Innovations in the Monitoring & Therapy of Sepsis

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Monitoring Sepsis: Blood cultures?

- **Most common ordered test in sepsis**
- Slow Turn-around time
- Low yield of viable pathogens
- Contamination risk
- Inadequate blood volumen
- Atb exposure or low bacterial burden
- RDT to guide atb at POC does not exist

- **Positive <30% of patients with sepsis**
- Virus also generate sepsis.
- A paradigm shift is required

Rello J & Watkins R. J Transl Crit Care Med 2022

Sepsis =

- Hypermetabolism
- Mitocondrial Dysfunction
- Increased blood levels of L-carnitine
- Facilitates fatty acid B-oxidation (FAO)

- Aberrant immune response !

Watkins RR, Bonomo RA, Rello J. Expert Review Anti-Infect Ther 2022;13:1-10

Pathophysiology of sepsis

The pathophysiology of sepsis is extremely complex and mechanisms of multiple organ system dysfunction and immune system alterations are reviewed here

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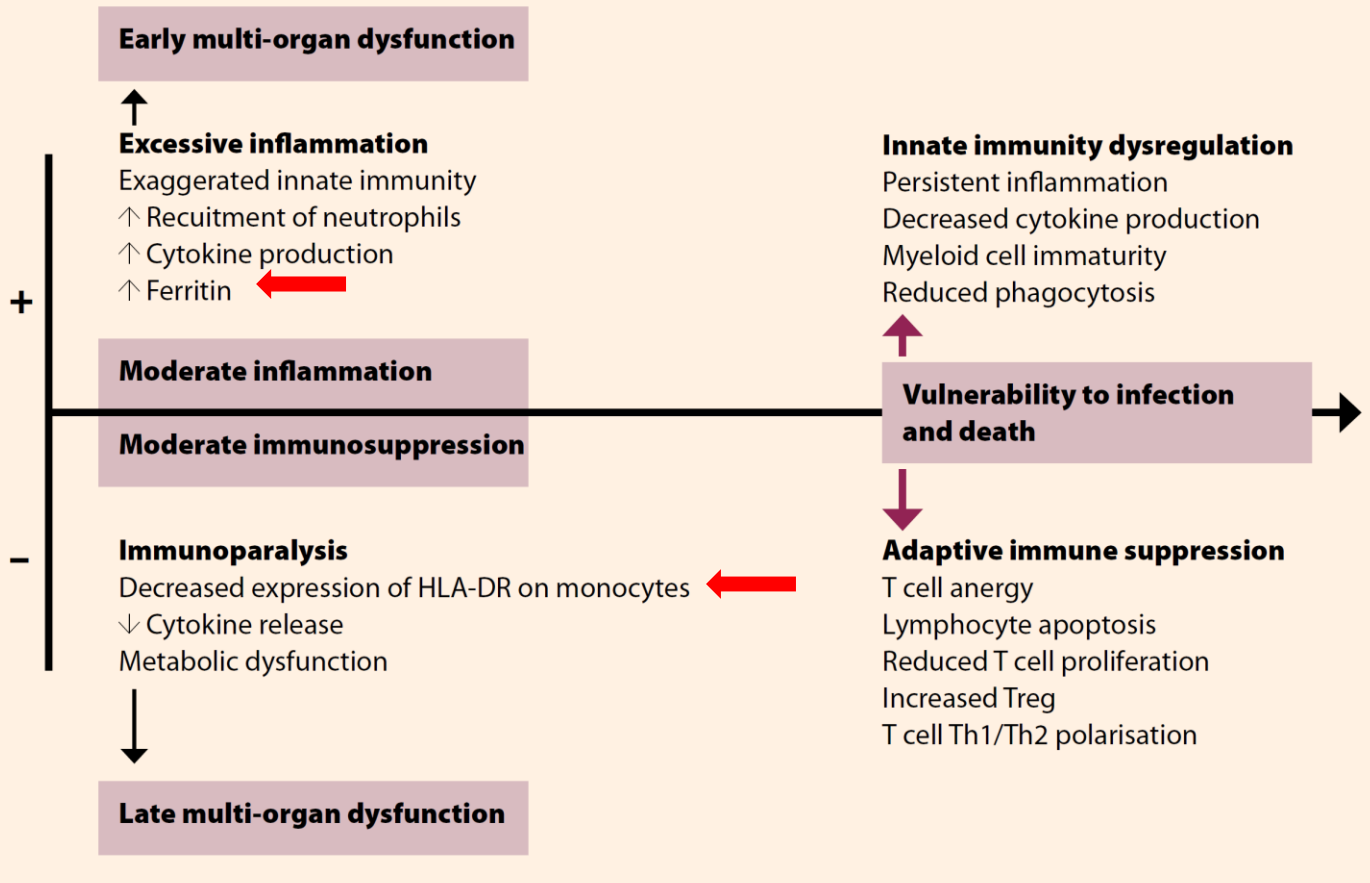
FIGURE 2

Immune dysregulation in sepsis

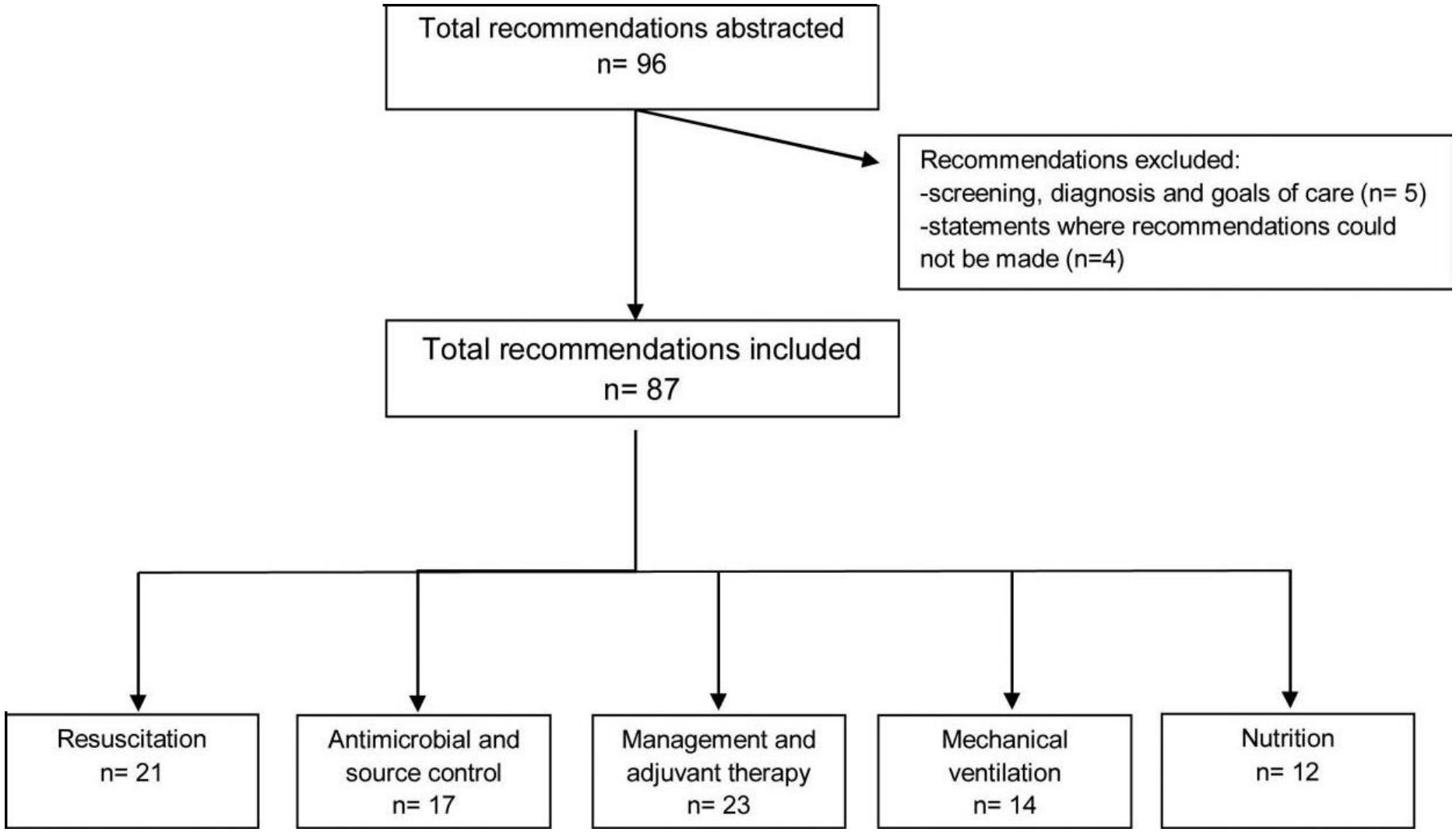


2017 SSC Recommendations
Quality of evidence

- 87/96 recommendations eligible
- Among 31 (43%) strong R, only 15.2% of High Q
- 37 (42.5%) Low Q & 7 (8%) were High Q.
- RCT supported 8.6% R management/adjuvant Rx
- None High Q supported atb use (82% Low-very Low evidence or BPS)

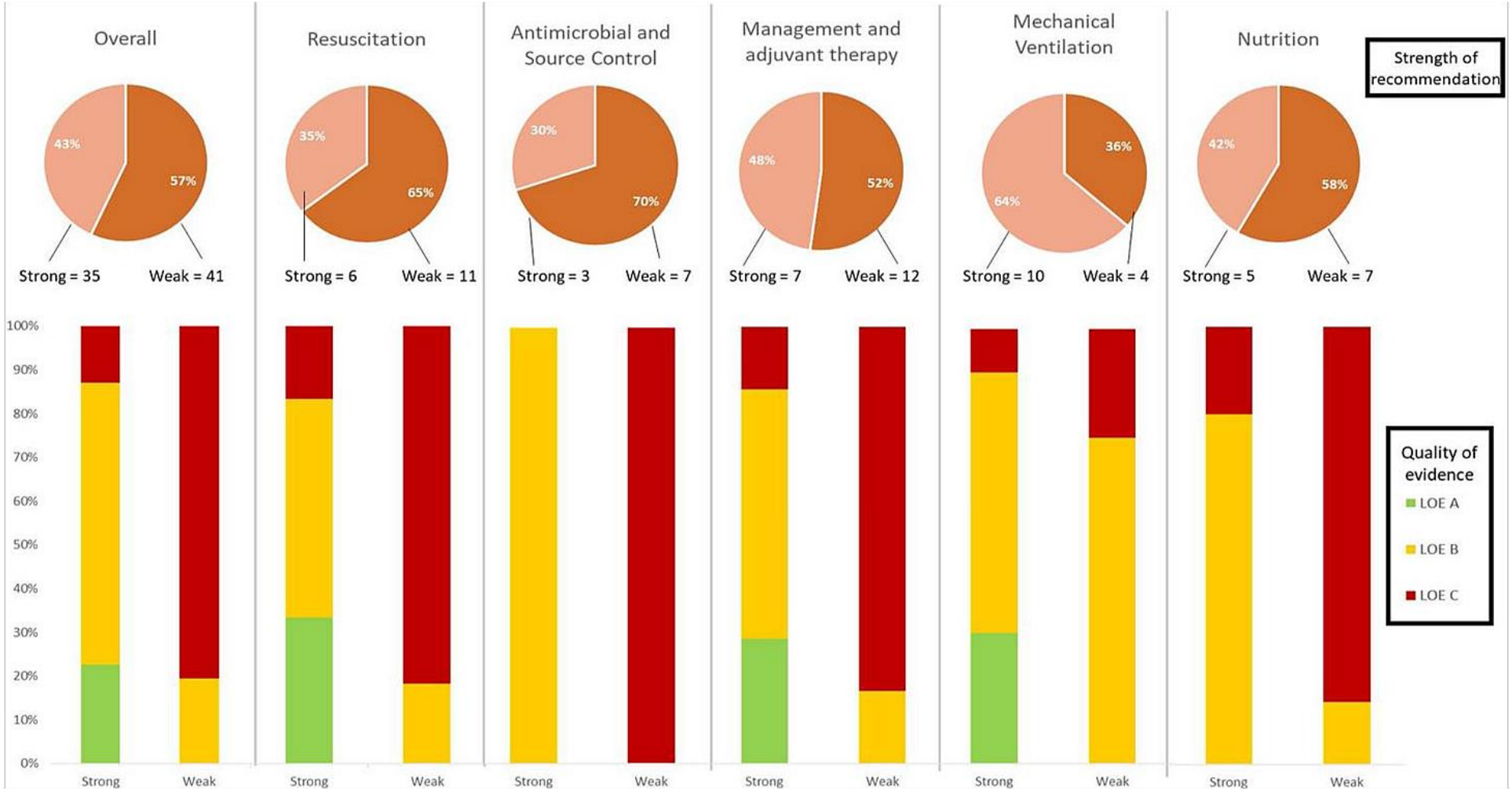
Rello J, et al. ACCPM 2020;39:497-502

PRISMA flow diagram of the study selection



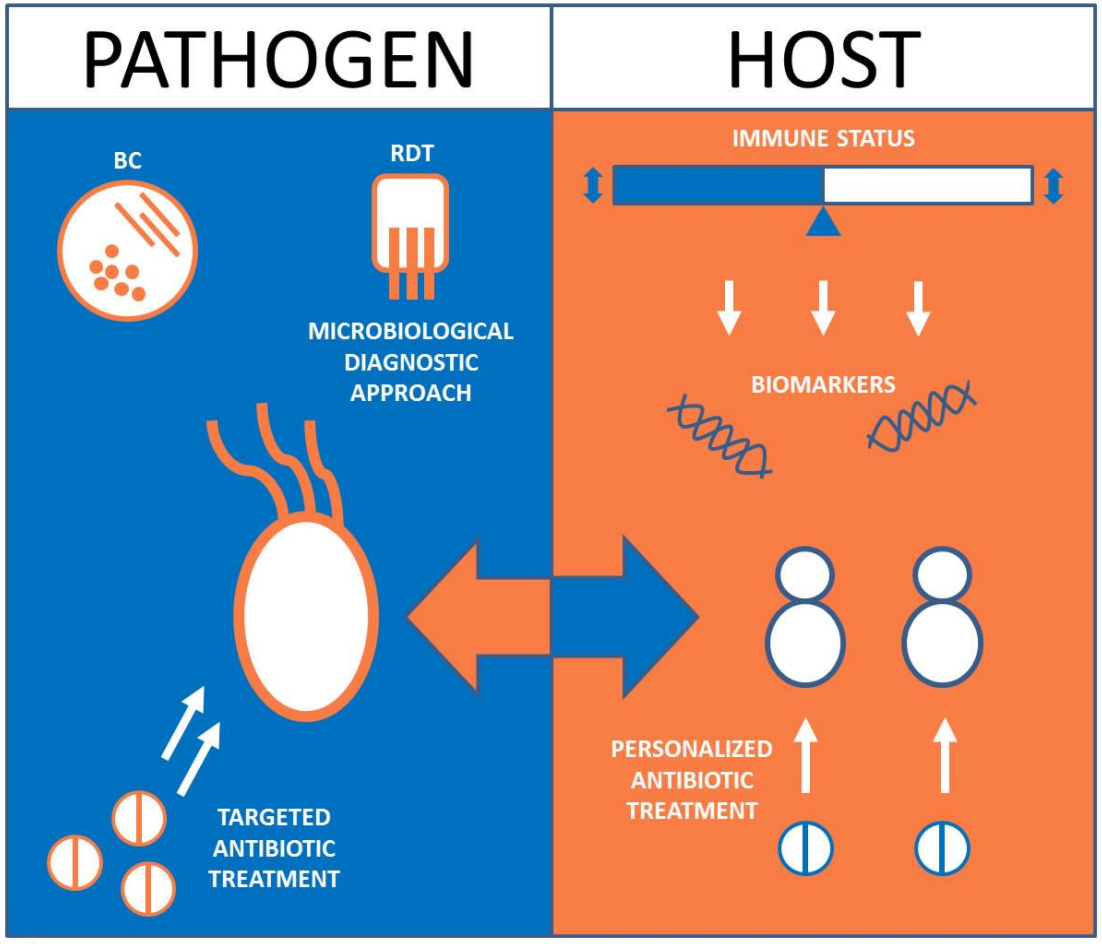
Rello J, et al. Anaesth Crit Care Pain Med 2020; 39: 497–502.

2017 SSC: Proportion of recommendations by the strength of recommendation and level of evidence.



Rello J, et al. Anaesth Crit Care Pain Med 2020; 39: 497–502.

Precision Medicine in Sepsis
ESCMID Position Paper



Rello J, et al. CMI 2018;24:1264-72.

Precision Medicine in Sepsis

- PubMed
- Adults
- RCT, SR & MA, CPG & Observational studies
- "**Precision Medicine", "Sepsis**", "Rapid Diagnosis", "Biomarkers", "Metabolomics", Immunomodulatory Therapies"
- January 2010- December 2021
- English language

Watkins RR, Bonomo RA, Rello J. Expert Review Anti-Infect Ther 2022;13:1-10.

Choosing antibiotics using a Personalized Approach: Rapid AST

- SRMA compared Varigene® & FilmaArray® for GNB-PBC in 20 studies with 3310 isolates.
- Both studies miss ceph/carbapenem resistance phenotypes in only a few cases.
- A SRMA compared RAST to standard susceptibility testing for BSI in 6 trials with 1638 participants.
- RAST did not improve mortality, time-to-discharge or time-to-appropriate antibiotics.

Anton-Vazquez V, et al. Cochrane database Syst Rev 2021;5:CD013235.
Venkatesh B, et al. NEJM 2018;378:797-808

Rapid AST in UTIs

- In a trial with 41 uropathogenic *E. coli* isolates, all were classified as S/R to cipro within 10 minutes
- It was used a direct single-cell imaging test.
- The trial needs validation to blood or other infectious sites.
- If confirmed, a POC test to direct therapy of urinary tract sepsis may be used, even at low bacterial concentrations

Baltekin et al. PNAS 2017;114:9170-75.

Rapid determination of Resistance should be the Key

- Unlike the genotypic ASTs, the phenotypic ASTs directly assess if the antibiotic inhibited bacterial growth, which should be the most relevant issue.

Rello J, Alonso-Tarres C. Clin Infect Dis 2021;73:1173-5

Vit C as adjunctive therapy?

- Observational retrospective study among adults: hidrocortisone, ascorbic acid & thiamine reduced hospital mortality (40.4% to 8.5%) in sepsis.

- Follow-up prospective studies reported reduction in vasopressor use but no reduction in mortality.

- A random-effects NMA found vit C, steroids, vit B1 or combo did not decrease long-term mortality in adults with sepsis /septic shock.

Marik PE, et al. CHEST 2017;151:1229-1238.
Fujii T, et al. ICM 2022;48:16-24.

Vit D as adjunctive therapie?

- VITdAL-ICU study: RCT large vit D dosing vs placebo in ICU adults with sepsis

- Intervention has lower mortality, after 7 days, in subgroup with vitamin deficiency.

- Measuring serum vitamin D in sepsis holds promise from a precision medicine standpoint

Miri A, et al. Eur Rev Med Pharmacol Sci 2019;23:4033-43.

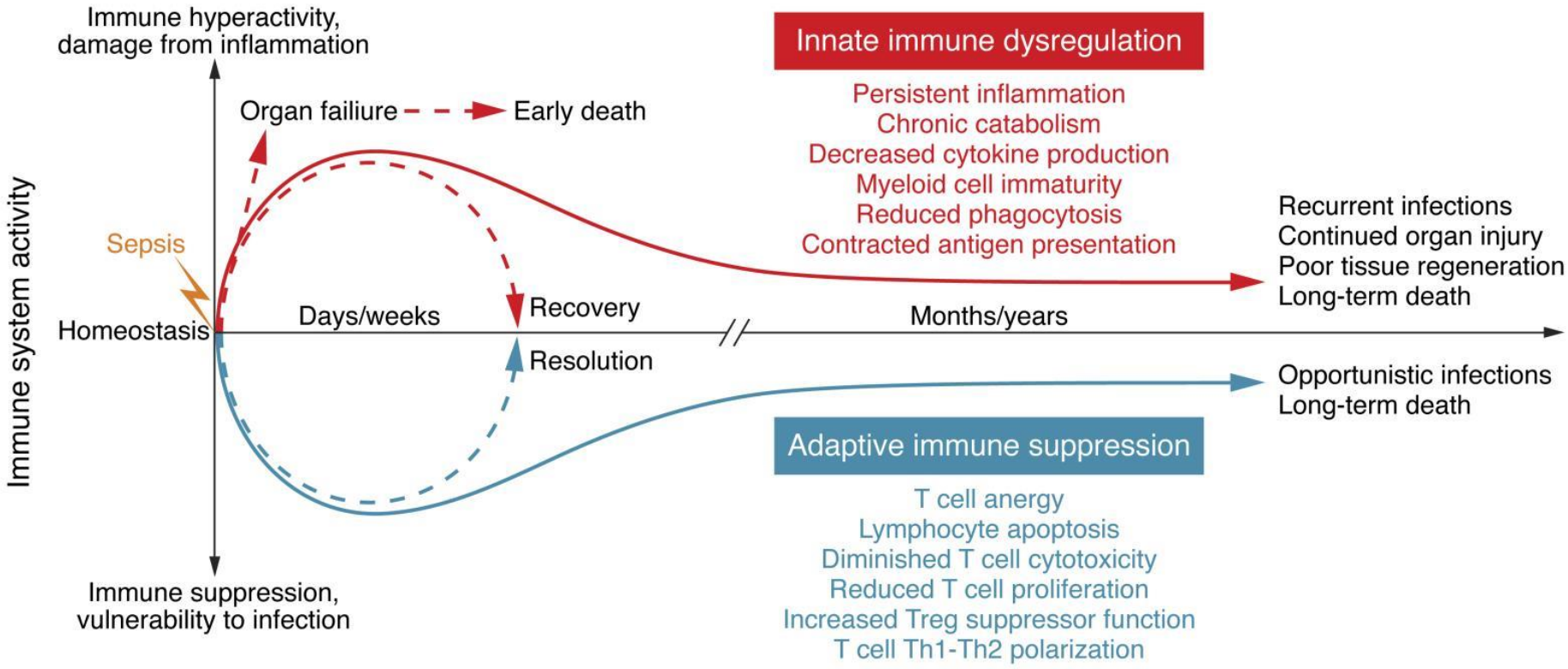
Immunomodulatory therapies

- 2021 SSC recommend iv steroids for adults with septic shock & vasopressors use.
- Early vs late onset & dosage are issues.
- Infectious site, microbiota & genetic signatures cause heterogeneity.

- CPG vs Actual Clinical Practice: Need of more evidences & different paradigms

Evans L, et al. Eur Rev Med Pharmacol 2021;47:1181-1247
Rello J, Waterer GW. ACCPM 2020;39:699-701
Rello J, Waterer GD, CID 2021;73:e1611-e1612.

Sepsis: Dysregulated Immune Response
Can immune therapies reduce mortality?



Delano MJ et al. J Clin Invest. 2016;126:23-31

Steroids & Genetic signatures

- SRS1 & SRS2 transcriptomic sepsis response signatures were identified in a RCT on septic shock
- SRS2 endotype had significantly higher mortality with steroids compared with placebo.
- In children, the risk of mortality was three-fold higher when endotype A received steroids compared with placebo (p= 0.05).

Antcliffe DB et al. AJRCCM 2019;199:980-6
Wong HR, et al. CCM 2021;49:e98-e101

Immunophenotypes: Influenza Pneumonia

Ferritin< 325 ng/mL

HLA-DR <4500 MFI

Group 1 normal (N)

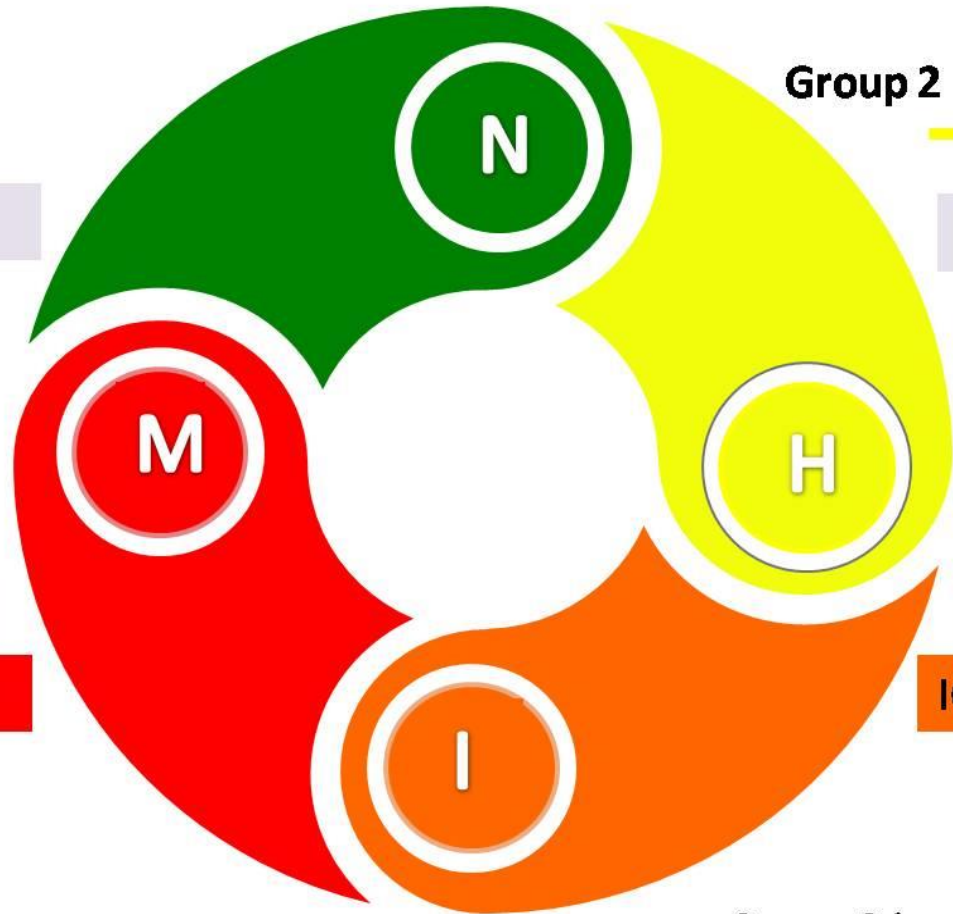
ICU admission: 6.6%
Mortality: 0%

Ferritin>325 ng/mL

HLA-DR > 4500 MFI

Group 2 hyperinflammation (HI)

ICU admission: 27.5%
Mortality: 0%



Mortality: 40 %
ICU admission: 92.3%

Ferritin > 325 ng/mL

HLA-DR <4500 MFI

Group 4 mixed (HI+ID)

Mortality: 22.2 %
ICU admission: 81.8 %

Ferritin < 325 ng/mL

HLA-DR <4500 MFI

Group 3 immunocompromised (ID)

Monitoring cellular host response

- The intelliSept® test (Cytovale, CA) measures biophysical properties of WBC in a microfluidic channel.

  A 23-mRNA response has been described to predict bacterial infections in suspected sepsis.

- InSep® (inflammatix, inc) uses a 29-mRNA panel to determine risk of bacterial infection & risk of physiologic decompensation.

  A pilot study correlated the test with infection response.

- These results should serve to stratify patients based on their immune response in a personalized way, anticipating the response that can be monitored at the bedside

Crawford K, et al. AJRCCM 2018;198:280-2
He YD, et al. J Pers Med 2021;11.735-9.

Septicyte® Rapid

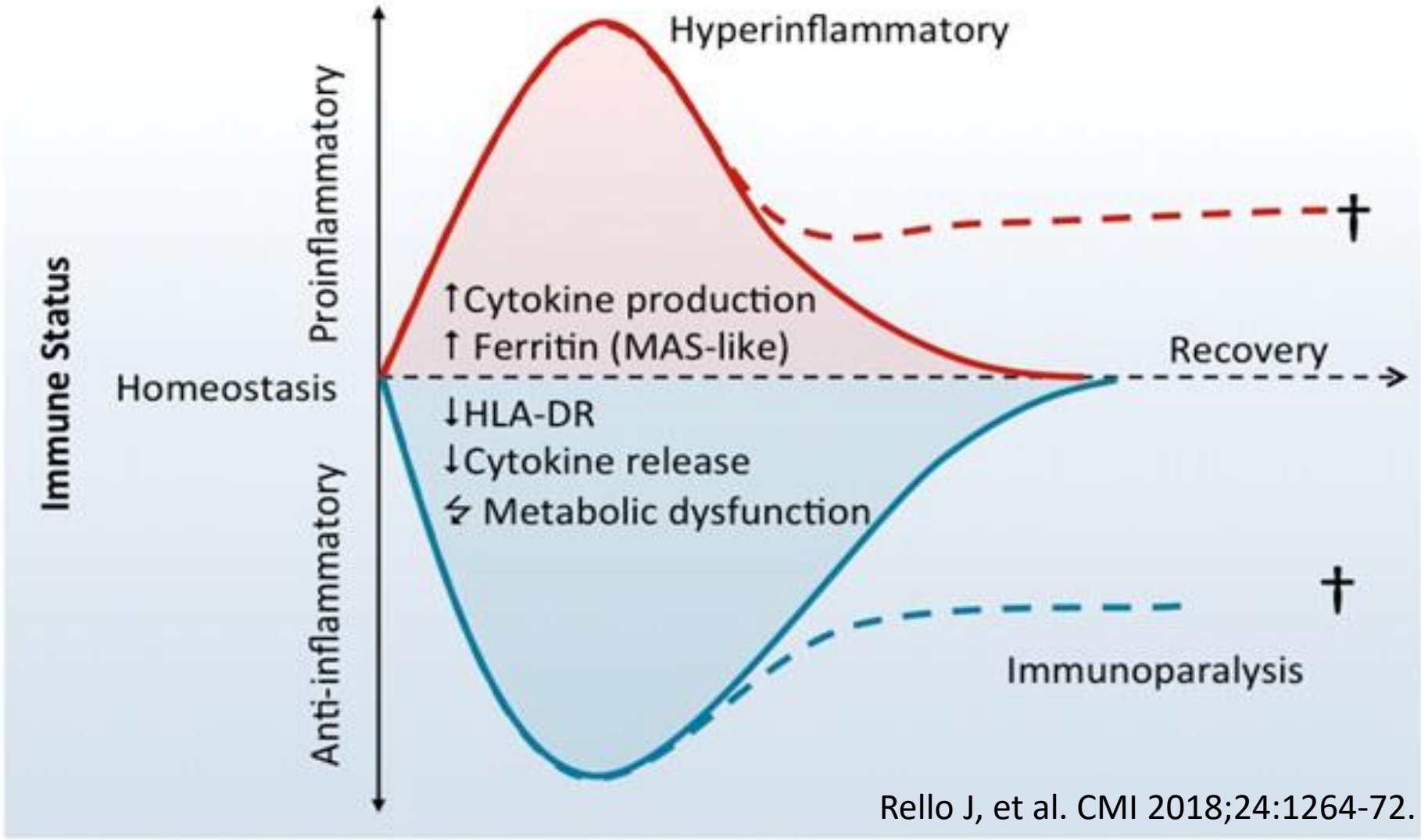
- Transcriptomic technology detects an early sepsis signature.
- First FDA approved test to diagnose sepsis
- Targets: PLCAC8, PLA2G7
- Signature validated with AUC 0.901
- SeptiScore® 0-15 with three Bands
- Outperforms lactate, pro-C and others

Personalized therapy:
CMV in Transplant patients

- This principle has already inspired personalized pre-emptive therapy of cytomegalovirus in kidney transplant patients, using cell-mediated immune assays.

Manuel O, et al. Curr Op Infect Dis 2021;34:307-313.

Sepsis:
Dysregulated Immune Response



Rello J, et al. CMI 2018;24:1264-72.

Innovation priorities in Sepsis

- RDT for sepsis should be POC test delivering phenotypic susceptibility within 30-60 minutes
- Therapy should be targeted to personalized responses
- **Early identification of an aberrant immune activation is the most important unmet clinical need in sepsis**

How succesful to innovate?
Personal vision

- Today’s best … is never quite enough
- Survival of the best
- Creative destruction & benefits it brings people
- Easy experimentation, greater access & trust of the new.

Group culture should keep risk

- Spea
- Cons
- Acad