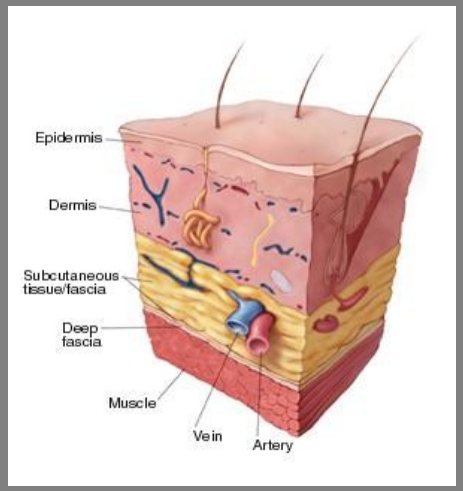
Caso Clinico

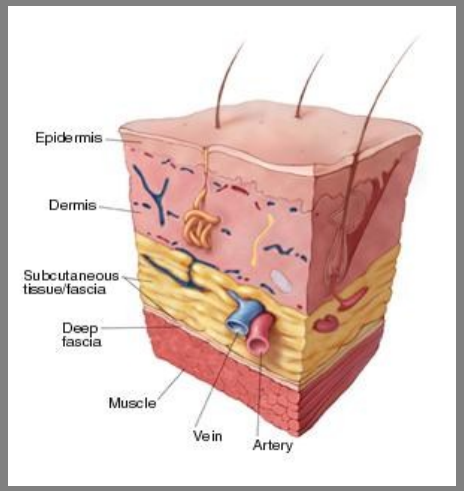
- ✓ M.B.M. donna 34 anni giunge al DEA trasferita da altro nosocomio per comparsa da alcune ore di:
- Iperpiressia (TC 40 °C)
- Spiccata dolorabilità arto inferiore dx
- Alvo diarroico
- ✓ APR: non eventi patologici di rilievo. Non allergie a farmaci
- ✓ Significativa familiarità per diabete mellito

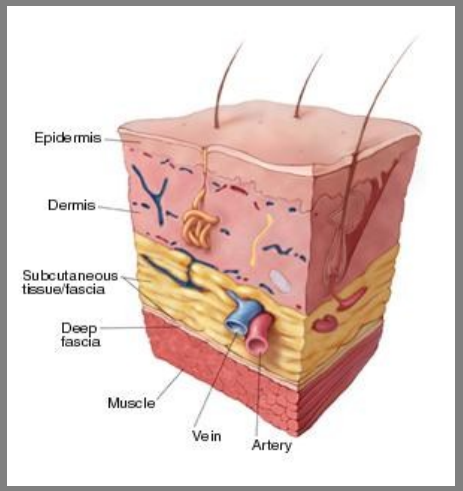
Azienda
Unità Sanitaria Locale
Latina

Condizioni generali gravissime

- Iperpiressia (TC 40°C)
- Vigile, sofferente, anurica
- Diarrea profusa
- Ipotensione (85/40 mmHg)
- Tachipnea (FR 40 °C)
- Tachicardia (FC 120 bpm)
- SatO2 93% in aria ambiente
- IRA (anuria)







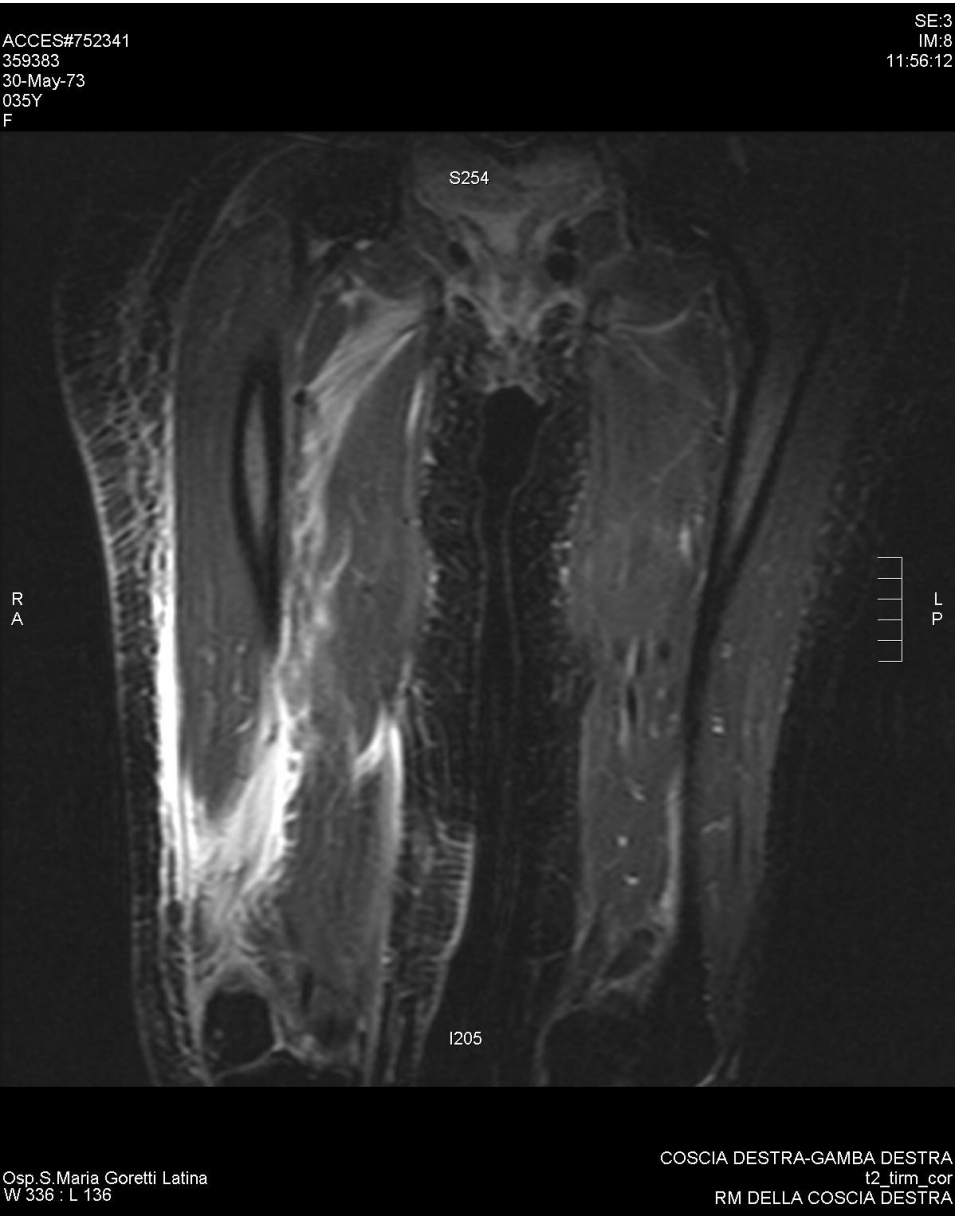
- ✓ Gamba dx: lesione necrotica di circa 8 cm di diametro superficie laterale circondata da area eritematosa
- ✓ Sovrastante piccola lesione ulcerata di circa 1 cm diametro (follicolo pilifero)
- ✓ Spiccata dolorabilità spontanea ed al tatto diffusa dal piede alla coscia

Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score

Variable, Units	β	Score
C-Reactive Protein, mg/L		
<150	0	0
≥150	3.5	4
Total white cell count, per mm^3		
<15	0	0
15–25	0.5	1
>25	2.1	2
Hemoglobin, g/dL		
>13.5	0	0
11–13.5	0.6	1
<11	1.8	2
Sodium, mmol/L		
≥135	0	0
<135	1.8	2
Creatinine, μmol/L		
≤141	0	0
>141	1.8	2
Glucose, mmol/L		
≤10	0	0
>10	1.2	1

Final model constructed using factors found to be independently predictive of necrotizing fasciitis on multivariate analysis. β values are the regression coefficients of our model after adjusting for a shrinkage factor of .89. The maximum score is 13; a score of ≥6 should raise the suspicion of necrotizing fasciitis and a score of ≥8 is strongly predictive of this disease. To convert the values of glucose to mg/dL, multiply by 18.015. To convert the values of creatinine to mg/dL, multiply by 0.01131.

SCORE della pz: 8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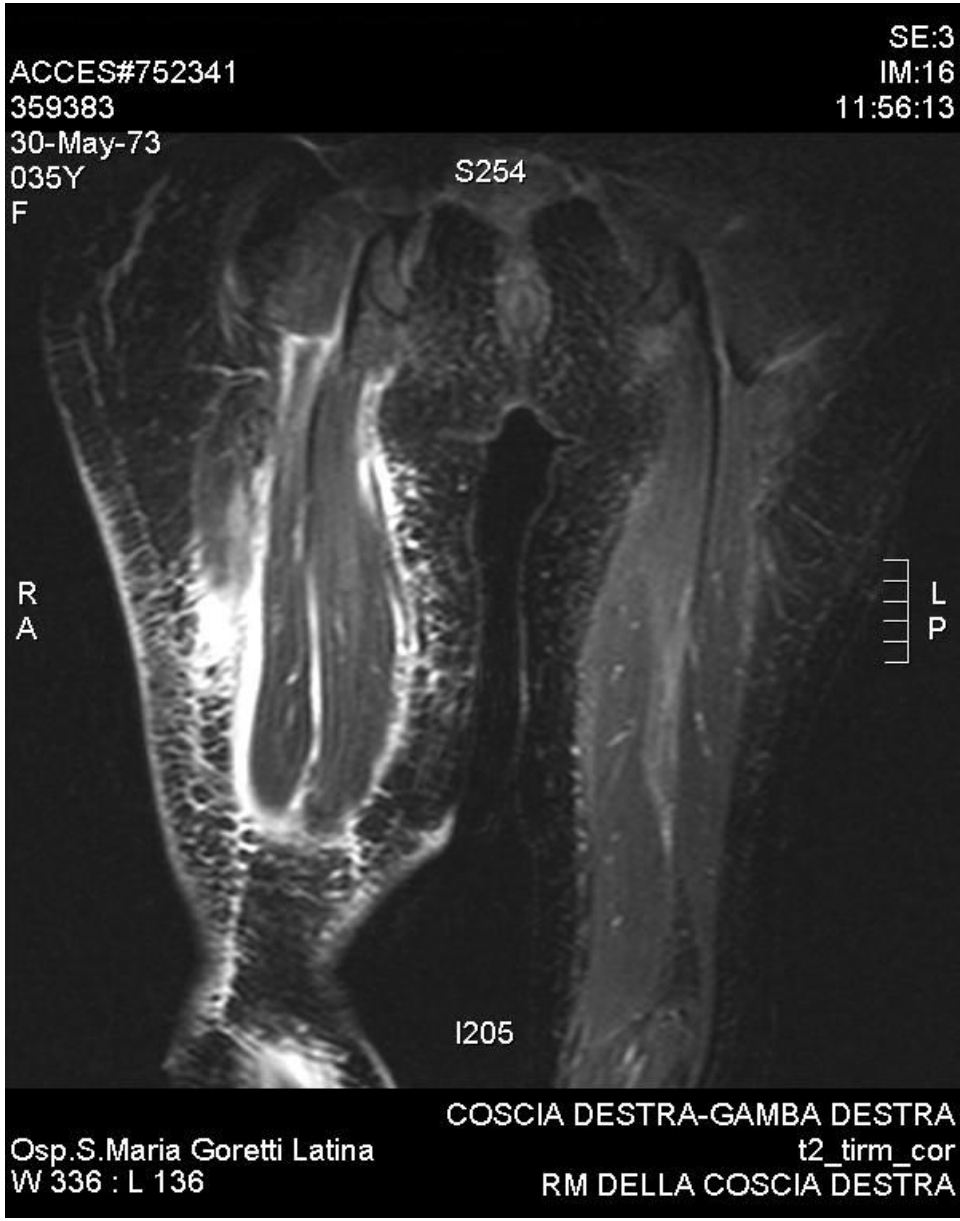
30-May-73
035Y
F
SE:3
IM:8
11:56:12
S254
R
A
L
P
I205
Osp.S.Maria Goretti Latina
W 336 : L 136
COSCIA DESTRA-GAMBA DESTRA
t2_tirm_cor
RM DELLA COSCIA DESTRA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W 336 : L 136
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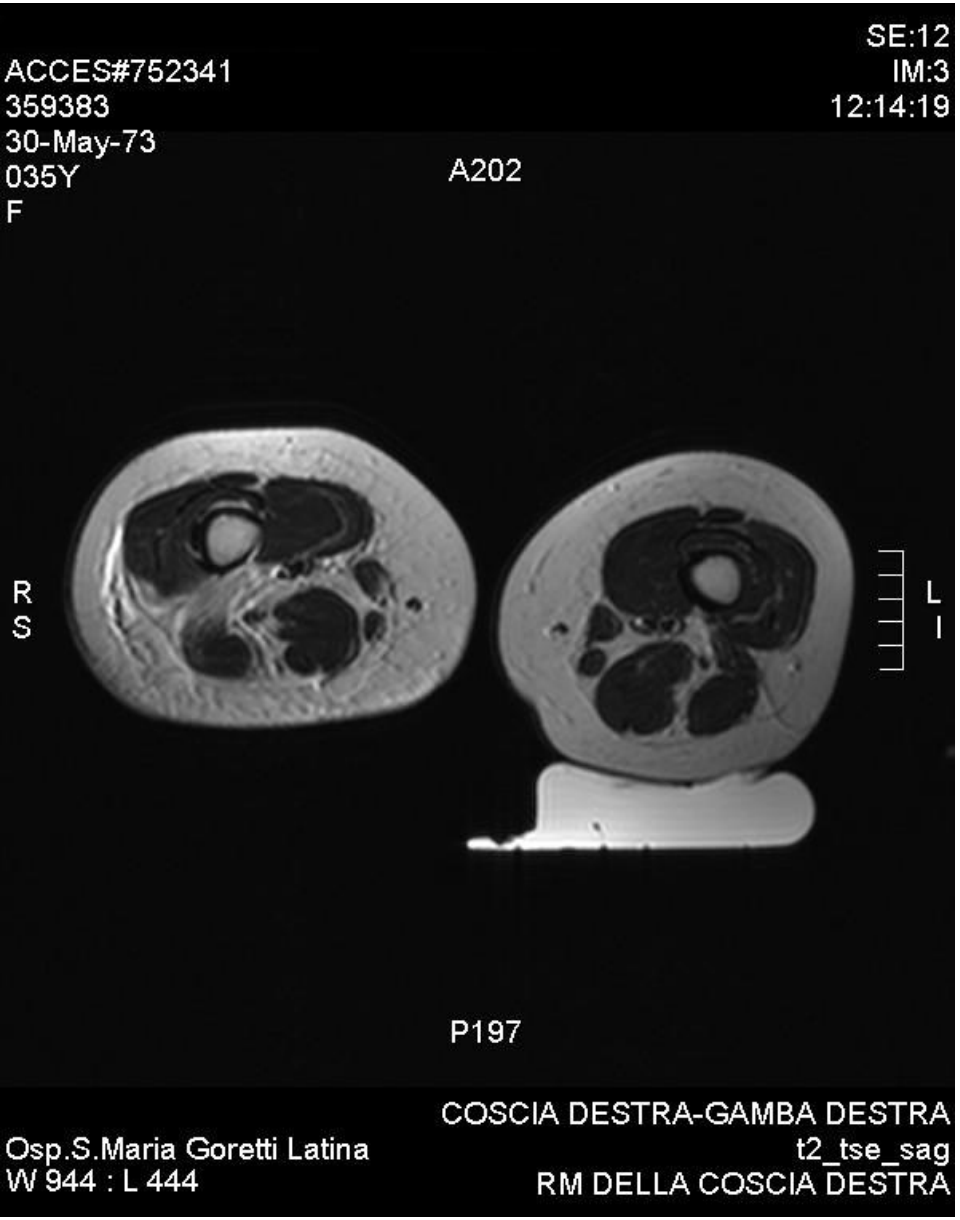
t2_tirm_cor
RM DELLA COSCIA DESTRA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30-May-73
035Y
A202
F
R
S
L
I
P197
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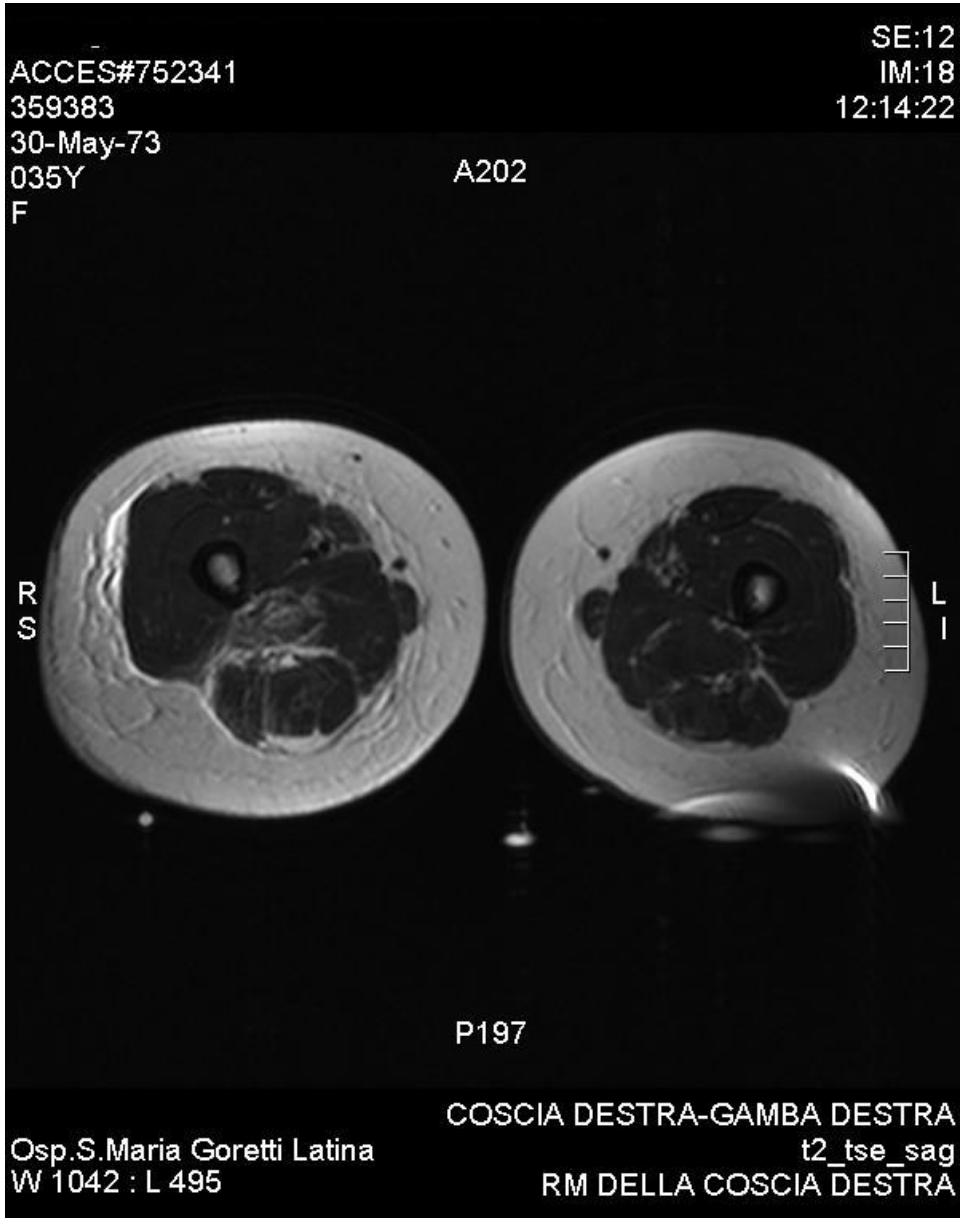
Osp.S.Maria Goretti Latina
t2_tse_sag
W 944 : L 444
RM DELLA COSCIA DESTRA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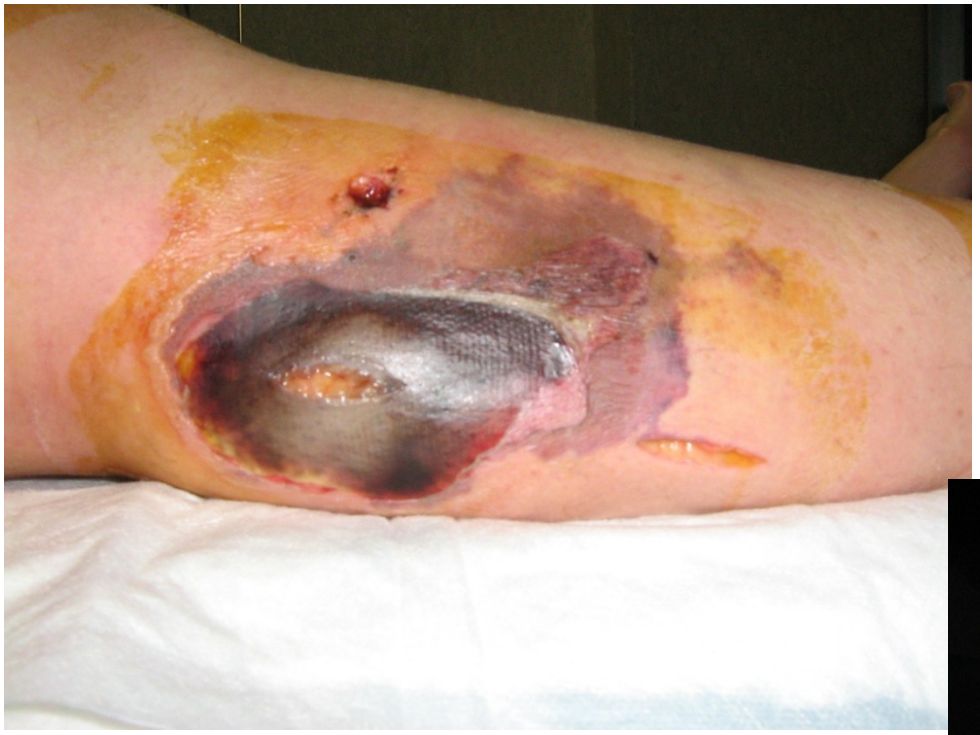
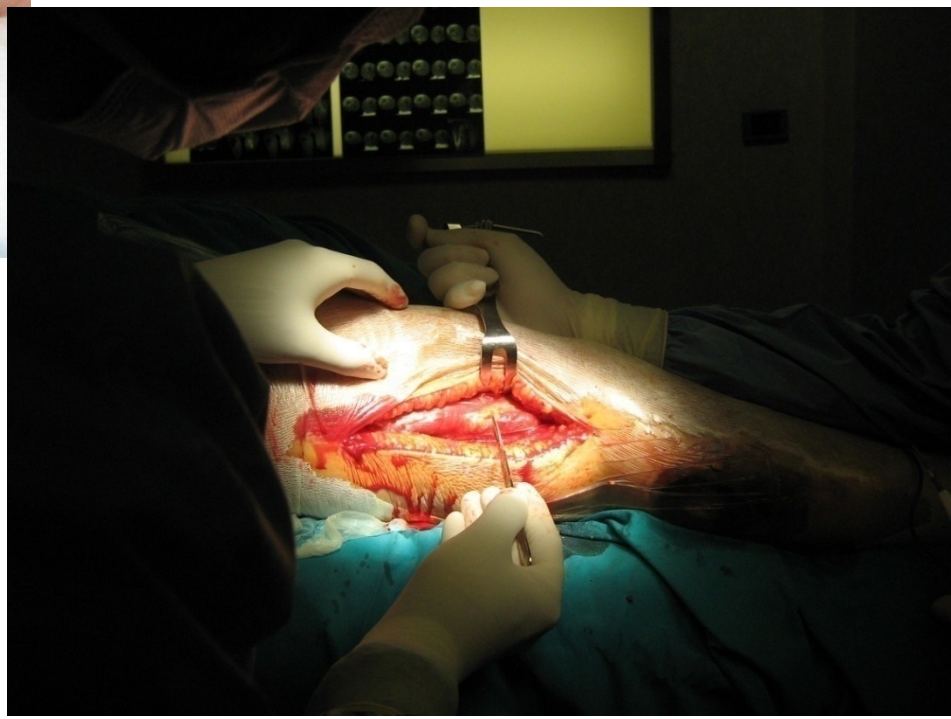
035Y
A202
F
R
S
L
I
P197
COSCIA DESTRA-GAMBA DESTRA
Osp.S.Maria Goretti Latina
t2_tse_sag
W 1042 : L 495
RM DELLA COSCIA DESTRA

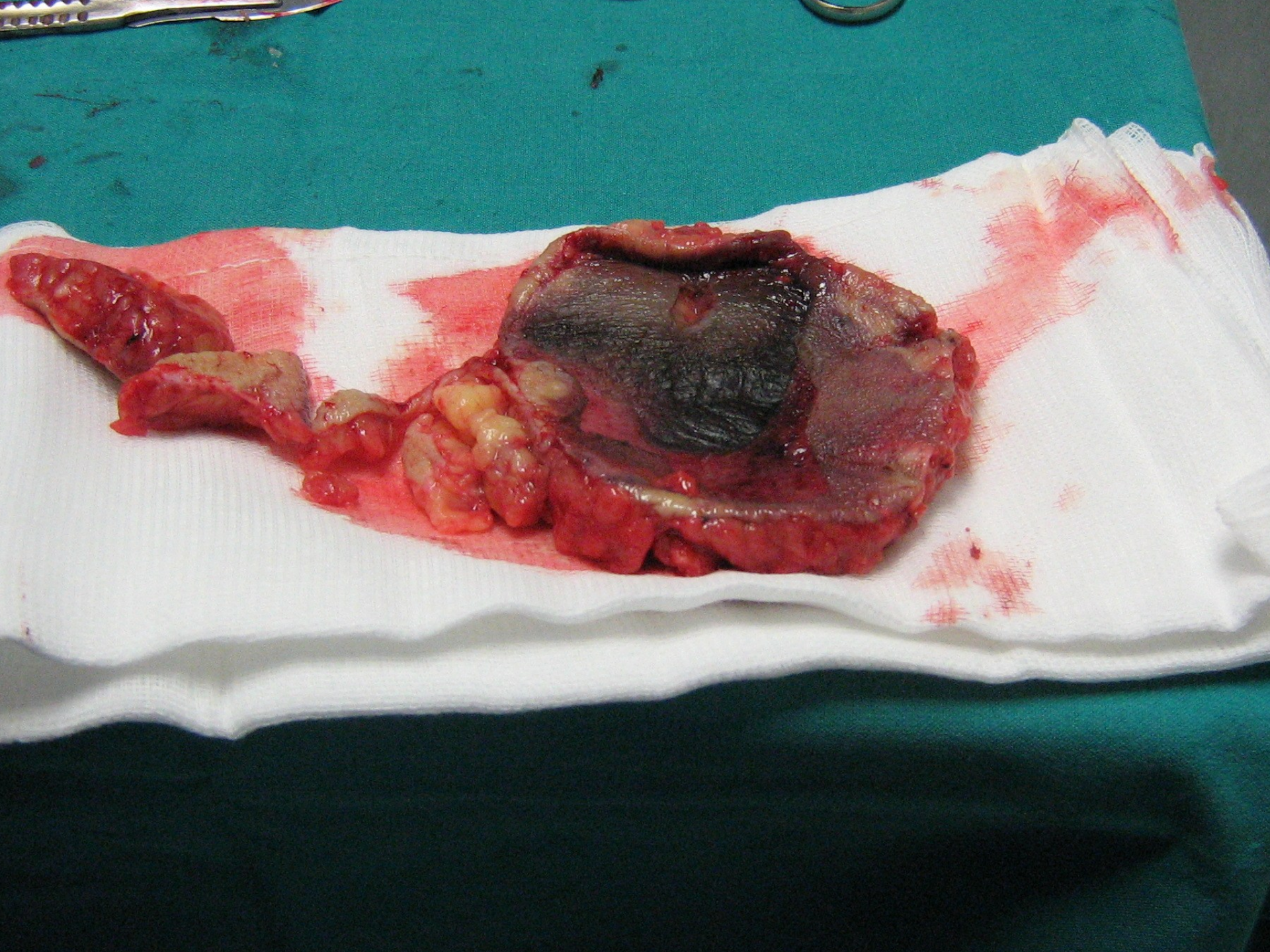
Intervento chirurgico

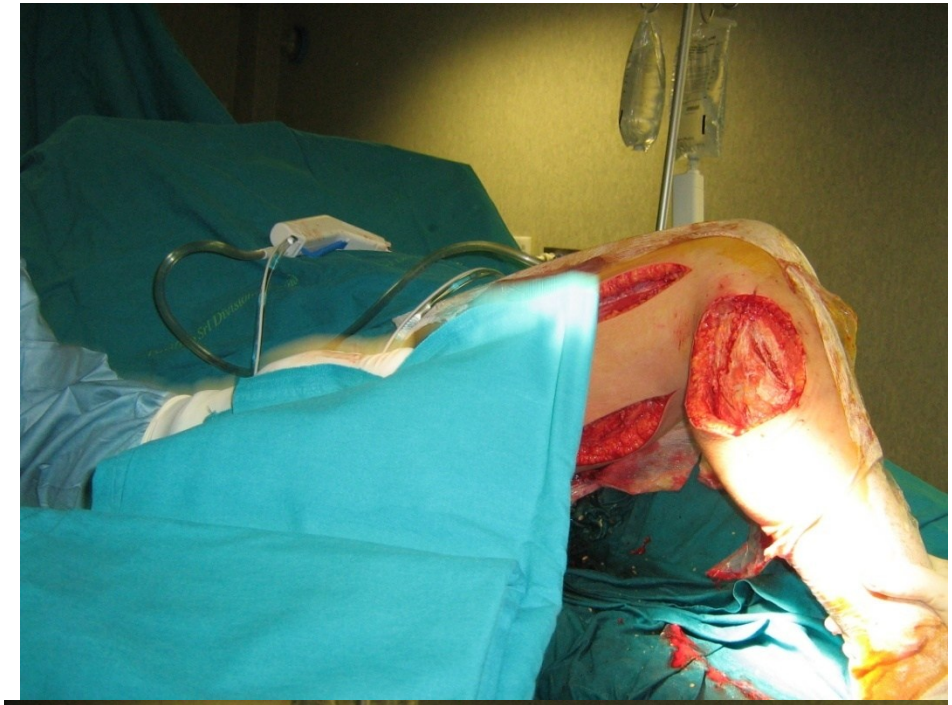
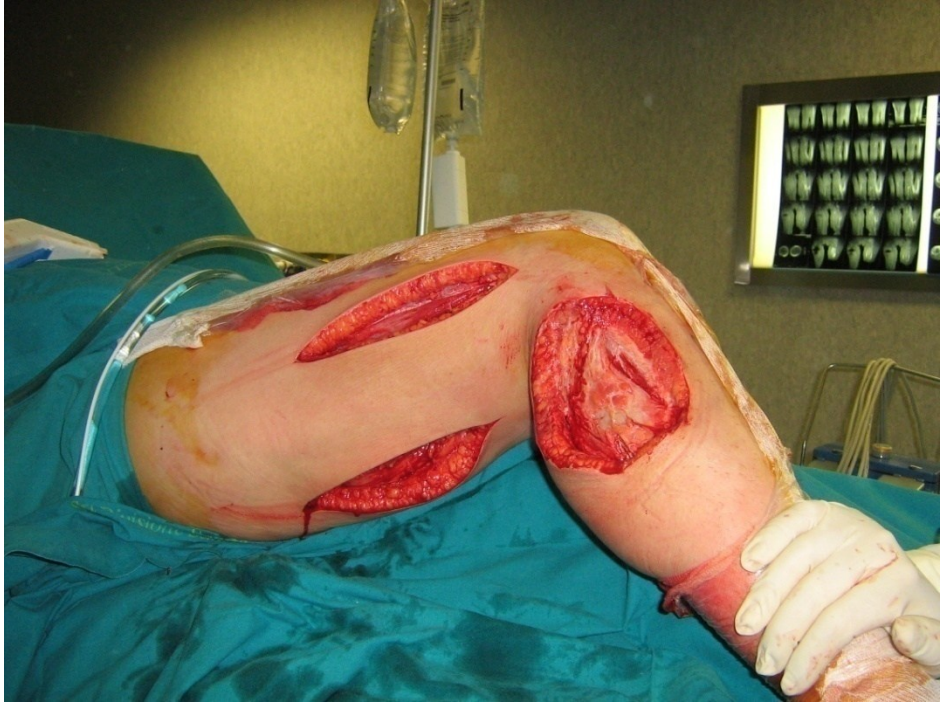
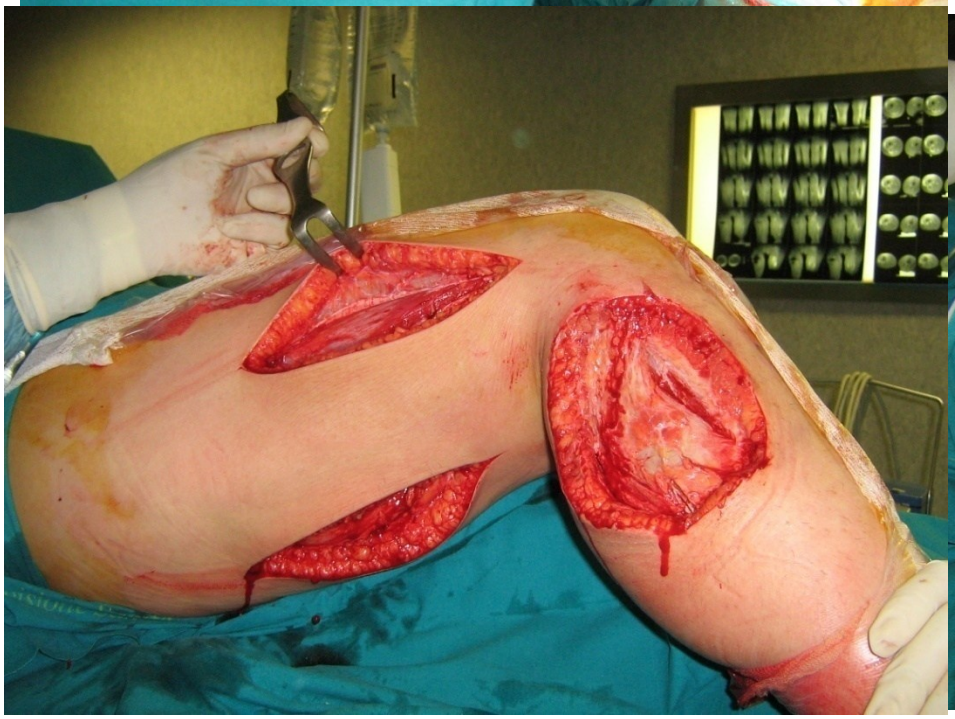
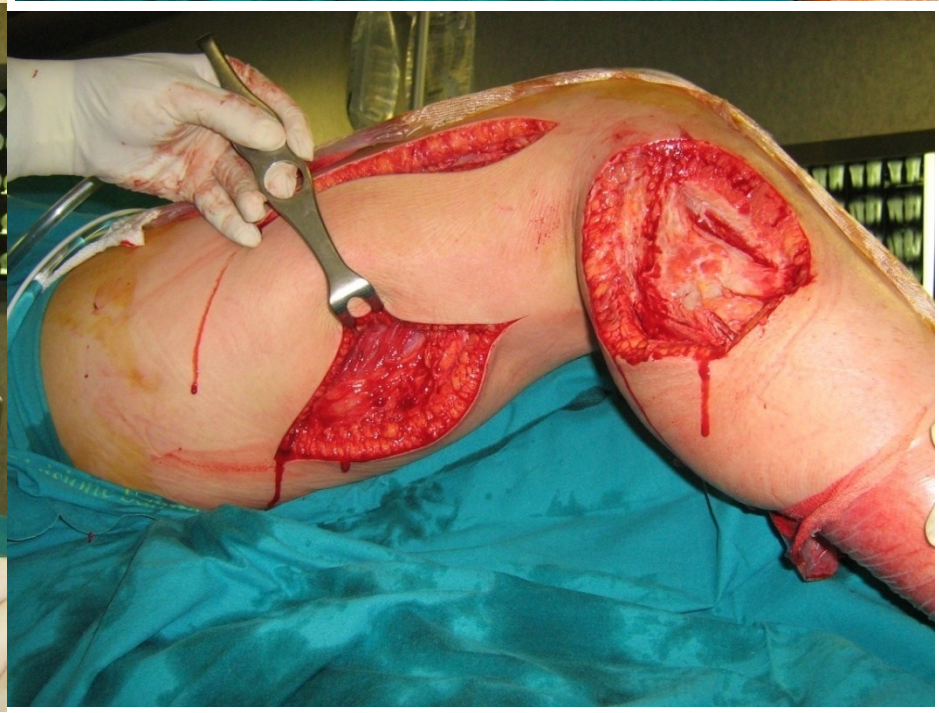
- **Intervento di fasciotomia allargata**

- **La paziente ha inoltre effettuato sedute di camera iperbarica**

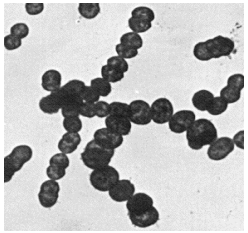






Esami microbiologici



- Tampone Intraoperatorio
- Esame colturale
- Ricerca DNA batterico

STREPTOCOCCO β emolitico di gruppo A

Sepsi

SAPIENZA
UNIVERSITÀ DI ROMA

Prof. Claudio Mastroianni

La sepsi è una sindrome eterogenea che risulta da una complessa interazione tra difese dell'ospite e patogeno invasore

Sepsis

(as 700 BCE, the Greeks recognized Σήψις)

- **Common and lethal syndrome: although outcomes have improved, mortality remains high.**
- **No specific anti-sepsis treatments exist;**
- **Early recognition**
- **Therapeutic measures to be started rapidly, including:**
  - **administration of appropriate antibiotics**
  - **source control measures when necessary**
  - **resuscitation with intravenous fluids and vasoactive drugs when needed.**

Sepsi: una sfida per il sistema sanitario

- **750.000 casi/anno**
- **Sepsi severa: 51-95 pz. per 100.000 abitanti**
- **Negli USA 500 persone muoiono al giorno per sepsi grave**
  - Incremento nei pazienti anziani
  - Malattie croniche/comorbidità
  - Aumento delle procedure invasive
  - Aumentato uso degli antibiotici/resistenza
  - Pazienti immunosoppressi/steroidi

Surviving sepsis campaigne

- Riconoscimento
- Principi guida di trattamento
- Progettazione bundles terapeutici relativi alle prime 6 ore di trattamento ed in misura specifica per il Dipartimento di Emergenza
- Modifica dell'organizzazione ospedaliera sul principio delle "golden hours" già in atto per l'IMA o lo stroke
- Riprogettazione della risposta assistenziale orientata al principio della intensità assistenziale

Intensive Care Med
DOI 10.1007/s00134-007-0934-2

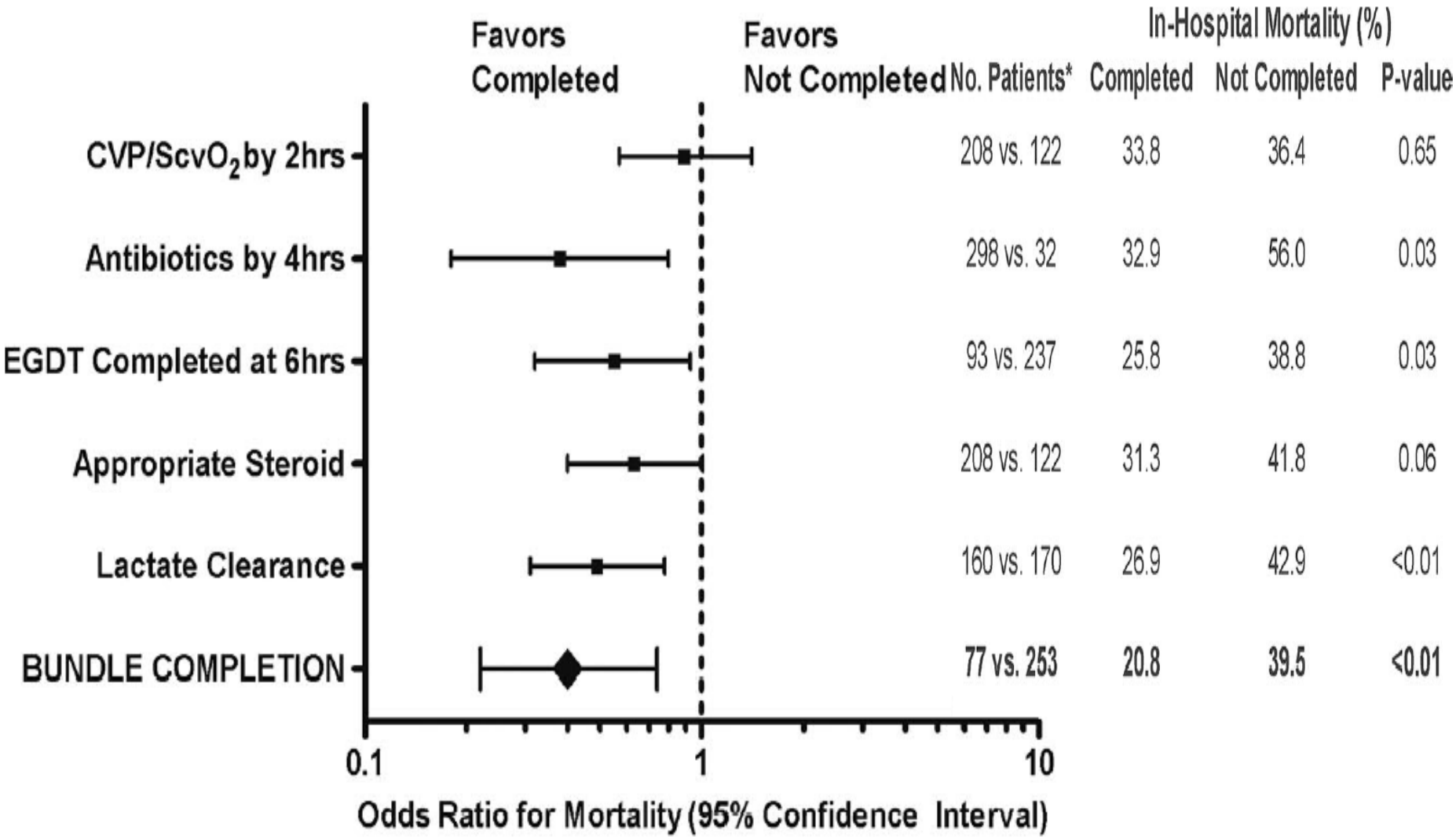
SPECIAL ARTICLE

Perché ?

Patologia acuta	**Mortalità (%)**
Stroke	9.3
Rottura di aneurisma aortico addominale	50.0 – 73.3
IMA	2.7 – 9.6
Sepsi	28 – 50

Implementation of a bundle of quality indicators for the early management of severe sepsis and septic shock is associated with decreased mortality

Nguyen BH et al, Crit Care Med 2007; 35 (4): 1106-1112



Sepsis incidence and outcome: Contrasting the ICU with the hospital ward

Esteban A et al, Crit Care Med 2007

Impiego della terapia Intensiva e mortalità

	Sepsi	Sepsi grave	Shock settico
numero	702	199	59
Incidenza (x 100,000)	367	104	31
Ricovero in UTI %	12%	32%	75%
Mortalità non in UTI		36%	53.3%
mortalità in UTI		11%	33%

Prima qualche definizione….

- ***Batteriemia:*** i batteri responsabili di un processo morboso localizzato (polmonite,enterite) invadono, anche se transitoriamente, il circolo ematico, dove possono essere identificati mediante adeguate indagini microbiologiche(emocolture)

  Può determinare la diffusione metastatica dell'infezione in altre sedi dell'organismo

- ***SEPSI:*** risposta infiammatoria sistemica che in genere consegue alla presenza di gravi e consistenti infezioni (polmone, addome, vie urinarie)

  -invasione microbica del circolo ematico non è indispensabile dal momento che la diffusione sistemica dei prodotti microbici è sufficiente a innescare tale risposta.

  -massiccia rilascio di citochine infiammatorie(TNF, IL-1, IL-6, IFN-γ, IL-12, IL-8)

What is sepsis?

SIRS

at least 2 of the following

T°>38°C or < 37°C

•Pulse >90 beats/ min

•RR > 20 breaths/min

•WBC > 12,000 cells/ml,
<4,000 cells/ml
or >10% immature forms

Sepsis

SIRS plus Documented Infection

Severe Sepsis

Sepsis plus organ failure

Septic shock

Severe sepsis and

•Hypotension despite
adequate ressucitation

Definizioni

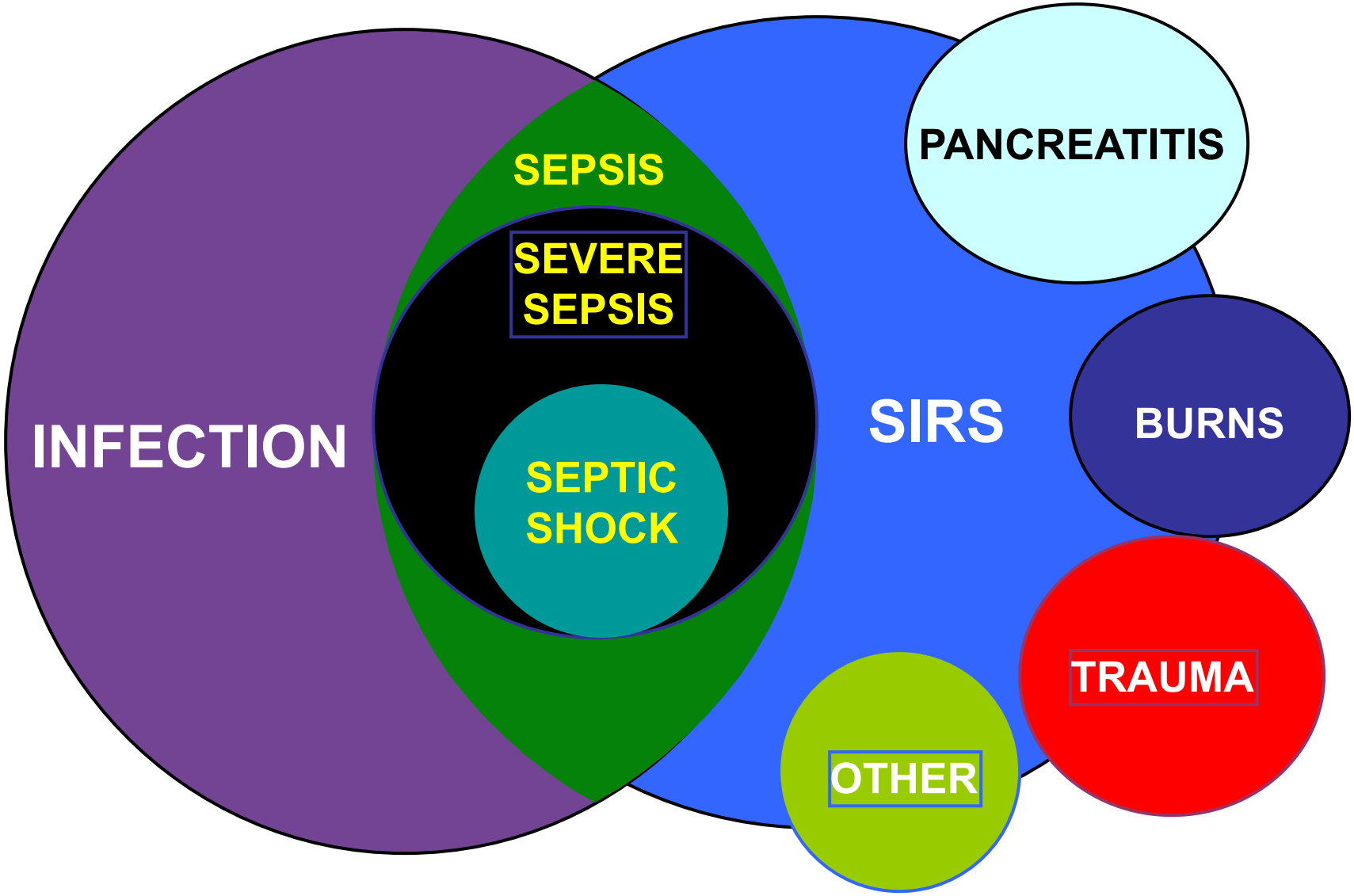
SIRS

Sindrome da Risposta Infiammatoria Sistemica: risposta infiammatoria sistemica ad una varietà di insulti clinici di una certa gravità.

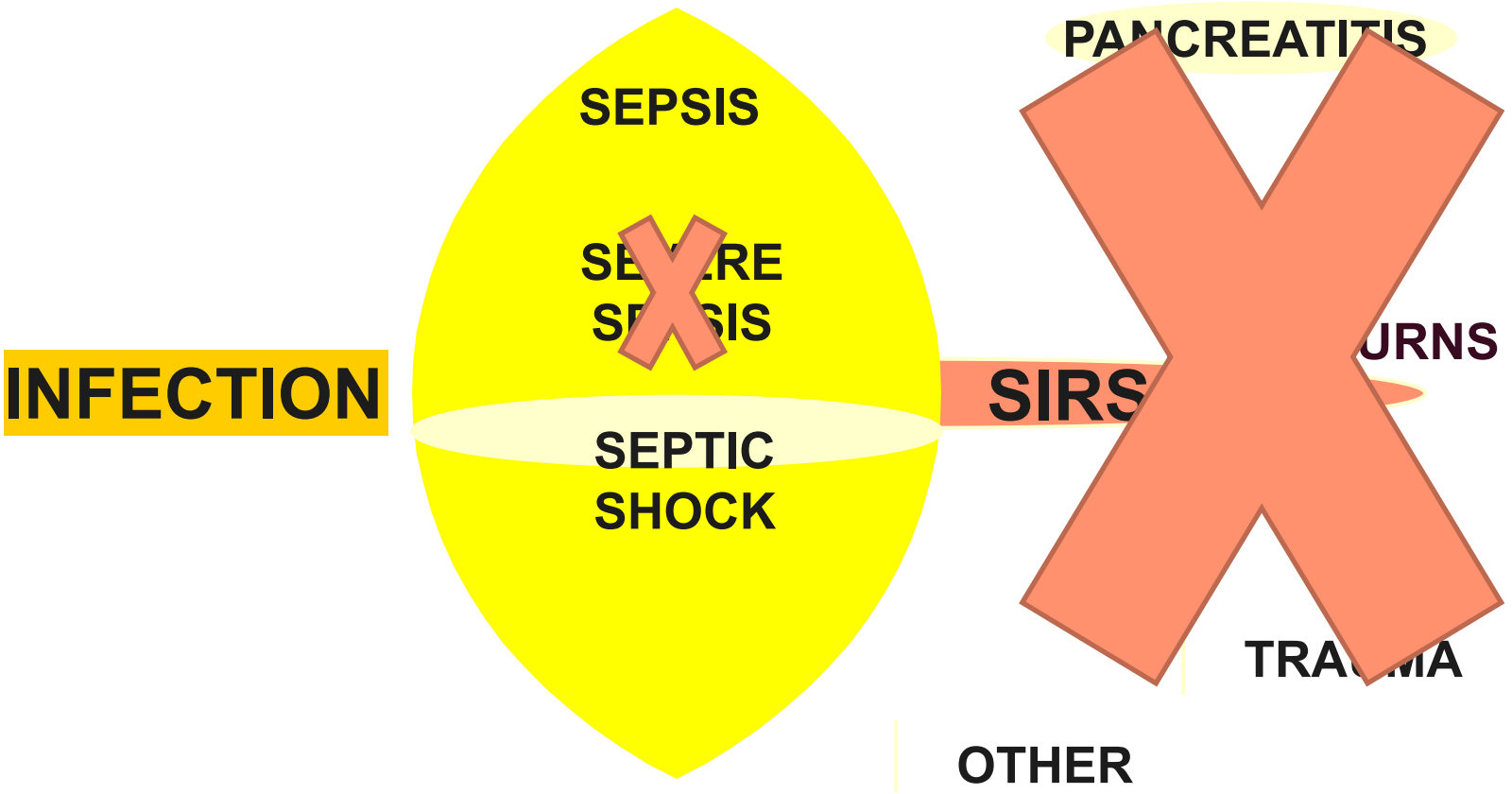
E' caratterizzata da due o più delle seguenti condizioni:

- temperatura >38°C o < 36 ° C
- frequenza cardiaca > 90 battiti/minuto
- frequenza respiratoria > 20 atti/min. o $PaCO_2$<32 mmHg
- globuli bianchi >12000/mmc, < 4000/mmc o più del 10% di forme immature

SIRS, Sepsi, Sepsi Severa e Shock Settico: quadri strettamente collegati



SIRS, Sepsi, Sepsi Severa e Shock Settico



Bone et al.1992;101:1644

Definitions (ACCP/SCCM, 1991)

- **Systemic Inflamatory Response Syndrome (SIRS):** **the systemic inflammatory response to a variety of severe clinical insults (For example, infection).**

- **Sepsis:** **the systemic inflammatory response to infection.**

Clinical Review & Education

Special Communication | CARING FOR THE CRITICALLY ILL PATIENT

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

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

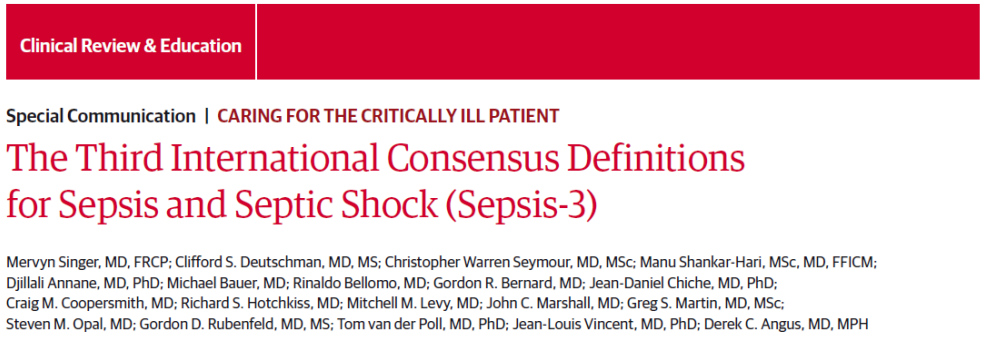
JAMA. 2016;315(8):801-810. doi:10.1001/jama.2016.0287

Increased Understanding of Sepsis Pathobiology

- Pathways are activated with differing kinetics in individuals with sepsis and involve
  - inflammatory and anti-inflammatory signaling
  - innate and adaptive immune response, apoptosis, mitochondrial function
  - translational and transcriptional regulation, and oxidative biology

The Definition of Sepsis

Sepsis is life-threatening organ dysfunction caused by a dysregulated host response to infection



Clinical Review & Education

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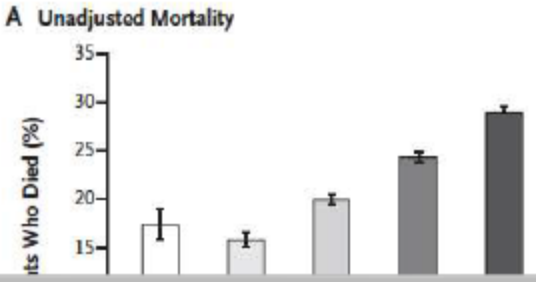
SIRS Sensitivity

Systemic Inflammatory Response Syndrome Criteria in Defining Severe Sepsis

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

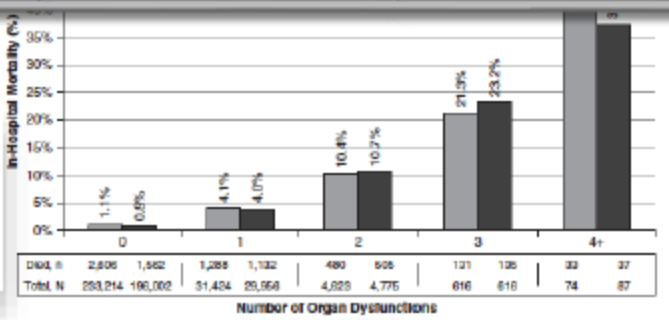
N Engl J Med 2015;372:1629-38.



SIRS is an *appropriate* response to infection – or any other stimulus that activates inflammation

Am J Respir Crit Care Med 2015; 192:958-964

Conclusions: Almost half of patients hospitalized on the wards developed SIRS at least once during their ward stay. Our findings suggest that screening ward patients using SIRS criteria for identifying those with sepsis would be impractical.



Society of Critical Care Medicine


SIRS vs SOFA

Table 1. Sequential [Sepsis-Related] Organ Failure Assessment Score[a]

System	Score 0	1	2	3	4
Respiration					
Pao_2/Fio_2, mm Hg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation					
Platelets, $\times 10^3/\mu L$	≥150	<150	<100	<50	<20
Liver					
Bilirubin, mg/dL (μmol/L)	<1.2 (20)	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (204)
Cardiovascular	MAP ≥70 mm Hg	MAP <70 mm Hg	Dopamine <5 or dobutamine (any dose)[b]	Dopamine 5.1-15 or epinephrine ≤0.1 or norepinephrine ≤0.1[b]	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1[b]
Central nervous system					
Glasgow Coma Scale score[c]	15	13-14	10-12	6-9	<6
Renal					
Creatinine, mg/dL (μmol/L)	<1.2 (110)	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440)	>5.0 (440)
Urine output, mL/d				<500	<200

Abbreviations: Fio_2, fraction of inspired oxygen; MAP, mean arterial pressure; Pao_2, partial pressure of oxygen.

[a] Adapted from Vincent et al.[27]

[b] Catecholamine doses are given as μg/kg/min for at least 1 hour.

[c] Glasgow Coma Scale scores range from 3-15; higher score indicates better neurological function.

HOW CAN QUICKLY RECOGNIZE SEPSIS

- **q**uick
- **S**epsis-related
- **O**rgan
- **F**ailure
- **A**ssesment

qSOFA

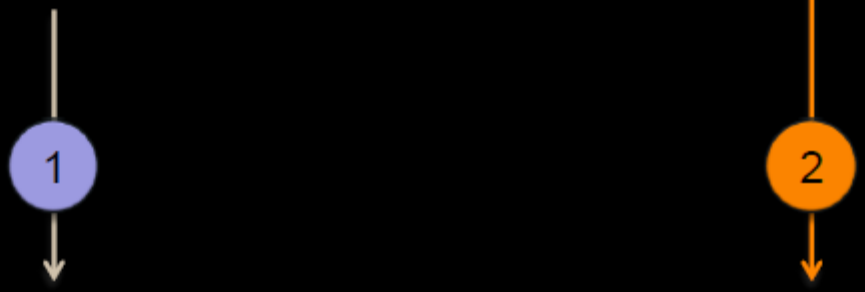
A simple tool to identify infected patients who are likely to be septic outside ICU

qSOFA


Hypotension
Systolic BP
<100 mmHg
Altered
Mental
Status
Tachypnea
RR >22/Min
Score of ≥2 Criteria Suggests a Greater Risk of a Poor Outcome

What is sepsis ?

A life threatening organ dysfunction caused by a dysregulated host response to infection.



Among patients with suspected infection,

who is really sick?

- Outside the ICU, patients with suspected or presumed infection who are highly likely to have poor outcomes can be clinically identified using qSOFA
  - **SBP < 100mm Hg**
  - **RR > 22 breath/min**
  - **Altered mental status**

- In the ICU, patients with suspected or presumed infection who are highly likely to have poor outcomes can be clinically identified by the presence of 2 or more SOFA points

Consensus definitions of Sepsis-3: no longer include SIRS

- Components of SIRS include tachycardia, tachypnea, hyperthermia or hypothermia, and abnormalities in peripheral white blood cell count.

- Many studies have shown that the presence of SIRS is nearly ubiquitous in hospitalized patients and occurs in many benign conditions, both related and not related to infection, **and thus is not adequately specific for the diagnosis of sepsis.**

«L'uso corrente della definizione di SEPSI in base alla presenza di 2 o più parametri di SIRS è considerato in maniera unanime non funzionale…»

Box 1. SIRS (Systemic Inflammatory Response Syndrome)

Two or more of:

- Temperature >38°C or <36°C
- Heart rate >90/min
- Respiratory rate >20/min or $Paco_2$ <32 mm Hg (4.3 kPa)
- White blood cell count >12 000/mm^3 or <4000/mm^3 or >10% immature bands

From Bone et al.[9]

«…i criteri di SIRS non indicano necessariamente una risposta disfunzionale e minacciosa per la vita. Sono presenti in molti pazienti ospedalizzati, inclusi quelli che non svilupperanno mai infezione, né indicano quelli con evoluzione in prognosi peggiore»

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

qSOFA (1)

- Given the limited use of SOFAs outside the ICU (no time to sit down in ED), and its complicated nature, the quick SOFA (qSOFA) has been suggested as a bedside aide-memoire to identify sepsis
- The SOFA score is not intended to be used as a tool for patient management but as a means to clinically characterize a septic patient

qSOFA (2)

- Although qSOFA is less robust than a SOFA score of 2 or greater in the ICU, it does not require laboratory tests and can be assessed quickly and repeatedly.
- qSOFA criteria be used to prompt clinicians to further investigate:
  - **for possible infection not previously recognized**
  - **for organ dysfunction**
  - **to initiate or escalate therapy as appropriate**
  - **to consider referral to critical care or increase the frequency of monitoring**

In pratica…

- Si passa da una definizione diagnostica a una definizione prognostica

- PUNTO DI FORZA: rapido assessment del paziente a rischio di potenziale evoluzione settica
- PUNTO DI DEBOLEZZA: sovrastima delle diagnosi di sepsi

The Definition of Septic Shock

- What tangibly differentiates septic shock from sepsis ?
  - MORTALITY
    - Septic shock is "really, really, really bad" sepsis

Septic shock is a subset of sepsis in which profound circulatory, cellular and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone

What is septic shock ?

A subset of sepsis in which

profound circulatory, cellular and metabolic abnormalities are associated with

a greater **risk** of mortality than with sepsis alone

1

Among patients with sepsis (that is, who have suspected infection and are *really sick*)

2

Hospital mortality

2

Who is *really, really, really* sick ?
(eg, has a 50:50 chance of dying)

New Clinical Criteria for Septic Shock

Septic shock is a subset of sepsis in which profound circulatory, cellular and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone

- Patients with septic shock can be clinically identified if, despite adequate resuscitation,

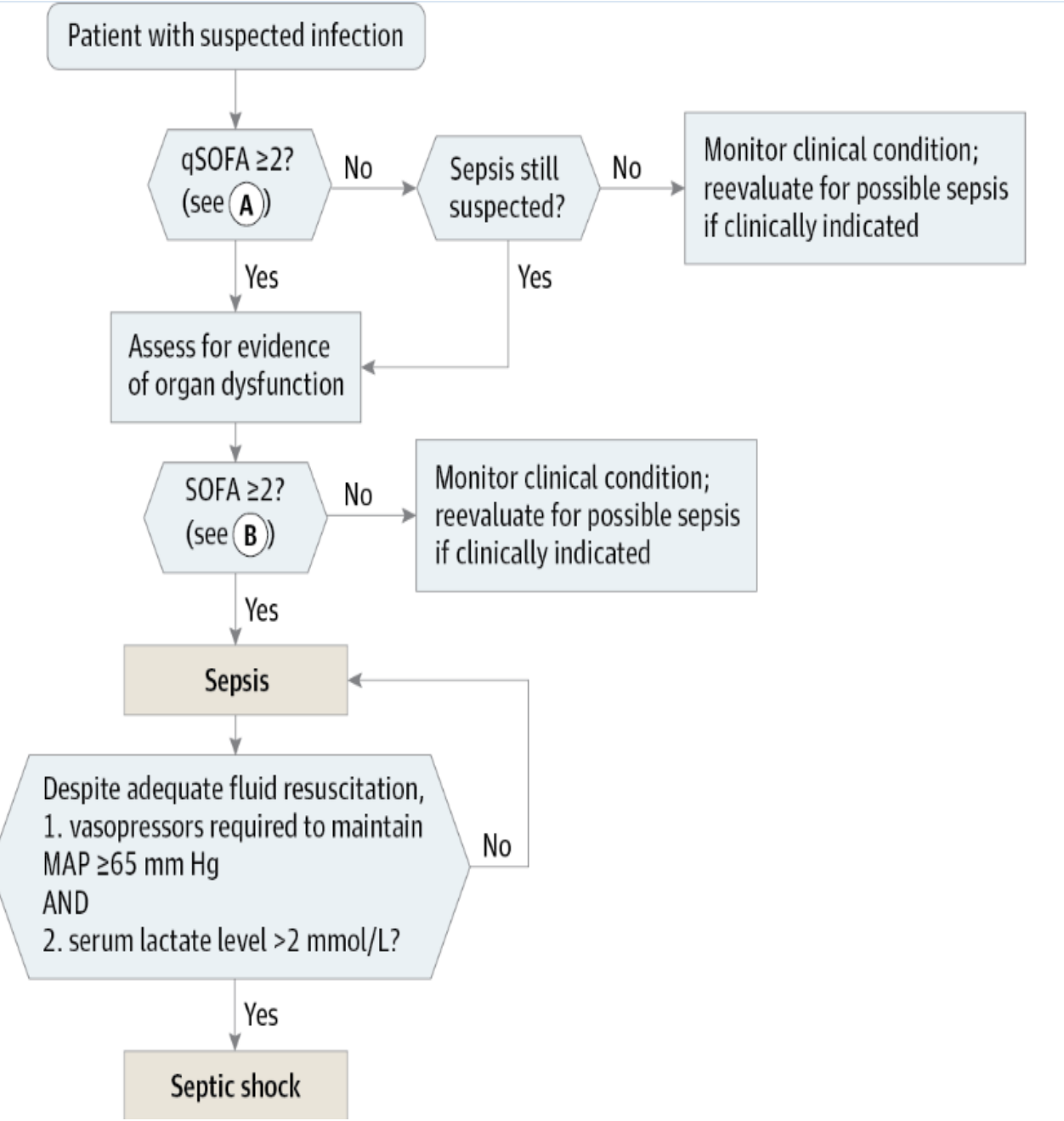
  ▪ They require **vasopressors to maintain MAP ≥65 mmHg**

  AND

  ▪ Their serum **lactate level is > 2 mmol/l**

Sepsis I-II: Sepsis = [Suspected infection] + [SIRS]

Sepsis-III: Sepsis = [Suspected infection] + [qSOFA] + [SOFA]



A qSOFA Variables

- Respiratory rate
- Mental status
- Systolic blood pressure

B SOFA Variables

- PaO_2/FiO_2 ratio
- Glasgow Coma Scale score
- Mean arterial pressure
- Administration of vasopressors with type and dose rate of infusion
- Serum creatinine or urine output
- Bilirubin
- Platelet count

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Derivation, Validation, and Potential Treatment Implications of Novel Clinical Phenotypes for Sepsis

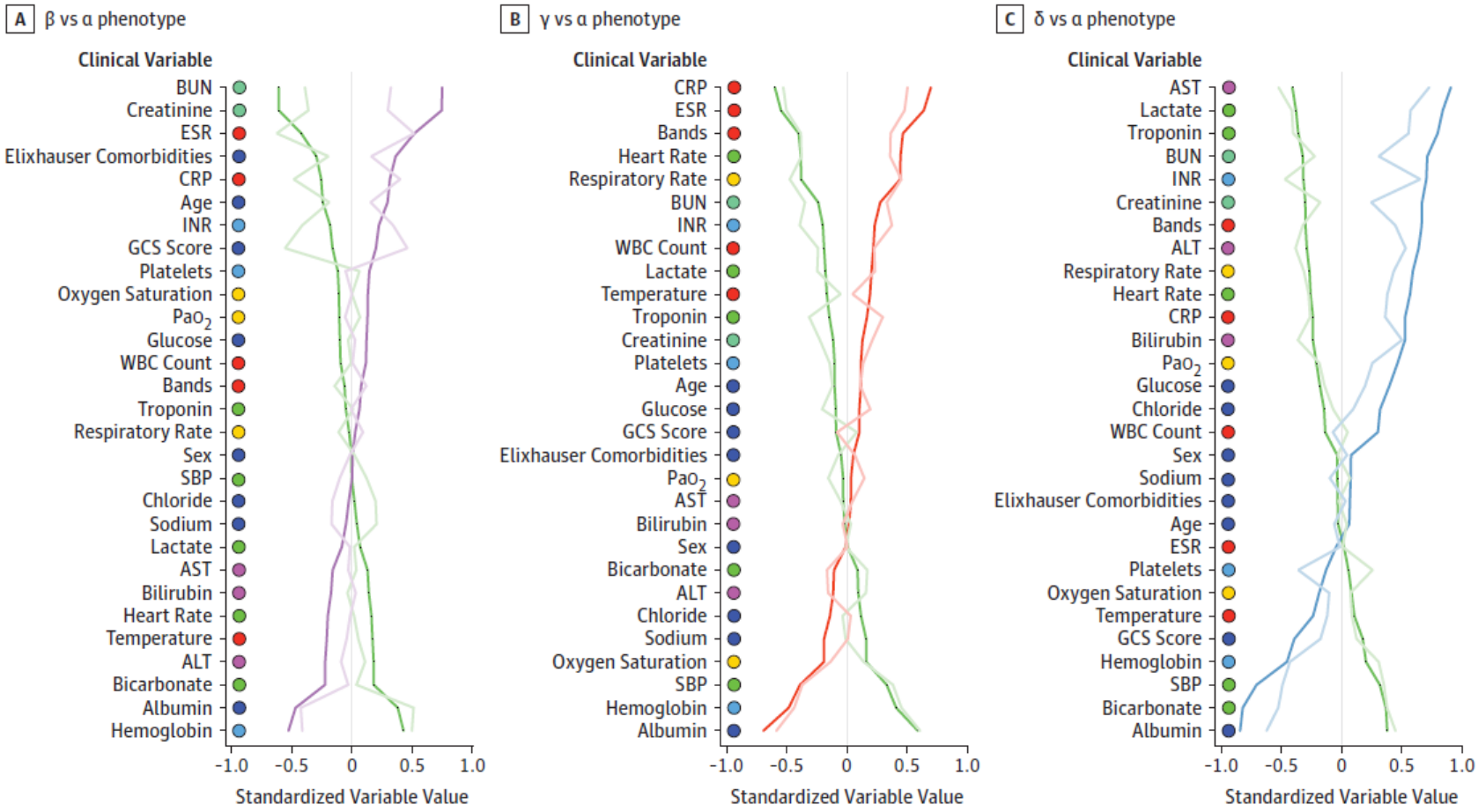
Christopher W. Seymour, MD, MSc; Jason N. Kennedy, MS; Shu Wang, MS; Chung-Chou H. Chang, PhD; Corrine F. Elliott, MS; Zhongying Xu, MS; Scott Berry, PhD; Gilles Clermont, MD, MSc; Gregory Cooper, MD, PhD; Hernando Gomez, MD, MPH; David T. Huang, MD, MPH; John A. Kellum, MD, FACP, MCCM; Qi Mi, PhD; Steven M. Opal, MD; Victor Talisa, MS; Tom van der Poll, MD, PhD; Shyam Visweswaran, MD, PhD; Yoram Vodovotz, PhD; Jeremy C. Weiss, MD, PhD; Donald M. Yealy, MD, FACEP; Sachin Yende, MD, MS; Derek C. Angus, MD, MPH

EDITORIAL

New Phenotypes for Sepsis

The Promise and Problem of Applying Machine Learning and Artificial Intelligence in Clinical Research

William A. Knaus, MD; Richard D. Marks, JD


A β vs α phenotype
Clinical Variable
BUN
Creatinine
ESR
Elixhauser Comorbidities
CRP
Age
INR
GCS Score
Platelets
Oxygen Saturation
PaO2
Glucose
WBC Count
Bands
Troponin
Respiratory Rate
Sex
SBP
Chloride
Sodium
Lactate
AST
Bilirubin
Heart Rate
Temperature
ALT
Bicarbonate
Albumin
Hemoglobin
-1.0 -0.5 0 0.5 1.0
Standardized Variable Value
B γ vs α phenotype
Clinical Variable
CRP
ESR
Bands
Heart Rate
Respiratory Rate
BUN
INR
WBC Count
Lactate
Temperature
Troponin
Creatinine
Platelets
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Standardized Variable Value
C δ vs α phenotype
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Age
ESR
Platelets
Oxygen Saturation
Temperature
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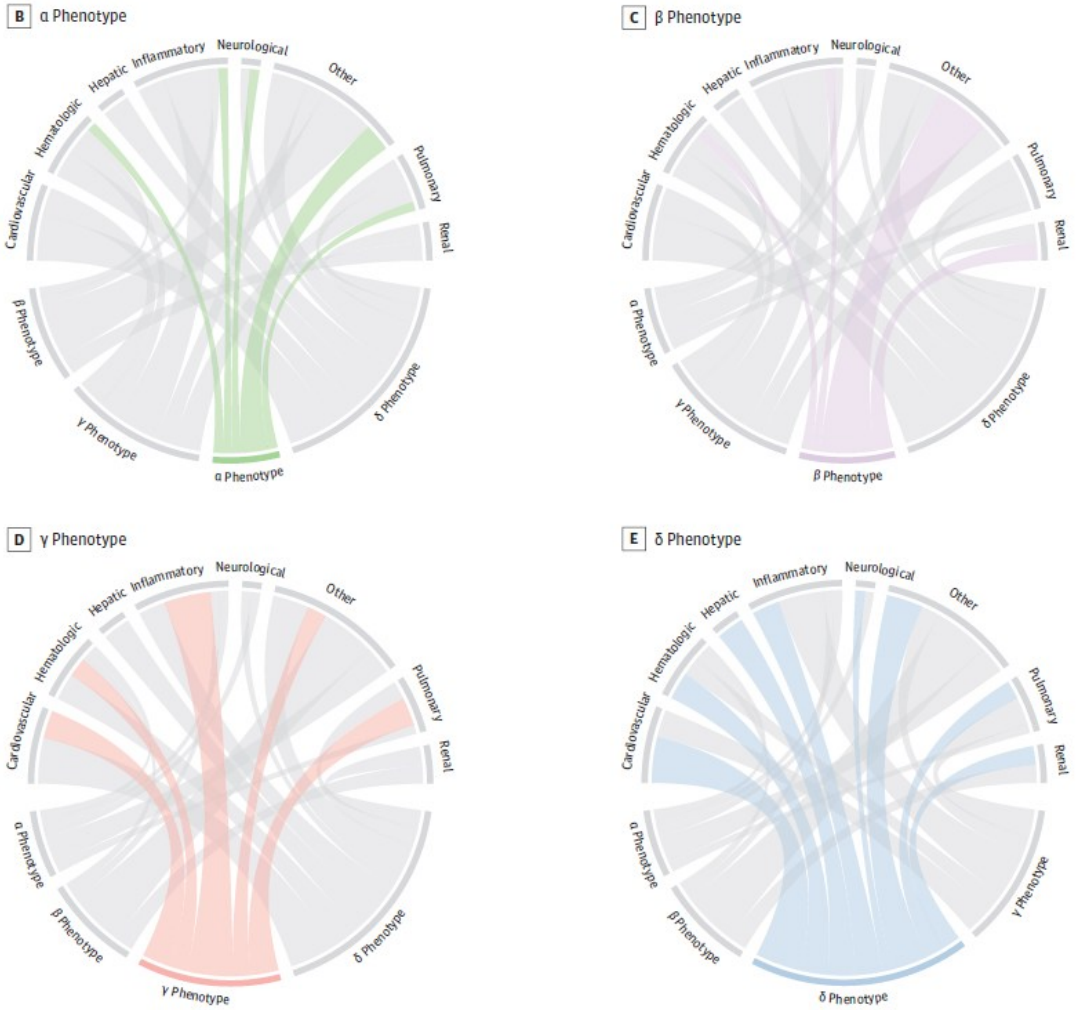
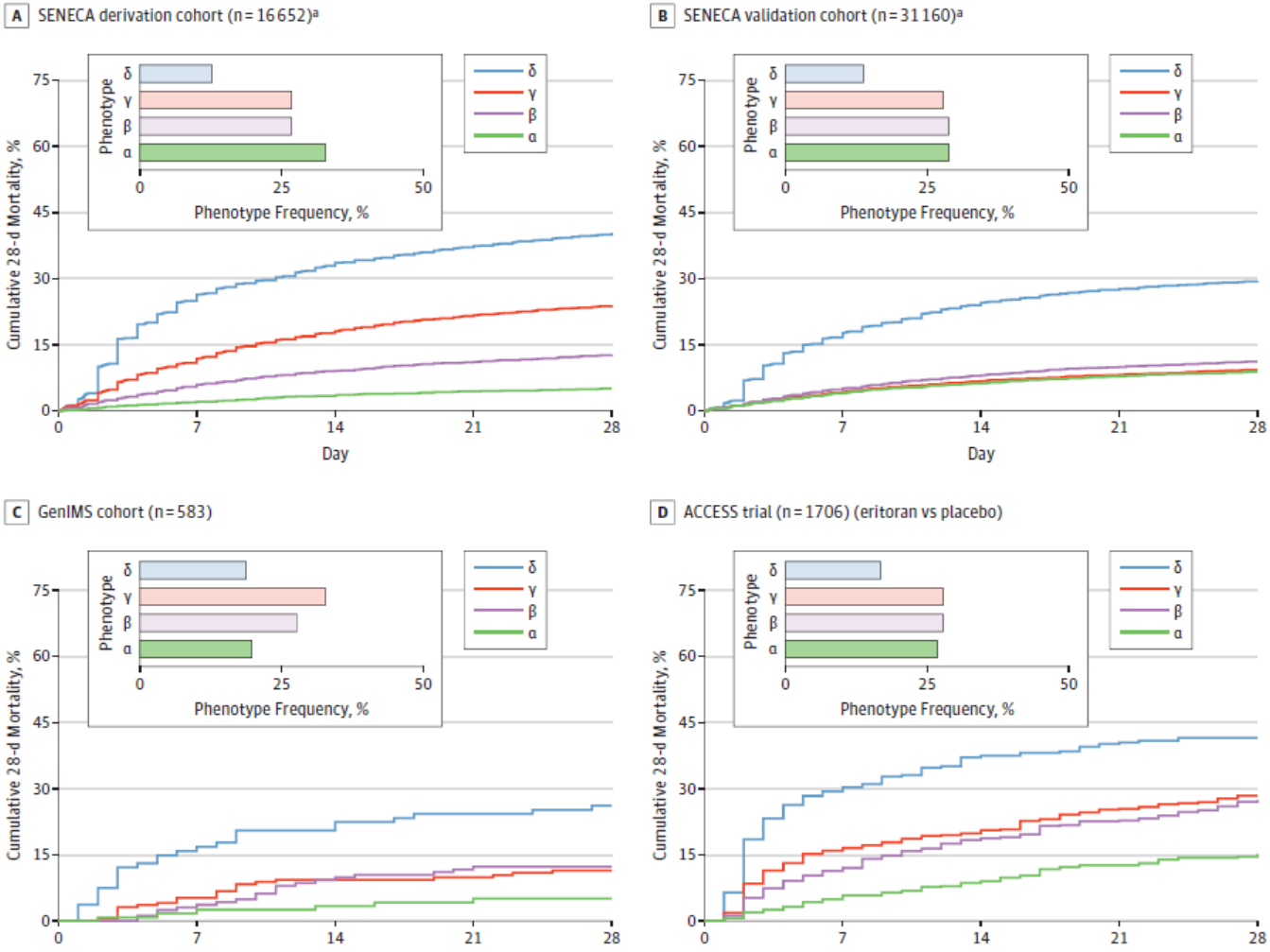
Hemoglobin
SBP
Bicarbonate
Albumin
-1.0 -0.5 0 0.5 1.0
Standardized Variable Value


B α Phenotype
Neurological
Other
Pulmonary
Renal
δ Phenotype
α Phenotype
γ Phenotype
β Phenotype
Cardiovascular
Hematologic
Hepatic
Inflammatory
C β Phenotype
D γ Phenotype
E δ Phenotype

- **α phenotype:**
  - few abnormal laboratory values, less organ system dysfunction, and the lowest mortality rate.
- **β phenotype:**
  - older, frequent chronic illness, kidney disease.
- **γ phenotype:**
  - more likely to have measures of inflammation, lower albumin levels, and higher temperatures.
- **δ phenotype:**
  - high serum lactate levels, elevated levels of transaminases, hypotension, and the highest mortality rate.


A SENECA derivation cohort (n = 16 652)[a]
B SENECA validation cohort (n = 31 160)[a]
C GenIMS cohort (n = 583)
D ACCESS trial (n = 1706) (eritoran vs placebo)
Cumulative 28-d Mortality, %
Day
Phenotype
Phenotype Frequency, %
δ
γ
β
α
0
7
14
21
28
15
30
45
60
75
25
50

- The study by Seymour and colleagues represents the brave new world of attempting to apply patient data, machine learning, and artificial intelligence to better understand complex, serious clinical problems.

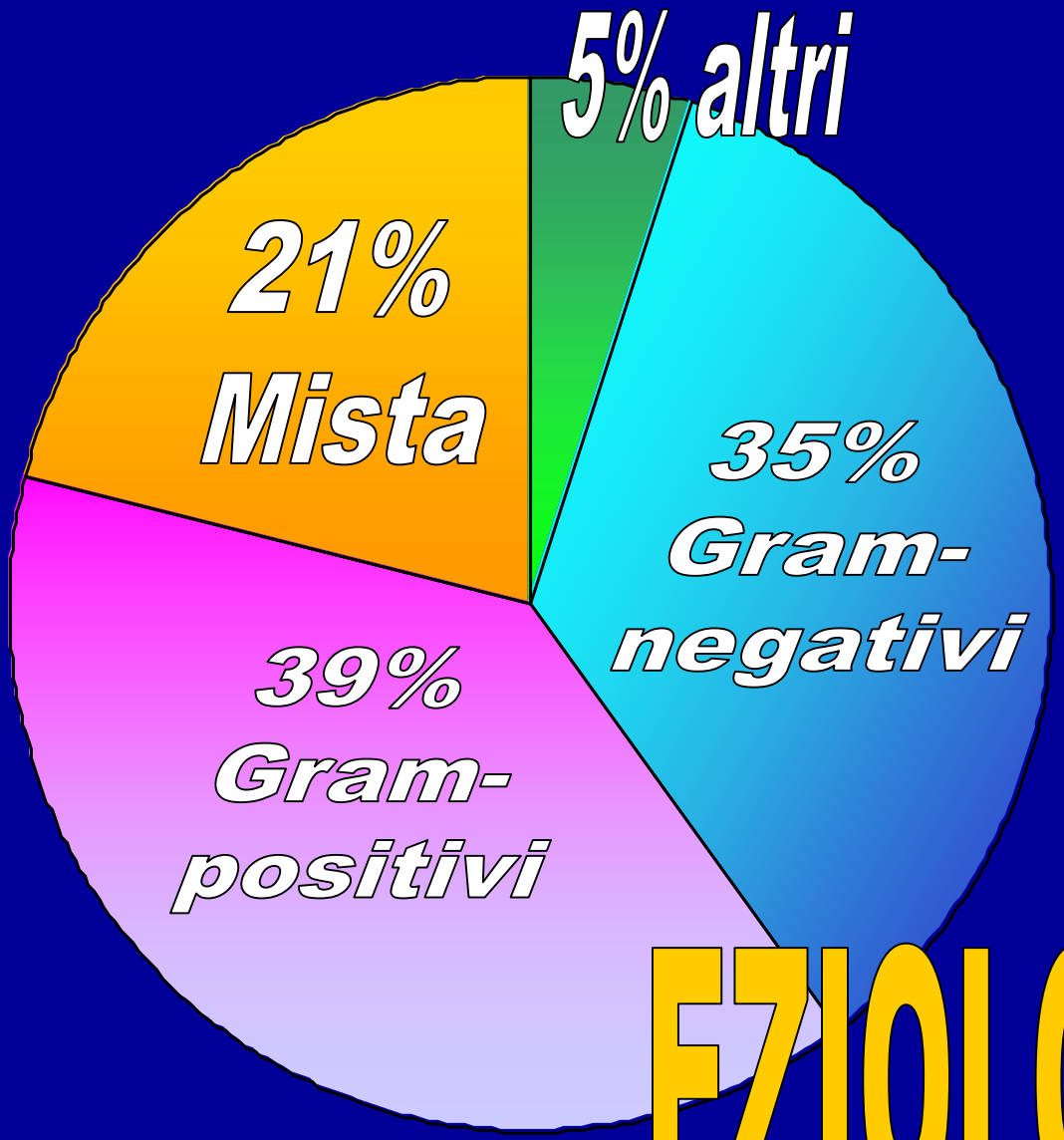
- However, the ultimate answer to the question “will this approach improve patient outcomes?” remains unknown.

Clinical management of sepsis

- **Screening**
- **Diagnosis**
- **Antimicrobial therapy**
- **Source control**
- **Selective decontamination**

Principali patogeni

Gram-positive bacteria	**30–50%**
Meticillin-susceptible *S aureus*	14–24%
Meticillin-resistant *S aureus*	5–11%
Other *Staphylococcus* spp	1–3%
Streptococcus pneumoniae	9–12%
Other *Streptococcus* spp	6–11%
Enterococcus spp	3–13%
Anaerobes	1–2%
Other gram-positive bacteria	1–5%
Gram-negative bacteria	**25–30%**
E coli	9–27%
Pseudomonas aeruginosa	8–15%
Klebsiella pneumoniae	2–7%
Other *Enterobacter* spp	6–16%
Haemophilus influenzae	2–10%
Anaerobes	3–7%
Other gram-negative bacteria	3–12%
Fungus	
Candida albicans	1–3%
Other *Candida* spp	1–2%
Yeast	1%
Parasites	1–3%
Viruses	2–4%



EZIOLOGIA

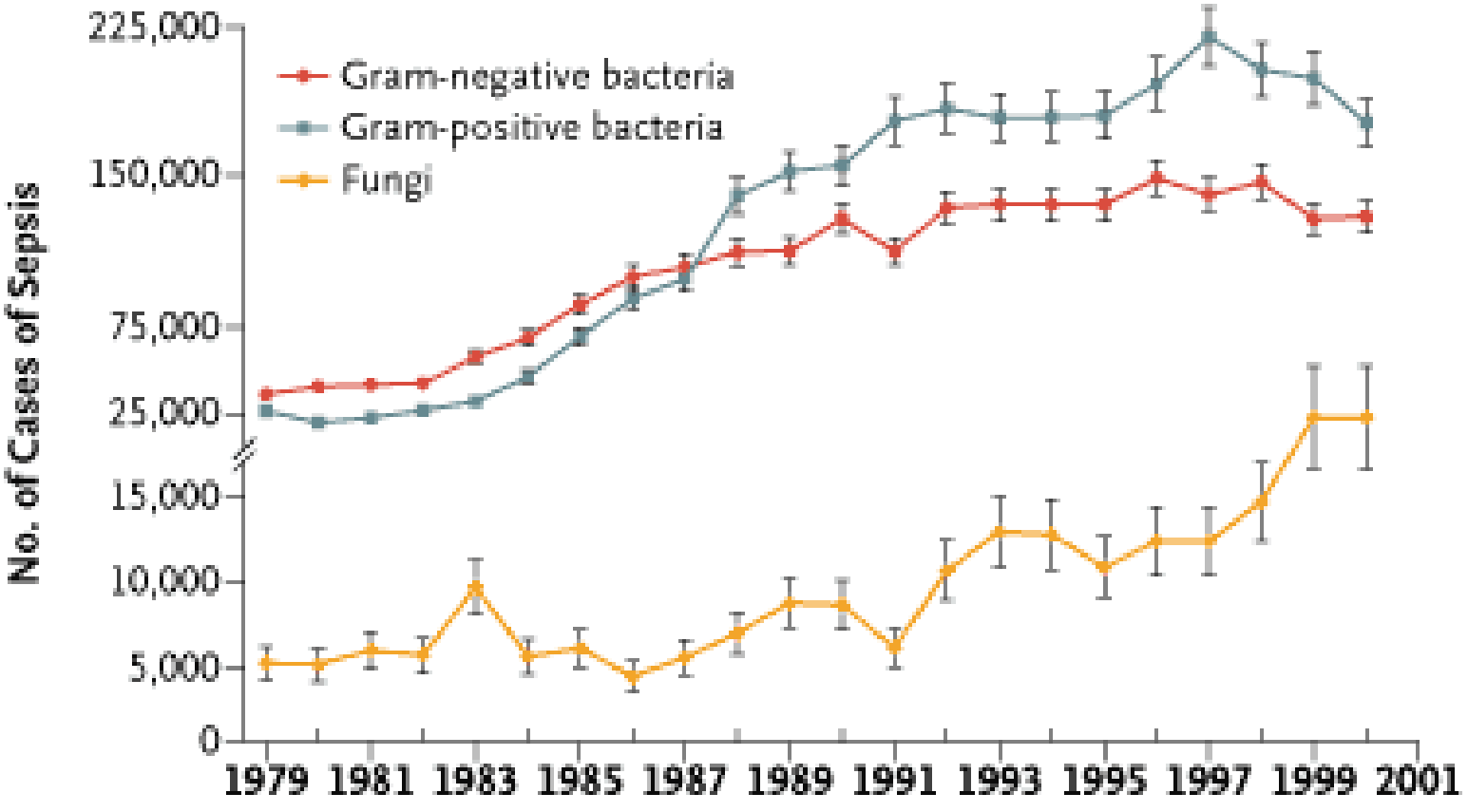
Batteremia in era Preantibiotica

- Streptococcus pneumoniae
- Str. group A streptococcus
- Staphylococcus aureus
- Haemophilus influenzae
- Neisseria mennigitidis
- Salmonella spp.

Emergenza di Gram-Negativi

- L’uso indiscriminato di antibiotici
- L’utilizzo di dispositivi centrali (CVC)
- Lo stato di immunodepressione

Sepsi: eziologia



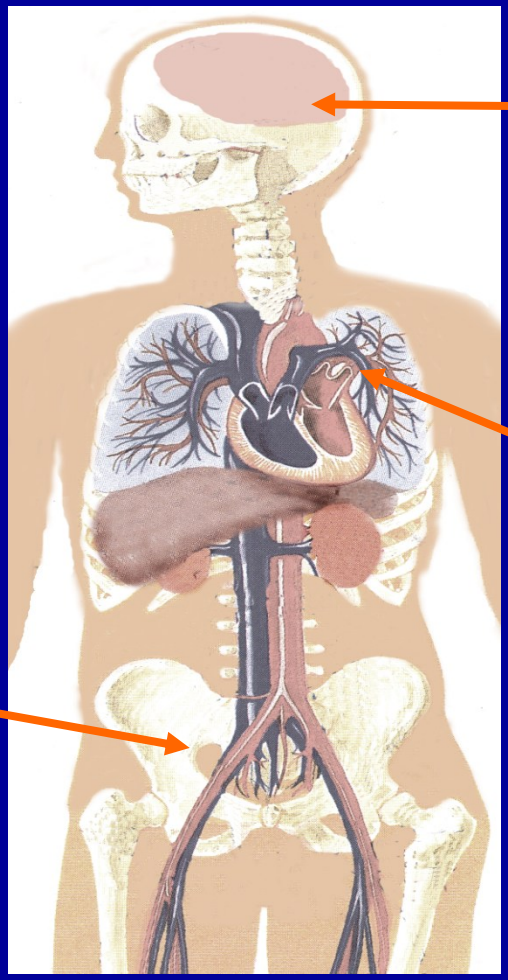
EZIOLOGIA

La frequenza dei microrganismi varia a seconda delle cause predisponenti:

- ferite chirurgiche, CVC, protesi, neutropenia
  Stafilococchi
- infezioni urinarie, cateteri vescicali
  E. coli
- insorgenza nosocomiale, immunodeficit
  P. aeruginosa

Focolaio sepsigeno sito in qualsiasi parte dell'organismo.

Immissione in circolo dei patogeni con formazione di focolai metastatici.



Meningococco

Streptococco

Stafilococchi

REVIEW

Virulence 5:1, 154–160; January 1, 2014; © 2014 Landes Bioscience

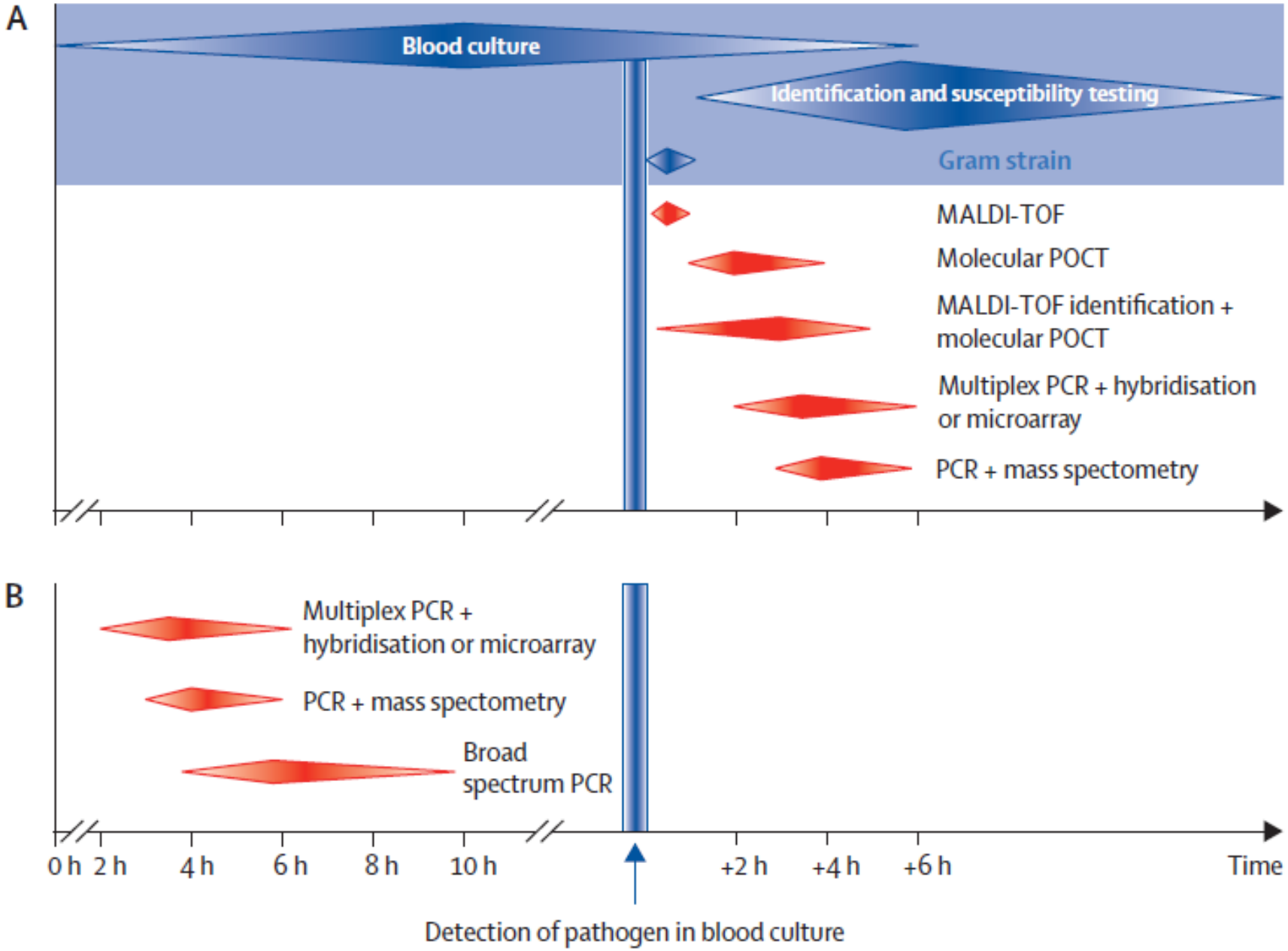
Rapid diagnosis of sepsis

Frank Bloos and Konrad Reinhart*

Department of Anesthesiology and Intensive Care Medicine; Jena University Hospital; Jena, Germany

Keywords: sepsis, diagnosis, biomarker, cytokines, procalcitonin, PCR

Abbreviations: CRP, C-reactive protein; ICU, intensive care unit; IL, interleukin; LBP, lipopolysaccharide binding protein; MD2, myeloid differentiation factor 2; PCR, polymerase chain reaction; PCT, procalcitonin; *s*TREM-1, soluble triggering receptor expressed on myeloid cells 1; suPAR, soluble urokinase plasminogen activator receptor; TNF, tumor necrosis factor


A
Blood culture
Identification and susceptibility testing
Gram strain
MALDI-TOF
Molecular POCT
MALDI-TOF identification + molecular POCT
Multiplex PCR + hybridisation or microarray
PCR + mass spectometry
B
Multiplex PCR + hybridisation or microarray
PCR + mass spectometry
Broad spectrum PCR
0 h
2 h
4 h
6 h
8 h
10 h
+2 h
+4 h
+6 h
Time
Detection of pathogen in blood culture

Laboratory Detection of Sepsis

Biomarkers and Molecular Approaches

Stefan Riedel, MD, PhD, D(ABMM)[a,*], Karen C. Carroll, MD[b]

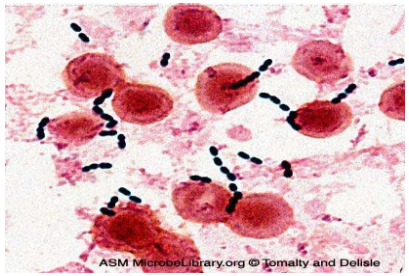
Clinics in Laboratory Medicine
33, 413-748; 2013

KEYWORDS

• Biomarkers • Procalcitonin • C-reactive protein • Molecular diagnostics
• Nucleic acid amplification testing • Sepsis • Bacteremia

KEY POINTS

- Sepsis, severe sepsis, and septic shock are significant medical problems worldwide; sepsis is the 10th leading cause of death in the United States.
- Although numerous biomarkers are available no single assay has consistently emerged for use as a single marker with high diagnostic accuracy for the prediction and outcome assessment of sepsis.
- The best evidence in support of usefulness and diagnostic and prognostic performance in the management of patients with sepsis exists for the following biomarkers: C-reactive protein, procalcitonin, adrenomedullin, and a few select interleukins (IL-6 and IL-8).
- Although blood cultures are still considered the gold standard in clinical practice for the detection of sepsis, molecular technologies provide more rapid organism identification from positive blood cultures in patients with bacteremia/sepsis. Direct whole-blood assays are not yet sensitive enough to replace existing culture amplification.
- Diagnostic approaches for early sepsis diagnosis using biomarkers, together with rapid organism identification by molecular technologies, will likely lead to a reduction of turnaround time for test results and subsequent improvements of therapeutic interventions and patient care outcomes.



Sepsi batterica

- **Sepsi da Gram-**

  Enterobatteriacee: E.coli Klebsiella, P.aeruginosa

- **Sepsi da Gram+**

  Stafilococchi: S.aureus

  S.coagulasi negativi

  Streptococchi:

  S.pyogenes

  S.viridans

  S.pneumoniae

FOCOLAIO SEPSIGENO:
polmone, cavità addominale, tratto urinario

FOCOLAIO SEPSIGENO:
cute, tessuti molli, app.respiratorio

CASO CLINICO:

- Donna, 58 anni
- APR: Edentulia totale, eterozigosi per G6P-DH, tabagismo
- APP: Dolore pelvico, stranguria, ematuria 3 mesi prima, regrediti spontaneamente; nei 15 gg precedenti dolore pelvico, stranguria, pollachiuria, febbre fino a 40°C con brividi scuotenti, resistente a Ciprofloxacina e Ceftriaxone
- DEA: GCS 15, **TC 38.6 °C**, PA 110/70 mmHg, **FC 117 bpm**, FR 18 /min, spO2 97%
- *Hb 8.7 g/dL,* ***GB 17660/µl*** *(87% N, 7.2% L), PLTs 330000/µl,* creatinina 0.7 mg/dl, azoto 8 mg/dl, *AST 51 U/l, ALT 19 U/l, γGT 109 UI/l, bilirubina tot* 0.56 mg/dl, diretta 0.38 mg/dl, *LDH 264 UI/l,* P*CR 24.66 mg/dl (RR 0-0.5), PCT 23.88 ng/ml (RR 0.02-0.064), fibrinogeno 550 g/dl, D-dimero 1252 µ/l*
- Stick urine: negativo
- RX torace: non processi flogistici in atto
- ETT: minima insufficienza mitralica, FE 60%

➢ **MEROPENEM 1g q8h ev**

SOFA SCORE (Sequential Organ Failure Assessment)

Organ system	1	2	3	4
Respiratory PaO_2/FiO_2, (mmHg)	<400	<300	<200	<100
Hematologic Platelets/ nl	<150	<100	<50	<20
Hepatic Bilirubin, mg/dl (µmol/l)	1,2–1,9 (20–32)	2,0–5,9 (33–101)	6,0–11,9 (102–204)	>12,0 (>204)
Cardiovascular Hypotension	MAP[2] <70 mmHG	Dopamine ≤ 5[1] or dobutamine (any dose)	Dopamine >5 or epinephrine ≤0,1[1] or Norepinephrine ≤0,1[1]	Dopamine >15 epinephrine > 0 or norepinehrine 0,1
Neurologic Glasgow Coma Score	13–14	10–12	6–9	<6
Renal Creatinine, mg/dl (µmol/l) urine output	1,2–1,9 (110–170)	2,0–3,4 (171–299)	3,5–4,9 (300–440) <500 ml/day	>5,0 (>440) <200 ml/day

Vincent JL, de Mendonça A, Cantraine F, et al. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Working group on "sepsis-related problems" of the European Society of Intensive Care Medicine. ***Crit Care Med***. 1998;26 (11):1793-800.

Ferreira FL, Bota DP, Bross A, et al. Serial evaluation of the SOFA score to predict outcome in critically ill patients. ***JAMA***. 2001;286(14):1754-8.

SEPSI

Infezione + SOFA ≥ 2

- PaO2/FiO2
- Piastrine
- Bilirubina
- PAM + inotropi/vasocostr.
- GCS
- Creatinina
- Diuresi

Infezione + qSOFA ≥ 2

- PAS ≤ 100 mmHg
- GCS < 15
- FR ≥ 22

SHOCK SETTICO

Sepsi
+
Ipotensione refrattaria
che richiede vasopressori per mantenere PAM ≥ 65 mmHg
e
Iperlattatemia > 18 mg/dl o 2 mml/L
nonostante adeguato riempimento volemico

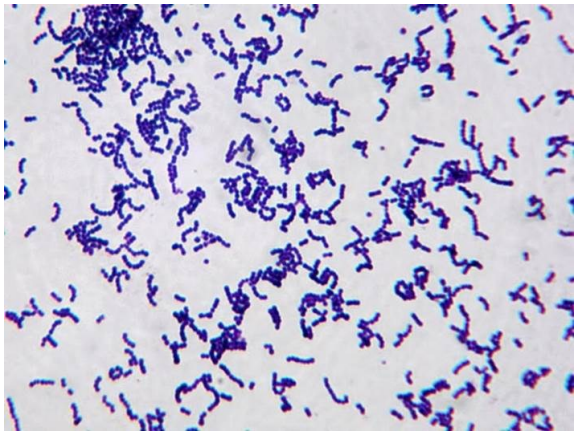
Score Trend (first 48 hrs)	Mortality
Increasing	> 50%
Unchanged	27 - 35%
Decreasing	< 27%

Maximum SOFA Score	Mortality
0 to 6	< 10%
7 to 9	15 - 20%
10 to 12	40 - 50%
13 to 14	50 - 60%
15	> 80%
15 to 24	> 90%

- Emocolture (2 set): ***Streptococcus constellatus***

Antibiogramma	Ceppo 1	
ANTIBIOTICI	*MIC*	
Ampicillina		S
Benzylpenicillin	0.064	S
Cefepime		S
Cefotaxime		S
Ceftriaxone		S
Cefuroxime		S
Meropenem		S
Teicoplanin	0.5	S
Vancomicina	0.5	S

➔ Gruppo Streptococcus anginosus
➔ Commensale mucosa orale, tratto respiratorio superiore, gastro-intestinale, genito-urinario
➔ Infezioni piogeniche opportunistiche: per via ematica (ascessi epatici, cerebrali, endocarditi), diretta (trauma o chirurgia), aspirazione (polmoni), per contiguità
➔ Frequenti coinfezioni con anaerobi obbligati
➔ Casi di tromboflebite settica (seni cavernosi)

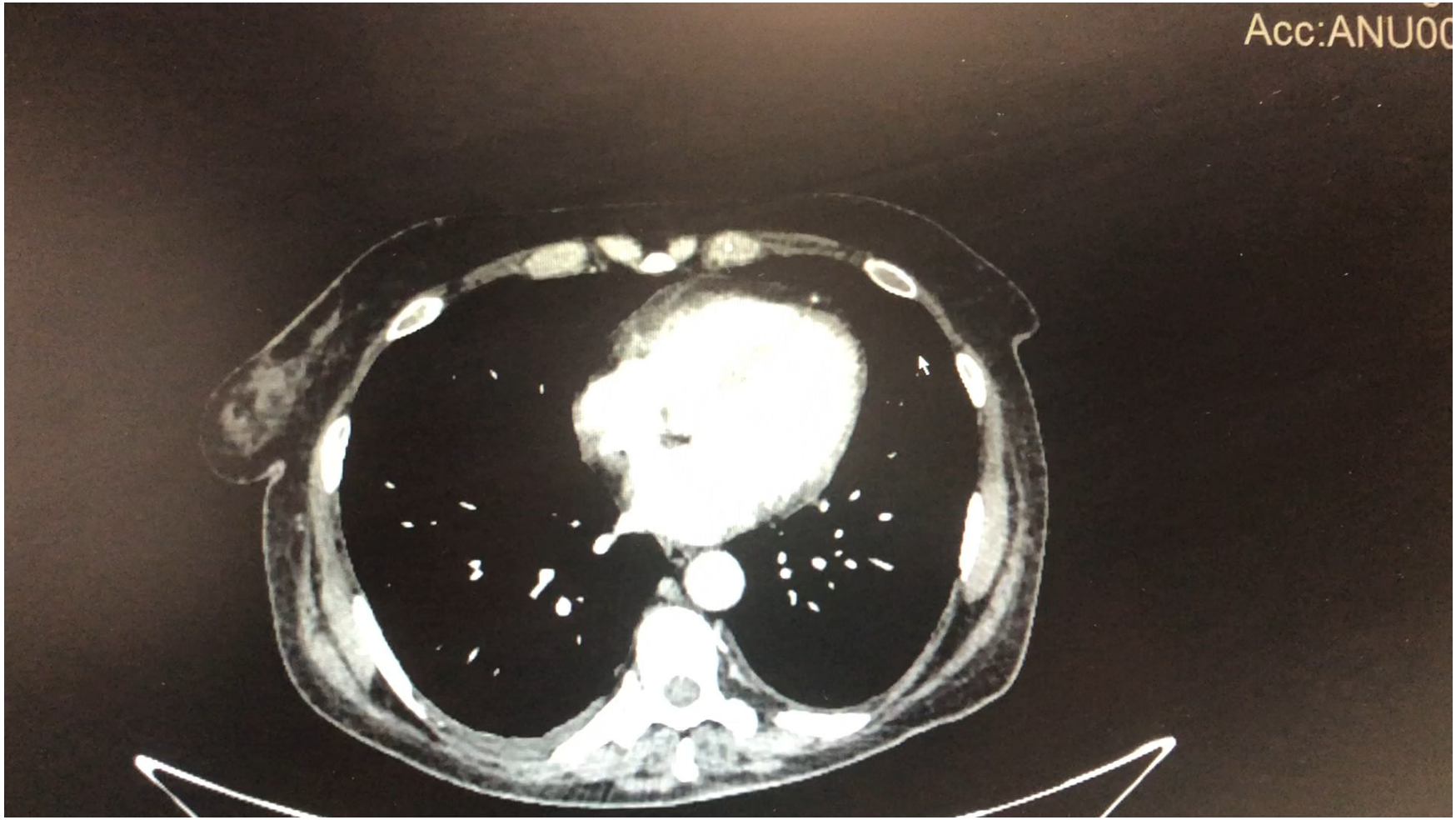


- Ecografia addominale: «*Fegato di dimensioni aumentate ad ecostruttura omogenea… colecisti normodistesa contenente almeno tre formazioni litiasiche…**ectasia della vena porta (DT21mm) con immagine debolmente iperecogena al suo interno che si estende ai rami secondari del lobo epatico sinistro con presenza di segnale colordoppler, da riferire verosimilmente a trombosi parziale dei rami principali; fenomeno analogo a livello della vena splenica**…»*

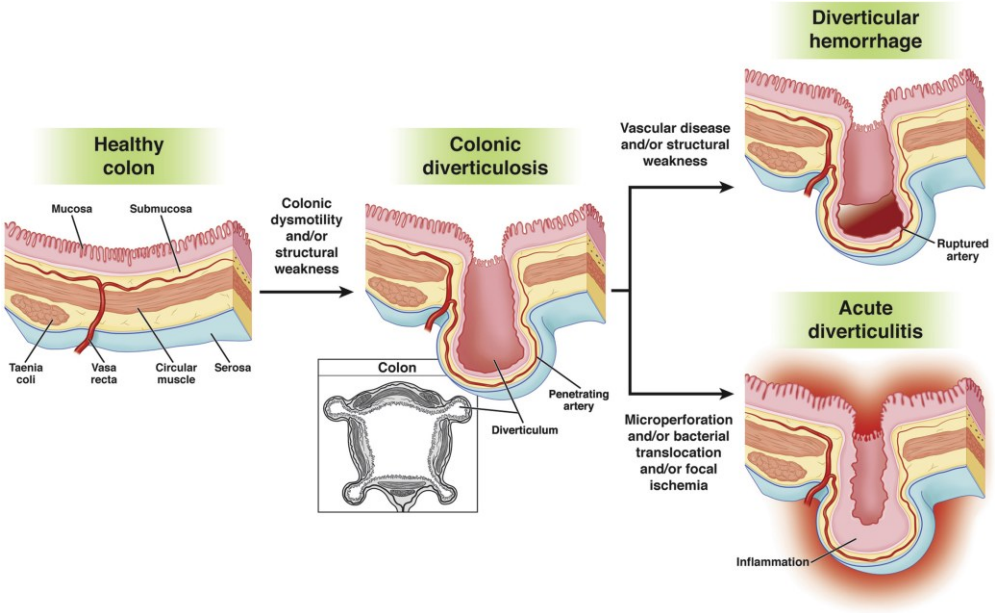
➔ FONDAPARINUX 7.5 mg sc /die

- TC total body: «…***estesa trombosi massiva a carico della vena porta intra ed extraepatica a partire dalla confluenza con la vena splenica e mesenterica superiore con coinvolgimento delle diramazioni portali principali e secondarie in entrambi i lobi epatici****; la vena porta e le principali diramazioni presentano* ***calibro aumentato (fino a 2 cm) e pareti ispessite ed iperemiche, come per condizione di tromboflebite****. La vena splenica e la mesenterica superiore appaiono pervie ed opacizzate. Regolare opacizzazione anche delle vene sovraepatiche e della VCI. Fegato di forma normale e dimensioni modicamente aumentate; dopo somministrazione di mdc, sia in fase arteriosa che portale, si osserva una* ***estesa area ipodensa a limiti sfumati ed a prevalente disposizione pericolecistica, che si omogenizza in fase tardiva, coinvolgente principalmente il III, IV, V, e VIII segmento epatico, in prima ipotesi per fenomeni di alterata perfusione****. Concomita imbibizione del tessuto adiposo in sede ilare, ove si rileva la presenza di alcuni linfonodi di aspetto reattivo, il maggiore di 14 mm.* ***Modesta quota di versamento libero in sede periepatica, lungo la doccia parietocolica di destra ed in pelvi****…»*

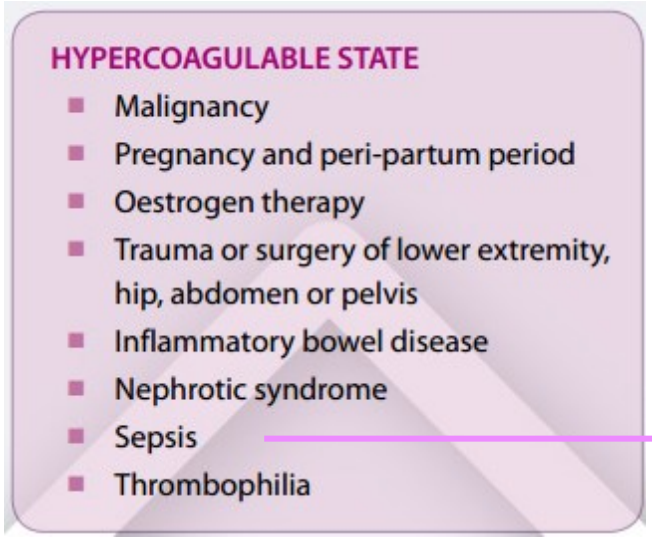
- RM addome mdc: «*Si conferma l´****estesa trombosi massiva della vena porta a partire dalla confluenza con la vena splenica e mesenterica superiore, con coinvolgimento delle diramazioni portali principali e secondarie in entrambi i lobi epatici; la vena porta e le principali diramazioni presentano calibro aumentato e pareti ispessite ed iperemiche, come per condizione di tromboflebite associata****... Fegato di forma normale con dimensioni aumentate; stabile la condizione di* ***ipoperfusione del parenchima epatico*** *che appare esente da patologia…*»


Acc:ANU0

- Emocolture (2 set) dopo 6 giorni: ***Streptococcus constellatus*** e ***Bacteroides fragilis***
- SOF: positivo
- Pancolonscopia: Emorroidi e **diverticolosi del sigma**



- ETE: Lieve insufficienza mitralica; non evidenti masse vegetanti



- Marcatori tumorali: CEA, AFP-2, CA 19.9: negativi

- Screening trombofilico: mutazioni **MTHFR 667C>T e 1298A>C in eterozigosi**; **omocisteina 17.5 µmol/L**; mutazione di fattore V, fattore II, PAI-1: assenti; anticorpi anticardiolipina e anti β-2-microglobulina: negativi

Tromboflebite settica

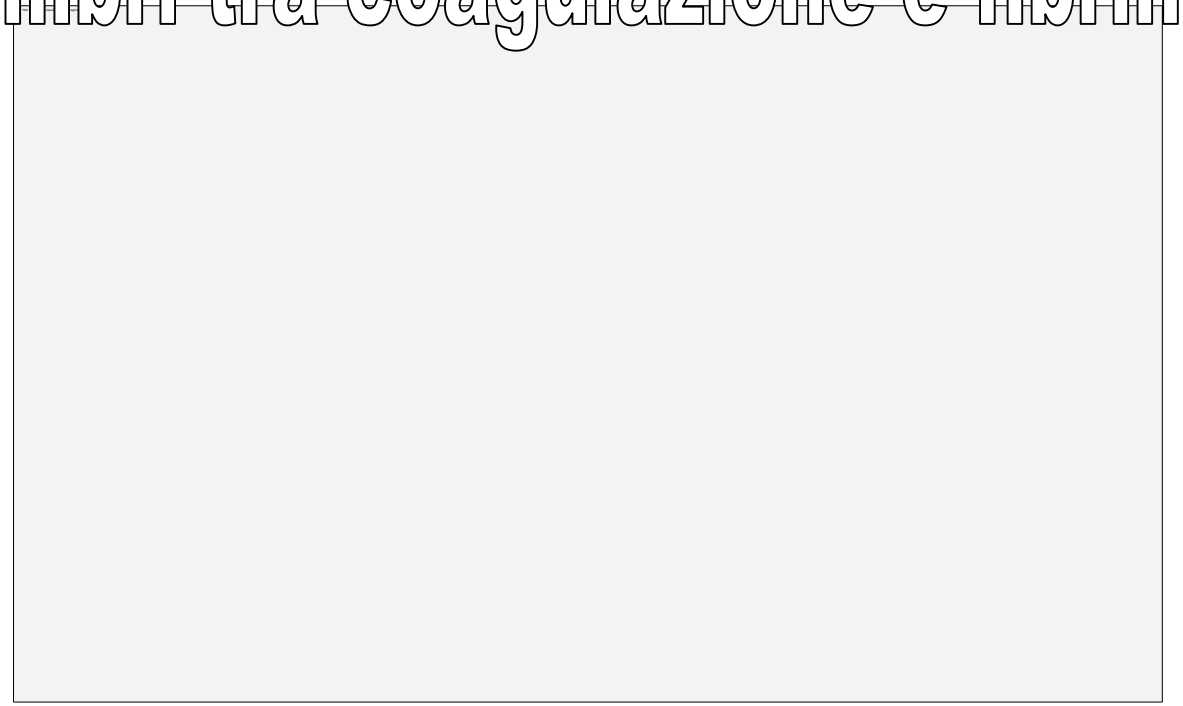
- Ecografia addome: «*Estesa trombosi della vena porta coinvolgente anche l'origine della vena splenica e le vene mesenteriche; minimo flusso periferico nei rami distali del IV-VIII segmento epatico*»

➢ Dimissione: **AMOXICILLINA/CLAVULANATO 2.2 g x2/die fino a completare le 6 settimane + WARFARIN 5 mg secondo INR + ACIDO FOLICO 5 mg**

Classificazione delle sepsi

- Sepsi di origine ignota
  - Di comunità
  - Nosocomiale
- Sepsi da catetere intravascolare o da catetere venoso centrale
- Sepsi in ospite immunocompromesso
  - Tossicodipendente
  - Splenectomizzato
  - Neutropenico
- Sepsi in corso di polmonite (comunitaria /nosocomiale)
- Urosepsi (comunitaria /nosocomiale)
- Sepsi in infezione endo-addominale (comunitaria /nosocomiale)
- Sepsi in paziente ustionato
- Sepsi in paziente con meningite
- Sepsi in corso di artrite settica/osteomielite
- Sepsi a partenza da cute e tessuti molli (fascite necrotizzante)
- Sepsi nel piede diabetico
- Sepsi in paziente con malattia infiammatoria pelvica

Sepsi: Disfunzione endoteliale e squilibri tra coagulazione e fibrinolisi



- **La disfunzione progressiva dell'endotelio microvascolare nella sepsi è causata in parte da uno squilibrio tra coagulazione e fibrinolisi**
- **Il progressivo consumo della proteina C ne riduce i livelli pregiudicando la capacità dell'organismo di modulare l'infiammazione, la coagulazione, la fibrinolisi e di ripristinare l'omeostasi**

Sepsi e danno d'organo
Dov'è il legame?

- Microtrombosi
- Apoptosi
- Disfunzione mitocondriale

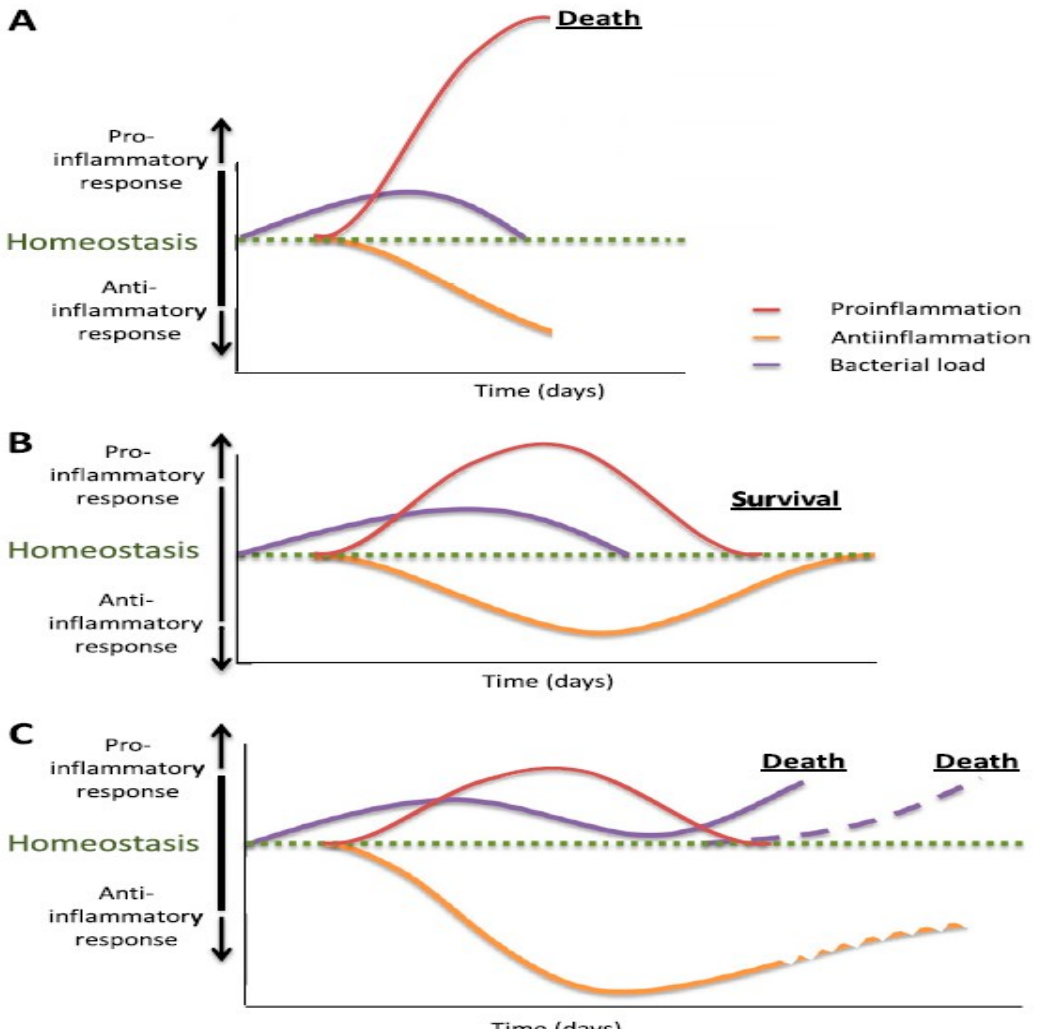
INFLAMMATORY-IMMUNE RESPONSE IN SEPSIS

Immunotherapy for the Adjunctive Treatment of Sepsis: From Immunosuppression to Immunostimulation
Time for a Paradigm Change?
Am J Respir Crit Care Med Vol 187, Iss. 12, pp 1287–1293, Jun 15, 2013

The inflammatory-immune response may vary and depends on

@ Microorganism(s) load and virulence

@ Host genetic factors and comorbidities



Healthy young adult with meningococcemia:
Overwhelming proinflammatory response which is likely to eradicate bacteria but lead to tissue damage and multiorgan failure

Healthy young adult with CAP responsive to Abx :
adequate proinflammatory re-sponse, combined with an adequate non-sustained antiinflammatory response to pre-vent tissue damage

Patient with candidemia after postoperative abdominal sepsis:
Proinflammatory response combined with a pronounced or sustained anti inflammatory state with persisting bacterial or secondary (opportunistic) infections

Diagnosis of sepsis

There is no specific pathognomic clinical or laboratory parameter of sepsis

The diagnoses should be based on

- the clinical signs of infection +
- the correct evaluation of aspecific clinical signs and lab parameters of organ dysfunctions

Critical parameters

Blood white cell count

Thrombocyte count

Serum bilirubin, SGOT, SGPT

Serum creatinine

Prothrombin, D-dimer

Serum lactate

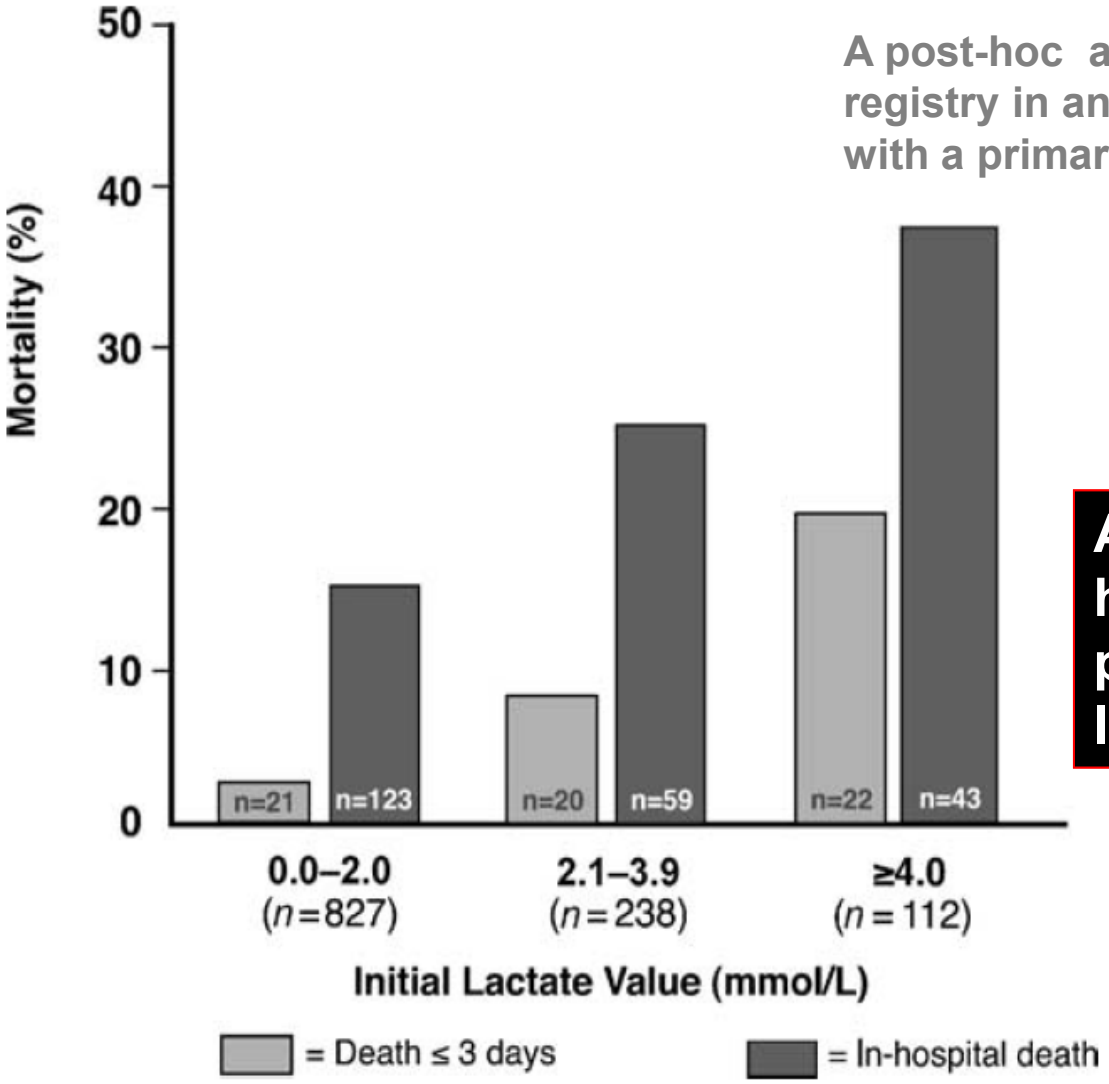
CRP (C reactive protein)

PCT (procalcitonin)

Serum lactate as a predictor of mortality in patients with infection

TrzeciaK S et al, Intensive Care Med, 2007

A post-hoc analysis of a prospectively compiled registry in an urban academic hospital in patients with a primary or secondary diagnosis of infection



Acute-phase deaths and in-hospital deaths in infected patients stratified by initial lactate value.

Proteina C Reattiva (PCR)

- *storicamente più utilizzata*
- *molto sensibile*

Procalcitonina (PCT)

- *più specifica rispetto alla PCR nella diagnosi di sepsi*
- *correla in maniera significativa alla gravità del quadro clinico*

Luzzani A et al.. Crit Care Med 2003;31:1737-41

PROCALCITONINA

- Prodotta dalle **cellule C della tiroide** e da **cellule neuroendocrine extratiroidee:**
  (soprattutto: polmone, intestino, fegato)
- **Emivita di 25-30 h**
- Prodotta selettivamente in risposta ad infezioni batteriche (stimolo più potente è l'endotossina batterica) e in corso di MOFs
- Non aumenta (se non in modo poco significativo) nelle infezioni fungine, virali, in malattie autoimmunitarie e neoplasie
- **individuo sano**: indosabile o < 0.1 ng/mL
- **in corso di infezione:** 1 - 1000 ng/mL

PCT as a tool to guide Antimicrobial Therapy

- PCT level
- Less than 0.1ng/ml: absence of infection
- 0.1 to 0.25 ng/ml: bacterial infection unlikelly and use of antibiotic discouraged.
- 0.25 to 0.5 ng/ml: indicate possible bacterial infection, initiate antimicrobial therapy
- More than 0.5 ng/ml: suggestive of presence of bacterial infection and antibiotic treatment is strongly recommended

Approccio al paziente con sepsi

- Accurati e ripetuti esami obiettivi
- Identificazione focus infettivo
- Terapia mirata al sito di infezione

POSSIBILI SEDI DEI FOCOLAI INFETTIVI

- Polmone
- Tratto urinario
- Regione addomino-pelvica
- Vie biliari
- Cute e tessuti
- Cateteri intravascolari

	sepsis (*n* = 134)	Septic shock (*n* = 53)
	Source of infection (%)	
Lung	63 (47)	22 (42)
Abdomen	45 (34)	20 (38)
Urethra	3 (2)	3 (6)
SNC	2 (1)	1 (2)
Blood	3 (2)	0
Skin	9 (7)	5 (9)
Other	9 (7)	2 (4)

SINTOMATOLOGIA

- spesso **aspecifica**: febbre con brividi, nausea, cefalea, confusione (10-30%, specie negli anziani)
- alcuni sintomi come tosse, disuria, cefalea associata a sindrome meningea, possono rivelare la **patologia sottostante**
- **verificare** la presenza di cateteri, terapie immunosoppressive, recenti interventi chirurgici

SINTOMATOLOGIA

Il paziente tipico con sepsi presenta:

- febbre
- tachicardia
- estremità calde

- tachipnea
- confusione
- oliguria

Aggravamento

SINTOMATOLOGIA

Cuore

Minore contrattilità

Riduzione del ritorno venoso

Riduzione della portata cardiaca

Insufficienza miocardica irreversibile

Alterazioni dello stato mentale

- Disorientamento lieve
- Confusione
- Letargia
- Agitazione psico-motoria
- Coma

Meccanismo Fisiopatologico

- Effetto di mediatori infiammatori a livello neurologico (fase iniziale)
- Alterato trasporto di aminoacidi con alterata sintesi di neurotrasmettitori
- Riduzione locale o globale del fluso ematico cerebrale

Le alterazioni dello stato mentale vanno calcolate secondo i criteri del Glasgow Coma Scale (GCS)
Nell'anziano le alterazioni dello stato mentale possono rappresentare le uniche menifestazioni della sepsi

Manifestazioni Ematologiche

Leucocitosi neutrofila con granulazioni tossiche e vacuolizzazioni intracitoplasmatiche

Meccanismo fisiopatologico

- Demarginazione dei polimorfonucleati
- Immissione in circolo di granulociti immaturi
- Stimolo midollare da parte del Colony Stimulating Factor (CSF)

Neutropenia specie sepsi da Gram negativi

Meccanismo fisiopatologico

- Sequestro splenico
- Aggregazione neutrofila per attivazione complementare

Piastrinopenia di grado diverso (50.000-150.000/mm3), isolata o associata a CID

Coagulazione Intravascolare Disseminata (CID)

Situazione caratterizzata dall'attivazione sistemica della coagulazione e/o del sistema fibrinolitico che determina generazione di trombina e deposito di fibrina, consumo di fattori della coagulazione e piastrine, con fibrinolisi secondaria

Dati di laboratorio

- Allungamento del PT e PTT
- Diminuzione dei fattori II, V, VIII
- Diminuzione della proteina C coagulativa
- Diminuzione dell'antitrombina III
- Diminuzione de fibrinogeno
- Aumento del D-Dimero
- Piastrinopenia

Clinica

- Eventi emorragici e trombotici

Complicanze Renali

Insufficienza Renale Acuta (IRA)

- Oliguria (<0.5 ml/kg/h) o poliuria
- Iperazotemia ed aumento della creatinina con clearances ridotte
- Bassa soduria (IRA pre-renale) o alta soduria (necrosi tubulare acuta
- Protenuria (variabile)
- Cilindri granulosi e cellule epiteliali tubulari

Meccanismo fisopatologico

- Ridotta pressione arteriosa media
- Ipoperfusione renale
- Riduzione/ridistribuzione flusso renale
- Aumento resistenze vascolari intrarenali
- Alterazioni funzionali per effetto di mediatori infiammatori e neuro-ormonali
- Apoptosi
- Necrosi tubulare

Complicanze Polmonari

- **Danno acuto polmonare (ALI)**
- **Sindrome di distress respiratorio acuto (ARDS)**

	Insorgenza	Difetto di ossigenazione	Aspetto radiologico	Pressione idrostatica
ALI	Acuta	PaO2/FIO2 <300	Infiltrati bilaterali	PAOP<18
ARDS	Acuta	PaO2/FIO2 <300	Infiltrati bilaterali	PAOP<18

EGA: Inizialmente ipossiemia non responsiva all'o2 terapia – alcalosi respiratoria

Rx torace: Infiltrati diffusi bilateralmente che risparmiano gli angoli costofrenici e che non si associano a cardiomegalia

PAOP: Pressione di incuneamento capillare in arteria polmonare

Manifestazioni epatiche

- **Iperbilirubinemia:**

Bilirubina > 2.0 mg/dl per motivi non altrimenti spiegati

Manifestazioni metaboliche

- **Acidosi metabolica da alterata perfusione:**

Ph 7.30 o deficit base ≥ 50 mEq/l con lattacidemia > 4 mmol/l

Alterazioni metaboliche glicidiche

- Glucosio è il substrato principale per processi di difesa e riparazione
- La principale sorgente endogena di glucosio sono gli AA attraverso la

Per il fenomeno di Insulinoresistenza le EMULSIONI LIPIDICHE quali ACIDO LINOLEICO φ6 e ACIDO α-LINOLEICO ϕ3 che interferiscono sui processi della membrana cellulare, produzione di eicosanoidi, rigenerazione cellule sistema immunitario SONO UN OTTIMO SUSBSTRATO PER IL METABOLISMO ENERGETICO

- Febbre
- Iperventilzione
- Iperdinamismo cardiocircolatorio
- ↑ Perspiratio Insensibilis

Quadro clinico dello shock settico

Fase iniziale

- **Shock "Caldo ed Iperdinamico"** (pazienti con cute calda senza compromissione della perfusione delle estremità, polso frequente con aumento della pressione differenziale)
- **Iperventilazione, Alcalosi Respiratoria** (PaCO2 <32 mmHg)
- **Alterazione dello stato mentale** (stato di agitazione o di lieve euforia)

Fase tardiva

- **Comparsa dei segni di vasocostrizione, di bassa portata e di insufficienza d'organo:**
  - Peggioramento dello stato mentale
  - Cute fredda, umida marmorizzata
  - Ipotensione
  - Oliguria
  - Ipossiemia
  - Acidosi metabolica con elevati livelli di acido lattico

Sindrome da Disfunzione d'Organo Multipla (MODS)

Presenza di alterazione della funzione d'organo in un paziente critico tale che rendere impossibile il mantenimento dell'omeostasi senza intervento esterno

Bone RC, Chest 1992

Multi Organ Failure

Organo	Fisiopatologia	Meccanismo
Sist.vascolare periferico	Vasodilatazione, ipotensione refrattaria,coaguopatia, CID	NO, espressione del fatt. tissutale, migrazione neutrofili
Miocardio	Depressione miocardica, aritmie	Alterato flusso di calcio, F.E.ridotta
Polmone	A.R.D.S.	⇑ permeabilità endolteliale, migrazione neutrofili
Rene	Necrosi tubulare acuta	ipoperfusione renale
Fegato	Necrosi zonale	Ipoperfusione, acidosi
Intestino	Alterazione integrità dell'epitelio	Ipoperfusione, acidosi
Cervello	Encefalopatia	Ipoperfusione, acidosi

Approccio al paziente con sepsi

- Accurato esame obiettivo
- Terapia mirata al sito di infezione
- Ripetuti esami obiettivo

Impossibilità di identificare un'infezione

- **Microrganismo infettante insolito o inatteso**
  - ✓Toxoplasmosi
  - ✓Tubercolosi
  - ✓Varie infezioni fungine
  - ✓Infezione virale
- **Processo in cui è difficile identificare i microrganismi**
  - ✓Sinusite
  - ✓Diverticolite
  - ✓Colecistite alitisiaca
- **Terapia precedente con antibiotici**
- **Limitazioni nella campionatura microbiologica**

PROGNOSI

L'evoluzione dipende anche dal microrganismo in causa

Letalità

- **15% stafilococchi coagulasi negativi**
- **25% bacilli gram negativi**
- **30% enterococchi**
- **40% Candida spp.**

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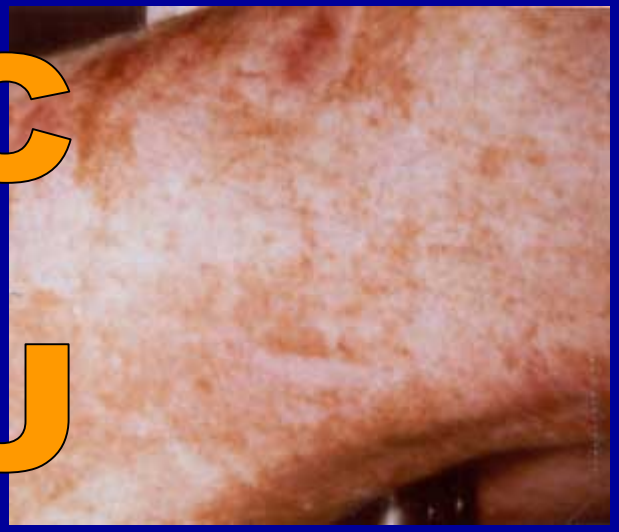
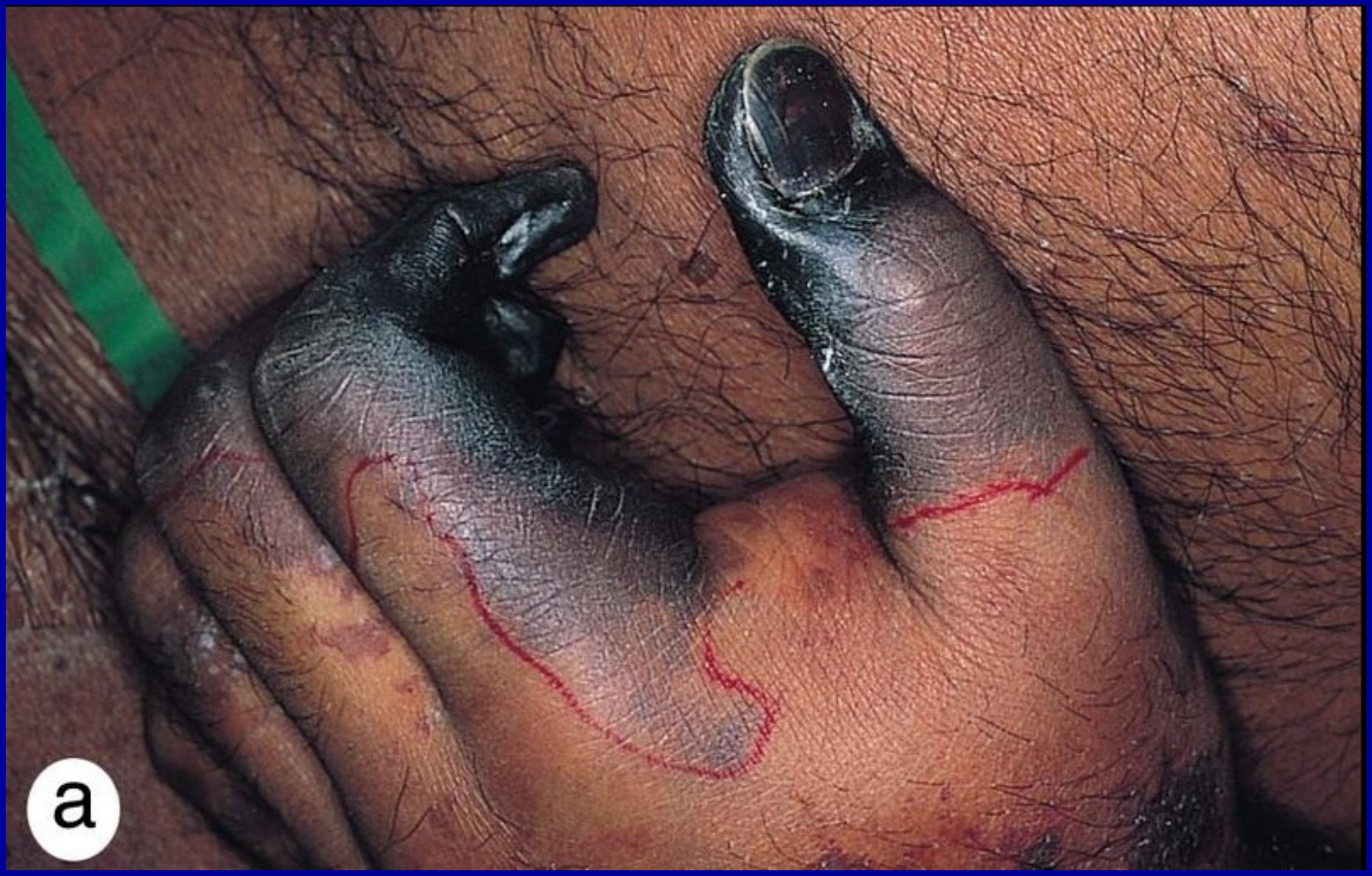


- Ulcere
- Lesioni cutanee
- Petecchie
- Eritema nodulare
- Ectima gangrenoso
- Porpora cutanea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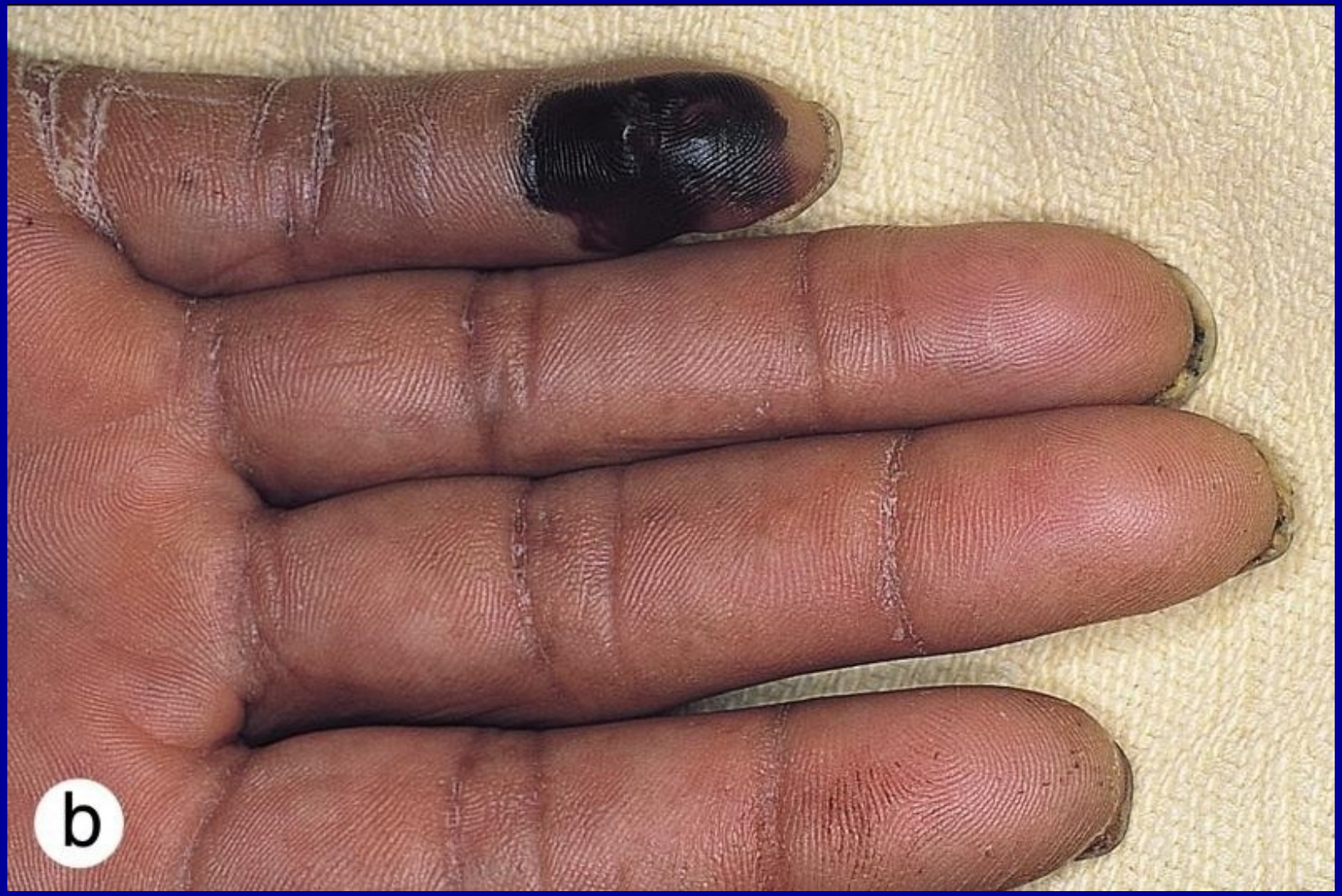
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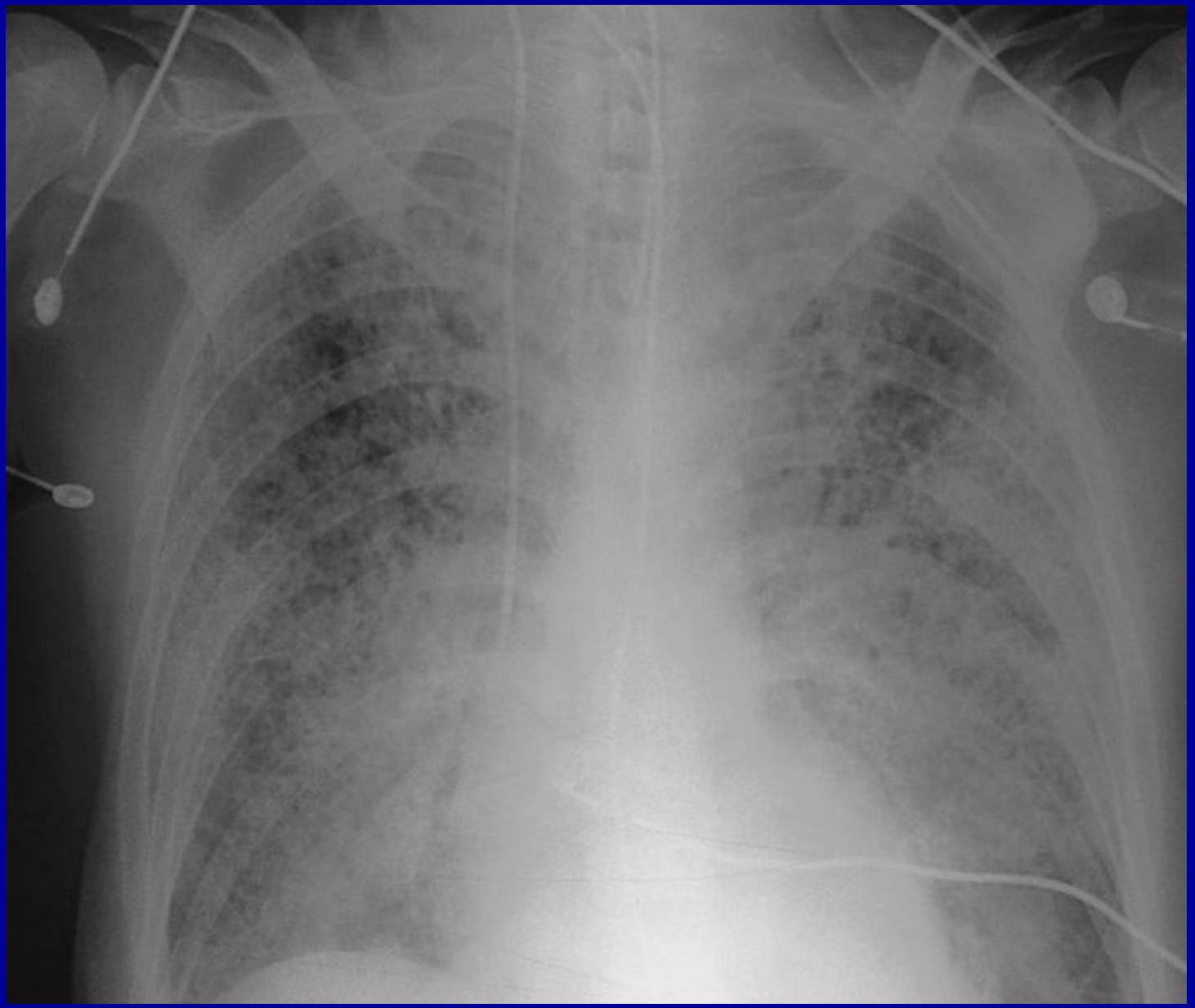


Sepsi: interventi per ridurre la mortalità

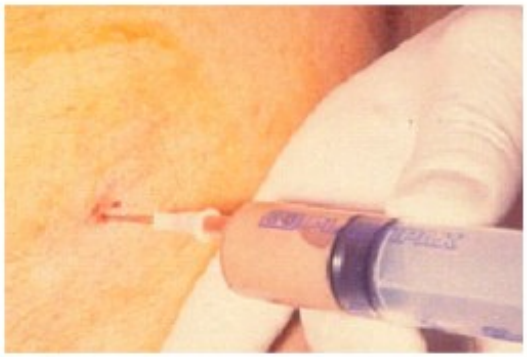
- **Diagnosi precoce**
- **Immediata correzione della ipoperfusione**
- **Steroidi**
  - **Shock settico refrattario**
- **Proteina C attivata**
- **Controllo precoce dell'infezione**
  - **Identificazione della sorgente e terapia antibiotica**

Controllo precoce dell'infezione

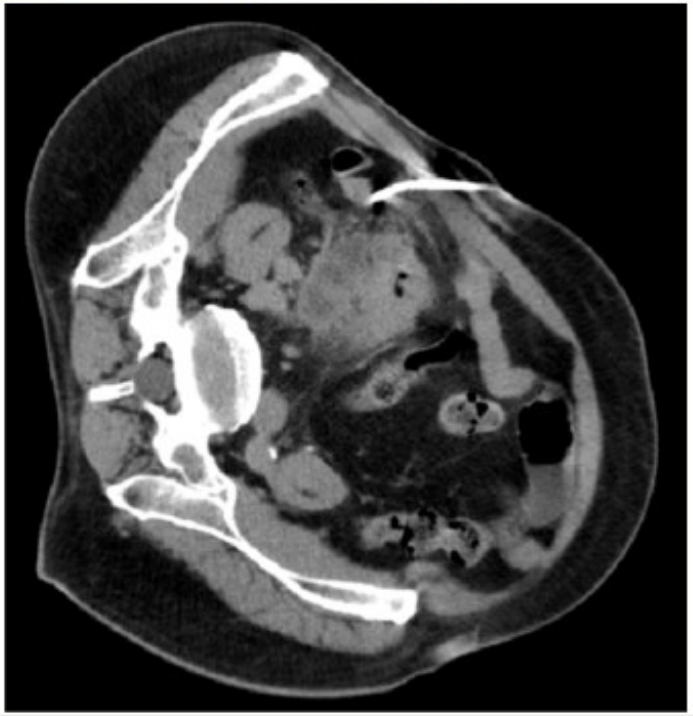
- **Identificazione sorgente**
  - **Tessuti necrotici**
  - **Polmone**
  - **Ascessi**
  - **Cateteri urinari**
  - **Dispositivi protesici**
  - **CVC**

Fighting infection in the first hours

Sampling
Including invasive procedures when needed (BAL…)



Rapid tests
When available. Gram stain!!! When needed



Start adequate antibiotic coverage
(within 1 hour?)
Tillou A et al. Am Surg 2004;70:841-4

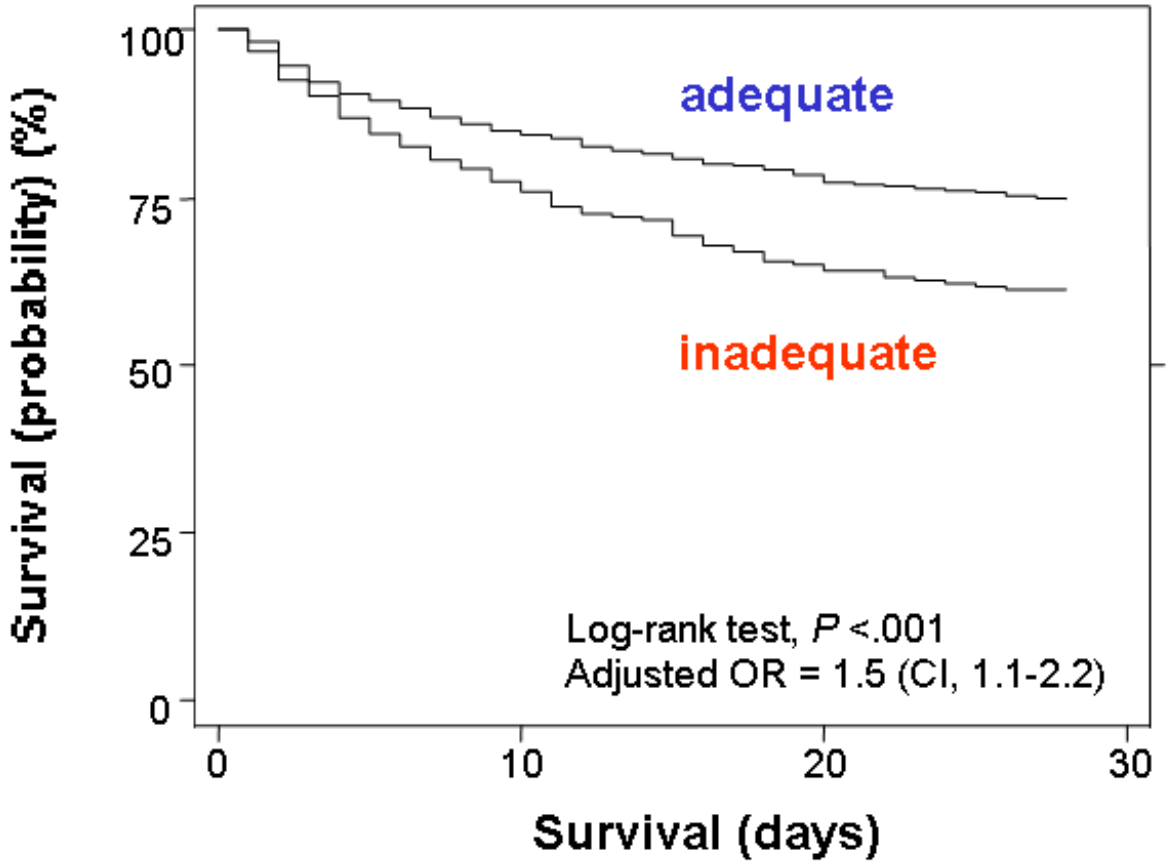
Drain purulent collection

TERAPIA

- Antibiotici battericidi e non batteriostatici
- Terapia associata
  (p.e. ß-Lattamico/glicopeptide + aminoglicoside) per via e.v.
- Terapia empirica in base a
  - sede dell'infezione
  - tipo di esposizione
  - stato immunologico
  - allergie farmacologiche
- Messa in evidenza e rimozione di materiale infetto **(drenaggio ascessi, rimozione cateteri…)**

Survival of patients with sepsis

(1,342 severe sepsis and septic shocks LENERCEPT study)



Harbarth, Giarbino, Pugin et al. Am J Med, 2004

CENNI DI TERAPIA

Controllo del focus infettivo

Terapia antibiotica

Supporto respiratorio/ventilatorio

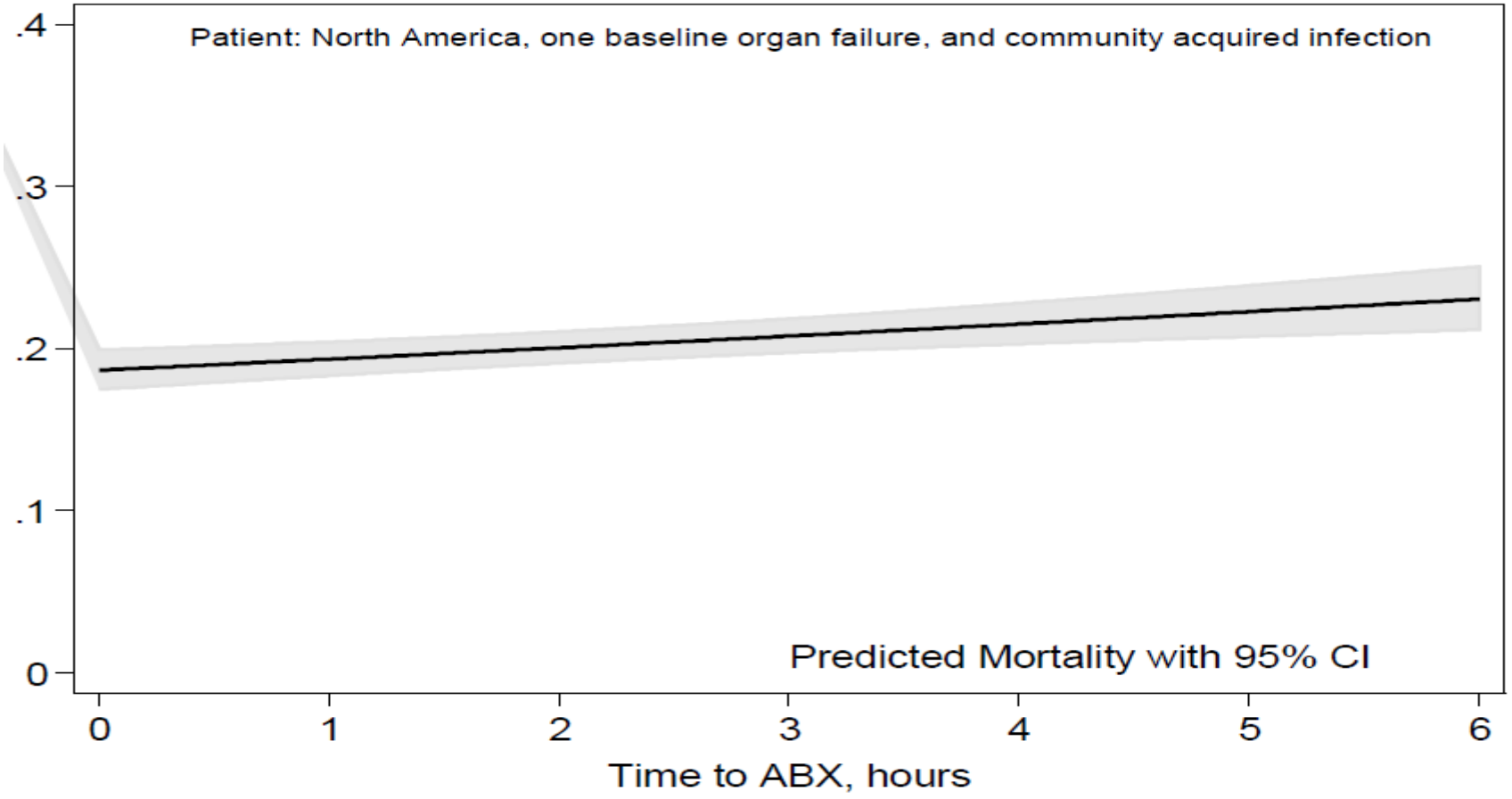
Supporto di volume ed emodinamico

Supporto nutrizionale

Therapeutic measures

- Timing of antibiotic treatment
- Appropriate antibiotic treatment

Hospital Mortality by Time to Antibiotics



Hospital Mortality by Time to Antibiotics

Time to ABX[1], hrs	OR[2]	95% CI		*p*-value	Probability of mortality[3]	95% CI	
0 (ref)	1.00	---	---	---	18.7	17.5	19.9
1	1.05	1.02	1.07	< 0.001	19.3	18.3	20.4
2	1.09	1.04	1.15	< 0.001	20.0	19.1	21.0
3	1.14	1.06	1.23	< 0.001	20.8	19.7	21.8
4	1.19	1.08	1.32	< 0.001	21.5	20.3	22.8
5	1.25	1.11	1.41	< 0.001	22.3	20.7	23.9
6	1.31	1.13	1.51	< 0.001	23.1	21.2	25.1

[1]Time to ABX is based on 15,948 observations that are greater than or equal to zero

[2]Hospital mortality odds ratio referent group is 0 hours for the time to ABX and is adjusted by the number of baseline organ failures, infection type (community vs. nosocomial), and geographic region (Europe, North America, and South America)

Inappropriate Initial Therapy

- The antibiotic does not cover the infecting pathogens
- The pathogen is resistant to antibiotics
- Combination therapy is not used, if indicated
- Dosing is not adequate
- Not adequate tissue penetration

Risk Factors

MDR/Health-care associated pathogens	Fungemia
• broad spectrum antibiotics within 90 d • hospitalization >2 day • local high antibiotic resistance rates • residence in LTCF • chronic dialysis within 30 d • home wound care • family member with MDR infection • mechanical ventilation ≥5 d • immunosuppression • structural lung disease • IV drug use • COPD (*Pseudomonas spp.*) • Influenza infection (MRSA)	• broad-spectrum antibiotics • central venous catheter • parenteral nutrition • renal replacement therapy in ICU • neutropenia • hematologic malignancy • implantable prosthetic devices • immunosuppression • chemotherapy

Clin Infect Dis 2007;44:S27-72
Am J Respir Crit Care Med 2005;171:388-416
Clin Infect Dis 2009;49:1-45
Clin Infect Dis 2009;48:503-35

REVIEW

Virulence 5:1, 206–212; January 1, 2014; © 2014 Landes Bioscience

The clinical impact of multidrug-resistant gram-negative bacilli in the management of septic shock

Aurora Pop-Vicas[1,2,*] and Steven M Opal[1,2]

- In studies of *Pseudomonas aeruginosa* bloodstream infections, mortality ranged from 39% to 42% in patients with stem-cell or solid organ transplants
- Patients with ICU infections with MDR *Pseudomonas* or *Acinetobacter* species have a significantly worse outcome than ICU patients with other types of infection
- In patients infected with carbapenem-resistant organisms from the KPC-producing family, mortality ranged from 24% to 65%

- The impact of inadequate empiric antimicrobial therapy on mortality was illustrated in a study of 186 patients with bloodstream infections caused by ESBL producing organisms. The 3 week mortality associated with receipt of inadequate vs. adequate initial therapy was 60% vs. 19%, respectively

Batteri
Gram-positivi *"non positivi"*

- ***S. aureus*** **meticillino-resistente (MRSA)**
- ***S. aureus*** **intermedio/resistente alla vancomicina (VISA/VRSA) e problema dei ceppi con MIC elevate (>1 mg/L) alla vancomicina**
- **Stafilococchi coagulasi negativi (CoNS) multiresistenti**
- **Enterococchi vancomicino-resistenti (VRE)**
- ***Clostridium difficile***

Etiology of BSI episodes

PATHOGENS	*Clostridium*/BSI+ n= 72
Enterobacteriaceae	14 (19.4%)
***Enterococcus* species**	10 (13.9%)
***Candida* species**	34 (47.3%)
C. albicans	15 (44.1%)
C. glabrata	9 (26.5%)
C. tropicalis	5 (14.7%)
C. parapsilosis	3 (8.9%)
C. krusei	1 (2.9%)
C. guilliermondii	1 (2.9%)
Mixed BSI**	14 (19.4%)
Candida albicans + Enterococcus faecalis	6 (42.9%)
Enterococcus faecalis + Klebsiella pneumoniae	3 (21.5%)
Candida glabrata + Klebsiella pneumoniae	2 (14.3%)
Candida tropicalis + Klebsiella pneumoniae	1 (7.1%)
Enterococcus faecium + Klebsiella pneumoniae	1 (7.1%)
Candida tropicalis + Enterococcus faecium	1 (7.1%)

AAC Accepted Manuscript Posted Online 19 October 2015
Antimicrob. Agents Chemother. doi:10.1128/AAC.01927-15

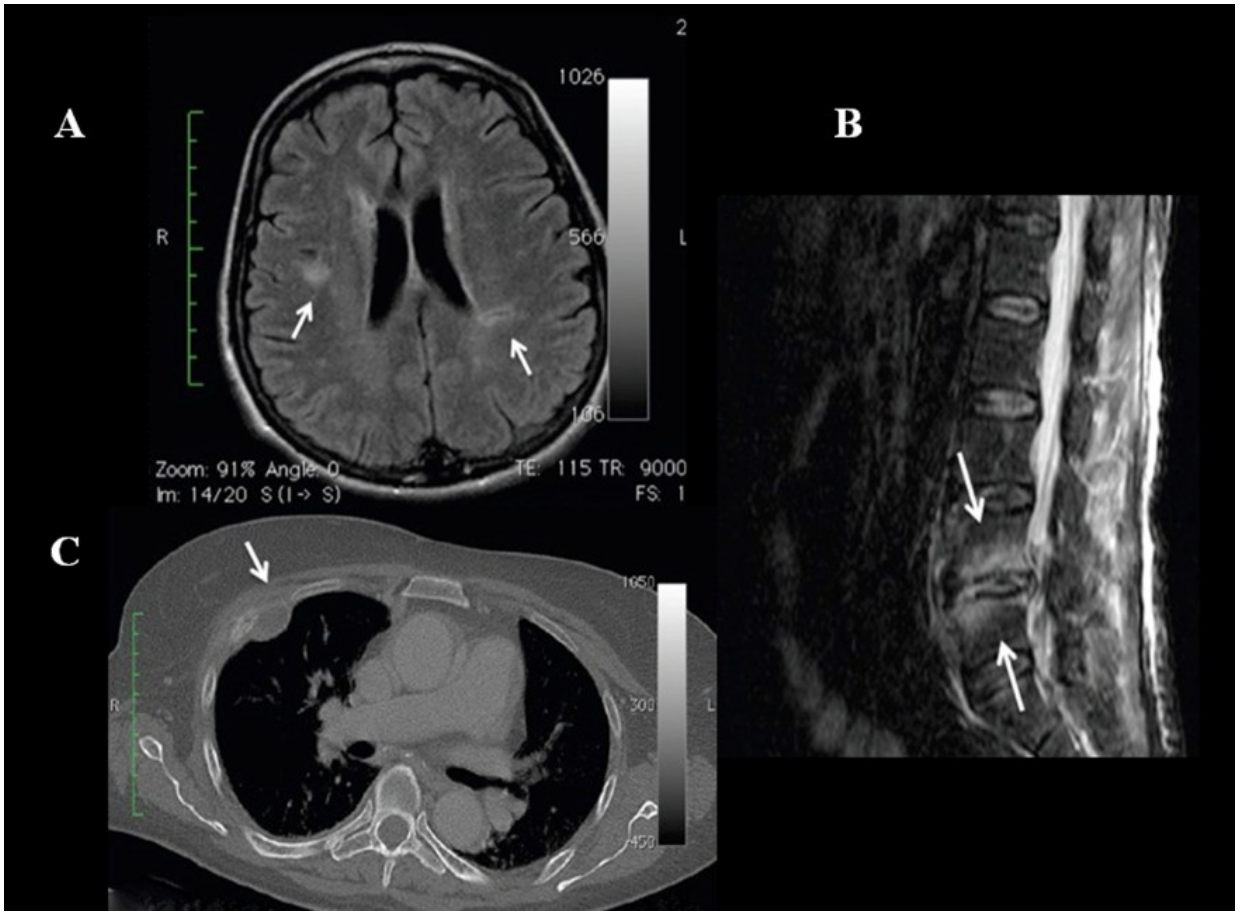
1 Bloodstream infections secondary to *Clostridium difficile* infection:
2 risk factors and outcomes
3
4
5 Marco Falcone[1], Alessandro Russo[1], Federica Iraci[2], Paolo Carfagna[3], Paola Goldoni[1],
6 Vincenzo Vullo[1], and Mario Venditti[1]
7

Late onset invasive pneumococcal disease in a liver transplanted patient: beyond the Austrian syndrome

V. Belvisi, C. Del Borgo, F. Morelli, R. Marocco, T. Tieghi, P. Fabietti, A. Vetica, M. Lichtner, C.M. Mastroianni. Late onset invasive pneumococcal disease in a liver transplanted patient: beyond the Austrian syndrome.
Transpl Infect Dis 2013: **15**: E111–E114. All rights reserved

V. Belvisi, C. Del Borgo, F. Morelli, R. Marocco, T. Tieghi, P. Fabietti, A. Vetica, M. Lichtner, C.M. Mastroianni

Infectious Disease Unit, SM Goretti Hospital, Fondazione Eleonora Lorillard Spencer Cenci, Sapienza University,



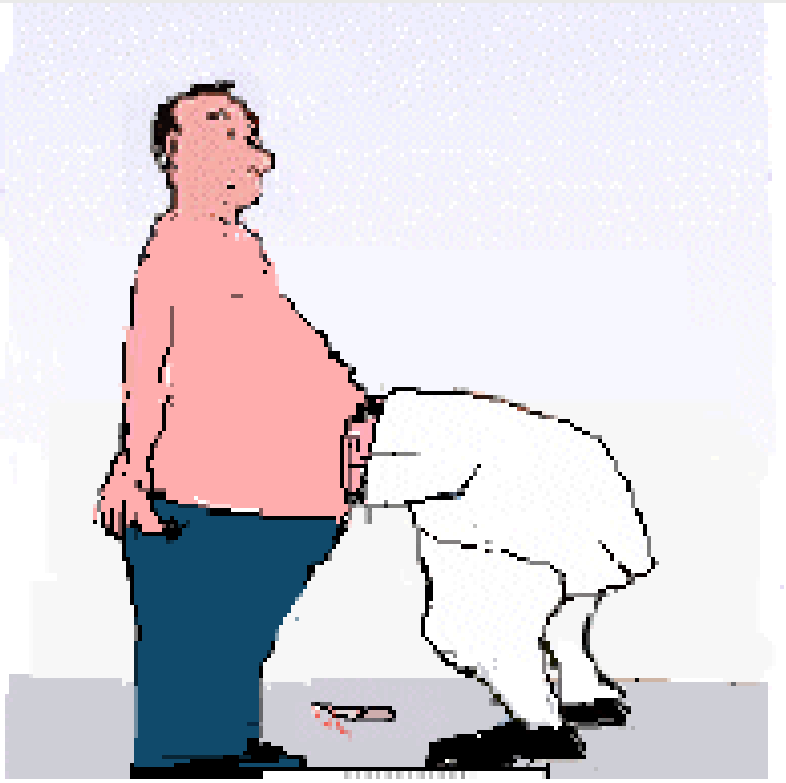
Meningitis
Endocarditis
Spondylodiscitis
Muscle abscess

Clinical management of sepsis

- **Screening**
- **Diagnosis**
- **Antimicrobial therapy**
- **Source control**
- **Selective decontamination**

Il controllo del focus infettivo

Convincere i chirurghi a dare un'occhiata



Source control

Ricerca ed eliminazione del focolaio settico

- **Drenaggio**
  - Ascesso intra-addominale
  - Empiema pleurico
  - Pielonefrite, colangite
- **Asportazione**
  - Infarto intestinale
  - Fascite necrotizzante
  - Necrosi pancreratica infetta
- **Rimozione presidi**
  - Catetere vascolare infetto
  - Catetere vescicale
  - Tubo endotracheale colonizzato
- **Controllo definitivo**
  - Resezione sigma per diverticolite
  - Colecistectomia per colecistite
  - Amputazione per mionecrosi

Clinical Case

- A 37-year-old woman was hospitalized due to a two-week history of persistent fever.
- Thirty days before she had given birth to a healthy child through normal vaginal delivery in the 39th week
- The patient had a history of asymptomatic uterine fibroid, but no systematic follow-up had been performed

Examination

- Fever 39°C, blood pressure 105/50 mmHg, and pulse 100 beats/min. Her respiratory rate was 30 breaths/min.
- Tenderness in lower abdominal quadrants.
- Gynaecological examination revealed an enlarged uterus with tenderness upon deep palpation.
- Laboratory tests: WBC 14,200/mm^3 PLT count of 95,000/mm^3, CRP=10.8 mg/dL PCT=59.71 ng/mL

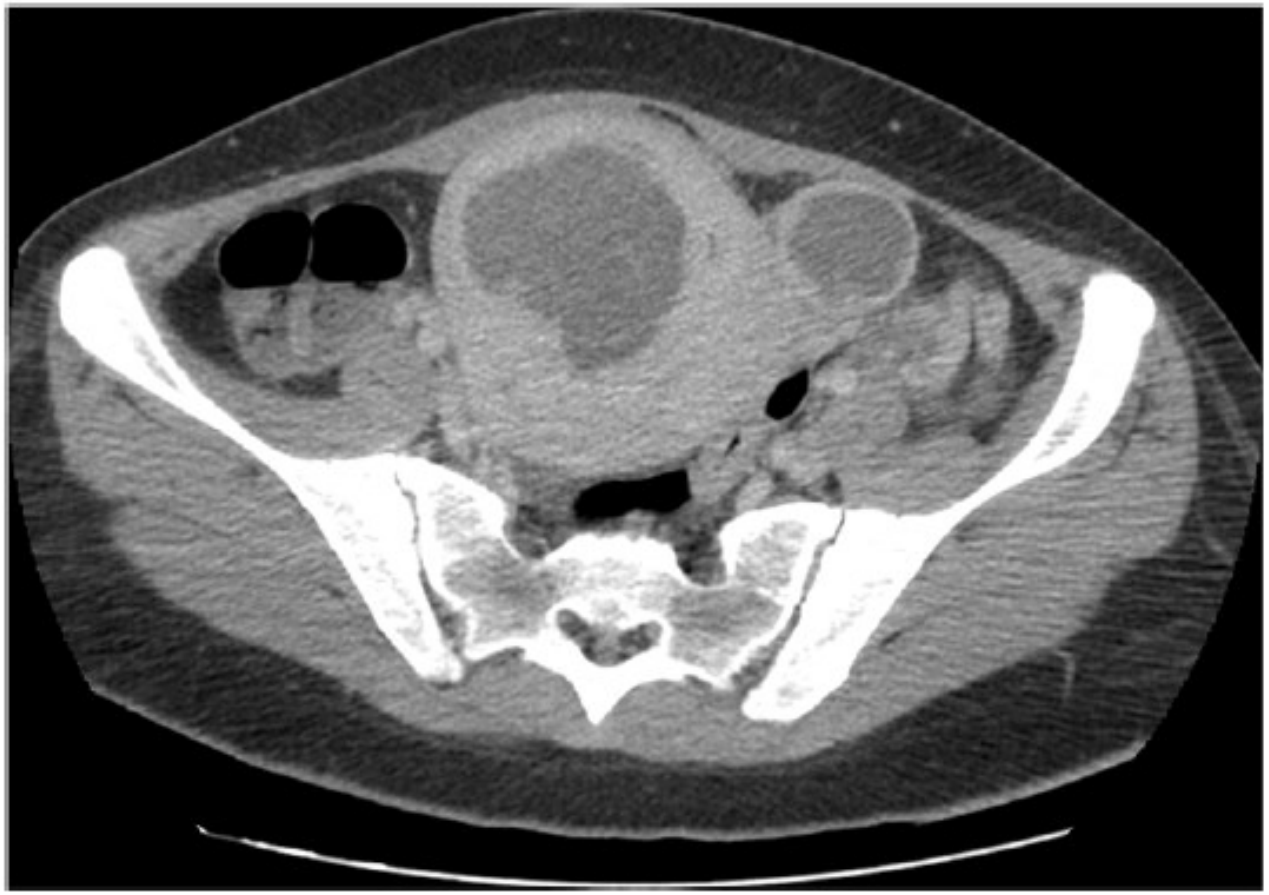


Figure 1 CT scan, abdominal view: mild bilateral hydroureteronephrosis and enlarged uterus with heterogeneous masses.

Antibiotic treatment

- Meropenem, metronidazole, teicoplanin
- No improvement

Blood cultures: Sphingomonas paucimobilis

Table 1 Antimicrobial drug susceptibility of *Sphingomonas paucimobilis*

Antimicrobial drug	Susceptibility	MIC (µg/ml)
Ampicillin	S	<=2
Cefotaxime	S	<=1
Gentamicin	S	<=1
Amikacin	S	<=2
Levofloxacin	S	<=0.12
Meropenem	S	<=0.25
Cefepime	S	<=1
Tygeciclin	S	<=0.5

S, susceptible. MICs are based on EUCAST breakpoints.

Explorative laparotomy and source control

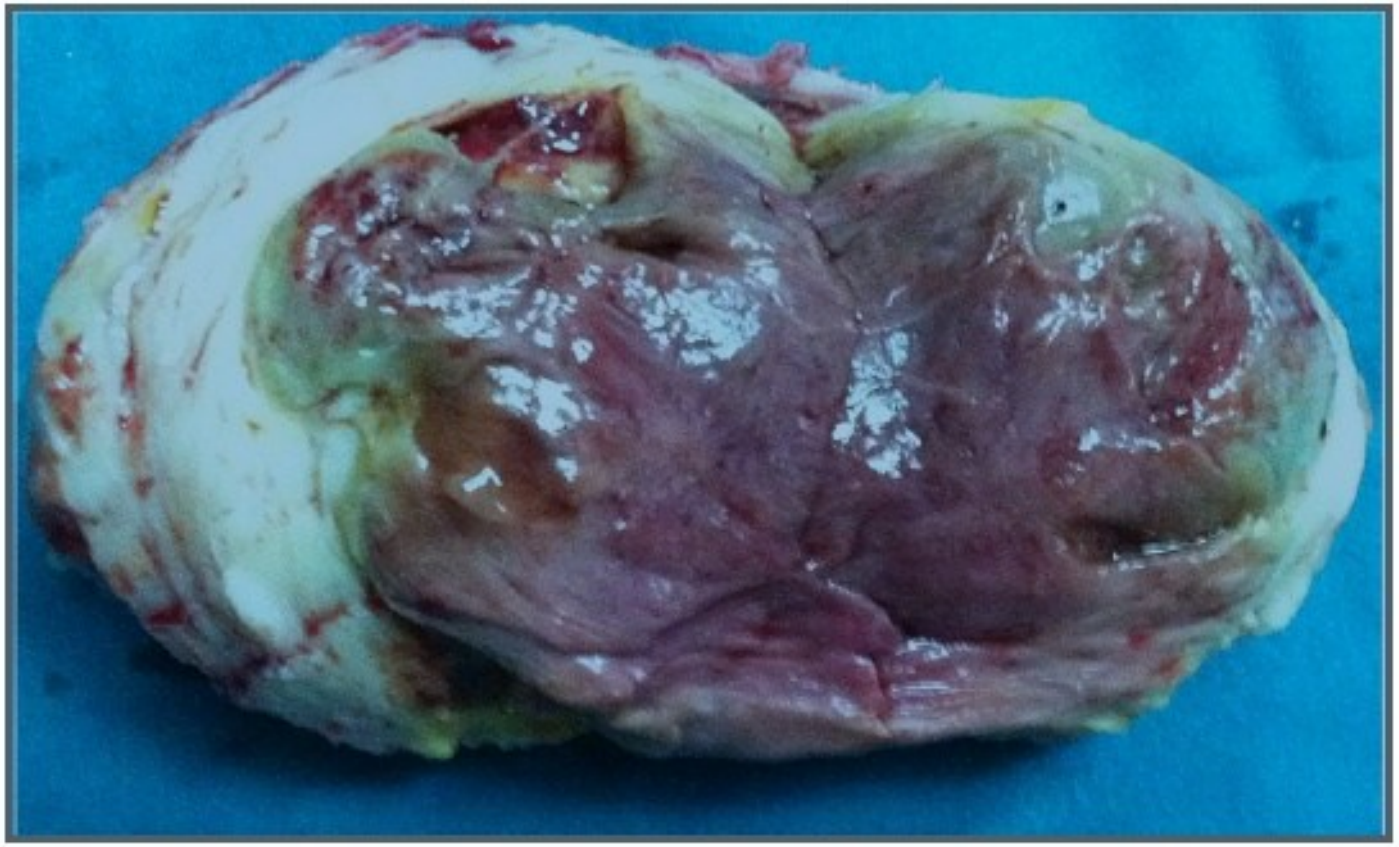


Figure 2 Surgical specimen: anterior view of 10 cm dissected pyomioma of uterine fundus.

Del Borgo *et al. BMC Infectious Diseases* 2013, **13**:574
http://www.biomedcentral.com/1471-2334/13/574

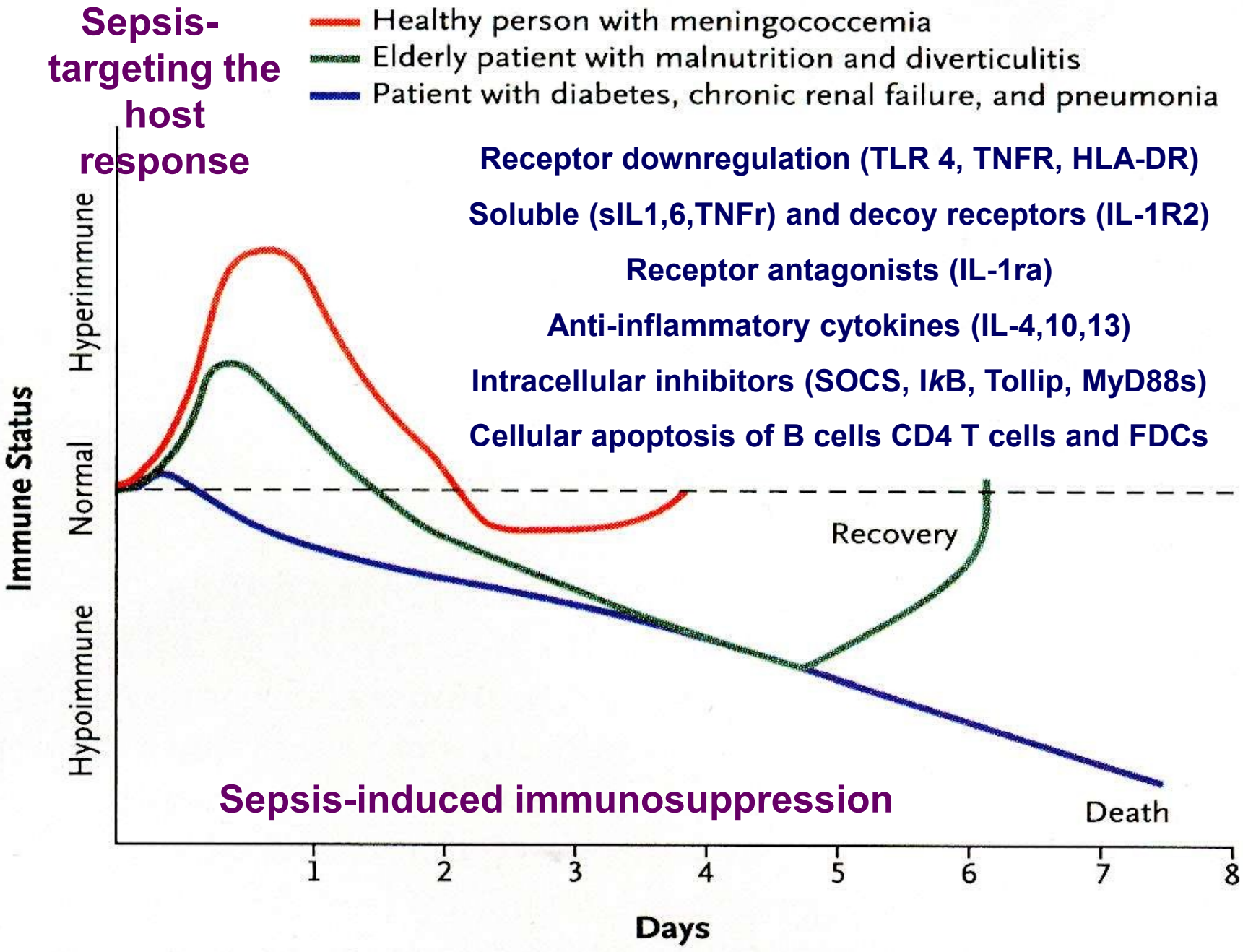
BMC
Infectious Diseases

CASE REPORT Open Access

Postpartum fever in the presence of a fibroid: *Sphingomonas paucimobilis* sepsis associated with pyomyoma

Cosmo Del Borgo[1], Francesco Maneschi[2], Valeria Belvisi[1], Francesca Morelli[1], Angelo Vetica[1], Raffaella Marocco[1], Tiziana Tieghi[1], Miriam Lichtner[1] and Claudio M Mastroianni[1*]

Sepsis-targeting the host response



Receptor downregulation (TLR 4, TNFR, HLA-DR)

Soluble (sIL1,6,TNFr) and decoy receptors (IL-1R2)

Receptor antagonists (IL-1ra)

Anti-inflammatory cytokines (IL-4,10,13)

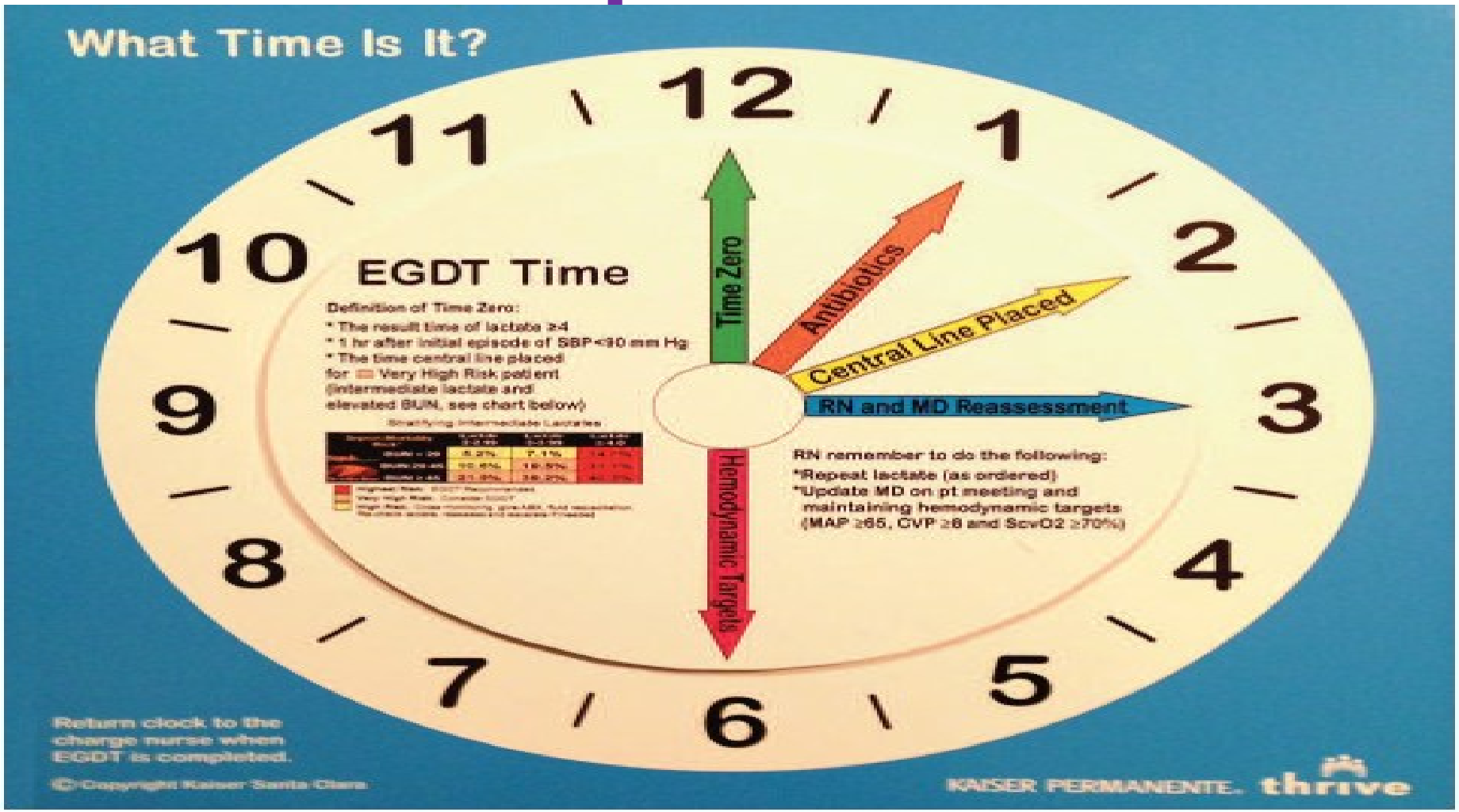
Intracellular inhibitors (SOCS, I*k*B, Tollip, MyD88s)

Cellular apoptosis of B cells CD4 T cells and FDCs

Sepsis-induced immunosuppression

Hotchkiss and Karl NEJM 2003;348:138

Sepsis Clock



Each minute without

DIAGNOSIS and TREATMENT

reduces survival