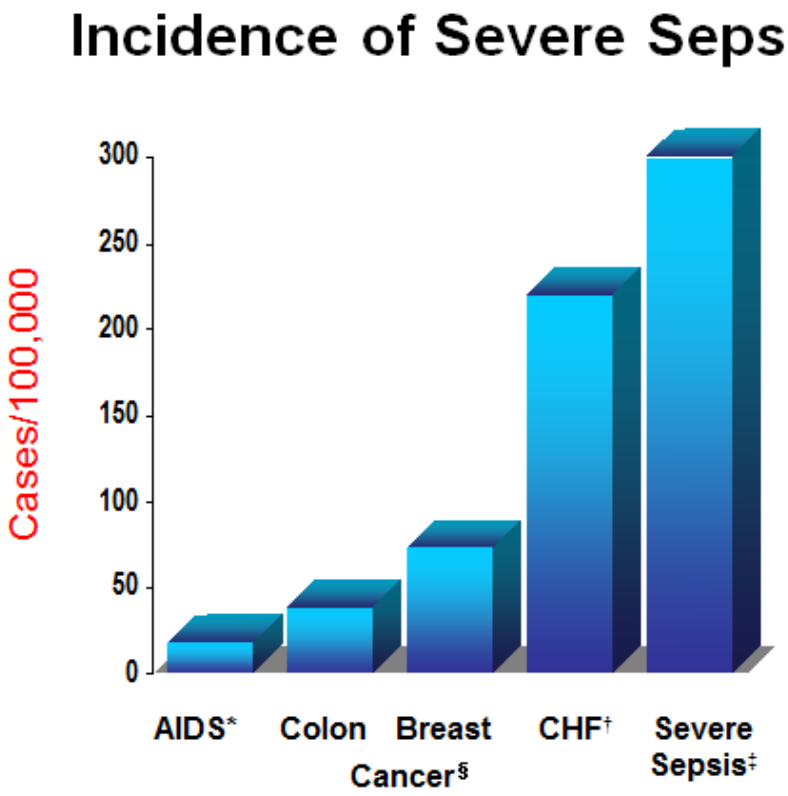
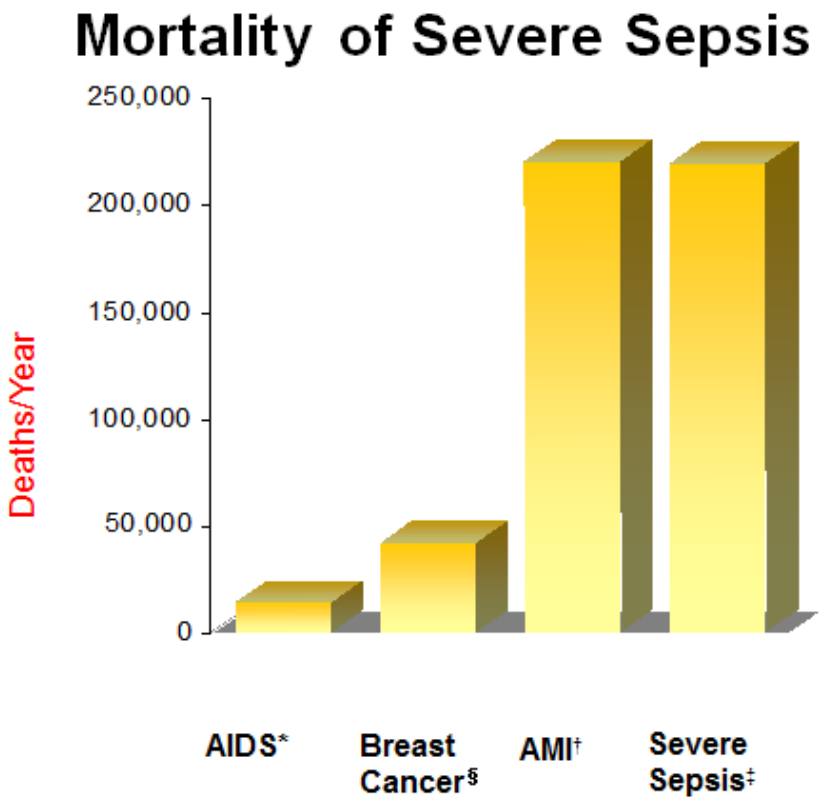
# What is sepsis?

- Infection
- SIRS (systemic inflammatory response syndrome)
- Severe sepsis
- Septic shock

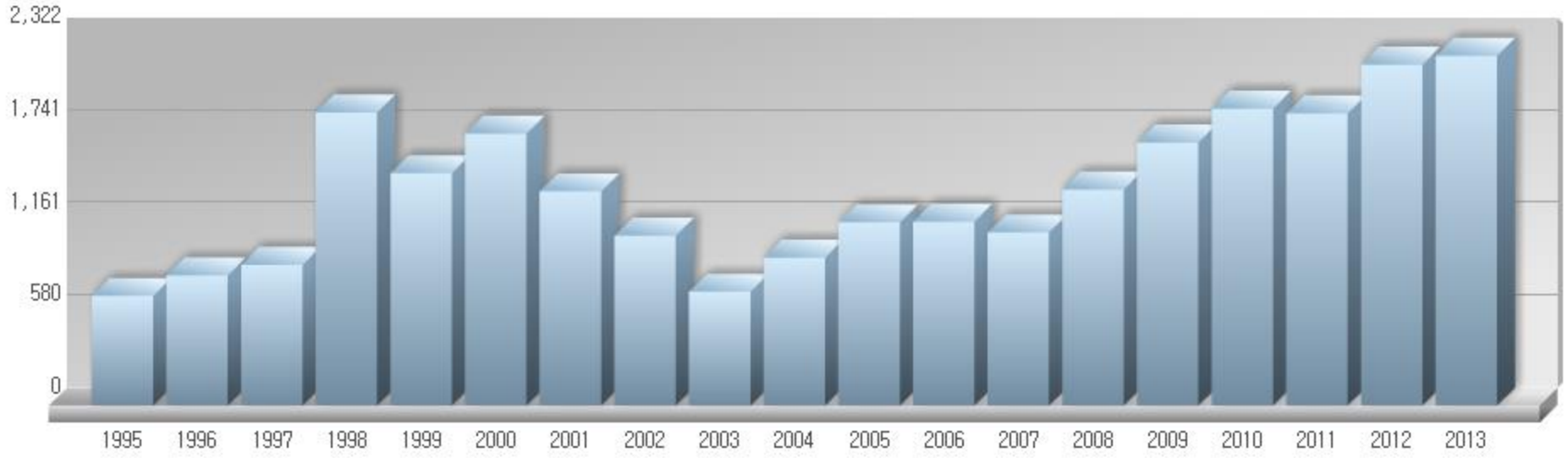
# Comparison with Other Major Diseases




†National Center for Health Statistics, 2001. § American Cancer Society, 2001. *American Heart Association. 2000. ‡Angus DC et al. *Crit Care Med.* 2001

# Mortality of Severe Sepsis in Korea




KOSIS 국가통계포털
KOrean Statistical Information Service

# Diagnositc criteria

**Sepsis (documented or suspected infection plus ≥1 of the following)†**

General variables

- Fever (core temperature, >38.3°C)
- Hypothermia (core temperature, <36°C)
- Elevated heart rate (>90 beats per min or >2 SD above the upper limit of the normal range for age)
- Tachypnea
- Altered mental status
- Substantial edema or positive fluid balance (>20 ml/kg of body weight over a 24-hr period)
- Hyperglycemia (plasma glucose, >120 mg/dl [6.7 mmol/liter]) in the absence of diabetes

Inflammatory variables

- Leukocytosis (white-cell count, >12,000/mm$^3$)
- Leukopenia (white-cell count, <4000/mm$^3$)
- Normal white-cell count with >10% immature forms
- Elevated plasma C-reactive protein (>2 SD above the upper limit of the normal range)
- Elevated plasma procalcitonin (>2 SD above the upper limit of the normal range)

Hemodynamic variables

- Arterial hypotension (systolic pressure, <90 mm Hg; mean arterial pressure, <70 mm Hg; or decrease in systolic pressure of >40 mm Hg in adults or to >2 SD below the lower limit of the normal range for age)
- Elevated mixed venous oxygen saturation (>70%)‡
- Elevated cardiac index (>3.5 liters/min/square meter of body-surface area)§

Organ-dysfunction variables

- Arterial hypoxemia (ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen, <300)
- Acute oliguria (urine output, <0.5 ml/kg/hr or 45 ml/hr for at least 2 hr)
- Increase in creatinine level of >0.5 mg/dl (>44 μmol/liter)
- Coagulation abnormalities (international normalized ratio, >1.5; or activated partial-thromboplastin time, >60 sec)
- Paralytic ileus (absence of bowel sounds)
- Thrombocytopenia (platelet count, <100,000/mm$^3$)
- Hyperbilirubinemia (plasma total bilirubin, >4 mg/dl [68 μmol/liter])

Tissue-perfusion variables

- Hyperlactatemia (lactate, >1 mmol/liter)
- Decreased capillary refill or mottling

**Severe sepsis (sepsis plus organ dysfunction)**

**Septic shock (sepsis plus either hypotension [refractory to intravenous fluids] or hyperlactatemia)¶**

*N Engl J Med 2013; 369:840-851*

# SCCM Consensus Definitions

- Infection
  - Inflammatory response to microorganisms, or invasion of normally sterile tissues
- Systemic Inflammatory Response Syndrome (SIRS)
  - Systemic response to a variety of processes
- Sepsis
  - Infection with ≥ 2 SIRS criteria

# ACCP/SCCM Consensus Definitions

- Severe Sepsis
  - Sepsis with organ dysfunction
- Septic shock
  - Sepsis with hypotension despite fluid resuscitation

# SIRS

- A systemic response to a nonspecific insult
  - **Infection**, trauma, surgery, massive transfusion, etc
- Defined as 2 of the following:

General variables

- Fever (core temperature, >38.3°C)
- Hypothermia (core temperature, <36°C)
- Elevated heart rate (>90 beats per min or >2 SD above the upper limit of the normal range for age)
- Tachypnea
- Altered mental status
- Substantial edema or positive fluid balance (>20 ml/kg of body weight over a 24-hr period)
- Hyperglycemia (plasma glucose, >120 mg/dl [6.7 mmol/liter]) in the absence of diabetes

Inflammatory variables

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*N Engl J Med 2013; 369:840-851*

# Sepsis

- SIRS due to an infection

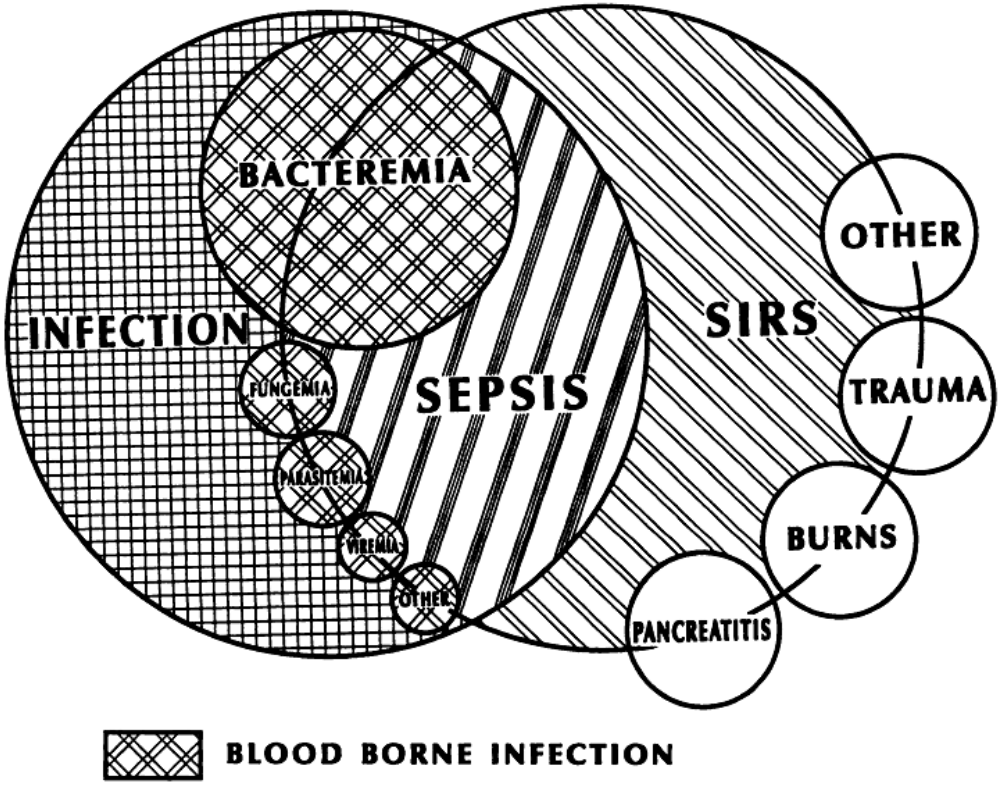
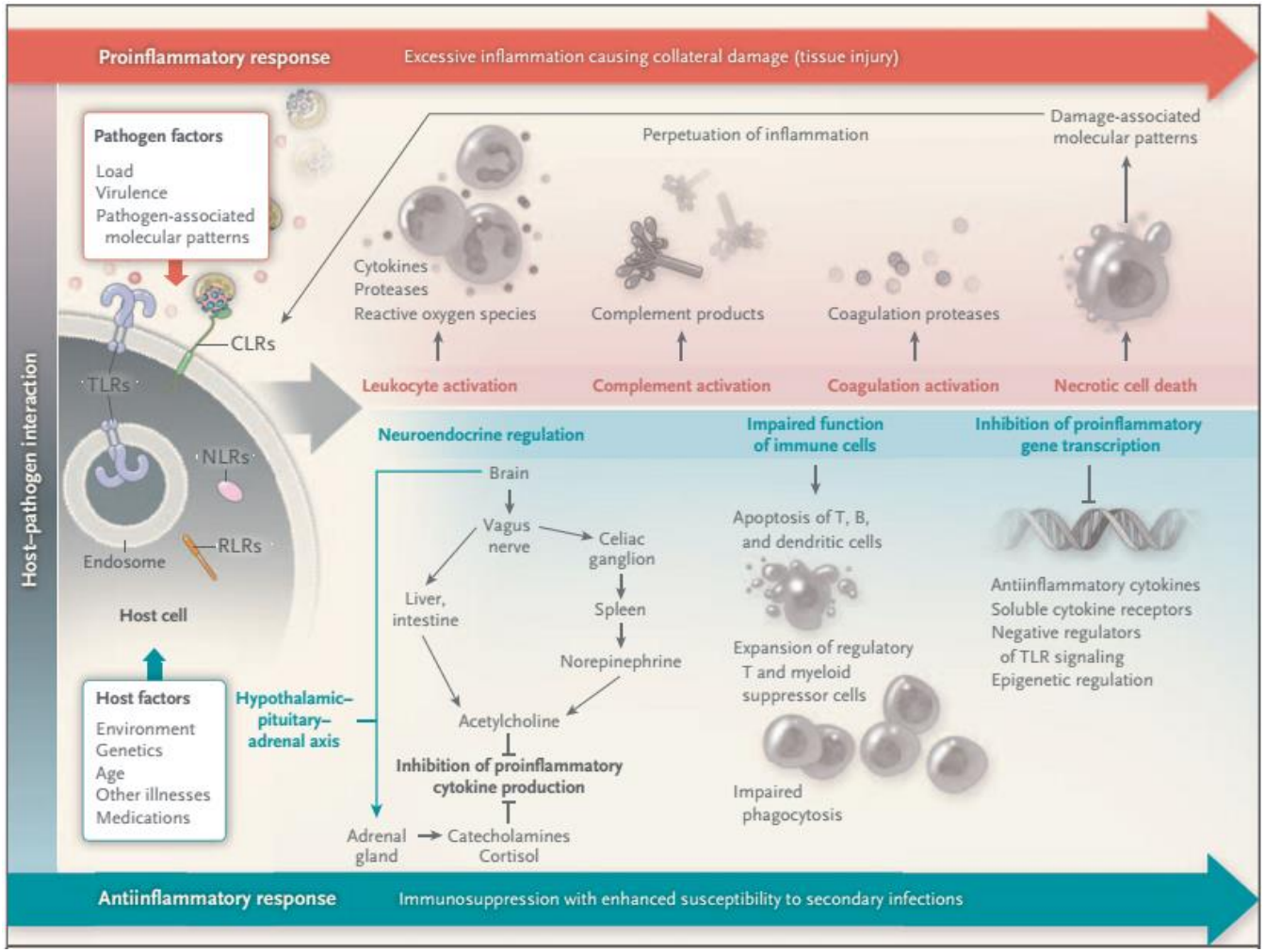



FIGURE 1. The interrelationship between systemic inflammatory response syndrome (SIRS), sepsis, and infection.

*Chest 1992;101:1644*

# Host response to sepsis




*N Engl J Med 2013; 369:840-851*

# Severe sepsis

- Sepsis with organ dysfunction, hypoperfusion or hypotension

Organ-dysfunction variables

- Arterial hypoxemia (ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen, <300)
- Acute oliguria (urine output, <0.5 ml/kg/hr or 45 ml/hr for at least 2 hr)
- Increase in creatinine level of >0.5 mg/dl (>44 μmol/liter)
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- Thrombocytopenia (platelet count, <100,000/mm$^3$)
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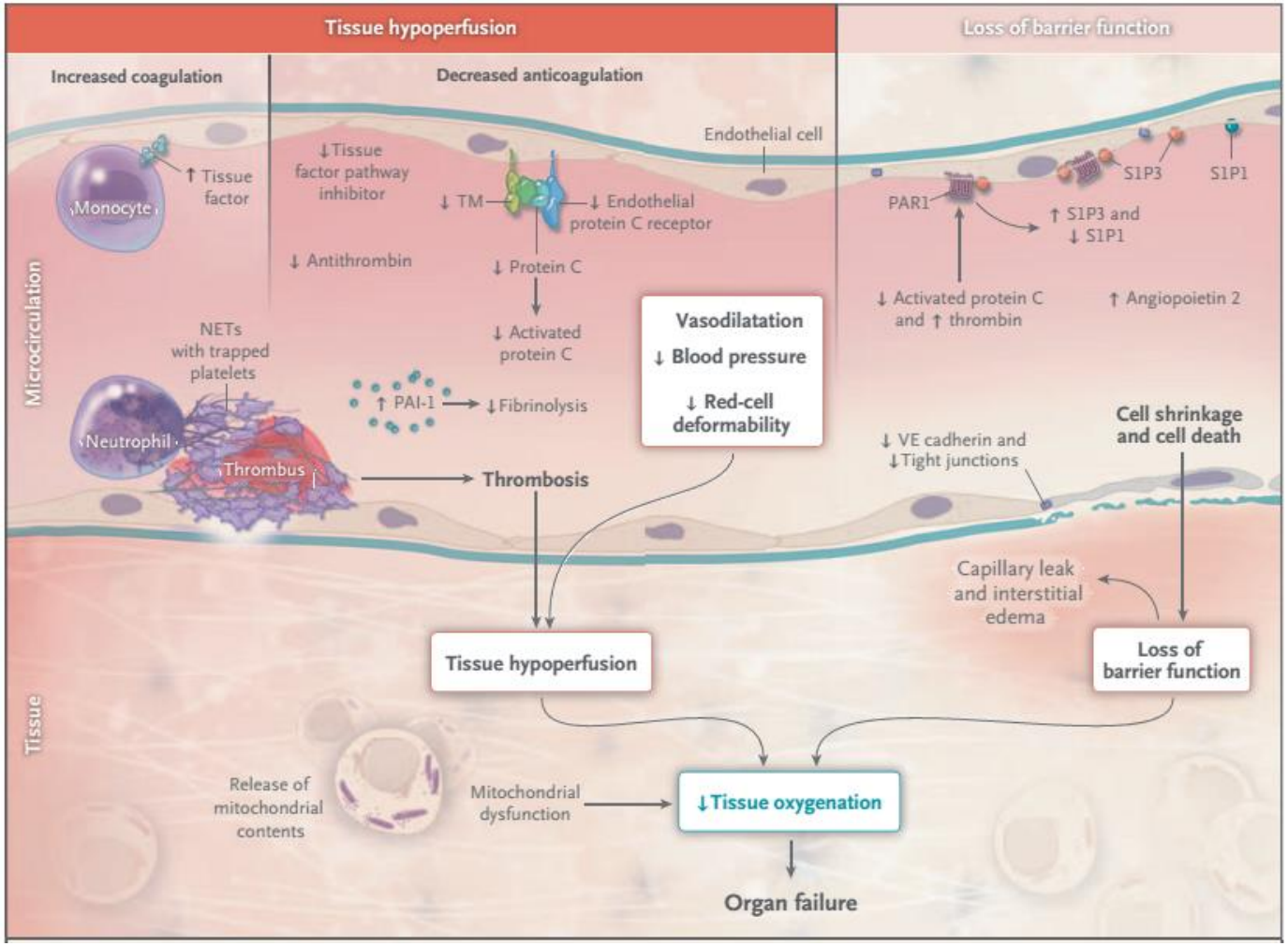
*N Engl J Med 2013; 369:840-851*

# Organ faiulre in severe sepsis




*N Engl J Med 2013; 369:840-851*

# Septic shock

- Shock
  - Tissue perfusion is not adequate for the tissues' metabolic requirements
  - Type : cardiogenic, neurogenic, hypovolemic, anaphylactic…
- Septic shock
  - Shock secondary to systemic inflammatory response to a new infection

# Septic shock

- Sepsis plus
  - Refractory hypotension
    - persistent hypotension or a requirement for vasopressors after the administration of an intravenous fluid bolus
  - Hyperlactatemia

Hemodynamic variables

Arterial hypotension (systolic pressure, <90 mm Hg; mean arterial pressure, <70 mm Hg; or decrease in systolic pressure of >40 mm Hg in adults or to >2 SD below the lower limit of the normal range for age)

Elevated mixed venous oxygen saturation (>70%)‡

Elevated cardiac index (>3.5 liters/min/square meter of body-surface area)§

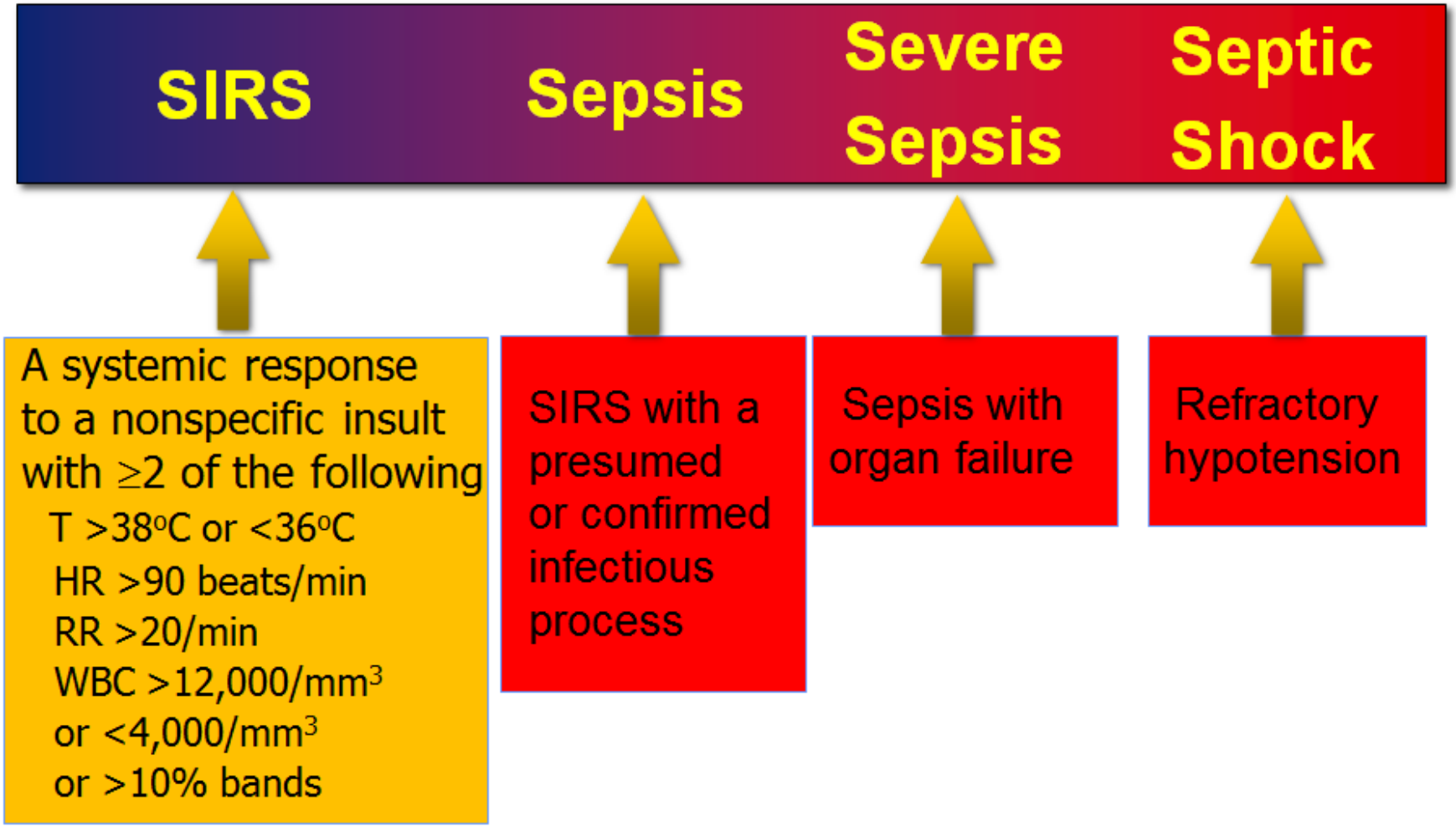
Tissue-perfusion variables

Hyperlactatemia (lactate, >1 mmol/liter)

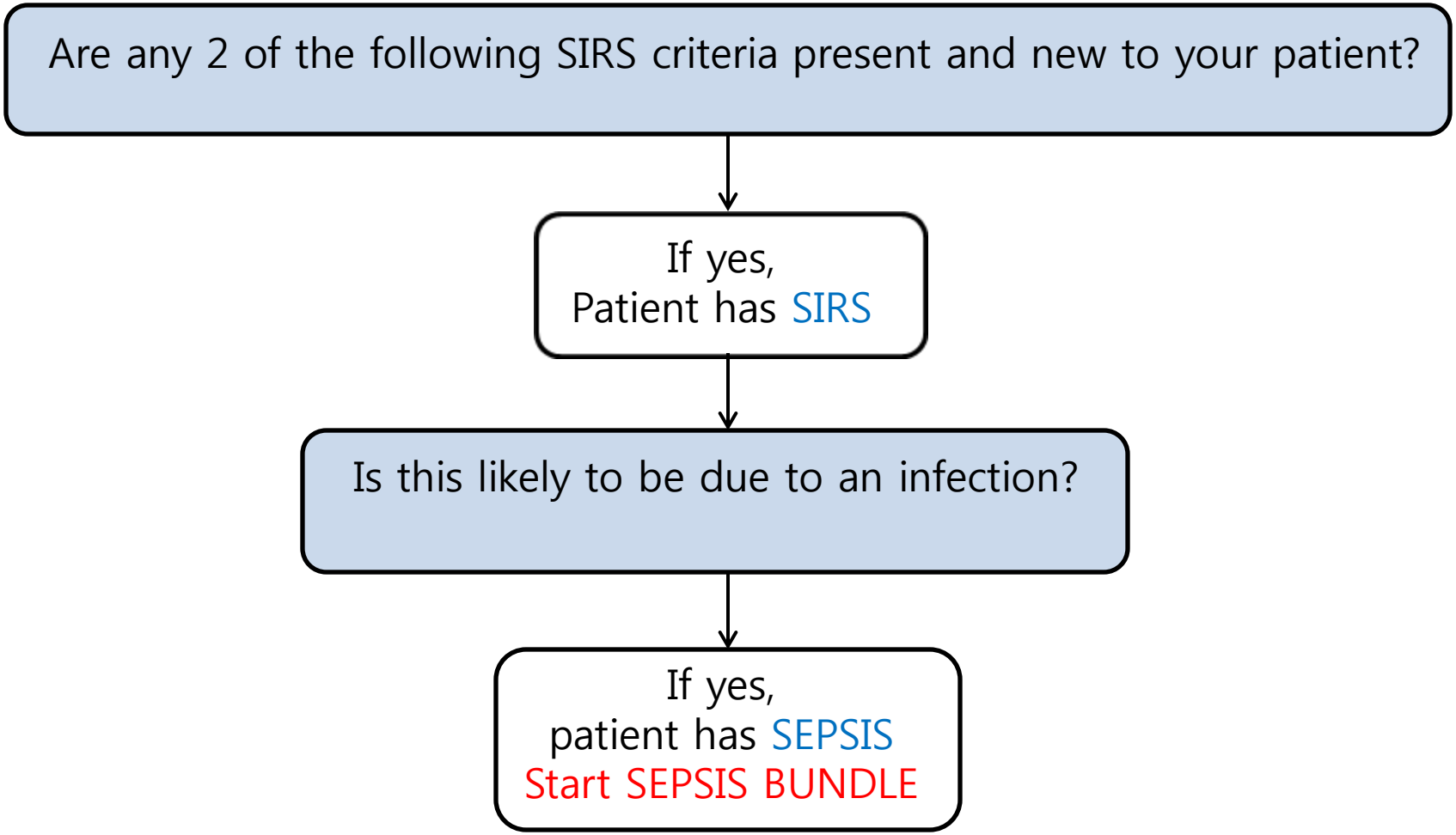
Decreased capillary refill or mottling

*N Engl J Med 2013; 369:840-851*

# The Sepsis Continuum



# Severe Sepsis Screening



# What is a Bundle?

- From evidence based guidelines
- Specifically selected care elements
- Implemented together provide improved outcomes compared to individual elements alone

# Initial Resuscitation Bundle

- To Be Completed in 3 hours:
  - Measure *lactate* level
  - Obtain *cultures* prior to administration of antibiotics
  - Administer broad spectrum *antibiotics*
  - Administer 30ml/kg *crystalloid* for hypotension or lactate greater than or equal to 4mmol/kg

*Crit Care Med. 2013 Feb;41(2):580-637*

# Septic Shock Bundle

- To be Completed Within 6 Hours:
  - Apply *vasopressors* (for hypotension that does not respond to initial fluid resuscitation) to maintain a *mean arterial pressure* (MAP) greater than or equal to 65mmHg
  - In the event of persistent arterial hypotension despite volume resuscitation (septic shock) or initial lactate greater than or equal to 4mmol/L
    - Measure *central venous pressure* (CVP)*
    - Measure *central venous oxygen saturation* (ScvO2)*
  - Remeasure *lactate* if initial lactate was elevated*

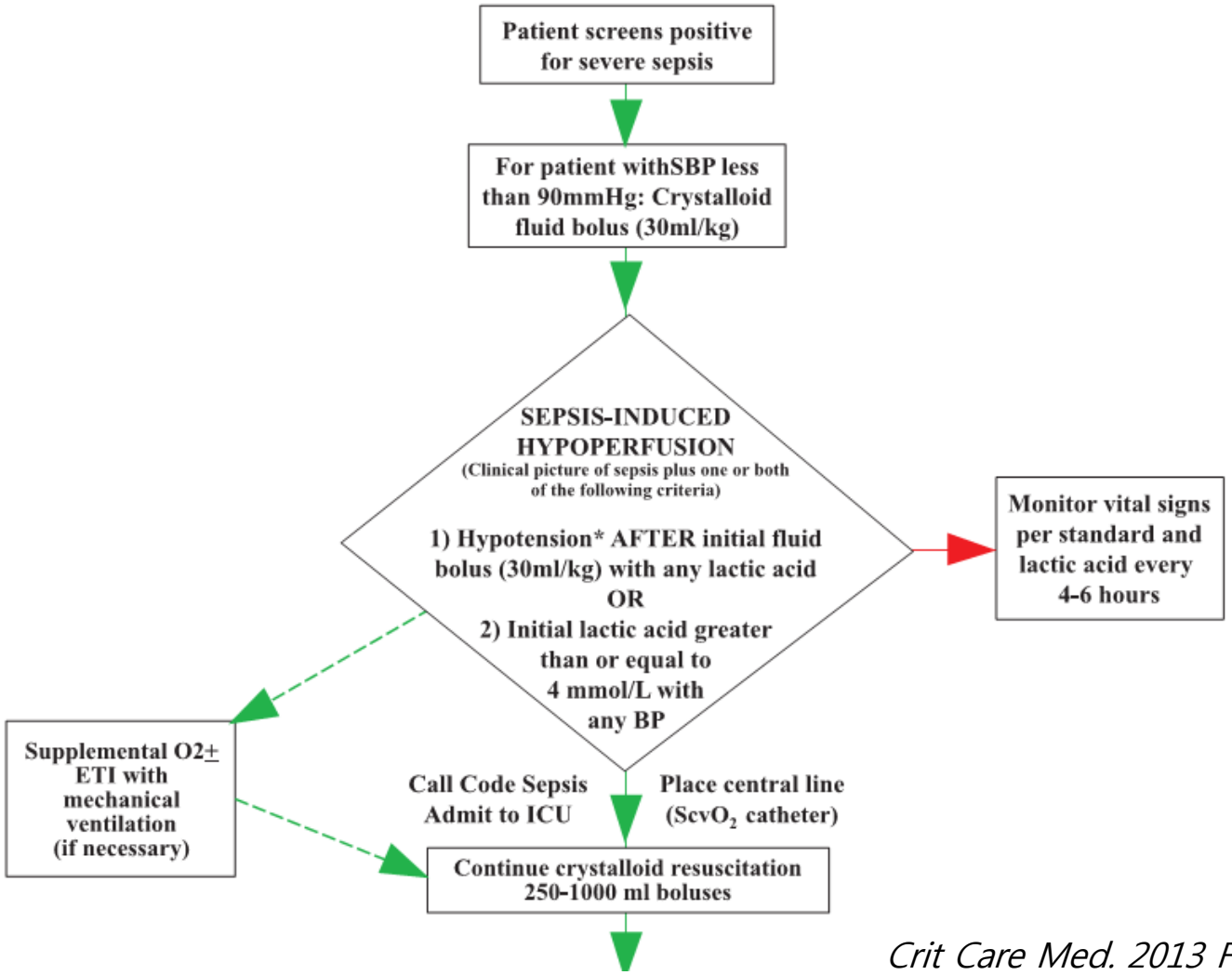
*Crit Care Med. 2013 Feb;41(2):580-637*

# Septic Shock Bundle

- Targets for quantitative resuscitation
  - CVP greater than or equal to 8mmHg
  - ScvO2 greater than or equal to 70%
  - Normalization of lactate

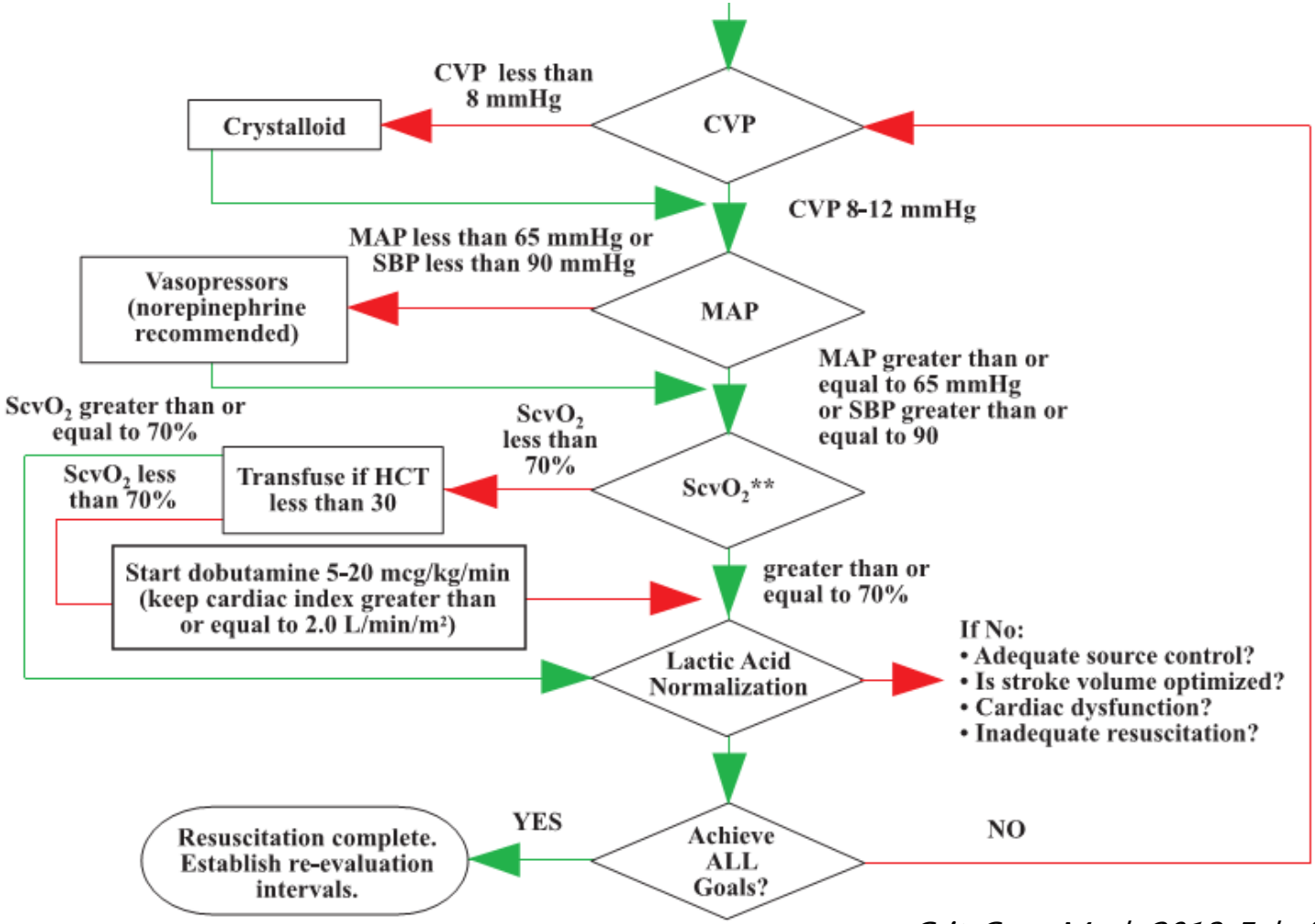
*Crit Care Med. 2013 Feb;41(2):580-637*

# Septic Shock Resuscitation Algorithm




*Crit Care Med. 2013 Feb;41(2):580-637*

# Septic Shock Resuscitaion Algorithm




*Crit Care Med. 2013 Feb;41(2):580-637*

# Oxygen Kinetics

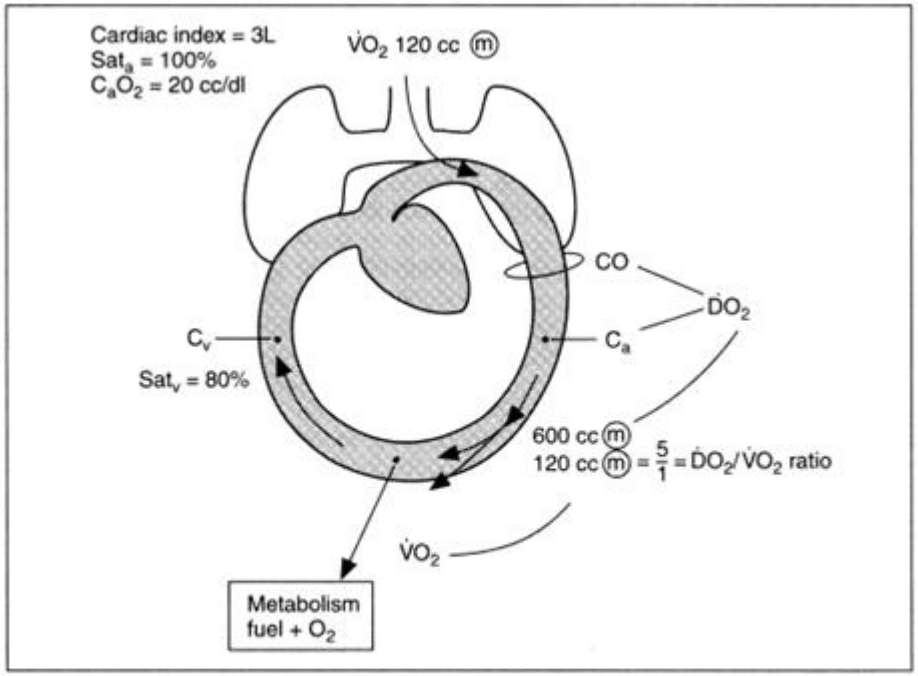



**FIGURE 1-1.** Oxygen kinetics. Oxygen delivery ($\dot{D}O_2$) is the product of cardiac output ($CO$) times the arterial oxygen content ($C_a$). Oxygen delivery is normally four to five times oxygen consumption ($\dot{V}O_2$). ($C_v$ = venous oxygen content; ⓜ = /min/m$^2$; Sat$_a$ = arterial saturation; Sat$_v$ = venous saturation.)

*Critical Care Physiology, Robert H. Bartlett, p2*

# Relationship between $VO_2$ and $DO_2$

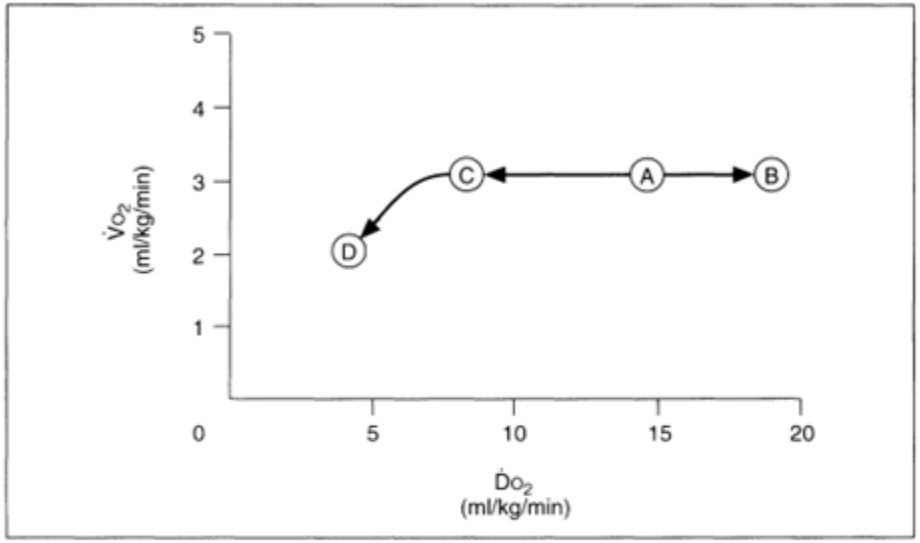



**FIGURE 1-11.** The normal relationship between $\dot{V}O_2$ and $\dot{D}O_2$. The normal point (*A*) is shown as $\dot{V}O_2$ 120 cc/m$^2$/min and $\dot{D}O_2$ 600 cc/m$^2$/min. If $\dot{D}O_2$ is increased by transfusion (*B*), $\dot{V}O_2$ remains constant. If $\dot{D}O_2$ is progressively decreased (*A* to *C*), $\dot{V}O_2$ remains constant until the ratio of $\dot{D}O_2/\dot{V}O_2$ falls below 2:1 (*C* to *D*).

*Critical Care Physiology, Robert H. Bartlett, p16*

# $VO_2$ and $DO_2$

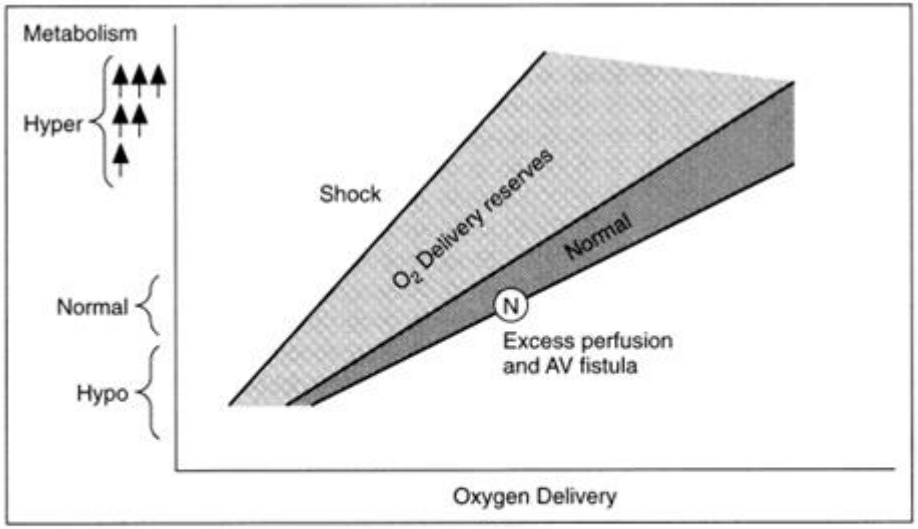


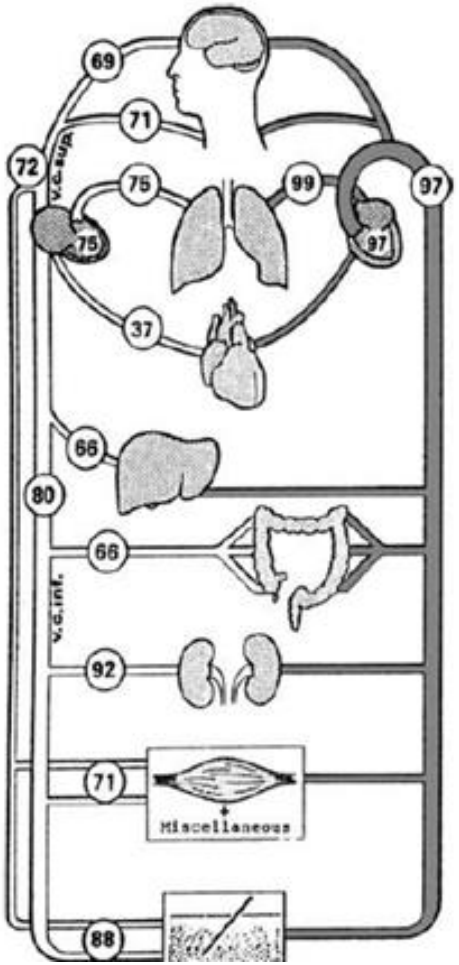

**FIGURE 1-13.** Interpreting the $\dot{D}O_2/\dot{V}O_2$ diagram. In this diagram the relationships shown in Figures 1-11 and 1-12 are demonstrated without specific numerical values to emphasize the difference between normal relationships, the utilization of oxygen delivery reserves, and shock. (AV = arteriovenous; Ⓝ = normal.)

*Critical Care Physiology, Robert H. Bartlett, p17*

# $SvO_2$

- In an average adult
  - $DO_2$ : 1000ml/min, $VO_2$ : 200ml/min
  - $DO_2/VO_2$ = 5:1
- The amount of $O_2$ extracted : 20% of delivery
- 80% of $O_2$ : in venous blood → return to heart
- The saturation of mixed venous blood : 80%

# Mixed venous blood



# $SvO_2$ and $DO_2/VO_2$ ratio

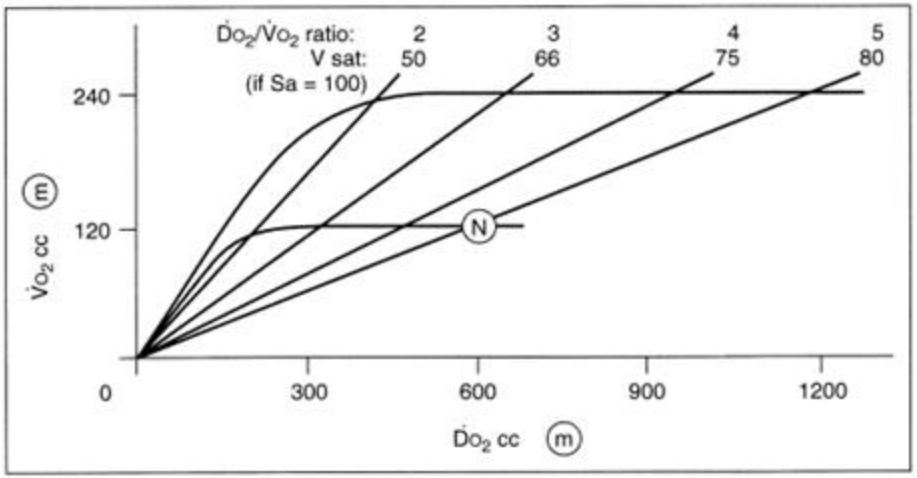


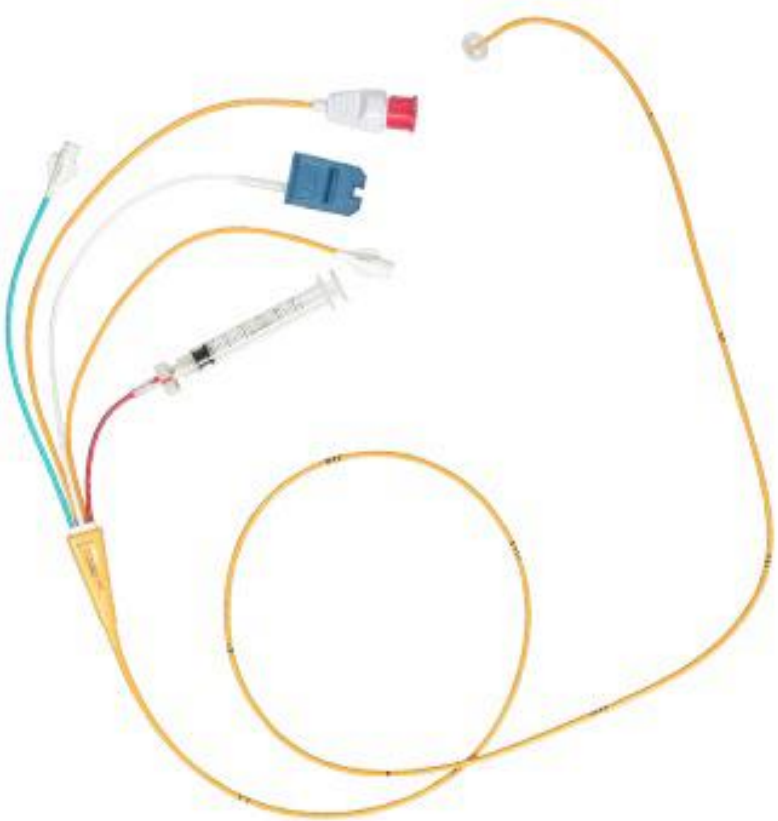

**FIGURE 1-12.** $\dot{D}O_2/\dot{V}O_2$ relationships during normal metabolism (as in Figure 1-11) and during hypermetabolism. During normal, hypometabolic, or hypermetabolic states the normal ratio of delivery to consumption is 5:1. This results in 80% venous saturation (*V sat*) if the arterial blood is 100% saturated. The isobar for the 5:1 ratio is demonstrated in this diagram, as well as the isobar for the 4:1, 3:1, and 2:1 ratios. Corresponding levels of venous saturation are shown. A state of decreasing oxygen consumption in which consumption is supply dependent occurs when the ratio is less than 2:1. (ⓜ = /min/$m^2$; Sa = arterial saturation.)

*Critical Care Physiology, Robert H. Bartlett, p17*

# $SvO_2$ monitoring

- Accurate representation of $DO_2/VO_2$ ratio
- Can be monitored continuously
  - in the pulmonary artery
  - with the Swan-Ganz Oximetry catheter

# Swan-Ganz catheter



# Reflection spectrophotometry

- Transmitting light of selected wavelengths
  - Through fiberoptic filament in the catheter body
  - To the blood flowing past the catheter tip

- Reflected light is then transmitted back
  - Through the second fiberoptic filament
  - To a photodetector located in the optical module
  - Hemoglobin and oxyhemoglobin absorb light differently at the selected wavelengths

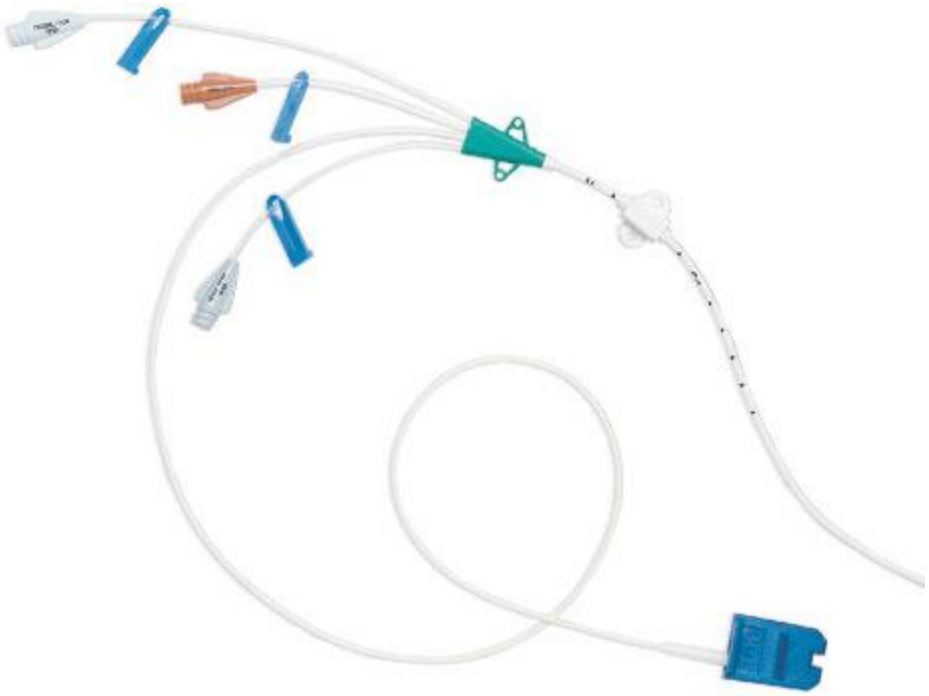
# Complications of Swan-Ganz catheter

- Pulmonary artery perforation
  - Occur during insertion
  - Mortality > 30 %
  - Usually requires emergent thoracotomy
- Pulmonary infarction
  - Migration of the catheter tip
  - Balloon left inflated in the wedge position
- Thromboembolic events, Arrhythmia

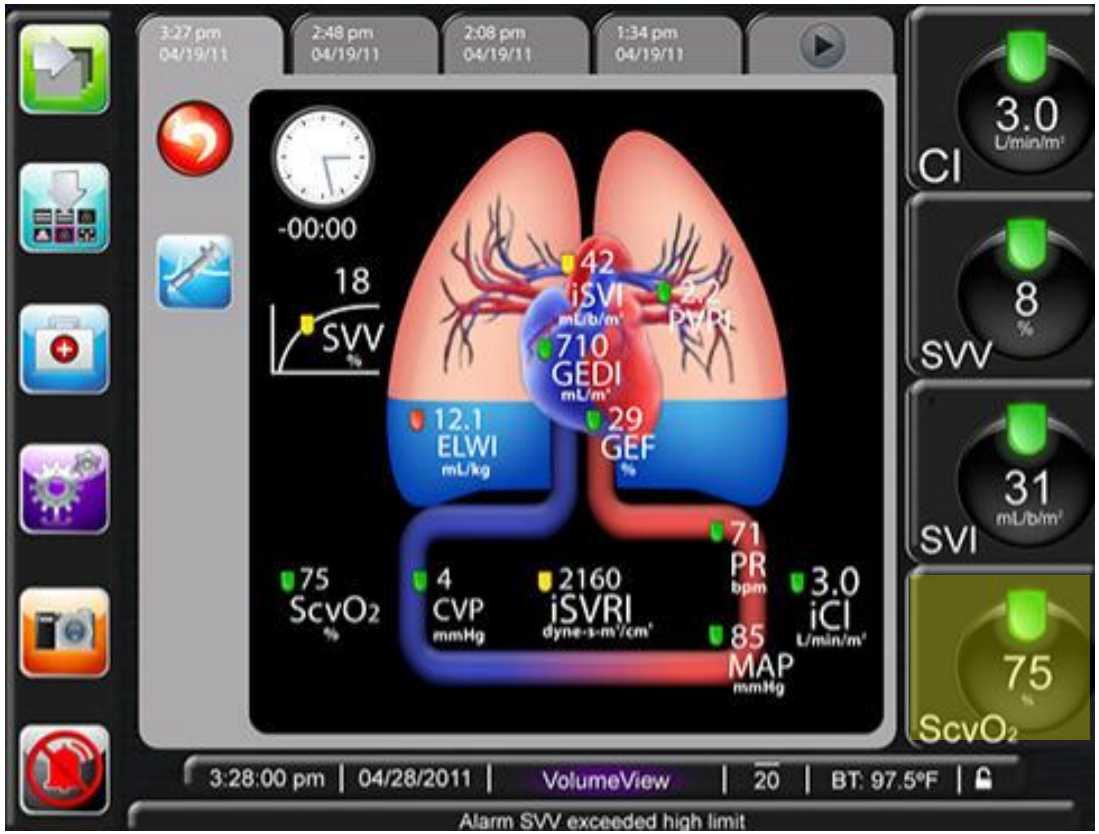
# $ScvO_2$

- Central venous oxygen saturation
- Regular central venous catheter coupled with a fiberoptic lumen
- Placed through a jugular or a subclavian vein at the SVC

# $ScvO_2$ monitoring



# $ScvO_2$ monitoring



# $SvO_2$ and $ScvO_2$

- $SvO_2$ : surrogate for global tissue oxygenation
  - Upper body + Lower body + coronary sinus

- $ScvO_2$ : essentially reflects the oxygenation of the upper part of the body
  - Head, neck, upper limbs, and upper part of trunk
  - $ScvO_2 > SvO_2$

# $ScvO_2$ – Validated Parameter ?

Table 1: Summary of the studies comparing $SvO_2$ and $ScvO_2$ in humans or in experimental models.

| Author (year) | Type of patients ($n$) | Conclusion | Correlation coefficient |
|---|---|---|---|
| Tahvanainen et al. [13] (1982) | Intensive care (42) | $ScvO_2 = SvO_2$ | NC |
| Wendt et al. [14] (1990) | Intensive care (19) | $ScvO_2 \sim SvO_2$ | 0,78 |
| Kong et al. [15] (1990) | Kidney failure (8) | $ScvO_2 \sim SvO_2$ | NC |
| Berridge et al. [16] (1992) | Intensive care (51) | $ScvO_2 = SvO_2$ | 0,92 |
| Herrera et al. [17] (1993) | Thoracic surgery (23) | $ScvO_2 = SvO_2$ | NC |
| Pieri et al. [18] (1995) | Major surgery (39) | $ScvO_2 \neq SvO_2$, nonsubstituable | 0,90 |
| Ladakis et al. [19] (2001) | Intensive care (61) | $ScvO_2 = SvO_2$ | 0,94 |
| Reinhart et al. [11] (2004) | Intensive care (32) | $ScvO_2 \sim SvO_2$ | 0,81 |
| Chawla et al. [20] (2004) | Intensive care (53) | $ScvO_2 > SvO_2$ | 0.88 |
| Dueck et al. [21] (2005) | Neurosurgery (70) | $ScvO_2 \neq SvO_2$, substituable evolution | $\geq$0,75 |
| Ho et al. [22] (2010) | Intensive care | $ScVO_2 \neq SvO_2$, nonsubstituable | NC |

*Cardiology Research and Practice 2012; Article ID 370697*

# $ScvO_2$ – Clinical Validation

- Considered as a suitable prognosis factor in many clinical situations
  - Myocardial infarction
  - Acute heart failure
  - Severe sepsis
    - Surviving Sepsis Campaign, European guidelines
    - First 6 hours of management ($ScvO_2$ > 70%)

# $ScvO_2$ – Theoretical Limit

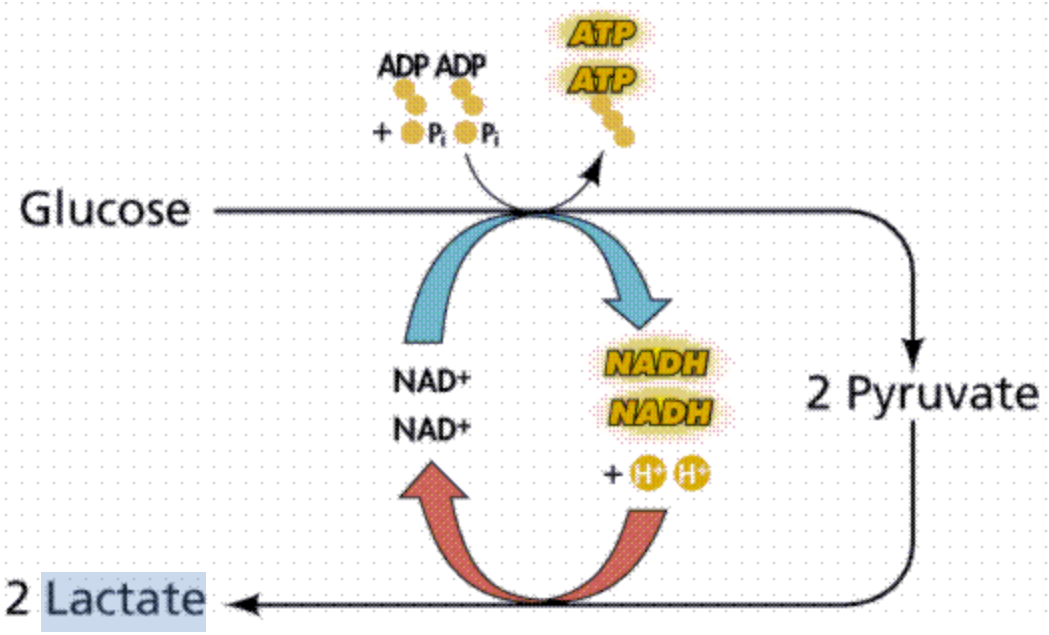
- Does **not** include venous blood coming from **coronary sinus**
  - The most deoxygenated venous blood (40%)
- Does **not** take into account the **myocardial $O_2$ supply/demand** adequacy
- Major increase in myocardial $O_2$ consumption
  - No impact on $ScvO_2$ monitoring

# $ScvO_2$ – Clinical Limit

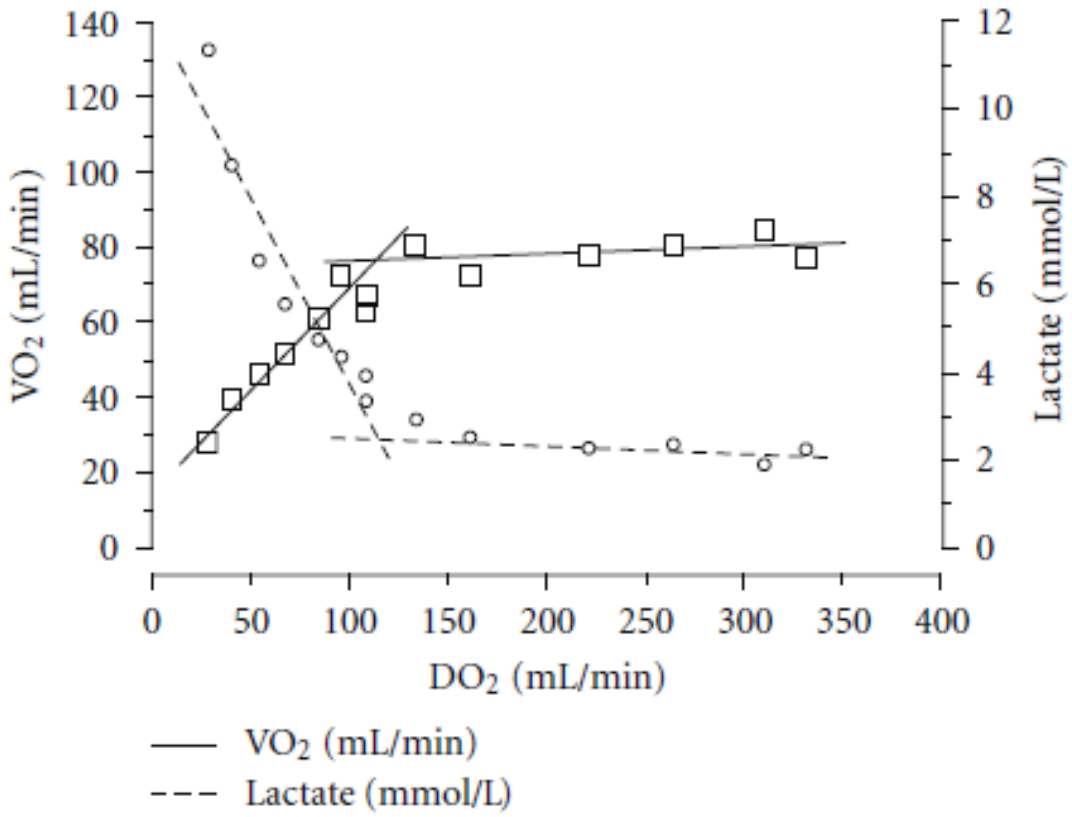
- Early stage of sepsis
  - Tissue hypoperfusion : low $ScvO_2$
- After the first 6 hours of resuscitation
  - Paradoxically normal or even raised $ScvO_2$
    - Tissue $O_2$ extraction capacity ↓
    - Capillary shunt ↑
    - Changes in hemoglobin affinity for $O_2$

# Lactate

- The result of inadequate $DO_2$
  - slows mitochondrial metabolism → pyruvate is converted to lactate → anaerobic metabolism



# Lactate




*Intensive Care Medicine, vol. 30, no. 11, pp. 1990–1996, 2004*

# Lactate + $ScvO_2$

## Early Lactate-Guided Therapy in Intensive Care Unit Patients

### A Multicenter, Open-Label, Randomized Controlled Trial

Tim C. Jansen[1], Jasper van Bommel[1], F. Jeanette Schoonderbeek[3], Steven J. Sleeswijk Visser[4], Johan M. van der Klooster[5], Alex P. Lima[1], Sten P. Willemsen[2], and Jan Bakker[1], for the LACTATE study group*

[1]Department of Intensive Care, Erasmus MC University Medical Centre, Rotterdam, The Netherlands; [2]Department of Biostatistics, University Medical Centre Rotterdam, Rotterdam, The Netherlands; [3]Department of Intensive Care, Ikazia Hospital, Rotterdam, The Netherlands; [4]Department of Intensive Care, Reinier de Graaf Hospital, Delft, The Netherlands; and [5]Department of Intensive Care, St. Franciscus Gasthuis, Rotterdam, The Netherlands

348 patients with lactate levels ≥3 mmol/L
≥ 20% decrease in lactate levels per 2 hrs of the first 8 hrs
ScvO2 target achievement

9.6% absolute reduction in mortality

*Am J Respir Crit Care Med 2010; 182:752–761*

# Lactate vs $ScvO_2$

**Lactate Clearance vs Central Venous Oxygen Saturation as Goals of Early Sepsis Therapy: A Randomized Clinical Trial**

**Dr. Alan E. Jones, MD**, **Dr. Nathan I. Shapiro, MD, MPH**, **Dr. Stephen Trzeciak, MD, MPH**, **Dr. Ryan C. Arnold, MD**, **Ms. Heather A. Claremont, BFA**, and **Dr. Jeffrey A. Kline, MD for the Emergency Medicine Shock Research Network (EMShockNet) Investigators**
Department of Emergency Medicine, Carolinas Medical Center, Charlotte, North Carolina (Drs Jones and Kline and Ms Claremont); Department of Emergency Medicine and Center for Vascular Biology Research, Beth Israel Deaconess Medical Center, Boston, Massachusetts (Dr Shapiro); and Departments of Medicine, Division of Critical Care Medicine (Dr Trzeciak), and Emergency Medicine (Drs Trzeciak and Arnold), Cooper University Hospital, Camden, New Jersey

30 patients with lactate levels ≥4 mmol/L

Lactate clearance (decrease by at least 10%) was noninferior to early quantitative resuscitation based on achieving ScvO2 of 70% or more

*JAMA 2010; 303:739–746*

# Optimization strategy

- Low $ScvO_2$ & Hyperlactatemia reflects an adaptive mechanism to an unsuitable $O_2$ supply
- $DO_2 = [(SaO_2 \times \mathbf{Hb} \times 1.36) + (PaO_2 \times 0.003)] \times \mathbf{CO}$
- Dobutamine infusion (to a maximum of 20 μg/kg/min)
- Transfusion of packed RBC to achieve a hematocrit of greater than or equal to 30%


# Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2012

R. Phillip Dellinger, MD[1]; Mitchell M. Levy, MD[2]; Andrew Rhodes, MB BS[3]; Djillali Annane, MD[4]; Herwig Gerlach, MD, PhD[5]; Steven M. Opal, MD[6]; Jonathan E. Sevransky, MD[7]; Charles L. Sprung, MD[8]; Ivor S. Douglas, MD[9]; Roman Jaeschke, MD[10]; Tiffany M. Osborn, MD, MPH[11]; Mark E. Nunnally, MD[12]; Sean R. Townsend, MD[13]; Konrad Reinhart, MD[14]; Ruth M. Kleinpell, PhD, RN-CS[15]; Derek C. Angus, MD, MPH[16]; Clifford S. Deutschman, MD, MS[17]; Flavia R. Machado, MD, PhD[18]; Gordon D. Rubenfeld, MD[19]; Steven A. Webb, MB BS, PhD[20]; Richard J. Beale, MB BS[21]; Jean-Louis Vincent, MD, PhD[22]; Rui Moreno, MD, PhD[23]; and the Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup*

# Guidelines

**A. Initial Resuscitation**

1. Protocolized, quantitative resuscitation of patients with sepsis- induced tissue hypoperfusion (defined in this document as hypotension persisting after initial fluid challenge or blood lactate concentration ≥ 4 mmol/L). Goals during the first 6 hrs of resuscitation:
   a) Central venous pressure 8–12 mm Hg
   b) Mean arterial pressure (MAP) ≥ 65 mm Hg
   c) Urine output ≥ 0.5 mL/kg/hr
   d) Central venous (superior vena cava) or mixed venous oxygen saturation 70% or 65%, respectively (grade 1C).
2. In patients with elevated lactate levels targeting resuscitation to normalize lactate (grade 2C).

**B. Screening for Sepsis and Performance Improvement**

1. Routine screening of potentially infected seriously ill patients for severe sepsis to allow earlier implementation of therapy (grade 1C).
2. Hospital–based performance improvement efforts in severe sepsis (UG).

**C. Diagnosis**

1. Cultures as clinically appropriate before antimicrobial therapy if no significant delay (> 45 mins) in the start of antimicrobial(s) (grade 1C). At least 2 sets of blood cultures (both aerobic and anaerobic bottles) be obtained before antimicrobial therapy with at least 1 drawn percutaneously and 1 drawn through each vascular access device, unless the device was recently (<48 hrs) inserted (grade 1C).
2. Use of the 1,3 beta-D-glucan assay (grade 2B), mannan and anti-mannan antibody assays (2C), if available and invasive candidiasis is in differential diagnosis of cause of infection.
3. Imaging studies performed promptly to confirm a potential source of infection (UG).

# Guidelines

**D. Antimicrobial Therapy**

1. Administration of effective intravenous antimicrobials within the first hour of recognition of septic shock (grade 1B) and severe sepsis without septic shock (grade 1C) as the goal of therapy.

2a. Initial empiric anti-infective therapy of one or more drugs that have activity against all likely pathogens (bacterial and/or fungal or viral) and that penetrate in adequate concentrations into tissues presumed to be the source of sepsis (grade 1B).

2b. Antimicrobial regimen should be reassessed daily for potential deescalation (grade 1B).

3. Use of low procalcitonin levels or similar biomarkers to assist the clinician in the discontinuation of empiric antibiotics in patients who initially appeared septic, but have no subsequent evidence of infection (grade 2C).

4a. Combination empirical therapy for neutropenic patients with severe sepsis (grade 2B) and for patients with difficult-to-treat, multidrug-resistant bacterial pathogens such as *Acinetobacter* and *Pseudomonas* spp. (grade 2B). For patients with severe infections associated with respiratory failure and septic shock, combination therapy with an extended spectrum beta-lactam and either an aminoglycoside or a fluoroquinolone is for *P. aeruginosa* bacteremia (grade 2B). A combination of beta-lactam and macrolide for patients with septic shock from bacteremic *Streptococcus pneumoniae* infections (grade 2B).

4b. Empiric combination therapy should not be administered for more than 3–5 days. De-escalation to the most appropriate single therapy should be performed as soon as the susceptibility profile is known (grade 2B).

5. Duration of therapy typically 7–10 days; longer courses may be appropriate in patients who have a slow clinical response, undrainable foci of infection, bacteremia with *S. aureus;* some fungal and viral infections or immunologic deficiencies, including neutropenia (grade 2C).

6. Antiviral therapy initiated as early as possible in patients with severe sepsis or septic shock of viral origin (grade 2C).

7. Antimicrobial agents should not be used in patients with severe inflammatory states determined to be of noninfectious cause (UG).

# Guidelines

**E. Source Control**

1. A specific anatomical diagnosis of infection requiring consideration for emergent source control be sought and diagnosed or excluded as rapidly as possible, and intervention be undertaken for source control within the first 12 hr after the diagnosis is made, if feasible (grade 1C).
2. When infected peripancreatic necrosis is identified as a potential source of infection, definitive intervention is best delayed until adequate demarcation of viable and nonviable tissues has occurred (grade 2B).
3. When source control in a severely septic patient is required, the effective intervention associated with the least physiologic insult should be used (eg, percutaneous rather than surgical drainage of an abscess) (UG).
4. If intravascular access devices are a possible source of severe sepsis or septic shock, they should be removed promptly after other vascular access has been established (UG).

**F. Infection Prevention**

1a. Selective oral decontamination and selective digestive decontamination should be introduced and investigated as a method to reduce the incidence of ventilator-associated pneumonia; This infection control measure can then be instituted in health care settings and regions where this methodology is found to be effective (grade 2B).

1b. Oral chlorhexidine gluconate be used as a form of oropharyngeal decontamination to reduce the risk of ventilator-associated pneumonia in ICU patients with severe sepsis (grade 2B).

# Guidelines

**G. Fluid Therapy of Severe Sepsis**

1. Crystalloids as the initial fluid of choice in the resuscitation of severe sepsis and septic shock (grade 1B).
2. Against the use of hydroxyethyl starches for fluid resuscitation of severe sepsis and septic shock (grade 1B).
3. Albumin in the fluid resuscitation of severe sepsis and septic shock when patients require substantial amounts of crystalloids (grade 2C).
4. Initial fluid challenge in patients with sepsis-induced tissue hypoperfusion with suspicion of hypovolemia to achieve a minimum of 30 mL/kg of crystalloids (a portion of this may be albumin equivalent). More rapid administration and greater amounts of fluid may be needed in some patients (grade 1C).
5. Fluid challenge technique be applied wherein fluid administration is continued as long as there is hemodynamic improvement either based on dynamic (eg, change in pulse pressure, stroke volume variation) or static (eg, arterial pressure, heart rate) variables (UG).

# Guidelines

**H. Vasopressors**

1. Vasopressor therapy initially to target a mean arterial pressure (MAP) of 65 mm Hg (grade 1C).
2. Norepinephrine as the first choice vasopressor (grade 1B).
3. Epinephrine (added to and potentially substituted for norepinephrine) when an additional agent is needed to maintain adequate blood pressure (grade 2B).
4. Vasopressin 0.03 units/minute can be added to norepinephrine (NE) with intent of either raising MAP or decreasing NE dosage (UG).
5. Low dose vasopressin is not recommended as the single initial vasopressor for treatment of sepsis-induced hypotension and vasopressin doses higher than 0.03-0.04 units/minute should be reserved for salvage therapy (failure to achieve adequate MAP with other vasopressor agents) (UG).
6. Dopamine as an alternative vasopressor agent to norepinephrine only in highly selected patients (eg, patients with low risk of tachyarrhythmias and absolute or relative bradycardia) (grade 2C).
7. Phenylephrine is not recommended in the treatment of septic shock except in circumstances where (a) norepinephrine is associated with serious arrhythmias, (b) cardiac output is known to be high and blood pressure persistently low or (c) as salvage therapy when combined inotrope/vasopressor drugs and low dose vasopressin have failed to achieve MAP target (grade 1C).
8. Low-dose dopamine should not be used for renal protection (grade 1A).
9. All patients requiring vasopressors have an arterial catheter placed as soon as practical if resources are available (UG).

# Guidelines

**I. Inotropic Therapy**

1. A trial of dobutamine infusion up to 20 micrograms/kg/min be administered or added to vasopressor (if in use) in the presence of (a) myocardial dysfunction as suggested by elevated cardiac filling pressures and low cardiac output, or (b) ongoing signs of hypoperfusion, despite achieving adequate intravascular volume and adequate MAP (grade 1C).
2. Not using a strategy to increase cardiac index to predetermined supranormal levels (grade 1B).

**J. Corticosteroids**

1. Not using intravenous hydrocortisone to treat adult septic shock patients if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability (see goals for Initial Resuscitation). In case this is not achievable, we suggest intravenous hydrocortisone alone at a dose of 200 mg per day (grade 2C).
2. Not using the ACTH stimulation test to identify adults with septic shock who should receive hydrocortisone (grade 2B).
3. In treated patients hydrocortisone tapered when vasopressors are no longer required (grade 2D).
4. Corticosteroids not be administered for the treatment of sepsis in the absence of shock (grade 1D).
5. When hydrocortisone is given, use continuous flow (grade 2D).

# Guidelines

- Are not perfect
- Are still evolving and always will be
- Attempt to provide the best quality for the “Typical” patient in the ICU with the matched disorder
- Will never replace clinical decision-making by expert

# Vasopressor

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# MAP - Rationale

- Below a threshold MAP, autoregulation in critical vascular beds can be lost
- Perfusion : linearly dependent on pressure
- Vasopressor therapy to achieve a minimal perfusion pressure and maintain adequate flow
- The titration of norepinephrine to a MAP as low as 65 mmHg : preserve tissue perfusion

# MAP - Rationale

## Effects of perfusion pressure on tissue perfusion in septic shock

David LeDoux, MD; Mark E. Astiz, MD, FCCM; Charles M. Carpati, MD; Eric C. Rackow, MD, FCCM

*Objective:* To measure the effects of increasing mean arterial pressure (MAP) on systemic oxygen metabolism and regional tissue perfusion in septic shock.

*Design:* Prospective study.

*Setting:* Medical and surgical intensive care units of a tertiary care teaching hospital.

*Patients:* Ten patients with the diagnosis of septic shock who required pressor agents to maintain a MAP ≥ 60 mm Hg after fluid resuscitation to a pulmonary artery occlusion pressure (PAOP) ≥ 12 mm Hg.

*Interventions:* Norepinephrine was titrated to MAPs of 65, 75, and 85 mm Hg in 10 patients with septic shock.

*Measurements and Main Results:* At each level of MAP, hemodynamic parameters (heart rate, PAOP, cardiac index, left ventricular stroke work index, and systemic vascular resistance index), metabolic parameters (oxygen delivery, oxygen consumption, arterial lactate), and regional perfusion parameters (gastric mucosal $P_{CO_2}$, skin capillary blood flow and red blood cell velocity, urine output) were measured.

Increasing the MAP from 65 to 85 mm Hg with norepinephrine resulted in increases in cardiac index from 4.7 ± 0.5 L/min/m$^2$ to 5.5 ± 0.6 L/min/m$^2$ ($p < 0.03$). Arterial lactate was 3.1 ± 0.9 mEq/L at a MAP of 65 mm Hg and 3.0 ± 0.9 mEq/L at 85 mm Hg (NS). The gradient between arterial $P_{CO_2}$ and gastric intramucosal $P_{CO_2}$ was 13 ± 3 mm Hg (1.7 ± 0.4 kPa) at a MAP of 65 mm Hg and 16 ± 3 at 85 mm Hg (2.1 ± 0.4 kPa) (NS). Urine output at 65 mm Hg was 49 ± 18 mL/hr and was 43 ± 13 mL/hr at 85 mm Hg (NS). As the MAP was raised, there were no significant changes in skin capillary blood flow or red blood cell velocity.

*Conclusions:* Increasing the MAP from 65 mm Hg to 85 mm Hg with norepinephrine does not significantly affect systemic oxygen metabolism, skin microcirculatory blood flow, urine output, or splanchnic perfusion. (Crit Care Med 2000; 28:2729–2732)

KEY WORDS: sepsis; sepsis syndrome; septic shock; norepinephrine; systemic hypotension; regional blood flow; gastric tonometry; lactate; arterial pressure; tissue oxygenation; laser-Doppler

# MAP

- Optimal MAP: should be individualized
  - higher in patients with atherosclerosis and/or previous hypertension than in young patients without cardiovascular comorbidity

# Norepinephrine

- The first-choice vasopressor for treatment of sepsis-induced hypotension
- Powerful catecholamine with both α and β adrenergic properties
  - Increases MAP due to its predominant α effects
  - Little change in heart rate and less increase in stroke volume compared with dopamine
- Effective at reversing hypotension in patients with septic shock

# Dopamine

- 5 randomized trials (n= 1993 patients with septic shock) comparing norepinephrine to dopamine
  - Does not support the routine use of dopamine
  - Risk of short-term mortality (RR : 0.91)
- Recent meta-analysis (*Crit Care Med 2012; 40:725–730*)
  - Dopamine was associated with an increased risk (RR : 1.10)
  - More frequent arrhythmias with dopamine than with norepinephrine

# Dopamine

- Increases MAP & cardiac output
  - Primarily due to an increase in stroke volume & heart rate
- Causes more tachycardia and may be more arrhythmogenic than norepinephrine
- Particularly useful in patients with compromised systolic function

# Epinephrine

- Potent β1-inotropic agent that increases cardiac output by an increase in heart rate & contractility
- May increase aerobic lactate production via stimulation of skeletal muscles' β2-adrenergic receptors
  - Type B lactic acidosis (not associated with tissue hypoxia)
- 4 randomized trials (n= 540) comparing norepinephrine to epinephrine
  - No evidence for differences in the risk of dying (RR : 0.96)
- It should be the first alternative to norepinephrine

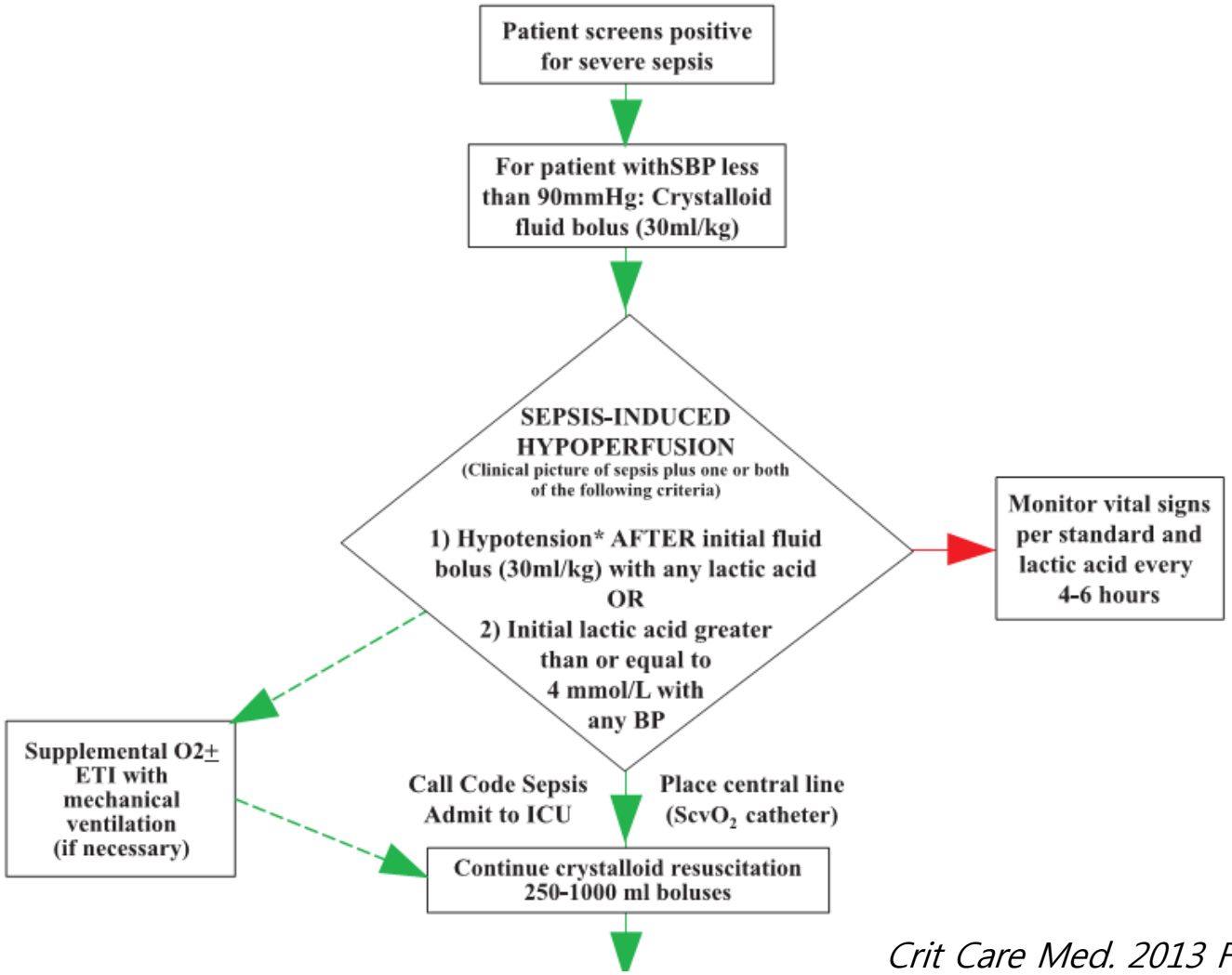
# Vasopressin

- RCT comparing norepinephrine alone to norepinephrine plus vasopressin at 0.03 U/min
  - No difference in outcome (*N Engl J Med 2008; 358:877–887*)
- Seven trials (n= 963 patients with septic shock) comparing norepinephrine with vasopressin
  - Does not support the routine use of vasopressin (RR : 1.12)

# Vasopressin

- Endogenous hormone secreted by the posterior pituitary
- Activation of V1a receptors on vascular smooth muscle
  - Vasoconstriction and increased SVR
  - Activation of baroreceptor reflexes : reduce heart rate and cardiac output
  - Little effect on arterial pressure at physiologic concentrations during normal conditions
  - Impaired baroreceptor reflexes during septic shock : little change in heart rate
  - Greatly enhanced pressor activity of vasopressin
- May be effective in raising blood pressure in patients who are refractory to other vasopressors

# Septic Shock Resuscitation Algorithm

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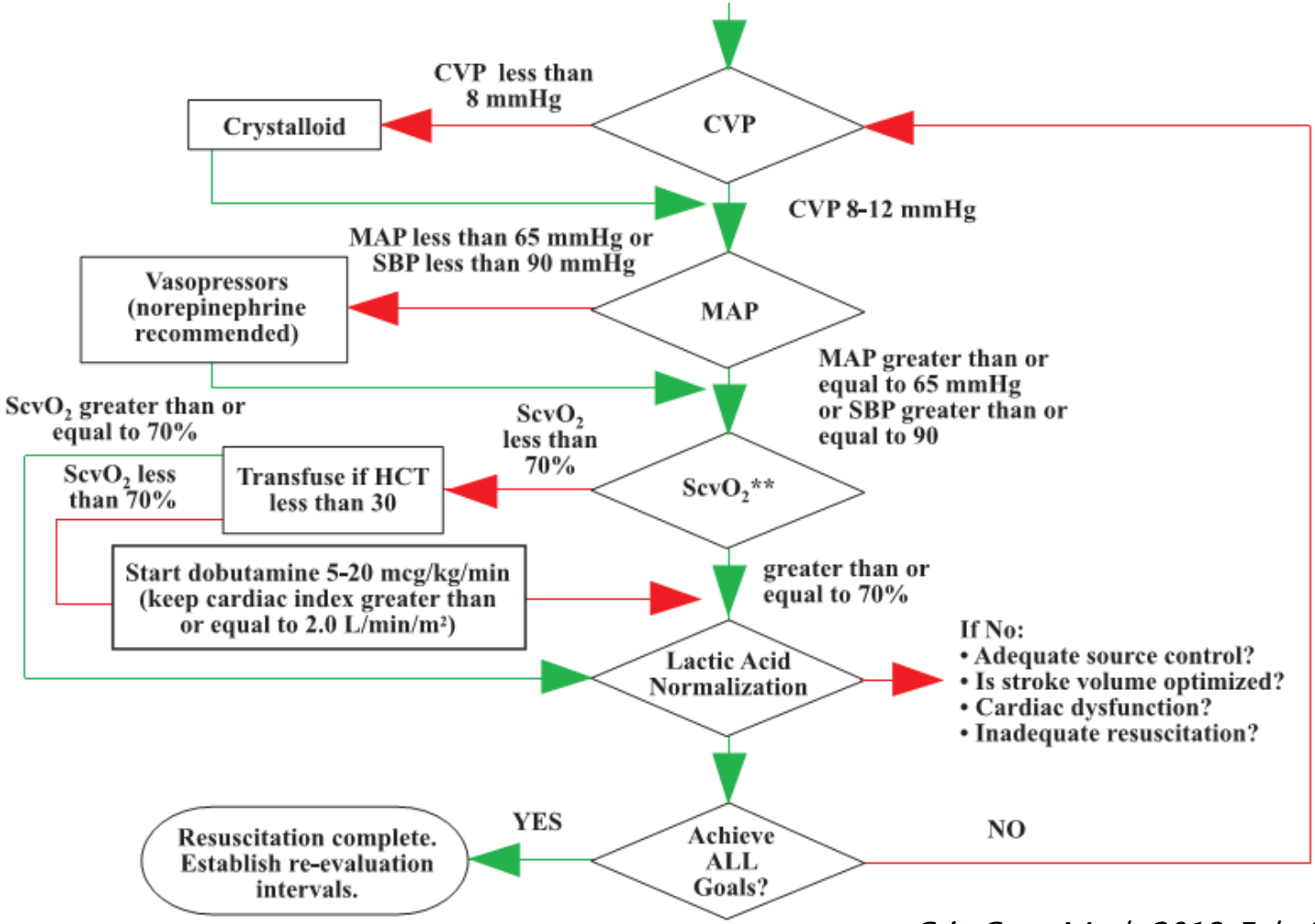
# Septic Shock Resuscitaion Algorithm

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# Summary

- Key mechanism : Tissue hypoperfusion
- Measure lactate level
- Maintain MAP ≥ 65mmHg
  - Volume (Crystalloid) + Vasopressor (Norepinephrine)
- Measure $ScvO_2$ : DO2
  - Dobutamine infusion : cardiac output
  - Transfusion of packed RBC : oxygen content
- Normalization of lactate
- Guidelines are not perfect
  - It will never replace clinical decision-making by expert