SOCIETÀ MEDICA DI SANTA MARIA NUOVA

IX EDIZIONE

Giornate Mediche di Santa Maria Nuova 2017

L'Ospedale dei Fiorentini

LA DIMISSIONE OSPEDALIERA "RITARDATA":
Complicanze intraospedaliere e criticità gestionali

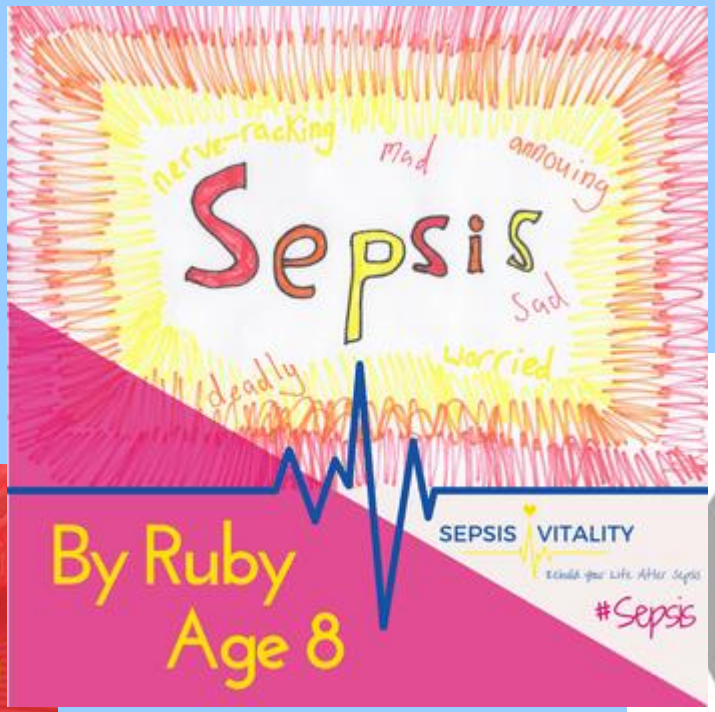
5-6 Ottobre 2017

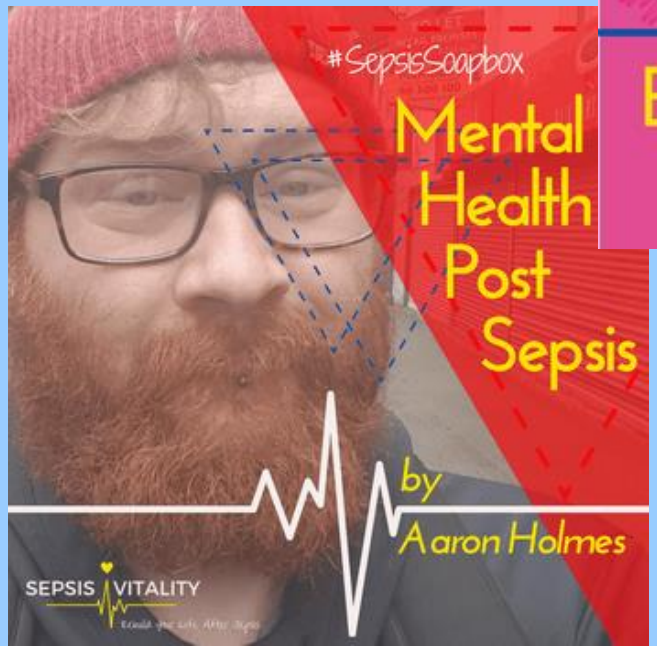
• Il ruolo dei biomarcatori di flogosi e di sepsi

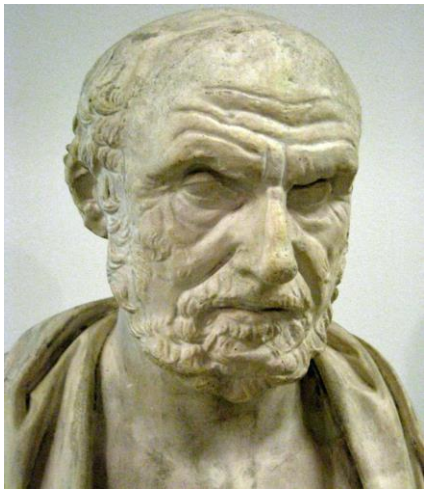
D.ssa Francesca Veneziani

SEPSIS VITALITY

REBUILD YOUR LIFE AFTER SEPSIS







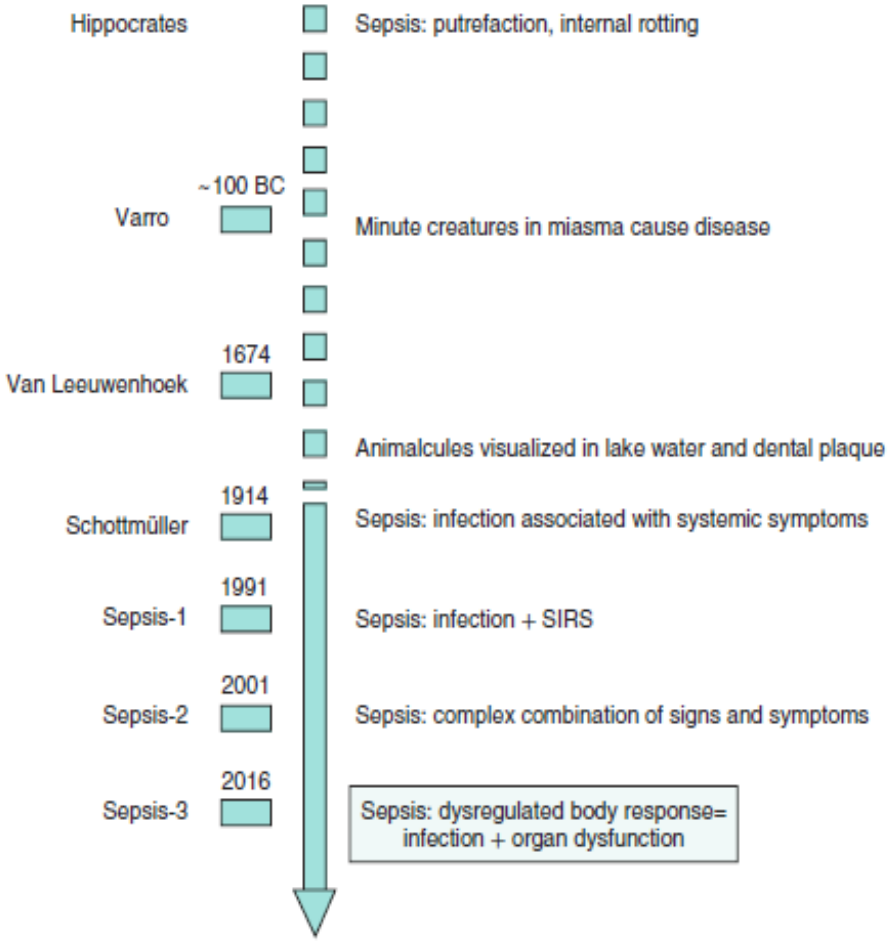


Fig. 1 Sepsis: key definition concepts over time

Vincent JL, *BJS* 2017; **104**: e34–e40

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

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

SEPTIC SHOCK is a subset of sepsis in which particularly profound circolatory , cellular and metabolic abnomalities are associated with a greater risk of morbidity than with sepsi alone

GET AHEAD OF SEPSIS

KNOW THE RISKS. SPOT THE SIGNS. ACT FAST.

PROTECT YOUR PATIENTS FROM SEPSIS.

Infections put your patients at risk for sepsis. Be alert to the signs and, if suspected, act fast.

Sepsis is the body's extreme response to an infection. It is life-threatening, and without prompt treatment, often rapidly leads to tissue damage, organ failure, and death.

SEPSIS STATS

More than **1.5 MILLION** people get sepsis each year in the U.S.

At least **250,000** Americans die from sepsis each year

About **1 IN 3 PATIENTS** who die in a hospital have sepsis

WHAT CAUSES SEPSIS?

The most frequently identified pathogens that cause infections that can develop into sepsis include *Staphylococcus aureus* (staph), *Escherichia coli* (E. coli), and some types of *Streptococcus* (strep).

Four types of infections that are often linked with sepsis:

- Lungs (e.g., pneumonia)
- Urinary tract (e.g., kidney)
- Skin
- Gut

WHO IS AT RISK?

Anyone can get an infection, and almost any infection can lead to sepsis. Certain patients are at increased risk for developing sepsis:

- **65+** Adults 65 or older
- People with chronic medical conditions, such as diabetes, lung disease, cancer, and kidney disease
- People with weakened immune systems
- Children younger than one

Sepsis

- Sepsis affects approximately 700.000 people annually in the United States
- Over 25% of these patiens die before leaving the hospital making sepsis the ninth leading cause of death
- Over 20% of sepsis survivor are readmitted within 30 days
- Nearly 30% of these patients have recurrent sepsis.

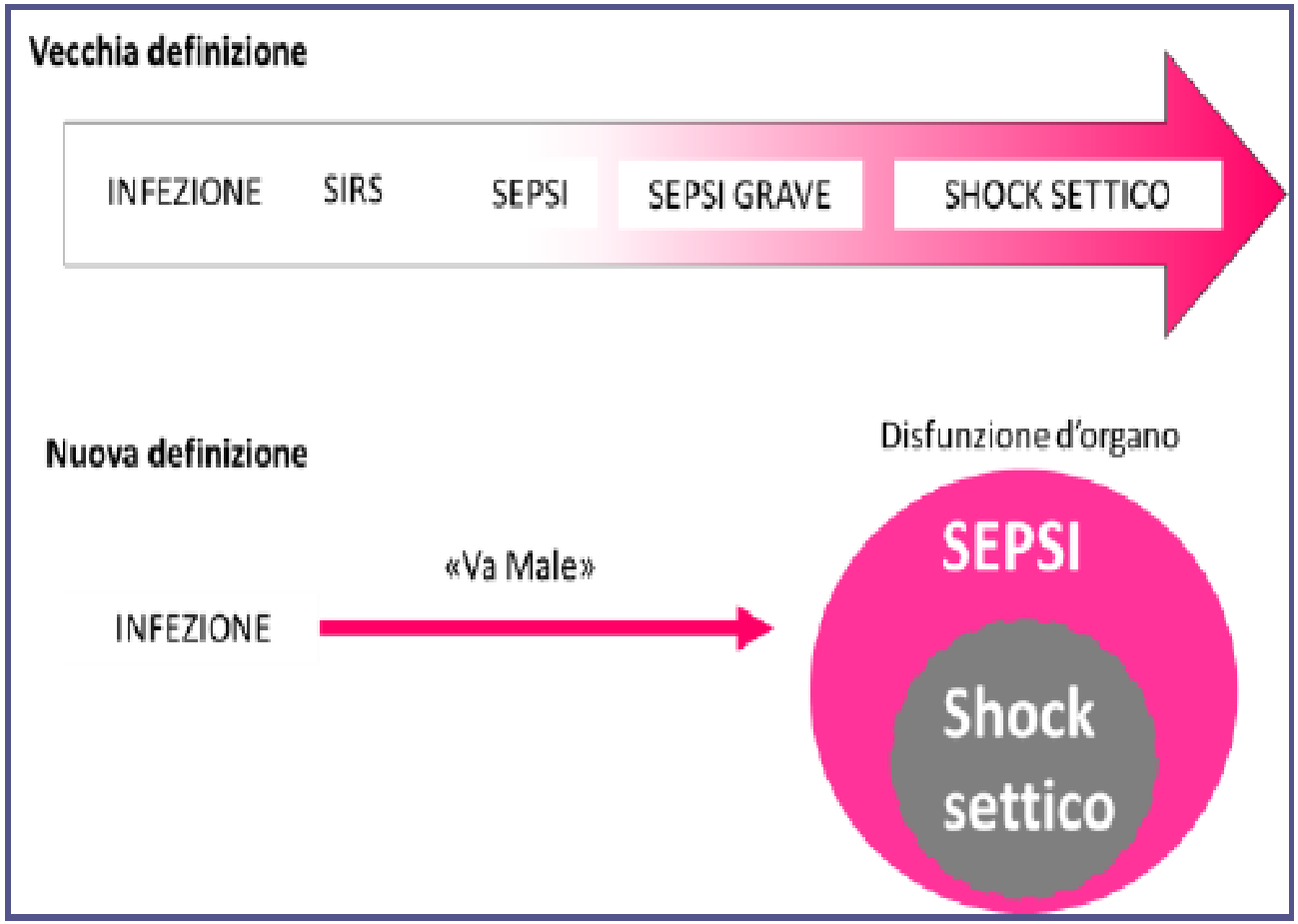

Vecchia definizione
INFEZIONE
SIRS
SEPSI
SEPSI GRAVE
SHOCK SETTICO
Nuova definizione
Disfunzione d'organo
«Va Male»
INFEZIONE
SEPSI
Shock settico

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

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

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

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

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

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

Criteri clinici di Sepsi: Almeno 2 punti al SOFA Score

qSOFA: Frequenza respiratoria ≥ 22/ min

Alterato stato mentale

Pressione arteriosa ≤ 100 mmHg

CRITICAL CARE

COMMENTARY

Don't miss the diagnosis of sepsis!

Paul E Marik

Table 1 Diagnostic features suggestive of sepsis

Diagnostic criteria	Threshold
Fever	>38.3°C
Tachycardia	>120/minute
Systolic blood pressure	<90 mmHg
Procalcitonin	>0.5 ng/ml
Bandemia	>5%
Lymphocytopenia	$<0.5 \times 10^3$ ul
or neurophil/lymphocyte ratio	>10
Thrombocytopenia	$<150 \times 10^3$ ul
Lactate	>2.0 meq/l

Biomarcatore

- Con il termine biomarcatore si intende un analita quantificabile in laboratorio , che consenta di migliorare l'accuratezza diagnostica, di semplificare algoritmi clinici complessi e migliorare il processo decisionale clinico. Nell'ambito specifico della sepsi, un marcatore ideale dovrebbe consentire una diagnosi precoce, essere sensibile e specifico, fornire informazioni sul decorso e la prognosi della malattia, fornire indicazioni per guidare la terapia antibiotica

Table 1
Uses of biomarkers

Screening
To identify patients at increased risk of adverse outcome to inform a prophylactic intervention or further diagnostic test
Diagnosis
To establish a diagnosis to inform a treatment decision and to do so more reliably, more rapidly, or more inexpensively than available methods
Risk stratification
To identify subgroups of patients within a particular diagnostic group who may experience greater benefit or harm with therapeutic intervention
Monitoring
To measure response to intervention to permit the titration of dose or duration of treatment
Surrogate end point
To provide a more sensitive measure of the consequences of treatment that can substitute for a direct measure of a patient-centered outcome

From Marshall JC and Reinhart K. Biomarkers of sepsis Critical Care Medicine 2009, 37, 2290–22

Table 1. Acute Phase Reactants

ESR	Extremely elevated ESR (>100 mm/hour)-high specificity for infection, malignancy, or arteritis. Rises within 24–48 hours of the onset of inflammation and falls back slowly with resolution.
CRP	Begins to rise after 12–24 hours and peaks within 2–3 days. Low levels of CRP elevation with values between 2 and 10 mg/L measured by a "high sensitivity CRP" assay seen in noninfectious "metabolic inflammatory" states such as cardiac ischemia, uremia, or smoking.
PCT	Detectable within 3–4 hours and peaks within 6–24 hours. Elevated levels not seen in other noninfectious inflammatory conditions such as polymyalgia, inflammatory bowel disease, polyarteritis nodosa, systemic lupus erythematosus, gout, and temporal arteritis. More sensitive and specific than CRP for distinguishing bacterial from noninfectious causes of inflammation
Others	Apolipoproteins: SAA proteins Coagulation Pathway: Fibrinogen, Protein S, Plasminogen Complement System: C3, C4, C9, Factor B, C1 inhibitor Antiproteases: Alpha-1 antitrypsin, Alpha-1 acid glycoprotein Proteins: Haptoglobin, Hemopexin, Hepcidin, Ferritin, Ceruloplasmin Cytokines: IL-1, IL-6, tumor necrosis factor-alpha

Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IL, interleukin; PCT, procalcitonin; SAA, serum amyloid A.

Table 1: Role of biomarkers of sepsis.

Biomarkers of sepsis	Prognostic value	Diagnostic value	Syndrome/disease
CRP	No	Yes	Sepsis
Procalcitonin	Yes	Yes	Sepsis/respiratory tract infections/pneumonia/
sTREM-1	Yes	Yes	Sepsis/pneumonia/ meningitis
Pro-ADM	Yes	No	Pneumonia
suPAR	Yes	No	Sepsis/tuberculosis
Presepsin	Yes	Yes	SIRS/sepsis

Presepsina

- E’ una glicoproteina presente sulla membrana di superficie di monociti-macrofagi. E’ un recettore dei complessi lipopolisaccaride(LPS)-proteina legante il lipopolisaccaride (LPB) presente sulla membrana delle cellule fagocitarie , in grado di attivare la cascata infiammatoria dell’immunità innata. Normalmente presente nel siero di pazienti sani , aumenta significativamente nei pazienti settici e l’ incremento è correlato alla gravità della malattia.
- Può essere dosato con metodiche automatizzate in chemiluminescenza
- Cut off 600 pg/ml con sensibilità 78% e specificità 61%

Citochine

- Le citochine sono regolatori pleiotropici della risposta immune che giocano un ruolo chiave nei complessi meccanismi patogenetici della sepsi
- IL-6: azione pro-infiammatoria- stimola la produzione di proteine della fase acuta
- IL-8: chemochina. Prodotta dai macrofagi, agisce nella chemiotassi neutrofilica
- IL-10: azione antiinfiammatoria
- Alti livelli di IL6 e IL10 sono predittivi di un'elevata mortalità nei pazienti settici. IL8 è considerato un marcatore di severità della sepsi, soprattutto nei bambini.
- Nessuno studio ha al momento dimostrato che il trattamento della sepsi basato su questi marcatori, influenzi la strategia terapeutica o migliori l'outcome del paziente

Pro-adrenomedullina

- E’ un polipeptide con attività immunomodulante, metabolica e vasodilatante.
- Gioca un ruolo decisivo nell’induzione della vasodilatazione nei primi stadi di sepsi e nella progressione verso lo shock settico
- Ha azione battericida e potrebbe essere utile nella stratificazione prognostica per identificare pazienti a rischio di sepsi severa.
- In combinazione con la PCT potrebbe migliorare la diagnosi precoce di sepsi

Time course of the mean CRP concentration

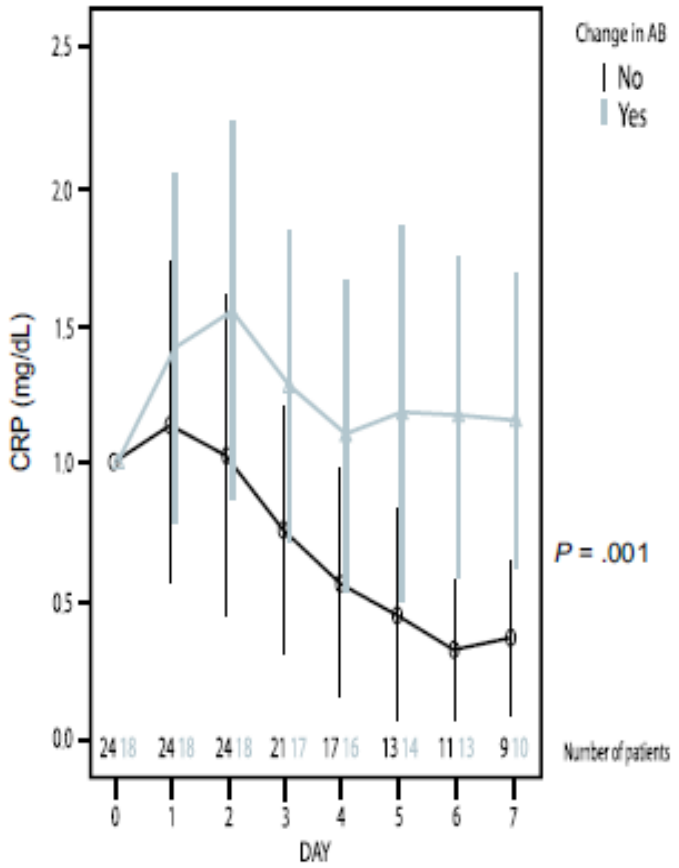


Fig. 1. Time course of the mean CRP concentration in patients with a favorable response to initial antibiotics (AB) (*black line*) and in patients who required a change in antibiotic therapy (*gray line*). Differences, $P = .001$. (*From* Schmit X, Vincent JL. The time course of blood C-reactive protein concentrations in relation to the response to initial antimicrobial therapy in patients with sepsis. Infection 2008;36:217; with permission.)

CRP

- I livelli plasmatici di CRP aumentano tardivamente, oltre 24 ore dopo l'ammissione, rispetto a PCT e Citochine
- Le concentrazioni di CRP possono aumentare in corso di infezioni minori e non riflettono adeguatamente la severità dell'infezione
- I livelli di CRP permangono elevati per diversi giorni anche quando l'infezione è stata superata
- Livelli elevati di CRP si ritrovano in corso di patologie infiammatorie non infettive es. malattie autoimmuni, malattie reumatiche, infarto del miocardio, neoplasie….

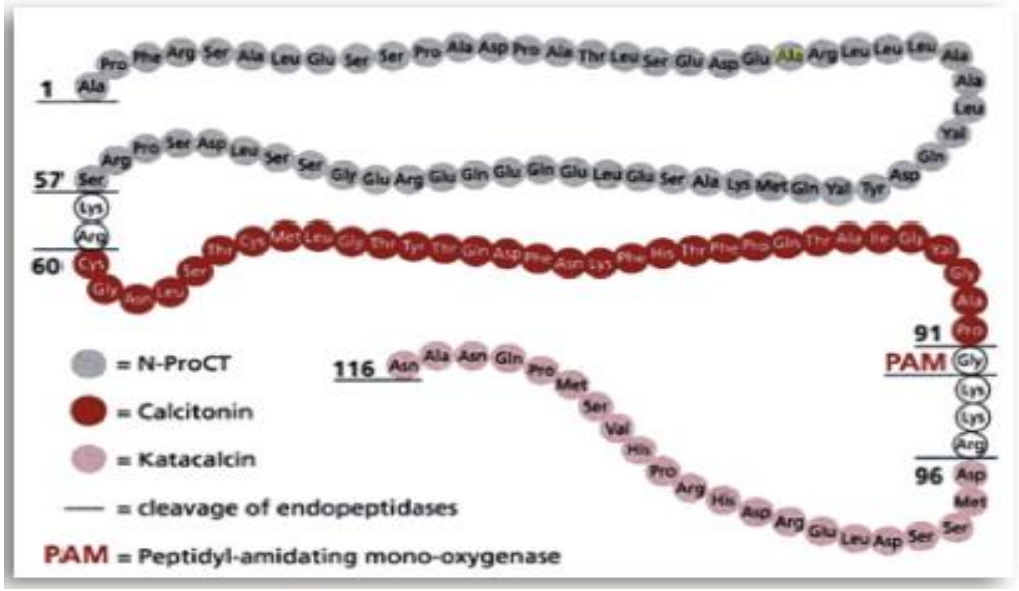
CRP

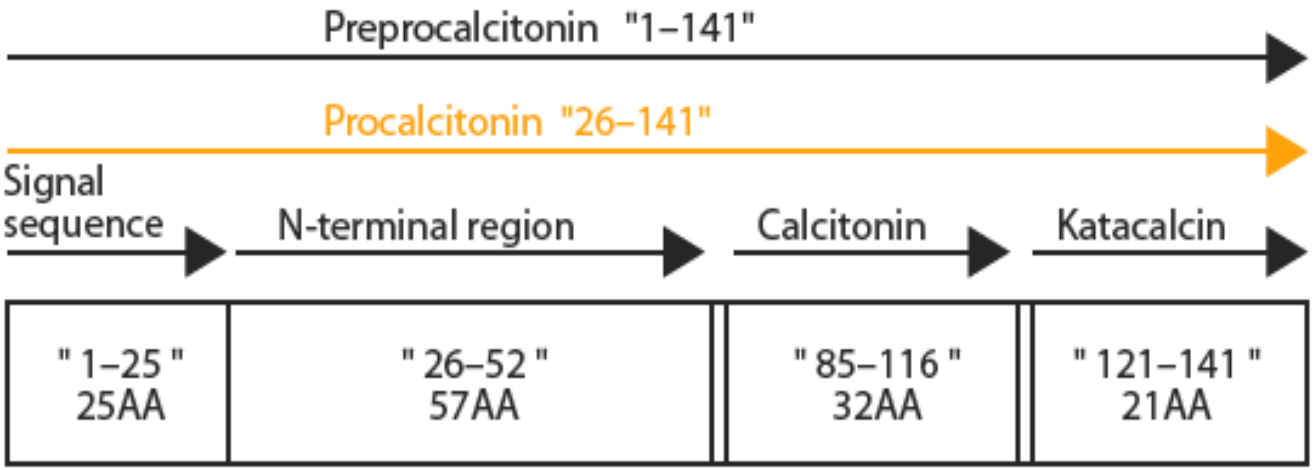
In conclusion, when considering the use of serum CRP levels in critically ill patients, 3 key principles should be remembered:

1. CRP levels, as with other sepsis biomarkers, are more useful to rule out than to rule in sepsis: An elevated value does not necessarily mean that sepsis is present, but a completely normal value makes a diagnosis of sepsis unlikely.
2. Time course is more important that a single value. An increasing CRP level suggests that infection is developing or worsening, whereas a decreasing CRP level during treatment is reassuring in terms of the adequacy of therapy.
3. Serum CRP levels should always be interpreted in the clinical context. CRP levels alone can never be diagnostic, but should be used to support other clinical signs and symptoms.

Crit Care Clin 27 (2011) 241–251

Struttura della procalcitonina





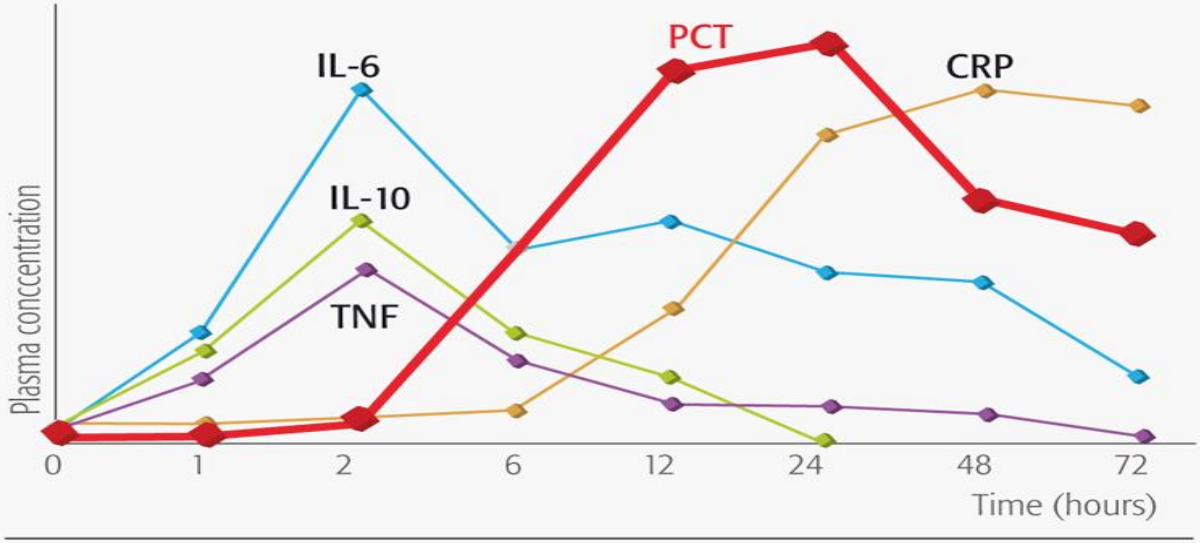
Procalcitonina

- Precursore della calcitonina prodotta dalle cellule C della tiroide
- In corso di infezione batterica viene prodotta da cellule epatiche, monociti e macrofagi
- Aumenta nelle infezioni batteriche
- Elevato VPN
- Valori > 5 ng/ml indicativi di sepsi

- Aumenta già dopo 4 ore
- Le concentrazioni di PCT raggiungono un picco tra 8-24 ore
- Emivita 22-29 ore
- Dopo cessazione dello stimolo si normalizza entro 48-72 ore
- Non è influenzata dalla concomitante terapia steroidea e con FANS
- Non è influenzata dai livelli di WBC

Cinetica della PCT vs. altri biomarkers

- **PCT mostra un profilo cinetico favorevole per l'uso come marker clinico.**
  - misurabile a 3-6 ore dalla stimolazione
  - plateau dopo 12-24 ore e riduzione quando l'infezione è controllata.
  - ridotta half-life (~ 20-35 h) independente dalla funzionalità renale.

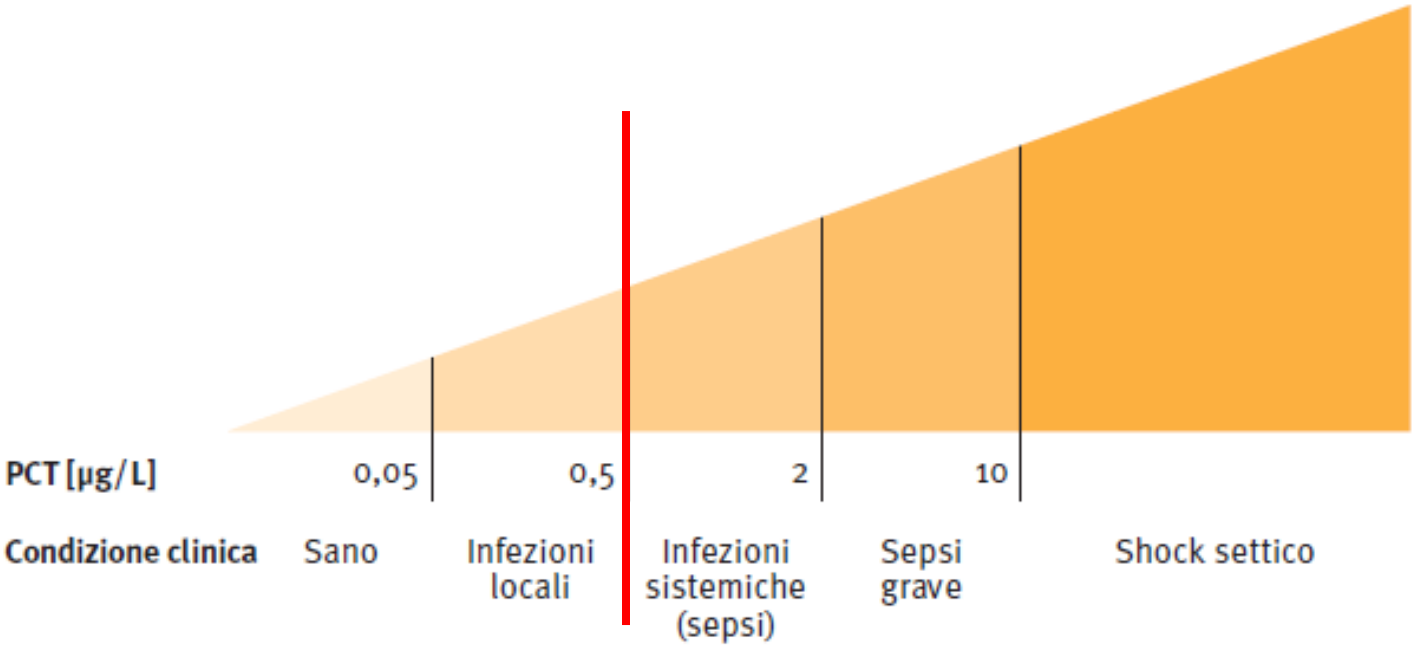


Kinetic profiles of different biomarkers of bacterial infection.
Adapted from Meisner M.[1]

ıb Med (1999)

Caratteristiche

- Correla significativamente con la severità della sepsi



L'aumento della PCT corrisponde fedelmente alla progressione da una condizione clinica **sana** fino agli **stadi più gravi** della patologia (sepsi grave e shock settico)

Oberhoffer, M et al.(1999) Clin Chem Lab Med 37:363-8

Table 1 **PCT Levels and Possible Interpretation**[23]

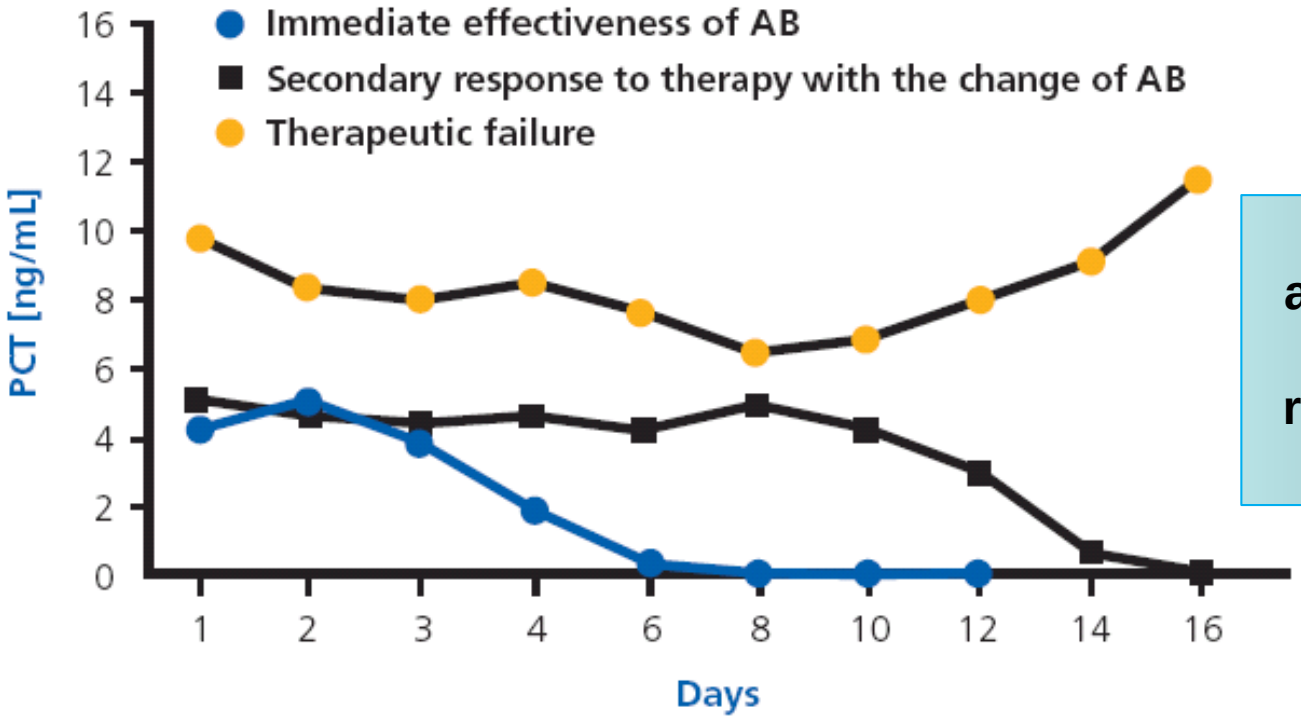
PCT (ng/mL)	Possible Clinical Interpretation
< 0.1	Normal Values Infection very unlikely; systemic inflammatory response unlikely
< 0.5	On first day of ICU admission this indicates a low risk for progression to severe sepsis and/or septic shock, sepsis unlikely Local inflammation or infection is possible: systemic inflammatory response unlikely
≥ 0.5 and < 2.0	Severe trauma, major surgery or cardiogenic shock, If the patient has a proven infection it is likely sepsis Moderate risk for progression to severe systemic infection (severe sepsis) The patient should be closely monitored both clinically and by re-assessing PCT within 6-24 hours
≥ 2.0 and < 10	Very likely to be sepsis On first day of ICU admission this indicates a high risk for progression to severe sepsis and/or septic shock
≥ 10	Severe sepsis or septic shock Organ dysfunction High risk of death

Table 1
Potential benefits of the measurement of PCT levels

Aim of the Study	Findings	References
PCT levels in patients with sepsis, severe sepsis, and septic shock	PCT is significantly elevated in patients with sepsis, severe sepsis, and septic shock. Especially high concentrations were found in patients with severe stages of the disease (severe sepsis, septic shock)	6–13
PCT in severe bacterial infection	PCT levels were significantly higher in patients with bacterial infection than in those with viral and fungal infections and sepsis	14–18
PCT as a marker for effectiveness of source control and prognosis	PCT levels decline by successful measures of source control, and sustained elevated PCT levels are associated with poor prognosis. This finding was demonstrated in adult and pediatric patients with sepsis, VAP, and CAP	6,19–25
Usefulness of PCT for antibiotic stewardship	PCT-guided antibiotic therapy may result in a 20%–70% decrease in antibiotic exposure without a negative effect on patient outcome	26–29

PCT: Monitoraggio Terapia Antibiotica

- La cinetica della PCT si può usare per valutare l‘efficacia della terapia antibiotica e monitorare la risposta dell‘ospite all‘infezione.



Un trattamento antibiotico efficace si riflette nella riduzione dei valori di PCT.

F. Stüber, University Bonn, Lecture at ISICEM, Brussels 2001

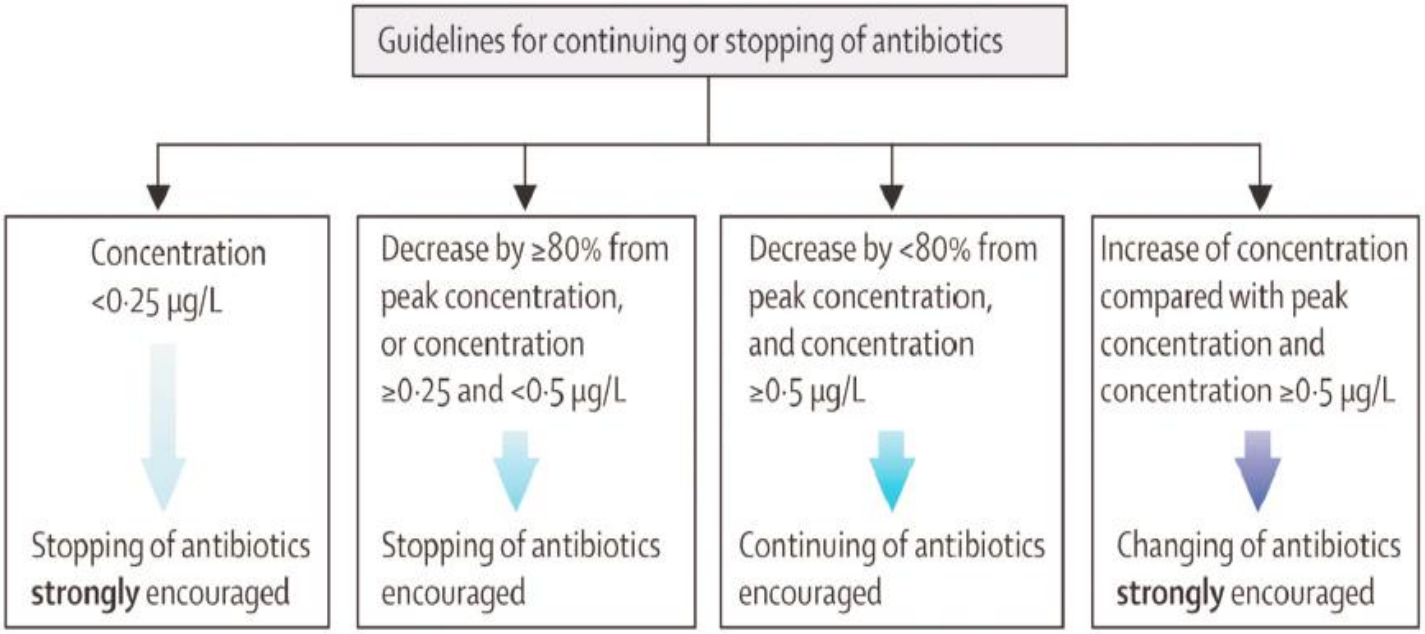


Figura 1
Schema del protocollo consigliato per l'impiego del dosaggio della procalcitonina sierica nei pazienti ricoverati in terapia intensiva al fine di decidere se continuare o cessare una terapia antibiotica. Riprodotta da Bouadma L, Luyt CE, Tubach F, et al. Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial. Lancet 2010;375:463–74 con il permesso dell'Editore.

Numerosi RCT con pazienti arruolati in differenti scenari clinici dimostrano come l'impiego di algoritmi basati sul dosaggio seriato della PCT permetta un uso più giudizioso degli antibiotici sia in PS che in ICU.
La PCT non avrebbe quindi un ruolo primariamente diagnostico ma come importante ausilio nell'incrementare l'appropriatezza delle scelte terapeutiche.

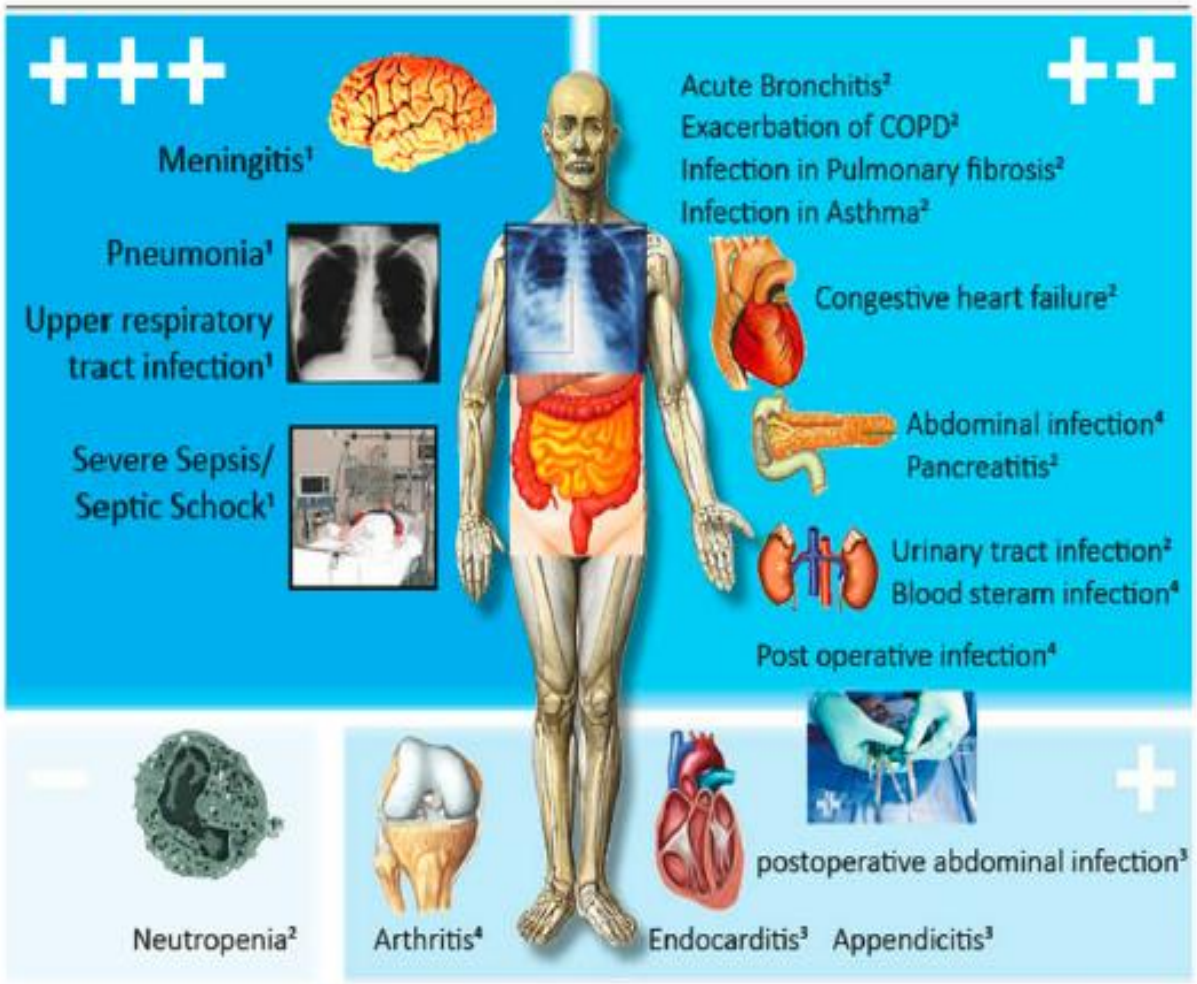
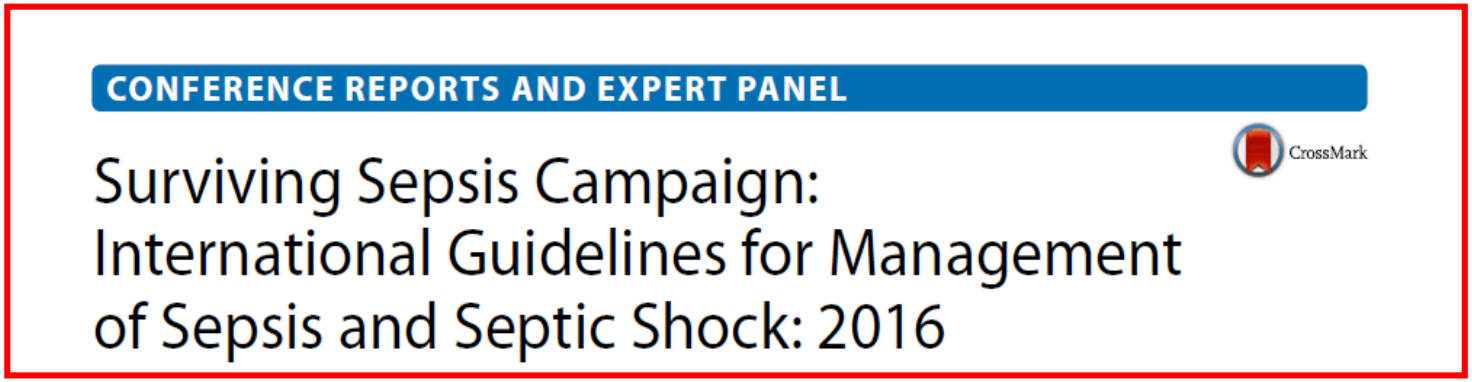


Fig. 1 Summary of evidence regarding procalcitonin (PCT) for diagnosis and antibiotic stewardship in organ-related infections. While for some infections, intervention studies have investigated benefit and harm of using PCT for diagnosis and antibiotic stewardship (*left side*), for other infections only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



- 14. We suggest that measurement of procalcitonin levels can be used to support shortening the duration of antimicrobial therapy in sepsis patients (weak recommendation,low quality of evidence).

- 15. We suggest that procalcitonin levels can be used to support the discontinuation of empiric antibiotics in patients who initially appeared to have sepsis, but subsequently have limited clinical evidence of infection (weak recommendation, low quality of evidence).

CONFERENCE REPORTS AND EXPERT PANEL

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

- It is important to note that procalcitonin and all other biomarkers can provide only supportive and supplemental data to clinical assessment.

- Decisions on initiating, altering, or discontinuing antimicrobial therapy should never be made solely on the basis of changes in any biomarker, including procalcitonin

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

Condition	Comments /Peak	Expected range	Reference
Surgery, trauma, burn, and inhalation trauma. Surgery/ trauma, thoracic surgery	Maximum values on day 1, rapidly declining CRP peak day 2 or 3, slow decline (1–2 weeks)	<0.5–1 ng/mL for peripheral, non-abdominal trauma or minor abdominal surgery) <2 ng/mL for abdominal surgery or trauma, cardiac surgery. >2 ng/mL expected in patients with major retroperitoneal or abdominal surgery, liver transplantation	[23, 68, 69] [70, 71] [72–75]
Cardiogenic shock	Initially low, but increasing within 1–3 days, if vasopressor support is required	May be intermediate to high (e.g. >0.5 ng/mL to >10 ng/mL)	[76–78]
MODS, severe SIRS (various etiology: severe viral infection, pancreatitis, heat stroke)	Increases with severity. After injection of proinflammatory cytokines or application of anti-lymphocyte antibodies (attenuated by corticosteroids)	0.5 ng/mL–2 ng/mL, rarely >10 ng/mL	[79, 80] [28, 81, 82]
Pancreatitis, severe	Low PCT indicates less severe or edematous pancreatitis. Infection not likely. High levels are related with severity, organ dysfunction and infected necrosis	<0.2 ng/mL: mild or edematous pancreatitis. Severe pancreatitis: 0.5 ng/mL–>10 ng/mL	[37–39, 83]
Autoimmune disorders	Induction depends on the type: No or minor induction in: Rheumatoid arthritis, chronic arthritis, systemic scleroderma, amyloidosis, thyroiditis, psoriasis, inflammatory bowel disease, systemic lupus erythematous. May be elevated in: Kawasaki Syndrome, Good pasture's Syndrome, Anti-neutrophil antibody-positive vasculitis, autoimmune hepatitis or primary sclerosing cholangitis, M. Still	Usually less than 0.3–0.5 ng/mL, in some types significant increase >1 ng/mL–10 ng/mL	[84–90]
Severe renal or liver dysfunction	Chronic and moderate elevation, only at severe dysfunction (dialysis, prior to dialysis, Child C). May decline during hemofiltration and after onset of hemodialysis. Cases with increase reported during acute liver failure	In the lower range, 0.1–2 ng/mL, constant elevation	[44, 91–94] [95, 96]
After prolonged resuscitation, myocardial infarction	Peak Day 1	Only In case of prolonged CPR, levels are related with prognosis after CPR. Very faint increase after myocardial infarction.	[97, 98]
Neonates after birth	Peak Day 1–2	Use adapted reference range	[99–102]
End stage of tumor disease	Slow increase. Para neoplastic induction very rare, always by C-cell carcinoma.	Low (0.5–2 ng/mL)	[103] [104]
Rhabdomyolysis	Acute	May be very high	Individual reports

Metodi di dosaggio

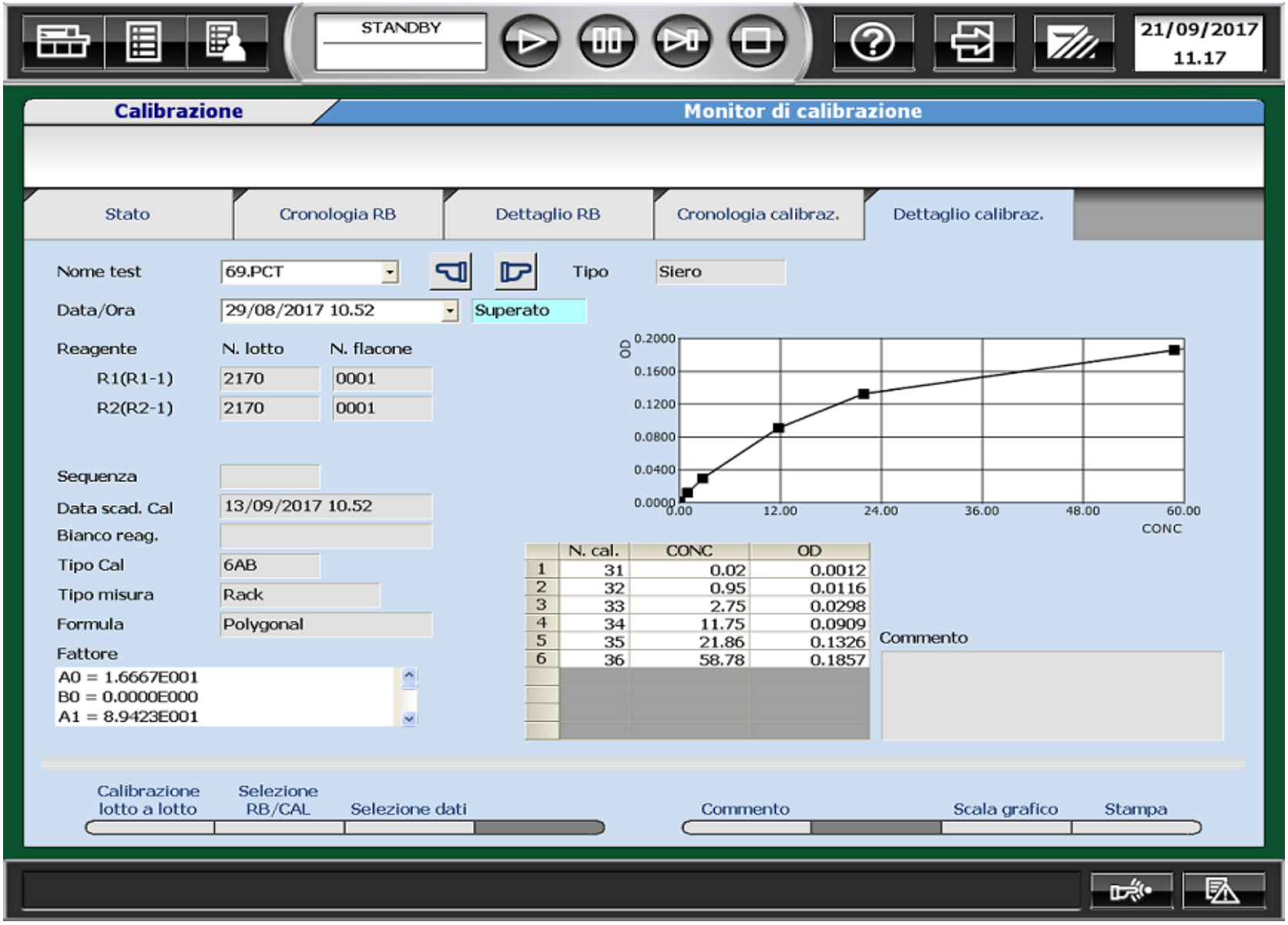
Tabella 1
Metodologie disponibili commercialmente per il dosaggio della procalcitonina

Ditta/Analizzatore	Principio analitico	LOD, µg/L	LOQ, µg/L	Intervallo misurazione, µg/L
Brahms LUMItest	Immunoluminometrico	0,08	0,30	0,1-500
DiaSorin Liaison	Immunoluminometrico	0,04	0,30	0,1-500
ThermoFisher Kryptor	"Time resolved amplified cryptate emission" (TRACE)	0,02	0,06	0,02-5000
BioMérieux Vidas	ELFA ("enzyme-linked fluorescent immunoassay")	0,05	0,09	0,09-200
Siemens Advia Centaur	Chemiluminescenza	0,02	0,05	0,02-75
Roche Elecsys	Elettrochemiluminescenza	0,02	0,06	0,02-100

LOD, limite di rilevabilità; LOQ, limite di quantificazione ("functional sensitivity"): la più bassa concentrazione di analita che può essere misurata con un CV <20%.

Biochimica clinica , 2013

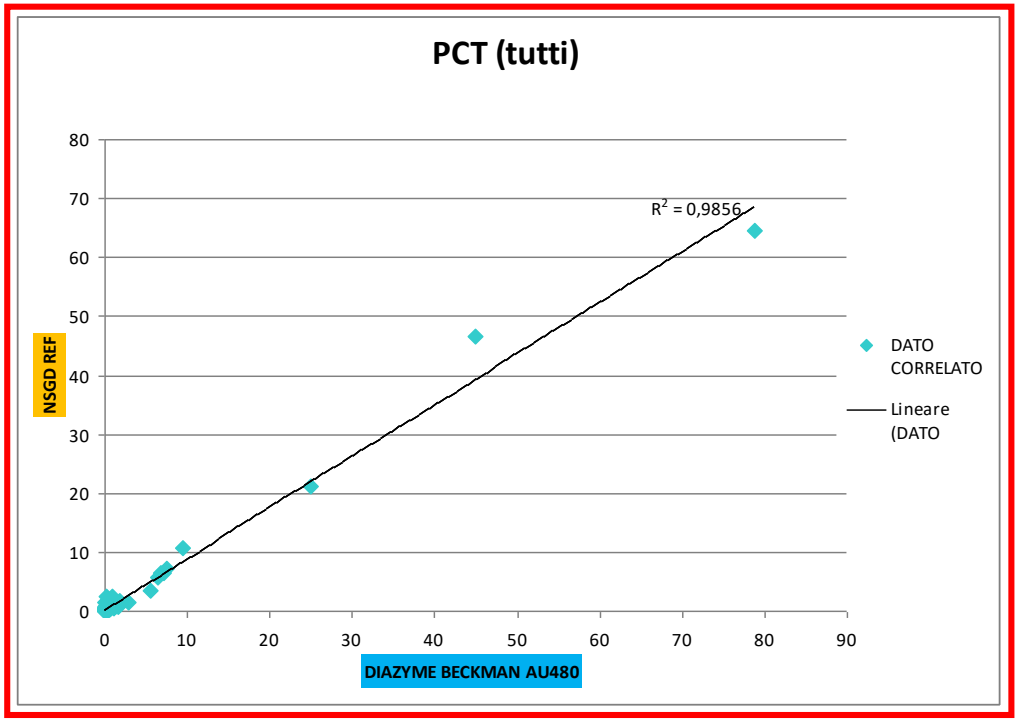
PCT Dyazime - Calibrazione



PCT metodo turbidimetrico vs PCT chemiluminescenza

Dati di precisione metodo Diazyme

Precisione metodo Diazyme su AU480	
Media ng/ml	**CV %**
0,75	5,44
1,2	4,51
2,37	2,03
6,59	2,05
11,32	2,18



I risultati ottenuti con il metodo Dyazime sono compresi in un range compreso fra 0,01 e 64,59 ng/ml. Il confronto con il metodo di riferimento Brahams mostra una buona correlazione (R^2= 0.9838). Le prove di precisione sono state eseguite a vari livelli di concentrazione: ***Media*** *= 0.75 ng/mL* ***CV%*** *= 5.44;* ***Media*** *= 1.20 ng/mL* ***CV%*** *= 4.51;* ***Media*** *= 2.37 ng/mL* ***CV%*** *= 2.03;* ***Media*** *= 6.59 ng/mL* ***CV%*** *= 2.05;* ***Media*** *= 11.32 ng/mL* ***CV%*** *= 2.18.*

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Effectiveness and safety of procalcitonin evaluation for reducing mortality in adult patients with sepsis, severe sepsis and septic shock (Protocol)

- Further high-quality research are needed to confirm the safety of procalcitonin algorithms in critical care settings and for guiding treatment of nonrespiratory infections.

  Future trials should evaluate the cost-effectiveness of procalcitonin algorithms by considering country specific costs of procalcitonin measurements and potential savings and health benefits by reducing antibiotic prescription rates.

Procalcitonin testing for diagnosing and monitoring sepsis (ADVIA Centaur BRAHMS PCT assay, BRAHMS PCT Sensitive Kryptor assay, Elecsys BRAHMS PCT assay, LIAISON BRAHMS PCT assay and VIDAS BRAHMS PCT assay)

NICE guidance

- There was not enough evidence to recommend that these tests are used in the NHS. But NICE has recommended further research and data collection to show the impact of adding procalcitonin testing to standard clinical practice in the NHS.

- The Procalcitonin test show promise but further research are recommended for guiding decisions to stop antibiotic treatment in people with confirmed or highly suspected sepsis in the ICU or start and stop antibiotic treatment in people with suspected bacterial infections presenting to the ED

The “Choosing Wisely” initiative in infectious diseases

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Do not treat an elevated C-reactive protein (CRP) or procalcitonin in serum with antibiotics for patients not presenting signs or symptoms of infection

Elevated systemic inflammatory biomarkers reflect an inflammatory condition in the body. They are not solely specific for infections and especially not for bacterial infection. However, they could be evaluated in the context of specific clinical presentation. High inflammatory biomarkers might prompt a search for an infection. Though, biomarkers without any clinical signs for an infection (for example pneumonia, urinary tract infection or blood stream infection) do not represent an indication to initiate antibiotic treatment [29–32].