XII congresso nazionale
simeu
RICCIONE 13-15 MAGGIO 2022

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XII CONGRESSO NAZIONALE SIMEU

Riccione: 13 -15 Maggio 2022
Palazzo dei Congressi di Riccione

16h00 I biomarcatori precoci
C Tascini

Prof Carlo Tascini
Direttore Clinica Malattie Infettive – ASUFC
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Conflict of interest Disclosure

prof. Carlo Tascini has received in the last two years grants as a speaker at symposia from:

- Astrazeneca
- AVIR Pharma
- Merck
- Pfizer
- Astellas
- Angelini
- Gilead
- Novartis
- Biotest
- Thermofischer
- Correvio/Advanz Pharma
- Basilea
- Biomerieux
- Hikma
- Zambon

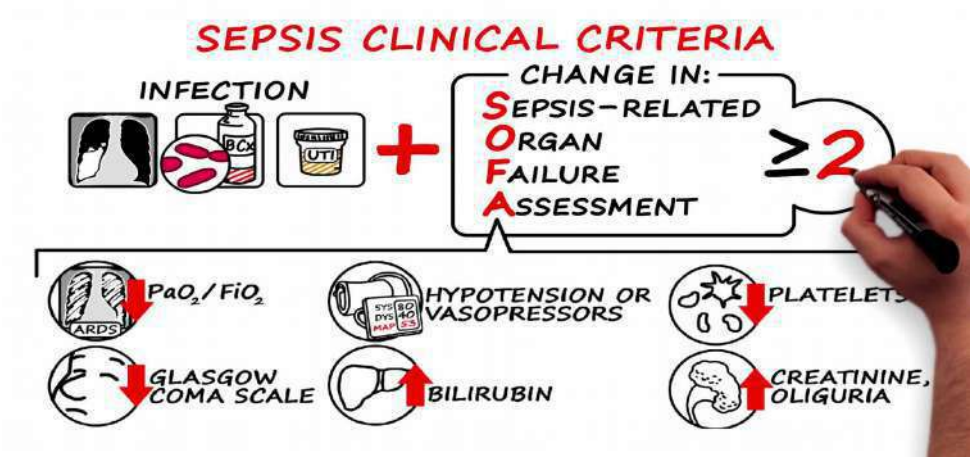
- Emergency Medicine is the most interesting 15 minutes of every other specialty.»

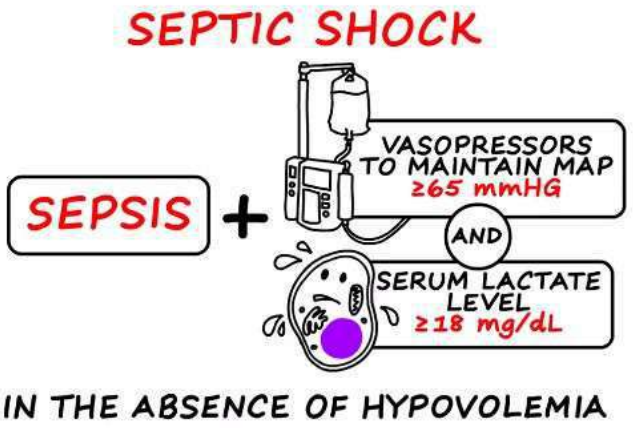
- «While other doctors dwell on the question *What does this patient **have**?*, emergency physicians are constantly thinking *What does this patient **need**? Now? In 5 minutes? In 2 hours?*» My answer: **a doctor!!!**

- **Author: Joe Lex, Clinical Professor of Emergency Medicine, Temple University School of Medicine – Philadelphia**

SEPSIS-3: simple Key Points (…as emergency physicians like it!)

- ✓ Sepsis is the primary cause of death from infection, especially if not recognized and treated promptly. Its recognition mandates urgent attention
- ✓ Sepsis is a syndrome shaped by pathogen factors and host factors with characteristics that evolve over time. What differentiates sepsis from infection is an aberrant or dysregulated host response and the presence of organ dysfunction.
- ✓ Sepsis-induced organ dysfunction may be occult; therefore, its presence should be considered in any patient presenting with infection. Conversely, unrecognized infection may be the cause of new-onset organ dysfunction. Any unexplained organ dysfunction should thus raise the possibility of underlying infection.
- ✓ Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection





INFLAMMATORY-IMMUNE RESPONSE IN SEPSIS

The Journal of Clinical Investigation REVIEW

Sepsis-induced immune dysfunction: can immune therapies reduce mortality?

jci.org Volume 126 Number 1 January 2016

Matthew J. Delano[1] and Peter A. Ward[2]

[1]Department of Surgery, Division of Acute Care Surgery, University of Michigan, Ann Arbor, Michigan, USA. [2]Department of Pathology, University of Michigan Medical School, Ann Arbor, Michigan, USA.

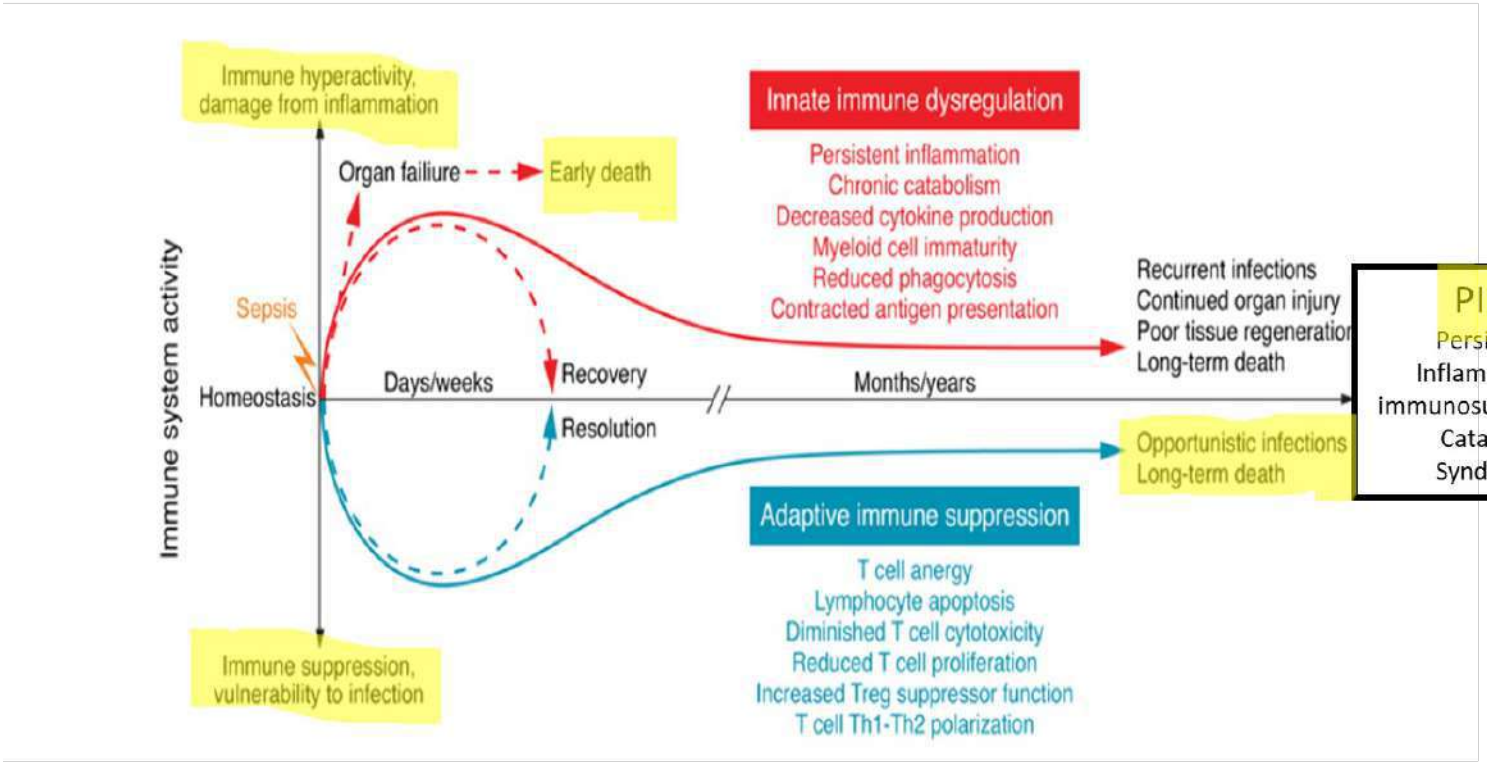


Figure 2. Immune dysregulation in sepsis. New insights into immune dysregulation have been gained using samples from deceased septic patients as well as from severely injured trauma patients. These studies demonstrate an enduring inflammatory state driven by dysfunctional innate and suppressed adaptive immunity that culminates in persistent organ injury and death of the patient. Although the initial inflammatory process, if unabated, contributes to organ failure and early mortality, this process is largely ameliorated by improvements in patient management protocols. However, considering that the vast majority of sepsis survivors are elderly with highly comorbid conditions, the short-term gains in survival have merely been pushed back by several months to a year. Although theories about the processes underlying this observation are numerous, the widespread consensus is that persistent derangements in innate and adaptive immune system cellular function are the main culprits driving long-term mortality.

Cortesia M. Girardis

N. meningitidis gruppo Y

- Paziente di 13 anni arriva in coma all'Ospedale Cotugno: rigidità nucale e febbre
- Nessuna petecchia
- Ricovero in UTI: si programma PL
- Arriva anche il fratello di 11 anni: febbre, nessun segno neurologico
- EO: negativo, torace, addome, cuore, non rigidità nucale: non si tolgono le calze

N. meningitidis gruppo Y

- Dopo due ore, il paziente rientra con numerose petecchie
- Sia lui che il fratello hanno *N. meningitidis* gruppo Y , lui isolato solo da sangue, il fratello solo da liquor

Med Intensiva. 2014;38(6):356–362

medicina *intensiva*

www.elsevier.es/medintensiva

ORIGINAL

TLR2–TLR4/CD14 polymorphisms and predisposition to severe invasive infections by *Neisseria meningitidis* and *Streptococcus pneumoniae*☆

J.J. Tellería-Orriols[b], A. García-Salido[a,*], D. Varillas[b], A. Serrano-González[a], J. Casado-Flores[a]

Conclusions: Genetical variations in the innate immune system by polymorphisms in the TLR2 and CD14, could be related with an increases susceptibility to severe invasive infections by *S. pneumoniae* and *N. meningitidis*.

Intensive Care Med (2018) 44:1502–1511
https://doi.org/10.1007/s00134-018-5341-3

ORIGINAL

Clinical spectrum and short-term outcome of adult patients with purpura fulminans: a French multicenter retrospective cohort study

Damien Contou[1,2*], Romain Sonneville[3], Florence Canoui-Poitrine[4,5], Gwenhaël Colin[6], Rémi Coudroy[7,8], Frédéric Pène[9], Jean-Marc Tadié[10], Martin Cour[11], Gaëtan Béduneau[12], Antoine Marchalot[13], Laurent Guérin[14], Sébastien Jochmans[15], Stephan Ehrmann[15], Nicolas Terzi[17], Sébastien Préau[18], François Barbier[19], Guillaume Schnell[20], Damien Roux[21], Olivier Leroy[22], Claire Pichereau[23], Elodie Gélisse[24], Lara Zafrani[25], Richard Layese[4], Christian Brun-Buisson[1], Armand Mekontso Dessap[1] and Nicolas de Prost[1] for the Hopeful Study Group

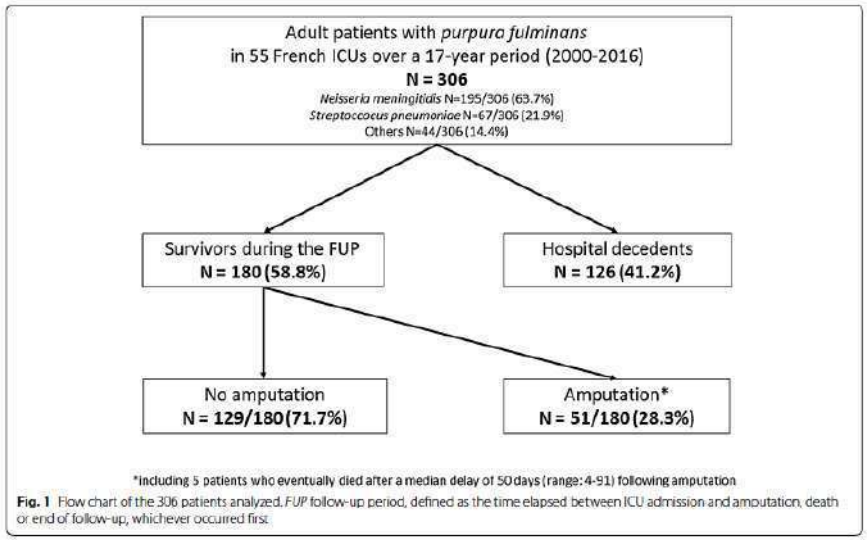


Fig. 1 Flow chart of the 306 patients analyzed. *FUP* follow-up period, defined as the time elapsed between ICU admission and amputation, death or end of follow-up, whichever occurred first

Intensive Care Med (2018) 44:1502–1511
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ORIGINAL

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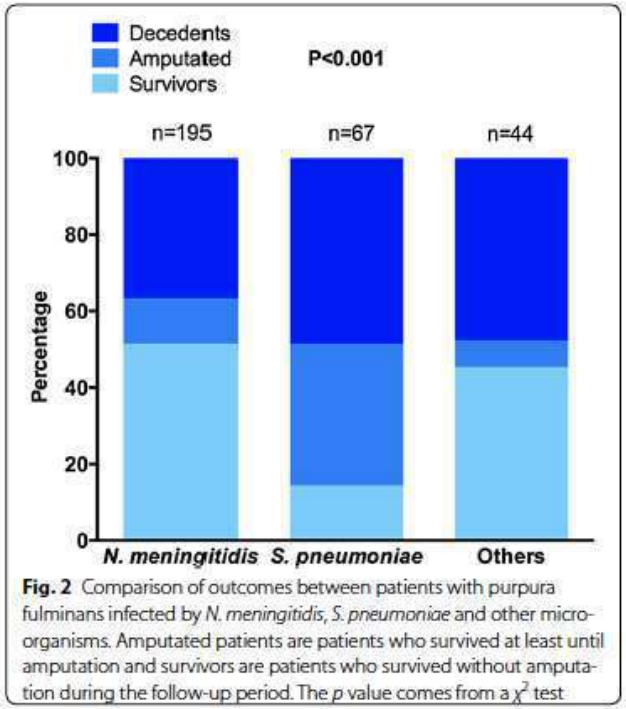

Fig. 2 Comparison of outcomes between patients with purpura fulminans infected by *N. meningitidis*, *S. pneumoniae* and other micro-organisms. Amputated patients are patients who survived at least until amputation and survivors are patients who survived without amputation during the follow-up period. The *p* value comes from a χ^2 test

Table 3 Multivariable Cox model for hospital death (censored at day 30) after multiple imputations and adjustment for center size and year of admission ($n = 301$)

	Hospital death ($n = 301$, number of events = 114)	
	HR (95% CI)	*p*
SAPS II	1.03 (1.02–1.04)	< 0.001
Neck stiffness	0.51 (0.28–0.92)	0.026
Leukocytes count, 10^3 mm^{-3}	0.83 (0.69–0.99)	0.034
Arterial lactate, mmol/L[a]	2.71 (1.68–4.38)	< 0.001
Platelets count, 10^3.mm^{-3} [a]	0.77 (0.60–0.91)	0.007
Center size ≥ 4 patients	0.45 (0.27–0.97)	0.028
Year of admission		0.32
2000–2004	1.00	
2005–2008	1.11 (0.64–1.94)	0.71
2009–2012	0.75 (0.43–1.32)	0.32
2013–2016	0.97 (0.55–1.72)	0.93

HR adjusted hazard-ratio, *CI* confidence interval

[a] Log-transformed variables and expressed for one unit of the log

frontiers in Medicine

ORIGINAL RESEARCH
published: 15 April 2021
doi: 10.3389/fmed.2021.627830

D-Dimer as Biomarker for Early Prediction of Clinical Outcomes in Patients With Severe Invasive Infections Due to *Streptococcus Pneumoniae* and *Neisseria Meningitidis*

Simone Meini[1], Emanuela Sozio[2], Giacomo Bertolino[3], Francesco Sbrana[4], Andrea Ripoli[4], Carlo Pallotto[5,6], Bruno Viaggi[7], Roberto Andreini[1], Vittorio Attanasio[8], Carolina Rescigno[8], Luigi Atripaldi[9], Silvia Leonardi[9], Mariano Bernardo[9] and Carlo Tascini[2,8]*

OPEN ACCESS

D-dimer values. In conclusion, D-dimer is rapid to be obtained, at low cost and available everywhere, and can help stratify the risk of in-hospital mortality and complications in patients with invasive infections due to *N. meningitidis*: D-dimer <500 ng/mL excludes any further complications, and a cut-off of 7,000 ng/mL seems able to predict a significantly increased mortality risk from much <10% to over 25%.

We focused on the role of D-dimer assessed within 24 h after admission in predicting clinical outcomes in a cohort of 270 patients hospitalized in a 79 months period for meningitis and/or bloodstream infections due to *Streptococcus pneumoniae* (n = 162) or *Neisseria meningitidis* (n = 108). Comparisons were performed with

frontiers in Medicine

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D-Dimer as Biomarker for Early Prediction of Clinical Outcomes in Patients With Severe Invasive Infections Due to *Streptococcus Pneumoniae* and *Neisseria Meningitidis*

Simone Meini[1], *Emanuela Sozio[2]*, *Giacomo Bertolino[3]*, *Francesco Sbrana[4]*, *Andrea Ripoli[4]*, *Carlo Pallotto[5,6]*, *Bruno Viaggi[7]*, *Roberto Andreini[1]*, *Vittorio Attanasio[8]*, *Carolina Rescigno[8]*, *Luigi Atripaldi[9]*, *Silvia Leonardi[9]*, *Mariano Bernardo[9]* and *Carlo Tascini[2,3]*

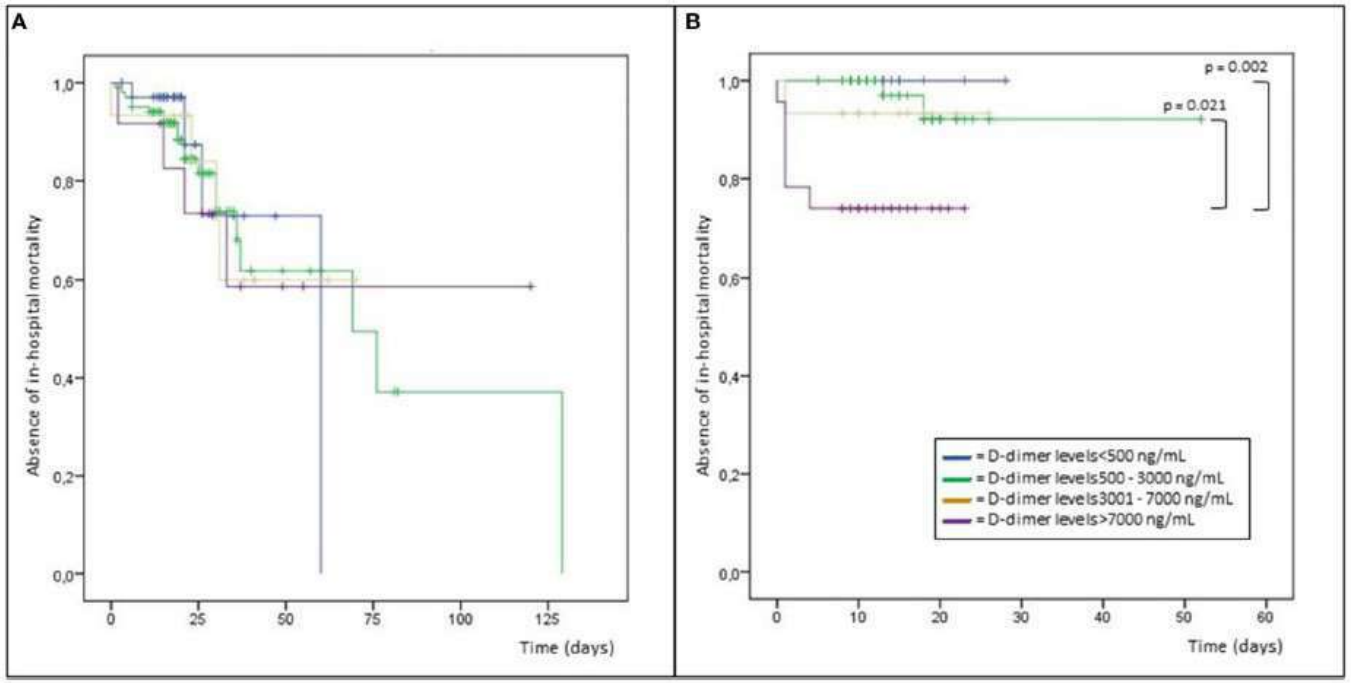
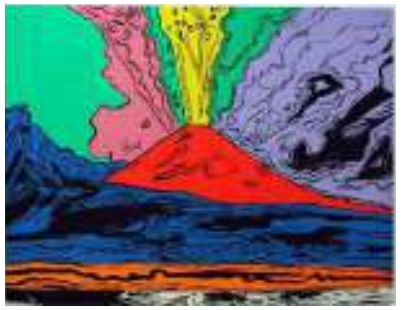


FIGURE 1 | Kaplan-Meier analysis of in-hospital mortality in patients with infections due to *Streptococcus pneumoniae* **(A)** and *Neisseria meningitidis* **(B)**.

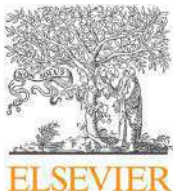


- Purulent meningitis: dexamethasone NNT 1:10
- Mortality from 15 to 7%
- Glasgow score 8-11
- Pneumococcus: dexamethasone NNT 1:4
- Mortality from 34% to 14%
- **Steroid should be administered within 4 hours from antibiotic administration**

Reasearch aim for us as a doctor

- How I can reduce the disproportionate response to infection that lead to sepsis and septic shock?

Journal of Infection (2016) xx, 1–4



LETTER TO THE EDITOR

Clinical presentation and outcome of twenty cases of Invasive Meningococcal Disease due to Serogroup C – Clonal complex 11 in the Florence province, Italy, 2015–2016

Francesco Maria Fusco*
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Table 1 Demographical and clinical characteris
ical presentation, from January 2015 to June 20

Characteristics (n available data/total)[a]	All patients (20 cases)	Septic shock with *Purpura fulminans* (9 cases)
Male sex (%, 20/20)	55%	66%
Years (mean, 20/20)	40 (13–83)	39 (13–83)
Main presenting symptoms (20/20)	Fever (Mean 38.7 °C) and petechiae (different degrees) always present	Confluent petechiae, fever
Hours between symptoms onset and referral to ED (mean, 13/20)	24	22
MEWS score at presentation to ED (mean, 13/20)	1,8	1,5
Selected bio-chemistry parameters		
White blood cells (mean, 16/20)	13,1 × 10^3	6,3 × 10^3
Platelets (mean, 16/20)	119 × 10^3	68 × 10^3
C-reactive protein (mean, 14/20)	18	11
Procalcitonin (mean, 10/20)	80	127
Cerebrospinal fluid		
Proteins (mean, 13/13)		30 (20–40)[b]
Cells (mean, 13/13)		5 (2–8)[b]
Glucose (mean, 13/13)		55 (50–65)[b]
Need for intensive care (IC) (20/20)	17/20	9/9
Mean length of stay in IC (days)		Not calculable[c]
Letality (20/20)	7/20; 35%	7/9; 77%

Vaccine 36 (2018) 5962–5966

Contents lists available at ScienceDirect

Vaccine

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

Invasive Meningococcal Disease due to group C N. meningitidis ST11 (cc11): The Tuscany cluster 2015–2016

Francesco Menichetti [a,⇑], Simona Fortunato [a], Andrea Ricci [a], Francesca Salani [a], Andrea Ripoli [b], Carlo Tascini [c], Francesco Maria Fusco [d], Jessica Mencarini [e], Alessandro Bartoloni [e], Massimo Di Pietro [f]

Table 2
Patient outcome according to demographic, clinical and management variables.

	Recovered (n = 38)	Sequelae or death (n = 15)	P value univariate analysis	OR[b]
Males	17 (45%)	9 (60%)	0.486	–
Mean age (range)	33.9 (3–70)	35.5 (17–75)	0.799	**1.003**
Previous Vaccination[a]	9 (24%)	2 (13%)	0.645	–
Meningitis	6 (16%)	2 (13%)	1	–
Meningitidis + meningococcemia	16 (42%)	7 (47%)	1	–
Meningococcemia	16 (42%)	6 (40%)	1	–
Septic shock	**14 (37%)**	**12 (80%)**	**0.011**	**1.211**
Multi-organ failure	11 (29%)	8 (53%)	0.177	–
Disseminate intravascular coagulophaty	**7 (18%)**	**9 (60%)**	**0.008**	–
Purpura fulminans	**6 (16%)**	**9 (60%)**	**0.004**	**6.641**
Adequate Antibiotic therapy	38 (100%)	15 (100%)	**1**	–
Steroid treatment	28 (74%)	11 (74%)	1	–
Pentaglobin®	8 (21%)	2 (13%)	0.797	–
ICU	25 (66%)	14 (93%)	0.089	–
Tertiary-care Universitary Hospital	**13 (34%)**	**0 (0%)**	**0.024**	**0.111**

[a] Previous receipt of a serogroup C-containing meningococcal conjugate vaccine.
[b] OR were calculated with a multivariate analysis on a total of 53 patients with the availability of all the listed variables.

Steroid

Grade A	Empiric treatment with dexamethasone is strongly recommended for all adults (10 mg qid for 4 days) and children (0.15 mg/kg qid for 4 days) with acute bacterial meningitis in the setting of high-income countries.
Grade A	Treatment with dexamethasone is strongly recommended to be initiated with the first dose of antibiotic treatment.
Grade C	If intravenous antibiotic treatment has already been started, dexamethasone can still be administered up to 4 hours after start of the first dose of intravenous antibiotics.
Grade B	It is recommended to stop dexamethasone if the patient is discovered not to have bacterial meningitis or if the bacterium causing the meningitis is a species other than *H. influenzae* or *S. pneumoniae,* although some experts advise that adjunctive treatment should be continued irrespective of the causative bacterium.

Bretonnière *et al. Critical Care* (2015) 19:303
DOI 10.1186/s13054-015-1021-7

CRITICAL CARE

RESEARCH Open Access

Rifampin use in acute community-acquired meningitis in intensive care units: the French retrospective cohort ACAM-ICU study

Cédric Bretonnière[1,2*], Mathieu Jozwiak[1,3], Christophe Girault[4,5], Pascal Beuret[6], Jean-Louis Trouillet[7], Nadia Anguel[3], Jocelyne Caillon[2,8], Gilles Potel[2,9], Daniel Villers[1], David Boutoille[2,10] and Christophe Guitton[1]

Table 2 Correlation between ICU mortality and rifampin treatment in critically ill patients admitted with bacterial meningitis

Rifampin use	Non-survivors		Survivors		*p* Value
Entire population	n=23		n=134		
Rifampin during hospitalization	2/23	8.7 %	30/134	22.4 %	NS
Rifampin during first 48 h of hospitalization	1/23	4.3 %	23/134	17.2 %	NS
Rifampin during first 24 h of hospitalization	0/23	0.0 %	19/134	14.2 %	0.078
Streptococcus pneumoniae meningitis	n=18		n=58		
Rifampin during hospitalization	2/18	11.1 %	18/58	31.0 %	NS
Rifampin during first 48 h of hospitalization	1/18	5.6 %	15/58	25.9 %	0.097
Rifampin during first 24 h of hospitalization	0/18	0.0 %	13/58	22.4 %	**0.031**

NS not significant
Data are proportions of patients. They were compared with Fisher's exact test
p Values <0.1 are detailed. *p* Values <0.05 were considered significant (bold)

Intensive Care Med
DOI 10.1007/s00134-017-4957-z

LETTER

Potential role of IgM-enriched immunoglobulin as adjuvant treatment for invasive meningococcal disease

Carlo Tascini[1], Fiorentino Fraganza[2], Francesca Salani[3], Emanuela Sozio[4], Marco Rossi[1], Francesco Sbrana[5], Novella Carannante[1], Maria Daniela Chiesa[2], Andrea Ripoli[5], Giacomo Bertolino[6], Massimo Di Pietro[7], Alessandro Bartoloni[8,9] and Francesco Menichetti[3*], on behalf of GISA/SIMIT Meningitis Study Group

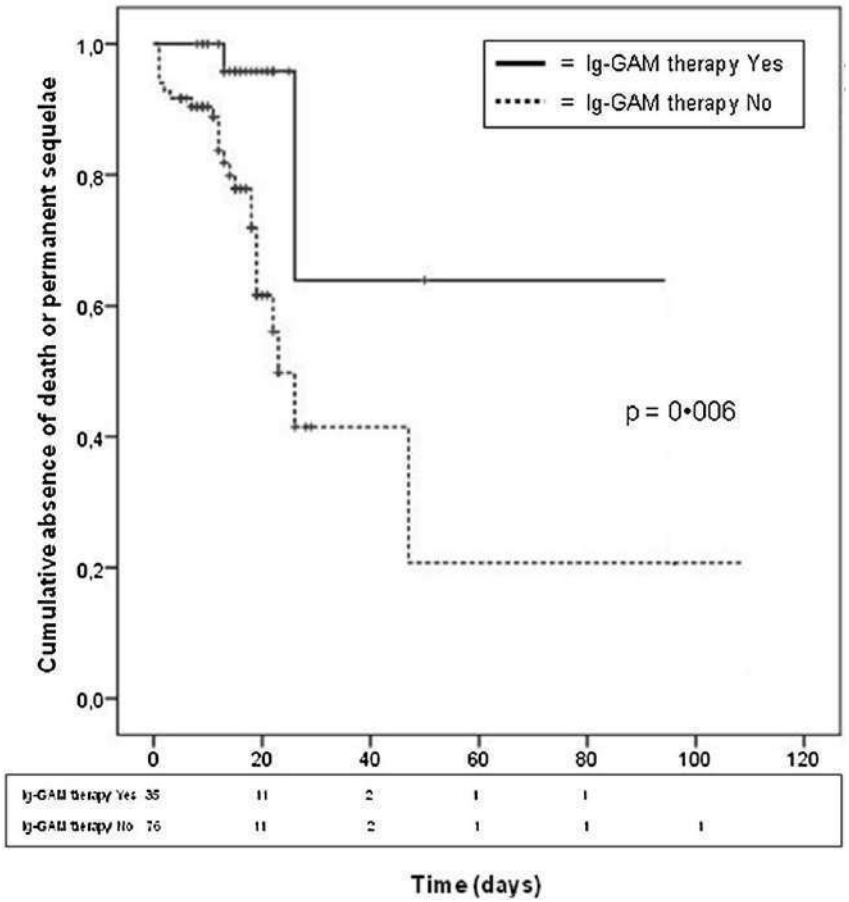

Fig. 1 Kaplan–Meier analysis of aggregated data on death and permanent sequelae in patients treated or not with Ig-GAM

Clinical Infectious Diseases

MAJOR ARTICLE

Interleukin (IL)-1β and IL-10 Host Responses in Patients With *Staphylococcus aureus* Bacteremia Determined by Antimicrobial Therapy

Cecilia F. Volk,[1] Sarah Burgdorf,[2] Graham Edwardson,[1] Victor Nizet,[2] George Sakoulas,[2] and Warren E. Rose[1]

[1]School of Pharmacy, University of Wisconsin–Madison; and [2]Department of Pediatrics, University of California–San Diego School of Medicine, La Jolla

clinical implications. Here, we demonstrate that monotherapy with vancomycin or daptomycin does not elicit a robust IL-1β response in patients. However, β-lactam therapy that includes oxacillin, cefazolin, or ceftaroline, either alone or in combination with vancomycin or daptomycin, enhanced IL-1β at days 3 and 7 of therapy. We suspect that the muted IL-1β response with non–β-lactam therapy may be a predisposing factor for the longer bacteremia that has been reported in MRSA compared to MSSA [19, 20].

Volk et al., CID 2020

Clinical Infectious Diseases

MAJOR ARTICLE

Interleukin (IL)-1β and IL-10 Host Responses in Patients With *Staphylococcus aureus* Bacteremia Determined by Antimicrobial Therapy

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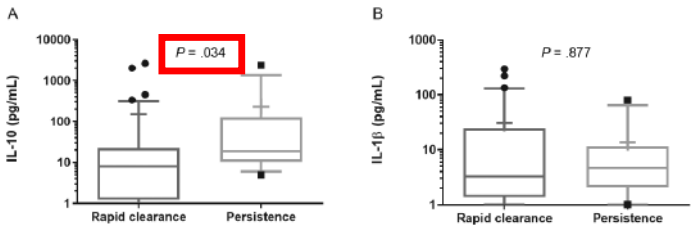


Figure 2. (*A*) IL-10 and (*B*) IL-1β concentrations in patient sera on day 1 of presentation compared by outcome of rapid bacteremia clearance (≤4 days) or persistent bacteremia (>4 days). The Mann-Whitney *U* test was used for statistical analysis. Median (line) and mean (+). Abbreviation: IL, interleukin.

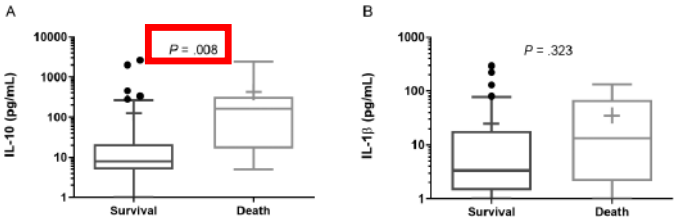


Figure 1. (*A*) IL-10 and (*B*) IL-1β concentrations in patient sera on day 1 of presentation compared by outcome of 30-Day survival or mortality. The Mann-Whitney *U* test was used for statistical analysis. Median (line) and mean (+). Abbreviation: IL, interleukin.

Persistent bacteremia

Mortality

Volk et al., CID 2020

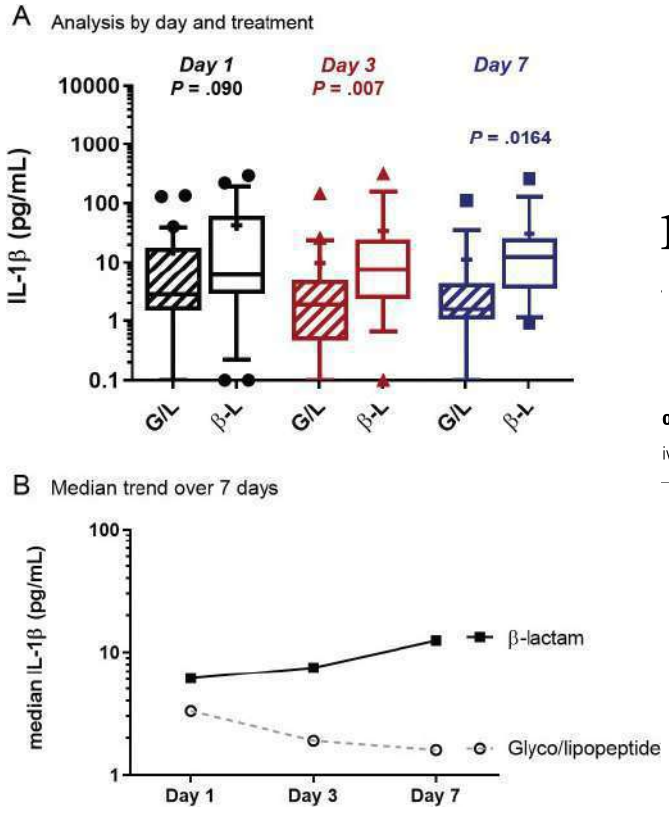


Figure 3. IL-1β concentrations in patient sera treated with G/L or β-L antibiotic at day 1, day 3, and day 7 of therapy. The Mann-Whitney U test was used for statistical analysis. Median (line) and mean (+). Abbreviations: B-L, β-lactam; G/L, glyco/lipopeptide; IL, interleukin.

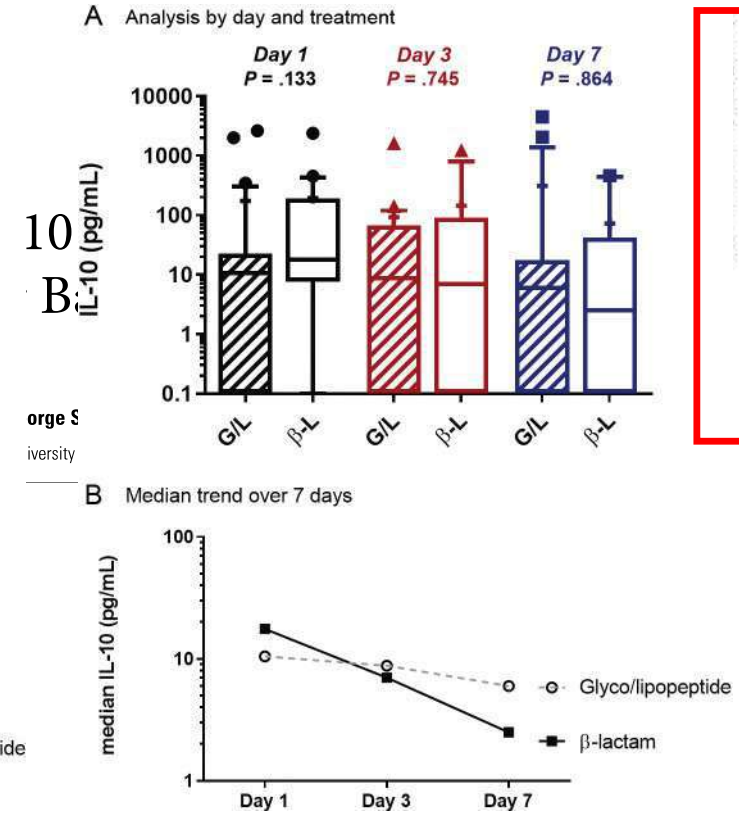
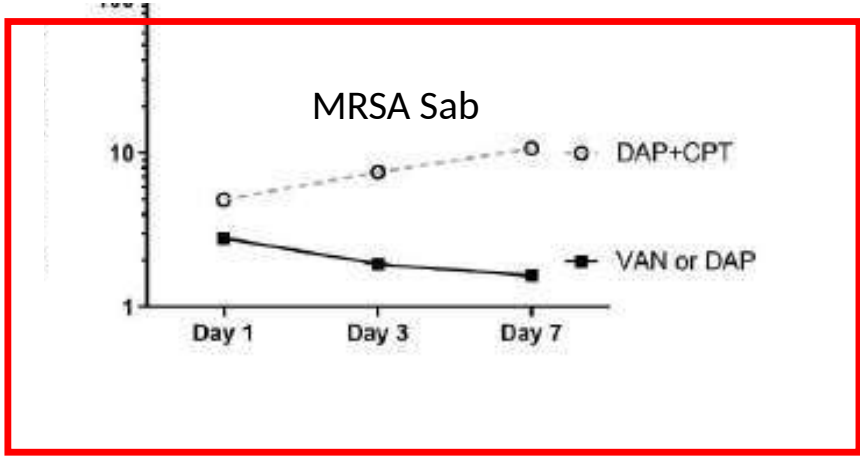


Figure 4. IL-10 concentrations in patient sera treated with G/L or β-L antibiotic at day 1, day 3, and day 7 of therapy. The Mann-Whitney *U* test was used for statistical analysis. Median (line) and mean (+). Abbreviations: B-L, β-lactam; G/L, glyco/lipopeptide; IL, interleukin.



IL-1b trend in MRSA blood-stream infections

β-lactam had higher IL-1β on days 3 (median +5.6 pg/mL; *P* = .007) and 7 (+10.9 pg/mL; *P* = .016). Ex vivo, addition of the IL-1 receptor antagonist anakinra to whole blood reduced staphylococcal killing, supporting an IL-1β functional significance in SaB clearance. β-lactam–treated patients had sharper declines in IL-10 than vancomycin or daptomycin –treated patients over 7 days. Volk et al., CID 2020

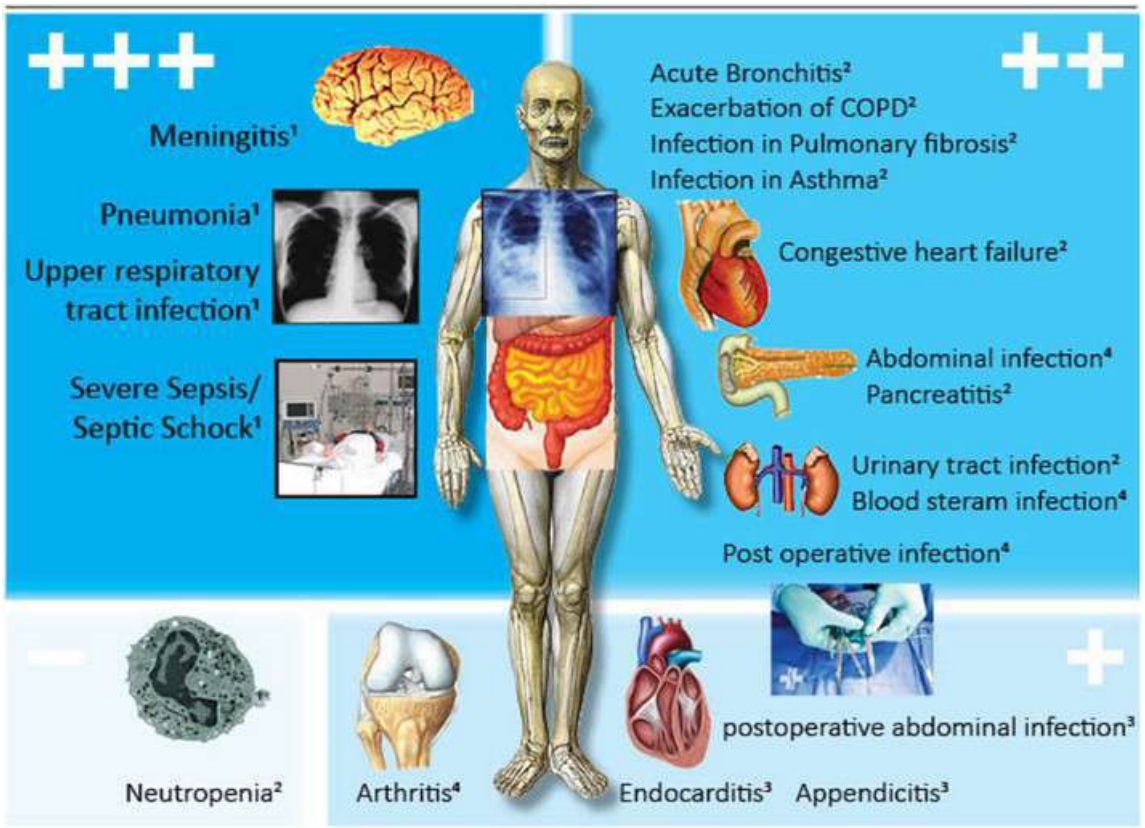


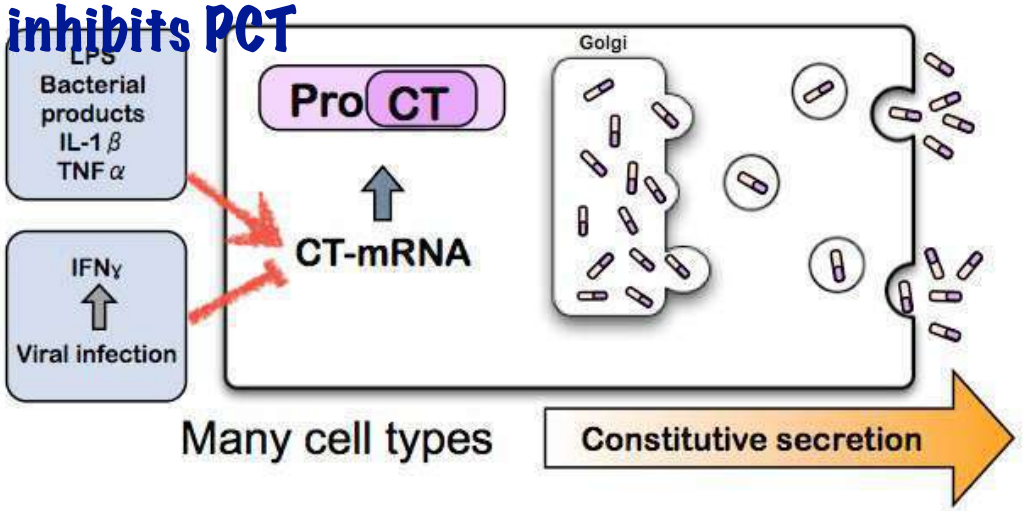
Fig. 1 Summary of evidence regarding procalcitonin (PCT) for diagnosis and antibiotic stewardship in organ-related infections. While for some infections, intervention studies have investigated benefit and harm of using PCT for diagnosis and antibiotic stewardship (*left side*), for other infections only results from diagnostic (observation) studies are available (*right side*). +: moderate evidence in favor of PCT; ++: good evidence in favor of PCT; +++: strong evidence in favor of PCT; – no evidence in favor of PCT

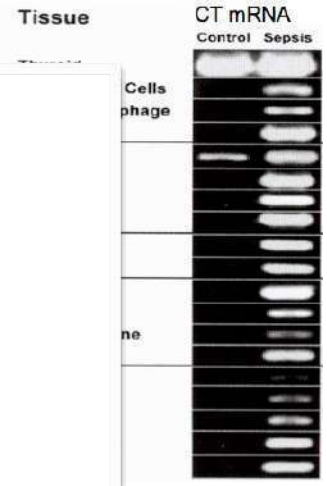
During bacterial infection

Biochemistry of PCT

IFN_{χ}

inhibits PCT





Inflamm Res 2012 DOI 10.1007/s00011-012-0439-5

Luzzani Aldo

Comparison of procalcitonin and C-reactive protein as markers of sepsis

as marker of severity of infection and organ dysfunction

Table 3. PCT and CRP plasma concentrations in the SOFA score groups

SOFA Score	PCT Median (Interquartile Range)	CRP Median (Interquartile Range)
1–6	3.1 (1.2–4.9)	135.9 (85.8–178.9)
7–12	3.9 (1.8–7.3)[a]	82.9 (59.4–149.2)[a]
13–18	31.0 (4.8–62.1)[a]	113.5 (107.9–222.9)[a]

PCT, procalcitonin; CRP, C-reactive protein; SOFA, sepsis-related organ failure assessment.
[a] $p < .001$.

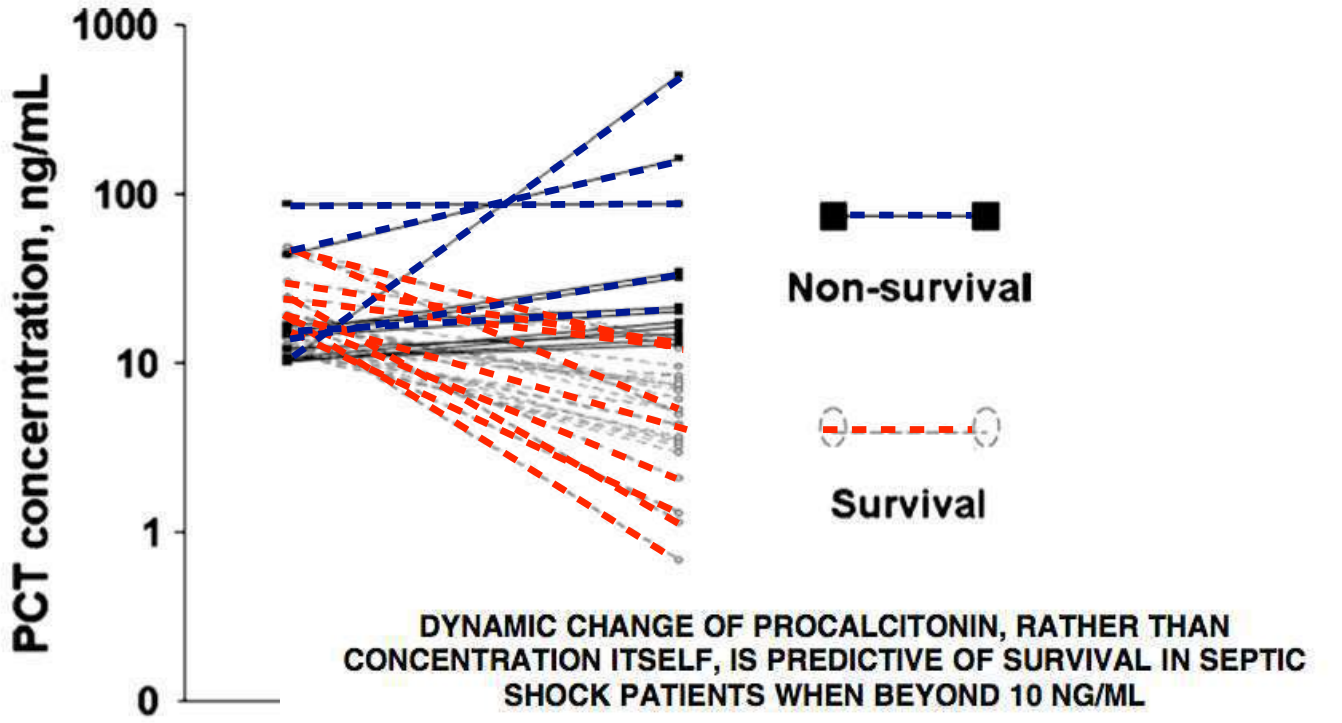
Conclusion: PCT is a better marker of sepsis than CRP. The course of PCT shows a closer correlation than that of CRP with the severity of infection and organ dysfunction.

Crit Care Med 2003;31:1737-1741

.. The dynamic change is more important than the PCT

Guan J

PCT Kinetics



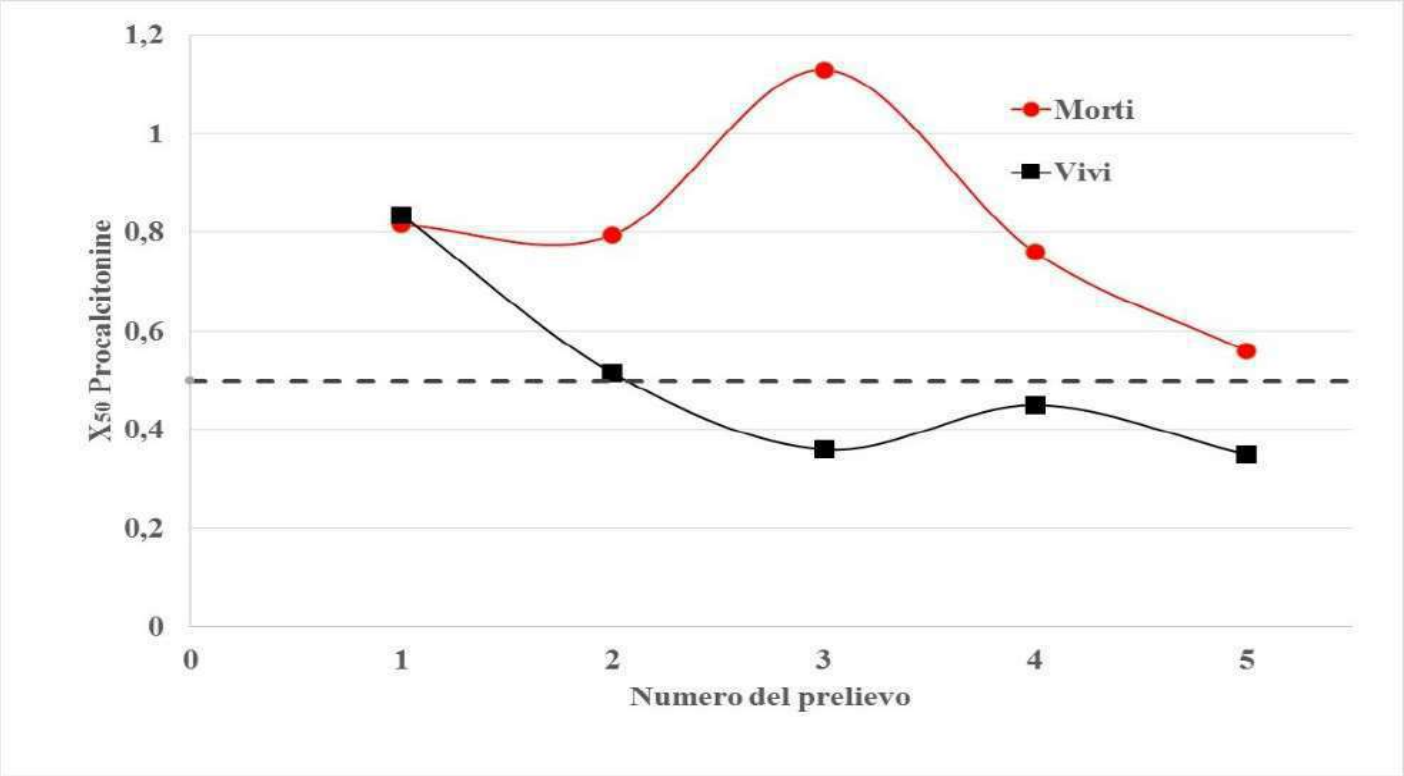
DYNAMIC CHANGE OF PROCALCITONIN, RATHER THAN CONCENTRATION ITSELF, IS PREDICTIVE OF SURVIVAL IN SEPTIC SHOCK PATIENTS WHEN BEYOND 10 NG/ML

Jun Guan,* Zhaofen Lin,* and Hong Lue†

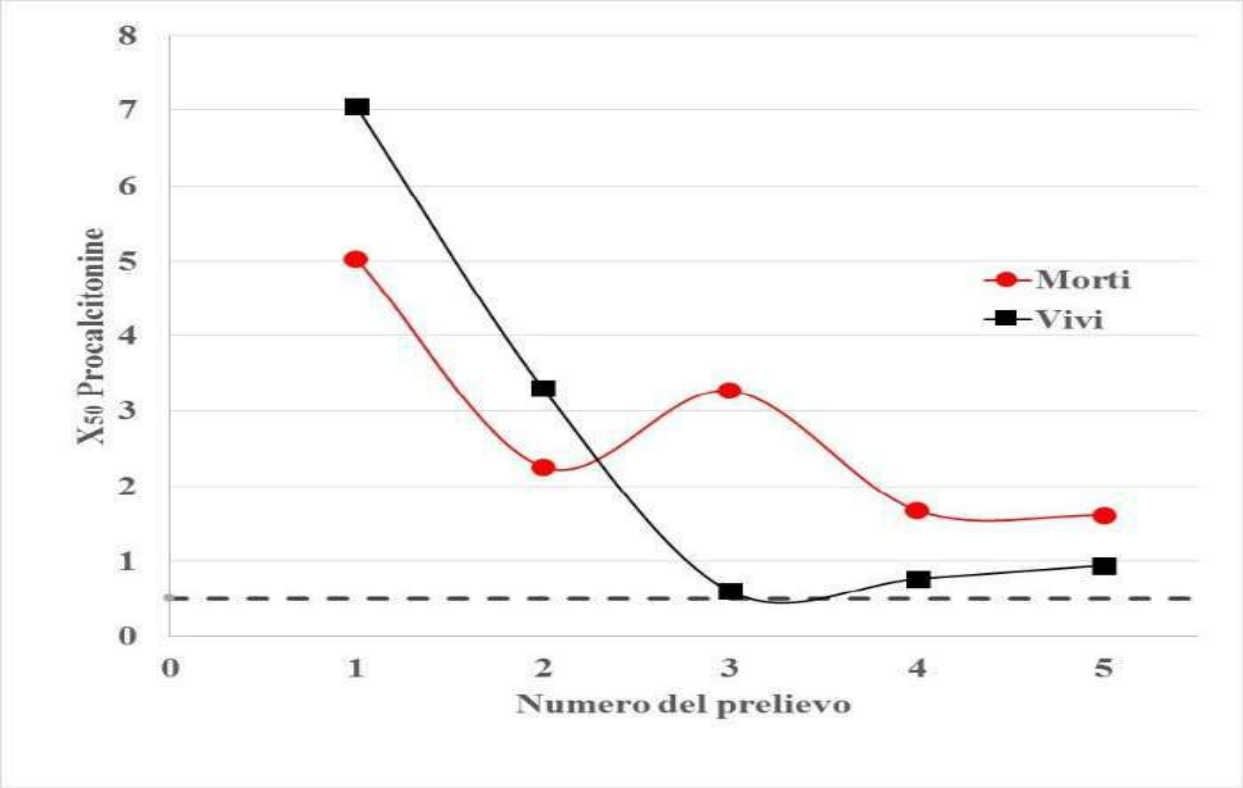
**Shanghai Changzheng Hospital, Second Military Medical University, Shanghai; and †Taicang Chinese Medicine Hospital, Taicang, Jiangsu, China*

J Shock 2011;36(6):570-574

PCT polmoniti (tesi Vanna Caccavo)



PCT sepsi (tesi Vanna Caccavo)



Schuetz P

Effect of Procalcitonin-Based Guidelines vs Standard Guidelines on Antibiotic Use in Lower Respiratory Tract Infections

The ProHOSP Randomized Controlled Trial

ProHOSP study

1359 patients 6 centers

eFigure 1. PCT Algorithm for Antibiotic Stewardship

Procalcitonin (PCT) algorithm for stewardship of antibiotic therapy in patients with LRTI

< 0.1 µg/l	0.1 - 0.25 µg/l	>0.25 – 0.5 µg/l	>0.5 µg/l
Bacterial etiology **very unlikely**	Bacterial etiology **unlikely**	Bacterial etiology **likely**	Bacterial etiology **Very likely**
NO antibiotics !	**no antibiotics**	**Antibiotics yes**	**Antibiotics YES !**

Control PCT after 6-24 hours

Initial antibiotics can be considered in case of:
- Respiratory or hemodynamic instability
- Life-threatening comorbidity
- Need for ICU admission
- **PCT < 0.1** µg/l: CAP with PSI V or CURB65 >3, COPD with GOLD IV
- **PCT < 0.25** µg/l: CAP with PSI ≥IV or CURB 65>2, COPD with GOLD > III
- Localised infection (abscess, empyema), L.pneumophilia
- Compromised host defense (e.g. immuno-suppression other than corticosteroids)
- Concomitant infection in need of antibiotics

Consider the course of PCT

If antibiotics are initiated:
- Repeated measurement of PCT on days 3, 5, 7
- Stop antibiotics using the same cut offs above
- If initial PCT levels are >5-10 µg/l, then stop when 80-90% decrease of peak PCT
- If initial PCT remains high, consider treatment failure (e.g. resistant strain, empyema, ARDS)
- **Outpatients**: duration of antibiotics according to the last PCT result:
  - **>0.25-0.5 µg/l:** 3 days
  - **>0.5 - 1.0 µg/l:** 5 days
  - **>1.0 µg/l:** 7 days

Abbreviations: PCT *procalcitonin*, CAP *community-acquired pneumonia*, PSI *pneumonia severity index*, COPD *chronic obstructive pulmonary disease*, GOLD *global initiative for obstructive lung disease*,

JAMA 2009;302(10):1059-1066

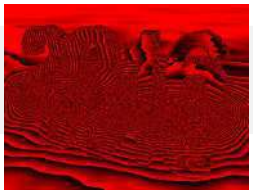
	Procalcitonin group (n=307)	Control group (n=314)	Between-group absolute difference	p value
Primary endpoints				
28-day mortality*	65 (21·2%)	64 (20·4%)	0·8% (–4·6 to 6·2)	NA
60-day mortality*	92 (30·0%)	82 (26·1%)	3·8% (–2·1 to 9·7)	NA
Number of days without antibiotics	14·3 (9·1)	11·6 (8·2)	2·7 (1·4 to 4·1)	<0·0001
Secondary endpoints (days 1–28)				
Relapse	20 (6·5%)	16 (5·1%)	1·4% (–2·3 to 5·1)	0·45
Superinfection	106 (34·5%)	97 (30·9%)	3·6% (–3·8 to 11·0)	0·29
Number of days without mechanical ventilation	16·2 (11·1)	16·9 (10·9)	–0·7 (–2·4 to 1·1)	0·47
SOFA score				
Day 1	7·5 (4·4)	7·2 (4·4)	0·3 (–0·4 to 1·0)	0·39
Day 7	4·1 (4·2)	4·0 (4·2)	0·1 (–0·6 to 0·8)	0·73
Day 14	2·8 (3·5)	2·8 (3·6)	0 (–0·6 to 0·7)	0·87
Day 21	2·1 (3·3)	1·9 (3·1)	0·2 (–0·4 to 0·8)	0·52
Day 28	1·5 (3·0)	0·9 (2·4)	0·6 (0·0 to 1·1)	0·0370
Length of stay in ICU from inclusion (days)	15·9 (16·1)	14·4 (14·1)	1·5 (–0·9 to 3·9)	0·23
Length of stay in hospital from inclusion (days)	26·1 (19·3)	26·4 (18·3)	–0·3 (–3·2 to 2·7)	0·87
Multidrug-resistant bacteria†	55 (17·9%)	52 (16·6%)	1·3% (–4·6 to 7·2)	0·67
Days of antibiotic exposure per 1000 inpatient days	653	812	–159 (–185 to –131)	<0·0001
Duration of first episode of antibiotic treatment (number [%]; days [SD])				
Overall population	307 (100%); 6·1 (6·0)	314 (100%); 9·9 (7·1)	–3·8 (–4·8 to –2·7)	<0·0001
Community-acquired pneumonia	79 (26%); 5·5 (4·0)	101 (32%); 10·5 (6·4)	–5·0 (–6·6 to –3·4)	<0·0001
Ventilator-associated pneumonia	75 (24%); 7·3 (5·3)	66 (21%); 9·4 (5·7)	–2·1 (–4·0 to –0·3)	0·0210
Intra-abdominal infection	14 (5%); 8·1 (7·7)	20 (6%); 10·8 (6·7)	–2·7 (–7·7 to 2·4)	0·29
Urinary tract infection	24 (8%), 7·4 (6·3)	18 (6%), 14·5 (9·3)	–7·1 (–11·9 to –2·2)	0·0053
Infection with positive blood culture	55 (18%), 9·8 (7·7)	53 (17%), 12·8 (8·1)	–3·0 (–6·0 to 0·1)	0·06

Data are number (%), difference (95% CI), or mean (SD), unless otherwise indicated. NA=not applicable. SOFA=sequential organ-failure assessment. ICU=intensive care unit.
*Difference (90% CI).

Table 2: **Main outcome variables**

De Jong E

Efficacy and safety of procalcitonin guidance in reducing the duration of antibiotic treatment in critically ill patients: a randomised, controlled, open-label trial



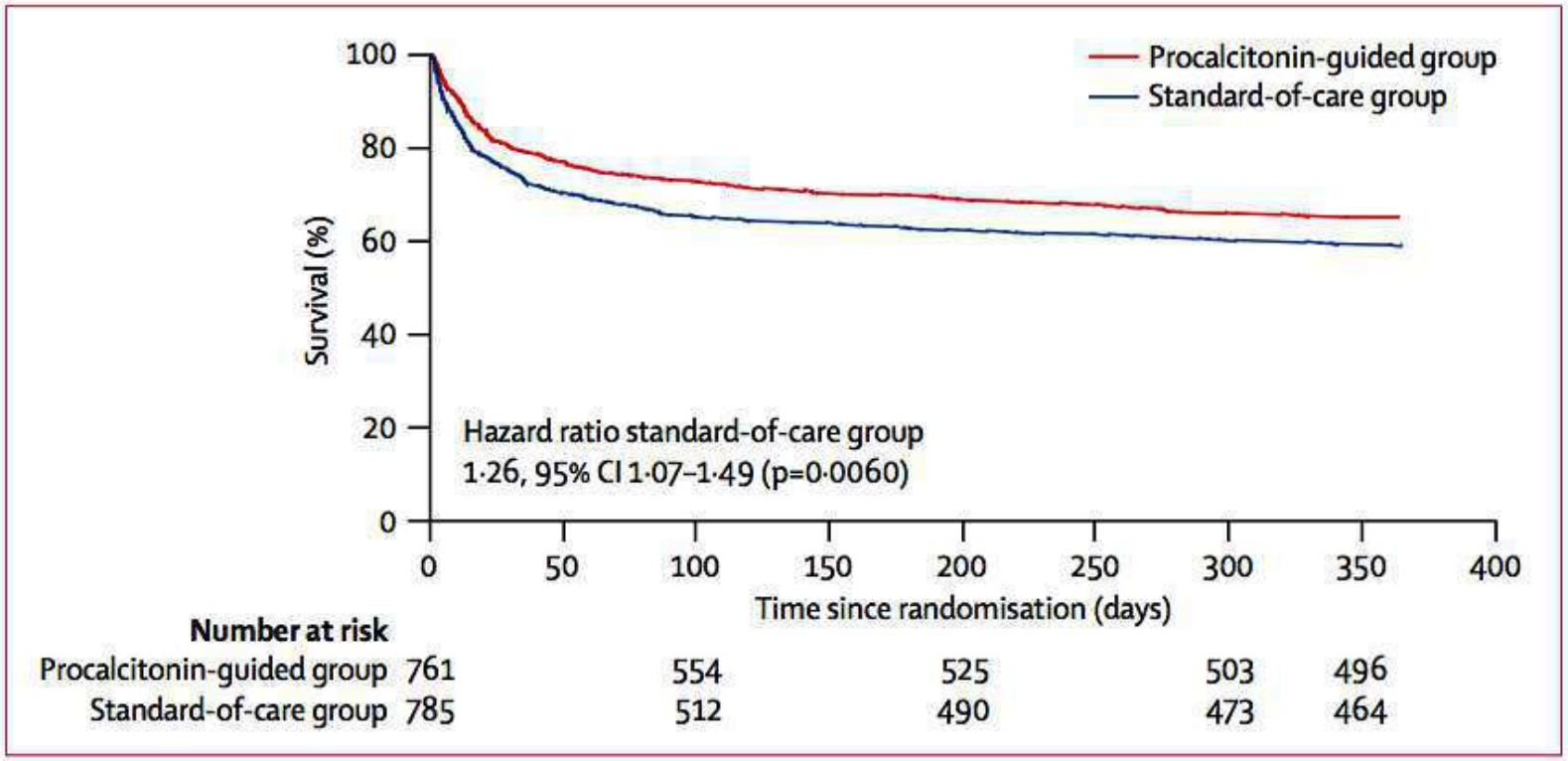


Figure 2: **Kaplan-Meier plot for probability of survival from random assignment to day 365, in the modified intention-to-treat population**

Lancet Infect Dis 2016

Thomas-Rüddel *et al. Critical Care* (2018) 22:128
https://doi.org/10.1186/s13054-018-2050-9

Critical Care

RESEARCH Open Access

Influence of pathogen and focus of infection on procalcitonin values in sepsis patients with bacteremia or candidemia

Daniel O. Thomas-Rüddel[1,2*], Bernhard Poidinger[1,2], Matthias Kott[3], Manfred Weiss[4], Konrad Reinhart[1,2], Frank Bloos[1,2] for the MEDUSA study group

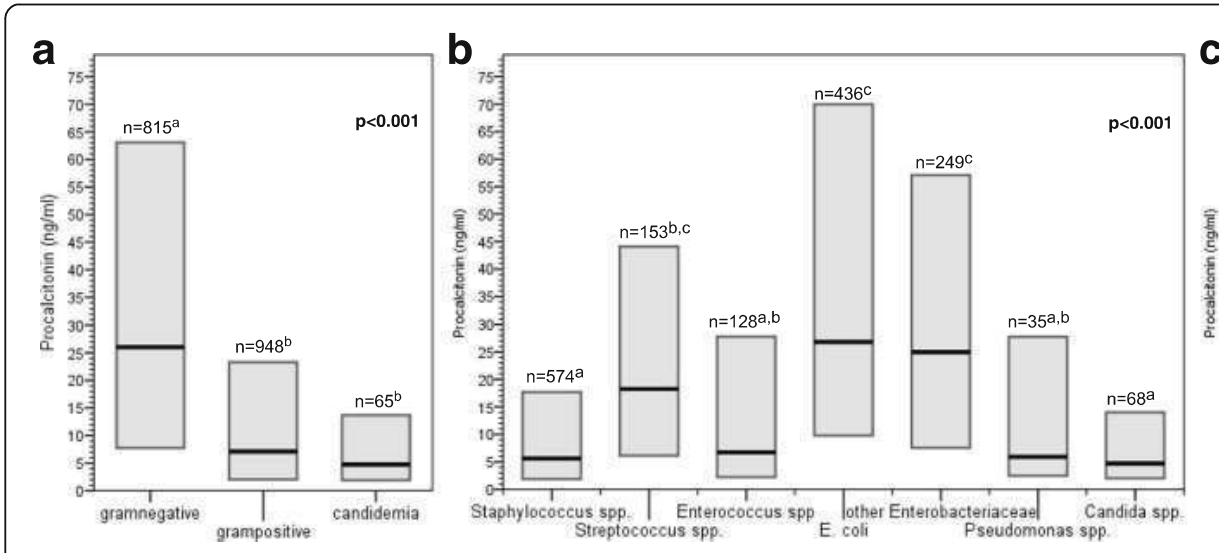


Table 3 Test performance of procalcitonin for prediction of Gram-negative bacteremia

Classification	Optimal cutoff (ng/ml)	SENS	SPEC	PPV	NPV	PLR	NLR	ACC
Gram-negative bacteremia vs Gram-positive/candidemia	17.5	0.59	0.70	0.61	0.68	1.98	0.59	0.65
Gram-negative bacteremia vs all other blood culture results	10	0.69	0.65	0.33	0.9	1.97	0.47	0.66

Optimal cutoff values derived from receiver operating characteristics by Youden's index and sensitivity (SENS), specificity (SPEC), positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (PLR), negative likelihood ratio (NLR) and accuracy (ACC) calculated from the resulting 2 × 2 tables

Table 4 Procalcitonin values associated with different pathogens

Pathogen species detected from blood cultures	Number	PCT (IQR)
***Staphylococcus* spp.**	574	5.6 (1.9–17.7)
Staphylococcus aureus, methicillin sensitive	272	7.2 (2.7–20.7)
Staphylococcus aureus, methicillin resistant	58	4.7 (1.4–10.6)
Coagulase-negative Staphylococci, methicillin sensitive	151	5.2 (1.4–16.1)
Coagulase-negative Staphylococci, methicillin resistant	65	3.8 (1.3–12.8)
***Streptococcus* spp.**	153	18.2 (6.2–44.1)
Streptococci, Group A, B, C or G	59	18.2 (8.4–47.3)
Streptococcus pneumoniae	63	21.6 (7–48.3)
Other Streptococci (*Streptococcus mutans*, other viridans Streptococci)	26	6.8 (3.6–44.1)
***Enterococcus* spp.**	128	6.8 (2.2–27.8)
Enterococcus faecalis	41	8.7 (2.1–54)
Enterococcus faecium	71	6.7 (2.3–25.3)
Vancomycin-resistant Enterococci	7	1.9 (0.5–99.3)

Table 4 Procalcitonin values associated with different pathogens

Pathogen species detected from blood cultures	Number	PCT (IQR)
Escherichia coli	436	26.8 (9.8–70)
Enterobacteriaceae* other than *E. coli	249	24.9 (7.6–57.1)
Enterobacter spp.	38	21.1 (7.6–56.8)
Klebsiella spp.	123	21.5 (6–49.7)
Proteus spp.	47	46.8 (9.1–97.6)
Serratia spp.	20	12.1 (6.5–42.4)
Citrobacter spp.	9	37.8 (15.1–113.1)
Enterobacteriaceae, other	2	3.7 (2.4–5)
***Pseudomonas* spp.**	35	5.9 (2.1–28.4)
Pseudomonas aeruginosa	32	6.1 (3.1–30.6)
Pseudomonas, other	3	2.0 (0.6–28.4)

Table 4 Procalcitonin values associated with different pathogens

Pathogen species detected from blood cultures	Number	PCT (IQR)
Candida spp.	68	4.7 (2–14)
Candida albicans	57	5.3 (2.1–15.3)
Candida, other	37	6.5 (2.2–17.4)
Rare pathogens		
Listeria monocytogenes	7	8.0 (0.8–19.7)
Acinetobacter spp.	7	5.8 (0.9–39.0)
Haemophilus spp.	4	29.9 (17.3–36.6)

proADM is a good biomarker for the diagnosis and prognosis of sepsis and septic shock patients as well as for organ failure

→ wide variety of physiological functions:
  → Endogenous immunomodulatory factor with predominant anti-inflammatory effects in various models of sepsis and septic shock,
  → Antimicrobial activity (Gram+, Gram-, fungi)
  → Diuretic and Vasodilatory activity

and, under normal conditions, circulates at low concentrations

<u>Increase in ADM in sepsis is explained by 2 mechanisms:</u>

1) ADM synthesis increases during severe infections because it is a peptide related to the calcitonin gene
2) Bacterial endotoxins and pro-inflammatory citokines lead increased ADM gene expression in several tissues

Mid-regional pro-adrenomedullina

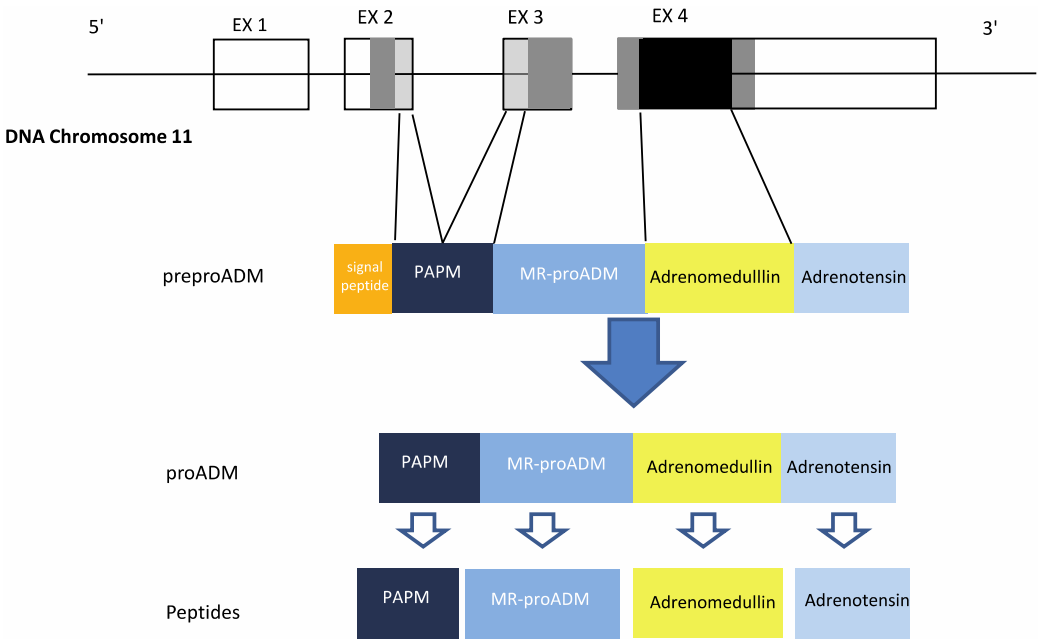


Figure 1 Schematic representation of the pre-proadrenomedullin gene and biosynthesis of the peptides: aminoterminal peptide of proadrenomedullin (PAMP), the mid-regional pro-adrenomedullin (MR-proADM), adrenomedullin and adrenotensin.

Andaluz-Ojeda *et al. Ann. Intensive Care (2017) 7:15*
DOI 10.1186/s13613-017-0238-9

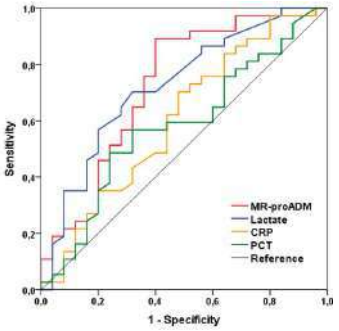
Annals of Intensive Care

RESEARCH Open Access

Superior accuracy of mid-regional proadrenomedullin for mortality prediction in sepsis with varying levels of illness severity

David Andaluz-Ojeda[1,2], H. Bryant Nguyen[3], Nicolas Meunier-Beillard[4], Ramón Cicuéndez[1,2], Jean-Pierre Quenot[4], Dolores Calvo[5], Auguste Dargent[4], Esther Zarca[5], Cristina Andrés[5], Leonor Nogales[1,2], Jose María Eiros[6], Eduardo Tamayo[2,7], Francisco Gandía[1,2], Jesús F. Bermejo-Martín[2*] and Pierre Emmanuel Charles[4]

SOFA ≥ 13
N= 62 patients



	AUROC [95%CI]	*p*
MR-proADM	0.73 [0.59 - 0.86]	0.003
Lactate	0.72 [0.59 - 0.86]	0.003
CRP	0.6 0 [0.46 - 0.75]	0.168
PCT	0.58 [0.44 - 0.73]	0.279

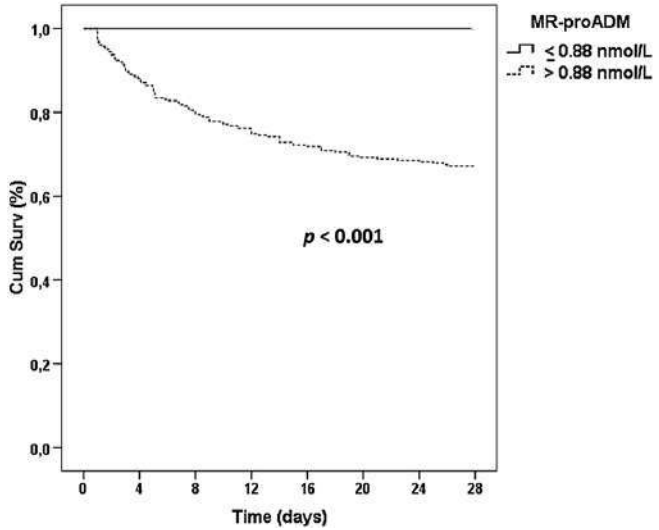


Fig. 1 Kaplan–Meier analysis for mortality prediction at 28 days

Journal of Infection (2015) xx, 1—4

LETTER TO THE EDITOR

Sustained value of proadrenomedullin as mortality predictor in severe sepsis

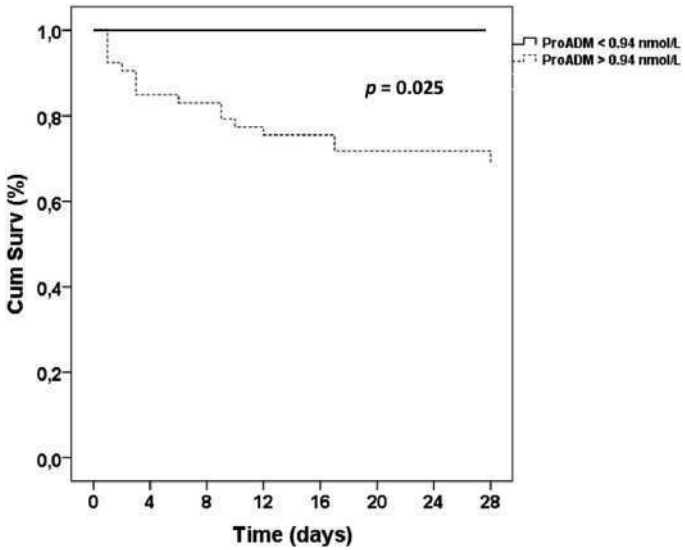
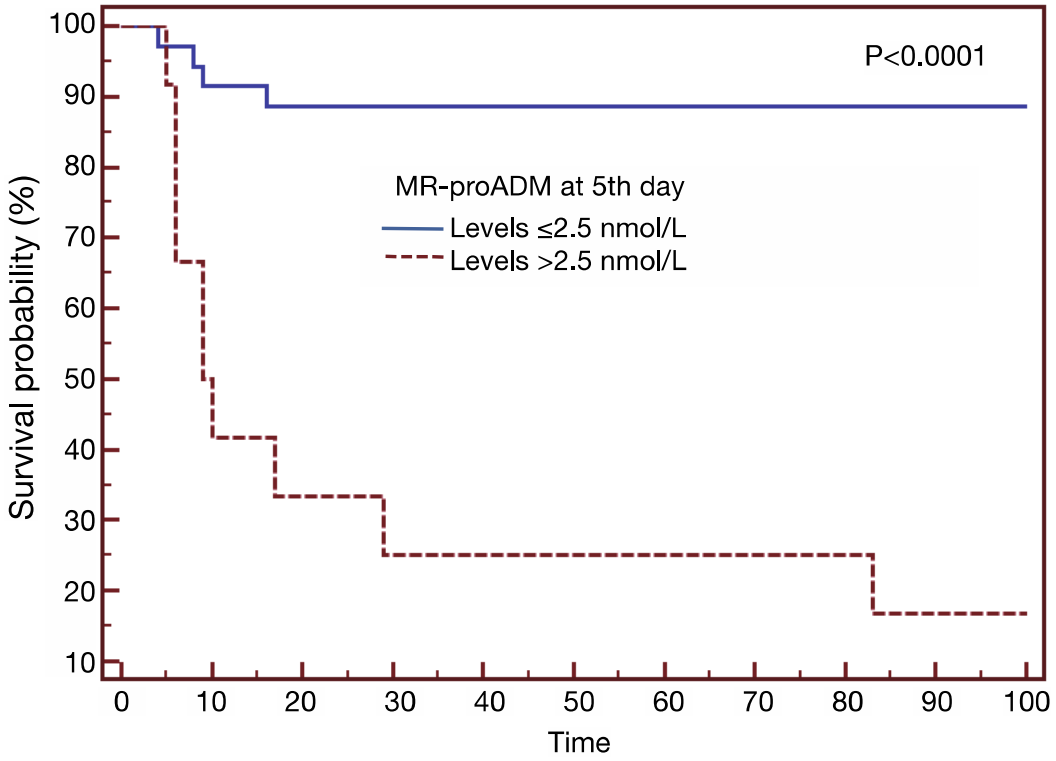
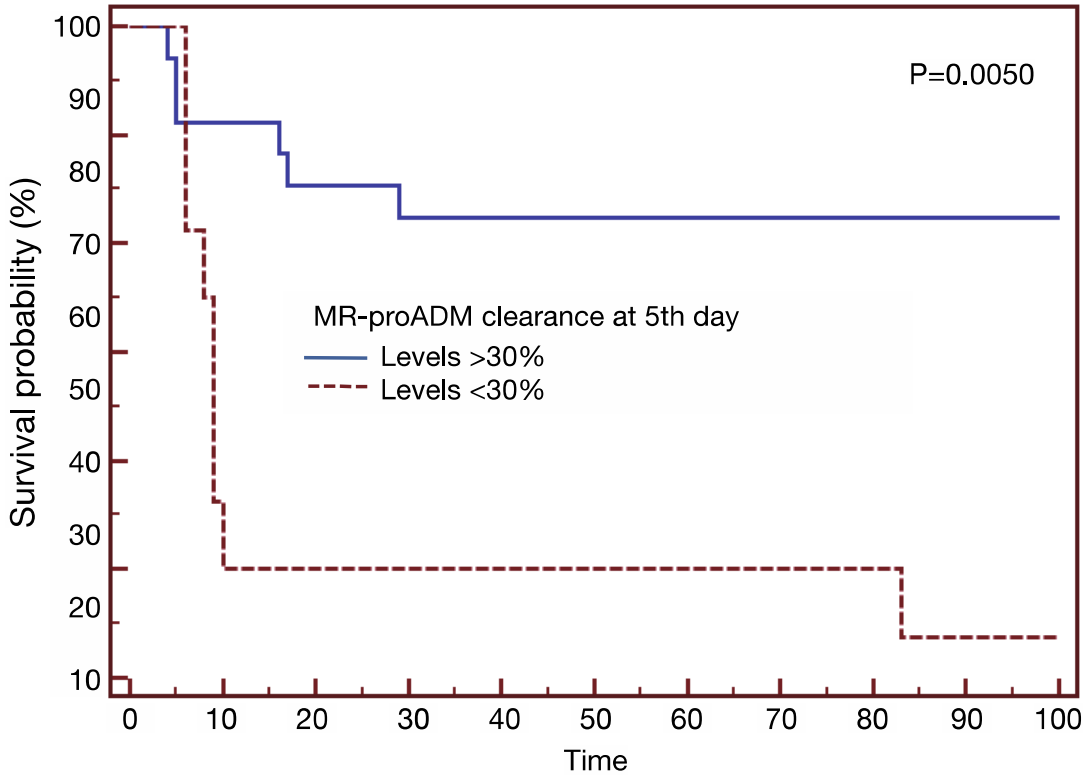


Figure 2 Kaplan Meier survival curves based on ProADM levels at day 1. Deciles from percentile 10 to percentile 90 of ProADM were calculated and used to compare survival times in those patients with low or high concentrations of this biomarker. The first decile showing significant differences between groups based upon the log-rank test (Mantel—Haenzel) was represented.

Pro ADM 2,5


P<0.0001
MR-proADM at 5th day
Levels ≤2.5 nmol/L
Levels >2.5 nmol/L
Survival probability (%)
100
90
80
70
60
50
40
30
20
10
0
10
20
30
40
50
60
70
80
90
100
Time

Pro ADM riduzione del 30% del valore iniziale



Elke et al. Critical Care (2018) 22:79
https://doi.org/10.1186/s13054-018-2001-5

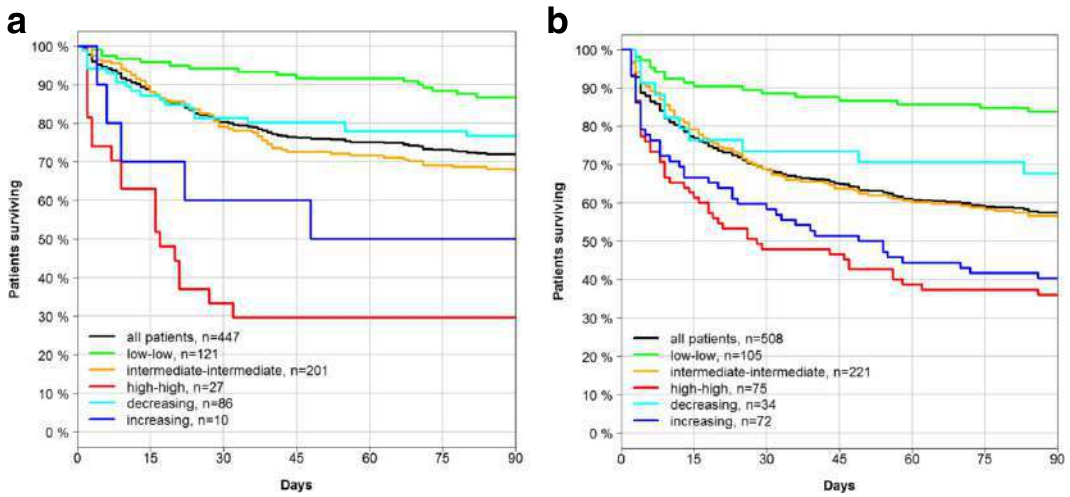
Critical Care

RESEARCH Open Access

The use of mid-regional proadrenomedullin to identify disease severity and treatment response to sepsis - a secondary analysis of a large randomised controlled trial

Gunnar Elke[1*], Frank Bloos[2,3], Darius Cameron Wilson[4], Frank Martin Brunkhorst[2,3], Josef Briegel[5], Konrad Reinhart[2,3], Markus Loeffler[6], Stefan Kluge[7], Axel Nierhaus[7], Ulrich Jaschinski[8], Onnen Moerer[9], Andreas Weyland[10], Patrick Meybohm[11] and the SepNet Critical Care Trials Group

Results: 1089 patients with a 28-day mortality rate of 26.9% were analysed. According to the Sepsis-3 definition, 41.2% and 58.8% fulfilled the criteria for sepsis and septic shock, with respective mortality rates of 20.0% and 32.1%. MR-proADM had the strongest association with mortality across all Sepsis-1 and Sepsis-3 subgroups and could facilitate a more accurate classification of low (e.g. MR-proADM vs. SOFA: *N* = 265 vs. 232; 9.8% vs. 13.8% mortality) and high (e.g. MR-proADM vs. SOFA: *N* = 161 vs. 155; 55.9% vs. 41.3% mortality) disease severity. Patients with decreasing PCT concentrations of either ≥ 20% (baseline to day 1) or ≥ 50% (baseline to day 4) but continuously high MR-proADM concentrations had a significantly increased mortality risk (HR (95% CI): 19.1 (8.0–45.9) and 43.1 (10.1–184.0)).



	Biomarker Kinetics		28 day mortality			90 day mortality		
	Baseline	Day 1	N	%	HR [95% CI]	N	%	HR [95% CI]
PCT decrease ≥20%			458	18.3%		447	28.2%	
MR-proADM severity level	Low	Low	125	5.6%	3.6 [1.6 - 8.1]*	121	13.2%	2.7 [1.6 - 4.8]*
	Intermediate	Intermediate	204	19.1%	5.3 [3.0 - 9.3]**	201	32.3%	3.8 [2.3 – 6.3]**
	High	High	27	66.7%	19.1 [8.0 - 45.9]***	27	70.4%	10.4 [5.3 - 20.2]***
	Increasing							
	Low	Intermediate	2	50.0%	-	2	50.0%	-
	Intermediate	High	10	40.0%	2.5 [0.9 - 7.0]††	10	50.0%	1.9 [0.8 - 4.8]††
	Decreasing							
	High	Intermediate	30	36.7%	0.4 [0.2 - 0.9]‡	29	44.8%	0.5 [0.2 - 0.9]‡
	Intermediate	Low	60	8.3%	0.4 [0.2 - 1.0]‡‡	57	12.3%	0.3 [0.2 - 0.7]‡‡
PCT decrease <20%			522	29.7%		508	42.5%	
MR-proADM severity level	Low	Low	106	10.4%	3.1 [1.7 - 5.9]*	105	16.2%	3.2 [1.9 - 5.3]*
	Intermediate	Intermediate	229	29.7%	2.0 [1.3 - 2.9]**	221	43.4%	1.9 [1.3 - 2.6]**
	High	High	77	49.4%	6.2 [3.2 - 12.2]***	75	64.0%	5.9 [3.4 - 10.3]***
	Increasing							
	Low	Intermediate	29	17.2%	1.8 [0.6 - 5.2]†	27	44.4%	3.2 [1.5 - 6.7]†
	Intermediate	High	45	53.3%	2.3 [1.4 - 3.6]††	45	68.9%	2.1 [1.4 - 3.2]††
	Decreasing							
	High	Intermediate	11	54.5%	-	11	72.7%	-
	High	Low	1	0.0%	-	1	100.0%	-
	Intermediate	Low	24	12.5%	0.4 [0.1 - 1.2]‡‡	23	13.0%	0.2 [0.1 - 0.8]‡‡

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Procalcitonin and MR-proAdrenomedullin combination in the etiological diagnosis and prognosis of sepsis and septic shock

Silvia Spoto[a], Marta Fogolari[b], Lucia De Florio[b], Marilena Minieri[c,d], Giuseppe Vicino[d], Jacopo Legramante[e,f], Maria Stella Lia[a], Alessandro Terrinoni[g], Damiano Caputo[g], Sebastiano Costantino[a], Sergio Bernardini[c,d], Massimo Ciccozzi[h], Silvia Angeletti[h,*]

Retrospective analysis of PCT and MR-proADM on 571 consecutive patients with sepsis

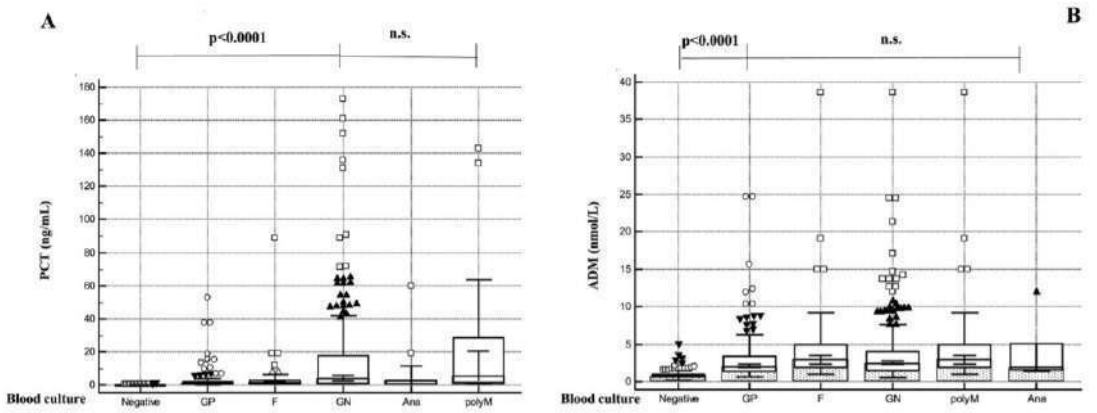

Fig. 1. PCT median values according to BC result: Mann-Whitney comparison between gram-negative (GN) vs, gram-positive (GP), fungi (F), anaerobes (Ana), polymicrobial (polyM) and negative BCs (panel A); ADM median values according to BC result: Mann-Whitney comparison between Fungi (F) vs negative, gram-positive (GP), gram-negative (GN), anaerobes (Ana) and polymicrobial (polyM) BCs (panel B).

- ✓ PCT: excellent in gram-negative, but less performant in gram-positive and fungal etiologies.
- ✓ MR-proADM: homogenously distributed within the different microbial classes and increased significantly in septic shock
- ✓ MR-proADM discriminating cut-offs were homogeneously distributed in Gram-negative and Gram-positive sepsis and were higher in septic shock, but not influenced by pathogen etiologies. MR-proADM cut-off values > 3.39 nmol/L in sepsis and > 4.33 nmol/L in septic shock were associated with significant higher risk of 90-days mortality.

S. Spoto et al. *Microbial Pathogenesis*(2019)

PLOS ONE

RESEARCH ARTICLE

Mid regional pro-adrenomedullin for the prediction of organ failure in infection. Results from a single centre study

Bruno Viaggi[1], Daniele Poole[2]*, Omar Tujjar[3], Silvia Marchiani[1], Agostino Ognibene[4], Stefano Finazzi[5]

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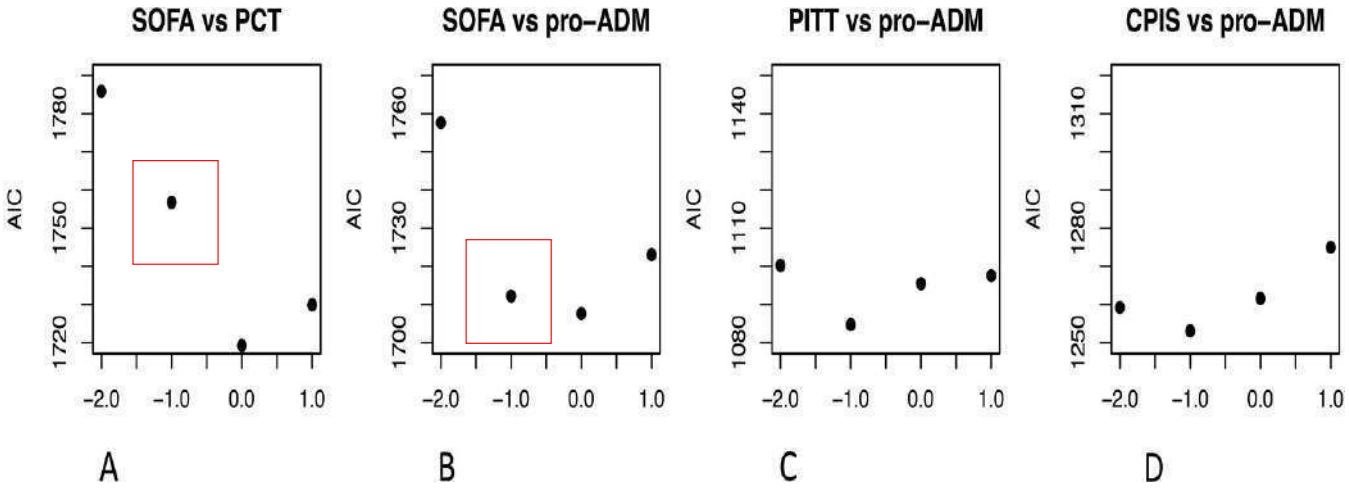

Fig 1. AIC of LME models with the biomarker measured two days before, one day before, the same day, the day after the score measurement (-2, -1, 0, and +1 on the x-axis). In panel A, we illustrate AIC values for LME models analyzing PCT and SOFA. In panels B, C, and D, the AIC values for the models correlating MR-proADM with SOFA, Pitt, and CPIS respectively. AIC: Akaike Information Criterion; LME: Linear Multiple-Effect; SOFA: daily Sequential Organ Failure Assessment; CPIS: Clinical Pulmonary Infection Score.

https://doi.org/10.1371/journal.pone.0201491.g001

Saeed *et al. Critical Care* (2019) 23:40
https://doi.org/10.1186/s13054-019-2329-5

Critical Care

RESEARCH Open Access

The early identification of disease progression in patients with suspected infection presenting to the emergency department: a multi-centre derivation and validation study

Kordo Saeed[1,2*], Darius Cameron Wilson[3], Frank Bloos[4,5], Philipp Schuetz[6,7], Yuri van der Does[8], Olle Melander[9,10], Pierre Hausfater[11], Jacopo M. Legramante[12,13], Yann-Erick Claessens[14], Deveendra Amin[15], Mari Rosenqvist[10,16], Graham White[17], Beat Mueller[6,7], Maarten Limper[18], Carlota Clemente Callejo[19], Antonella Brandi[12], Marc-Alexis Macchi[14], Nicholas Cortes[1,2,20], Alexander Kutz[6], Peter Patka[8], María Cecilia Yañez[19], Sergio Bernardini[21,22], Nathalie Beau[14], Matthew Dryden[1,2,23], Eric C. M. van Gorp[24,25], Marilena Minieri[21], Louisa Chan[26], Pleunie P. M. Rood[8] and Juan Gonzalez del Castillo[27]

Based on the results of this study, two clinically important uses for MR-proADM can be proposed: (i) an early escalation of treatment in patients with MR-proADM concentrations ≥ 1.5 nmol/L, thus identifying an already high level of disease severity or a high potential for further development and progression, and (ii) a decreased number of hospital admissions allowing a safe increase in out-patient treatment in patients with MR-proADM concentrations < 0.9 nmol/L.

Conclusions: In patients presenting to the ED with a suspected infection, the blood biomarker MR-proADM could most accurately identify the likelihood of further disease progression. Incorporation into an early sepsis management protocol may therefore aid rapid decision-making in order to either initiate, escalate or intensify early treatment strategies, or identify patients suitable for safe out-patient treatment.

Saeed et al. Critical Care (2019) 23:40
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Critical Care

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MR-proADM concentrations (e.g. > 2.75 nmol/L [19]), with the early admission onto a high dependency or intensive care unit to initiate aggressive therapeutic strategies, such as those targeting extravascular fluid accumulation, potentially decreasing further organ dysfunction or progression towards multiple organ failure [20, 32]. Interestingly, MR-proADM concentrations > 2.75 nmol/L in our study ($N = 126$; 10.7%) resulted in a 28-day mortality rate of 30.2%, similar to the 32.5% found in the intensive care study of Elke et al. [19] in patients with corresponding concentrations ($N = 759$; 73.7%).

Zampino et al. BMC Infectious Diseases (2021) 21:23
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BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Prognostic value of pro-adrenomedullin and copeptin in acute infective endocarditis

Rosa Zampino[1,2], Domenico Iossa[3], Maria Paola Ursi[1], Lorenzo Bertolino[1], Roberto Andini[2], Rosa Molaro[3], Oriana Fabrazzo[1], Silvia Leonardi[4], Luigi Atripaldi[4] and Emanuele Durante-Mangoni[1,2*]

- ✓ 196 patients with definite IE. Clinical, laboratory and echocardiography parameters were analyzed, with a focus on comorbidities. PCT, pro-ADM and copeptin were measured on stored plasma samples obtained on admission
- ✓ Pro-ADM and copeptin were significantly higher in older patients and associated with prior chronic kidney disease.
- ✓ Pro-ADM was an independent predictor of hospital mortality (OR 3.29 [95%C.I. 1.04–11.5]; p = 0.042)
- ✓ copeptin independently predicted 1-year mortality (OR 2.55 [95%C.I. 1.18–5.54]; p = 0.017).
- ✓ A high PCT value was strictly tied with *S. aureus* etiology (p = 0.001).
- ✓ CRP was the only biomarker associated with embolic events (p = 0.003).

Zampino et al. BMC Infectious Diseases (2021)

NUM	PAZIENTE	PCT	ADM	BNP
1	IM	3,28	2,76	nd
2	TD	0,25	2,35	nd
3	PR	nd	3,12	nd
4	RM	0,16	1,23	26841
5	IS	>100	5,11	3256
6	PN	0,85	3,5	26638
7	AL	0,68	1,3	1071
8	SL	1,06	2,15	6439
9	INC	1,28	3,24	9799
10	MA	0,17	3,19	5525
11	IzMa	17,3	1,68	7248
12	LI	0,01	0,46	88
13	AR	0,08	1	209
14	D'AA	0,5	2	2382
15	SG	0,48	5,65	16486

Data courtesy of Prof Carlo Tascini—Personal Experience

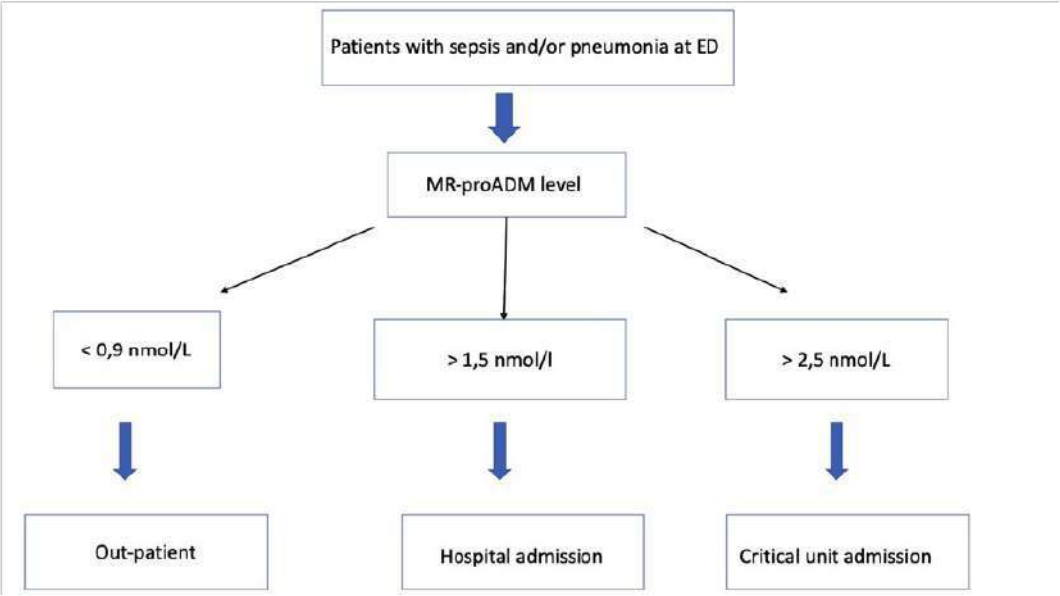
Pro-ADM e PCT Liquor

Paziente	PCT Sangue	PCT liquor	Pro-ADM sangue	Pro-ADM liquor	Patologia
Paziente di 80 anni	0,07	0,07	0,67	0,95	Meningitie liquor limpido primo prelievo
Paziente di 70 anni	10,42	2,7	--	11	Meningitie S. agalactiae primo prelievo
Paziente di 68 anni	2,39	0,4	1,71	8,33	Meningite pneumococcica primo prelievo
Paziente 40 anni		0,68		3,58	Meningite pneumococcica primo
Paziente 75 anni	0,38	3,48	1,22	14,21	Meningite S. agalactiae primo prelievo
Paziente di 78 anni	0,66	0,09	1,66	1,79	Meningite pneumococcica controllo
Paziente di 60 anni	0,05	0,02	0,99	1,73	Meningite pneumococcica controllo
Paziente 5 anni	125	1,54	1,32	6,22	Meningite pneumococcica primo prelievo
Paziente 10 anni	0,1	0,11	0,73	1,4	Meningite pneumococcica primo prelievo
Paziente di 68 anni	0,13	0,07	2,7	1,8	Controllo in meningite ipoglicorrachica

Data courtesy of Prof Carlo Tascini—
Personal Experience

Clinical Benefits of MR-proADM

Interviewee: Professor Carlo Tascini | Head of Infectious Diseases Clinic | Udine University Hospital | Italy



Wilson et al. Critical Care (2020) 24:411
https://doi.org/10.1186/s13054-020-03151-7

Critical Care

LETTER Open Access

Adrenomedullin in COVID-19 induced endotheliitis

Darius Cameron Wilson[1*], Joerg C. Schefold[2], Jaume Baldirà[3], Thibaud Spinetti[2], Kordo Saeed[4] and Gunnar Elke[5]

Whilst numerous pro-inflammatory cytokines and blood biomarkers have already been compared in patients with different severities of COVID-19 - to date - no study, report or editorial has described the potential role of adrenomedullin (ADM) during the host response to COVID-19. This is surprising, since ADM has been shown to play a key role in reducing vascular (hyper) permeability and promoting endothelial stability and integrity following severe infection [2]. Thus, ADM may also be of interest (MR-proADM), found that its assessment could accurately identify disease progression in patients with non-severe clinical signs and symptoms, safely increase outpatient treatment with decreased readmission rates and no subsequent mortalities [4], and identify patients requiring a rapid administration of antibiotics or triage to the ICU [5]. Despite the low number of severe viral cases within each of these studies (between 2.1% [3] and 3.4% [4]), similar hypotheses can also be formulated for patient populations with COVID-19.

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MR-proADM as prognostic factor of outcome in COVID-19 patients

Emanuela Sozio[1], Carlo Tascini[1]✉, Martina Fabris[2], Federica D'Aurizio[2], Chiara De Carlo[1], Elena Graziano[1], Flavio Bassi[3], Francesco Sbrana[4], Andrea Ripoli[5], Alberto Pagotto[1], Alessandro Giacinta[1], Valentina Gerussi[1], Daniela Visentini[2], Paola De Stefanis[3], Maria Merelli[1], Kordo Saeed[6] & Francesco Curcio[2]

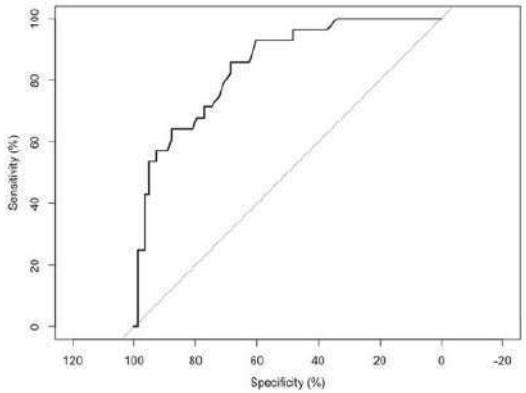

Figure 1. AUROC analysis: MR-proADM on combined event of death or orotracheal intubation (IOT). AUROC: 0.849 [0.771–0.730], $p < 0.0001$. Optimal cut-off value of MR-proADM: 0.895; a sensitivity of 0.857 [0.728–0.987] and a specificity of 0.687 [0.587–0.787] correspond to this cutoff value.

	Overall (n = 111)	Not death and not IOT (n = 83)	Death or IOT (n = 28)	p
Males	66 (59.5%)	44 (53.0%)	22 (78.6%)	0.0308
Age (years)	62.29 ± 13.63	61.73 ± 14.28	63.93 ± 11.6	0.4191
WHO disease severity	2.24 ± 1.03	1.86 ± 0.72	3.39 ± 0.96	< 0.0001
SIMEU disease severity	2 [2–3]	2 [2–3]	5 [4–5]	< 0.0001
PaO_2/FiO_2 ratio	292.5 ± 109.4	330.9 ± 85.6	183.2 ± 96.2	< 0.0001
SOFA score	2 [1–3]	2 [1–2]	3 [3–4]	< 0.0001
Charlson Comorbidity Index	2 [1–4]	2 [1–4]	2.5 [1.75–4]	0.4477
Length of hospital stay (days)	9 [6–22]	7 [4.5–10]	30 [23–47]	< 0.0001
MR-proADM (nMol/L)	0.82 [0.64–1.08]	0.73 [0.56–0.94]	1.38 [0.94–1.73]	< 0.0001
IL-6 (pg/mL)	30.0 [7.7–82.3]	21.9 [4.2–51.0]	175.7 [48.0–1070.0]	< 0.0001
IL-1b (pg/ml)	0.33 [0.18–0.48]	0.28 [0.15–0.42]	0.48 [0.26–0.88]	0.0069
IL-8 (pg/mL)	32.0 [21.0–43.1]	27.7 [18.3–38.4]	37.5 [30.0–62.6]	0.0018
TNFα (pg/mL)	17.0 [13.3–21.8]	16.0 [12.8–19.1]	23.7 [17.6–31.4]	0.0001
C reactive protein (mg/dl)	71.0 [16.9–117.0]	48.0 [10.3–99.5]	108.5 [72.3–200.8]	0.0002
Procalcitonine (mg/dL)	0.07 [0.02–0.29]	0.04 [0.02–0.14]	0.31 [0.18–0.47]	< 0.0001
White blood cell (/mmc)	6020 [4745–7925]	5760 [4330–7465]	7030 [5892–12725]	0.001
Neutrophils (/mmc)	4420 [3130–6680]	3900 [2720–5945]	6175 [4898–11510]	< 0.0001
Lymphocytes (/mmc)	914 ± 435	1007 ± 442	639 ± 268	< 0.0001
CD4/CD8	2.1 [1.4–2.9]	2.0 [1.3–2.9]	2.2 [1.8–4.2]	0.1016
D-dimer (FEUng/ml)	751 [403–1200]	690 [343–1045]	1157 [759.5–1959]	0.0008
LDH (U/L)	517 [375–735]	452 [350–646]	758 [637–951]	< 0.0001
CK (U/L)	92 [55–178]	78 [53–127]	185 [106–333]	0.0002
B-type natriuretic peptide (pg/ml)	28 [12–66]	25 [11–63]	34 [20–92]	0.2634
High-sensitive cardiac troponin (ng/L)	0.02 [0.00–0.02]	0.02 [0.00–0.02]	0.02 [0.00–0.02]	0.3407
Bilirubin (mg/dl)	0.55 [0.40–0.78]	0.51 [0.38–0.78]	0.60 [0.50–0.78]	0.1638
Platelets (/mmc)	224,189 ± 98,333	220,398 ± 85,808	235,429 ± 129,834	0.571
Creatinine (mg/dl)	1.00 ± 0.48	0.98 ± 0.51	1.08 ± 0.37	0.2636

Table 1. Overall study population and comparison between the group with combined event of Death or IOT and the group without combined event.

	Univariate analysis		Multivariate analysis
Variables	OR [95% CI]	p	OR [95% CI]
Males	3.25 [1.2565–9.5691]	0.0209	–
Age (years)	1.0122 [0.9806–1.0465]	0.4607	–
WHO disease severity	8.55 [4.1473–21.841]	< 0.0001	7.632 [5.871–19.496]
SIMEU disease severity	4.9577 [3.0004–9.3041]	< 0.0001	–
PaO_2/FiO_2 ratio	0.9816 [0.9731–0.9883]	< 0.0001	–
SOFA score	4.1475 [2.4822–7.9195]	< 0.0001	–
Charlson Comorbidity Index	1.0953 [0.9548–1.2742]	0.1949	–
Length of hospital stay (days)	1.1121 [1.0697–1.168]	< 0.0001	–
MR-proADM (nMol/L)	4.329 [1.9178–12.4701]	0.0024	4.284 [1.893–11.413]
IL-6 (pg/mL)	1.0081 [1.0038–1.0146]	0.0025	–
IL-1b (pg/ml)	0.9702 [0.5885–1.2803]	0.8516	–
IL-8 (pg/mL)	1.0119 [0.9995–1.0289]	0.0979	–
TNFα (pg/mL)	1.1302 [1.0637–1.2223]	0.0005	–
C reactive protein (mg/dl)	1.0107 [1.0053–1.0169]	0.0003	–
Procalcitonine (mg/dL)	1.0236 [0.7832–1.2445]	0.7954	–
White blood cell (/mmc)	1.0187 [1.0081–1.0316]	0.0015	–
Neutrophils (/mmc)	1.0243 [1.0119–1.0394]	0.0004	1.029 [1.011–1.049]

Internal and Emergency Medicine
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CE-RESEARCH LETTER TO THE EDITOR

Pooled analysis of mid-regional pro-adrenomedullin values in COVID-19 patients with critical illness

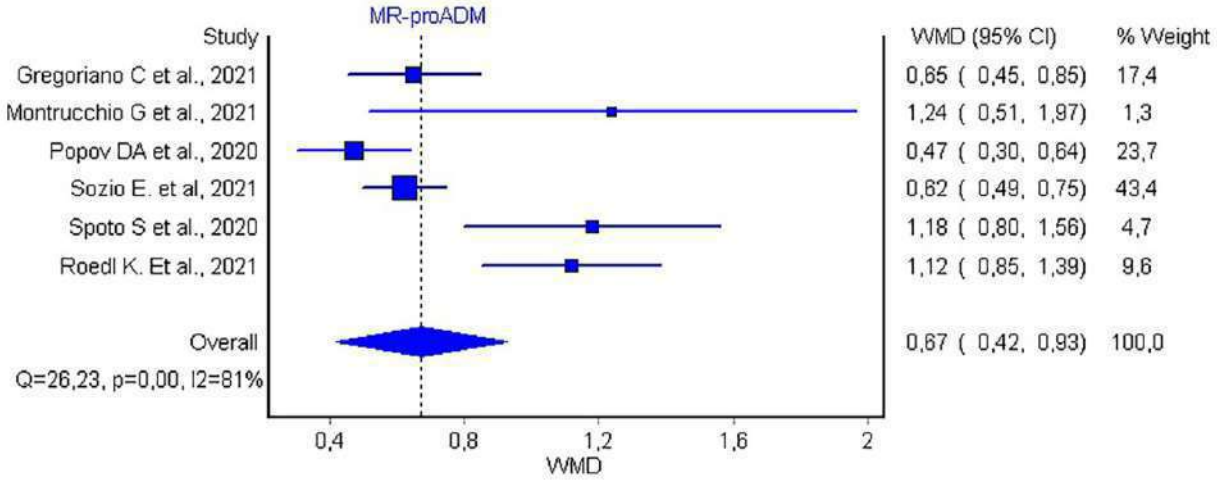
Giuseppe Lippi[1] · Brandon Michael Henry[2]

Received: 2 March 2021 / Accepted: 29 April 2021

Table 1 Summary of clinical studies which explored mid-regional pro-adrenomedullin (MR-proADM) levels in coronavirus disease 2019 (COVID-19) patients with or without critical illness

Authors	Setting	Sample size	Endpoint	Values (severe vs. non-severe; nmol/L)
Gregoriano C et al. (2021) [7]	Switzerland	89 (19% severe)	Death	1.50 ± 0.40 vs. 0.85 ± 0.23
Montrucchio G et al. (2021) [8]	Italy	57 (54% severe)	ICU admission or death	2.37 ± 1.63 vs. 1.13 ± 1.16
Popov DA et al. (2020) [9]	Russia	97 (14% severe)	Death	1.25 ± 0.31 vs. 0.78 ± 0.22
Roedl K. et al. (2021) [10]	Germany	64 (45% severe)	RRT	2.46 ± 0.64 vs.1.34 ± 0.39
Sozio E et al. (2021) [11]	Italy	111 (25% severe)	Death or intubation	1.36 ± 0.31 vs. 0.74 ± 0.23
Spoto S et al. (2021) [12]	Italy	69 (58% severe)	ARDS	2.30 ± 1.11 vs. 1.12 ± 0.45

ARDS acute respiratory distress syndrome, *ICU* intensive care unit, *RRT* renal replacement therapy



G. Lippi, B. M. Henry *Internal and Emergency Medicine*(2021)

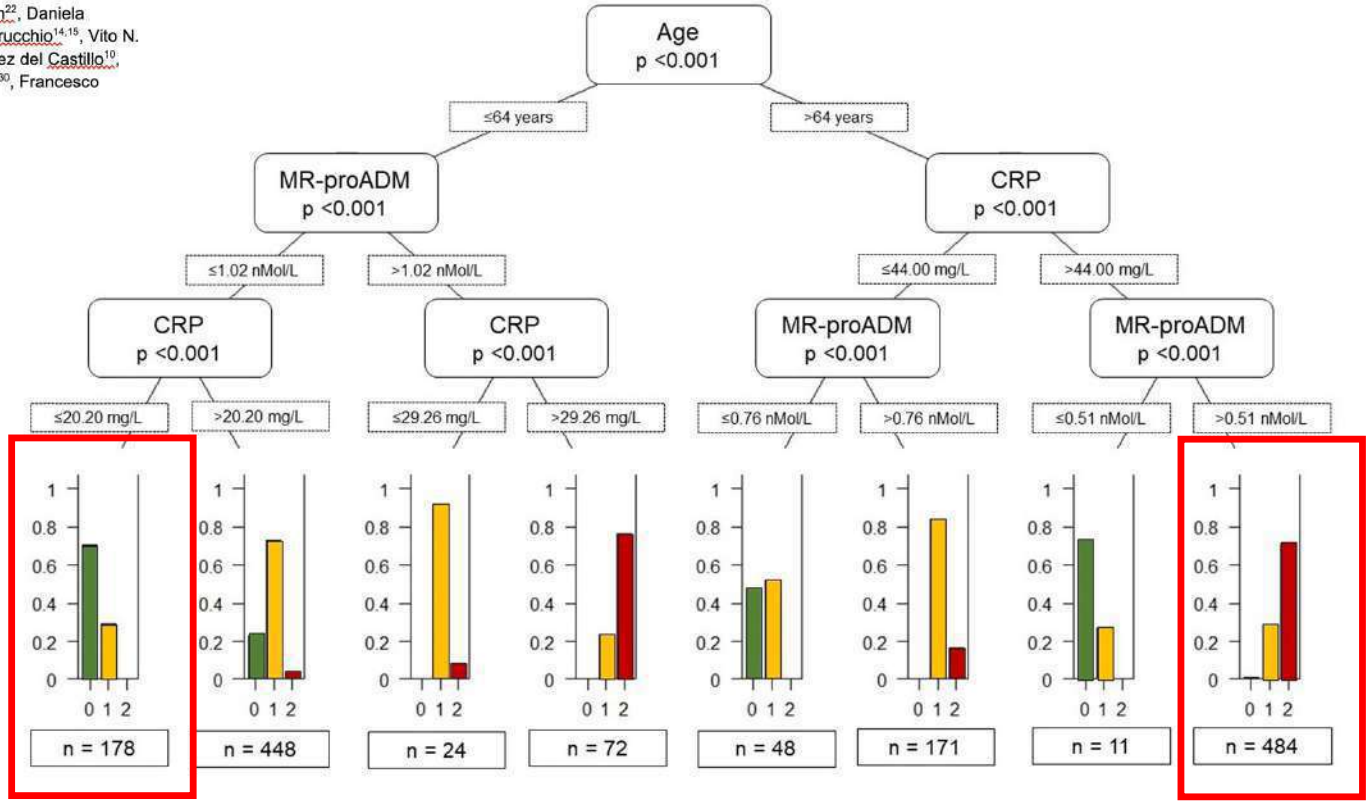
article to be published, confidential data

Identification of COVID-19 Patients at Risk of Hospital Admission and Mortality: a European Multicentre Retrospective Analysis

Authors/ Affiliations

Emanuela Sozio[†,1], Nathan Moore[1,2], Martina Fabris[3], Andrea Ripoli[4], Francesca Rumbolo[5], Marilena Minieri[6,7], Riccardo Boverio[8], María Dolores Rodríguez Mulero[9], Sara Lainez-Martinez[10], Mónica Martínez Martínez[11], Dolores Calvo[12], Claudia Gregoriano[13], Rebecca Williams[2], Luca Brazzi[14,15], Alessandro Terrinoni[5], Tiziana Callegari[16], Marta Hernández Olivo[17], Patricia Esteban-Torrella[18], Ismael Calcerrada[19], Luca Bernasconi[20], Stephen P. Kidd[2], Francesco Sbrana[4], Iria Miguens[21], Kirsty Gordon[22], Daniela Visentini[3], Jacopo M. Legramante[23,24], Flavio Bassi[25], Nicholas Cortes[2,26], Giorgia Montrucchio[14,15], Vito N. Di Lecce[24], Ernesto C. Lauritano[8], Luis García de Guadiana-Romualdo[27], Juan González del Castillo[10], Enrique Bernal-Morell[11,28], David Andaluz-Ojeda[29], Luca Bernasconi, Philipp Schuetz[13,30], Francesco Curcio[3,31], Carlo Tascini[1,31] & Kordo Saeed[26,32]

1436 patients
10 Hospitals across Europe



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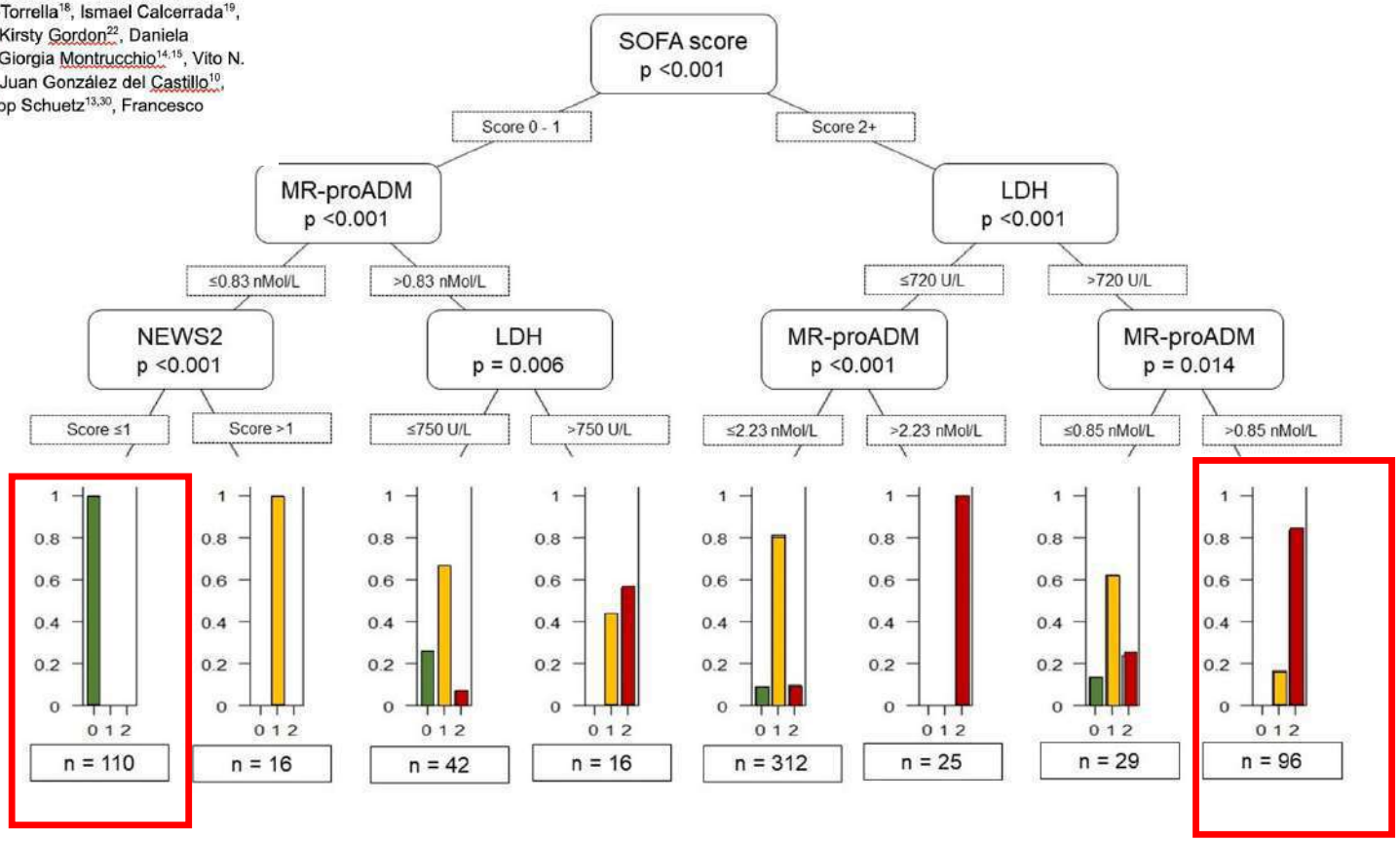
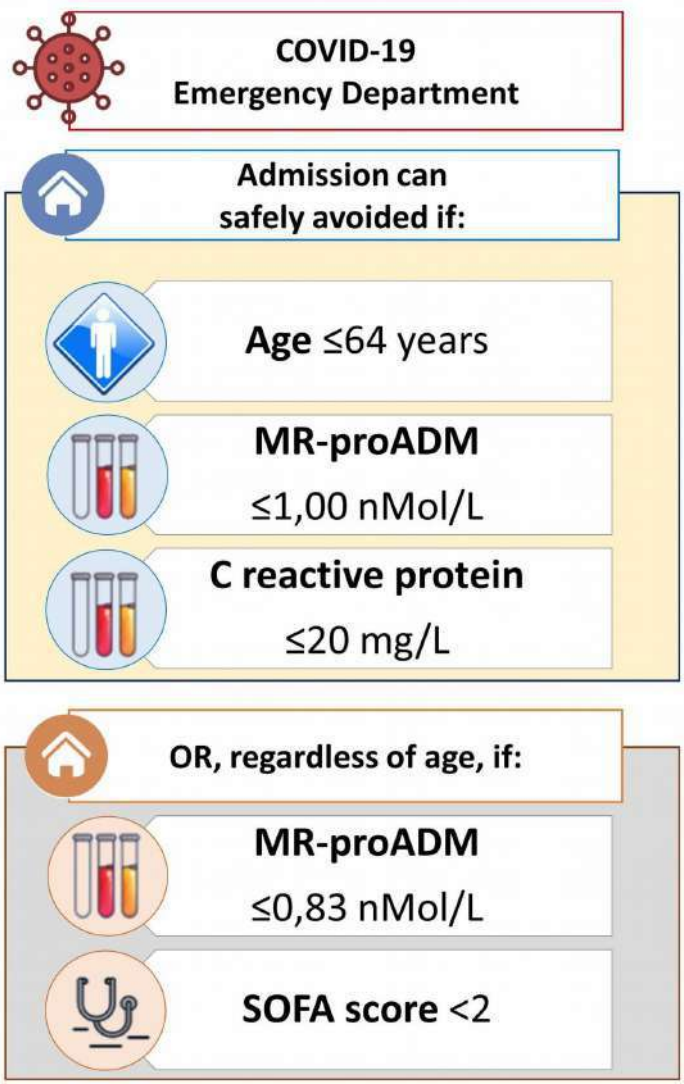
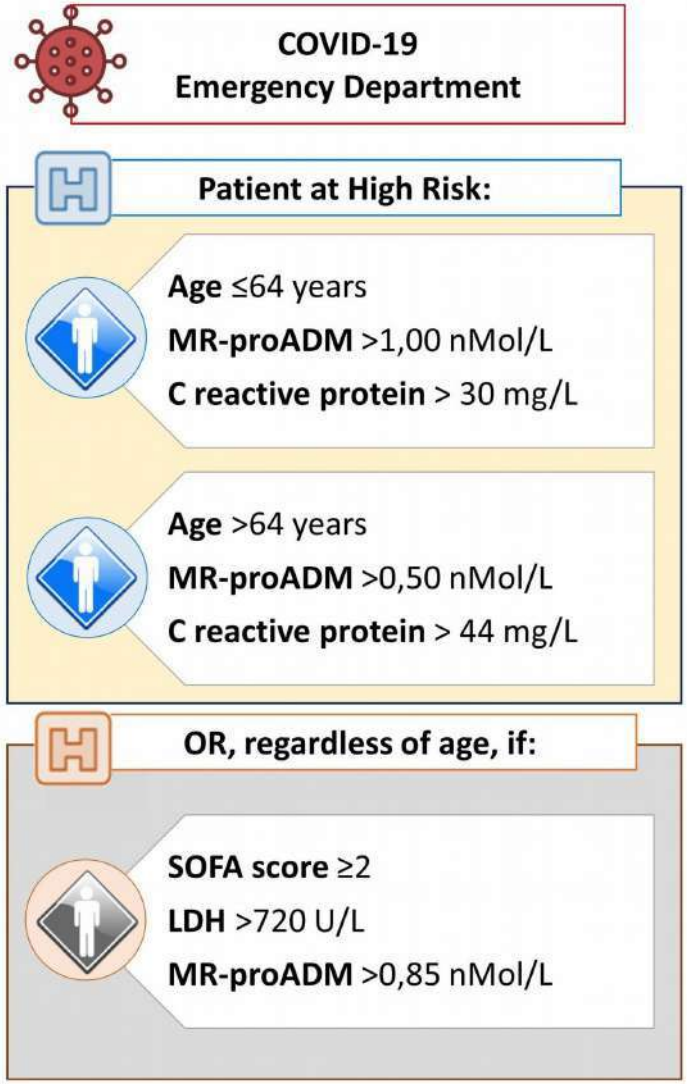
646 patients





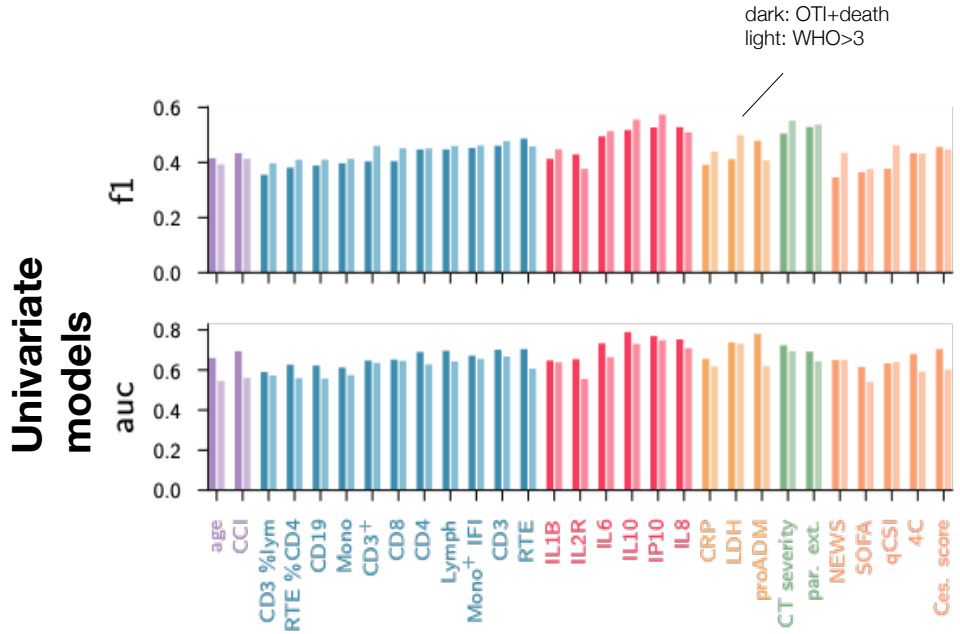


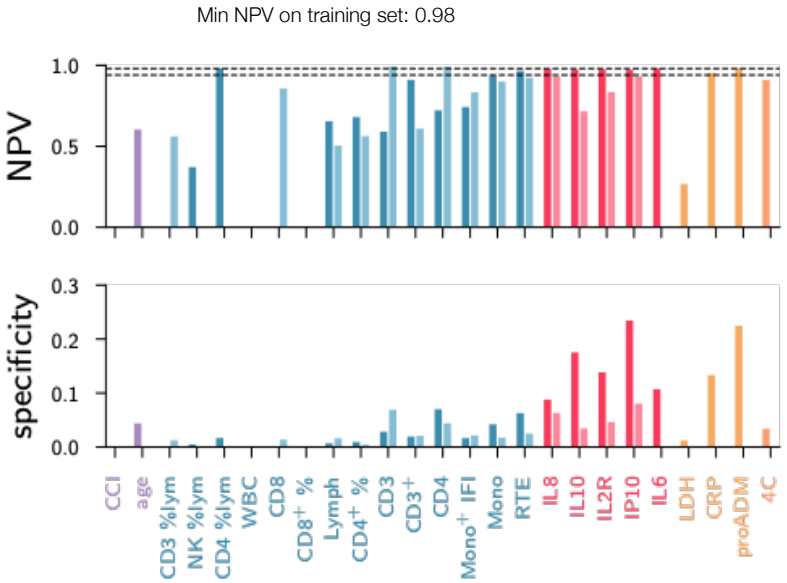
article to be published, confidential data

COVID-19 set: 897 patients hospitalised (March 2020 -April 2021)
Control set: 382 healthy patients.

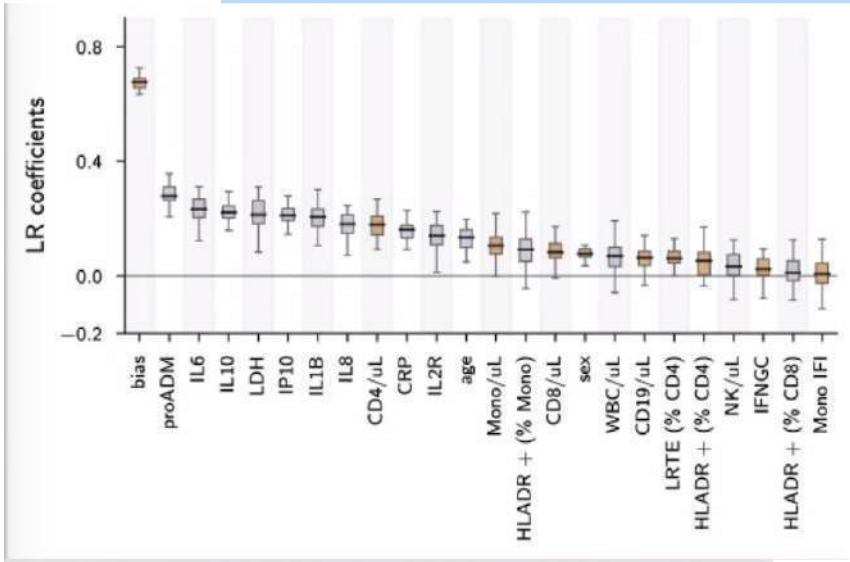
Variables:

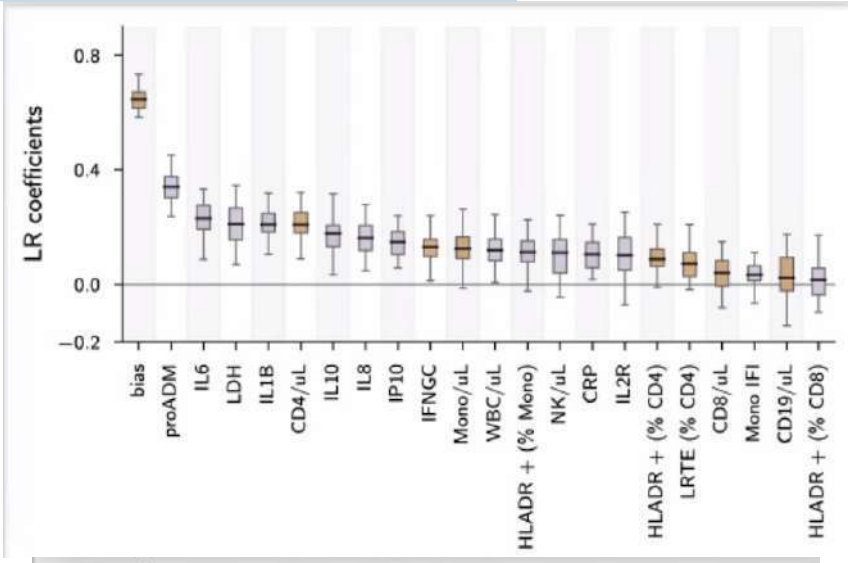
- Immune cells: WBC, lymphocytes and monocytes, subpopulations of T CD3, T CD4, T CD8 (%, abs, HLADR), T NK, B CD19, LRTE % CD4, monocyte HLADR and mean intensity fluorescence (IFI).
- Cytokines: IL2R , IP10, IL10, IL6, IL8, INFγ
- Biomarkers: LDH, CRP, proADM.
- Clinical Scores: SOFA score, 4C score, qCSI, NEWS
- Outcome data: orotracheal intubation (OTI), death, WHO*, days of hospital stay.
- **Age, Sex, Charlson Comorbidity Index (CCI).**

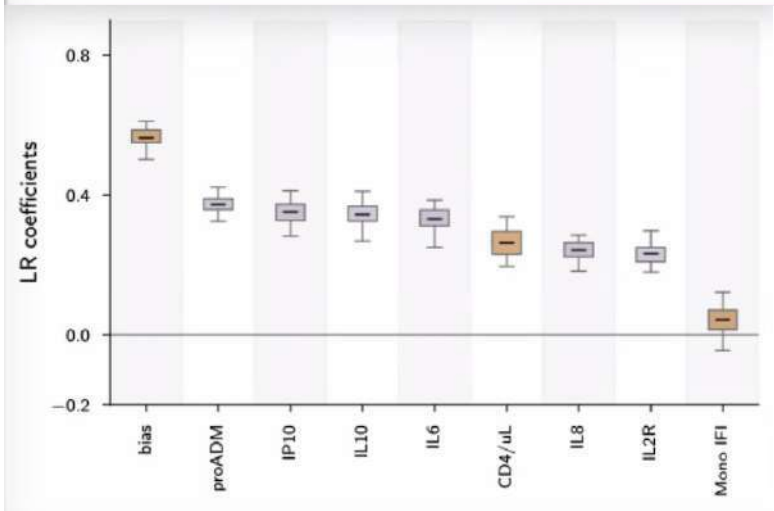


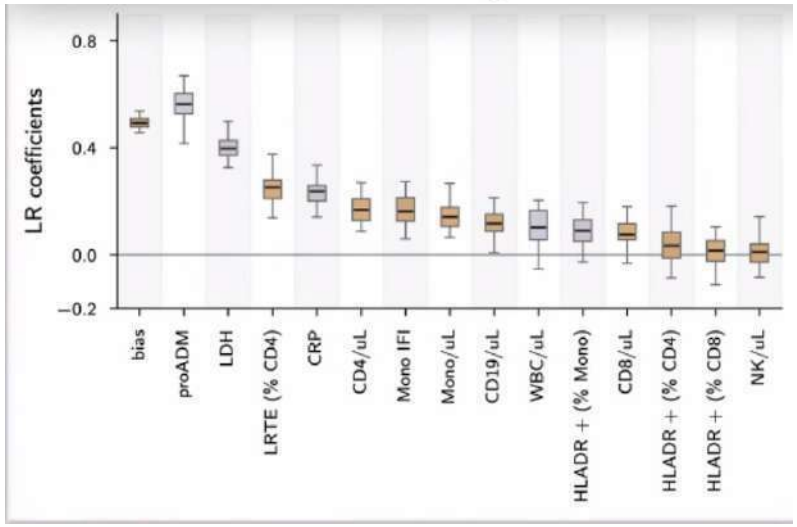


Multivariate models - Coefficients logistic regression. Negative sign in yellow.









Quando e perché utilizzo pro-ADM ?

- ✓ Nel paziente con COVID-19 per dimissione precoce se clinica stabile e pro-ADM bassa
- ✓ Nel paziente con infezione per dimissione precoce se clinica stabile e pro-ADM bassa
- ✓ Nel paziente con COVID-19 come «red flag» di possibile aggravamento
- ✓ Nel paziente con sepsi come «red flag» di possibile aggravamento

Quali vantaggi e quali limiti?

Vantaggi:

- ✓ Buon biomarker di danno d'organo → performance simile se non migliore agli score clinici (SOFA score, NEWS etc)
- ✓ Predizione di aggravamento (necessità di setting ad alta intensità di cure e terapie tempestive)
- ✓ Predizione di mortalità
- ✓ Nelle infezioni è indipendente dall'eziologia

Svantaggi

- ✓ Cut-off non ancora ben definiti (studi eterogenei ma anche probabilmente cut-off eterogenei per alcuni outcome)
- ✓ Età e Comorbidità possono essere un fattore confondente (es IRC)

Come implementarne l'uso in ambito clinico?

- ✓ «Triage» guidati da MR-proADM
- ✓ Patologie cardiovascolari
- ✓ Meningoencefaliti (su liquor?)
- ✓ Altri fluidi?

Conclusioni

- Il paziente settico deve ricevere una terapia personalizzata