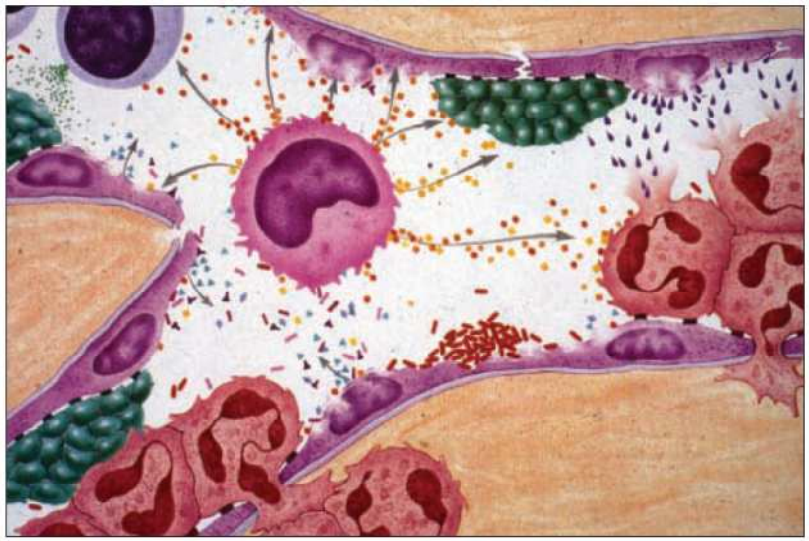
Journal Club del Venerdì

REVISIONE DEI CRITERI DIAGNOSTICI PER LA SEPSI



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Dipartimento Medicina e Riabilitazione
Istituto Clinico Sant'Anna - Brescia

Brescia, 24 Novembre 2017

68° CONGRESSO NAZIONALE SIGG
NAPOLI2017
29 novembre - 2 dicembre
INVECCHIAMENTO: SCENARIO 2.0

Venerdì 1 Dicembre 2017

17:15—18:45 **SIMPOSIO**

SEPSIS IN OLDER ADULTS

Moderatori: Amato De Paulis (Napoli), Fabio Di Stefano (Verbania)

Fisiopatologia della sepsi e nuove Guidelines SEPSIS 3: criticità, rivisitazione e loro impatto e conseguenze
Luca Laghi (Birmingham)

Presentazione clinica negli anziani ed organi bersaglio
Ciro Paolillo (Udine)

Sepsi e shock settico degli anziani in Pronto Soccorso
Antonio Cherubini (Ancona)

Sepsis non batterica e biomarkers della infezione
Giovanni Ricevuti (Pavia)

Patogeni coinvolti, antibioticoterapia e strategie antimicrobiche
Piero Marone (Pavia)

Discussione e indicazioni linee guida

Highlights

- Sepsis definition
- Sepsis: epidemiology, pathophysiology, diagnosis
- Sepsis: a new definition
- Treatment guidelines: Early Goal Directed Therapy (EGDT) and the Surviving Sepsis Campaign

Definition

Clinical Review & Education

Special Communication | CARING FOR THE CRITICALLY ILL PATIENT

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

Mervyn Singer, MD, FRCP; Clifford S. Deutschman, MD, MS; Christopher Warren Seymour, MD, MSc; Manu Shankar-Hari, MSc, MD, FFICM; Djillali Annane, MD, PhD; Michael Bauer, MD; Rinaldo Bellomo, MD; Gordon R. Bernard, MD; Jean-Daniel Chiche, MD, PhD; Craig M. Coopersmith, MD; Richard S. Hotchkiss, MD; Mitchell M. Levy, MD; John C. Marshall, MD; Greg S. Martin, MD, MSc; Steven M. Opal, MD; Gordon D. Rubenfeld, MD, MS; Tom van der Poll, MD, PhD; Jean-Louis Vincent, MD, PhD; Derek C. Angus, MD, MPH

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

Definition

In the early 1990s, a consensus statement was developed by the American College of Chest Physicians and the Society of Critical Care Medicine (SCCM) that defined

Systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, and septic shock in terms of both clinical and laboratory abnormalities, emphasizing a continuum of acute inflammation and organ dysfunction.

: *BMJ* 2016;353:i1585

Definition

Revised modestly in 2001, these definitions have formed the basis of the past quarter century of research into sepsis and catalyzed the evolution of its clinical recognition and management, and the design of clinical trials.

However, the sensitivity and specificity of SIRS criteria have been questioned, as has the contention that SIRS, sepsis, severe sepsis, and septic shock occur along a continuum rather than as discrete clinical entities.

: *BMJ* 2016;353:i1585

Definition

In February 2016, the European Society of Intensive Care Medicine and the SCCM published new consensus definitions of sepsis and related clinical criteria (Sepsis-3).

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

Definition

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Septic shock	Sepsis with persistent hypotension after fluid resuscitation
REVISED DEFINITIONS	
Sepsis	Life threatening organ dysfunction* caused by a dysregulated host response to infection
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JAMA. 2016;315(8):801-810. doi:10.1001/jama.2016.0287

thebmj

STATE OF THE ART REVIEW

Sepsis: pathophysiology and clinical management

Jeffrey E Gotts, Michael A Matthay

: *BMJ* 2016;353:i1585

Epidemiology

Over the past 40 years the incidence of severe sepsis has substantially increased, partly because of the increasing age of the population.

The latest estimates in the United States, Europe, and the United Kingdom range between

0,4/1000 and 1/1000 of the population.

Remarkably, in-hospital mortality for patients with sepsis during this period has decreased from 28 to 18%.

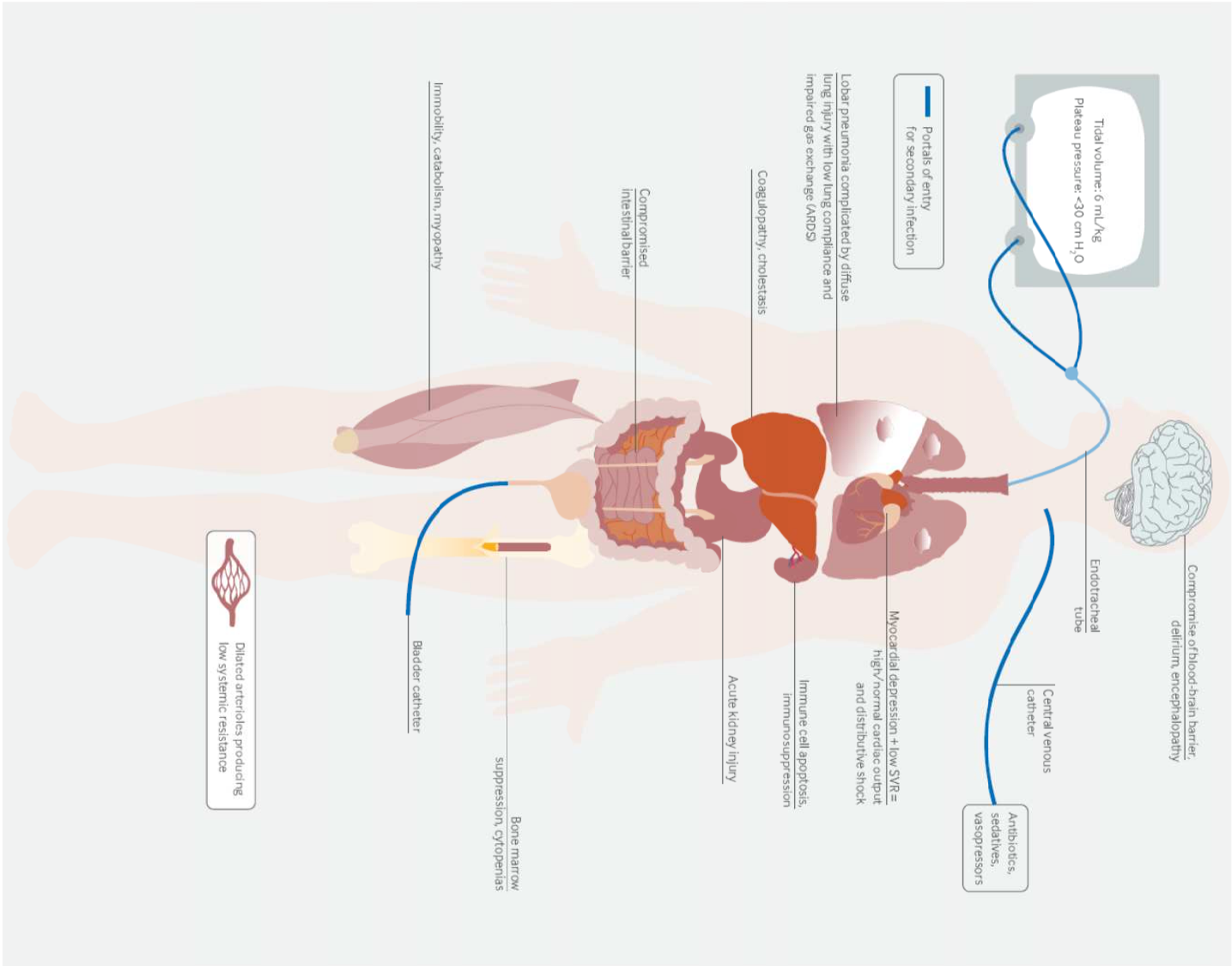
Using objective definitions of acute organ dysfunction, severe sepsis in patients admitted to the ICU was estimated to increase from 7,2% to 11,1% during the study period.

At the same time, hospital mortality in severe sepsis declined from 35% to 18%.

Epidemiology

Organism	Western Europe	Eastern Europe	Central/ South America	North America	Oceania	Africa	Asia
Staphylococcus aureus/MRSA	20/9	22/10	19/11	27/18	28/9	30/20	16/10
Staphylococcus epidermidis	11	12	9	12	8	15	9
Streptococcus pneumoniae	5	5	3	4	3	6	2
VSE	9	10	2	5	4	0	4
VRE	4	5	2	5	5	0	2
Escherichia coli	17	15	14	14	13	11	17
Enterobacter spp	7	8	9	8	3	7	5
Klebsiella spp	10	21	16	9	12	19	21
Pseudomonas spp	17	29	26	13	15	15	29
Acinetobacter spp	6	17	14	4	4	15	19
ESBL producing GNR	2	2	3	0	0	2	3
Anaerobes	5	3	1	8	3	2	3
Candida spp	19	19	13	18	13	11	16
Aspergillus spp	2	0	0	3	2	0	1
Parasites	1	1	1	1	1	0	1

Pathophysiology



Pathophysiology

- **the cardiovascular system** undergoes major perturbations.
- Use of pulmonary arterial catheters in the 1980s, it became clear that after intravascular volume is restored, most patients with sepsis have a normal or raised cardiac output with low systemic vascular resistance.
- The preservation or enhancement in cardiac output occurs despite acute biventricular dysfunction that can last longer than a week

: *BMJ* 2016;353:i1585

Pathophysiology

- Increased **lactate** in these patients predicts mortality.
- This has traditionally been thought to reflect tissue hypoxia as a result of hypoperfusion

- In sepsis, profound alterations to the **endothelium** occur, including increased leukocyte adhesion, a shift to a procoagulant state, vasodilation, and loss of barrier function, which all lead to widespread tissue edema

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Pathophysiology

- Widespread tissue factor expression, fibrin deposition, and impaired anticoagulant mechanisms (including activated protein C) can produce **disseminated intravascular coagulation** (DIC)

- The endothelial changes in severe sepsis are associated with altered barrier function in other organs.

: *BMJ* 2016;353:i1585

Pathophysiology

- More permeable lung capillaries result in the accumulation of protein-rich edema fluid in the **interstitial spaces of the lung**, and in the presence of sepsis induced alveolar epithelial barrier dysfunction, the interstitial edema fluid floods into the alveoli.
- These changes result in perfusion-ventilation mismatch, arterial hypoxemia, and reduced lung compliance: ARDS.

: *BMJ* 2016;353:i1585

Pathophysiology

- **Gut epithelium** becomes more permeable in the setting of hypercytokinemia.
- This increased permeability sets in motion a vicious cycle of bacterial translocation, gut injury by luminal contents including activated pancreatic enzymes (autodigestion)

: *BMJ* 2016;353:i1585

Pathophysiology

- **Acute kidney injury (AKI)** is common in severe sepsis and substantially increases the risk of death

- The **nervous system** is not simply an injured bystander in severe sepsis but an active participant in its early development, playing mostly an anti-inflammatory role.

: *BMJ* 2016;353:i1585

Pathophysiology

- **Encephalopathy** is an early and common clinical finding in severe sepsis that can range from mildly impaired concentration to deep coma.

- **Delirium**, as assessed by the confusion assessment method (CAM)-ICU method, is very common in ventilated patients, and it is independently associated with mortality and long lasting neurocognitive deficits

: *BMJ* 2016;353:i1585

Pathophysiology

- Coincident **hepatic and renal dysfunction** exacerbate toxin influx into the CNS.
- In addition, coagulopathy and impaired autoregulation of cerebral blood flow can together produce areas of ischemia and hemorrhage.

: *BMJ* 2016;353:i1585

Inflammatory system

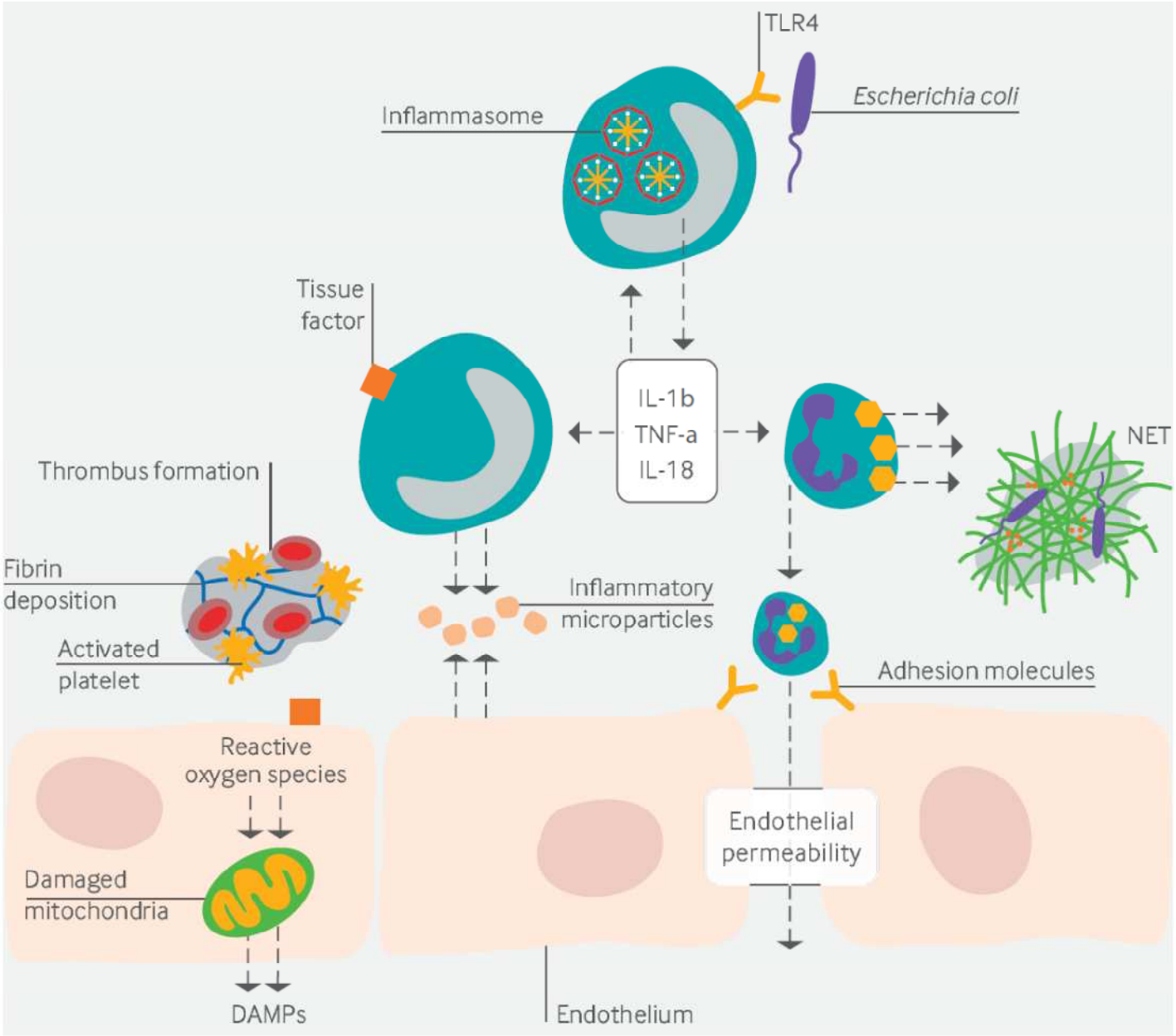

Fig 4| The self reinforcing pathophysiologic processes involved in sepsis. Endothelial injury results in activation of monocytes and granulocytes, endothelial barrier breakdown, immunothrombosis, and disseminated intravascular coagulation. DAMPs= damage associated molecular patterns; IL= interleukin; TLR4= Toll-like receptor 4; TNF-α=tumor necrosis factor α

Pathophysiology

- Septic organ dysfunction often **perpetuates critical illness** in a **self reinforcing** manner through several pathways:
- ARDS often requires **mechanical ventilation**, which itself can further injure the lungs and enhance systemic inflammation
- **Sedatives** needed for ventilation can worsen septic associated encephalopathy and delirium, leading to reduced mobility, worsened catabolism, severe **neuromuscular weakness**
- Intestinal barrier dysfunction causes ongoing systemic translocation of pathogenic organisms and **impaired nutritional** status

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SIRS

SINDROME di RISPOSTA INFIAMMATORIA SISTEMICA

Risposta infiammatoria sistemica
a VARIE TIPOLOGIE di grave insulto clinico

Due o più dei seguenti segni e sintomi

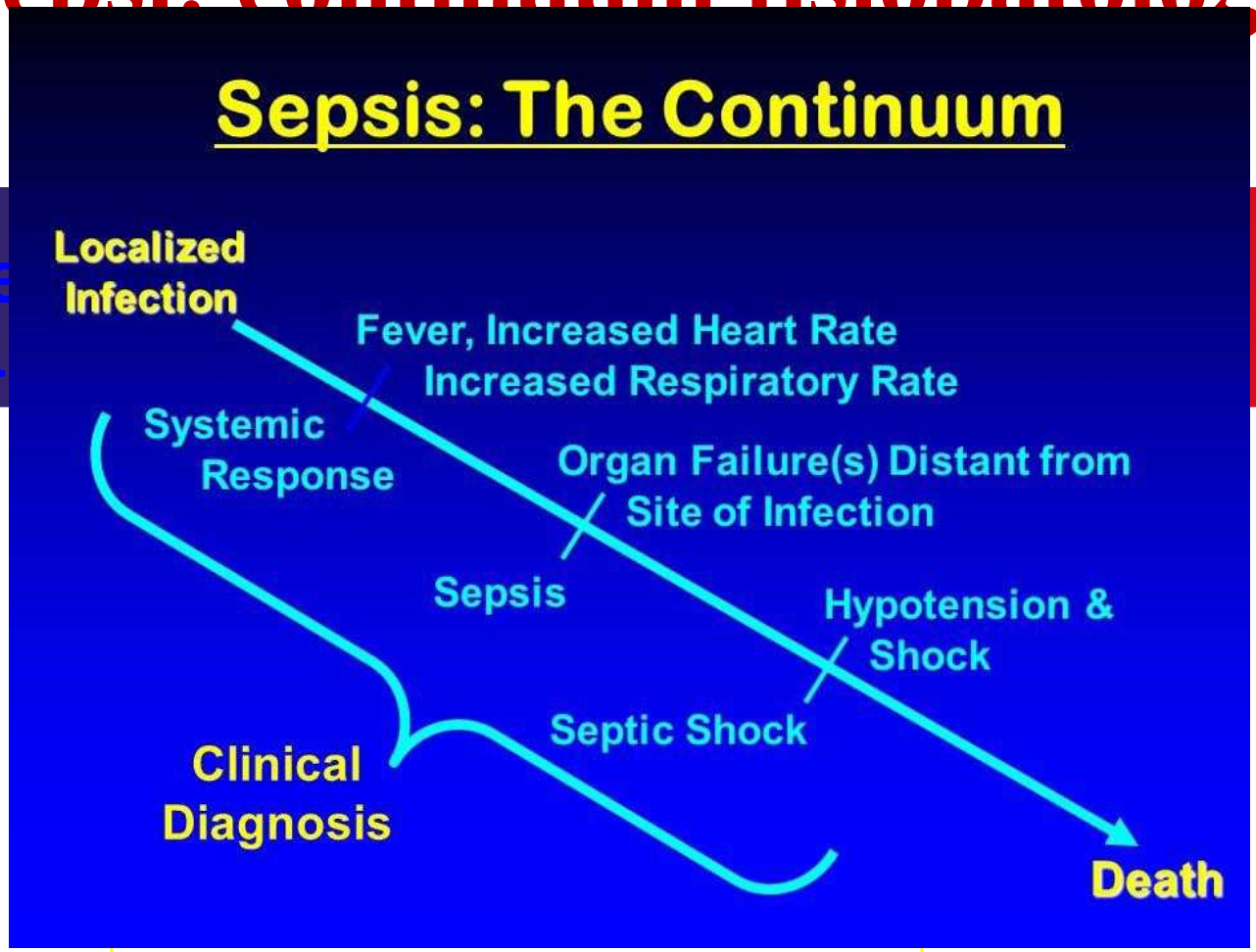
- **Temperatura >38°C o <36°C**
- **frequenza cardiaca >90 bpm**
- **Frequenza respiratoria >20 atti/min o $PaCO_2$<32 mm Hg**
- **Leucociti >12.000/mm^3 o <4.000/mm^3 oppure >10% forme immature**

ACCP/SCCM CONSENSUS CONFERENCE. Chest, 1992;101(6):1644-55

SEPSI

SIRS + infezione accertata (documentata microbiologicamente) o sospettata clinicamente

Sepsi: continuum fisiopatologico



-Acidosi metabolica (aumento dei lattati)

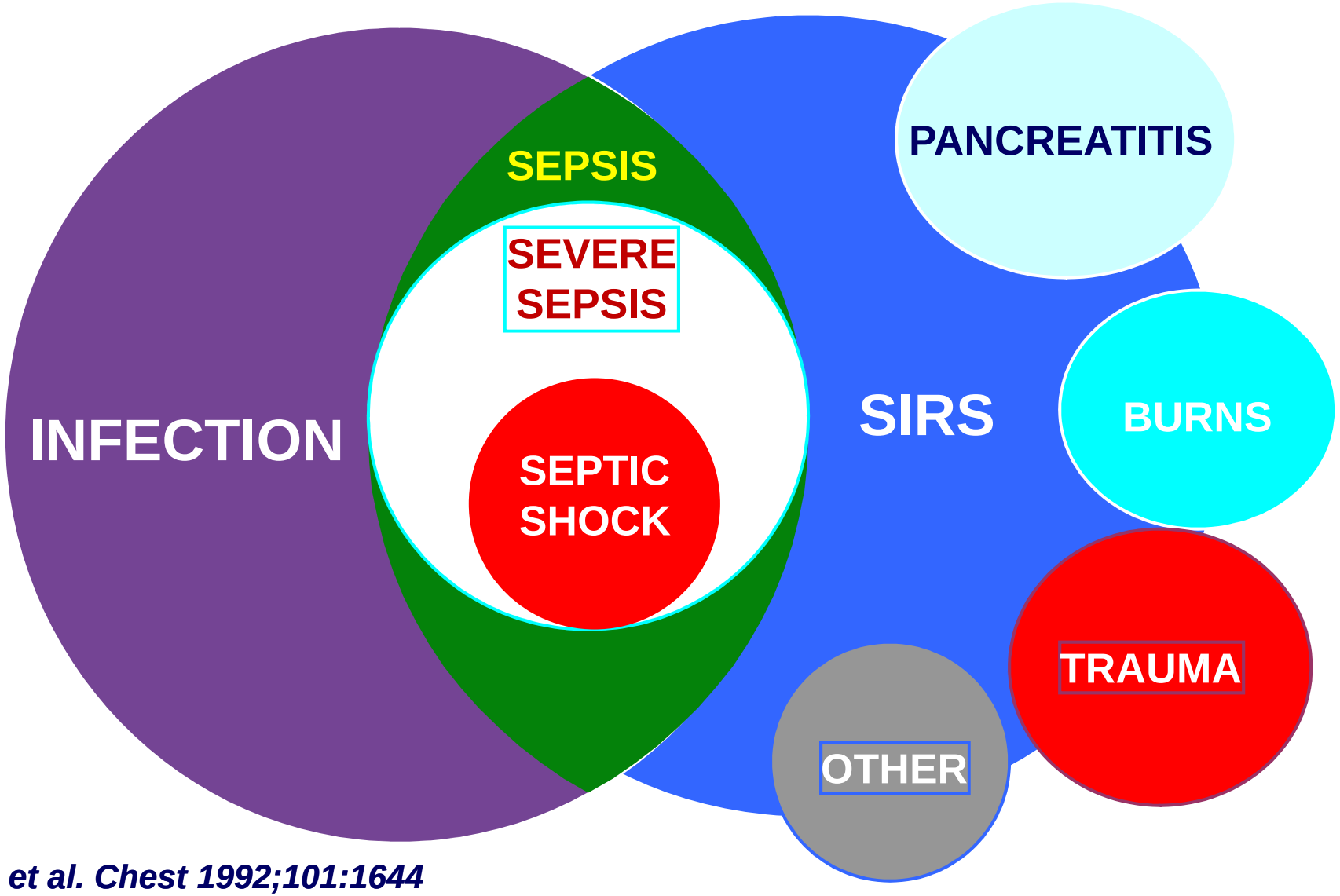
Bone et al. Chest 1992;101:1644; Wheeler and Bernard. N Engl J Med 1999;340:207

SEPTIC SHOCK

" …a state of **acute circulatory failure** characterized by persistent arterial hypotension unexplained by other causes. Hypotension is defined by a systolic arterial pressure below 90 mmHg, a mean arterial pressure < 60, or a reduction in systolic blood pressure of > 40 mmHg from baseline, despite adequate volume resuscitation…"

2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference

Relationship Of Infection, SIRS, Sepsis Severe Sepsis and Septic Shock



Bone et al. Chest 1992;101:1644

La terza definizione della sepsi: Luci ed Ombre

JAMA The Journal of the American Medical Association

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

Mervyn Singer, MD, FRCP[1]; Clifford S. Deutschman, MD, MS[2]; Christopher Warren Seymour, MD, MSc[3]; Manu Shankar-Hari, MSc, MD, FFICM[4]; Djillali Annane, MD, PhD[5]; Michael Bauer, MD[6]; Rinaldo Bellomo, MD[7]; Gordon R. Bernard, MD[8]; Jean-Daniel Chiche, MD, PhD[9]; Craig M. Coopersmith, MD[10]; Richard S. Hotchkiss, MD[11]; Mitchell M. Levy, MD[12]; John C. Marshall, MD[13]; Greg S. Martin, MD, MSc[14]; Steven M. Opal, MD[12]; Gordon D. Rubenfeld, MD, MS[15,16]; Tom van der Poll, MD, PhD[17]; Jean-Louis Vincent, MD, PhD[18]; Derek C. Angus, MD, MPH[19,20]

LIMITI DELLA PRECEDENTE DEFINIZIONE:

Ad amplificare la risposta all' infezione nella sepsi concorrono:

- **fattori endogeni (età, sesso, razza, comorbilità, determinanti genetici)**
- **Fattori esogeni (caratteristiche del patogeno)**

Segue attivazione pro- ed antinfiammatoria, m**odificazioni cardiovascolari, neuronali, ormonali, metabolici ed altre modificazioni non immunologiche.**

1) **I criteri SIRS :**
   - **focalizzano solo sull'infiammazione sistemica**
   - **1/8 con sepsi non mostrano SIRS**
   - **aspecifici riscontrabili anche in altri tipi di insulto**

2) **I pazienti affetti mostrano eterogeneità clinica e biologica non ben definita dalla definizione sepsi I-II**

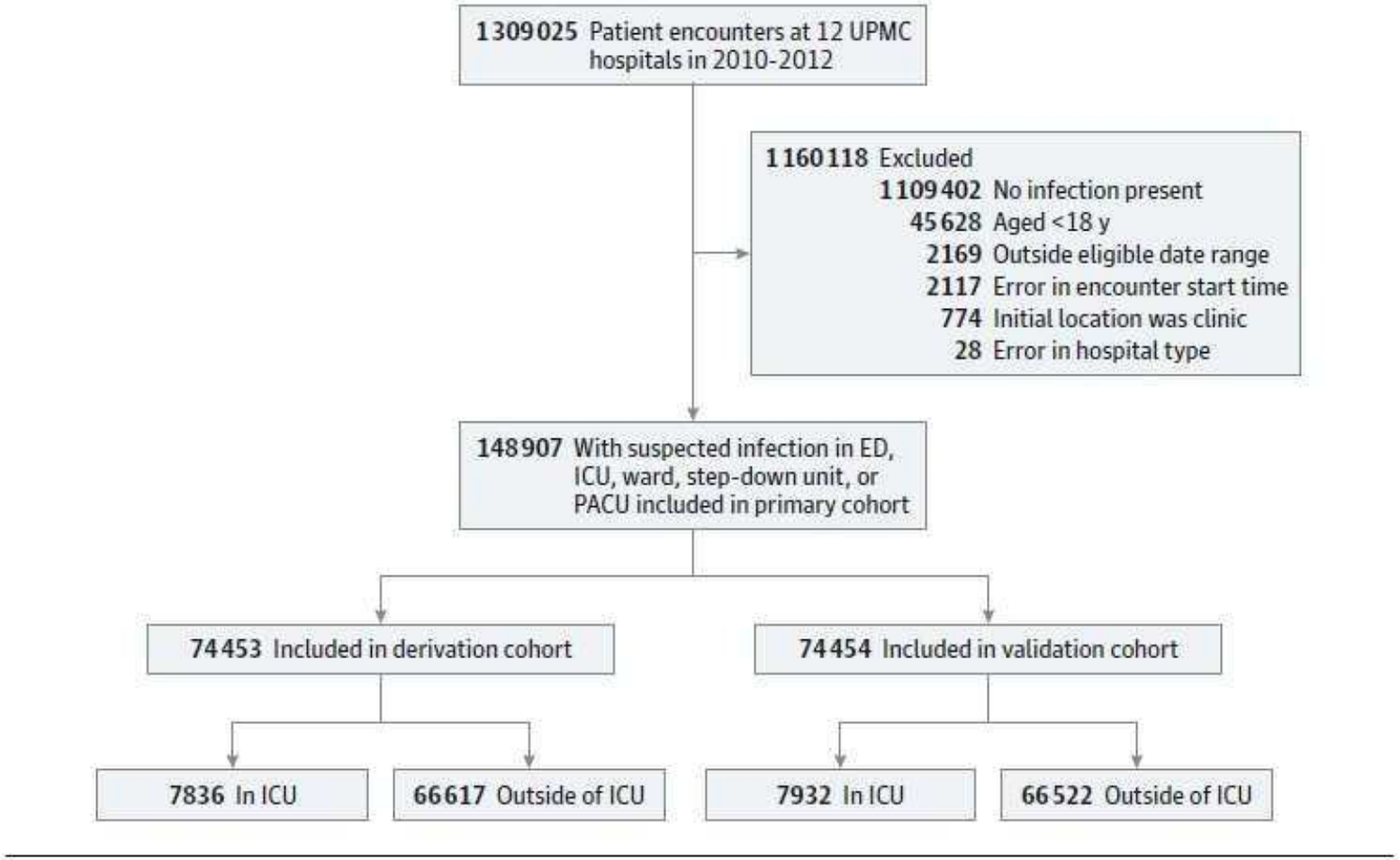
Study Design, Setting, and Population

A retrospective cohort study was performed among adult encounters (age ≥18 years) with suspected infection. The primary cohort was all hospital encounters from 2010 to 2012 at 12 community and academic hospitals in the UPMC health care

Summary of Data Sets

Characteristics	UPMC[a]	KPNC	VA	ALERTS	KCEMS
Years of cohort	2010-2012	2009-2013	2008-2010	2011-2012	2009-2010
No. of hospitals	12	20	130	1	14
Total No. of encounters	1 309 025	1 847 165	1 640 543	38 098	50 727
Data source and study design	Retrospective study of EHRs	Retrospective study of EHRs	Retrospective study of EHRs	Prospective cohort study	Retrospective study of administrative records
Setting	Integrated health system in southwestern Pennsylvania	Integrated health system in northern California	All hospitals in the US VA system	Single university hospital, Jena, Germany	Out-of-hospital records from integrated emergency medical services system in King County, Washington
Definition of suspected infection	Combination of body fluid culture and nonprophylactic antibiotic administration in the EHR[b]	Combination of body fluid culture and nonprophylactic antibiotic administration in the EHR[b]	Combination of body fluid culture and nonprophylactic antibiotic administration in the EHR[b]	CDC criteria for hospital-acquired infections[c]	*ICD-9-CM* codes for infection, with present-on-admission indicators[d]
No. with suspected infection (% of total)	148 907 (11)	321 380 (17)	377 325 (23)	1186 (3)	6508 (13)
Location at onset of infection, No. (%) infected					
Intensive care unit	15 768 (11)	7031 (2)	73 264 (19)	300 (25)	0
Outside of intensive care unit	133 139 (89)	314 349 (98)	304 061 (81)	886 (75)	6508 (100)
In-hospital mortality, No. (%) infected[e]	6347 (4)	16 092 (5)	22 593 (6)	210 (18)	700 (11)

Accrual of Encounters for Primary Cohort



What clinical criteria to study

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)[a] (Range, 0-22 Points)
Respiratory rate, breaths per minute	Pao_2/Fio_2 ratio	Pao_2/Fio_2 ratio
White blood cell count, $10^9/L$	Glasgow Coma Scale score	Glasgow Coma Scale score
Bands, %	Mean arterial 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

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.

La terza definizione della sepsi: Luci ed Ombre

DEFINIZIONE SEPSIS-III: **La sepsi è una disfunzione d'organo potenzialmente fatale causata da una sregolata risposta dell'ospite ad un infezione**

Abolito il concetto di SIRS e sepsi severa

la sepsi è una condizione severa per definizione

La disfunzione d'organo può essere definita come cambiamento acuto ≥ 2 punti rispetto al basale del SOFA score (Sequential Organ Failure Assessment Score)

(sofa >2 = mortalità 10%)

Enfatizza il concetto di risposta non omeostatica

Infezione ≠ Sepsi

Criteri Diagnostici SEPSIS III:

Infezione sospetta + SOFA ≥2

SOFA: score disfunzione organo:

- **Respirazione: P/F**
- **Coagulazione: PLT**
- **Fegato: Bilirubina**
- **Cardiovascolare: MAP e vasopressori**
- **SNC: GCS**
- **Rene: Creatinina e Diuresi**

12% sepsi occulte (1/8 pz)

criteri SIRS non adeguati

Nuova Definizione di Shock Settico

Shock Settico III: Sottotipo di sepsi in cui le alterazioni del metabolismo cellulare e circolatorie sono tali da aumentarne la mortalità

La task force 2016 vuole:
ampliare la visione rispetto al passato concetto di "Circulatory failure" del 2001 per differenziarlo dagli altri tipi di shock

Ipotensione + lact >2+ vasopressore	→ mortalità 42-50%
Solo Ipotensione	→ mortalità 18-25%
Solo Lact >2 (cryptic shock)	→ mortalità 6.8-18%
Solo Sepsi con disfunzione d'organo	→ mortalità 20%

Modificato da Shankar-Hari et al. JAMA 02-2016

Criteri Diagnostici Shock Settico

Necessità di terapia vasopressoria per mantenere una pressione arteriosa media ≥ 65mmHg

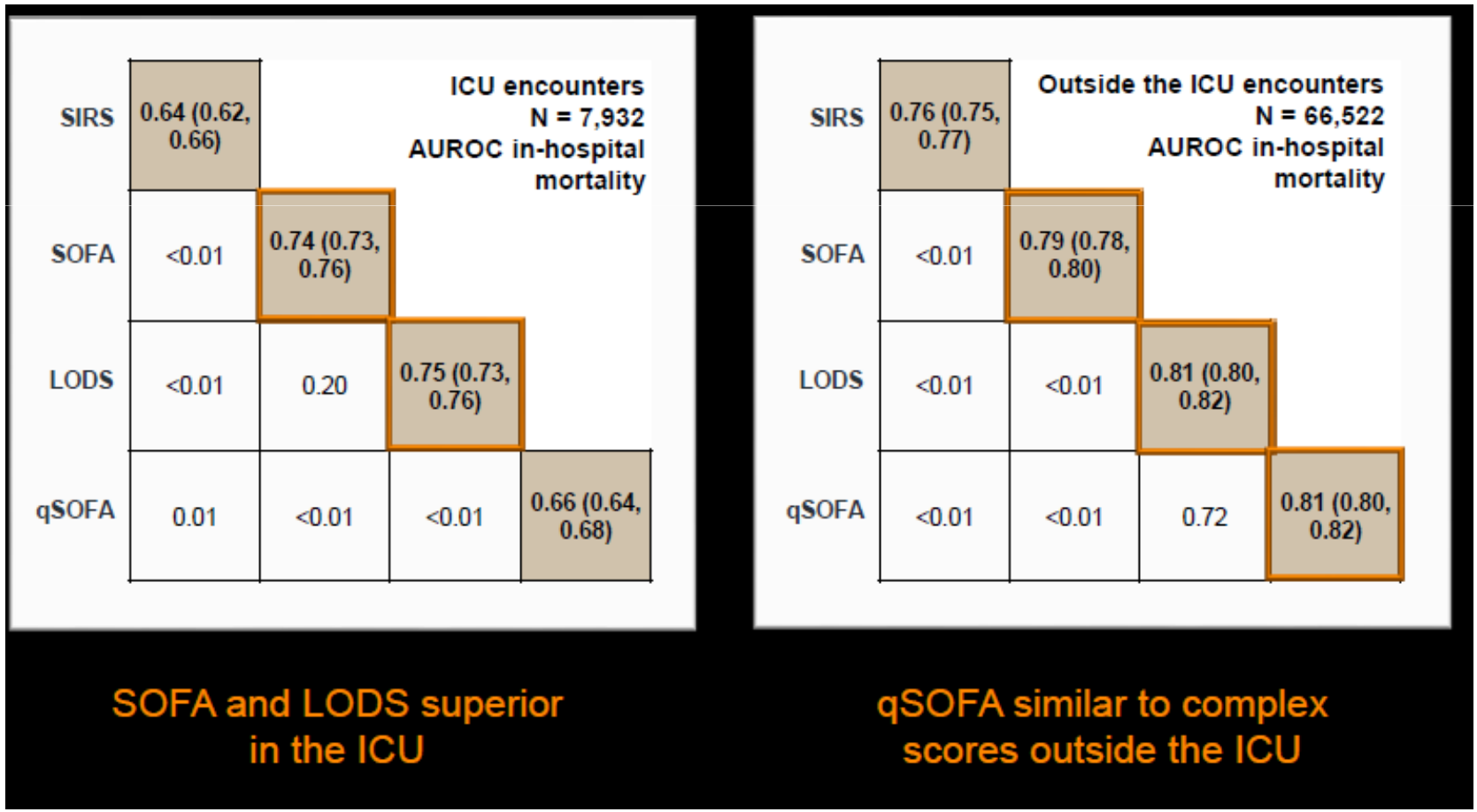
SEPSI +
- **PAM < 65 mmHg**
- **Lact > 2 mmol/L**
- **Bisogno di Vasopressore**

Which score to use !!

- "The SOFA score found patients more likely to be septic both in and out of the ICU. But it involves the use of many lab tests and is a bit complex.

- For patients not in the ICU, the performance of Quick SOFA score was similar to that of the sequential organ failure assessment score.

Area Under the Receiver Operating Characteristic Curve and 95%Confidence Intervals for In-Hospital Mortality of Candidate Criteria (SIRS, SOFA, LODS, and qSOFA) Among Suspected Infection Encounters in the UPMC Validation Cohort (N = 74 454)



Box 4. qSOFA (Quick SOFA) Criteria

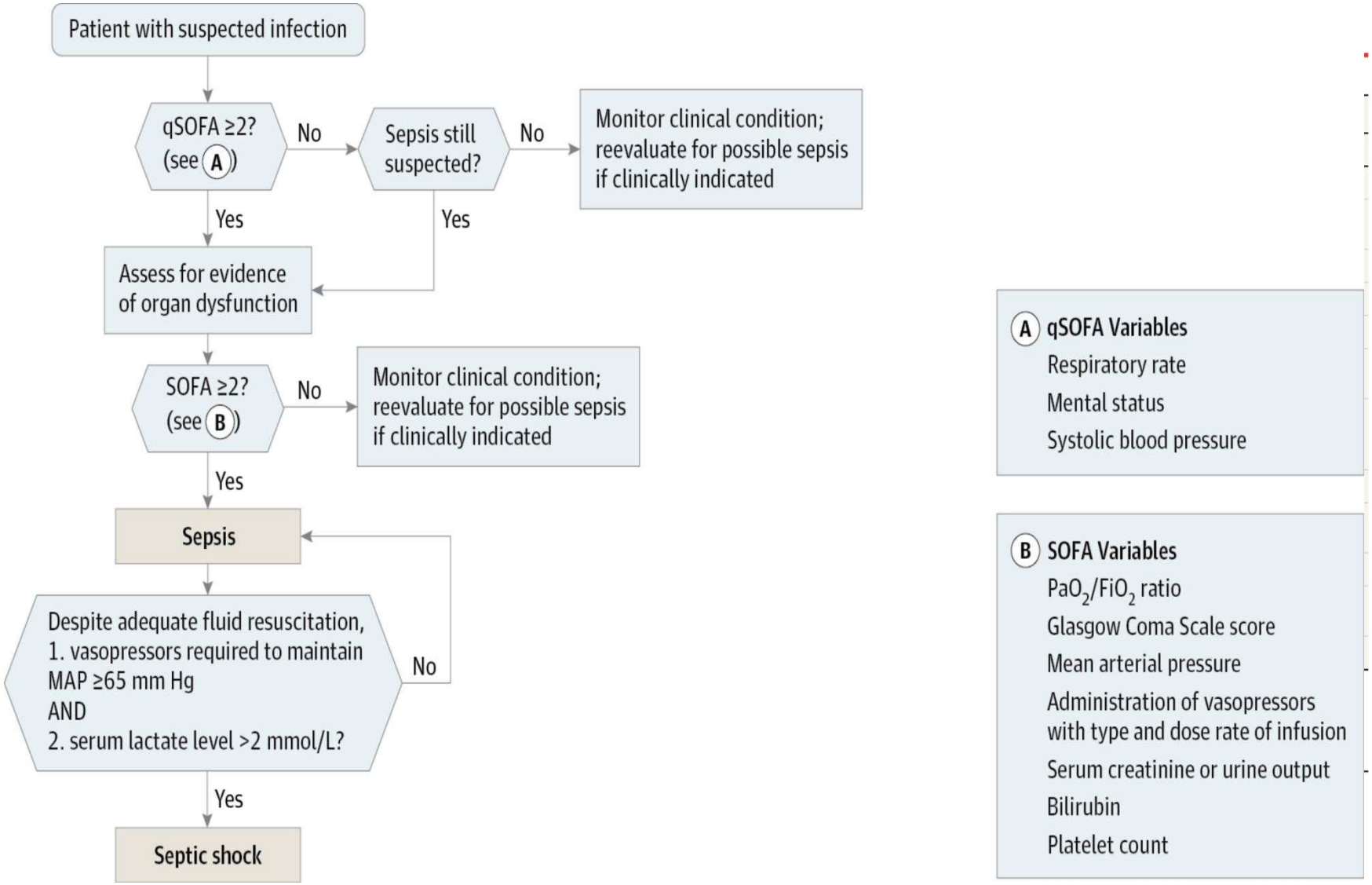
Respiratory rate ≥22/min

Altered mentation

Systolic blood pressure ≤100 mm Hg

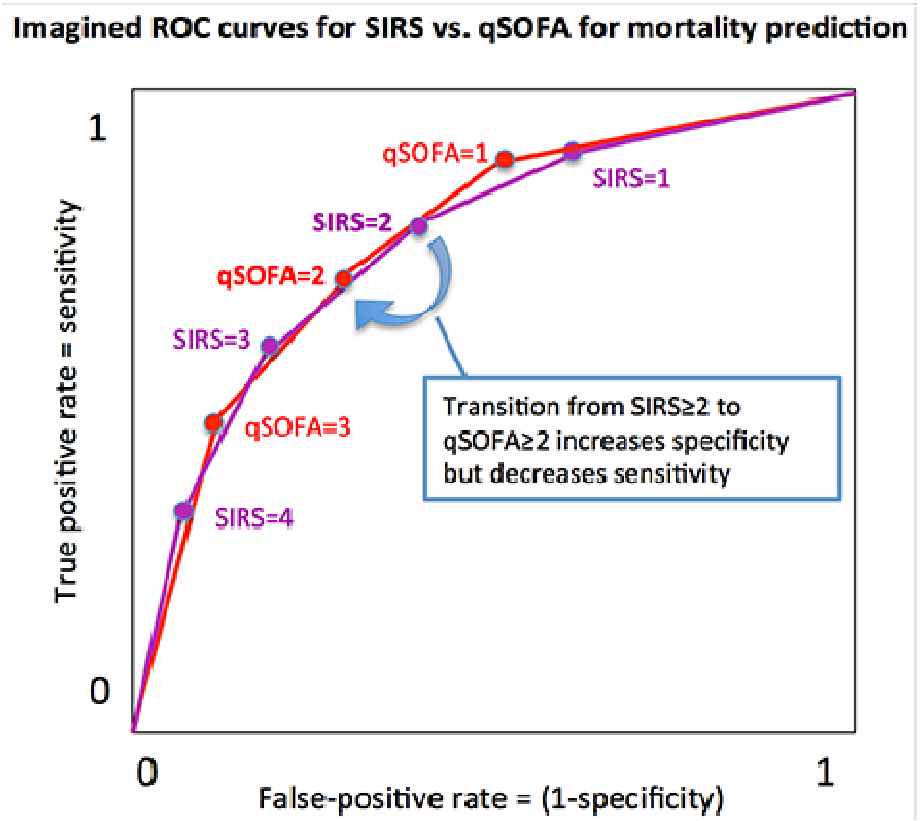
JAMA. 2016;315(8):801-810. doi:10.1001/jama.2016.0287

qSOFA SOFA ed Algoritmo Diagnostico



Il dibattito è aperto…

1) Il sospetto d'infezione resta soggettivo
2) SEPSI-III è meno specifica per infezione rispetto a SEPSI II ("mancano" criteri SIRS)
3) I criteri SIRS criticati per ipo-sensibilità hanno performance simili a qSOFA
4) SOFA e qSOFA sono test di severità e predittori di Mortalità non Test per Sepsi
5) qSOFA non è screen test → pericolo di sottodiagnosi
6) Sospetto + Tardivo?
7) La sequenza qSOFA →SOFA non è ottima consecutio test sensibile→ test Specifico
8) La nuova definizione renderà inutilizzabili i dati degli ultimi 20 anni ?
9) La sensibilità per sepsi III al di fuori da UTI potrebbe essere <50%



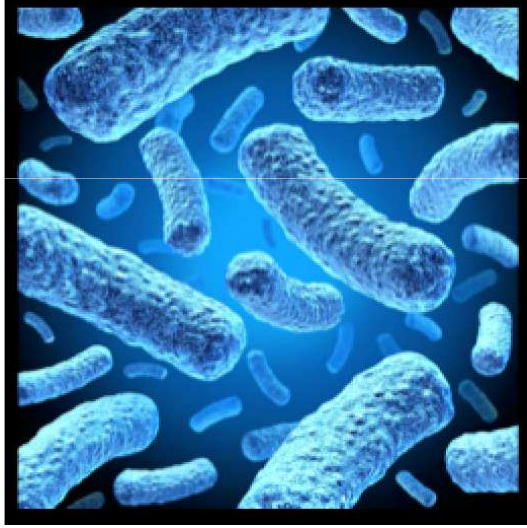
Ability to predict mortality among patients with possible infection outside the ICU

Test	Area under ROC curve	Sensitivity for mortality	Specificity for mortality
SIRS ≥ 2	0.76	64%	65%
SOFA ≥ 2	0.79	68%	67%
qSOFA ≥ 2	0.81	55%	84%

Josh Farkas - University of Vermont - USA
American College of Physicians
Simpson - CHEST 02-2016

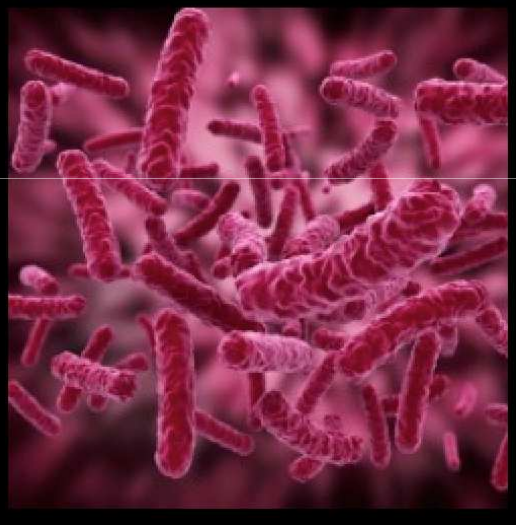
The Sepsis Trilogy

ProCESS



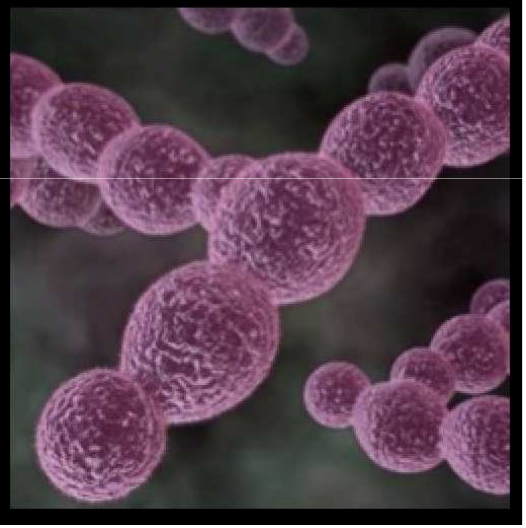
Protocolized Care for Early Septic Shock (ProCESS) – 31 ED's in US

ARISE



Australasian Resuscitation in Sepsis Evaluation (ARISE) – 51 ED's in Australia, New Zealand, Finland, Hong Kong, Ireland

ProMISe



The Protocolised Management in Sepsis (ProMISe) Trial – 56 ED's in the UK

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

Surviving Sepsis Campaign

Society of Critical Care Medicine
The Intensive Care Professionals

ESICM
European Society of Intensive Care Medicine
The Intensive Connection

CONFERENCE REPORTS AND EXPERT PANEL

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

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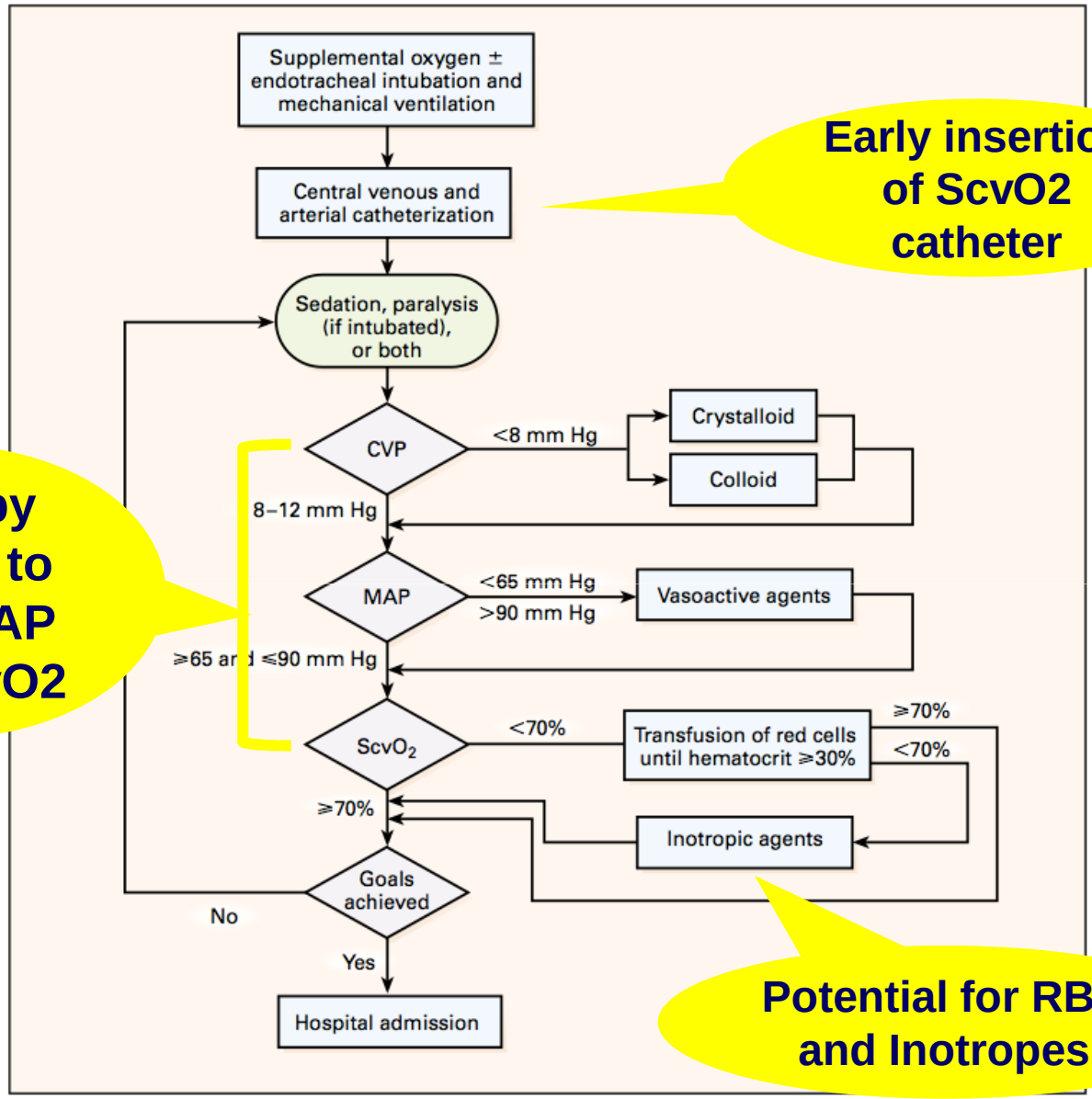
2012 Recommendation for Initial Resuscitation.

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:

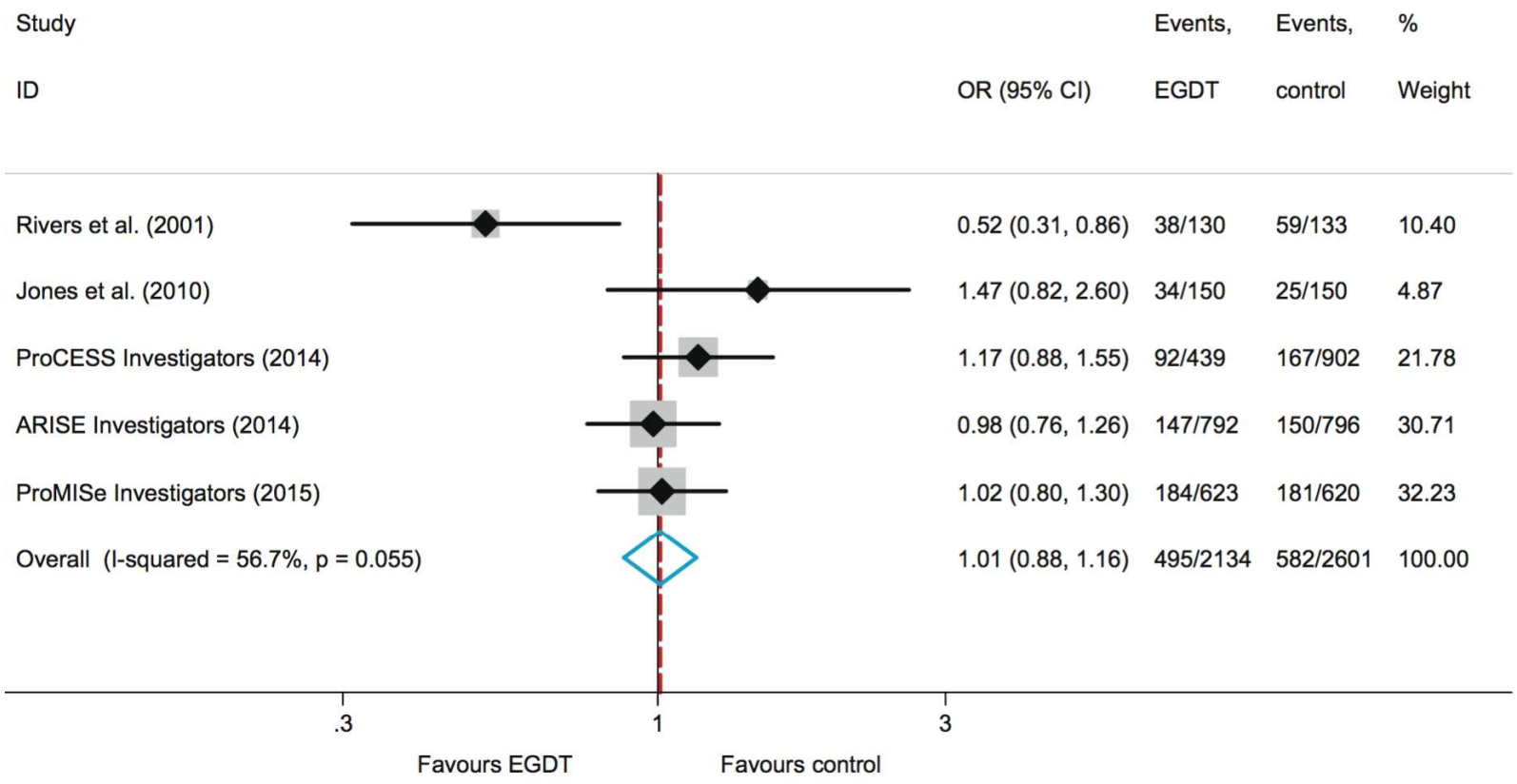
a) CVP 8–12 mm Hg
b) MAP ≥ 65 mm Hg
c) Urine output ≥ 0.5 mL/kg/hr
d) Scvo2 ≥ 70%.



N Engl J Med, Vol. 345, No. 19 · November 8, 2001

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

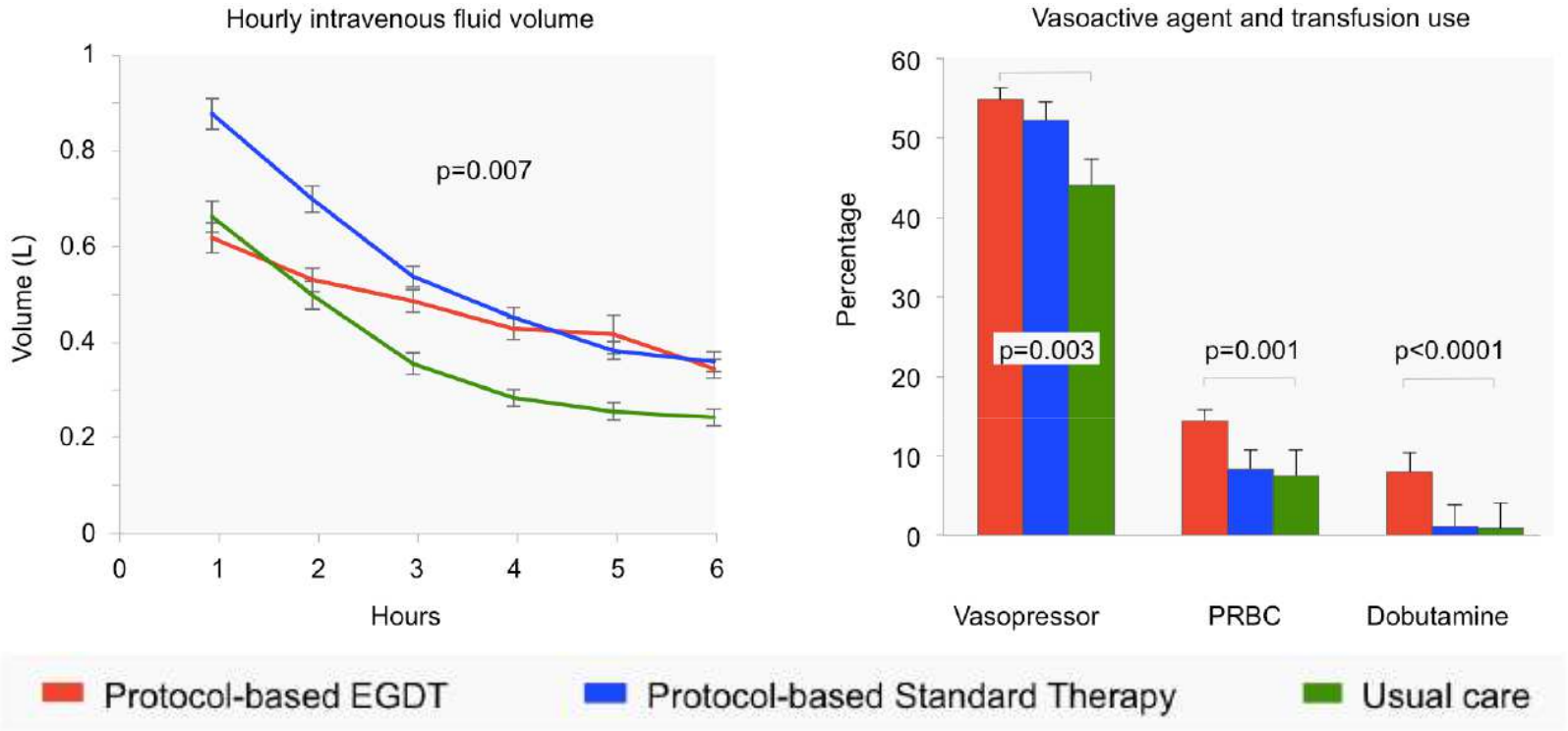
A Primary mortality outcome of each study



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

A Randomized Trial of Protocol-Based Care for Early Septic Shock

The ProCESS Investigators*



Intravenous Fluids

EGDT

Usual Care

Intravenous Antibiotics

EGDT

Usual Care

DOI: 10.1056/NEJMoa1401602

Caveats / Limitations of ProCESS, ARISE & Promise

- **The overall management of sepsis has changed…**
  - **In all three studies patients had early antibiotics, > 30ml/kg of intravenous fluid prior to randomization.**
- **We need therefore to be very careful about over interpreting the results in areas where this paradgim is not valid.**

The River's work was useful….

- **As it provided us a construct on how to understand resuscitation:**
  - **Start early- (give antibiotics)**
  - **Correct hypovolaemia**
  - **Restore perfusion pressure**
  - **And in some cases a little more may be required..!**
- **These concepts are as important today as they ever were.**

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

Best Practice Statement

Source Control

- **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).

Antibiotics

- **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).

Initial Resuscitation

- **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)

Fluid Therapy

- **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

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

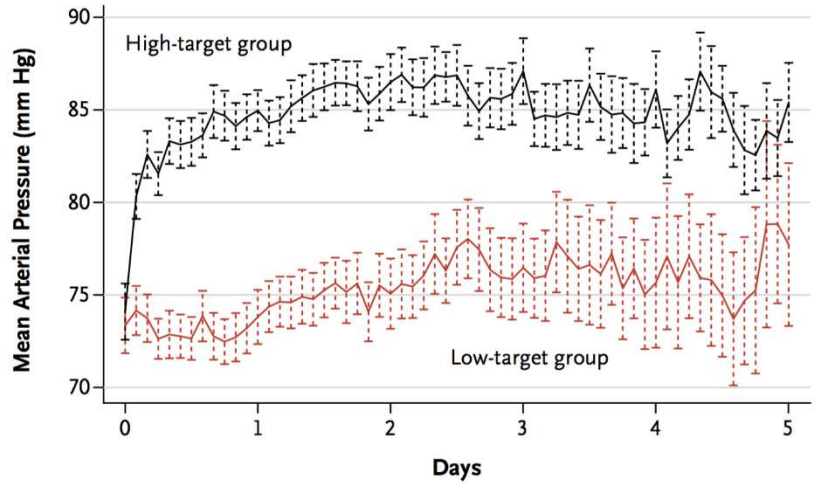


Figure 2. Mean Arterial Pressure during the 5-Day Study Period.

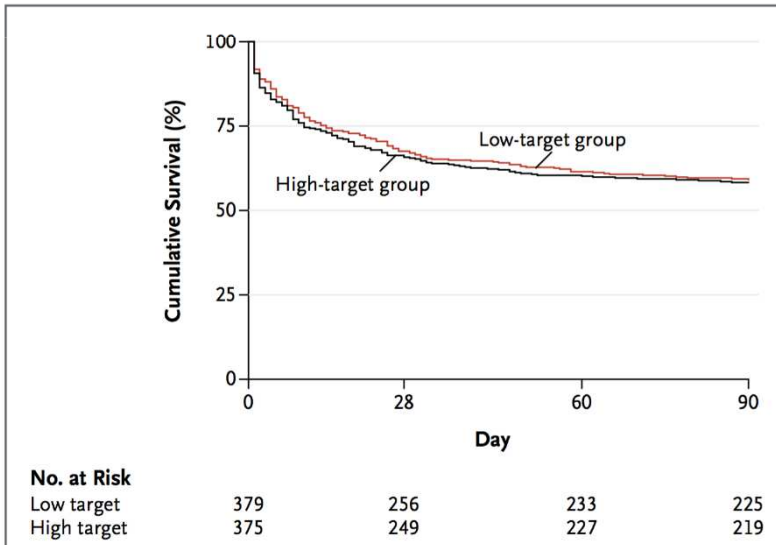


Figure 3. Kaplan–Meier Curves for Cumulative Survival.

DOI: 10.1056/NEJMoa1312173

Vasoactive agents

- **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)

If shock is not resolving quickly…..

- **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)

Lactate can help guide resuscitation

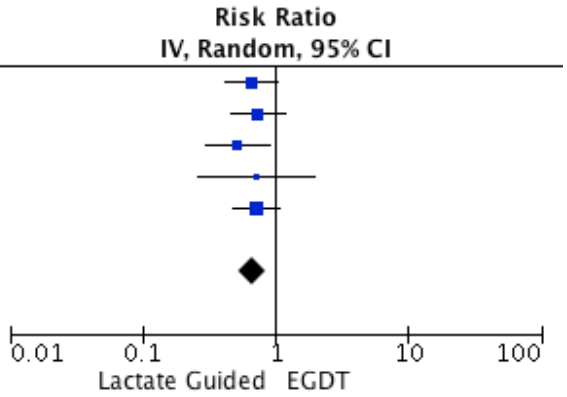
- **We suggest guiding resuscitation to normalize lactate in patients with elevated lactate levels as a marker of tissue hypoperfusion.**

(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)



Summary

- **Start resuscitation early with source control, intravenous fluids and antibiotics.**
- **Frequent assessment of the patients' volume status is crucial throughout the resuscitation period.**
- **We suggest guiding resuscitation to normalize lactate in patients with elevated lactate levels as a marker of tissue hypoperfusion.**

SCREENING FOR SEPSIS AND PERFORMANCE IMPROVEMENT

1. **We recommend that hospitals and hospital systems have a performance improvement program for sepsis including sepsis screening for acutely ill, high-risk patients. (BPS)**

Diagnosis

- **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).**

Antibiotics

- **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)**

Antibiotics

- **We suggest that combination therapy not be routinely used for on-going treatment of most other serious infections, including bacteremia and sepsis without shock.**
  - **(Weak recommendation; low quality of evidence).**

- **We recommend against combination therapy for the routine treatment of neutropenic sepsis/bacteremia.**
  - **(Strong recommendation; moderate quality of evidence).**

Antimicrobial Therapy

Antibiotic Stewardship

- **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)**

Sistema Socio Sanitario
Regione Lombardia
ASST Spedali Civili

Linee di Indirizzo

Progetto

Scimmia

Saper Come Impostare al Meglio il MIglior Antimicrobico

UU.OO. Malattie Infettive
ASST Spedali Civili di Brescia

Clinica Malattie Infettive e Tropicali
Università degli Studi di Brescia

CORTICOSTEROIDS

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.**

   (Weak recommendation; low quality of evidence)

Mechanical Ventilation

- **We suggest using higher PEEP over lower PEEP in adult patients with sepsis-induced moderate to severe ARDS.**
  - **Weak recommendation; moderate quality of evidence**
- **We recommend using prone over supine position in adult patients with sepsis-induced ARDS and a PaO_2/FIO_2 ratio <150.**
  - **(Strong recommendation; moderate quality of evidence)**

Mechanical Ventilation

- **We recommend against the use of HFOV in adult patients with sepsis-induced ARDS.**
  - **(Strong recommendation; moderate quality of evidence)**
- **We recommend against the use of beta-2 agonists for the treatment of patients with sepsis- induced ARDS without bronchospasm.**
  - **(Strong recommendation; moderate quality of evidence)**

GLUCOSE CONTROL

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)**

Renal Replacement Therapy

- **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)**

Nutrition

- **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)**

Nutrition

- **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).**

Nutrition

- **We suggest the early initiation of enteral feeding rather than a complete fast or only IV glucose in critically ill patients with sepsis or septic shock who can be fed enterally. (Weak recommendation; low quality of evidence)**
- **We suggest either early trophic/hypocaloric or early full enteral feeding in critically ill patients with sepsis or septic shock; if trophic/hypocaloric feeding is the initial strategy, then feeds should be advanced according to patient tolerance. (Weak recommendation; moderate quality of evidence)**

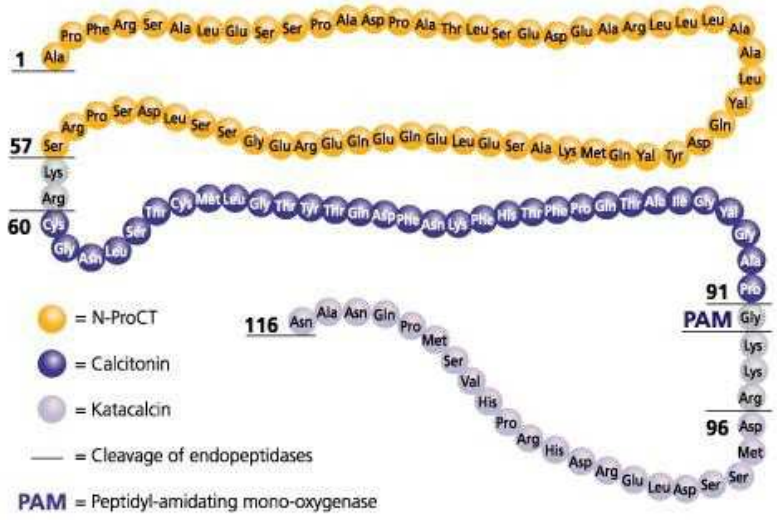
Nutrition

- **We suggest against routinely monitoring gastric residual volumes in critically ill patients with sepsis or septic shock. (Weak recommendation; low quality of evidence). However, we suggest measurement of gastric residuals in patients with feeding intolerance or who are considered to be high risk for aspiration. (Weak recommendation; very low quality of evidence)**

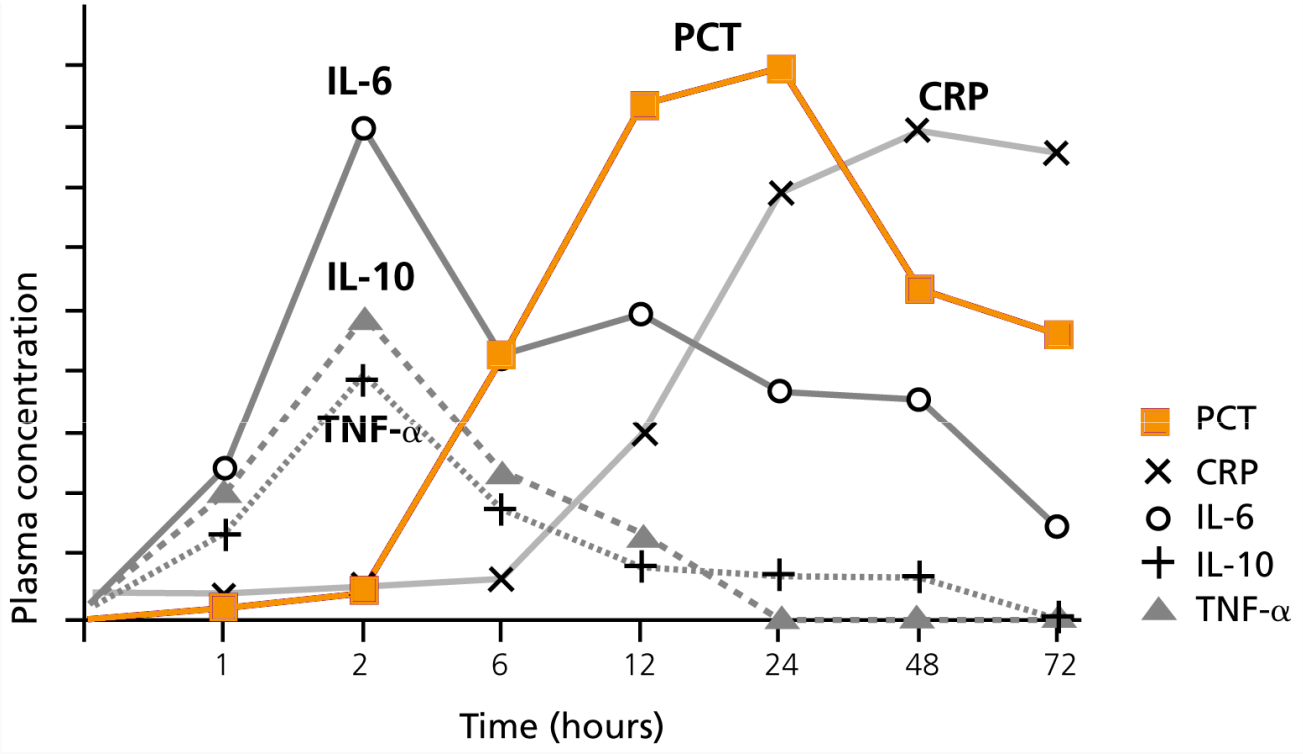
- **We suggest the use of prokinetic agents in critically ill patients with sepsis or septic shock and feeding intolerance. (Weak recommendation; low quality of evidence)**

Biomarkers infiammatori

- VES
- PCR
- Procalcitonina

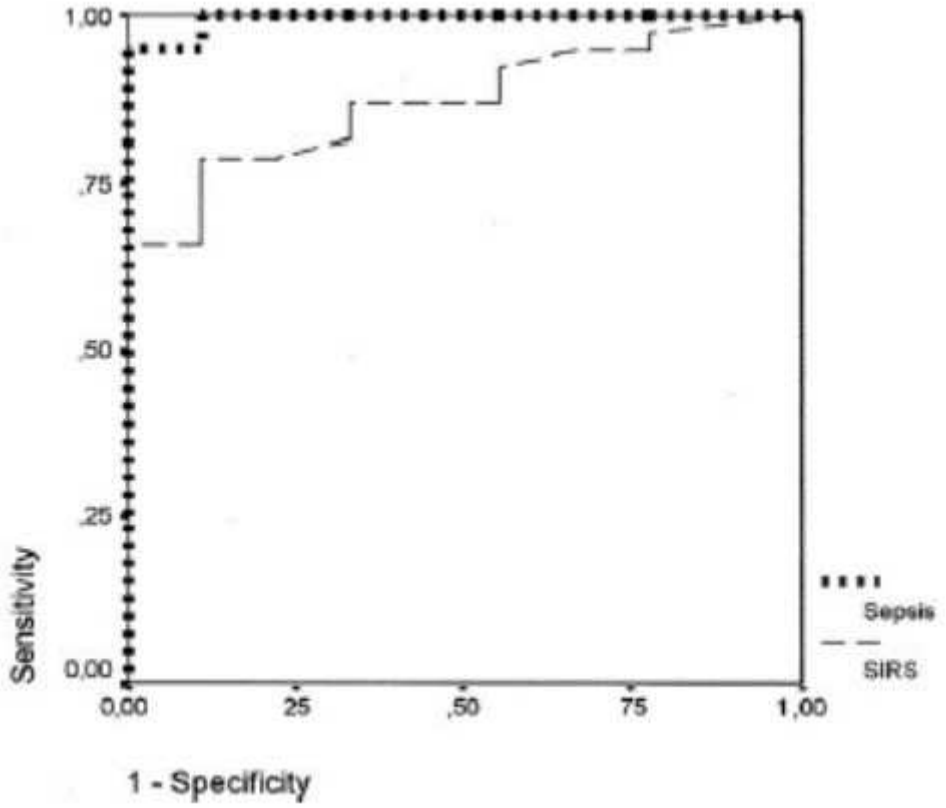


Biomarkers infiammatori



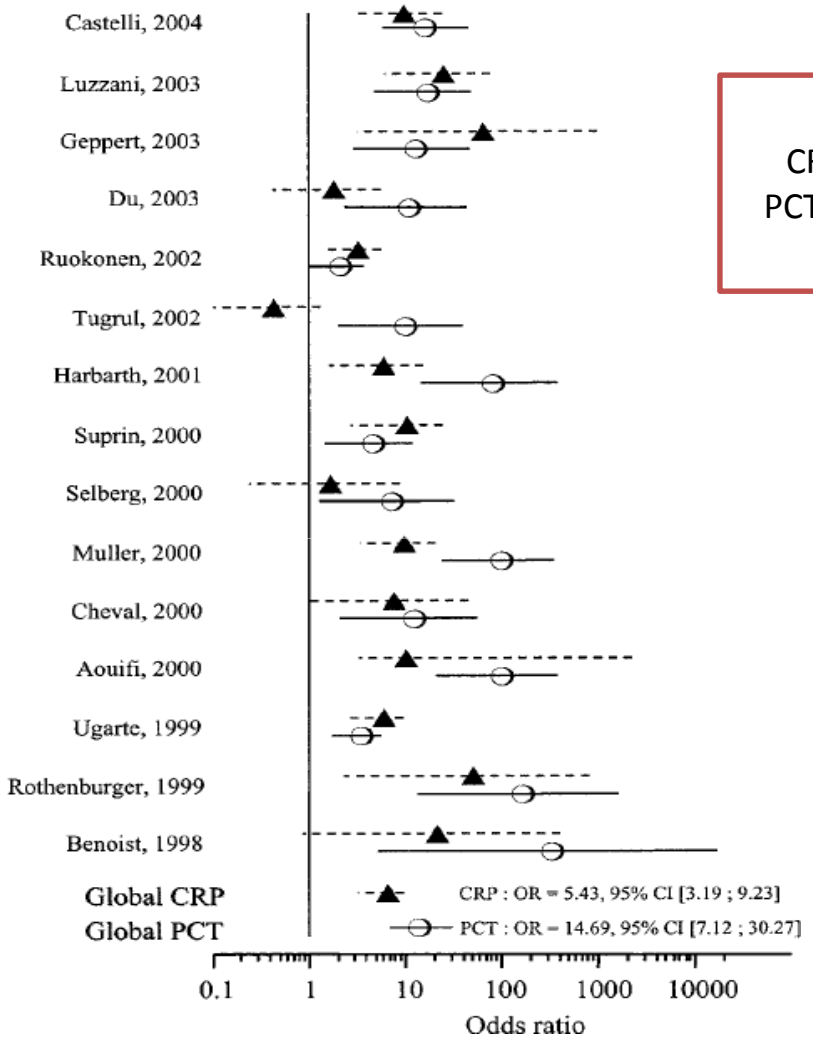
Brunkhorst FM et al., Intens. Care Med (1998) 24: 888-892

Biomarkers infiammatori / Procalcitonina



Giamarellos-Bourboulis EJ et al; J Crit Care 2004 Sep;19(3):152-7.

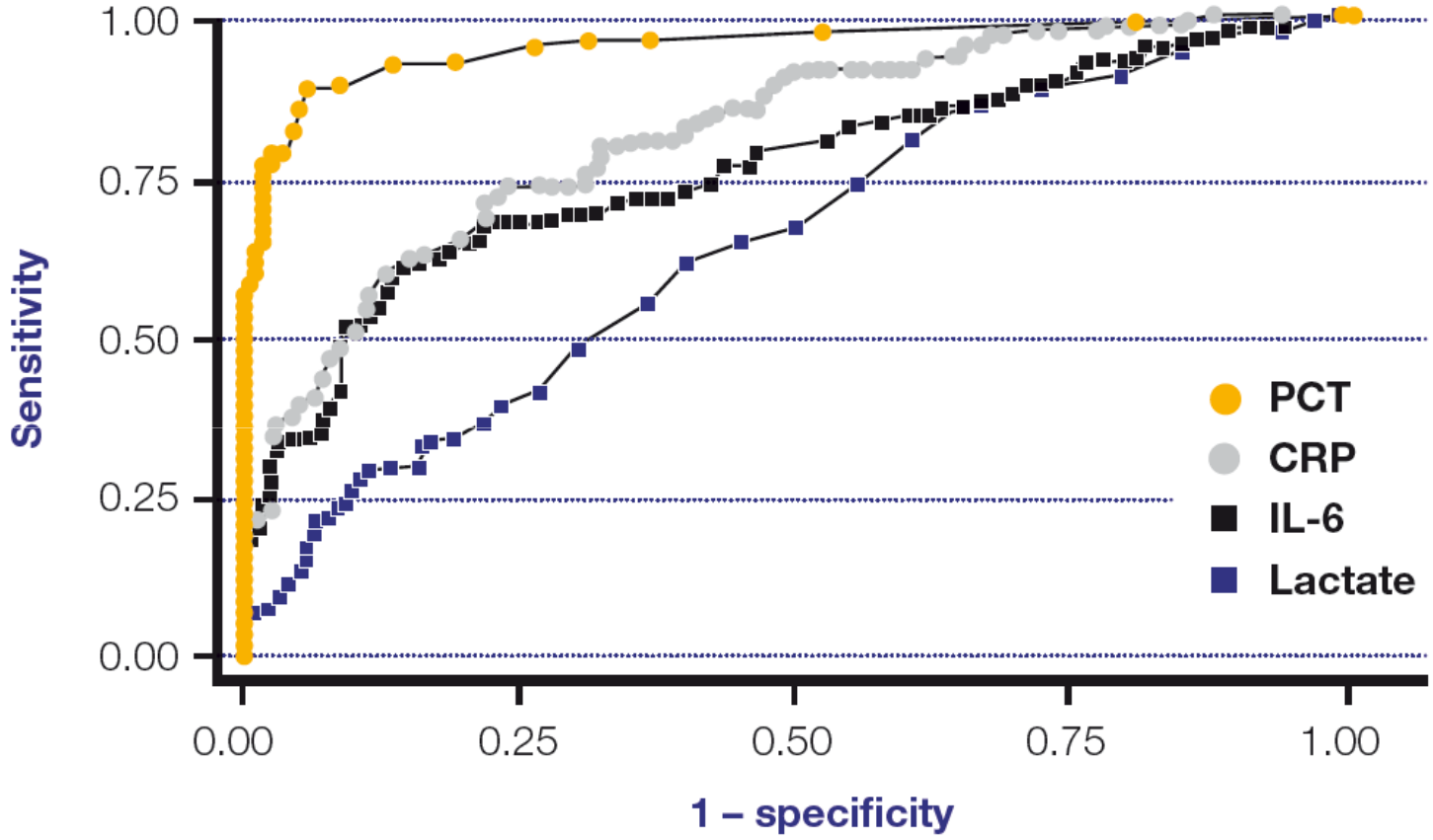
Biomarkers infiammatori



CRP OR: 5,43, 95% CI [3,19 ; 9,23]
PCT OR: 14,99, 95% CI [7,12 ; 30,27]

Uzzan B et al; Crit care Med 2006 Jul;34(7):1996-2003

Biomarkers infiammatori



Simon L. et al. Clin Infect Dis. 2004;39:206-217.

Biomarkers infiammatori

Table 1. Indications for PCT measurement other than bacterial or fungal infection

Condition	Comments /Peak	Expected range	Reference
Surgery, trauma, burn, and inhalation trauma. Surgery/ trauma, thoracic surgery	Maximum values on day 1, rapidly declining CRP peak day 2 or 3, slow decline (1-2 weeks)	<0.5-1 ng/mL for peripheral, non-abdominal trauma or minor abdominal surgery) <2 ng/mL for abdominal surgery or trauma, cardiac surgery. >2 ng/mL expected in patients with major retroperitoneal or abdominal surgery, liver transplantation	[23, 68, 69] [70, 71] [72-75]
Cardiogenic shock	Initially low, but increasing within 1-3 days, if vasopressor support is required	May be intermediate to high (e.g. >0.5 ng/mL to >10 ng/mL)	[76-78]
MODS, severe SIRS (various etiology, severe viral	Increases with severity. After injection of proinflammatory cytokines or	0.5 ng/mL-2 ng/mL, rarely >10 ng/mL	[79, 80] [28, 81, 82]

sepsis remains undefined. The utility of procalcitonin levels or other biomarkers (such as C-reactive protein) to discriminate the acute inflammatory pattern of sepsis from other causes of generalized inflammation (eg, postoperative, other forms of shock) has not been demonstrated. No recommendation can be given for the use of these markers to distinguish between severe infection and other acute inflammatory states (56–58).

	hemodialysis. Cases with increase reported during acute liver failure		
After prolonged resuscitation, myocardial infarction	Peak Day 1	Only In case of prolonged CPR, levels are related with prognosis after CPR. Very faint increase after myocardial infarction.	[97, 98]
Neonates after birth	Peak Day 1-2	Use adapted reference range	[99-102]
End stage of tumor disease	Slow increase. Para neoplastic induction very rare, always by C-cell carcinoma.	Low (0.5-2 ng/mL)	[103] [104]
Rhabdomyolysis	Acute	May be very high	Individual reports

Meisner et al; Ann Lab Med 2014 Jul;34(4):263-73

Take Home

- La necessità di ridefinire la sepsi dimostra la complessità della problematica;

- La diagnosi di sepsi è prevalentemente clinica e ogni tentativo di definire un chiaro e rigido protocollo diagnostico potrebbe risultare inadeguato per la diagnosi, vista l'eterogeneità dei quadri clinici;

- I markers infiammatori e di sepsi supportano la diagnosi clinica, non «fanno» la diagnosi;

- La gran parte dei dati in letteratura su sepsi e shock settico deriva da casistiche di pazienti di terapia intensiva.

GRAZIE