Overview of Clinical and Basic Science in Sepsis Diagnosis and Definitions

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NHS Foundation Trust

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- Research funding
  Primary = NIHR Clinician Scientist Award

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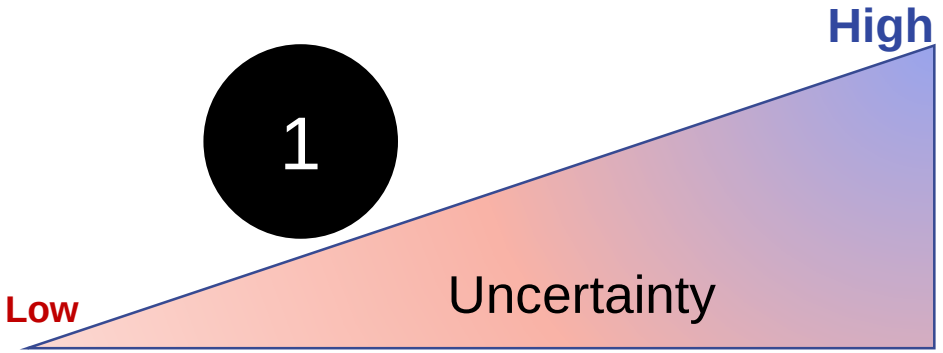
- Department of Health disclaimer
  The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

- No COI directly relevant to this talk

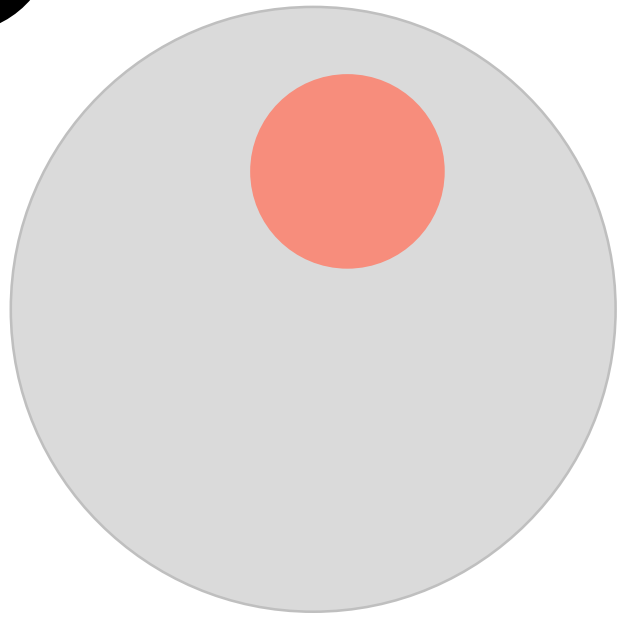
Why?

Infection



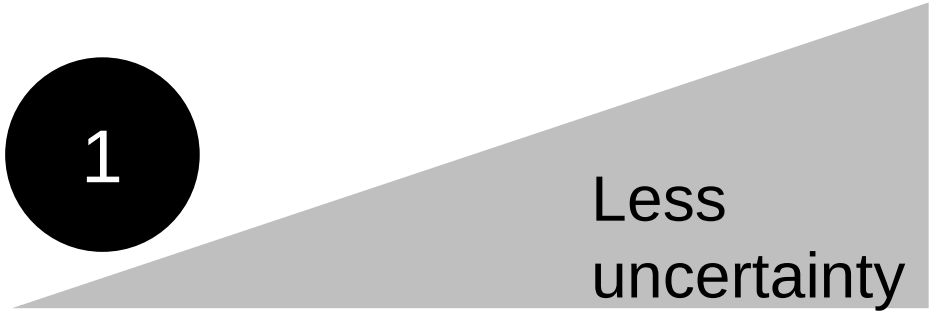
2

Uncomplicated

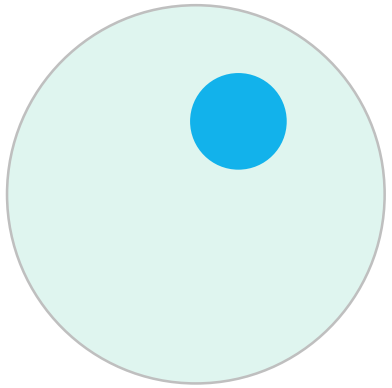


Sepsis

Organ dysfunction (e.g. SOFA score)

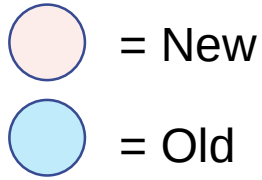


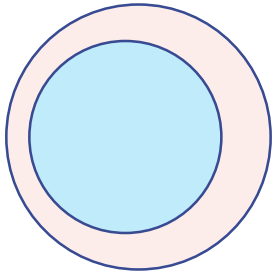
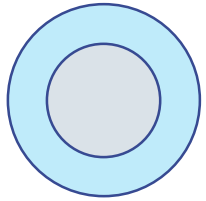
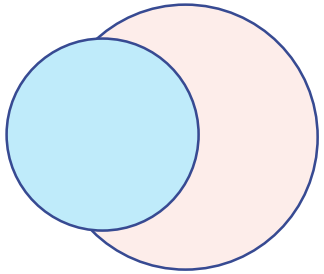
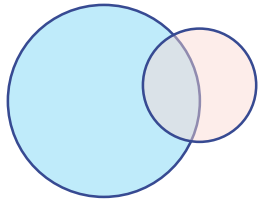
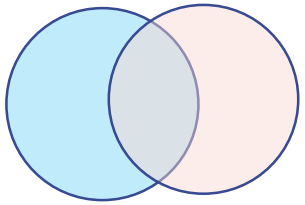
Not causal



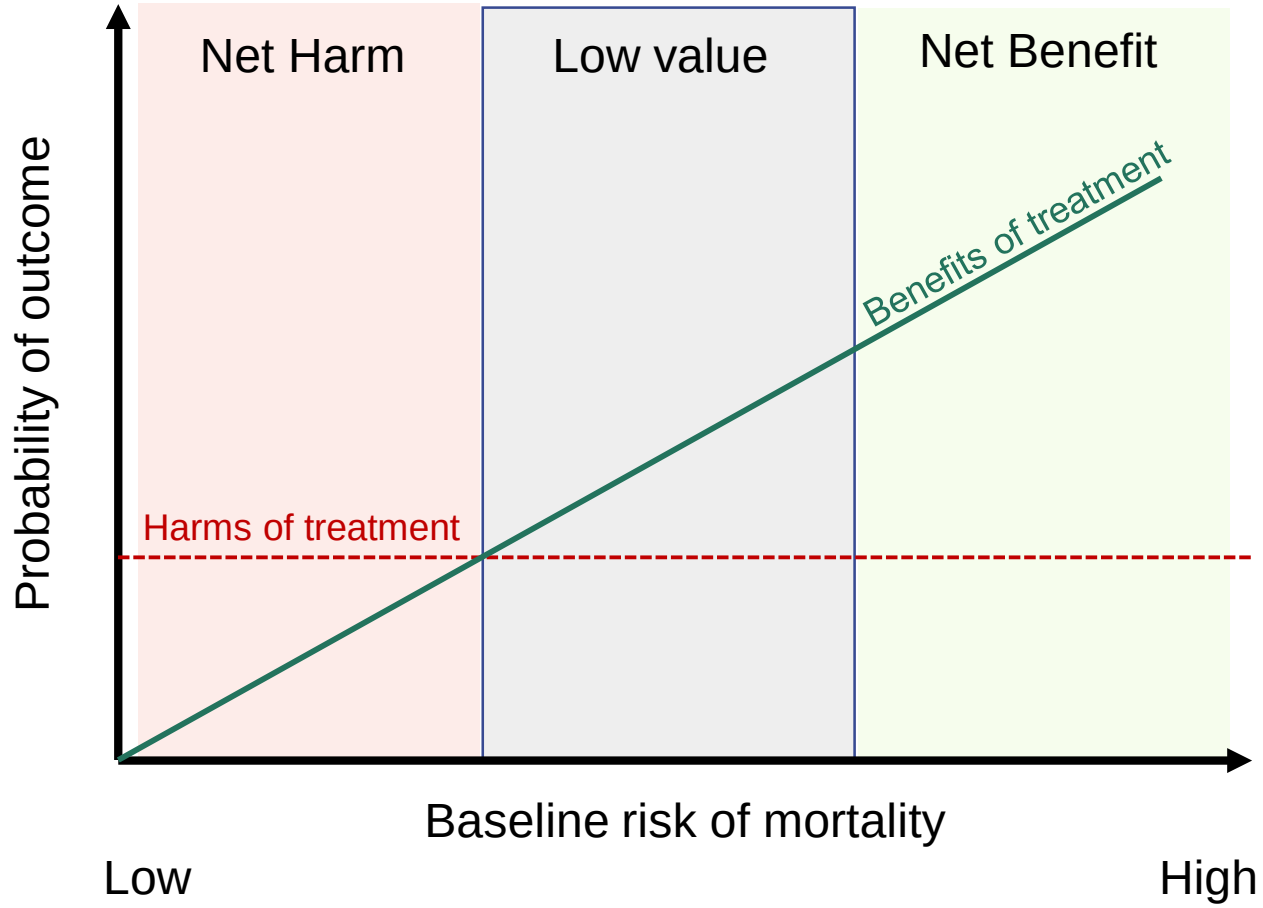
Causal

Potential impact-1



	Increase	Decrease	No change
Same TEST, Change in threshold			Not applicable
New TEST			

Potential Impact-2



Goals = Overview of

1. Sepsis definitions and criteria

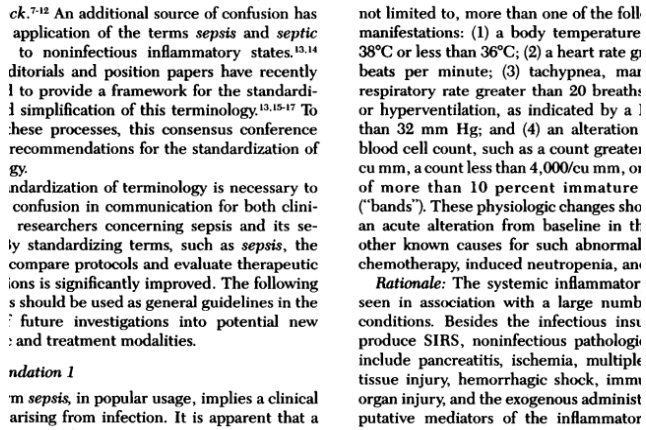
2. Biology of sepsis

Sepsis definitions and criteria

Sepsis-1
(1991)

Sepsis-2
(2001)

Sepsis-3.0
(2016)



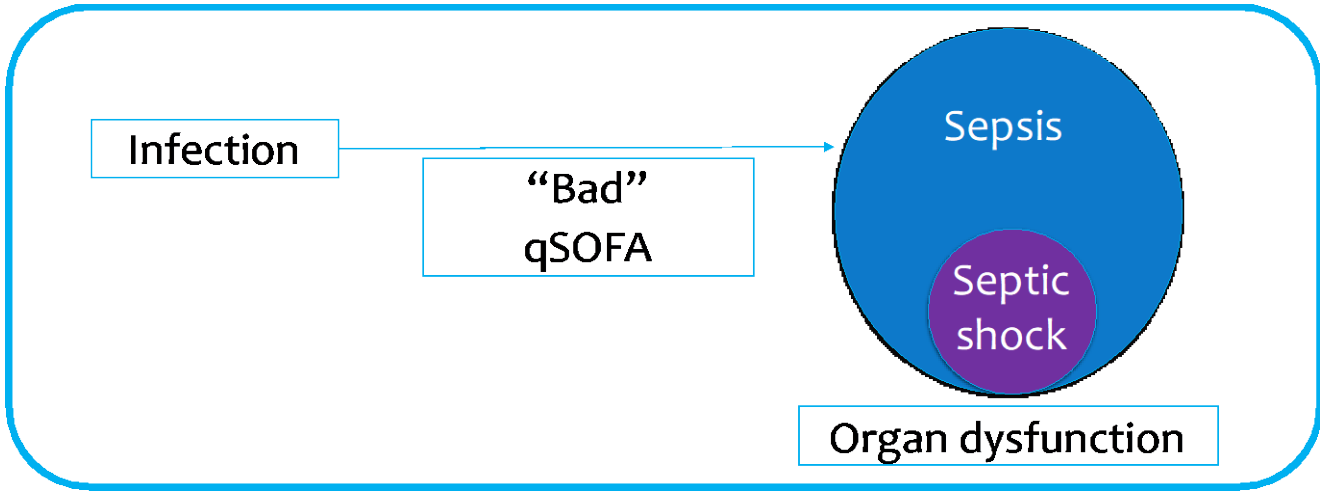
ck.[7-12] An additional source of confusion has
application of the terms *sepsis* and *septic*
to noninfectious inflammatory states.[13,14]
ditorials and position papers have recently
l to provide a framework for the standardi-
l simplification of this terminology.[13,15-17] To
hese processes, this consensus conference
recommendations for the standardization of
gy.
ndardization of terminology is necessary to
confusion in communication for both clini-
researchers concerning sepsis and its se-
y standardizing terms, such as *sepsis*, the
compare protocols and evaluate therapeutic
ions is significantly improved. The following
s should be used as general guidelines in the
future investigations into potential new
and treatment modalities.

ndation 1

m *sepsis*, in popular usage, implies a clinical
arising from infection. It is apparent that a

not limited to, more than one of the foll
manifestations: (1) a body temperature
38°C or less than 36°C; (2) a heart rate g
beats per minute; (3) tachypnea, ma
respiratory rate greater than 20 breath
or hyperventilation, as indicated by a
than 32 mm Hg; and (4) an alteration
blood cell count, such as a count greate
cu mm, a count less than 4,000/cu mm, o
of more than 10 percent immature
("bands"). These physiologic changes sho
an acute alteration from baseline in th
other known causes for such abnormal
chemotherapy, induced neutropenia, an

Rationale: The systemic inflammator
seen in association with a large numb
conditions. Besides the infectious inst
produce SIRS, noninfectious pathologi
include pancreatitis, ischemia, multipl
tissue injury, hemorrhagic shock, imm
organ injury, and the exogenous administ
putative mediators of the inflammator



Sepsis-3

Differences between Sepsis-2 vs Sepsis-3

Differences between Sepsis-3 vs Sepsis-2

- Definitions and explicit data-driven* criteria
  - Definitions = Illness description or concept
  - Criteria = Clinical & lab variables

- Terminology simplified
  - SIRS discarded
  - ‘Severe’ discarded
  - Septic shock explicitly made a subset of sepsis

Differences between Sepsis-3 vs Sepsis-2

- Sepsis-3 ‘Sepsis’
  - Definition =
    life-threatening organ dysfunction caused by a dysregulated host response to infection
  - Criteria =
    suspected or proven infection + change in SOFA score >=2 points

Sepsis 2.0 severe sepsis == Sepsis 3.0 ‘sepsis’

Differences between Sepsis-3 vs Sepsis-2

- Sepsis-2 “Septic shock’
  - Definition = a state of acute circulatory failure characterized by persistent arterial hypotension unexplained by other causes
  - Criteria =

Developing a New Definition and Assessing New Clinical Criteria for Septic Shock
For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

Manu Shankar-Hari, MD, MSc; Gary S. Phillips, MAS; Mitchell L. Levy, MD; Christopher W. Seymour, MD, MSc; Vincent X. Liu, MD, MSc; Clifford S. Deutschman, MD; Derek C. Angus, MD, MPh; Gordon D. Rubenfeld, MD, MSc; Mervyn Singer, MD, FRCP; for the Sepsis Definitions Task Force

Septic Shock Case Definition Criteria[a]	No.[b]	Mortality, No. of Events/ No. of Patients (%) [95% CI][c]
Consensus definitions cited (no description)	7	4954/9590 (51.6) [46.3-56.9]
Hypotension	6	15 003/51 976 (39.8) [30.1-49.5]
Hypotension + perfusion abnormalities and/or vasopressor therapy	3	830/1323 (63.3) [48.3-78.4]
Hypotension + vasopressor therapy	11	18 446/32 095 (48.9) [40.5-57.4]
Hypotension + vasopressor therapy + serum lactate level >2 mmol/L	1	3602/8520 (42.3) [41.2-43.3]
Hypotension + perfusion abnormalities + vasopressor therapy	3	4175/8972 (47.0) [45.0-49.0]
Hypotension ± vasopressor therapy or metabolic abnormalities	1	75/324 (23.1) [18.6-27.7]
Hypotension or vasopressor therapy	13	1286/2971 (48.4) [41.3-55.5]
Hypotension or serum lactate any value or vasopressor therapy	2	7383/21 376 (33.9) [31.8-36.0]
International Classification of Diseases codes	3	13 843/28 055 (38.9) [22.5-55.2]
Serum lactate level >4 mmol/L	2	461/1277 (38.3) [21.5-55.1]
Overall	52	70 058/166 479 (46.5) [42.7-50.3]

Differences between Sepsis-3 vs Sepsis-2

- Sepsis-3 ‘Septic shock’
  - Definition =
    as a subset of sepsis in which underlying circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than sepsis alone
  - Criteria =
    hypotension requiring vasopressor therapy to maintain mean BP 65 mm Hg or greater and having a serum lactate level greater than 2 mmol/L after adequate fluid resuscitation

qSOFA

Amongst patients with suspected or proven infection, who are at risk of bad outcomes?

qSOFA

Sepsis =

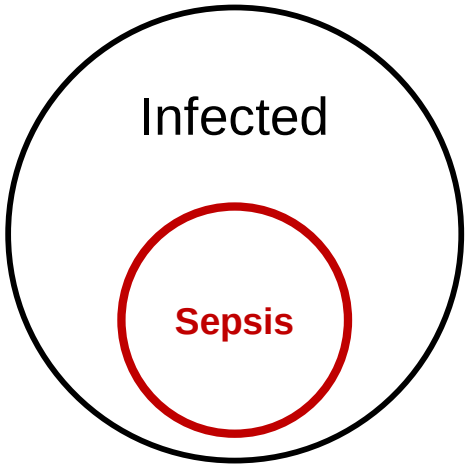
life threatening organ dysfunction caused by a dysregulated host response to infection

Among encounters with suspected infection,

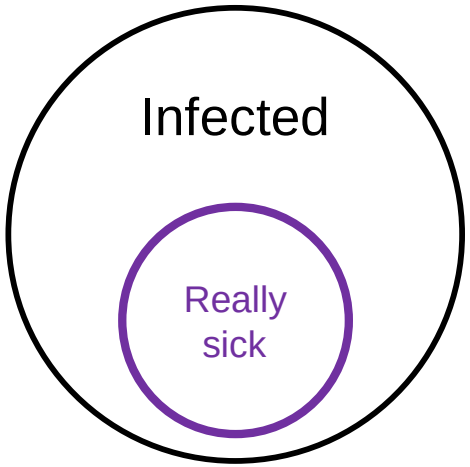
who is sick?

qSOFA = Identifies ‘BAD’

qSOFA IS NOT Criteria for infection



- There are no gold standard test(s) for or clinical feature(s) of sepsis



- “Really sick” is a proxy
- More common among infected patients who are septic than those who are not
  - Death in the hospital
  - Prolonged stay in the ICU >3 days

qSOFA = Identifies ‘BAD’

- Studied 21 variables from Sepsis-2
- Multivariable logistic regression for in-hospital mortality

Respiratory rate ≥ 22 bpm

Altered mentation

Systolic blood pressure ≤ 100 mmHg

Sepsis Biology

Sepsis immunobiology

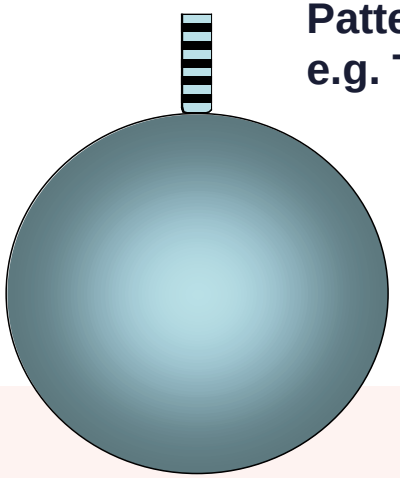
Avoidance

Resistance
- To reduce pathogen burden → Immune responses

Tolerance
- To reduce negative impact of infection on host fitness → Minimise damage
  - Pathogen-induced
  - Immune response induced

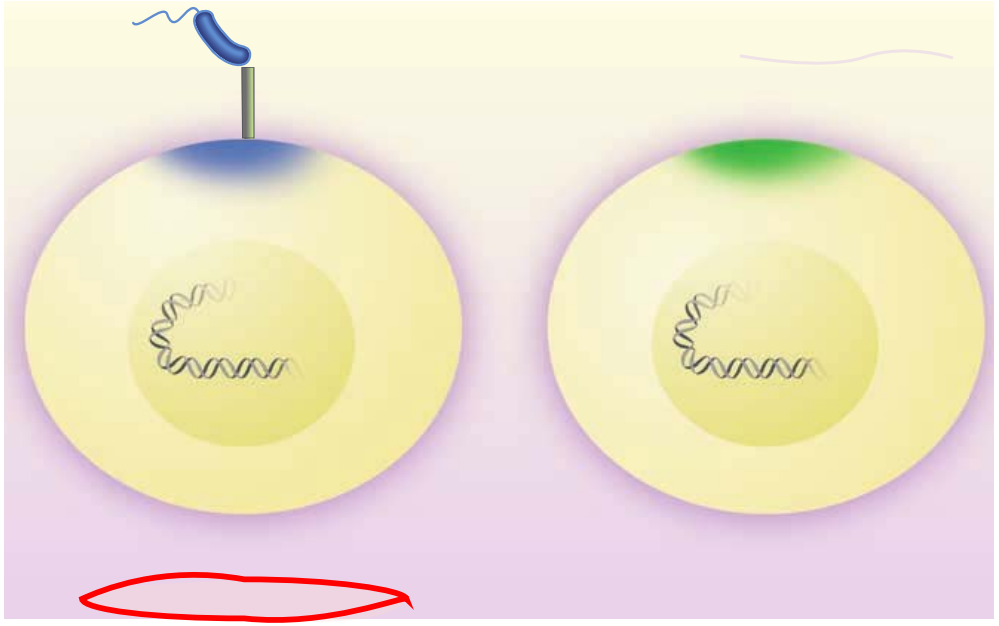
Sepsis biology - resistance

Infections → **Danger signals = Patterns of microbial non-self** → **Pattern recognition**



Patter recognition receptors
e.g. Toll like receptors

APC = Antigen Presenting Cells
e.g. Dendritic cells



Secondary lymphoid organs
e.g. spleen
Lymph nodes

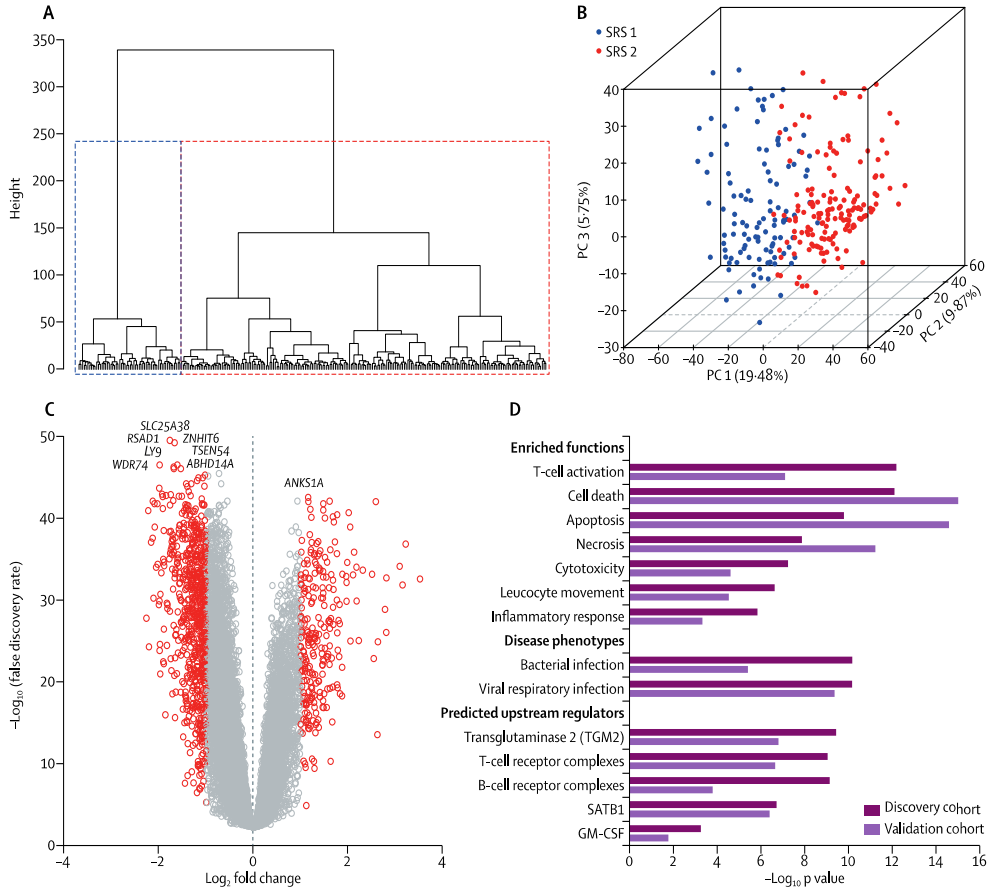
↓

Adaptive immune system responses

Immune responses in sepsis ≠ infection

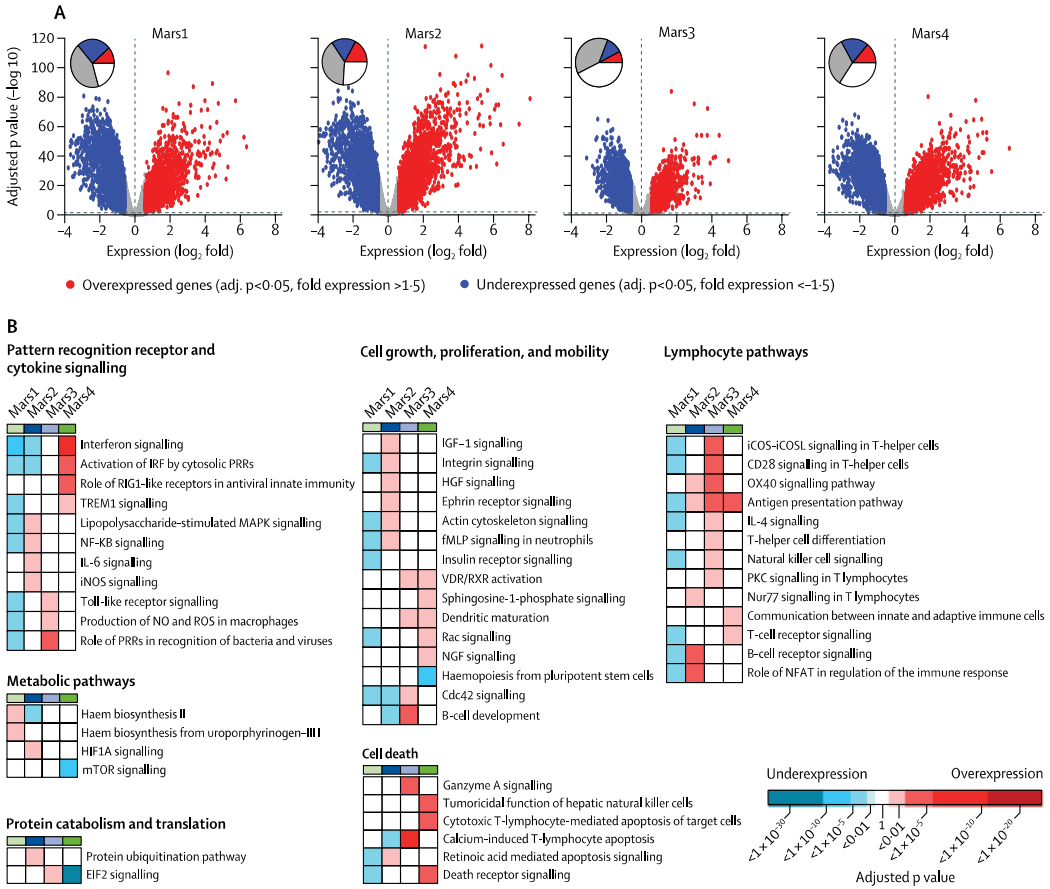
Genomic landscape of the individual host response and outcomes in sepsis: a prospective cohort study

Emma E Davenport, Katie L Burnham, Jayachandran Radhakrishnan*, Peter Humburg, Paula Hutton, Tara C Mills, Anna Rautanen, Anthony C Gordon, Christopher Garrard, Adrian V S Hill, Charles J Hinds, Julian C Knight*

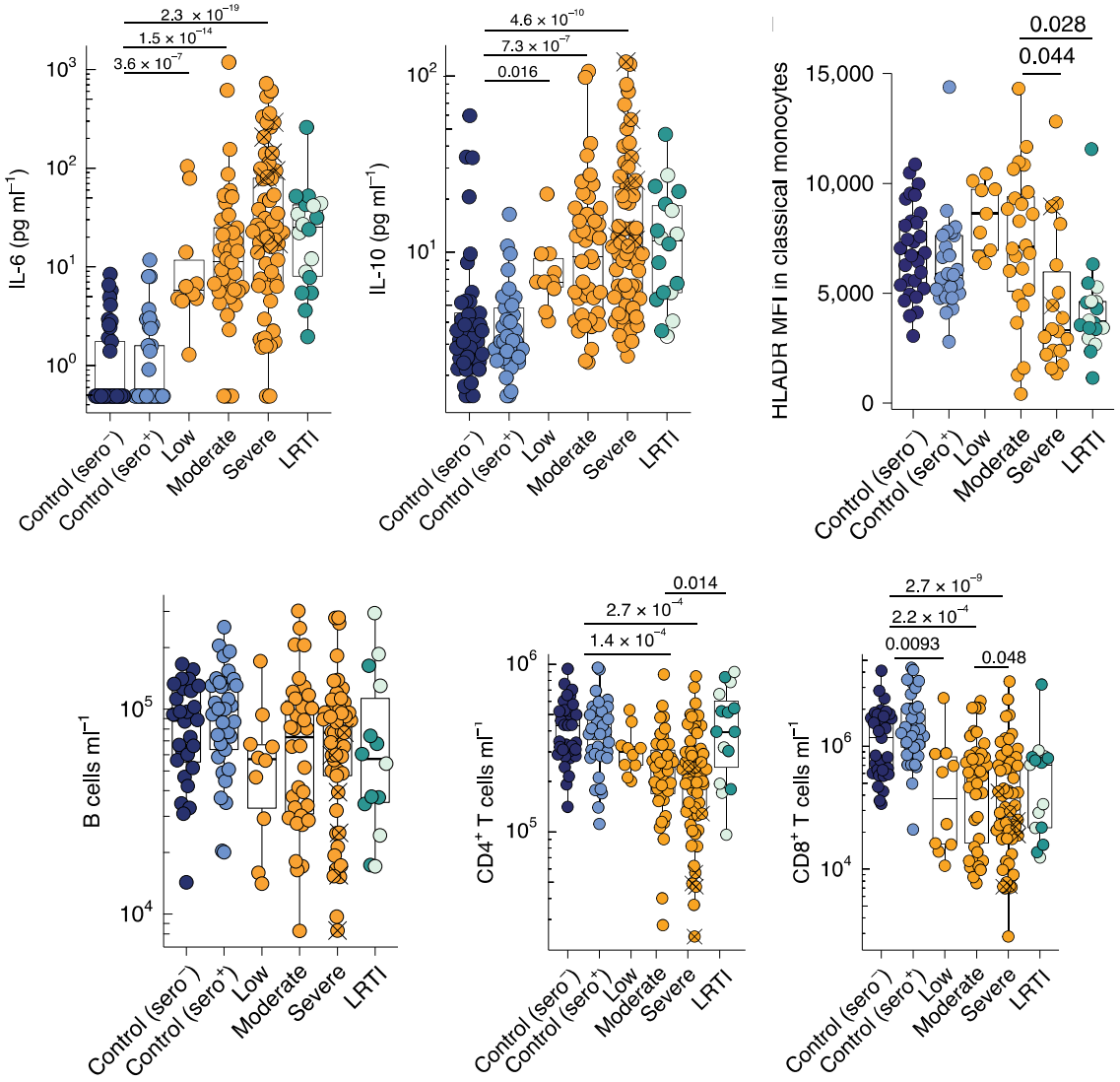


Classification of patients with sepsis according to blood genomic endotype: a prospective cohort study

*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**



Sepsis is not always ‘bacterial’ infection



nature medicine

ARTICLES

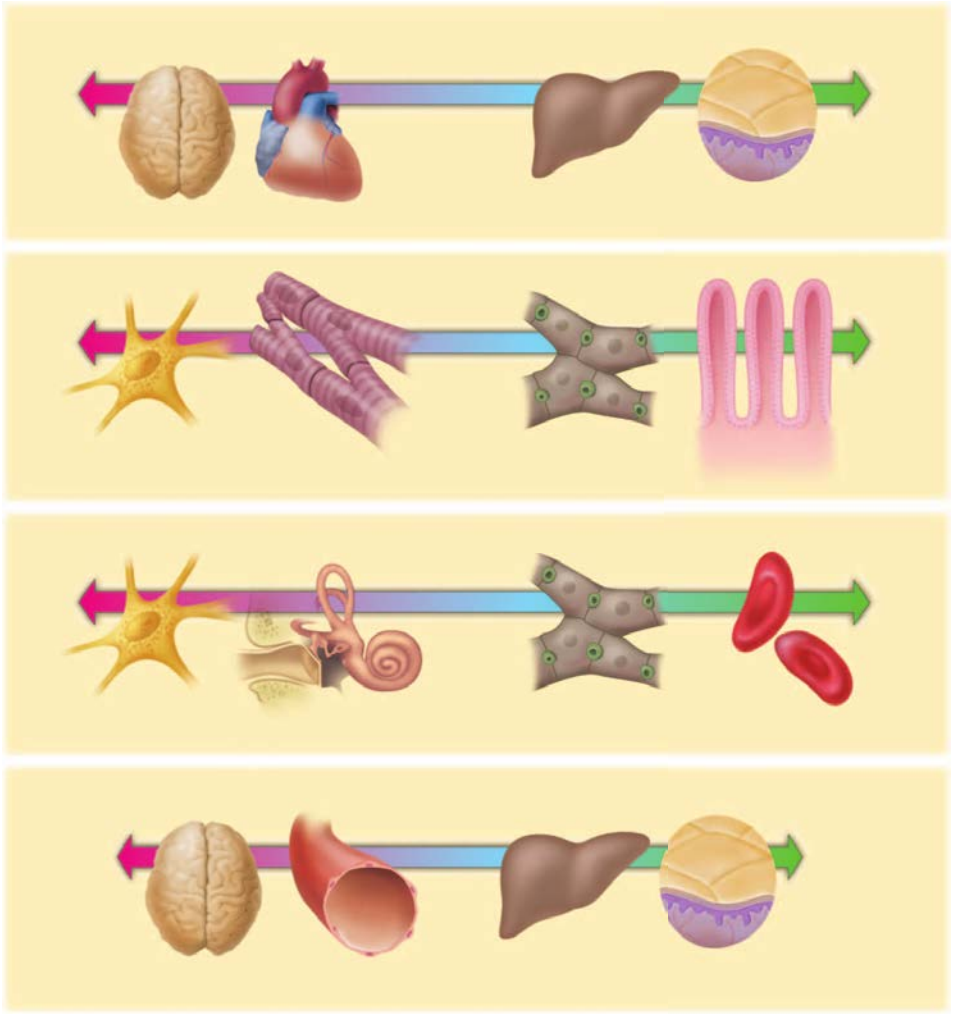
https://doi.org/10.1038/s41591-020-1038-6

Check for updates

A dynamic COVID-19 immune signature includes associations with poor prognosis

Adam G. Laing[1,19], Anna Lorenc[1,19], Irene del Molino del Barrio[1,2,19], Abhishek Das[1,3,19], Matthew Fish[1,4,19], Leticia Monin[5,19], Miguel Muñoz-Ruiz[5,19], Duncan R. McKenzie[5,19], Thomas S. Hayday[1,19], Isaac Francos-Quijorna[6,19], Shraddha Kamdar[1,19], Magdalene Joseph[1], Daniel Davies[1,7], Richard Davis[1], Aislinn Jennings[1,4], Iva Zlatareva[1], Pierre Vantourout[1], Yin Wu[1,2,5], Vasiliki Sofra[1], Florencia Cano[5], Maria Greco[5], Efstathios Theodoridis[1], Joshua Freedman[1], Sarah Gee[1], Julie Nuo En Chan[8], Sarah Ryan[9], Eva Bugallo-Blanco[8], Pärt Peterson[10], Kai Kisand[10], Liis Haljasmägi[10], Loubna Chadli[11], Philippe Moingeon[11], Lauren Martinez[12], Blair Merrick[13], Karen Bisnauthsing[13], Kate Brooks[12], Mohammad A. A. Ibrahim[14], Jeremy Mason[15], Federico Lopez Gomez[15], Kola Babalola[15], Sultan Abdul-Jawad[8], John Cason[16,17], Christine Mant[16,17], Jeffrey Seow[16], Carl Graham[16], Katie J. Doores[16], Francesca Di Rosa[18], Jonathan Edgeworth[13], Manu Shankar-Hari[1,4]✉ and Adrian C. Hayday[1,5]✉

Sepsis biology - Tolerance



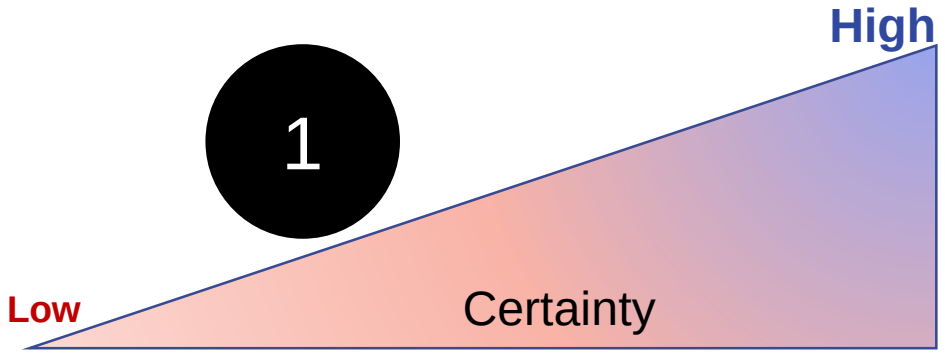
Although tissues generally tend to fall at the same ends of the four spectra, the four characteristics do not necessarily correlate with each other.

- Intrinsic damage susceptibility
- Renewal capacity
- Repair capacity
- Functional autonomy
- Damage sequelae

Disease Tolerance as a Defense Strategy
Ruslan Medzhitov *et al.*
Science **335**, 936 (2012);
DOI: 10.1126/science.1214935

Summary (Problems to tackle)

- Increase certainty of infection diagnosis



- Identify risk of
  - Infection
  - Sepsis in infected

- Ensure organ dysfunction is *caused* by infection