La sepsi: nuovi indicatori

Slide and discussion
e-mail: girardis@unimo.it
@maxdulac

Disclosures

POTENTIAL CONFLICT OF INTEREST
Unrestricted grant, lectures, advisory boards, etc.

AOP Health
BioMerieux
Baxter
Beckman Coulter
Biotest
CSL-Bhering
Kedrion
Estor
Gilead
MSD
Novonordisk
Orion Pharma
Pfizer
Shionogi
Thermofisher

I trust in PHYSIOLOGY & EBM*

* that does not mean only Large-Mega RCTs

BASIC KNOWLEDGE

SEPSIS DEFINITION

@ **Sepsis** is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection

@ **Organ dysfunction** can be identified as an acute change in total SOFA score ≥ 2 points consequent to the infection

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

JAMA. 2016;315(8):801-810.

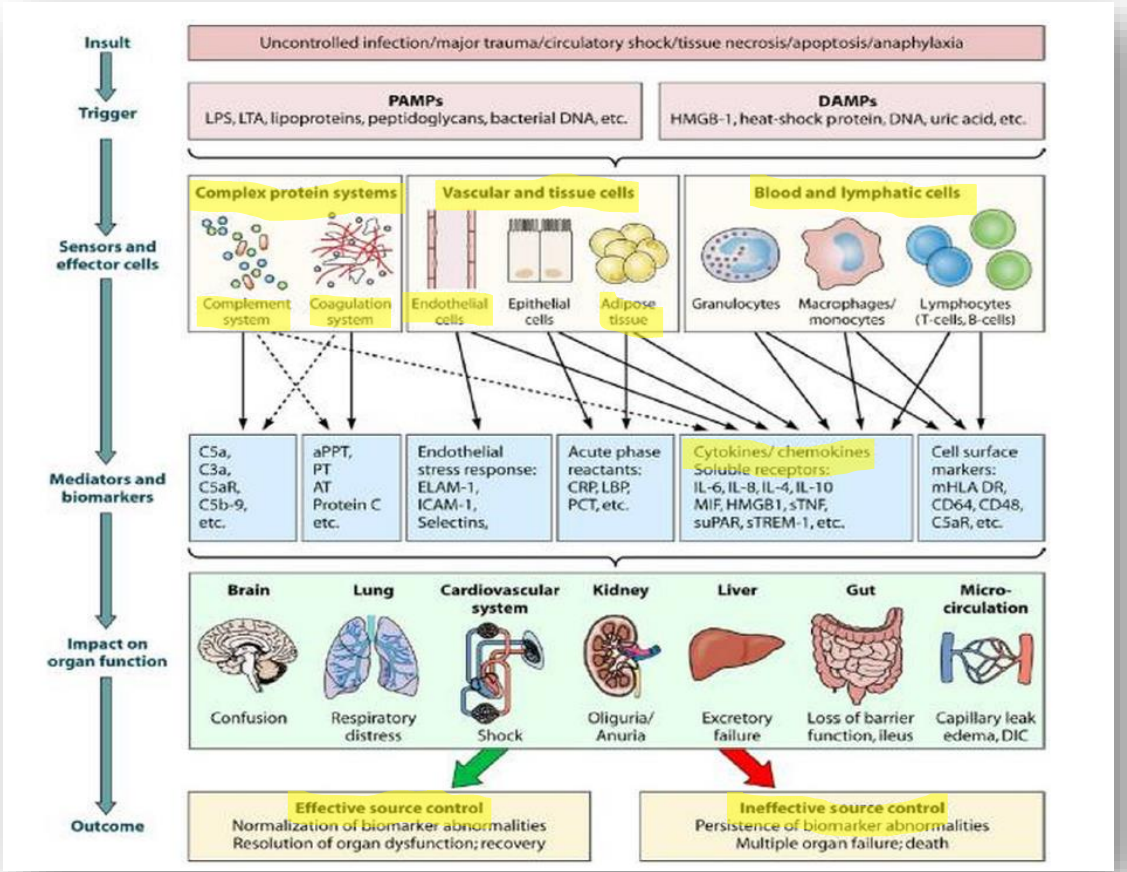
Mervyn Singer, MD, FRCP; Clifford S. Deutschman, MD, MS; Christopher Warren Seymour, MD, MSc; Manu Shankar-Hari, MSc, MD, FFICM;

Mechanisms of sepsis-induced organ dysfunction

Edward Abraham, MD; Mervyn Singer, MD, FRCP

Crit Care Med 2007 Vol. 35, No. 10

SEPSIS PATHOBIOLOGY



Early Identification of Sepsis on the Hospital Floors:

Insights for Implementation of the Hour-1 Bundle

1. Measure Lactate Level

Serum lactate can be a surrogate for tissue perfusion (4,5). Studies have shown a significant reduction in mortality via lactate-guided resuscitation (6–10).

If initial lactate is >2mmol/L, the guidelines recommend remeasurement within 2 to 4 hours to guide resuscitation to normalize lactate (6).

The SSC Guideline for lactate measurement is a weak recommendation, low quality of evidence.

2. Obtain Blood Cultures Before Administering Antibiotics

Optimizing the identification of pathogens to improve outcomes is crucial. Because cultures can be sterilized within minutes of delivery of the appropriate antimicrobial (11,12), cultures should be drawn before antimicrobials are introduced. Appropriate blood cultures include at least two sets (aerobic and anaerobic). Administration of appropriate antimicrobials should not be delayed.

The SSC Guidelines consider this a best practice statement.

3. Administer Broad-Spectrum Antibiotics

One or more intravenous antimicrobials should be started immediately (13). Once pathogen identification and sensitivities are established, empiric antimicrobial therapy should be narrowed or discontinued if the patient does not have an infection. The consideration of early administration of antibiotics for suspected infection and antibiotic stewardship are essential to high-quality sepsis management.

The SSC Guideline is a strong recommendation, moderate quality of evidence.

4. Administer IV Fluid

Initial fluid resuscitation should begin immediately upon recognizing a patient with sepsis and/or hypotension and elevated lactate. The guidelines recommend a minimum of 30 mL/kg of intravenous crystalloid fluid to be completed within 3 hours of recognition. Observational evidence supports this volume (1,14). Fluid administration beyond initial resuscitation should be carefully monitored to ensure that the patient remains fluid responsive.

The SSC Guideline is a strong recommendation, low quality of evidence.

5. Apply Vasopressors

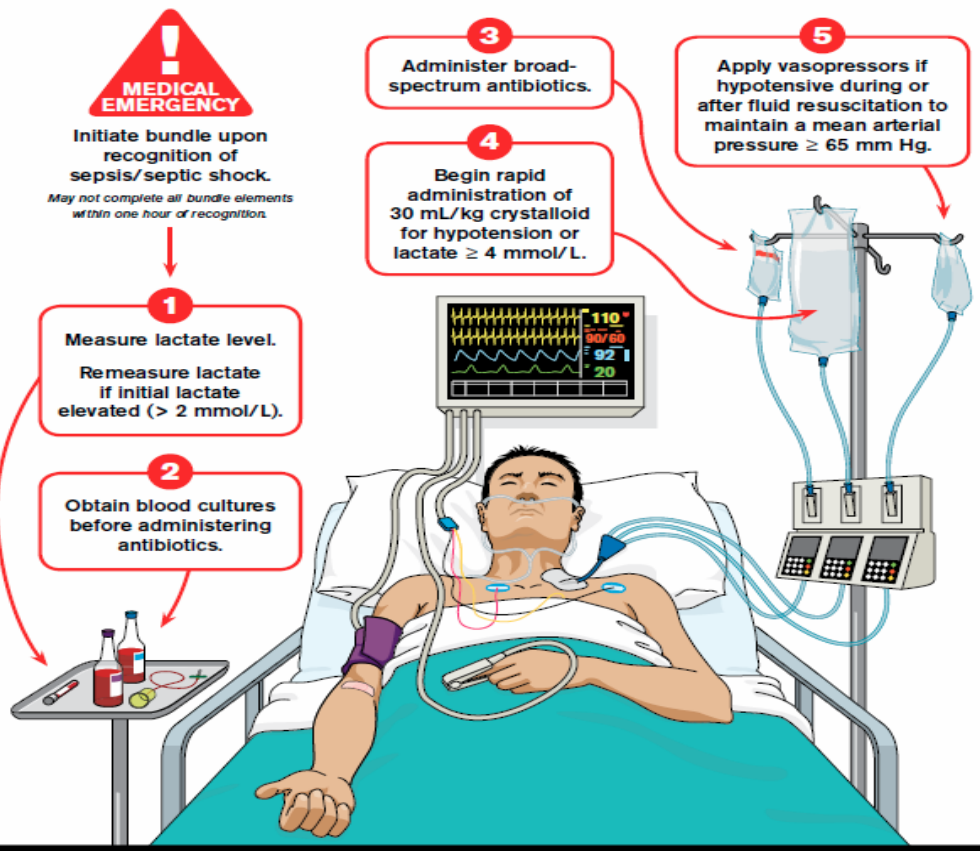
Restoration of adequate perfusion pressure to the vital organs is essential. Vasopressors should be started within the first hour to achieve MAP of ≥ 65 mm Hg if initial fluid resuscitation is not adequate.

The SSC Guideline is a strong recommendation, moderate quality of evidence.

Hour-1 Bundle

Initial Resuscitation for Sepsis and Septic Shock

Surviving Sepsis Campaign



Bundle: SurvivingSepsis.org/Bundle **Complete Guidelines: SurvivingSepsis.org/Guidelines**

Society of Critical Care Medicine

ESICM

Surviving Sepsis Campaign

SPECIFIC ADJUNCTIVE THERAPIES & SSC GUIDELINES

	2004	2008	2012	2016	2021
STEROIDS	shocked	refractory shock	refractory shock	refractory shock	
TIGHT GLYCEMIC CONTROL (<150 mg/dl)					
rhAPC					Not mentioned
VIT C	Not mentioned	Not mentioned	Not mentioned	Not mentioned	
IMMUNOGLOBULINS	pediatric	pediatric			
BLOOD PURIFICATION	Not mentioned	Not mentioned	Not mentioned		

ONE SIZE DOES NOT FIT ALL

Table 1 Twenty recommendations to individualize interventions in the early resuscitation of patients with sepsis

1. We recommend individualizing the timing of ICU admission. It should ideally be within minutes in severely ill patients but can be less urgent in less severe cases. No time limit is applicable for *all* patients. The decision may be influenced by the level of care available within ward areas and by ICU bed availability and, of course, by the physiological status and reserve of the patient
2. We recommend individualizing the decision to admit to the ICU. Many patients develop sepsis at the end of their life. Patients with palliative care orders and treatment escalation plans that preclude advanced organ support should generally not be admitted
3. We recommend individualizing the timing of antibiotic therapy. Administration should be prompt in the presence of septic shock but less urgent in less severe cases, enabling more time to perform investigations, confirm the diagnosis and likely source, and seek expert advice
4. We recommend individualizing the need for and timing of tracheal intubation, based on careful clinical assessment, including level of consciousness, respiratory rate and work of breathing, hemodynamic status, and assessment of gas exchange. Delaying tracheal intubation may lead to respiratory and even cardiac arrest, with dire consequences, yet premature use of invasive mechanical ventilation can expose the patient to ventilator-induced lung injury, distant organ complications, and increased risk of nosocomial lung infection
5. We recommend individualizing respiratory settings in mechanically ventilated patients, including driving pressure, tidal volume and level of positive end-expiratory pressure (PEEP), aiming at the lowest possible mechanical power. PEEP could be adjusted to lung recruitment capacity
6. We recommend individualizing oxygenation targets, taking oxygen delivery into account. Exposure to high PaO_2 levels may be associated with worse outcomes, except perhaps in necrotizing infections. Extreme oxygenation values (too conservative or too liberal) should generally be avoided
7. We recommend individualizing sedation therapies, recognizing that many septic patients need little or even no sedation. Tracheal intubation per se is not a sufficient indication for administration of sedative agents. Sedative agents reduce vascular tone and myocardial contractility, and may also alter immune function
8. We recommend individualizing initial fluid resuscitation. No single formula can be applied to all patients, as fluid requirements vary substantially (depending on the source of sepsis and preexisting cardiovascular function). This is particularly true for the suggestion to give at least 30 mL/kg of fluid within the first 3 h. A young patient without comorbidities is more likely to tolerate administration of a large volume of fluid than a fragile elderly patient with severe cardiac or renal disease
9. We recommend individualizing fluid therapy using dynamic challenges. Assessment of pulse pressure variation (PPV) or stroke volume variation (SVV) is possible only in deeply sedated mechanically ventilated patients with no spontaneous breathing. Alternative methods, including fluid challenges or passive leg raising, are therefore more widely applicable
10. We recommend individualizing the type of intravenous fluid administered. For example, albumin administration may be considered in an edematous patient with profound hypoalbuminemia or prolonged non-response to crystalloids
11. We recommend monitoring of chloride levels if saline solutions are administered. Saline solutions should not be banned, but one must keep in mind that liberal administration of saline results in hyperchloremia, and this may result in a worsening metabolic acidosis and renal impairment
12. We recommend individualizing the initiation of vasopressor therapy. Fluid *pre*-loading may be considered in less severe cases, whereas fluid *co*-loading parallel to vasopressor initiation should be preferred in cases of life-threatening hypotension or a low diastolic arterial pressure
13. We recommend individualizing arterial blood pressure levels. Although a mean value of 65 mmHg may be recommended as an initial goal, the optimal level may be higher in patients with a history of hypertension, atherosclerosis or chronic kidney disease. Conversely it may be lower in younger patients without previous vascular problems, in those with chronically low arterial pressure, or in whom adequate tissue perfusion is maintained
14. We recommend optimizing oxygen delivery, based on clinical assessment complemented by careful hemodynamic assessment including measurement of mixed (or central) venous oxygen saturation (SvO_2) and even carbon dioxide-derived variables. A low SvO_2 in the presence of a normal SaO_2 indicates inadequate overall oxygen delivery to the tissues. More importantly, a normal or high SvO_2 does not exclude tissue hypoxia
15. We recommend a multimodal approach to assessing tissue perfusion, including mental status, urine output, peripheral perfusion, and blood lactate levels, taking into consideration the physiological reserve of the patient
16. We recommend individualizing blood transfusion. Transfusion should be based not only on measurements of hemoglobin concentration, but on clinical evaluation including persisting signs of tissue hypoperfusion, and measurements of SvO_2 and lactate
17. We recommend individualizing administration of inotropic agents when tissue hypoperfusion relates to impaired cardiac function (documented at least by echocardiography). The choice and the dose of the inotropic agent should be based on individual hemodynamic monitoring with repeated measurements
18. We recommend individualizing the decision to administer corticosteroids, not only for septic shock, but also for other conditions such as severe pneumonia and ARDS
19. We recommend involving senior colleagues and consultants, especially since guidelines are most useful for non-experts. Team work, communication and multidisciplinary teams are essential aspects. One of the most overarching recommendations is to seek for guidance from other colleagues and to clearly document the rationale for an intervention –be it recommended or not in the guidelines
20. We recommend carefully measuring and monitoring the effects of any therapeutic measures undertaken and deciding whether or not to continue or adjust treatment accordingly

EDITORIAL Open Access

Equilibrating SSC guidelines with individualized care

Jean-Louis Vincent[1*], Mervyn Singer[2], Sharon Einav[3], Rui Moreno[4], Julia Wendon[5], Jean-Louis Teboul[6],

Vincent *et al. Critical Care* (2021) 25:397
https://doi.org/10.1186/s13054-021-03813-0

FROM ONE SIZE FITS ALL to PERSONALIZED APPROACH

Enhanced understanding of the host-pathogen interaction in sepsis: new opportunities for omic approaches

Cyndi Goh, Julian C Knight

Lancet Respir Med 2017; 5: 212–23

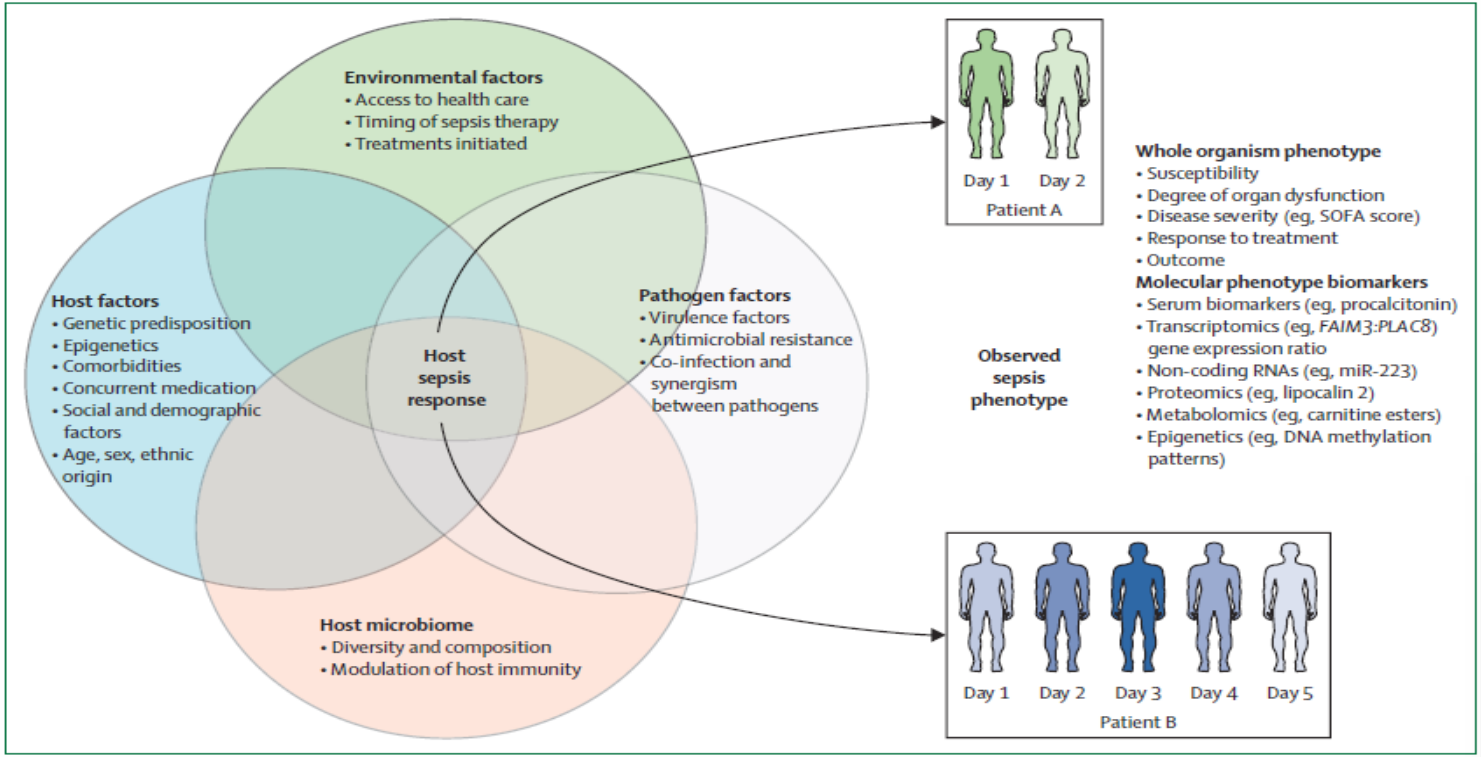


Figure 1: **Factors influencing the heterogeneous host sepsis response**
A complex interaction of factors involving the host, microbiome, pathogen, and the environment results in a heterogeneous sepsis disease phenotype, which varies between individuals during the dynamic time course of their illness. This phenotype can be observed at both whole organism and molecular levels (see example biomarkers).[14–20] During the course of an individual's illness, a variable host response is observed over different timescales—eg, patient A's illness peaks on day 1 and resolves by day 2, while patient B's illness peaks on day 3, leading to recovery by day 5. The optimal therapy for an individual at a given time needs to reflect the composite phenotype (arising through the interaction of host, microbiome, pathogen, and environment) and requires a precision medicine approach. *FAIM3*=Fc fragment of IgM receptor. miR=microRNA. *PLAC8*=placenta specific 8. SOFA=Sequential Organ Failure Assessment.

Panel: Translational goals for omics research in sepsis

Diagnosis
- Early recognition of patients at risk for sepsis
- Differentiation from non-infective causes
- Rapid, accurate microbiological diagnosis

Treatment
- Precision therapy for specific sepsis subphenotypes
- Identification of novel therapeutic targets
- Targeted, effective antimicrobial therapy
- Biomarker development for definition of disease subphenotypes and monitoring response to therapy

Prognosis
- Identification of patients at risk of specific organ failure or poor outcome

The Journal of Clinical Investigation REVIEW

Sepsis-induced immune dysfunction: can immune therapies reduce mortality?

jci.org Volume 126 Number 1 January 2016

Matthew J. Delano[1] and Peter A. Ward[2]

[1]Department of Surgery, Division of Acute Care Surgery, University of Michigan, Ann Arbor, Michigan, USA. [2]Department of Pathology, University of Michigan Medical School, Ann Arbor, Michigan, USA.

SEPTIC SHOCK
Timing of Death

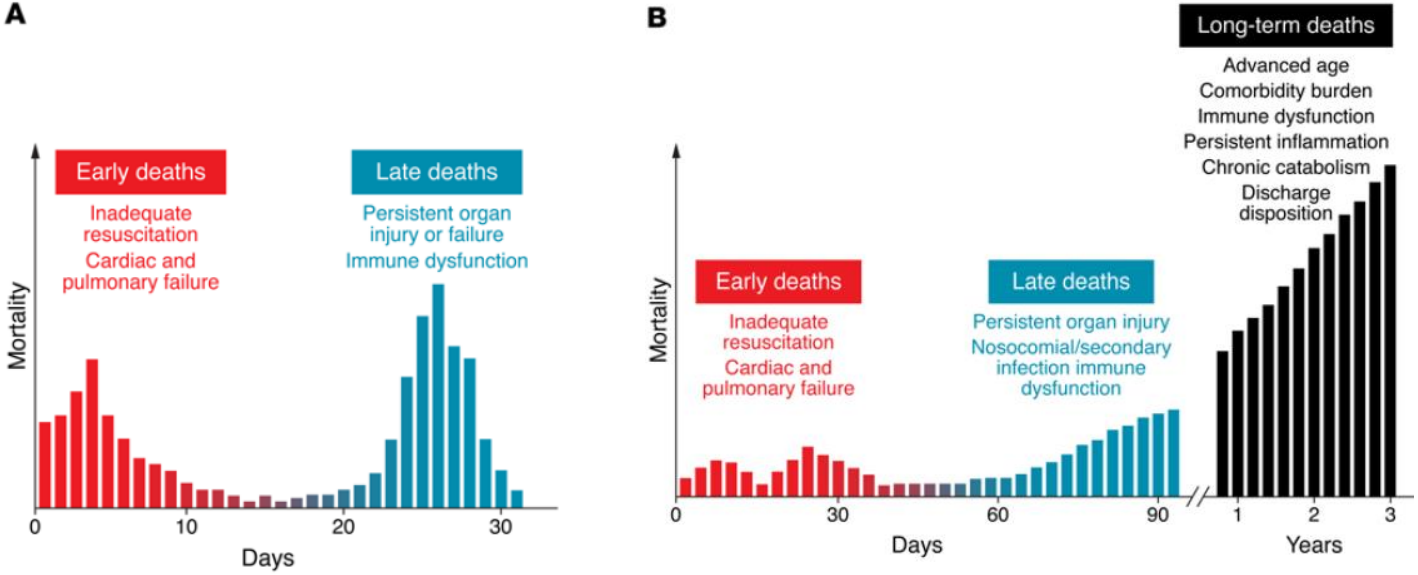


Figure 1. Historical and current sepsis mortality distribution. (**A**) Historically, sepsis deaths have occurred in a biphasic distribution, with an initial early peak at several days due to inadequate resuscitation, resulting in cardiac and pulmonary failure, and a late peak at several weeks due to persistent organ injury and failure. Considering the recent trend in sepsis outcomes, the elderly population, and mounting long-term mortality, a trimodal distribution may be more indicative of the current sepsis-associated death distribution. (**B**) The two early peaks in mortality exist, albeit with much lower magnitude than in the past. The third upswing occurs approximately 60 to 90 days after sepsis and continues to soar as time progresses. This delay in sepsis mortality is thought to be the consequence of the more sophisticated ICU care that keeps elderly and comorbidly challenged patients alive longer in spite of ongoing immune, physiologic, and biochemical aberrations.

From One Size Fits All To Personalized Approach
PHENOTYPING-CLINICAL DATA

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

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

JAMA. doi:10.1001/jama.2019.5791
Published online May 19, 2019.

Christopher W. Seymour, MD, MSc; Jason N. Kennedy, MS; Shu Wang, MS; Chung-Chou H. Chang, PhD; Corrine F. Elliott, MS; Zhongying Xu, MS;

OBJECTIVE To derive sepsis phenotypes from **clinical data**, determine their reproducibility and correlation with host-response biomarkers and clinical outcomes, and assess the potential causal relationship with results from randomized clinical trials.

METHODS:

i) Retrospective analysis of data sets using statistical, machine learning, and simulation tools. Phenotypes were derived among 20 189 total patients (16 552 unique patients) who met Sepsis-3 criteria within 6 hours of hospital presentation at 12 Pennsylvania hospitals (2010-2012) using 29 variables.

ii) Reproducibility and correlation with biological parameters and clinical outcomes were assessed in a second database (2013-2014; n = 43 086 total patients and n = 31 160 unique patients), in a prospective cohort study of sepsis due to pneumonia(n = 583), and in 3 sepsis RCTs (n = 4737).

α phenotype: the most common (n = 6625; 33%) and included patients with the lowest administration of a vasopressor

β phenotype (n = 5512; 27%), patients were older and had more chronic illness and renal dysfunction

γ phenotype (n = 5385; 27%), patients had more inflammation and pulmonary dysfunction;

δ phenotype (n = 2667; 13%), patients had more liver dysfunction and septic shock

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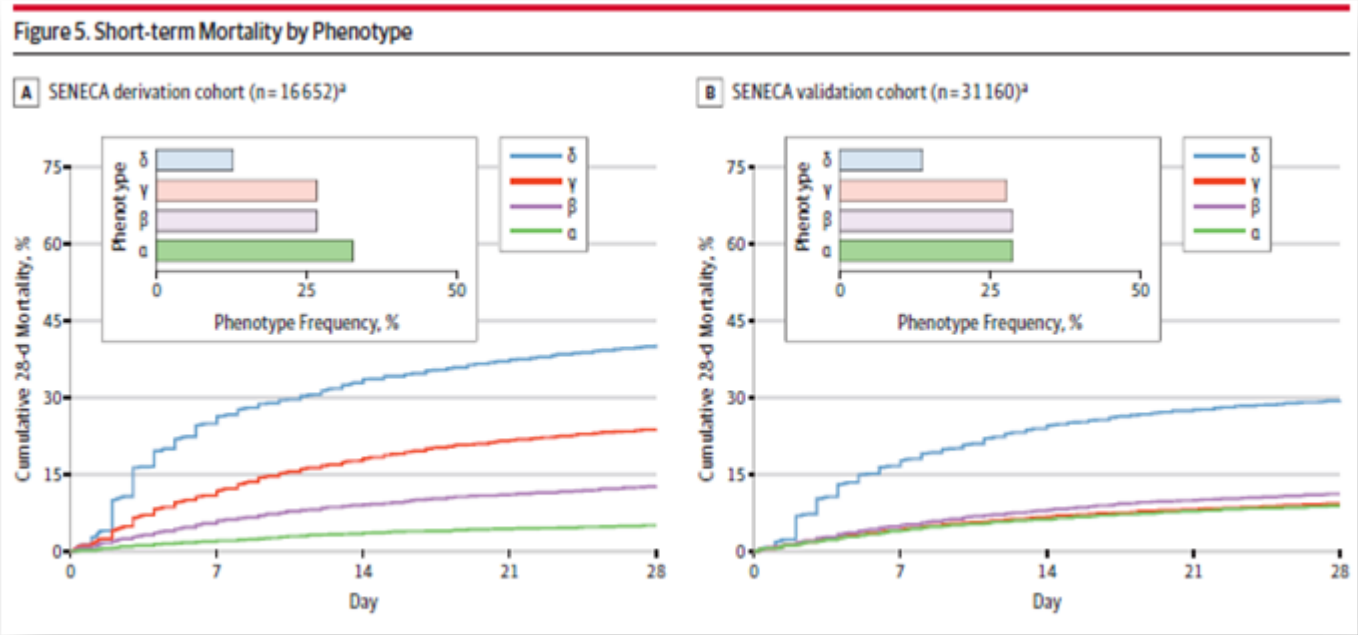

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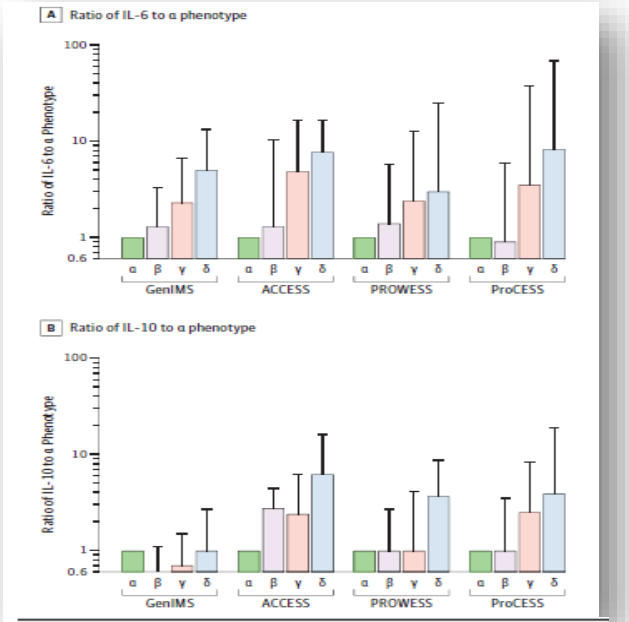
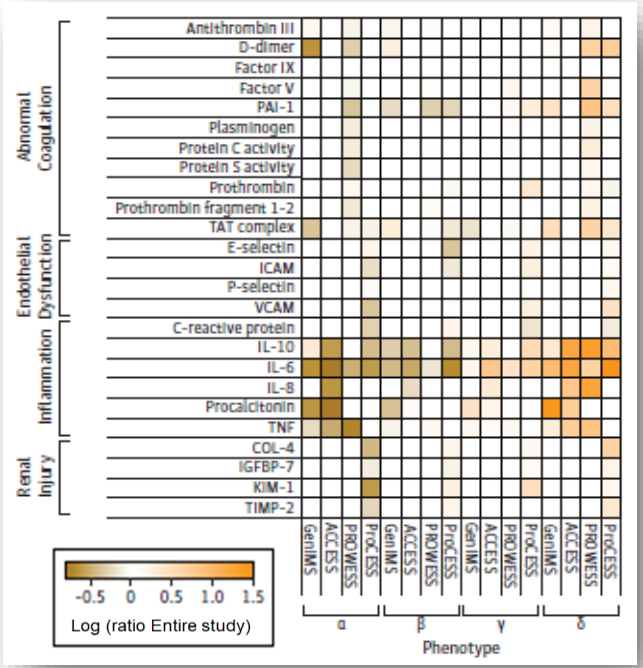
Correlation CLINICAL phenotypes with BIOMARKER profile



Ratio of IL-6 was calculated as the cytokine value standardized by the median value for the α phenotype in each study (referent) illustrated on a log scale. All comparisons within data sets across phenotypes were significant ($P < .001$).



From One Size Fits All To Personalized Approach
PHENOTYPING-CLINICAL DATA

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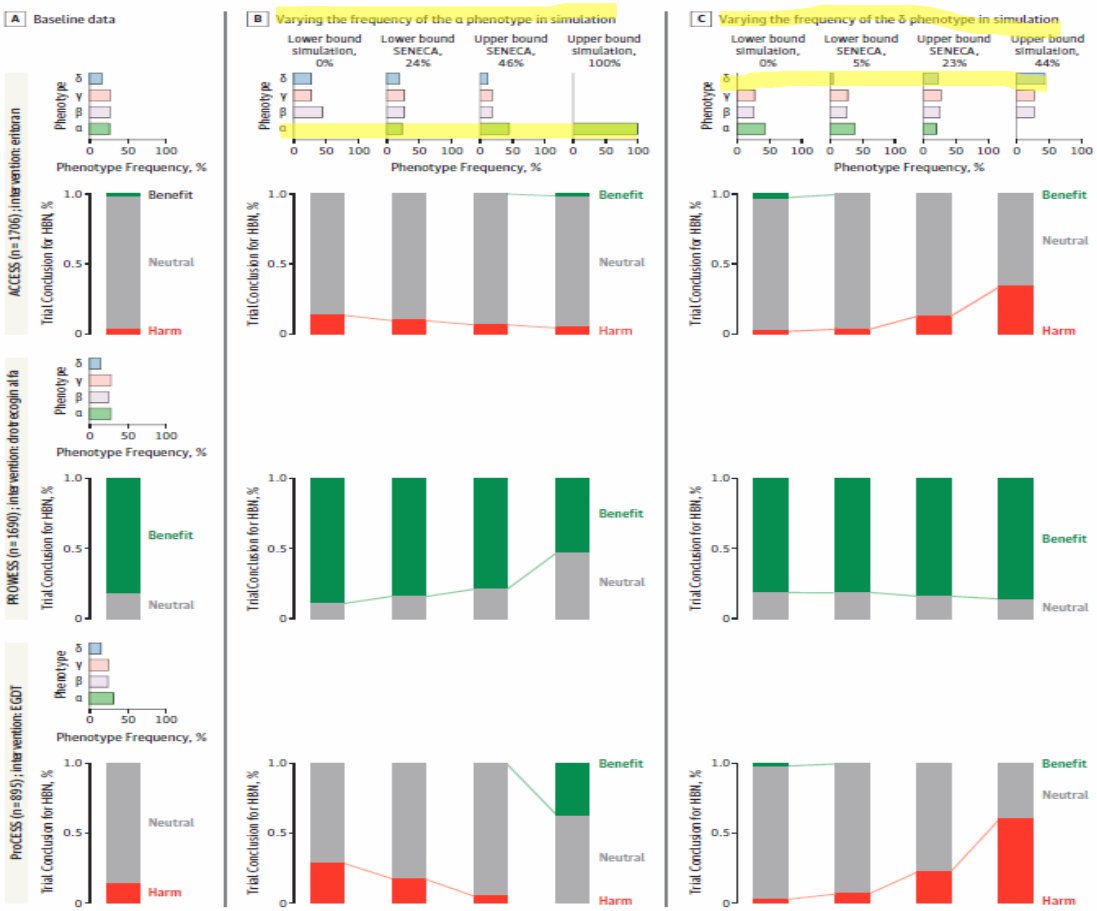
Conclusions

In this retrospective analysis of data sets from patients with sepsis, 4 clinical phenotypes were identified that correlated with host-response patterns and clinical outcomes, and simulations suggested these phenotypes may help in understanding heterogeneity of treatment effects. Further research is needed to determine the utility of these phenotypes in clinical care and for informing trial design and interpretation.

Figure 6. Sensitivity of Clinical Trial Results to the Relative Frequency of Phenotypes in Monte Carlo Simulation



For each trial (ACCESS, PROWESS, and ProCESS), panel A shows the actual distribution of the 4 phenotypes in that trial (horizontal bar graph) and the observed proportion of trials concluding no difference (neutral), harm, or benefit in simulation (vertical stacked bar graph). Each simulation represents 10 000 iterations using sampling with replacement. Panel B shows how simulated trial results vary when the case mix is changed to the distributions shown in the top set of graphs by varying α (panel B) and δ (panel C). ACCESS indicates A Controlled Comparison of Eritoran in Severe Sepsis; EGDT, early goal-directed therapy; HBN, harm, benefit, or neutral; ProCESS, Protocol-Based Care for Early Septic Shock; PROWESS, Activated Protein C Worldwide Evaluation in Severe Sepsis; SENECA, Sepsis Endotyping in Emergency Care.

From One Size Fits All To Personalized Approach
PHENOTYPING-CLINICAL DATA (VITAL SIGNS)

Int Care Med 2022

ORIGINAL

Development and validation of novel sepsis subphenotypes using trajectories of vital signs

Sivasubramanium V. Bhavani[1,2,10*], Matthew Semler[3], Edward T. Qian[3], Philip A. Verhoef[4,5], Chad Robichaux[6], Matthew M. Churpek[7,8] and Craig M. Coopersmith[2,9]

@ Most studies have identified sub-phenotypes using static measurements of biomarkers or vital signs

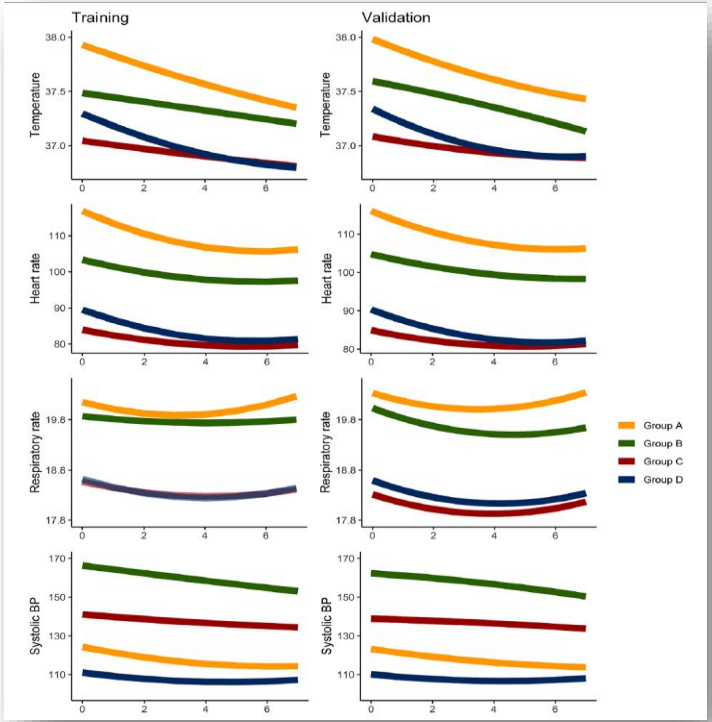
@ "Temporal instability" of sepsis suggests that static snapshots of labs and vitals may not identify sub-phenotypes that are consistent over time.

@ Routine bedside measurements as vital signs may increased feasibility in precision enrollment for clinical trials.

@ 12473 patients with suspected infection admitted to four academic hospitals in Emory Healthcare between 2014–2017 (training cohort) and 8256 between 2018–2019 (validation cohort)

@ Group-based trajectory modeling to vital signs from the first 8 h of hospitalization to develop and validate vitals trajectory sub-phenotypes.

@ treatment with balanced crystalloids versus saline was tested in 1641 patients a secondary analysis of SMART(Isotonic Solutions and Major Adverse Renal Events Trial).



A: (N = 3483, 28%) were hyperthermic, tachycardic, tachypneic and were relatively hypotensive.

B: (N = 1578, 13%) were also hyperthermic, tachycardic and tachypneic and hypertensive.

C:(N = 4044, 32%) lower temperatures, heart rates, and respiratory rates, normotensive

D: (N = 3368, 27%) lower temperatures, heart rates, and respiratory rates, hypotensive

From One Size Fits All To Personalized Approach
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Lab values

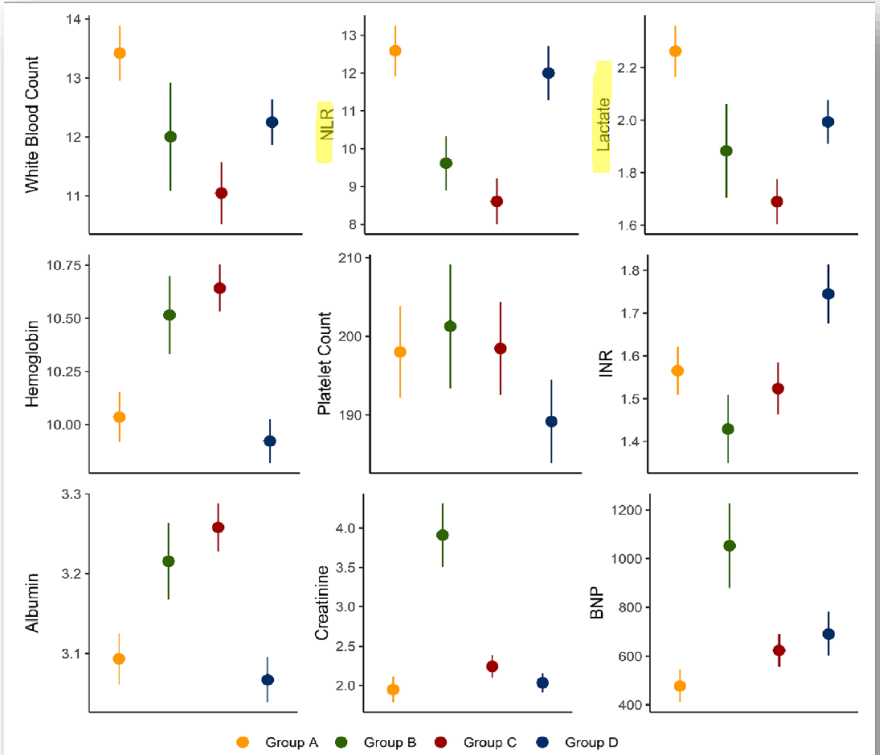

Fig. 2 Laboratory values compared between vitals trajectory sub-phenotypes in sepsis patients in the training cohort. Laboratory values (most abnormal values in the first 24 h of hospitalization) were compared between the vitals trajectory sub-phenotypes using ANOVA testing. All laboratory values presented were significantly different between sub-phenotypes after multiple testing correction either in the training or validation cohorts. Group A had the highest white blood cell count, neutrophil-to-lymphocyte ratio, and lactic acid levels ($p < 0.001$). Group B had the highest creatinine and BNP levels ($p < 0.001$). Group D had the lowest hemoglobin ($p < 0.001$). These relative distributions of labs were similar in the validation cohort. *NLR* neutrophil-to-lymphocyte ratio, *INR* international normalized ratio, *BNP* Brain natriuretic peptide

Mortality 30-day (group C reference)

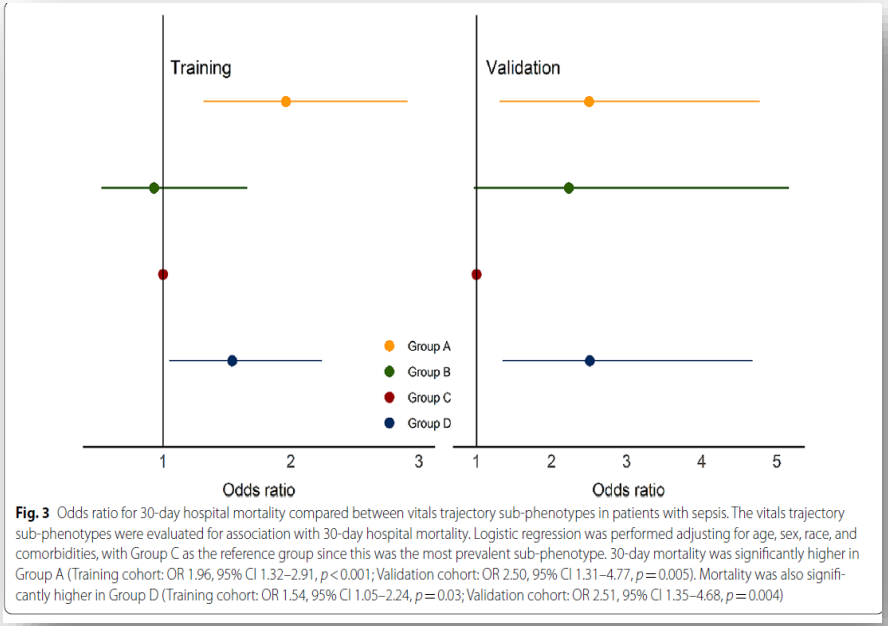

Fig. 3 Odds ratio for 30-day hospital mortality compared between vitals trajectory sub-phenotypes in patients with sepsis. The vitals trajectory sub-phenotypes were evaluated for association with 30-day hospital mortality. Logistic regression was performed adjusting for age, sex, race, and comorbidities, with Group C as the reference group since this was the most prevalent sub-phenotype. 30-day mortality was significantly higher in Group A (Training cohort: OR 1.96, 95% CI 1.32–2.91, $p < 0.001$; Validation cohort: OR 2.50, 95% CI 1.31–4.77, $p = 0.005$). Mortality was also significantly higher in Group D (Training cohort: OR 1.54, 95% CI 1.05–2.24, $p = 0.03$; Validation cohort: OR 2.51, 95% CI 1.35–4.68, $p = 0.004$)

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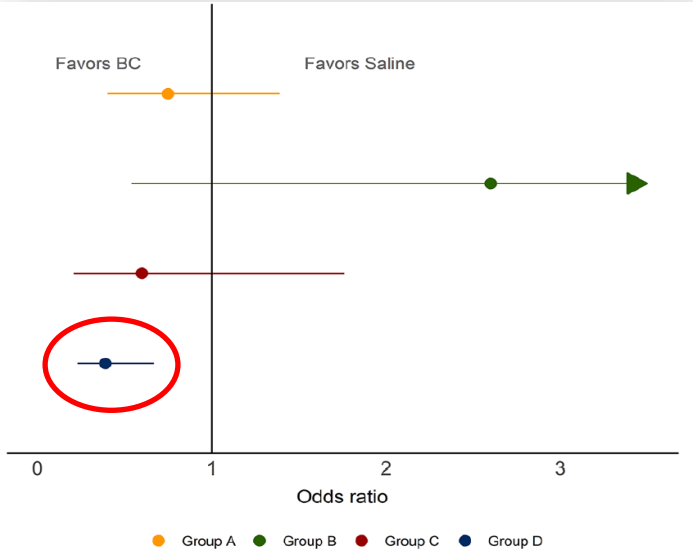


Fig. 4 Heterogeneity of treatment effect to balanced crystalloids (BC) and saline. In this secondary analysis of the Isotonic Solutions and Major Adverse Renal Events Trial (SMART), Group D had a significantly lower OR of 30-day mortality with balanced crystalloid treatment compared to saline (OR 0.39, 95% CI 0.23–0.67, $p < 0.001$). The other sub-phenotypes were not significantly associated with mortality: Group A OR 0.75 (95% CI 0.40–1.39, $p = 0.4$); Group B OR 2.60 (95% CI 0.54–12.53, $p = 0.2$); Group C OR 0.60 (95% CI 0.21–1.76, $p = 0.4$). Since the entire confidence interval for Group B could not be presented in the figure, the arrow signifies that the confidence interval extends beyond the axis. There was significant heterogeneity of treatment effect between sub-phenotypes and treatment assignment in predicting 30-day mortality ($p = 0.03$)

@ Subphenotypes based on trajectories of vital signs over the first 8 hours of hospitalization had DISTINCT:

- baseline clinical characteristics,
- lab abnormalities,
- organ dysfunction profiles
- outcomes.

@ Subphenotype significantly modified the effect of intravenous fluid on mortality.

Take-home message

mortality. The four sepsis subphenotypes based on universally available vital signs may have different responses to treatment and could inform precision enrollment for clinical trials.

ARE ALL THE SEPTIC PATIENTS SIMILAR ?

PREDISPOSITION:	Pre-existing illness, genetic polymorphisms	Difficult Patient
INSULT:	Site of infection, type of infection, virulence and sensitivity of infecting pathogens;	Difficult Micro-organisms Or Site
RESPONSE	SIRS, other signs of sepsis, activated inflammation (PCT or IL-6) or impaired host responsiveness (HLA-DR)	Difficult Immune Inflammatory Response
ORGAN DYSFUNCTION	Time and number of failing organs	

IMMUNE RESPONSE IN SEPSIS

Current gaps in sepsis immunology: new opportunities for translational research

Lancet Infect Dis 2019

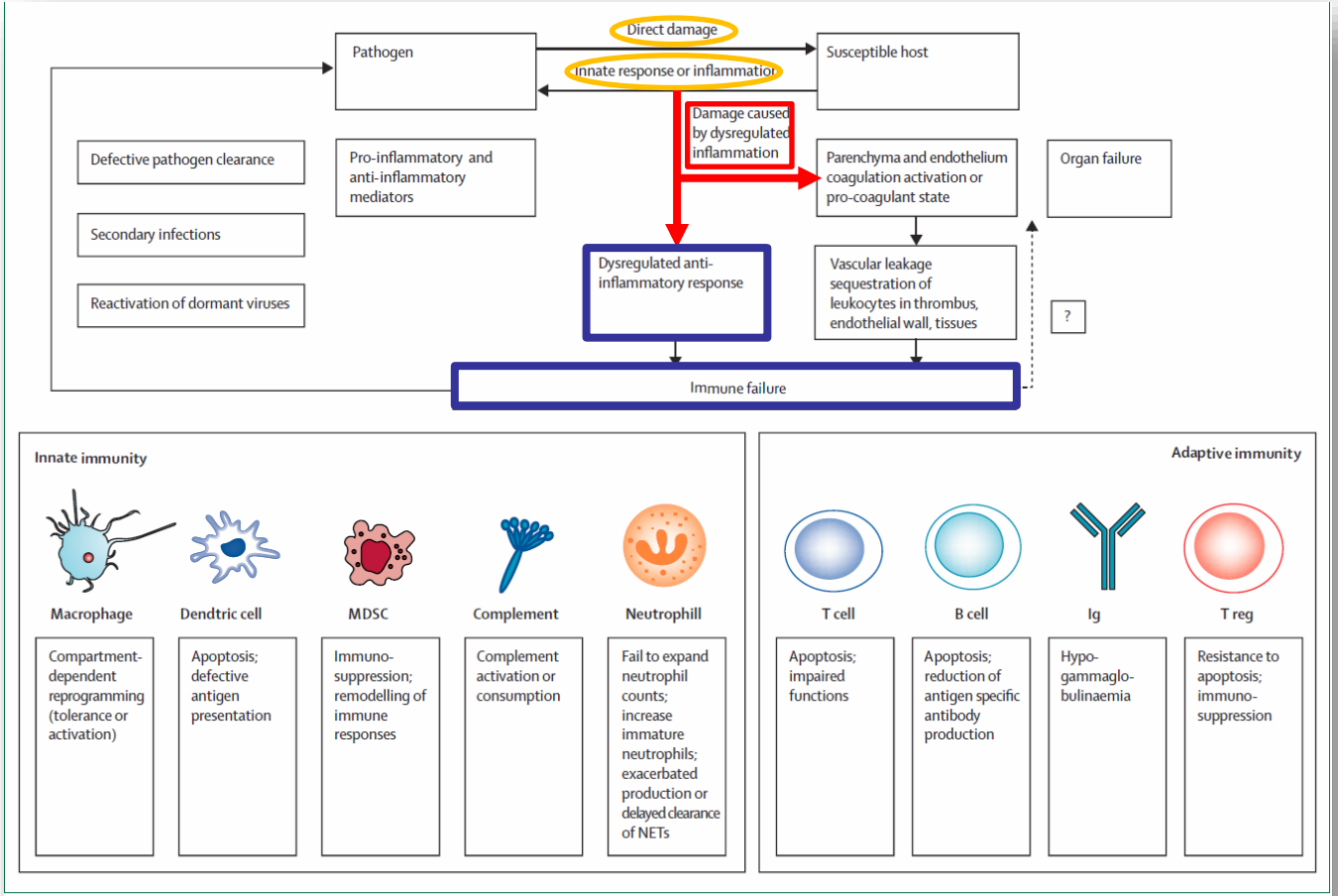


Figure 1: Key events in sepsis immunopathology

INFLAMMATORY-IMMUNE RESPONSE IN SEPSIS

The Journal of Clinical Investigation REVIEW

Sepsis-induced immune dysfunction: can immune therapies reduce mortality?

jci.org Volume 126 Number 1 January 2016

Matthew J. Delano[1] and Peter A. Ward[2]

[1]Department of Surgery, Division of Acute Care Surgery, University of Michigan, Ann Arbor, Michigan, USA. [2]Department of Pathology, University of Michigan Medical School, Ann Arbor, Michigan, USA.

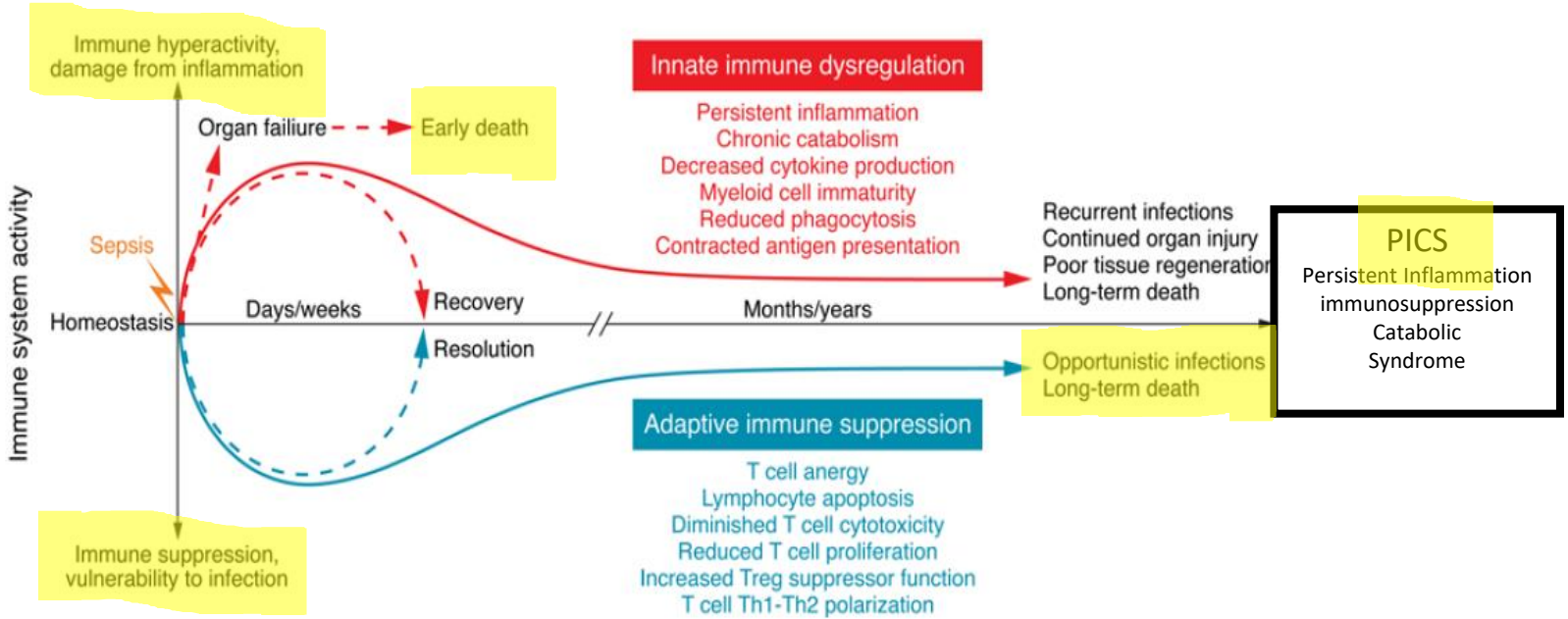


Figure 2. Immune dysregulation in sepsis. New insights into immune dysregulation have been gained using samples from deceased septic patients as well as from severely injured trauma patients. These studies demonstrate an enduring inflammatory state driven by dysfunctional innate and suppressed adaptive immunity that culminates in persistent organ injury and death of the patient. Although the initial inflammatory process, if unabated, contributes to organ failure and early mortality, this process is largely ameliorated by improvements in patient management protocols. However, considering that the vast majority of sepsis survivors are elderly with highly comorbid conditions, the short-term gains in survival have merely been pushed back by several months to a year. Although theories about the processes underlying this observation are numerous, the widespread consensus is that persistent derangements in innate and adaptive immune system cellular function are the main culprits driving long-term mortality.

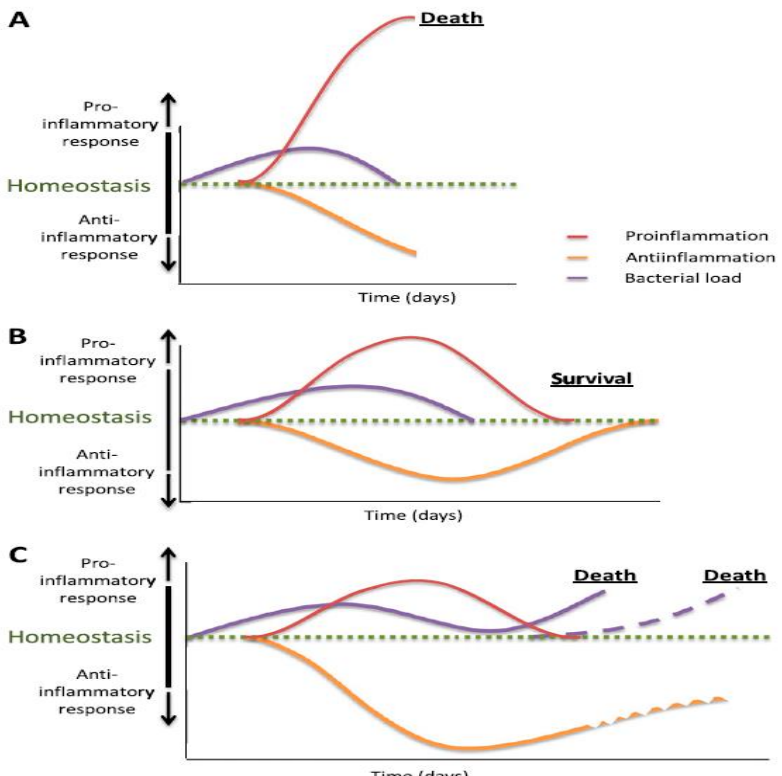
INFLAMMATORY-IMMUNE RESPONSE IN SEPSIS

Immunotherapy for the Adjunctive Treatment of Sepsis: From Immunosuppression to Immunostimulation
Time for a Paradigm Change?
Jenneke Leentjens[1,2,3], Matthijs Kox[1,3,4], Johannes G. van der Hoeven[1,3], Mihai G. Netea[2,3], and Peter Pickkers[1,3]
Am J Respir Crit Care Med Vol 187, Iss. 12, pp 1287–1293, Jun 15, 2013

The inflammatory-immune response may vary and depends on

@ Microorganism(s) load and virulence

@ Host genetic factors and comorbidities

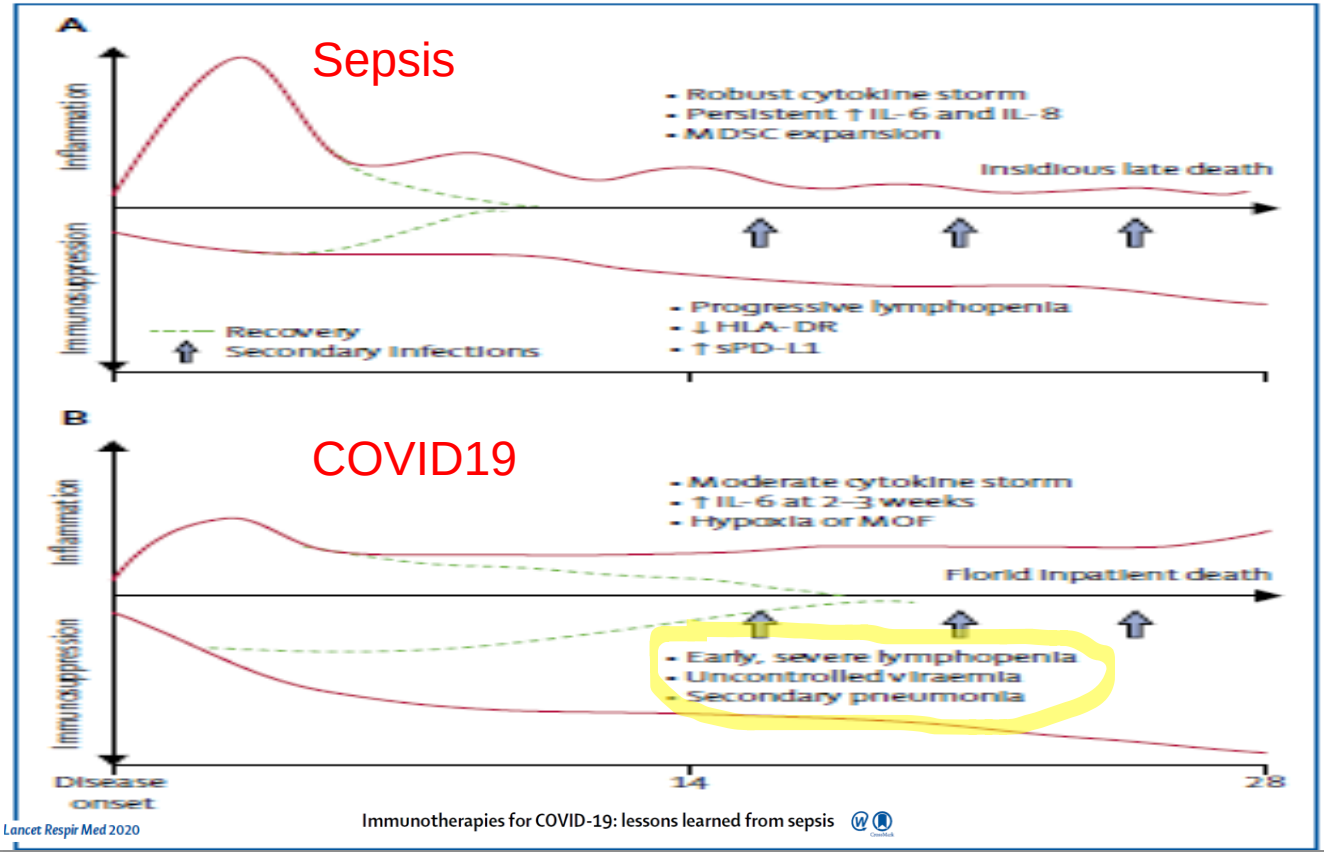


***Healthy young adult with meningococcemia**:*
Overwhelming proinflammatory response which is likely to eradicate bacteria but lead to tissue damage and multiorgan failure

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

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

IMMUNE RESPONSE IN COVID19



INFLAMMATORY-IMMUNE RESPONSE IN SEPSIS

BIOLOGICAL MARKERS OF INJURY-INDUCED IMMUNOSUPPRESSION

Christelle ROUGET, Thibaut GIRARDOT, Julien TEXTORIS, Guillaume MONNERET, Thomas RIMMELé, Fabienne VENET

Minerva Anestesiol 2016 Jun 17 [Epub ahead of print]

Innate immunity

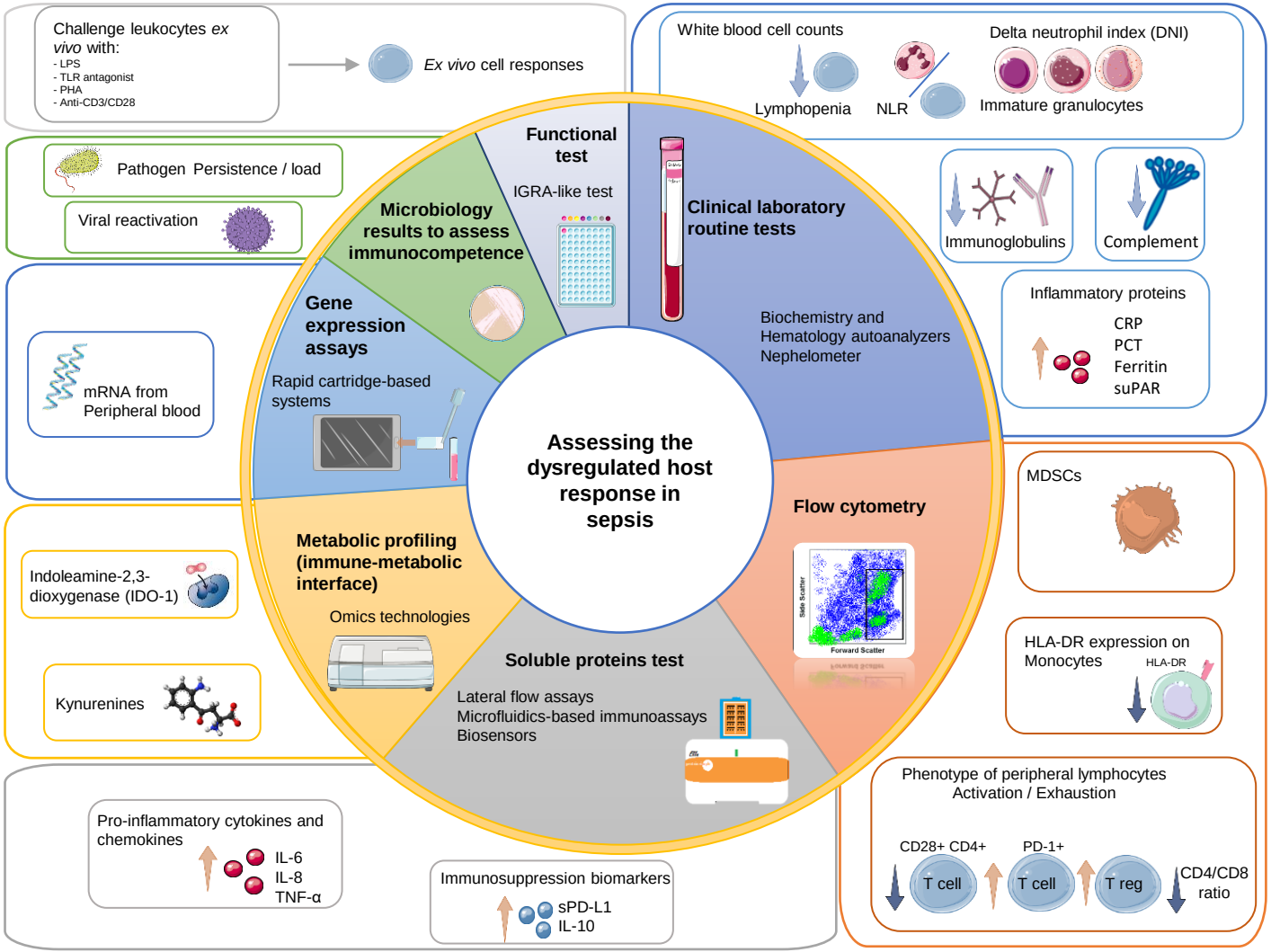
- HLA-DR expression on monocytes.
- Tumour necrosis factor (TNF) production by lipopolysaccharide-stimulated whole blood cells.
- Programmed cell death ligand 1 expression on monocytes.

Adaptive immunity

- Persistent severe lymphopenia.
- Reactivation of cytomegalovirus or herpes simplex virus infections.
- Programmed cell death 1 expression on $CD4^+$ or $CD8^+$ cells.
- Number of circulating regulatory T cells.
- Interferon-γ production by T cells.
- T cell proliferation.

Innate and adaptive immunity

- Infections with relatively avirulent or opportunistic pathogens, such as *Enteroroccus* spp., *Acinetobacter* spp. or *Candida* spp.
- Interleukin-10/TNF ratio.
- Delayed-type hypersensitivity response.


Challenge leukocytes *ex vivo* with:
- LPS
- TLR antagonist
- PHA
- Anti-CD3/CD28
Ex vivo cell responses
White blood cell counts
Lymphopenia
NLR
Delta neutrophil index (DNI)
Immature granulocytes
Pathogen Persistence / load
Viral reactivation
Functional test
IGRA-like test
Microbiology results to assess immunocompetence
Clinical laboratory routine tests
Biochemistry and Hematology autoanalyzers Nephelometer
Immunoglobulins
Complement
Inflammatory proteins
CRP
PCT
Ferritin
suPAR
Gene expression assays
Rapid cartridge-based systems
mRNA from Peripheral blood
Assessing the dysregulated host response in sepsis
Flow cytometry
Side Scatter
Forward Scatter
MDSCs
Metabolic profiling (immune-metabolic interface)
Omics technologies
Indoleamine-2,3-dioxygenase (IDO-1)
Kynurenines
Soluble proteins test
Lateral flow assays
Microfluidics-based immunoassays
Biosensors
HLA-DR expression on Monocytes
HLA-DR
Phenotype of peripheral lymphocytes Activation / Exhaustion
CD28+ CD4+
T cell
PD-1+
T cell
T reg
CD4/CD8 ratio
Pro-inflammatory cytokines and chemokines
IL-6
IL-8
TNF-α
Immunosuppression biomarkers
sPD-L1
IL-10

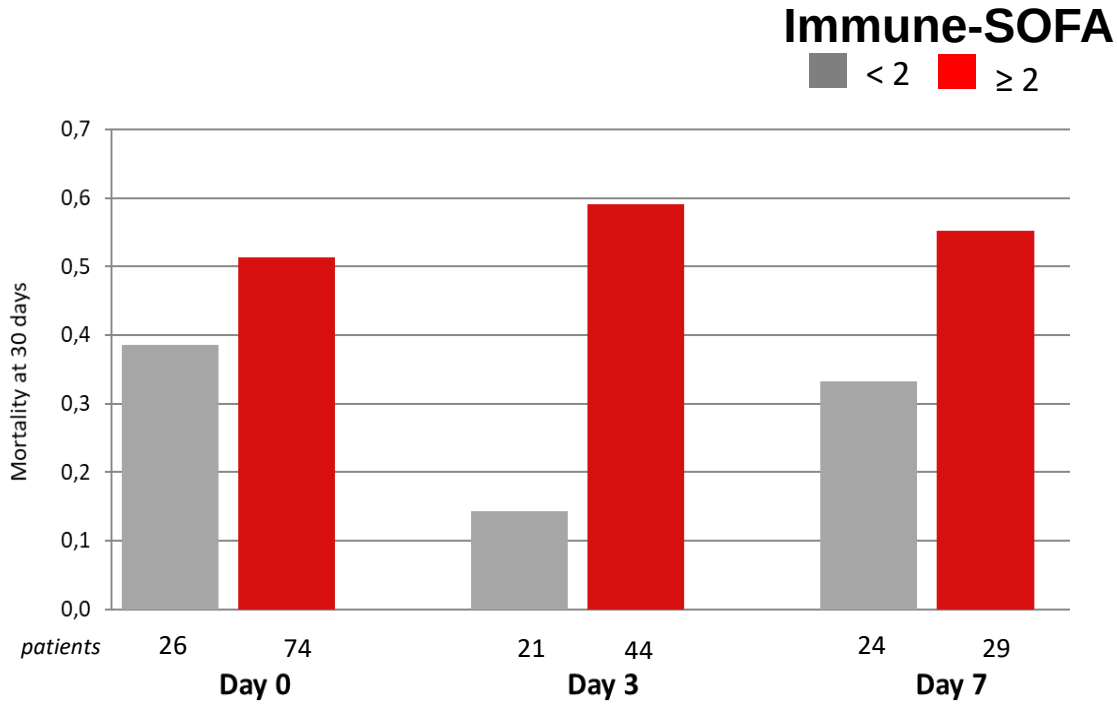
Submitted

Immune System	0	1	2	3	4
Monocyte HLA-DR (mAb) or Lymphocytes (n/mcl) or HSV/CMV reactivation	8000 or > 1200 or NO	6-8000 or 900—1200 or NO	5000-8000 or 600-900 or YES/NO	2500- 5000 or 400-600 or YES	<2500 or < 400 or YES

ICU–Modena University
2016-2017
100 septic shock

ImmunoMonitoring
HLA-DR*; CMV; Lympho
DAY-0 (shock onset)
DAY-3
DAY-7
DAY-14

*** Not available**
WEND



From One Size Fits All To Personalized Approach
PHENOTYPING-BIOMARKERS

Intensive Care Med
https://doi.org/10.1007/s00134-022-06869-w

ORIGINAL

Coronavirus disease 2019 subphenotypes and differential treatment response to convalescent plasma in critically ill adults: secondary analyses of a randomized clinical trial

@ COVID-19 patients are immunologically heterogeneous, immunologically similar COVID-19 subphenotypes may differ in their treatment responses to convalescent plasma
@ 1239 patients (REMAP-CAP) subphenotypes by measuring 26 biomarkers (cytokines, chemokines, endothelial biomarkers)
@ Unsupervised analyses identified 3 subphenotypes/endotypes
  i. subphenotype-1 (70.2%) variable biomarker pattern, dysregulated response
  ii. subphenotype-2 (10.3%) mixed immune response
  iii. subphenotype-3 (19.5%) with exaggerated inflammation
@ Subphenotypes similar age, sex, comorbidities, illness severity, types of respiratory support, and prevalence of immu-nosuppression
@ Subphenotypes-2, and -3 had worse outcomes,
@ Subphenotype-1 had better outcomes with convalescent plasma therapy

Organ support-free days, median (IQR)	Convalescent plasma	Control	Odds ratio (95% CI)	P-value
Overall	0 (-1 to 16)	4 (-1 to 16)	0.91 (0.74 to 1.12)	
Subphenotype-1	0 (-1 to 21)	0 (-1 to 21)	1.05 (0.81 to 1.36)	
Subphenotype-2	0 (-1 to 21)	10 (-1 to 21)	0.66 (0.37 to 1.19)	0.008
Subphenotype-3	1.5 (-1 to 21)	12 (-1 to 21)	0.71 (0.45 to 1.12)	

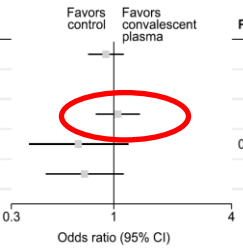
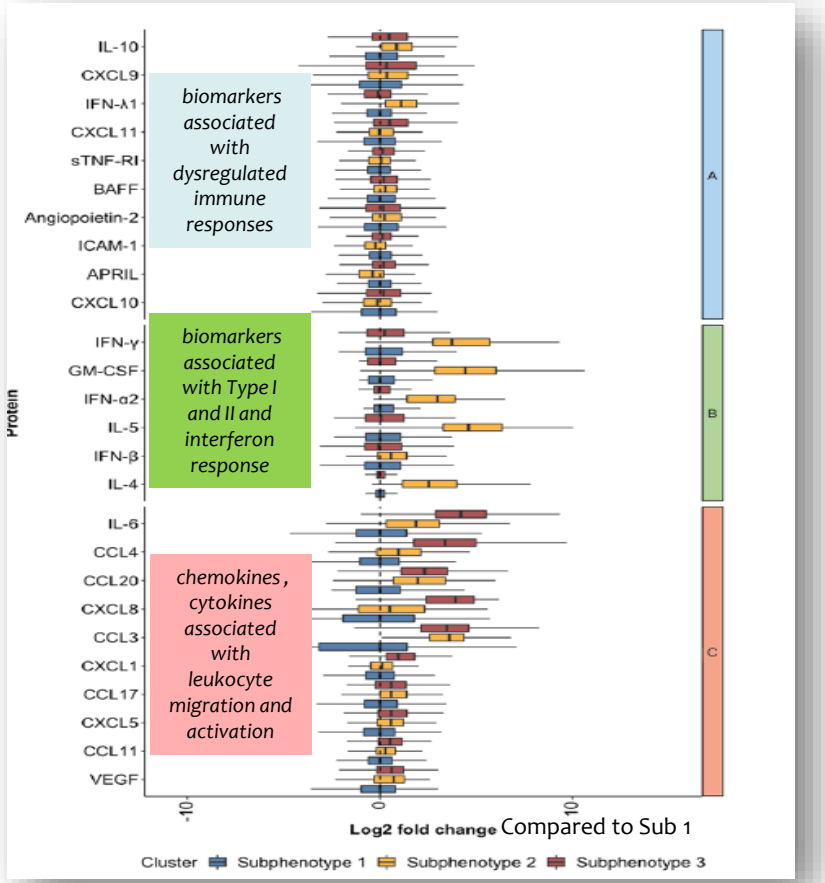
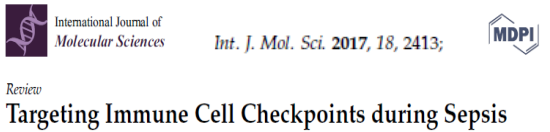


Fig. 4 Treatment effect of convalescent plasma compared to usual care for organ support-free days by subphenotypes. Forest plot comparing organ support-free days at day 21 (OSFD-21) of the overall cohort and by subphenotypes when treated with convalescent plasma, compared to usual care population. Median and inter-quartile ranges (IQR) for OFSD are displayed. Odds ratio was calculated using ordered logistic regression,



From One Size Fits All To Personalized Approach
IMMUNE-PHENOTYPE



@Steroids

@Blood purification

@Immunoglobulins

@G-CSF/GM-CSF

@IL 3/7/15

@Interferon-γ

@Anti PD1/PDL1 (programmed death; ligand)

@Anti-BTLA (B and T Lymphocyte Attenuator)

@Anti-CTLA-4 (Cytotoxic T Lymphocyte Antigen-4)

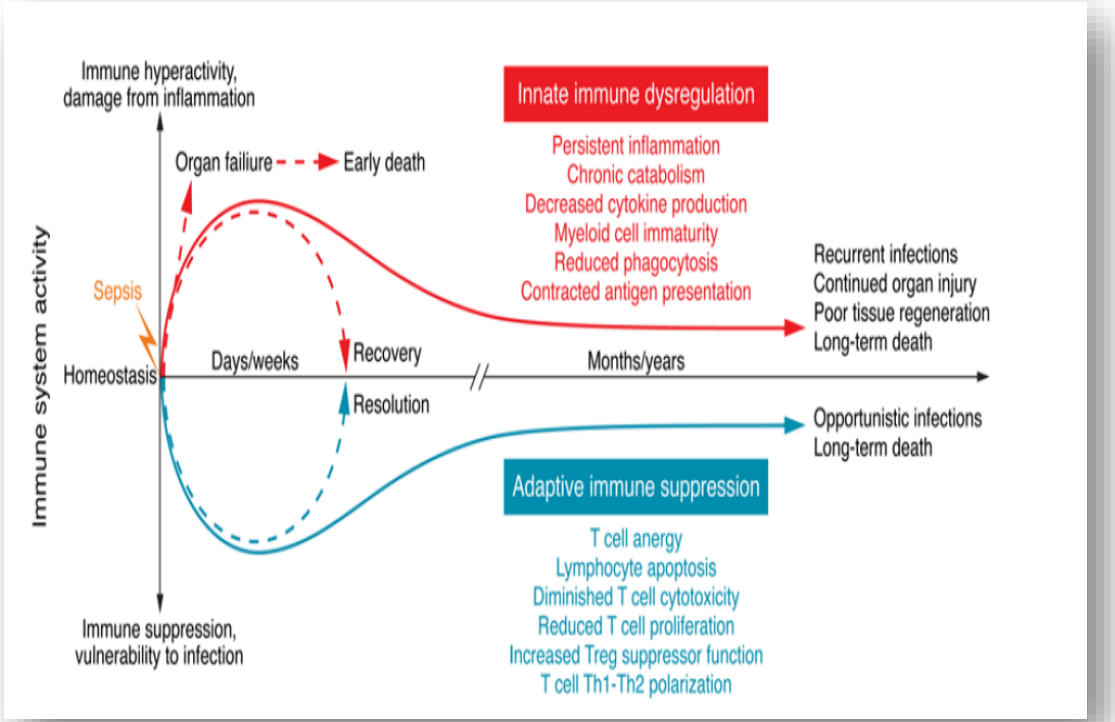
@Combination:

@IL-7 with anti-PD-1/anti-PD-L1 in patients with lymphopenia and T cell exhaustion

@Anti-PD-1/anti-PD-L1 or IL-7 and IFN-gamma in patients with decreased HLA-DR expression on monocytes and T cell dysfunction

TAKE HOME PICTURE

ADJUNCTIVE THERAPIES FOR SEPSIS (included the new trigger)



ADRECIZUMAB

ORIGINAL

Safety and tolerability of non-neutralizing adrenomedullin antibody adrecizumab (HAM8101) in septic shock patients: the AdrenOSS-2 phase 2a biomarker-guided trial

Intensive Care Med (2021) 47:1284–1294

Pierre-François Laterre[1], Peter Pickkers[2], Gernot Marx[3], Xavier Wittebole[4], Ferhat Meziani[5,6], Thierry Dugernier[7],

RATIONALE

@ *Bioactive ADM (bio-ADM) is an active, short-lived circulating peptide essential for endothelial barrier development and stability*

@ *Elevated plasma levels of bio-ADM are associated with severe multiple organ dysfunction and an elevated mortality risk in septic shock patients*

@ *Bystander of endothelial dysfunc-tion or a counterregulatory response to the impairment of vascular integrity ?.*

@ *Pre-clinical models showed that modulating the ADM path-way with the high-affinity, non-neutralizing monoclonal anti-ADM antibody adrecizumab, improved endothelial homeostasis and survival.*

TRIAL

@ Phase-2a, double-blind, randomized, placebo-controlled biomarker-guided trial

@ 301 (72+77 vs 152) patients with adrenomedullin > 70 pg/mL, < 12 h of vasopressor start for septic shock.

@ Single infusion of adrecizumab (2 or 4 mg/kg b.w.). Randomization was 1:1:2.

@ Primary safety: 90-day mortality, treatment emergent adverse events and tolerability (drug interruption, hemodynamics)

@ Efficacy endpoints: Sepsis Support Index (SSI, reflecting ventilator- and shock-free days alive), change in Sequential-related Organ Failure Assessment (SOFA) and 28-day mortality.

Personalized Medicine in sepsis…."*Trial designs should combine biomarker-guided enrichment of enrolled patients to reduce heterogeneity and biomarker-guided therapy to enhance likelihood of success for novel therapies…"*

ENDOTHELIUM and COVID19

N Engl J Med 2020;383:120-8.
DOI: 10.1056/NEJMoa2015432

Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19

Maximilian Ackermann, M.D., Stijn E. Verleden, Ph.D., Mark Kuehnel, Ph.D.,

INFLAMMATION & COAGULATION

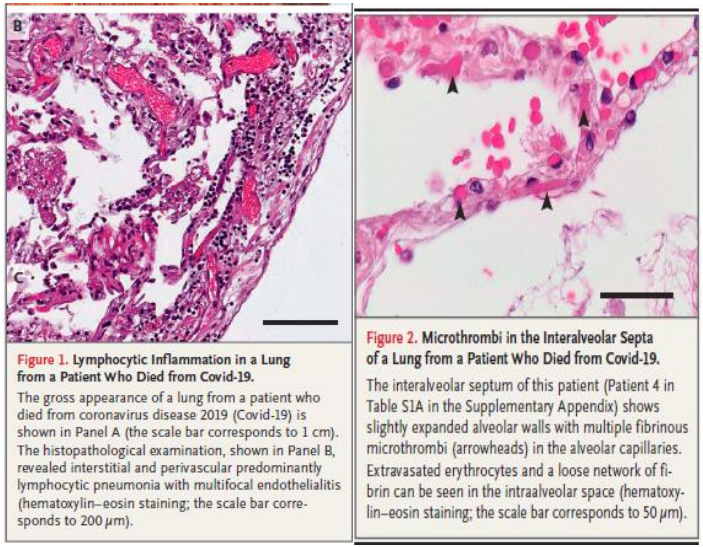
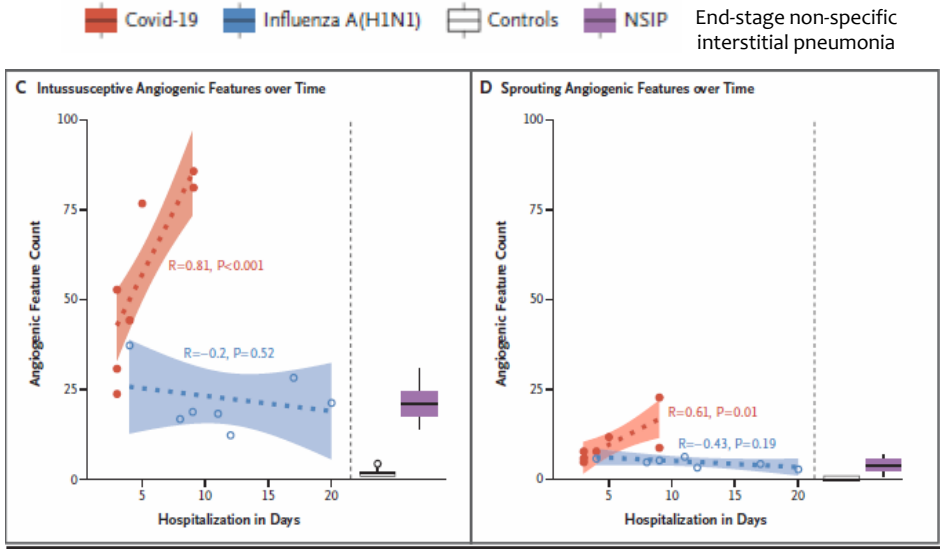


Figure 1. Lymphocytic Inflammation in a Lung from a Patient Who Died from Covid-19.
The gross appearance of a lung from a patient who died from coronavirus disease 2019 (Covid-19) is shown in Panel A (the scale bar corresponds to 1 cm). The histopathological examination, shown in Panel B, revealed interstitial and perivascular predominantly lymphocytic pneumonia with multifocal endothelialitis (hematoxylin–eosin staining; the scale bar corresponds to 200 μm).

Figure 2. Microthrombi in the Interalveolar Septa of a Lung from a Patient Who Died from Covid-19.
The interalveolar septum of this patient (Patient 4 in Table S1A in the Supplementary Appendix) shows slightly expanded alveolar walls with multiple fibrinous microthrombi (arrowheads) in the alveolar capillaries. Extravasated erythrocytes and a loose network of fibrin can be seen in the intraalveolar space (hematoxylin–eosin staining; the scale bar corresponds to 50 μm).

ANGIOGENESIS



@ **In Covid-19** (n =7) and **influenza** (n = 7) respiratory failure: histologic pattern of **diffuse alveolar damage with perivascular T-cell infiltration.**
@ **In Covid-19** endothelial injury associated with the **presence of intracellular virus, thrombosis and microangiopathy.**
@ **In Covid-19** alveolar capillary **microthrombi were 9** times than patients with **influenza**
@ **In Covid-19** the amount of **new vessel growth was 2.7** times than in the lungs from patients with **influenza**

In our small series, vascular angiogenesis distinguished the pulmonary pathobiology of Covid-19 from that of equally severe influenza virus infection.

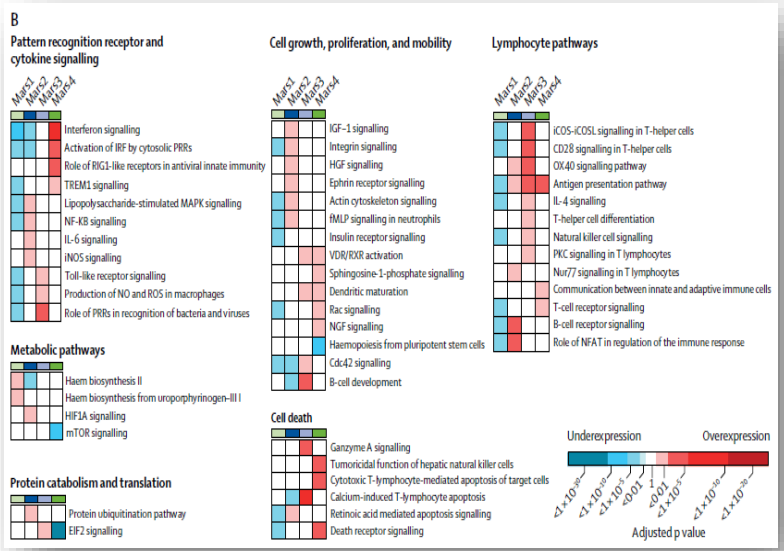
FROM ONE SIZE FITS ALL to PERSONALIZED APPROACH

ENDOTYPE-Gene expression

Classification of patients with sepsis according to blood genomic endotype: a prospective cohort study

*Brendon P Scicluna, Lonneke A van Vught, Aeilko H Zwinderman, Maryse A Wiewel, Emma E Davenport, Katie L Burnham, Peter Nürnberg, Marcus J Schultz, Janneke Horn, Olaf L Cremer, Marc J Bonten, Charles J Hinds, Hector R Wong, Julian C Knight, Tom van der Poll, on behalf of the MARS consortium**

Lancet Respir Med 2017



We identified four blood gene expression endotypes in patients from the UK and the Netherlands, one of which (Mars1) was consistently significantly associated with acute (28-day) and late (1-year) mortality. Furthermore, combining Acute Physiology and Chronic Health Evaluation IV scores and endotype significantly improved patient risk stratification. The four endotypes could not be predicted by demographic or clinical covariates. We also showed that the blood transcriptomes of these four endotypes had distinct host response signatures, including endotypes attuned to immunosuppression, hyperinflammation, or adaptive immune functions, showing great potential for more targeted patient management and clinical trial design.

Implications of all the available evidence

The substantial heterogeneity in the host response to sepsis has hindered patient management and therapeutic discoveries. Our study and others have shown that using the concepts of unsupervised blood genomic analysis, patients can be classified into molecular endotypes with important prognostic and pathophysiological value. The distinct host response signatures between the four endotypes have important implications that include development of precision therapeutics and practices of clinical trial design.

ADRECIZUMAB

Intensive Care Med (2021) 47:1284–1294

Primary Endpoint: Adrecizumab was well tolerated (one interruption, no hemodynamic alteration) with no differences in frequency and severity in TEAEs between treatment arms (TEAE of grade 3 or higher: 70.5% in the adrecizumab group and 71.1% in the placebo group) nor in 90-day mortality.

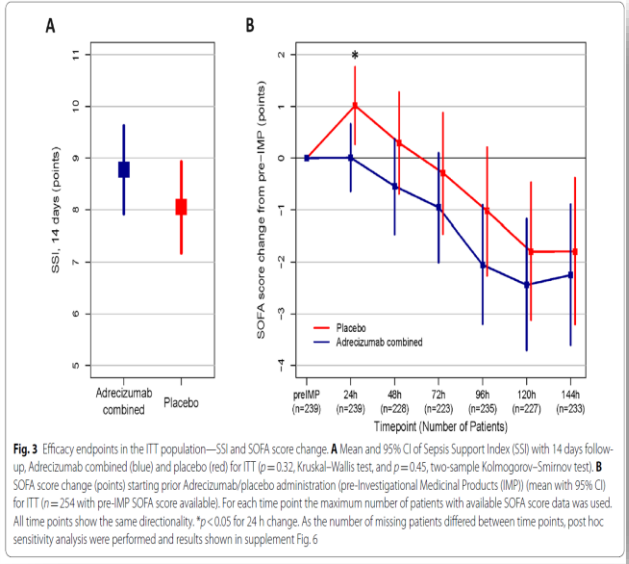


Fig. 3 Efficacy endpoints in the ITT population—SSI and SOFA score change. **A** Mean and 95% CI of Sepsis Support Index (SSI) with 14 days follow-up, Adrecizumab combined (blue) and placebo (red) for ITT ($p = 0.32$, Kruskal–Wallis test, and $p = 0.45$, two-sample Kolmogorov–Smirnov test). **B** SOFA score change (points) starting prior Adrecizumab/placebo administration (pre-Investigational Medicinal Products (IMP)) (mean with 95% CI) for ITT ($n = 254$ with pre-IMP SOFA score available). For each time point the maximum number of patients with available SOFA score data was used. All time points show the same directionality. *$p < 0.05$ for 24 h change. As the number of missing patients differed between time points, post hoc sensitivity analysis were performed and results shown in supplement Fig. 6

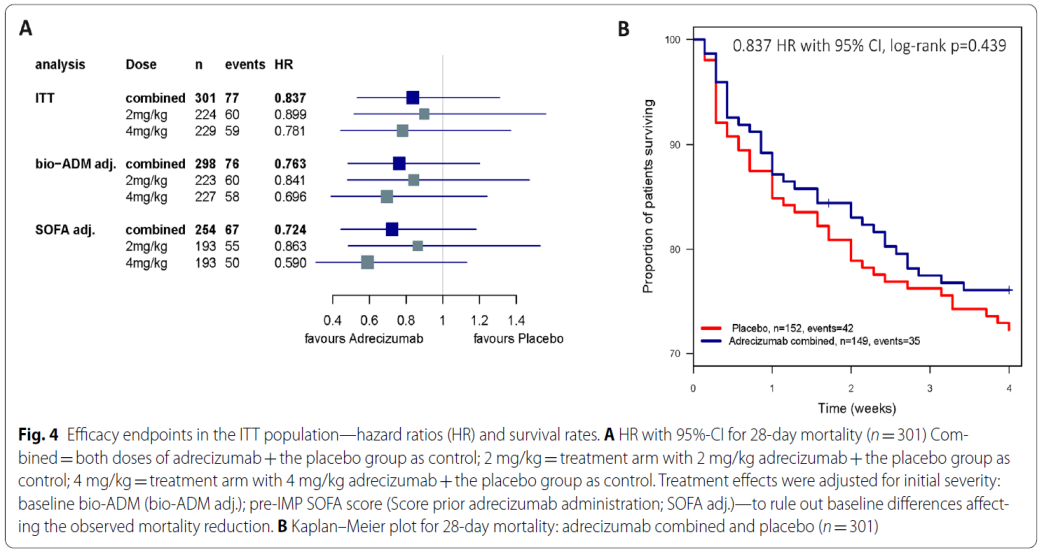


Fig. 4 Efficacy endpoints in the ITT population—hazard ratios (HR) and survival rates. **A** HR with 95%-CI for 28-day mortality ($n = 301$) Combined = both doses of adrecizumab + the placebo group as control; 2 mg/kg = treatment arm with 2 mg/kg adrecizumab + the placebo group as control; 4 mg/kg = treatment arm with 4 mg/kg adrecizumab + the placebo group as control. Treatment effects were adjusted for initial severity: baseline bio-ADM (bio-ADM adj.); pre-IMP SOFA score (Score prior adrecizumab administration; SOFA adj.)—to rule out baseline differences affecting the observed mortality reduction. **B** Kaplan–Meier plot for 28-day mortality: adrecizumab combined and placebo ($n = 301$)

Take-home message

The primary endpoint of AdrenOSS-2 was achieved as adrecizumab was well tolerated and showed a favorable safety profile. In this biomarker-guided trial, the mode of action was confirmed: adrecizumab rapidly increased plasma levels of bioactive adrenomedullin, a key hormone restoring and maintaining vascular integrity and endothelial function.

FROM ONE SIZE FITS ALL to PERSONALIZED APPROACH

Treatable traits and therapeutic targets: Goals for systems biology in infectious disease

Clark D. Russell[a] and J. Kenneth Baillie[a,b]

Current Opinion in Systems Biology 2017, 2:140–146

Box 1: Terminology

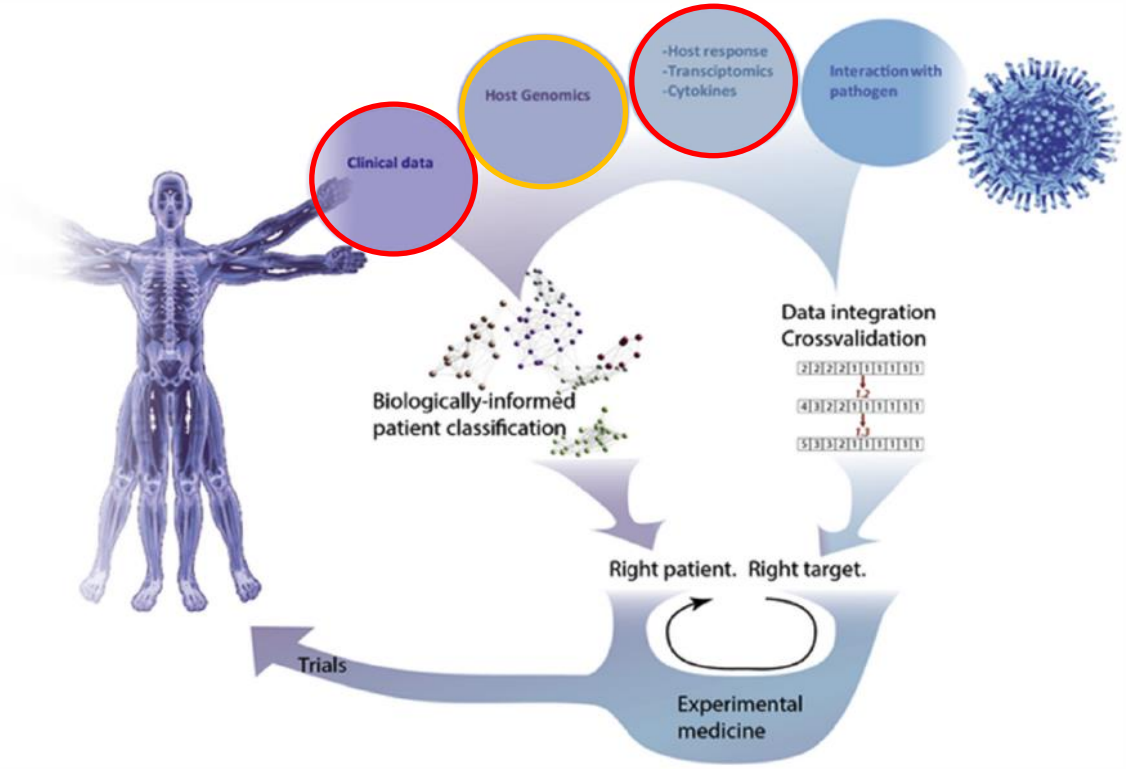
Term	Definition
Host-directed therapy	Therapeutic intervention to modulate an aspect of the host response to infection to alter the biology of a susceptible host to induce a response more similar to a host who survives.
Clinical syndrome	A collection of clinical symptoms and signs that tend to occur together. Depth of characterisation is limited by the range of observations available.
Disease	A clinical syndrome for which at least some of the underlying pathophysiological processes are thought to be known.
Subgroup	A smaller set within any population of patients, who are linked by some clinical feature or group of features.
Endotype	A subgroup within a population of patients who are distinguished by a shared disease process.
Treatable trait	The pathophysiological feature (or, in a looser sense, a biomarker or group of biomarkers for that feature) that determines whether a given therapy will improve a given patient's outcome. The same trait may be present in many different clinical syndromes or disease processes.

We suggest there are two major goals for systems biology in infection medicine:

(1) to identify subgroups of patients that share treatable features

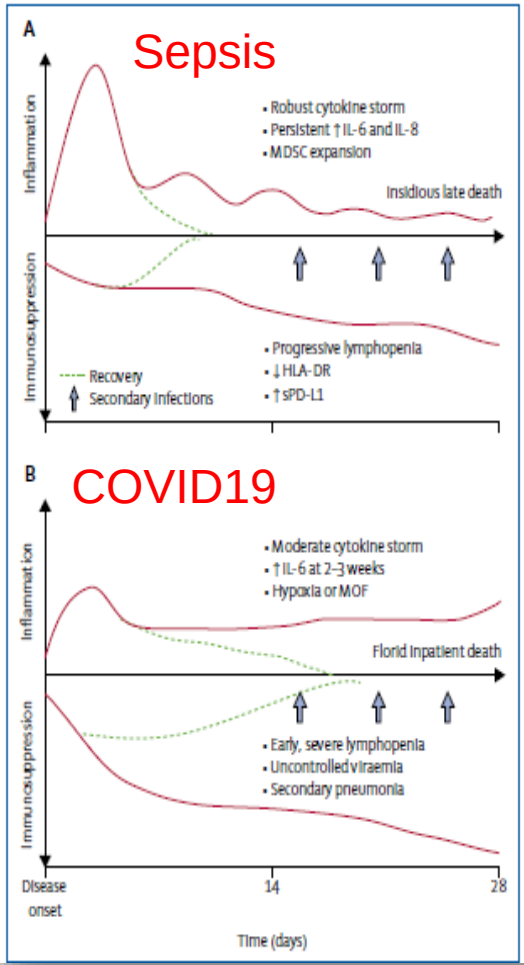
(2) to integrate high-throughput data from clinical and in vitro sources in order to predict tractable therapeutic targets with the potential to alter disease trajectories for individual patients.

Figure 1



Summary of a systems medicine approach to infection. A wide range of data sources can be combined using various methods (see text) to achieve two fundamental goals – clinically-informative phenotyping of patients, and identification of therapeutic targets.

THE 'NEW' TRIGGER



Bacterial sepsis and COVID19: analogies and differences

	Analogies	Differences
Pathobiology (viral sepsis)	• Dysregulated host response • Early Endothelial involvement • Multiple organ dysfunction • High heterogeneity	• **BACTERIAL SEPSIS: more frequent shock and rapid MOF** • **COVID19: Severe coagulopathy leading to thrombosis/ embolism**
Cytokine storm (yes, no, maybe)	• Early phase	• **BACTERIAL SEPSIS: Robust in the early phase** • **COVID19: Moderate in the early phase but persisting in late phase**
Immune dysfunction (when and how much)	• Mechanisms involved • Immune and clinical consequences (immune-paralysis and secondary infections)	• **BACTERIAL SEPSIS: Progressive** • **COVID19: Earlier and more pronounced (persisting viremia/viral replication ?)**

Olwal CO, Nganyewo NN, Tapela K, Djomkam Zune AL, Owoicho O, Bediako Y, Duodu S. Parallels in Sepsis and COVID-19 Conditions: Implications for Managing Severe COVID-19. Front Immunol. 2021 Feb 3;12:602848.