Clinical Utility of Sepsis Biomarkers

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Conflict of Interest / Disclosures

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- Thermo-Fisher, Scientific, Middletown, VA*,[a]
- OpGen, Inc., Gaithersburg, MD *,[a]

Expert Review Committees:

- U.S. Committee for Antimicrobial Susceptibility Testing (USCAST)*,[a]

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Objectives

- Describe the role of the clinical laboratories in the diagnosis and management of sepsis and bacterial infections
- Describe the biology & kinetics of key biomarkers used in the diagnosis management of sepsis
- Describe the role of biomarkers and other rapid tests in the management of sepsis and their ability to predict clinical outcome
- Describe the limitations of biomarkers as single tests for the diagnosis of sepsis

Sepsis

From Global Burden – To Global Health Priority

- incidence is rising rapidly
- high mortality rate
  14% (community-onset BSI) - 34% to 60% (nosocomial BSI)
- risk of death from septic shock increases by 7.6% with every hour until start of appropriate therapy
- 10th leading cause of death in U.S

- <u>True global burden</u> of sepsis is difficult to assess
- Estimated 30 million cases of sepsis per year, worldwide
- Estimated 6 million deaths per year, worldwide, due to sepsis

Global Sepsis Alliance

May 26, 2017

Misdiagnosed 'Sepsis' Now a Global Health Priority for World Health Organization

GENEVA – Sepsis, one of the most prevalent but misdiagnosed, deadly diseases, was established as a global priority today by the World Health Assembly (WHA), the decision-making body of the World Health Organization (WHO).

On the unanimous recommendation of the Executive Board of the WHO, the WHA adopted the resolution to improve, prevent, diagnose, and manage sepsis through a series of actions directed at developed and developing countries around the world. The resolution was adopted at the seventieth WHA, which is meeting between May 22-31 in Geneva.

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May 26th, 2017

WHA Adopts Resolution on Sepsis

On Friday, May 26th, 2017, the World Health Assembly and the World Health Organization made sepsis a global health priority, by adopting a resolution to improve, prevent, diagnose, and manage sepsis. This marks a quantum leap in the global fight against sepsis.

Sepsis, commonly referred to as 'blood poisoning', is the life-threatening condition that arises when the body's response to infection results in organ dysfunction or failure. Sepsis is often confused with other conditions in its early stages, with delayed recognition of the signs and symptoms quickly leading to multi-system organ failure and ultimately death.

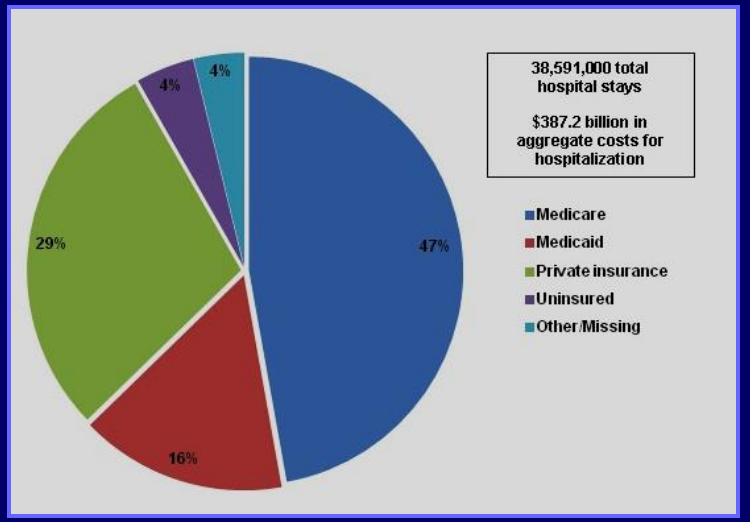
The resolution urges the 194 United Nation Member States to implement appropriate measures to reduce the human and health economic burden of sepsis. In the USA alone, sepsis causes or contributes to half of all deaths in hospitals and has become the leading cause of annual hospitals costs, at over 24 billion USD per year.

Sepsis – Healthcare Cost

Aggregate hospital cost (2011, USA) ; $ 20.3 billion

5.2% of total aggregate cost; most expensive condition treated

1.	Septicemia	$ 20,298 million
2.	Osteoarthritis	$ 14,810 million
3.	Complication of device (graft, implant)	$ 12,881 million
4.	Liveborn	$ 12,390 million
5.	Acute Myocardial Infarction	$ 11,504 million



Rank of Expense and number of discharge codes ***in thousands**

- **Most expensive to Medicare (722)**
- **2nd most expensive to Medicaid (113) and Uninsured (44)**
- **4th most expensive to private insurance (189)**

Tiru B et al. *Pharmaco Economics* 2015; 33 (9): 925-937
Prescott HC, et al. *Am J Resp Critical Care* 2014; 190: 62-69

Earlier is Better !

Time in the Context of Acute Illness

Funk DJ, Kumar A. *Crit Care Clin* 2011; 27: 53-76

Laboratory interventions that decrease TAT can be effective

The "Golden Hour"

R. Adams Cowley, M.D. – University of Maryland Medical Center, Baltimore

From his personal experiences and observations in post-World War II Europe, and then in Baltimore (1960s), he recognized that the sooner trauma patients reached definitive care, the better their chance of survival.

- 1970s/1980s — importance of early antimicrobial therapy for pediatric meningitis
- 1990s — rapid initiation of antimicrobial therapy for community-acquired pneumonia
- 2000s — effective antimicrobial therapy for severe sepsis / septic shock

Sepsis & Septic Shock

Initiate Antimicrobial Therapy within 1 hour of recognition of sepsis

Dellinger RP, et al. 2013; *Crit Care Med* 41 (2): 580-630

Early Sepsis Recognition – Early Pathogen Detection

SSC : Focus on improving outcomes in sepsis

- hemodynamic resuscitation
- development of novel & adjunctive therapies
- development of novel antimicrobials

Early recognition & appropriate antimicrobial therapy
Improves sepsis survival

Dellinger RP, et al. 2013; *Crit Care Med* 41 (2): 580-630
Funk DJ, Kumar A. *Crit Care Clin* 2011; 27: 53-76

Kumar A, et al. *Chest* 2009; 136: 1237-1248
Kumar A, et al. *Crit Care Med* 2006; 34: 1589-1596

"Time is Tissue"

Revascularization of arteries in acute MI and Stroke

Clinical signs of sepsis have been used for hundreds of years !
(hyperthermia ; hypothermia ; tachycardia ; tachypnea ; elevated WBC counts – SIRS)

Hyperthermia / fever is a poor predictor of sepsis and yield of positive blood cultures

Bates DW et al, *Ann Int Med* 1990; 113: 495-500 ; Circiumaru B, et al. *Intensive Care Med* 1999; 25: 668-673
Jaimes F et al, *CID* 2004; 38: 357-362 ; Riedel S et al, *J Clin Micro 2008*; 46: 1381-1385

Early Sepsis Recognition – Early Pathogen Detection

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Kumar A, et al. *Crit Care Med* 2006; 34: 1589-1596

Sepsis & Septic Shock

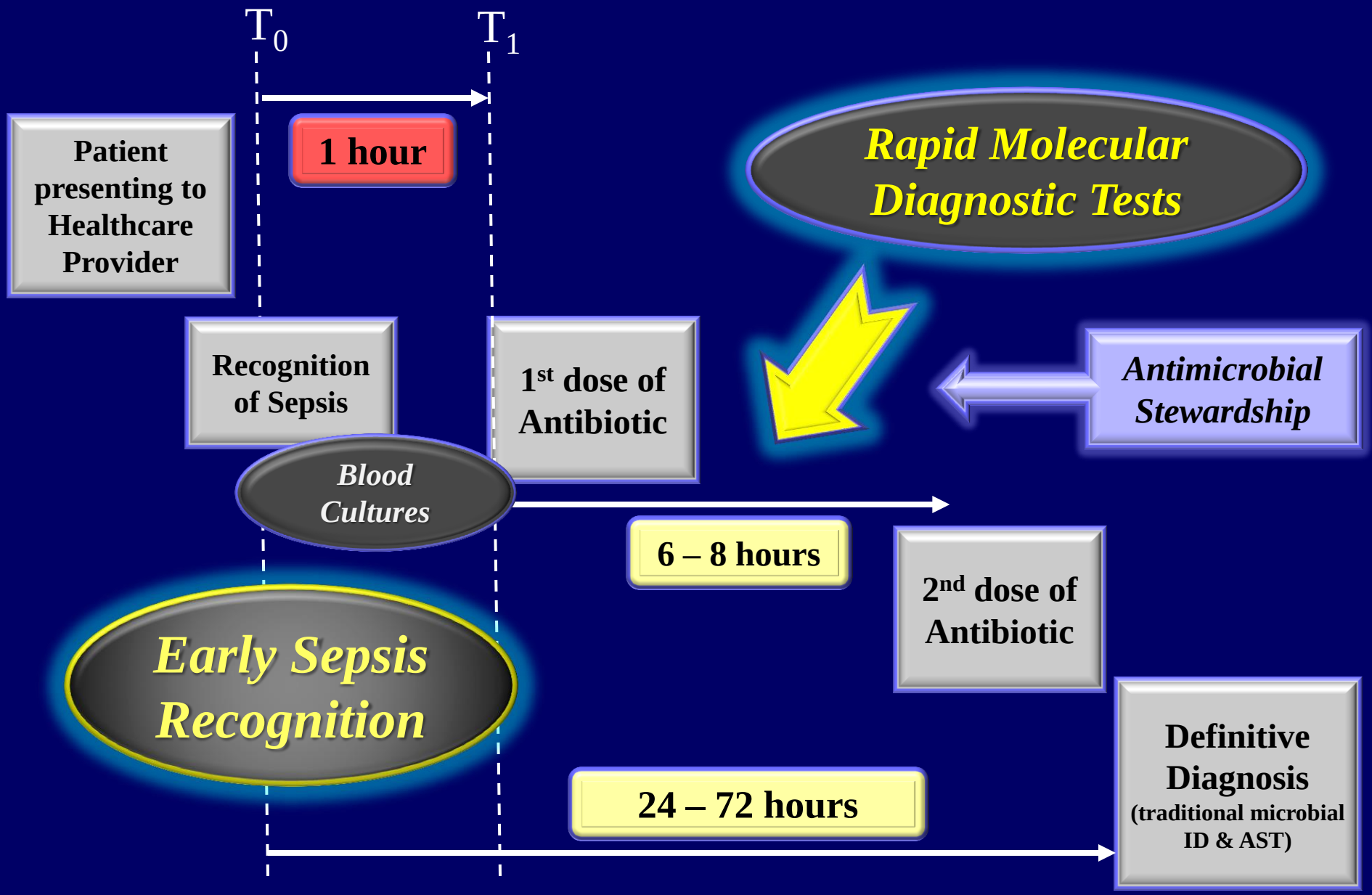
"Speed is Life"

Continued & growing interest in biomarkers as predictors of sepsis !

Riedel S, Carroll KC . *Clin Lab Med* 2013; 33: 413-437
Albrich WC, Mueller B. *Expert Rev Anti Infect Ther* 2011; 9: 653-656

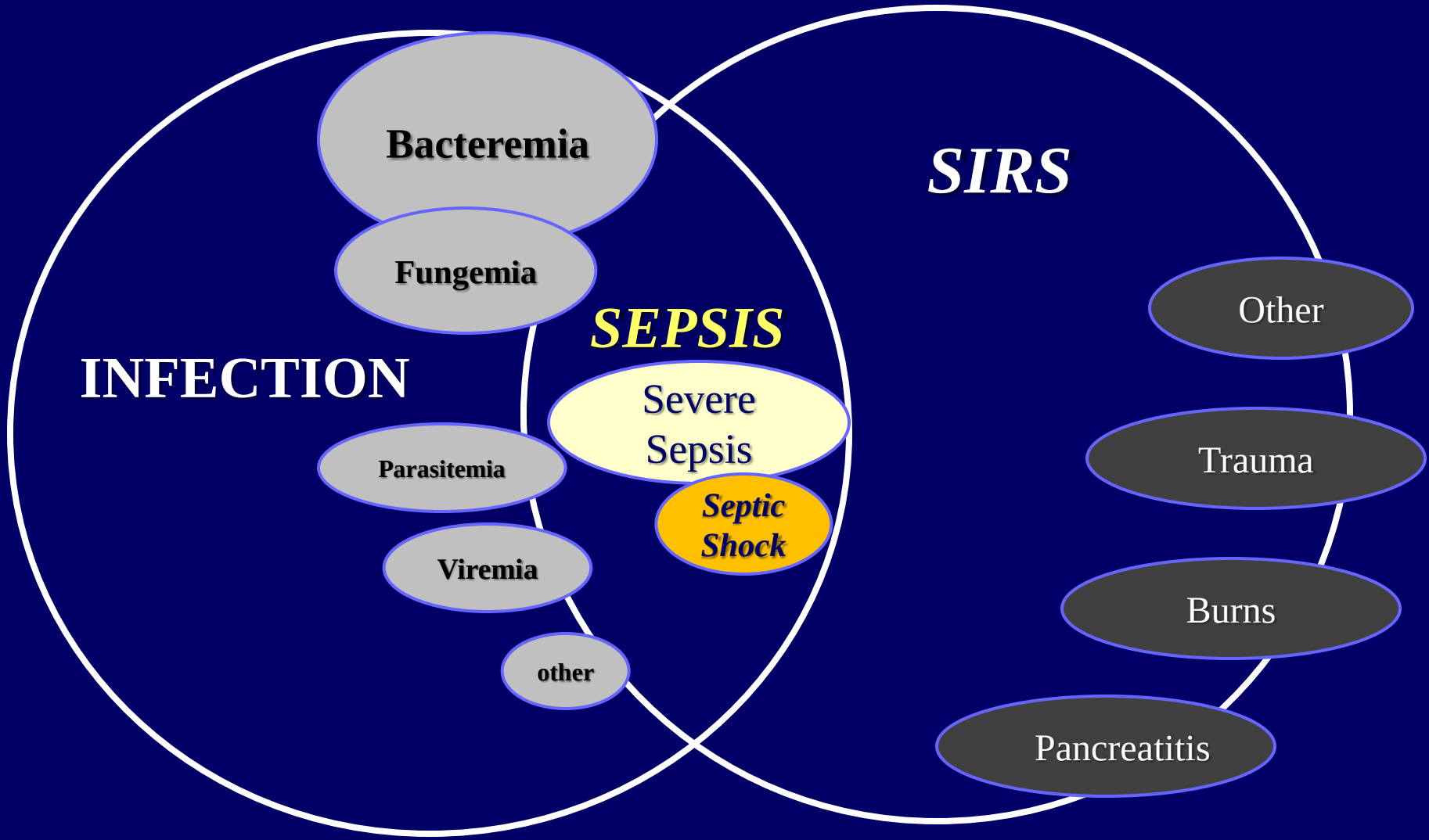
Vincent J-L, Beumier M . *Expert Rev Anti Infect Ther* 2013; 11: 265-275
Riedel S, Carroll KC. *Clin Chest Med* 2016; 37: 191-207

Time of Diagnostic Uncertainty & Empiric Therapy



A "simplistic view" of sepsis and infection

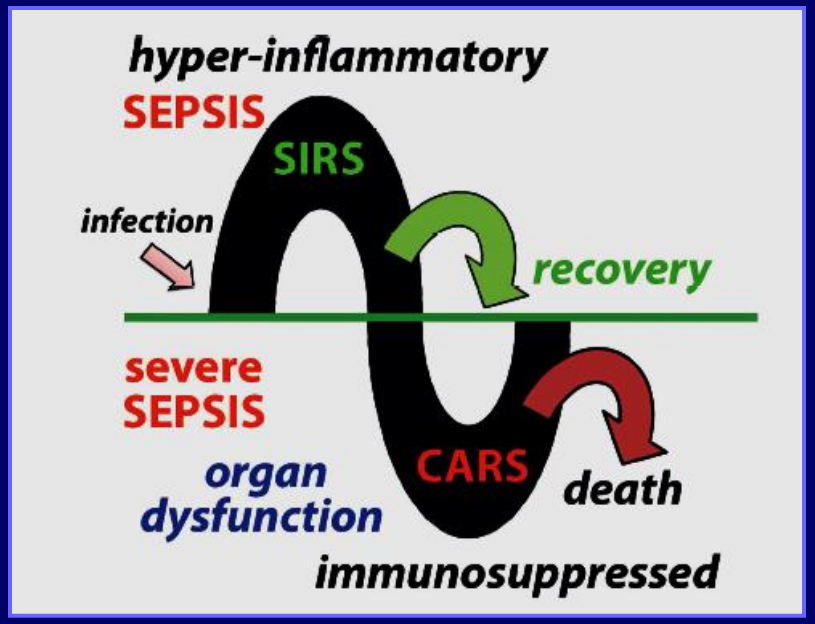
SIRS : Systemic Inflammatory Response Syndrome



Sepsis may be divided into two phases

Faix JD. *Crit Rev Clin Lab Sci* 2013; 50 (1): 23-36

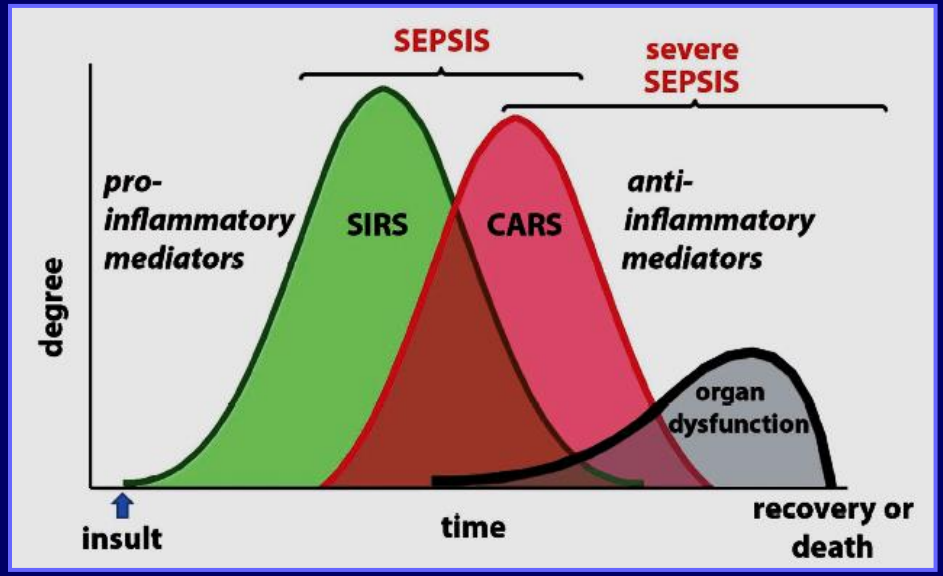
Systemic Inflammatory Response Syndrome (SIRS)



SIRS criteria; two or more of the following:

- body temperature > 38ºC or < 36ºC
- heart rate > 90 beats/min
- respiratory rate > 20 breaths/min (or arterial pCO_2 < 32 mmHg)
- WBC > 12.0 x 10^9/L or < 4.0 x 10^9/L (or >10% immature forms)

Compensatory Anti-Inflammatory Response Syndrome (CARS)



Alternative model:

- CARS begins while pro-inflammatory SIRS is still present

Sepsis is NOT a "single / definitive" Diagnosis

Difficulty to define sepsis based on its pathophysiology

from localized infection to "Cytokine Storm"

Revised Sepsis Definition (2016)

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

[Sepsis is a life-threatening condition that arises when the body's response to an infection injures its own tissues and organs.]

JAMA 2016: 315 (8): 801-810

The Inflammatory Response to Sepsis

Adapted from: *Clin Microbiol Rev* 2012; 25 (4): 609-634

Insult

Trigger

Sensor & Effector cells

Mediators & Biomarkers

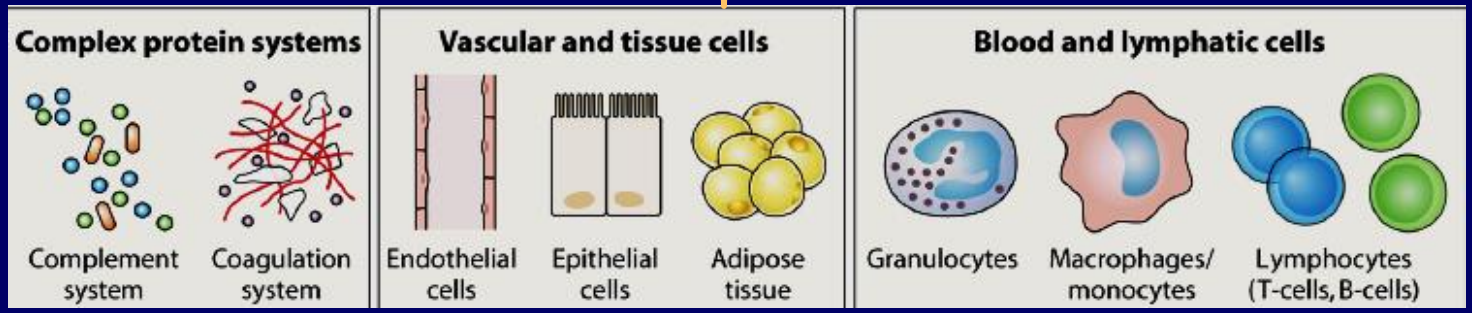
Impact on Organ Function

Outcome

Uncontrolled infection and/or major trauma (shock, tissue damage, etc.)

PAMPs
(pathogen-associated molecular patterns)
LPS ; LTA ; bacterial DNA ; etc.

DAMPs
(danger-associated molecular patterns)
heat-shock protein ; DNA ; uric acid ; etc.



Complement System | Endothelial Stress Response | Coagulation System

Acute Phase Reactants | Cell Surface Markers | Chemokines / Cytokines

MODS : brain ; lung ; cardiovascular ; kidney ; liver ; intestines

respiratory distress ; shock ; oliguria/anuria ; capillary leakage, edema ; DIC ; etc.

Effective source control
(normalization of biomarkers & resolution of organ dysfunction)

Ineffective source control
(persistent biomarker abnormalities; multi-organ failure ; death)

Biomarkers : Definition & Utility

Biomarker: "...a characteristic that can be objectively measured and evaluated as an indicator of normal biological processes, pathological processes, or pharmacological responses to a therapeutic intervention." (NIH, 2001)

Clin Pharmacol Ther 2001; 69 (3): 89-95

1) Screening patients at risk for sepsis
2) Establish early diagnosis in order to assist initial management of sepsis
3) Risk stratification to identify patients at risk for poor/adverse outcome
4) Predict (overall) outcome
5) Monitoring the response to therapeutic intervention(s)

Biomarkers & Sepsis

Myocardial infarction – 14 biomarkers ; Alzheimer's disease – 8 markers

Sepsis – 34 biomarkers (178 markers in 3370 studies, 160 clinical studies)

Coagulation, complement, inflammation, apoptosis

Complex pathophysiology of sepsis

Many mediators of inflammation

Most biomarkers are evaluated clinically but not experimentally

Is there a single, best biomarker to establish the diagnosis of sepsis ?

Examples of Potential / Actual Biomarkers

Riedel S. *Clin Lab Med 2019;* 39: 453-472

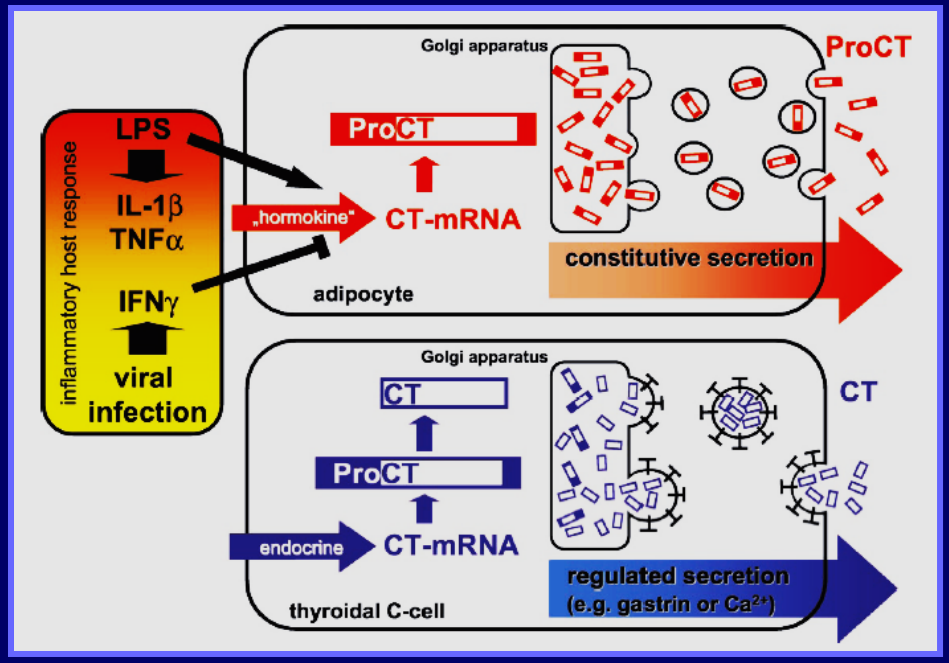
FDA-approved tests for Sepsis	Procalcitonin (PCT)
FDA-approved tests, but not specifically approved for Sepsis	Lactate ; CRP ; IL-6 ; IL-8 ; IL-10
Other biomarkers / tests	Proadrenomedullin (pro-ADM); CD-14 (presepsin) ; CD-64
Experimental biomarkers	sTREM-1 ; Pentraxin-3

Procalcitonin

(clinical utility first discovered in the 1990s)

Prohormone (PCT) for calcitonin (CT)

⟶ but different biologic activities



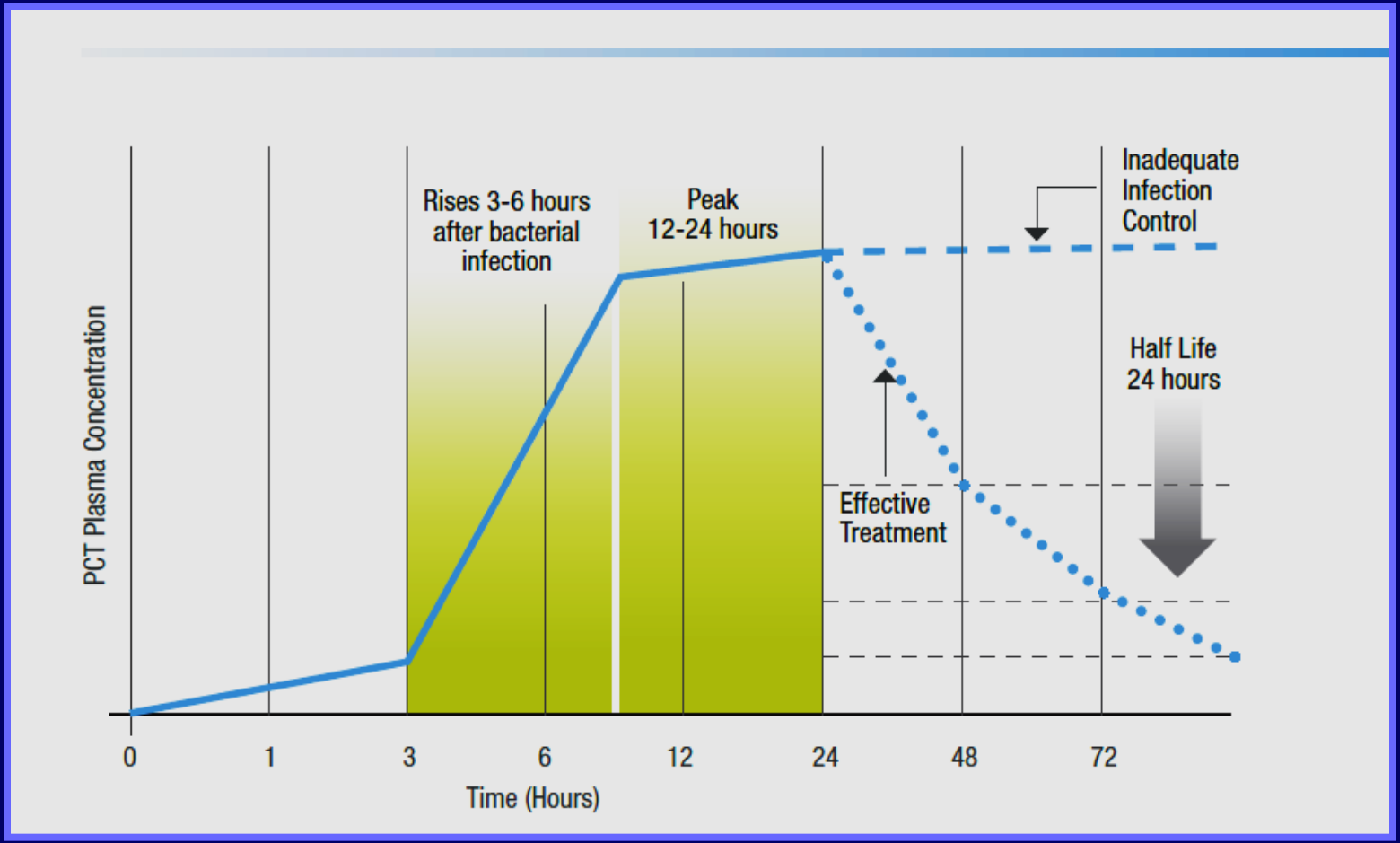
- produced in C-cells of thyroid and K-cells of the lung
- elevated serum Ca^{++} concentrations and neoplastic changes result in transcription & increased production of PCT
  - Calcitonin lowers serum Ca^{++} concentrations
- PCT can <u>also</u> be induced by
  - Bacterial endotoxins
  - Pro-inflammatory cytokines
  - Trauma and cardiogenic shock

increase within 2-4 hours after onset of inflammation

- No response to viral etiologies of infection

Christ-Crain M, Müller B. *Swiss Med Wkly* 2005; 135: 451-460
Linscheid P, et al. *Endocrinology* 2003; 144 (12): 5578-5584

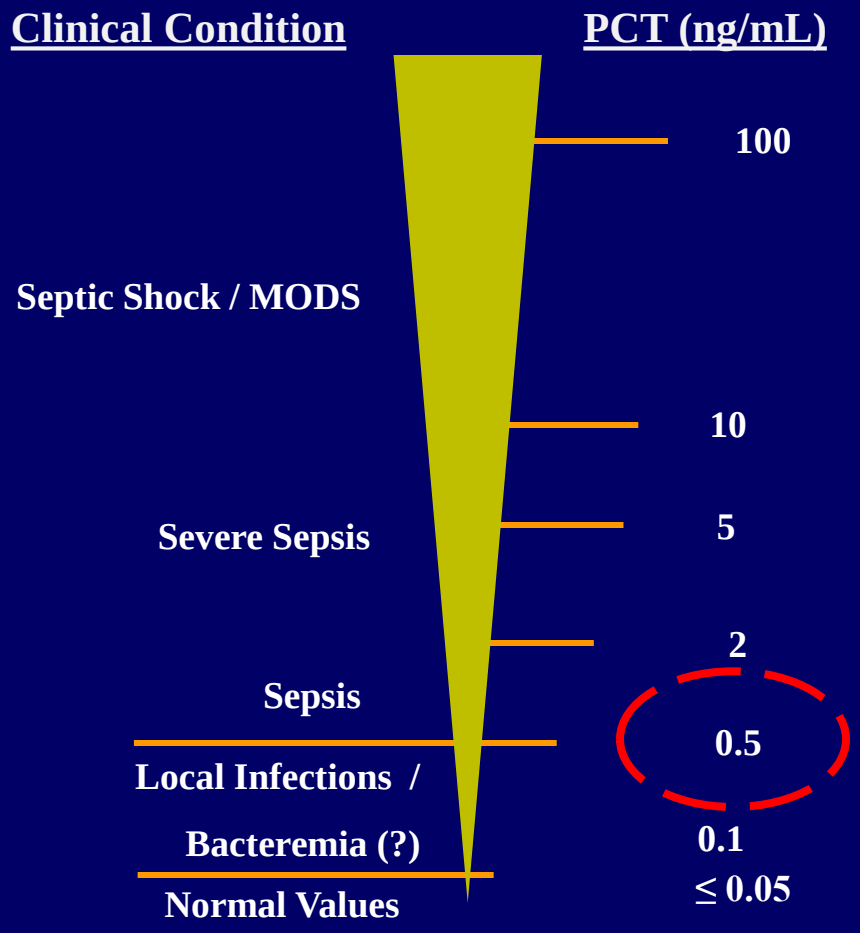
Kinetics of Procalcitonin



- Rapid and sustained response to bacterially induced systemic inflammation
- Half-life : 24 hours
- If the pathogen is not contained, infection spreads and the body up-regulates pro-inflammatory mediators

The Progression of Procalcitonin Levels

From *Healthy State* to *Sepsis – Utility of a Biomarker*



less than 0.5 ng/mL

Low risk for progression to severe sepsis / septic shock

0.5 and 2.0 ng/mL

Sepsis should be considered

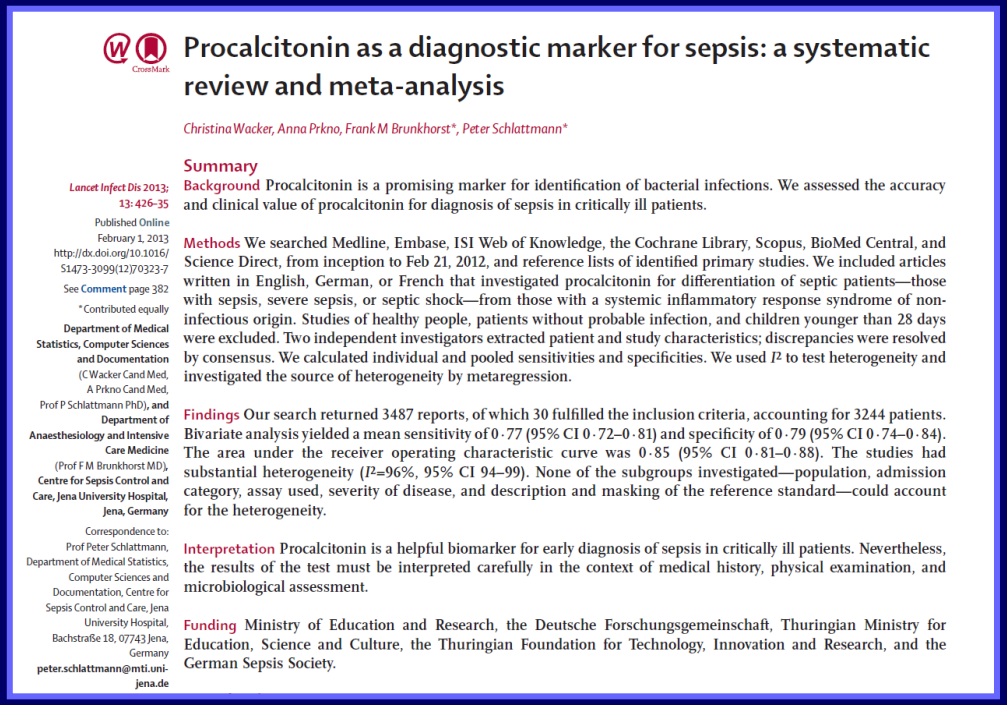
greater than 2.0 ng/mL

High risk for progression to severe sepsis / septic shock

PCT – Sepsis – SIRS : "how useful is it?"

Lancet Infect Dis 2013; 13 (5): 426-435
Clin Chim Acta 2016; 460: 203-210

- Meta-analysis of 30 studies (initial search looked at 3487 reports)
- Meta-analysis included reports for a total of 3244 patients
- PCT may accurately differentiate sepsis from SIRS
- Mean Sensitivity : 77%
- Mean Specificity : 79%
- Area under ROC curve (AUC) : 0.85



Procalcitonin as a diagnostic marker for sepsis: a systematic review and meta-analysis

Christina Wacker, Anna Prkno, Frank M Brunkhorst*, Peter Schlattmann*

Lancet Infect Dis 2013; 13: 426-35
Published Online February 1, 2013 http://dx.doi.org/10.1016/S1473-3099(12)70323-7
See Comment page 382

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Summary

Background Procalcitonin is a promising marker for identification of bacterial infections. We assessed the accuracy and clinical value of procalcitonin for diagnosis of sepsis in critically ill patients.

Methods We searched Medline, Embase, ISI Web of Knowledge, the Cochrane Library, Scopus, BioMed Central, and Science Direct, from inception to Feb 21, 2012, and reference lists of identified primary studies. We included articles written in English, German, or French that investigated procalcitonin for differentiation of septic patients—those with sepsis, severe sepsis, or septic shock—from those with a systemic inflammatory response syndrome of non-infectious origin. Studies of healthy people, patients without probable infection, and children younger than 28 days were excluded. Two independent investigators extracted patient and study characteristics; discrepancies were resolved by consensus. We calculated individual and pooled sensitivities and specificities. We used I^2 to test heterogeneity and investigated the source of heterogeneity by metaregression.

Findings Our search returned 3487 reports, of which 30 fulfilled the inclusion criteria, accounting for 3244 patients. Bivariate analysis yielded a mean sensitivity of 0·77 (95% CI 0·72–0·81) and specificity of 0·79 (95% CI 0·74–0·84). The area under the receiver operating characteristic curve was 0·85 (95% CI 0·81–0·88). The studies had substantial heterogeneity (I^2=96%, 95% CI 94–99). None of the subgroups investigated—population, admission category, assay used, severity of disease, and description and masking of the reference standard—could account for the heterogeneity.

Interpretation Procalcitonin is a helpful biomarker for early diagnosis of sepsis in critically ill patients. Nevertheless, the results of the test must be interpreted carefully in the context of medical history, physical examination, and microbiological assessment.

Funding Ministry of Education and Research, the Deutsche Forschungsgemeinschaft, Thuringian Ministry for Education, Science and Culture, the Thuringian Foundation for Technology, Innovation and Research, and the German Sepsis Society.

Limitations

- substantial heterogeneity among studies
- reliable, "gold standard" test is absent
- differences in study implementations
- publication bias may have been present
- differences in cut-off values among studies

PCT is a helpful biomarker for early diagnosis of sepsis in critically ill patients.

The Power of the Negative Predictive Value

Representative negative predictive values (NPV) of serum procalcitonin levels in patients with possible severe sepsis

Ref No.	Clinical Setting	Clinical Endpoint	Procalcitonin "Cutoff" Concentration, ng/mL	NPV, %
Reitman et al,[24] 2012	Febrile neutropenia in children	Bacteremia	<0.5	93
Riedel et al,[80] 2011	Sepsis in emergency department	Bacteremia	<0.1	98
Garcia-Granero et al,[81] 2013	Gastrointestinal surgery	Anastomotic leak	<0.35	100
Markogiannakis et al,[82] 2011	Bowel obstruction	Ischemic bowel	<0.25	95
Menacci et al,[83] 2012	Hospitalized with sepsis syndrome	Bacteremia	<0.25	99
Menendez et al,[84] 2012	Community-acquired pneumonia	Bacteremia	<0.36	98

Normal PCT values in a hypotensive/febrile patient virtually exclude bacteremia/sepsis as an etiology !

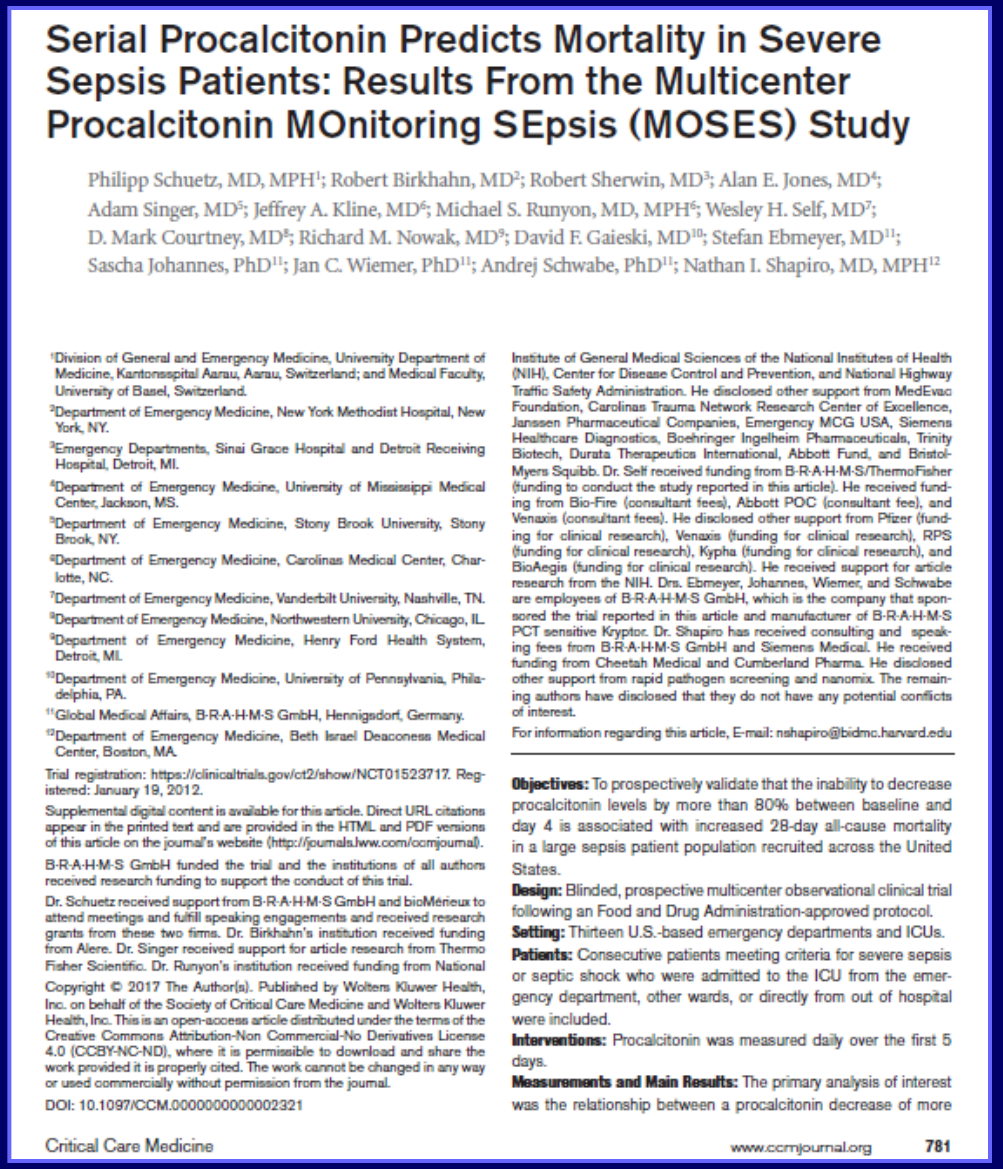
- serum PCT levels take 4-5 hours to increase
- with an acute illness: consider a second PCT level (after 4-6 hours)

Multicenter Procalcitonin Monitoring Sepsis (MOSES) Study

- Blinded, prospective multicenter, observational clinical trial, following a Food and Drug Administration (FDA) approved protocol
- Thirteen U.S.-based emergency departments and ICUs
- Consecutive patients meeting criteria for severe sepsis or septic shock, who are admitted to the ICU from the emergency department, other wards, or directly from out-of-hospital
- Procalcitonin was measured daily over the first 5 days of admission

OBJECTIVE

To prospectively validate that the inability to decrease PCT levels by more than 80% between baseline and day 4 is associated with increased 28-day all-cause mortality



Serial Procalcitonin Predicts Mortality in Severe Sepsis Patients: Results From the Multicenter Procalcitonin MOnitoring SEpsis (MOSES) Study

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[11]Global Medical Affairs, B·R·A·H·M·S GmbH, Hennigsdorf, Germany.
[12]Department of Emergency Medicine, Beth Israel Deaconess Medical Center, Boston, MA.

Trial registration: https://clinicaltrials.gov/ct2/show/NCT01523717. Registered: January 19, 2012.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (http://journals.lww.com/ccmjournal).

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For information regarding this article, E-mail: nshapiro@bidmc.harvard.edu

DOI: 10.1097/CCM.0000000000002321

Objectives: To prospectively validate that the inability to decrease procalcitonin levels by more than 80% between baseline and day 4 is associated with increased 28-day all-cause mortality in a large sepsis patient population recruited across the United States.

Design: Blinded, prospective multicenter observational clinical trial following an Food and Drug Administration-approved protocol.

Setting: Thirteen U.S.-based emergency departments and ICUs.

Patients: Consecutive patients meeting criteria for severe sepsis or septic shock who were admitted to the ICU from the emergency department, other wards, or directly from out of hospital were included.

Interventions: Procalcitonin was measured daily over the first 5 days.

Measurements and Main Results: The primary analysis of interest was the relationship between a procalcitonin decrease of more

Schuetz P, et al. *Crit Care Med* 2017; 45 (5): 781-789

Prognostic Performance of PCT Decrease

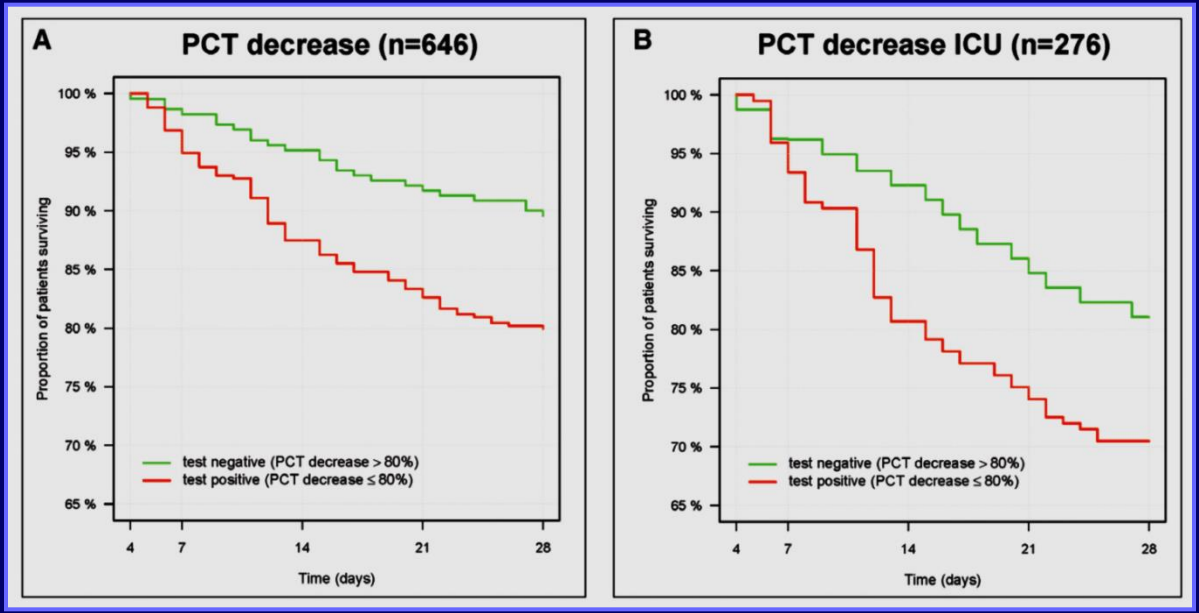
(baseline to day 4)

Intention-to-diagnose population	Dead	Alive	Total	Mortality	
				ΔPCT decrease ≤ 80%	20.0% (16.2–23.9%)
				ΔPCT decrease > 80%	10.4% (6.5–14.4%)
ΔPCT decrease ≤ 80%	83	330	413	Sensitivity	77.3% (69.3–85.3%)
ΔPCT decrease > 80%	24	209	233	Specificity	38.8% (34.6–43.0%)
Total	107	539	646	Positive predictive value	20.0% (16.2–23.9%)
				Negative predictive value	89.6% (85.6–93.5%)
Subpopulation with ICU care on day 4	Dead	Alive	Total	Mortality	
				ΔPCT decrease ≤ 80%	29.5% (23.1–35.9%)
				ΔPCT decrease > 80%	18.9% (10.3–27.6%)
ΔPCT decrease ≤ 80%	58	138	196	Sensitivity	79.2% (69.8–88.6%)
ΔPCT decrease > 80%	15	65	80	Specificity	32.1% (25.6–38.5%)
Total	73	203	276	Positive predictive value	29.5% (23.1–35.9%)
				Negative predictive value	81.1% (72.4–89.7%)
Subpopulation without ICU care on day 4	Dead	Alive	Total	Mortality	
				ΔPCT decrease ≤ 80%	11.5% (7.2–15.7%)
				ΔPCT decrease > 80%	5.9% (2.2–9.7%)
ΔPCT decrease ≤ 80%	25	192	217	Sensitivity	73.3% (58.3–88.2%)
ΔPCT decrease > 80%	9	144	153	Specificity	42.9% (37.4–48.4%)
Total	34	336	370	Positive predictive value	11.5% (7.2–15.7%)
				Negative predictive value	94.1% (90.3–97.8%)

Schuetz P, et al. *Crit Care Med* 2017; 45 (5): 781-789

Multicenter Procalcitonin Monitoring Sepsis (MOSES) Study

Schuetz P, et al. *Crit Care Med* 2017; 45 (5): 781-789



Kaplan-Meier survival curves, comparing survival of patients with PCT decrease of at least 80% (red, high-risk group) and patients with PCT decrease > 80% (green, low risk group)

A. overall population
B. in patients in the ICU on day 4

The 80% PCT decrease cutoff from baseline to day 4 significantly separated survivors from non-survivors

- 2-fold higher risk of death for patients with a decrease in PCT ≤ 80%, as compared to those with > 80% decrease in the first 4 days following ICU admission
- baseline PCT > 2.0 ng/mL has three-fold greater mortality, if PCT did not drop by > 80%

Limitations of Procalcitonin as a Sepsis Biomarker

J Leukoc Biol 2002; 72: 643-649
Clin Chim Acta 2016; 460: 203-210
BMC Medicine 2011; 9: 107
Infect Dis Clin N Am 2017; 31: 435-453

Good news: kinetics of PCT are less influenced by corticosteroids !

DO Increase Serum PCT to ≥0.25 ng/mL	DO NOT Increase Serum PCT to ≥0.25 ng/mL
Microorganisms	
Bacteria: • Alone or with viral coinfection[9,15,16] • Gram-positive and gram-negative pathogens • *Legionella* species[118,119] • *Mycobacteria* species[a,97,98] • Scrub typhus[96] Bacterial toxin-mediated inflammation: • *Clostridium difficile* toxin[120] • Toxic shock syndrome toxins[62] Fungi: *Candida* species[122] Parasites: *Plasmodium* species (malaria)[121] Viruses: None, so far	Bacteria: • *Chlamydia* species[26] • *Mycoplasma pneumoniae*[26] • *Mycobacteria* species[a,97,98] • Lyme borreliosis[131] Fungi[122–124]: • Aspergillosis • Coccidioidomycosis[123] • Mucormycosis[124] Viruses: Virtually all, so far
Clinical Syndromes	
Bacterial: • Aspiration pneumonia[125–127] • Bacterial meningitis[30–32] • Bacterial pancreatitis[99,100] • Bacterial peritonitis[132] • Bacterial pneumonia[7,9,15,17] • Bacterial septic shock[135] • Febrile neutropenia[24,128] • Mushroom poisoning[130] • Pyelonephritis[129] • Renal insufficiency[45,46] • Septic arthritis[108,109] • Shock[54–62,117,133]: anaphylactic, bacteremic, cardiogenic, toxic shock syndrome, adrenal insufficiency, hemorrhagic, obstructive • Thermal injury, burns[133] • Trauma: crush injury (case reports)[134]	Viral: respiratory tract infections[9,15,17] • Meningitis[30–32] Abscess, chronic: for example, empyema[36] Gout, pseudogout[108] Inflammatory bowel disease[101–103] Rheumatic diseases[104–108]: • Behcet syndrome • Polyarteritis nodosa • Rheumatoid arthritis • Systemic lupus erythematosus • Still disease • Temporal arteritis • Wegener granulomatosis

- specifically treatments that can cause a cytokine storm e.g. OKT3, anti-lymphocyte globulins
- drugs that increase serum PCT levels:
  - Alemtuzumab (CD52 antibody)
  - Granulocyte transfusions
  - Interleukin-2
  - Rituximab (anti-CD20 antibody)
  - T-cell antibodies
- PCT increased in newborns during first 48hrs of life
  - on 3rd day after birth, normal adult reference ranges apply

FDA-approved tests; NOT specifically approved for Sepsis

Lactate

Clin Chim Acta 2016; 460: 203-210

Lactate levels are a useful marker for organ dysfunction

- included in the 2016 *Sepsis-3* definitions
- may serve as endpoint for resuscitation in patients with severe sepsis / shock
- > 2 mmol/L - severe sepsis / > 4 mmol/L - septic shock
- elevated levels are strongly associated with poor outcome and high mortality

Limitations:

- elevated levels are not specific for sepsis and/or predicting mortality

CRP

Clin Chim Acta 2016; 460: 203-210

CRP is an acute phase reactant synthesized in the liver

- diagnostic and prognostic marker for variety of infections
- widely available and reproducible assay
- elevated levels are strongly associated with poor outcome and high mortality

Limitations:

- elevated levels are not specific for sepsis and/or predicting of mortality

Cytokines / Chemokines

- IL-6, IL-8, and IL-10 have been most widely studied to diagnose sepsis
  - IL-6 : pro-inflammatory cytokine
  - IL-8 : chemokine (neutrophil chemotactic factor)
  - IL-10 : anti-inflammatory cytokine

- **IL-6, IL-8, and IL-10** serum levels are increased in patients with sepsis
- increased serum levels correlate with organ dysfunction and mortality
- IL-6 can differentiate sepsis from SIRS
- IL-8 has a good predictive value for severity of sepsis and 28-day mortality

Pinsky MR, et al. *Chest* 1993; 103: 565-575
Bozza FA, et al. *Crit Care* 2007; 11: R48
Calfee CS, et al. *Crit Care Med* 2010; 38: 1436-1441
Oberholzer A, et al. *Shock* 2005; 23: 488-493
Uusitalo-Seppälä R, et al. *Scand J Infect Dis* 2011; 43: 883-1890
Wong HR, et al. *Am J Respir Crit Care Med* 2008; 178: 276-282

NO greater sensitivity or specificity compared to PCT and/or CRP

May be valuable to monitor intensity of inflammation

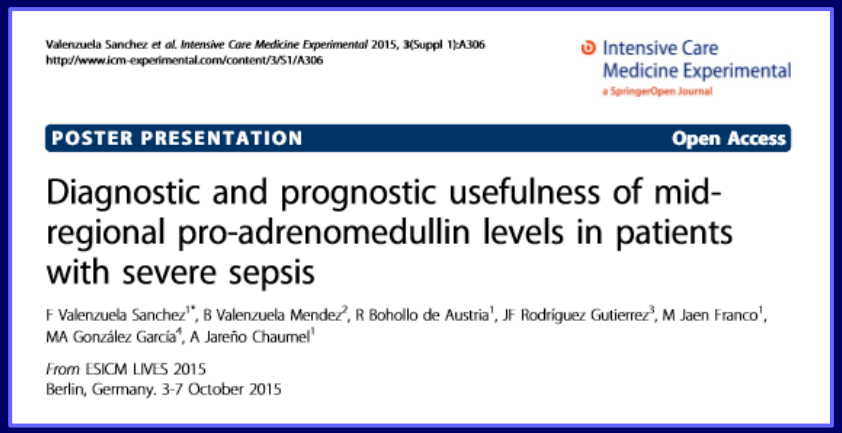
Clin Chim Acta 2016; 460: 203-210

Other Biomarkers - proADM

Ann Transl Med 2016; 4 (17): 329 *Clin Chim Acta* 2016; 460: 203-210 *Clin Chem Lab Med* 2015; 53: 521-539

Pro-adrenomedullin (proADM)

- first isolated from extracts of pheochromocytoma in 1993
- is ubiquitously expressed in many tissues
- belongs to Calcitonin gene peptide superfamily: PCT, calcitonin gene-related peptide
- primarily vasoactive effects (hypotensive)
- pulmonary circulation is place of ADM clearance (half-life: 22 min)



Valenzuela Sanchez *et al. Intensive Care Medicine Experimental* 2015, 3(Suppl 1):A306
http://www.icm-experimental.com/content/3/S1/A306

Intensive Care Medicine Experimental
a SpringerOpen Journal

POSTER PRESENTATION Open Access

Diagnostic and prognostic usefulness of mid-regional pro-adrenomedullin levels in patients with severe sepsis

F Valenzuela Sanchez[1*], B Valenzuela Mendez[2], R Bohollo de Austria[1], JF Rodríguez Gutierrez[3], M Jaen Franco[1], MA González García[4], A Jareño Chaumel[1]

From ESICM LIVES 2015
Berlin, Germany. 3-7 October 2015

Care Med Exp 2015; 3: A306

- 120 ICU patients: 104 with confirmed sepsis and 16 with SIRS without sepsis
- pro-ADM (sepsis) : 4.05 nmol/L
- pro-ADM (SIRS) : 0.309 nmol/L
- $p < 0.001$

- predictive diagnostic power: AUC of 0.95
- cut-off value established at 1.42 nmol/L
- PPV : 99% ; NPV: 42%

Pro-ADM & Sepsis

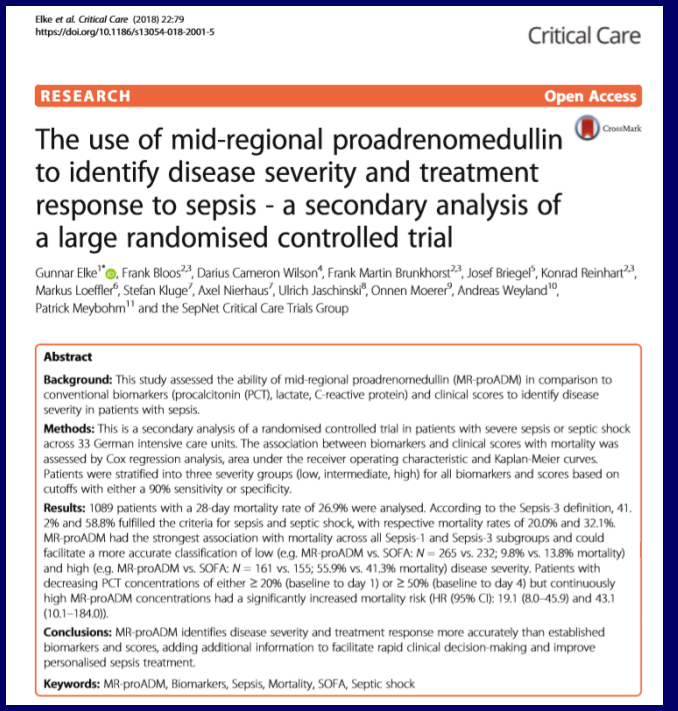
Diagnostic Value (initial proADM levels)

proADM levels help to identify the infectious origin in patients with systemic inflammatory response syndrome (SIRS) and organ dysfunction

Clin Chim Acta 2016; 460: 203-210

Prognostic Value (ongoing proADM levels)

proADM identifies disease severity and treatment response more accurately than established biomarkers and clinical scores



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

Critical Care

RESEARCH Open Access

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

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

Abstract

Background: This study assessed the ability of mid-regional proadrenomedullin (MR-proADM) in comparison to conventional biomarkers (procalcitonin (PCT), lactate, C-reactive protein) and clinical scores to identify disease severity in patients with sepsis.

Methods: This is a secondary analysis of a randomised controlled trial in patients with severe sepsis or septic shock across 33 German intensive care units. The association between biomarkers and clinical scores with mortality was assessed by Cox regression analysis, area under the receiver operating characteristic and Kaplan-Meier curves. Patients were stratified into three severity groups (low, intermediate, high) for all biomarkers and scores based on cutoffs with either a 90% sensitivity or specificity.

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

Conclusions: MR-proADM identifies disease severity and treatment response more accurately than established biomarkers and scores, adding additional information to facilitate rapid clinical decision-making and improve personalised sepsis treatment.

Keywords: MR-proADM, Biomarkers, Sepsis, Mortality, SOFA, Septic shock

Crit Care 2018; 22 (1): 79

- 1089 patients with sepsis and a 28-day mortality rate of 26.9%
- proADM, SOFA, APACHE II, PCT, lactate, CRP
- proADM had the strongest association with mortality

Biomarker Panels

- various biomarkers combined (panels) provide **improved sensitivity and specificity** for both **diagnostic AND prognostic** purposes of biomarker testing
- development of "bioscores" based on combination biomarkers
- Examples:
  - PCT, C3a — differentiation sepsis *vs.* SIRS
  - sTREM, PCT, CD64 — diagnosis of sepsis
  - PCT, presepsin, sTREM-1 — prediction of mortality of sepsis

Emerging Biomarkers

- microRNAs are a newly identified class of "biomarkers"
- short fragments of endogenous RNA involved in translational gene regulation
- may serve diagnostic & prognostic role for sepsis

Expert Rev Clin Immunol 2014; 10 (10): 1349-1356 *Eur J Intern Med* 2017; 45: 46-50

Is it really that simple ?

Obviously NOT !

- many studies, but variation in design (observational vs. randomized controlled)
- different cut-off values for various biomarkers among different studies
- differences in biomarker expression during various stages of sepsis
- different laboratory assays/methods used to measure various biomarkers
  - PCT : Kryptor compact (TRACE technology); VIDAS ELISA; COBAS (ECLIA); Architect (chemiluminescent microparticle immunoassay)
  - other methods for other biomarkers: flow-cytometry, immunoluminometric assays; LDTs

Different Performance = Different Clinical Utility

OPEN ACCESS Freely available online PLOS ONE

Transcriptional Instability during Evolving Sepsis May Limit Biomarker Based Risk Stratification

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Abstract

Background: Sepsis causes extensive morbidity and mortality in children worldwide. Prompt recognition and timely treatment of sepsis is critical in reducing morbidity and mortality. Genomic approaches are used to discover novel pathways, therapeutic targets and biomarkers. These may facilitate diagnosis and risk stratification to tailor treatment strategies.

Objective: To investigate the temporal gene expression during the evolution of sepsis induced multi-organ failure in response to a single organism, *Neisseria meningitidis*, in previously healthy children.

Method: RNA was extracted from serial blood samples (6 time points over 48 hours from presentation) from five critically ill children with meningococcal sepsis. Extracted RNA was hybridized to Affymetrix arrays. The RNA underwent strict quality control and standardized quantitation. Gene expression results were analyzed using GeneSpring software and Ingenuity Pathway Analysis.

Result: A marked variability in differential gene expression was observed between time points and between patients revealing dynamic expression changes during the evolution of sepsis. While there was evidence of time-dependent changes in expected gene networks including those involving immune responses and inflammatory pathways, temporal variation was also evident in specific "biomarkers" that have been proposed for diagnostic and risk stratification functions. The extent and nature of this variability was not readily explained by clinical phenotype.

Conclusion: This is the first study of its kind detailing extensive expression changes in children during the evolution of sepsis. This highlights a limitation of static or single time point biomarker estimation. Serial estimations or more comprehensive network approaches may be required to optimize risk stratification in complex, time-critical conditions such as evolving sepsis.

Citation: Kwan A, Hubank M, Rashid A, Klein N, Peters MJ (2013) Transcriptional Instability during Evolving Sepsis May Limit Biomarker Based Risk Stratification. PLoS ONE 8(3): e60501. doi:10.1371/journal.pone.0060501

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Competing Interests: The authors have declared that no competing interests exist.

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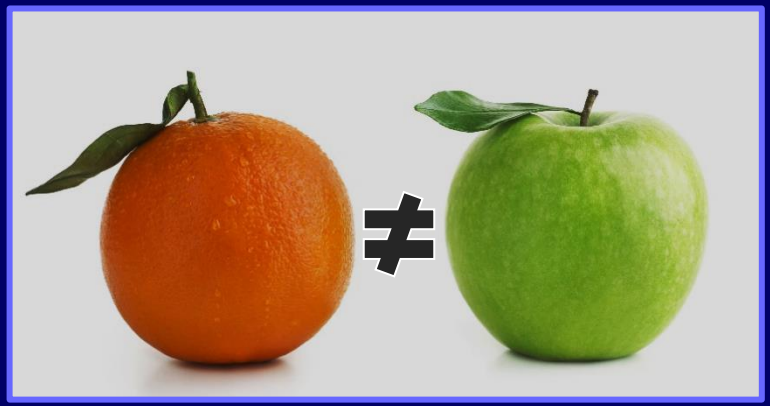

The Traditional & Current Approach to Sepsis Diagnosis

A two bottle system with blood specimen split evenly between an *AEROBIC* and an *ANAEROBIC* bottle.

Traditional BC Culture Methods

- up to 50% of sepsis patients have negative BCs
- preliminary results within 1-3 days
- definitive results often require more than 3-5 days
- ineffective for modification and/or de-escalation of antimicrobial therapy

Rapid Diagnostic Test Methods

- e.g. ePlex; BioFire; Verigene
- provide rapid ID for select organisms
- provide rapid detection of select AR mechanisms (e.g. *vanA*, KPC)

The Dilemma of a Diagnostic "*Gold Standard*"

the example case: **Biomarkers & Sepsis**

Blood Cultures are considered the Gold Standard for Detection of Bacteremia / Sepsis

- between 30% and 50% of sepsis patients have negative BCs
- problem with contaminant organisms (e.g. CoNS)
- problems with preceding / concomitant antimicrobial therapy

Sepsis is NOT a single diagnosis, but rather a clinical syndrome encompassing highly heterogeneous groups of disorders !

Differences in site and etiology of infection used in various studies.

What is the definition of a true "Gold Standard" ?

Early Sepsis Recognition – Ideal Biomarkers?

Riedel S. *Clin Lab Med 2019;* 39: 453-472
Riedel S. *Diagn Microbiol Infect Dis* 2012; 73: 221-227
Riedel S, Carroll KC . *Clin Lab Med* 2013; 33: 413-437
Vincent J-L, Beumier M . *Expert Rev Anti Infect Ther* 2013; 11: 265-275

Clinically relevant

- reflects underlying biological process
- predicts clinical events

High diagnostic accuracy

(high sensitivity, specificity, PPV, NPV)

➢ Indicator of

- Normal physiological processes
- Pathogenic processes
- Pharmacological response to a therapeutic intervention

Quickly obtainable & affordable

Common Misconceptions / Diagnostic Challenges

The search for specific marker(s) of sepsis

There is NOT and there will NEVER be one single marker for the diagnosis of sepsis.

Establish the etiology of the illness

- Blood cultures
- Molecular diagnostic tests
- MALDI-TOF/MS
- Direct organism detection in blood
- **Biomarkers (e.g. PCT, CRP, sTREM-1, presepsin, IL-6)**

Evaluate vital organ function & prognosis

- Hypotension
- Hypoperfusion
- Altered mental status
- Acid-base imbalance / **lactate levels**
- Hypoxemia
- Renal & liver dysfunction
- **Biomarkers (e.g. PCT, IL-6, presepsin)**

Conclusions

The clinical utility of biomarkers lies in their ability to …

support earlier detection of sepsis.

support earlier detection of high-risk subgroups of patients.

support antimicrobial stewardship efforts and potential de-escalation of antimicrobial therapy.

provide prognostic information for outcome.

Future Considerations

Continued development of new technologies for diagnosis of bacterial infections, incl. biomarkers, and other laboratory methods

- **PCT and CRP are commonly used in current practice**
- **Ongoing need for development of additional biomarkers (e.g. microRNAs)**

Develop integrated diagnostic & treatment algorithms

(include companion diagnostic tests, such as biomarkers, with traditional pathogen detection methods)

Need for comprehensive, prospective, clinical trials for evaluation of (combination) biomarkers to improve sensitivity & specificity

(consider the complexity and time-sensitivity of sepsis)

Need for expert groups and engagement of all clinical stakeholders

(individual clinicians , healthcare systems, professional societies, funding & regulatory bodies, diagnostics industry, public health agencies)

THANK YOU !