One size does not fit all. Individual sepsis therapy in the Emergency Room?

Peter Kanizsai

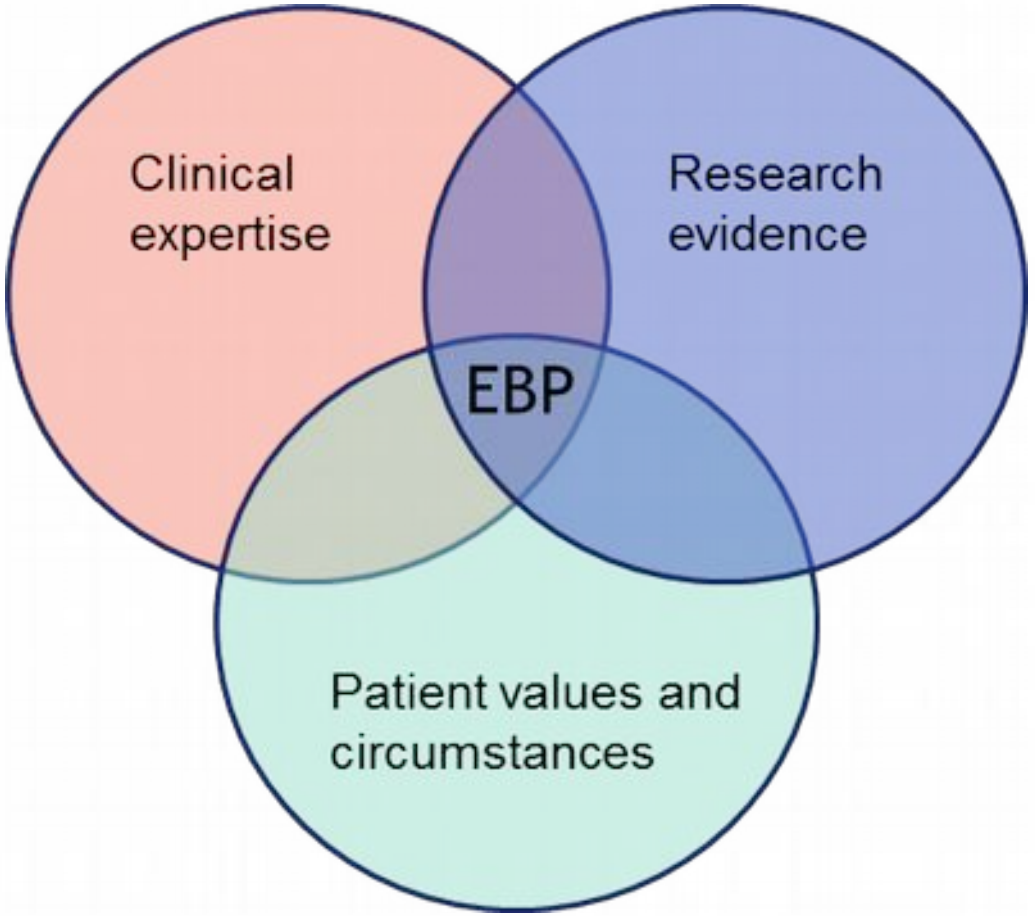
lead emergency physician

University of Pécs

Clinical Centre

Emergency Department

The 5 Steps of Evidence-Based Medicine



https://www.healthcatalyst.com/5-reasons-practice-evidence-based-medicine-is-hot-topic

of

Evidence-Based Medicine: A Unified Approach

Two approaches to using evidence to solve clinical problems, and how to unify them.

by David M. Eddy

HEALTH AFFAIRS · Volume 24, Number 1

2005

EBG (guidelines)

EBID(individual decisions)

- Daily examination of the patients
- Daily drug and fluid chart assessment
- Practice of adequate infection control
- Daily revision of individual treatment/nursing plan

COLOURS of Sepsis

Primary insult

Da ma ge

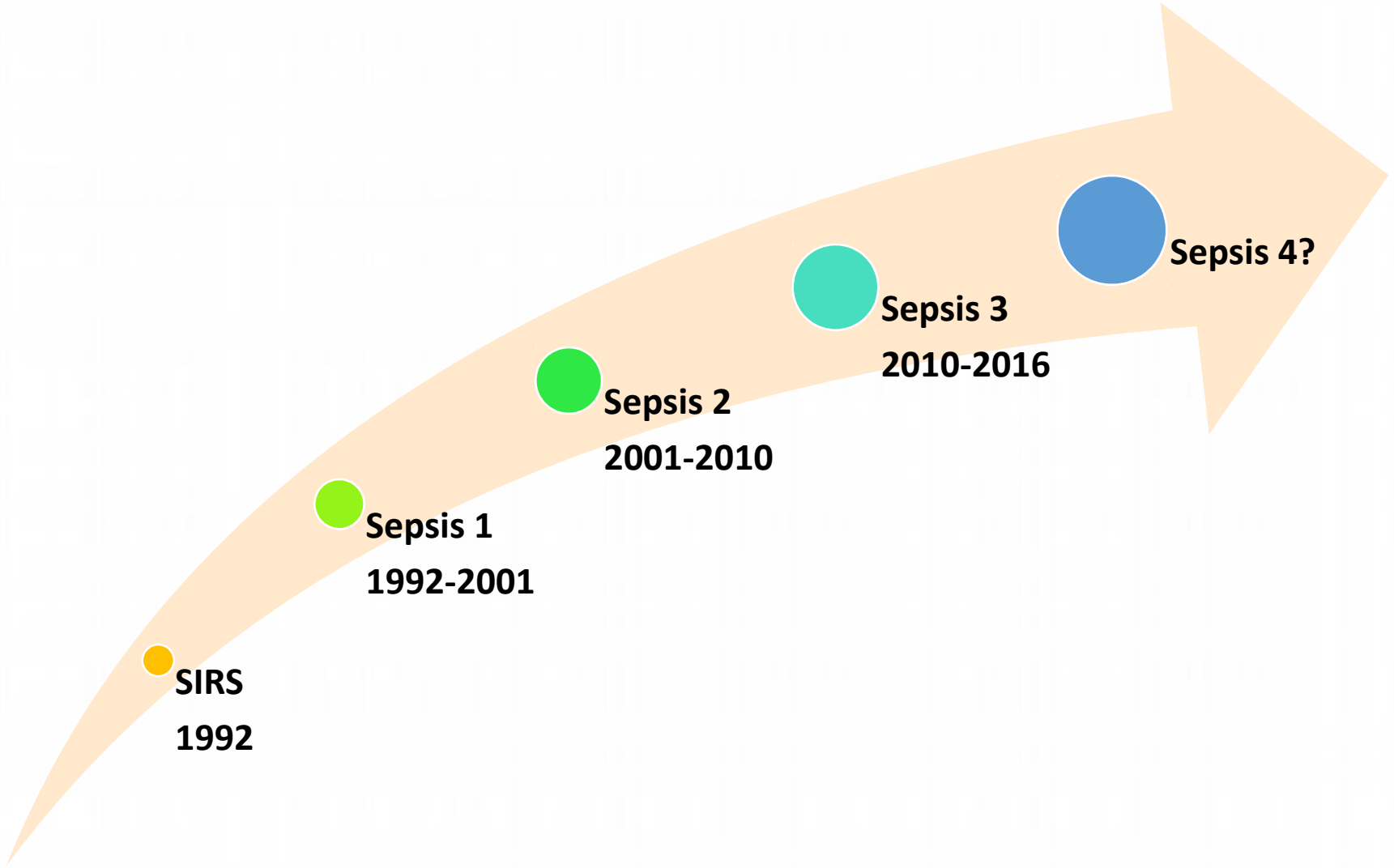
Secondary insult

Perfusion defect

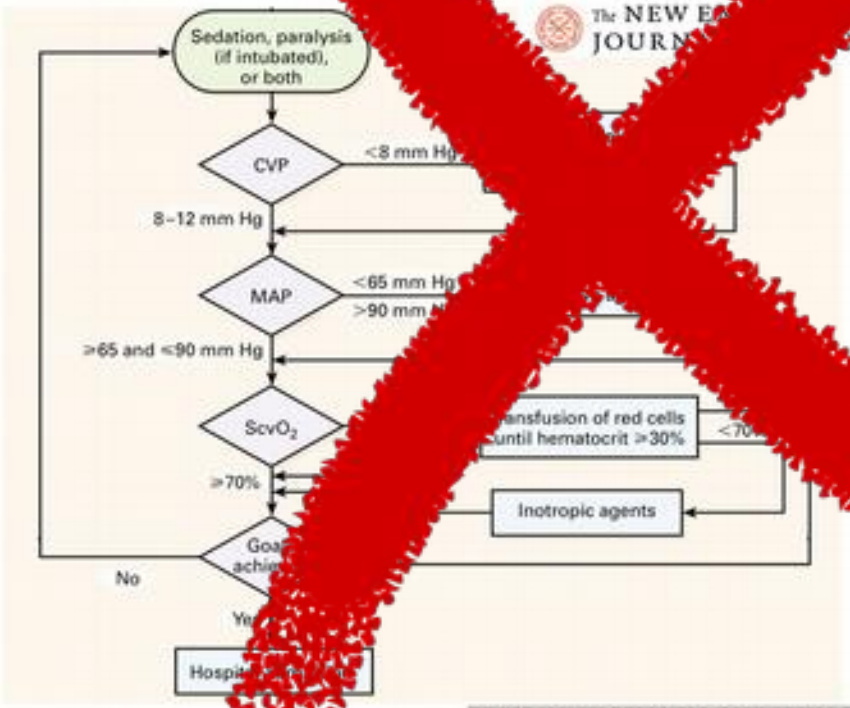
Individual reactivity

Outcome

COLOURS of Sepsis



COLOURS of Sepsis



Rivers E et al. N Engl J Med. 2001

ProCESS

ProMISe

Arise

COLOURS of Sepsis

Surviving Sepsis Campaign

2013

SURVIVING SEPSIS CAMPAIGN BUNDLES

TO BE COMPLETED WITHIN 3 HOURS:

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

TO BE COMPLETED WITHIN 6 HOURS:

5) Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (MAP) ≥ 65 mm Hg
6) In the event of persistent arterial hypotension despite volume resuscitation (septic shock) or initial lactate ≥4 mmol/L (36 mg/dL):
   - Measure central venous pressure (CVP)*
   - Measure central venous oxygen saturation ($Scvo_2$)*
7) Remeasure lactate if initial lactate was elevated*

*Targets for quantitative resuscitation included in the guidelines are CVP of ≥8 mm Hg, $Scvo_2$ of ≥70%, and normalization of lactate.

COLOURS of Sepsis

Intensive Care Med
https://doi.org/10.1007/s00134-018-5085-0

SPECIAL EDITORIAL

The Surviving Sepsis Campaign Bundle: 2018 update

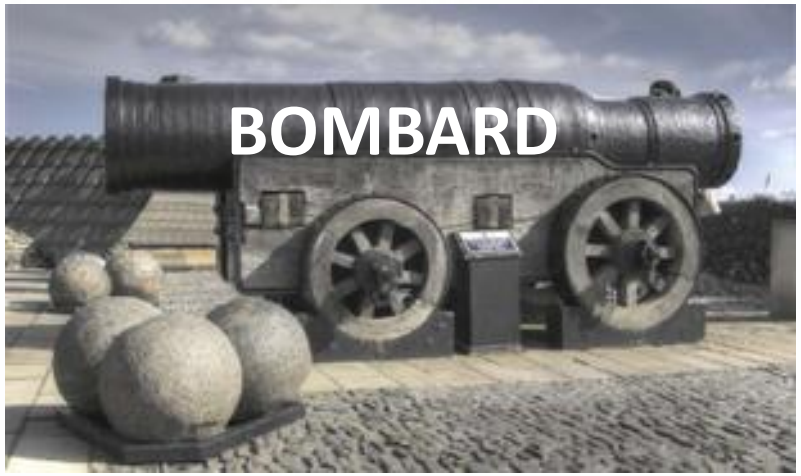
Mitchell M. Levy[1*], Laura E. Evans[2] and Andrew Rhodes[3]

Surviving Sepsis Campaign **2018**

Bundle element
Measure lactate level. Re-measure if initial lactate is > 2 mmol/L
Obtain blood cultures prior to administration of antibiotics
Administer broad-spectrum antibiotics
Rapidly administer 30 ml/kg crystalloid for hypotension or lactate ≥ 4 mmol/L
Apply vasopressors if patient is hypotensive during or after fluid resuscitation to maintain MAP ≥ 65 mm Hg

COLOURS of Sepsis

Score systems



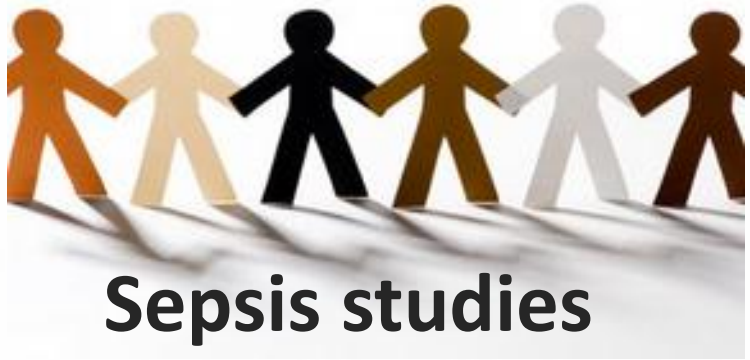
COLOURS of Sepsis

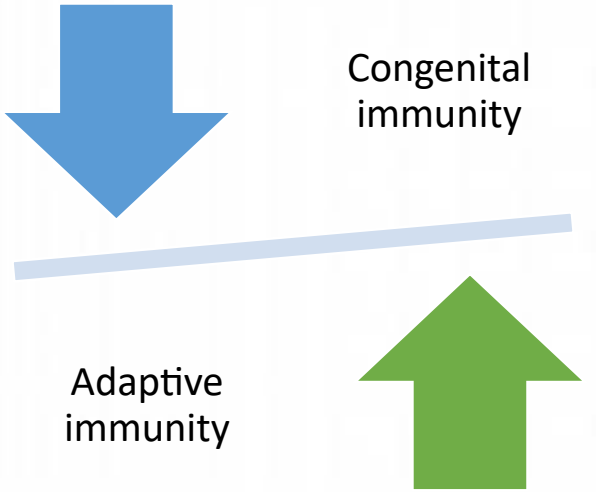
CLINICAL GENETICS An International Journal of Genetics, Molecular and Personalized Medicine
Clin Genet 2014: 86: 56–61
Printed in Singapore. All rights reserved

Published by John Wiley & Sons Ltd
CLINICAL GENETICS
doi: 10.1111/cge.12368

Review

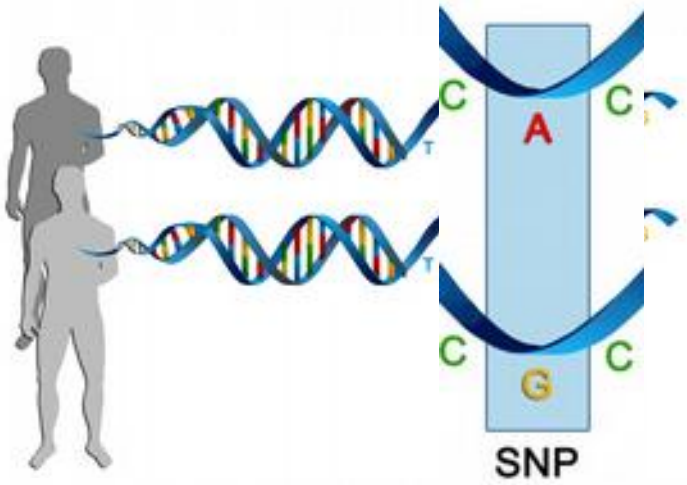
The beginning of personalized medicine in sepsis: small steps to a bright future





Genetic background

single nucleotide polymorphisms (SNPs)



MIF, TLR,

TNF →

Better bacterial kill, but higher mortality of septic shock especially when induced by DAMP

Alleles	Mortality
AA	48,7 %
AG	30,5 %
GG	29,5 %

AA genotype ADRB2 rs1042717 G/A polymorphism and beta-blocker treatment:

- increased heart rate
- more organ failure
- higher mortality

But can be reversed by low dose steroids!

Gene Expression Profiles Differentiate Between Sterile SIRS and Early Sepsis

Steven B. Johnson, MD, Matthew Lissauer, MD,* Grant V. Bochicchio, MD, MPH,* Richard Moore, MD, PhD,† Alan S. Cross, MD,‡ and Thomas M. Scalea, MD**

Annals of Surgery • Volume 245, Number 4, April 2007

12,782 genes (23.4%) with different expression within 0-48 hrs in sepsis compared to SIRS

Innate immunity: via TLR és MAPK
Citokine receptors: IL22 soluble receptor, citokine-citokine receptor interaction, IL-1R signal transduction
T-cell differentiation: Interferon Signaling Pathway, TH1/TH2 Differentiation Pathway, IL-12 and STAT4 Dependent Signaling Pathway
Protein synthesis regulation: apoptosis, eIF-4E and p70 S6 Kinase Pathway

Tang et al. Critical Care 2010, 14:R237
http://ccforum.com/content/14/6/R237

CRITICAL CARE

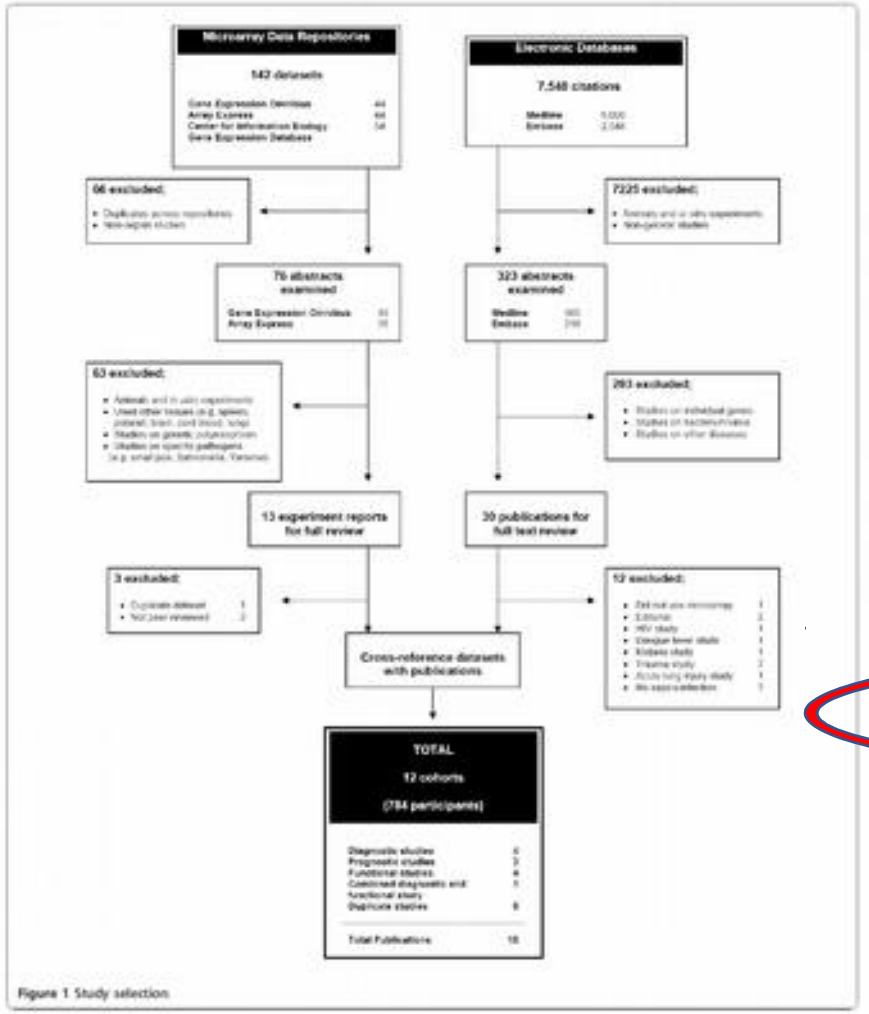


Figure 1 Study selection

RESEARCH Open Access

Genome-wide transcription profiling of human sepsis: a systematic review

Benjamin M Tang[1,2*], Stephen J Huang[1], Anthony S McLean[1]

Results: We identified 12 cohorts consisting of 784 individuals providing genome-wide expression data in early and late sepsis. Sepsis elicited an immediate activation of pathogen recognition receptors, accompanied by an increase in the activities of signal transduction cascades. These changes were consistent across most cohorts. However, changes in inflammation related genes were highly variable. Established inflammatory markers, such as tumour necrosis factor-α (TNF-α), interleukin (IL)-1 or interleukin-10, did not show any consistent pattern in their gene-expression across cohorts. The finding remains the same even after the cohorts were stratified by timing (early vs. late sepsis), patient groups (paediatric vs. adult patients) or settings (clinical sepsis vs. endotoxemia model). Neither a distinctive pro/anti-inflammatory phase nor a clear transition from a pro-inflammatory to anti-inflammatory phase could be observed during sepsis.

Conclusions: Sepsis related inflammatory changes are highly variable on a transcriptional level. We did not find strong genomic evidence that supports the classic two phase model of sepsis.

PRR, signal trasduction: similar
Inflammatory citokines (TNF, IL-1, IL-10): totally inhomogenous activation

Lu et al. Critical Care (2019) 23:26
https://doi.org/10.1186/s13054-019-2313-0

Critical Care

RESEARCH Open Access

Host genetic variants in sepsis risk: a field synopsis and meta-analysis

Hongxiang Lu[1], Dalin Wen[1], Xu Wang[1,2], Lebin Gan[1,3], Juan Du[1], Jianhui Sun[1], Ling Zeng[1], Jianxin Jiang[1*] and Anqiang Zhang[1*]

- 349 eligible articles focusing on 405 variants of 172 distinct genes.
- 29 variants of 23 genes significantly associated with the ***risk of sepsis*** (8 for PRRs, 14 for cytokines, 1 immune-related gene and 6 variants of other genes)
- Several genetic variants that could influence the ***susceptibility to sepsis***

EBioMedicine 2 (2015) 2087–2093

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

Research Article

Prospective Testing and Redesign of a Temporal Biomarker Based Risk Model for Patients With Septic Shock: Implications for Septic Shock Biology

Hector R. Wong [a,b,*], Natalie Z. Cvijanovich [c], Nick Anas [d], Geoffrey L. Allen [e], Neal J. Thomas [f], Michael T. Bigham [g], Scott L. Weiss [h], Julie Fitzgerald [b], Paul A. Checchia [i], Keith Meyer [j], Michael Quasney [k], Mark Hall [l], Rainer Gedeit [m], Robert J. Freishtat [n], Jeffrey Nowak [o], Shekhar S. Raj [p], Shira Gertz [q], Kelli Howard [d], Kelli Harmon [a], Patrick Lahni [a], Erin Frank [d], Kimberly W. Hart [r], Christopher J. Lindsell [r]

Based on measurements on day 1. and 3.

- Interleukin- 8 (IL8)
- C chemokine ligand 3 (CCL3)
- Matrix metallopeptidase 9 (MMP8)

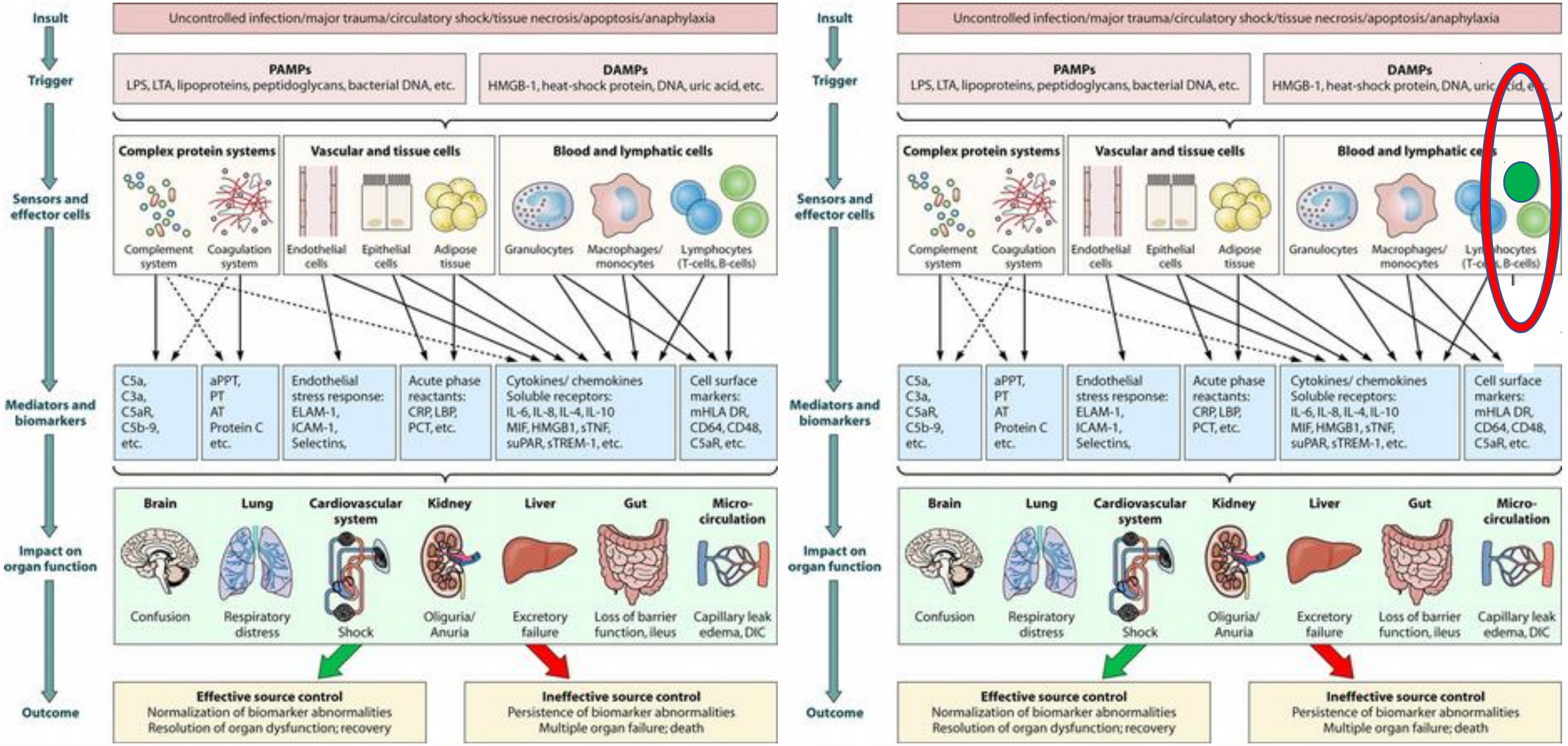
temporal version of the pediatric sepsis biomarker risk model (tPERSEVERE) modell

excessive inflammation

strong immunosuppression

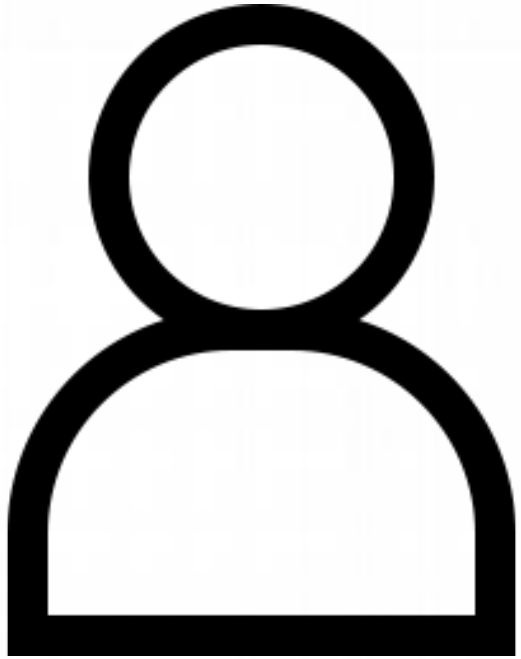
High mortality in each case but with different causes!

COLOURS of Sepsis



Insult
Trigger
Sensors and effector cells
Mediators and biomarkers
Impact on organ function
Outcome
Uncontrolled infection/major trauma/circulatory shock/tissue necrosis/apoptosis/anaphylaxia
PAMPs
LPS, LTA, lipoproteins, peptidoglycans, bacterial DNA, etc.
DAMPs
Complex protein systems
Complement system
Coagulation system
Vascular and tissue cells
Endothelial cells
Epithelial cells
Adipose tissue
Granulocytes
Macrophages/ monocytes
C5a, C3a, C5aR, C5b-9, etc.
aPPT, PT AT Protein C etc.
Endothelial stress response: ELAM-1, ICAM-1, Selectins,
Acute phase reactants: CRP, LBP, PCT, etc.
Cytokines/ chemokines Soluble receptors: IL-6, IL-8, IL-4, IL-10 MIF, HMGB1, sTNF, suPAR, sTREM-1, etc.
Cell surface markers: mHLA DR, CD64, CD48, C5aR, etc.
Brain
Lung
Cardiovascular system
Kidney
Liver
Gut
Micro-circulation
Confusion
Respiratory distress
Shock
Oliguria/ Anuria
Excretory failure
Loss of barrier function, ileus
Capillary leak edema, DIC
Effective source control
Normalization of biomarker abnormalities
Resolution of organ dysfunction; recovery
Ineffective source control
Persistence of biomarker abnormalities
Multiple organ failure; death

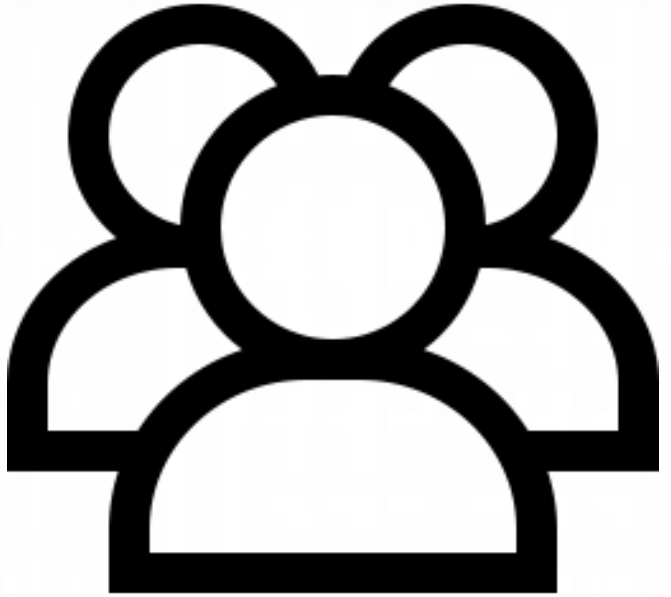
Biomarkers



Persistent **changes** in immunity

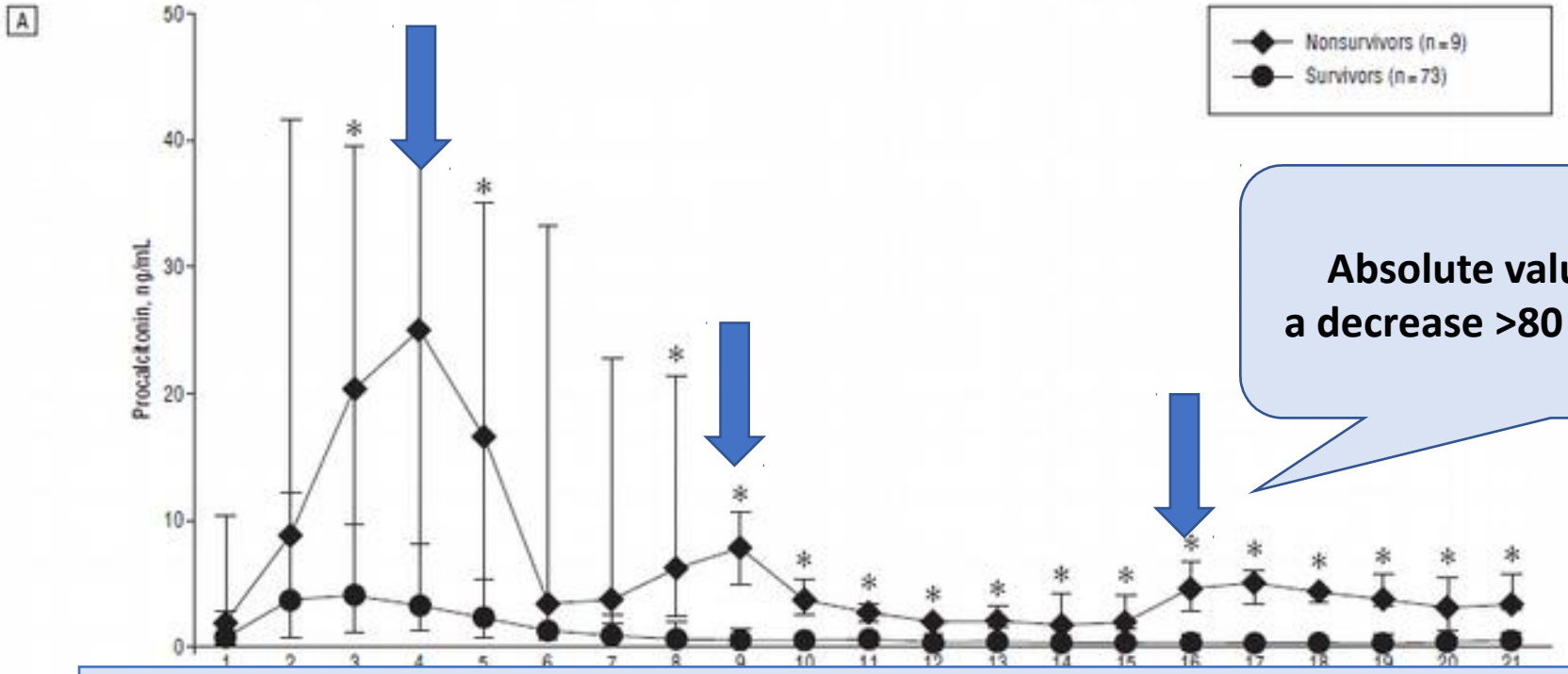
Individual differences

Interindividual differences



Evaluation of Procalcitonin for Predicting Septic Multiorgan Failure and Overall Prognosis in Secondary Peritonitis

Arch Surg. 2007;142:134-142



Absolute value < 0.5 ng/ml OR a decrease >80 % of the peak value

- Procalcitonin concentrations were most closely correlated with the development of septic multiorgan dysfunction syndrome.
- **Persisting procalcitonin levels** greater than 1.0 ng/mL beyond the first week after disease onset **strongly indicated nonsurvival** and were significantly better than CRP in assessing overall prognosis (P<.001).

Clec'h et al.: Differential diagnostic value of procalcitonin in surgical and medical patients with septic shock

Crit Care Med. 2006, 34:102-107

Medical patients:

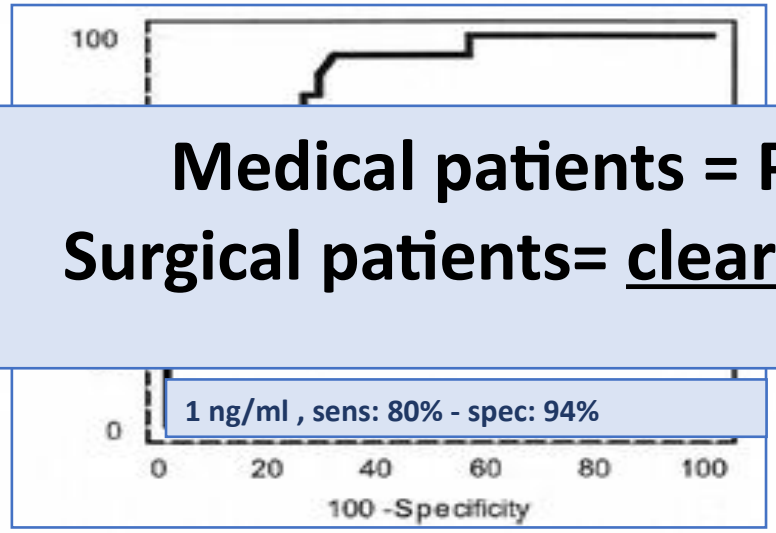
SIRS PCT: 0,3 ng/ml (0,1-1)

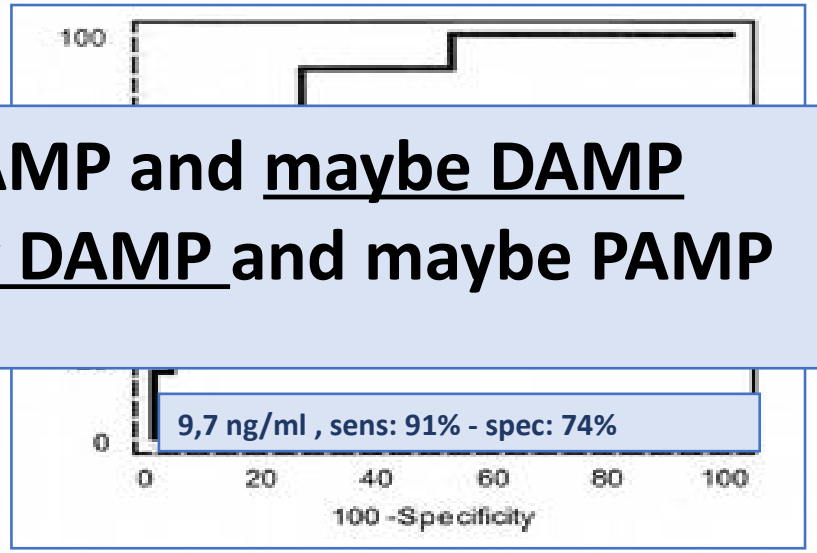
Septic shock PCT: 8,4 ng/ml (3,6-76)

Surgical patients:

SIRS PCT: 5,7 ng/ml (2,6-8.35)

Septic shock PCT: 34 ng/ml (7-76)





Medical patients = PAMP and <u>maybe DAMP</u>

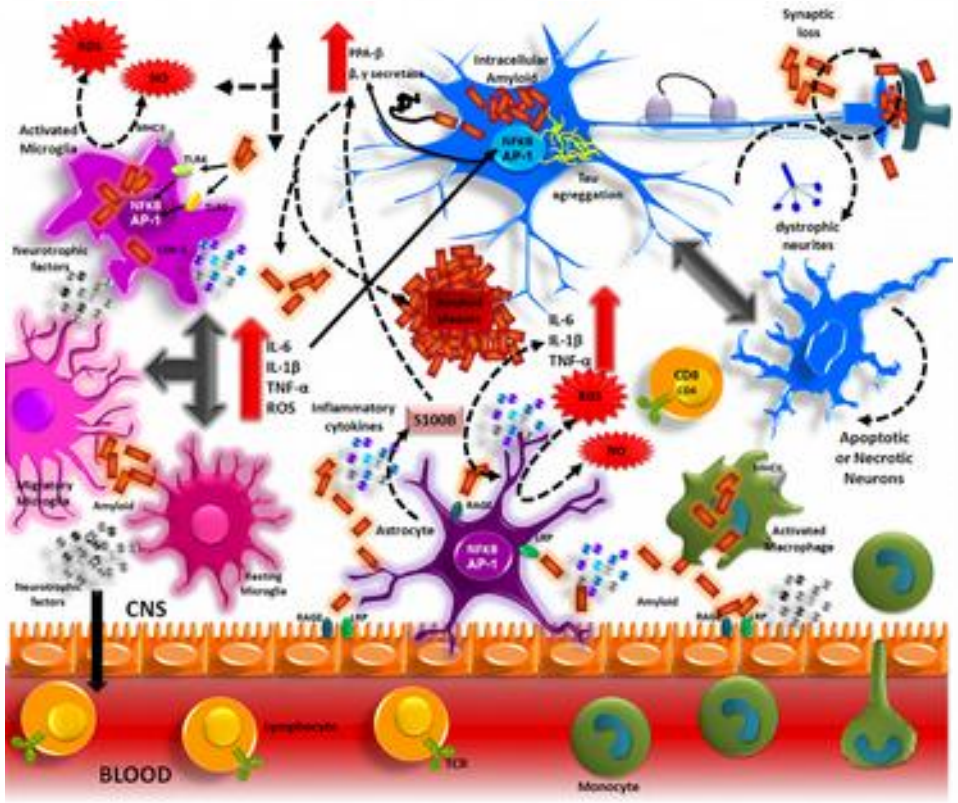
Surgical patients= <u>clearly DAMP</u> and maybe PAMP

https://myheart.net/heart-disease/heart-failure/

AHF → Mesenteric ischaemia → Acute inflammation → PCT?

Anker SD, Egerer KR, Volk HD, Kox WJ, Poole-Wilson PA, Coats AJ. Elevated soluble CD14 receptors and altered cytokines in chronic heart failure. Am J Cardiol 1997; 79: 1426–1430.

Antibiotics for what?



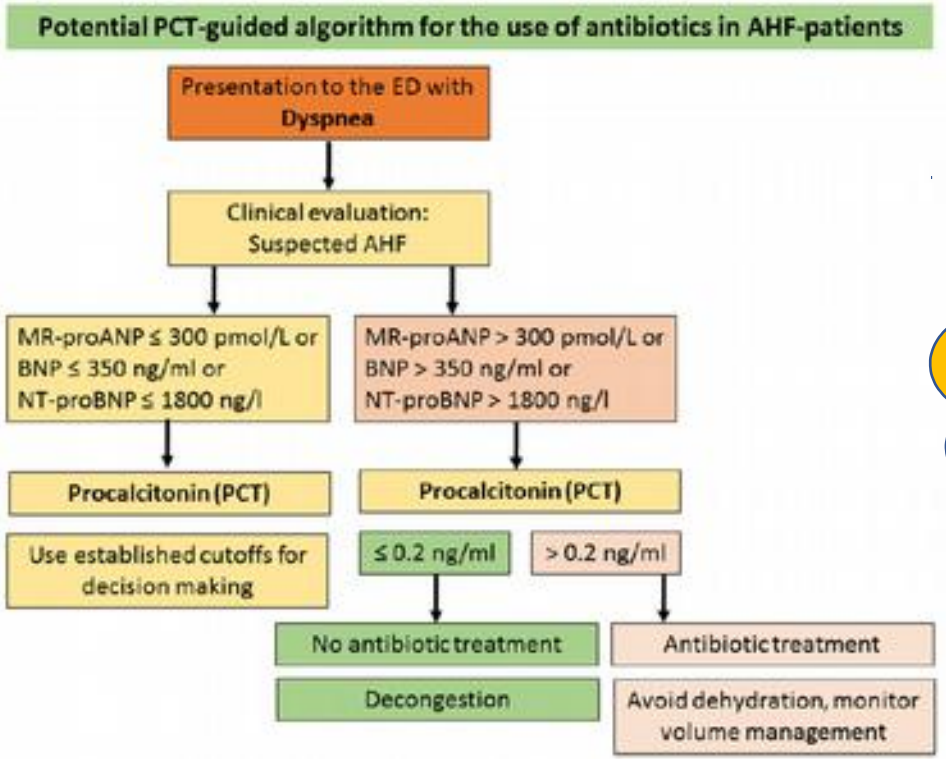
ESC HEART FAILURE
ESC Heart Failure 2017; 4: 203–208
Published online in Wiley Online Library (wileyonlinelibrary.com) DOI: 10.1002/ehf2.12189

REVIEW

The role of procalcitonin in acute heart failure patients

Martin Möckel[1,2*], Julia Searle[2] and Alan Maisel[3]

Figure 1 Proposed future use of procalcitonin in acute heart failure (AHF) using the cut-offs currently investigated in the IMPACT study. Established cut-offs are listed in *Table 1*. BNP, brain natriuretic peptide; ED, emergency department; MR-proANP, midregional pro-atrial natriuretic peptide; NT-proBNP, N terminal pro brain natriuretic peptide.



Multimarker approach…

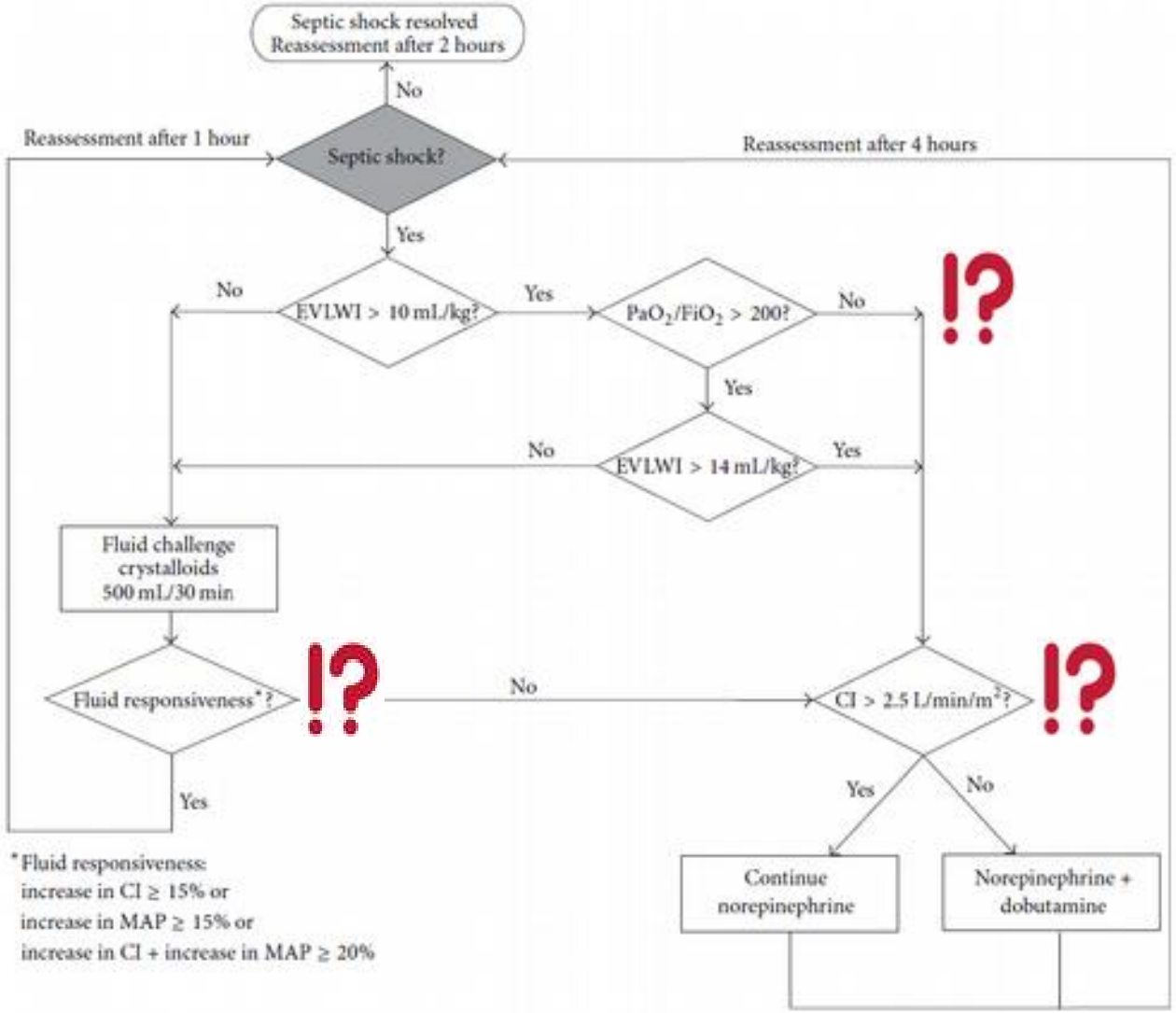
COLOURS of Sepsis

Hindawi Publishing Corporation
BioMed Research International
Volume 2016, Article ID 8260569, 11 pages
http://dx.doi.org/10.1155/2016/8260569

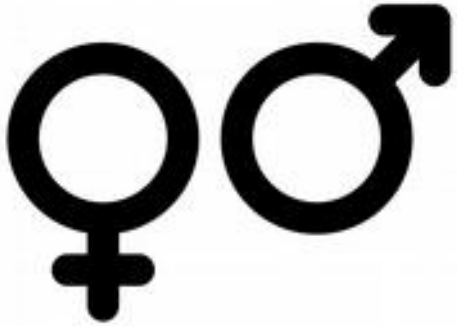
Review Article

Advanced Hemodynamic Management in Patients with Septic Shock

Bernd Saugel,[1] Wolfgang Huber,[2] Axel Nierhaus,[3] Stefan Kluge,[3] Daniel A. Reuter,[1] and Julia Y. Wagner[1]



Initial values?
Individual figures?
Are you OK with 140/85?



Sex-Specific Analysis of Cardiovascular Function pp 307-328 | Cite as

Sex-Specific Characteristics of the Microcirculation

Authors | Authors and affiliations

Virginia H. Huxley, Scott S. Kemp

Chapter
First Online: 27 July 2018

1 318

„…focusing on the constituents of the microcirculation identifies what is known presently about the role sex plays in matching metabolic demand with microvascular function and areas requiring additional study. Many of the identified sex differences are subtle and easily ignored. In the aggregate, though, they can profoundly alter phenotype, especially under stressful conditions including pregnancy, exercise, and disease states ranging from diabetes to heart failure.”

COLOURS of Sepsis

Multifactorial

Insult
(i) Infection, SIRS, surgery, trauma, burns, I-R injury, and so forth
(ii) DO_2/VO_2 imbalance

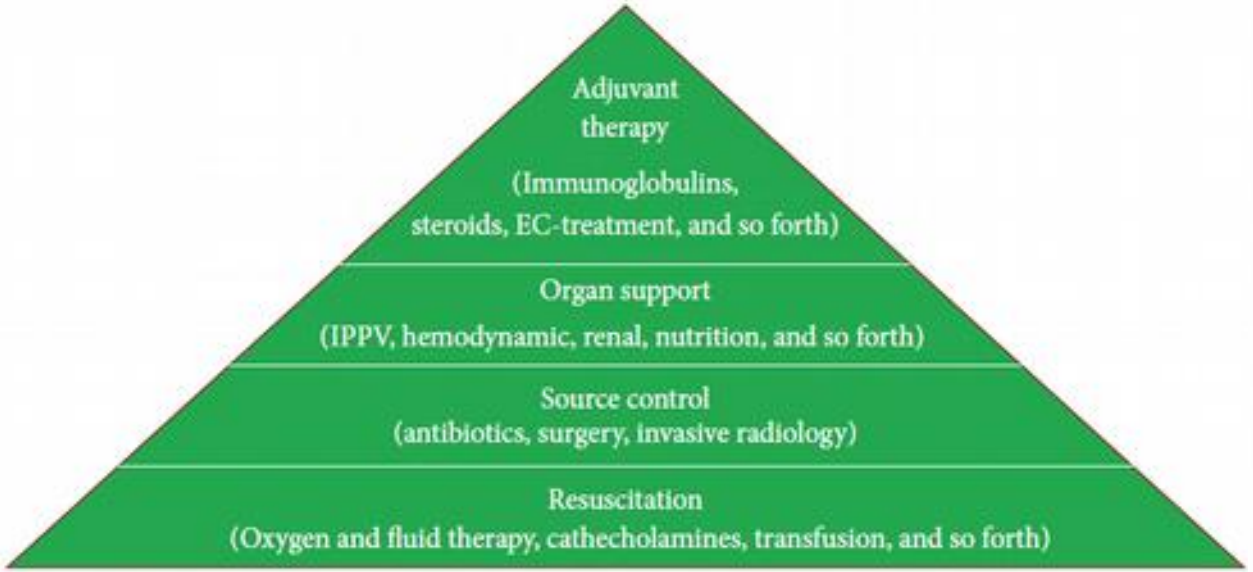
"Sepsis" triangle

Host response
(i) PAMP, DAMP
(ii) Innate, adaptive immunity

Immune status dependent

Severity and outcome

(a)



Review Article

Sepsis: From Pathophysiology to Individualized Patient Care

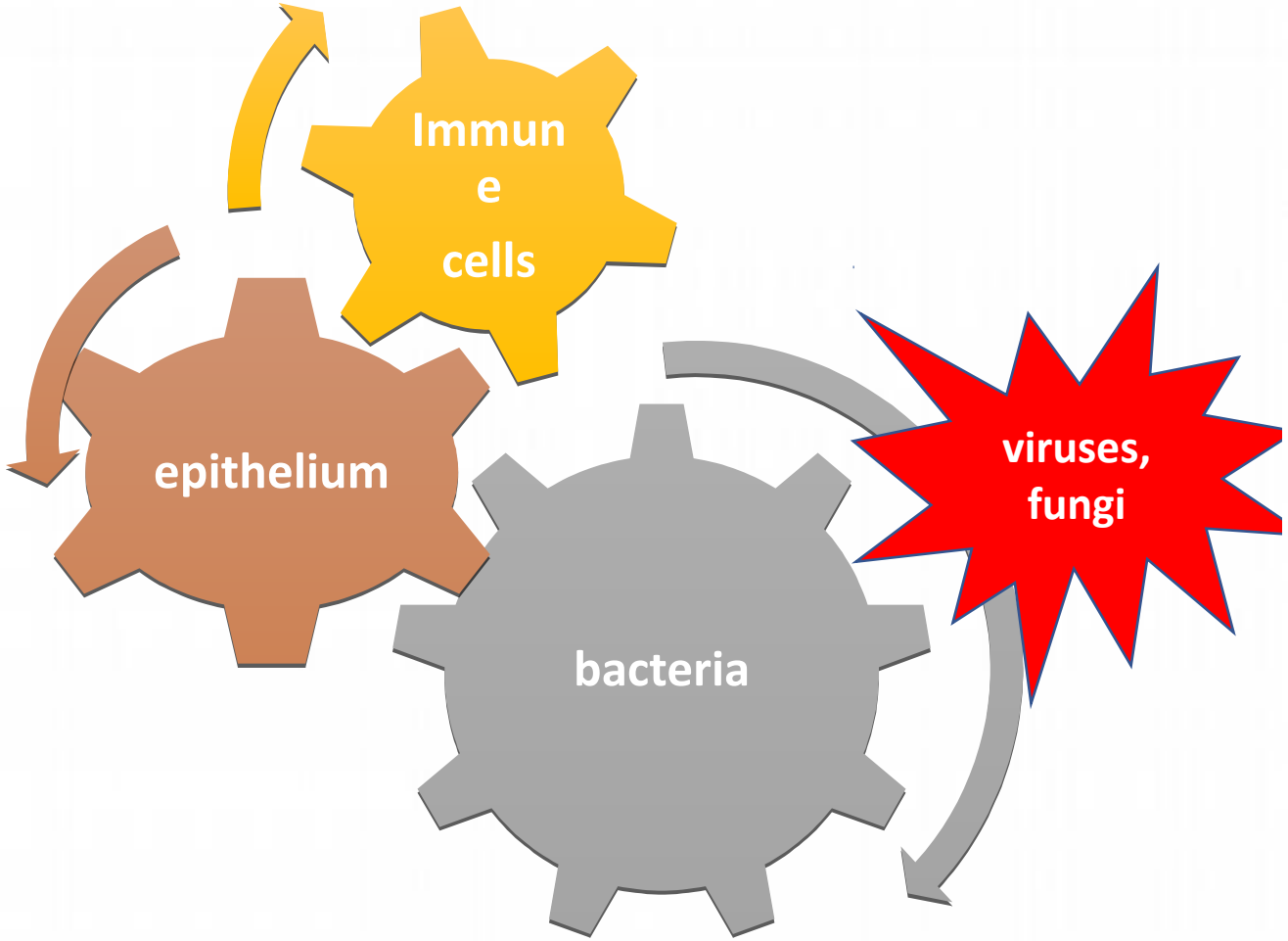
J Immun Res, 2015, AID:510436

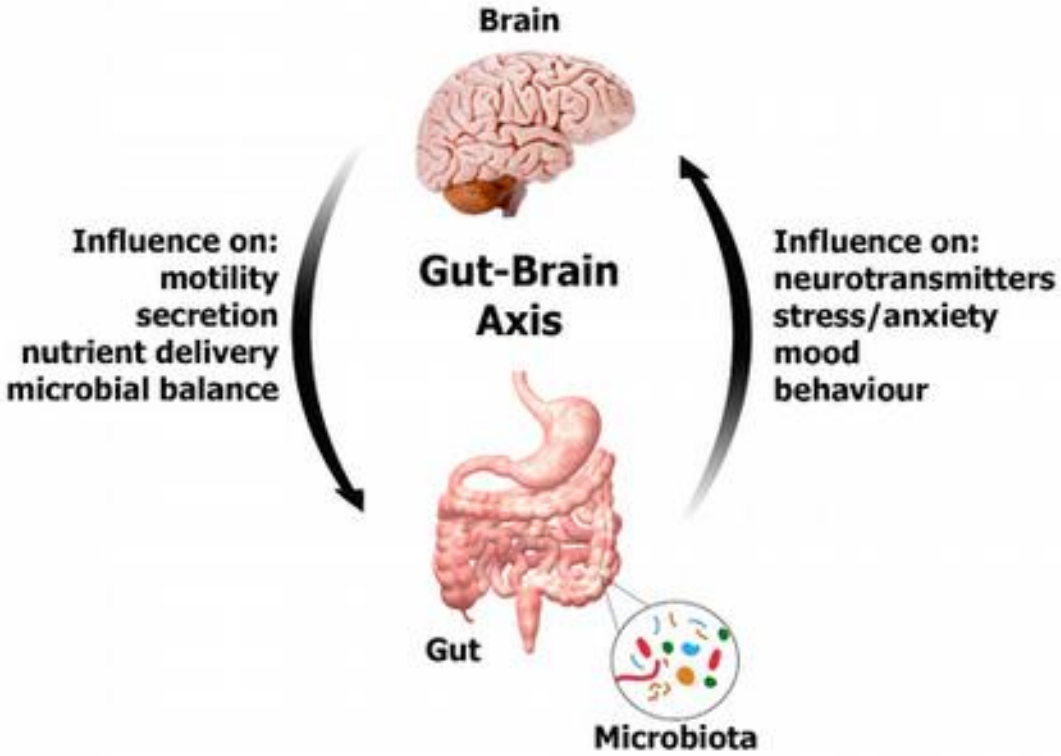
https://www.sott.net/article/318261-Dr-Justin-Sonnenburg-Is-a-disrupted-gut-microbiome-at-the-root-of-modern-disease

STATE OF THE ART REVIEW

The role of the microbiome in human health and disease: an introduction for clinicians

Vincent B Young





Functions – superficial overlook

Own microbial needs

Needs of host organism

„Messed up" processes of host organism

Local and systemic events

COLOURS of Sepsis

Possible sites of intervention

Approach	Rational	Example
Antibiotics	Target specific members or groups of the microbiota and suppress them, allowing expansion of desirable species	Small intestinal bacterial overgrowth Hepatic encephalopathy
Bacteriophages	Use naturally occurring bacterial viruses to target specific members of a community that are disruptive or are carrying out pathogenic processes	Pathogen targeted therapy to spare the microbiota from collateral damage
Probiotics (single species)	Replace a presumably missing organism and thus a missing function in the form of an organism	*Sacchromyces boulardii* for prevention of antibiotic associated diarrhea
Multispecies/designer communities	As with single species probiotics, use a collection of organisms to replace a missing function in the microbiome	Feces derived communities, multispecies
Prebiotics	Supply a complex food product (often carbohydrates) that is not digestible by the host to stimulate specific members of the microbiota. The prebiotic is meant to be metabolized by the microbiota to compounds beneficial to the host	Inulin, resistant starch
Synbiotics	Supply a complex of a microbe or microbes along with a prebiotic that is meant to be used by these organisms replace a missing function in a microbiome	
Nutritional therapy	Complete redesign of a diet to promote beneficial microbial communities and function	Low FODMAP diet for IBS. Exclusive enteral nutritional therapy for IBD
Community replacement, "microbiota restoration"	To restore a "deficient" microbiota, harvest a presumably normal microbiota from a healthy person and administer it to a patient	Fecal transplantation

FODMAP=fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; IBS=irritable bowel syndrome; IBD=inflammatory bowel disease.

COLOURS of Sepsis

Intensive Care Med
https://doi.org/10.1007/s00134-018-5085-0

SPECIAL EDITORIAL

The Surviving Sepsis Campaign Bundle: 2018 update

Mitchell M. Levy[1*], Laura E. Evans[2] and Andrew Rhodes[3]

Surviving Sepsis Campaign 2018

Bundle element	Grade of recommendation and level of evidence
Measure lactate level. Re-measure if initial lactate is > 2 mmol/L	Weak recommendation, low quality of evidence
Obtain blood cultures prior to administration of antibiotics	Best practice statement
Administer broad-spectrum antibiotics	Strong recommendation, moderate quality of evidence
Rapidly administer 30 ml/kg crystalloid for hypotension or lactate ≥ 4 mmol/L	Strong recommendation, low quality of evidence
Apply vasopressors if patient is hypotensive during or after fluid resuscitation to maintain MAP ≥ 65 mm Hg	Strong recommendation, moderate quality of evidence

Antibiotics vs microbiome

COLOURS of Sepsis

[Original Research **Critical Care**]

CHEST

Effect of Procalcitonin Testing on Health-care Utilization and Costs in Critically Ill Patients in the United States

Robert A. Balk, MD; Sameer S. Kadri, MD; Zhun Cao, PhD; Scott B. Robinson, MA, MPH; Craig Lipkin, MS; and Samuel A. Bozzette, MD, PhD

CHEST 2017; 151(1):23-33

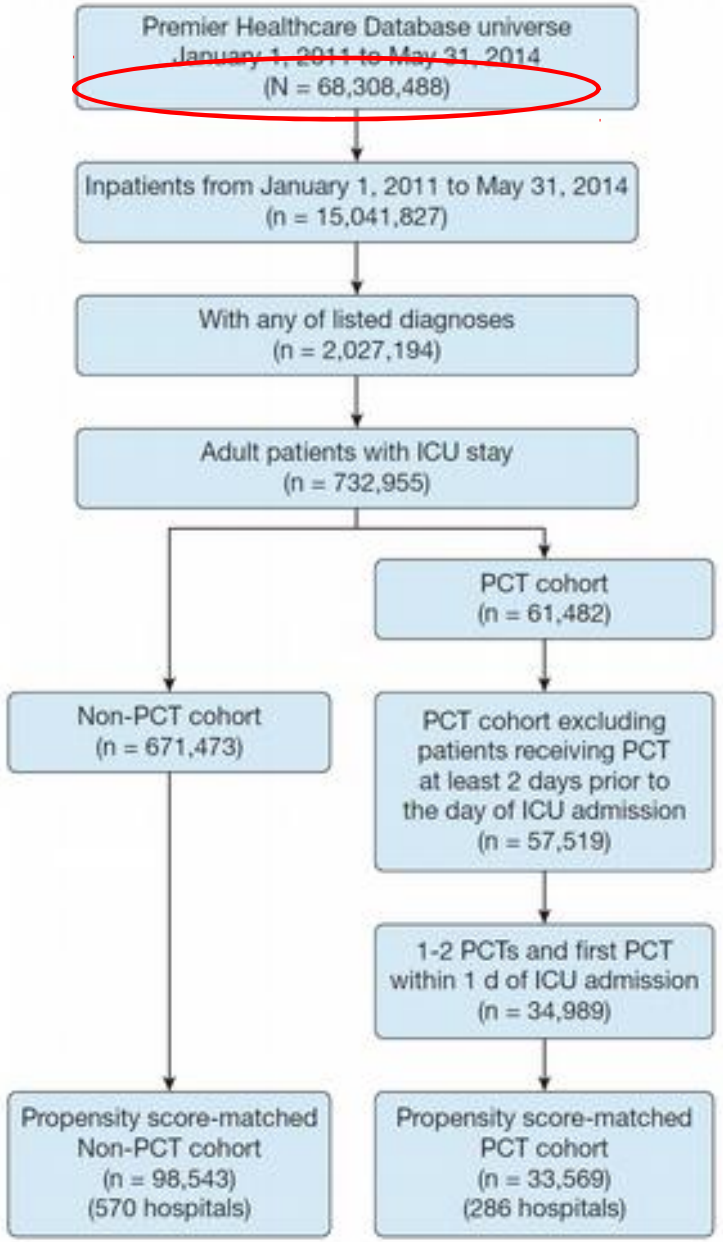
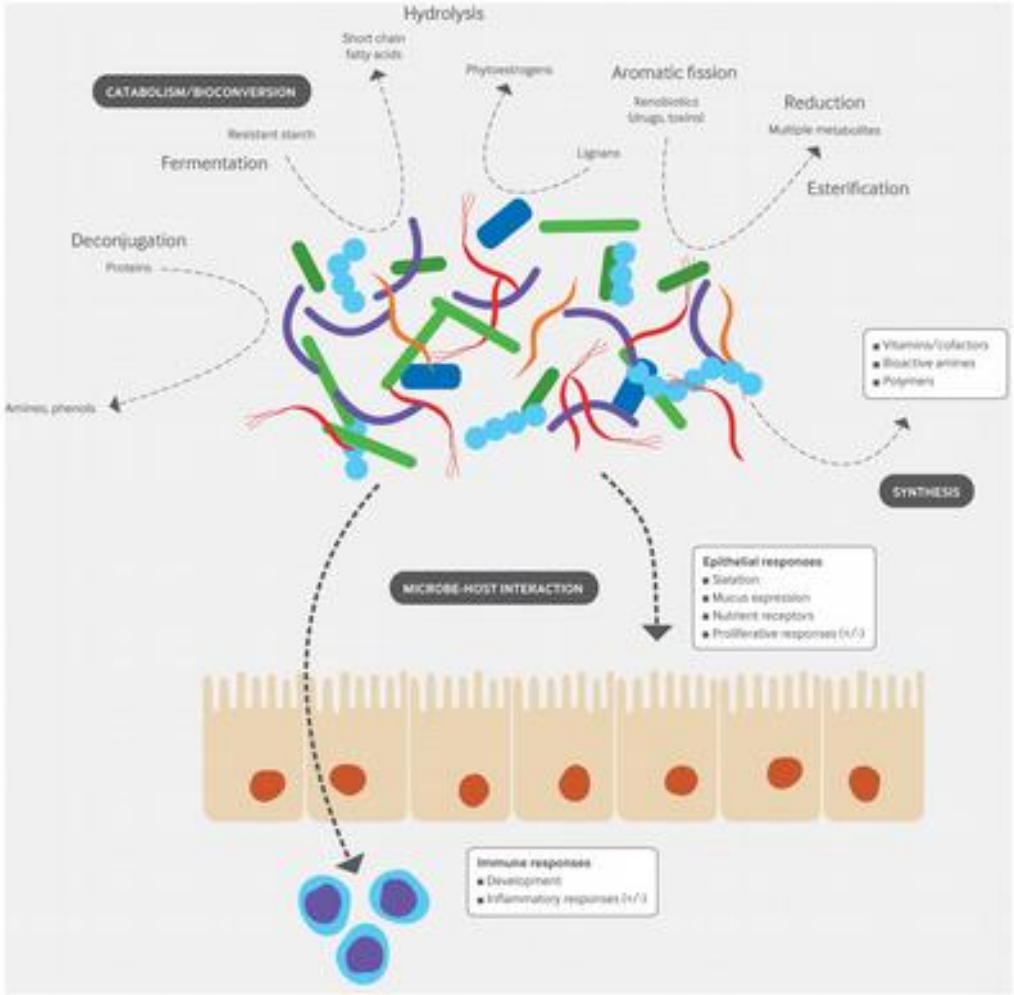


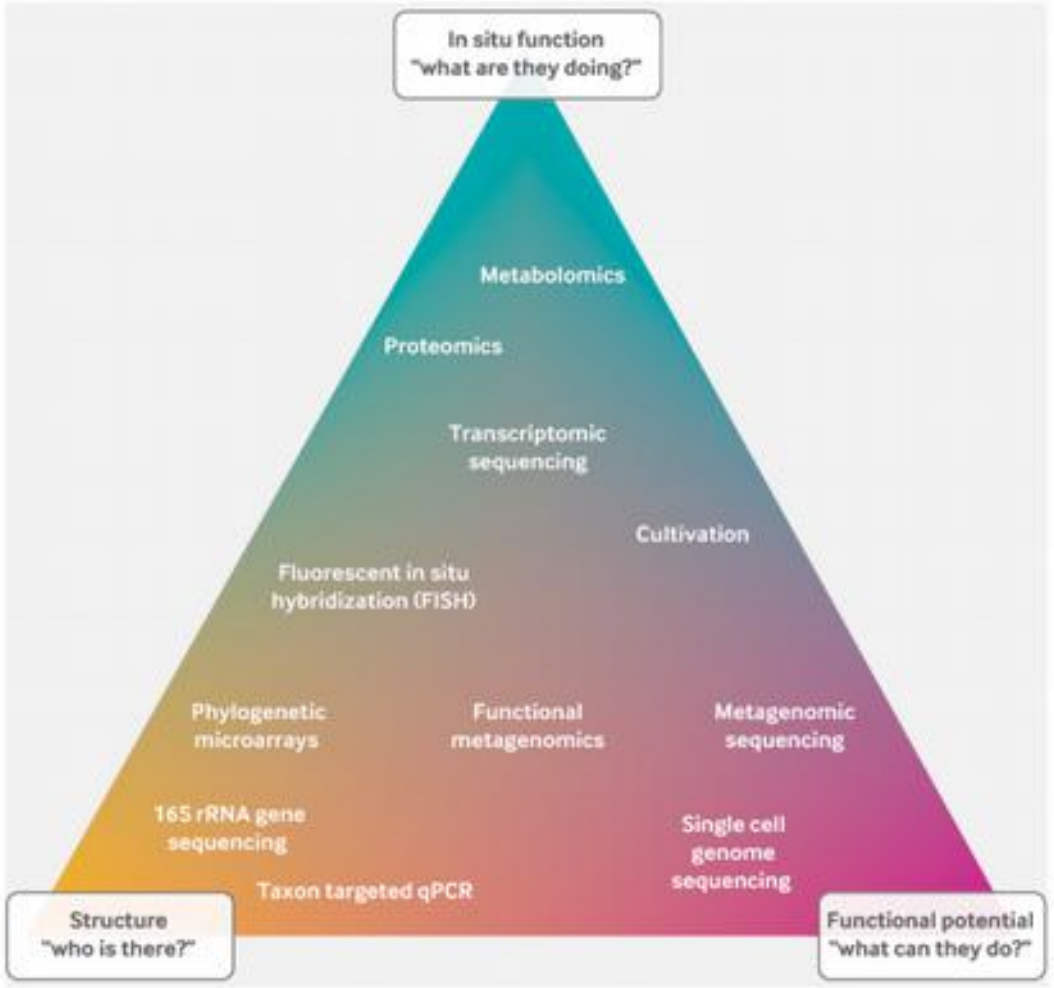
TABLE 2 | Matched Outcomes Without Regression Adjustment

Variable	1 to 2 PCT Assessments Within 1 Day of ICU Admission (n = 33,569 discharges)		No PCT (n = 98,543 discharges)		Difference		PCT vs No PCT, *P* Value
	Mean	95% CI	Mean	95% CI	Mean	95% CI	
LOS, d	10.5	10.4 to 10.6	12.8	12.7 to 12.9	−2.3	−2.4 to −2.2	< .001
ICU LOS, d	4.8	4.8 to 4.9	5.6	5.5 to 5.6	−0.7	−0.8 to −0.7	< .001
Total cost, $	25,513	25,163 to 25,864	33,164	32,898 to 33,429	−7,650	−8,090 to −7,211	< .001
ICU cost, $	16,814	16,560 to 17,069	21,630	21,429 to 21,832	−4,816	−5,140 to −4,492	< .001
Pharmacy cost, $	3,866	3,694 to 4,038	4,589	4,494 to 4,684	−723	−920 to −527	< .001
Antibiotic cost, $	832	768 to 897	936	911 to 961	−103	−173 to −34	< .001
Laboratory cost, $	1457	1,442 to 1,472	1,710	1,697 to 1,724	−253	−274 to −233	< .001
Room and board cost, $	12,212	12,053 to 12,370	15,379	15,254 to 15,503	−3,167	−3,369 to −2,965	< .001
Total antibiotic exposure[†]	14.9	14.7 to 15.0	17.3	17.2 to 17.4	−2.4	−2.6 to −2.3	< .001
Inpatient mortality	19.3%	18.8 to 19.7	18.2%	18.0 to 18.5	1.1%	0.6 to 1.5	< .001
Home	43.8%	43.3 to 44.4	41.4%	41.1 to 41.7	2.4%	1.8 to 3.1	< .001
Hospice	6.3%	6.1 to 6.6	6.4%	6.2 to 6.6	−0.1%	−0.4 to 0.2	.617
Other	1.7%	1.6 to 1.9	1.6%	1.5 to 1.7	0.1%	0 to 0.3	.122
Transfer to SNF/ICF/LTC	22.7%	22.2 to 23.1	25.2%	24.9 to 25.4	−2.5%	−3.0 to −2.0	< .001
Transfer to acute care	6.2%	5.9 to 6.4	7.2%	7.0 to 7.4	−1.0%	−1.3 to −0.7	< .001

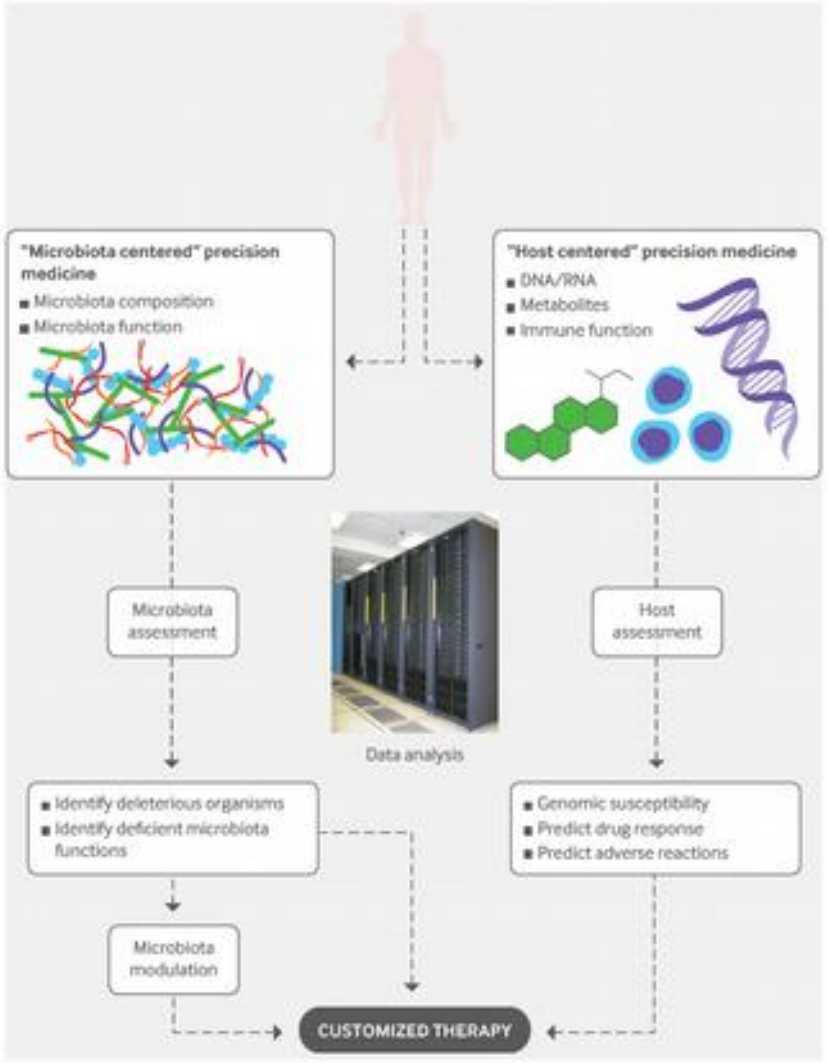
- Decreased LoS and ICU LoS
- Lower hospital costs
- Less total antibiotic exposure
- **More patients to be discharged to home**

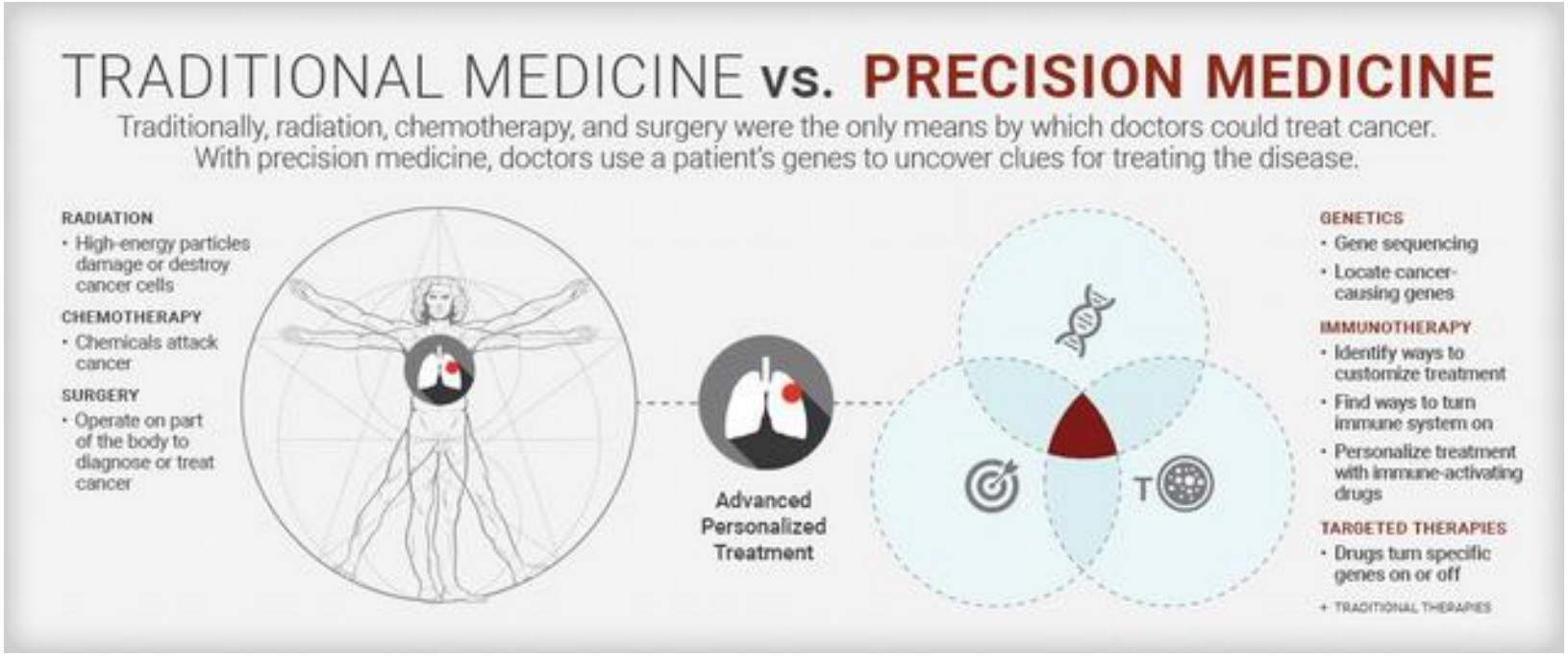
OMICS…


Hydrolysis
Short chain fatty acids
Phytoestrogens
Aromatic fission
Xenobiotics (drugs, toxins)
Reduction
Multiple metabolites
CATABOLISM/BIOCONVERSION
Resistant starch
Fermentation
Lignans
Esterification
Deconjugation
Proteins
Amines, phenols
Vitamins/cofactors
Bioactive amines
Polymers
SYNTHESIS
MICROBE-HOST INTERACTION
Epithelial responses
Sialation
Mucus expression
Nutrient receptors
Proliferative responses (+/-)
Immune responses
Development
Inflammatory responses (+/-)


In situ function
"what are they doing?"
Metabolomics
Proteomics
Transcriptomic sequencing
Cultivation
Fluorescent in situ hybridization (FISH)
Phylogenetic microarrays
Functional metagenomics
Metagenomic sequencing
165 rRNA gene sequencing
Single cell genome sequencing
Taxon targeted qPCR
Structure
"who is there?"
Functional potential
"what can they do?"

Precision medicine





https://healthmatters.nyp.org/precision-medicine/

Street lamp effect vs panorama picture

COLOURS of Sepsis