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敗血症國際指引

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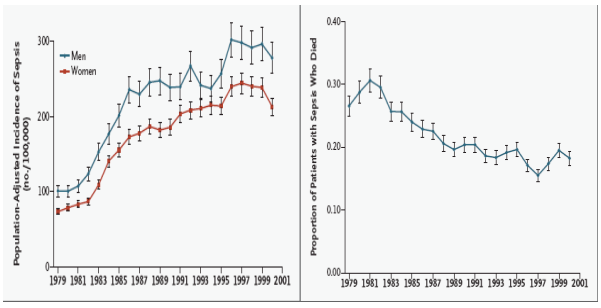
Surviving Sepsis Campaign:
International Guidelines for Management of Severe Sepsis and Septic Shock: 2012

主題大綱

- 敗血症相關定義
- 敗血症診斷標準
- 敗血症復甦目標
- 感染源診斷控制
- 血行動力學支持

Clinician's
decision-making capability
V
Guideline recommendations

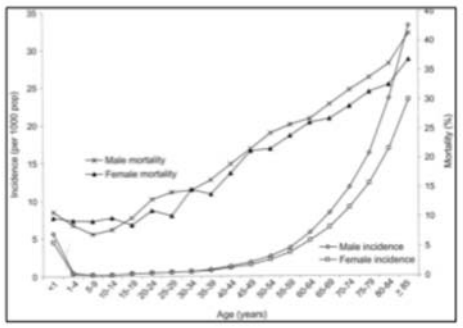
Sepsis is an important issue



28.7% ➔17.9%

N Engl J Med 2003;348:1546-54

Figure 2

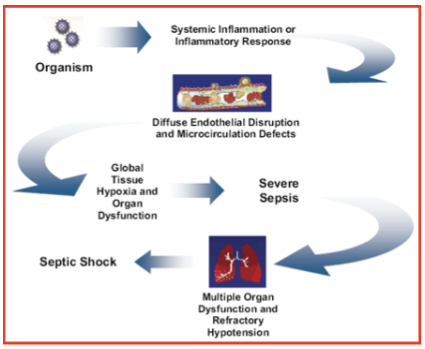


Epidemiology of severe sepsis in the United States: Analysis of incidence, outcome, and associated costs of care.
Angus, Derek, MD, MPH; Linde-Zwirble, Walter; Lidicker, Jeffrey; Clermont, Gilles; Carcillo, Joseph; Pinsky, Michael, MD FCCM
Critical Care Medicine. 29(7):1303-1310, July 2001.

Figure 2. National age-specific incidence and mortality rates for all cases of severe sepsis by gender, excluding those with HIV disease. National estimates are generated from the seven-state cohort using state and national age-specific population estimates from the National Center for Health Statistics and the U.S. Census. The incidence among women was equivalent to that of men 5 yrs younger. A similar age-based difference was seen in mortality but, in multivariate regression, this difference was explained by underlying comorbidity and site of infection. pop, population.

Severe Sepsis 751,000 cases/y
Mortality 28.6%

From Infection to Septic Shock



Definition

- SIRS
- Sepsis
- Severe Sepsis
  - sepsis-induced hypotension
  - sepsis-induced hypoperfusion
- Septic shock

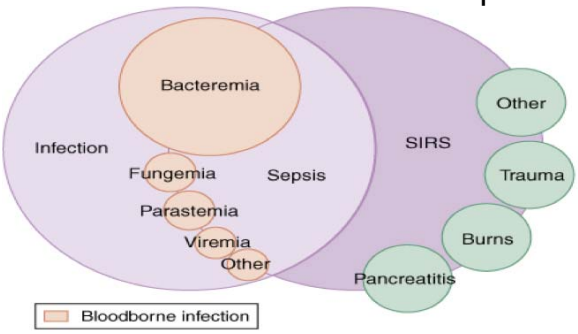
SIRS

(Systematic Inflammatory Response Syndrome)

- BT > 38℃ or <36℃
- HR > 90 bpm
- RR > 20 bpm or PaCO2 < 32 mmHg
- WBC > 12K , < 4K or > 10% bands

Sepsis = SIRS +

Presumed or confirmed infectious process



"Dear SIRS, I don't like you"

- Dear SIRS, you are too sensitive
- Dear SIRS, you do not help us understand the pathophysiology of sepsis
- Dear SIRS, you do not reflect the severity of the disease
- Dear SIRS, you detract us from searching for the infection
- Dear SIRS, I am afraid we don't need you

Diagnostic criteria for Sepsis GIHOT

- General variables
- Inflammatory variables
- Hemodynamic variables
- Organ dysfunction variables
- Tissue perfusion variables

Diagnostic criteria for Sepsis GIHOT

- General variables

  Fever (core temperature > 38.3°C)

  Hypothermia (core temperature < 36°C)

  Heart rate > 90 bpm or >2 SD above the normal value

  Tachypnea

  Altered mental status

  Significant edema or positive fluid balance (>20 mL/kg over 24 hrs)

  Hyperglycemia (plasma glucose >140 mg/dL) in the absence of diabetes

Diagnostic criteria for Sepsis GIHOT

- Inflammatory variables

  Leukocytosis (WBC count > 12,000/ μ L)

  Leukopenia (WBC count < 4000/ μ L)

  Normal WBC count with > 10% immature forms

  Plasma C-reactive protein > 2 SD above the normal value

  Plasma procalcitonin > 2 SD above the normal value

Diagnostic criteria for Sepsis GIHOT

- Hemodynamic variables
  - Arterial hypotension

    SBP < 90 mm Hg,

    MAP < 70 mm Hg, or

    SBP decrease > 40 mm Hg in adults or < 2 SD below normal for age
  - Bundle thresholds ≥ 65 mmHg

Diagnostic criteria for Sepsis GIHOT

- Organ dysfunction variables

  Arterial hypoxemia (PaO2/FiO2 < 300)

  Acute oliguria (urine output < 0.5 mL/kg/hr for at least 2 hrs despite adequate fluid resuscitation)

  Creatinine increase > 0.5 mg/dL

  Coagulation abnormalities (INR > 1.5 or aPTT > 60 secs)

  Ileus (absent bowel sounds)

  Thrombocytopenia (platelet count < 100,000 / μ L)

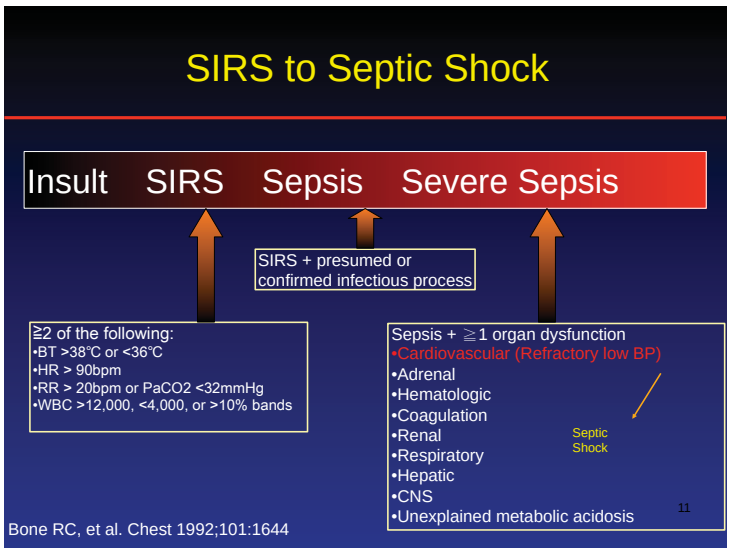
  Hyperbilirubinemia (plasma total bilirubin > 4 mg/dL)

Diagnostic criteria for Sepsis GIHOT

- Tissue perfusion variables

  Hyperlactatemia (> 1 mmol/L)

  Decreased capillary refill or mottling



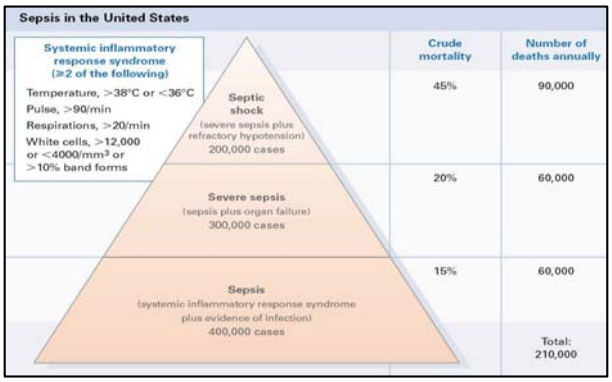
Severe Sepsis

Sepsis induced tissue hypoperfusion or organ dysfunction

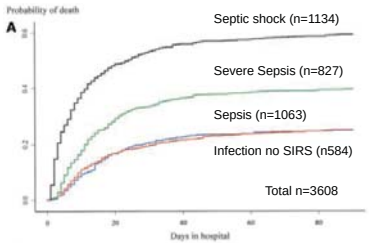
Sepsis-induced hypotension
Lactate > normal UL
Urine output < 0.5 mL/kg/hr for > 2 hrs despite adequate fluid resuscitation
Acute lung injury with PaO2/FiO2 < 250 for those w/o pneumonia as source
Acute lung injury with PaO2/FiO2 < 200 for those w/ pneumonia as source
Creatinine increase > 2.0 mg/dL
Bilirubin > 2 mg/dL
Platelet < 100K
Coagulopathy (INR > 1.5)

- Sepsis-induced tissue hypoperfusion
- infection-induced hypotension, elevated lactate, or oliguria
- Septic shock
- sepsis-induced hypotension persisting despite adequate fluid resuscitation

Epidemiology of Sepsis in US (1979-2000)



Organ dysfunction is a major outcome parameter



GRADE

Methodology

A
B
C
D

Decrease strength

Factors

Increase strength

建議強度考量因素 1 or 2

- 証據力
- 確定性
- 一致性
- 可行性

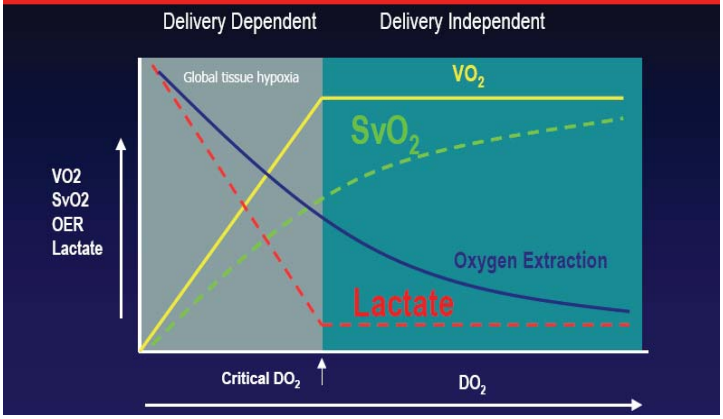
Strong recommendation

≠

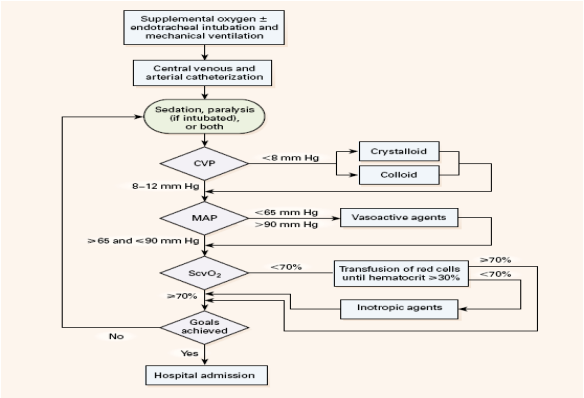
Standard of care

How do we recognize sepsis and global tissue hypoxia in the pre-ICU period?

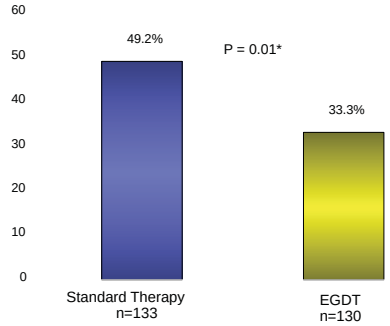
SvO_2 and Lactate as Markers of Global Tissue Hypoxia in Sepsis



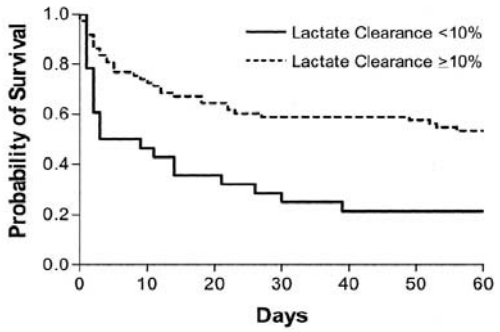
Early Goal-Directed Therapy



EGDT
28 day mortality



Early lactate clearance is associated with improved outcome



Initial resuscitation

- Protocol with quantitative resuscitation
- Sepsis-induced tissue hypoperfusion
- Goals within first 6 hours
  1. CVP 8-12 mmHg (MV 12-15 mmHg)
  2. MAP ≥ 65 mmHg
  3. Urine output ≥ 0.5 mL/kg/hr
  4. ScvO2 ≥ 70 % or SvO2 ≥ 65% (IC)
- Lactate normalization (2C)

Fluid therapy

- Crystalloids: initial fluid of choice (1B)
- Hydroxyethyl starches: against (1B)
- Albumin: supplement of crystalloids (2C)
- Volume: minimun 30 mL/kg (1C)
- Challenge technique (UG)
- Responsiveness: dynamic or static (UG)

Vasopressors

- Target: MAP ≥ 65 mmHg (1C)
- Norepinephrine: first choice (1B)
- Epinephrine: additional agent (2B)
- Vasopressin 0.03 U/min (UG)
  - to raise MAP or decrease NE dosage
  - not for single use
  - higher dose only for salvage therapy

NE is superior to dopamine

TABLE 7. Norepinephrine Compared With Dopamine in Severe Sepsis Summary of Evidence

Norepinephrine compared with dopamine in severe sepsis

Patient or population: Patients with severe sepsis
Settings: Intensive care unit
Intervention: Norepinephrine
Comparison: Dopamine
Sources: Analysis performed by Djillali Annane for Surviving Sepsis Campaign using following publications: De Backer D. *N Engl J Med* 2010; 362:779–789; Marik PE. *JAMA* 1994; 272:1354–1357; Mathur RDAC. *Indian J Crit Care Med* 2007; 11:186–191; Martin C. Chest 1993; 103:1826–1831; Patel GP. *Shock* 2010; 33:375–380; Ruokonen E. *Crit Care Med* 1993; 21:1296–1303

Outcomes	Illustrative Comparative Risks[a] (95% CI) Assumed Risk	Corresponding Risk	Relative Effect (95% CI)	No. of Participants (Studies)	Quality of the Evidence (GRADE)	Comments
	Dopamine	Norepinephrine				
Short-term mortality	530 per 1000	Study population 482 per 1000 (440 to 524)	RR 0.91 (0.83 to 0.99)	2043 (6 studies)	⊕⊕⊕⊖ moderate[b,c]	
Serious adverse events —Supraventricular arrhythmias	229 per 1000	Study population 82 per 1000 (34 to 195)	RR 0.47 (0.38 to 0.58)	1931 (2 studies)	⊕⊕⊕⊖ moderate[b,c]	
Serious adverse events —Ventricular arrhythmias	39 per 1000	Study population 15 per 1000 (8 to 27)	RR 0.35 (0.19 to 0.66)	1931 (2 studies)	⊕⊕⊕⊖ moderate[b,c]	

[a]The assumed risk is the control group risk across studies. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI = confidence interval; RR = risk ratio.
[b]Strong heterogeneity in the results (I^2 = 85%), however this reflects degree of effect, not direction of effect. We have decided not to lower the evidence quality.
[c]Effect results in part from hypovolemic and cardiogenic shock patients in De Backer, *N Engl J Med* 2010. We have lowered the quality of evidence one level for indirectness.

Vasopressors

- Dopamine (2C)
  - low risk of tachyarrhythmias
  - absolute or relative bradycardia
- Phenylephrine only for (1C)
  - NE associated with arrhythmias
  - High CO and Low BP
  - Salvage therapy
- Low-dose dopamine: not for renal protection (1A)
- Arterial catheter if available (UG)

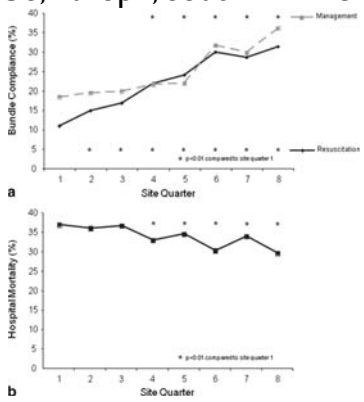
Inotropic therapy

- Dobutamine up to 20 μ g/kg/min (1C)
  - myocardial dysfunction
    - elevated cardiac filling pressure
    - low cardiac output
  - ongoing hypoperfusion
- Not for supranormal cardiac index (1B)

Corticosteroids

- Hydrocortisone
  - refractory septic shock (2C)
  - 200 mg/day (2C)
  - continous flow (2D)
  - no role for ACTH stimulation test (2B)
  - no vasopressor, no steroid (2D)
  - no shock, no steroid (1D)

SSC performance improvement program
US, Europe, South America



Low CVP and ScvO2 achievement

Table 3. Change in achievement of bundle targets

	Initial Quarter Achieved, %	Final Quarter Achieved, %[a]	*p* Value Compared With Initial	Remaining Quarters Achieved, %	*p* Value Compared With Initial
Initial care bundle (first 6 hrs of presentation)					
Measure lactate	61.0	78.7	≤.0001	72.5	≤.0001
Blood cultures before antibiotics	64.5	78.3	≤.0001	76.3	≤.0001
Broad-spectrum antibiotics	60.4	67.9	.0002	67.0	≤.0001
Fluids and vasopressors	59.8	77.0	≤.0001	71.1	≤.0001
CVP >8 mm Hg	26.3	38.0	≤.0001	33.9	≤.0001
$Scvo_2$ >70%	13.3	24.3	≤.0001	21.7	≤.0001
All resuscitative measures	10.9	21.5	≤.0001	21.1	≤.0001
Management bundle (first 24 hrs after presentation)					
Steroid policy	58.5	73.9	≤.0001	66.8	≤.0001
Administration of drotrecogin alfa policy	47.4	53.5	.003	49.9	.02
Glucose control	51.4	56.8	.0009	55.4	≤.0001
Plateau pressure control	80.8	83.8	.24	82.6	.09
All management measures	18.4	25.5	≤.0001	23.3	≤.0001

CVP, central venous pressure; $Scvo_2$, central venous oxygen saturation.
[a]Represents the last quarter of data submission from each institution during the 2-yr data analysis period, regardless of total number of quarter of each institution's participation.

BP & Lactate in Sepsis

	Low BP + Lac ≥ 4	Low BP	Lac ≥ 4
Prevalence	16.6%	49.5%	5.4%
Mortality	46.1%	36.7%	30%

ScvO2 70% vs Lac clearance 10%

Table 5. Hospital Mortality and Length of Stay

Variable	Lactate Clearance Group (n = 150)	$Scvo_2$ Group (n = 150)	Proportion Difference (95% Confidence Interval)	*P* Value[b]
In-hospital mortality, No. (%)[a]				
Intent to treat	25 (17)	34 (23)	6 (–3 to 15)	
Per protocol	25 (17)	33 (22)	5 (–3 to 14)	
Length of stay, mean (SD), d				
ICU	5.9 (8.46)	5.6 (7.39)		.75
Hospital	11.4 (10.89)	12.1 (11.68)		.60
Hospital complications				
Ventilator-free days, mean (SD)	9.3 (10.31)	9.9 (11.09)		.67
Multiple organ failure, No. (%)	37 (25)	33 (22)		.68
Care withdrawn, No. (%)	14 (9)	23 (15)		.15

Abbreviations: ICU, intensive care unit; $Scvo_2$, central venous oxygen saturation.
[a]Primary study end point.
[b]Continuous data are compared using an unpaired *t* test; categorical variables, using the χ^2 test.

Screening

- Earlier screening, earlier therapy implementation (1C)
- Hospital-based performance improvement (UG)
  - consistent education
  - protocol development & implementation
  - data collection
  - measurement of indicators
  - feedback to facilitate continuous improvement

SSC bundles (3 hrs)

- 測量Lactate數值
- 投予抗生素前取得血液培養
- 投予廣效抗生素
- 針對低血壓或Lactate ≥ 36 mg/dL (4 mmol/L)者，給予30 mL/kg膠體溶液

SSC bundles (6 hrs)

- 對輸液無反應者給予升壓劑以維持MAP ≥ 65 mmHg
- 僅管給了輸液仍持續低血壓的敗血性休克或初始Lactate ≥ 36 mg/dL (4 mmol/L)者
  - 測量中央靜脈壓力 (CVP) *
  - 測量中央靜脈氧氣飽合度 (ScvO2) *
- 對初始Lactate上升者再度測量Lactate值 *

- 治療目標 (*):
  - CVP ≥ 8 mmHg
  - ScvO2 ≥ 70%
  - Normalization of lactate

Data collection

Severe Sepsis Chart Review data collection tool for educational purposes

Based on the Evaluation for Severe Sepsis Screening Tool
☐ Does the patient history suggest a new infection? If yes,
☐ Does the patient present with two or more new signs or symptoms of infection? If yes,
☐ Does the patient have evidence of organ dysfunction due to the infection?

If ALL of the screening elements above are answered YES, initiate the Severe Sepsis Protocol.
1. Met Criteria for ☐Severe Sepsis ☐Septic Shock
2. Determine the date and time of presentation ___/___/___ ___:___
   - Time of presentation is equal to ED triage time or documentation (date and time) supporting the diagnosis of severe sepsis in the progress notes for non-ED admissions.
3. Admission Category:
   ☐ ED ☐ Transferred to Critical Care Unit from unit other than ED ☐ Currently in the ICU
   Patients on the floor/unit outside the ED, enter date and time of last sepsis screen ___/___/___ ___:___
   Hospital Admission ___/___/___ ___:___ Critical Care Unit admission ___/___/___ ___:___

3hr bundle

3 hour BUNDLE
Check if completed, proceed to enter date, time, and Y/N as appropriate

The goal is to start immediately and complete within 3 hours.
4.☐ Measure serum lactate ___Yes _____mmol/L mg/dl ___/___/___ ___:___ ___No
5.☐ Obtain blood cultures prior to antibiotic administration ___Yes ___/___/___ ___:___ ___No
☐ Collected before the patient was started on an antibiotic for a suspected infection other than severe sepsis and continued until the time of presentation
6.☐ Administer broad-spectrum antibiotic, ***Minimize time to administration with a maximum of 3 hours***
1. _____ ___/___/___ ___:___ 2._____ ___/___/___ ___:___
☐ A broad spectrum antibiotic was initiated for a suspected infection other than severe sepsis and continued until the time of presentation with severe sepsis

In the event of hypotension and/or a serum lactate ≥ 4 mmol/L
7. ☐ Was the patient hypotensive? ___Yes ___No
7b. ☐SBP<90 mmHg Y/N MAP <65 mmHg Y/N SBP decrease of >=40 mmHg Y/N
7c. ☐Deliver an initial minimum of 30 ml/kg of crystalloid ___Yes ___/___/___ ___:___ ___No
7d. ☐Did MAP rise to and remain ≥65 after initial fluid resuscitation? ___Yes ___No

6hr bundle

6 hour BUNDLE (measured +/- achieved)

To be started immediately and completed within 6 hours
7e. ☐ Apply vasopressors for hypotension not responding to initial fluid resuscitation to maintain mean arterial pressure (MAP) ≥65 mm Hg ___Yes ___No
7f. ☐ Did MAP remain >=65 without the use of vasopressors? ___Yes ___No

In the event of persistent hypotension despite fluid resuscitation (septic shock) and/or lactate ≥4 mmol/L
8. ☐ Insert a central line ___Yes ___/___/___ ___:___ ___No
9. ☐ Measure a central venous pressure (CVP) ___Yes ___/___/___ ___:___ ___No
   ☐ Achieve a central venous pressure (CVP) >=8 mm Hg ___Yes ___/___/___ ___:___ ___No
10. ☐ Measure a central venous oxygen saturation (ScvO2) or mixed venous oxygen saturation (SvO2) ___Yes ___/___/___ ___:___ ___No
   ☐ Achieve a central venous oxygen saturation (ScvO2) ≥ 70% or mixed venous oxygen saturation (SvO2) ≥ 65% ___Yes ___/___/___ ___:___ ___No
   10a. Type of catheter monitoring ☐Intermittent ☐Continuous ☐N/A
11. ☐ Remeasure lactate, if initial lactate was elevated >2 mmol/L (18mg/dl)
   ___Yes ___/___/___ ___:___ ___No

12. Critical Care Unit Discharge ___/___/___ ___:___

Hospital Discharge ___/___/___ ___:___ Status ☐ Alive ☐Deceased

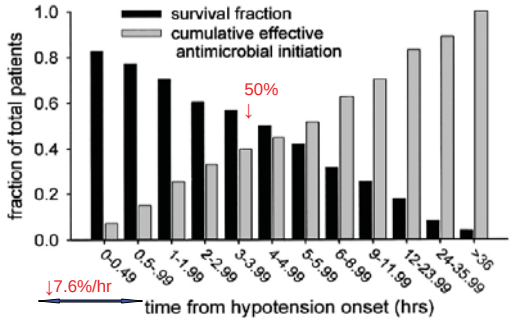
Diagnosis

- Cultures (1C)
  - Before antibiotics (no delay > 45 min)
  - At least 2 sets of B/C (1C as potential source)
  - Volume of blood for culture ≥ 10 mL
  - Cultures of other sites
  - Rapid influenza test during pandemic periods
- 1,3 β-D-glucan assay (2B), mannan and anti-mannan antibody assay(2C) for invasive candidiasis

Diagnosis

- Imaging
  - Seek for source of infection (UG)
- Biomarkers
  - No recommendation to distinguish between sepsis and inflammation

The earlier the antibiotics, the better the survival



Main causative organisms

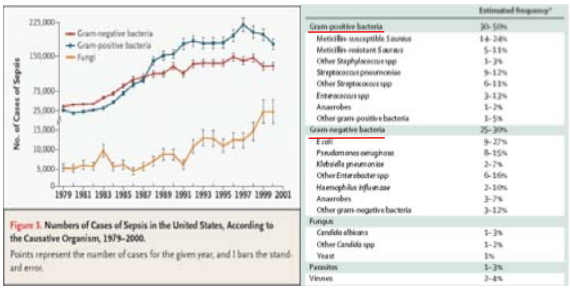


Figure 3. Numbers of Cases of Sepsis in the United States, According to the Causative Organism, 1979–2000.

Points represent the number of cases for the given year, and I bars the standard error.

	Estimated frequency*
Gram-positive bacteria	30–50%
Methicillin-susceptible S.aureus	14–24%
Methicillin-resistant S.aureus	5–11%
Other Staphylococcus spp	1–3%
Streptococcus pneumoniae	9–12%
Other Streptococcus spp	6–11%
Enterococcus spp	3–12%
Anaerobes	1–2%
Other gram-positive bacteria	1–5%
Gram-negative bacteria	25–30%
E.coli	9–27%
Pseudomonas aeruginosa	8–15%
Klebsiella pneumoniae	2–7%
Other Enterobacter spp	6–16%
Haemophilus influenzae	2–10%
Anaerobes	3–7%
Other gram-negative bacteria	3–12%
Fungus	
Candida albicans	1–3%
Other Candida spp	1–2%
Yeast	1%
Parasites	1–3%
Viruses	2–4%

Antimicrobial therapy

- Goal of antimicrobial therapy (ideal but not standard)
  - for septic shock: < 1hr (1B)
  - for severe sepsis: < 1hr (1C)
- Broad spectrum with good penetration (1B)
- Reassess daily for potential deescalation (1B)
- Low biomarker to assist stop antibiotics (2C)

Antimicrobial therapy

- Combination therapy
  - for neutropenic p' t (2B)
  - for difficult / resistant pathogens (2B)
  - for resp. failure & septic shock by bacteremic P. aeruginosa, extended beta-lactam & AM or FQ (2B)
  - for septic shock from bacteremic Streptococcus pneumonia, beta-lactam + macrolide (2B)
  - no more than 3-5 days & de-escalation ASAP (2B)

Antimicrobial therapy

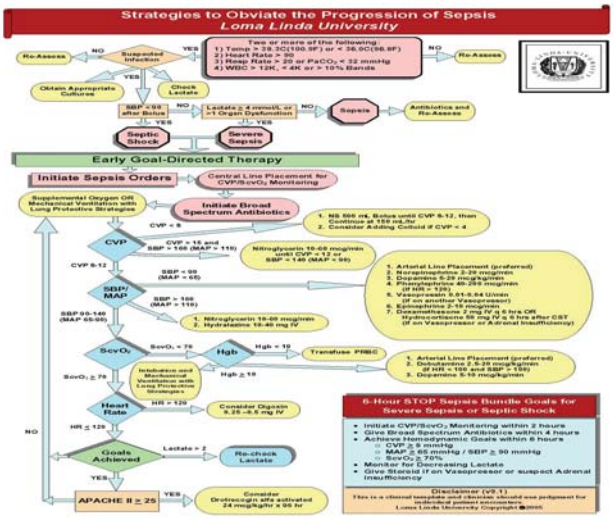
- Duration for 7-10 days
- Longer course for
  - slow clinical response
  - undrainable foci of infection
  - bacteremia with S. aureus
  - special situations (fungal, viral , neutrpenic) (2C)
- Antiviral therapy for severe viral origin sepsis (2C)
- Not for SIRS with noninfectious cause (UG)

Source control

- Anatomical diagnosis & source control < first 12 hours; risk vs benefit (1C)
- Delayed intervention until adequate demarcation for necrotizing pancreatitis (2B)
- Intervention with least physiologic insult (UG)
- Remove suspicious IV devices ASAP (UG)

Prevention

- Reducing VAP (ventilator-associated pneumonia) in health care setting (2B)
  - selective oral decontamination (SOD)
  - selective digestive decontamination (SDD)
- Reducing risk of VAP in ICU
  - Oral chlohexidine gluconate (CHG) (2B)



ProCESS

- Protocolized Care for Early Septic Shock
  - NEJM 2013

ProCESS: did not improve outcomes

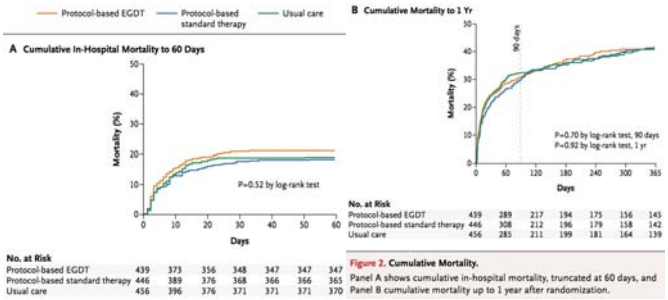


Figure 2. Cumulative Mortality.
Panel A shows cumulative in-hospital mortality, truncated at 60 days, and Panel B cumulative mortality up to 1 year after randomization.

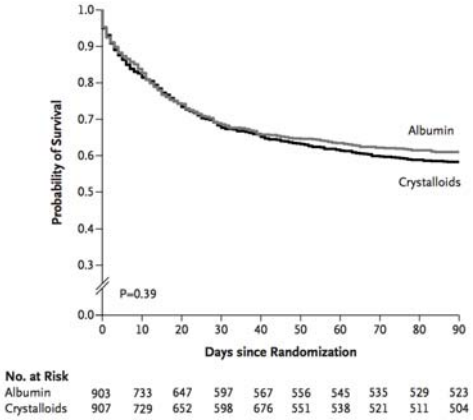
ProCESS trial elements

- early recognition of sepsis
- early administration of antibiotics
- early adequate volume resuscitation
- clinical assessment of the adequacy of circulation

Albumin replacement for severe sepsis or septic shock ??

- Albumin Italian Outcome Sepsis (ALBIOS) study
- NEJM 2013

Albumin did not improve survival



High BP or Low BP for septic shock ??

- Sepsis and Mean Arterial Pressure (SEPSISPAM) trial
- NEJM 2013

Higher MAP is not better

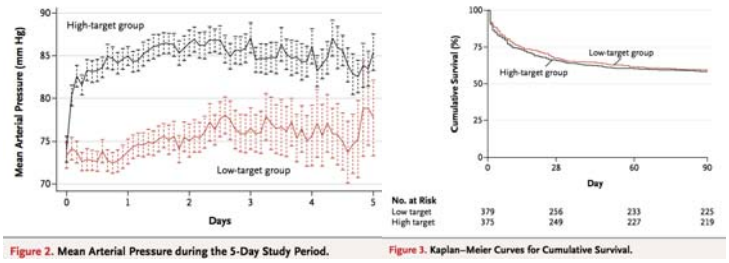


Figure 2. Mean Arterial Pressure during the 5-Day Study Period.

Figure 3. Kaplan–Meier Curves for Cumulative Survival.

Heads of Sepsis

hypotension, hypoperfusion, and organ dysfunction

We can conquer sepsis !!