Biomarkers contro LLGG nell'inquadramento della sepsi in PS

IX congresso nazionale
SIMEU
TORINO 6-8 NOVEMBRE 2014

Marco ULLA

Franco APRA'

- ✓ ULLA: BIOMARCATORI “CLASSICI” DI INFEZIONE E DI SHOCK
- ✓ APRA’: APPROCCIO CLINICO RAGIONATO AL PAZIENTE SETTICO
- ✓ ULLA: “NUOVI” BIOMARCATORI E RUOLO DEI POINT-OF-CARE PER LA GESTIONE DELLA SEPSI IN PS
- ✓ APRA’: LE CRITICHE ALLE LINEE GUIDA (TRIALS PROCESS, ARISE…) STIAMO FACENDO LE COSE GIUSTE?...

Pierrakos and Vincent *Critical Care* 2010, **14**:R15
http://ccforum.com/content/14/1/R15

CRITICAL CARE

RESEARCH Open Access

Sepsis biomarkers: a review

Charalampos Pierrakos, Jean-Louis Vincent*

Abstract

Introduction: Biomarkers can be useful for identifying or ruling out sepsis, identifying patients who may benefit from specific therapies or assessing the response to therapy.

Methods: We used an electronic search of the PubMed database using the key words "sepsis" and "biomarker" to identify clinical and experimental studies which evaluated a biomarker in sepsis.

Results: The search retrieved 3370 references covering 178 different biomarkers.

Conclusions: Many biomarkers have been evaluated for use in sepsis. Most of the biomarkers had been tested clinically, primarily as prognostic markers in sepsis; relatively few have been used for diagnosis. None has sufficient specificity or sensitivity to be routinely employed in clinical practice. PCT and CRP have been most widely used, but even these have limited ability to distinguish sepsis from other inflammatory conditions or to predict outcome.

Table 1 Cytokine/chemokine biomarkers identified in the li

Sepsis marker	Evaluated in experimental studies	Evaluated in clinical studies
GRO-alpha [49,50]		
High mobility protei		
IL-1 re		
ADAMTS-13		
Angiopoietir		
Endocan [12		
Endothelial molecule (El soluble) [12		
Endothelial		
Intracellular 1 (soluble) [		
Laminin [13		
Neopterin [1		
Platelet-deri BB [135]		
E-Selectin (c [123,136]		
L-Selectin (s		
P-Selectin [1		
Vascular cell (VCAM)-1 [1		
Vascular enc (VEGF) [141,		
von Willebran [143,144]	factor and antigen	B(m)

Table 2 Cell marker biomarl

Table 7 Biomarkers of organ dysfunction ident

Sepsis marker	Evaluated in experimental studies
Atrial natriuretic peptide (ANP) [168,169]	
Protein S-100b [187,190]	√
Surfactant protein (A, B, C, D) [191,192]	√
Troponin [193]	

Table 8 Acute phase protein biomarkers ident

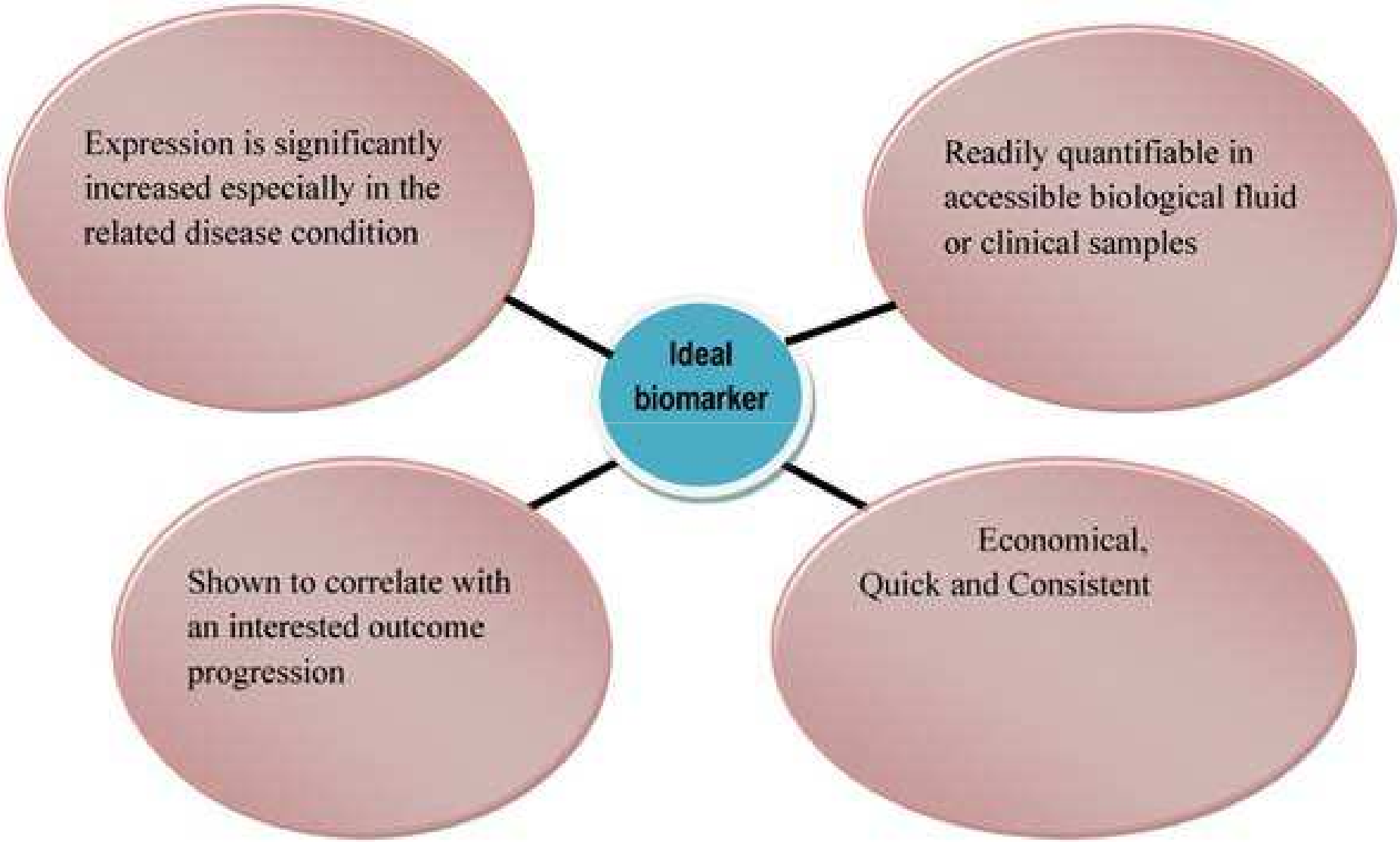
Sepsis Marker	Evaluated in experimental studies	Ev
Serum amyloid A (SAA) [194,195]	√	
Ceruloplasmin [196,197]		
C-reactive protein (CRP) [11,198,199]		
Ferritin [200]		
Alpha1-acid glycoprotein [201,202]	√	
Hepcidin [203]		
Lipopolysaccharide binding protein (LBP) [39,204]	√	
Procalcitonin [21,134,205]	√	
Pentraxin 3 [206,207]		

Table 9 Other biomarkers identified in the literature search (with some selected references)

Sepsis marker	Evaluated in experimental studies	Evaluated in clinical studies	Evaluated as a prognostic factor	Comment
Alpha2 macroglobulin [196,208]	√			
Albumin [209]	√			
Anti-endotoxin core antibodies (EndoCab) [210]		A	√	Distinguished between survivors and non-survivors at 28 days
Apolipoprotein CI [211-213]		C	√	Distinguished between survivors and non-survivors at 28 days
Bcl-2 [214]		A	√	Distinguished between survivors and non-survivors at 28 days
Beta-thromboglobulin [215]		B	√	Predicted response to therapy
Caspase-1 [216]		A		Increased in septic shock compared with healthy controls
Ceramide [217]		B	√**	Predicted development of MOF
Cholesterol [218]		C	√	Distinguished between survivors and non-survivors at 28 days in patients with severe sepsis
Complement (C3, C4, C5a levels) [219,220]		B(m)	√	Distinguished between survivors and non-survivors at 28 days
Terminal complement complex [221]	√			
Dendritic cell [222,223]	√	B	√	Distinguished between survivors and non-survivors at 28 days, correlated with SOFA score
[250]				correlation with SAPS II score
Inter-alpha inhibitor proteins (Ialpha1p) [251]		C	√	Predicted development of MOF
Intracellular nitric oxide in leukocyte [252]		B	√	Negatively correlated with SOFA score
IP-10 [30]		C		Increased in sepsis compared with healthy controls
Lactate [253,254]		C	√	Distinguished between survivors and non-survivors at 28 days, predicted response to therapy

Conclusions

Our literature review indicates that there are many biomarkers that can be used in sepsis, but none has sufficient specificity or sensitivity to be routinely employed in clinical practice. PCT and CRP have been most widely used, but even these have limited abilities to distinguish sepsis from other inflammatory conditions or to predict outcome. In view of the complexity of the sepsis response, it is unlikely that a single ideal biomarker will ever be found. A combination of several sepsis biomarkers may be more effective, but this requires further evaluation.


Ideal biomarker
Expression is significantly increased especially in the related disease condition
Readily quantifiable in accessible biological fluid or clinical samples
Shown to correlate with an interested outcome progression
Economical, Quick and Consistent

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

R. Phillip Dellinger, MD[1]; Mitchell M. Levy, MD[2]; Andrew Rhodes, MB BS[3]; Djillali Annane, MD[4]; Herwig Gerlach, MD, PhD[5]; Steven M. Opal, MD[6]; Jonathan E. Sevransky, MD[7]; Charles L. Sprung, MD[8]; Ivor S. Douglas, MD[9]; Roman Jaeschke, MD[10]; Tiffany M. Osborn, MD, MPH[11]; Mark E. Nunnally, MD[12]; Sean R. Townsend, MD[13]; Konrad Reinhart, MD[14]; Ruth M. Kleinpell, PhD, RN-CS[15]; Derek C. Angus, MD, MPH[16]; Clifford S. Deutschman, MD, MS[17]; Flavia R. Machado, MD, PhD[18]; Gordon D. Rubenfeld, MD[19]; Steven A. Webb, MB BS, PhD[20]; Richard J. Beale, MB BS[21]; Jean-Louis Vincent, MD, PhD[22]; Rui Moreno, MD, PhD[23]; and the Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup*

TABLE 1. Diagnostic Criteria for Sepsis

Infection, documented or suspected, and some of the following:
General variables
Fever (> 38.3°C)
Hypothermia (core temperature < 36°C)
Heart rate > 90/min^{-1} or more than two SD above the normal value for age
Tachypnea
Altered mental status
Significant edema or positive fluid balance (> 20 mL/kg over 24 hr)
Hyperglycemia (plasma glucose > 140 mg/dL or 7.7 mmol/L) in the absence of diabetes
Inflammatory variables
Leukocytosis (WBC count > 12,000 μL^{-1})
Leukopenia (WBC count < 4000 μL^{-1})
Normal WBC count with greater than 10% immature forms
Plasma C-reactive protein more than two SD above the normal value
Plasma procalcitonin more than two SD above the normal value
Hemodynamic variables
Arterial hypotension (SBP < 90 mm Hg, MAP < 70 mm Hg, or an SBP decrease > 40 mm Hg in adults or less than two SD below normal for age)
Organ dysfunction variables
Arterial hypoxemia (Pao_2/Fio_2 < 300)
Acute oliguria (urine output < 0.5 mL/kg/hr for at least 2 hrs despite adequate fluid resuscitation)
Creatinine increase > 0.5 mg/dL or 44.2 μmol/L
Coagulation abnormalities (INR > 1.5 or aPTT > 60 s)
Ileus (absent bowel sounds)
Thrombocytopenia (platelet count < 100,000 μL^{-1})
Hyperbilirubinemia (plasma total bilirubin > 4 mg/dL or 70 μmol/L)
Tissue perfusion variables
Hyperlactatemia (> 1 mmol/L)
Decreased capillary refill or mottling

TABLE 2. Severe Sepsis

Severe sepsis definition = sepsis-induced tissue hypoperfusion or organ dysfunction (any of the following thought to be due to the infection)
Sepsis-induced hypotension
Lactate above upper limits laboratory normal
Urine output < 0.5 mL/kg/hr for more than 2 hrs despite adequate fluid resuscitation
Acute lung injury with Pao_2/Fio_2 < 250 in the absence of pneumonia as infection source
Acute lung injury with Pao_2/Fio_2 < 200 in the presence of pneumonia as infection source
Creatinine > 2.0 mg/dL (176.8
Bilirubin > 2 mg/dL (34.2 µmol
Platelet count < 100,000 µL
Coagulopathy (international no

C. Diagnosis

1. Cultures as clinically appropriate
   1C). At least 2 sets of blood cult
   percutaneously and 1 drawn thr
2. Use of the 1,3 beta-D-glucan
   candidiasis is in differential dia
3. Imaging studies performed pro

SURVIVING SEPSIS CAMPAIGN BUNDLES

TO BE COMPLETED WITHIN 3 HOURS:

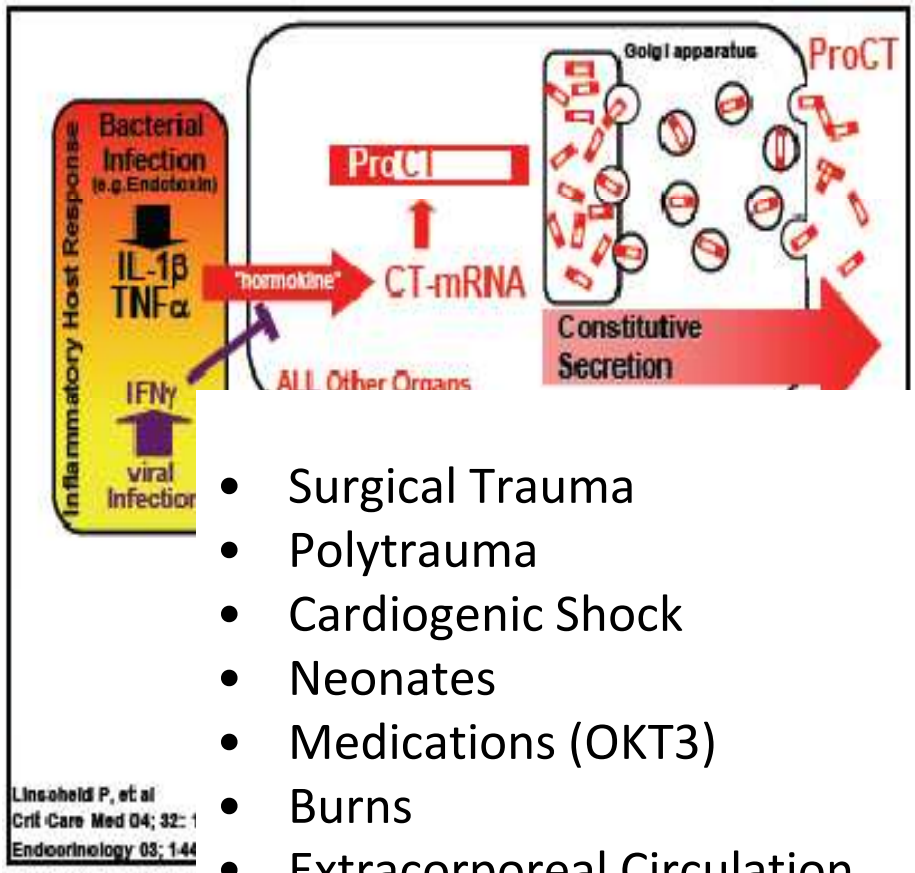
1) Measure lactate level
2) Obtain blood cultures prior to administration of antibiotics
3) Administer broad spectrum antibiotics
4) Administer 30 mL/kg crystalloid for hypotension or lactate ≥4mmol/L

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 arterial hypotension despite volume resuscitation (septic shock) or initial lactate ≥4 mmol/L (36 mg/dL):
   - Measure central venous pressure (CVP)*
   - Measure central venous oxygen saturation ($Scvo_2$)*
7) Remeasure lactate if initial lactate was elevated*

*Targets for quantitative resuscitation included in the guidelines are CVP of ≥8 mm Hg, $Scvo_2$ of ≥70%, and normalization of lactate.

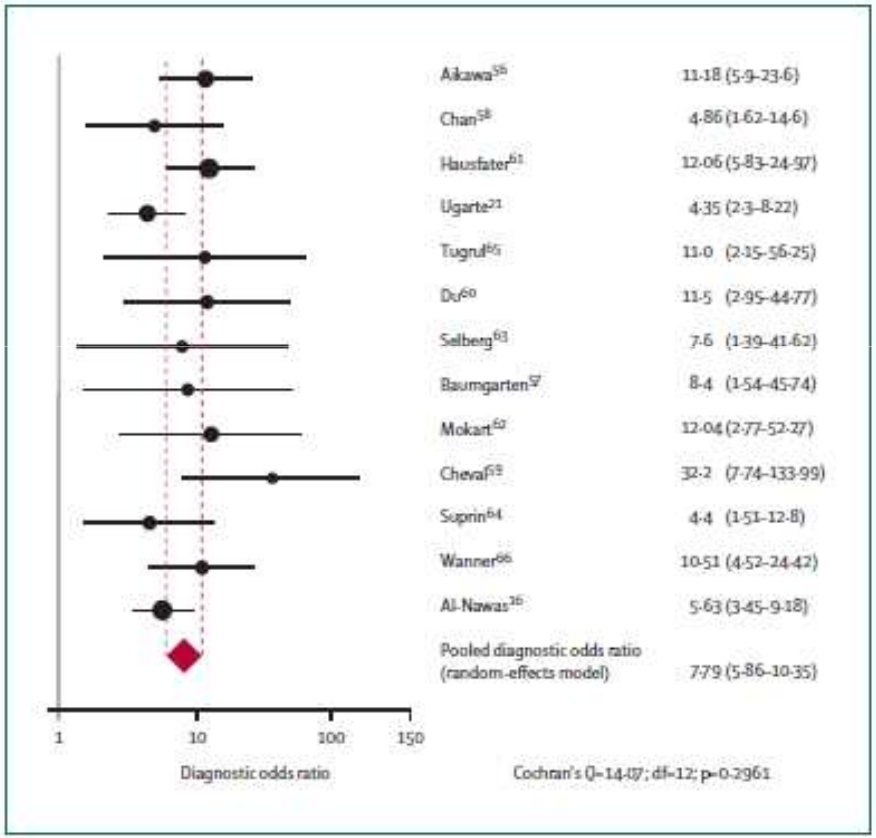
PROCALCITONINA

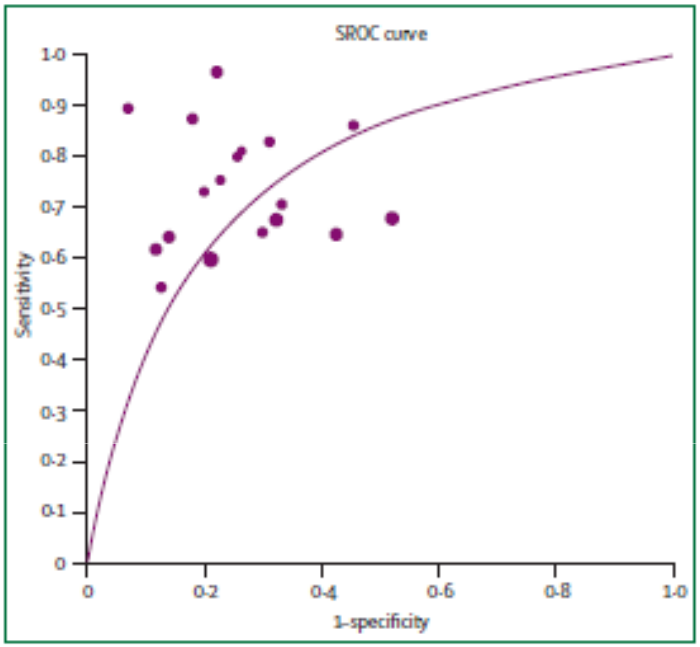


• Surgical Trauma	up to 7 ng/ml
• Polytrauma	around 5 ng/ml
• Cardiogenic Shock	up to 10 ng/ml
• Neonates	up to 20 ng/ml day 2
• Medications (OKT3)	up to 50 ng/ml
• Burns	around 2 ng/ml
• Extracorporeal Circulation	2 – 100 ng/ml
• Tumors	up to 50 ng/ml
• Liver cirrhosis	up to 4 ng/ml
• Haemodialysis	around 1 ng/ml
• Goodpasture Syndrome	av. 34 ng/ml
• Alzheimer, Dementia	up to 0,6 ng/ml

Accuracy of procalcitonin for sepsis diagnosis in critically ill patients: systematic review and meta-analysis

Benjamin M P Tang, Guy D Eslick, Jonathan C Craig, Anthony S McLean





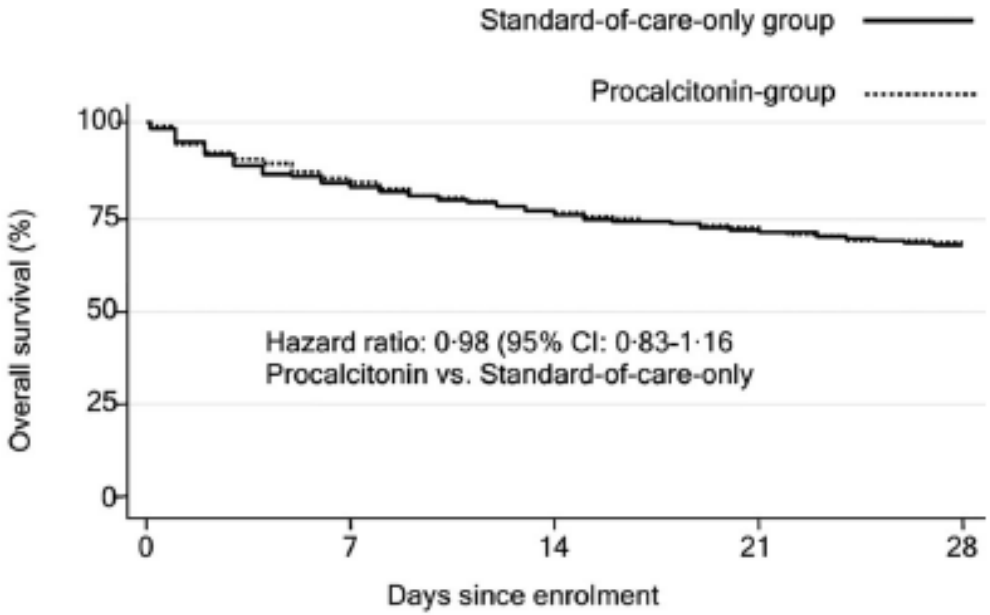
In summary, we found that procalcitonin had a low diagnostic performance in differentiating sepsis from SIRS in critically ill adult patients. The evidence presented in this review does not lend support to the widespread use of the procalcitonin test for sepsis diagnosis in critical care settings.

Guidelines for starting antibiotics[a]			
If the blood sample taken for procalcitonin level was taken at the early stage of the episode, obtain a second procalcitonin level at 6–12 h			
[a]Excludes situations requiring immediate antibiotic treatment (e.g. septic shock, purulent meningitis)			
Concentration <0.25 μg/L	Concentration ≥0.25 to <0.5 μg/L	Concentration ≥0.5 to <1 μg/L	Concentration ≥1 μg/L
⇓	⇓	⇓	⇓
Antibiotics strongly discouraged	Antibiotics discouraged	Antibiotics encouraged	Antibiotics strongly encouraged
Guidelines for continuing or stopping of antibiotics			
Concentration <0.25 μg/L	Concentration decrease by ≥80% from peak OR ≥0.25 to <0.5 μg/L	Concentration decrease by <80% from peak AND ≥0.5 μg/L	Concentration increase compared with peak AND ≥0.5 μg/L
⇓	⇓	⇓	⇓
Stopping of antibiotics strongly encouraged	Stopping of antibiotics encouraged	Continuing antibiotics encouraged	Changing antibiotics strongly encouraged

J Antimicrob Chemother 2011; **66** Suppl 2: ii33–ii40
doi:10.1093/jac/dkq523

Procalcitonin-guided interventions against infections to increase early appropriate antibiotics and improve survival in the intensive care unit: A randomized trial*

Jens U. Jensen, MD, PhD; Lars Hein, MD; Bettina Lundgren, MD, DMSc; Morten H. Bestle, MD, PhD; Thomas T. Mohr, MD, PhD; Mads H. Andersen, MD; Klaus J. Thornberg, MD; Jesper Løken, MD; Morten Steensen, MD; Zoe Fox, MD, PhD; Hamid Tousi, MD; Peter Søe-Jensen, MD; Anne Ø. Lauritsen, MD; Ditte Strange, MD; Pernille L. Petersen, MD; Nanna Reiter, MD; Søren Hestad, MD; Katrin Thormar, MD; Paul Fjeldborg, MD; Kim M. Larsen, MD; Niels E. Drenck, MD; Christian Østergaard, MD, PhD, DMSc; Jesper Kjær, MSc; Jesper Grarup, DVM; Jens D. Lundgren, MD, DMSc; for The Procalcitonin And Survival Study (PASS) Group



A strategy with escalation of broad-spectrum antimicrobials in the intensive care unit guided by daily procalcitonin measurements as used in this trial did not improve survival and did lead to an increased use of broad-spectrum antimicrobials, which is concerning in regard to toxicity, resistance, and economics. We observed deleterious effects on organ function and length of stay in the intensive care unit and the strategy cannot be recommended.

Procalcitonin for reduced antibiotic exposure in the critical care setting: A systematic review and an economic evaluation*

Daren K. Heyland, MD, FRCPC, MSc; Ana P. Johnson, PhD; Steven C. Reynolds, MD, FRCPC; John Muscedere, MD, FRCPC

Conclusions: **Procalcitonin-guided antibiotic therapy is associated with a reduction in antibiotic usage that, under certain assumptions, may reduce overall costs of care. However, the overall estimate cannot rule out a 7% increase in hospital mortality. (Crit Care Med 2011; 39:1792–1799)**

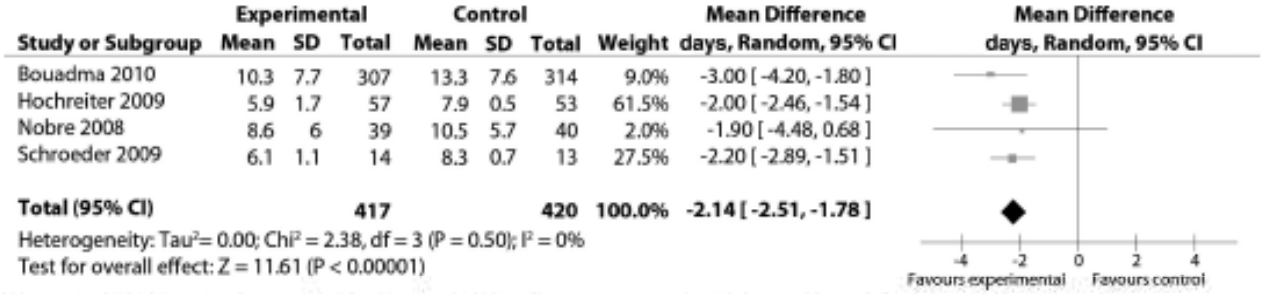


Figure 1. Effect of procalcitonin-guided therapy on duration of antibiotic utilization. *Gray squares* represent the point estimate and 95% confidence intervals (*CIs*) around the treatment effect of each individual study. The *black diamond* is the summary or overall combined estimate of treatment effect. *df*, degrees of freedom.

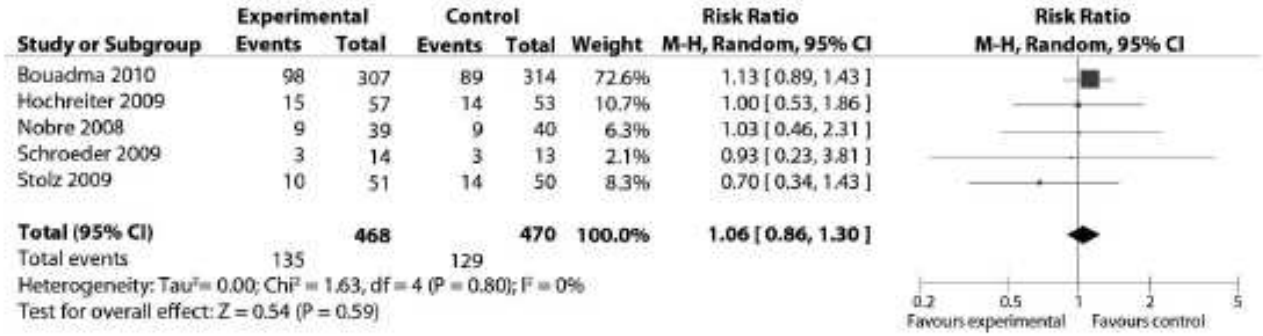
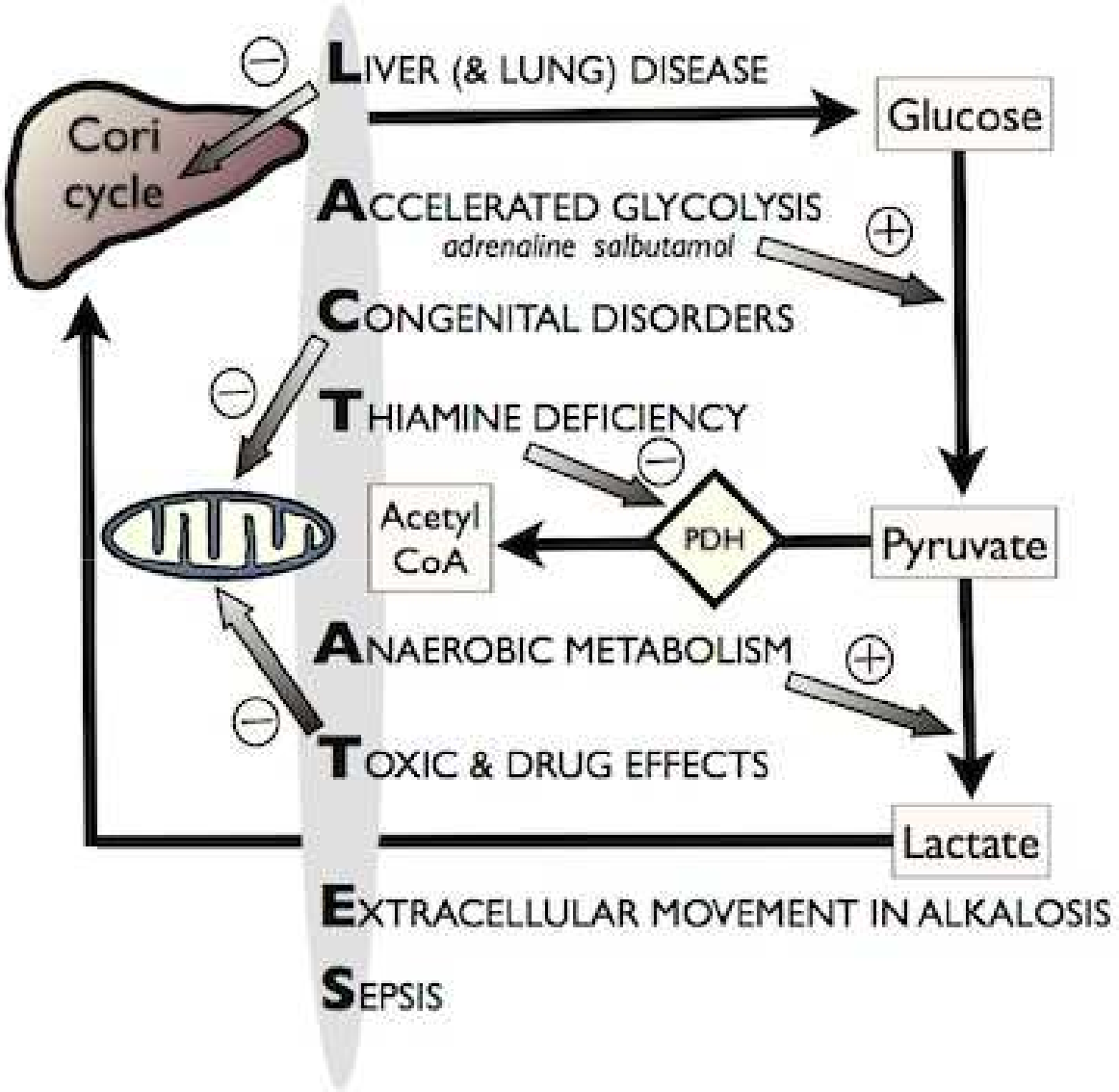


Figure 2. Effect of procalcitonin-guided therapy on hospital mortality. *Gray squares* represent the point estimate and 95% confidence intervals (*CIs*) around the treatment effect of each individual study. The *black diamond* is the summary or overall combined estimate of treatment effect. *M-H*, Mantel-Hanzel; *df*, degrees of freedom.

3. We suggest the use of low procalcitonin levels or similar biomarkers to assist the clinician in the discontinuation of empiric antibiotics in patients who appeared septic, but have no subsequent evidence of infection (grade 2C).

Rationale. This suggestion is predicated on the preponderance of the published literature relating to the use of procalcitonin as a tool to discontinue unnecessary antimicrobials (58, 83). However, clinical experience with this strategy is limited and the potential for harm remains a concern (83). No evidence demonstrates that this practice reduces the prevalence of antimicrobial resistance or the risk of antibiotic-related diarrhea from *C. difficile*. One recent study failed to show any benefit of daily procalcitonin measurement in early antibiotic therapy or survival (84).


LIVER (& LUNG) DISEASE
Glucose
Cori cycle
ACCELERATED GLYCOLYSIS
adrenaline salbutamol
CONGENITAL DISORDERS
THIAMINE DEFICIENCY
Acetyl CoA
PDH
Pyruvate
ANAEROBIC METABOLISM
TOXIC & DRUG EFFECTS
Lactate
EXTRACELLULAR MOVEMENT IN ALKALOSIS
SEPSIS

Nei quadri di shock i valori di LAC sierico correlano in maniera diretta con la mortalità; valori iniziali ≥ 4mmol/l associano ad un aumento di mortalità a 72h.

Intensive Care Med (2007) 33:970–977
DOI 10.1007/s00134-007-0563-9

ORIGINAL

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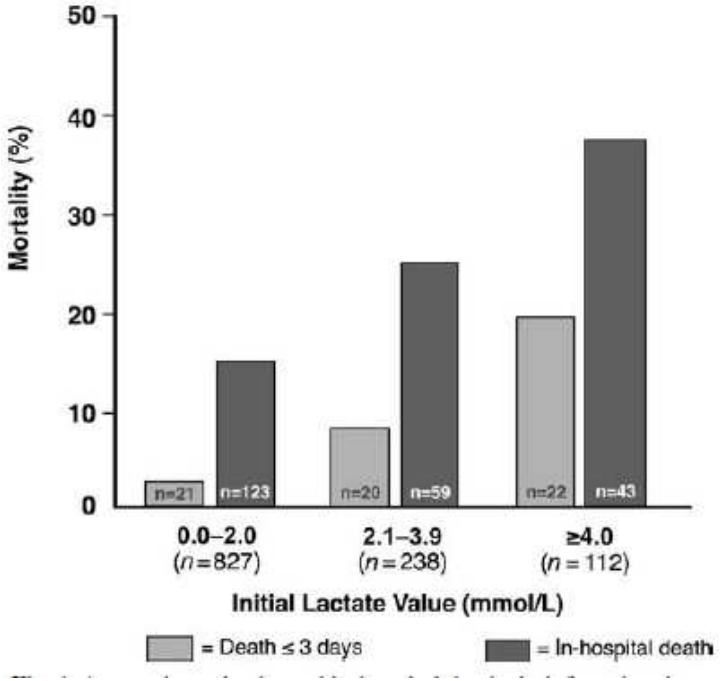
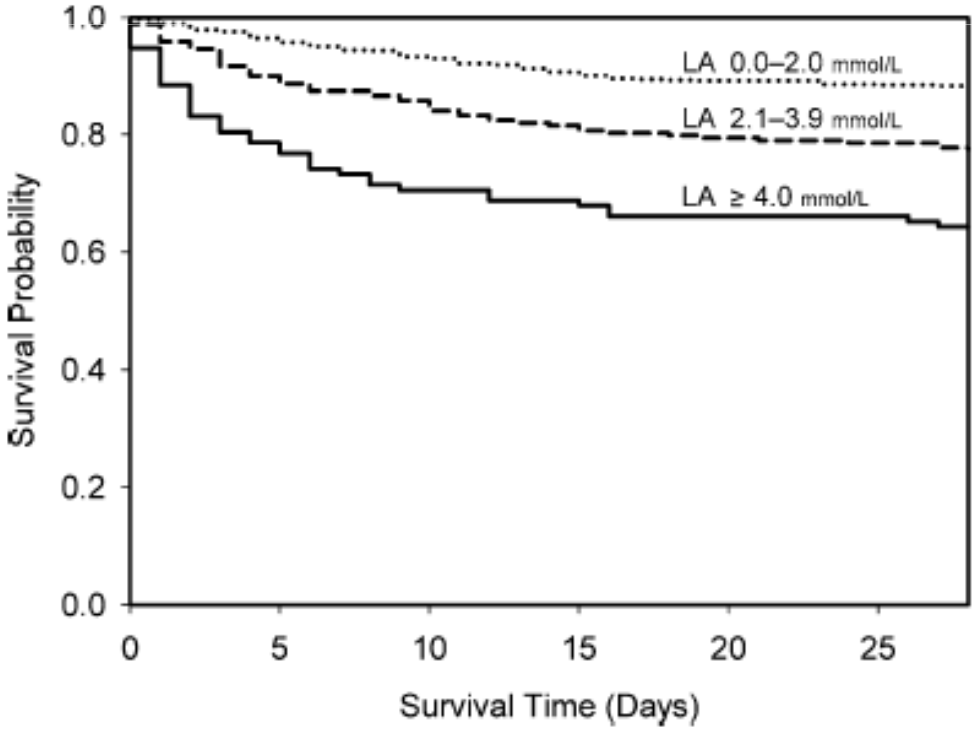
Christa Schorr
Barry Milcarek
Steven M. Hollenberg
Joseph E. Parrillo

Serum lactate as a predictor of mortality in patients with infection





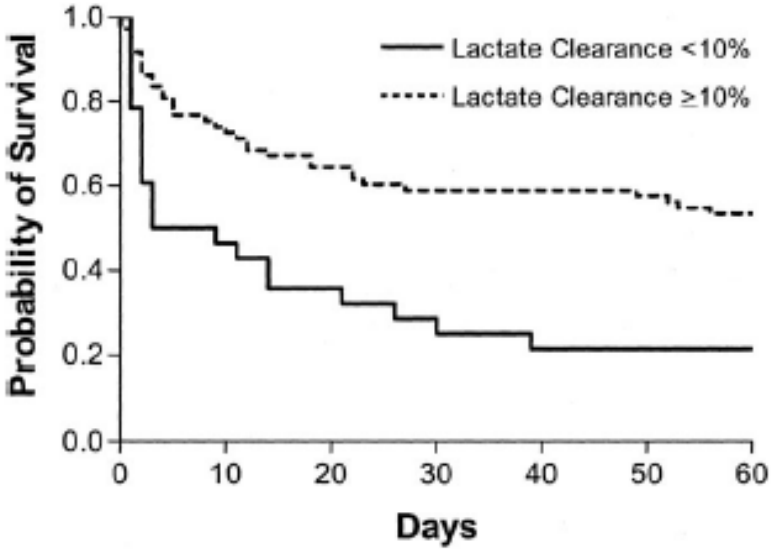
La Clearance dei LAC ha valore prognostico più accurato dei valori iniziali. Normalizzazione a 24h associa con migliore sopravvivenza.

Early lactate clearance is associated with improved outcome in severe sepsis and septic shock*

H. Bryant Nguyen, MD, MS; Emanuel P. Rivers, MD, MPH; Bernhard P. Knoblich, MD; Gordon Jacobsen, MS; Alexandria Muzzin, BS; Julie A. Ressler, BS; Michael C. Tomlanovich, MD

Crit Care Med 2004 Vol. 32, No. 8

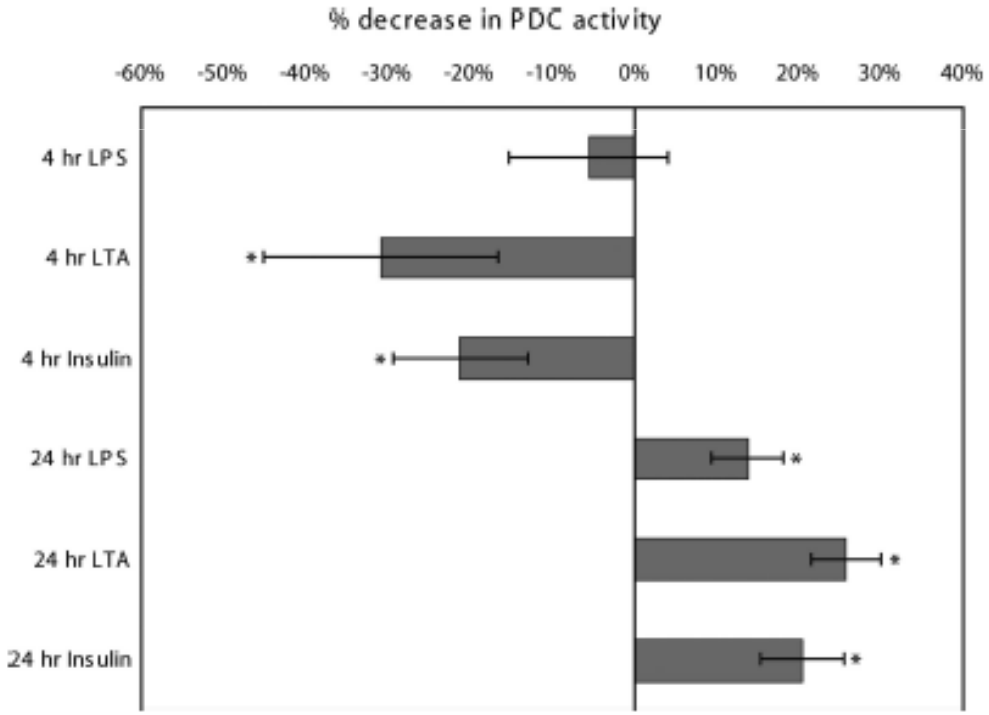
$$\text{Lactate clearance} = \frac{(\text{Lactate}^{\text{ED Presentation}} - \text{Lactate}^{\text{Hour 6}}) \times 100}{\text{Lactate}^{\text{ED Presentation}}}$$



Accumulo di LAC nei quadri settici non sarebbe il risultato di un inefficace DO_2, ma di un accumulo di piruvato per inibizione dell'enzima PiruvatoDH.

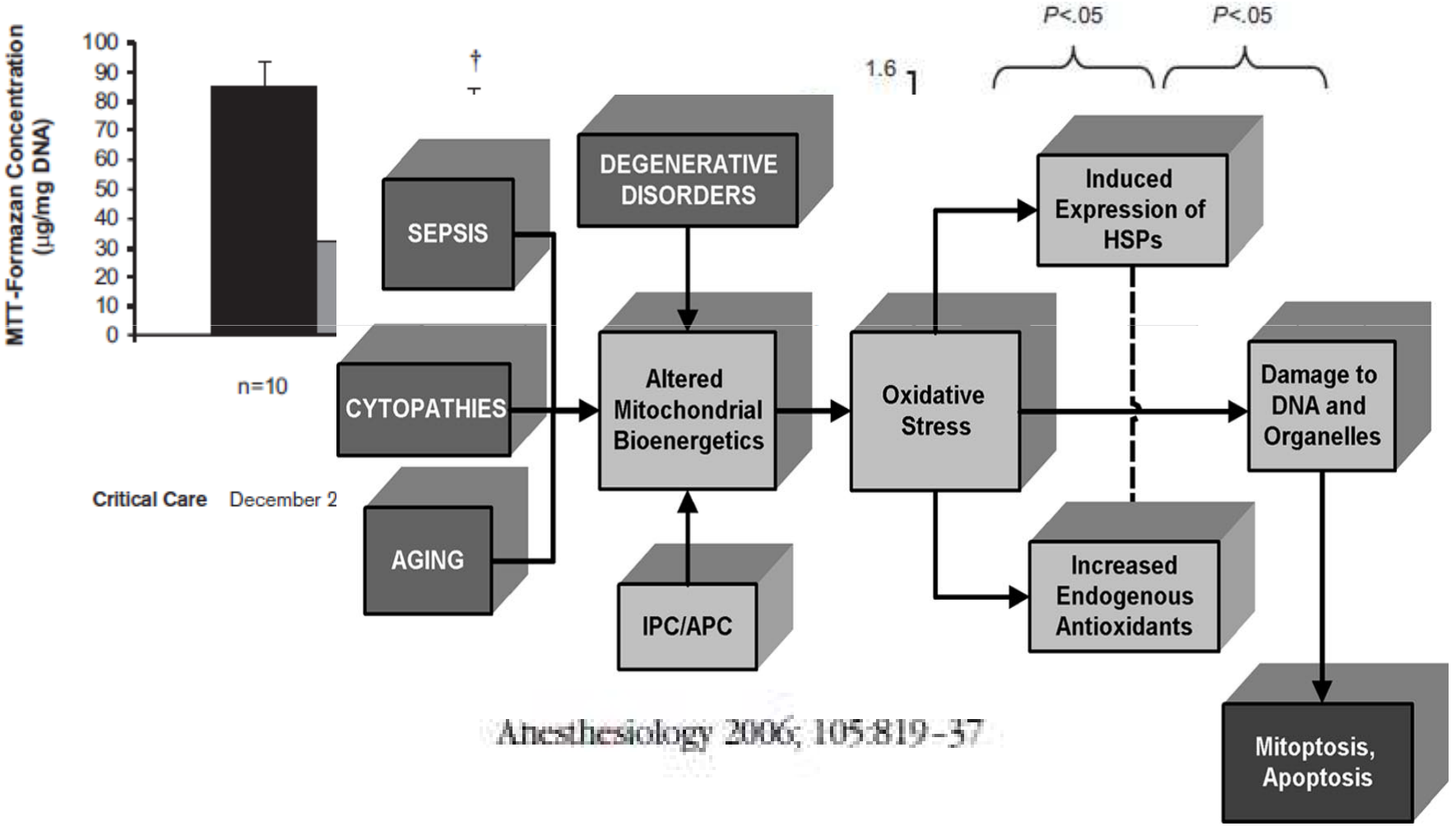
Potential Dysregulation of the Pyruvate Dehydrogenase Complex by Bacterial Toxins and Insulin

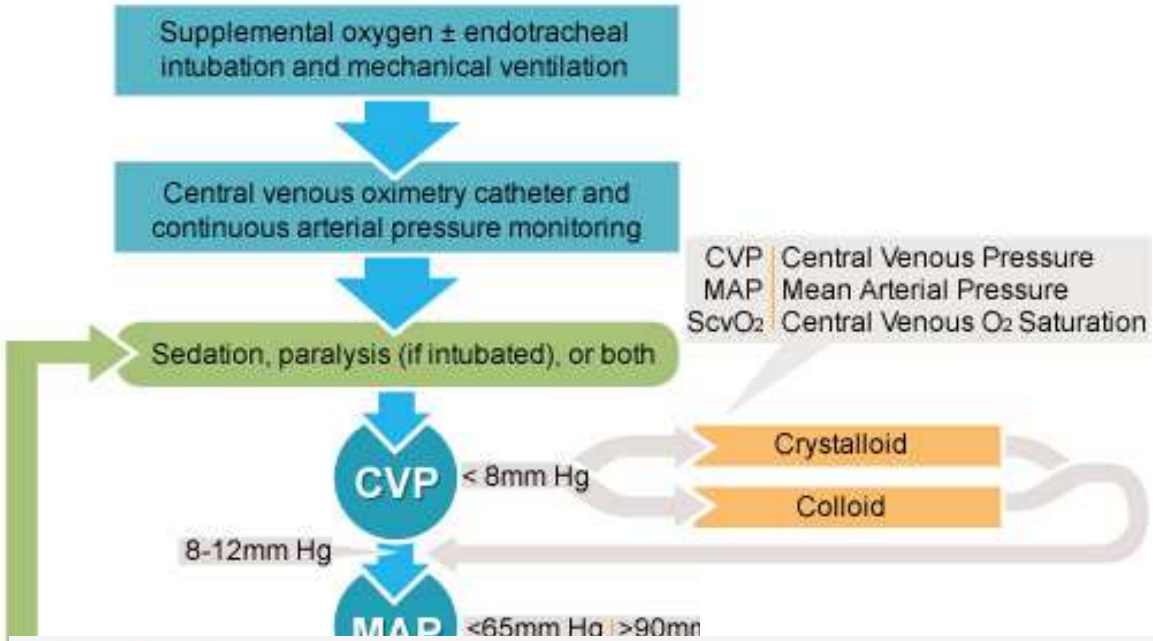
Gregory W. Thomas, BS, Charles W. Mains, MD, Denetta Sue Slone, MD, Michael L. Craun, MD, and David Bar-Or, MD



The Journal of TRAUMA® *Injury, Infection, and Critical Care* • Volume 67, Number 3, September 2009

Non si assiste a ipossia tissutale nei pazienti con sepsi grave/shock settico, ma un alterato utilizzo del O_2 da parte dei mitocondri (*cytopathic hypoxia*). PO2 a livello muscolare ↑ nella sepsi grave.





- SvO_2 65-75%
- ↓ 65% = ↓ DO_2
- < 50% = inadeguata ossigeazione tissutale
- > 75% = difetto di utilizzo O2 a livello tissutale (danno infiammatorio cellulare - sepsi grave/shock settico).

A. Initial Resuscitation

1. Protocolized, quantitative resuscitation of patients with sepsis- induced tissue hypoperfusion (defined in this document as hypotension persisting after initial fluid challenge or blood lactate concentration ≥ 4 mmol/L). Goals during the first 6 hrs of resuscitation:
   a) Central venous pressure 8–12 mm Hg
   b) Mean arterial pressure (MAP) ≥ 65 mm Hg
   c) Urine output ≥ 0.5 mL/kg/hr
   d) Central venous (superior vena cava) or mixed venous oxygen saturation 70% or 65%, respectively (grade 1C).
2. In patients with elevated lactate levels targeting resuscitation to normalize lactate (grade 2C).

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

R. Phillip Dellinger, MD[1]; Mitchell M. Levy, MD[2]; Andrew Rhodes, MB BS[3]; Djillali Annane, MD[4]; Herwig Gerlach, MD, PhD[5]; Steven M. Opal, MD[6]; Jonathan E. Sevransky, MD[7]; Charles L. Sprung, MD[8]; Ivor S. Douglas, MD[9]; Roman Jaeschke, MD[10]; Tiffany M. Osborn, MD, MPH[11]; Mark E. Nunnally, MD[12]; Sean R. Townsend, MD[13]; Konrad Reinhart, MD[14]; Ruth M. Kleinpell, PhD, RN-CS[15]; Derek C. Angus, MD, MPH[16]; Clifford S. Deutschman, MD, MS[17]; Flavia R. Machado, MD, PhD[18]; Gordon D. Rubenfeld, MD[19]; Steven A. Webb, MB BS, PhD[20]; Richard J. Beale, MB BS[21]; Jean-Louis Vincent, MD, PhD[22]; Rui Moreno, MD, PhD[23]; and the Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup*

Se cerco qualcosa sulla diagnosi della sepsi nelle lineeguida cosa trovo?

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Hyperbilirubinemia (plasma total bilirubin > 4 mg/dL or 70 μmol/L)
Tissue perfusion variables
Hyperlactatemia (> 1 mmol/L)
Decreased capillary refill or mottling

WBC = white blood cell; SBP = systolic blood pressure; MAP = mean arterial pressure; INR = international normalized ratio; aPTT = activated partial thromboplastin time.

Diagnostic criteria for sepsis in the pediatric population are signs and symptoms of inflammation plus infection with hyper- or hypothermia (rectal temperature > 38.5° or < 35°C), tachycardia (may be absent in hypothermic patients), and at least one of the following indications of altered organ function: altered mental status, hypoxemia, increased serum lactate level, or bounding pulses.

Adapted from Levy MM, Fink MP, Marshall JC, et al: 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med* 2003; 31: 1250–1256.

TABLE 2. Severe Sepsis

Severe sepsis definition = sepsis-induced tissue hypoperfusion or organ dysfunction (any of the following thought to be due to the infection)
Sepsis-induced hypotension
Lactate above upper limits laboratory normal
Urine output < 0.5 mL/kg/hr for more than 2 hrs despite adequate fluid resuscitation
Acute lung injury with Pao_2/Fio_2 < 250 in the absence of pneumonia as infection source
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Creatinine > 2.0 mg/dL (176.8 μmol/L)
Bilirubin > 2 mg/dL (34.2 μmol/L)
Platelet count < 100,000 μL
Coagulopathy (international normalized ratio > 1.5)

Adapted from Levy MM, Fink MP, Marshall JC, et al: 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med* 2003; 31: 1250–1256.

Cerco di leggere il testo e dopo l’introduzione metodologica cosa trovo?

heads and then by the entire committee. To satisfy peer review during the final stages of manuscript approval for publication, several recommendations were edited with approval of the SSC executive committee group head for that recommendation and the EBM lead.

Conflict of Interest Policy

Since the inception of the SSC guidelines in 2004, no members of the committee represented industry; there was no industry input into guidelines development; and no industry representatives were present at any of the meetings. Industry awareness or comment on the recommendations was not allowed. No member of the guidelines committee received honoraria for any role in the 2004, 2008, or 2012 guidelines process.

additional COI issues were reported that required further adjudication.

MANAGEMENT OF SEVERE SEPSIS

Initial Resuscitation and Infection Issues (Table 5)

A. Initial Resuscitation

1. We recommend the protocolized, quantitative resuscitation of patients with sepsis- induced tissue hypoperfusion (defined in this document as hypotension persisting after initial fluid challenge or blood lactate concentration ≥ 4 mmol/L). This protocol should be initiated as soon as hypoperfusion is recognized and should not be delayed pending ICU admission. During the first 6 hrs of resuscitation, the goals of initial resuscitation of

Cosa sappiamo:

- la sepsi è un disturbo funzionale
- dobbiamo individuare l'ipoperfusione prima che il danno sia irreversibile

- la precocità della stratificazione del paziente è probabilmente un punto critico

Quali sono gli elementi clinici diagnostici

General variables
Fever (> 38.3°C)
Hypothermia (core temperature < 36°C)
Heart rate > 90/min^{-1} or more than two SD above the normal value for age
Tachypnea
Altered mental status
Significant edema or positive fluid balance (> 20 mL/kg over 24 hr)
Hyperglycemia (plasma glucose > 140 mg/dL or 7.7 mmol/L) in the absence of diabetes

Forse sono aiutato dai marker infiammatori?

Inflammatory variables
Leukocytosis (WBC count $>$ 12,000 μL^{-1})
Leukopenia (WBC count $<$ 4000 μL^{-1})
Normal WBC count with greater than 10% immature forms
Plasma C-reactive protein more than two SD above the normal value
Plasma procalcitonin more than two SD above the normal value

Ho degli elementi per valutare l'ipoperfusione e la disfunzione d'organo?

Hemodynamic variables
Arterial hypotension (SBP < 90 mm Hg, MAP < 70 mm Hg, or an SBP decrease > 40 mm Hg in adults or less than two SD below normal for age)
Organ dysfunction variables
Arterial hypoxemia ($Pao_2/FIO_2 < 300$)
Acute oliguria (urine output < 0.5 mL/kg/hr for at least 2 hrs despite adequate fluid resuscitation)
Creatinine increase > 0.5 mg/dL or 44.2 μmol/L
Coagulation abnormalities (INR > 1.5 or aPTT > 60 s)
Ileus (absent bowel sounds)
Thrombocytopenia (platelet count < 100,000 μL^{-1})
Hyperbilirubinemia (plasma total bilirubin > 4 mg/dL or 70 μmol/L)
Tissue perfusion variables
Hyperlactatemia (> 1 mmol/L)
Decreased capillary refill or mottling

I criteri diagnostici di ipoperfusione precoci continuano ad essere clinici e sono questi che attivano il processo diagnostico e il trattamento

Infatti le azioni che intraprendo inizialmente e rapidamente sono probabilmente le più efficaci

SURVIVING SEPSIS CAMPAIGN 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

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 arterial hypotension despite volume resuscitation (septic shock) or initial lactate ≥4 mmol/L (36 mg/dL):
   - Measure central venous pressure (CVP)*
   - Measure central venous oxygen saturation ($Scvo_2$)*
7) Remeasure lactate if initial lactate was elevated*

*Targets for quantitative resuscitation included in the guidelines are CVP of ≥8 mm Hg, $Scvo_2$ of ≥70%, and normalization of lactate.

- I rilievo dei marcatori biologici è innescato dal rilievo clinico
- La selezione dei pazienti è cruciale perché la probabilità pretest determina l'accuratezza del test diagnostico

Valore Predittivo Positivo (VPP)

$$VPP = \frac{\text{sensibilità x prevalenza sepsi}}{\text{(sensibilità x prevalenza sepsi) + [(1 – specificità) x (1 - prevalenza sepsi)]}}$$

Tutte le altre indicazioni delle lineeguida sono di gestione trattamento

In pronto soccorso qual è il momento che attiva la *macchina della sepsi* ?

Surviving Sepsis Campaign

Statement from SSC Leadership on Time Zero in the Emergency Department

The conclusions and recommendations for the next phase of the Surviving Sepsis Campaign performance improvement initiative are to:

- Continue to use triage time as time zero in patients presenting to the ED
- Maximize the bundle's effectiveness for diagnosis as well as treatment
- Acknowledge that a percentage of patients may not meet criteria for severe sepsis or septic shock at ED triage

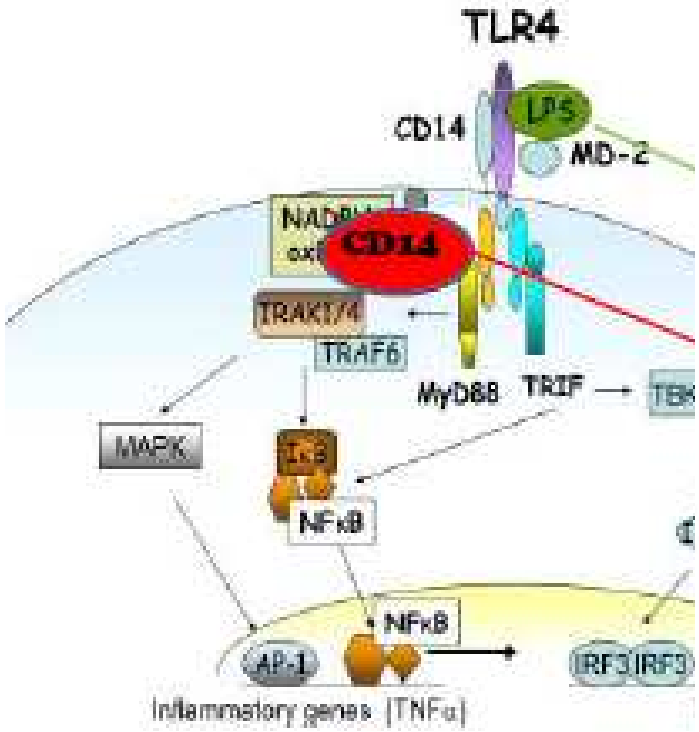
Ulla et al. Critical Care 2013, 17:R168
http://ccforum.com/content/17/4/R168

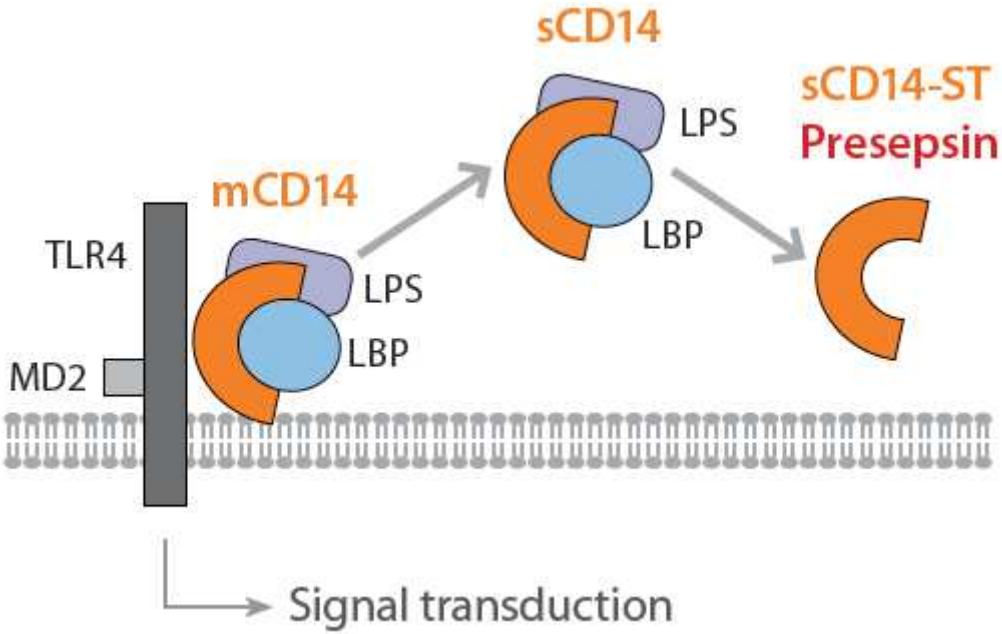
CRITICAL CARE

RESEARCH Open Access

Diagnostic and prognostic value of presepsin in the management of sepsis in the emergency department: a multicenter prospective study

Marco Ulla[1,3*†], Elisa Pizzolato[1†], Manuela Lucchiari[2], Maria Loiacono[2], Flavia Soardo[1], Daniela Forno[1], Fulvio Morello[1], Enrico Lupia[1], Corrado Moiraghi[1], Giulio Mengozzi[2] and Stefania Battista[1]





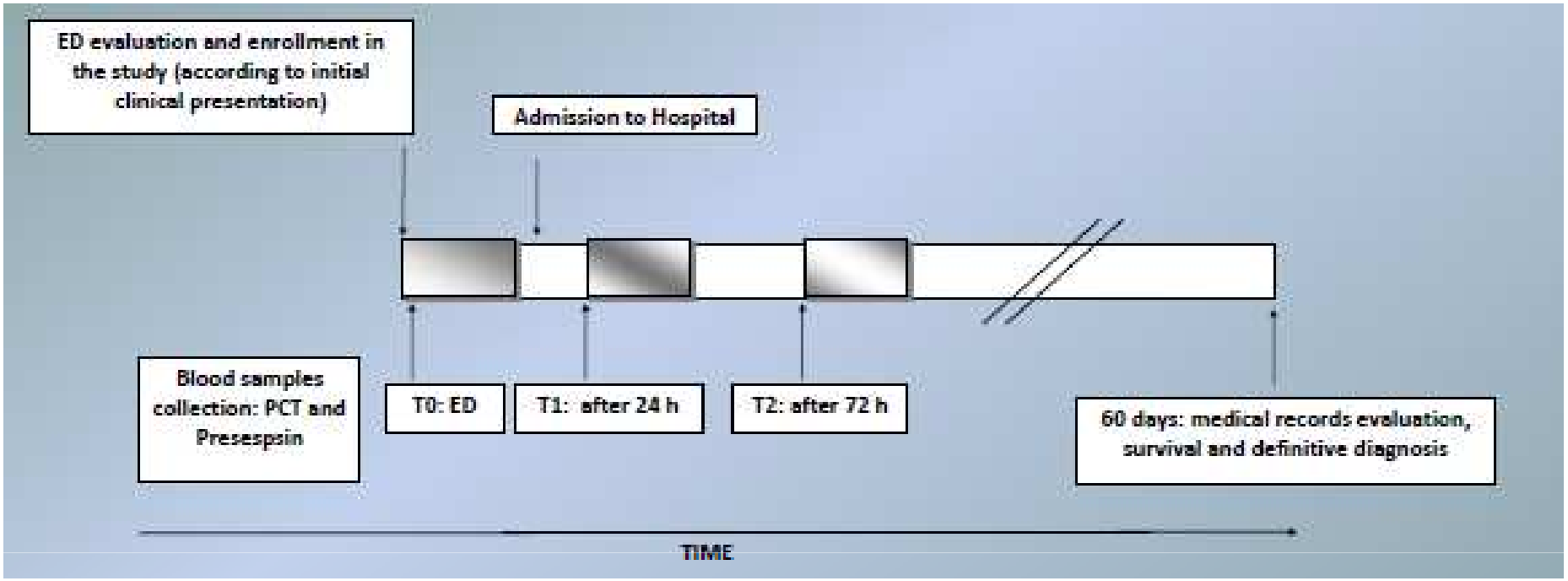
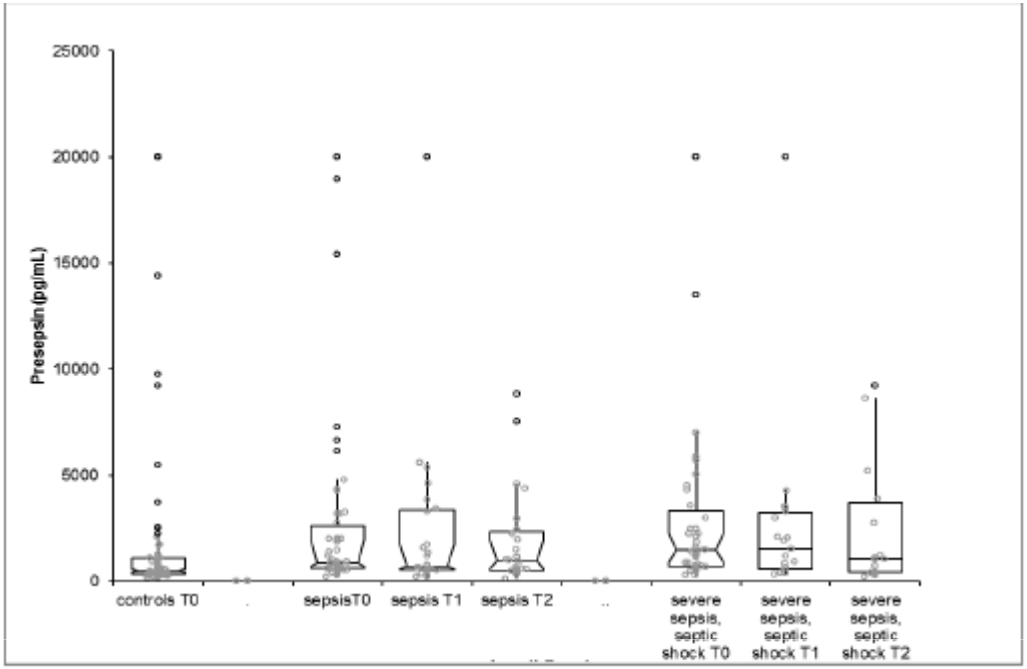
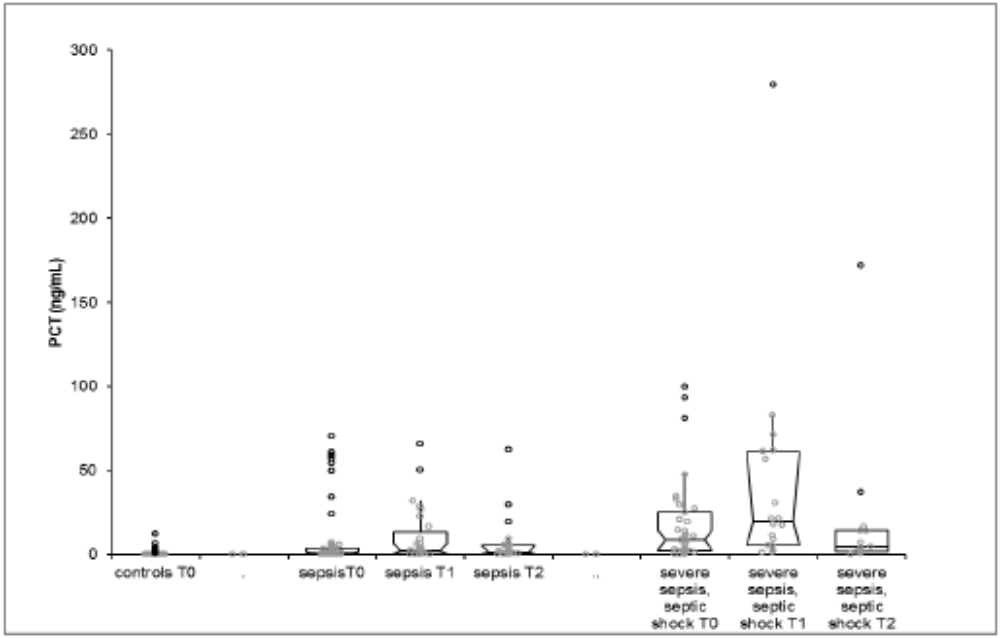


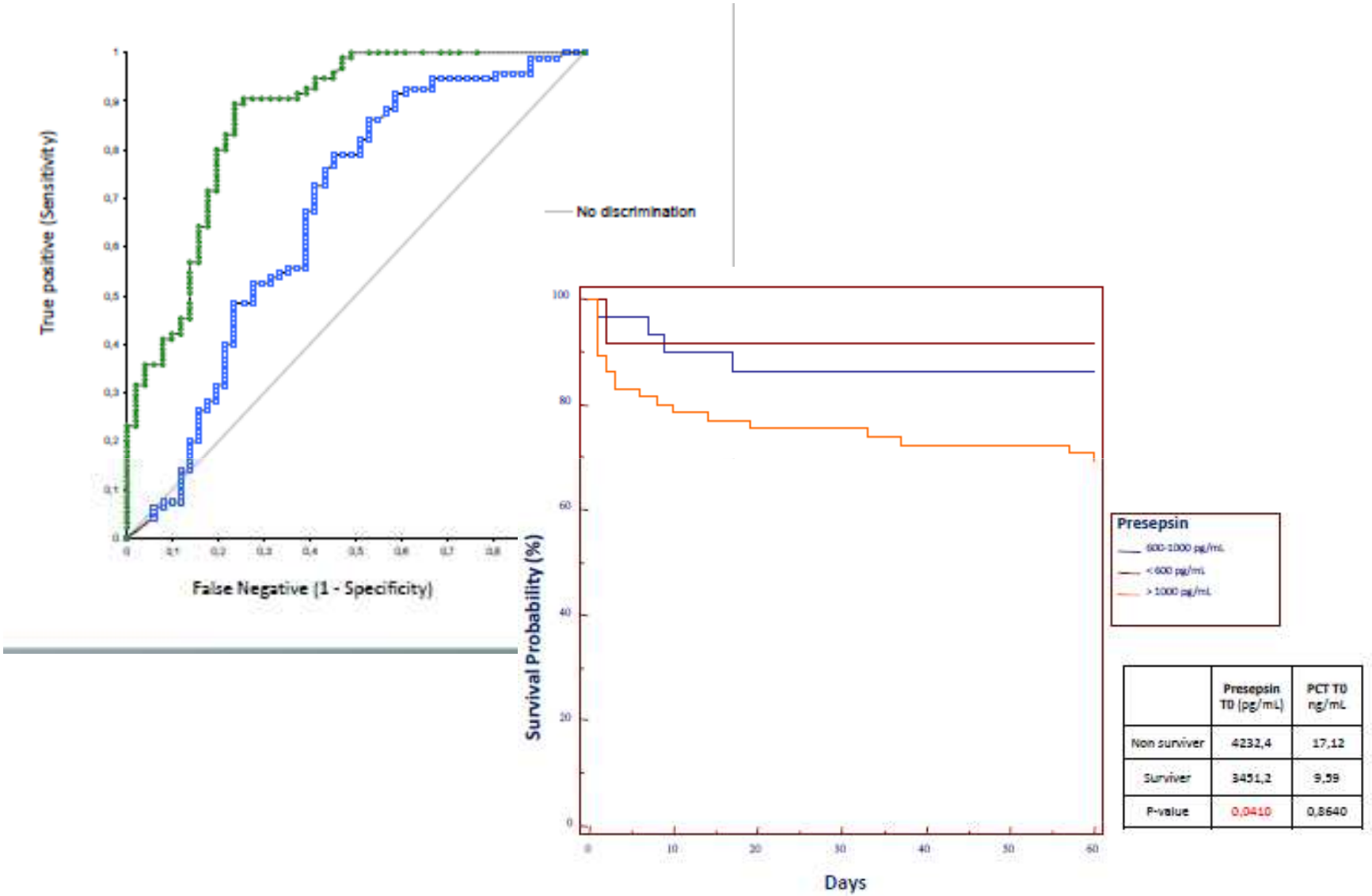
Table 1 Demographic and clinical characteristics of the subjects in the study.[a]

	SIRS (n = 83)	Sepsis (n = 55)	Severe sepsis/septic shock (n = 51)
Male	53	32	31
Female	30	23	20
Age	56 (19 to 92)	71 (27 to 99)	71 (22 to 90)
SOFA score	2 (0 to 8)	3 (0 to 9)	5 (0 to 15)
APACHE II score	7 (0 to 19)	11 (2 to 26)	14 (4 to 33)



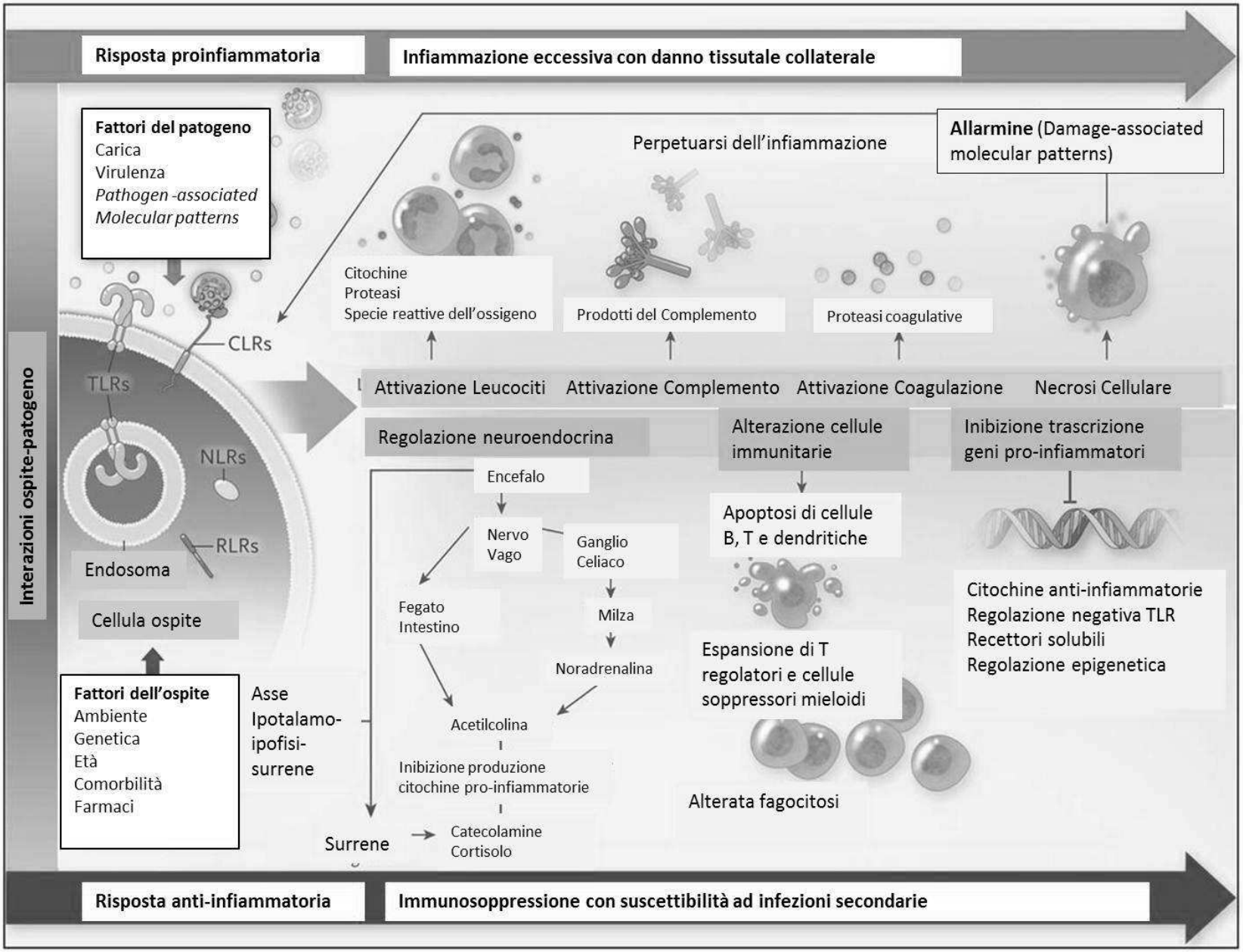


Ulla *et al. Critical Care* 2013, **17**:R168
http://ccforum.com/content/17/4/R168

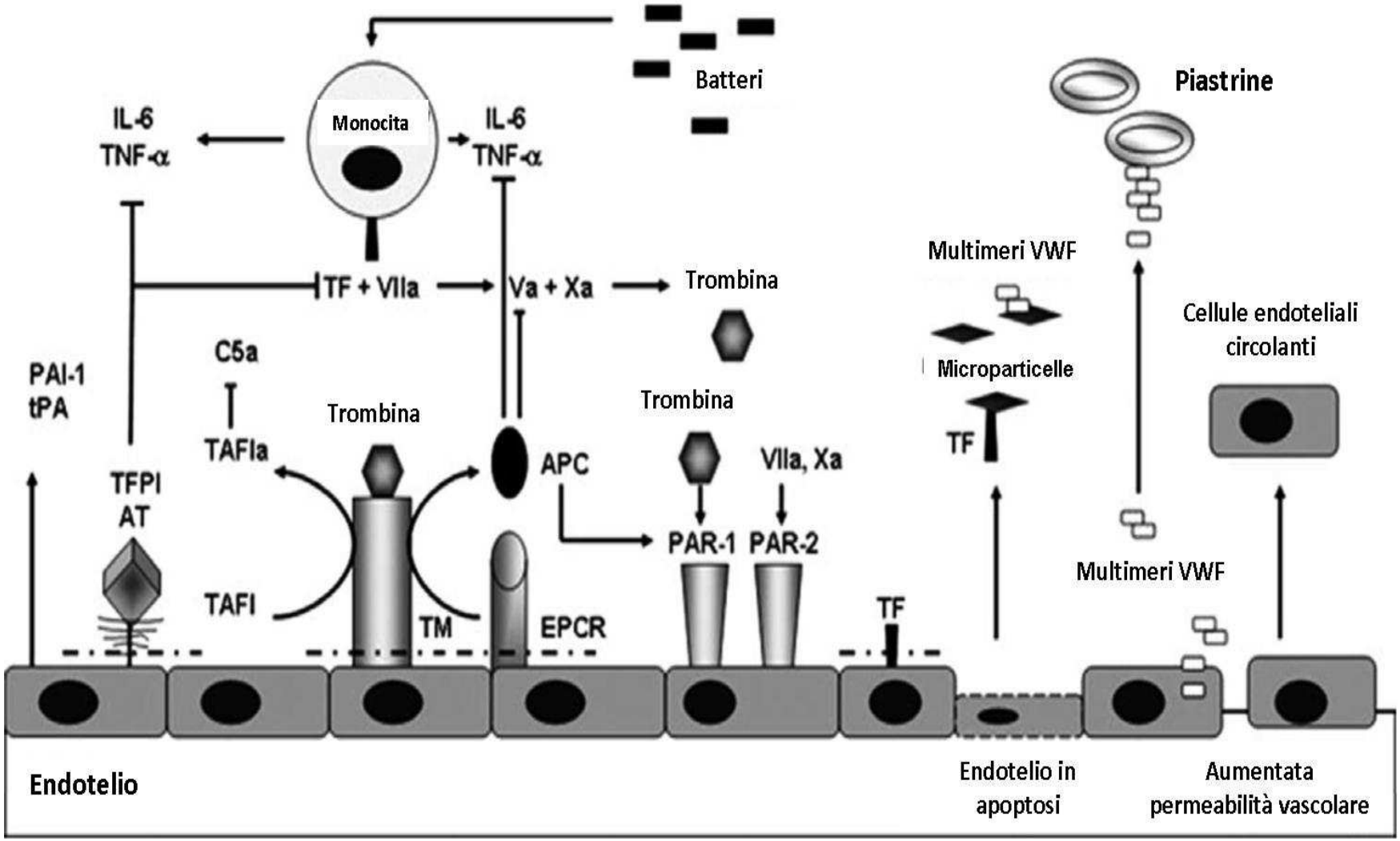


	Presepsin T0 (pg/mL)	PCT T0 ng/mL
Non survivor	4232,4	17,12
Survivor	3451,2	9,59
P-value	0,0410	0,8640

Ulla *et al. Critical Care* 2013, **17**:R168
http://ccforum.com/content/17/4/R168



Modificato da Angus DC et al. N Engl J Med 2013; 369:840-51.



Modificato da Marcel Levi, Tom van der Poll. Crit Care Med 2010 Vol. 38, No. 2.

Adamzik *et al. Critical Care* 2010, **14**:R178
http://ccforum.com/content/14/5/R178

CRITICAL CARE

RESEARCH Open Access

Comparison of thromboelastometry with procalcitonin, interleukin 6, and C-reactive protein as diagnostic tests for severe sepsis in critically ill adults

Michael Adamzik[1], Martin Eggmann[1], Ulrich H Frey[1], Klaus Görlinger[1], Martina Bröcker-Preuß[2], Günter Marggraf[3], Fuat Saner[4], Holger Eggebrecht[5], Jürgen Peters[1], Matthias Hartmann[1*]

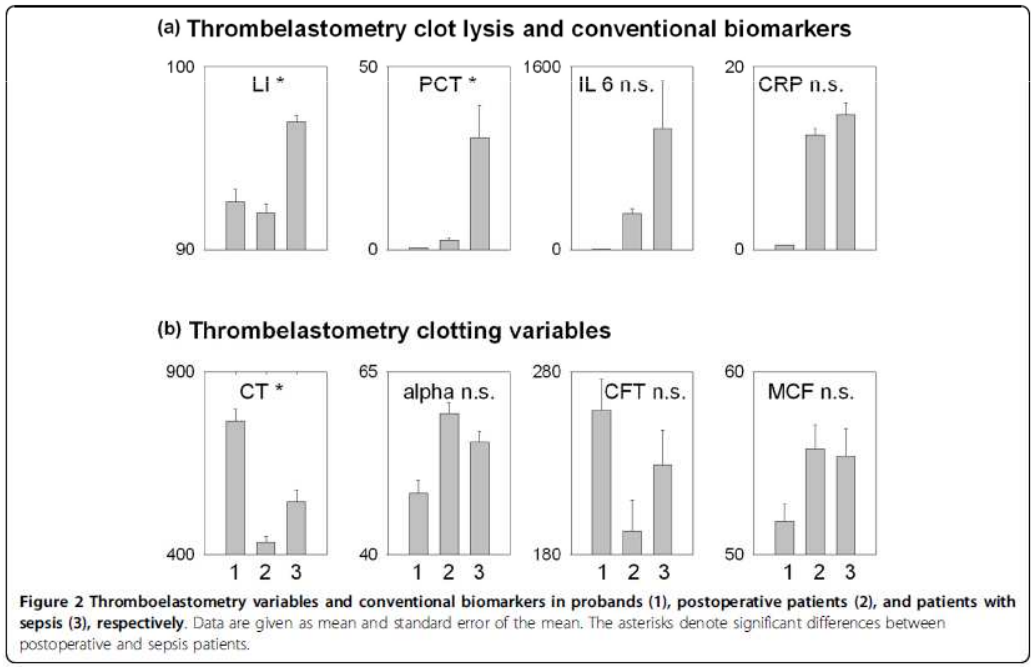


Figure 2 Thromboelastometry variables and conventional biomarkers in probands (1), postoperative patients (2), and patients with sepsis (3), respectively. Data are given as mean and standard error of the mean. The asterisks denote significant differences between postoperative and sepsis patients.

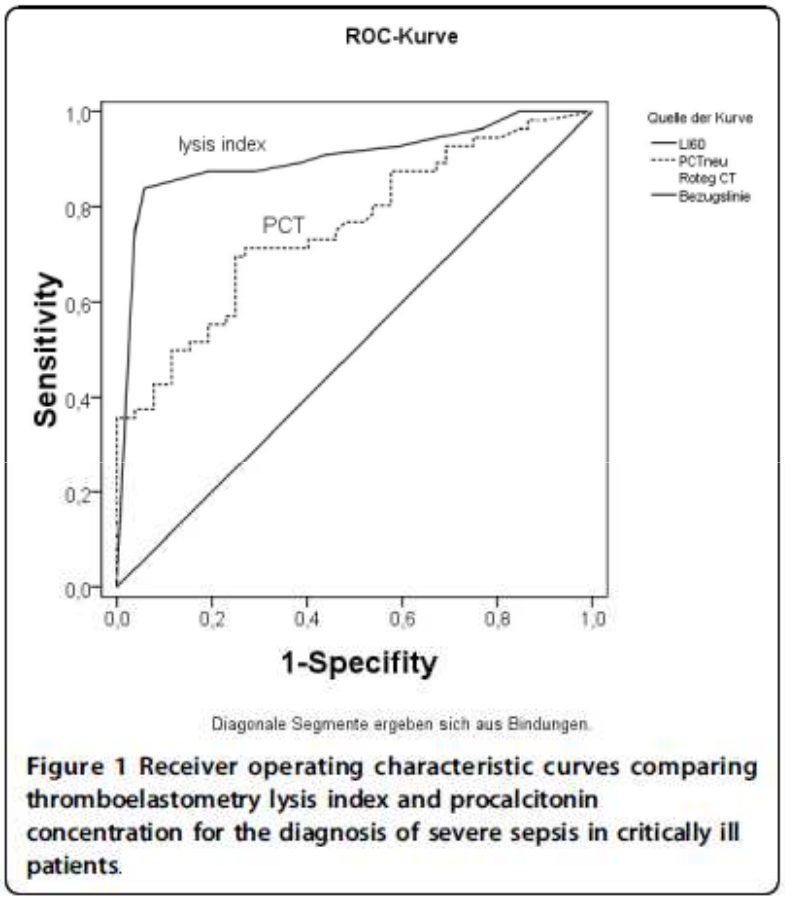


Figure 1 Receiver operating characteristic curves comparing thromboelastometry lysis index and procalcitonin concentration for the diagnosis of severe sepsis in critically ill patients.

Adamzik M, et al. Crit Care 2010; 14: R178.

Adamzik et al. Critical Care 2012, 16:R204
http://ccforum.com/content/16/5/R204

CRITICAL CARE

RESEARCH Open Access

Whole blood impedance aggregometry as a biomarker for the diagnosis and prognosis of severe sepsis

Michael Adamzik†, Klaus Görlinger†, Jürgen Peters and Matthias Hartmann*

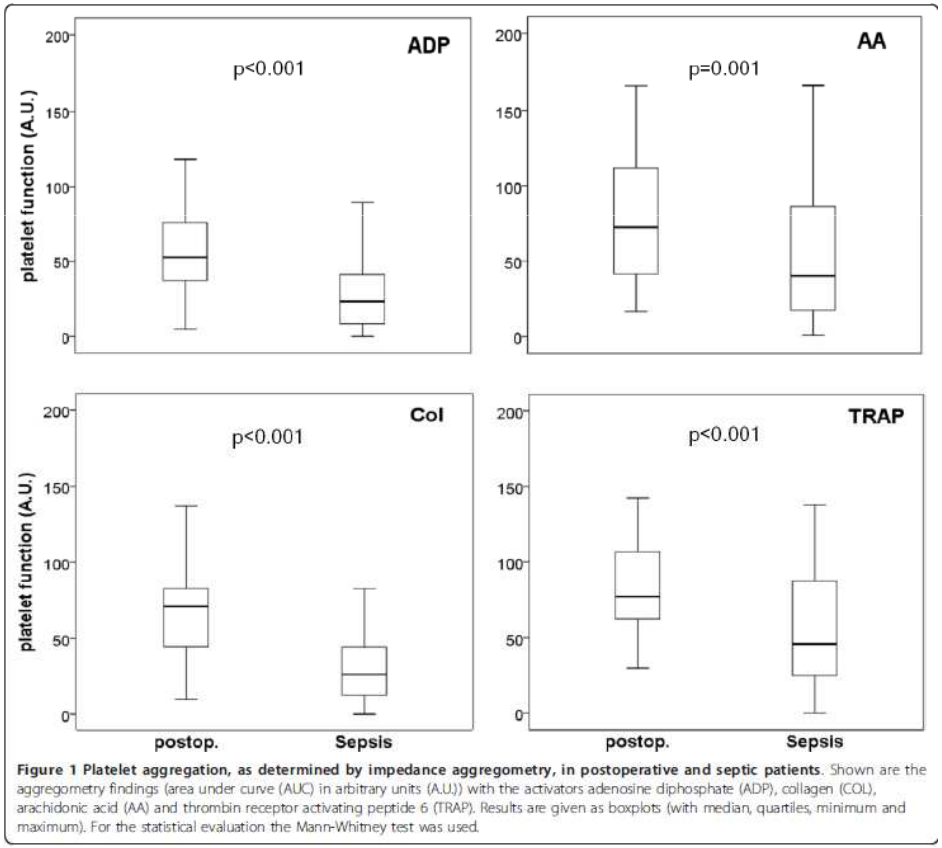


Figure 1 Platelet aggregation, as determined by impedance aggregometry, in postoperative and septic patients. Shown are the aggregometry findings (area under curve (AUC) in arbitrary units (A.U.)) with the activators adenosine diphosphate (ADP), collagen (COL), arachidonic acid (AA) and thrombin receptor activating peptide 6 (TRAP). Results are given as boxplots (with median, quartiles, minimum and maximum). For the statistical evaluation the Mann-Whitney test was used.

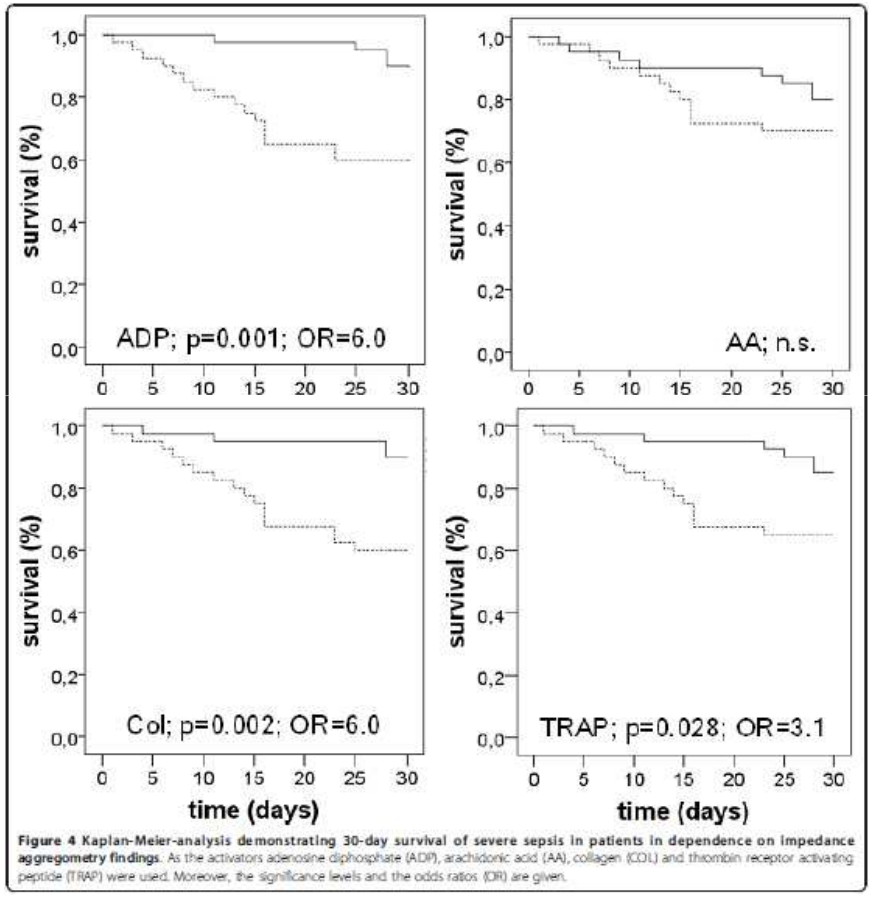


Figure 4 Kaplan-Meier-analysis demonstrating 30-day survival of severe sepsis in patients in dependence on impedance aggregometry findings. As the activators adenosine diphosphate (ADP), arachidonic acid (AA), collagen (COL) and thrombin receptor activating peptide (TRAP) were used. Moreover, the significance levels and the odds ratios (OR) are given.

Adamzik M, et al. Crit Care 2012; 16: R204.

PROTOCOLLO MULTITEM

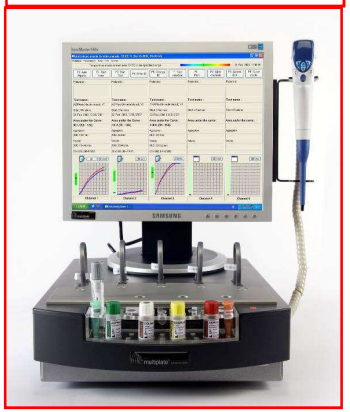
AZIENDA OSPEDALIERO-UNIVERSITARIA
Città della Salute e della Scienza di Torino

SEPSI, SEPSI GRAVE/SHOCK SETTICO

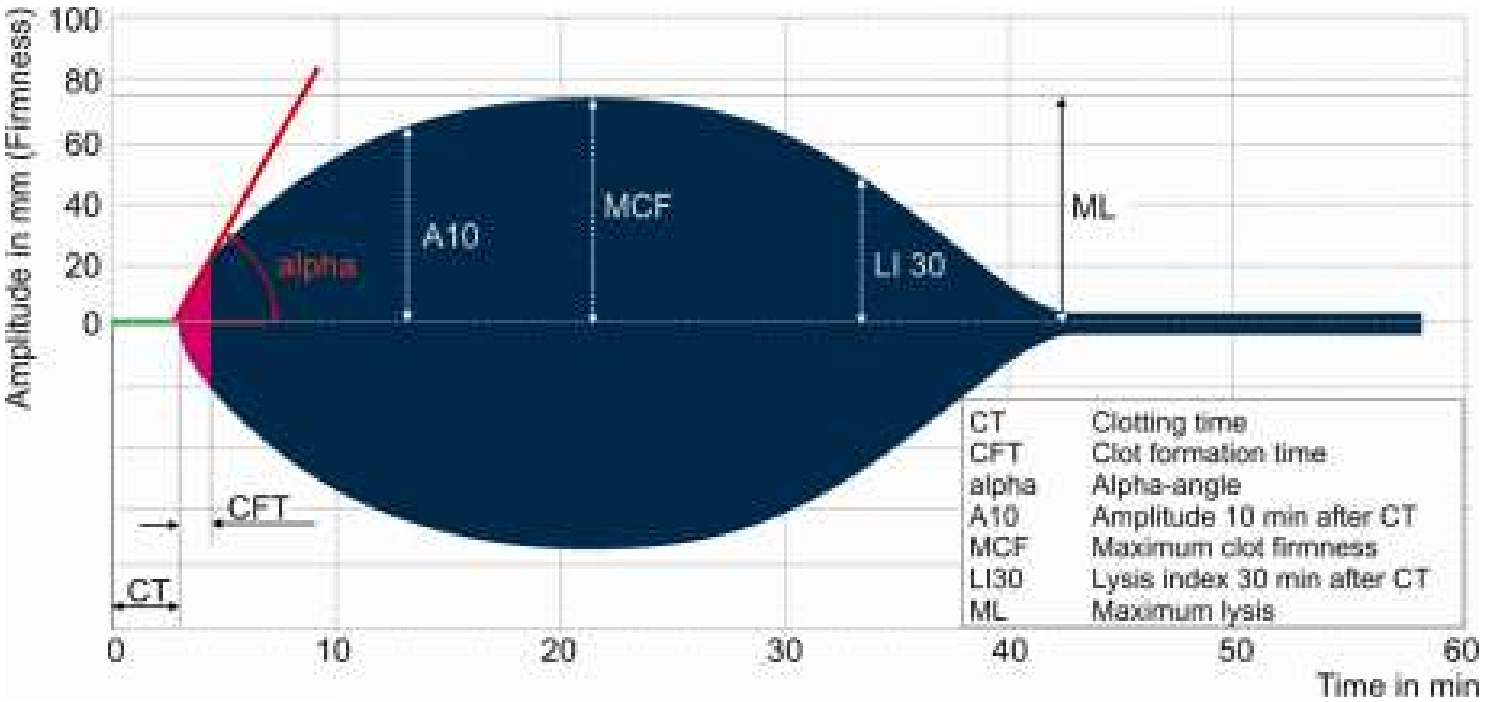
POLI-TRAUMA (ISS>15)

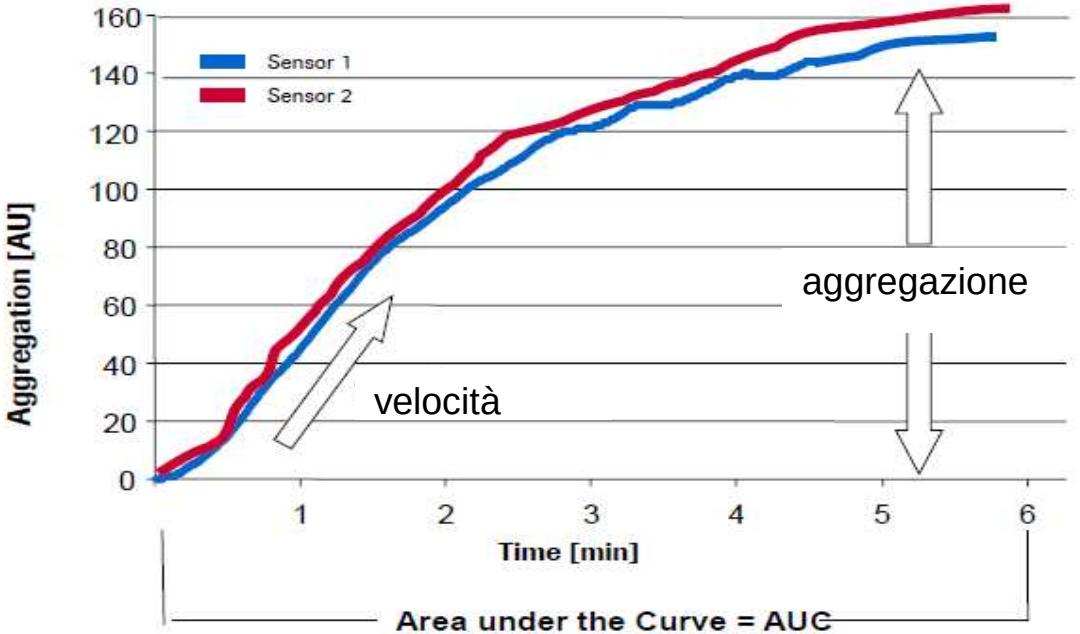
VALUTAZIONE IN EMERGENZA IN PS
Parametri clinici (CRF)
Ematochimici di Routine

MULTIPLATE®

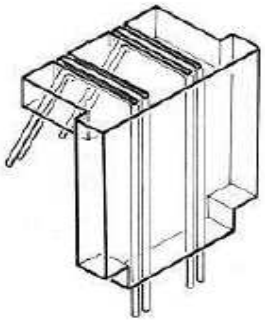


ROTEM®





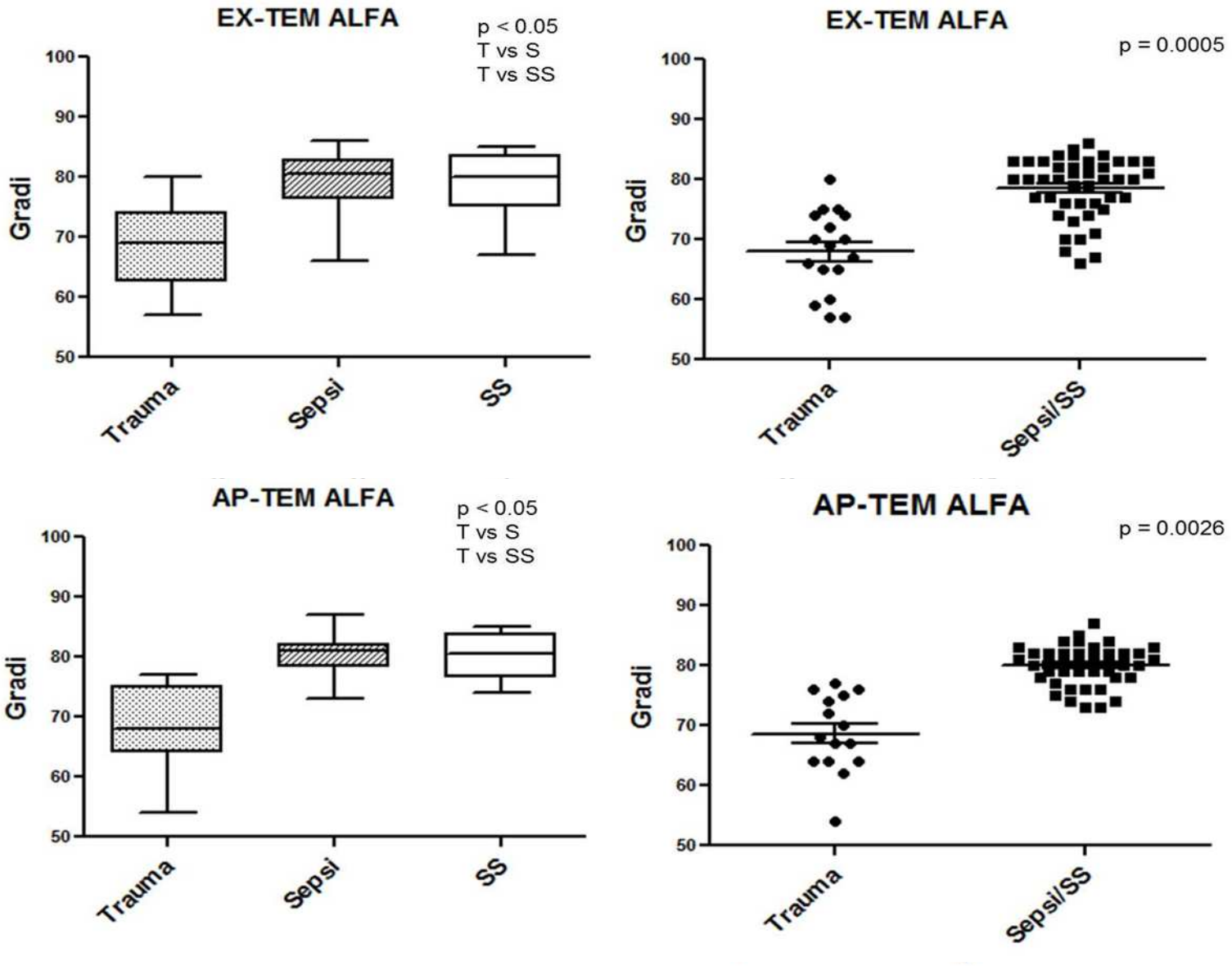
- E' l'unità di misura più importante
- espressa in AU*min o **U** (10 AU*min = 1 U)



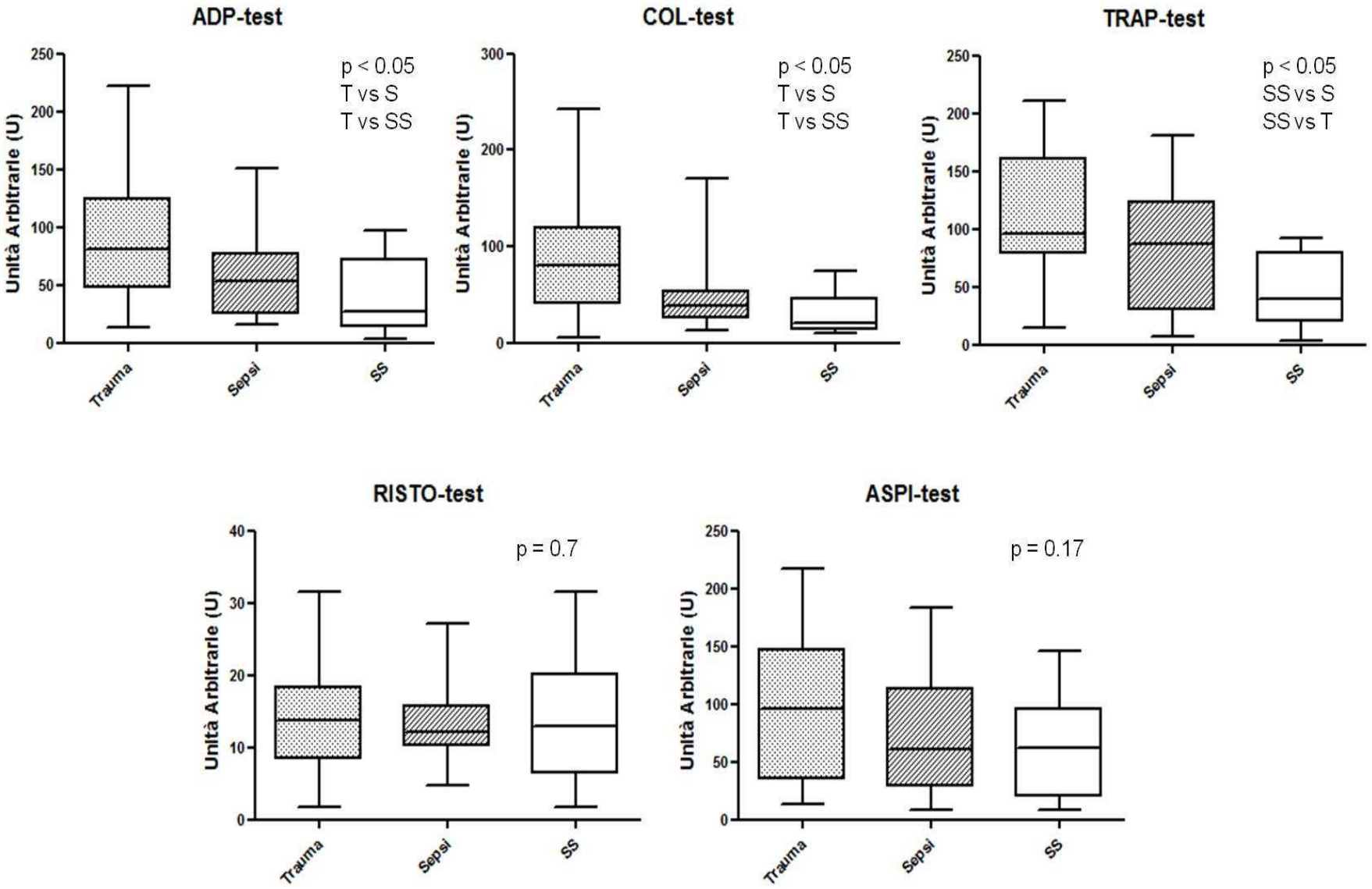
sensor 1+2

Variabili CLINICHE	TRAUMA (T)	SEPSI (S)	SEPSI GRAVE SHOCK SETTICO (SS)	p-VALUE
PAM mmHg	93 (4)	91 (2.3)	62 (1.8)	<0.05 (SS vs S e T)
TC °	36.1 (0.16)	38.2 (0.18)	37.9 (0.23)	<0.05 (T vs S e SS)
GCS	11 (1)	15 (0.06)	14 (0.6)	<0.05 (T vs S e SS)
IOT e VM	9 (42%)	/	1 (3%)	
AMINE	5 (24%)	/	5 (26%)	
TERAPIA ANTICOAGULANTE	/	6 (18%)	6 (31%)	
TERAPIA ANTIAGGREGANTE	2 (1%)	8 (25%)	4 (19%)	
EXITUS A 28 GIORNI	1 (3,7%)	/	6 (23%)	
DURATA RICOVERO (Range)	18 (1-45)*	11 (1-42)	14 (5-30)**	

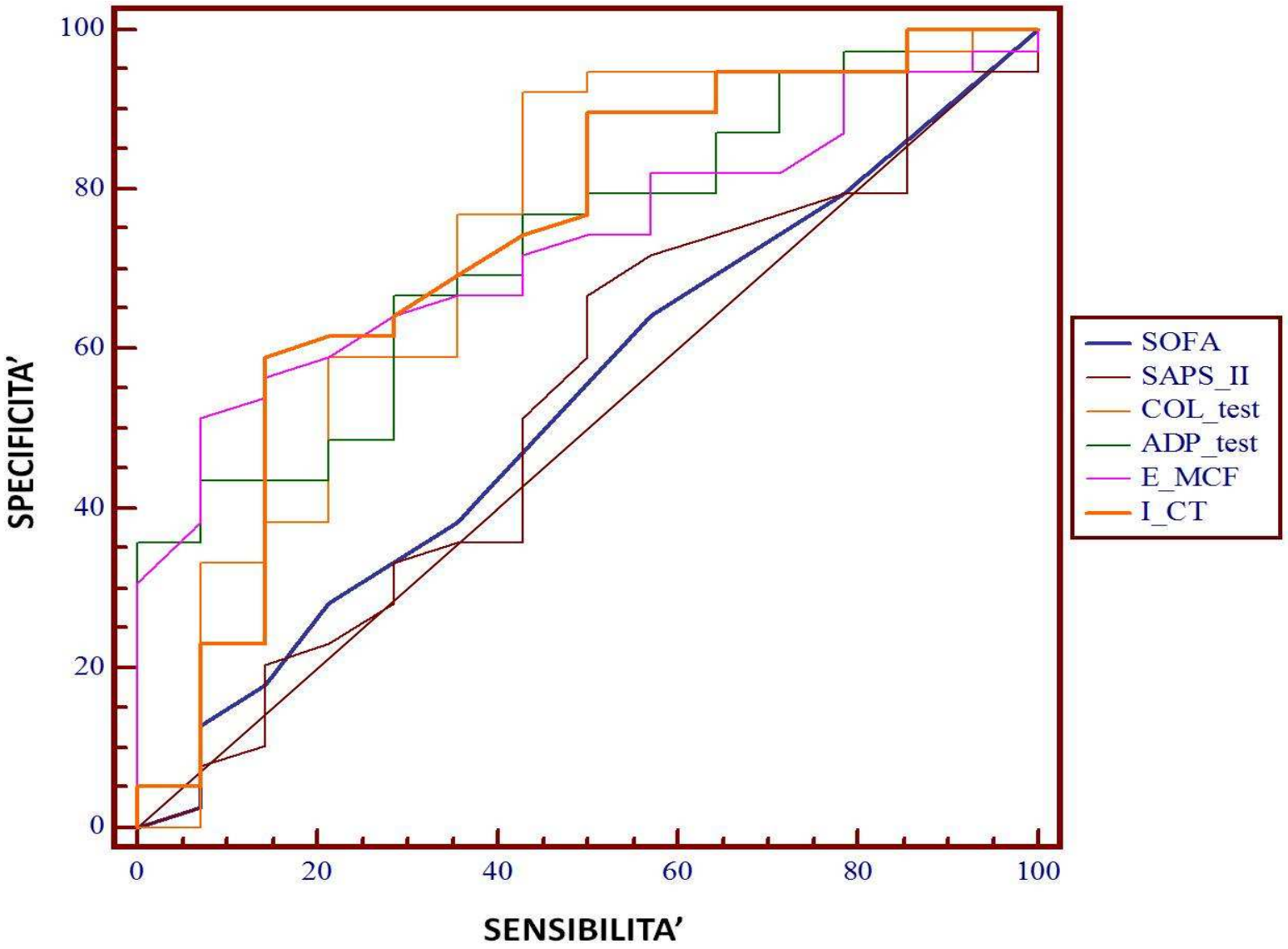
Variabili di LABORATORIO	TRAUMA	SEPSI	SEPSI GRAVE SHOCK SETTICO	p-VALUE
FIBRINOGENO mg/dL	270 (21)	566 (30)	531 (30)	<0.05 (T vs S e SS)
AT III %	95.7 (4.7)	86.5 (3.2)	85.3 (6.1)	NS
D-DIMERO µg/mL	20.4 (3.9)	2.4 (0.3)	10.5 (2.9)	<0.05
BE	-2.7 (1)	-0.7 (0.7)	-2.9 (0.7)	NS
LATTATO mmol/L	2.9 (0.5)	1.4 (0.11)	3.48 (0.5)	<0.05 (S vs T e SS)
CREATININA mg/dL	0.97 (0.05)	1.25 (0.16)	1.9 (0.3)	<0.05 (SS vs S e T)
PCR mg/L	/	132 (17)	128 (31)	NS
PCT ng/mL	0.074 (0.01)	4.89 (3.2)	20.8 (8.7)	<0.05



Tromboelastometria - MULTITEM study



Aggregometria - MULTITEM study



Accuratezza - MULTITEM study

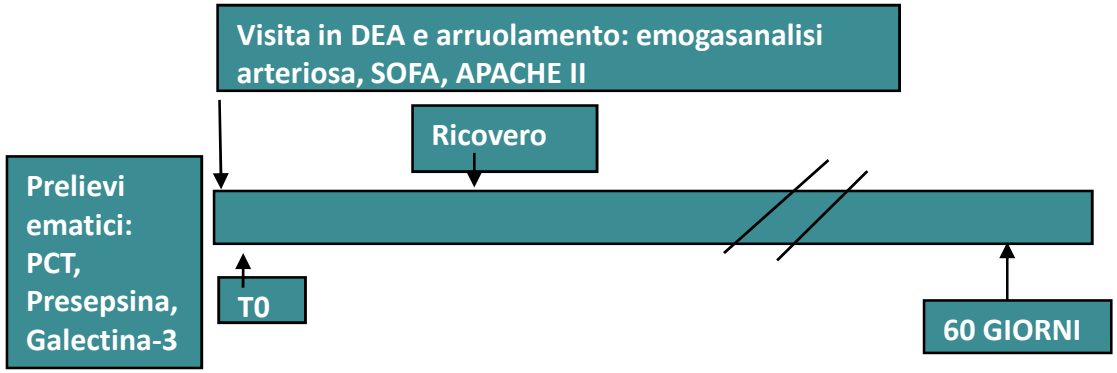
- Questo lavoro rappresenta il primo esempio di applicazione congiunta di metodiche **Point-of-Care** per la valutazione della coagulazione plasmatica (Rotem®) e della funzionalità piastrinica (Multiplate®) in pazienti affetti da SIRS infettiva e non infettiva in pronto soccorso e **nell'ambito dell'emergenza**.

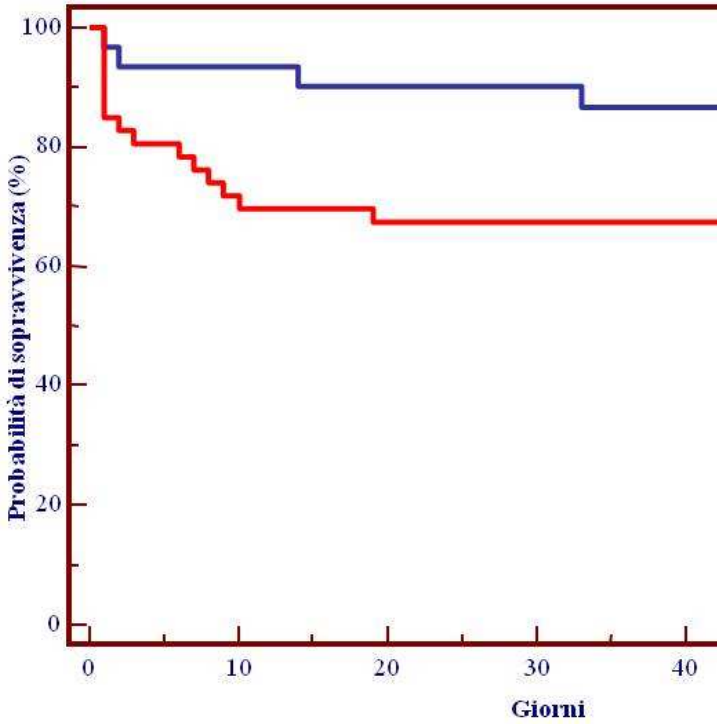
- Si sono osservate **alterazioni peculiari** a carico del sistema coagulativo (allungamento del CT, incremento di MCF, A10, angolo α) e della aggregabilità piastrinica (ipo-aggregabilità su ADP-test, COL-test e TRAP-test) **in pazienti affetti da sepsi, sepsi grave e shock settico** sin dalla prima valutazione in pronto soccorso.

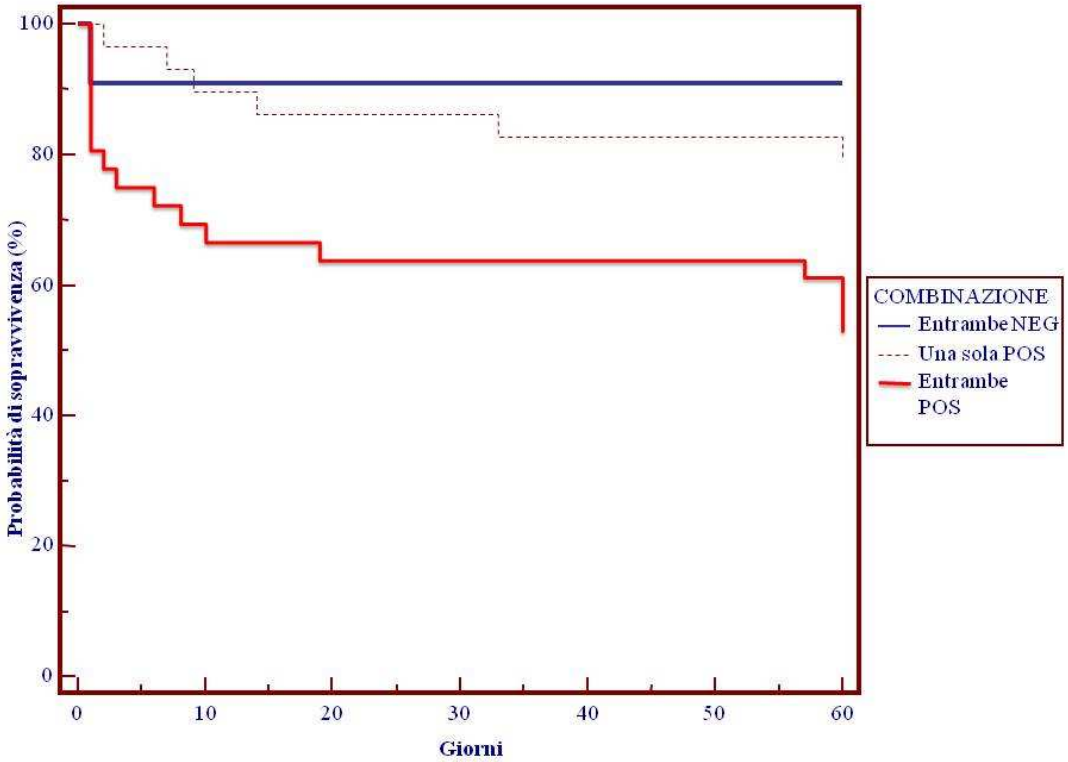
- Tali alterazioni sono in grado di **distinguere** in maniera significativa e con una buona accuratezza le condizioni di SIRS a genesi infettiva rispetto a quadri di SIRS ad eziologia non infettiva.

CONCLUSIONI - MULTITEM study

GALECTINA-3







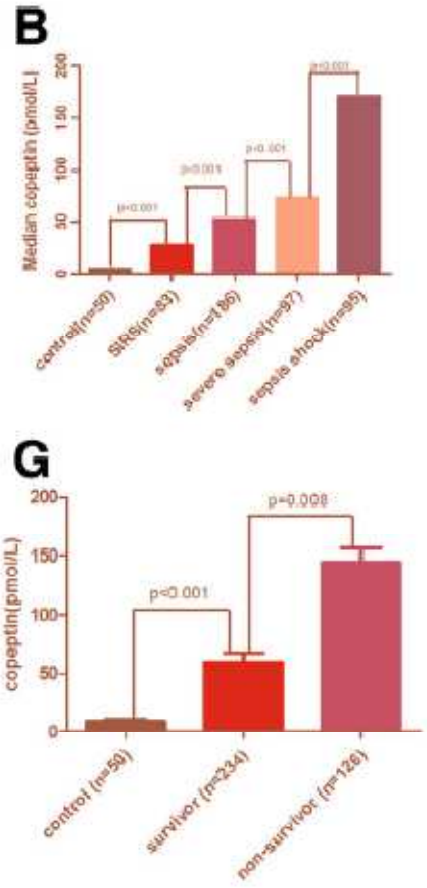
Galluzzo et al. *In press*

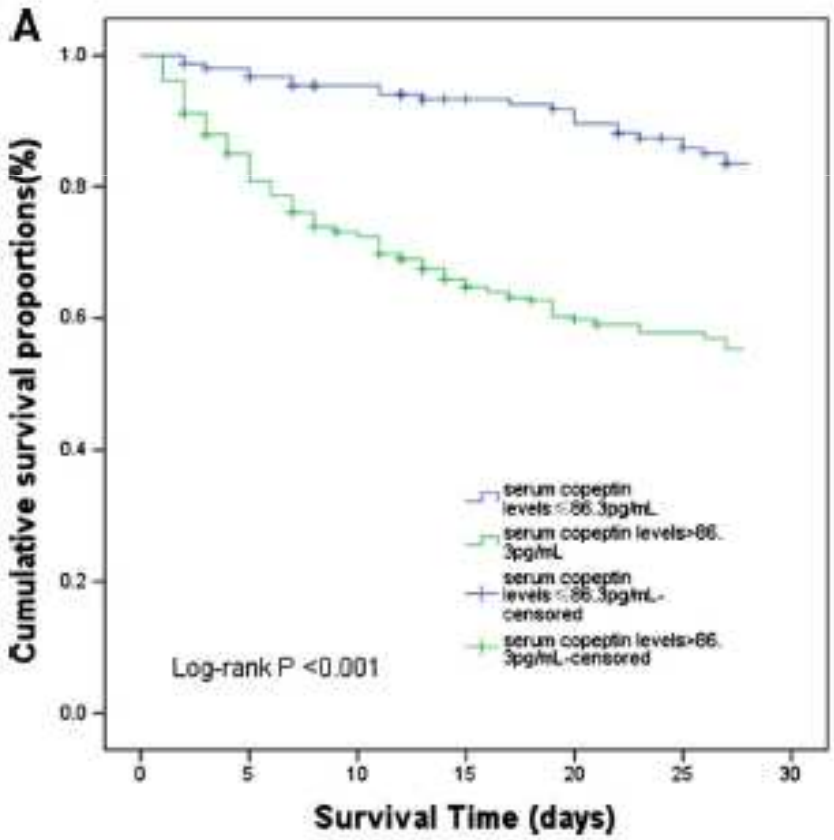
Intensive Care Med (2014) 40:1499–1508
DOI 10.1007/s00134-014-3468-4

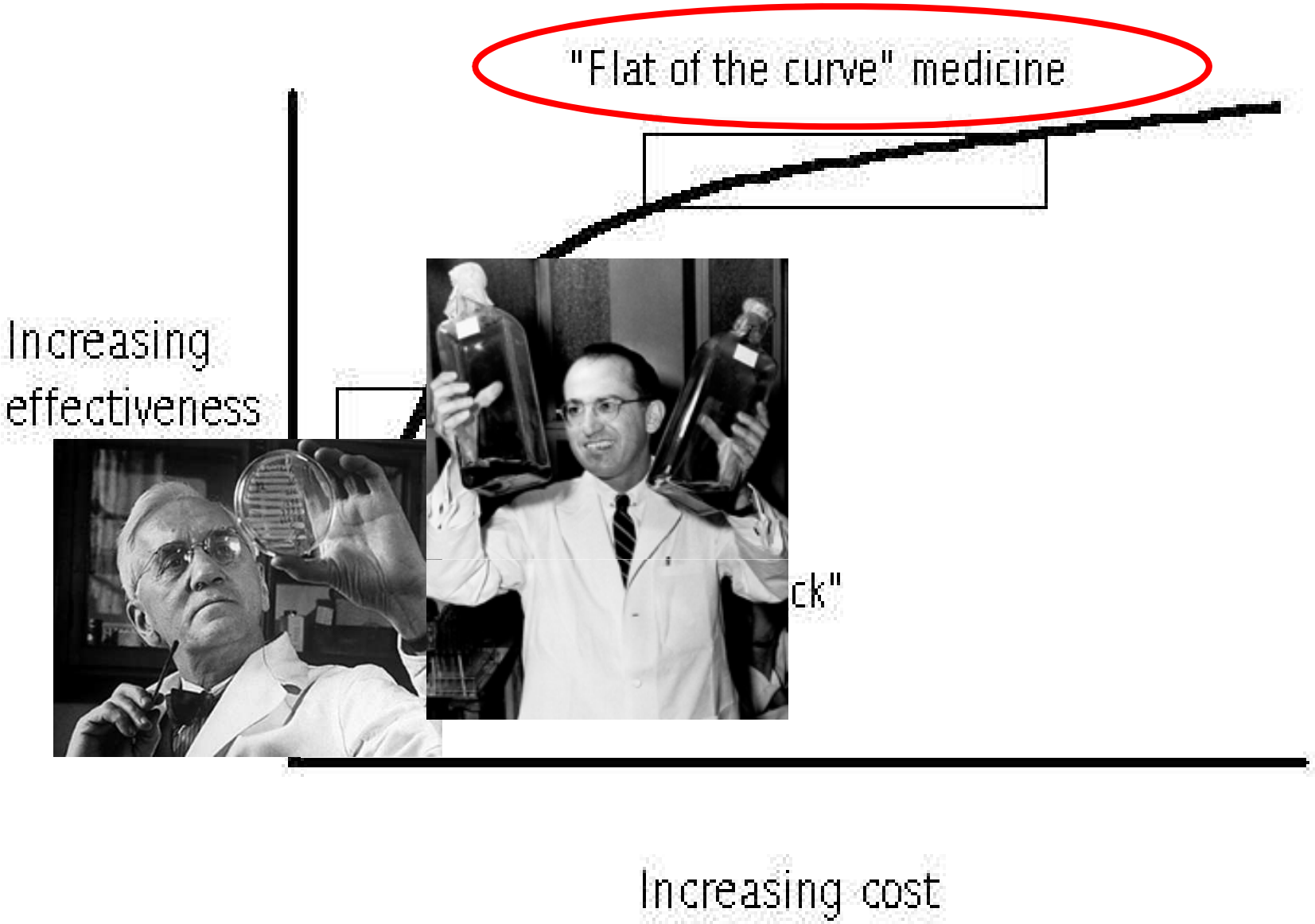
ORIGINAL

Qian Zhang
Guijuan Dong
Xin Zhao
Miaomiao Wang
Chun-Sheng Li

Prognostic significance of hypothalamic–pituitary–adrenal axis hormones in early sepsis: a study performed in the emergency department





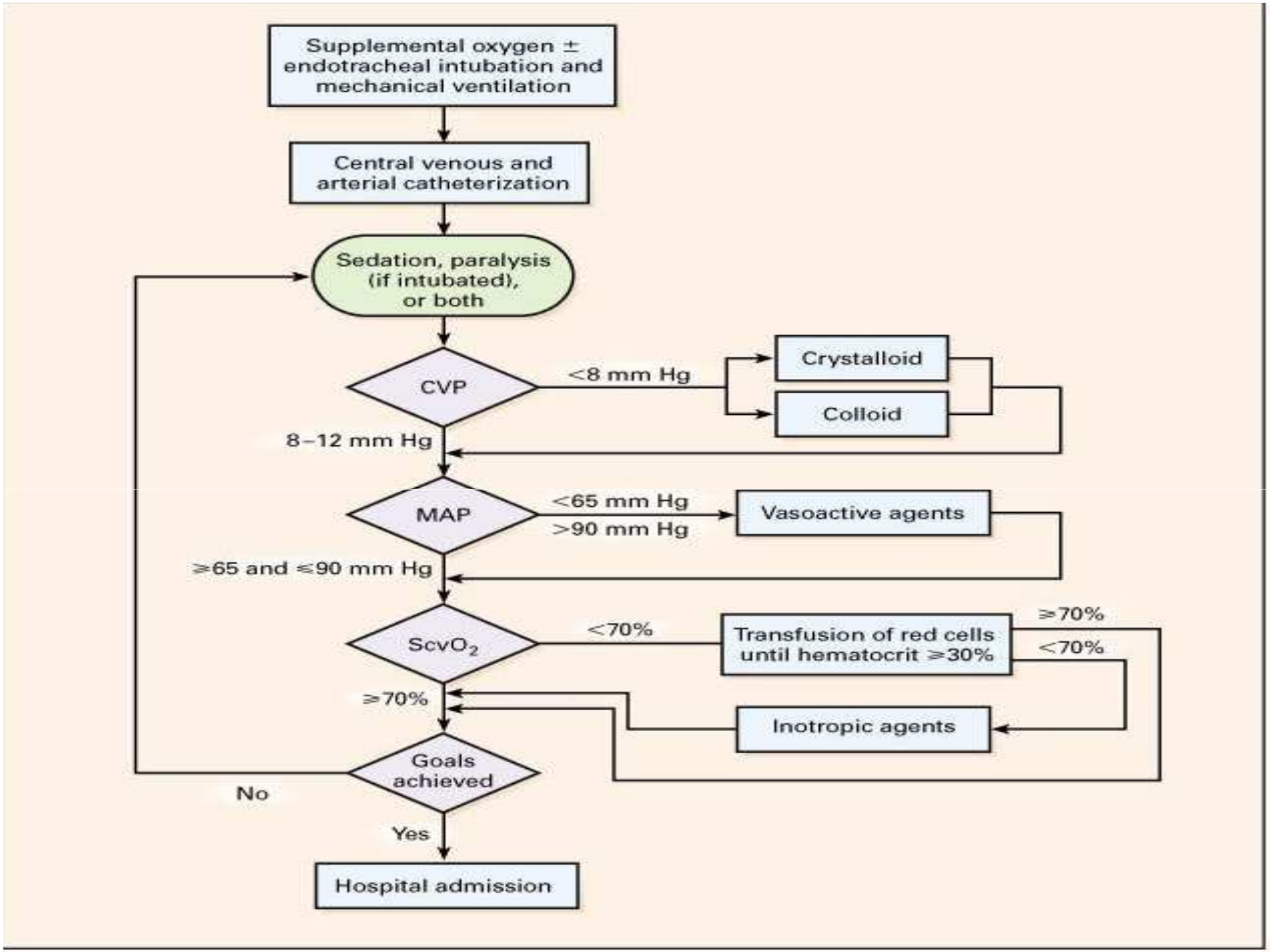


“Who owns the patent on this vaccine?'
'Well, the people, I would say. There is no patent. Could you patent the sun?”

Jonas Salk

APRA’ SECONDA PARTE

Quando eravamo felici (2000-2013)


Supplemental oxygen ± endotracheal intubation and mechanical ventilation
Central venous and arterial catheterization
Sedation, paralysis (if intubated), or both
CVP
<8 mm Hg
Crystalloid
Colloid
8–12 mm Hg
MAP
<65 mm Hg
>90 mm Hg
Vasoactive agents
≥65 and ≤90 mm Hg
ScvO2
<70%
Transfusion of red cells until hematocrit ≥30%
≥70%
<70%
≥70%
Inotropic agents
Goals achieved
No
Yes
Hospital admission

These articles were published on March 18, 2014, at NEJM.org.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

The ProCESS Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

EDITORIAL

The ProCESS Trial — A New Era of Sepsis Management

Craig M. Lilly, M.D.

The importance of early detection and treatment for reducing the mortality associated with sepsis has been a tenet of medical training since the middle ages, when it was noted that ". . . the physicians say it happens in hectic fever, that in the beginning of the malady it is easy to cure but creased mortality to delays in the administration of appropriate antibiotics[6] suggested that early administration of antibiotics increased survival in all groups of the trial. Indeed, in the ProCESS trial, the early or facilitated recognition of septic shock, administration of intravenous antibi-

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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., Bruno Megarbane, M.D., Ph.D., Nadia Anguel, M.D., Jean-Paul Mira, M.D., Ph.D., Pierre-François Dequin, M.D., Ph.D., Soizic Gergaud, M.D., Nicolas Weiss, M.D., Ph.D., François Legay, M.D., Yves Le Tulzo, M.D., Ph.D., Marie Conrad, M.D., René Robert, M.D., Ph.D., Frédéric Gonzalez, M.D., Christophe Guitton, M.D., Ph.D., Fabienne Tamion, M.D., Ph.D., Jean-Marie Tonnelier, M.D., Pierre Guezennec, M.D., Thierry Van Der Linden, M.D., Antoine Vieillard-Baron, M.D., Ph.D., Eric Mariotte, M.D., Gaël Pradel, M.D., Olivier Lesieur, M.D., Jean-Damien Ricard, M.D., Ph.D., Fabien Hervé, M.D., Damien Du Cheyron, M.D., Ph.D., Claude Guerin, M.D., Ph.D., Alain Mercat, M.D., Ph.D., Jean-Louis Teboul, M.D., Ph.D., and Peter Radermacher, M.D., Ph.D. for the SEPSISPAM Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

EDITORIAL

Is There a Good MAP for Septic Shock?

James A. Russell, M.D.

As fundamental as the issue is, there is no clear, high-level evidence to determine the most effective mean arterial pressure (MAP) for resuscitation of patients with septic shock. During hypotions are based on low-quality evidence. Accordingly, Asfar et al.[4] now report in the *Journal* the results of a large, randomized, controlled trial of targeting a low MAP (65 to 70 mm Hg) ver-

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Albumin Replacement in Patients with Severe Sepsis or Septic Shock

Pietro Caironi, M.D., Gianni Tognoni, M.D., Serge Masson, Ph.D., Roberto Fumagalli, M.D., Antonio Pesenti, M.D., Marilena Romero, Ph.D., Caterina Fanizza, M.Stat., Luisa Caspani, M.D., Stefano Faenza, M.D., Giacomo Grasselli, M.D., Gaetano Iapichino, M.D., Massimo Antonelli, M.D., Vieri Parrini, M.D., Gilberto Fiore, M.D., Roberto Latini, M.D., and Luciano Gattinoni, M.D., for the ALBIOS Study Investigators*

- Perché è successo tutto questo?

- EGDT non è servito a niente?

Surviving Sepsis Campaign

Surviving Sepsis Campaign Responds to ProCESS Trial
Updated 19 May 2014

The Surviving Sepsis Campaign (SSC) has received many inquiries regarding the recent publication of the Protocol-Based Care for Early Septic Shock (ProCESS) trial's effect on the continuing activities of the Campaign. (1)

(1) The ProCESS trial reflects the consensus that early diagnosis of septic shock is essential. Notably, all groups in the study received on average more than 2 liters of fluid prior to randomization and more than 75% received antibiotics prior to randomization--both elements of the 3-hour Surviving Sepsis Campaign bundle. (2) The editorial accompanying the ProCESS study highlights these points. (3)

Surviving Sepsis Campaign

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(2) The 18% mortality rate in the "usual care" arm of ProCESS illustrates a dramatic change in the management and outcomes of patients with septic shock. (1) In comparison, septic shock mortality was 46.5% in the 2001 early goal-directed therapy trial by Rivers. (4)

Surviving Sepsis Campaign

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(3) Given the remarkably low mortality rate in the control arm of ProCESS, and the pending results of 2 large ongoing trials (the Australian Resuscitation In Sepsis Evaluation Randomised Controlled Trial [ARISE] and The Protocolised Management in Sepsis Trial [ProMISe]), the SSC will determine any appropriate revisions to the bundle elements when these study results are available.

Bisogna stare attenti a quello che si dice!

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Surviving Sepsis Campaign Responds to ProCESS Trial
Updated 19 May 2014

(4) ProCESS does not address the protocolized management of patients with severe sepsis without septic shock, a group of patients for whom early detection and treatment remain critical. The aggressive protocolized management of these patients who do not yet have shock has likely lowered severe sepsis and septic shock mortality since the inception of the SSC. The recently formed Society of Critical Care Medicine/Society of Hospital Medicine (SCCM/SHM) Early Diagnosis and Treatment of Severe Sepsis on the Hospital Floors Collaboratives will focus in large part on this population. Further, the ProCESS results have no impact on the 3-hour bundle, which is the primary focus for the Collaboratives.

Ancora una volta gli studi non si occupano dei pazienti più comuni, a di quelli che interessano più i medici!

Surviving Sepsis Campaign

Surviving Sepsis Campaign Responds to ProCESS Trial
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(5) Regarding the SSC 6-hour bundle (2):

a. A companion paper appears to support a mean initial arterial pressure (MAP) target of 65 mm Hg, which is one of the indicators in this bundle. (5)

b. The ProCESS paper does not address repeating lactate measures in patients with elevated lactate while literature supports doing so. (6,7)

c. When measured, the first $ScvO_2$ was 71 ± 13%, which is another of the indication of the bundle.

d. The majority of the patients in the usual care (56.5%) and protocol-based standard care arms (57.9%) of ProCESS had central lines inserted as part of clinical care. (1) The 6-hour bundle currently asks only that central venous pressure (CVP) be measured and that a venous blood gas be sent from that line to obtain the central venous oxygen saturation ($ScvO_2$). SSC recognizes that alternate means of obtaining results exist and will address specific ways of including those data in future iterations of the quality improvement database.

Tutti d’accordo?

The effect of goal-directed therapy on mortality in patients with sepsis - earlier is better: a meta-analysis of randomized controlled trials

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Complotto?

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Harmonizing international trials of early goal-directed resuscitation for severe sepsis and septic shock: methodology of ProCESS, ARISE, and ProMISe

The ProCESS/ARISE/ProMISe Methodology Writing Committee

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Goal-Directed Resuscitation for Patients with Early Septic Shock

The ARISE Investigators and the ANZICS Clinical Trials Group*

Oltre a confermare quanto detto nel Process, il trattamento più messo in discussione è l'uso dei vasopressori

L’uso di liquidi è solo futile o peggio?

ORIGINAL ARTICLE

Comparison of Two Fluid-Management Strategies in Acute Lung Injury

The National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network*

CONCLUSIONS

Although there was no significant difference in the primary outcome of 60-day mortality, the conservative strategy of fluid management improved lung function and shortened the duration of mechanical ventilation and intensive care without increasing nonpulmonary-organ failures. These results support the use of a conservative strategy of fluid management in patients with acute lung injury. (ClinicalTrials.gov number, NCT00281268.)

N Engl J Med 2006;354:2564-75.

From Critical Care Medicine

Fluid Resuscitation in Septic Shock

A Positive Fluid Balance and Elevated Central Venous Pressure Are Associated With Increased Mortality

John H. Boyd, MD, FRCP(C); Jason Forbes, MD; Taka-aki Nakada, MD, PhD; Keith R. Walley, MD, FRCP(C); James A. Russell, MD, FRCP(C)

Posted: 02/21/2011; Crit Care Med. 2011;39(2):259-65.

Abstract and Introduction

Abstract

Objective: To determine whether central venous pressure and fluid balance after resuscitation for septic shock are associated with mortality.

Design: We conducted a retrospective review of the use of intravenous fluids during the first 4 days of care.

Setting: Multicenter randomized controlled trial.

Patients: The Vasopressin in Septic Shock Trial (VASST) study enrolled 778 patients who had septic shock and who were receiving a minimum of 5 μg of norepinephrine per minute.

Interventions: None.

Measurements and Main Results: Based on net fluid balance, we determined whether one's fluid balance quartile was correlated with 28-day mortality. We also analyzed whether fluid balance was predictive of central venous pressure and furthermore whether a guideline-recommended central venous pressure of 8–12 mm Hg yielded a mortality advantage. At enrollment, which occurred on average 12 hrs after presentation, the average fluid balance was +4.2 L. By day 4, the cumulative average fluid balance was +11 L. After correcting for age and Acute Physiology and Chronic Health Evaluation II score, a more positive fluid balance at both at 12 hrs and day 4 correlated significantly with increased mortality. Central venous pressure was correlated with fluid balance at 12 hrs, whereas on days 1–4, there was no significant correlation. At 12 hrs, patients with central venous pressure <8 mm Hg had the lowest mortality rate followed by those with central venous pressure 8–12 mm Hg. The highest mortality rate was observed in those with central venous pressure >12 mm Hg. Contrary to the overall effect, patients whose central venous pressure was <8 mm Hg had improved survival with a more positive fluid balance.

Conclusions: A more positive fluid balance both early in resuscitation and cumulatively over 4 days is associated with an increased risk of mortality in septic shock. Central venous pressure may be used to gauge fluid balance ≤12 hrs into septic shock but becomes an unreliable marker of fluid balance thereafter. Optimal survival in the VASST study occurred with a positive fluid balance of approximately 3 L at 12 hrs.

Shock, Publish Ahead of Print
DOI: 10.1097/SHK.0000000000000268

Fluid Overload in Patients with Severe Sepsis and Septic Shock Treated with Early-Goal Directed Therapy is Associated with Increased Acute Need for Fluid-Related Medical Interventions and Hospital Death

Diana J. Kelm MD[1,2]; Jared T. Perrin MD[1]; Rodrigo Cartin-Ceba MD[1,2]; Ognjen Gajic MD[1,2]; Louis Schenck MS[3]; Cassie C. Kennedy, MD[1,2]

Perchè

For sepsis, the drugs don't work

On Oct 25, 2011, Eli Lilly announced the voluntarily withdrawal from the market of drotrecogin alfa (activated), marketed as Xigris, a drug licensed for the treatment of severe sepsis. Drotrecogin alfa, a recombinant form of human activated protein C with anticoagulant and anti-inflammatory activity, was the only pharmaceutical available designed specifically to treat sepsis. Its withdrawal marks the end of another chapter in the inglorious history of the search for a specific treatment for sepsis.

Sepsis is a systemic response to infection, characterised by heamodynamic instability, mental confusion, and tachypnoea. Gram negative bacteria account for most cases of sepsis, but the disorder can also be caused by Gram positive organisms and fungi. Sepsis manifests in its most severe form as septic shock, when patients display hypotension and organ failure, caused by dysregulation of the immune response to infection. The key to managing sepsis is early treatment, but it can be difficult to diagnose

US Navy/Erica Mater

For **European Medicine Agency**

COMMENTARY

The Search for Effective Therapy for Sepsis

Back to the Drawing Board?

Derek C. Angus, MD, MPH

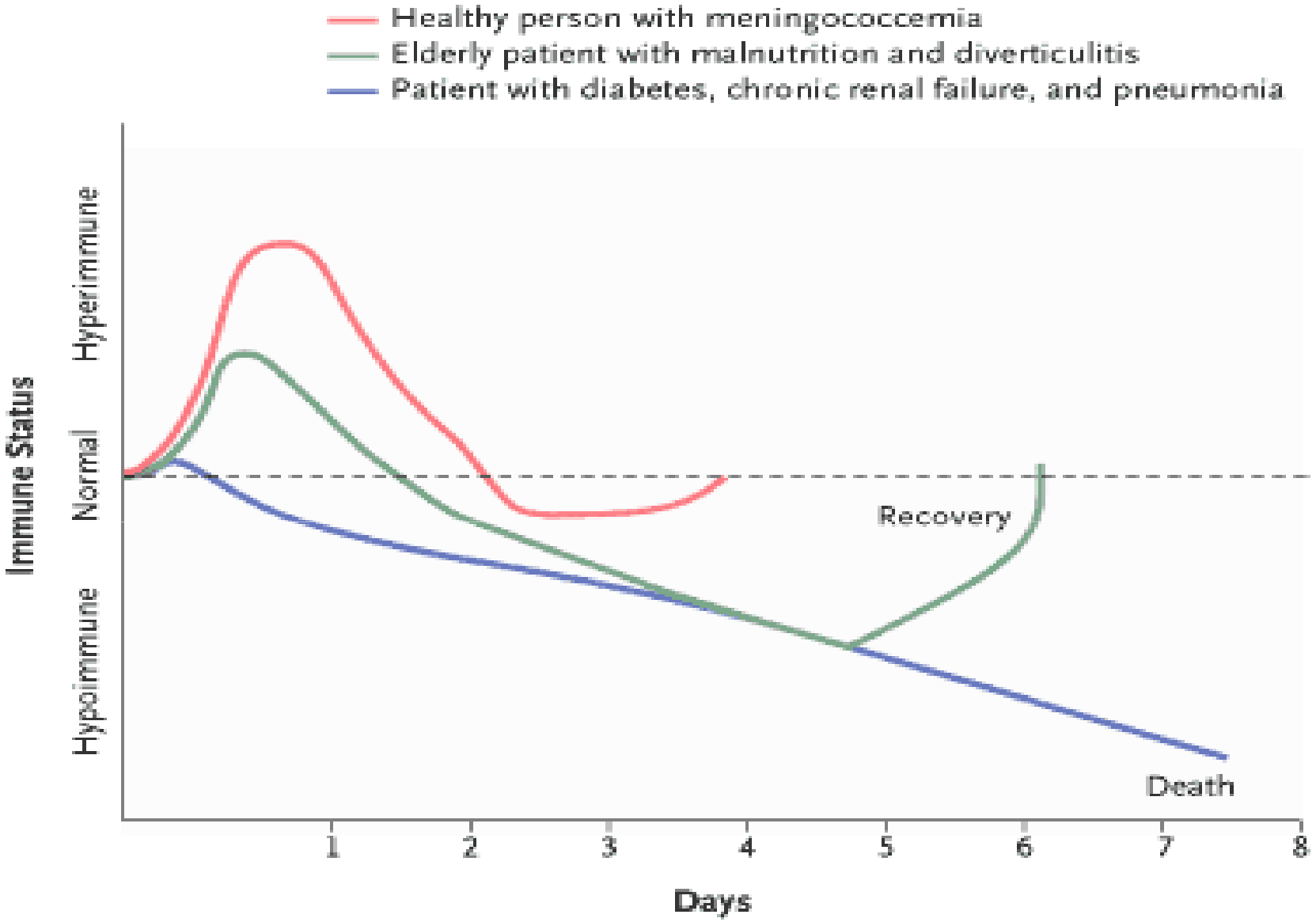
NEW THERAPEUTIC APPROACHES FOR SEPSIS HAVE NOT fared well recently. In January, Eisai announced that its worldwide phase 3 randomized trial of a novel anti–Toll-like receptor (TLR)-4 compound, eritoran tetrasodium, had failed to demonstrate an

saccharide (LPS), rapidly produce a broad array of cytokines, chemokines, and other proteins to sequester and eradicate invading pathogens. However, these same proteins can profoundly disturb and harm host tissue function and anatomy, a form of "friendly fire."

These findings led to 2 central tenets of current sepsis research. First, the host response in sepsis is unhelpfully exu-

La sepsi

- È una sindrome e non una malattia
- Non abbiamo un modello affidabile
- Non abbiamo nessuna capacità prognostica per poter stratificare i pazienti



R S Hotchkiss, I E Karl NEJM 348:138-150

Statement from the Surviving Sepsis Campaign Leadership on CVP, $ScvO_2$, and Lactate Measurements

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journal homepage: www.elsevier.com/locate/ajem

Original Contribution

Towards a less invasive approach to the early goal-directed treatment of septic shock in the ED☆,☆☆

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J R Coll Physicians Edinb 2014; 44:133
http://dx.doi.org/10.4997/JRCPE.2014.210

Major sepsis study confirms back to basics approach

D Nathwani
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TITLE A randomized trial of protocol-based care for early septic shock

AUTHORS The ProCESS Investigators

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DECLARATION OF INTERESTS No conflicts of interest declared.

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SUMMARY

COMMENTARY

In summary, more technical care is not always better; simple interventions applied consistently and timeously are equally effective. We continue to streamline the effective interventions for improved sepsis management.

Chissà come finisce?