SCUOLA DI SPECIALIZZAZIONE IN MALATTIE INFETTIVE E TROPICALI

PANDORA ID - 24

TIME TO WEBINAR IN INFECTIOUS DISEASES

PROGETTO DI FORMAZIONE

Anno Accademico 23/24

STEWARDSHIP ANTIMICROBICA IN DIFFERENTI SETTING OSPEDALIERI E TERRITORIALI

21 Ottobre 2024 – Ore 16.00-19.00 VIRTUAL EDITION

16.45 **Il ruolo dell'infettivologo in Pronto Soccorso e indicazioni di terapia empirica**
Carlo Tascini (Udine)

17.15 **Discussione**

PROF CARLO TASCINI
Direttore Clinica Malattie Infettive
Università di Udine – ASUFC
c.tascini@gmail.com

Conflicts of interest

In the last two years I had direct financial relationships with the following companies:

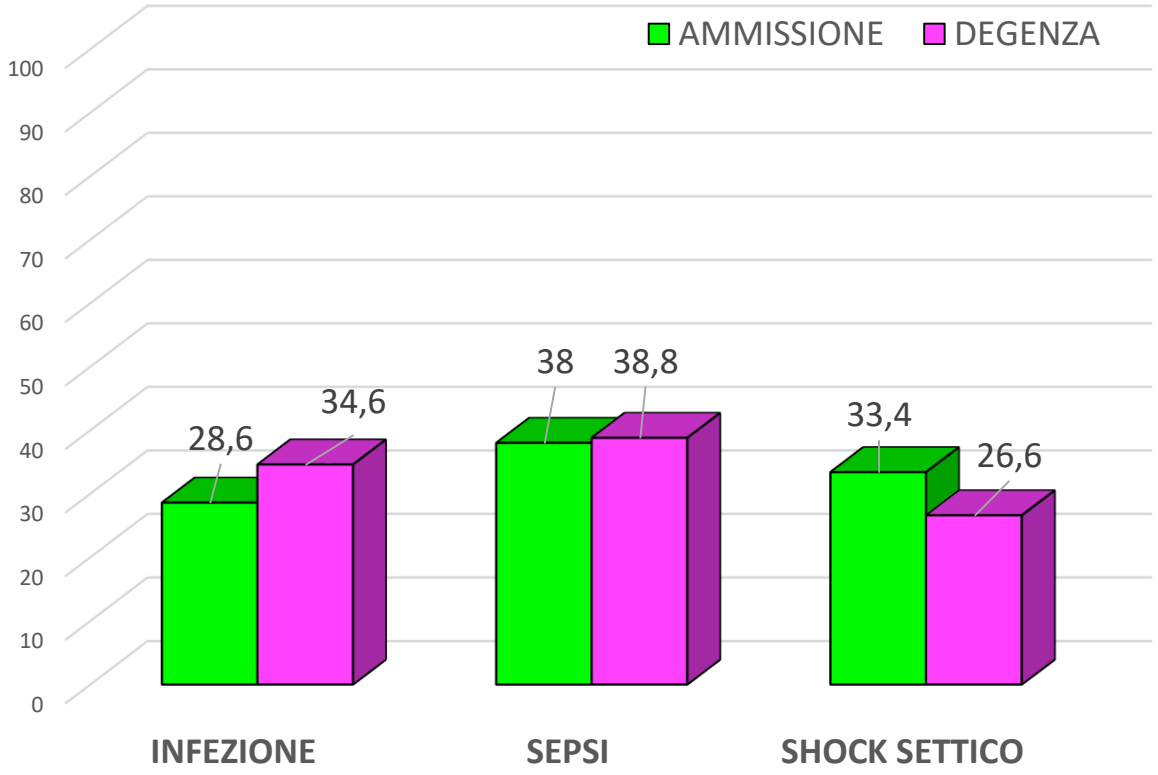
- *Menarini*
- *Merck*
- *Pfizer*
- *Angelini*
- *Gilead*
- *Novartis*
- *Biomerieux*
- *Thermofisher*
- *Zambon*
- *Hikma*
- *Avir Pharma*
- *Shionogi*
- *Biotest*
- *Viatris*
- *Diasorin*

PROGETTO SORVEGLIANZA INFEZIONI 2022

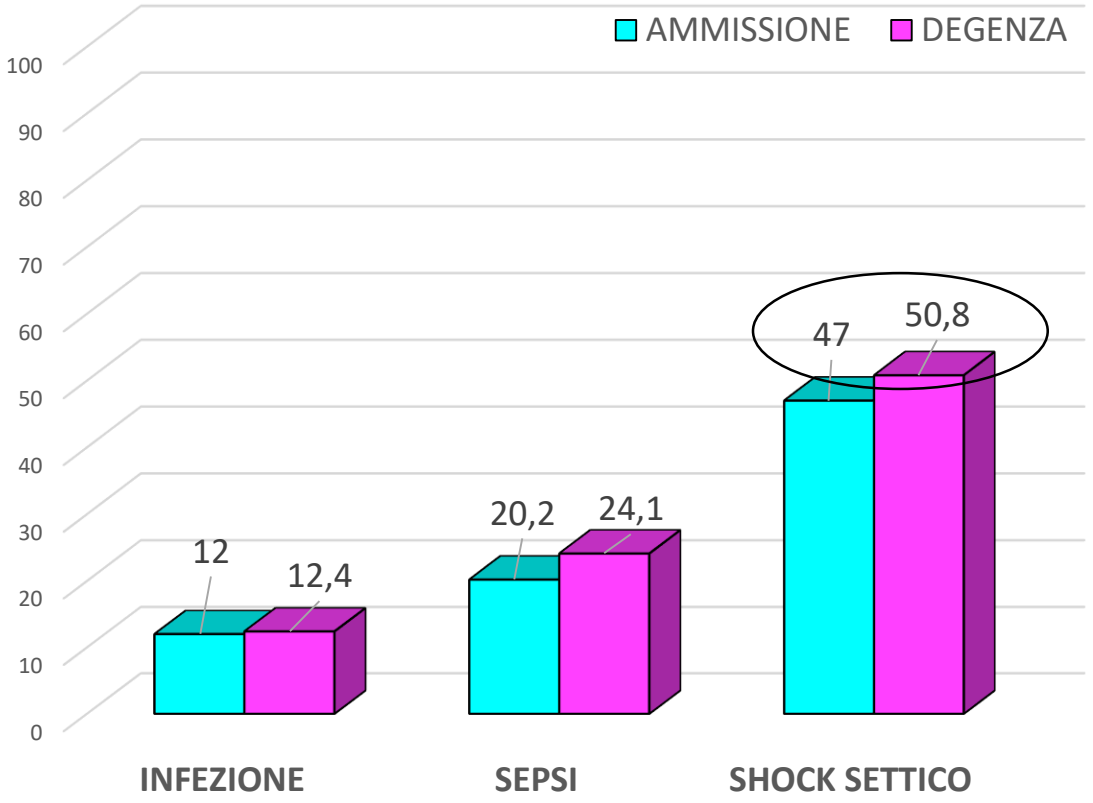
100 TI (N = 26 343)

INFEZIONI 40.5% (N = 10 661)

GRAVITA' CLINICA



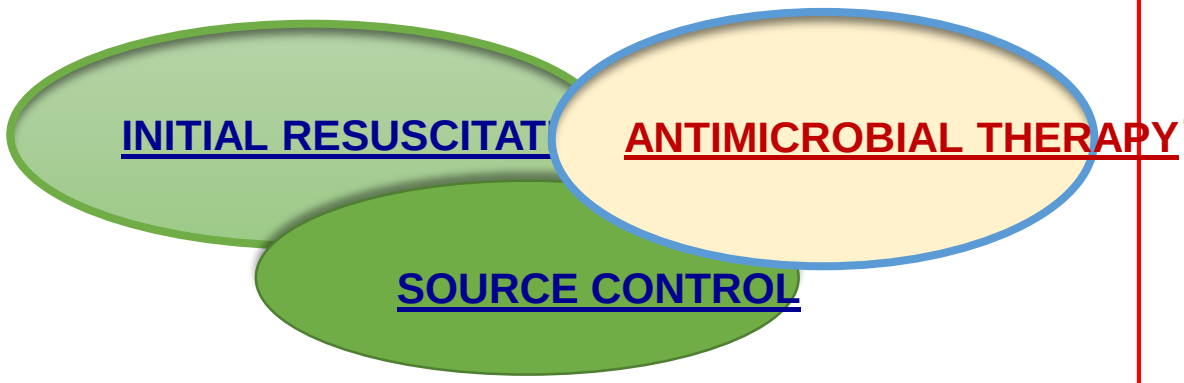
MORTALITA' STRATIFICATA PER GRAVITA'



SEPSIS IN THE ICU: GUIDELINES

BUNDLE APPROACH FOR SEPSIS AND SEPTIC SHOCK

Surviving Sepsis Campaign



TO BE COMPLETED WITHIN 3 HOURS OF TIME OF PRESENTATION*:

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

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

TO BE COMPLETED WITHIN 6 HOURS OF TIME OF PRESENTATION:

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

Clinical Microbiology and Infection 30 (2024) 1384–1407

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

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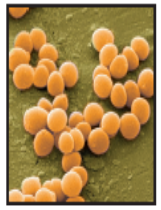
Teske Schoffelen [1, 2, *, †], Cihan Papan [3, 4, †], Elena Carrara [5], Khalid Eljaaly [6, 7], Mical Paul [8], Emma Keuleyan [9, 10], Alejandro Martin Quirós [11)], Nathan Peiffer-Smadja [12, 13, 14], Carlos Palos [15], Larissa May [16], Michael Pulia [17], Bojana Beovic [18], Eric Batard [19, 20], Fredrik Resman [21], Marlies Hulscher [22], Jeroen Schouten [1, 23], on behalf of the ESCMID Study Group for Antimicrobial Stewardship (ESGAP)

We suggest against the use of CRP in the ED to guide the initiation of antibiotics for patients with respiratory tract infections	Weak	Very low
Rapid pathogen tests		
We suggest against the use of rapid NAAT or rapid antigen tests for influenza to reduce the initiation of antibiotics in the ED	Weak	Low
We suggest against the use of multiplex PCR for respiratory pathogens to reduce the initiation of antibiotics in the ED	Weak	Low
We suggest against the routine use of urinary antigen testing for *Streptococcus pneumoniae* in patients with LRTI in the ED	Weak	Very low
We suggest against the routine use of urinary antigen testing for *Legionella pneumophila* in patients with LRTI in the ED	Weak	Very low
We suggest the use of urinary antigen testing for *Legionella pneumophila* in patients with LRTI in the ED with suspected legionellosis or in outbreak settings to guide the use of narrow-spectrum antibiotic therapy	Good practice statement	Expert opinion
We suggest MRSA PCR for purulent skin and soft tissue infections in the ED to guide antibiotic therapy in setting with high prevalence of community-acquired MRSA	Weak	Very low

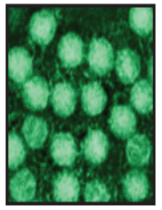
Blood cultures

BioFire FilmArray ME: falsi negative con HSV1-2 e Criptococco



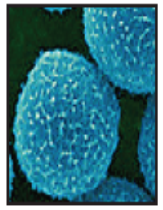
Bacteria

Escherichia coli K1
Haemophilus influenzae
Listeria monocytogenes
Neisseria meningitidis
Streptococcus agalactiae
Streptococcus pneumoniae



Viruses

Cytomegalovirus (CMV)
Enterovirus
Herpes simplex virus 1 (HSV-1)
Herpes simplex virus 2 (HSV-2)
Human herpesvirus 6 (HHV-6)
Human parechovirus
Varicella zoster virus (VZV)



Fungi

Cryptococcus neoformans/gattii

BioFire® FilmArray®

Pneumonia Panel *plus* Investigational Use Only

34 Targets

Bacterial Targets:

Acinetobacter calcoaceticus-baumannii complex
Enterobacter aerogenes
Enterobacter cloacae complex
Escherichia coli
Haemophilus influenzae
Klebsiella oxytoca
Klebsiella pneumoniae group
Moraxella catarrhalis
Proteus spp.
Pseudomonas aeruginosa
Serratia marcescens
Staphylococcus aureus
Streptococcus agalactiae
Streptococcus pneumoniae
Streptococcus pyogenes

Atypical Bacterial:

Chlamydia pneumoniae
Legionella pneumophila
Mycoplasma pneumoni

Viruses:

Adenovirus
Coronavirus
Human Metapneumovirus
Human Rhinovirus/Enterovirus
Influenza A
Influenza B
Parainfluenza Virus
Respiratory Syncytial Virus

Assay Result		Reported Result and Bin Result	
Negative OR	<10^3.5 copies/mL	Not Detected	
Positive AND	≥10^3.5 – <10^4.5 copies/mL	Detected	10^4 copies/mL
Positive AND	≥10^4.5 – <10^5.5 copies/mL	Detected	10^5 copies/mL
Positive AND	≥10^5.5 – <10^6.5 copies/mL	Detected	10^6 copies/mL
Positive AND	≥10^6.5 copies/mL	Detected	≥10^7 copies/mL

mecA/C and MREJ (Methicillin resistance)
NDM (Carbapenem resistance)
Oxa48-like (Carbapenem resistance)
VIM (Carbapenem resistance)

FilmArray GI Panel

BIOFIRE

www.BioFireDx.com

Run Summary

Sample ID:	-	**Run Date:**	03 Oct 2018 1:35 PM
Detected:	*Campylobacter* *Plesiomonas shigelloides* *Vibrio* *Vibrio cholerae* Enteroaggregative *E. coli* (EAEC) Enteropathogenic *E. coli* (EPEC) Enterotoxigenic *E. coli* (ETEC) *lt/st* *Shigella*/Enteroinvasive *E. coli* (EIEC) Norovirus GI/GII	**Controls:**	Passed

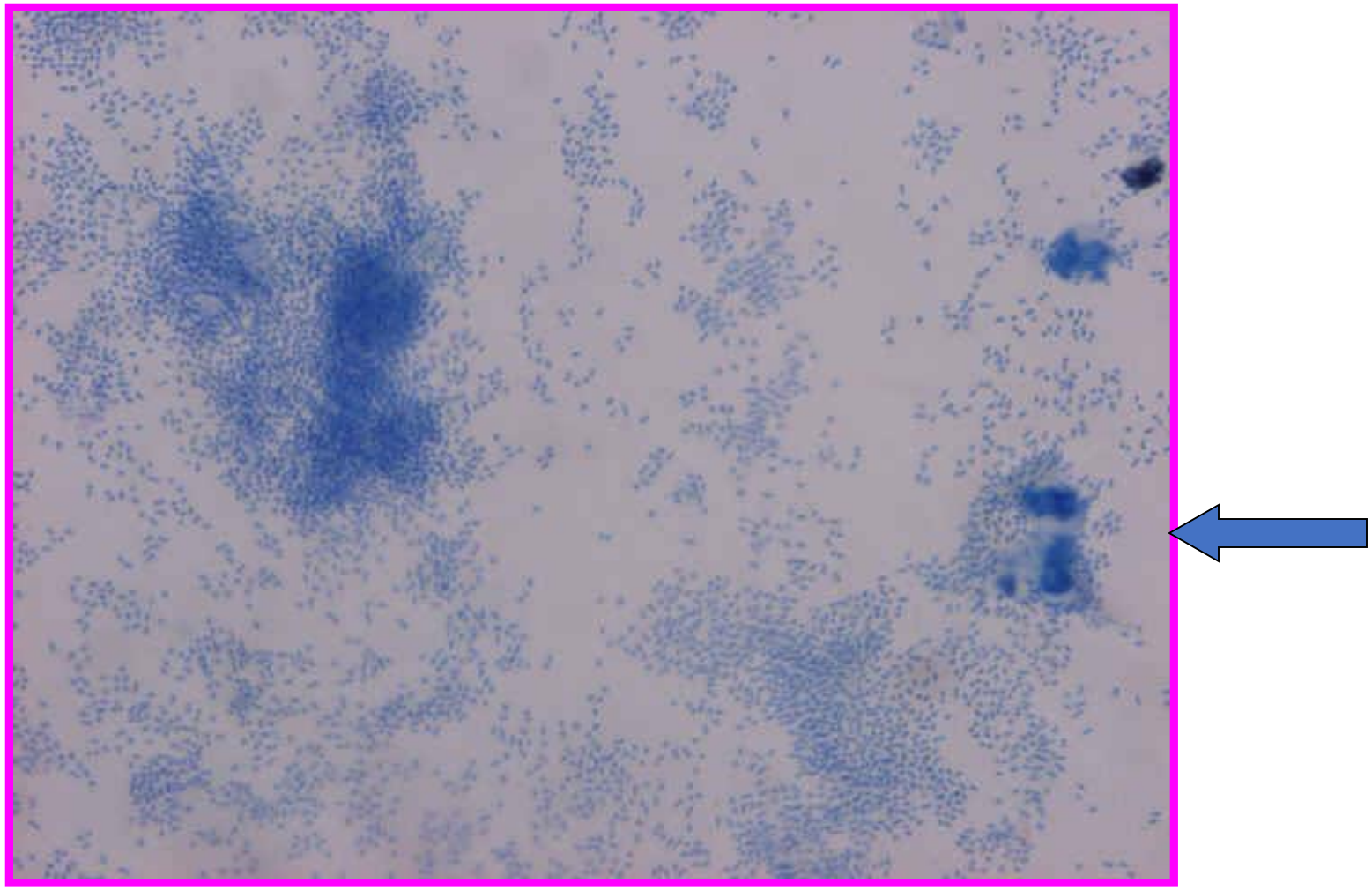
Result Summary

	Bacteria	
✓	Detected	*Campylobacter*
	Not Detected	*Clostridium difficile* toxin A/B
✓	Detected	*Plesiomonas shigelloides*
	Not Detected	*Salmonella*
✓	Detected	*Vibrio*
✓	Detected	*Vibrio cholerae* -
	Not Detected	*Yersinia enterocolitica*
	Diarrheagenic *E. coli/Shigella*	
✓	Detected	Enteroaggregative *E. coli* (EAEC)
✓	Detected	Enteropathogenic *E. coli* (EPEC)
✓	Detected	Enterotoxigenic *E. coli* (ETEC) *lt/st*
	Not Detected	Shiga-like toxin-producing *E. coli* (STEC) *stx1/stx2*
⊘	N/A	*E. coli* O157
✓	Detected	*Shigella*/Enteroinvasive *E. coli* (EIEC)
	Parasites	
	Not Detected	*Cryptosporidium*
	Not Detected	*Cyclospora cayetanensis*
	Not Detected	*Entamoeba histolytica*
	Not Detected	*Giardia lamblia*
	Viruses	
	Not Detected	Adenovirus F 40/41
	Not Detected	Astrovirus
✓	Detected	Norovirus GI/GII
	Not Detected	Rotavirus A
	Not Detected	Sapovirus

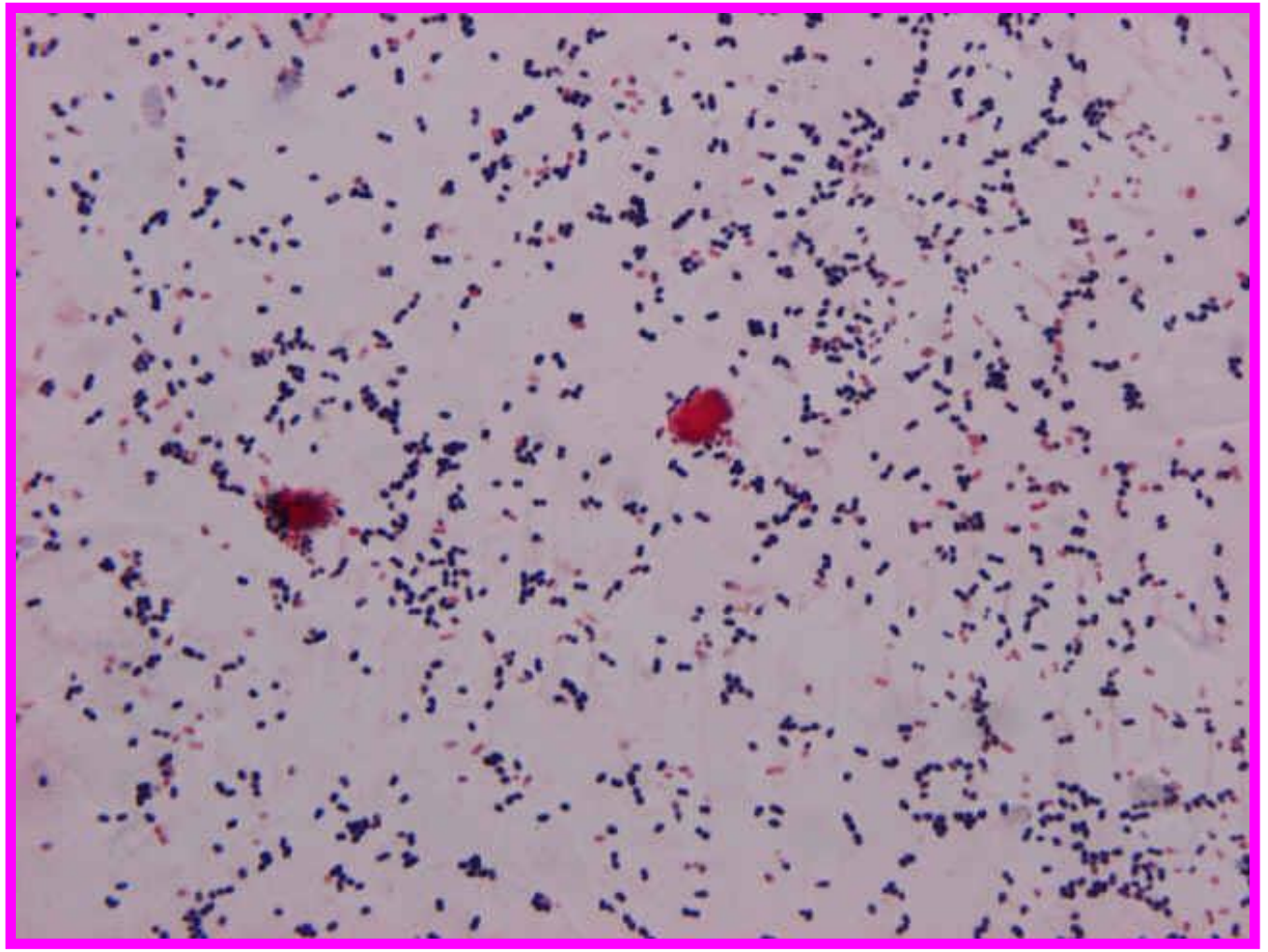
Run Details

Pouch:	GI Panel v2.1	**Protocol:**	Stool FA v3.3
Run Status:	Completed	**Operator:**	
Serial No.:	15713451	**Instrument:**	TM00757
Lot No.:	995918		

Blu di metilene del liquor



Gram dal liquor



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Biomarkers

We suggest the use of procalcitonin in the ED to guide the initiation of antibiotics for patients with suspected LRTI who are likely to be admitted to the hospital	Weak	Moderate
We suggest the use of procalcitonin in the ED to guide the initiation of antibiotics for patients with acute exacerbation of asthma who are likely to be admitted to the hospital	Weak	Low
We suggest the use of procalcitonin in the ED to guide the initiation of antibiotics for patients with acute exacerbation of COPD who are likely to be admitted to the hospital	Weak	Moderate
We suggest against the use of procalcitonin in the ED to guide the initiation of antibiotics for patients with dyspnea and suspected or known heart disease who are likely to be admitted to the hospital	Weak	Low
We suggest against the use of procalcitonin based on the criterion of fever alone in patients in the ED to guide the initiation of antibiotics	Weak	Very low
We suggest against the use of CRP in the ED to guide the initiation of antibiotics for patients with respiratory tract infections	Weak	Very low

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

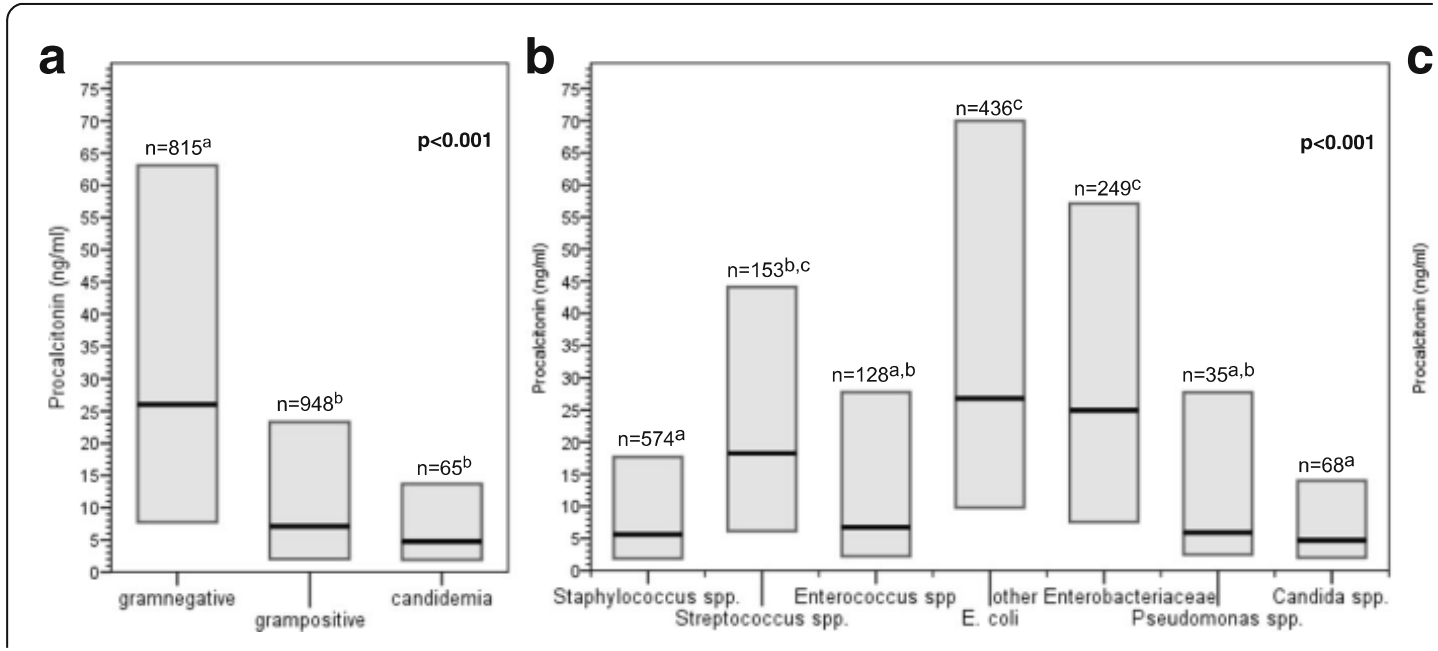


Table 3 Test performance of procalcitonin for prediction of Gram-negative bacteremia

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)

Gonzalez del Castillo *et al. Critical Care* (2019) 23:335
https://doi.org/10.1186/s13054-019-2613-4

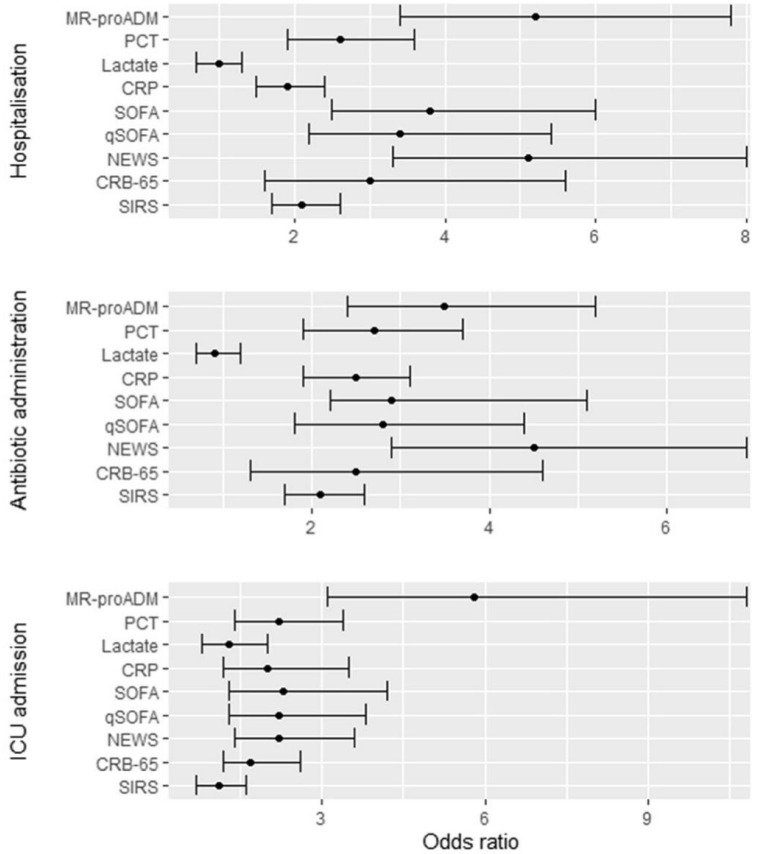
Critical Care

RESEARCH Open Access

Biomarkers and clinical scores to identify patient populations at risk of delayed antibiotic administration or intensive care admission

Juan Gonzalez del Castillo[1,2], Darius Cameron Wilson[3*], Carlota Clemente-Callejo[1], Francisco Román[4], Ignasi Bardés-Robles[5], Inmaculada Jiménez[4], Eva Orviz[6], Macarena Dastis-Arias[7], Begoña Espinosa[4], Fernando Tornero-Romero[6], Jordi Giol-Amich[5], Veronica González[4], Ferran Llopis-Roca[5] on behalf of the INFURG-SEMES investigators

- ✓ Prospective observational study
- ✓ 3 EDs
- ✓ 684 patients were enrolled with hospitalization (72.8%), ICU admission (3.4%), and infection-related 28-day mortality rates (4.4%).
- ✓ MR-proADM and NEWS had the strongest association with hospitalisation and the requirement for antibiotic administration,
- ✓ MR-proADM alone had the strongest association with ICU admission (OR: 5.8 [3.1 - 10.8]) and mortality (HR: 3.8 [2.2 - 6.5]).



- ✓ Patient subgroups with high MR-proADM concentrations (≥ 1.77 nmol/L) and low NEWS (< 5 points) had:
  - significantly higher rates of ICU admission (8.1% vs 1.6%; p < 0.001),
  - hospital readmission (18.9% vs. 5.9%; p < 0.001),
  - infection-related mortality (13.5% vs. 0.2%; p < 0.001),
  - disease progression (29.7% vs. 4.9%; p < 0.001)

ICU admission was delayed by 1.5 [0.25 – 5.0] days in patients with high MR-proADM and low NEWS compared to high NEWS, despite similar 28-day mortality rates (13.5% vs. 16.5%).

Antibiotics were withheld in 17.4% of patients with high MR-proADM and low NEWS values

J. Gonzalez Del Castillo et al.*Critical Care*(2019)

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Community acquired pneumonia		
We suggest against obtaining blood cultures routinely in patients presenting to the ED with a diagnosis of non-severe CAP	Weak	Low
We suggest obtaining blood cultures in patients admitted with severe CAP, e.g. patients with PSI score IV or V or with indications for ICU admission	Good practice statement	Expert opinion
We suggest obtaining blood cultures in patients admitted with CAP and risk factors for or initiated on therapy for unusual or resistant pathogens[a]	Good practice statement	Expert opinion
We suggest obtaining blood cultures in patients admitted with CAP and immunocompromised state[b]	Good practice statement	Expert opinion
Urinary tract infection with systemic symptoms		
We suggest against obtaining blood cultures routinely in patients presenting to the ED with UTI with systemic symptoms without anatomical abnormalities of the urinary tract in whom a good-quality urine sample for culture is available	Weak	Very low
We suggest obtaining blood cultures in patients presenting to the ED with UTI with systemic symptoms and antibiotic pretreatment	Good practice statement	Expert opinion
We suggest obtaining blood cultures in patients presenting to the ED with a chronic indwelling catheter and UTI with systemic symptoms	Good practice statement	Expert opinion
We suggest obtaining blood cultures in immunocompromised[b] patients presenting to the ED with UTI with systemic symptoms	Good practice statement	Expert opinion
Skin and soft tissue infections		
We suggest against routinely obtaining blood cultures in patients presenting to the ED with cellulitis/erysipelas	Weak	Very low
We suggest obtaining blood cultures in immunocompromised[b] patients presenting to the ED with cellulitis/erysipelas	Good practice statement	Expert opinion
We suggest obtaining blood cultures in patients presenting to the ED with cellulitis/erysipelas in clinical situations associated with high risk of non-standard pathogens[c]	Good practice statement	Expert opinion
We suggest obtaining blood cultures in patients presenting to the ED with cellulitis/erysipelas who have an intravascular prosthesis, a pacemaker or a valvular prosthesis	Good practice statement	Expert opinion

Emocolture

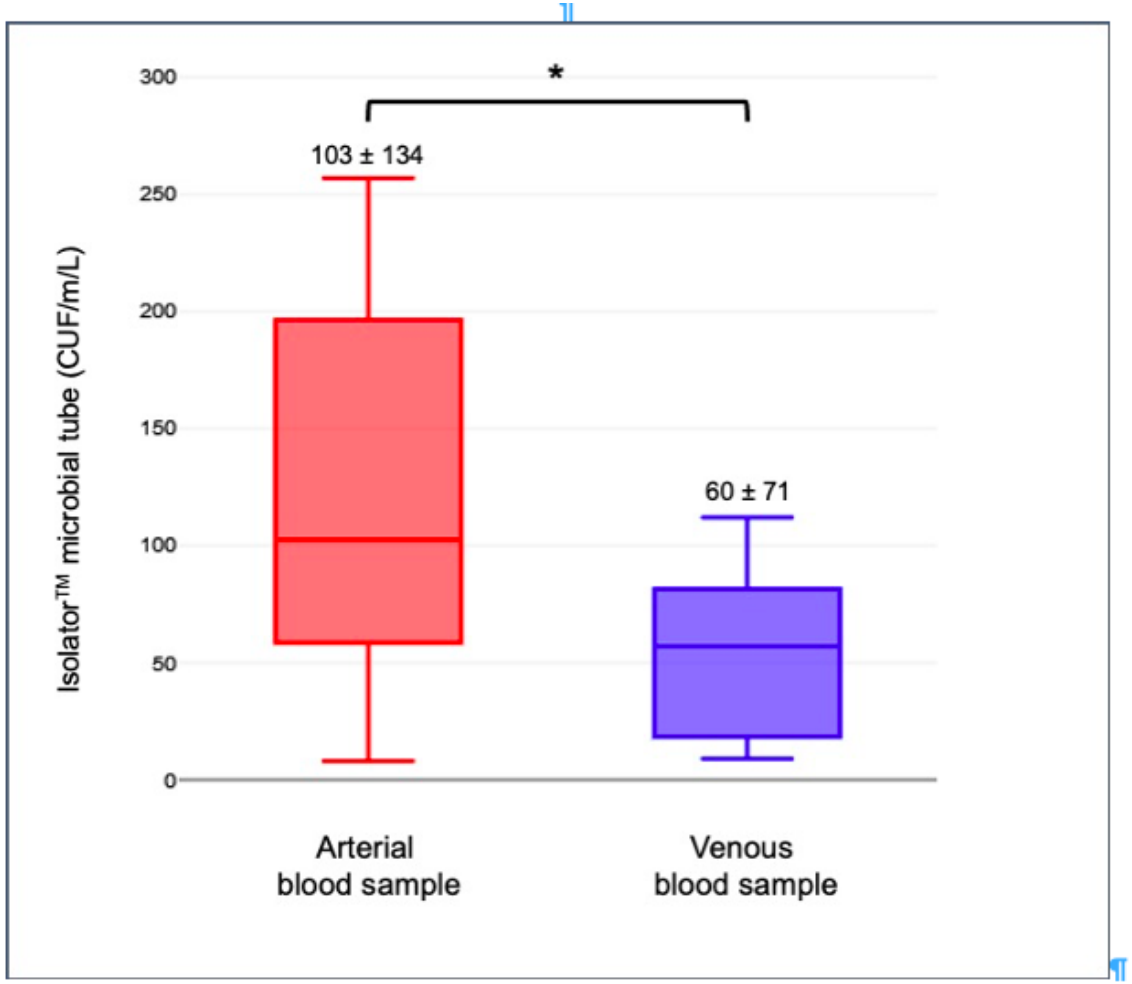
- Arteria versus vena
- CVC versus VP (time differenziale di due ore)
- Singola venipuntura
- Pannelli sindromici emocolture
- Perché solo emocolture: liquor, materiale ascessi, biopsie
- Perché solo batteri: pannelli virali, ricerca funghi, parassiti (malaria)

FREQUENZA DI POSITIVITA' DI EMOCOLTURE DA PAZIENTI ADULTI CON DIFFERENTI INFEZIONI

Cellulite acuta	**2%**
Infezione del piede diabetico/vascolare	**10%**
Malattia febbrile acuta del neutropenico	**20%**
Pielonefrite	**20%**
Polmonite acquisita in comunità	**30%**
Meningite batterica acuta	**50%**
Osteomielite acuta	**50%**
Cellulite necrotizzante	**80%**
Endocardite batterica	**95%**
Tromboflebite batterica suppurativa	**100%**

Stratton CW Antimicrobics Infect Dis Newsletter 2000; 18:9-13

Protocollo emocoltura da vena periferica versus arteria: Isolator con conta colonie

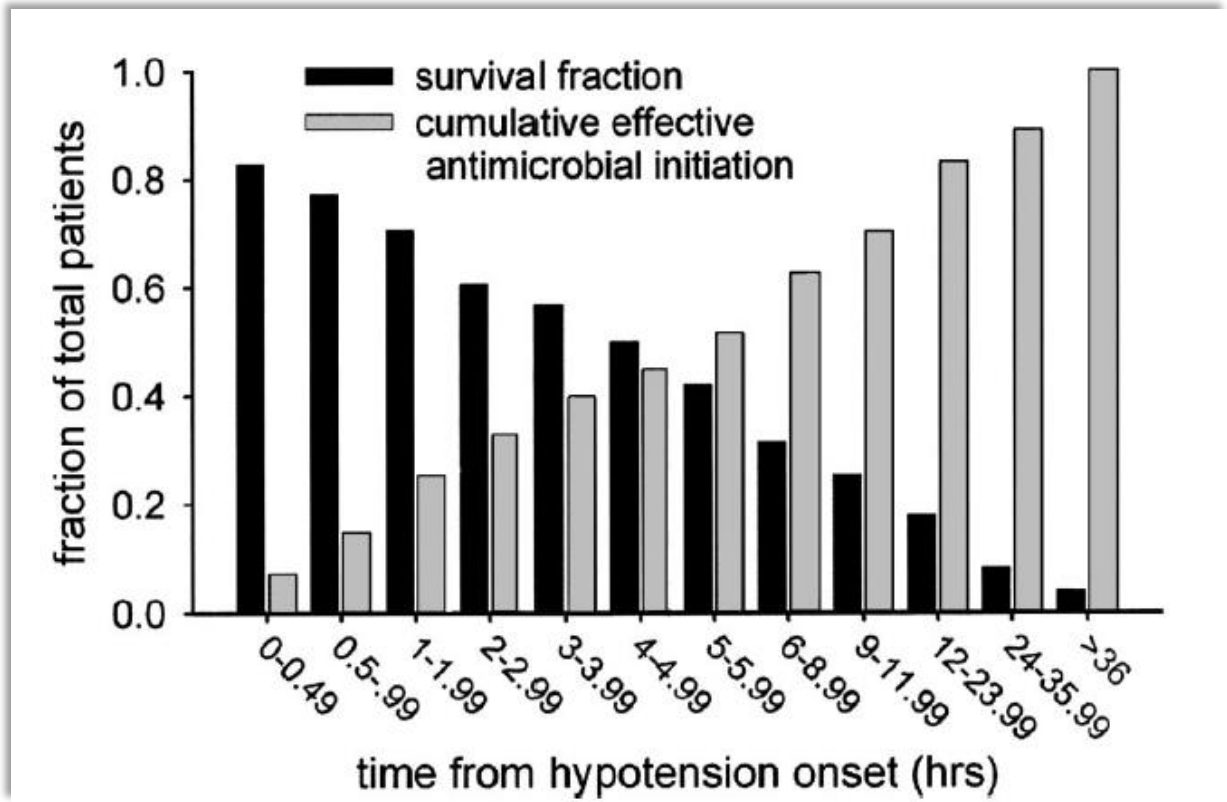


Terapia empirica

Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock*

Anand Kumar, MD; Daniel Roberts, MD; Kenneth E. Wood, DO; Bruce Light, MD; Joseph E. Parrillo, MD; Satendra Sharma, MD; Robert Suppes, BSc; Daniel Feinstein, MD; Sergio Zanotti, MD; Leo Taiberg, MD; David Gurka, MD; Aseem Kumar, PhD; Mary Cheang, MSc

2,731 adult ICU patients with septic shock.



- **Median time from hypotension to antibiotic administration: 6 hours after the recognition of shock.**
- **Overall mortality rate: 56.2%**

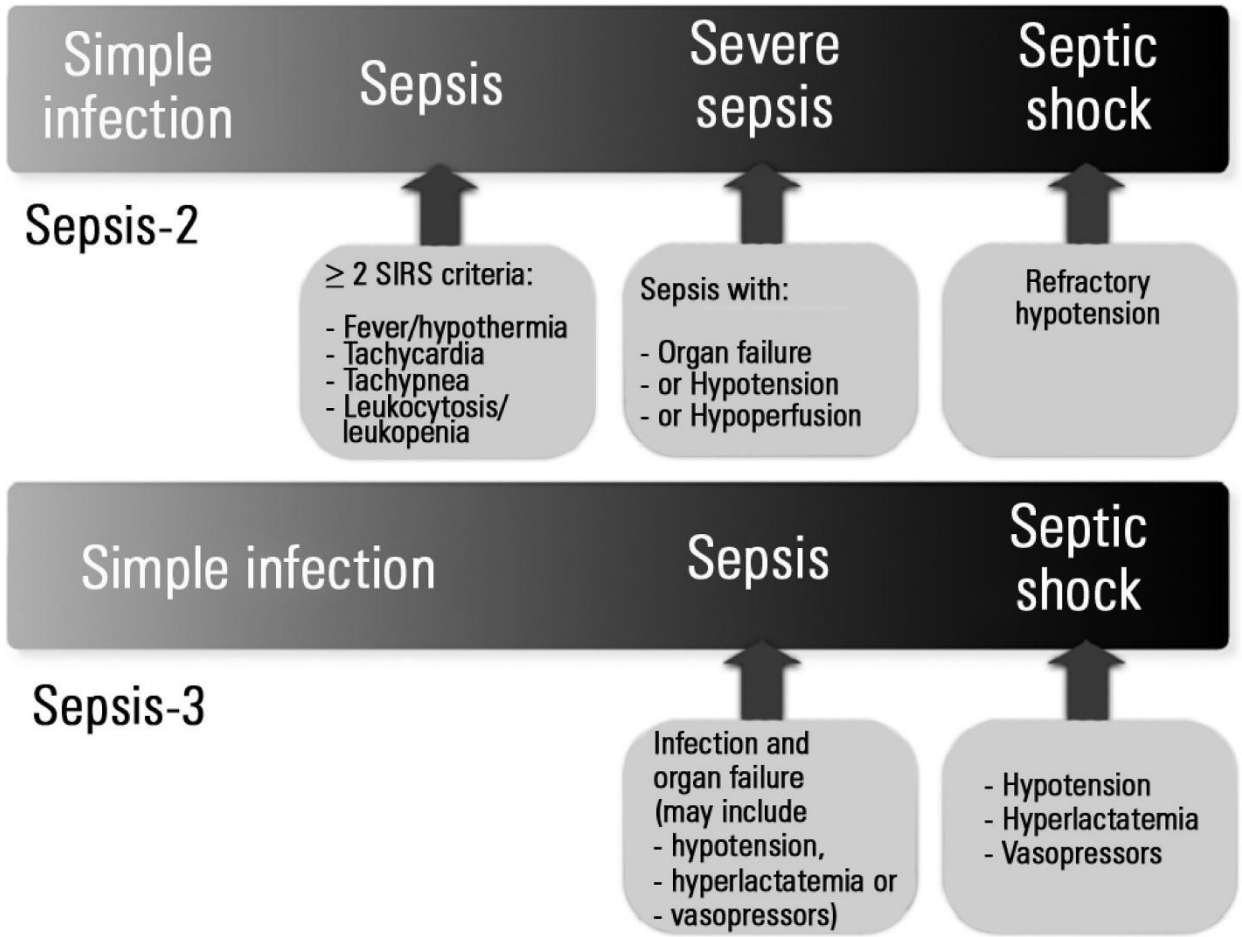
(Crit Care Med 2006; 34:1589–1596)

Clinical Review & Education

Special Communication | CARING FOR THE CRITICALLY ILL PATIENT

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

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



	1991 Consensus Definitions	2016 Consensus Definitions
SIRS (Systemic Inflammatory Response Syndrome)	Due o più tra i seguenti criteri: 1) T° corporea > 38°C o < 36°C 2) Frequenza cardiaca > 90 bpm 3) Frequenza respiratoria > 20 atti/min o paCO2 < 32 mmHg 4) Leucociti > 12.000/mm3 o Leucociti < 4000/mm3 o forme immature > 10%	---
Sepsi	SIRS + Infezione	Infezione + delta SOFA ≥ 2
Sepsi grave	Sepsi + insufficienza d'organo, ipoperfusione o ipotensione (pressione sistolica < 90 mmHg o una riduzione ≥ 40 mmhg rispetto ai valori di partenza in assenza di altre potenziali cause di ipotensione). L'ipoperfusione può includere ma non è limitata a, acidosi lattica, alterazione dello stato di coscienza e oliguria.	---
Shock settico	Shock indotto da sepsi nonostante adeguato riempimento volemico associate alla presenza di alterazioni della perfusione che possono includere, ma non sono limitate a, acidosi lattica, alterazione dello stato di coscienza e oliguria.	Sepsi associata a: 1. Necessità di impiego di vasopressori per mantenere MAP ≥ 65 mmHg e 2. Lattato sierico ≥ 2 mmol/l

Tabella 1. Sintesi e confronto dei criteri diagnostici derivati dalla Consensus Conference del 1992 e i cosiddetti criteri SEPSIS-3.

https://www.empillsblog.com

CLINICAL CHALLENGE 1#

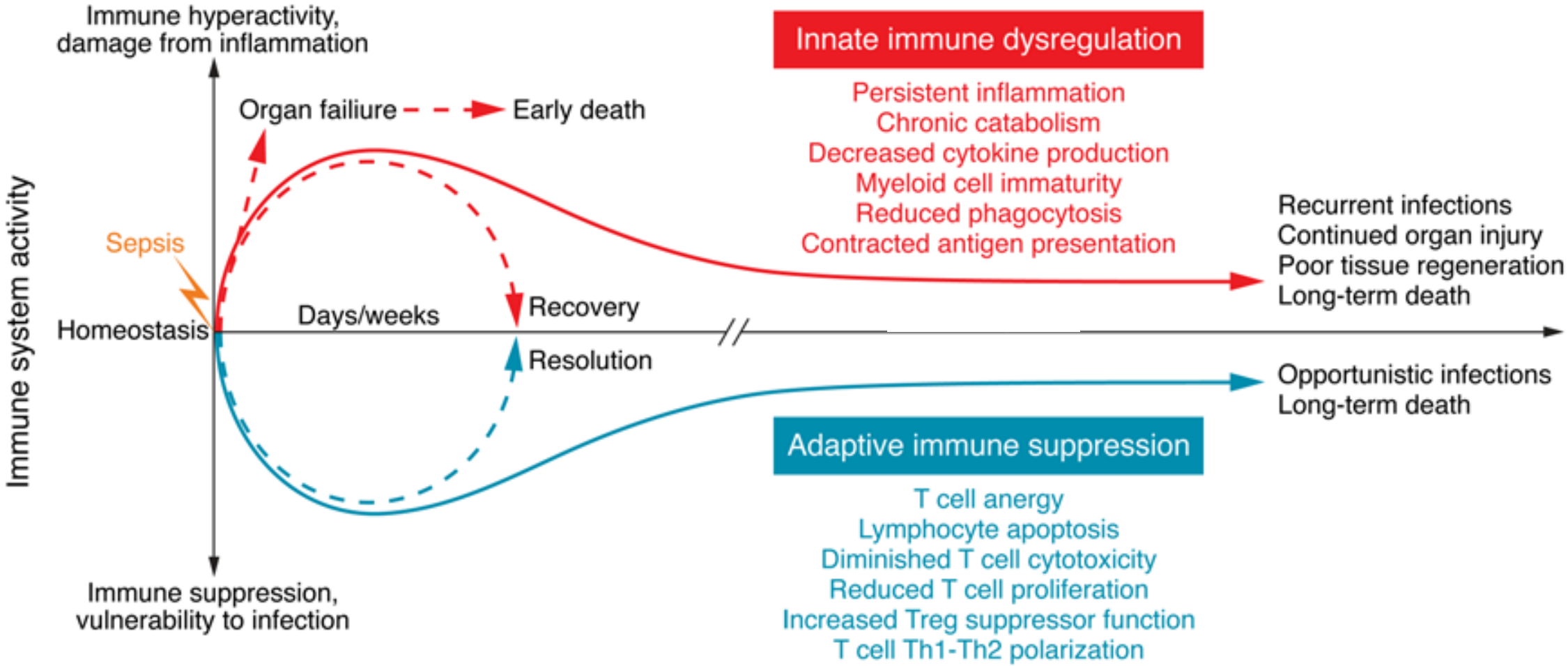
Noninfectious Causes of New Fever in ICU Patients

Acalculous Cholecystitis
Acute myocardial infarction
Adrenal insufficiency
Atelectasis
Blood product transfusion
Cytokine release syndrome
Dressler syndrome (pericardial injury syndrome)
Drug fever
Fat emboli
Fibroproliferative phase of acute respiratory distress syndrome
Gout
Heterotopic ossification
Immune reconstitution inflammatory syndrome

Intracranial bleed
Jarisch-Herxheimer reaction
Malignant hyperthermia
Neuroleptic malignant syndrome
Nonconvulsive status epilepticus
Pancreatitis
Pulmonary infarction
Pneumonitis without infection
Serotonin syndrome
Stroke
Thyroid storm
Transplant rejection
Tumor lysis syndrome
Venous thrombosis
Withdrawal from certain substances including alcohol, opiates, barbiturates, benzodiazepines

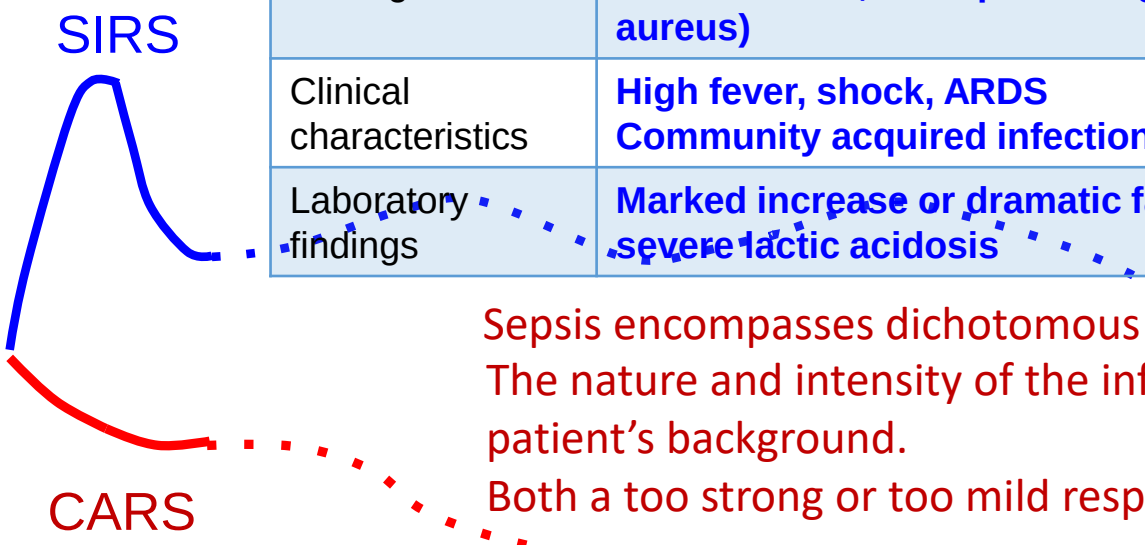
Naomi P. O'Grady, et al. Crit Care Med, 2023

TODAY'S ICU PATIENTS



Delano MJ, Ward PA. J Clin Invest, 2016

Immuno-inflammatory response during critical illness



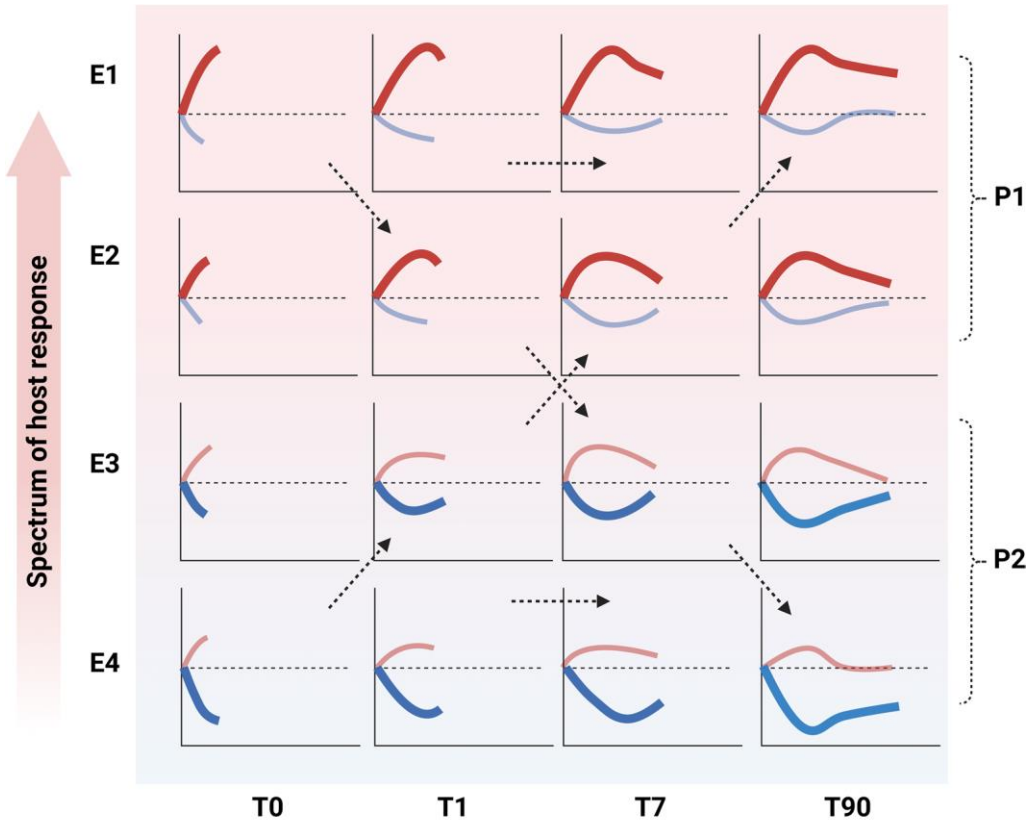
Patient population	**Healty, young or middle-aged**
Pathogen	**Often virulent, toxin producing (N. meningitis, S. pyogenes, S. aureus)**
Clinical characteristics	**High fever, shock, ARDS** **Community acquired infections**
Laboratory findings	**Marked increase or dramatic fall in absolute granulocyte count, severe lactic acidosis**

Sepsis encompasses dichotomous clinical presentations.
The nature and intensity of the inflammatory response is mainly determined by the patient's background.
Both a too strong or too mild response may adversely affect outcome

Patient population	**Elderly, malnourished, with comorbidities, chronic critically ill**
Pathogen	**May be weakly virulent or opportunistic (Acinetobacter, Stenotrophomonas, Enterococcus, fungi)**
Clinical characteristics	**More blunted response with subtle findings: altered mental status, hypothermia**
Laboratory findings	**Low absolute lymphocyte count persisting beyond 3-4 days**

Intensive Care Med (2016) 42:1051–1054

An evolving paradigm of dysfunctional host response in critical illness



Hyperinflammatory phenotype

Sustained and unchecked hyperinflammation.

Hypoinflammatory phenotype

Overactivation of anti-inflammatory pathways

Temporal subclass switching over the course of critical illness

Stevens J et al. Crit Care, 2024

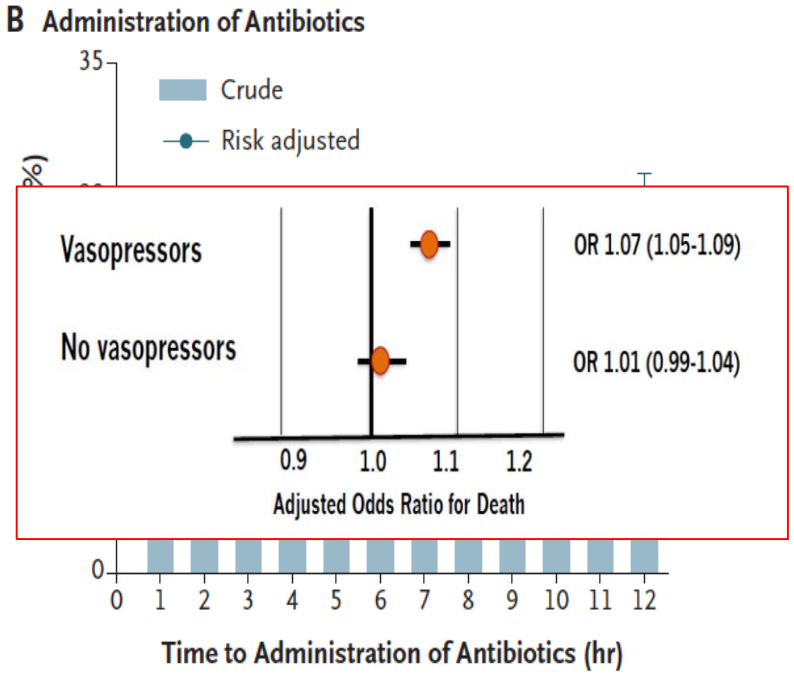
Facts: in septic shock time matters

ORIGINAL ARTICLE

Time to Treatment and Mortality during Mandated Emergency Care for Sepsis

Christopher W. Seymour, M.D., Foster Gesten, M.D., Hallie C. Prescott, M.D., Marcus E. Friedrich, M.D., Theodore J. Iwashyna, M.D., Ph.D., Gary S. Phillips, M.A.S., Stanley Lemeshow, Ph.D., Tiffany Osborn, M.D., M.P.H., Kathleen M. Terry, Ph.D., and Mitchell M. Levy, M.D.

49,331 patients at 149 hospitals

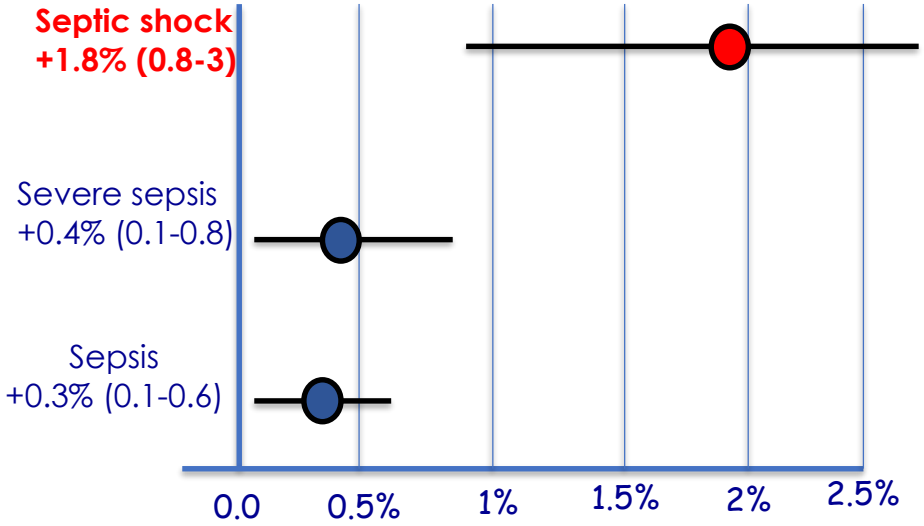


N Engl J Med, 2017

The Timing of Early Antibiotics and Hospital Mortality in Sepsis

Vincent X. Liu[1], Vikram Fielding-Singh[2], John D. Greene[1], Jennifer M. Baker[1], Theodore J. Iwashyna[3,4], Jay Bhattacharya[5], and Gabriel J. Escobar[1]

35,000 patients

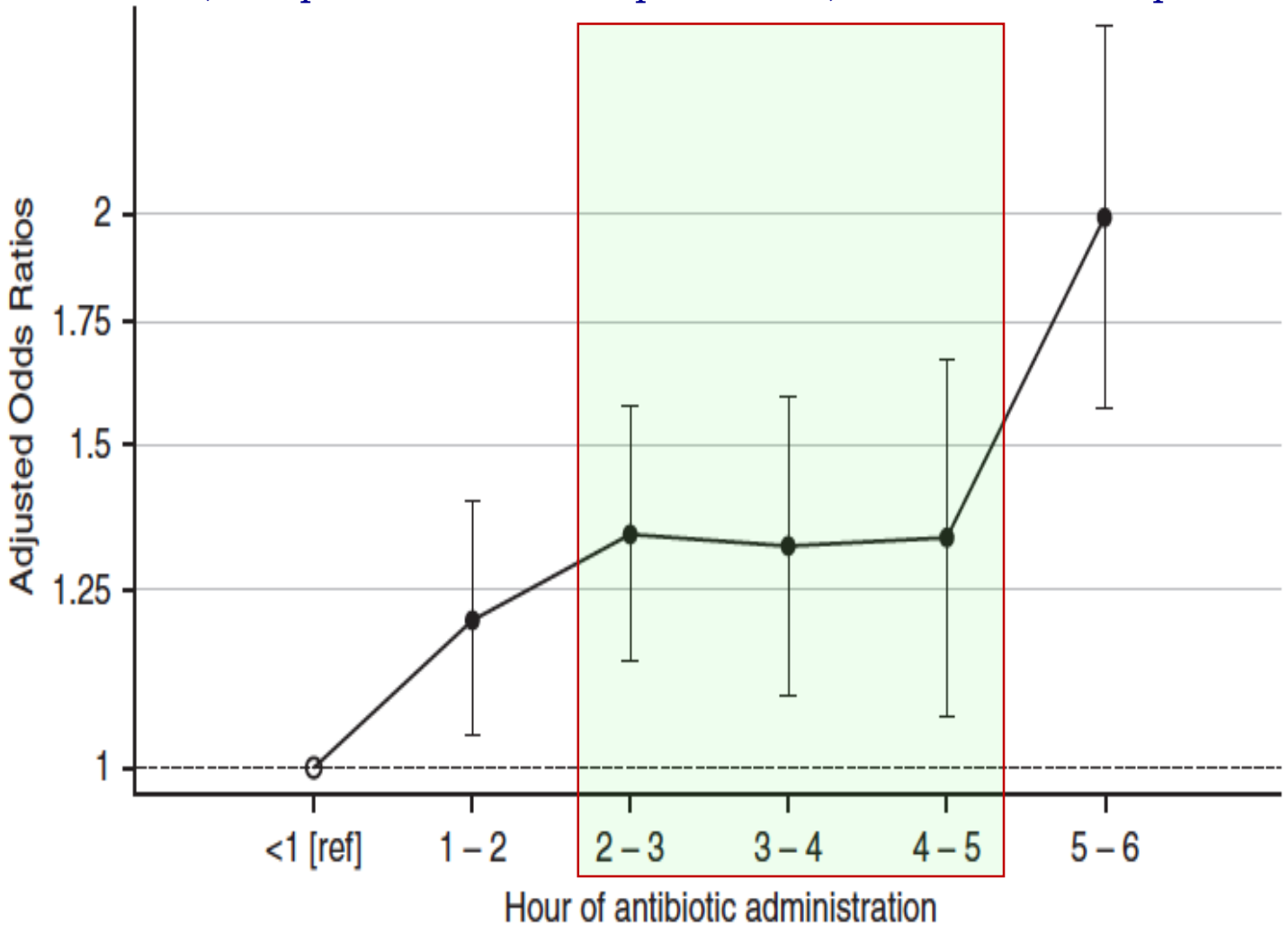


Absolute increase in mortality per hour delay

Liu VX, et al. American Journal of Respiratory and Critical Care, 2017

How early is early enough for antibiotic administration in sepsis and septic shock?

35,000 patients:13.3% septic shock, 52.0% severe sepsis.



Antibiotics given between hours 2 and 5 were associated with similar odds of mortality.

Liu VX, et al. Am J Resp Crit Care Med, 2017

Rüddel et al. Critical Care (2022) 26:51
https://doi.org/10.1186/s13054-022-03901-9

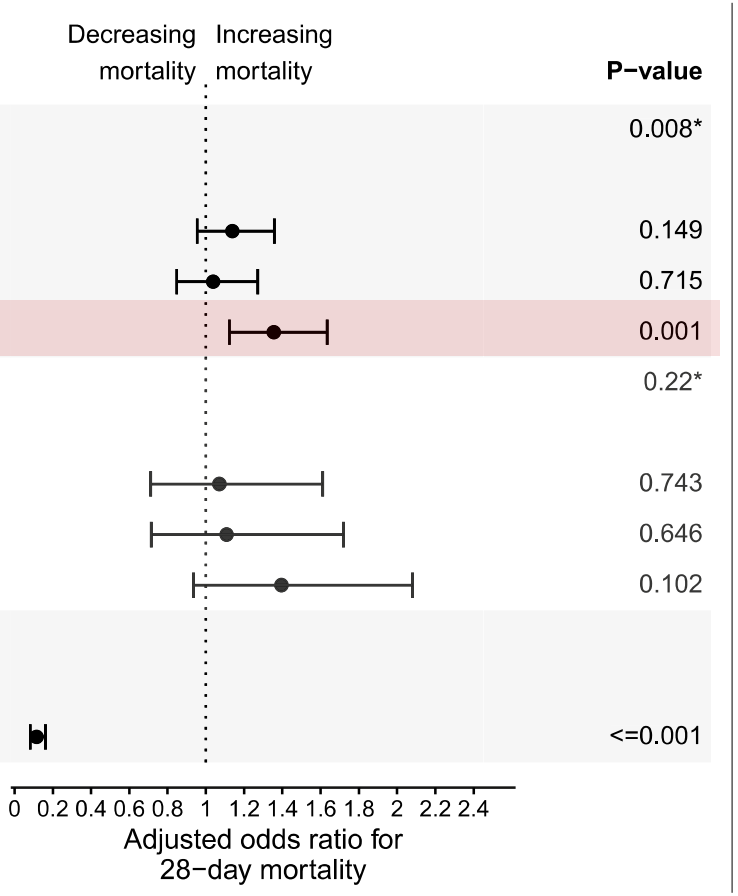
Critical Care

RESEARCH Open Access

Adverse effects of delayed antimicrobial treatment and surgical source control in adults with sepsis: results of a planned secondary analysis of a cluster-randomized controlled trial

Hendrik Rüddel[1,2], Daniel O. Thomas-Rüddel[1,2], Konrad Reinhart[3,4], Friedhelm Bach[5], Herwig Gerlach[6], Matthias Lindner[7], John C. Marshall[8], Philipp Simon[9], Manfred Weiss[10], Frank Bloos[1,2], Daniel Schwarzkopf[1,2,11*] and the MEDUSA study group

Predictor	No. of patients	Observed mortality	Risk−adjusted mortality	OR (95% CI)	P−value
Timing of antimicrobial therapy	4659/4792				0.008*
0−1 hr		364/1270 (28.7)	25.3 (22, 28.9)	1	
1−3 hrs		418/1352 (30.9)	27.8 (24.4, 31.6)	1.14 (0.95, 1.36)	0.149
3−6 hrs		255/836 (30.5)	26 (22.3, 30.2)	1.04 (0.85, 1.27)	0.715
>6 hrs		437/1201 (36.4)	31.5 (27.5, 35.7)	1.36 (1.12, 1.63)	0.001
Timing of surgical source control	1563/1595				0.22*
0−1 hr		92/327 (28.1)	25.1 (19.1, 32.3)	1	
1−3 hrs		85/287 (29.6)	26.4 (20.8, 32.9)	1.07 (0.71, 1.61)	0.743
3−6 hrs		93/293 (31.7)	27.1 (21.3, 33.8)	1.11 (0.71, 1.72)	0.646
>6 hrs		240/656 (36.6)	31.9 (26.7, 37.5)	1.4 (0.94, 2.08)	0.102
Success of source control	1563/1595				
Not successful		179/262 (68.3)	68.7 (60.7, 75.7)	1	
Successful		331/1301 (25.4)	20.2 (16.5, 24.5)	0.12 (0.08, 0.16)	<=0.001



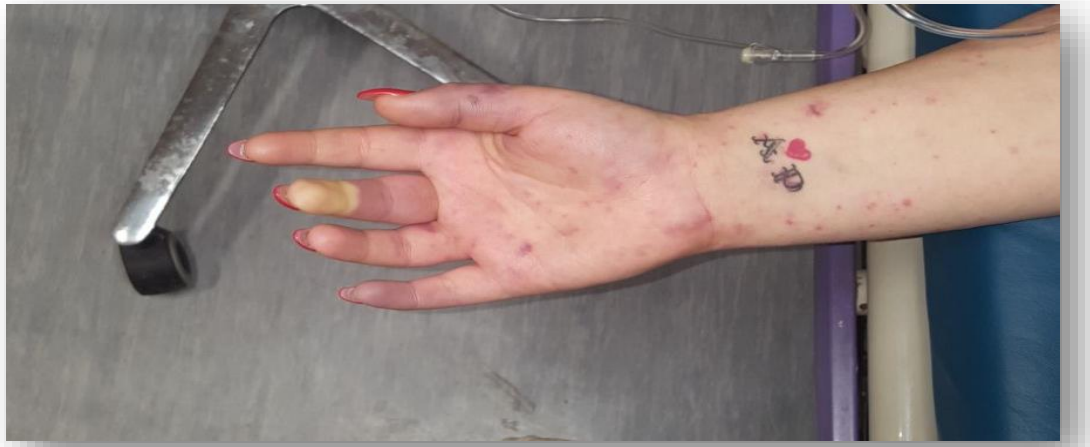
Terapia empirica

- Si può aspettare, anche nella sepsi, almeno 6 ore

Terapia iniziale

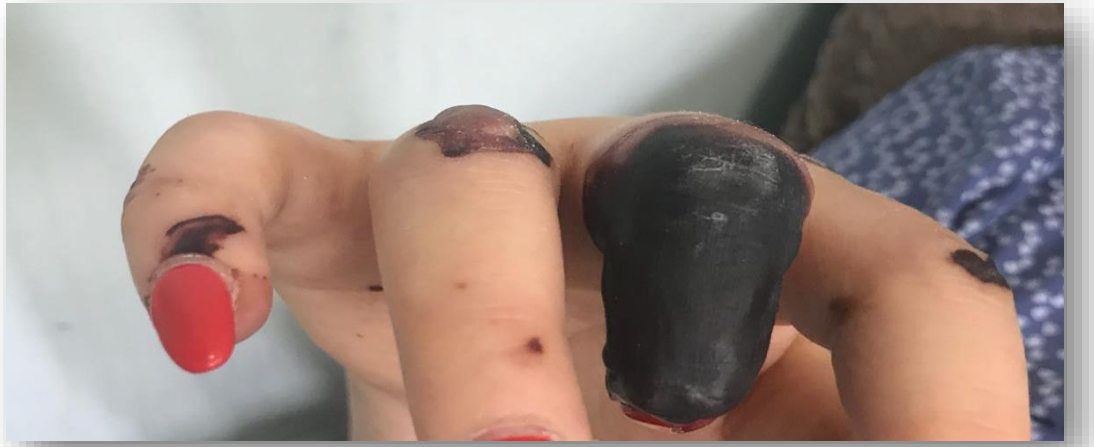
- Bisogna sempre essere veloci indipendentente dalla infiammazione?
- La sepsi non è una risposta abnorme?

N. meningitidis: Purpura fulminans



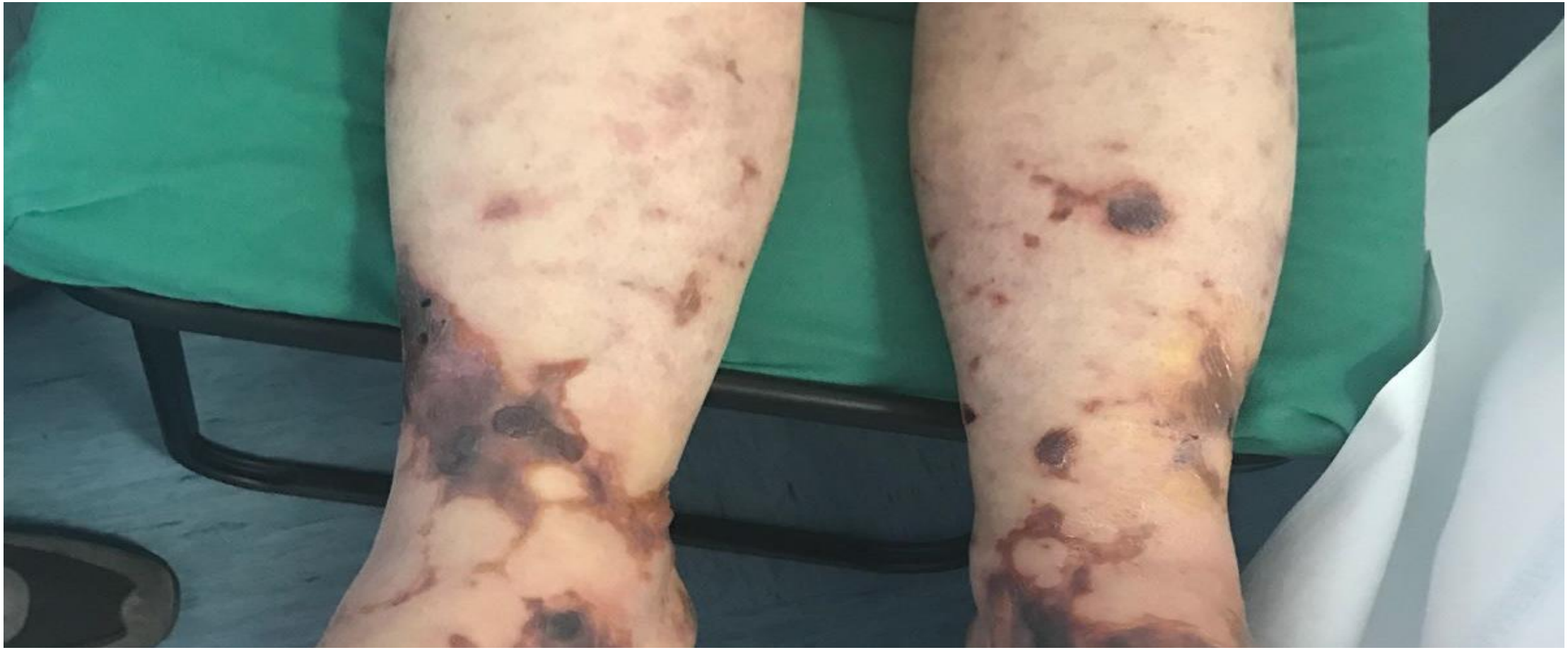
Dismissed from ED: Doppler advised

After 12 hrs back to ICU

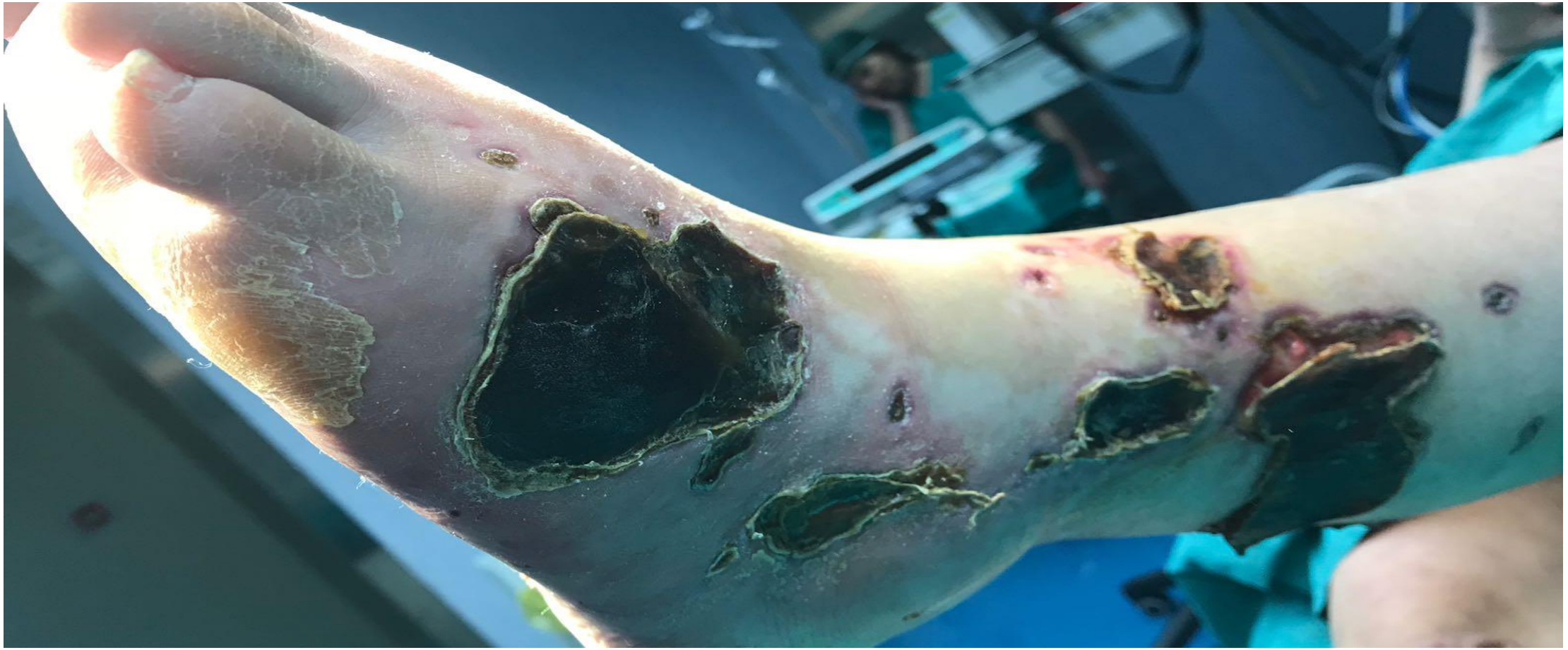


After two months

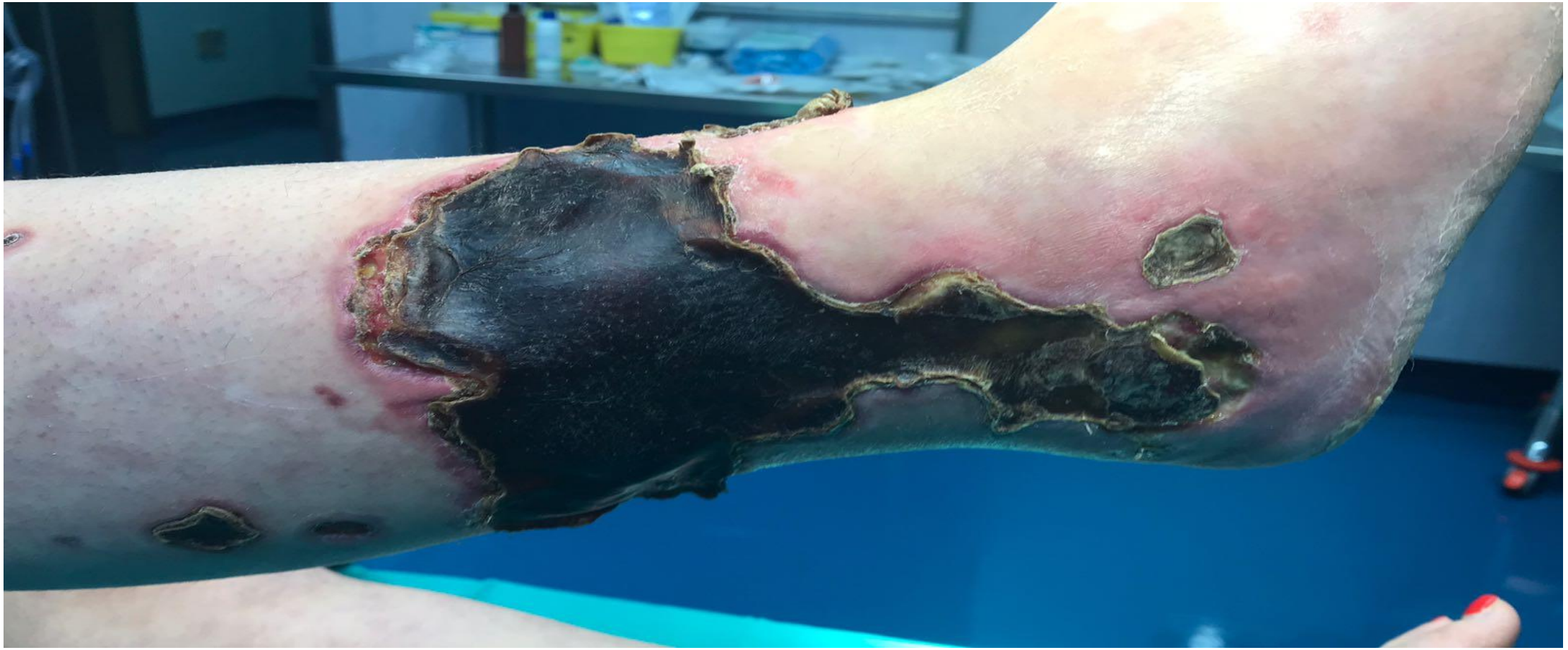
After one year



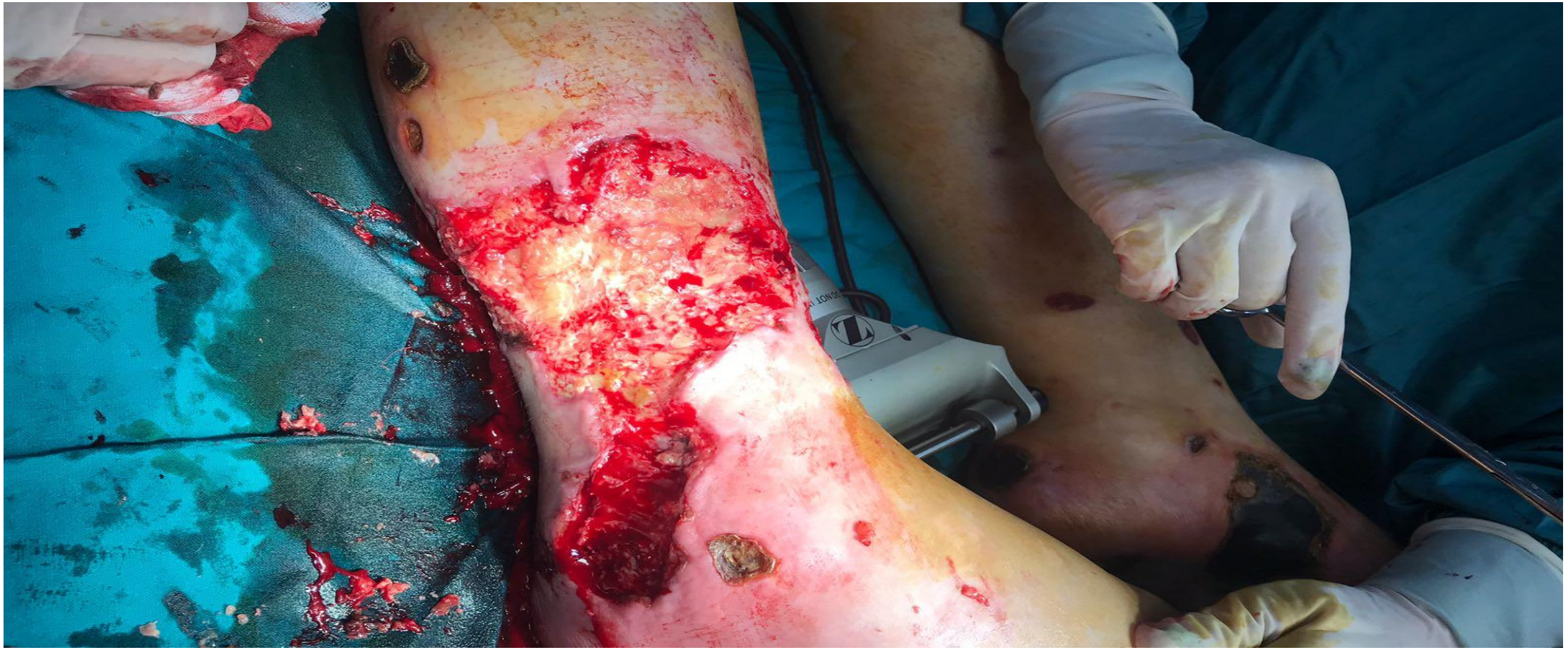
Esiti tardivi a 2 mesi: escara



Esiti tardivi a 2 mesi: escara



Intervento



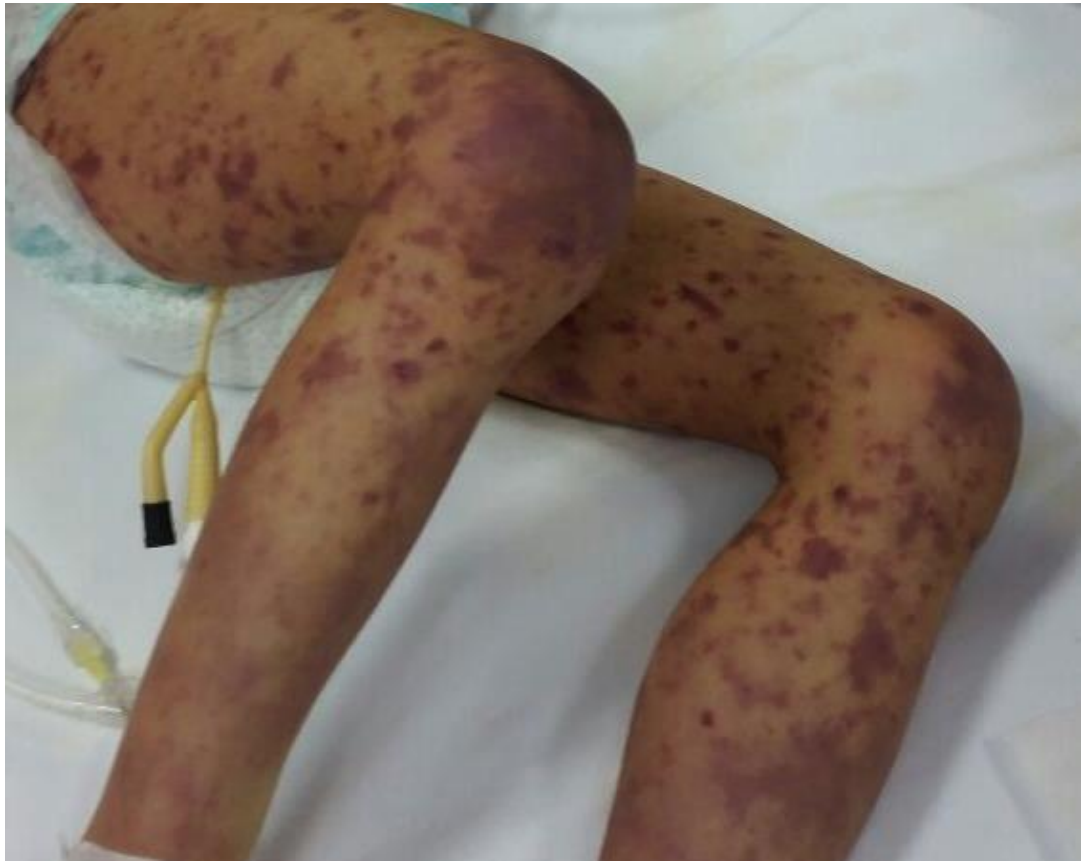
Purpura fulminans

- Cotugno Hospital, Naples, Italy
- Admitted to ICU, sedated and intubated
- **Therapy**: Dexamethasone, rifampicin 600 mg, than ceftriaxone 2 g slowly, IGAM 5 mL/kg Continuous Infusion (CI) for the first 3 days

Purpura fulminans

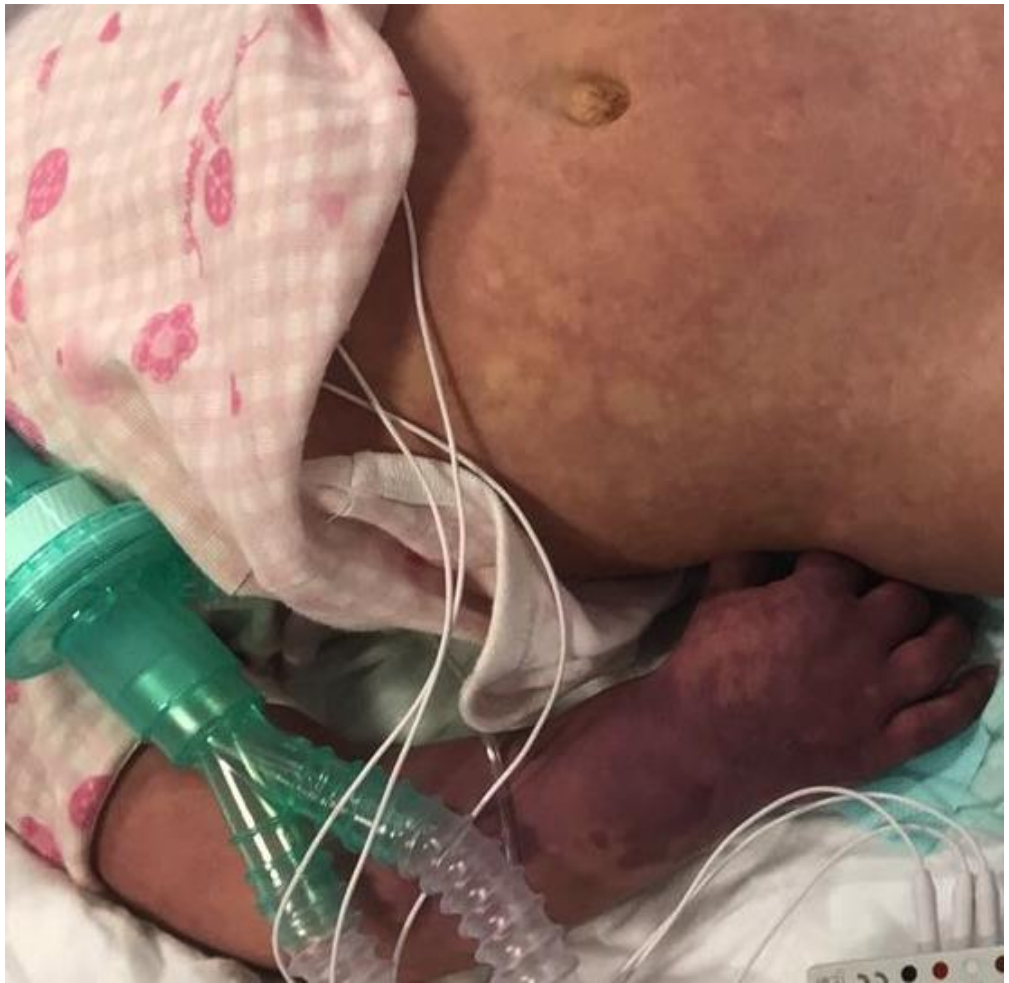
- Lumbar Puncture (LP) and filmarray performed on CSF: tested positive for Meningococcus
- Group C serotype
- Strain sent to National Health Institute (ISS-Istituto Superiore di Sanità) for further characterization: C St type 11, P1.5,-1.,10-8:F3-6,
- Result: Tuscany outbreak serotype

Case - 2018: *N. meningitidis* group C, ST11; unvaccinated 5-year-old boy, cardiac arrest after steroid and during antibiotic ceftriaxone therapy: endotoxin 1 EU/ml, procalcitonin 80 ng/ml.



Courtesy Prof. Tascini

2018: *N. meningitidis* group W, st type 11,
12 month old girl
Expired following cortisone and ceftriaxone administration:
endotoxin values= 1,2, PCT=100



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[16], 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

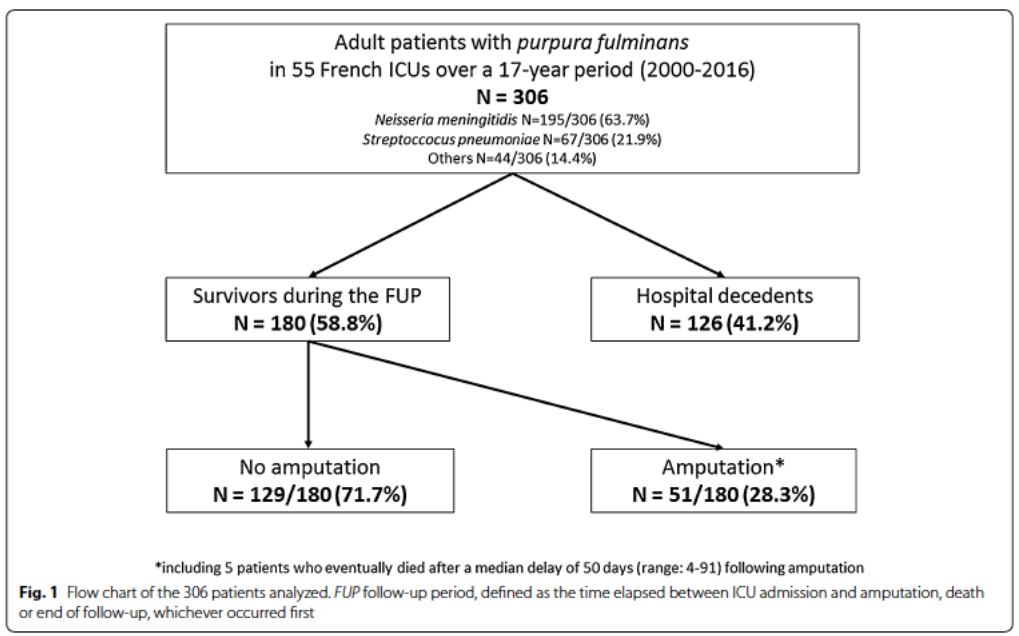


Fig. 1 Flow chart of the 306 patients analyzed. *FUP* follow-up period, defined as the time elapsed between ICU admission and amputation, death or end of follow-up, whichever occurred first

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

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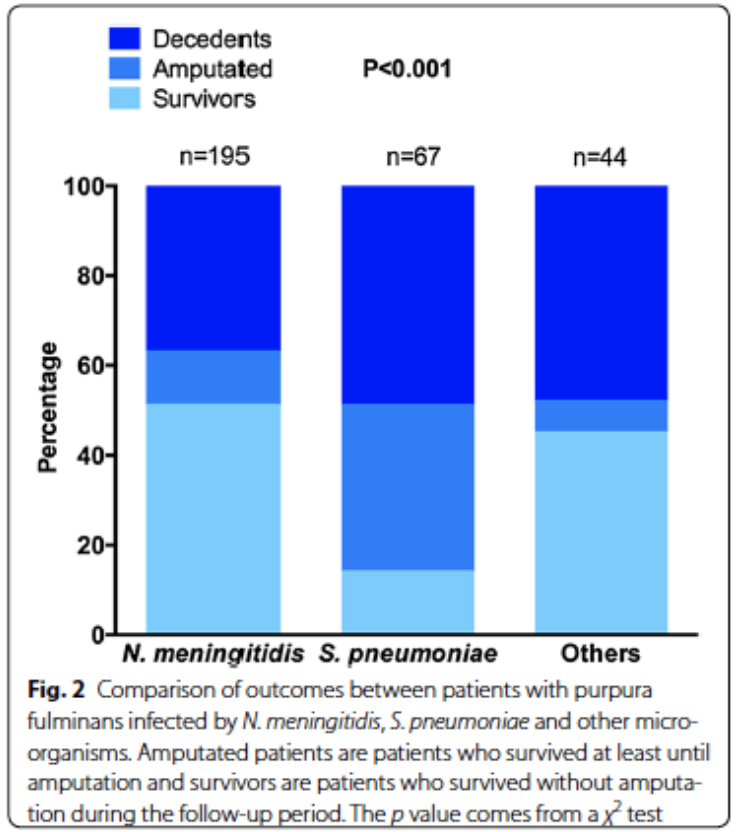


Fig. 2 Comparison of outcomes between patients with purpura fulminans infected by *N. meningitidis*, *S. pneumoniae* and other micro-organisms. Amputated patients are patients who survived at least until amputation and survivors are patients who survived without amputation during the follow-up period. 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		0.52
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

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.

Partiamo dalla meningite batterica comunitaria

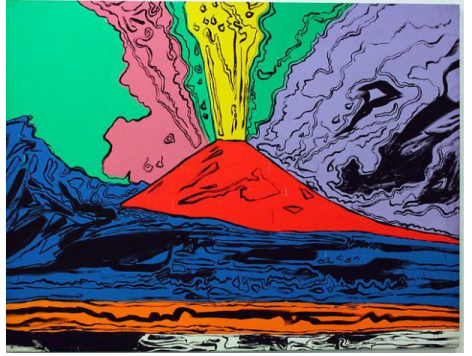
The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

CURRENT CONCEPTS

Community-Acquired Bacterial Meningitis in Adults

Diederik van de Beek, M.D., Ph.D., Jan de Gans, M.D., Ph.D.,
Allan R. Tunkel, M.D., Ph.D., and Eelco F.M. Wijdicks, M.D., Ph.D.



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

Steroids

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.

Adjunctive dexamethasone in adults with meningococcal meningitis

Sebastiaan G.B. Heckenberg, MD*
Matthijs C. Brouwer, MD, PhD*
Arie van der Ende, PhD
Diederik van de Beek, MD, PhD

Dexamethasone, 10 mg IV, given every 6 hours for 4 days was started before or with the first dose of parenteral antibiotics in 78 of 96 episodes (81%). In 6 patients (6%), dexamethasone was discontinued after cultures grew meningococci. Dexamethasone was prescribed in 35 of 39 patients (90%) with a rash on admission. Adjunctive dexamethasone was administered in 43 episodes (17%) in the 1998–2002 cohort. Twelve of these patients were included in the European dexamethasone in adulthood bacterial meningitis study and received dexamethasone 10 mg IV, given every 6 hours for 4 days, started before or with first dose of parenteral antibiotics; dexamethasone was initiated after clinical deterioration in all other episodes.[4,13]

Steroid use in non-pneumococcal and non-Haemophilus bacterial meningitis

Lancet 2022 Feb 19;399(10326):717-718.

Steroide per tutte le meningiti comunitarie batteriche

To conclude, dexamethasone should be initiated with the first dose of antibiotics in all patients with community-acquired bacterial meningitis beyond the neonatal age. On the basis of available evidence, we advise to continue dexamethasone treatment in this patient group for 4 days regardless of microbial cause, except in patients with *Listeria monocytogenes*.

We declare no competing interests.

*Diederik van de Beek,
Matthijs C Brouwer, Uwe Koedel,
Emma C Wall
d.vandebeek@amsterdamumc.nl

Adjunctive dexamethasone treatment in adults with listeria monocytogenes meningitis: a prospective nationwide cohort study

Matthijs C. Brouwer* and Diederik van de Beek**

dexamethasone. The case fatality rate was 51 of 162 (31%) and an unfavourable outcome occurred in 91 of 162 patients (56%). Age and the standard regimen of adjunctive dexamethasone were independent predictors for an unfavourable outcome and mortality. The adjusted odds ratio of dexamethasone treatment for unfavourable outcome was 0.40 (95% confidence interval 0.19–0.81).

Interpretation Adjunctive dexamethasone is associated with an improved outcome in patients with *L. monocytogenes* meningitis and should not be withheld if *L. monocytogenes* is suspected or detected as causative pathogen.

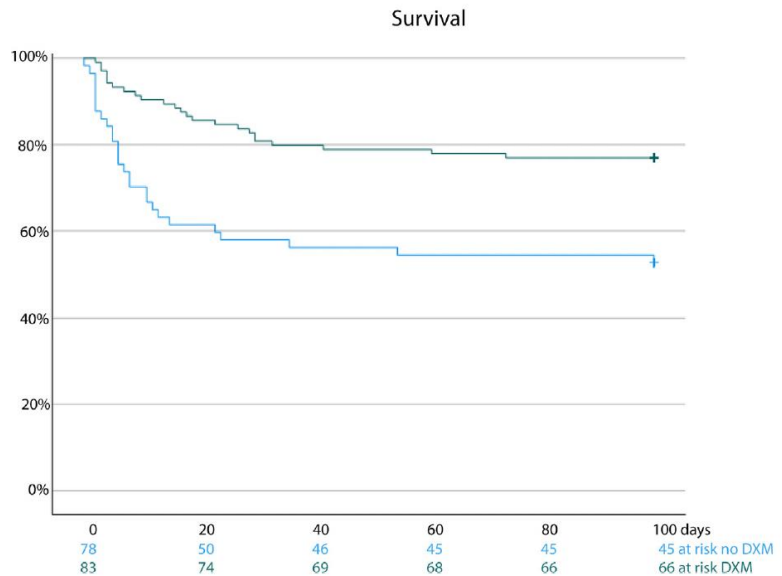


Fig. 2: Kaplan-Meijer estimates of survival for listeria meningitis patients receiving standard dexamethasone treatment and those receiving no dexamethasone or a non-standard regimen (log-Rank test P < 0.001).

Antibiotico batteriolitico ed infiammazione

Spoke Hospital, Udine Province, Italy

- 67-year old male, previous pneumococcal meningitis
- Fever, headache, Glasgow coma scale: 9, lumbar puncture: purulent CSF
- Centralized to Udine Hospital
- Started on intravenous ceftriaxone 2 g, and ampicillin 2 g

Time 13:38 spoke Hospital –Time 20:08 Udine Hub Hospital after antibiotics without steroid administration

Esame Emocromocitometrico				
Globuli Bianchi	13.25	>	x10^3/µL	4.00 - 11.00
Globuli Rossi	5.42		x10^6/µL	4.60 - 5.60
Emoglobina	16.7		g/dL	14.0 - 18.0
Ematocrito	51.5	>	%	40.0 - 50.0
MCV	95.1	>	fL	80.0 - 94.0
MCH	30.8		pg	27.0 - 32.0
MCHC	32.4		g/dL	32.0 - 35.0
RDW (CV Distrib. Vol. Eritrocitari)	13.9		%	11.0 - 14.0
Piastrine	197		x10^3/µL	150 - 400

Proteina C reattiva	19.00	>	mg/L	0.00 - 5.00
Procalcitonina	0.60		ng/mL	< 0.10

Rischio per sepsi:
0.10 - 0.50 basso
0.50 - 2.00 moderato
2.00 - 10.00 alto
> 10.00 molto alto

Esame Emocromocitometrico				
Globuli Bianchi	31.24	>	x10^3/µL	4.00 - 11.00
Globuli Rossi	5.12		x10^6/µL	4.60 - 5.60
Emoglobina	16.1		g/dL	14.0 - 18.0
Ematocrito	48.6		%	40.0 - 50.0
MCV	94.9	>	fL	80.0 - 94.0
MCH	31.4		pg	27.0 - 32.0
MCHC	33.1		g/dL	32.0 - 35.0
RDW (CV Distrib. Vol. Eritrocitari)	13.8		%	11.0 - 14.0
Piastrine	191		x10^3/µL	150 - 400
Formula Leucocitaria				
Neutrofili %	87.8		%	
Linfociti %	1.7		%	
Monociti %	10.2		%	
Eosinofili %	0.0		%	
Basofili %	0.2		%	
Neutrofili	27.44	>	x10^3/µL	2.00 - 7.50
Linfociti	0.54	<	x10^3/µL	1.00 - 4.00
Monociti	3.19	>	x10^3/µL	0.10 - 1.00
Eosinofili	0.01	<	x10^3/µL	0.04 - 0.65
Basofili	0.06		x10^3/µL	0.00 - 0.20

Formula Strumentale non verificata al Microscopio; Presenza di aggregati piastrinici. Conteggio sottostimato.

Proteina C reattiva	63.99	>	mg/L	0.00 - 5.00
Procalcitonina	34.55		ng/mL	< 0.10

Clinical case: patient Z.A.

- Female, 69 years old
- No known comorbidities, no chronic therapy. No allergies.
- Clinical onset on November 26th, 2022, pain localized at right ear.
- From 02/12/2022 morning walking difficulties with mental confusion.
- Access to emergency room on the 2nd of December: «alert, febrile (TC 38°), no focal deficit, neck stiffness and altered mental status»
- Empirically started on dexamethasone 8 mg IV + ceftriaxone 2 g IV+ ampicillin 4 g IV and aciclovir 800 mg IV.
- Centralized in Udine and hospitalized in the Infectious Diseases Unit.

Materiale: Liquor

Ag Cryptococcus neoformans test IC	**Negativo**
Ricerca diretta molecolare multiplex	
BATTERI	
Escherichia coli K1	**Negativa**
Haemophilus influenzae	**Negativa**
Listeria monocytogenes	**Negativa**
Neisseria meningitidis	**Negativa**
Streptococcus agalactiae	**Negativa**
Streptococcus pneumoniae	**Positiva**

Dato comunicato il 03/12/2022 alle ore 14:08, mediante modalità read back.

Glucosio	**160** >	mg/dL	74 - 109

Indagini su Liquido Cefalo-Rachidiano

Liquido cefalo rachidiano			
Aspetto	**Limpido**		
Aspetto dopo centrifugazione	**Limpido**		
Colore	*LEGG XANTOCROMICO*		
Volume	**0.5**	mL	
Glucosio	**<2**	mg/dL	
Proteine totali	**3551** >	mg/L	150 - 450
Lattato	**14.6** >	mMol/L	0.0 - 2.8
Conta leucociti	**14.0** >	/µL	0.0 - 3.0
Polimorfonucleati	**24**	%	
Linfociti	**12**	%	
Mononucleate	**64**	%	
	RARE EMAZIE		

Richiesta: **55333178** del: **03/12/2022** Ore: 12:17
(UD)-2° piano, Pad. 9

Off-Label
CSF Pro ADM

Esame	*Esito*	*U.M.*	*Intervalli di riferimento*

Indagini su Liquido Cefalo-Rachidiano

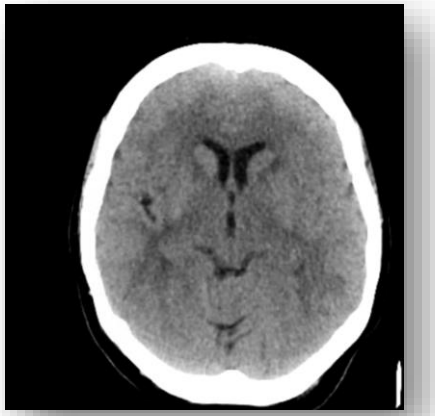
Pro-adrenomedullina liquido cefalo rachidiano	**16.77**	nMol/L
Ratio pro-adren.liquor/sangue	**7.7**	

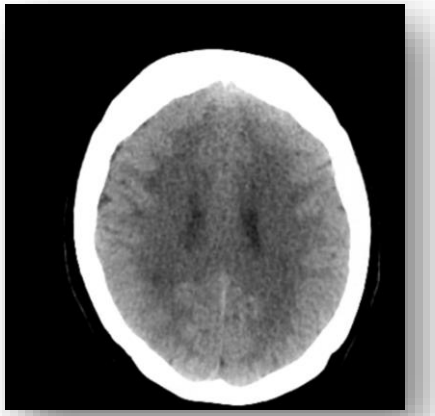
Proadrenomedullina eseguita su richiesta n. 55331420

Plasma Pro-ADM: 2,17 mMol/L

Clinical case: patient Z.A.

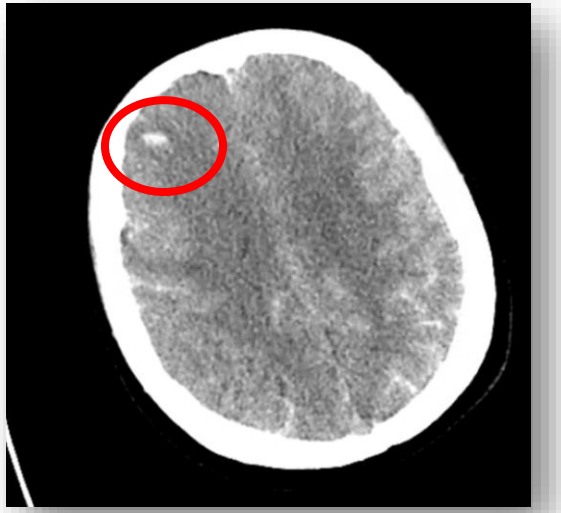
- Ampicillin and acyclovir therapy discontinued. Ceftriaxone and dexamethasone continued.
- On the 5th of December 2022: patient locked her gaze and no longer replied if not with the emission of incomprehensible sounds; presented deviation of buccal line and flattening of the nasolabial fold with flaccid paresis on the right side (ischemic stroke)

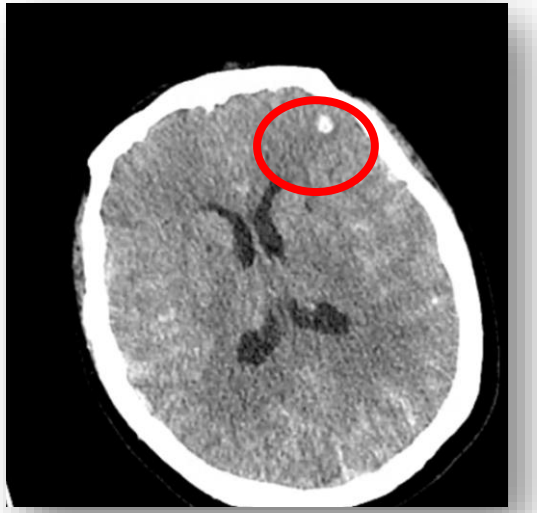




Clinical case: patient Z.A.

- CT scan: negative. Started fibrinolysis with alteplase.
- Approximately 30 mins following the end of alteplase infusion, further neurological deterioration was observed: the patient appeared no longer responsive to the call. She presented afinalistic movements of the upper left limb alternating with a state of drowsiness with snoring breath with respiratory pauses. Normally reactive myotic pupils (haemorragic stroke)





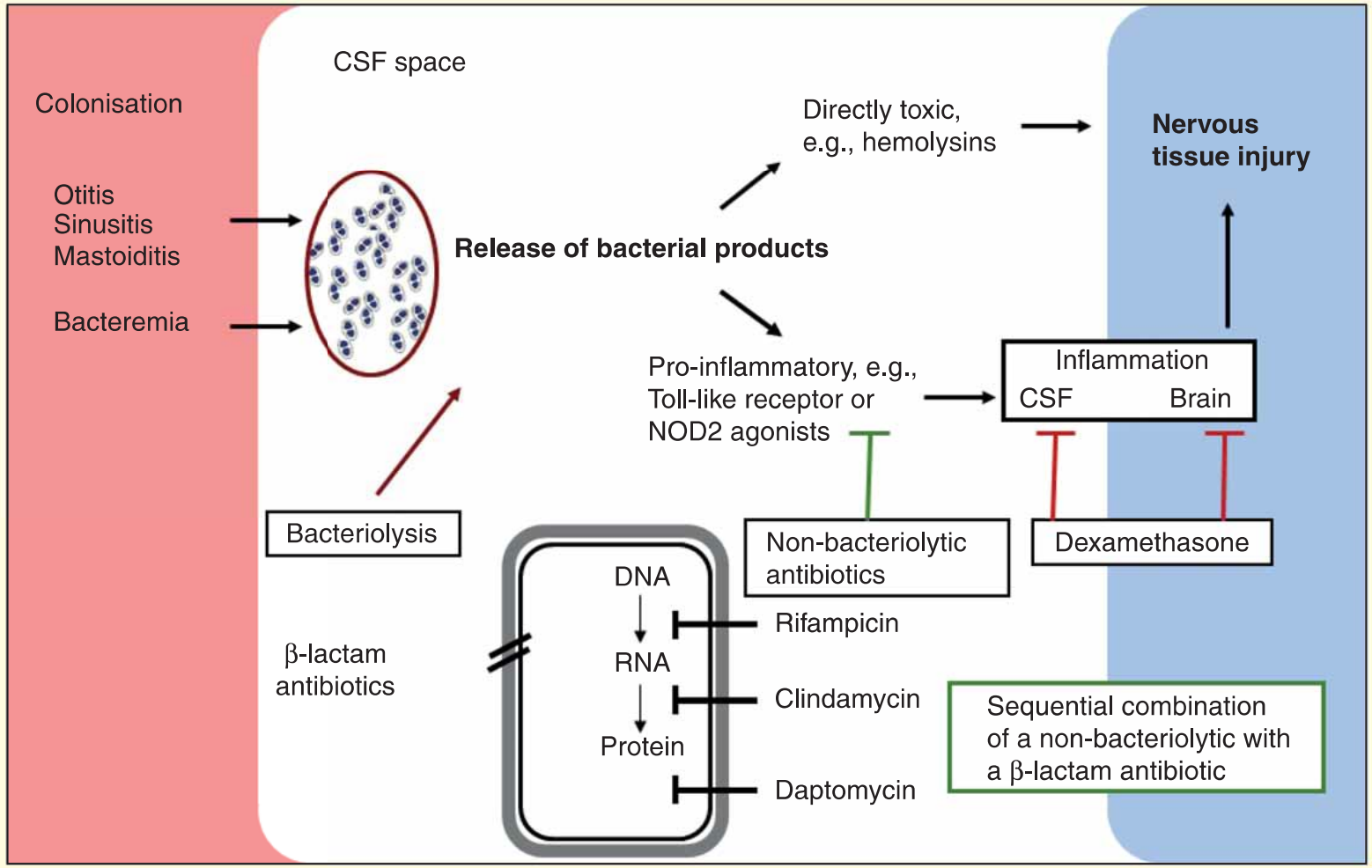
Clinical case: patient Z.A.

27th April 2023, discharge from the Hospital after 6 months: with 16 of Mr-ProADM in CSF, I have to use the standard protocol???

Diagnosi di dimissione:

"Afasia, doppia emiplegia flaccida in postumi di meningite, dubbia mastoidite e batteriemia da S. pneumoniae complicata da ischemia cerebrale a verosimile patogenesi vasculitica sottoposta a fibrinolisi complicata da emorragia subaracnoidea e intraparenchimale fronto-parieto-temporale bilaterale, LDD sacrale in terapia a pressione negativa".

Quick and dirty versus killing bacteria softly



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)

MENING-*Italy* Study

Penalized multivariate logistic regression

Chronic renal insufficiency	**1,12**
Immuno-suppression	**1,26**
GCS	**0,90**
SOFA	**1,11**
White Blood cells	**0,99**
Platekletes	**0,99**
Glucose	**1,001**
Cetriaxon	**0,89**
Rifampicin	**0,89**
Male	**0,43**
Fever	**1,16**
Age	**1,01**
S. pneumoniae	**1,67**

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

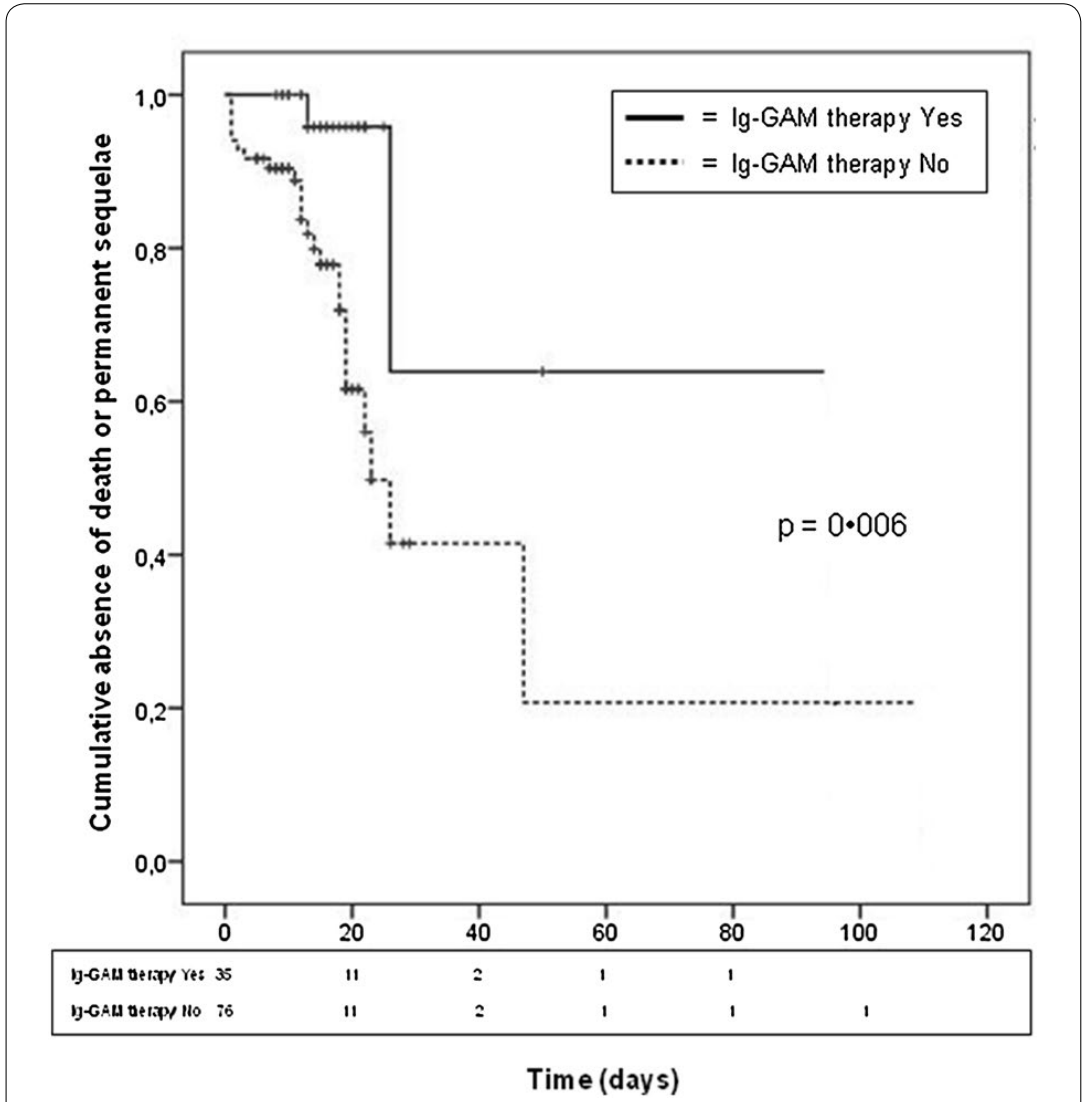


Fig. 1 Kaplan–Meier analysis of aggregated data on death and permanent sequelae in patients treated or not with Ig-GAM

Quale terapia empirica e come somministrare

Enterobatteri e penicilline negli anni: *2021*

***Enterobacterales* ***

Expert Rules and Intrinsic Resistance Tables

EUCAST Clinical Breakpoint Tables v. 11.0, valid from 2021-01-01

An MIC breakpoint of S ≤ 0.001 mg/L is an arbitrary, "off scale" breakpoint (corresponding to a zone diameter breakpoint of "S ≥ 50 mm") which categorises wild-type organisms (organisms without phenotypically detectable resistance mechanisms to the agent) as "Susceptible, increased exposure" (I). For these organism-agent combinations, never report "Susceptible, standard dosing regimen" (S).

MIC determination (broth microdilution according to ISO standard 20776-1 except for mecillinam and fosfomycin where agar dilution is used)
Medium: Mueller-Hinton broth (for cefiderocol, see http://www.eucast.org/guidance_documents/)
Inoculum: $5x10^5$ CFU/mL
Incubation: Sealed panels, air, 35±1°C, 18±2h
Reading: Unless otherwise stated, read MICs at the lowest concentration of the agent that completely inhibits visible growth.
Quality control: *Escherichia coli* ATCC 25922. For agents not covered by this strain and for control of the inhibitor component of beta-lactam inhibitor combinations, see EUCAST QC Tables.

Disk diffusion (EUCAST standardised disk diffusion method)
Medium: Mueller-Hinton agar
Inoculum: McFarland 0.5
Incubation: Air, 35±1°C, 18±2h
Reading: Unless otherwise stated, read zone edges as the point showing no growth viewed from the back of the plate against a dark background illuminated with reflected light.
Quality control: *Escherichia coli* ATCC 25922. For agents not covered by this strain and for control of the inhibitor component of beta-lactam inhibitor-combination disks, see EUCAST QC Tables.

*** Recent taxonomic studies have narrowed the definition of the family Enterobacteriaceae. Some previous members of this family are now included in other families within the Order *Enterobacterales*. Breakpoints in this table apply to all members of the *Enterobacterales*.**

Penicillins[1]	MIC breakpoints (mg/L)			Disk content (µg)	Zone diameter breakpoints (mm)		
	S ≤	R >	ATU		S ≥	R <	ATU
Benzylpenicillin	-	-			-	-	
Ampicillin[1]	8	8		10	14[A]	14[A]	
Ampicillin-sulbactam[1]	8[2]	8[2]		10-10	14[A]	14[A]	
Amoxicillin[1]	8	8		-	Note[B]	Note[B]	
Amoxicillin-clavulanic acid[1]	8[3]	8[3]		20-10	19[A]	19[A]	19-20
Amoxicillin-clavulanic acid (uncomplicated UTI only)	32[3]	32[3]		20-10	16[A]	16[A]	
Piperacillin	8	8		30	20	20	
Piperacillin-tazobactam	8[4]	8[4]	16	30-6	20	20	19
Ticarcillin	8	8		75	23	20	
Ticarcillin-clavulanic acid	8[3]	16[3]		75-10	23	20	
Temocillin (infections originating from the urinary tract), *E. coli*, *Klebsiella* spp. (except *K. aerogenes*) and *P. mirabilis*	0.001	16		30	50[C]	17[C]	
Phenoxymethylpenicillin	-	-			-	-	
Oxacillin	-	-			-	-	
Cloxacillin	-	-			-	-	
Dicloxacillin	-	-			-	-	
Flucloxacillin	-	-			-	-	
Mecillinam oral (pivmecillinam) (uncomplicated UTI only), *E. coli*, *Citrobacter* spp., *Klebsiella* spp., *Raoultella* spp., *Enterobacter* spp. and *P. mirabilis*	8[5]	8[5]		10	15[C]	15[C]	

Notes
Numbered notes relate to general comments and/or MIC breakpoints.
Lettered notes relate to the disk diffusion method.

1. Aminopenicillin breakpoints in *Enterobacterales* are based on intravenous administration. For oral administration the breakpoints are relevant for urinary tract infections only. Breakpoints for other infections are under review.
2. For susceptibility testing purposes, the concentration of sulbactam is fixed at 4 mg/L.
3. For susceptibility testing purposes, the concentration of clavulanic acid is fixed at 2 mg/L.
4. For susceptibility testing purposes, the concentration of tazobactam is fixed at 4 mg/L.
~~**5/C. Breakpoints still under consideration.**~~
5. Agar dilution is the reference method for mecillinam MIC determination.

A. Ignore growth that may appear as a thin inner zone on some batches of Mueller-Hinton agars.
B. Susceptibility inferred from ampicillin.
C. Ignore isolated colonies within the inhibition zone.

EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING
European Society of Clinical Microbiology and Infectious Diseases

- **Terapia antibiotica appropriata: criteri microbiologici e clinici**

Frequently Asked Questions: FAQ

Dosages **EUCAST Clinical Breakpoint Tables v. 12.0, valid from 2022-01-01**

Penicillins	Standard dosage	High dosage	Uncomplicated UTI	Special situations
Piperacillin-tazobactam	(4 g piperacillin + 0.5 g tazobactam) x 4 iv 30-minute infusion or x 3 iv by extended 4-hour infusion	(4 g piperacillin + 0.5 g tazobactam) x 4 iv by extended 3-hour infusion		A lower dosage of (4 g piperacillin + 0.5 g tazobactam) x 3 iv, 30-minute infusion, is adequate for some infections such as complicated UTI, intraabdominal infections and diabetic foot infections, but not for infections caused by isolates resistant to third-generation cephalosporins.

I BP per *Enterobacterales* e piperacillina-tazobactam sono stati cambiati nel 2021, perché è stata rimossa la categoria «I»?

- **Per riuscire a coprire isolati con MIC 16 mg/L occorrerebbe un dosaggio di 4 g x 4 con un tempo di infusione esteso**
  - **Pratica non ben stabilita**
  - **Incertezza sull'outcome clinico per questo livello di MIC**
- **Problema dell' incertezza tecnica (ATU) per questo valore di MIC**

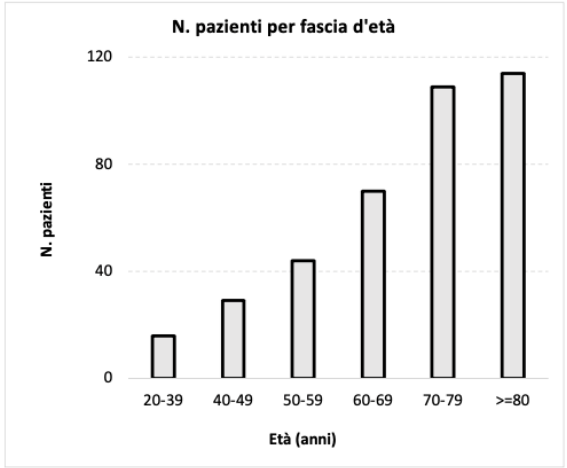
Table 2: Target attainment artes for piperacillin-tazobactam 4.5 g x 3 and 4.5 g x 4 iv [4], based on PK described by Felton et al. [5]

MIC (mg/L)	Target attainment rate at *f*T>MIC of 50%		
	4 g x 3 iv 4h infusion	4 g x 4 30' infusion	4 g x 4 iv 3h infusion
64	9	9.5	18
32	44	38	67
16	93	76	99
8	100	95	100
4	100	99	100
≤ 2	100	100	100

Piperacillin-tazobactam, beakpoint for Enterobacterales. **General Consultation 10 july – 18 september 2020**

Piperacillin/tazobactam continuous infusion: 2023 Udine University Hospital, Target PK/PD Conc/MIC > 4 piperacillin

Figura 1 *Distribuzione dei pazienti per fascia d'età*



Pazienti	N.
N. totale pazienti	382
Sesso M	228
Sesso F	154

Parametri	Media	Dev. St.	Mediana	1° quartile	3° quartile
Età (anni)	70	15	72	61	81
Peso (Kg)	75	18	75	63	85
Altezza (m)	1,70	0,10	1,70	1,63	1,76
BMI (Kg/mq)	25,99	5,53	25,39	22,50	28,86
Creatinina (mg/dL)	1,50	1,29	1,05	0,74	1,62
eGFR (mL/min)	70,32	49,64	61,23	37,65	94,05
Dose media iniziale (g)	15,16	4,50	18,00	11,25	18,00

Target PK/PD Conc/MIC > 4 piperacillin, conc > 64 mg/L

Tabella 2 *Concentrazioni di piperacillina rilevate*

[piperacillina] (mg/L)	N.	Media	Dev. St.	Mediana	1° quartile	3° quartile	Min	Max
Tutti i campioni								
	701	82,71	61,28	66,53	45,56	98,24	1,32	539,16
Sesso								
M	423	77,19	61,78	61,36	43,13	90,93	1,57	539,16
F	278	91,11	59,66	76,35	50,49	113,88	1,32	414,17
Fasce d'età								
20-39	33	49,40	25,47	47,12	32,96	55,36	13,47	127,36
40-49	49	63,32	43,90	55,77	30,03	90,87	15,52	246,49
50-59	99	69,98	57,34	52,23	34,75	87,63	2,01	375,02
60-69	134	84,16	75,30	62,93	45,22	92,12	1,65	457,82
70-79	182	90,66	65,37	77,64	54,17	101,90	1,32	539,16
>=80	205	93,17	54,18	77,64	56,22	119,29	2,05	282,81
eGFR								
<20	67	101,91	61,00	82,24	65,22	134,26	2,64	282,81
20-39	125	111,42	69,52	97,38	59,39	141,76	1,32	414,17
40-89	315	82,85	60,76	69,36	49,64	97,20	1,57	539,16
90-119	109	62,91	41,03	54,84	39,41	74,31	1,32	242,09
>=120	85	50,20	46,65	39,16	30,38	54,17	2,01	395,11
BMI								
sottopeso: < 18	29	103,25	67,64	77,77	56,95	123,95	13,47	282,81
normopeso: 18 - 24.9	288	80,19	53,23	67,46	47,18	94,41	4,41	457,82
sovrappeso: 25 - 29.9	242	85,73	65,36	67,37	44,06	108,00	2,05	395,11
obeso: > 30	142	78,47	67,33	61,52	43,24	96,63	1,32	539,16

Paziente clinica medica,

- switch da terapia ev a sottocute
- 18 g pip/tazo ic
- 4,5 g ogni 6 ore con ago flessibile sottocute addome

Pre: endovena 3° giorno

Post: sottocute terzo giorno

Pre

Data Nascita: 22/07/1962 Età: 60 Anni
Richiesta: **55693011** del: **13/02/2023**
(UD)-1° piano, Pad. 8

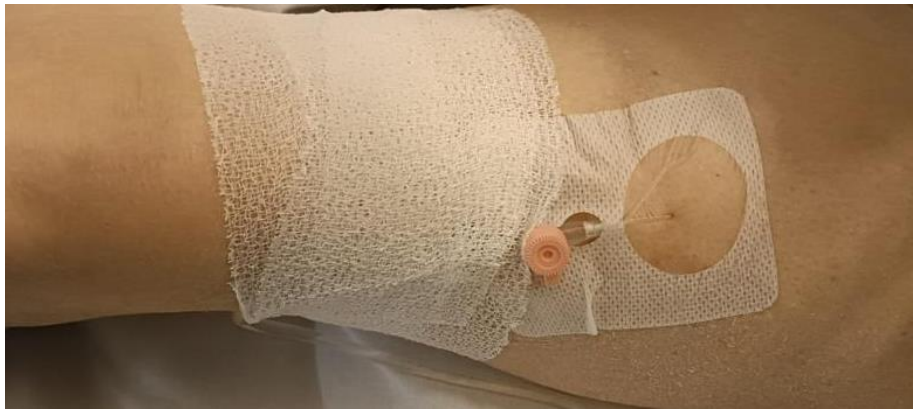
Esame	*Esito*	*U.M.*	*Intervalli di*
Peso del paziente	**60**	kg	
Altezza	**182**	cm	
Data-ora del prelievo pre-dose	**13.02.23 12.00**		
PIPERACILLINA: Concentrazione pre-dose	**69.59**	mg/L	
Dose consigliata	**18 gr ev ic**	mg	
Intervallo di somministrazione	**24**	Ore	
Commento	**Concentrazione in ambito di efficacia terapeutica**		

Post

Richiesta: **55693053** del: **13/02/2023**
(UD)-1° piano, Pad. 8

Esame	*Esito*	*U.M.*	*Intervalli di*
Peso del paziente	**60**	kg	
Altezza	**180**	cm	
Data-ora del prelievo pre-dose	**13.02.23 13.30**		
PIPERACILLINA: Concentrazione pre-dose	**85.22**	mg/L	
Dose consigliata	**4.5 gr SC II**	mg	
Intervallo di somministrazione	**6**	Ore	
Data in cui ripetere il monitoraggio	**mercoledi**		
Commento	**Concentrazione in ambito di efficacia terapeutica**		

Pre: 18 g infusione continua



Post: 4,5 g infuso ogni 6 ore sottocute

Richiesta: **55694135** del: **14/02/2023**
(UD)-1° piano, Pad. 8

Esame	*Esito*	*U.M.*	*Intervalli di*
Peso del paziente	**60**	kg	
Altezza	**180**	cm	
Data-ora del prelievo pre-dose	**14.02.23 12.00**		
PIPERACILLINA: Concentrazione pre-dose	**84.50**	mg/L	
Dose consigliata	**4.5 gr SC II**	mg	
Intervallo di somministrazione	**6**	Ore	
Commento	**Concentrazione in ambito di efficacia terapeutica**		

Data Nascita: 22/07/1962 Età: 60 Anni
Richiesta: **55694190** del: **14/02/2023**
(UD)-1° piano, Pad. 8

Esame	*Esito*	*U.M.*	*Intervalli di*
Peso del paziente	**60**	kg	
Altezza	**180**	cm	
Data-ora del prelievo pre-dose	**14.02.23 13.30**		
PIPERACILLINA: Concentrazione pre-dose	**113.00**	mg/L	
Concentrazione post-dose, con data dell'ultima somminist. ore 12.00			
Dose consigliata	**4.5 gr SC II**	mg	
Intervallo di somministrazione	**6**	Ore	
Commento	**Concentrazione in ambito di efficacia terapeutica**		

Outline

- Detection of methicillin-resistance in *Staphylococcus aureus*

Recommended methods for detection of methicillin resistance in *S. aureus*

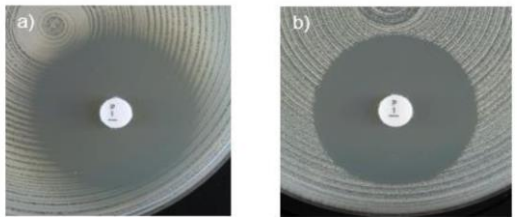
Staphylococcus aureus

Cefoxitin screening

BMD ≤ 4 mg/L
DD ≥ 22 mm

BMD > 4 mg/L
DD < 22 mm

PCR for *mecA/mecC*
latex agglutination for PBP2a protein



MSSA

MRSA

PSSA

BORSA
oxacillin MICs 1-8 mg/L

The European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters. Version 14.0, 2024. http://www.eucast.org; The EUCAST guideline on detection of resistance mechanisms v 2.0 (2017-07-11) ; EUCAST Expert Rules v 3.2 February 2023

Antibiotic susceptibility performed in physiologic media better predicts activity *in vivo* compared to susceptibility testing performed in bacteriological media

Ersoy SC et al. EBioMedicine. 2017 Jun;20:173-181

"Susceptible" MIC
"Intermediate" MIC
"Resistant" MIC

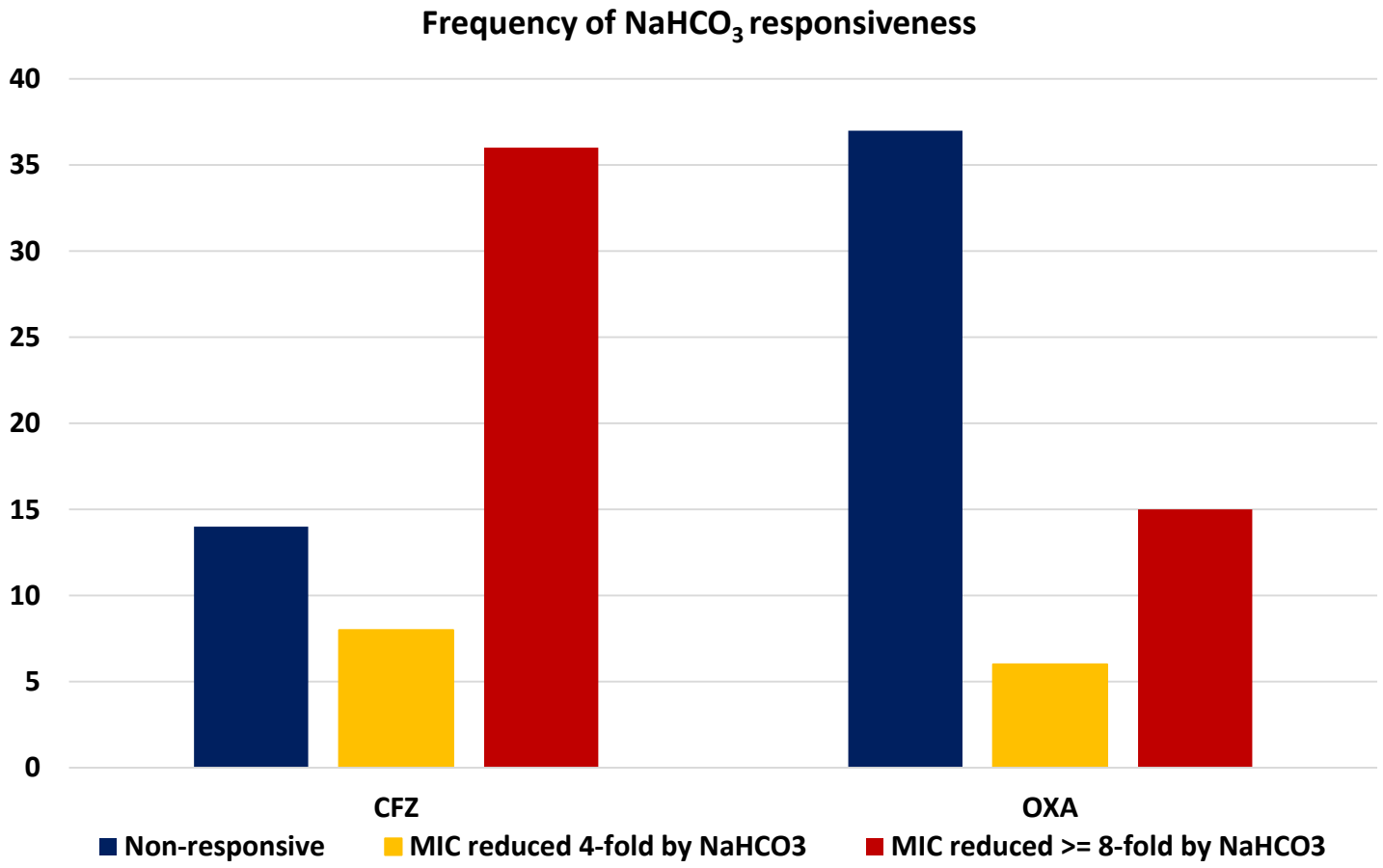
Supplementary Table 2A. Antimicrobial susceptibility test in media w/ and w/o $NaHCO_3$ (*Staphylococcus*)

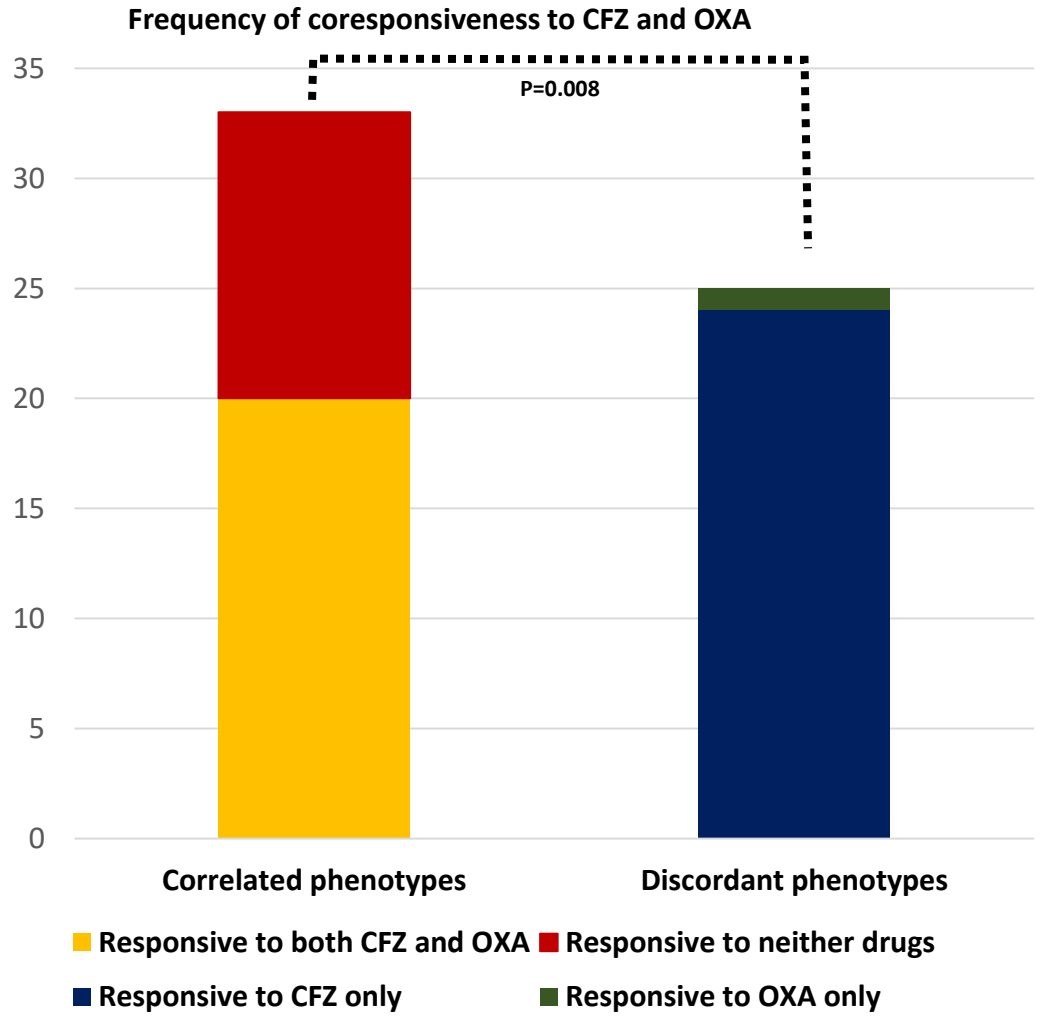
				Cephalothin MIC (µg/mL)
Clinical Breakpoints[a]:				S ≤ 8; I = 16; R ≥ 32[2]
Strain #	Strain Name	Ca-MHB pH 7.2	Ca-MHB 100 mM Tris pH 7.2	Ca-MHB 100 mM Tris 44 mM $NaHCO_3$ pH 7.4
MT3322	MRSA USA300	32	32	8
MT3315	MRSA Wound	8	4	1

				Ceftriaxone MIC (µg/mL)
Clinical Breakpoints:				S ≤ 8; I =16-32; R ≥ 64[2]
Strain #	Strain Name	Ca-MHB pH 7.2	Ca-MHB 100 mM Tris pH 7.2	Ca-MHB 100 mM Tris 44 mM $NaHCO_3$ pH 7.4
MT3322	MRSA USA300	512	256	16
MT3302	MRSA Blood	128	64	32
MT3315	MRSA Wound	64	64	32

				Oxacillin MIC (µg/mL)
Clinical Breakpoints:				S ≤ 2; R ≥ 4
Strain #	Strain Name	Ca-MHB pH 7.2	Ca-MHB 100 mM Tris pH 7.2	Ca-MHB 100 mM Tris 44 mM $NaHCO_3$ pH 7.4
MT3302	MRSA Blood	64	64	16
MT3315	MRSA Wound	32	64	32

Are MRSA really MRSA?: the curious case of “bicarbonate responder” MRSA

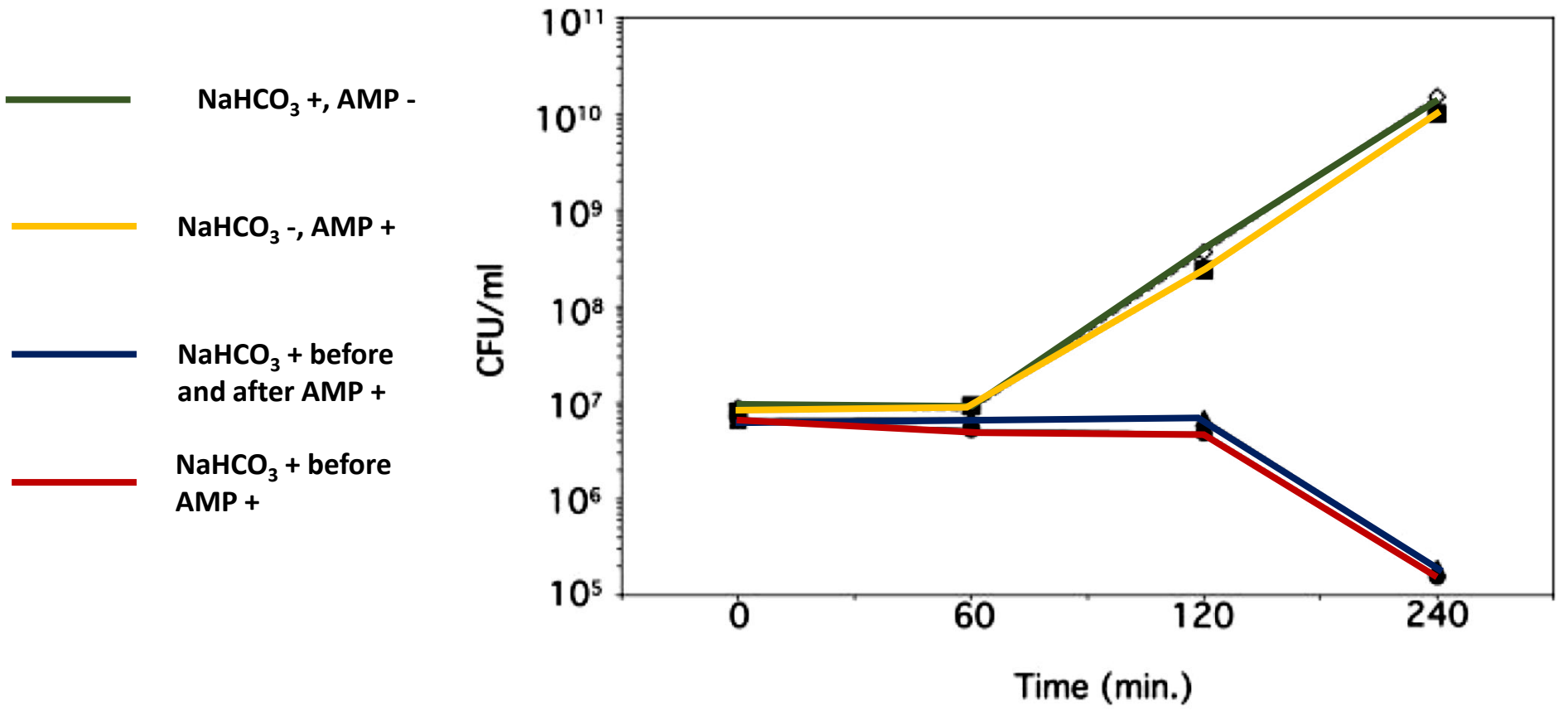




Ersoy SC et al. Antimicrob Agents Chemother. 2020 Apr 21;64(5):e02445-19.

Are MRSA really MRSA?: the curious case of “bicarbonate responder” MRSA

Exposure of MRSA to NaHCO3 enhances susceptibility to antimicrobial peptides



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Synergistic enhancement of in vitro antimicrobial activity of imipenem and cefazolin, cephalothin, cefotiam, cefamandole or cefoperazone in combination against methicillin-sensitive and -resistant Staphylococcus aureus

T Uete [1], K Matsuo

Affiliations + expand

PMID: 7752453

Uete T, Matsuo K. Synergistic enhancement of in vitro antimicrobial activity of imipenem and cefazolin, cephalothin, cefotiam, cefamandole or cefoperazone in combination against methicillin-sensitive and -resistant Staphylococcus aureus. Jpn J Antibiot. 1995 Mar;48(3):402-8. PMID: 7752453.

Abstract

Synergistic enhancement of the in vitro antimicrobial activity of imipenem combined with cephalosporins against methicillin-resistant Staphylococcus aureus (MRSA) has been reported. In order to investigate which cephalosporin is more effective in enhancing the activity of imipenem against MRSA, the in vitro antimicrobial activities of imipenem, cefazolin, cephalothin, cefotiam, cefamandole and cefoperazone, alone and in combination, against methicillin-sensitive Staphylococcus aureus (MSSA) and MRSA were assessed. Using the checkerboard Mueller-Hinton agar dilution method, strong synergy was found in 97% to 100% of MRSA strains for imipenem and all tested cephalosporins except cefoperazone; fractional inhibitory concentration (FIC) indices were < or = 0.5. Among the cephalosporins studied, cefamandole most markedly increased the activity of imipenem against MRSA, followed, in order of decreasing effect, by cefotiam, cephalothin, cefazolin, and cefoperazone. The synergistic effect of imipenem combined with cefamandole or cefotiam was confirmed using the broth dilution method with 2% of NaCl.

Imipenem e molte cefalosporine
sono sinergiche contro MRSA
miglior combinazione con cefamandolo

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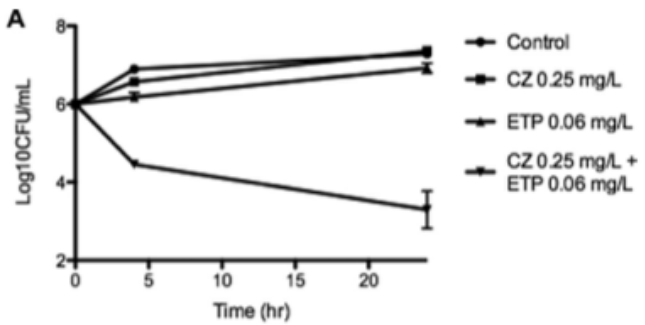
Cefazolin and Ertapenem, a Synergistic Combination Used To Clear Persistent *Staphylococcus aureus* Bacteremia

George Sakoulas,[a,b] Joshua Olson,[a] Juwon Yim,[c] Niedita B. Singh,[c] Monika Kumaraswamy,[a] Diana T. Quach,[d] Michael J. Rybak,[c] Joseph Pogliano,[d] Victor Nizet[a,e]

Killing contro MSSA dell'associazione a sub-MIC



Permeabilizzazione con associazione

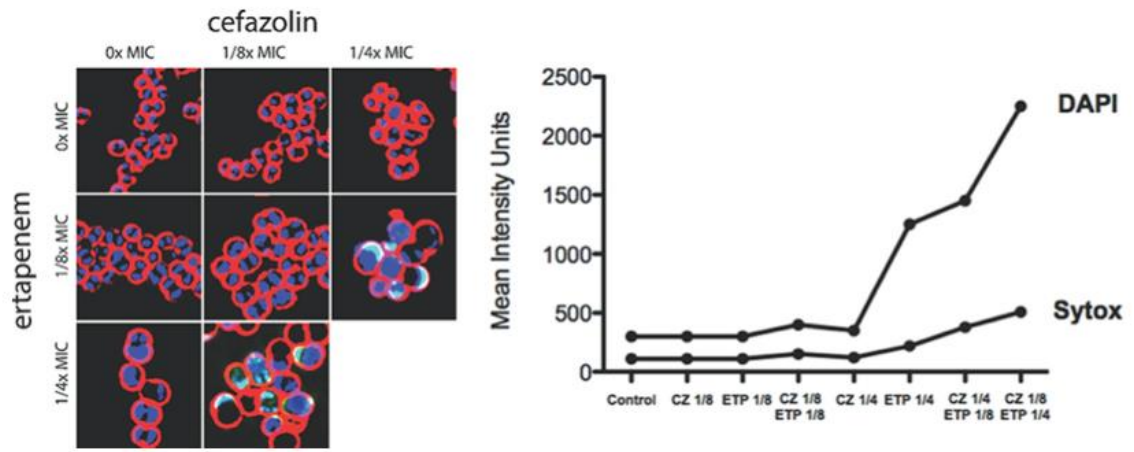


FIG 2 (Left) Microscopy comparing the effects of CZ or ETP alone and in combination on MSSA rus276 at sub-MICs. Sytox Green and DAPI stain uptake was used to measure cellular permeabilization. (Right) Quantification of DAPI and Sytox staining, reflective of increases in cellular permeability with combined ETP and CZ compared to either drug alone at concentrations relative to the MIC.

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Antimicrobial Chemotherapy | Minireview

Measuring beta-lactam minimum inhibitory concentrations in *Staphylococcus aureus* in the clinical microbiology laboratory: pinning the tail on the donkey

George Sakoulas,[1,2] Victor Nizet[2,3]

Daptomicina o peptidi naturali sono detergenti che fanno perdere la penicillinasi a *S. aureus*. Questi ceppi PSSA sono meno sensibili a peptidi naturali e pertanto più virulenti

Given that penicillin-susceptibility may be a marker of virulence in endovascular *S. aureus* infections, we encourage labs to take the extra steps to quantify penicillin MIC in documented endovascular infections. Further investigation of these isolates is warranted. Clinician awareness of penicillin-susceptible *S. aureus* endocarditis would potentially offer potential therapeutic cues, including the avoidance of daptomycin monotherapy given that the pathway to daptomycin resistance may have already begun before daptomycin is even used. Such cases would potentially be treated with combination therapy. Given the shortcomings of disk testing, we recommend that labs serious about adopting penicillin therapy for PSSA use PCR for blaZ testing, although they are not commercially available.

Interleukin (IL)-1β and IL-10 host responses in patients with SAB determined by antimicrobial therapy

- **IL-1β:**

  immunostimulatory response (high levels are good);

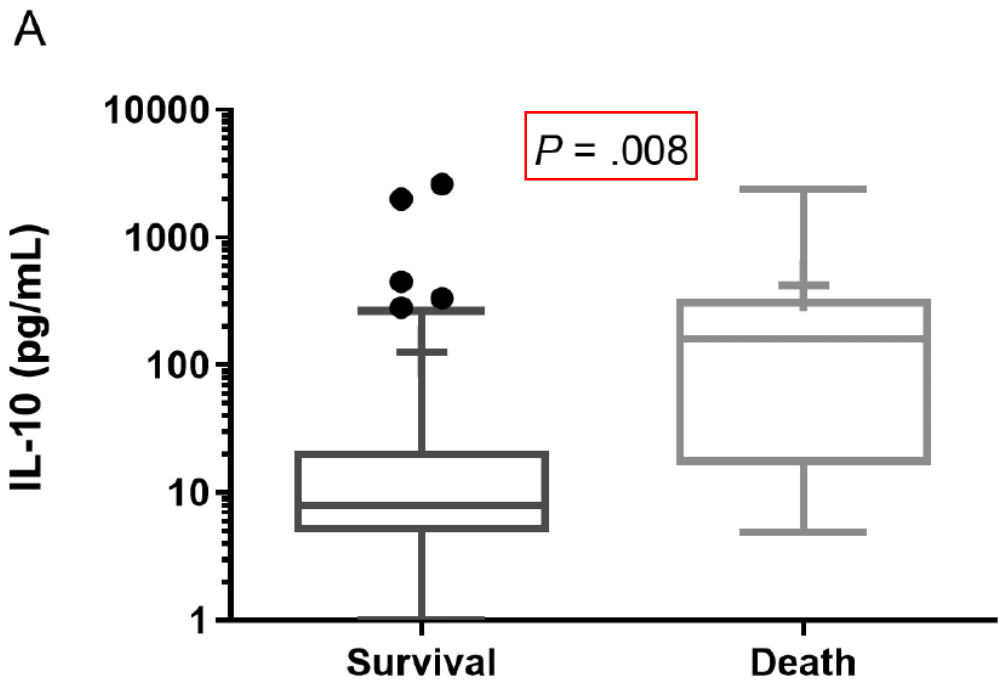
- **IL-10:**

  dysregulated immunosuppressive response (high levels are bad).

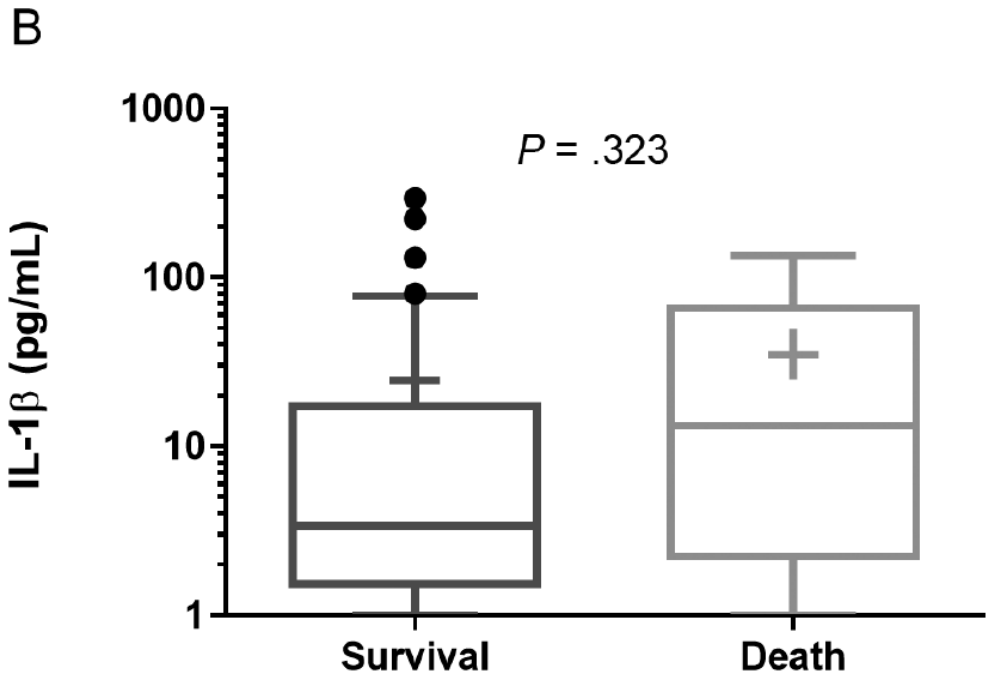
Clinical Infectious Diseases 2020;70(12):2634–40

Interleukin (IL)-1β and IL-10 host responses in patients with SAB (S. aureus bacteremia) determined by antimicrobial therapy

IL-10 concentrations in patient sera on day 1 of presentation compared by outcome of 30-Day survival or mortality.



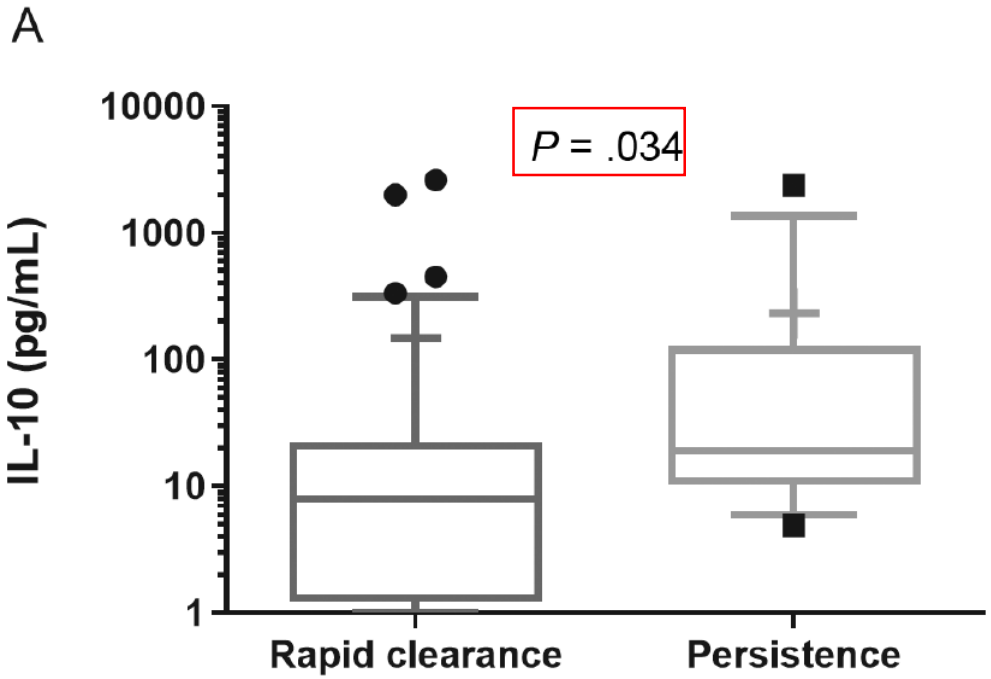
IL-1β concentrations in patient sera on day 1 of presentation compared by outcome of 30-Day survival or mortality.



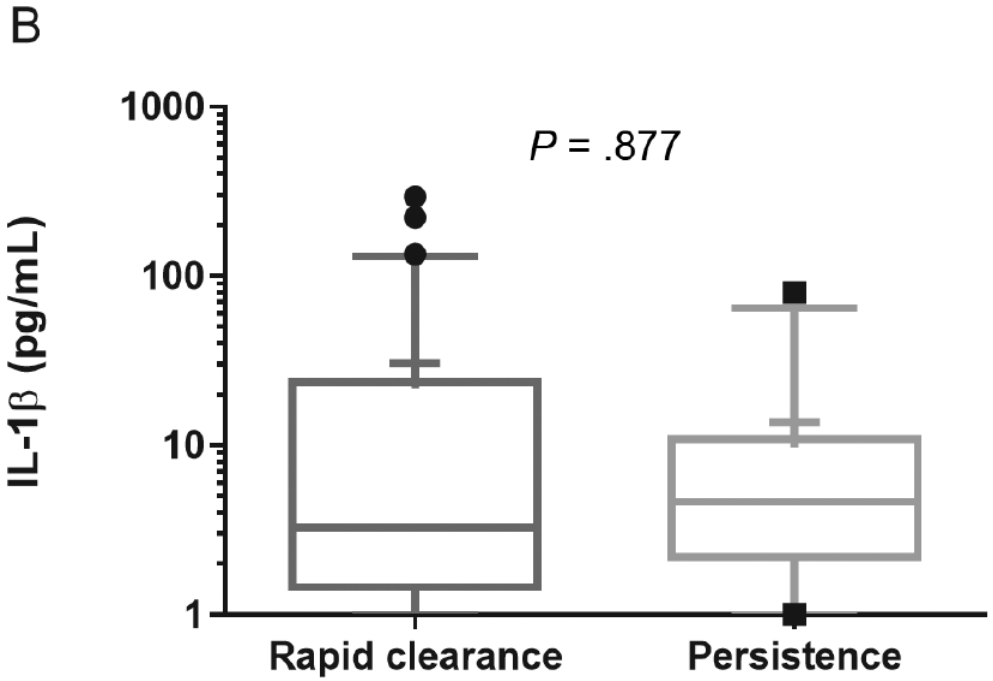
Clinical Infectious Diseases 2020;70(12):2634–40

Interleukin (IL)-1β and IL-10 host responses in patients with SAB determined by antimicrobial therapy

IL-10 concentrations in patient sera on day 1 of presentation compared by outcome of rapid bacteremia clearance (≤4 days) or persistent bacteremia (>4 days).



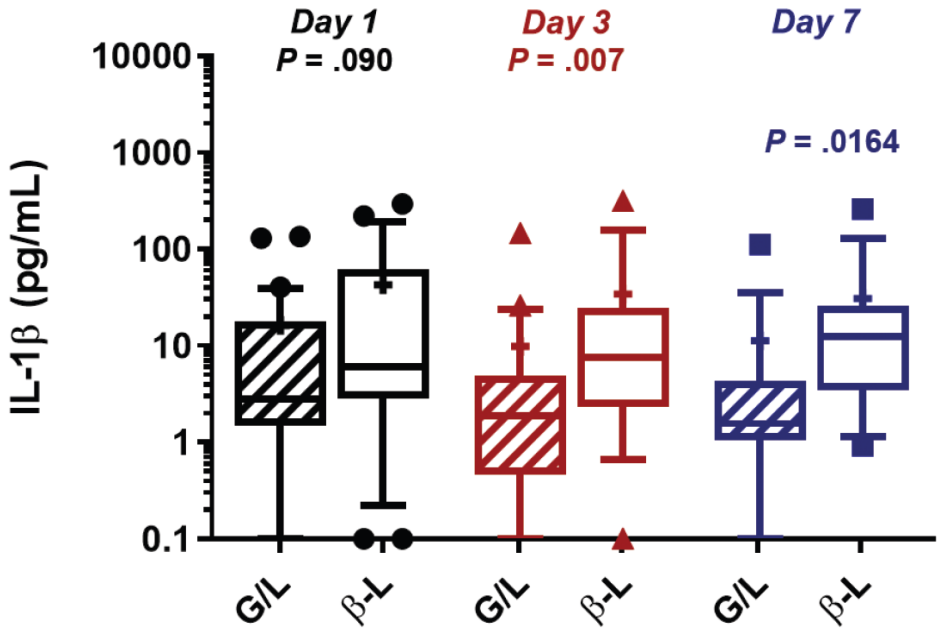
IL-1β concentrations in patient sera on day 1 of presentation compared by outcome of rapid bacteremia clearance (≤4 days) or persistent bacteremia (>4 days).



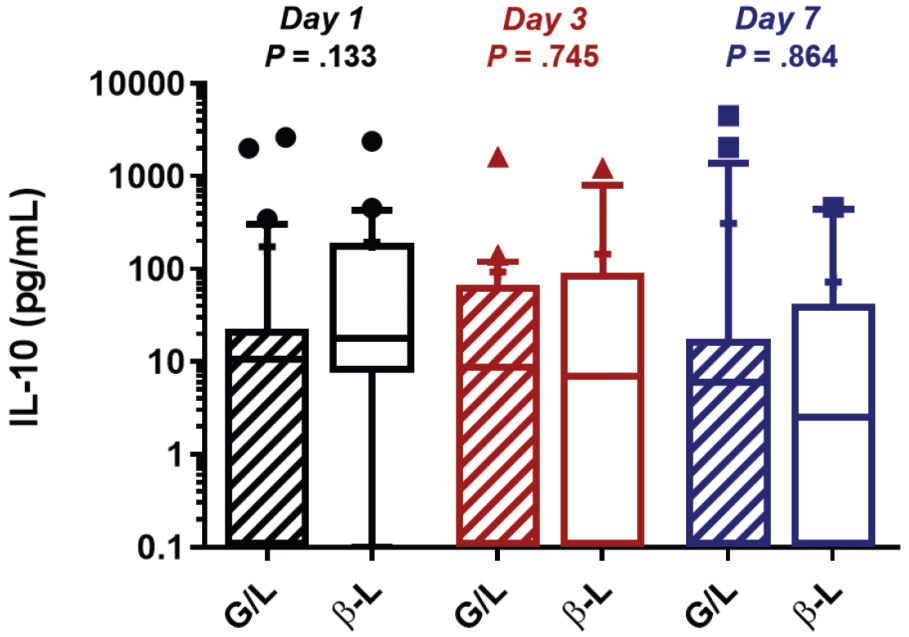
Clinical Infectious Diseases 2020;70(12):2634–40

Interleukin (IL)-1β and IL-10 host responses in patients with SAB determined by antimicrobial therapy

IL-1β concentrations in patient sera treated with G/L or β-L antibiotic at day 1, day 3, and day 7 of therapy.



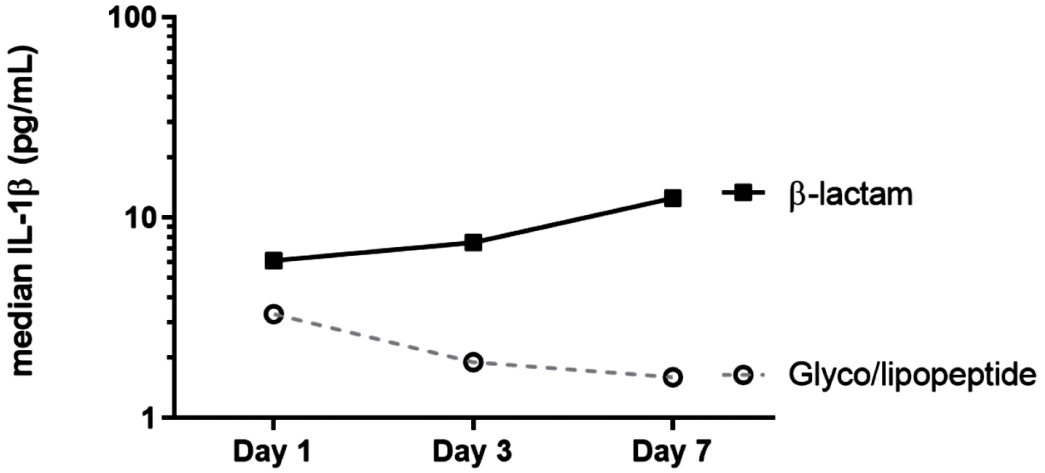
IL-10 concentrations in patient sera treated with G/L or β-L antibiotic at day 1, day 3, and day 7 of therapy.



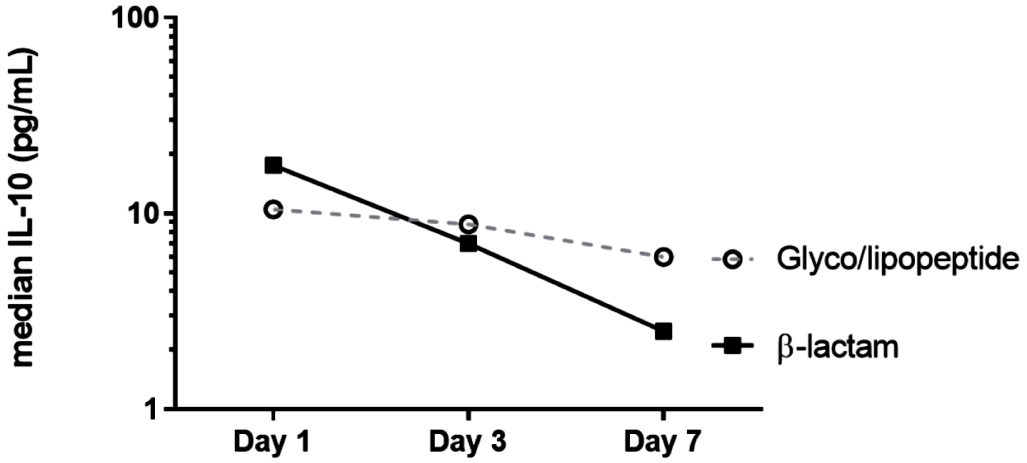
Clinical Infectious Diseases 2020;70(12):2634–40

Interleukin (IL)-1β and IL-10 host responses in patients with SAB determined by antimicrobial therapy

IL-1β concentrations in patient sera treated with G/L or β-L antibiotic: median trend over 7 days.



IL-10 concentrations in patient sera treated with G/L or β-L antibiotic: median trend over 7 days.



Clinical Infectious Diseases 2020;70(12):2634–40

Conclusioni

- Diagnosi corretta di infezione
- Iniziare terapia semi-targeted quando possibile (test rapidi)
- Terapia empirica quando necessario (biomarcatori)
- Ripensare l’infiammazione
- Somministrare al meglio le monoterapie