# SEPSIS MANAGEMENT

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THINK TREAT STOP! sepsis

# goals

- Treatment of pts. with septic shock consists of the following:
  1. **Resuscitate** the patient from septic shock using supportive measures to correct hypoxia, hypotension, and impaired tissue oxygenation.
  2. **Identify the source** of infection and treat with antimicrobial therapy, surgery, or both.
  3. **Maintain** adequate organ system **function** guided by cardiovascular monitoring and interrupt the pathogenesis of multiple organ dysfunction syndrome (MODS).

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# General Treatment Guidelines

- In 2004, the first set of formal treatment guidelines for septic shock were published.
- These guidelines were formulated by an international consensus group that was composed of experts from 11 organizations
- These guidelines, known as the **Surviving Sepsis Campaign**, were updated in 2008 and reflect the most modern opinion on the treatment of septic shock.


1. Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. *Crit Care Med*. Mar 2004.
2. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. *Crit Care Med*. Jan 2008

# early goal-directed therapy may improve 28-day survival

- N Engl J Med 2001 Nov
  - based on randomized trial
  - 263 patients with severe sepsis or septic shock randomized to 6 hours of **early goal-directed therapy vs. standard therapy** prior to admission to ICU
  - in-hospital mortality was 30.5% with early goal-directed therapy vs. 46.5% with standard therapy (p = 0.009, NNT 7)

- Zhongguo Wei Zhong Bing Ji Jiu Yi Xue 2010 Jun
  - based on randomized trial without intention-to-treat analysis
  - 341 patients with severe sepsis/septic shock randomized to early **goal-directed therapy vs. conventional treatment**
  - comparing early goal-directed therapy vs. conventional treatment
    - 28-day survival 75.2% vs. 57.5% (p = 0.001, NNT 6)
    - ICU mortality 30.5% vs. 50.7% (p = 0.035, NNT 5)

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- difficult to perform the full EGDT protocol in all EDs
  - because of the time needed to place the various invasive catheters and perform the complex resuscitation, and because many departments are not set up to measure ScvO2.


3. Protocolized Care for Early Septic Shock Investigators. Variability in management of early severe sepsis. Emerg Med J 2010.
5. Managing severe sepsis: A national survey of current practices. Am J Health Syst Pharm 2009


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- significant improvements in mortality of severely septic patients by implementing only key steps in the EGDT protocol rather than all steps.

6. Before-after study of a standardized hospital order set for the management of septic shock. Crit Care Med 2006;
9. Bundled care for septic shock: An analysis of clinical trials. Crit Care Med 2010;38:668-678.

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- 2012, the Surviving Sepsis Campaign developed and published international guidelines for the evaluation and treatment of patients in severe sepsis and septic shock.

- These guidelines updated previous recommendations published in 2008, based on literature published in the last 5 years.

- A consensus committee of 68 experts representing 30 international organizations:
- To provide an update to the "Surviving Sepsis Campaign Guidelines for Management of Severe Sepsis and Septic Shock," published in 2008.
- Followed principles of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to guide assessment of :
  - ***Quality*** of evidence from high (A) to very low (D) and
  - ***Strength*** of recommendations as strong (1) or weak (2).
  - Some recommendations were ungraded (UG).

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# 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*

**Objective:** To provide an update to the "Surviving Sepsis Campaign Guidelines for Management of Severe Sepsis and Septic Shock," last published in 2008.

**Design:** A consensus committee of 68 international experts representing 30 international organizations was convened. Nominal groups were assembled at key international meetings (for those committee members attending the conference). A formal conflict of interest policy was developed at the onset of the process and enforced throughout. The entire guidelines process was conducted independent of any industry funding. A stand-alone meeting was held for all subgroup heads, co- and vice-chairs, and selected individuals. Teleconferences and electronic-based discussion among subgroups and among the entire committee served as an integral part of the development.

**Methods:** The authors were advised to follow the principles of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to guide assessment of quality of evidence from high (A) to very low (D) and to determine the strength of recommendations as strong (1) or weak (2). The potential drawbacks of making strong recommendations in the presence of low-quality evidence were emphasized. Some recommendations were ungraded (UG). Recommendations were classified into three groups: 1) those directly targeting severe sepsis; 2) those targeting general care of the critically ill patient and considered high priority in severe sepsis; and 3) pediatric considerations.

**Results:** Key recommendations and suggestions, listed by category, include: early quantitative resuscitation of the septic patient during the first 6 hrs after recognition (1C); blood cultures

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* Members of the 2012 SSC Guidelines Committee and Pediatric Subgroup are listed in **Appendix A** at the end of this article.

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- From 2008 to 2012, the most relevant changes to use in clinical practice include the following instructions:

1) Use protocolized quantitative resuscitation with specific physiologic targets.
2) Preferentially use crystalloids, with or without albumin, for volume resuscitation.
3) Use albumin when patients require substantial amounts of crystalloids.
   - Do not use hydroxyethyl starches.

4) Norepinephrine as the first-choice vasopressor,
   - Vasopressin as an additional agent is needed; (up to 0.03 U/minute) to increase MAP to target or to reduce norepinephrine dosage.

5) Add lactate clearance as a marker of tissue hypo-perfusion.

6) Reduce emphasis on corticosteroid use.

7) Do not use activated protein C

6. Before-after study of a standardized hospital order set for the management of septic shock. Crit Care Med 2006;
8. A modified goal-directed protocol improves clinical outcomes in intensive care unit patients with septic shock: A randomized controlled trial. Shock 2006
11. Surviving Sepsis Campaign. The Surviving Sepsis Campaign: Results of an international guideline-based performance improvement program targeting severe sepsis. Crit Care Med 2010

- QUANTATAIVE Protocol improves the survival:
  - Crit Care Med 2008 Oct
    - systematic review of 9 randomized trials comparing **quantitative vs. standard resuscitation strategies** in 1,001 adults with presumed or confirmed sepsis
    - early quantitative resuscitation associated with decreased mortality (OR 0.5, 95% CI 0.37-0.69)
  - Crit Care Med 2010 Feb
    - systematic review of 8 evaluating efficacy of **protocol of combined therapies vs. nonprotocolized** care for adults with sepsis
    - increased survival (odds ratio [OR] 1.91, 95% CI 1.49-2.45)

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- Key steps are:
  A. **Screening of septic patients**
  B. **Identifying and controlling the source of sepsis**
  C. **Fluid resuscitation**
  D. **Monitoring serum lactate clearance**
  E. **Antibiotic administration**

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# Resuscitation Target


- Goals during the first 6 hrs of resuscitation:
  - Central venous pressure 8–12 mm Hg
  - Mean arterial pressure (MAP) ≥ 65 mm Hg
  - Urine output ≥ 0.5 mL/kg/hr
  - Central venous (superior vena cava) or mixed venous oxygen saturation 70% or 65%, respectively (grade 1C).
  - normalize lactate level (grade 2C).

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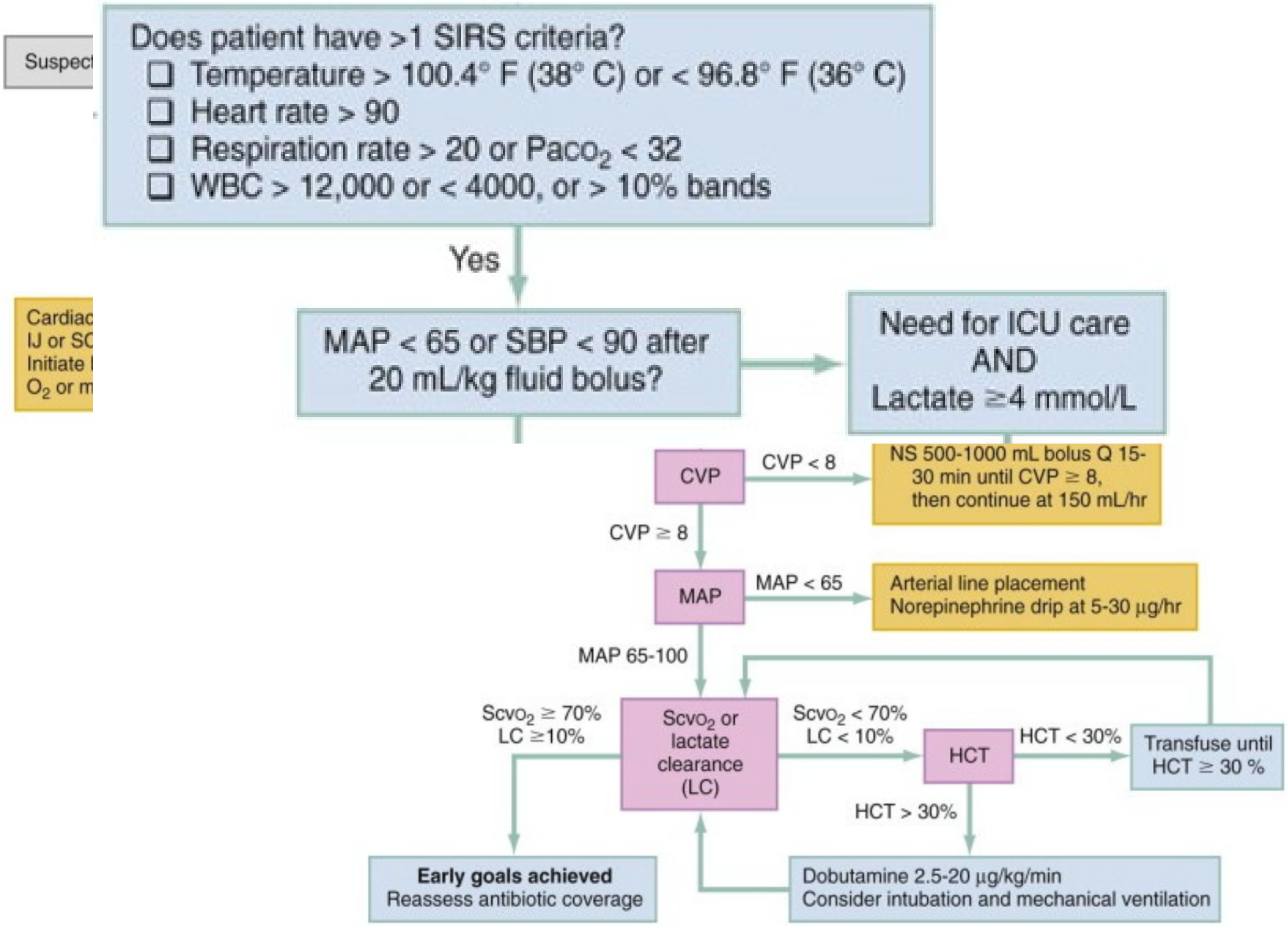
1. Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: Crit Care Med; 2013


Suspect
Does patient have >1 SIRS criteria?
Temperature > 100.4° F (38° C) or < 96.8° F (36° C)
Heart rate > 90
Respiration rate > 20 or $Paco_2$ < 32
WBC > 12,000 or < 4000, or > 10% bands
Yes
Cardiac
IJ or SC
Initiate
$O_2$ or m
MAP < 65 or SBP < 90 after 20 mL/kg fluid bolus?
Need for ICU care AND Lactate ≥4 mmol/L
CVP
CVP < 8
NS 500-1000 mL bolus Q 15-30 min until CVP ≥ 8, then continue at 150 mL/hr
CVP ≥ 8
MAP
MAP < 65
Arterial line placement
Norepinephrine drip at 5-30 µg/hr
MAP 65-100
$Scvo_2$ ≥ 70%
LC ≥10%
$Scvo_2$ or lactate clearance (LC)
$Scvo_2$ < 70%
LC < 10%
HCT
HCT < 30%
Transfuse until HCT ≥ 30 %
HCT > 30%
Early goals achieved
Reassess antibiotic coverage
Dobutamine 2.5-20 µg/kg/min
Consider intubation and mechanical ventilation

# A. Screening of septic pa

- high index of suspicion.
- 2 or more of (SIRS) criteria signify the presence of a potentially severe infection.
- elevated lactate levels are associated with an increased mortality.
  - even in the face of hemodynamic stability, pts with a serum lactate level > 4.0 mmol/L have a sharp decline in survival

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# B. Identifying and controlling the source of sepsis


- The Surviving Sepsis Campaign guidelines recommend within 6 hours of presentation.
  - blood cultures +/- others (urine, CSF, synovial fluid)
  - Cultures before antimicrobial therapy if no significant delay (> 45 mins) (grade1C).
  - Imaging studies performed promptly to confirm a potential source of infection (UG).

2. Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: Crit Care Med 2008

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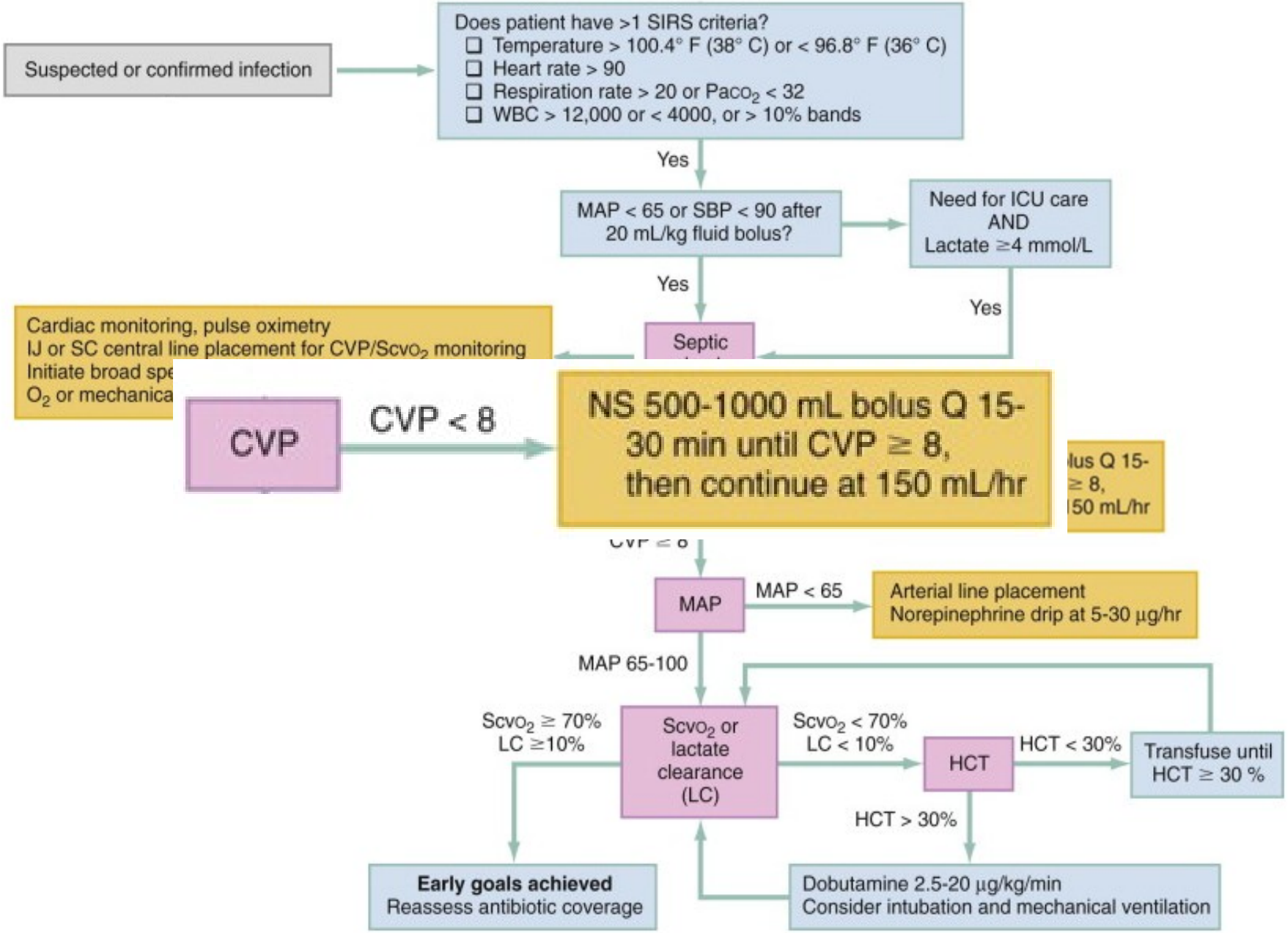
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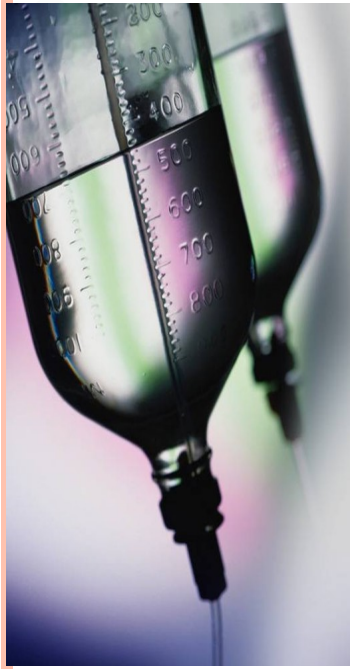
# C. Volume resuscitation:

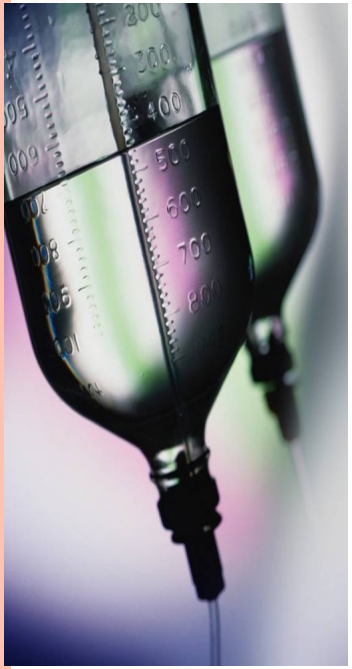


- Recommendations regarding initial resuscitation (first 6 hours)(1)
  - start resuscitation (crystalloids 30 mL/kg) immediately if hypotension or serum lactate > 4 mmol/L (4 mEq/L) (do not delay pending I.C.U. admission) (Grade 1C)

1. Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: Crit Care Med; 2013

# Fluid choice

- Recommendations regarding fluid therapy(1)
  - crystalloids recommended as initial fluid choice (Grade 1B)
  - do not use hydroxyethyl starches for fluid resuscitation (Grade 1B)
  - consider using albumin if patients require substantial amounts of crystalloids (Grade 2C)



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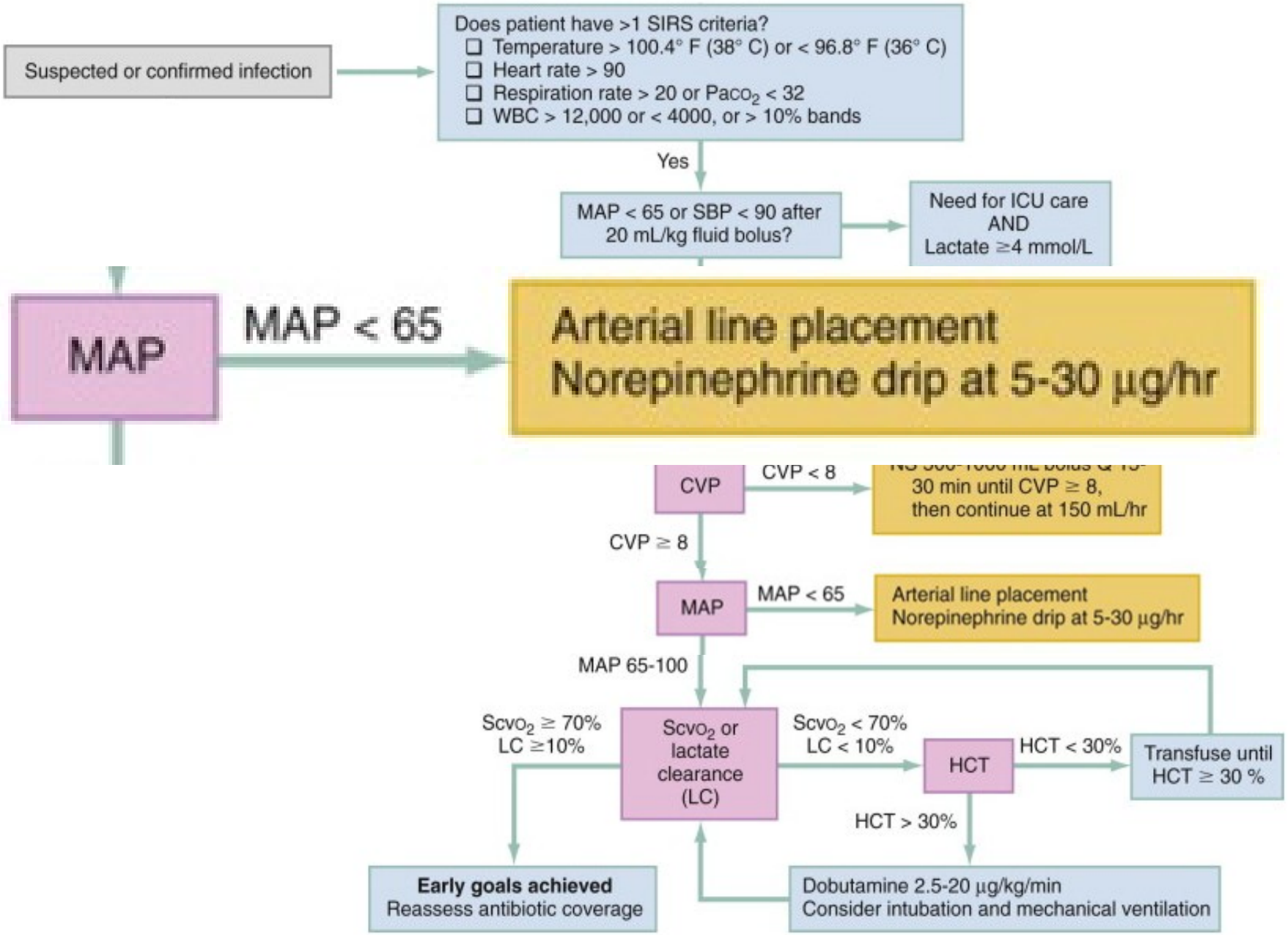
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Early goals achieved
Reassess antibiotic coverage
Dobutamine 2.5-20 µg/kg/min
Consider intubation and mechanical ventilation

# Vasopressors


- Recommendations regarding vasopressors(1)
  - target MAP ≥ 65 mm Hg (Grade 1C)
  - Norepinephrine recommended as first choice (Grade 1B)
  - if additional agent needed to maintain blood pressure epinephrine + norepinephrine (Grade 2B)
  - Vasopressin
    - vasopressin 0.03 units/minute can be subsequently added to norepinephrine
      - to increase MAP or
      - decrease norepinephrine dose

1. Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: Crit Care Med; 2013

# Vasopressin


- should not be used as the sole initial therapy for refractory septic shock.
  - trials demonstrated no change in mortality for patients with severe sepsis when vasopressin was added to other vasopressors.

# Vasopressors

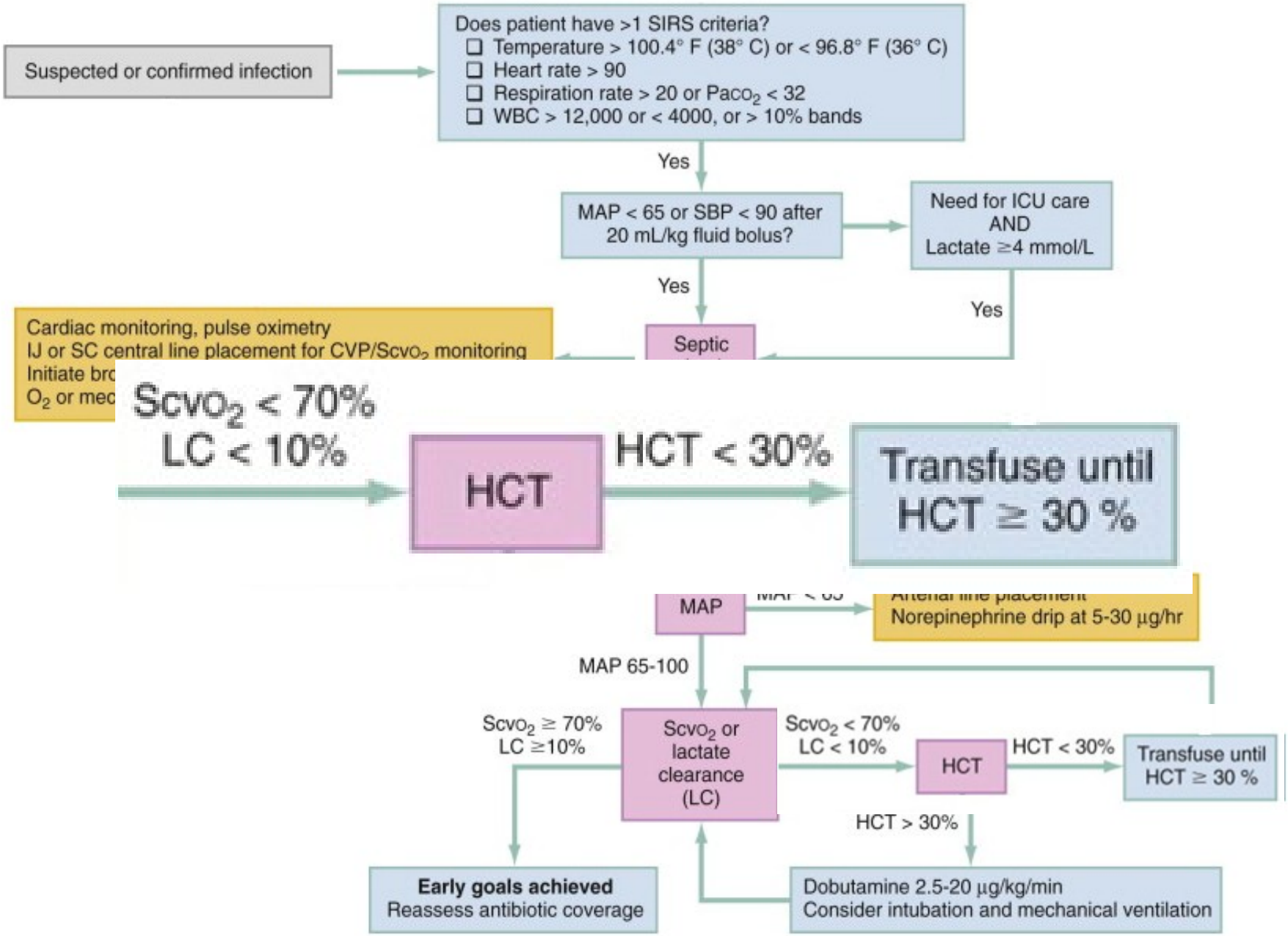

- Cochrane Database Syst Rev 2011 May
  - **no significant difference in 1-year mortality comparing vasopressors in patients with shock**
    - systematic review of 23 randomized trials evaluating vasopressor regimens in 3,212 patients with hypotensive shock (15 studies in pts with septic shock)
    - **no significant differences in 1-year mortality in comparisons of:**
      - norepinephrine vs. dopamine in analysis of 6 trials with 1,400 patients
      - norepinephrine vs. epinephrine in 1 trial with 269 patients
      - norepinephrine vs. terlipressin in analysis of 2 trials with 40 patients
      - norepinephrine vs. vasopressin in analysis of 3 trials with 812 patients
      - norepinephrine vs. norepinephrine plus terlipressin plus dobutamine
      - norepinephrine vs. phenylephrine in 1 trial with 32 patients
      - epinephrine vs. norepinephrine plus dobutamine
      - epinephrine vs. norepinephrine plus dopexamine
      - vasopressin vs. placebo in analysis of 4 trials with 157 patients
      - terlipressin vs. placebo in analysis of 3 trials with 127 patients
      - terlipressin vs. vasopressin in 1 trial with 30 patients

# DOPAMINE


- Crit Care Med 2012 Mar
  - **dopamine might increase 28-day mortality compared to norepinephrine in patients with septic shock (level 2 evidence)**
    - systematic review of 6 randomized trials and 5 observational studies comparing dopamine vs. norepinephrine for treatment of septic shock in 2,768 patients
    - dopamine associated with increased
      - 28-day mortality (risk ratio 1.12, 95% CI 1.01-1.2) in analysis of 6 trials with 1,408 patients
      - arrhythmias (risk ratio 2.34, 95% CI 1.46-3.77) in analysis of 2 trials with 1,296 patients

# Phenylephrine


- Phenylephrine NOT recommended in treatment of septic shock, except in cases where (Grade 1C)
  - norepinephrine associated with serious arrhythmias
  - high cardiac output and persistently low BP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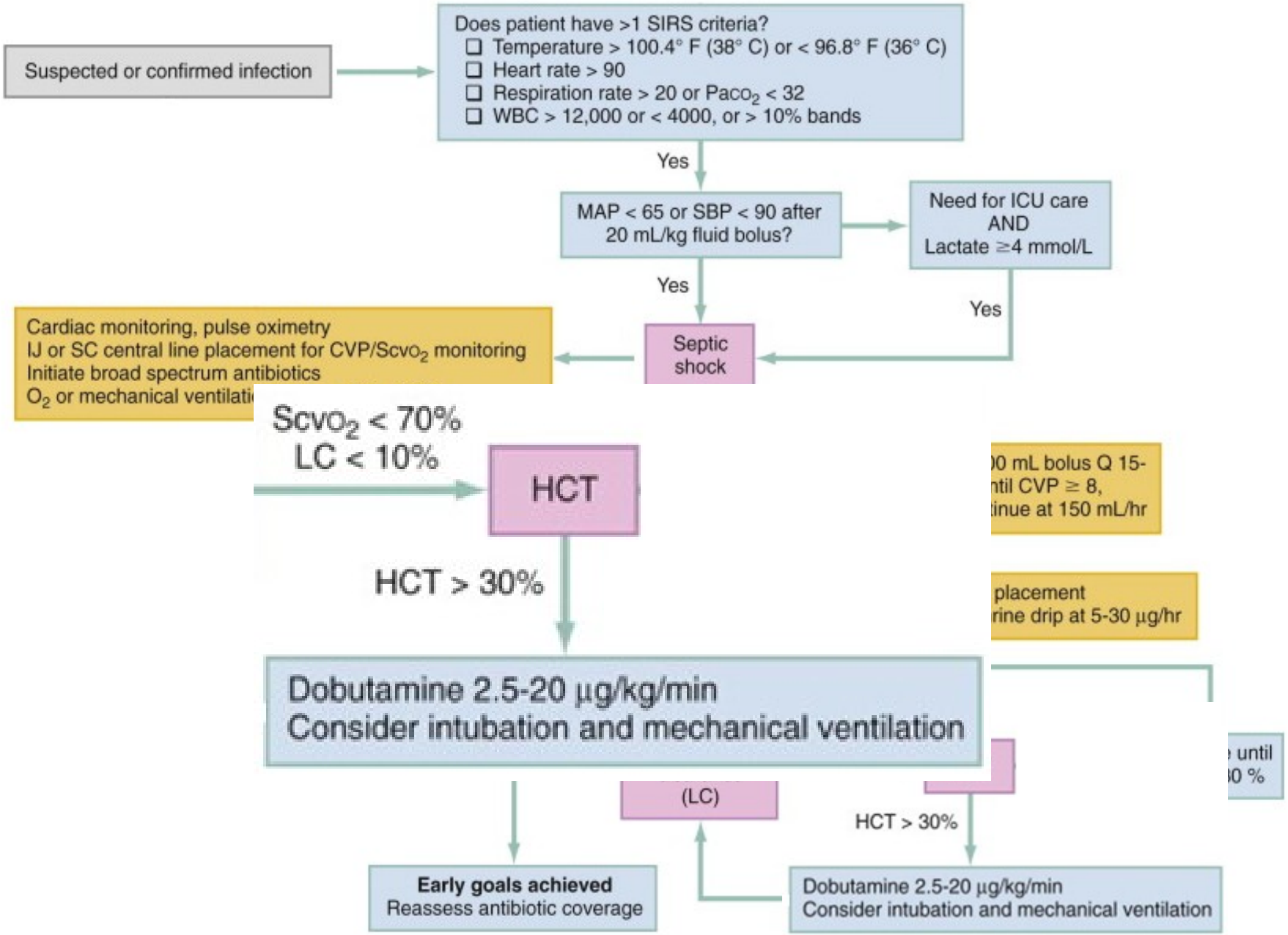
# Blood products

- Recommendations regarding blood product use(1)


- red blood cell transfusion recommended if hemoglobin level < 7 g/dL (Grade 1B)
  - target hemoglobin level 7-9 g/dL in adults
- prophylactic platelets suggested if (Grade 2D)
  - platelet counts < 10,000/mm3 in absence of apparent bleeding
  - platelet counts < 20,000/mm3 and significant risk for bleeding
  - platelet count < 50,000/mm3 and active bleeding or if surgery or invasive procedures needed
- interventions which are not recommended
  - antithrombin (Grade 1B)
  - erythropoietin for sepsis-related anemia (Grade 1B)
  - fresh frozen plasma in absence of planned invasive procedures or bleeding (Grade 2D)

1. Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: Crit Care Med; 2013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Consider intubation and mechanical ventilation
until
0 %
(LC)
HCT > 30%
Early goals achieved
Reassess antibiotic coverage
Dobutamine 2.5-20 µg/kg/min
Consider intubation and mechanical ventilation

# Inotropic therapy


- Recommendations regarding inotropic therapy(1)
  - trial of DOBUTAMINE infusion up to 20 mcg/kg/minute recommended in presence of: (Grade 1C)
    1. Myocardial dysfunction (elevated cardiac filling pressures and low cardiac output)
    2. Ongoing hypoperfusion despite adequate intravascular volume and adequate (MAP)



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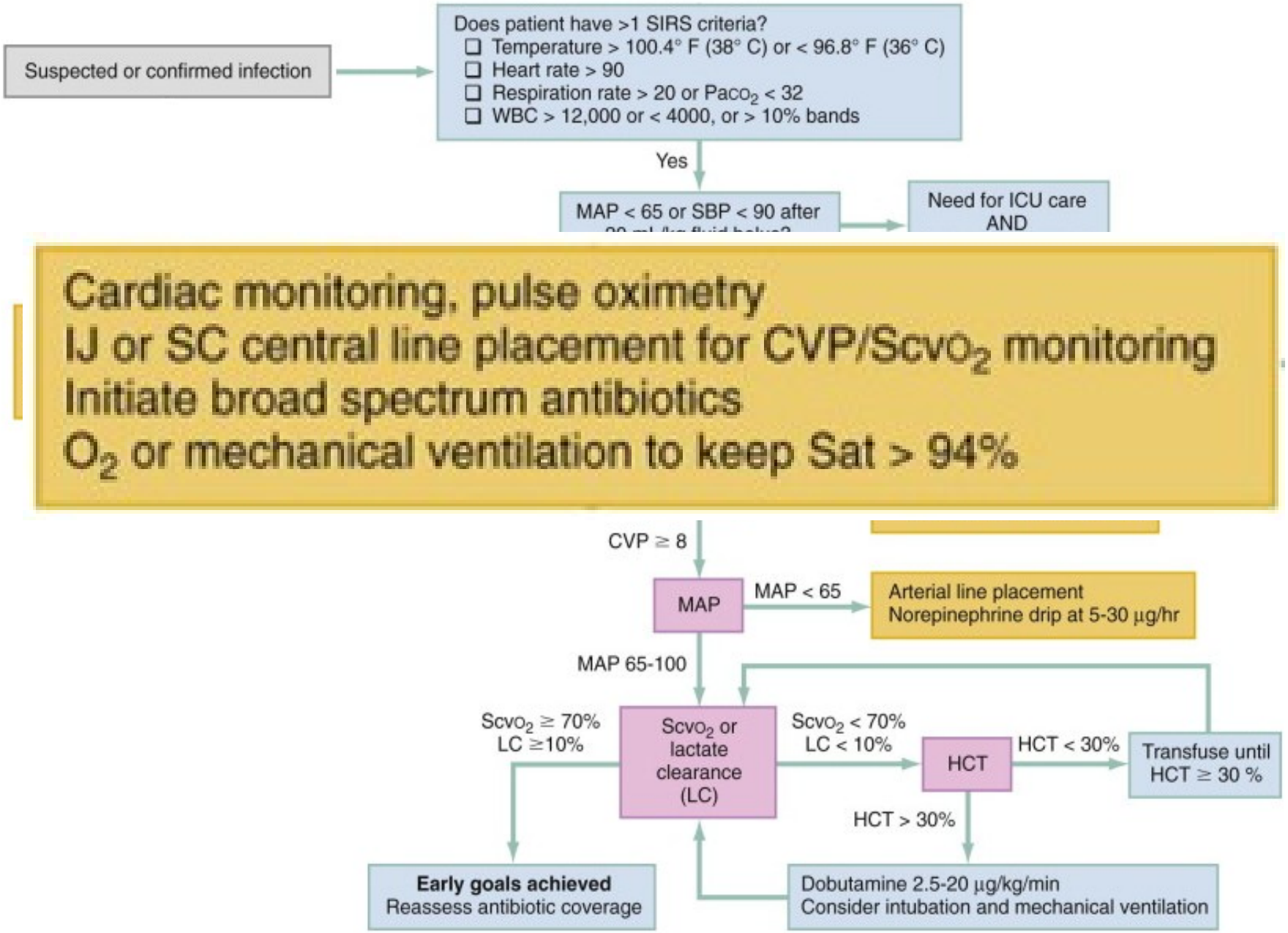
# DOBUTAMINE


- Crit Care Med 2011 Mar
  - **norepinephrine-dobutamine associated with similar mortality and may be safer compared to epinephrine in critically ill patients (level 2 evidence)**
    - small randomized trial without blinding
    - no significant difference in mortality
    - norepinephrine-dobutamine associated with
      - lower heart rates ($p < 0.05$)
      - decreased lactate level
    - epinephrine associated with
      - new arrhythmia in 3 patients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Initiate broad spectrum antibiotics
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CVP ≥ 8
MAP
MAP < 65
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Norepinephrine drip at 5-30 µg/hr
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HCT < 30%
Transfuse until HCT ≥ 30 %
HCT > 30%
Early goals achieved
Reassess antibiotic coverage
Dobutamine 2.5-20 µg/kg/min
Consider intubation and mechanical ventilation

# Antibiotic selection in adults

- choice of empirical antimicrobial therapy should be guided by(1)
  - patient history (underlying disease, immune status, prior antibiotic use, prior infection, or colonization with multidrug-resistant organisms)
  - potential source of infection
  - microbial resistance patterns within the community, hospital, or intensive care unit
  - patient organ dysfunction
  - associated drug toxicities (such as nephrotoxicity with aminoglycosides)

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# Antibiotics and Source Control-1

- Recommendations regarding antibiotic therapy(1)
  - begin IV antibiotics as soon as possible and within first hour of recognizing severe sepsis (Grade 1C) or septic shock (Grade 1B)
  - recommended initial therapy consists of 1 or more drugs with activity against all likely pathogens (bacterial, fungal, and/or viral) and with good penetration for presumed source (Grade 1B)

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# Antibiotics and Source Control-2

- Recommendations regarding antibiotic therapy(1)

  - combination empirical therapy
    - combination empirical therapy suggested for (Grade 2B)
      - neutropenic patients with severe sepsis
      - areas where *Acinetobacter* infections, *Pseudomonas* infections, or other difficult-to-treat, multidrug-resistant bacterial pathogens are prevalent
    - *Pseudomonas aeruginosa* is prevalent
      - combination therapy (extended-spectrum beta-lactam and either aminoglycoside or fluoroquinolone) (Grade 2B)
    - *Streptococcus pneumoniae* is prevalent
      - combination of beta-lactam and macrolide (Grade 2B)

1. Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: Crit Care Med; 2013

# combination therapy vs. monother

**ombination therapy may reduce mortality in atients with bacterial septic shock (level 2 [mid-vel] evidence)**

Crit Care Med 2010 Sep

- retrospective cohort study
- 4,662 patients with bacterial septic shock evaluated
- comparing combination therapy vs. monotherapy in propensity-matched cohort
- beta-lactam plus aminoglycoside, fluoroquinolone, or macrolide/clindamycin associated with reduced mortality

# Antibiotics and Source Control-3

- Recommendations regarding antibiotic therapy(1)

  - suggested to limit antibiotic therapy 7-10 days unless (Grade 2C)
    - slow response
    - undrainable foci of infection
    - bacteremia with *Staphylococcus aureus*
    - certain fungal and viral infections
    - immunologic deficiencies (including neutropenia)
  - start antiviral therapy in patients with severe sepsis or septic shock due to virus (Grade 2C)
  - consider using low procalcitonin levels or other biomarkers to inform discontinuation of empiric antibiotics in patients who initially appeared septic, but no longer have evidence of infection (Grade 2C)

1. Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: Crit Care Med; 2013

# Antibiotic administration

- Strong positive relationship between prompt antimicrobial administration and improved outcome in severe sepsis or septic shock.

44.Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med 2006
45. Time to initiation of fluconazole therapy impacts mortality in patients with candidemia: A multi-institutional study. Clin Infect Dis 2006
46. Impact of time to antibiotics on survival in patients with severe sepsis or septic shock in whom early goal-directed therapy was initiated in the emergency department. Crit Care Med 2010

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# Antibiotic administration

- The impact of each action in the Surviving Sepsis Campaign measures on hospital mortality of patients with severe sepsis/septic shock. Einstein 2008
  - interventions associated with lower mortality:
    - Early administration of antimicrobials (i.e., after less than 120 min from identification) and
    - early collection of blood for cultures.

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# Antibiotic administration

- Effectiveness of treatments for severe sepsis: A prospective, multicenter, observational study. Am J Respir Crit Care Med 2009
  - 2796 severe sepsis or septic shock patients
    - early administration of antimicrobials associated with significantly reduced mortality.

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# Time to antibiotics

- **each hour of delay of antimicrobial therapy after onset of hypotension in septic shock associated with increased mortality (<u>level 2 [mid-level] evidence</u>)**

  - <u>Crit Care Med 2006 Jun</u>
    - retrospective cohort study
    - 2,154 adults with septic shock in 14 ICU and 10 hospitals in United States and Canada
    - delay of effective therapy associated with increased risk of in-hospital mortality
      - adjusted odds ratio 1.119 per hour delay (95% CI 1.103-1.136)
      - **<u>survival decreased 7.6% with each hour effective treatment was delayed</u>**

# Time to antibiotics

- **starting antibiotics within 1 hour associated with lower mortality in patients with severe sepsis or septic shock (<u>level 2 [mid-level] evidence</u>)**
  - <u>Crit Care Med 2010 Apr</u>
    - retrospective cohort study
    - time from triage to antibiotics < 1 hour associated with lower mortality (19.5% vs. 33.2%, p = 0.02)
    - time to antibiotics < 1 hour associated with lower mortality (25% vs. 38.5%, p = 0.03)

# Procalcitonin-guided strategy

- Crit Care Med 2010 Nov
- Arch Intern Med 2011 Aug
  - **procalcitonin algorithms for antibiotic therapy decisions may decrease antibiotic exposure without increasing mortality (level 2 [mid-level] evidence)**
- Lancet 2010 Feb
  - **in nonsurgical patients in intensive care units, procalcitonin-guided strategy to treat suspected bacterial infections may reduce antibiotic exposure (level 2 [mid-level] evidence)**

# Procalcitonin

- Procalcitonin is the prohormone precursor of calcitonin that is expressed primarily in C-cells of the thyroid gland and to a smaller extent in neuroendocrine tissue of other organs, such as the lungs and intestines.
- The final step in conversion of procalcitonin to calcitonin is inhibited by various cytokines and bacterial endotoxins and, therefore, high levels of cytokines and/or bacterial endotoxins cause procalcitonin levels to rise.
- Cytokines are released nonspecifically in response to inflammation and infection, but endotoxins are released specifically during bacterial infections because since they are derived primarily from Gram-negative bacterial cell walls.
- There is some evidence that procalcitonin is more specific for bacterial infections with serum levels rising and falling more rapidly in bacterial infection.

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# Procalcitonin

- Procalcitonin's primary diagnostic utility is thought to be in establishing bacterial infections are present.
  - Viruses, parasites, and fungi can increase procalcitonin levels due to systemic inflammation, but higher levels of procalcitonin have been demonstrated to specifically occur with bacterial infections, with the highest levels seen in bacterial sepsis.
  - The diagnostic utility of procalcitonin is limited in fungal infections because the levels do not rise until 1 to 2 days after the onset of infection.
  - A greater increase in procalcitonin levels would be anticipated in Gram-negative versus Gram-positive bacterial infections due to the release of endotoxin from Gram-negative bacterial cell walls; however, few studies have demonstrated higher levels of procalcitonin with Gram-negative bacterial infections when compared to Gram-positive bacterial infections.5
- Procalcitonin appears to be a promising serum biomarker for infection, but its exact utility in diagnosing and managing patients with suspected infections remains unclear.

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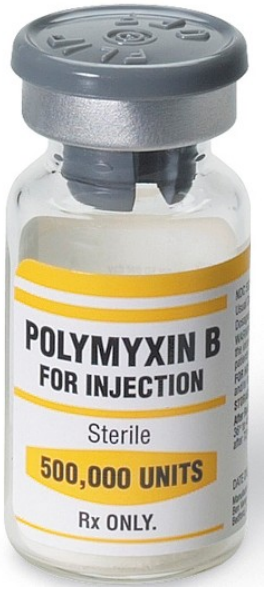
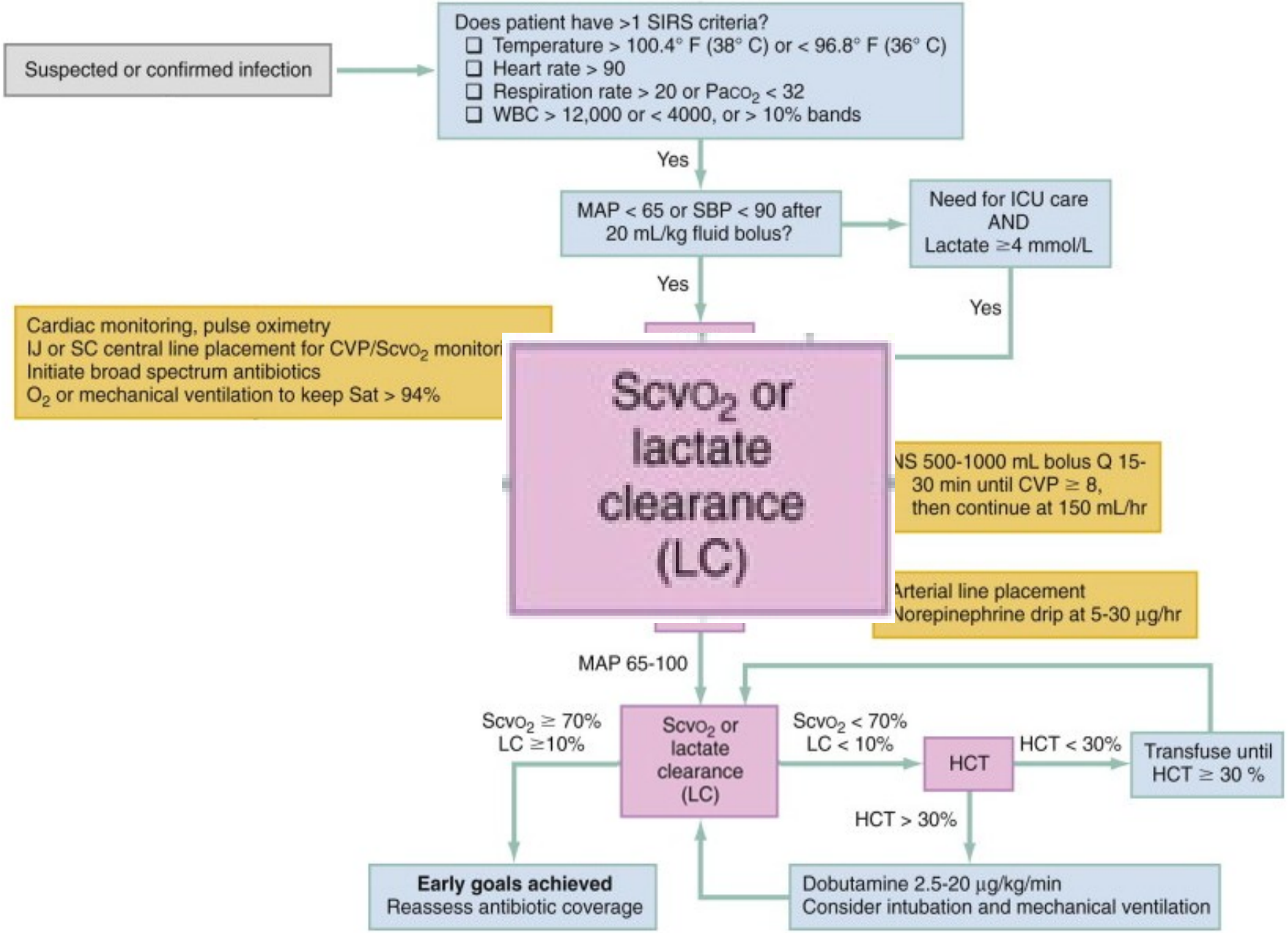
# Polymyxin-B

- EUPHAS trial, JAMA 2009 Jun




- **polymyxin B hemoperfusion reduces mortality in patients with septic shock due to intra-abdominal infection (level 1 evidence)**
- randomized trial
- 64 patients with severe sepsis or septic shock having emergency surgery for intra-abdominal infection randomized to conventional therapy plus 2 sessions of polymyxin B hemoperfusion vs. conventional therapy alone
- trial terminated early due to significant difference in mortality
- 28-day mortality 32% with polymyxin B vs. 53% with control ($p = 0.01$, NNT 5)
- changes from baseline with polymyxin B hemoperfusion
  - increased mean arterial pressure (76 mm Hg to 84 mm Hg, $p = 0.001$)
  - decreased vasopressor requirement (29.9 to 6.8 inotropic score, $p < 0.001$)
  - increased fraction of inspired oxygen ratio ($p = 0.049$)
  - improved Sequential Organ Failure Assessment (SOFA) scores ($p < 0.001$)
- no significant changes from baseline in control group


Suspected or confirmed infection
Does patient have >1 SIRS criteria?
❑ Temperature > 100.4° F (38° C) or < 96.8° F (36° C)
❑ Heart rate > 90
❑ Respiration rate > 20 or Paco2 < 32
❑ WBC > 12,000 or < 4000, or > 10% bands
Yes
MAP < 65 or SBP < 90 after 20 mL/kg fluid bolus?
Need for ICU care AND Lactate ≥4 mmol/L
Yes
Yes
Cardiac monitoring, pulse oximetry
IJ or SC central line placement for CVP/Scvo2 monitori
Initiate broad spectrum antibiotics
O2 or mechanical ventilation to keep Sat > 94%
Scvo2 or lactate clearance (LC)
NS 500-1000 mL bolus Q 15-30 min until CVP ≥ 8, then continue at 150 mL/hr
Arterial line placement
Norepinephrine drip at 5-30 µg/hr
MAP 65-100
Scvo2 ≥ 70%
LC ≥10%
Scvo2 or lactate clearance (LC)
Scvo2 < 70%
LC < 10%
HCT
HCT < 30%
Transfuse until HCT ≥ 30 %
HCT > 30%
Early goals achieved
Reassess antibiotic coverage
Dobutamine 2.5-20 µg/kg/min
Consider intubation and mechanical ventilation

# Monitoring serum lactate clearance


- serum lactate clearance a reasonable biomarker alternative to invasive resuscitation monitoring.
  - Studies have found that septic patients who do not clear serum lactate by 10% in the first 2 to 6 hours have an increased mortality.

39. Multicenter study of early lactate clearance as a determinant of survival in patients with presumed sepsis. Shock 2009
40. Early lactate clearance is associated with improved outcome in severe sepsis and septic shock. Crit Care Med 2004

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# EGDT Vs. lactate clearance

- association of targeting lactate clearance as a resuscitation goal with mortality.


1. Multicenter study of early lactate clearance as a determinant of survival in pts with sepsis. Shock 2009
    - patients were randomized to conventional invasive monitoring (EGDT) or a therapy target guided by serial lactate clearance of 20% every 2 hours in addition to conventional invasive monitoring.
    - They found a significantly reduced ICU length of stay and both ICU and hospital mortality in the lactate clearance.

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# EGDT Vs. lactate clearance


- association of targeting lactate clearance as a resuscitation goal with mortality.

2. Lactate clearance vs. central venous oxygen saturation as goals of early sepsis therapy: A randomized clinical trial. JAMA 2010

  - multicentre noninferiority trial, group assigned to normalization of CVP, MAP, and ScvO2 according to EGDT protocols, and one to normalization of CVP, MAP, and a lactate clearance of 10% in the first 6 hours.

  - lactate clearance may be used instead of central venous oxygen saturation as a resuscitation target in severe sepsis.

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# Others

- **Corticosteroids**
- **Source control measures**
- **Glucose Control**
- **Sedation and analgesia**
- **Mechanical Ventilation**
- **Renal Replacement Therapy**
- **Antithrombotic Treatments**
- **Prevention of Septic Shock**

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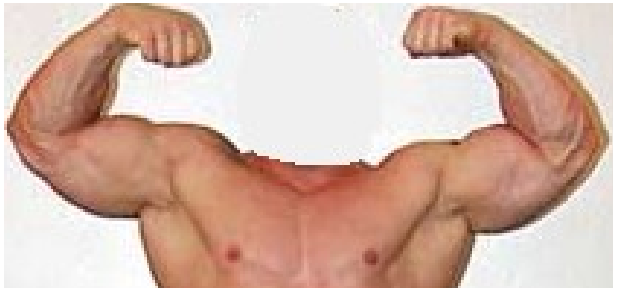
# Corticosteroids



- Recommendations regarding steroids(1)
  - IV hydrocortisone 200 mg/day suggested only for septic shock when hypotension responds poorly to fluids and vasopressors (Grade 2C)
    - adrenocorticotropic hormone (ACTH) stimulation test NOT suggested pre hydrocortisone (Grade 2B)
  - steroids may be weaned when vasopressors no longer needed (Grade 2D)
  - corticosteroids not recommended for treatment of sepsis in absence of shock (Grade 1D)





1. Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: Crit Care Med; 2013

# Source control measures


- Recommendations on source control measures(1)
  - seek and diagnose or exclude infection requiring emergent source control as quickly as possible, and give intervention within 12 hours of diagnosis if feasible (Grade 1C)
  - suggested exception for infected pancreatic necrosis, for which surgery should be delayed until adequate demarcation of viable and nonviable tissue achieved (Grade 2B)
  - choose source control measure with least physiologic upset (for example, percutaneous rather than surgical drainage of abscess) (Grade UG)
  - remove potentially infected intravascular access devices promptly after other vascular access established (Grade





1. Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: Crit Care Med; 2013

# Source control measures


- **examples of source control techniques:**
  - drainage for intra-abdominal abscess, thoracic empyema, or septic arthritis
  - debridement for pyelonephritis, cholangitis, infected pancreatic necrosis, intestinal infarction, or mediastinitis
  - device removal for infected vascular catheter, urinary catheter, or infected intrauterine contraceptive device
  - surgery for diverticulitis (sigmoid resection), gangrenous cholecystitis (cholecystectomy), or clostridial myonecrosis (amputation)

Crit Care Med 2008 Jan

SOURCE CONTYROL

# Glucose Control

- Recommendations for glucose control
  - begin insulin when 2 consecutive blood glucose levels are > 180 mg/dL (10 mmol/L), (Grade 1A)
  - monitor blood glucose levels every 1-2 hours (every 4 hours when stable) (Grade 1C)

1. Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: Crit Care Med; 2013

# Glucose Control

- **Intensive insulin therapy:**

  - NICE-SUGAR trial, N Engl J Med 2009 Mar
    - **intensive glucose control may be associated with increased risk for death and severe hypoglycemia in critically ill patients (level 2 evidence)**
  - N Engl J Med 2008 Jan
  - COIITSS trial, JAMA 2010 Jan
    - **intensive insulin therapy in patients with sepsis associated with higher risk of hypoglycemia and no reduction in mortality (level 2 evidence)**

TIGHT GLYCEM

# Tight Glycemic Control

- On the basis of the current evidence, the Surviving Sepsis Campaign recommends maintaining a glucose level of less than 150 mg/dL.[37, 71]

Van den Berghe documented benefit only once glucose levels were maintained below 110 mg/dl, with increased mortality when blood glucose levels were allowed to reach 130-150 mg/dL.[72]

- This same group recently finished a large prospective study in medical patients documenting similar benefits in these patients.[73]
- In elderly persons (>75 y) and in those patients with liver failure, excessive hypoglycemic reactions limits its use.

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# Other Supportive Care

- **Sedation and analgesia:**
  - Surviving Sepsis Campaign recommendations(1)
    - minimize continuous or intermittent sedation in mechanically ventilated sepsis patients, targeting specific titration endpoints (Grade 1B)
    - Neuromuscular blocking agents (NMBA)
      - in patients without ARDS , avoid NMBA if possible (Grade 1C)
      - if NMBA required, intermittent bolus as required or continuous infusion with train-of-four monitoring of blockade depth recommended (Grade 1C)
      - in patients with ARDS and PaO2/FiO2 < 150 mm Hg, short course of NMBA < 48 hours suggested (Grade 2C)

1. Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: Crit Care Med; 2013

# Mechanical Ventilation

- Surviving Sepsis Campaign guidelines on mechanical ventilation of sepsis-induced acute lung injury/acute respiratory distress syndrome (ALI/ARDS)(1)
  - settings for mechanical ventilation
    - target tidal volume 6 mL/kg predicted body weight (SCCM Grade 1A vs. 12 mL/kg)
    - target initial upper limit plateau pressure in passively inflated lung ≤ 30 cm H2O ( SCCM Grade 1B)
    - set positive end-expiratory pressure (PEEP) to avoid extensive lung collapse at end-expiration (SCCM Grade 1B)
    - consider strategies based on higher rather than lower levels of PEEP in patients with moderate or severe acute respiratory distress syndrome (ARDS) (SCCM Grade 2C)
  - recruitment maneuvers suggested in sepsis patients with severe refractory hypoxemia ( SCCM Grade 2C)
  - consider prone position for acute respiratory distress patients with partial pressure of arterial oxygen/fraction of inspired oxygen (PaO2/FiO2) ratio ≤ 100 mm Hg in facilities experienced with such practices (SCCM Grade 2B)
  - maintain semirecumbent position (head of bed raised to 30-45 degrees) (SCCM Grade 1B)
  - carefully consider noninvasive mask ventilation in patients if benefits outweigh risks ( SCCM Grade 2B)

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# Mechanical Ventilation

- Surviving Sepsis Campaign guidelines on mechanical ventilation of sepsis-induced acute lung injury/acute respiratory distress syndrome (ALI/ARDS)(1)
  - use weaning protocol and regular spontaneous breathing trials to evaluate ability to discontinue mechanical ventilation (SCCM Grade 1A)
    - spontaneous breathing trial options include low level of pressure support with continuous positive airway pressure 5 cm H2O or T-piece
    - patient criteria for spontaneous breathing trial
      - arousable
      - hemodynamically stable without vasopressors
      - no new potentially serious conditions
      - low ventilatory and end-expiratory pressure requirements
      - FiO2 levels can be safely delivered via face mask or nasal cannula
  - do not use pulmonary artery catheter for routine monitoring (SCCM Grade 1A)
  - use conservative fluid strategy if no evidence of tissue hypoperfusion (SCCM Grade 1C)
  - do not use beta-2 agonists in absence of specific indications, such as bronchospasm ( SCCM Grade 1B)

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# Renal Replacement Therapy

- Surviving Sepsis Campaign recommendations for renal replacement therapy(1)
  - intermittent hemodialysis and continuous renal replacement therapies considered equivalent (Grade 2B)
  - continuous therapies considered easier to manage in hemodynamically unstable patients (Grade 2D)

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# Renal Replacement Therapy

- Lancet 2006 Jul

  - **intermittent hemodialysis may be as effective as continuous hemodiafiltration in patients with multiple organ dysfunction (level 2 evidence)**

    - randomized trial with differential crossover rate
    - 360 critically ill patients with acute renal failure and multiple organ dysfunction syndrome were randomized to intermittent hemodialysis vs. continuous venovenous hemodiafiltration
    - 225 patients (62.7%) had sepsis
    - 6 patients in intermittent hemodialysis group and 31 in continuous venovenous hemodiafiltration group switched treatment
    - comparing intermittent hemodialysis vs. continuous venovenous hemodiafiltration
      - 30-day survival 41.8% vs. 38.9% (not significant)
      - 60-day survival 32% vs. 33% (not significant)
      - 90-day survival 27.2% vs. 28.5% (not significant)

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# Antithrombotic Treatments

- **Deep vein thrombosis prophylaxis:**
  - American College of Chest Physicians (ACCP) guidelines on antithrombotic and thrombolytic therapy (9th Edition)
  - Surviving Sepsis Campaign recommendations regarding deep vein thrombosis prophylaxis(1)
    - daily pharmaco-prophylaxis against DVT recommended for patients with severe sepsis (Grade 1B)
    - combination of pharmacologic therapy and intermittent pneumatic compression devices suggested for treatment of severe sepsis when possible (Grade 2C)

1. Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: Crit Care Med; 2013

# Limited evidence

- Crit Care Med 1999 Apr
  - **ibuprofen IV may decrease mortality in patients with hypothermic sepsis (level 2 evidence)**
    - 455 patients admitted to intensive care unit (ICU) for severe sepsis and suspected of having serious infection given ibuprofen 10 mg/kg (maximum 800 mg) IV over 30-60 minutes every 6 hours vs. placebo for 8 doses
    - mortality
      - 35% among 409 febrile patients
      - 70% among 44 hypothermic patients
    - among hypothermic patients, 30-day mortality was 54% with ibuprofen vs. 90% with placebo ($p < 0.05$, NNT 3)

# Limited evidence

- Crit Care Med 2010 Jan
  - **IV nitroglycerin might increase mortality in patients with severe sepsis (level 2 [mid-level] evidence)**
    - based on randomized trial without statistical significance
    - 70 patients ≥ 18 years old with sepsis and ≥ 1 early sign of organ dysfunction were randomized to nitroglycerin vs. placebo after protocol-driven resuscitation endpoints
    - in-hospital mortality 34.3% with nitroglycerin vs. 14.2% with placebo ($p = 0.09$)

# Limited evidence

- Cochrane Database Syst Rev 2003
  - **naloxone might improve blood pressure in patients with shock (level 3 [lacking direct] evidence)**
    - Cochrane review of trials without significant differences in clinical outcomes
    - systematic review identified 6 randomized trials evaluating naloxone in 126 patients with septic, cardiogenic, hemorrhagic, or spinal shock
    - naloxone associated with improved outcomes in analysis of 3 trials with 59 patients
      - significantly higher mean arterial blood pressure (weighted mean difference +9.33 mm Hg, 95% CI 7.07-11.59 mm Hg)
      - non-significant decrease in mortality (odds ratio 0.59, 95% CI 0.21-1.67), results limited by significant heterogeneity ($I^2$ = 0.05)

# Prevention of Septic Shock

- Ventilatory support and invasive catheters further worsen the risk of infection.
- Avoiding the use of catheters or removing them as soon as possible may prevent severe sepsis.
- Prophylactic antibiotics in the perioperative phase, particularly after GI surgery, may be beneficial.

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# Prevention of Septic Shock

- The use of topical antibiotics around invasive catheters and as part of dressing for patients with burns is helpful
- Prevention of sepsis with topical or systemic antibiotics is suggested for high-risk patients.
- Maintenance of adequate nutrition, administration of pneumococcal vaccine in patients who have had a splenectomy, and early enteral feeding are other preventive measures

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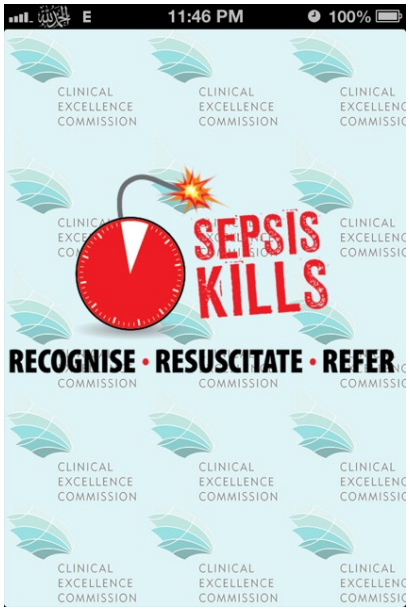


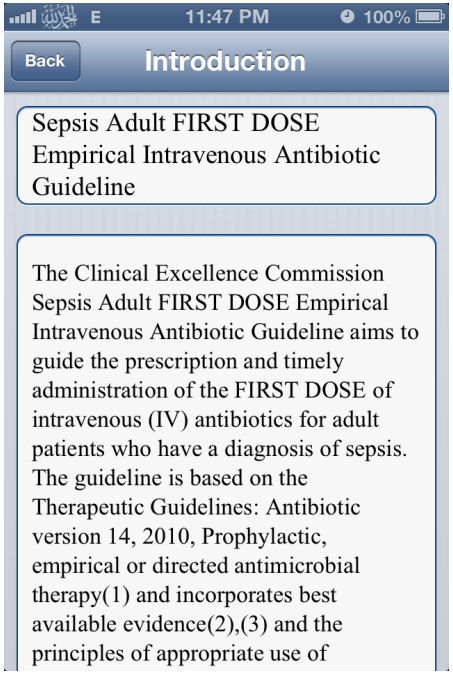


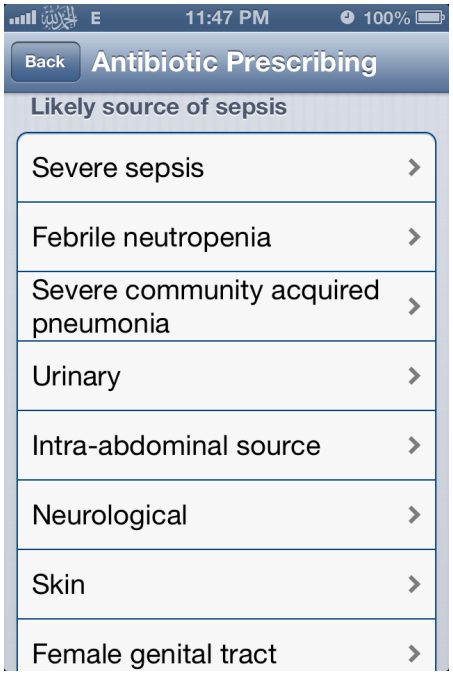


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- Progression from infection with SIRS, sepsis to severe sepsis with organ dysfunction to septic shock with refractory hypotension can often be reversed

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# Interventions within 3 hrs of triage:

- Measure lactate levels.
- Obtain at least 2 sets of blood cultures and relevant other sites +/- imaging.
- Give 30 mL/kg of crystalloid for hypotension or for lactate levels of at least 4 nmol/L.
- Give broad-spectrum antibiotics including at least 1 drug with activity against all likely pathogens (bacterial, fungal, or viral).

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# Interventions within 6 hrs of triage:

- Use vasopressors if no response to fluid to maintain mean arterial pressure of at least 65 mm Hg.
- Use targets for quantitative resuscitation:
  - normalization of lactate
  - urine output of at least 0.5 mL/kg per hour
  - CVP of at least 8 mm Hg
  - ScvO2 of at least 70%,

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# THINK TREAT STOP!

sepsis


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