IL LABORATORIO E LA DEFINIZIONE DEL RISCHIO

Elisa Pontoni, PS Pordenone

XIII congresso nazionale
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IL LABORATORIO E LA DEFINIZIONE DEL RISCHIO

Eventualità di subire un danno
Connessa a circostanze piu' o meno
prevedibili

TRA PALCO E REALTA'

Inge Morath

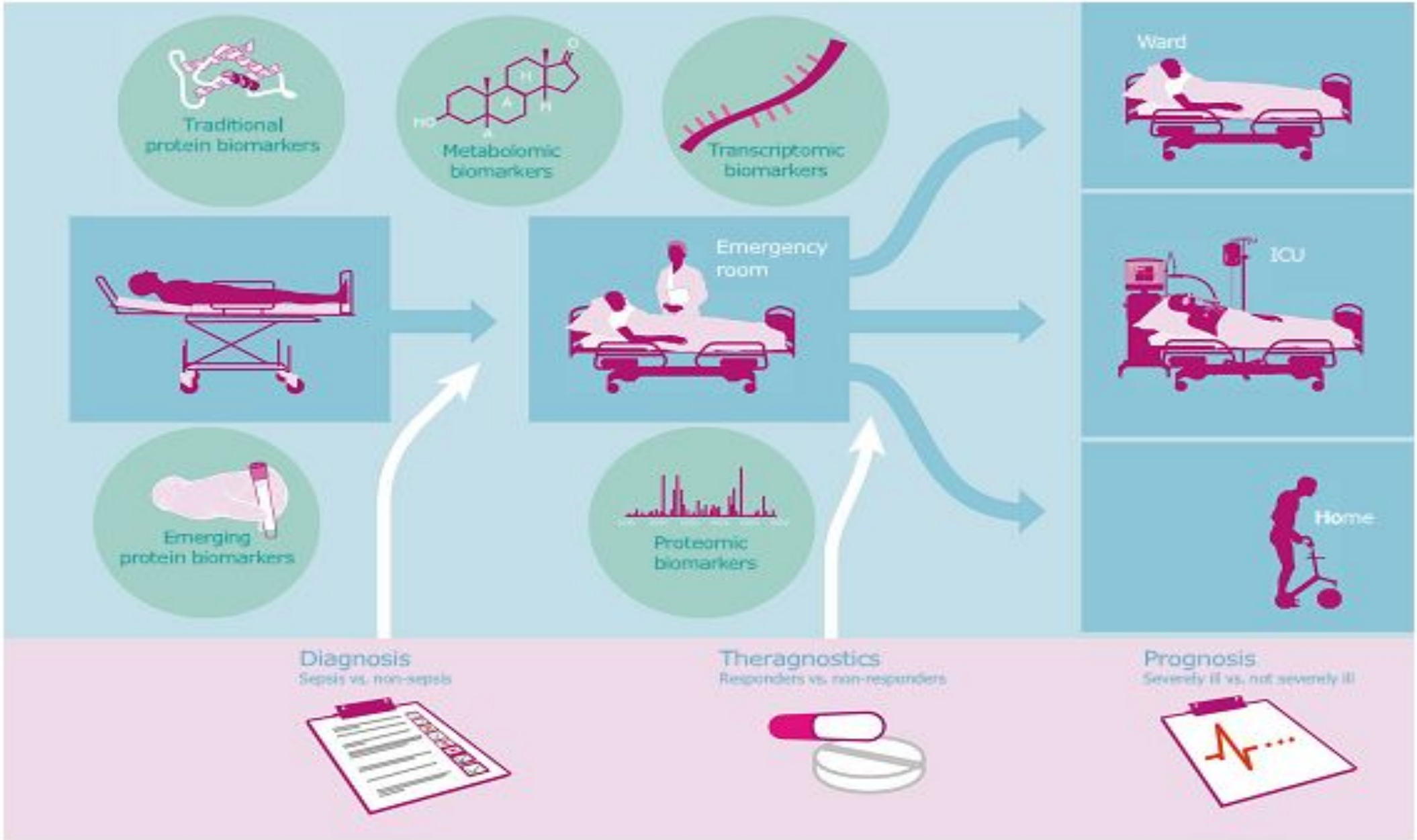


Fig. 1 Host response biomarkers for sepsis in the emergency room (ER). A visualization of the patient flow through the ER and of the different types of sepsis biomarkers and their respective roles in this process

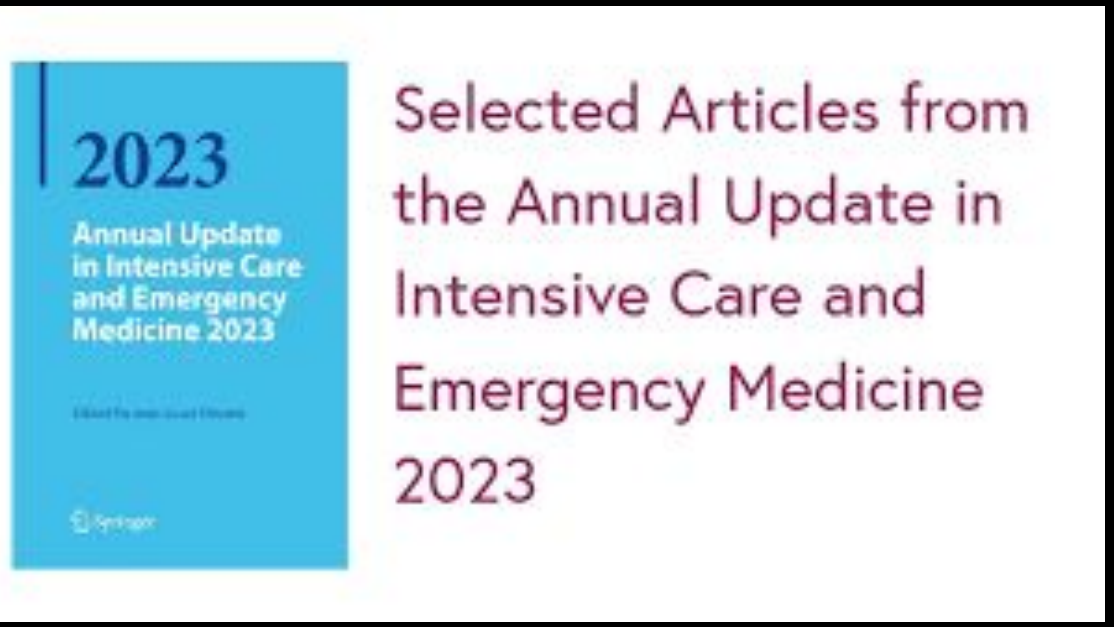
REVIEW ARTICLE

Surviving Sepsis Campaign Research Priorities 2023

De Backer, Daniel MD, PhD (Co-chair)[1]; Deutschman, Clifford S. MS, MD, MCCM[2,3]; Hellman, Judith MD[4]; Myatra, Sheila Nainan MD, FCCM[5]; Ostermann, Marlies MD, PhD[6]; Prescott, Hallie C. MD, MSc, FACP[7]; Talmor, Daniel MD, MPH[8]; Antonelli, Massimo MD, PhD[9,10]; Pontes Azevedo, Luciano Cesar MD, PhD[11]; Bauer, Seth R. PharmD, FCCM[12]; Kissoon, Niranjan MB BS, MCCM, FRCP(C), FACPE[13]; Loeches, Ignacio-Martin MD, PhD[14]; Nunnally, Mark MD, FCCM[15]; Tissieres, Pierre MD, DSc[16]; Vieillard-Baron, Antoine MD, PhD[17]; Coopersmith, Craig M. MD, MCCM (Co-chair)[18]; for the Surviving Sepsis Campaign Research Committee

Author Information

Critical Care Medicine 52(2):p 268-296, February 2024. | ***DOI:*** 10.1097/CCM.0000000000006135



Selected Articles from the Annual Update in Intensive Care and Emergency Medicine 2023

Turgman et al. Critical Care (2023) 27:97
https://doi.org/10.1186/s13054-023-04367-z

Critical Care

REVIEW Open Access

Host Response Biomarkers for Sepsis in the Emergency Room

Oren Turgman[1], Michiel Schinkel[1,2] and Willem Joost Wiersinga[1,2*]

Abstract

This article is one of ten reviews selected from the Annual Update in Intensive Care and Emergency Medicine 2023. Other selected articles can be found online at https://www.biomedcentral.com/collections/annualupdate2023. Further information about the Annual Update in Intensive Care and Emergency Medicine is available from https://link.springer.com/bookseries/8901.

Introduction

Sepsis is a medical emergency currently defined as life-threatening organ dysfunction caused by a dysregulated host response to infection [1]. With a recent estimate 6 of 11 million sepsis-related deaths out of 48.9 million yearly sepsis cases, it is a 7 global health priority [2]. Current sepsis treatment guidelines recommend general 8 measures, such as antibiotic treatment, source control, and resuscitation [3]. The 9 heterogeneity of the sepsis syndrome however makes early and consistent diagnosis difficult [4] and has resulted in a lack of sepsis-specific treatments [5, 6]. An essential factor limiting our ability to detect sepsis is the lack of clinically relevant biomarkers for the early phases of the syndrome.

The benefits of early diagnosis and treatment have been well-studied and protocolized in specialties such as trauma medicine, cardiology (e.g., myocardial infarction and cardiac arrest) and neurology (e.g., stroke management), but less so in the field of sepsis [7]. This can potentially lead to longer time-to-antibiotics and higher mortality [8]. Sepsis patients often undergo their first extensive evaluation in the emergency room (ER). Decisions made at this stage, such as choice of antibiotic treatment and discharge destination, are likely to highly impact the rest of the hospital stay. Biomarkers are able to reduce the heterogeneity among sepsis patients in the ER and could improve their care.

This review aims to provide a high-level overview of sepsis biomarkers that are relevant for the ER setting. It focuses on markers found in the systemic compartment and includes traditional and emerging protein biomarkers, but also those arising from the fields of transcriptomics, proteomics, and metabolomics (Fig. 1).

Biomarkers in the Context of Sepsis

Biomarkers can be defined as any objective, reproducible characteristics by which (patho)physiologic processes can be identified and measured [9]. Within the field of sepsis, one can differentiate between diagnostic, prognostic, and therapeutic bio- markers [10, 11]. Diagnostic biomarkers differentiate between infectious and non-infectious disease or help identify specific pathogens. Prognostic biomarkers are useful for assessing the risk of poor outcomes in septic patients and can help us stratify patients by their risk profiles. Lastly, therapeutic biomarkers are used to assess the effectiveness of a treatment. In recent years, biomarkers have been used for a fourth category: theragnostics. Theragnostics describes

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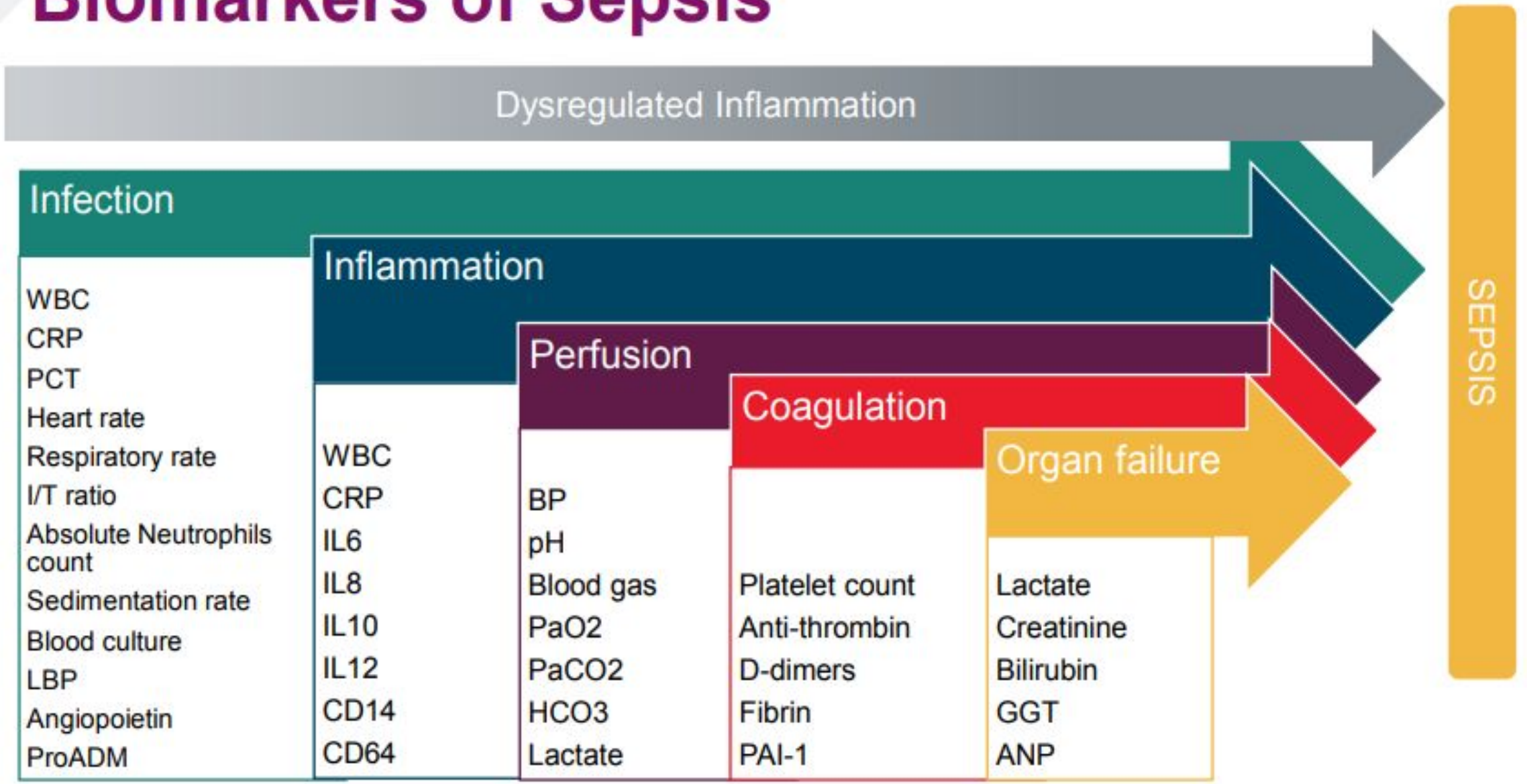
BIOMARKER IDEALE

- Non rilevabile in condizioni basali
- Sensibile e specifico
- Precoce
- Facilmente campionabile
- Facilmente misurabile
- Bedside/rapido TAT
- Economico
- Utile per decision-making in urgenza
- Capacità diagnostica/prognostica

Elliott Erwitt

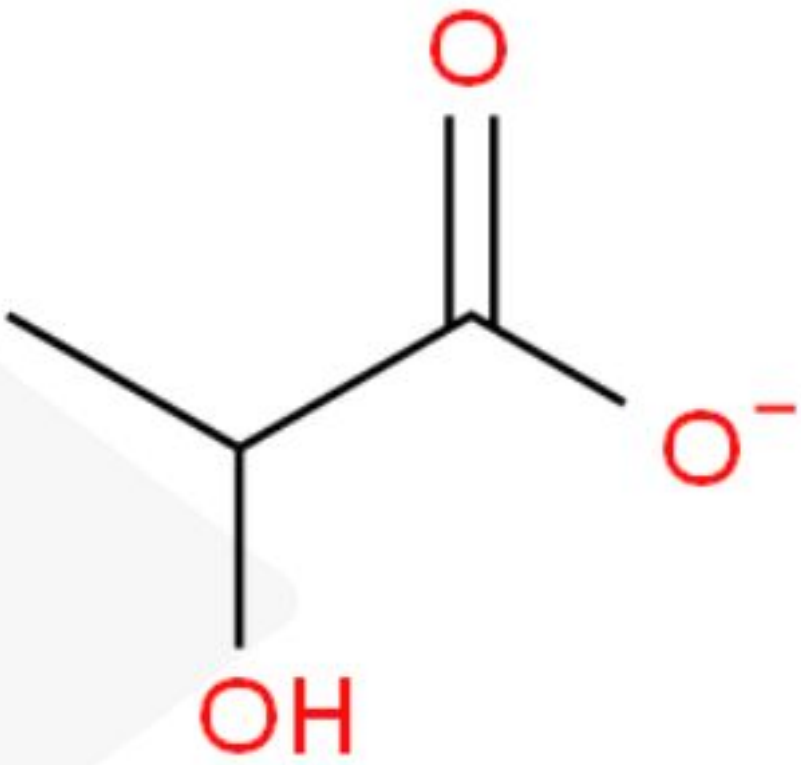

Nane
Zavagno

Biomarkers of Sepsis



Lactate

- Lactate is a byproduct of anaerobic metabolism from pyruvate
- With insufficient oxygenation, cells and tissues move from aerobic metabolism to anaerobic metabolism
- Used as a measure of tissue perfusion irrespective of blood pressure



Chertoff et al. Journal of Intensive Care (2015) 3:39
DOI 10.1186/s40560-015-0105-4

JOURNAL OF INTENSIVE CARE

REVIEW Open Access

Lactate kinetics in sepsis and septic shock: a review of the literature and rationale for further research

Jason Chertoff[1*], Michael Chisum[1], Bryan Garcia[2] and Jorge Lascano[3]

Abstract

Over the last two decades, there have been vast improvements in sepsis-related outcomes, largely resulting from the widespread adoption of aggressive fluid resuscitation and infection control. With increased understanding of the pathophysiology of sepsis, novel diagnostics and resuscitative interventions are being discovered. In recent years, few diagnostic tests like lactate have engendered more attention and research in the sepsis arena. Studies highlighting lactate's prognostic potential for mortality and other outcomes are ubiquitous and largely focus on the early stage of sepsis management, defined as the initial 6 h and widely referred to as the "golden hours." Additional investigations, although more representative of surgical and trauma patients, suggest that lactate measurements beyond 24 h from the initiation of resuscitation continue to have predictive and prognostic utility. This review summarizes the current research and evidence regarding lactate's utility as a prognosticator of clinical outcomes in both early and late sepsis management, defines the mechanism of lactate production and clearance, and identifies areas warranting further research.

Keywords: Lactate, Kinetics, Sepsis, Early sepsis, Late sepsis, Resuscitation, Microvascular, Shock

Intensive Care Med (2019) 45:82–85
https://doi.org/10.1007/s00134-018-5213-x

WHAT'S NEW IN INTENSIVE CARE

The ten pitfalls of lactate clearance in sepsis

Glenn Hernandez[1], Rinaldo Bellomo[2,3,4,5] and Jan Bakker[1,6,7,8*]

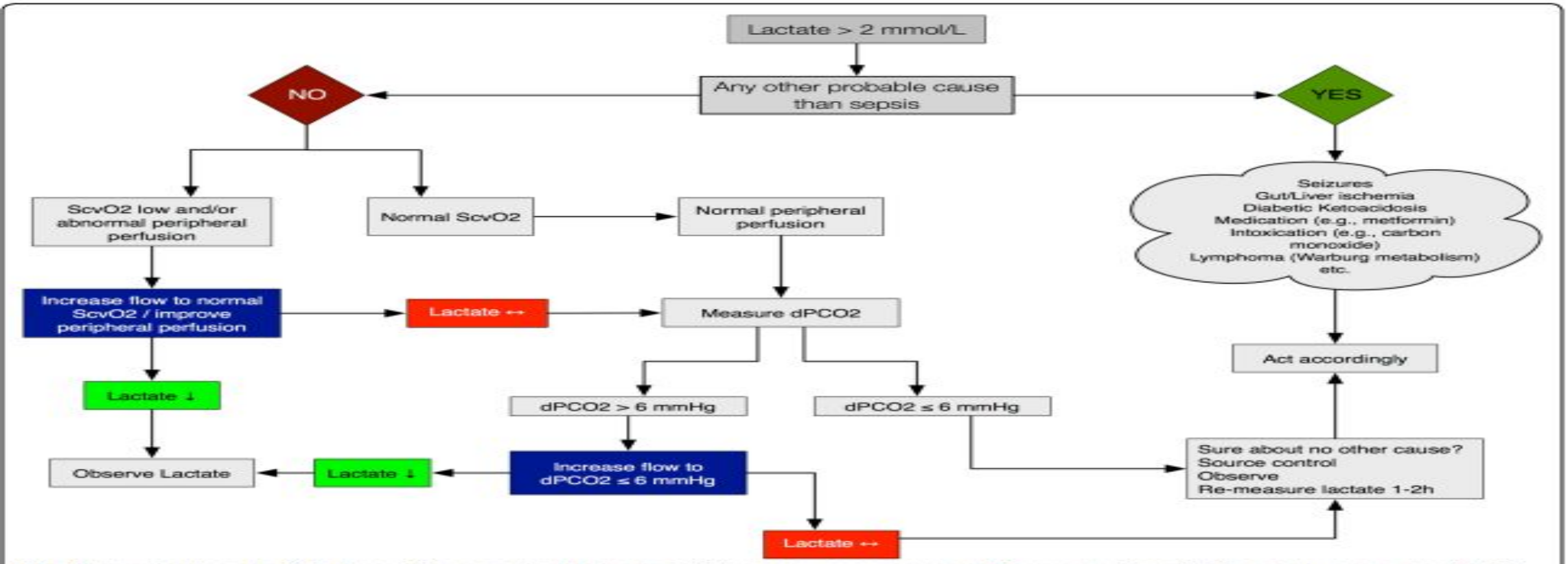
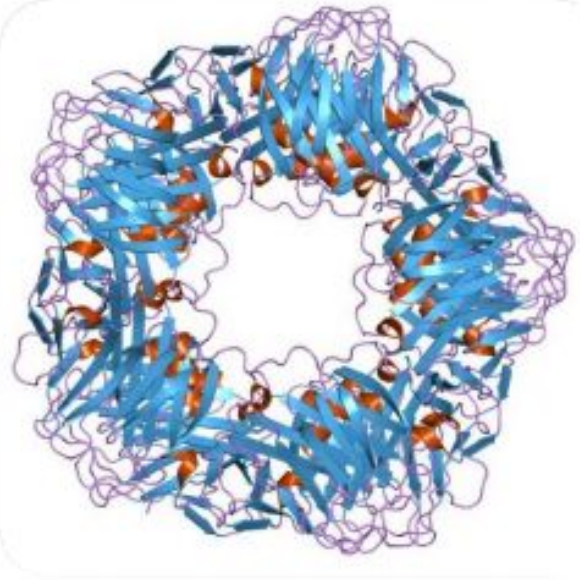
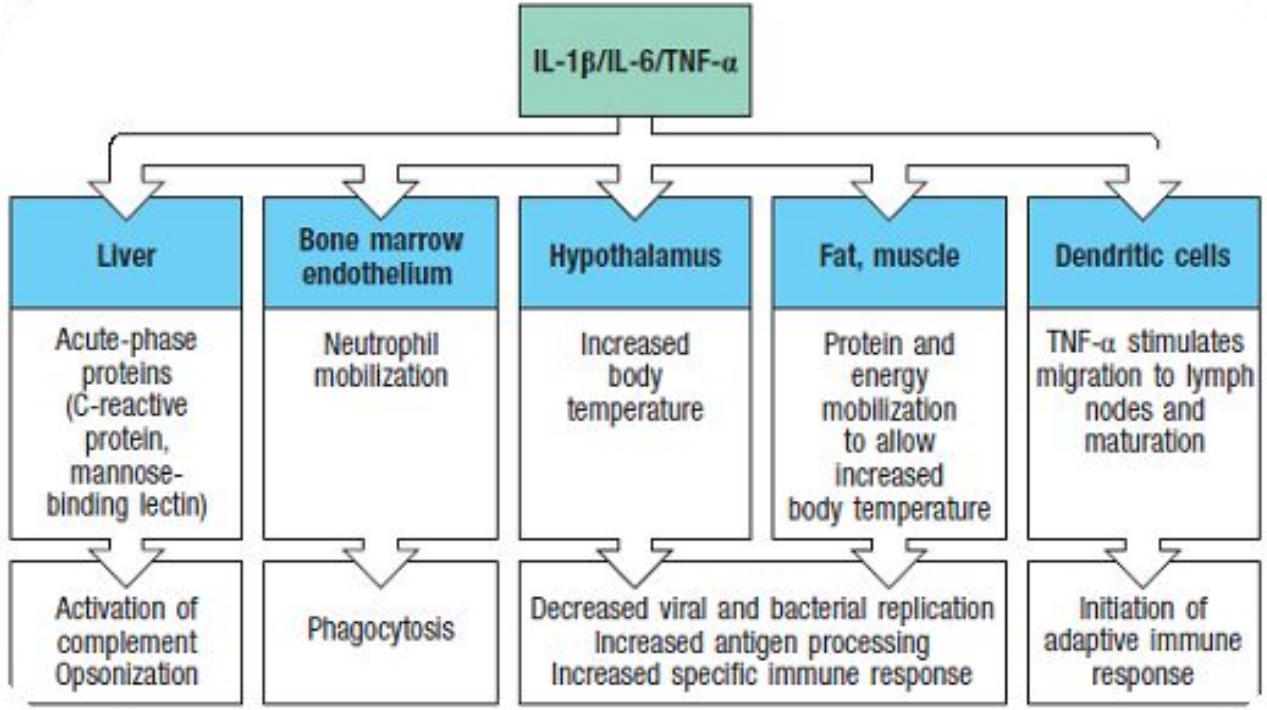


Fig. 1 Flowchart on the clinical use of increased lactate levels. *ScvO2* central venous hemoglobin oxygenation, *dPCO2* central venous–arterial PCO_2 difference

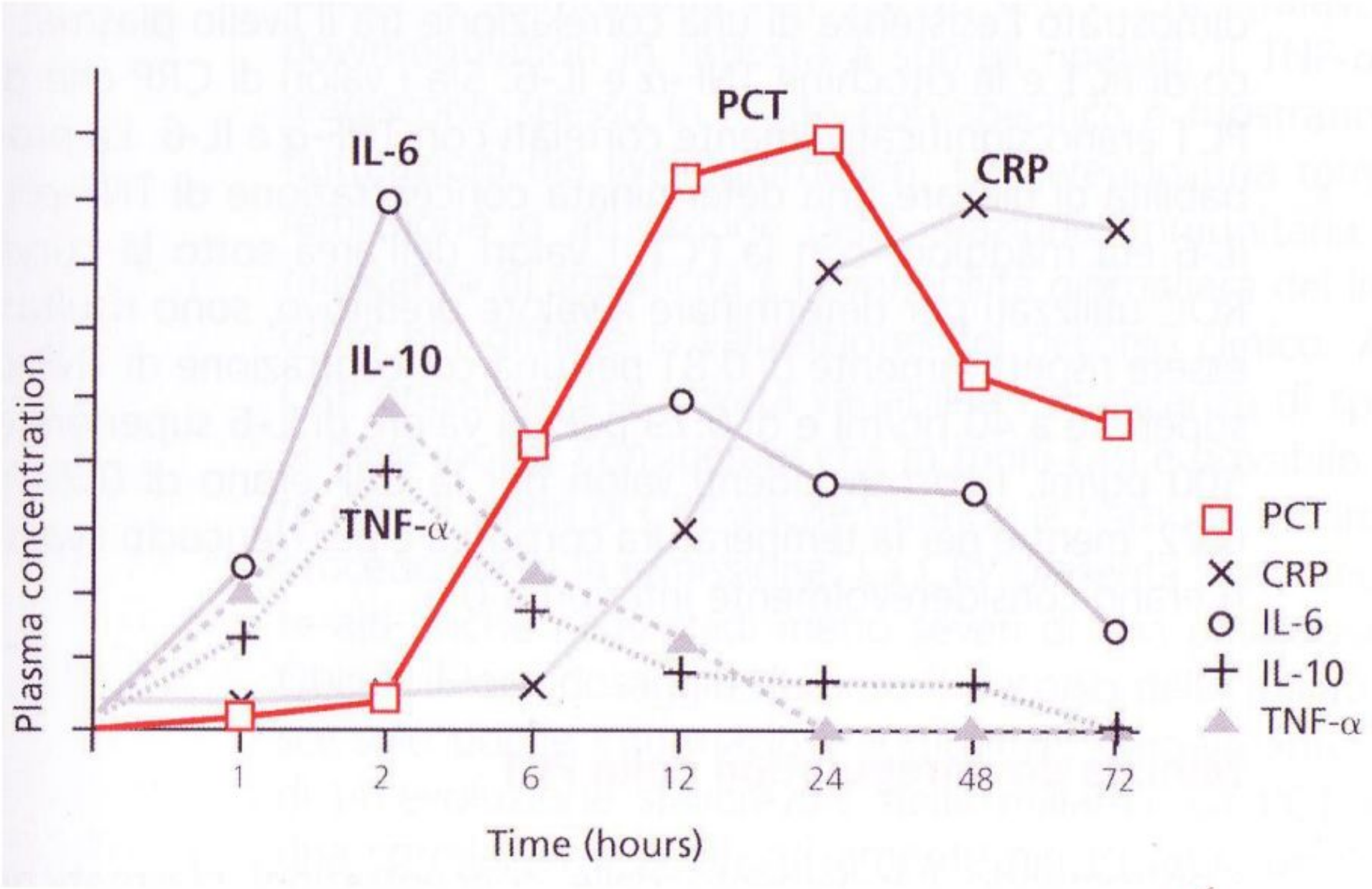
C-reactive protein

- Macrophages secrete IL's which stimulate the liver to initiate the acute-phase response and produce CRP
- Binds to phosphocholine, for uptake by phagocytes
- Bacteria binding to CRP can activate the complement cascade



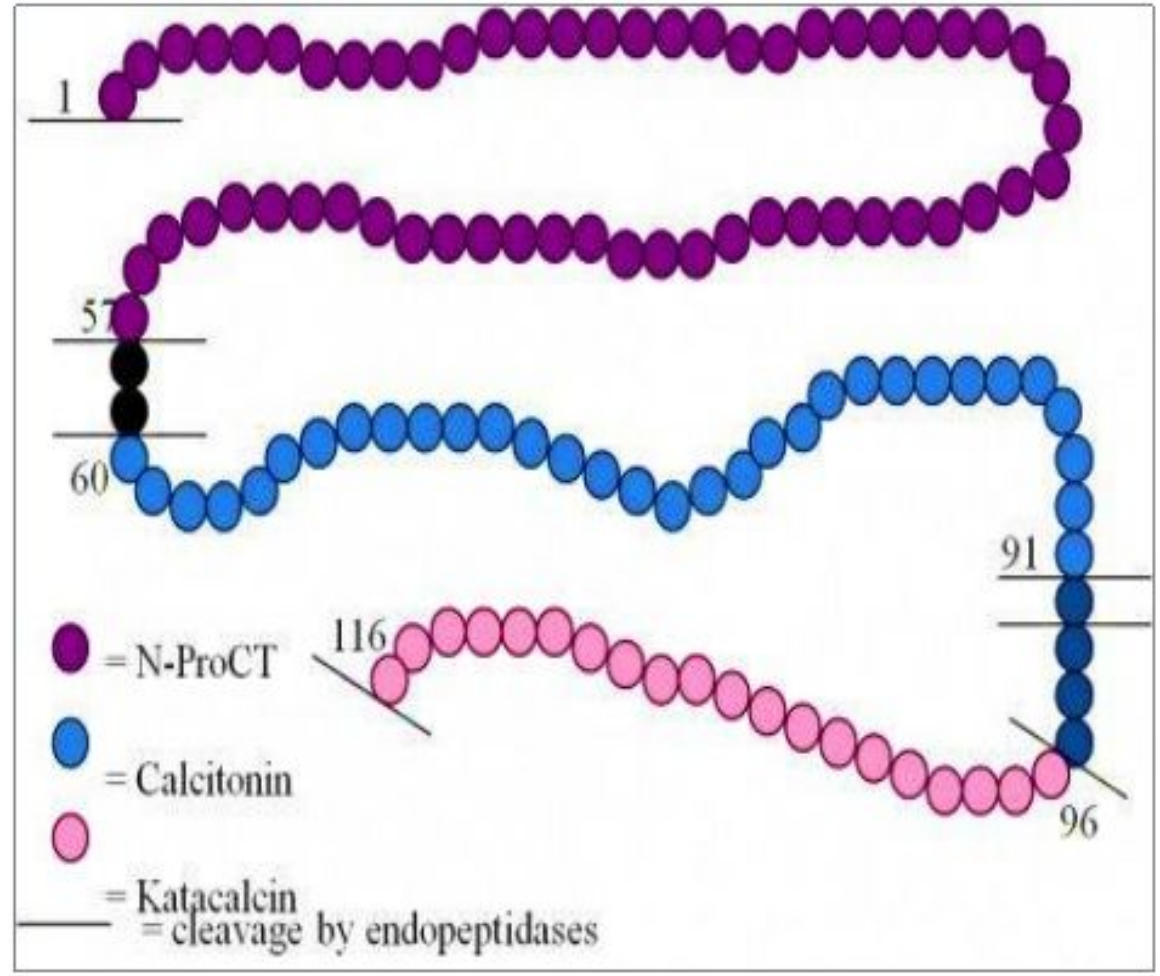


PCT E PCR A CONFRONTO (1)



Procalcitonin

- A prohormone of calcitonin
- In physiological conditions, calcitonin is secreted by parafollicular cells of the thyroid
- In sepsis the main producers of PCT are macrophages and monocytic cells of different organs, especially liver



Zaki et al. Systematic Reviews (2024) 13:37
https://doi.org/10.1186/s13643-023-02432-w

Systematic Reviews

SYSTEMATIC REVIEW UPDATE Open Access

Accuracy of procalcitonin for diagnosing sepsis in adult patients admitted to the emergency department: a systematic review and meta-analysis

Hany A. Zaki[1], Soumaya Bensliman[1], Khalid Bashir[1,2], Haris Iftikhar[1], Mohamed H. Fayed[1], Waleed Salem[1], Amr Elmoheen[1,2] and Yavuz Yigit[1,3*]

Abstract

Background Differentiating sepsis from non-infectious systemic inflammatory response syndrome (SIRS) is challenging. Biomarkers like procalcitonin (PCT) aid early risk assessment and guide antibiotic use. This study aims to ascertain PCT's accuracy as a sepsis biomarker among adult emergency department admissions.

Method The PRISMA guidelines were followed to search for relevant articles in five electronic databases between April 14th and August 4th, 2023: PubMed, Cochrane Library, ProQuest, EMBASEs, and ScienceDirect. Studies had to be published in English to avoid directly translating scientific terms. Besides, the inclusion criteria were based on the diagnosis of sepsis in adult patients admitted to an emergency department. QUADAS-2 tool provided by the Review Manager version 5.4.1 was utilized to assess the risk of bias in included studies. STATA (v. 16) software was used to perform the meta-analysis.

Results Ten of 2457 studies were included. We sampled 2980 adult sepsis patients for the under-investigated role of PCT in ED sepsis diagnosis. PCT emerged as the primary early diagnostic biomarker with high levels (29.3 ± 85.3 ng/mL) in sepsis patients. Heterogeneity in outcomes, possibly due to bias in cohort and observational studies, was observed.

Conclusion PCT tests offer moderate accuracy in diagnosing sepsis and stand out for rapidly and precisely distinguishing between viral and bacterial inflammations.

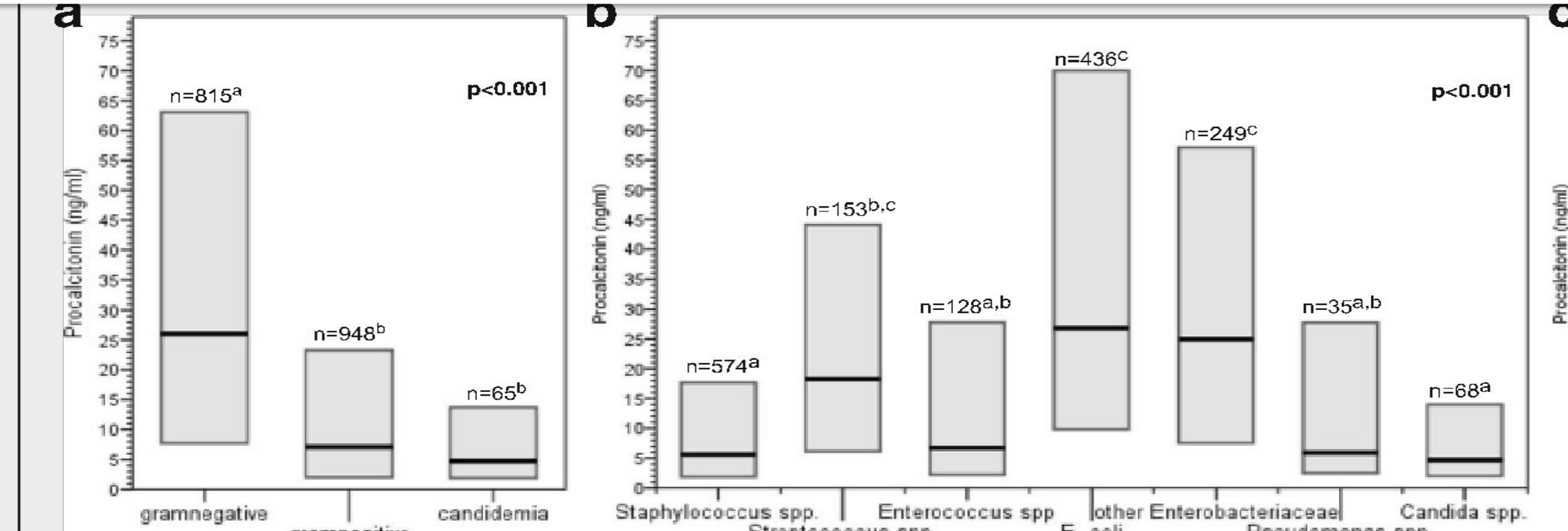
Thomas-Rüddel et al. Critical Care (2018) 22:128
https://doi.org/10.1186/s13054-018-2050-9

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[1], Konrad Reinhart[1,2], Frank Bloos[1,2] for the MEDUSA study group



DIFFERENZA PCT PER PATOGENO

- Maggiore incremento per gram negativi *Enterobacteriacae*
- Gli unici gram positivi che mantengono un incremento della PCT sono gli Streptococchi (le tossine come le pneumolisine attivano TLR che portano ad un incremento di IL-1beta) [1]
- Minor incremento per gram negativi fermentanti come *Pseudomonas* sp
- Minor incremento per gram positivi Stafilococchi

[1] Thomas-Rüddel DO, Poidinger B, Kott M et al.; MEDUSA study group. Influence of pathogen and focus of infection on procalcitonin values in sepsis patients with bacteremia or candidemia. Crit Care 2018 May 13;22(1):128.

PCT: FALSI POSITIVI

Tabella I - Condizioni cliniche caratterizzate da un aumento dei livelli di procalcitonina, non legato ad infezione batterica disseminata.

Carcinoma a cellule C della tiroide
Carcinoma polmonare a piccole cellule
Carcinoma broncogeno squamoso
Ipertensione portale (Stadio C di Child)
Granulomatosi di Wegener
Interventi chirurgici
Colpo di calore
Ustioni
Politraumatismi
Shock cardiogeno protratto
Multiple Organ Dysfunction Syndrome
Perfusione tissutale con TNF-α o IL-6
Neonati
Alte concentrazioni di citochine proinfiammatorie (?)

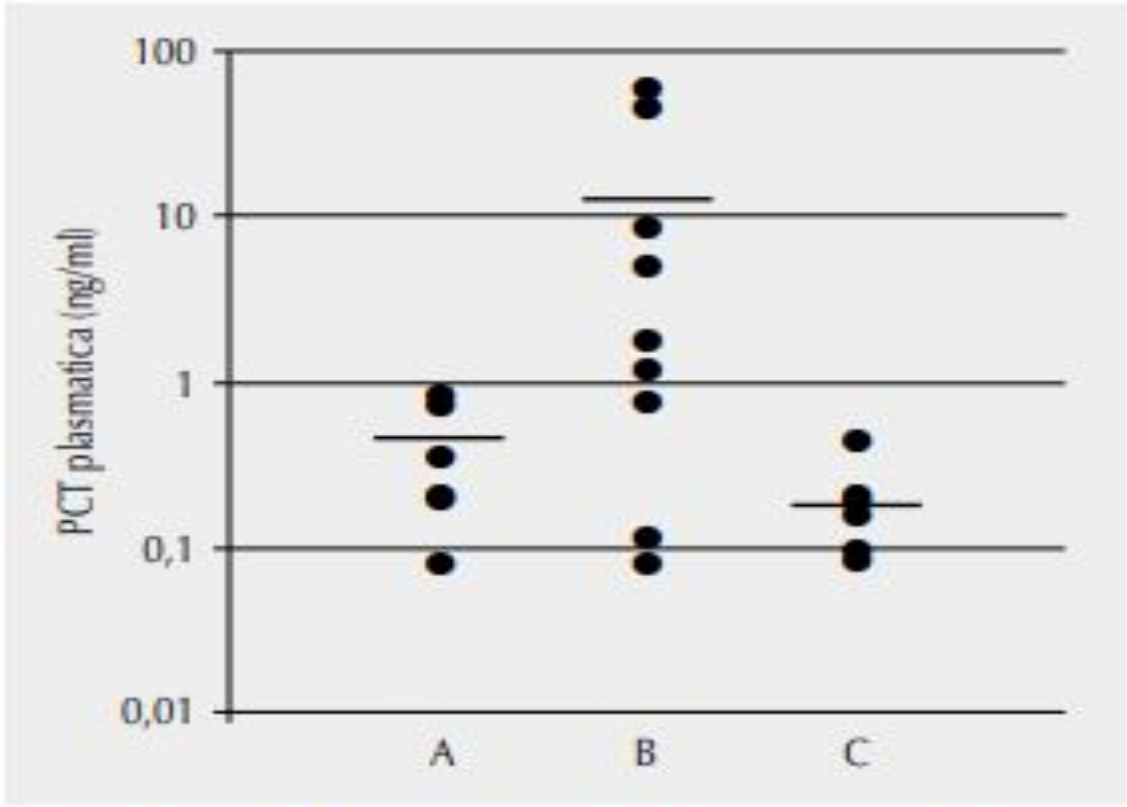


Figura 2 - Livelli di PCT in 7 pazienti febbrili con malattia autoimmune in fase attiva (3 AAV, 2 LES, 1 AR, 1 PM) senza complicanza infettiva (A), in 9 pazienti febbrili con malattia autoimmune sistemica (1 AAV, 4 LES, 1 AR, 2 PM, 1 SSc) e dimostrata infezione batterica in atto (B) e in 11 pazienti con malattia autoimmune sistemica in fase attiva (3 AAV, 2 LES, 3 AR, 2 PM, 1 SSc) ma non febbrili (C).

EARLY DISCONTINUATION OF ATB

IVYSPRING INTERNATIONAL PUBLISHER

International Journal of Medical Sciences

2020; 17(3): 332-337. doi: 10.7150/ijms.39367

Review

Procalcitonin: A promising tool or just another overhyped test?

Robin Paudel[1]✉, Prerna Dogra[2], Ashley A Montgomery-Yates[1], Angel Coz Yataco[3,4]

1. Division of Pulmonary and Critical Care, University of Kentucky, Lexington, Kentucky;
2. Division of Hospital Medicine, University of Kentucky, Lexington, Kentucky;
3. Lexington Veterans Affairs Medical Center, Lexington, Kentucky;
4. University of Kentucky College of Medicine

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Received: 16 June 2021 | Revised: 8 October 2021 | Accepted: 17 October 2021
DOI: 10.1111/jcpt.13554

ORIGINAL ARTICLE

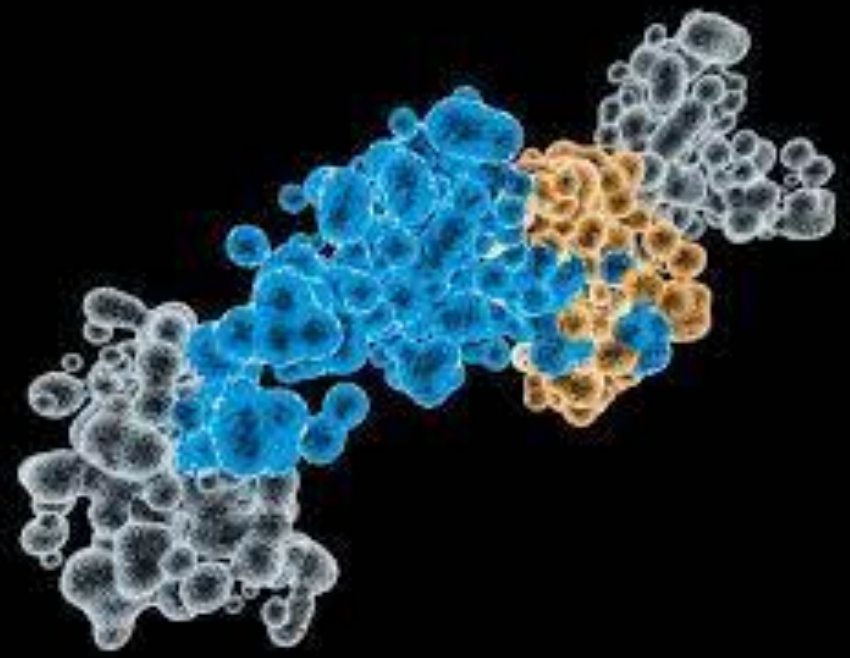
WILEY

Antibiotic stewardship: Early discontinuation of antibiotics based on procalcitonin level in COVID-19 pneumonia

Archana Roy MD[1] | Harry Ross Powers MD[2] | Emily C. Craver Biostatistician[3] | Mark D. Nazareno PharmD, RPh[4] | Siva Naga S. Yarrarapu Research fellow[5] | Devang K. Sanghavi MBBS, MD[6]

Pro-adrenomedullina

- L'**adrenomedullina (ADM)** è un peptide, membro delle calcitonine, inizialmente isolato nelle cellule dei feocromocitomi. La *clearance* è prevalentemente renale.
- Viene prodotta in vari organi (incluso il cuore) e tessuti, principalmente dalle **cellule endoteliali**.
- Il precursore dell'ADM, la **pro-adrenomedullina (pro-ADM)** è più stabile e può essere facilmente misurata come surrogato della concentrazione di ADM
- Uno dei primi tentativi di utilizzo è stato nello scompenso cardiaco, come indice prognostico.



> APMIS. 2015 Sep;123(9):740-8. doi: 10.1111/apm.12406. Epub 2015 Jun 8.

Diagnostic and prognostic role of procalcitonin (PCT) and MR-pro-Adrenomedullin (MR-proADM) in bacterial infections

Silvia Angeletti [1], Silvia Spoto [2], Marta Fogolari [2], Marco Cortigiani [2], Marta Fioravanti [1], Lucia De Florio [1], Brunella Curcio [2], Danilo Cavalieri [2], Sebastiano Costantino [2], Giordano Dicuonzo [1]

- La proADM risulta aumentata nelle **infezioni batteriche localizzate**
- Il valore di proADM è correlato alla severità di malattia, risultando più elevato nei quadri più gravi

Review > Respir Med. 2014 Nov;108(11):1569-80. doi: 10.1016/j.rmed.2014.09.018.

Midregional proadrenomedullin for prognosis in community-acquired pneumonia: a systematic review

Rodrigo Cavallazzi [1], Karim El-Kersh, Emran Abu-Atherah, Sonal Singh, Yoon K Loke, Timothy Wiemken, Julio Ramirez

- Elevati valori di proADM correlano con un maggior rischio di mortalità a breve termine e di sviluppo di complicanze nei pazienti con **polmonite acquisita in comunità (CAP)**

> Ann Intensive Care. 2017 Dec;7(1):15. doi: 10.1186/s13613-017-0238-9. Epub 2017 Feb 10.

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

David Andaluz-Ojeda [1 2], H Bryant Nguyen [3], Nicolas Meunier-Beillard [4], Ramón Cicuéndez [1 2], Jean-Pierre Quenot [4], Dolores Calvo [5], Auguste Dargent [4], Esther Zarca [5], Cristina Andrés [5], Leonor Nogales [1 2], Jose María Eiros [6], Eduardo Tamayo [2 7], Francisco Gandía [1 2], Jesús F Bermejo-Martín [8], Pierre Emmanuel Charles [4]

- I valori di proADM sono correlati con la mortalità dei pazienti con **sepsi o shock settico**
- La proADM è risultata migliore rispetto a PCR, pct e lattati nel predire la mortalità nei pazienti con malattia lieve o moderata (SOFA ≤ 12), paragonabile ai lattati in caso di malattia severa (SOFA > 13)

medicina

MDPI

Review

Proadrenomedullin in Sepsis and Septic Shock: A Role in the Emergency Department

Andrea Piccioni [1], Angela Saviano [1,*], Sara Cicchinelli [1], Federico Valletta [1], Michele Cosimo Santoro [1], Tommaso de Cunzo [1], Christian Zanza [1], Yaroslava Longhitano [2], Gianluca Tullo [1], Pietro Tilli [1], Marcello Candelli [1], Marcello Covino [1] and Francesco Franceschi [1]

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[2] Dietetics and Clinical Nutrition Unit, Department of Internal Medicine, University of Genoa, IRCCS Polyclinic Hospital San Martino, 16132 Genoa, Italy; lon.yaro@gmail.com

* Correspondence: saviange@libero.it

Abstract: Sepsis and septic shock represent a leading cause of mortality in the Emergency Department (ED) and in the Intensive Care Unit (ICU). For these life-threating conditions, different diagnostic and prognostic biomarkers have been studied. Proadrenomedullin (MR-proADM) is a biomarker that can predict organ damage and the risk of imminent death in patients with septic shock, as shown by a large amount of data in the literature. The aim of our narrative review is to evaluate the role of MR-proADM in the context of Emergency Medicine and to summarize the current knowledge of MR-proADM as a serum indicator that is useful in the Emergency Department (ED) to determine an early diagnosis and to predict the long-term mortality of patients with sepsis and septic shock. We performed an electronic literature review to investigate the role of MR-proADM in sepsis and septic shock in the context of ED. We searched papers on PubMed®, Cochrane®, UptoDate®, and Web of Science® that had been published in the last 10 years. Data extracted from this literature review are not conclusive, but they show that MR-proADM may be helpful as a prognostic biomarker to stratify the mortality risk in cases of sepsis and septic shock with different degrees of organ damage, guiding emergency physicians in the diagnosis and the succeeding therapeutic workup. Sepsis and septic shock are conditions of high complexity and have a high risk of mortality. In the ED, early diagnosis is crucial in order to provide an early treatment and to improve patient survival. Diagnosis and prognosis are often the result of a combination of several tests. In our opinion, testing for MR-proADM directly in the ED could contribute to improving the prognostic assessment of patients, facilitating the subsequent clinical management and intensive treatment by the emergency physicians, but more studies are needed to confirm these results.

Keywords: sepsis; septic shock; proadrenomedullin; MR-proADM; procalcitonin; emergency department

Citation: Piccioni, A.; Saviano, A.; Cicchinelli, S.; Valletta, F.; Santoro, M.C.; de Cunzo, T.; Zanza, C.; Longhitano, Y.; Tullo, G.; Tilli, P.; et al. Proadrenomedullin in Sepsis and Septic Shock: A Role in the Emergency Department. *Medicina* **2021**, *57*, 920. https://doi.org/10.3390/medicina57090920

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EXPERT REVIEW OF MOLECULAR DIAGNOSTICS
https://doi.org/10.1080/14737159.2021.1902312

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Taylor & Francis Group

REVIEW

Mid-regional pro-adrenomedullin as a supplementary tool to clinical parameters in cases of suspicion of infection in the emergency department

Kordo Saeed[a,b], Jacopo M. Legramante[c], Silvia Angeletti[d], Francesco Curcio[e], Iria Miguens[f], Stephen Poole[g], Carlo Tascini[h], Emanuela Sozio[h] and Juan González Del Castillo[i]

[a]Microbiology Innovation and Research UNIT, Department of Infection, University Hospitals Southampton NHS Foundation Trust, Southampton, UK; [b]School of Medicine, University of Southampton, Southampton, UK; [c]Emergency Department, University Hospital Tor Vergata, Rome, Italy; [d]Clinical Pathology, University Hospital Campus Bio-Medico of Rome Science Unit, University Campus Bio-Medico of Rome, Faculty of Medicine University Campus Bio-Medico of Rome, Italy; [e]Department of Medicine (DAME), University of Udine, Udine, Italy; [f]Hospital General Universitario Gregorio Marañón, Madrid, Spain; [g]NIHR Southampton Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust, Southampton, UK; [h]Infectious Diseases Clinic, Udine University Hospital, Udine, Italy; [i]Emergency Department, Hospital Clínico San Carlos, Madrid, Spain

ABSTRACT

Introduction: Mid-regional proadrenomedullin (MR-proADM), a novel biomarker, has recently gained interest particularly with regards to its potential in assisting clinicians' decision making in patients with suspicion of infection in the emergency department (ED). A group of international experts, with research and experience in MR-proADM applications, produced this review based on their own experience and the currently available literature.

Areas covered: The review provides evidence related to MR-proADM as a triaging tool in avoiding unnecessary admissions to hospital and/or inadequate discharge, and identifying patients most at risk of deterioration. It also covers the use of MR-proADM in the context of COVID-19. Moreover, the authors provide a proposal on how to incorporate MR-proADM into patients' clinical pathways in an ED setting.

Expert opinion: The data we have so far on the application of MR-proADM in the ED is promising. Incorporating it into clinical scoring systems may aid the clinician's decision making and recognizing the 'ill looking well' and the 'well looking ill' sooner. However there are still many gaps in our knowledge especially during the ongoing COVID-19 waves. There is also a need for cost-effectiveness analysis studies especially in the era of increasing cost pressures on health systems globally.

ARTICLE HISTORY
Received 8 January 2021
Accepted 9 March 2021

KEYWORDS
MR-proADM; emergency department; triage tool; admission; ICU

Observational Study > Int J Infect Dis. 2021 Oct;111:211-218. doi: 10.1016/j.ijid.2021.08.058. Epub 2021 Aug 28.

Circulating MR-proADM levels, as an indicator of endothelial dysfunction, for early risk stratification of mid-term mortality in COVID-19 patients

Luis Ga
María I
María
María
Carlos
Lucian
Enriqu

> J Clin Pathol. 2022 Jan 7;jclinpath-2021-207750. doi: 10.1136/jclinpath-2021-207750. Online ahead of print.

Mid-regional proadrenomedullin (MR-proADM), C-reactive protein (CRP) and other biomarkers in the early identification of disease progression in patients with COVID-19 in the acute NHS setting

Nathan Moore [1], Rebecca Williams [2], Matilde Mori [3], Beatrice Bertolusso [4], Gabrielle Vernet [5], Jessica Lynch [2], Pete Philipson [6], Thomas Ledgerwood [2], Stephen P Kidd [2], Claire Thomas [2 3],

Observational Study > Eur Rev Med Pharmacol Sci. 2021 Feb;25(3):1743-1751. doi: 10.26355/eurrev_202102_24885.

High levels of mid-regional proadrenomedullin in ARDS COVID-19 patients: the experience of a single, Italian Center

I Benedetti [1], D Spinelli, T Callegari, R Bonometti, E Molinaro, E Novara, M Cassinari, C Frino, R Guaschino, R Boverio, E C Lauritano

Observational Study > Eur J Clin Invest. 2021 May;51(5):e13511. doi: 10.1111/eci.13511. Epub 2021 Feb 20.

MR-proADM as marker of endotheliitis predicts COVID-19 severity

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María Dolores Rodríguez Mulero [3], Ismael Calcerrada Alises [4], Marta Hernández Olivo [5],
li Trapiello Fernández [2], Mercedes González Morales [1], Cristina Bolado Jiménez [6],
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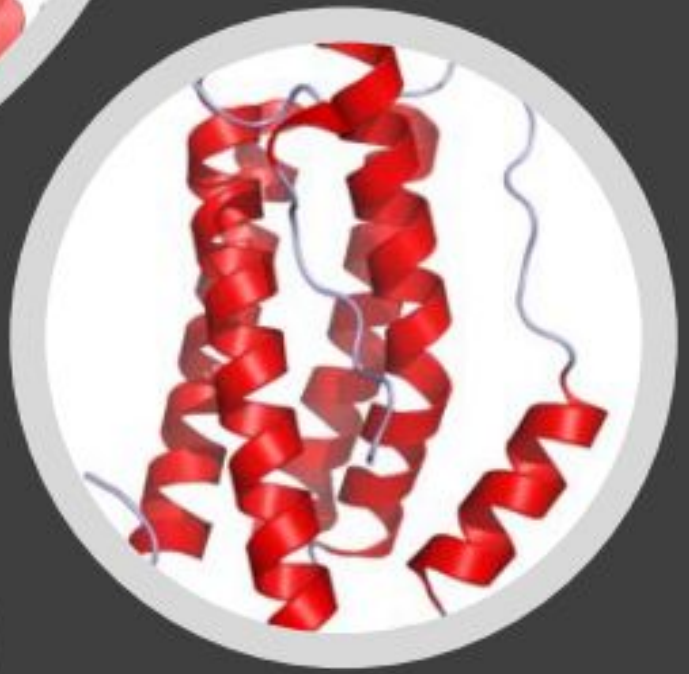
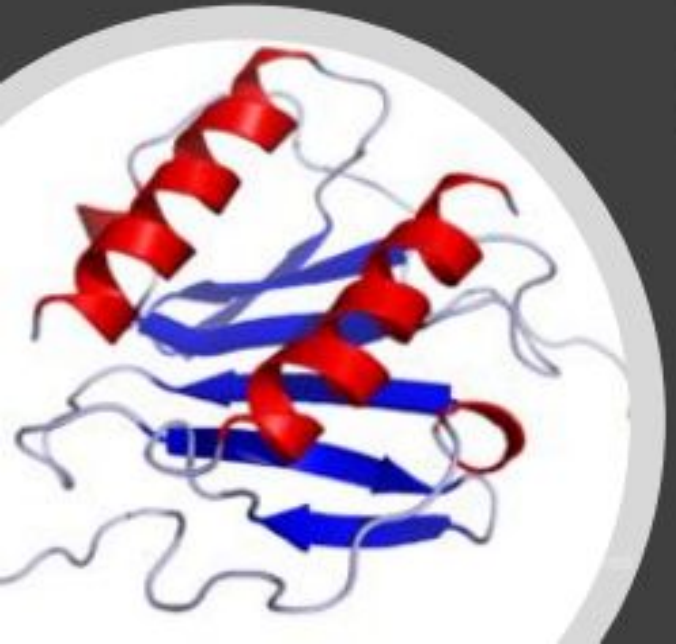
nio Azpeleta Manrique [6], Luciano Consuegra-Sánchez [10], Leonor Nogales Martín [11],
Conesa Zamora [1], David Andaluz-Ojeda [11]

Diversi studi su pro-ADM nei pazienti affetti da **COVID-19**:

- Il COVID determina danno endoteliale
- Il livello di pro-ADM correla con la mortalità (e con necessità di ventilazione invasiva/non invasiva)
- Solo pazienti ospedalizzati (popolazione selezionata)





Cytokines

IL-6 is produced by monocytes, fibroblasts, endothelial cells, keratinocytes, T-cells, and tumor cells.

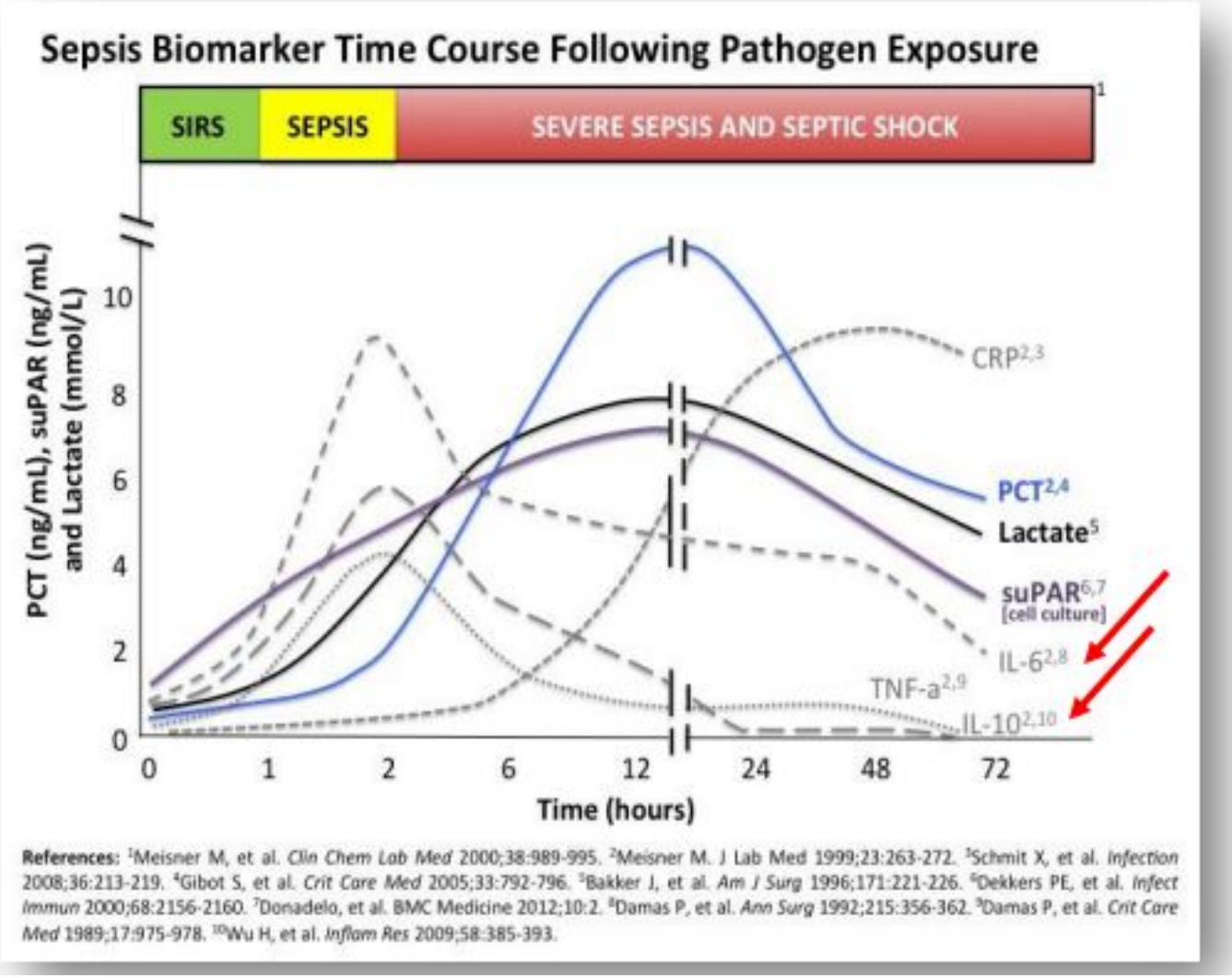
- Released into the bloodstream for 4–6 h, decreasing over the next 24–48 h.

IL-8 produced by macrophages and endothelial cells.

IL-10 is an anti-inflammatory cytokine produced by monocytes, macrophages, T and B cells, neutrophils and mesangial cells

Cytokines

- Measurements of CRP or PCT are more sensitive.
  - Elevated cytokine levels are **also seen in SIRS of noninfectious origin.**
- No studies prove that the treatment of sepsis based on these markers influences the treatment strategy or improves the clinical result.
- IL-6 and IL-10 can **predict higher mortality** for septic patients.



The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19

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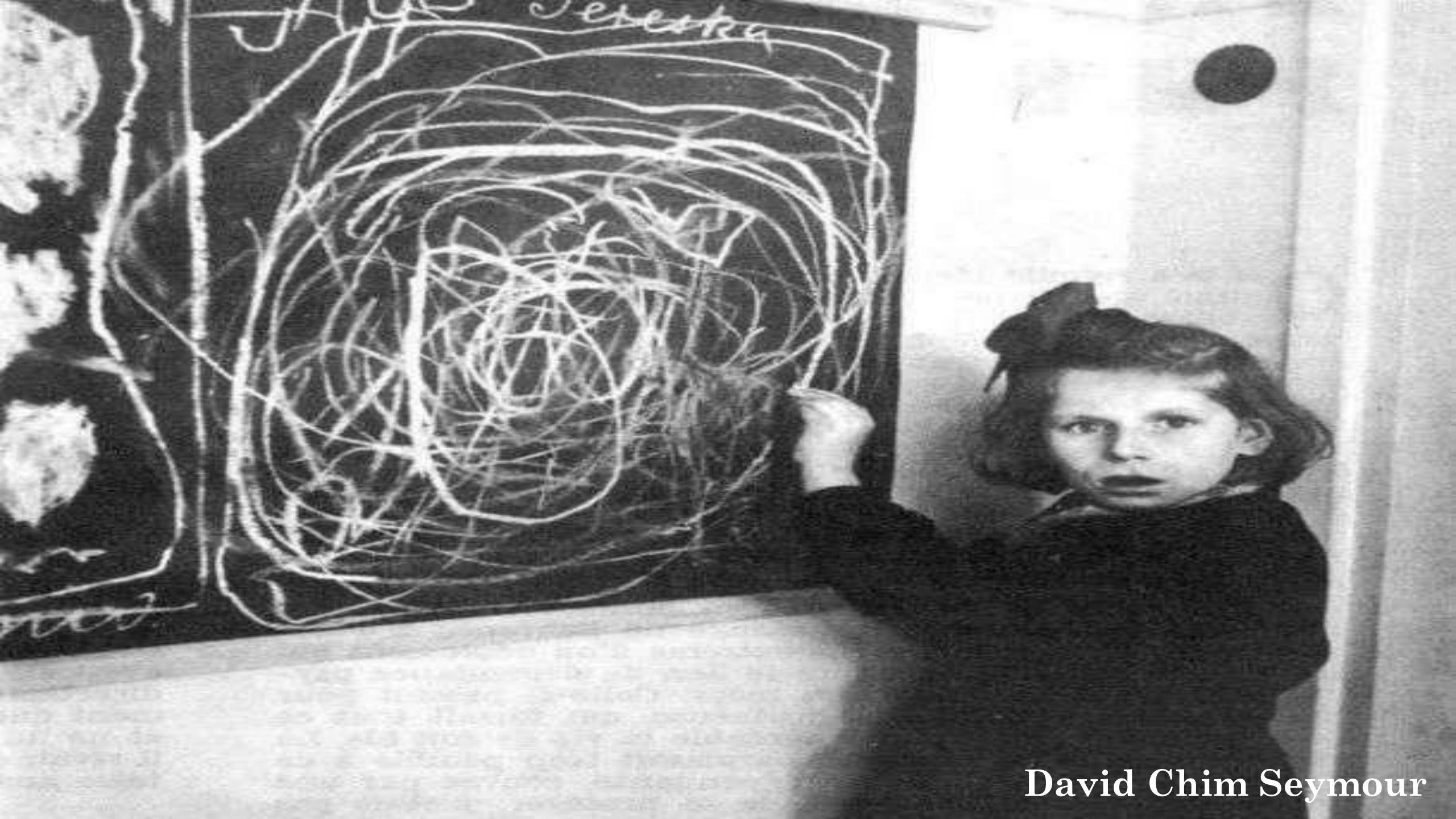


David Chim Seymour

IV. I test citofluorimetrici CD64/CD169 : **strumento utile in PS?**

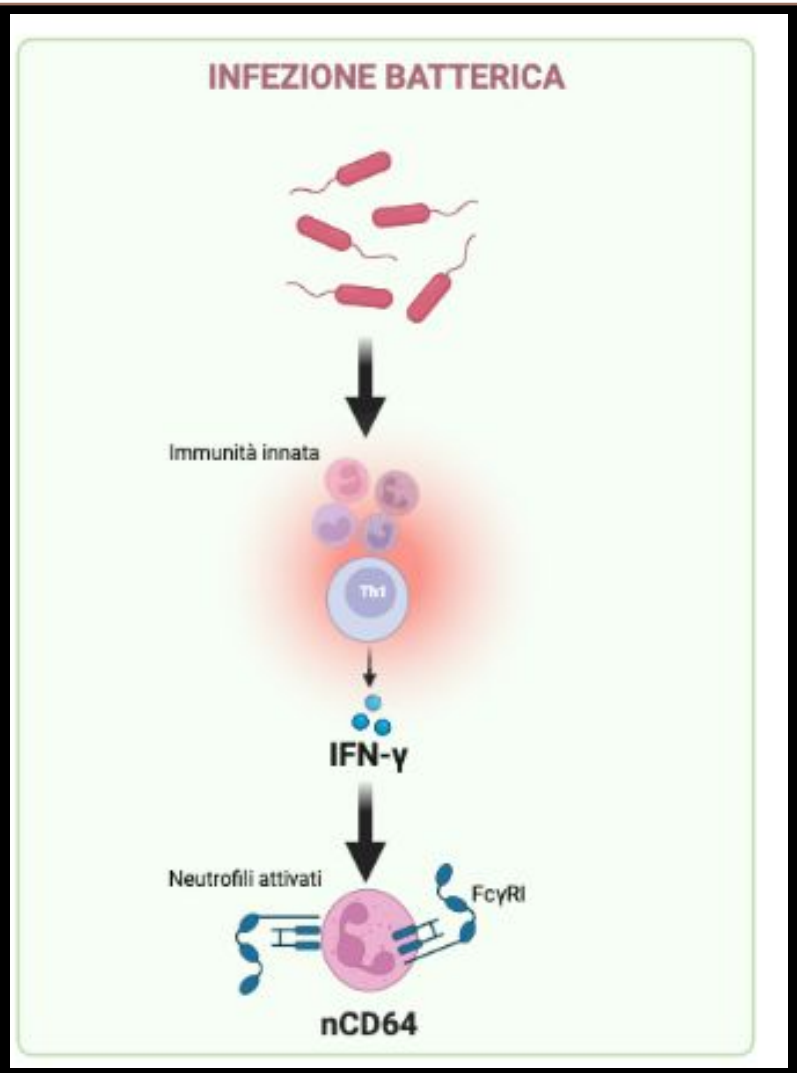
La citofluorimetria a flusso (*flow cytometry,* FCM) è una tecnica di analisi cellulare che sfrutta specifici anticorpi monoclonali associati a molecole fluorescenti per misurare, attraverso la fluorescenza emessa, l'espressione di specifiche proteine di membrana (denominate *cluster of differentiation*, CD) e quindi identificare specifiche sottopopolazioni cellulari [139]. Uno dei campi di utilizzo, ben noto nell'ambito infettivologico, è la stima del numero di linfociti CD4 e CD8 nei pazienti con infezione cronica da HIV. Il campo di applicazione è molto vasto: per lo scopo di questo lavoro sarà sufficiente analizzare il significato della misurazione in citofluorimetria dell'espressione del CD64 e del CD169.

risultato come *median fluorescence intensity* (MFI) oppure come *median fluorescence intensity ratio* (MFIR), ottenuta rapportando MFI dei neutrofili (nCD64) a quella dei linfociti (lCD64).

nCD64

Marker diagnostico di infezione batterica — sens: 76% spec: 85%

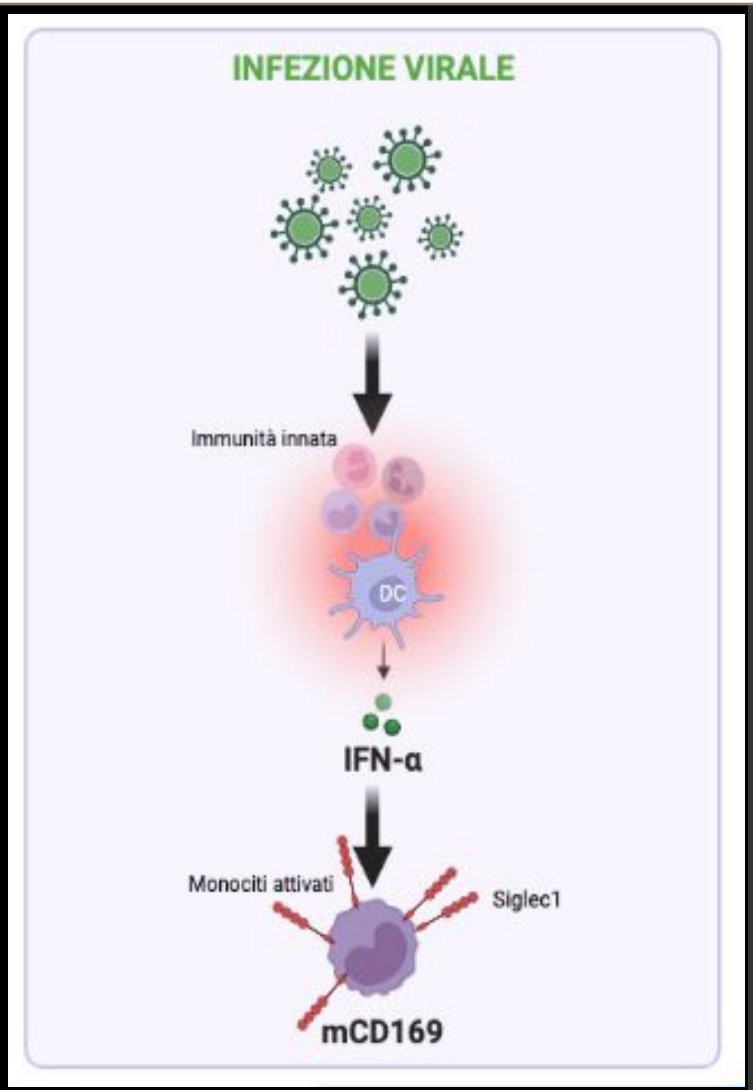
Utile anche in pazienti con:
- malattie autoimmuni
- infiammazione sistemica
- malattie ematologiche e tx d'organo



mCD169

Marker diagnostico *emergente* di infezione virale[8] — sens*: 78% spec*:91%

- HIV
- EBV[1]
- CMV[1]
- Dengue virus di Lassa e Marburg
- Zika
- Norovirus
- virus respiratorio sinciziale
- Influenza e SARS-CoV-2



Il *cluster of differentiation* CD64 corrisponde al recettore per la porzione Fc (conservata) delle immunoglobuline IgG (FcgRI), espresso a bassissimo livello sui neutrofili non attivati (circa 1400 recettori/cellula). In presenza di citochine infiammatorie, in particolare IFN-γ e *colony stimulating factor* (CSF), si sviluppa un'iperespressione del CD64 sui neutrofili

Per questo, in numerosi studi l'espressione del CD64 sui neutrofili circolanti è stata valutata come *marker* diagnostico di infezione batterica nella valutazione dei pazienti con infezione batterica o sepsi (Dimoula *et al.*, Li *et al.*, Cong *et al.*), riacutizzazione di BPCO (Quian *et al.*, Farah *et al.*), bronchiolite acuta severa (Garcia-Salido *et al.*), sepsi neonatale e febbre pediatrica (Garcia-Salido *et al.*, Song *et al.*, Lu *et al.*) [142–150]. Il test CD64 è stato impiegato anche per riconoscere forme infettive batteriche in corso di malattie autoimmuni, quali l'artrite reumatoide e il lupus eritematoso sistemico (Allen *et al.*, Hu *et al.*, Feng *et al.*), in corso di altre condizioni non-infettive di infiammazione sistemica, come l'epatite alcolica acuta, la pancreatite acuta e le ustioni severe (Pandey *et al.*, Wang *et al.*, Chen *et al.*) o in popolazioni particolari quali i pazienti ematologici (Liang *et al.*) o trapiantati d'organo solido (Grey *et al.*) [151–156].

Il *cluster of differentiation* CD169 corrisponde alla molecola di superficie sialoadesina (o siglec1) espressa in modo inducibile sulle cellule fagocitiche mononucleate del sistema immunitario (macrofagi, monociti, cellule dendritiche). La sialoadesina crea legami con ligandi sialilati patogenici endogeni o esogeni, permettendo l'interazione cellulare con tali molecole e favorendo il riconoscimento del patogeno, l'ingresso del patogeno e la presentazione del patogeno ai linfociti T e l'attivazione dei linfociti B e dei natural killer [165]. Sottopopolazioni macrofagiche CD169+ residenti sono identificabili a livello di linfonodi, milza, polmoni e midollo osseo (e in misura minore a livello di fegato, intestino, cuore e reni) [166]. L'espressione del CD169 monocitario (da qui in poi: mCD169) è modulata nei vari tessuti (compreso il sangue periferico) in presenza di processi patologici come malattie autoimmunitarie (sclerosi multipla, lupus eritematoso sistemico), patologie neoplastiche (carcinoma della mammella e dell'esofago) e infezioni virali [166–170].

EUSEM 2023
European Emergency Medicine Congress
16 – 17 September Pre-courses
17 – 20 September Congress
Barcelona - Spain

Monocites CD169/neutrophils CD64 and Mild-regional prodadrenomedullin in SARS-CoV-2 acute infection in Emergency Department: a retrospective study

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REGIONE AUTONOMA FRIULI VENEZIA GIULIA
As FO
Azienda sanitaria Friuli Occidentale

Background:

Over-expression of CD169 on circulating monocytes (mCD169)) has been observed in different viral infections, including SARS-CoV-2. Over-expression of CD64 on circulating neutrophils (nCD64) is a well-known marker of bacterial infection. However, it has been observed even during severe SARS-CoV-2 infections. Mild-regional proadrenomedullin (MR-proADM) is a new biomarker of endothelial damage and and its clinical use is increasing in sepsis, respiratory infections and Sars-Cov 2 infection: it might be a potential biomarker of COVID-19 severity and may be able to mimic disease progression.

We wanted to assess the applicability of mCD169 as a screening test in the Emergency Department (ED) to detect patients with acute SARS-CoV-2 infection and the usefulness of MD-proADM and nCD64 as a marker of severity and/or bacterial super-infection.

Methods:

Data of patients with confirmed SARS-CoV-2 infection (positive antigenic/molecular test) who underwent evaluation at the Emergency Department of the hospital "S. Maria degli Angeli" of Pordenone between November 2021 and January 2022 were retrospectively collected (figure 1). During the study period, cytofluorimetric measurement of mCD169 and nCD64, expressed as mean fluorescence intensity-ratio (MFIR), was performed systematically in all COVID-19 patients. The cut-offs for mCD169 and nCD64 were established from previously published studies and settled as ≥3.5 MFIR and ≥4.6 MFIR. Similarly, MR-proADM plasma concentrations were performed systematically in all COVID-19 patients admitted to the Emergency Department between November 2021 and January 2022, and the cut-off was estabilished from previously published studies and settled as 0.9 nMol/L.

Results:

Three hundred-forty five (345) patients with SARS-CoV-2 infection, mCD169/nCD64 test and MD-proADM test were included. In 93% of patients (N=320), mCD169was activated.Acute infection (symptoms ≤5 days) was associated with higher proportions of mCD169 activation compared to non-acute infection (95% vs. 92%, p <0.05). Not-vaccinated patients showed higher proportions of mCD169 activation compared to vaccinated patients (96% vs. 89%, p <0.05). Its expression was associated neither with the severity of COVID-19 nor the outcome. In 13% of patients (N=44) of patients nCD64 was activated. Higher proportions of nCD64 activation were found in patients with microbiologically-proven bacterial superinfection (N=5) compared to non-superinfected patients (60% vs. 12%) and severe compared to non-severe COVID-19 (21% vs. 1%, p <0.05). High MR-ProADM levels were significantly associated with negative outcome (death or orotracheal intubation) within 30 days. (Figure 2)

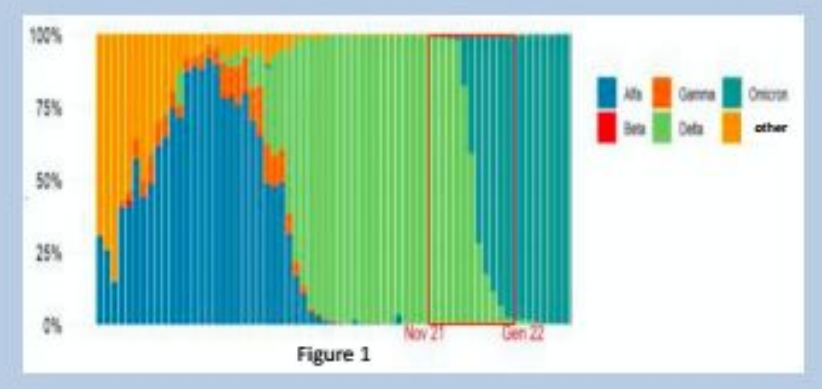


Figure 1

Conclusions:

Our data showed that mCD169 test is able to identify acute SARS-CoV-2 infection. During flu season and SARS-CoV-2 waves, it may be applied as a triage test for patients with acute respiratory infection in order to identify who needs isolation precautions. The nCD64 test may be useful to identify patients with bacterial infections and/or severe COVID-19. The association of mCD169 and nCD64 may help to discriminate fever of bacterial or viral origin. It appears a potentially useful test to limit antibiotic misprescription. The assessment of MR-proADM combined with clinical scoring systems could be of great value in triaging, evaluating possibile escalations of therapies.

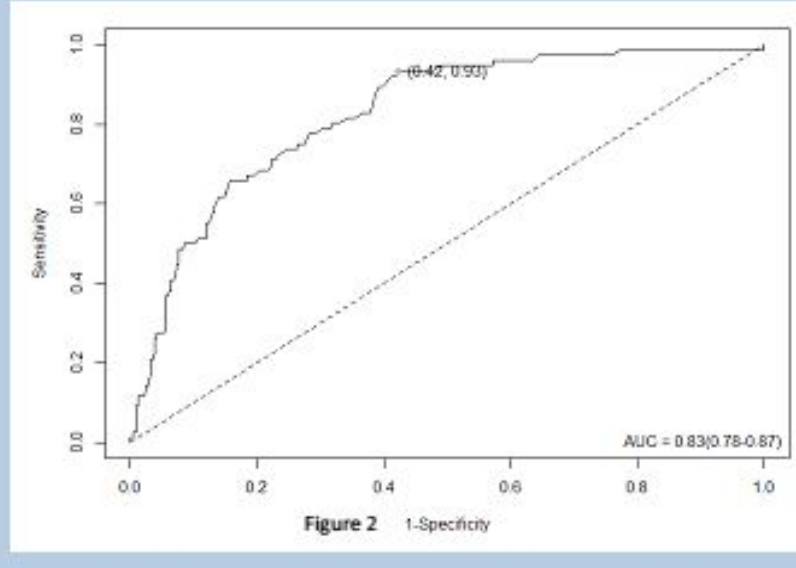


Figure 2

Received: 28 October 2020 | Revised: 15 December 2020 | Accepted: 18 December 2020
DOI: 10.1002/cyto.a.24314

ORIGINAL ARTICLE

MIFlowCyt
ISAC CYTOMETRY Journal of Quantitative Cell Science PART A

CD169 and CD64 could help differentiate bacterial from CoVID-19 or other viral infections in the Emergency Department

Pénélope Bourgoin[1,2] | Thomas Soliveres[3] | Alexandra Barbaresi[3] | Anderson Loundou[4] | Inès Ait Belkacem[1,5] | Isabelle Arnoux[6] | Denis Bernot[6] | Marie Loosveld[6] | Pierre-Emmanuel Morange[2,6] | Pierre Michelet[2,3] | Fabrice Malergue[1] | Thibaut Markarian[2,3]

Abstract

The identification of a bacterial, viral, or even noninfectious cause is essential in the management of febrile syndrome in the emergency department (ED), especially in epidemic contexts such as flu or CoVID-19. The aim was to assess discriminative performances of two biomarkers, CD64 on neutrophils (nCD64) and CD169 on monocytes (mCD169), using a new flow cytometry procedure, in patients presenting with fever to the ED during epidemics. Eighty five adult patients presenting with potential infection were included during the 2019 flu season in the ED of La Timone Hospital. They were divided into four diagnostic outcomes according to their clinical records: no-infection, bacterial infection, viral infection and co-infection. Seventy six patients with confirmed SARS-CoV-2 infection were also compared to 48 healthy volunteers. For the first cohort, 38 (45%) patients were diagnosed with bacterial infections, 11 (13%) with viral infections and 29 (34%) with co-infections. mCD169 was elevated in patients with viral infections, with a majority of *Flu A* virus or Respiratory Syncytial Virus, while nCD64 was elevated in subjects with bacterial infections, with a majority of *Streptococcus pneumoniae* and *Escherichia coli*. nCD64 and mCD169 showed 90% and 80% sensitivity, and 78% and 91% specificity, respectively, for identifying patients with bacterial or viral infections. When studied in a second cohort, mCD169 was elevated in 95% of patients with SARS-CoV-2 infections and remained at normal level in 100% of healthy volunteers. nCD64 and mCD169 have potential for accurately distinguishing bacterial and acute viral infections. Combined in an easy and rapid flow cytometry procedure, they constitute a potential improvement for infection management in the ED, and could even help for triage of patients during emerging epidemics.

KEYWORDS
bacterial infection, CoVID-19, emergency department, flow cytometry, viral infection

BMC Emergency Medicine

RESEARCH

Open Access

Point-of-care neutrophil CD64 as a rule in diagnostic test for bacterial infections in the emergency department

N. L. M. van de Ven[1], S. H. Bongers[1,2], R. Spijkerman[2,3], L. Koenderman[2,3], L. P. H. Leenen[1,2], F. Hietbrink[1,2*] and The COVPACH study group

Abstract

Introduction Bacterial infections are frequently seen in the emergency department (ED), but can be difficult to distinguish from viral infections and some non-infectious diseases. Common biomarkers such as c-reactive protein (CRP) and white blood cell (WBC) counts fail to aid in the differential diagnosis. Neutrophil CD64 (nCD64), an IgG receptor, is suggested to be more specific for bacterial infections. This study investigated if nCD64 can distinguish bacterial infections from other infectious and non-infectious diseases in the ED.

Methods All COVID-19 suspected patients who visited the ED and for which a definitive diagnosis was made, were included. Blood was analyzed using an automated flow cytometer within 2 h after presentation. Patients were divided into a bacterial, viral, and non-infectious disease group. We determined the diagnostic value of nCD64 and compared this to those of CRP and WBC counts.

Results Of the 291 patients presented at the ED, 182 patients were included with a definitive diagnosis (bacterial infection $n = 78$; viral infection $n = 64$; non-infectious disease $n = 40$). ROC-curves were plotted, with AUCs of 0.71 [95%CI: 0.64–0.79], 0.77 [0.69–0.84] and 0.64 [0.55–0.73] for nCD64, WBC counts and CRP, respectively. In the bacterial group, nCD64 MFI was significantly higher compared to the other groups ($p < 0.01$). A cut-off of 9.4 AU MFI for nCD64 corresponded with a positive predictive value of 1.00 (sensitivity of 0.27, a specificity of 1.00, and an NPV of 0.64). Furthermore, a diagnostic algorithm was constructed which can serve as an example of what a future biomarker prediction model could look like.

Conclusion For patients in the ED presenting with a suspected infection, nCD64 measured with automatic flow cytometry, has a high specificity and positive predictive value for diagnosing a bacterial infection. However, a low nCD64 cannot rule out a bacterial infection. For future purposes, nCD64 should be combined with additional tests to form an algorithm that adequately diagnoses infectious diseases.

Keywords nCD64, Bacterial infections, Viral infections, COVID-19, Inflammation, Point of care immunology

Federico
Garolla

K.H., 35 aa

Rientro da Ghana 10 gg prima

Febbre, tosse, dolore addominale da 4 gg

Rx minima consolidazione basale parilare dx

Negativo per malaria

GB 4020, PCR 7.5, ProCT 1.58

emocolture negative ag urinari negativi

Test attivazione mieloide: CD 64 4.6 ratio, CD 169 21.2 ratio, Compatibile con coinfezione virale e batterica

Tampone virus respiratori positivo per Virus Influenza A

Dimesso da DBI 3° giornata (7.9.2023)

T.I., 28 aa

Rientro da Messico da 72 h, soggiorno per 12 gg

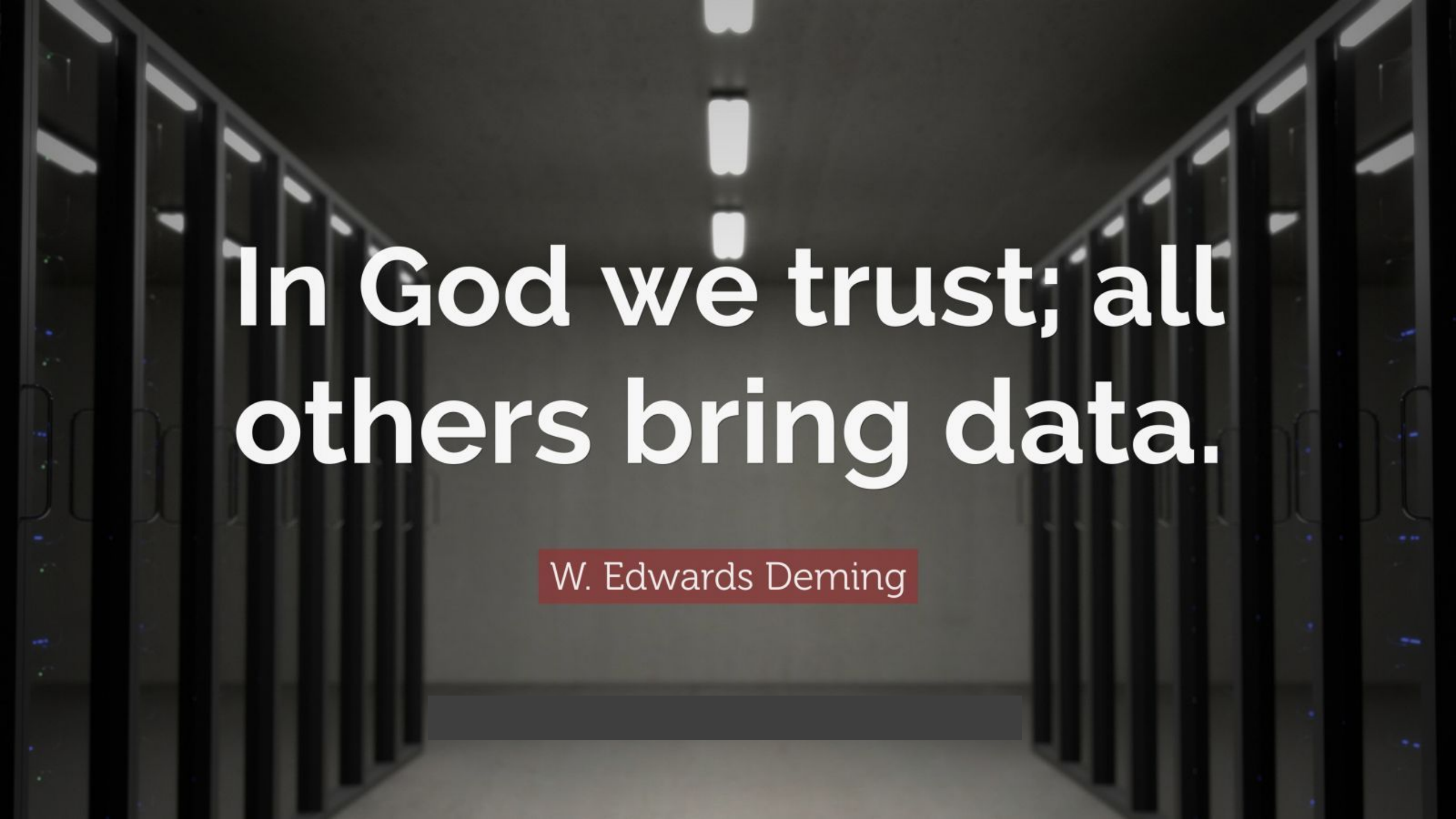
Febbre TT 40, cefalea, astenia, tosse

Non profilassi antimalarica

Tx negativo, lab lieve leucopenia (GB 3080), PCR 4.5. CD 169 fortemente attivati

DNA virale febbri tropicali positivo per Dengue (inviato molecolare sangue e urine TS)

Dimessa DBI in 3° giornata (28.8.2023)


In God we trust; all others bring data.
W. Edwards Deming

VALUTARE IL TEST DI ATTIVAZIONE MIELOIDE IN TERMINI DIAGNOSTICI PER DISCRIMINARE INFEZIONI RESPIRATORIE BATTERICHE E VIRALI

Abbiamo raccolto 778 pazienti dal 01/06/22 al 01/06/23 che hanno eseguito il test di attivazione mieloide CD64 e CD169 nei pazienti con sospetta infezione. Tra questi bisogna analizzare la motivazione per cui è stato eseguito e definire il sottogruppo delle infezioni respiratorie.

Nell'insieme infezioni respiratorie (sia batteriche che virali) valutare isolati microbiologici (Antigeni urinari, TNF virus respiratori, tampone per SARS-CoV-2), imaging (ecotorace, Rx torace o TC torace), esami bioumorali (PCR, PCT, emocromo con formula), terapie antibiotiche in corso, fattori confondenti in termini patologici (malattie ematologiche, reumatologiche in atto) o fattori iatrogeni (terapie immunosoppressive).

Una commissione *blind* valuta a posteriori se il caso è una infezione respiratoria batterica, virale o una sovrainfezione concomitante oppure se è una non infezione.

Al termine della raccolta dati sarà da definire la performance diagnostica del test di attivazione mieloide CD64 e CD169 nelle infezioni respiratorie nel setting dell'emergenza-urgenza.

Sospetta infezione respiratoria in ER

Eseguito emocromo+F, PCR, PCT, CD64 e CD169
Eseguito ecografia e/o Rx torace e/o TC
Eseguito TNF virus respiratori
Eseguito TNF SARS-CoV-2
Eseguito AgU

778 pazienti raccolti da 1 giugno 2022 al 1 giugno 2023

Analisi retrospettiva commissione per definire se infezione virale, batterica, coinfezione o non infezione

Steroide

Match CD169 con infezione virale

Fattori confondenti

Match CD64 con infezione batterica

Terapia atb eseguita

Stewardship e risparmio atb

Citofluorimetria CD 64 e CD 169: limiti

-vale per tutti i batteri?

-vale per tutti i virus?

-e i funghi?

-e per chi ha connettiviti o AR o neoplasie?

-e per chi ha tp immunosoppressive? Quali?

-e quanto dura over espressione?

-zone grigie?

-riattivazioni virali?

per gentile «concessione» DR.S.Venturini

Medicina delle differenze

Francesca Woodman

Per fortuna che c’è la microbiologia

VIROLOGIA DIRETTA MOLECOLARE

Ricerca DNA virus neurotropi nel liquor	
Citomegalovirus (CMV)	**Negativa**
Enterovirus	**Negativa**
Herpes simplex virus 1 (HSV-1)	**Negativa**
Herpes simplex virus 2 (HSV-2)	**Negativa**
Human herpes virus 6 (HHV-6)	**Negativa**
Human paraechovirus	**Negativa**
Varicella zoster virus (VZV)	**Negativa**

BATTERIOLOGIA, MICOLOGIA, PARASSITOLOGIA

Esame microbiologico liquor	
Esame microscopico	**Flora microbica assente.**
Esame colturale per batteri e miceti	**Negativo**
Ricerca DNA microrganismi nel liquor	
Escherichia coli K1	**Negativa**
Haemophilus influenzae	**Negativa**
Listeria monocytogenes	**Negativa**
Neisseria meningitidis	**Negativa**
Streptococcus agalactiae	**Negativa**
Streptococcus pneumoniae	**Negativa**

Per fortuna che c'è la microbiologia

Pordenone: Sperimentazione di un nuovo metodo molecolare per la diagnosi delle sepsi, in grado di rilevare oltre 30 target (attraverso la combinazione di diversi profili diagnostici) 4 marcatori di resistenza, possibilità di analizzare diverse matrici biologiche oltre il sangue, lavorando su un minimo volume (100µl), in modalità *open access*

PANNELLO SEPSI	PANNELLO RESPIRATORI
Staphylococcus spp	*Staphylococcus aureus*
Staphylococcus aureus	*Streptococcus pneumoniae*
Streptococcus spp	*Streptococcus pyogenes*
Streptococcus pneumoniae	*Streptococcus agalactiae*
Streptococcus pyogenes	*Enterococcus faecium*
Streptococcus agalactiae	*Enterococcus gallinarum*
Enterococcus faecium	*Enterococcus faecalis*
Enterococcus gallinarum	*Escherichia coli*
Enterococcus faecalis	*Pseudomonas aeruginosa*
Escherichia coli	*Proteus mirabilis*
Pseudomonas aeruginosa	*Acinetobacter baumannii*
Proteus mirabilis	*Klebsiella pneumoniae*
Acinetobacter baumannii	*Serratia marcesens*
Klebsiella spp	*Moraxella catarrhalis*
Enterobacter cloacae	*Haemophilus influenzae*
Enterobacter aerogenes	*Neisseria meningitidis*
Candida spp	*Bordetella pertussis*
Candida albicans	*Bordetella parapertussis*
Candida glabrata	*Legionella pneumophila*
Candida krusei	*Chlamydophila pneumoniae*
	Mycoplasma pneumoniae
ANTIBIOTICO-RESISTENZE SEPSI/RESPIRATORI	*Candida spp*
MRSA	*Candida albicans*
BLA KPC	*Candida glabrata*
Van A/B	*Aspergillus fumigatus*
	Pneumocystis jiroveci

PANNELLO MENINGITI

Streptococcus pneumoniae
Group B Streptococcus
Neisseria meningitidis
Haemophilus influenzae
Listeria monocytogenes
Escherichia coli

Pneumonia molecular panel

One sample, 26 targets. All in about 4 hours

Panel 1 — CE-IVD Marked

- Influenza A virus (Flu A)
- Influenza B virus (Flu B)
- Respiratory syncytial virus A (RSV A)
- Respiratory syncytial virus B (RSV B)
- Flu A-H1
- Flu A-H1pdm09
- Flu A-H3

Panel 2 — CE-IVD Marked

- Adenovirus (AdV)
- Enterovirus (HEV)
- Parainfluenza virus 1 (PIV 1)
- Parainfluenza virus 2 (PIV 2)
- Parainfluenza virus 3 (PIV 3)
- Parainfluenza virus 4 (PIV 4)
- Metapneumovirus (MPV)

Panel 3 — CE-IVD Marked

- Bocavirus (HBoV)
- Rhinovirus (HRV)
- Coronavirus NL63 (CoV NL63)
- Coronavirus 229E (CoV 229E)
- Coronavirus OC43 (CoV OC43)

Panel 4 — CE-IVD Marked

- *Mycoplasma pneumoniae* (MP)
- *Chlamydophila pneumoniae* (CP)
- *Legionella pneumophila* (LP)
- *Haemophilus influenzae* (HI)
- *Streptococcus pneumoniae* (SP)
- *Bordetella pertussis* (BP)
- *Bordetella parapertussis* (BPP)

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Narrative review

Rapid diagnostic tests for infectious diseases in the emergency department

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ABSTRACT

Background: Rapid diagnostic tests (RDTs) for infectious diseases, with a turnaround time of less than 2 hours, are promising tools that could improve patient care, antimicrobial stewardship and infection prevention in the emergency department (ED) setting. Numerous RDTs have been developed, although not necessarily for the ED environment. Their successful implementation in the ED relies on their performance and impact on patient management.

Objectives: The aim of this narrative review was to provide an overview of currently available RDTs for infectious diseases in the ED.

Sources: PubMed was searched through August 2019 for available studies on RDTs for infectious diseases. Inclusion criteria included: commercial tests approved by the US Food and Drug Administration (FDA) or Conformité Européenne (CE) *in vitro* diagnostic devices with data on clinical samples, ability to run on fully automated systems and result delivery within 2 hours.

Content: A nonexhaustive list of representative commercially available FDA- or CE-approved assays was categorized by clinical syndrome: pharyngitis and upper respiratory tract infection, lower respiratory tract infection, gastrointestinal infection, meningitis and encephalitis, fever in returning travellers and sexually transmitted infection, including HIV. The performance of tests was described on the basis of clinical validation studies. Further, their impact on clinical outcomes and anti-infective use was discussed with a focus on ED-based studies.

Implications: Clinicians should be familiar with the distinctive features of each RDT and individual performance characteristics for each target. Their integration into ED work flow should be preplanned considering local constraints of given settings. Additional clinical studies are needed to further evaluate their clinical effectiveness and cost-effectiveness. **D. Bouzid, Clin Microbiol Infect 2021;27:182**

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