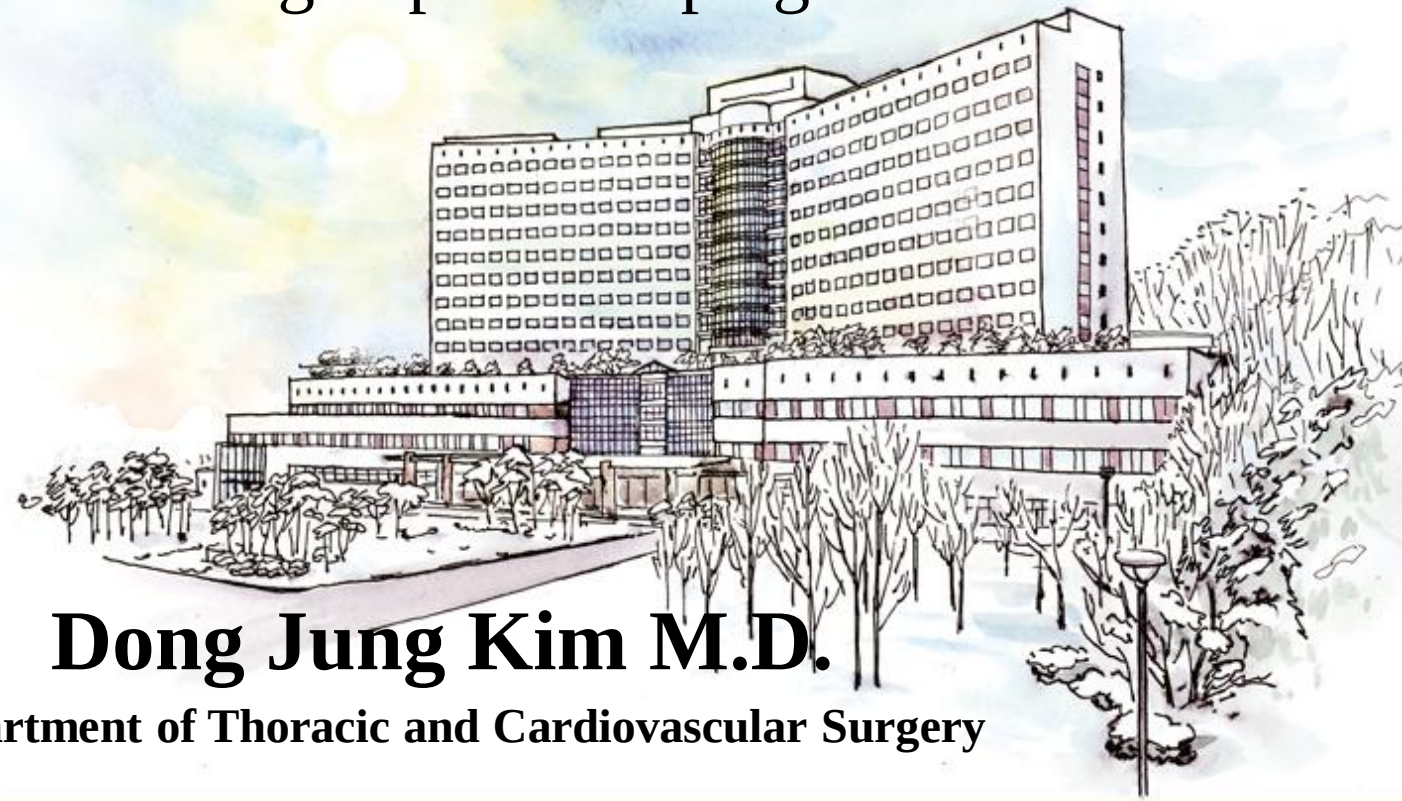
흉부외과 전공의 연수강좌

Sepsis and antibiotics

Surviving Sepsis Campaign



SNUH
SEOUL NATIONAL UNIVERSITY
BUNDANG HOSPITAL

Dong Jung Kim M.D.

Department of Thoracic and Cardiovascular Surgery

1. Sepsis

New definitions (Sepsis-3)

- Sepsis
  - life-threatening organ dysfunction
  - caused by dysregulated host response to infection

- Septic shock
  - subset of sepsis
  - with circulatory and cellular/metabolic dysfunction associated with a higher risk of mortality

(JAMA.2016;315(8):801-810)

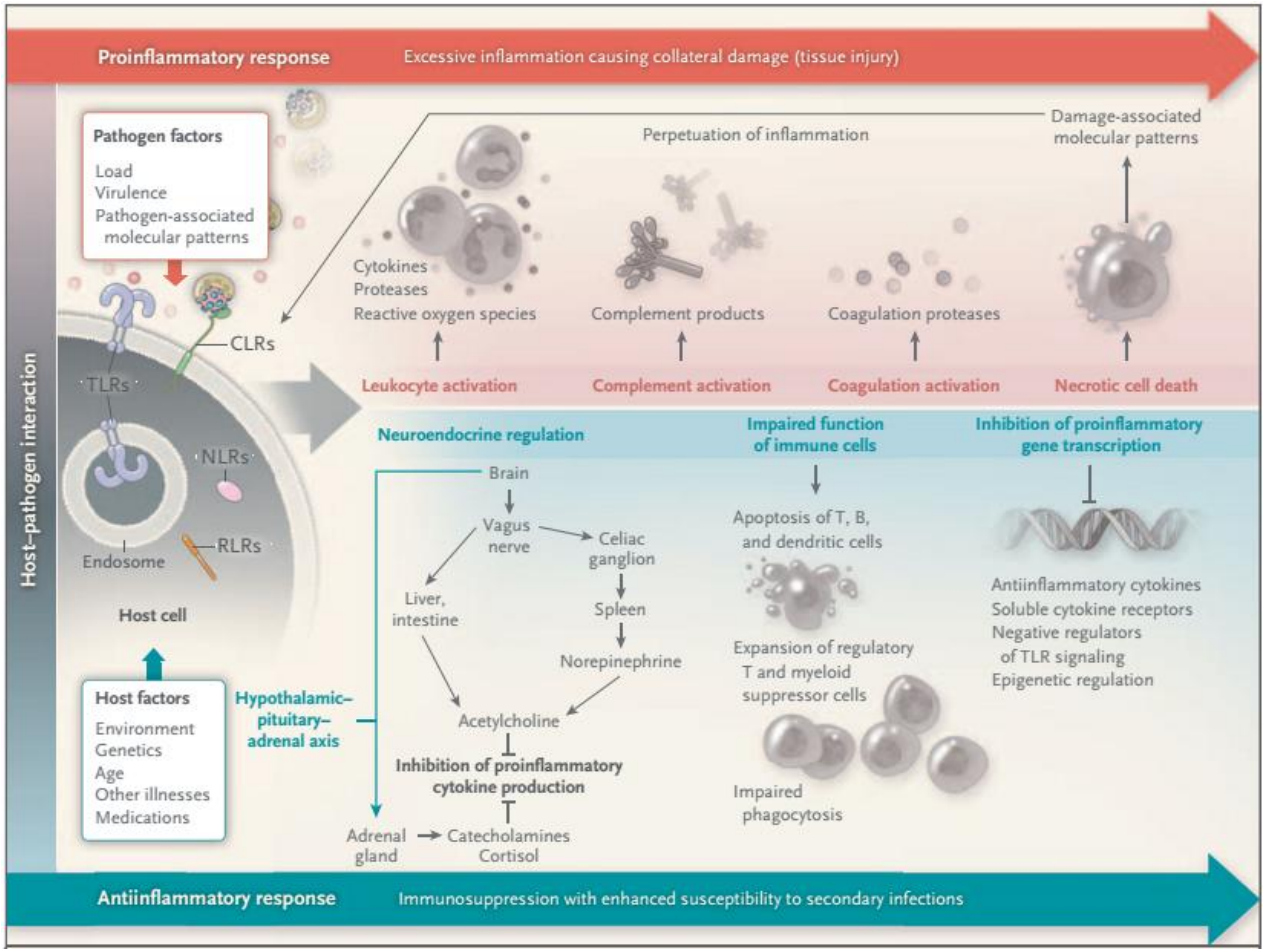
Sepsis

- Primary cause of death from infection
  - especially if not recognized and treated promptly
  - its recognition mandates urgent attention

- What differentiates sepsis from infection
  - aberrant or dysregulated host response
  - presence of organ dysfunction

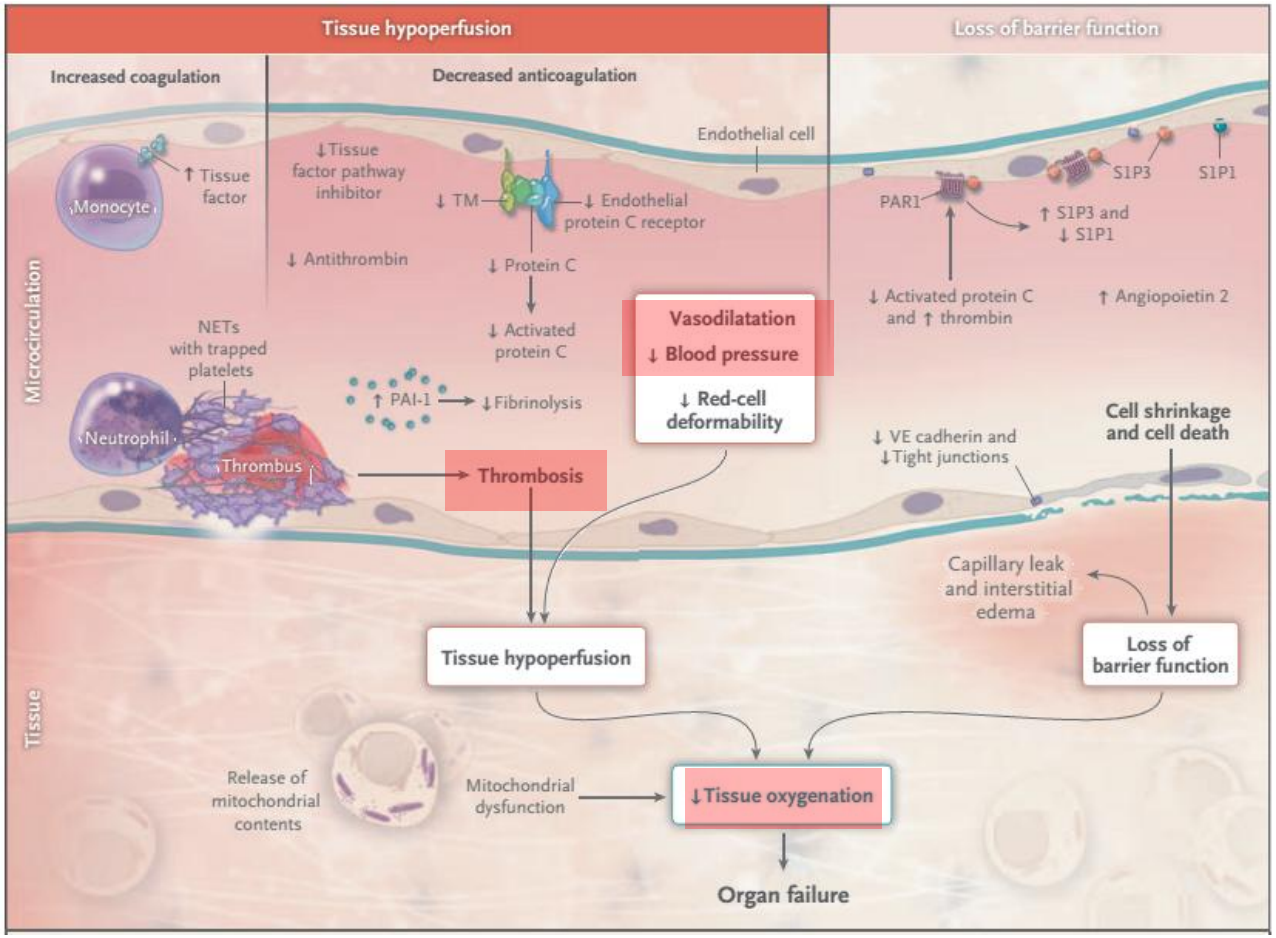
(JAMA.2016;315(8):801-810)

Host response to infection



(N Engl J Med 2013; 369:840-851)

Sepsis-induced organ dysfunction



(N Engl J Med 2013; 369:840-851)

Sepsis

- Sepsis-induced organ dysfunction
  - should be considered in any patient presenting with infection
  - conversely, unrecognized infection may be the cause of new-onset organ dysfunction
  - any unexplained organ dysfunction should raise the possibility of underlying infection

(JAMA.2016;315(8):801-810)

Sepsis

- Sepsis-induced organ dysfunction
  - identified as acute change in total SOFA score ≥ 2 consequent to infection
  - SOFA score ≥ 2
    - reflects an overall mortality risk of approximately 10% in a general hospital population with suspected infection
    - 2~25-fold increased risk of dying compared with patients with a SOFA score < 2

(JAMA.2016;315(8):801-810)

SOFA score

Table 1. Sequential [Sepsis-Related] Organ Failure Assessment Score[a]

	Score				
System	0	1	2	3	4
Respiration					
Pao_2/Fio_2, mm Hg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation					
Platelets, $\times 10^3/\mu L$	≥150	<150	<100	<50	<20
Liver					
Bilirubin, mg/dL (μmol/L)	<1.2 (20)	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (204)
Cardiovascular	MAP ≥70 mm Hg	MAP <70 mm Hg	Dopamine <5 or dobutamine (any dose)[b]	Dopamine 5.1-15 or epinephrine ≤0.1 or norepinephrine ≤0.1[b]	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1[b]
Central nervous system					
Glasgow Coma Scale score[c]	15	13-14	10-12	6-9	<6
Renal					
Creatinine, mg/dL (μmol/L)	<1.2 (110)	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440)	>5.0 (440)
Urine output, mL/d				<500	<200

Abbreviations: Fio_2, fraction of inspired oxygen; MAP, mean arterial pressure; Pao_2, partial pressure of oxygen.

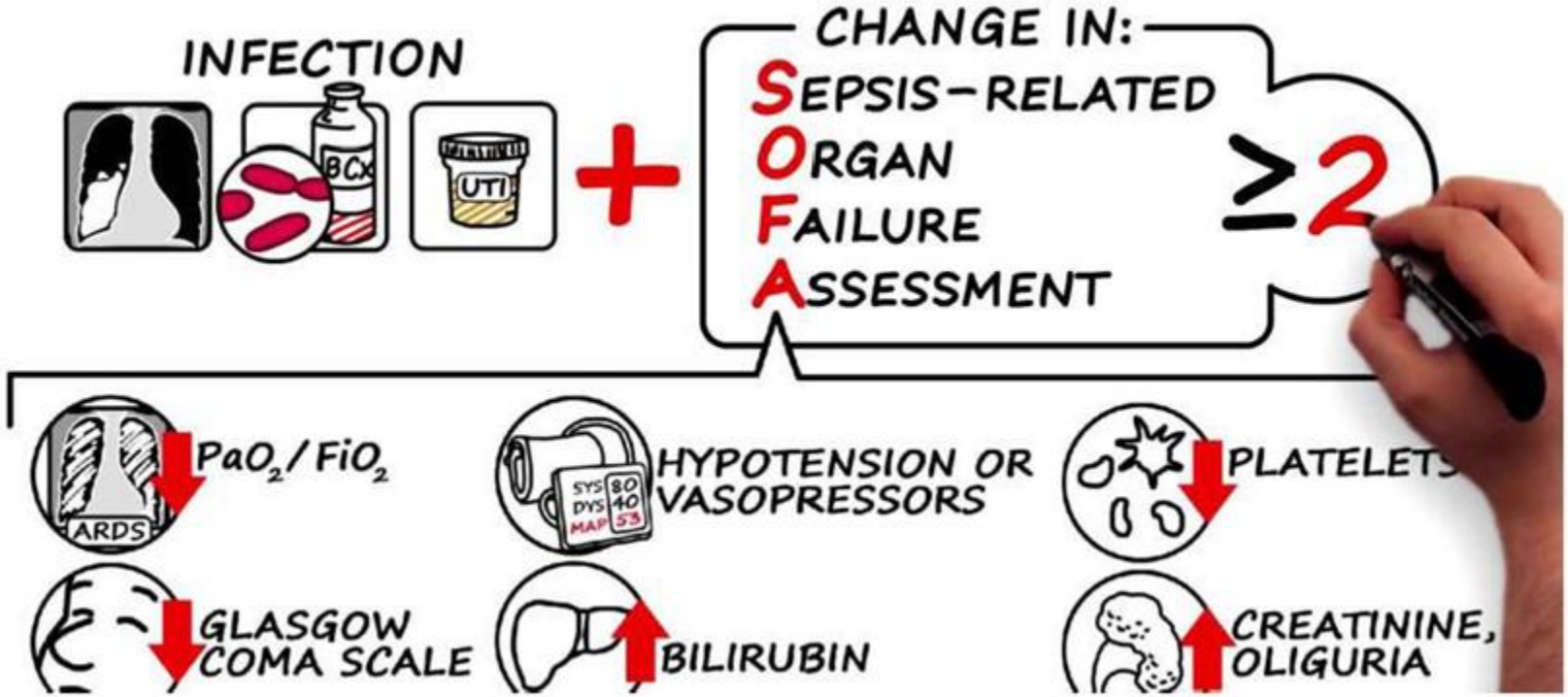
[a] Adapted from Vincent et al.[27]

[b] Catecholamine doses are given as μg/kg/min for at least 1 hour.

[c] Glasgow Coma Scale scores range from 3-15; higher score indicates better neurological function.

(JAMA.2016;315(8):801-810)

Sepsis : clinical criteria



qSOFA score

- Quick SOFA score
  - simple bedside criteria
    - to identify adult patients with suspected infection who are likely to have poor outcomes
  - respiratory rate ≥ 22/min
  - altered mentation
  - systolic blood pressure ≤ 100mmHg

(JAMA.2016;315(8):801-810)

qSOFA score


Hypotension
Systolic BP
<100 mmHg
Altered
Mental
Status
Tachypnea
RR >22/Min
Score of ≥2 Criteria Suggests a Greater Risk of a Poor Outcome

qSOFA score

- Quick SOFA score
  - does not define sepsis
  - does not require laboratory tests
  - can be assessed quickly and repeatedly
  - altered mentation vs GCS score < 15
    - reduce the measurement burden
    - predictive validity was unchanged (p = .55)

(JAMA.2016;315(8):801-810)

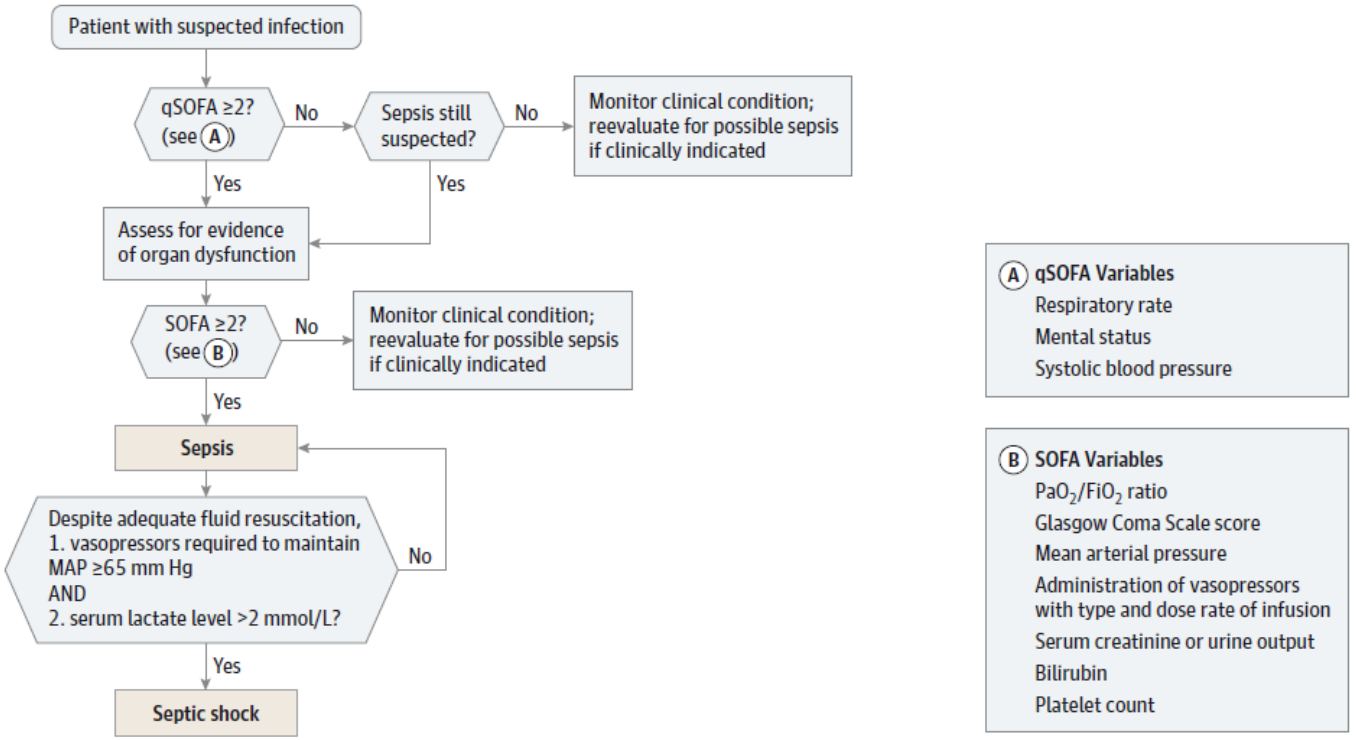
Septic shock

- Definition
  - sepsis with circulatory and cellular/metabolic dysfunction
  - shock secondary to systemic inflammatory response to infection
- Clinical criteria
  - vasopressor needed to elevate MAP ≥ 65 mmHg
  - lactate > 2 mmol/L (18 mg/dL)
    - despite adequate fluid resuscitation

(JAMA.2016;315(8):801-810)

Sepsis and septic shock

Figure. Operationalization of Clinical Criteria Identifying Patients With Sepsis and Septic Shock



The baseline Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score should be assumed to be zero unless the patient is known to have preexisting (acute or chronic) organ dysfunction before the onset of infection. qSOFA indicates quick SOFA; MAP, mean arterial pressure.

(JAMA.2016;315(8):801-810)

Surviving Sepsis Campaign

CONFERENCE REPORTS AND EXPERT PANEL

Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016

Andrew Rhodes[1*], Laura E. Evans[2], Waleed Alhazzani[3], Mitchell M. Levy[4], Massimo Antonelli[5], Ricard Ferrer[6], Anand Kumar[7], Jonathan E. Sevransky[8], Charles L. Sprung[9], Mark E. Nunnally[2], Bram Rochwerg[3], Gordon D. Rubenfeld[10], Derek C. Angus[11], Djillali Annane[12], Richard J. Beale[13], Geoffrey J. Bellinghan[14], Gordon R. Bernard[15], Jean-Daniel Chiche[16], Craig Coopersmith[8], Daniel P. De Backer[17], Craig J. French[18], Seitaro Fujishima[19], Herwig Gerlach[20], Jorge Luis Hidalgo[21], Steven M. Hollenberg[22], Alan E. Jones[23], Dilip R. Karnad[24], Ruth M. Kleinpell[25], Younsuk Koh[26], Thiago Costa Lisboa[27], Flavia R. Machado[28], John J. Marini[29], John C. Marshall[30], John E. Mazuski[31], Lauralyn A. McIntyre[32], Anthony S. McLean[33], Sangeeta Mehta[34], Rui P. Moreno[35], John Myburgh[36], Paolo Navalesi[37], Osamu Nishida[38], Tiffany M. Osborn[31], Anders Perner[39], Colleen M. Plunkett[25], Marco Ranieri[40], Christa A. Schorr[22], Maureen A. Seckel[41], Christopher W. Seymour[42], Lisa Shieh[43], Khalid A. Shukri[44], Steven Q. Simpson[45], Mervyn Singer[46], B. Taylor Thompson[47], Sean R. Townsend[48], Thomas Van der Poll[49], Jean-Louis Vincent[50], W. Joost Wiersinga[49], Janice L. Zimmerman[51] and R. Phillip Dellinger[22]

(Intensive Care Med (2017) 43:304–377)

Hour-1 bundle

- Measure lactate level. Remeasure if initial lactate is >2 mmol/L.
- Obtain blood cultures prior to administration of antibiotics.
- Administer broad-spectrum antibiotics.
- Begin rapid administration of 30ml/kg crystalloid for hypotension or lactate ≥4 mmol/L.
- Apply vasopressors if patient is hypotensive during or after fluid resuscitation to maintain MAP ≥65 mm Hg.

**"Time zero" or "time of presentation" is defined as the time of triage in the Emergency Department or, if presenting from another care venue, from the earliest chart annotation consistent with all elements of sepsis (formerly severe sepsis) or septic shock ascertained through chart review.*

Figure 1. Hour-1 Surviving Sepsis Campaign Bundle of Care.*

(Crit Care Med. 2018 Jun;46(6):997-1000)

Lactate : predictor of mortality

Stephen Trzeciak
R. Phillip Dellinger
Michael E. Chansky
Ryan C. Arnold
Christa Schorr
Barry Milcarek
Steven M. Hollenberg
Joseph E. Parrillo

Serum lactate as a predictor of mortality in patients with infection

1,177 patients with primary diagnosis of infection and serum lactate

Lactate levels were divided into low (0–2 mmol/L), intermediate (2.1–3.9 mmol/L), and high (>4.0 mmol/L)

A **lactate level of 4 mmol/L or more** was found to be highly specific (89%–99%) for predicting the acute phase of death and in-hospital death

(Intensive Care Med (2007) 33:970–977)

Lactate clearance

LACTATE CLEARANCE AND SURVIVAL FOLLOWING INJURY

David Abramson, MD, Thomas M. Scalea, MD, Robyn Hitchcock, MD, Stanley Z. Trooskin, MD, Sharon M. Henry, MD, and Joshua Greenspan, MD

76 patients with trauma and hemorrhagic shock

No death when lactate levels returned to normal within 24 hours

86% of patients died when lactate levels remained after 48 hours

(J Trauma. 1993 Oct;35(4):584-8)

ICU care

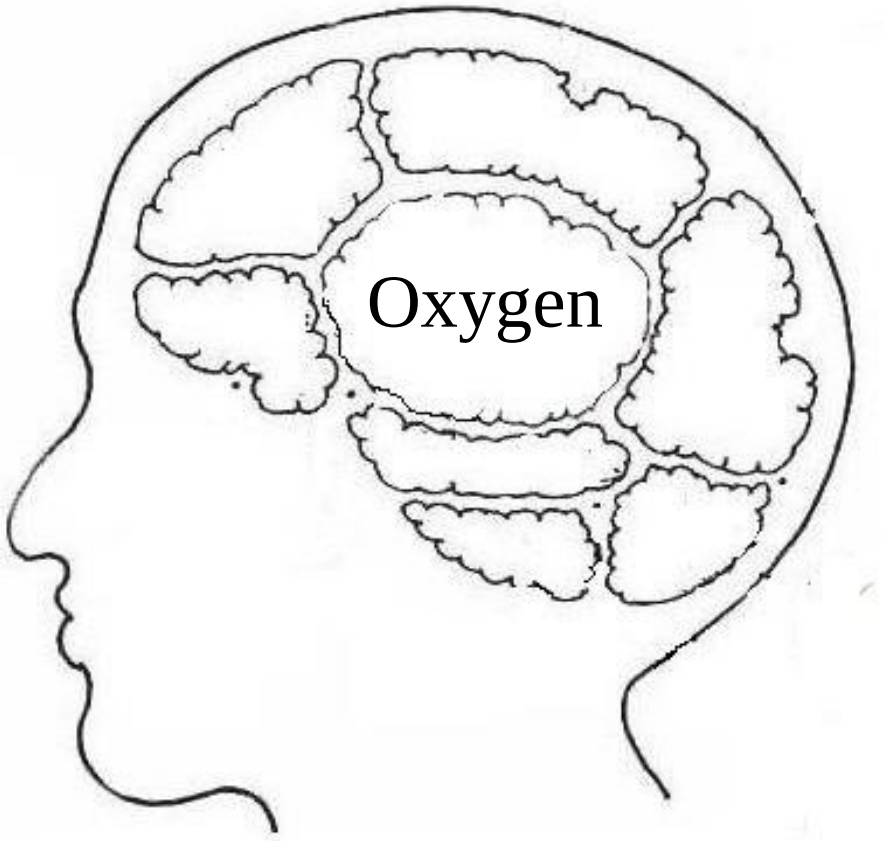
- Cardiovascular management
- Mechanical ventilation
- Fluid management
- Renal replacement
- Nutrition
- Metabolic, Endocrine, Neurologic problems
- Rehabilitation, etc…

Cardiopulmonary function

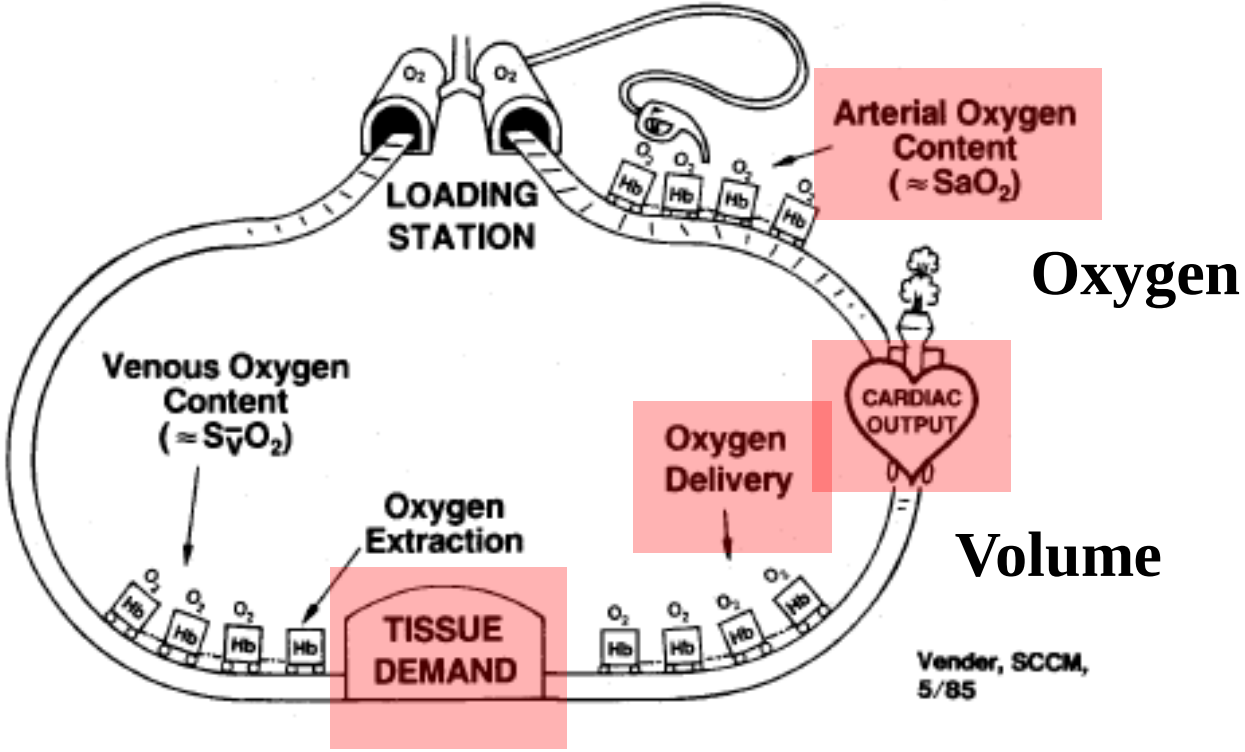
- Heart
  - Pumping blood to the organs and tissues
  - Delivery of nutrients and **oxygen** in blood to the organs and tissues

- Lung
  - Gas exchange : $O_2 \leftrightarrow CO_2$
  - Delivery of **oxygen** from the lungs to the blood

Priority



ICU care


LOADING STATION
Arterial Oxygen Content (≈ SaO_2)
Venous Oxygen Content (≈ $S\bar{v}O_2$)
Oxygen Extraction
Oxygen Delivery
CARDIAC OUTPUT
TISSUE DEMAND
Vender, SCCM, 5/85
Oxygen
Volume
Pressure

Shock

- Oxygen supply < Oxygen demand
- Tissue perfusion is not adequate for the tissues' metabolic requirements
- Type : cardiogenic, hypovolemic, septic…
- Key mechanism of septic shock
  - tissue hypoperfusion (tissue hypoxia)
    - ↓ perfusion pressure d/t vasodilation
    - microvascular thrombosis

Oxygen kinetics

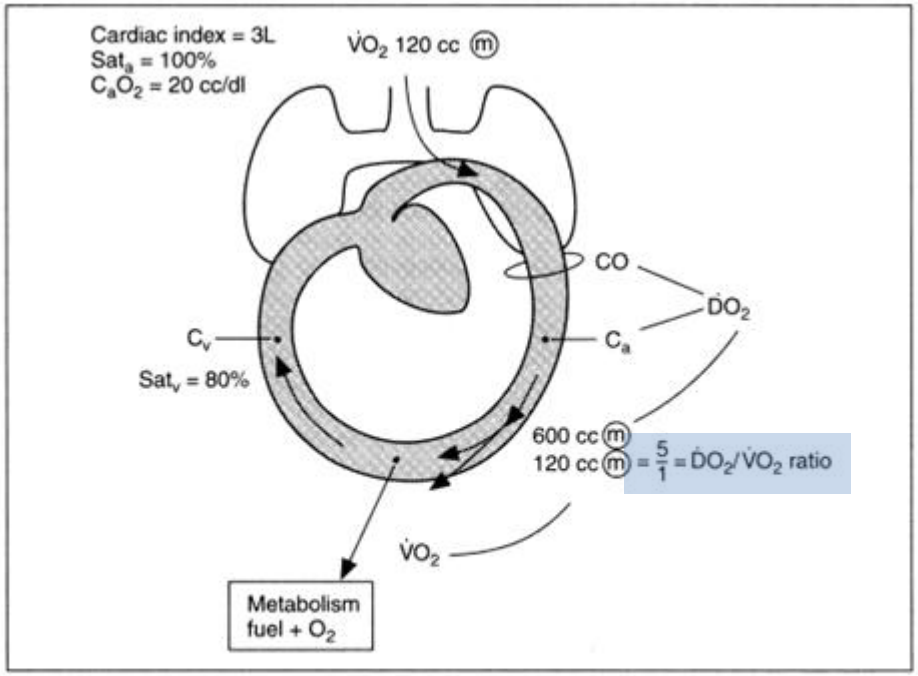


FIGURE 1-1. Oxygen kinetics. Oxygen delivery ($\dot{D}O_2$) is the product of cardiac output (CO) times the arterial oxygen content (C_a). Oxygen delivery is normally four to five times oxygen consumption ($\dot{V}O_2$). (C_v = venous oxygen content; ⓜ = /min/m^2; Sat$_a$ = arterial saturation; Sat$_v$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

(Critical Care Physiology, Robert H. Bartlett, p2)

VO_2 and DO_2

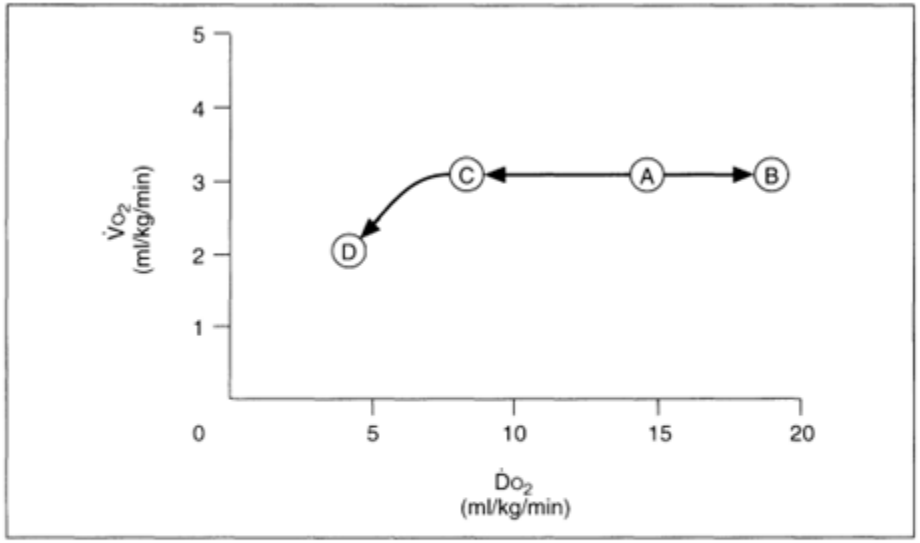


FIGURE 1-11. The normal relationship between $\dot{V}O_2$ and $\dot{D}O_2$. The normal point (*A*) is shown as $\dot{V}O_2$ 120 cc/m^2/min and $\dot{D}O_2$ 600 cc/m^2/min. If $\dot{D}O_2$ is increased by transfusion (*B*), $\dot{V}O_2$ remains constant. If $\dot{D}O_2$ is progressively decreased (*A*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

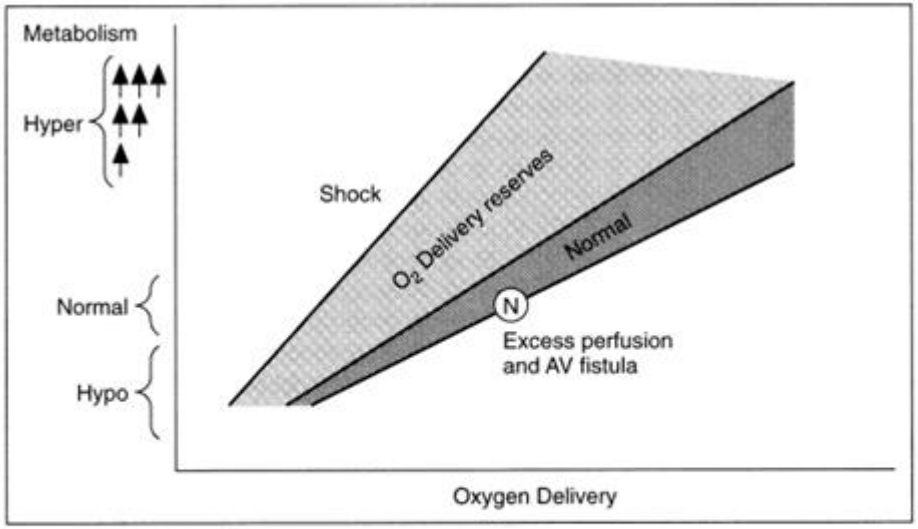
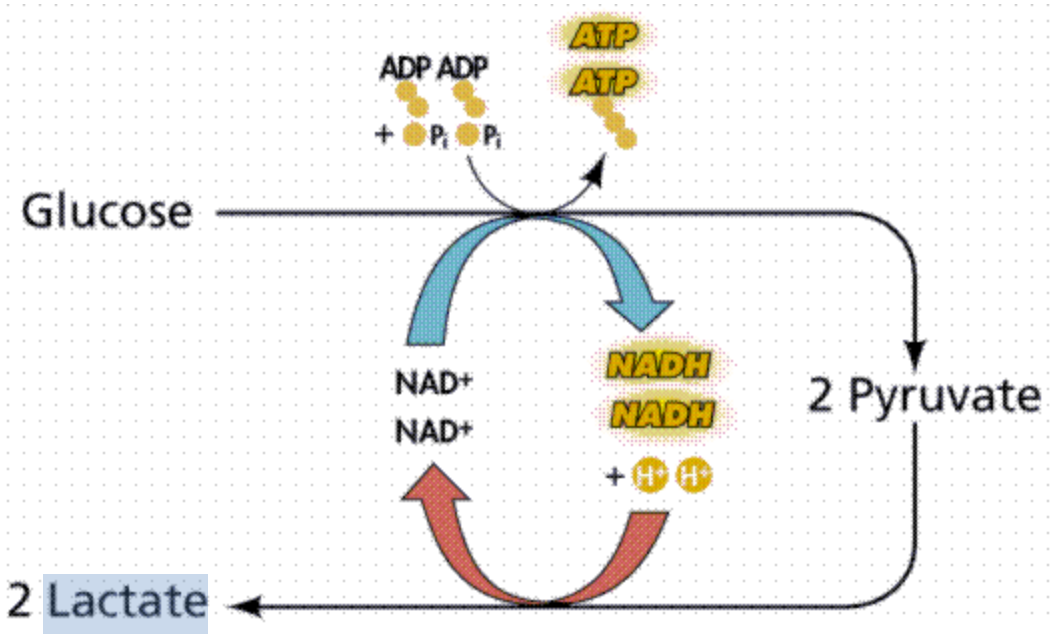


FIGURE 1-13. Interpreting the $\dot{D}O_2/\dot{V}O_2$ diagram. In this diagram the relationships shown in Figures 1-11 and 1-12 are demonstrated without specific numerical values to emphasize the difference between normal relationships, the utilization of oxygen delivery reserves, and shock. (AV = arteriovenous;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

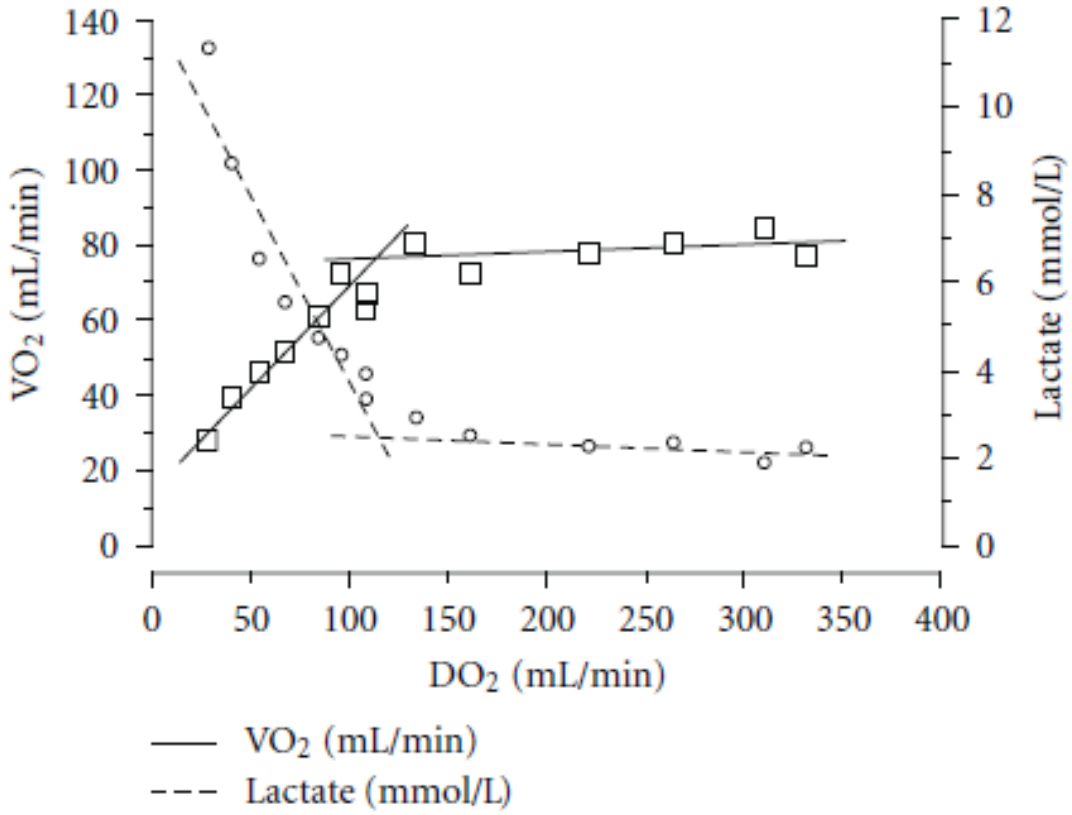
(Critical Care Physiology, Robert H. Bartlett, p17)

Lactate

- The result of inadequate oxygen delivery
  - slows mitochondrial metabolism → pyruvate is converted to lactate → anaerobic metabolism



Lactate

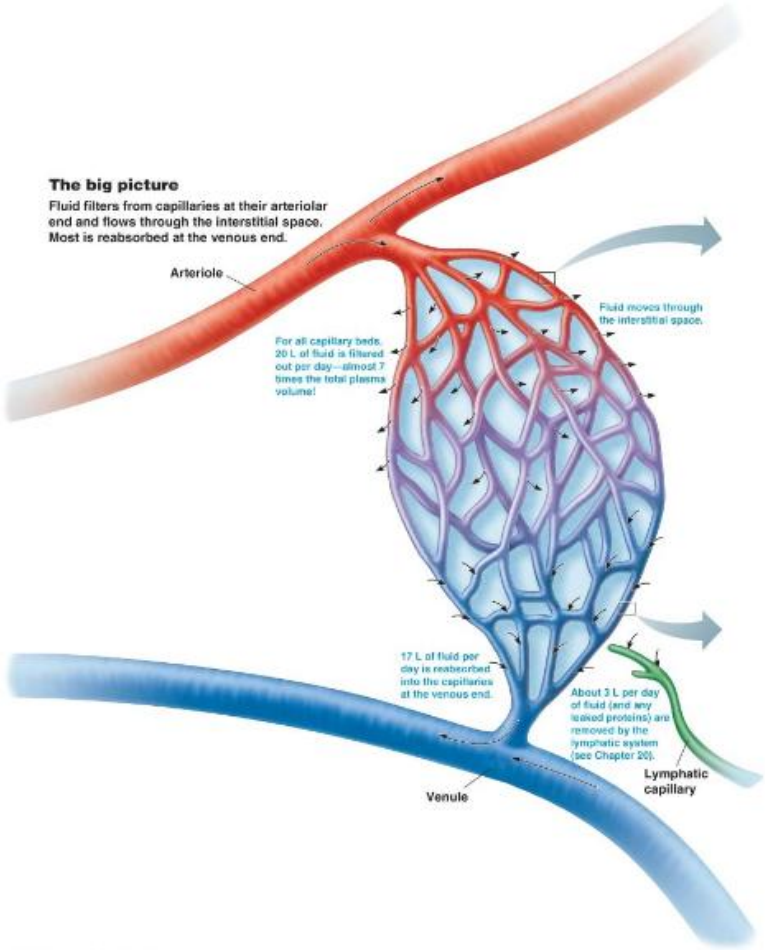


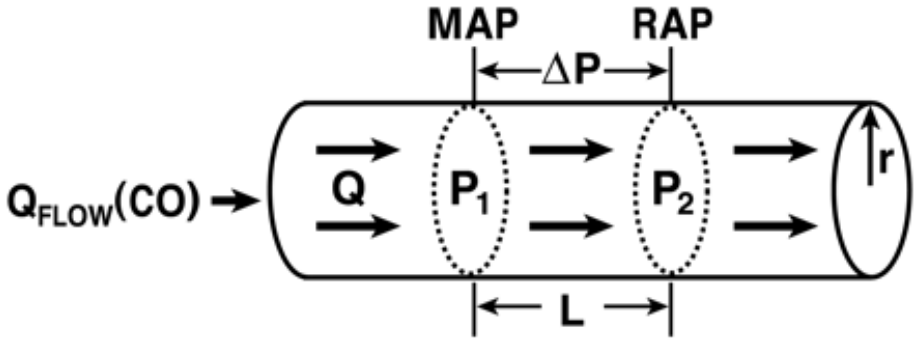
(Intensive Care Medicine, vol. 30, no. 11, pp. 1990–1996, 2004)

Blood pressure

- Intraventricular BP
  - Ejection of blood (Stroke volume)
- **Systemic arterial BP**
  - Blood flow to tissues (**Tissue perfusion**)
- Capillary hydrostatic pressure
  - Filtration (Tissue fluid formation)
- Systemic venous BP
  - Blood flow back to the heart (venous return)

Tissue perfusion





$$Q_{FLOW} = \frac{P_1 - P_2}{R = \frac{8\mu L}{\pi r^4}} \qquad CO = \frac{MAP - RAP}{SVR}$$

Arterial blood pressure

- Mean arterial pressure (MAP)
  - driving pressure of tissue perfusion
    - tissue perfusion becomes linearly dependent on MAP
  - indicator of peripheral tissue perfusion

A. INITIAL RESUSCITATION

1. Sepsis and septic shock are medical emergencies, and we recommend that treatment and resuscitation begin immediately (BPS).
2. We recommend that, in the resuscitation from sepsis-induced hypoperfusion, at least 30 mL/kg of IV crystalloid fluid be given within the first 3 hours (strong recommendation, low quality of evidence).
3. We recommend that, following initial fluid resuscitation, additional fluids be guided by frequent reassessment of hemodynamic status (BPS).

Remarks: Reassessment should include a thorough clinical examination and evaluation of available physiologic variables (heart rate, blood pressure, arterial oxygen saturation, respiratory rate, temperature, urine output, and others, as available) as well as other noninvasive or invasive monitoring, as available.

4. We recommend further hemodynamic assessment (such as assessing cardiac function) to determine the type of shock if the clinical examination does not lead to a clear diagnosis (BPS).
5. We suggest that dynamic over static variables be used to predict fluid responsiveness, where available (weak recommendation, low quality of evidence).
6. We recommend an initial target mean arterial pressure of 65 mm Hg in patients with septic shock requiring vasopressors (strong recommendation, moderate quality of evidence).
7. We suggest guiding resuscitation to normalize lactate in patients with elevated lactate levels as a marker of tissue hypoperfusion (weak recommendation, low quality of evidence).

(Surviving Sepsis Campaign : 2016)

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

(Crit Care Med 2000; 28:2729–2732)

MAP - Rationale

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 24, 2014 VOL. 370 NO. 17

High versus Low Blood-Pressure Target in Patients with Septic Shock

Pierre Asfar, M.D., Ph.D., Ferhat Meziani, M.D., Ph.D., Jean-François Hamel, M.D., Fabien Grelon, M.D.,

- Only one multicenter trial
- Norepinephrine dose titration to achieve a MAP of 65 mmHg vs 85 mmHg
- No significant difference in mortality at 28 days or 90 days
- Targeting a MAP of 85 mm Hg
  - resulted in a significantly higher risk of arrhythmias
  - subgroup of patients with previously diagnosed chronic hypertension had reduced need for RRT

(N Engl J Med 2014; 370:1583–1593)

Arterial blood pressure

- Optimal MAP: should be individualized
  - higher in patients with atherosclerosis and/or previous hypertension than in young patients without cardiovascular comorbidity
  - according to serum lactate monitoring
    - balance between DO_2 and VO_2

2. Antibiotics

Antimicrobial therapy

- IV antimicrobials
  - should be initiated ASAP after recognition and within one hour for both sepsis and septic shock

- Empiric broad-spectrum therapy
  - for patients presenting with sepsis or septic shock to cover all likely pathogens
  - should be narrowed once pathogen identification and sensitivities are established

(Crit Care Med. 2018 Jun;46(6):997-1000)

Antimicrobial therapy

- Empiric combination therapy
  - using at least two antibiotics of different classes
  - aimed at the most likely bacterial pathogen (s) for the initial management of septic shock
  - should not be routinely used for ongoing treatment of most other serious infections
  - de-escalation with discontinuation of combination therapy within the first few days

(Crit Care Med. 2018 Jun;46(6):997-1000)

Antimicrobial therapy

- Treatment duration
  - 7~10 days is adequate
    - for most serious infections ass. with sepsis & septic shock
  - longer courses
    - slow clinical response, undrainable foci of infection, bacteremia with S. aureus, fungal & viral infections, immunologic deficiencies (neutropenia)
  - shorter courses
    - rapid clinical resolution following effective source control (i.e., intra-abdominal or urinary sepsis)

(Crit Care Med. 2018 Jun;46(6):997-1000)

Antimicrobial therapy

- Procalcitonin
  - can be used to support shortening the duration of antimicrobial therapy in sepsis patients
  - can be used to support the discontinuation of empiric antibiotics
  - procalcitonin & all other biomarkers can provide only supportive & supplemental data to clinical assessment
    - decisions on initiating, altering, discontinuing antimicrobial therapy should never be made solely on the basis of changes in any biomarker, including procalcitonin

(Crit Care Med. 2018 Jun;46(6):997-1000)

Antibiotics : pulmonary

Infection	Regimens
CAP	β-lactam[1] + azithromycin
	β-lactam[1] + respiratory fluoroquinolone[2]
HAP	Anti-pseudomonal β-lactam[3]
	+ aminoglycoside[4] or anti-pseudomonal fluoroquinolone[5]
	+ vancomycin or linezolid

[1] ceftriaxone, cefotaxime, ampicillin/sulbactam

[2] levofloxacin, moxifloxacin

[3] piperacillin/tazobactam, cefepime, meropenem, imipenem, doripenem

[4] gentamicin, tobramycin, amikacin

[5] levofloxacin, ciprofloxacin

(Clin Infect Dis 2007;44:S27-72)

Antibiotics : CRBSI

Infection	Regimens
CRBSI	vancomycin or daptomycin[1]
	+ anti-pseudomonal β-lactam[2,3]
	+/− aminoglycoside[4]
Fungemia risk factors	+ fluconazole or echinocandin[5]

[1] if high rates of vancomycin MIC ≥ 2 μg/mL

[2] piperacillin/tazobactam, cefepime

[3] meropenem, imipenem, doripenem

[4] gentamicin, tobramycin, amikacin

[5] caspofungin, micafungin, anidulafungin

(Clin Infect Dis 2009;49:1-45)

Antibiotics : urinary

Infection	Regimens
Urosepsis	3rd generation cephalosporin[1]
	+/− aminoglycoside[2] or fluoroquinolone[3]
Urological interventions or MDR risk factors	Anti-pseudomonal β-lactam[4,5]

[1] ceftriaxone, cefotaxime

[2] gentamicin, tobramycin, amikacin

[3] levofloxacin, ciprofloxacin

[4] piperacillin/tazobactam, cefepime

[5] meropenem, imipenem, doripenem

(Int J Urol 2013; Epub)

Antibiotics : unknown

Infection	Regimens
Unknown	anti-pseudomonal β-lactam[1,2]
	+ aminoglycoside or anti-pseudomonal fluoroquinolone[3]
	+ vancomycin
Fungemia risk factors	+ fluconazole or echinocandin[4]

[1] piperacillin/tazobactam, cefepime

[2] meropenem, imipenem, doripenem

[3] levofloxacin, ciprofloxacin

[4] caspofungin, micafungin, anidulafungin

(Clin Infect Dis 2009;48:503-35)

Summary

- Key mechanism : tissue hypoperfusion
- Measure lactate level
- Maintain MAP ≥ 65mmHg
- IV antimicrobials : initiate ASAP
- Normalization of lactate
- Guidelines are not perfect
  - it will never replace clinical decision-making by expert

Thank you for your attention !

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