Σήψη, Σηπτικό Σοκ και Πολυοργανική Ανεπάρκεια

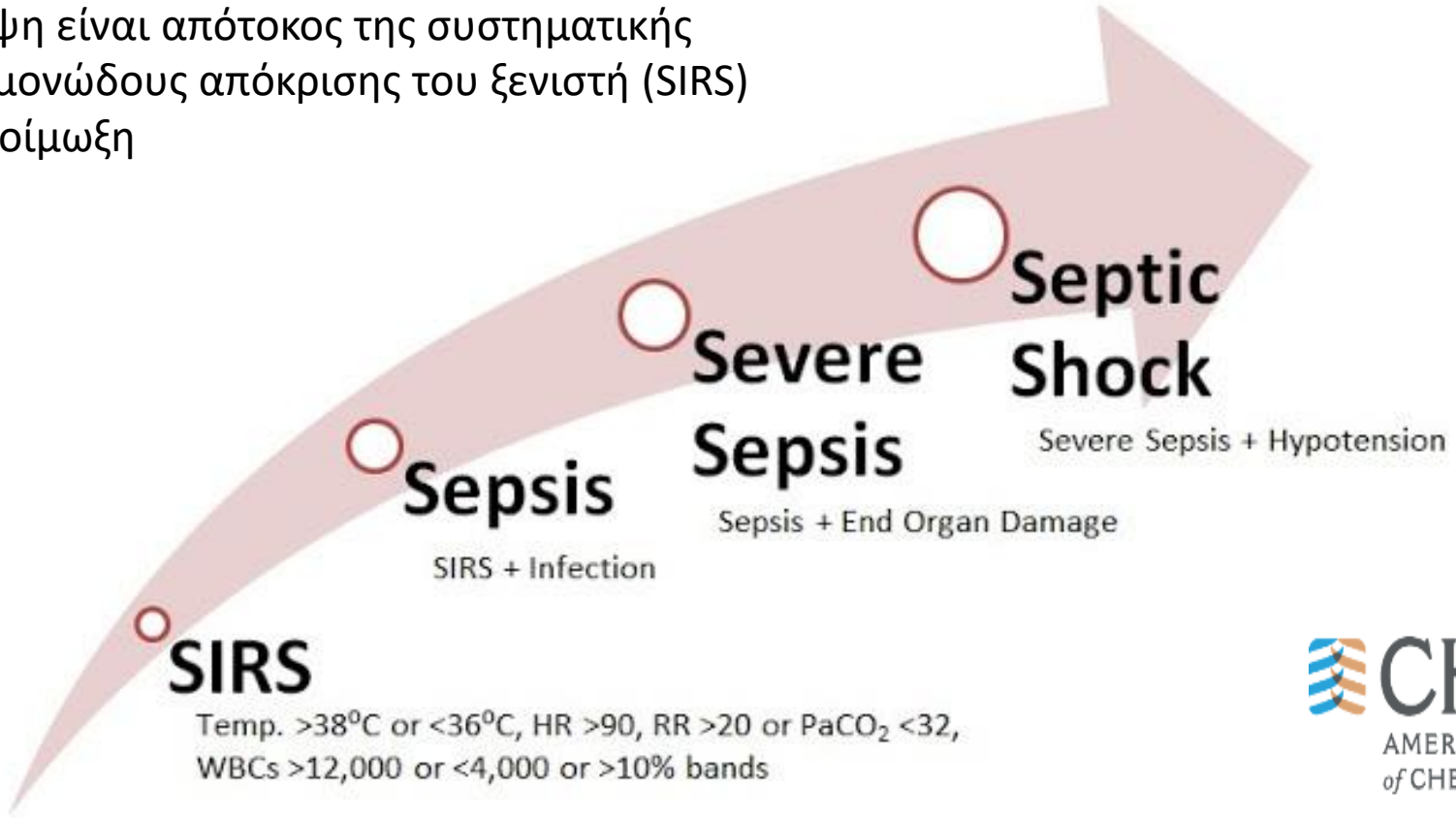
Φώτης Περλικός

Πνευμονολόγος – Εντατικολόγος

Ορισμοί

ACCP/SCCM Consensus Conference 1991 (Sepsis-1)

Η σήψη είναι απότοκος της συστηματικής φλεγμονώδους απόκρισης του ξενιστή (SIRS) στη λοίμωξη



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Society of Critical Care Medicine
The Intensive Care Professionals

ACCP/SCCM Consensus Conference 1991 (Sepsis-1)

Σήψη = Λοίμωξη + δύο ή περισσότερα κριτήρια SIRS

Σοβαρή Σήψη = Σήψη + Δυσλειτουργία Οργάνου ή υποάρδευση

Σηπτικό Σοκ = Σοβαρή Σήψη με εμμένουσα υπόταση παρά την επαρκή χορήγηση υγρών

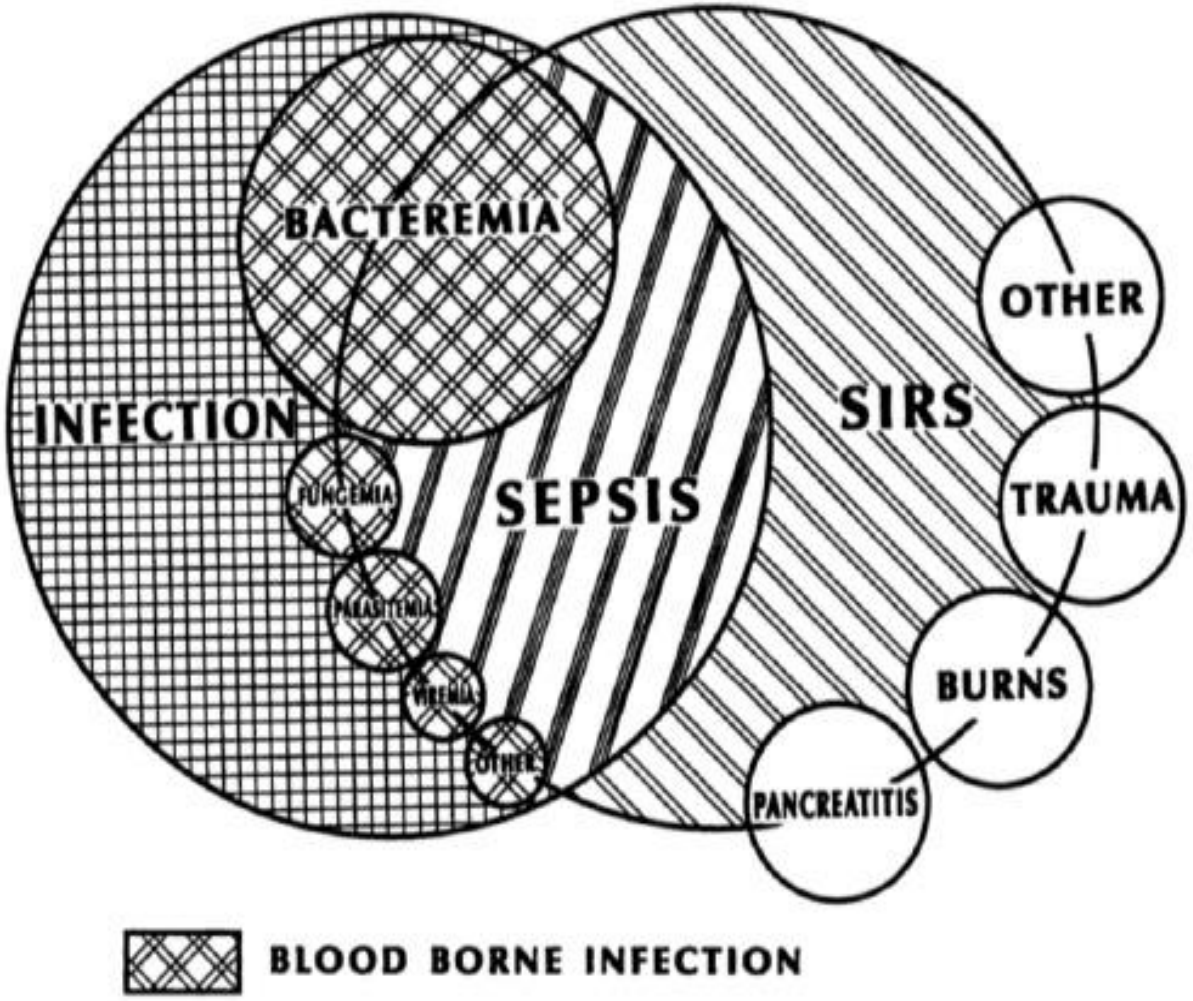

FIGURE 1. The interrelationship between systemic inflammatory response syndrome (SIRS), sepsis, and infection.

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SIRS	≥2 από τα παρακάτω: • θ>38 ◦C or <36 ◦C • HR > 90 beats/min • RR > 20 breaths/min • WBC >12000 /mm3 ή < 4000/mm3 ή 10% bands
Σήψη	≥2 κριτήρια SIRS και υποψία ή επιβεβαιωμένη λοίμωξη
Σοβαρή σήψη	Σήψη και δυσλειτουργία ≥ 1 όργανο: SBP< 90 παρά τα επαρκή υγρά Cr↑>0.5 επίπεδα αναφοράς ή HD PLT<10.000 PH<7.3 ή lactate>4mmol/l SGOT, SGPT>2x normal Χολερυθρίνη>4 Ειλεός ↓Κλίμακα Γλασκώβης (GCS) PaO2/FiO2<300, PEEP>7.5
Σηπτική καταπληξία	Σήψη **και** , παρά την επαρκή χορήγηση υγρών , SBP<90 ή MAP<60

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Το 2001 προστέθηκαν περισσότερες λεπτομέρειες για να βοηθηθούν οι κλινικοί ιατροί στην αναγνώριση της σήψης. (Sepsis-2)

Levy MM, et al. 2001CCM/ESICM/ACCP/ATS/SIS InternationalSepsis Definitions Conference.Crit Care Med 2003;31:1250-6.

Table 1. Diagnostic Criteria for Sepsis, Severe Sepsis, and Septic Shock.*

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)¶

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Systemic Inflammatory Response Syndrome Criteria in Defining Severe Sepsis

Kirsi-Maija Kaukonen, M.D., Ph.D., Michael Bailey, Ph.D., David Pilcher, F.C.I.C.M., D. Jamie Cooper, M.D., Ph.D., and Rinaldo Bellomo, M.D., Ph.D.

- 172 ICUs in Australia and New Zealand
- >100,000 patients retrospectively found from 2000-2013 with SIRS and sepsis
- SIRS missed 1 in 8 patients with sepsis!!
- No transition point in mortality with “2 or more SIRS criteria”!!

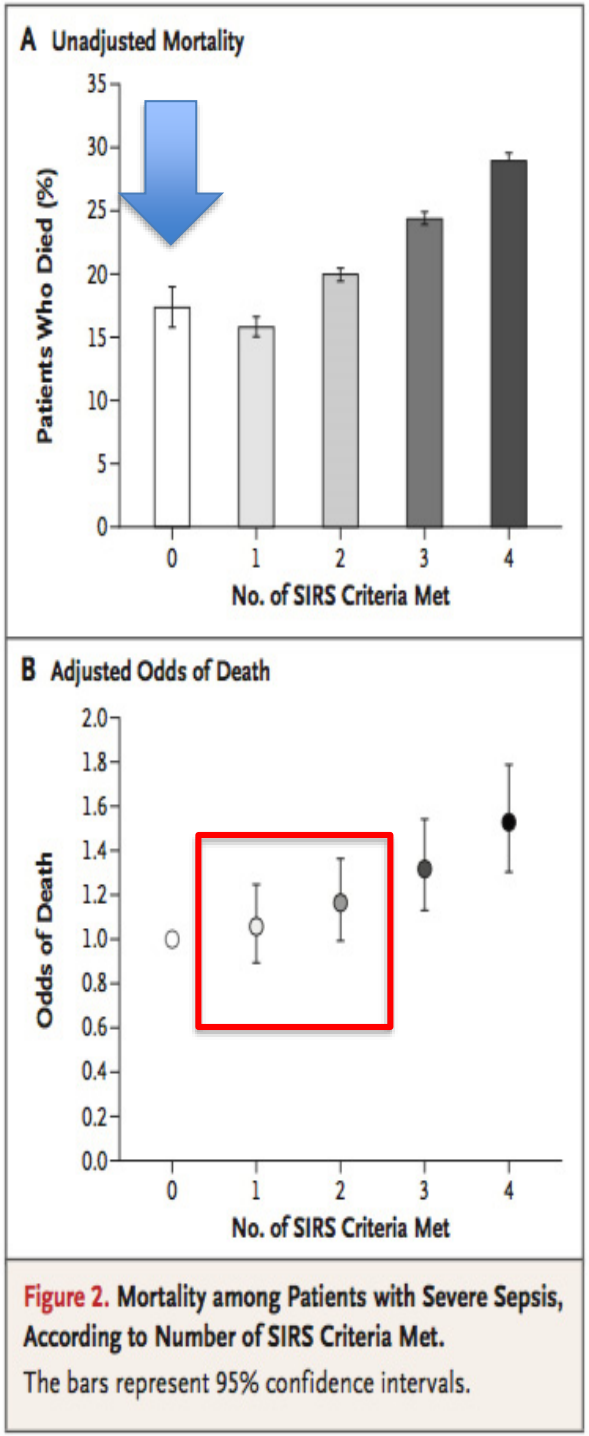

Figure 2. Mortality among Patients with Severe Sepsis, According to Number of SIRS Criteria Met.

The bars represent 95% confidence intervals.

The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

JAMA. 2016;315(8):801-810. doi:10.1001/jama.2016.0287

Task Force made up of 19 Intensivists convened to update Sepsis Definitions, understanding there's no validated diagnostic test (Gold Standard)

"The current use of 2 or more SIRS criteria to identify sepsis was unanimously considered by the task force to be unhelpful."

Severe sepsis definition removed – redundant with the new sepsis definition

Assessment of Clinical Criteria for Sepsis For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

JAMA. 2016;315(8):762-774. doi:10.1001/jama.2016.0288

ESICM EUROPEAN SOCIETY OF INTENSIVE CARE MEDICINE

Society of Critical Care Medicine
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Suggested Clinical Criteria for Sepsis (if in ICU?)

Infection + 2 or more SOFA points (above baseline)

Consider Sepsis outside ICU if

Infection + 2 or more qSOFA points

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.

Assessment of Clinical Criteria for Sepsis

For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

JAMA. 2016;315(8):762-774. doi:10.1001/jama.2016.0288

Taskforce wanted to predict:

- Increased mortality
- Increased ICU length of stay

REALLY SICK

Table 1. Variables for Candidate Sepsis Criteria Among Encounters With Suspected Infection

Systemic Inflammatory Response Syndrome (SIRS) Criteria (Range, 0-4 Criteria)	Sequential [Sepsis-related] Organ Failure Assessment (SOFA) (Range, 0-24 Points)	Logistic Organ Dysfunction System (LODS) (Range, 0-22 Points)[a]	Quick Sequential [Sepsis-related] Organ Failure Assessment (qSOFA) (Range, 0-3 Points)
Respiratory rate, breaths per minute	Pao_2/Fio_2 ratio	Pao_2/Fio_2 ratio	Respiratory rate, breaths per minute
White blood cell count, 10^9/L	Glasgow Coma Scale score	Glasgow Coma Scale score	Glasgow Coma Scale score
Bands, %	Mean arterial pressure, mm Hg	Systolic blood pressure, mm Hg	Systolic blood pressure, mm Hg
Heart rate, beats per minute	Administration of vasopressors with type/dose/rate of infusion	Heart rate, beats per minute	
Temperature, °C	Serum creatinine, mg/dL, or urine output, mL/d	Serum creatinine, mg/dL	
Arterial carbon dioxide tension, mm Hg	Bilirubin, mg/dL	Bilirubin, mg/dL	
	Platelet count, 10^9/L	Platelet count, 10^9/L	
		White blood cell count, 10^9/L	
		Urine output, L/d	
		Serum urea, mmol/L	
		Prothrombin time, % of standard	

ALTERED MENTAL STATUS

FAST RESPIRATORY RATE

LOW BLOOD PRESSURE

qSOFA

Glasgow Coma Scale

Άνοιγμα Ματιών		Ομιλία		Κίνηση	
					
Αυθόρμητο >	4	Προσανατολισμένη >	5	Υπακοή σε εντολές >	6
Με ήχο >	3	Σε σύγχυση >	4	Περιορισμένη >	5
Με πίεση >	2	Μόνο λέξεις >	3	Κανονικό λύγισμα >	4
Καθόλου >	1	Μόνο ήχους >	2	Αφύσικο λύγισμα >	3
		Καθόλου >	1	Έκταση άκρων >	2
				Καθόλου >	1

GLASGOW COMA SCALE SCORE

Ήπιο	Μέτριο	Σοβαρό
13-15	9-12	3-8

Surviving Sepsis Campaign

Ορισμοί με βάση το Sepsis-3

Σήψη είναι μια απειλητική για τη ζωή οργανική ανεπάρκεια που προκαλείται από την μη ρυθμισμένη απάντηση του ξενιστή στη λοίμωξη

Κλινικά : αύξηση του δείκτη SOFA κατά δύο ή περισσότερους βαθμούς

Σηπτική καταπληξία: υποκατηγορία σήψης με εκσεσημασμένες κυκλοφορικές, κυτταρικές και μεταβολικές δυλειτουργίες που σχετίζονται με μεγαλύτερη θνητότητα σε σχέση με τη σήψη

Κλινικά: Ανάγκη για ινότροπα προκειμένου να διατηρηθεί μέση αρτηριακή πίεση ≥65mmHg και επίπεδα γαλακτικού οξέος ≥2 απουσία υποογκαιμίας

JAMA. 2016;315(8):801-810. doi:10.1001/jama.2016.0287

Παθογενετικοί Μηχανισμοί

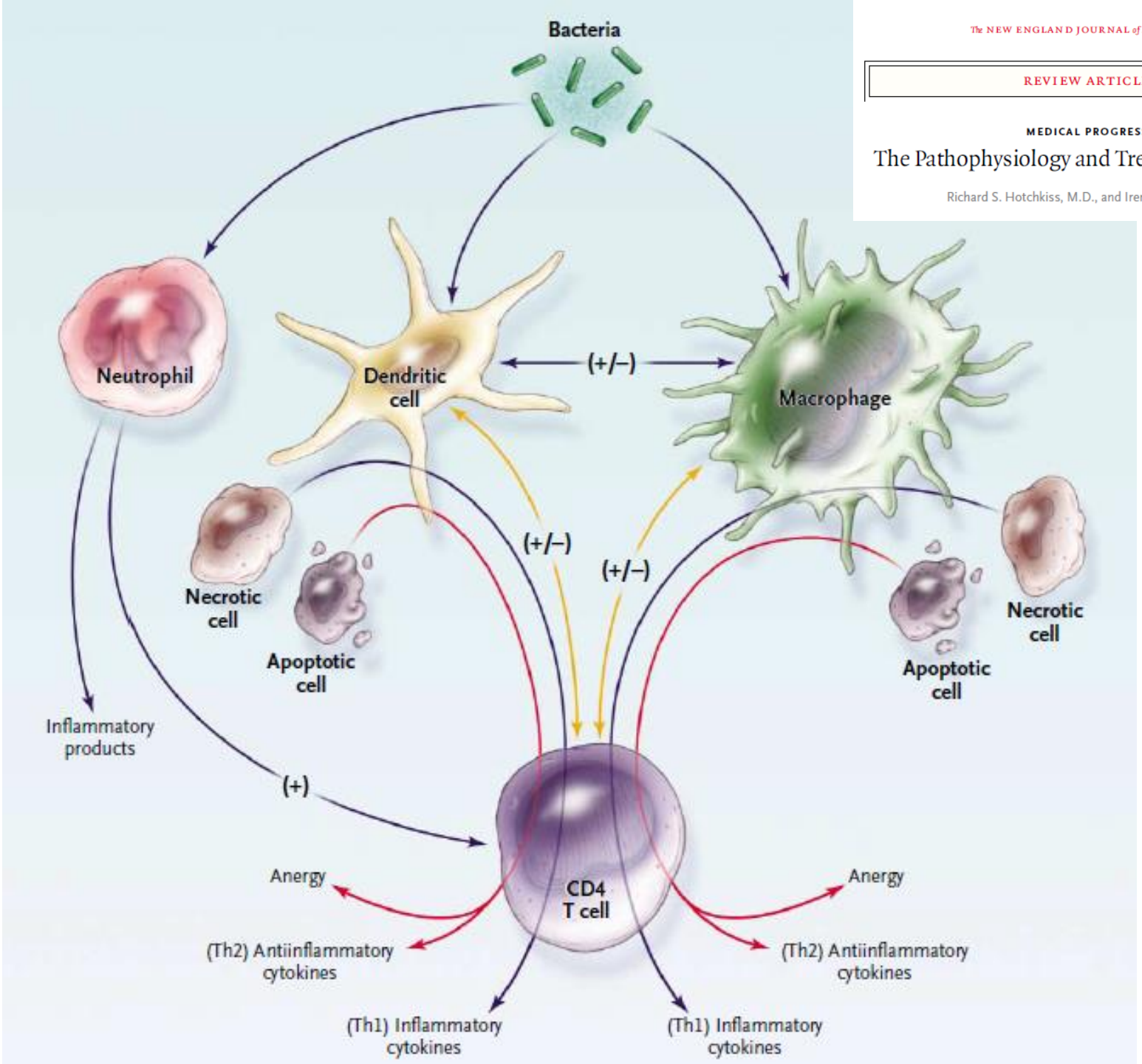
The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

MEDICAL PROGRESS

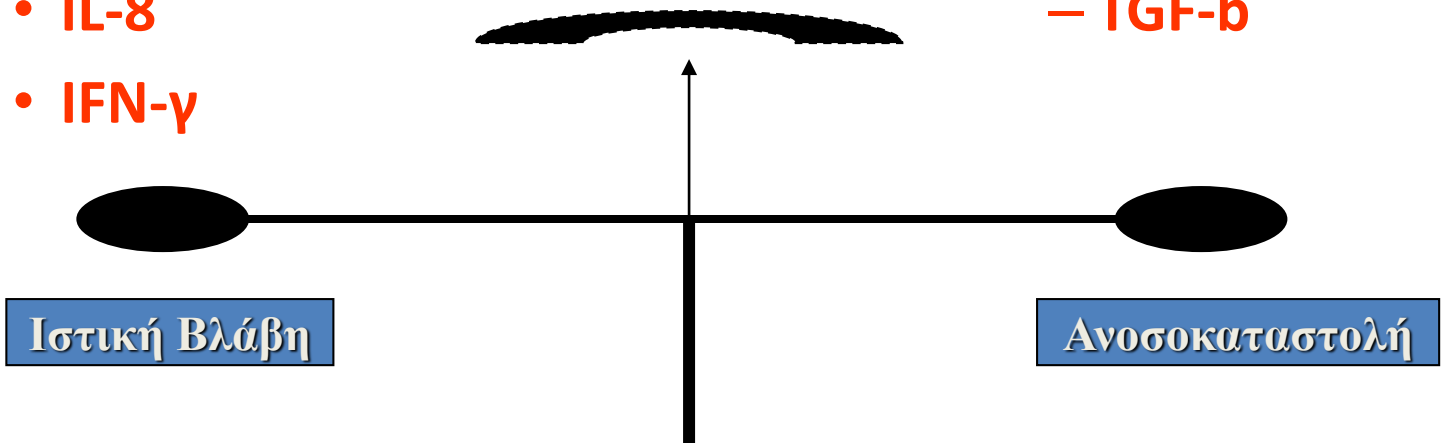
The Pathophysiology and Treatment of Sepsis

Richard S. Hotchkiss, M.D., and Irene E. Karl, Ph.D.

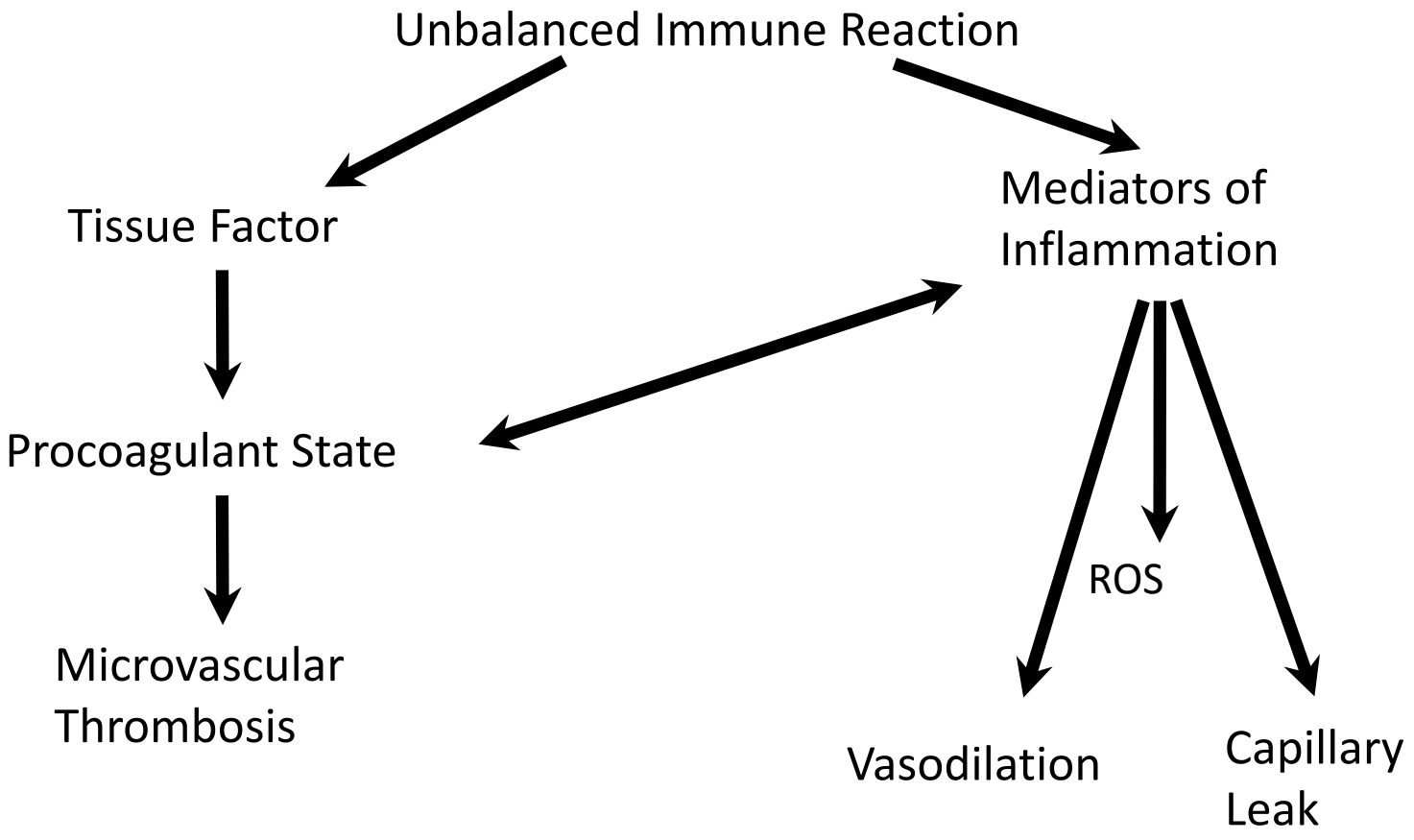


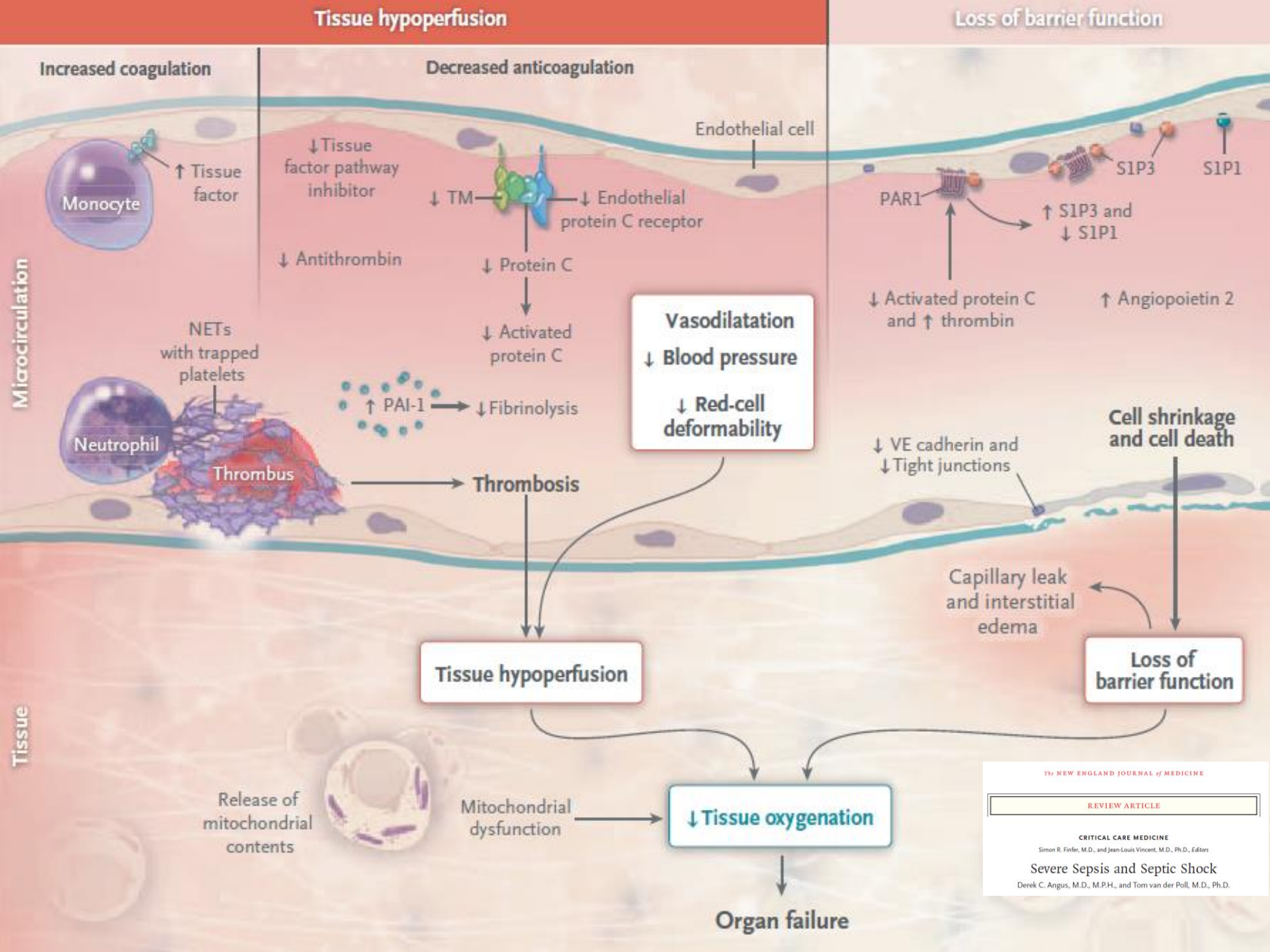
Κυτταροκίνες

- **Προφλεγμονώδεις**
  - IL-1b
  - TNF-a
  - IL-6
  - IL-12
  - IL-15
  - IL-18
  - IL-8
  - IFN-γ
- **Αντιφλεγμονώδεις**
  - IL-10
  - IL-13
  - IL-4
  - sTNFR-I
  - sTNFR-II
  - IL-1ra
  - TGF-b



Sepsis Pathogenesis





The NEW ENGLAND JOURNAL of MEDICINE
REVIEW ARTICLE
CRITICAL CARE MEDICINE
Simon R. Finfer, M.D., and Jean-Louis Vincent, M.D., Ph.D., *Editors*

Severe Sepsis and Septic Shock

Derek C. Angus, M.D., M.P.H., and Tom van der Poll, M.D., Ph.D.

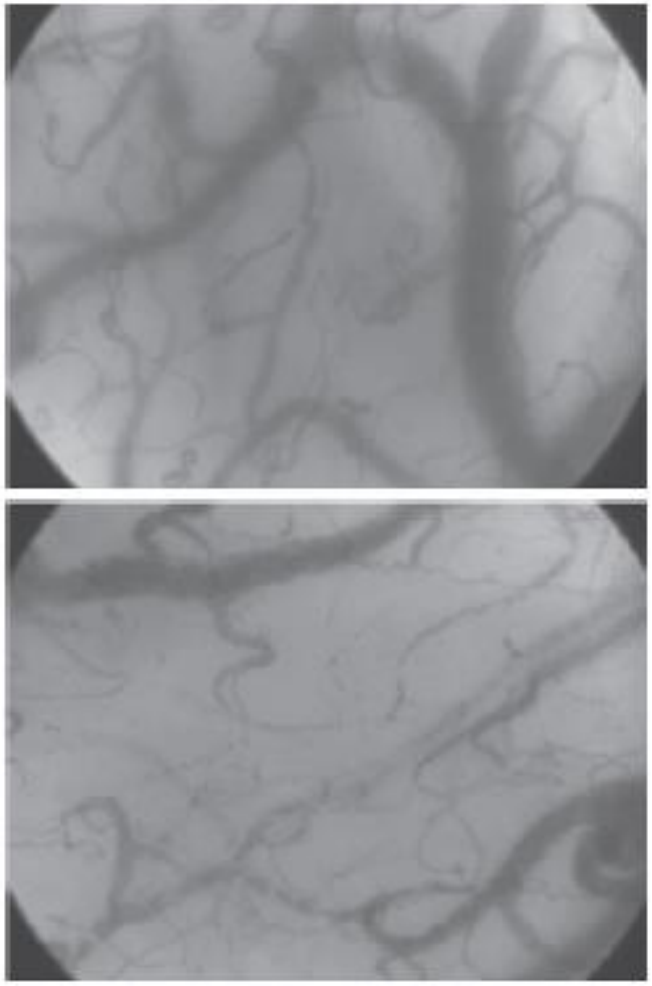
Virulence 5:1, 73–79; January 1, 2014; © 2014 Landes Bioscience

Pathophysiology of microcirculatory dysfunction and the pathogenesis of septic shock

Daniel De Backer*, Diego Orbegozo Cortes, Katia Donadello, and Jean-Louis Vincent

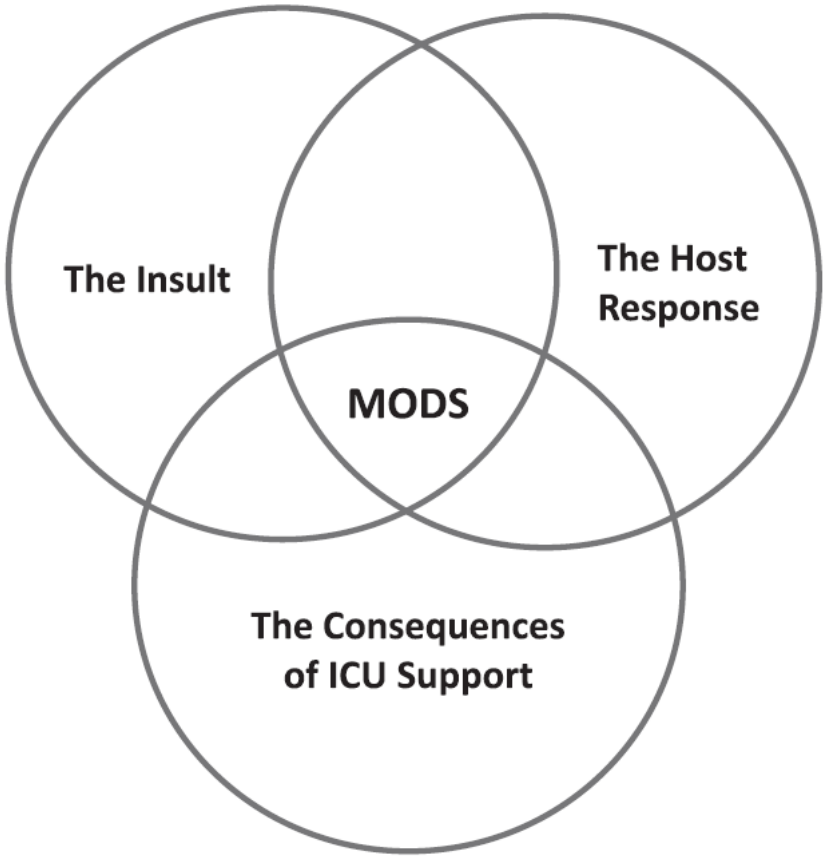
Φυσιολογική Μικροκυκλοφορία

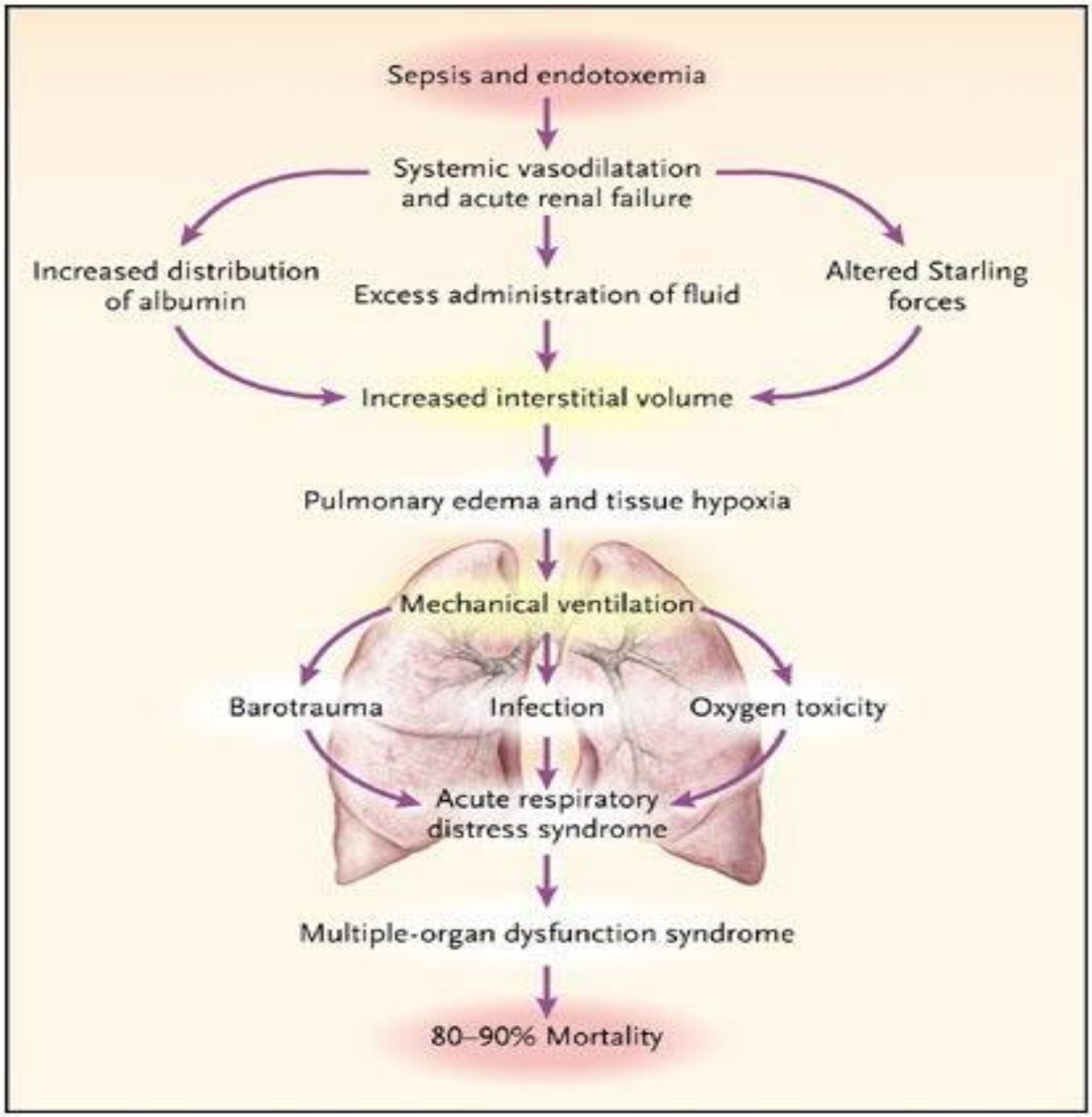
Σήψη



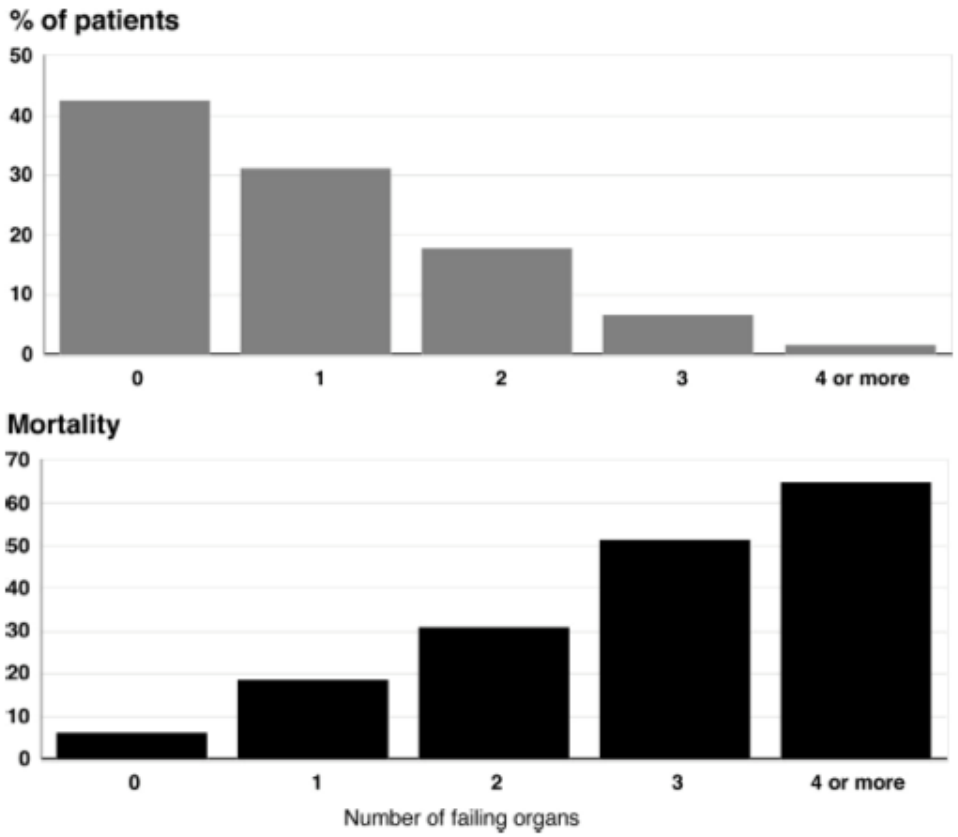
Multiple Organ Dysfunction: The Defining Syndrome of Sepsis

Markus T. Ziesmann and John C. Marshall




Sepsis and endotoxemia
Systemic vasodilatation and acute renal failure
Increased distribution of albumin
Excess administration of fluid
Altered Starling forces
Increased interstitial volume
Pulmonary edema and tissue hypoxia
Mechanical ventilation
Barotrauma
Infection
Oxygen toxicity
Acute respiratory distress syndrome
Multiple-organ dysfunction syndrome
80–90% Mortality

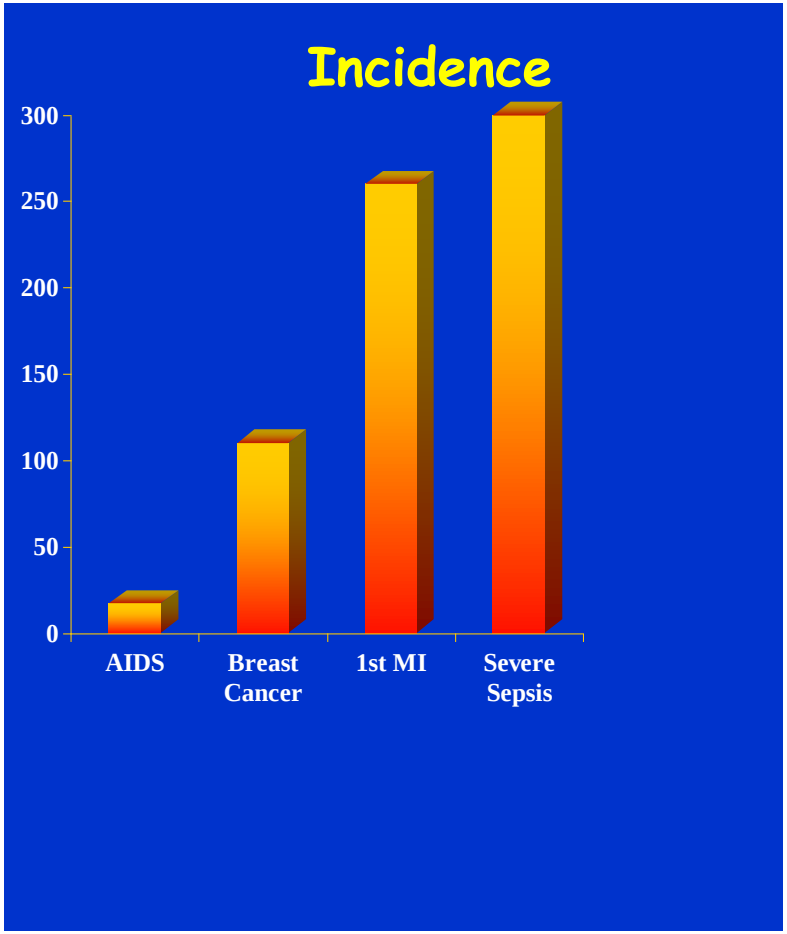
Η θνητότητα εξαρτάται από τον αριθμό των οργάνων που δυσλειτουργούν

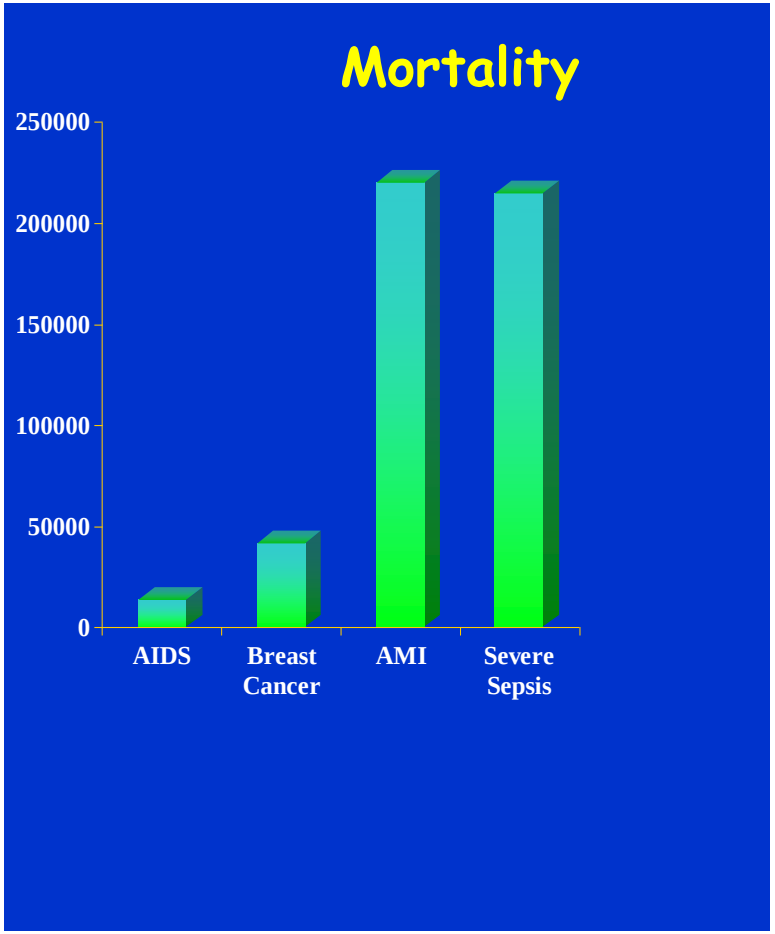


Vincent, J.-L., Sakr, Y., Sprung, C. L., Ranieri, V. M., Reinhart, K., Gerlach, H., Moreno, R., et al. (2006). Sepsis in European intensive care units: results of the SOAP study. *Critical Care Medicine*, *34*(2), 344–353.

Επιδημιολογία

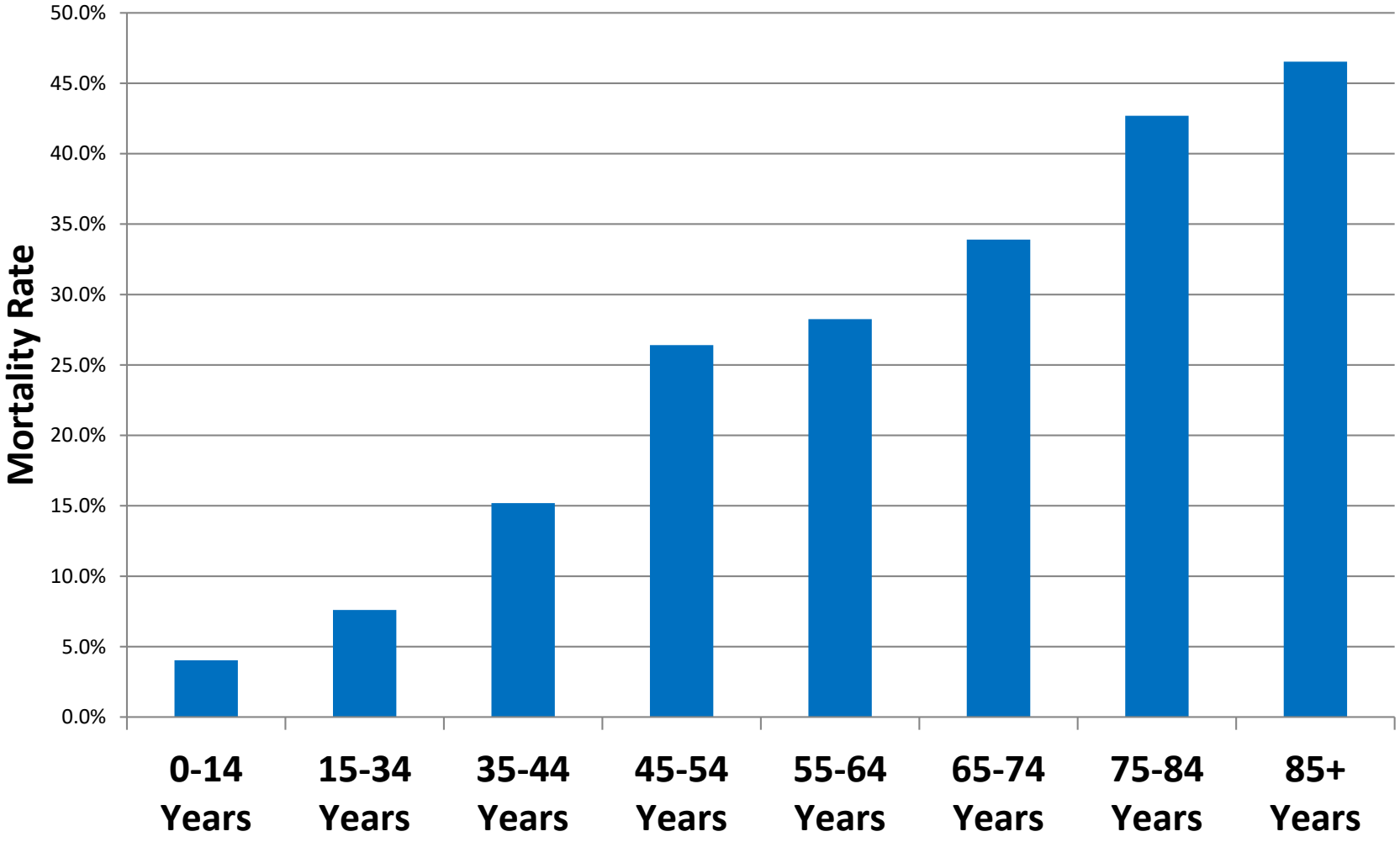
Σοβαρή Σήψη: Συγκριτική Επίπτωση και Θνητότητα





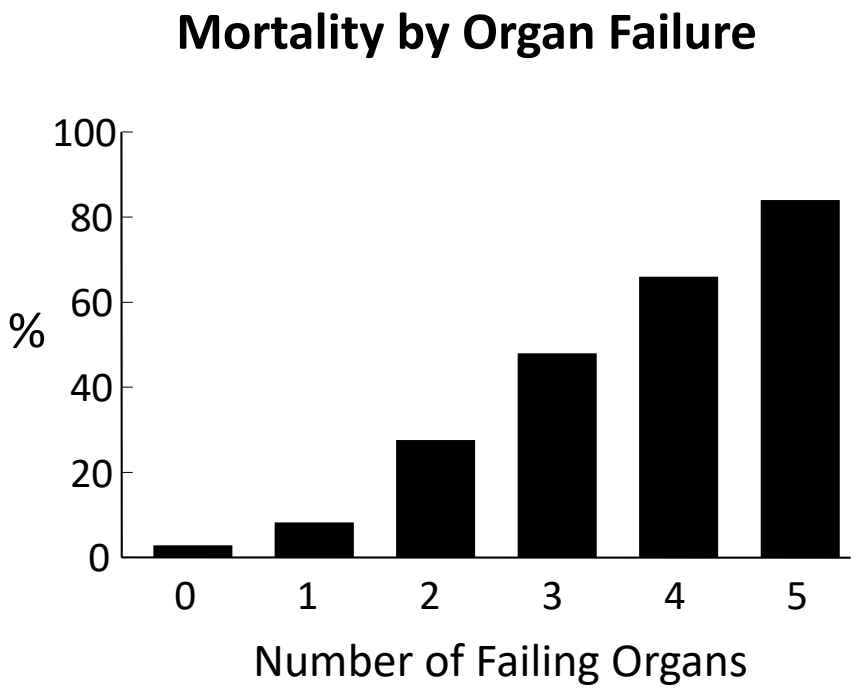
Angus DC, et al. Crit Care Med. 2001; ACS.

Hospital Inpatient Enquiry: Crude Mortality for Inpatients with a Diagnosis of Sepsis & Admission to Critical Care, by Age Group, 2015



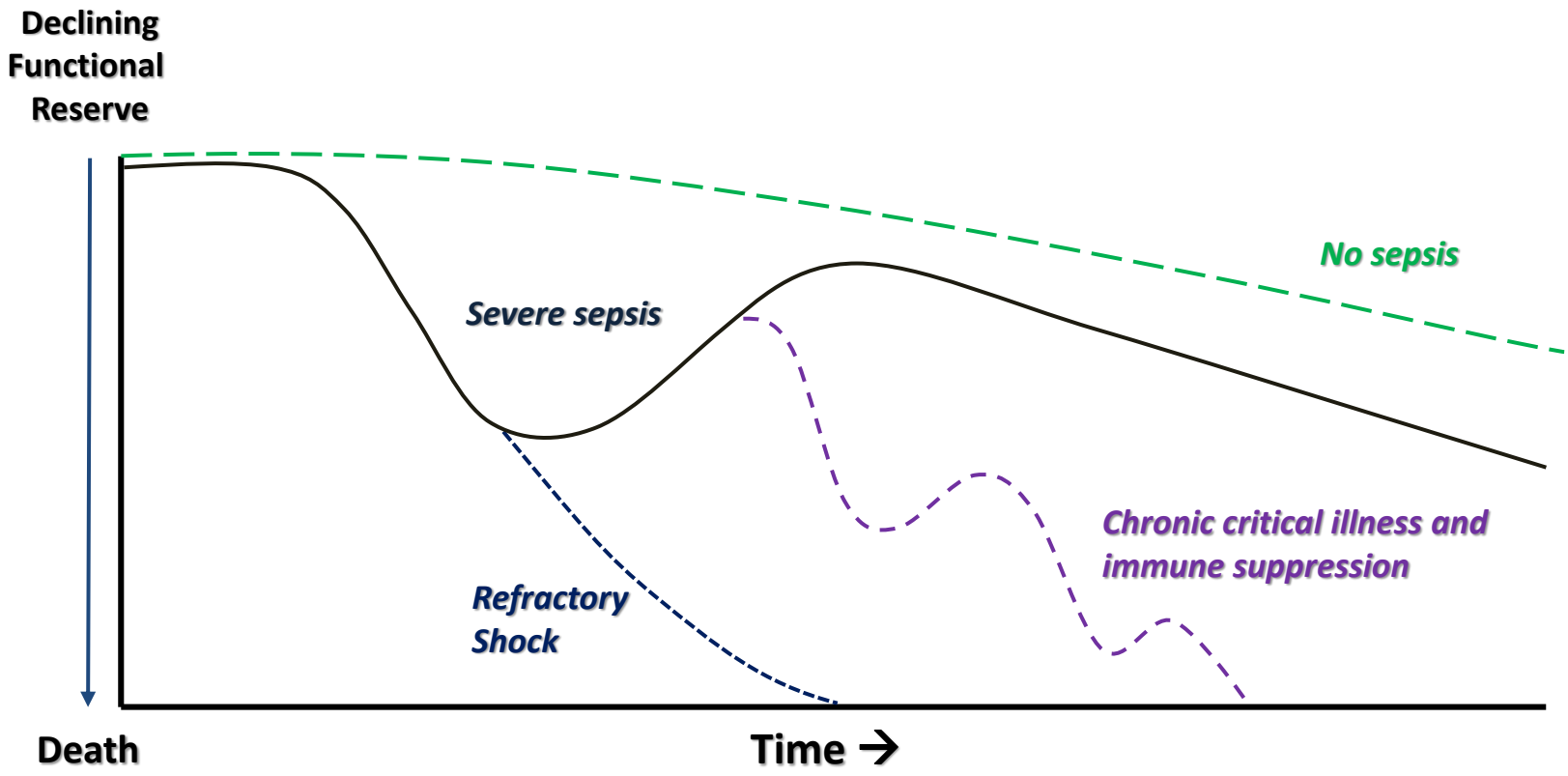
Θνητότητα

<u>Two of the most important factors affecting prognosis are organ failure and age</u>: Patients with sepsis generally die from multiple organ failure. Age is a major factor, especially after age 65

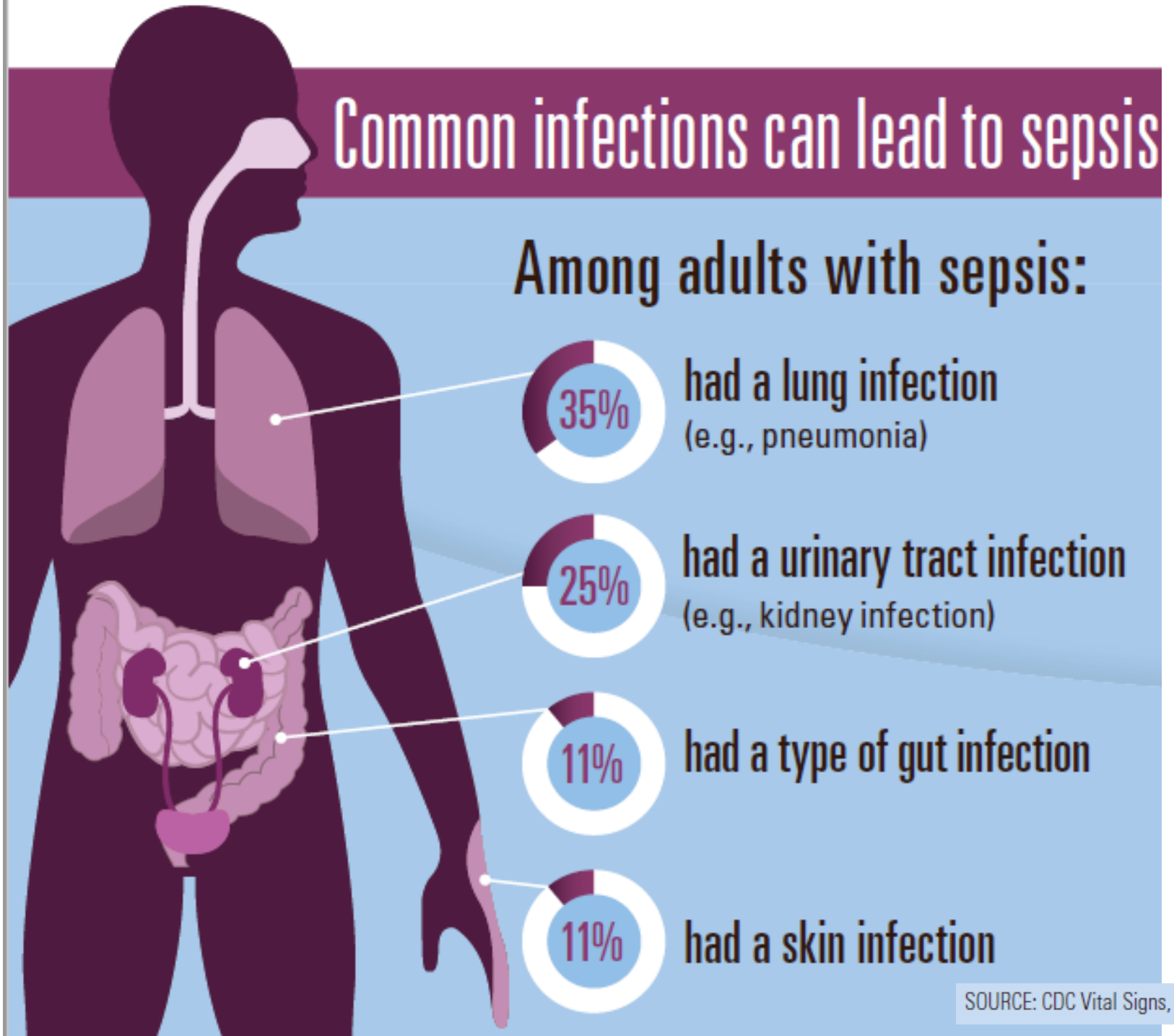


Mackenzie, I. et al. *BMJ* 335:929-932, 2007

Φυσική πορεία της Σήψης

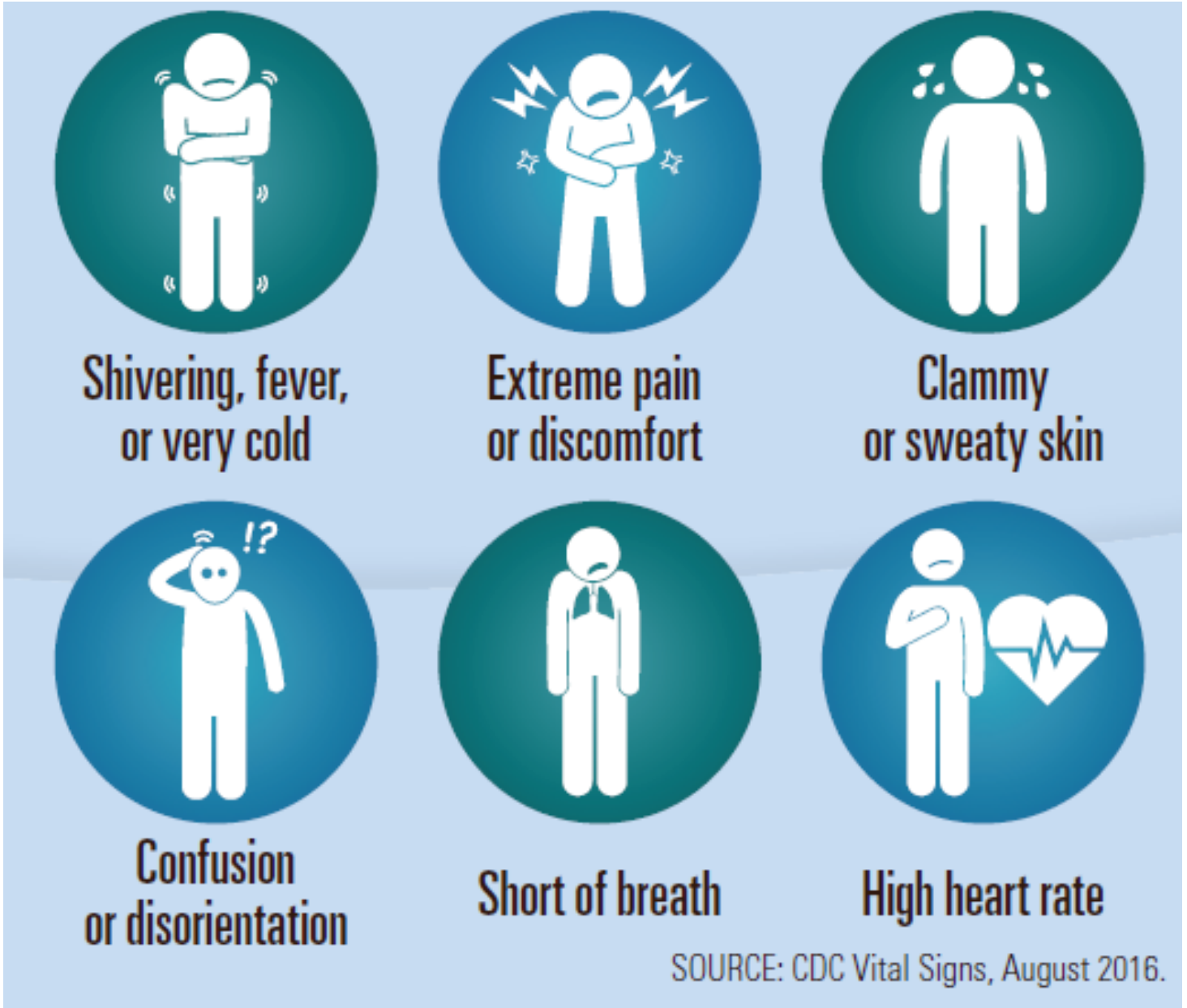


Yende S, Iwashyna TJ, and Angus DC. Interplay between sepsis and chronic health *Trends in Molecular Medicine*, 20, 4 , 2014.

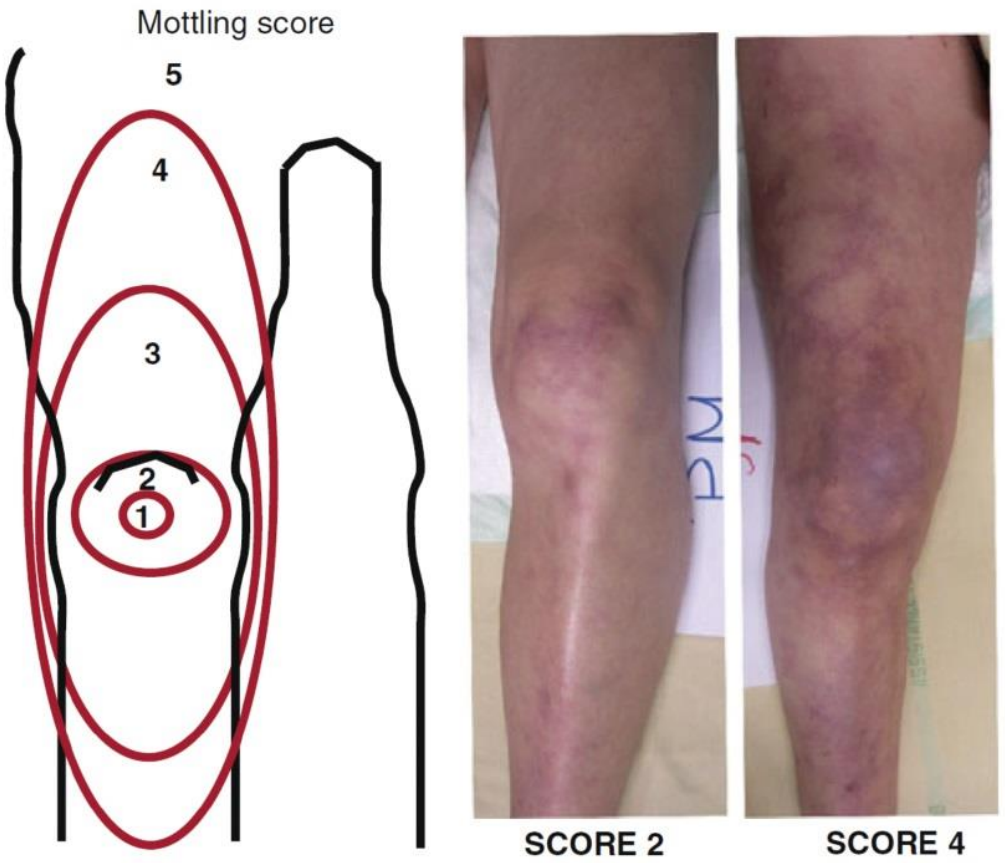

Common infections can lead to sepsis
Among adults with sepsis:
35%
had a lung infection
(e.g., pneumonia)
25%
had a urinary tract infection
(e.g., kidney infection)
11%
had a type of gut infection
11%
had a skin infection
SOURCE: CDC Vital Signs, August 2016.

Κλινικά Χαρακτηριστικά

Αναγνωρίστε τα Σημεία και τα Συμπτώματα



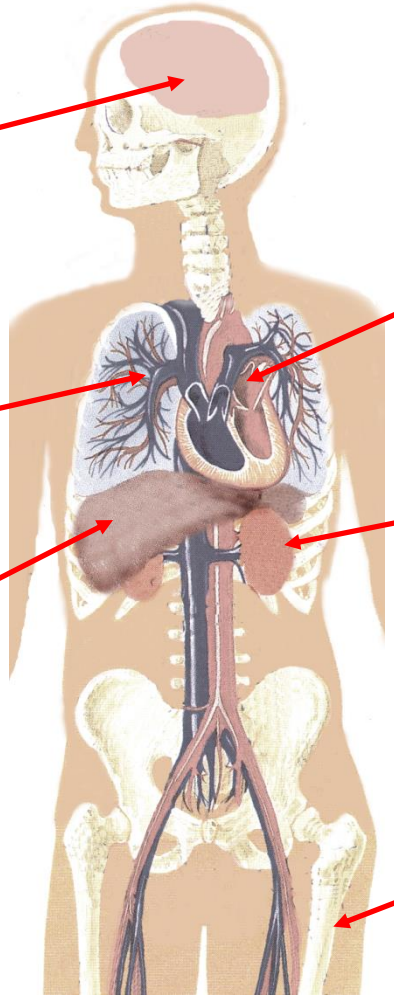
Δικτυωτή πελίωση - Mottling score



0 – No mottling
1 – Coin sized mottling area on the knee.
2 – To the superior area of the knee cap.
3 – Mottling up to the middle thigh
4 – Mottling up to the fold of the groin
5 – Severe mottling that extends beyond the the groin.

Quelle: Ait-Oufella et al., Intensive Care Med 2011

Διαταραχές οργάνων λόγω ανεπαρκούς άρδευσης



Αλλοίωση του επιπέδου συνείδησης
Σύγχυση

Ταχύπνοια
PaO_2 <70 mm Hg
SaO_2 <90%

Ίκτερος
↑ Ένζυμα
↓ Λευκωματίνες
↑ PT

Ταχυκαρδία
Υπόταση

Ολιγουρία
Διούρηση ≤ 0,5 ml/Kg/h
Ανουρία
↑ Κρεατινίνης

↓ Αιμοπετάλια
↑ aPTT
↓ Πρωτεΐνη C
↑ D-dimer

Αντιμετώπιση

Surviving Sepsis Campaign

Sepsis and septic shock are medical emergencies and we recommend that treatment and resuscitation begin immediately.

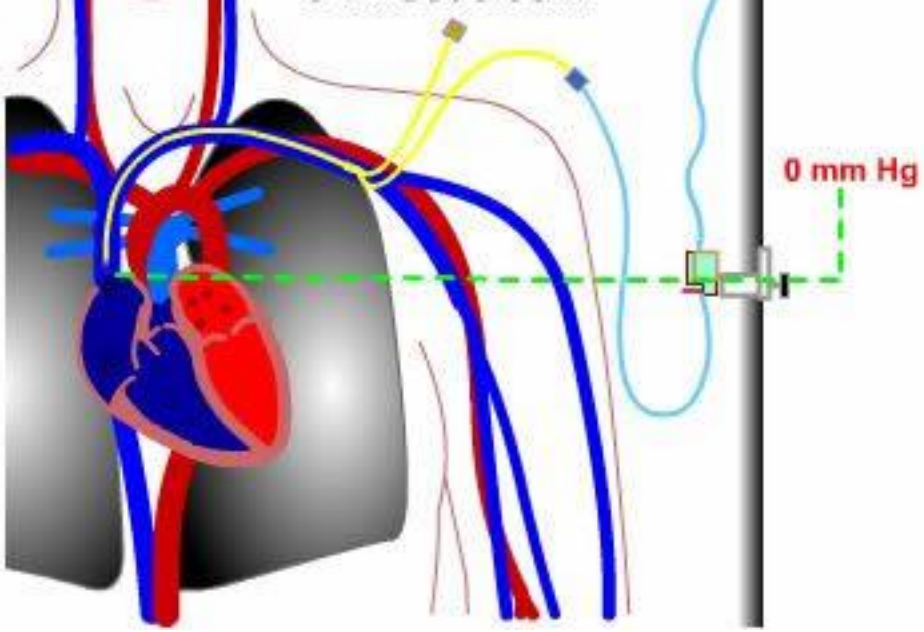
Best Practice Statement

Surviving Sepsis Campaign

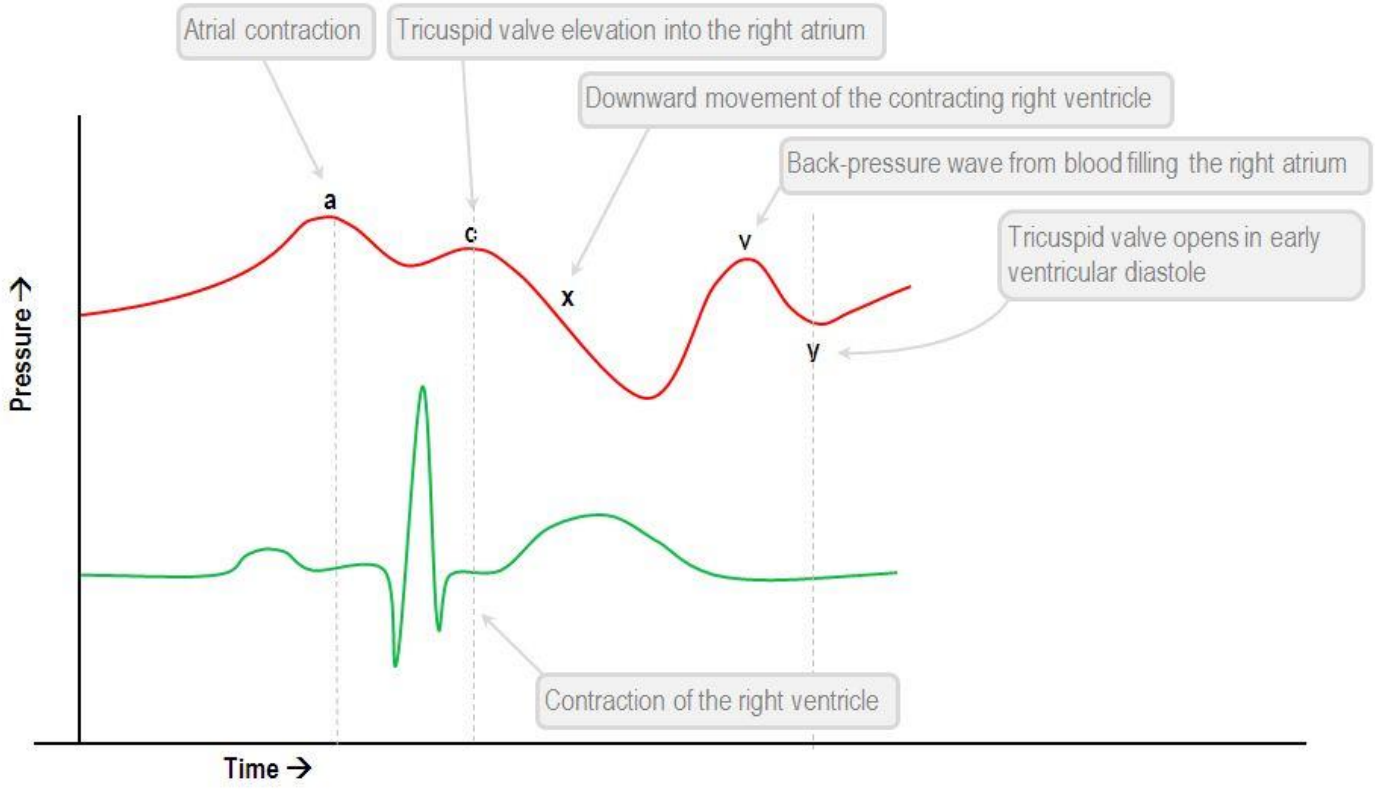
Αρχική Αντιμετώπιση

We recommend the protocolized, quantitative resuscitation of patients with sepsis- induced tissue hypoperfusion. During the first 6 hours of resuscitation, the goals of initial resuscitation should include all of the following as a part of a treatment protocol:

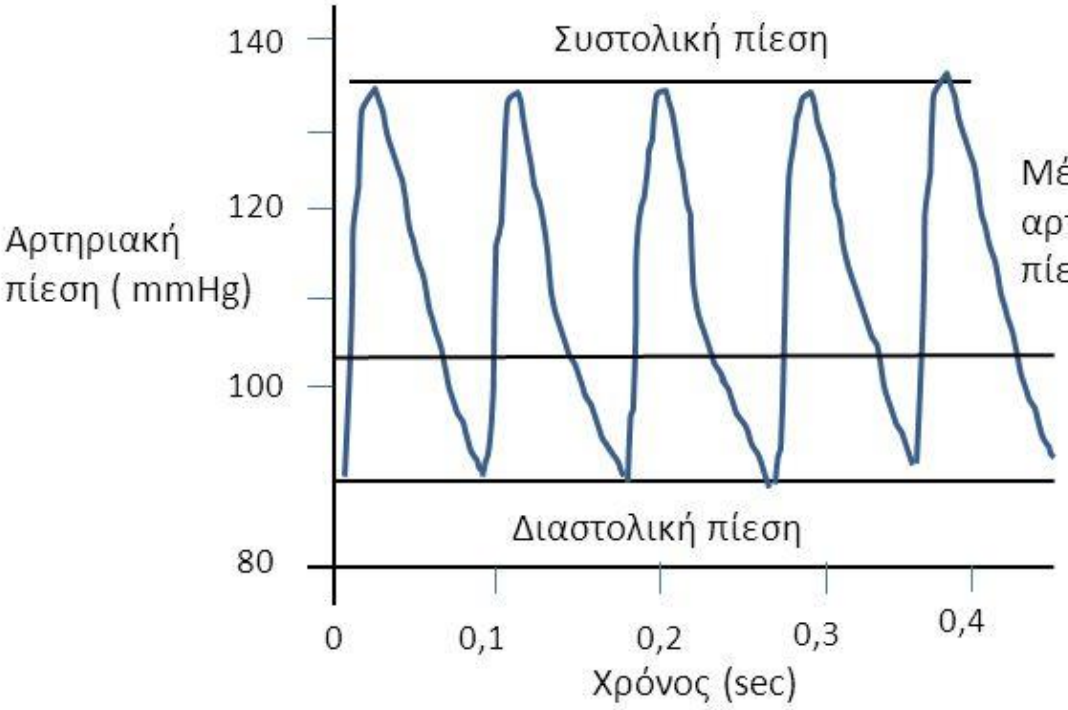
a) CVP 8–12 mm Hg
b) MAP ≥ 65 mm Hg
c) Urine output ≥ 0.5 mL/kg/hr
d) Scvo2 ≥ 70%.



Κεντρική Φλεβική Πίεση - CVP



Μέση Αρτηριακή Πίεση

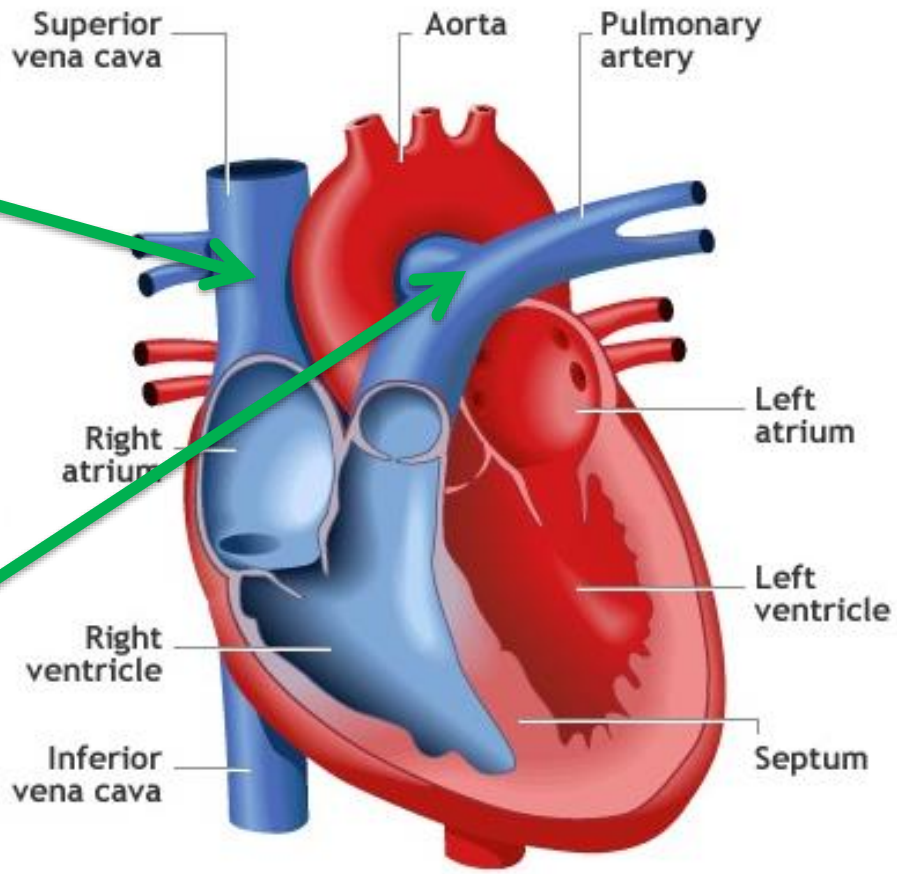


- **ΜΑΠ** = (ΣΑΠ + 2χΔΑΠ)/3,
- Οδηγός πίεση αιμάτωσης των οργάνων,

Λήψη ScvO2 και SvO2

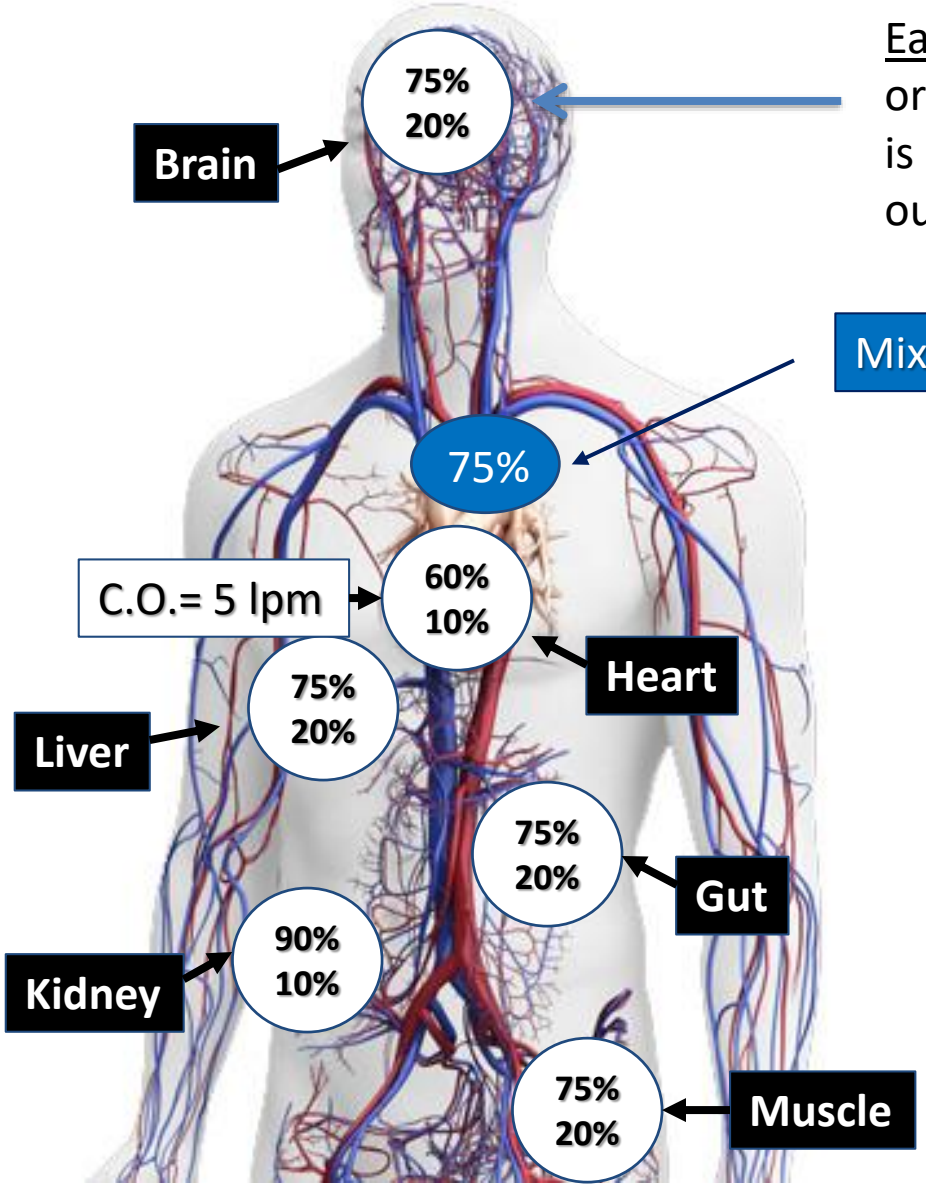
Central venous oxyhemoglobin saturation ($ScvO_2$) is measured here

Mixed venous oxyhemoglobin saturation (SvO_2) is measured here



We tend to check $ScVO_2$ rather than SvO_2 because the latter requires a PA catheter.

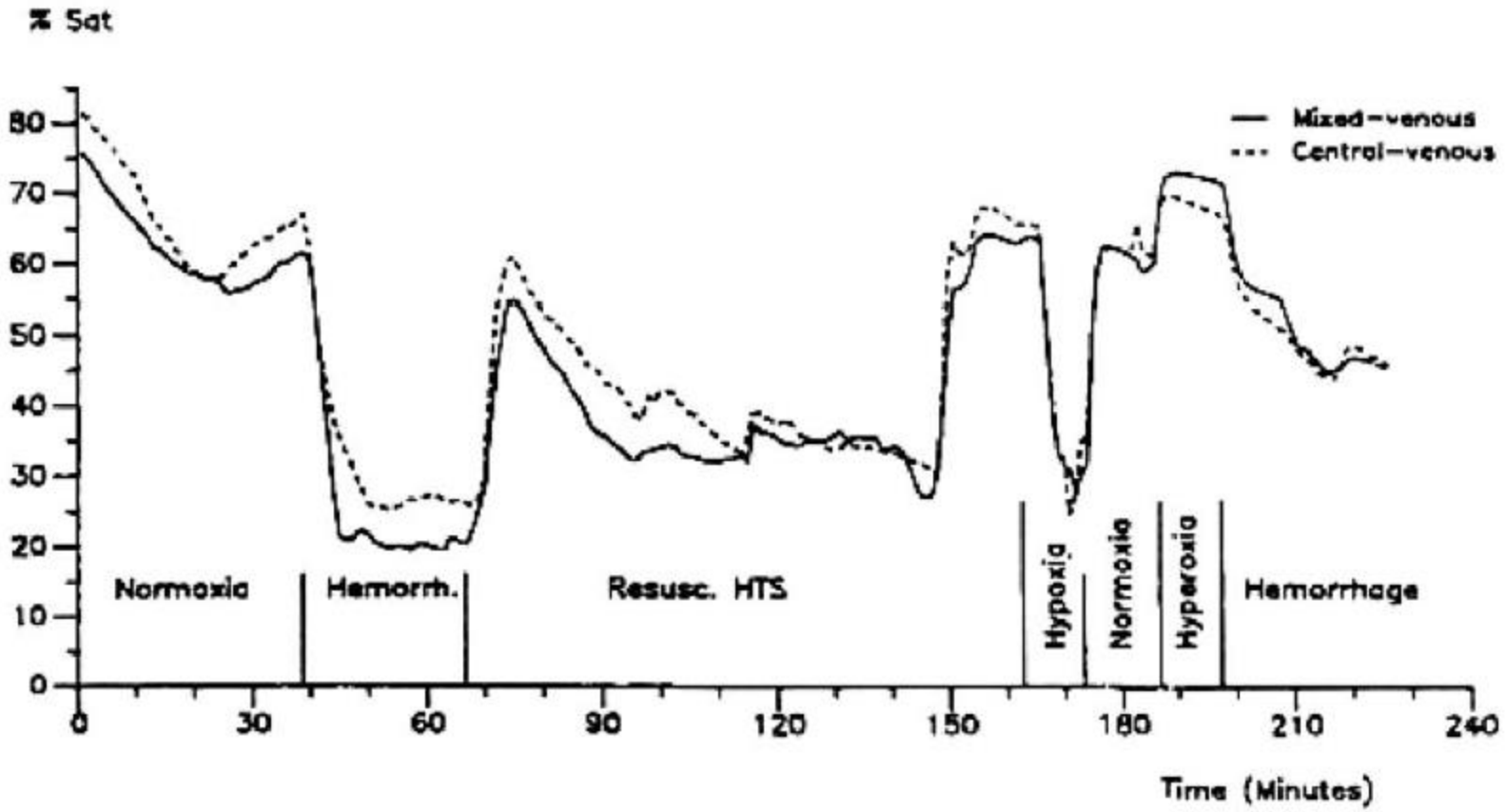
Κορεσμός Μεικτού Φλεβικού Αιματος - SvO2



Each circle is an organ. The top number is the organ-specific SvO_2% and the bottom number is organ blood flow as a % of the total cardiac output.

Organ	SvO_2	% CO	Weighted Contribution
Brain	75	20%	15
Heart	60	0.1	6
Liver	75	0.2	15
Gut	75	0.2	15
Kidney	90	0.1	9
Sk. Muscle	75	0.2	15
			SVO_2 = 75%

ScvO2 ως υποκατάστατο του SvO2



(Chest 1989; 95:1216-21)

Early Goal-Directed Therapy

The New England Journal of Medicine

EARLY GOAL-DIRECTED THERAPY IN THE TREATMENT OF SEVERE SEPSIS AND SEPTIC SHOCK

EMANUEL RIVERS, M.D., M.P.H., BRYANT NGUYEN, M.D., SUZANNE HAVSTAD, M.A., JULIE RESSLER, B.S., ALEXANDRIA MUZZIN, B.S., BERNHARD KNOBLICH, M.D., EDWARD PETERSON, PH.D., AND MICHAEL TOMLANOVICH, M.D., FOR THE EARLY GOAL-DIRECTED THERAPY COLLABORATIVE GROUP*

Rivers, E., Nguyen, B., Havstad, S., Ressler, J., Muzzin, A., Knoblich, B., Peterson, E., et al. (2001). Early goal-directed therapy in the treatment of severe sepsis and septic shock. *New England Journal of Medicine*, *345*(19), 1368–1377.

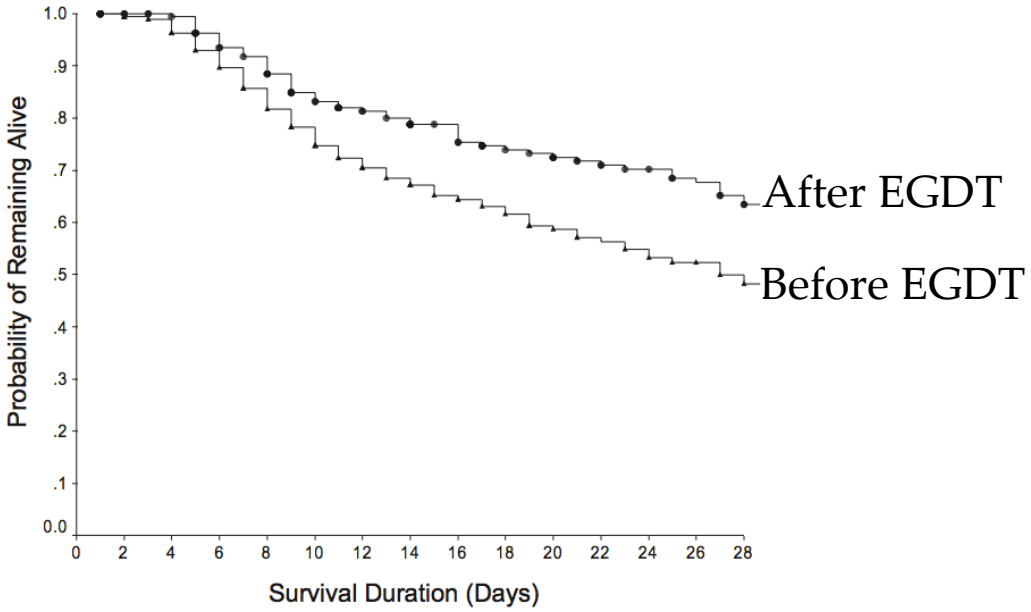
Early Goal-Directed Therapy

- INCLUSION = SEPSIS AND [BP < 90 after fluid OR Lactate > 4]

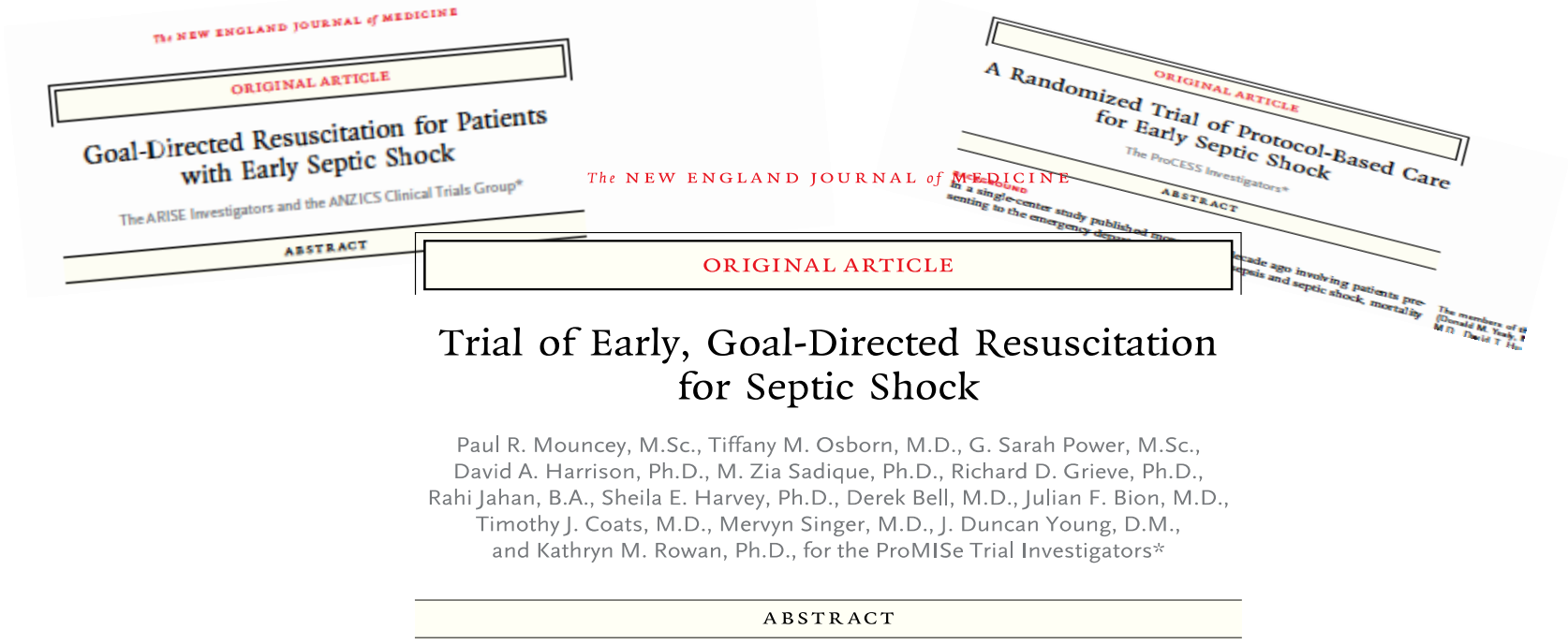
Control	Intervention	EGDT
CVP 8-12	Fluids	CVP 8-12
MAP > 65	Vasopressors	MAP > 65
	Transfusions Dobutamine	ScvO2 > 70%
49% mortality		33% mortality

Rivers, E., Nguyen, B., Havstad, S., Ressler, J., Muzzin, A., Knoblich, B., Peterson, E., et al. (2001). Early goal-directed therapy in the treatment of severe sepsis and septic shock. *New England Journal of Medicine*, *345*(19), 1368–1377.

Επίδραση από την άμεση εφαρμογή προτυποιημένων σετ ενεργειών



Thiel, S. W., Asghar, M. F., Micek, S. T., Reichley, R. M., Doherty, J. A., & Kollef, M. H. (2009). Hospital-wide impact of a standardized order set for the management of bacteremic severe sepsis*. *Critical Care Medicine*, *37*(3), 819–824. doi:10.1097/CCM.0b013e318196206b



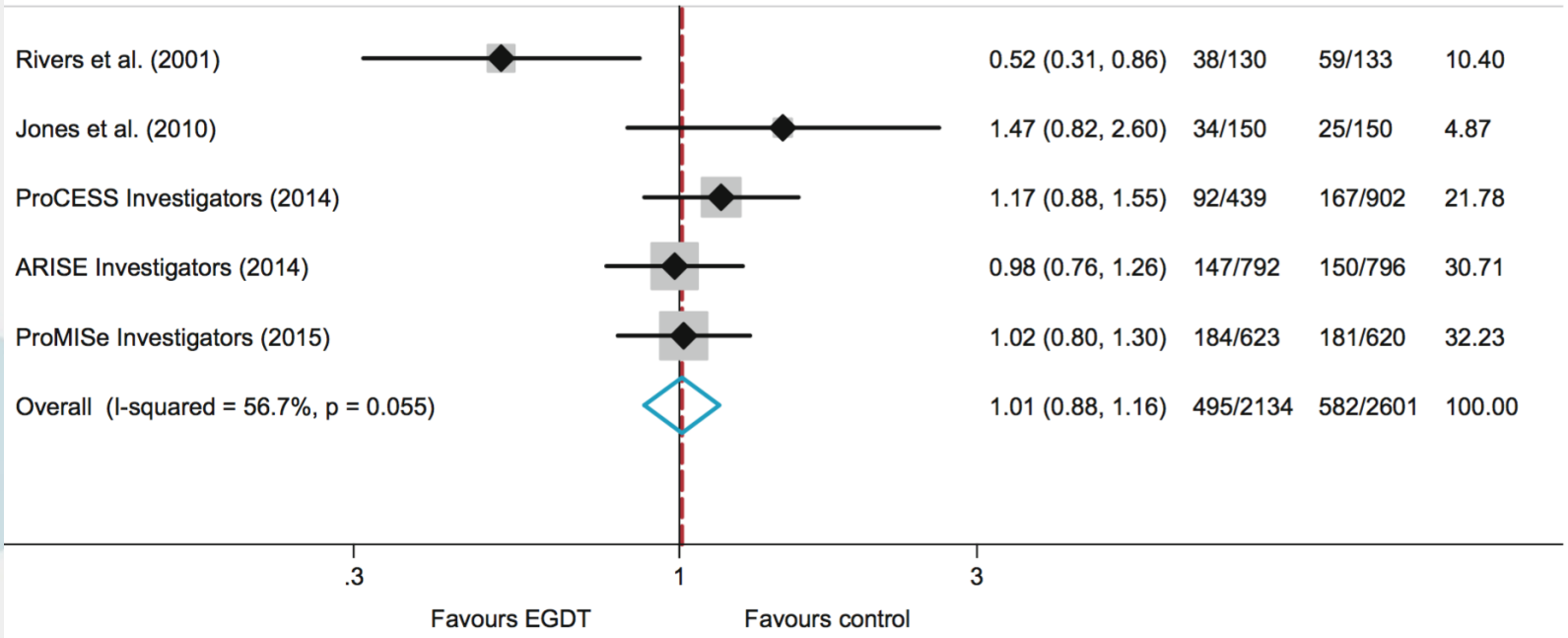
3 Recent Large Randomized Control Trials:

Although advanced severe sepsis therapies (such as central line placement, SVO2 goals, etc) did not show improved outcomes, **all were randomized after early recognition and standard therapies including antibiotics and fluid resuscitation which are the goals of UNC Code Sepsis**

Surviving Sepsis Campaign

A systematic review and meta-analysis of early goal-directed therapy for septic shock: the ARISE, ProCESS and ProMISe Investigators

A Primary mortality outcome of each study



Intensive Care Med (2015) 41:1549–1560
DOI 10.1007/s00134-015-3822-1

Society of Critical Care Medicine
The Intensive Care Professionals

ESICM
The Intensive Connection

Surviving Sepsis Campaign

Έτοιμες - Προτυποποιημένες Δέσμες Μέτρων Αντιμετώπισης

BUNDLES

TO BE COMPLETED WITHIN 3 HOURS:

1) Measure lactate level.
2) Obtain blood cultures prior to administration of antibiotics.
3) Administer broad spectrum antibiotics.
4) Administer 30 ml/kg crystalloid for hypotension or lactate ≥4mmol/L.

"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 severe sepsis or septic shock ascertained through chart review.

TO BE COMPLETED WITHIN 6 HOURS:

5) Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (MAP) ≥65 mm Hg.
6) In the event of persistent hypotension after initial fluid administration (MAP < 65 mm Hg) or if initial lactate was ≥4 mmol/L, re-assess volume status and tissue perfusion and document findings according to Table 1.
7. Re-measure lactate if initial lactate elevated.

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Έτοιμες - Προτυποποιημένες Δέσμες Μέτρων Αντμετώπισης

BUNDLES

TABLE 1

DOCUMENT REASSESSMENT OF VOLUME STATUS AND TISSUE PERFUSION WITH:

EITHER:

- Repeat focused exam (after initial fluid resuscitation) including vital signs, cardiopulmonary, capillary refill, pulse, and skin findings.

OR TWO OF THE FOLLOWING:

- Measure CVP.
- Measure $ScvO^2$.
- Perform bedside cardiovascular ultrasound.
- Perform dynamic assessment of fluid responsiveness with passive leg raise or fluid challenge.

www.survivingsepsis.org

Surviving Sepsis Campaign

Αρχική Χορήγηση Υγρών

- **We recommend that in the resuscitation from sepsis-induced hypoperfusion, at least 30ml/kg of intravenous crystalloid fluid be given within the first 3 hours.**

(Strong recommendation; low quality of evidence)

- **We recommend that following initial fluid resuscitation, additional fluids be guided by frequent reassessment of hemodynamic status.**

(Best Practice Statement)

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Χορήγηση Υγρών

- **We recommend crystalloids as the fluid of choice for initial resuscitation and subsequent intravascular volume replacement in patients with sepsis and septic shock**

(Strong recommendation, moderate quality of evidence).

- **We suggest using albumin in addition to crystalloids when patients require substantial amounts of crystalloids**

(weak recommendation, low quality of evidence).

Η χορήγηση υγρών πρέπει να διακόπτεται όταν δεν είναι πια οφέλιμη

Fluid overload

- prolongs mechanical ventilation and
- increases the mortality of critically ill patients in general and, more specifically, in patients with sepsis,
- acute respiratory distress syndrome (ARDS),
- intra-abdominal hypertension and
- acute kidney injury
- aggravate lung and tissue edema

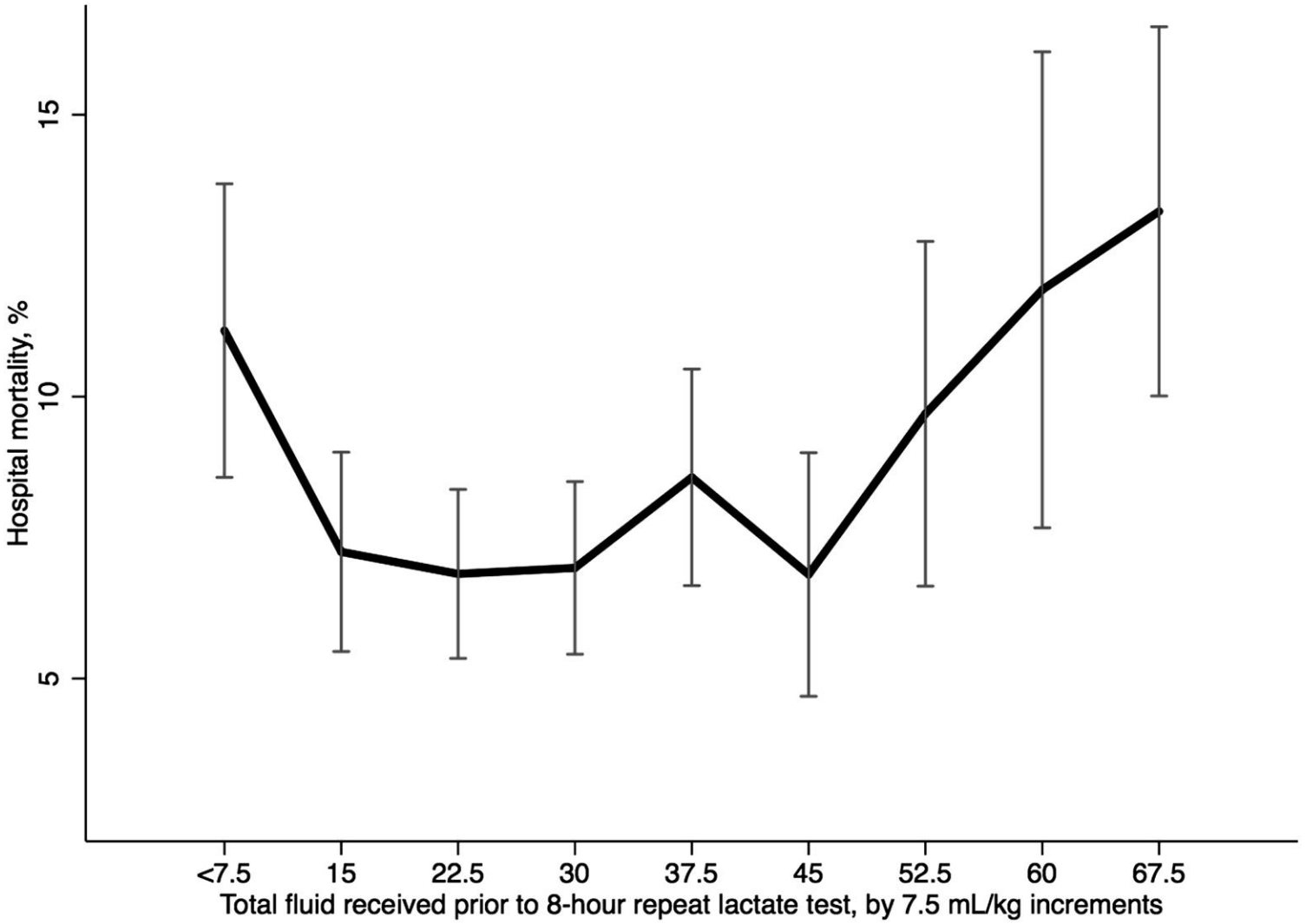
Crit Care Med. 2011;39:259–65.

Crit Care. 2013;17:R246.

Crit Care Med. 2013;41:472–80.

Intensive Care Med. 2013;39:1190–206.

Χορήγηση Υγρών και Θνητότητα



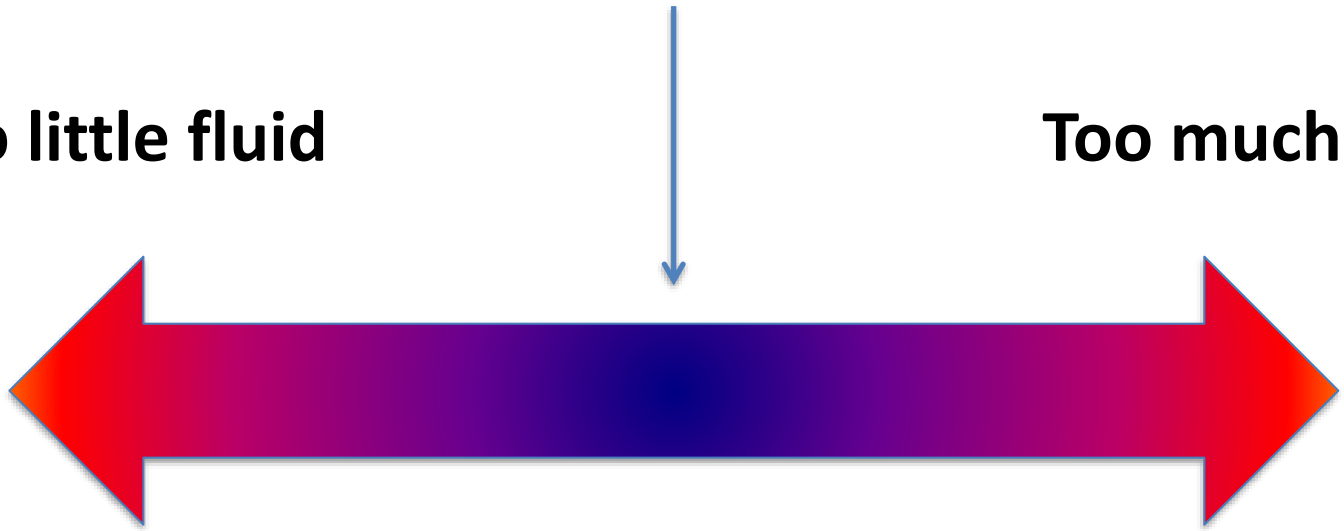
Mean hospital mortality among patients with decreased lactate within 8 hours of index test, stratified by total fluid received in increments of 7.5 ml/kg based on medication administration record. Annals ATS, 2013

Χορήγηση Υγρών

Finding the middle for each patient requires combining many variables: physical exam, straight leg raise, IVC ultrasound, lactate, $ScvO_2$, urine output, trial and error, etc.

Too little fluid

Too much fluid



- More organ injury
- Higher mortality
- Vasopressor-induced digital necrosis

- Worse edema
- Impaired oxygen diffusion
- Worse ARDS

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

We recommend an initial target mean arterial pressure of 65 mmHg in patients with septic shock requiring vasopressors.

(Strong recommendation; moderate quality of evidence)

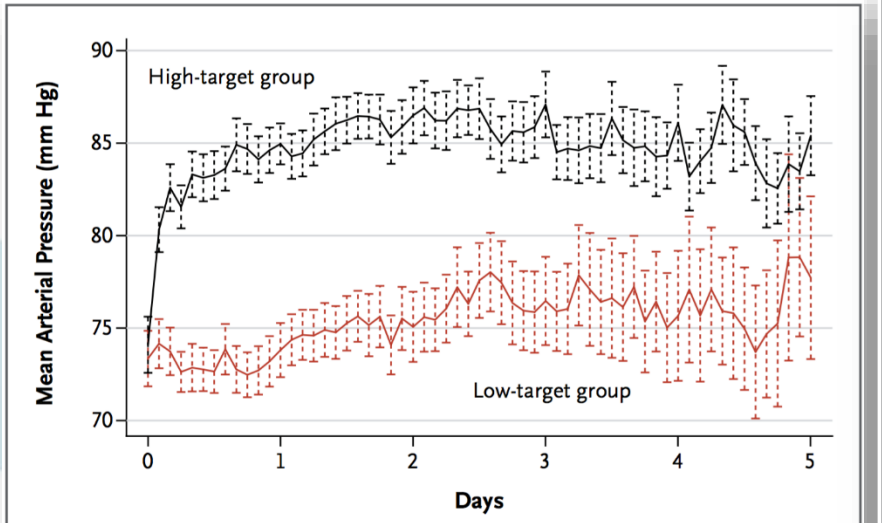

Figure 2. Mean Arterial Pressure during the 5-Day Study Period.

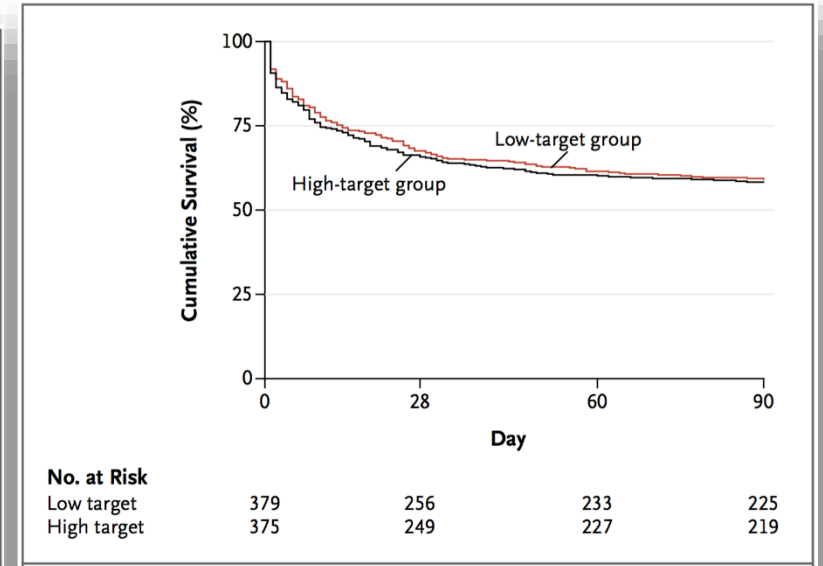

Figure 3. Kaplan–Meier Curves for Cumulative Survival.

DOI: 10.1056/NEJMoa1312173

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Διάγνωση

- **1. We recommend that appropriate routine microbiologic cultures (including blood) be obtained before starting antimicrobial therapy in patients with suspected sepsis and septic shock if doing so results in no substantial delay in the start of antimicrobials. (BPS)**
  - **Remarks: Appropriate routine microbiologic cultures always include at least two sets of blood cultures (aerobic and anaerobic).**

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Αντιβιοτική Θεραπεία

- **We recommend that administration of IV antimicrobials be initiated as soon as possible after recognition and within 1 h for both sepsis and septic shock.**

(strong recommendation, moderate quality of evidence).

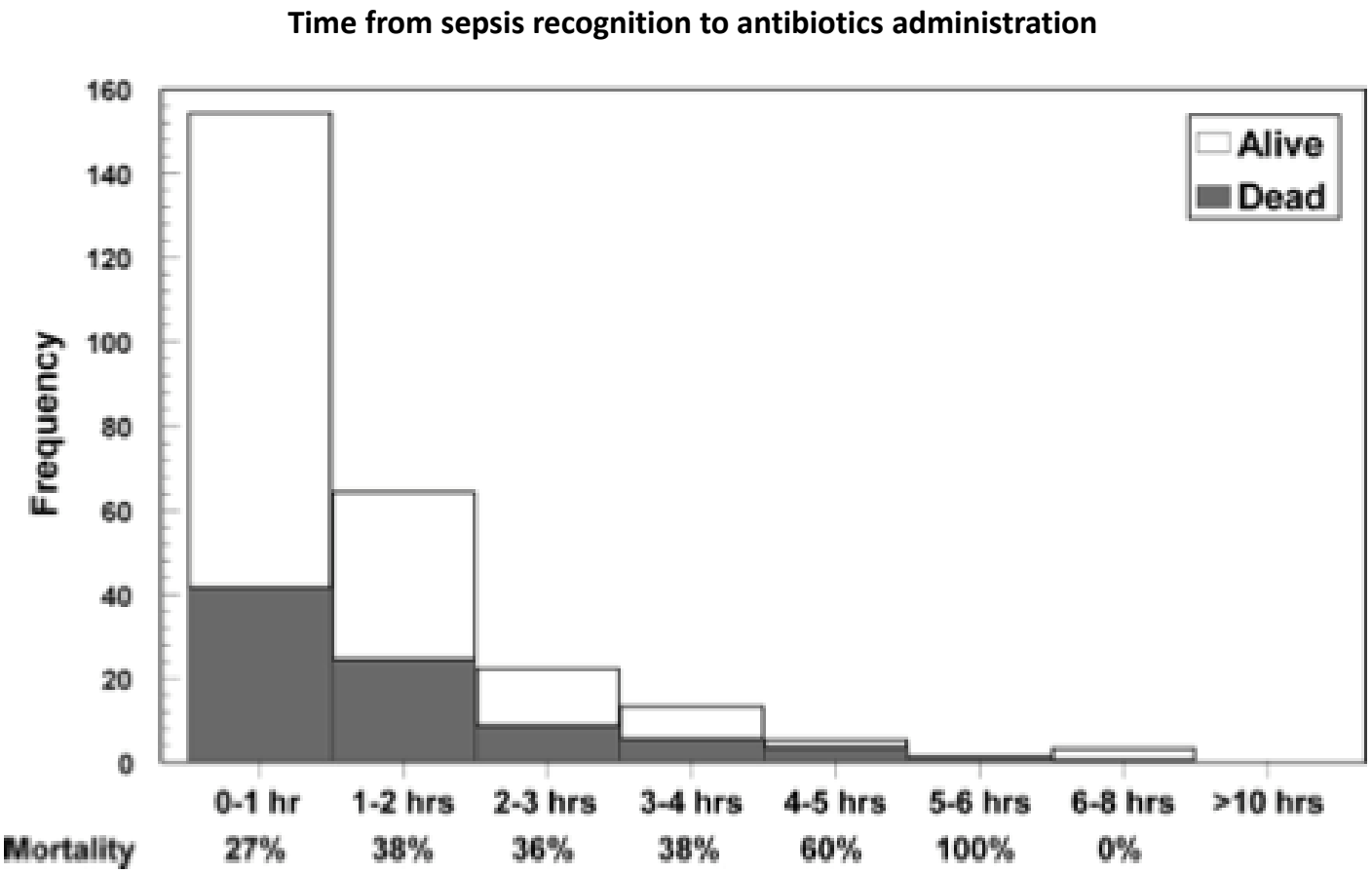
- **We recommend empiric broad-spectrum therapy with one or more antimicrobials to cover all likely pathogens.**

(strong recommendation, moderate quality of evidence).

Η έγκαιρη χορήγηση αντιβιοτικών μειώνει την πιθανότητα θανάτου

- Sepsis is a time-dependent medical emergency
- Mortality increases by 7.6% for each hour delay to appropriate antibiotics (Kumar CCM 2006)

Η έγκαιρη χορήγηση αντιβιοτικών μειώνει την πιθανότητα θανάτου



Gaieski DF, Mikkelsen ME, Band RA, et al. 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*. Critical Care Medicine 2010;38(4):1045–53.

Η έγκαιρη χορήγηση αντιβιοτικών μειώνει την πιθανότητα θανάτου

Author	N	Setting	Median time (mins)	Odds ratio for death
Gaieski CCM 2010; 38;1045-53	261	ED, USA (shock)	119	0.30 (1st hour vs all times)
Daniels Emerg Med J 2010; doi:10.1136	567	Whole hospital, UK	121	0.62 (1st hour vs all times)
Kumar CCM 2006; 34(6): 1589-1596	2154	ED, Canada (shock)	360	0.59 (1st 3 hours vs delayed)
Appelboam CCM 2010; 14(Suppl 1):50	375	Whole hospital, UK	240	0.74 (1st 3 hours vs delayed)
Levy CCM 2010; 38(2): 1-8	15022	Multi-centre		0.86 (1st 3 hours vs delayed)

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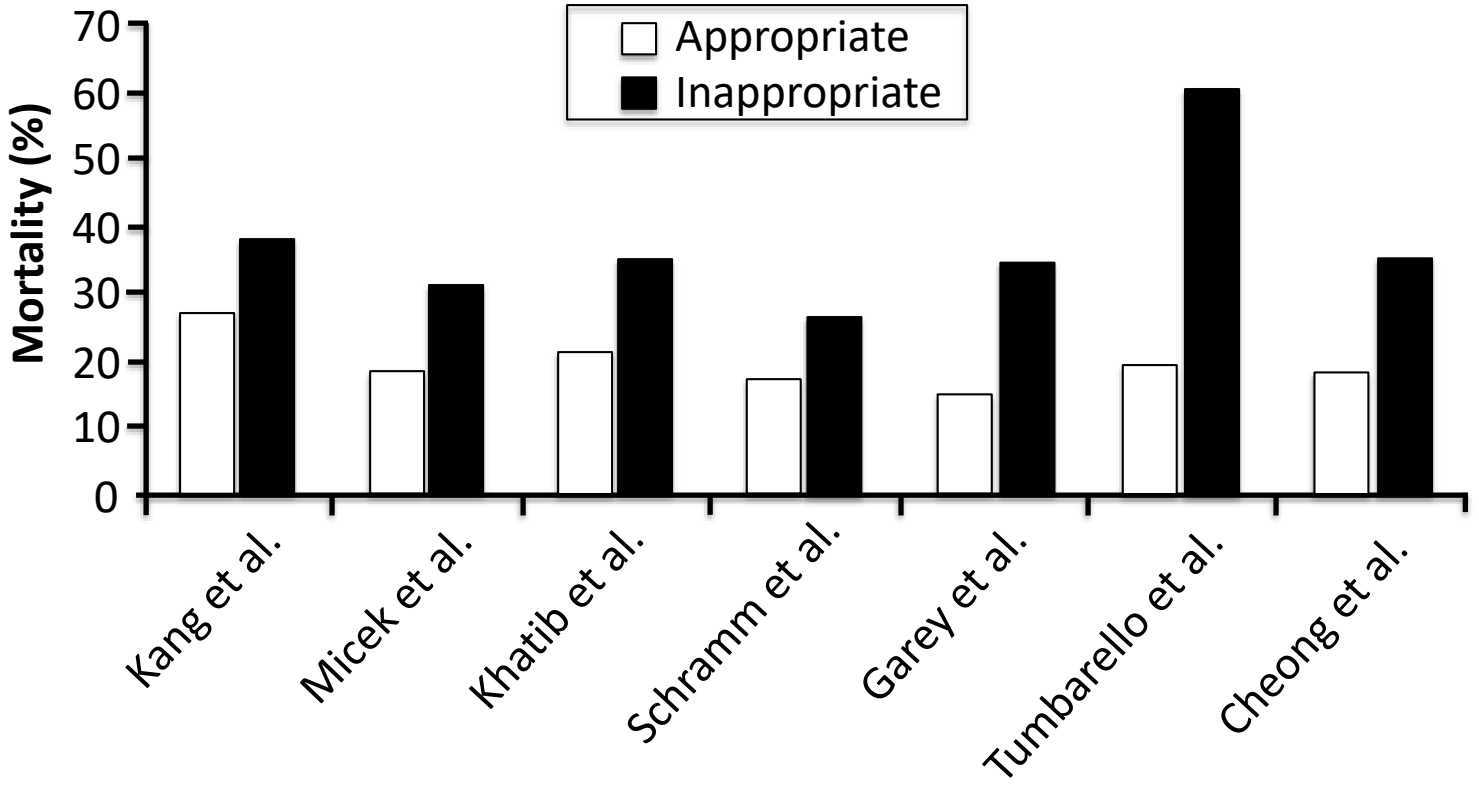
Αντιβιοτική Θεραπεία

- **We suggest empiric combination therapy (using at least two antibiotics of different antimicrobial classes) aimed at the most likely bacterial pathogen(s) for the initial management of septic shock.**
  - **(Weak recommendation; low quality of evidence)**

Γρήγορη επιλογή κατάλληλου αντιβιοτικού σχήματος

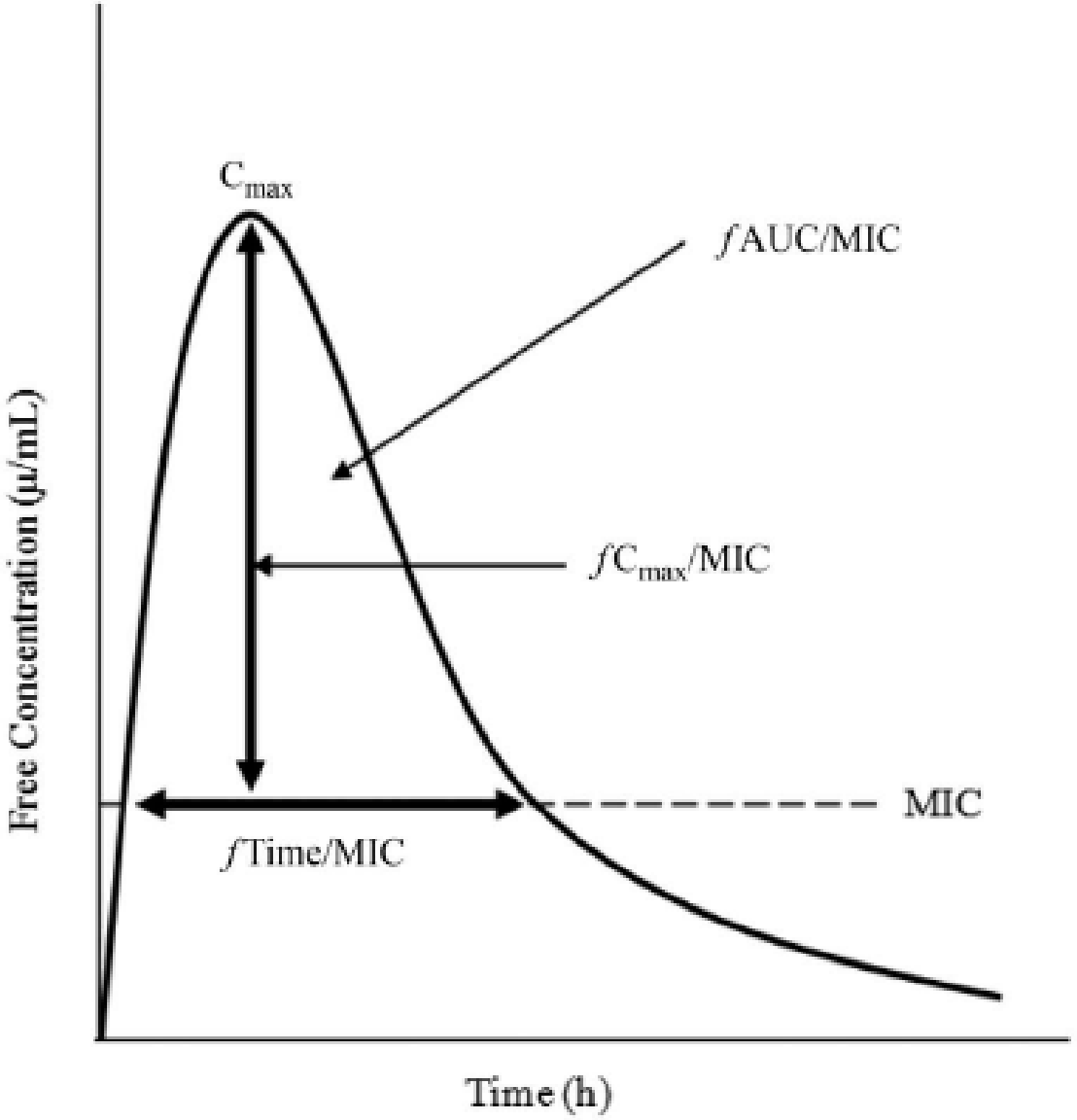
Early, broad-spectrum antibiotics are absolutely critical. Failure to treat up front with the right antibiotics increases mortality by 10-20 percentage points.



Morell MR et al. The Management of Severe Sepsis and Septic Shock
Infectious Disease Clinics of North America 23 (3): 485-501, 2009

Source	Initial Antibiotic Choice
Άγνωστη εστία	Carbapenem (imipenem/cilastin 500 mg IV every 6 h) Primaxin *Or* Third- or fourth-generation cephalosporin (ceftazidime 1 g IV every 8 h) Solvetan *Or* Anti-pseudomonal extended-spectrum penicillin (piperacillin/tazobactam 3.375 g IV every 6 h) Tazocin
Πνευμονία Κοινότητας	Beta-lactam (ceftriaxone 1 g IV every 12 h) Rocephin *Plus* Respiratory quinolone (moxifloxacin 400 mg IV every 24 h) Avelox *Or* Macrolide (azithromycin 500 mg IV every 24 hours) Zithromax **For penicillin-allergic patients:** Aztreonam 1-2 g IV every 8-12 h Azactam *Plus* Respiratory quinolone (moxifloxacin 400 mg IV every 24 h) Avelox
Νοσοκομειακή Πνευμονία ή Πνευμονία του Αναπνευστήρα	Anti-pseudomonal cephalosporin (ceftazidime 1 g IV every 8 h) Solvetan *Or* Carbapenem (imipenem/cilastin 500 mg IV every 6 h) Primaxin *Or* Anti-pseudomonal extended-spectrum penicillin (piperacillin/tazobactam 3.375 g IV every 6 h) Tazocin *Plus* Anti-pseudomonal fluoroquinolone (levofloxacin 750 mg IV every 12 h) Tavanic *Or* Aminoglycoside (amikacin 7.5 mg/kg IV every 12 h) Briklin
Ουροποιητικό	Anti-pseudomonal extended-spectrum penicillin (piperacillin/tazobactam 3.375 g IV every 6 h) Tazocin *Or* Carbapenem (imipenem/cilastin 500 mg IV every 6 h) Primaxin
Ενδοκοιλιακή Σήψη	Carbapenem (meropenem 1 g IV every 8 h) Meronem *Or* Tigecycline 50 mg IV every 12 h after a 100 mg initial dose Tygacil
Μαλακά Μόρια / Δέρμα	Anti-pseudomonal extended-spectrum penicillin (piperacillin/tazobactam 3.375 g IV every 6 h) Tazocin
Υψηλή αντοχή σε Gram + (πχ MRSA)	Glycopeptide (vancomycin 1 g IV every 12 h) Voncon *Or* Oxazolidinone (linezolid 600 mg IV every 12 h) Zyvoxid
Λοίμωξη από Μύκητες	Azole (fluconazole 400 mg IV every 24 h) Fungostatin *Or* Echinocandins (caspofungin 70 mg IV on day 1, then 50 mg IV every 24 h) Cancidas

Δοσοεξαρτώμενα και Χρονοεξαρτώμενα Αντιβιοτικά



Δοσοεξαρτώμενα και Χρονοεξαρτώμενα Αντιβιοτικά

Higher peak blood levels in relation to pathogen MIC

fluoroquinolones, aminoglycosides, vancomycin

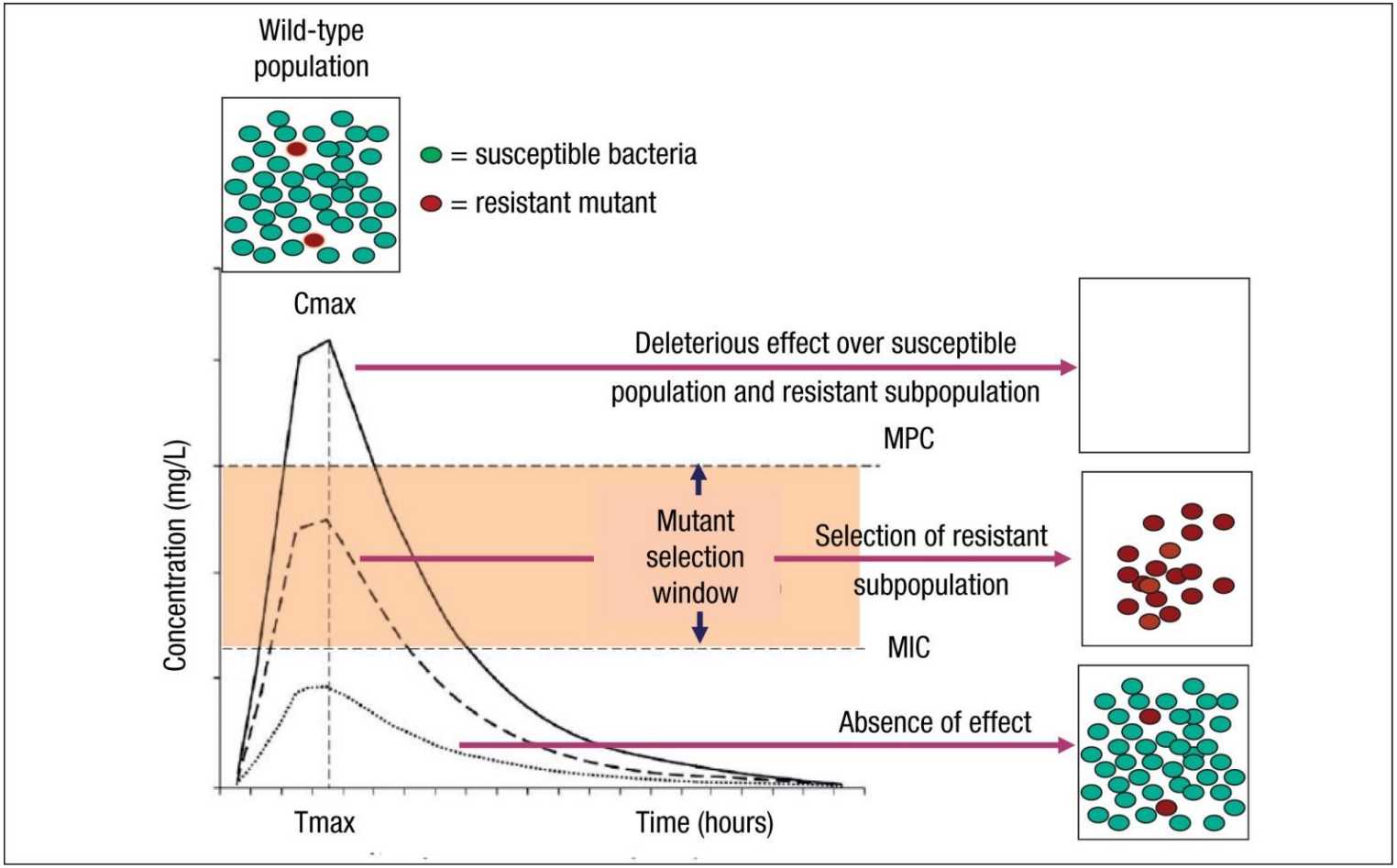
- Once-daily dosing
- equivalent dose in impaired renal function !!
- loading dose of 25–30 mg/kg (based on actual body weight)—> trough target of 15–20 mg/L

Longer duration of plasma concentration above the pathogen MIC

β-lactams

- loading dose (not affected by alterations of renal function)/rapid infusion !!
- T > MIC (60%-100%)/extended infusion !!

Χρήση ακατάλληλων αντιβιοτικών οδηγεί σε θεραπευτική αποτυχία



Inappropriate use of antibiotics in hospitals: the complex relationship between antibiotic use and antimicrobial resistance. Cantón R, et al. Enferm Infecc Microbiol Clin. 2013 Sep;31 Suppl 4:3-11

Οι ασθενείς με σήψη έχουν διαφορετικές συγκεντρώσεις αντιβιοτικών στο πλάσμα

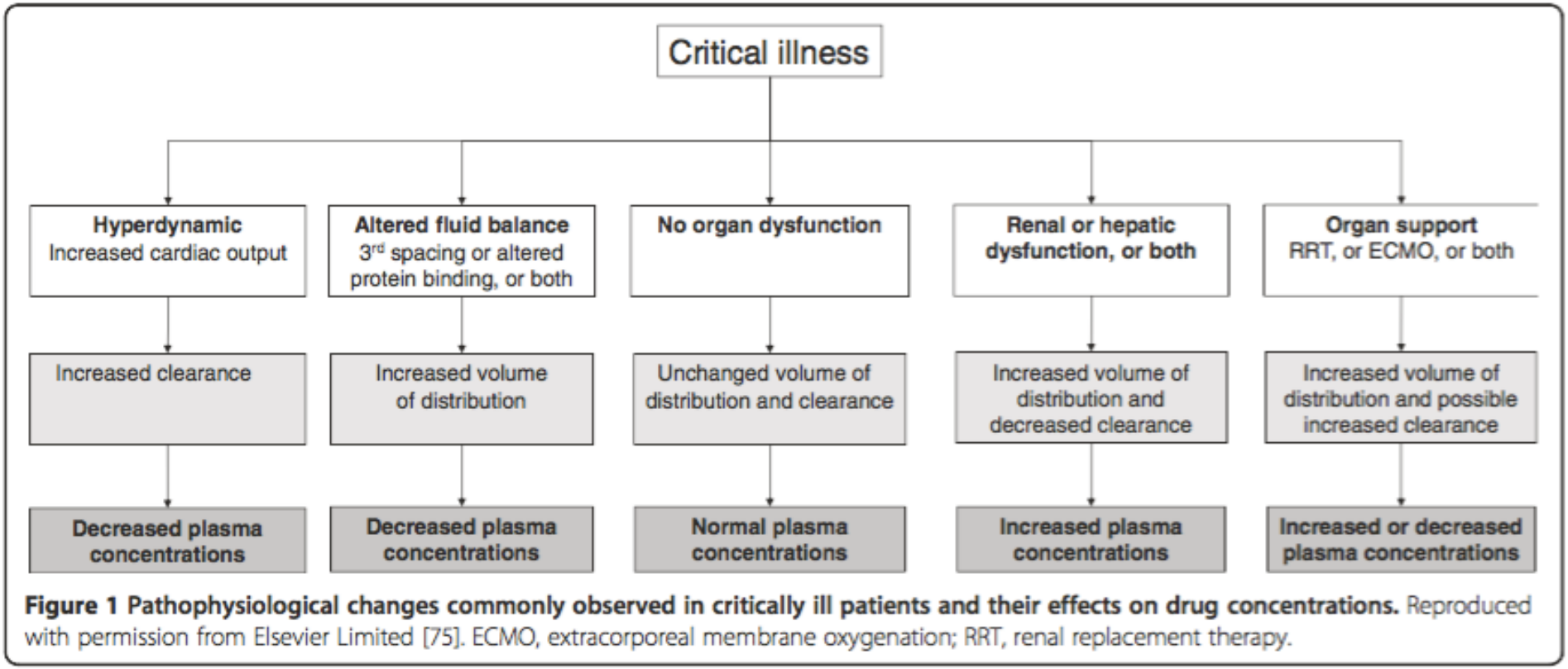


Figure 1 Pathophysiological changes commonly observed in critically ill patients and their effects on drug concentrations. Reproduced with permission from Elsevier Limited [75]. ECMO, extracorporeal membrane oxygenation; RRT, renal replacement therapy.

Surviving Sepsis Campaign

Αντιμικροβιακή Θεραπεία

- **We recommend that empiric antimicrobial therapy be narrowed once pathogen identification and sensitivities are established and/or adequate clinical improvement is noted.**
  - **(BPS)**
- **We suggest that an antimicrobial treatment duration of 7-10 days is adequate for most serious infections associated with sepsis and septic shock.**
  - **(Weak recommendation; low quality of evidence)**
- **We recommend daily assessment for de-escalation of antimicrobial therapy in patients with sepsis and septic shock.**
  - **(BPS)**
- **We suggest that measurement of procalcitonin levels can be used to support shortening the duration of antimicrobial therapy in sepsis patients.**
  - **(Weak recommendation; low quality of evidence)**

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Έλεγχος σηπτικής εστίας

- **We recommend that a specific anatomic diagnosis of infection requiring emergent source control be identified or excluded as rapidly as possible in patients with sepsis or septic shock, and that any required source control intervention be implemented as soon as medically and logistically practical after the diagnosis is made.**

(Best Practice Statement).

Τα αντιβιοτικά δεν μπορούν να διεισδύσουν σε μη-παροχετευμένα αποστήματα

- This means EARLY involvement of procedural and surgical colleagues for adequate source control:
  - E.g. inserting chest tubes for empyemas, biliary tubes for biliary obstructions, nephrostomy tubes for obstructing kidney stones, joint wash-out for septic arthritis, ex-laps for bowel perfs, etc.
- One caveat – patients much be stabilized for these procedures, which means they need to be fluid resuscitated first .
- It is also common for patients to *transiently worsen* following source control procedure (classically drainage of liver abscess) due to “stirring up infection”. Anticipate this and stay on top of it with fluids and vasopressors!
- Consider inadequate source control in a patient who fails to improve with fluids and antibiotics alone

Έλεγχος σηπτικής εστίας

- *Παροχέτευση*
  - ◊ Ενδο-κοιλιακού αποστήματος
  - ◊ Εμπυήματος θώρακα
  - ◊ Σηπτικής αρθρίτιδας
  - ◊ Εμπυήματος νεφρού
  - ◊ Χολαγγειΐτιδας
- *Χειρουργικός καθαρισμός νεκρωτικών εστιών*
  - ◊ Νεκρωτικής απονευρίτιδας
  - ◊ Νεκρωτικής παγκρεατίτιδας
  - ◊ Εντερικού εμφράκτου
  - ◊ Μεσοθωρακίτιδας

Έλεγχος σηπτικής εστίας

- *Αφαίρεση συσκευών*
  - ◊ Αγγειακοί καθετήρες
  - ◊ Ουροκαθετήρες
  - ◊ Ενδοτραχειακοί σωλήνες αποικισμένοι
  - ◊ Ενδομήτριες συσκευές επιμολυσμένες
- *Οριστική αντιμετώπιση*
  - ◊ Εκτομή εντέρου σε εκκολπωματίτιδα
  - ◊ Χολοκυστεκτομή για γαγγραινώδη χολοκυστίτιδα
  - ◊ Ακρωτηριασμός άκρου λόγω μυονέκρωσης από κλωστηρίδιο

Surviving Sepsis Campaign

Αγγειοσυσπαστικά

- **We recommend norepinephrine as the first choice vasopressor**

(strong recommendation, moderate quality of evidence).

- **We suggest adding either vasopressin (up to 0.03 U/min) or epinephrine to norepinephrine with the intent of raising MAP to target, or adding vasopressin (up to 0.03 U/min) to decrease norepinephrine dosage.**

(weak recommendation, low quality of evidence)

Pressor	Indications	Advantages	Disadvantages
Dopamine	• Dopamine is FDA indicated for all forms of shock and for treatment of decreased cardiac output • Poor cardiac function with poor perfusion • Post arrest hypotension/ myocardial stunning	• Effective at multiple receptors • Graded, dose-dependent receptor activity (not all or nothing) • Titrate to patient specific responses and hemodynamic monitoring	• "Dopaminergic" doses may improve urine output but do not improve renal function and generally are not helpful in addressing hypotension • May be arrhythmogenic at higher "alpha" doses • High doses may compromise urine output (consider using with dobutamine)
Norepinephrine **Levophed**	• Septic shock due to low SVR • Can be used in anaphylactic shock	Excellent at increasing systemic vascular resistance (SVR)	Increased risk of dysrhythmias and myocardial ischemia; increased oxygen consumption; may decrease intestinal perfusion and increase lactate levels
Phenylephrine	FDA indicated for use in hypotension	Good choice if tachycardia/arrhythmia limiting use	No effect on cardiac output
Dobutamine **Innotrex** **Dobutan**	• FDA indicated for decreased cardiac output and CHF • Best if used when there are signs/symptoms of shock without severe hypotension (< 90 mmHg)	• Inotropic agent: increases cardiac output • Good for congestive heart failure *without* hypotension	Can decrease SVR; may provoke hypotension. Potential solution: add dopamine or epinephrine to increase SVR **OR** consider switching to another class of inotropic agents, such as phosphodiesterase inhibitor (e.g., inamrinone and milrinone)
Epinephrine **Adrenaline**	• FDA indicated for use in anaphylactic shock • Intravenous form is FDA indicated for cardiac arrest	Does not require volume resuscitation prior to use (for the purely anaphylactic cause of shock)	Increased risk of dysrhythmias and myocardial ischemia
Vasopressin **Pitressin**	Consider in septic shock refractory to volume expansion and first line catecholamines	May decrease amount of other vasopressors needed	• Not a first line agent • Delayed onset of action • Its use in septic shock and for cardiac arrest are off-label

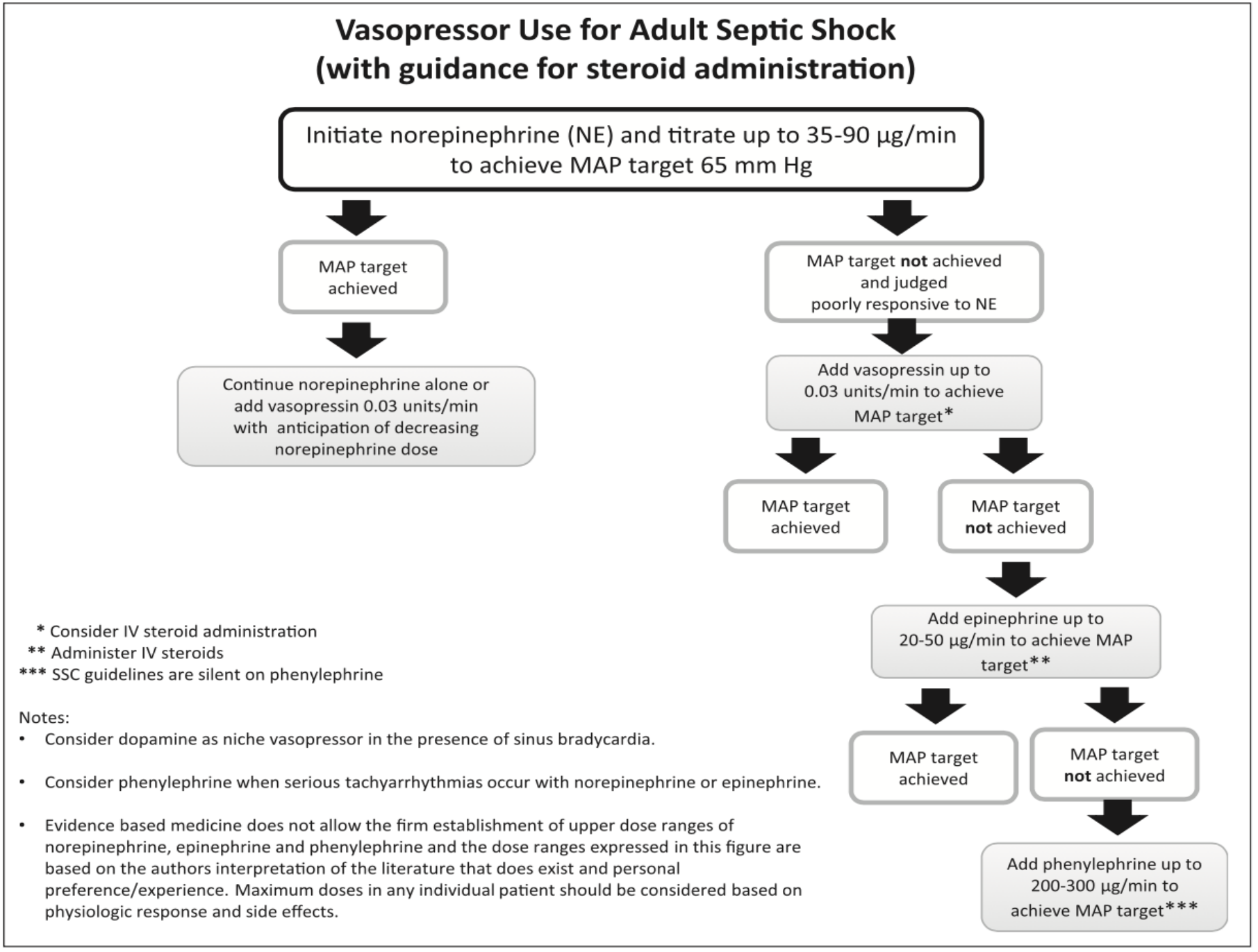

Figure 3. This figure demonstrates how the guideline recommendations on vasopressor and steroid use can be molded into a flow diagram approach to

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Αν το σοκ δεν βελτιώνεται άμεσα

- **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.**

(Best Practice Statement)

- **We suggest that dynamic over static variables be used to predict fluid responsiveness, where available.**

(Weak recommendation; low quality of evidence)

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Τα επίπεδα Γαλακτικού Οξέος μπορούν να καθοδηγήσουν την χορήγηση υγρών

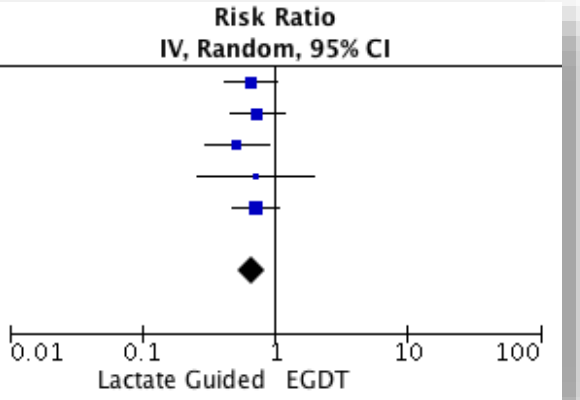
- **We suggest guiding resuscitation to normalize lactate in patients with elevated lactate levels as a marker of tissue hypoperfusion.**

(Weak recommendation; low quality of evidence)

Study or Subgroup	Lactate Guided Events	Total	Standard Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Year
Jansen, 2010	20	68	30	67	24.9%	0.66 [0.42, 1.03]	2010
Jones, 2010	25	150	34	150	23.8%	0.74 [0.46, 1.17]	2010
Tian, 2012	14	43	12	19	16.9%	0.52 [0.30, 0.89]	2012
Yu, 2013	5	25	7	25	5.1%	0.71 [0.26, 1.95]	2013
Lyu 2015	20	50	28	50	29.2%	0.71 [0.47, 1.09]	2015
Total (95% CI)		**336**		**311**	**100.0%**	**0.67 [0.53, 0.84]**	
Total events	84		111				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.14$, df = 4 (P = 0.89); $I^2 = 0\%$

Test for overall effect: Z = 3.51 (P = 0.0004)



Society of Critical Care Medicine
The Intensive Care Professionals

ESICM
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Κορτικοστεροειδή

1. **We suggest against using intravenous hydrocortisone to treat septic shock patients if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability. If this is not achievable, we suggest intravenous hydrocortisone at a dose of 200 mg per day.**

SoluCortef

(Weak recommendation; low quality of evidence)

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Έλεγχος Σακχάρου Αίματος

1. **We recommend a protocolized approach to blood glucose management in ICU patients with sepsis, commencing insulin dosing when 2 consecutive blood glucose levels are >180 mg/dL. This approach should target an upper blood glucose level ≤180 mg/dL rather than an upper target blood glucose ≤110 mg/dL. (Strong recommendation; high quality of evidence)**
2. **We recommend that blood glucose values be monitored every 1 to 2 hrs until glucose values and insulin infusion rates are stable, then every 4 hrs thereafter in patients receiving insulin infusions. (BPS)**

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Έλεγχος Σακχάρου Αίματος

3. We recommend that glucose levels obtained with point-of-care testing of capillary blood be interpreted with caution, as such measurements may not accurately estimate arterial blood or plasma glucose values. (BPS)

4. We suggest the use of arterial blood rather than capillary blood for point of care testing using glucose meters if patients have arterial catheters. (Weak recommendation; low quality of evidence)

Μηχανικός Αερισμός

- **We suggest using lower tidal volumes over higher tidal volumes in adult patients with sepsis-induced respiratory failure without ARDS.**
  - **(Weak recommendation; low quality of evidence)**

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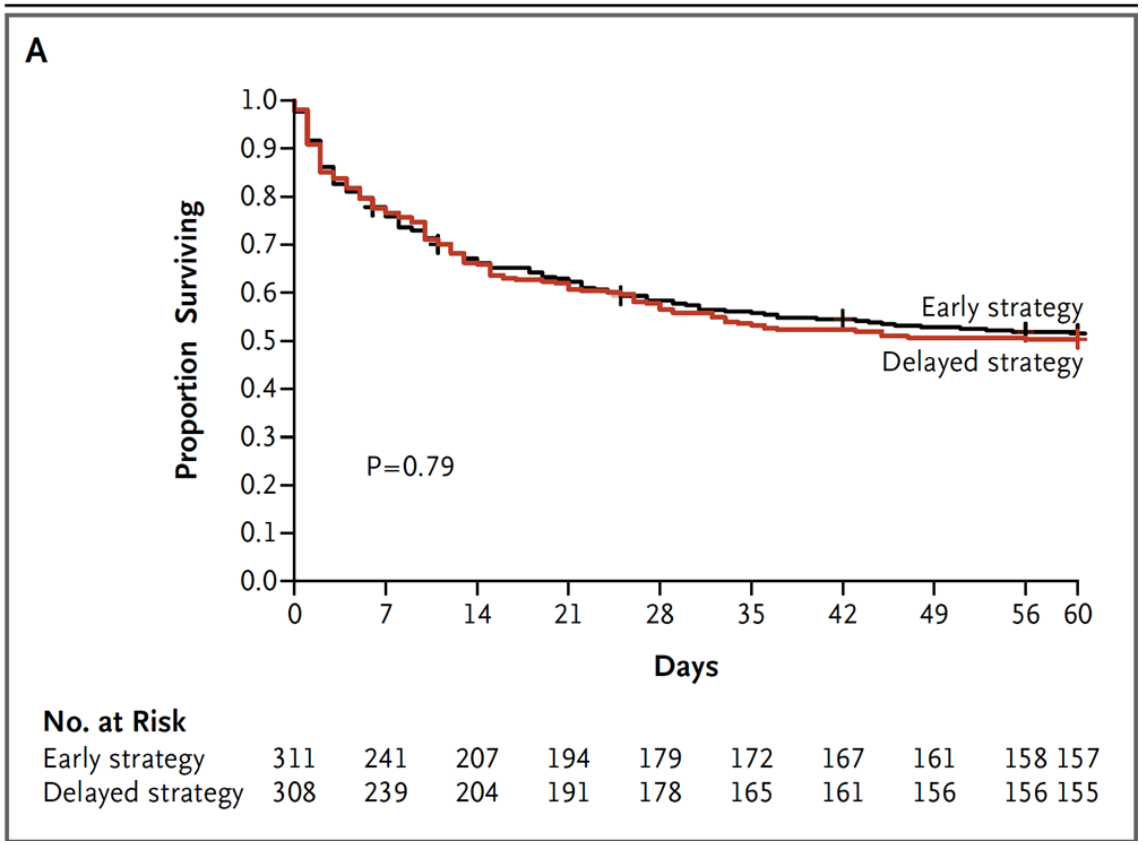
Θεραπεία νεφρικής υποκατάστασης

- **We suggest against the use of renal replacement therapy in patients with sepsis and acute kidney injury for increase in creatinine or oliguria without other definitive indications for dialysis.**
  - **(Weak recommendation; low quality of evidence)**

Πρώιμη vs Όψιμη έναρξη νεφρικής υποκατάστασης σε ασθενείς με σήψη



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Θρέψη

- **We recommend against the administration of early parenteral nutrition alone or parenteral nutrition in combination with enteral feedings (but rather initiate early enteral nutrition) in critically ill patients with sepsis or septic shock who can be fed enterally. (Strong recommendation; moderate quality of evidence)**

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Θρέψη

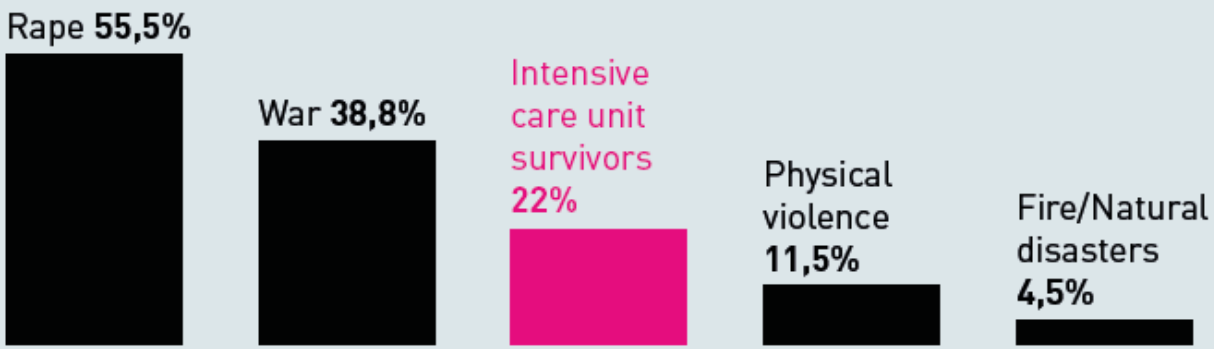
- **We recommend against the administration of parenteral nutrition alone or in combination with enteral feeds (but rather to initiate IV glucose and advance enteral feeds as tolerated) over the first 7 days in critically ill patients with sepsis or septic shock in whom early enteral feeding is not feasible. (Strong recommendation; moderate quality of evidence).**

Τα προβλήματα των ασθενών με σήψη δεν τελειώνουν με την έξοδο από την ΜΕΘ

Possible post-sepsis symptoms are:

_Neuromuscular weakness
_Chronic pain
_Post-traumatic stress disorder
_Cognitive impairment
_Depression

Incidence of post-traumatic stress disorder[1]



Sepsis accounts for 50–60 % of ICU cases.[1]

Other symptoms can include:

- Sleep disturbance, including insomnia
- Extreme tiredness and fatigue
- Inability to concentrate
- Loss of confidence and self-belief

1_ Kessler RC, Sonnega A, Bromet E, et al.: Posttraumatic stress disorder in the National Comorbidity Survey. Arch Gen Psychiatry, 52: 1048–60, 1995. // Davydow DS, Gifford JM, Desai SV, et al.: Posttraumatic stress disorder in general intensive care unit survivors: a systematic review. Gen Hosp Psychiatry, 30: 421-434, 2008.


QUESTIONS?