



PLATFORM OF LABORATORIES FOR ADVANCES IN CARDIAC EXPERIENCE

ROMA

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1 Ottobre
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Sessione: SCOMPENSO ACUTO e SHOCK CARDIOGENO

Sepsi e shock settico: come prevenire, come adattare il monitoraggio e il trattamento e quando curare



Prof. Alessandro Russo

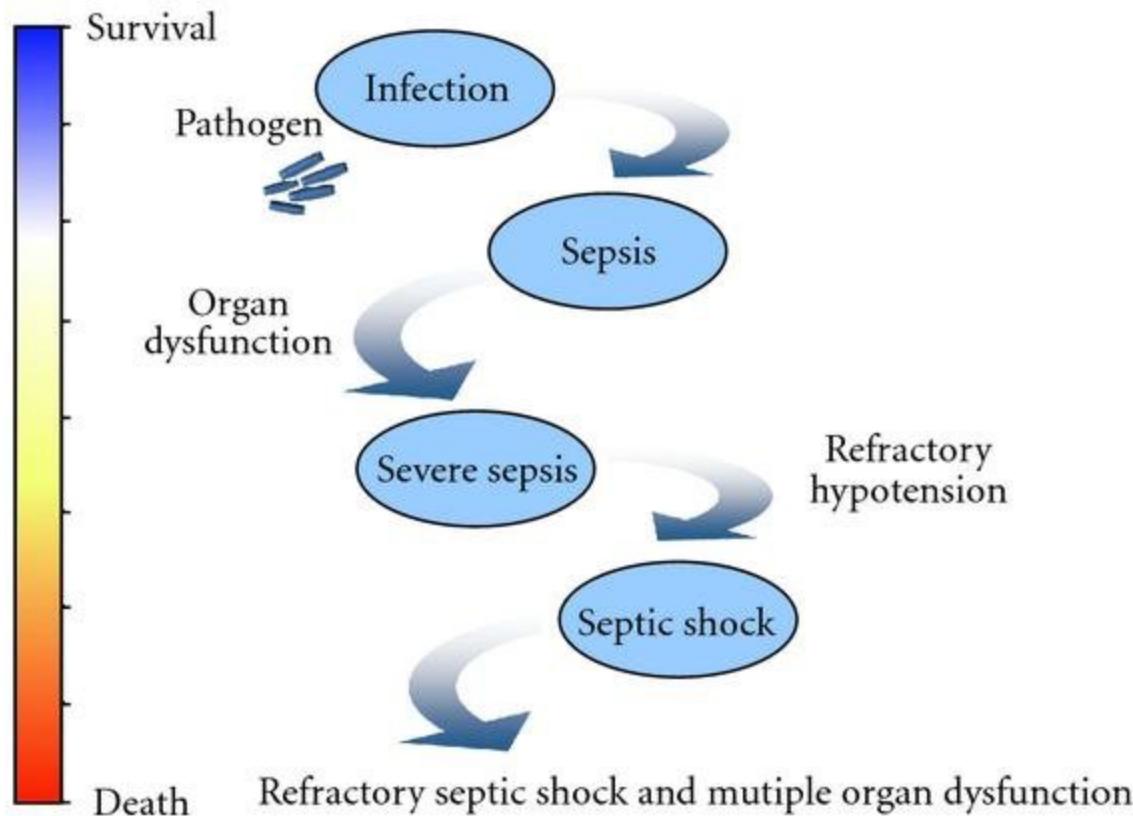
UOC Malattie Infettive e Tropicali

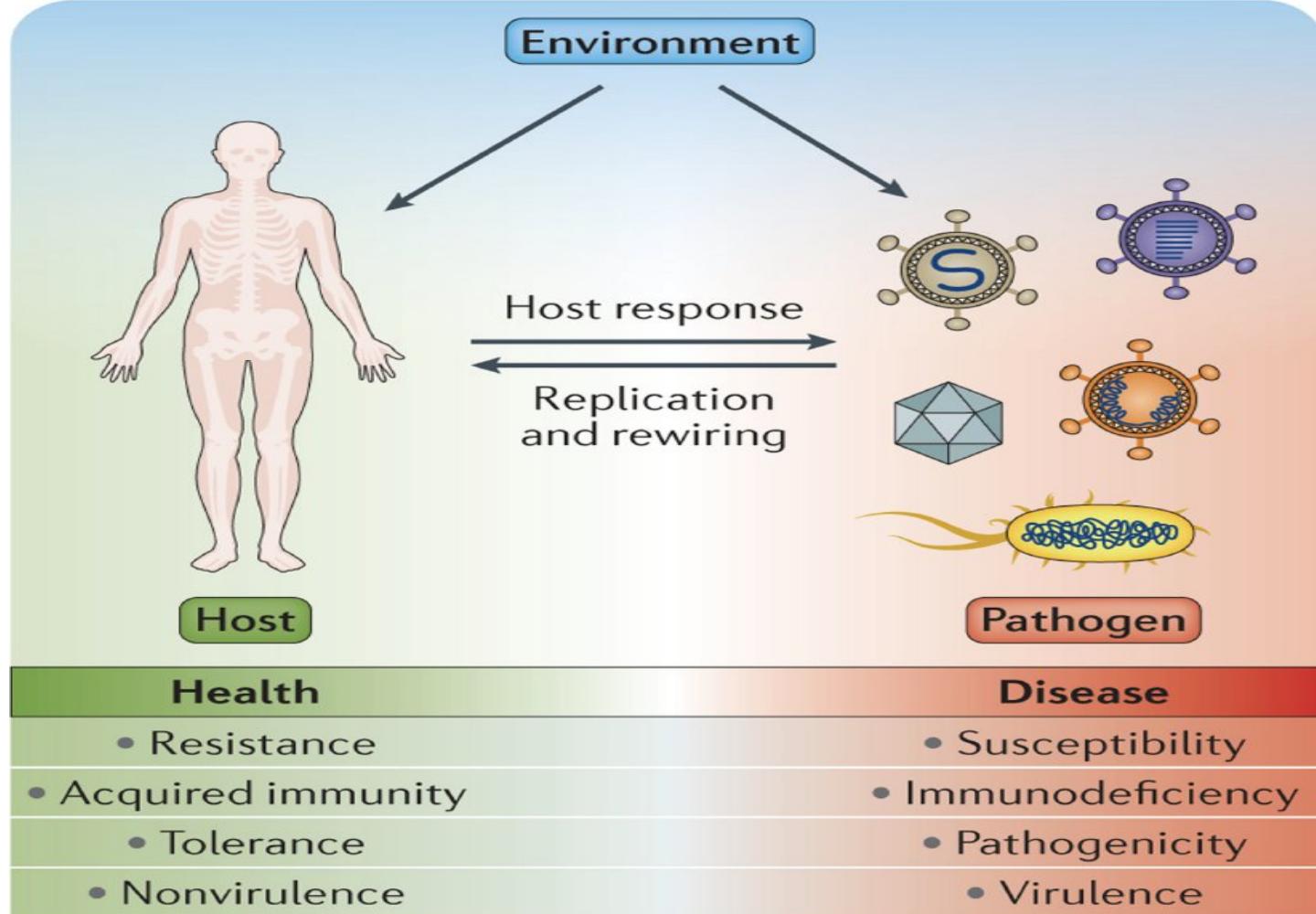
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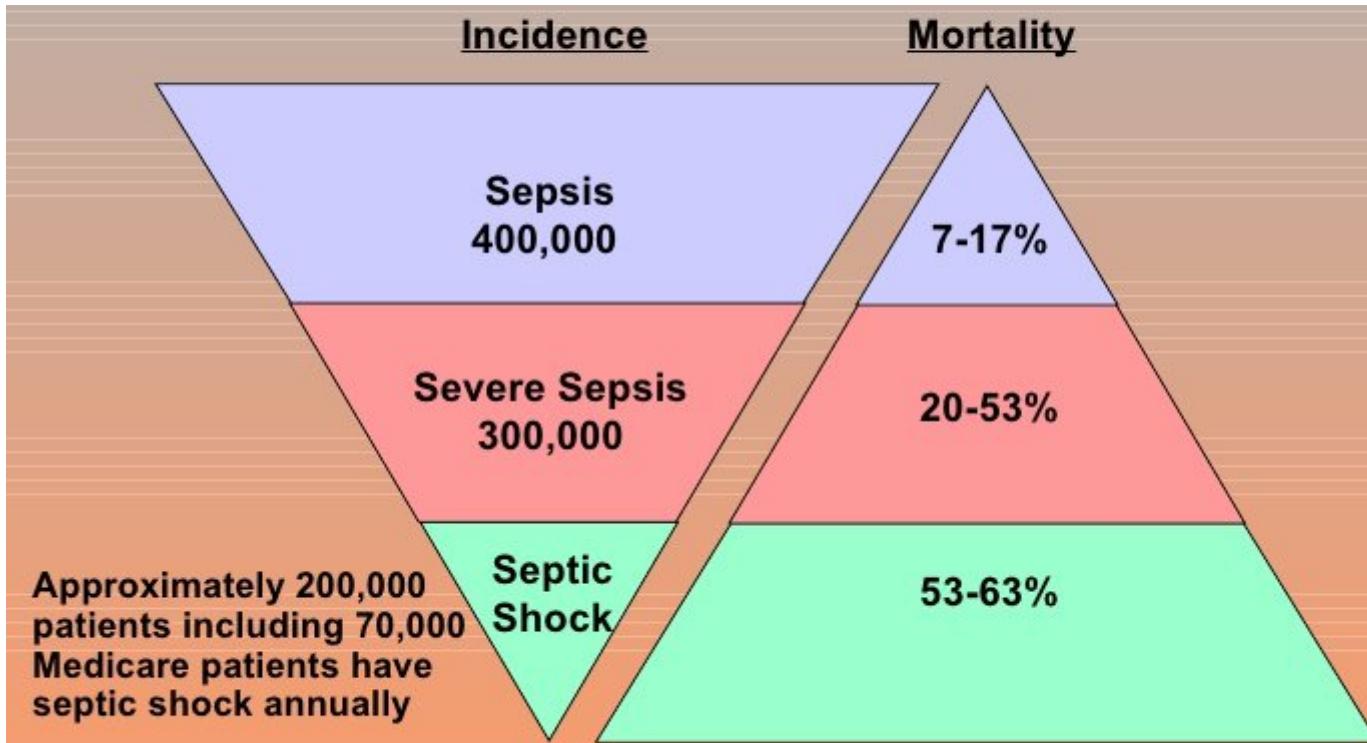


A continuum of severity describing the host systemic inflammatory response

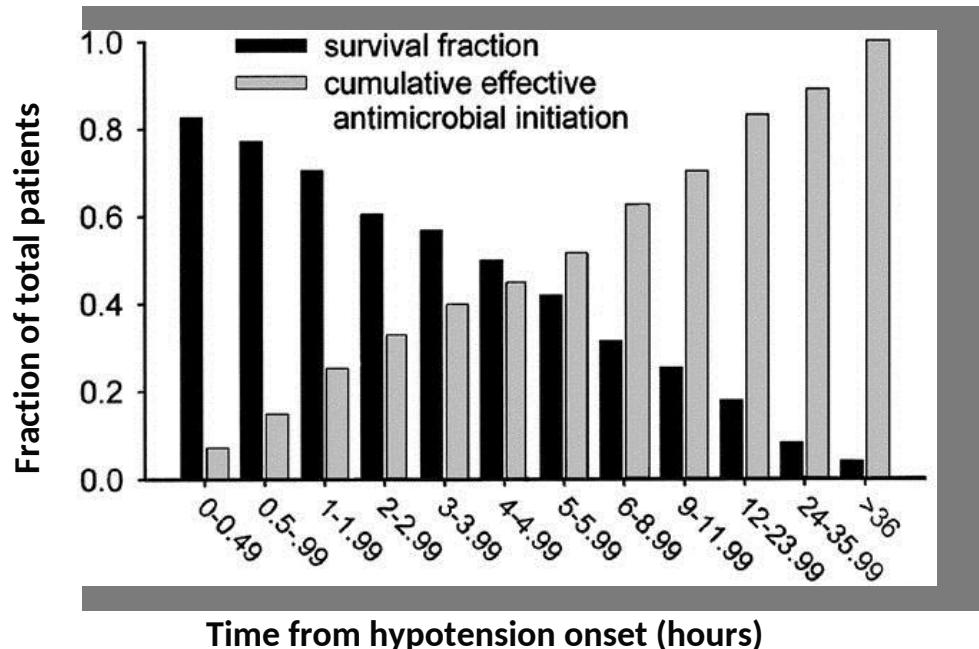




Crude mortality



Effect of timing on survival



De-escalation of empirical therapy is associated with lower mortality in patients with severe sepsis and septic shock

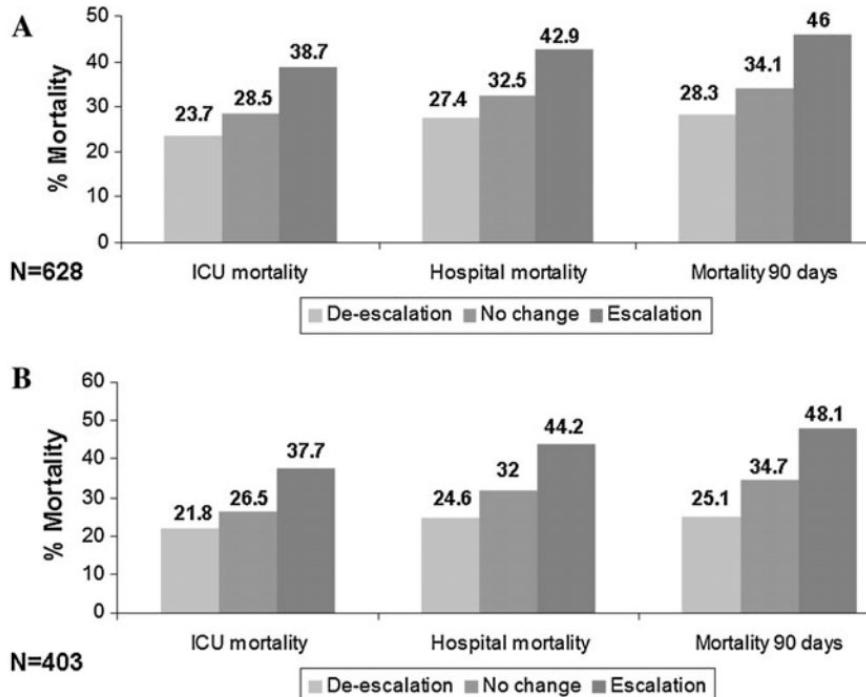


Fig. 1 Mortality rate according to therapeutic strategy: **a** total cohort and **b** patients with adequate empirical antimicrobial therapy

Sepsis in the era of MDR pathogens

Poor clinical condition

Vs

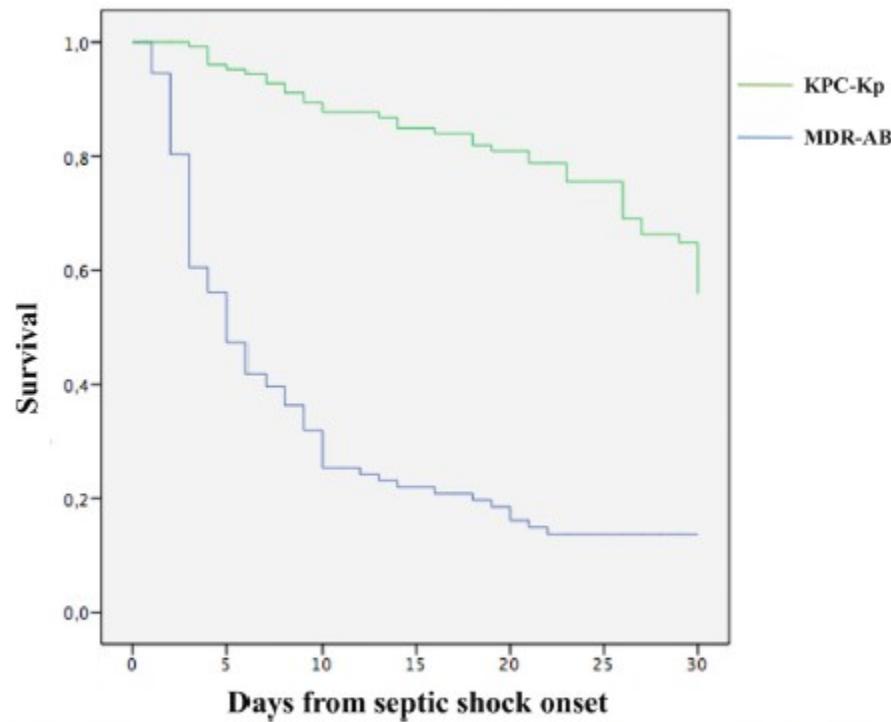
Antibiotic resistant pathogen

ESCAPE

E	<i>Enterococcus faecium</i>	
S	<i>Staphylococcus aureus</i> (MRSA)	
C	<i>Clostridium difficile</i>	→ Acknowledges the growing virulence of <i>C. difficile</i>
A	<i>Acinetobacter baumannii</i>	
P	<i>Pseudomonas aeruginosa</i>	Enterobacteriaceae captures: <i>K.pneumoniae</i> , <i>Enterobacter</i> spp., and other resistant species including <i>Escherichia coli</i> and <i>Proteus</i> spp.
E	<i>Enterobacteriaceae</i>	→



Comparison of Septic Shock Due to Multidrug-Resistant *Acinetobacter baumannii* or *Klebsiella pneumoniae* Carbapenemase-Producing *K. pneumoniae* In Intensive Care Unit Patients



Russo et al. AAC 2018

FIG 1 Kaplan-Meier curves for 30-day survival of KPC-Kp or MDR-AB infections. *, P < 0.001. KPC-Kp, *Klebsiella pneumoniae* carbapenem-resistant *K. pneumoniae*; MDR-AB, multidrug-resistant *Acinetobacter baumannii*.

Bed-side decision

Timing of prescription

Spectrum of causative pathogens

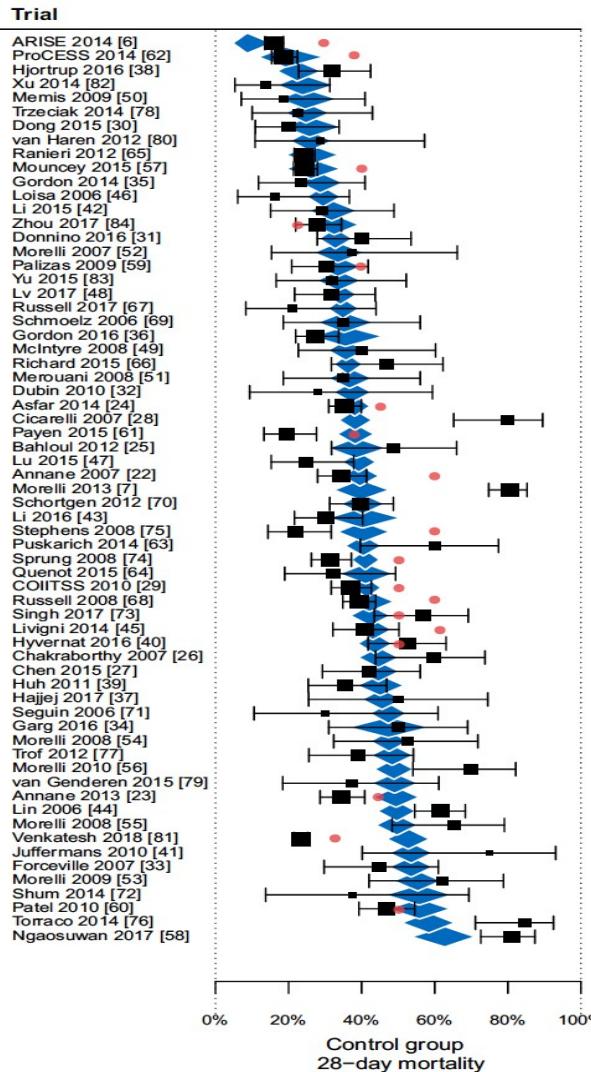
Recognition of risk factors for MDR pathogens

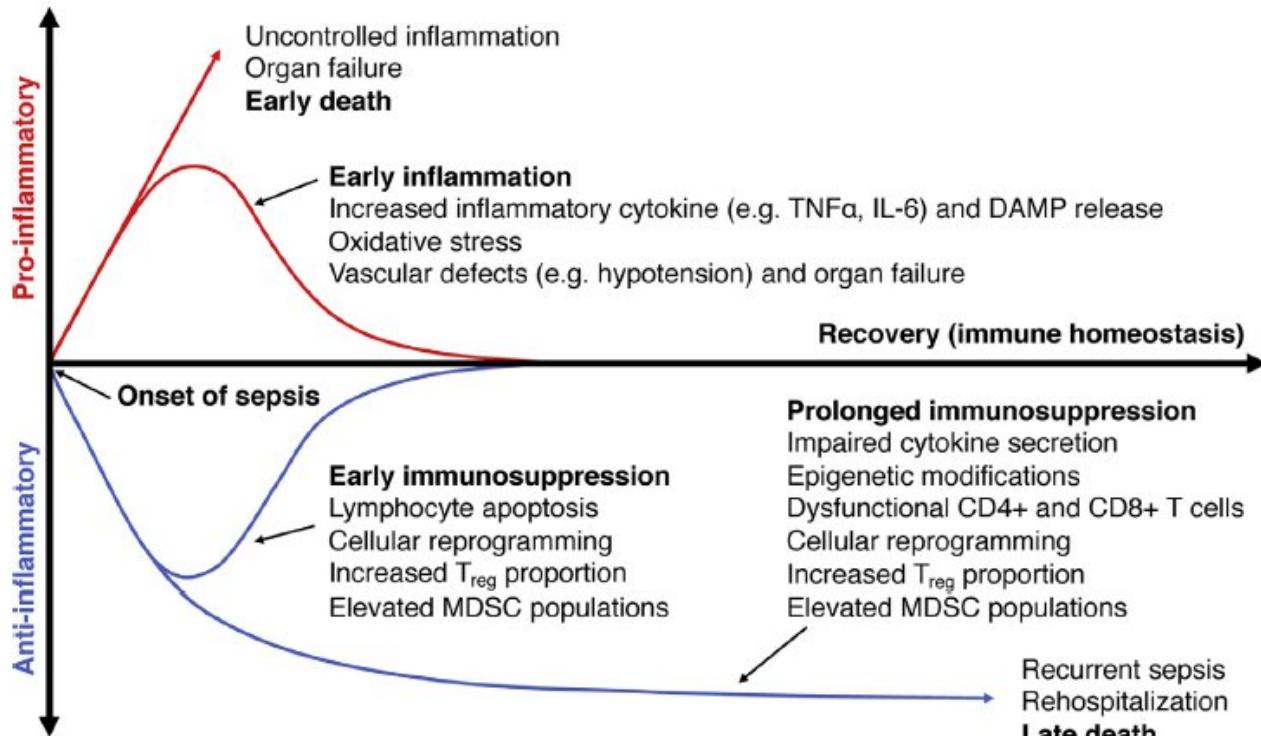
Monotherapy/combination therapy

PK/PD considerations

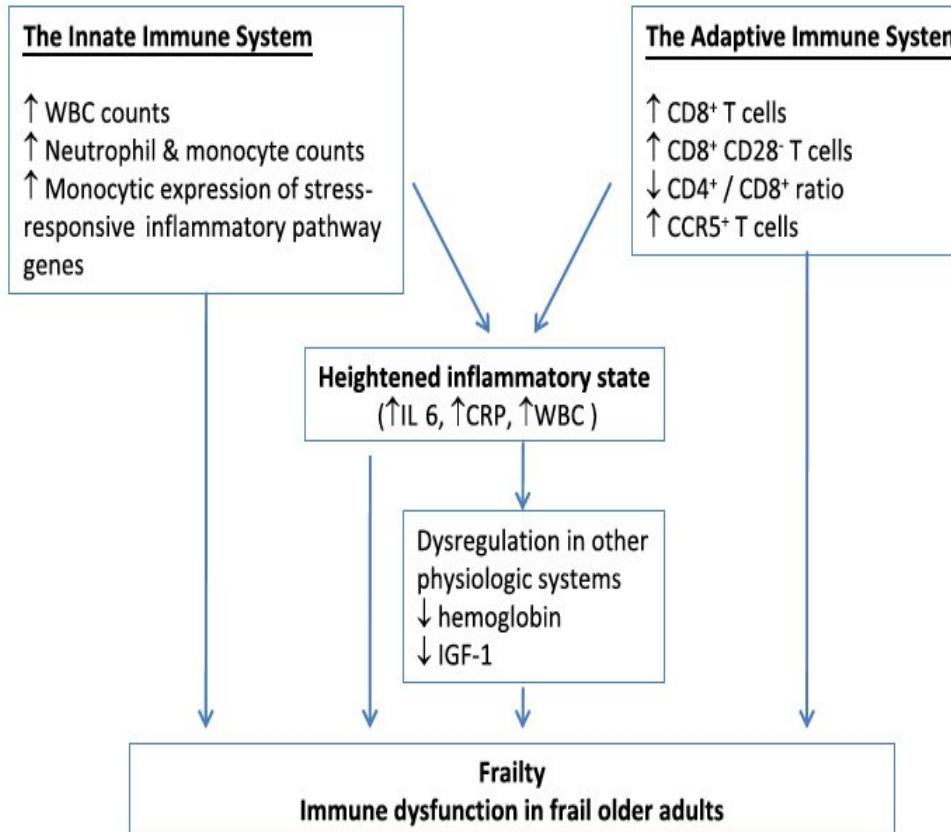
Unexplained mortality differences between septic shock trials: a systematic analysis of population characteristics and control-group mortality rates

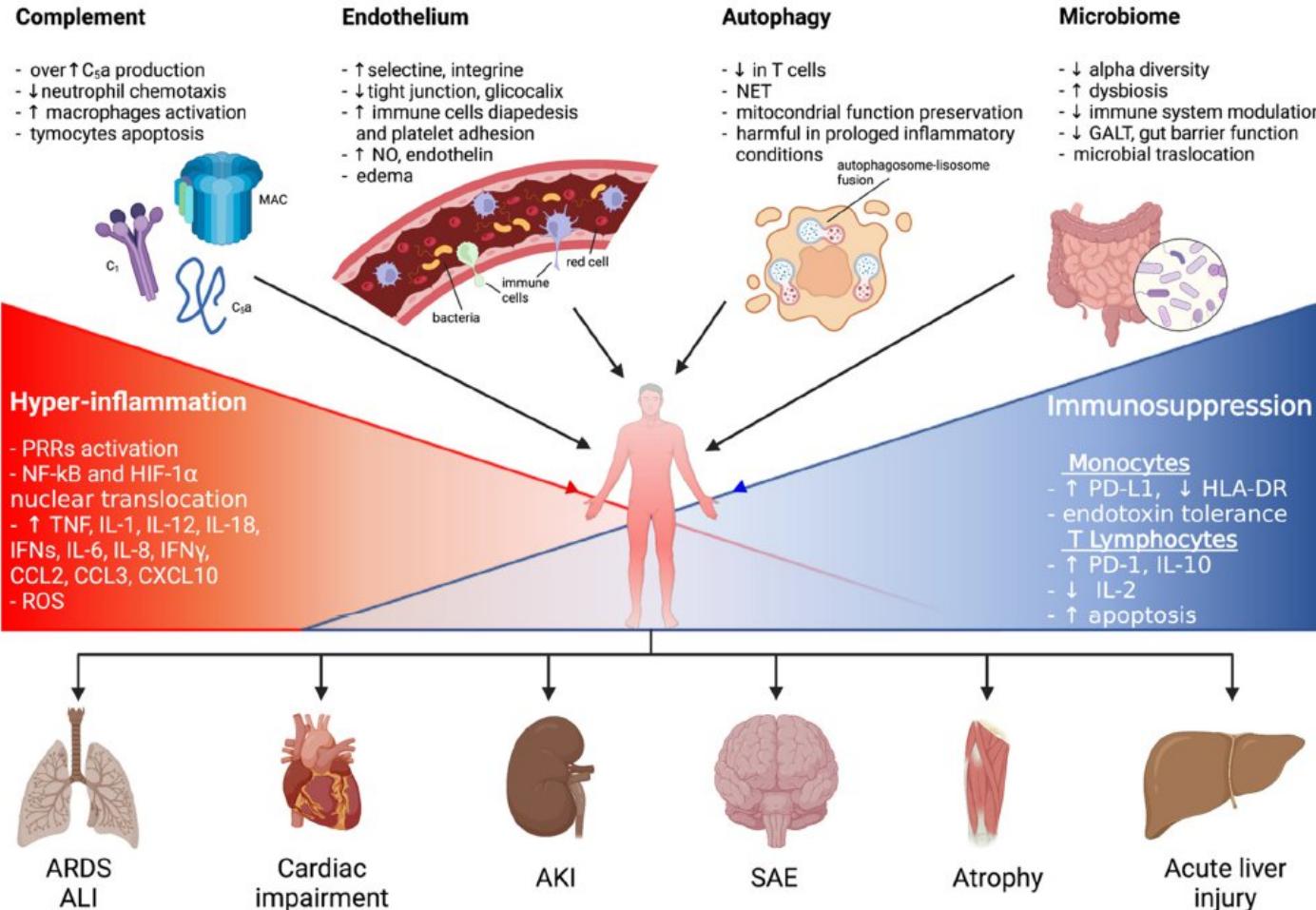
Intensive Care Med (2018) 44:311–322



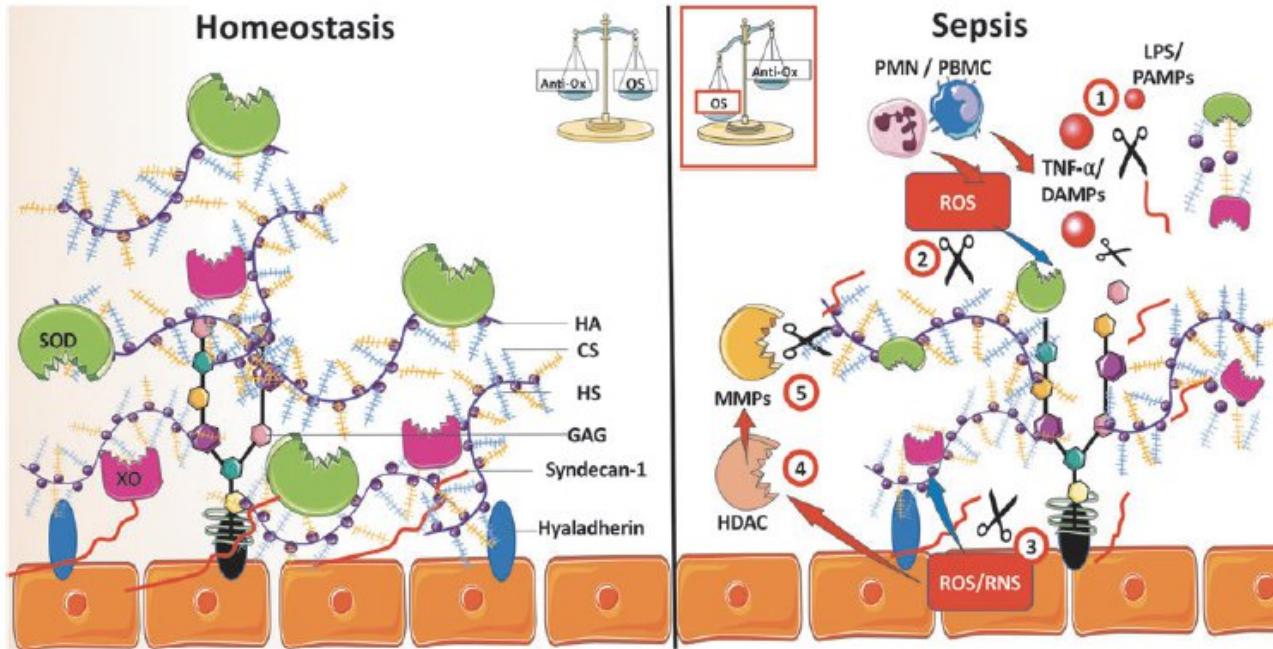


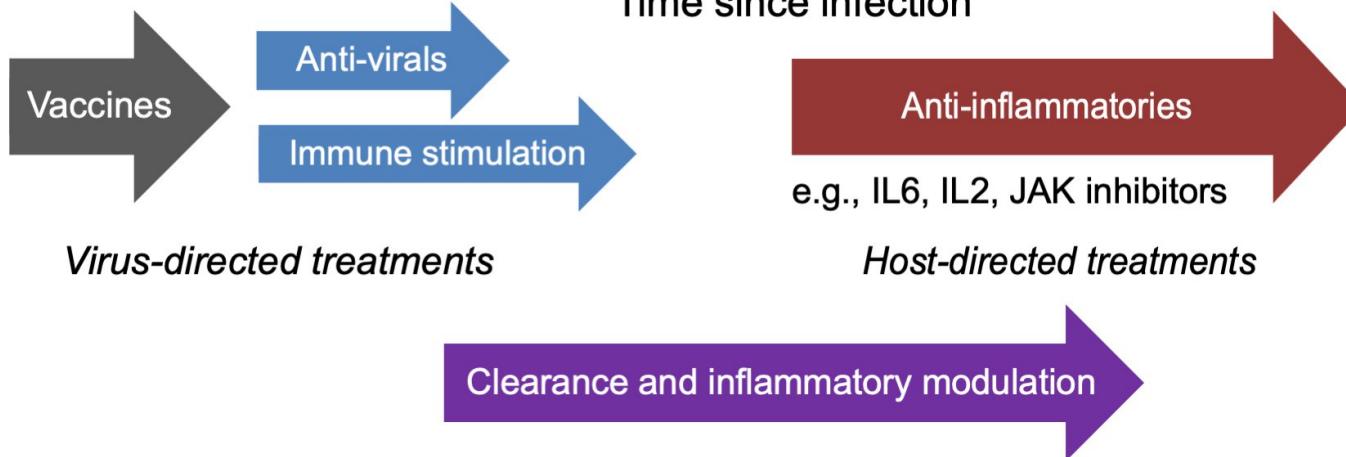
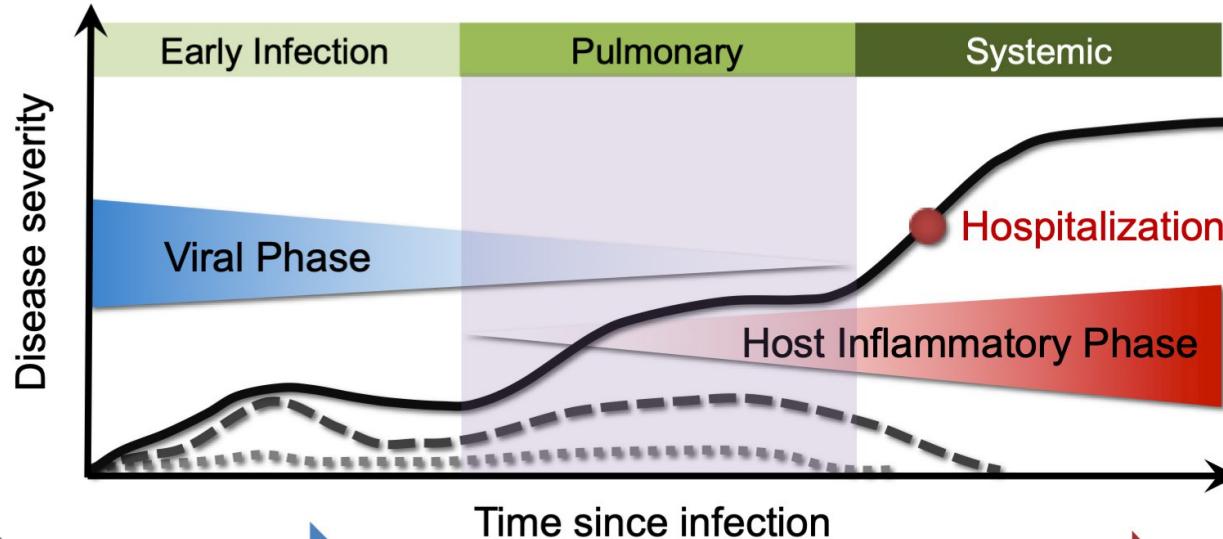
Frail patient and severe infection

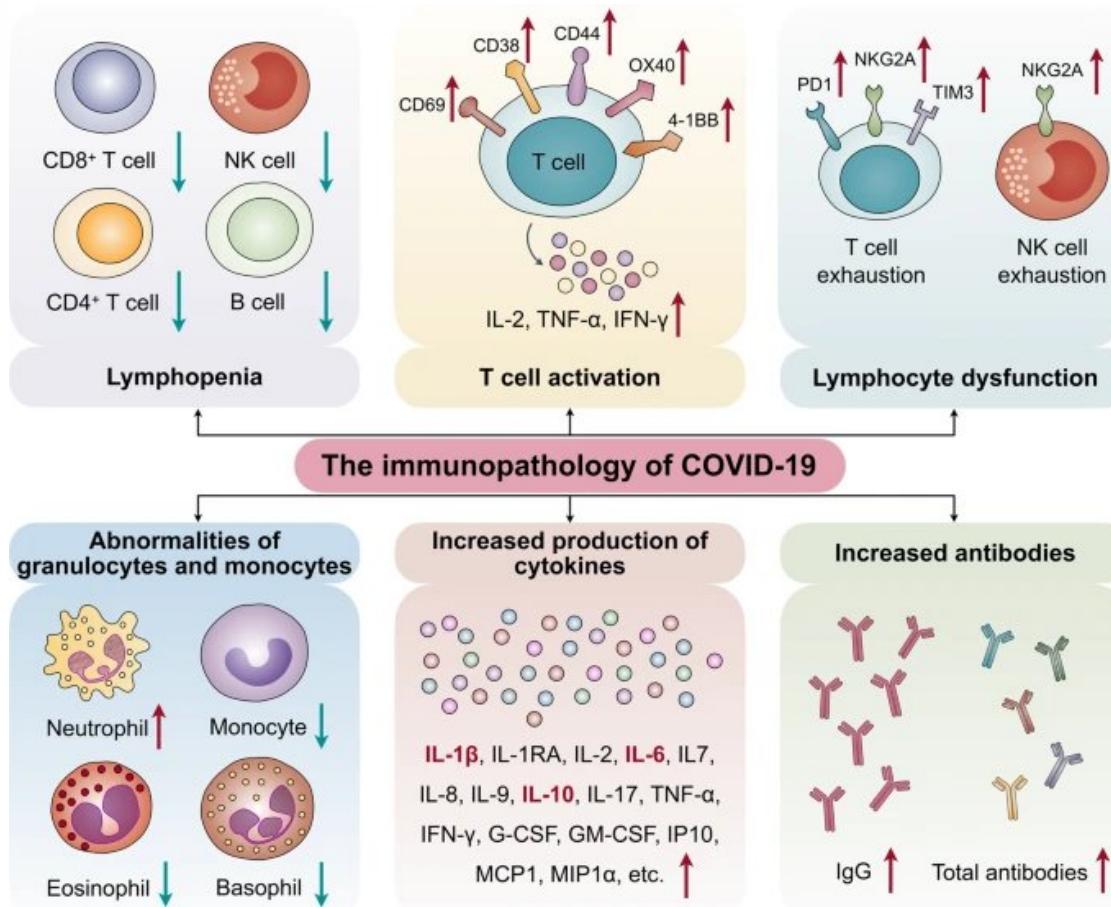


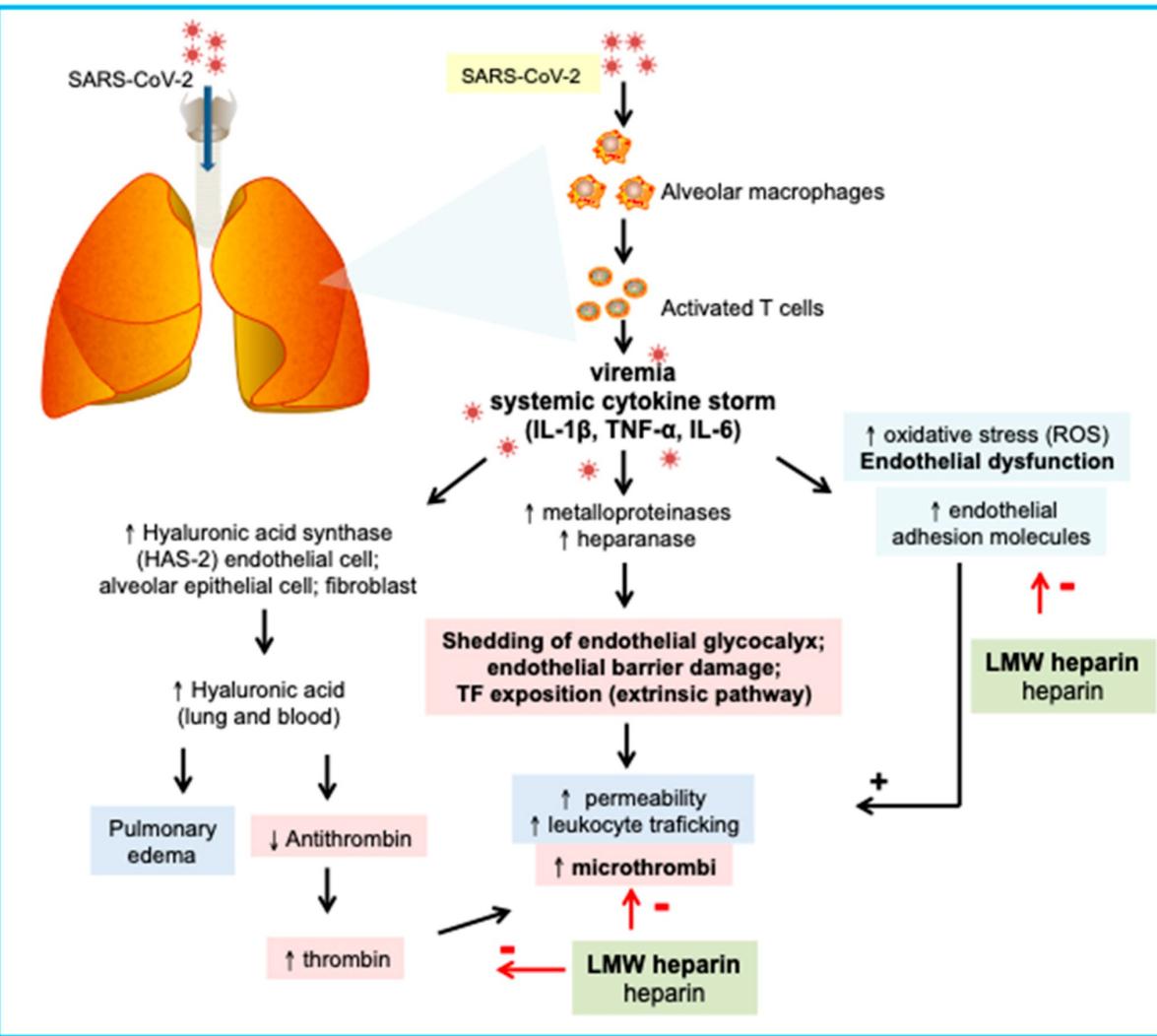


Oxidative Stress and Endothelial Dysfunction in Sepsis and Acute Inflammation





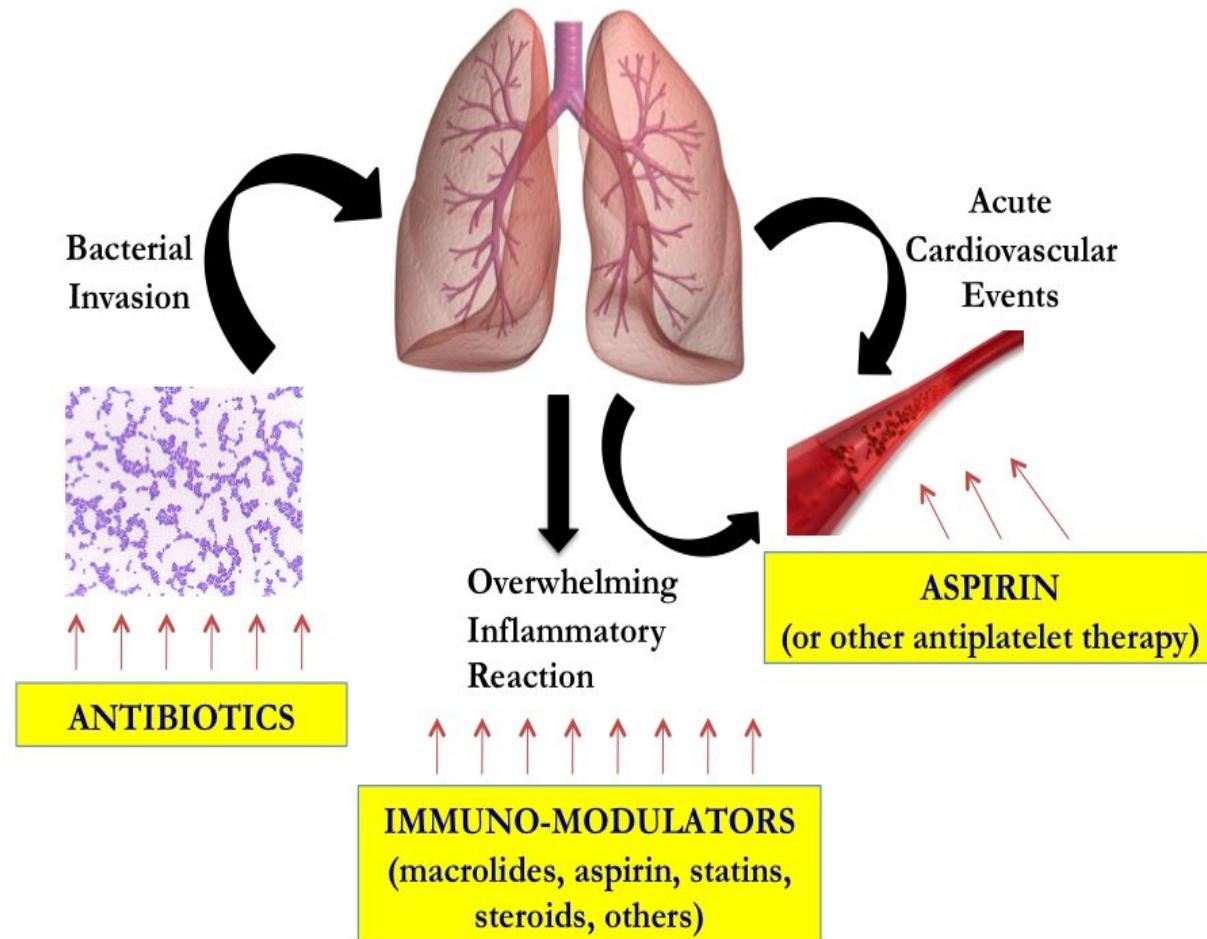




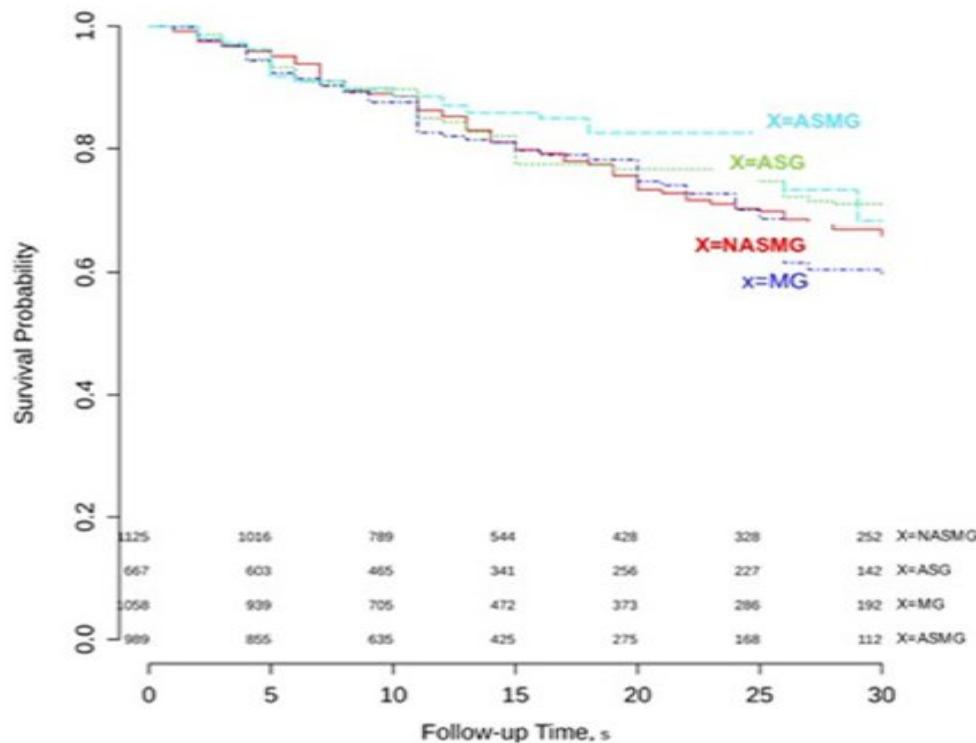


Few definitive data about COVID-19 are available, and all the proposed therapeutic approaches are based on management of 3 crucial points:

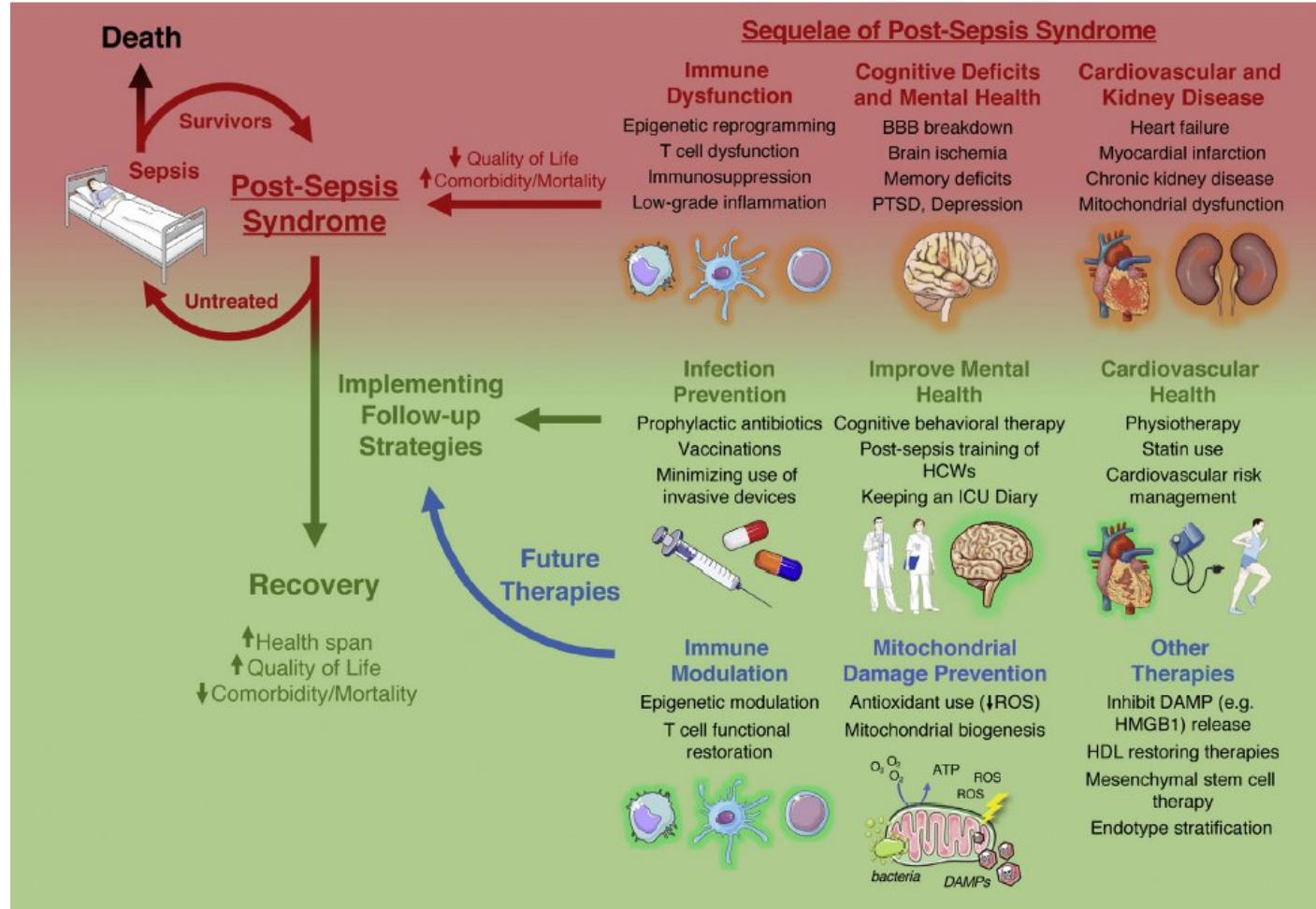
- viral replication and tissue invasion reduction
- abnormal immune response modulation
- systemic thromboembolism prevention



Combination of Aspirin plus Macrolides in Patients with Severe Community-Acquired Pneumonia

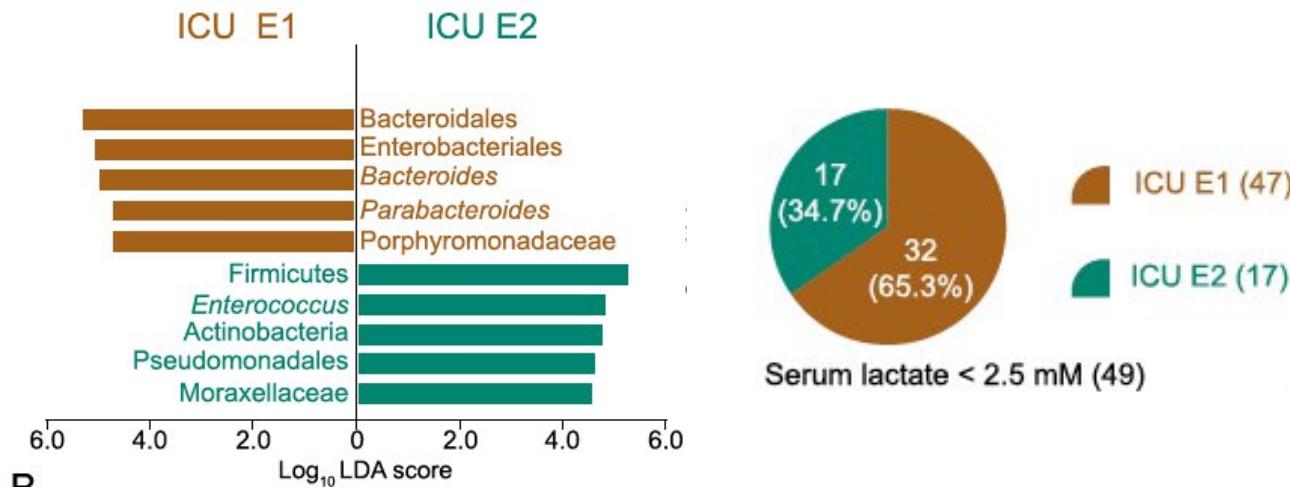


Falcone, Russo et al, AAC 2019



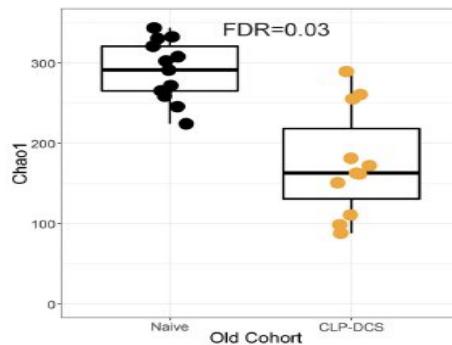
Classification of the Gut Microbiota of Patients in Intensive Care Units During Development of Sepsis and Septic Shock

A

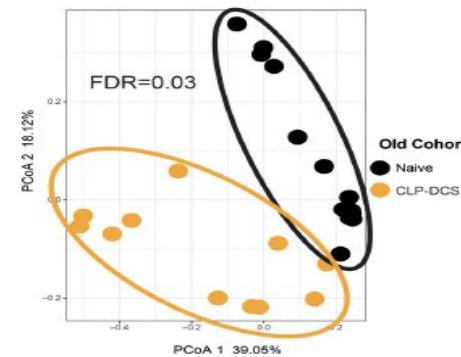


Gut Microbiota in Young Adult Mice Maintains Overall Stability after Sepsis Compared to Old Adult Mice

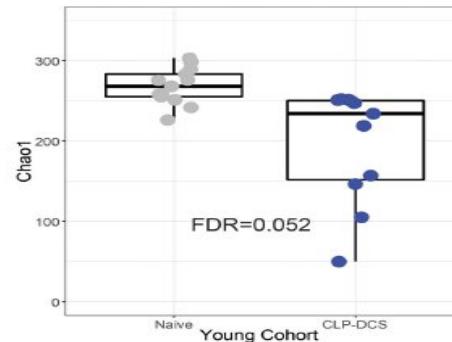
A.



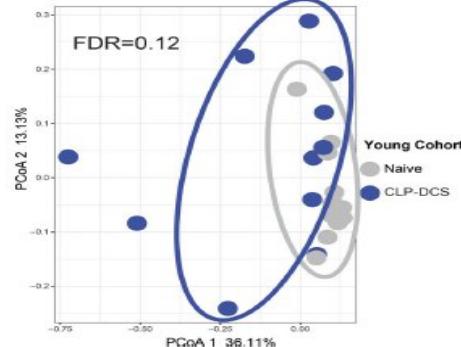
B.



C.



D.



Multidrug-resistant *Acinetobacter baumannii* infections in COVID-19 patients hospitalized in intensive care unit

Table 2 Relative risk* associated or not with MDR-AB infection in patients affected or not by COVID-19

Variables	RR	CI 95%	p value
Previous hospitalization (90 days)	0.4	0.2–0.9	0.031
COPD	0.3	0.1–0.9	0.029
Chronic steroid therapy	0.1	0.0–0.9	0.041
Infection at time of ICU admission	0.1	0.0–0.4	0.001
Serum lactate levels > 2 mmol/l	1.8	1.3–2.5	0.001
<i>Acinetobacter baumannii</i> colonization	7.9	4.0–15.7	<0.001
Bloodstream infection	6.5	3.2–13.5	<0.001
Steroid therapy	18.4	7.6–44.1	<0.001

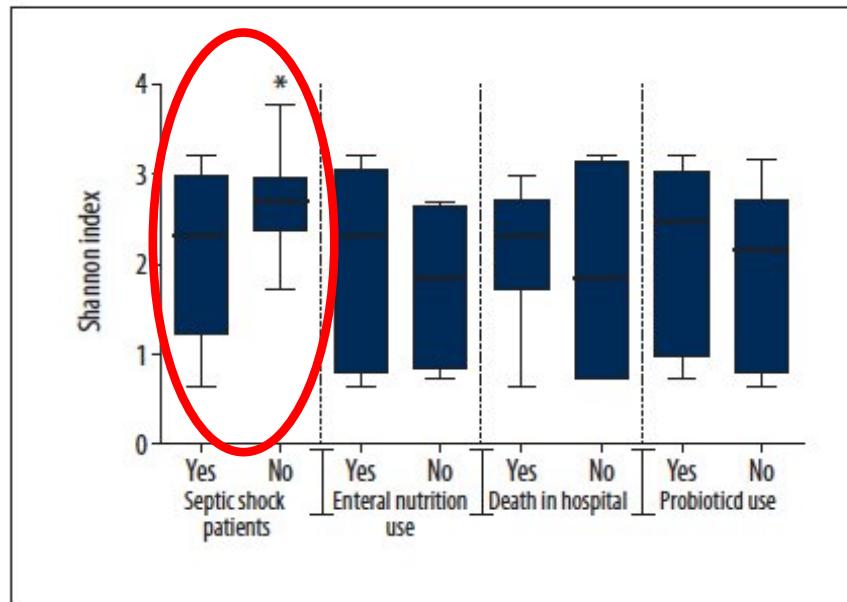
Table 3 Logistic regression analysis about risk factors associated with 30-days mortality

Variables	OR	CI 95%	p value
Serum lactate levels > 2 mmol/l	4.9	2.1–11.3	<0.001
<i>Acinetobacter baumannii</i> colonization	17.1	5.5–53.3	<0.001
Bloodstream infection	13.6	4.8–38.2	<0.001
Steroid therapy	46.9	13.9–157.5	<0.001

Table 5 Multivariate analysis about risk factors associated with development of bloodstream infection

Variables	OR	CI 95%	p value
Severe COVID-19	15.1	3.7–40.1	<0.001
WBC > 11,000 mm ³	5.2	2.1–11.5	<0.001
Serum lactate levels > 2 mmol/l	2.7	1.2–6.4	0.022
Infection at time of ICU admission	0.4	0.2–1	0.030
<i>Acinetobacter baumannii</i> colonization	4.8	1.9–12.1	<0.001
Steroid therapy	8.8	3.5–22.1	<0.001

Gut Microbiota Disruption in Septic Shock Patients



Appropriateness

STEP 1: The best drug

STEP 2: Alone or in combination?

STEP 3: Optimal dosage

STEP 4: De-escalate and stop therapy

Key issues for empirical antibiotic therapy

Site of infection

- Lung
- Urinary tract
- Abdomen
- Bloodstream infection

Type of infection

- Monomicrobial
- Polymicrobial
- Fungal infection

- Community acquired
- HC associated
- Nosocomial acquired

Severity of the infection

- Hematological patients
- Unstable patients
- With high severity score

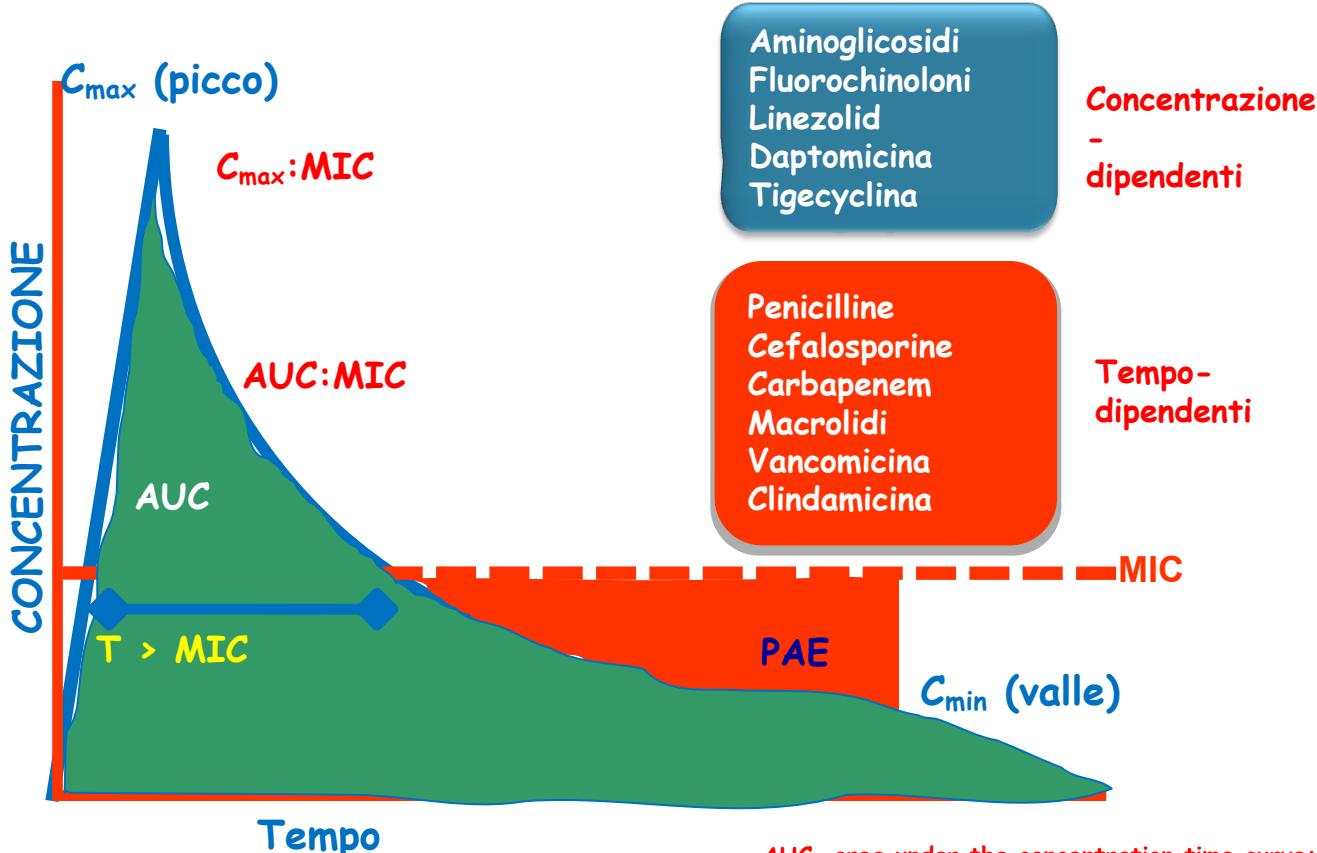
Comorbidities

- Age > 70 years
- Diabetes
- Charlson index > 3
- Use of corticosteroids
- COPD
- Renal impairment

Risk of resistance

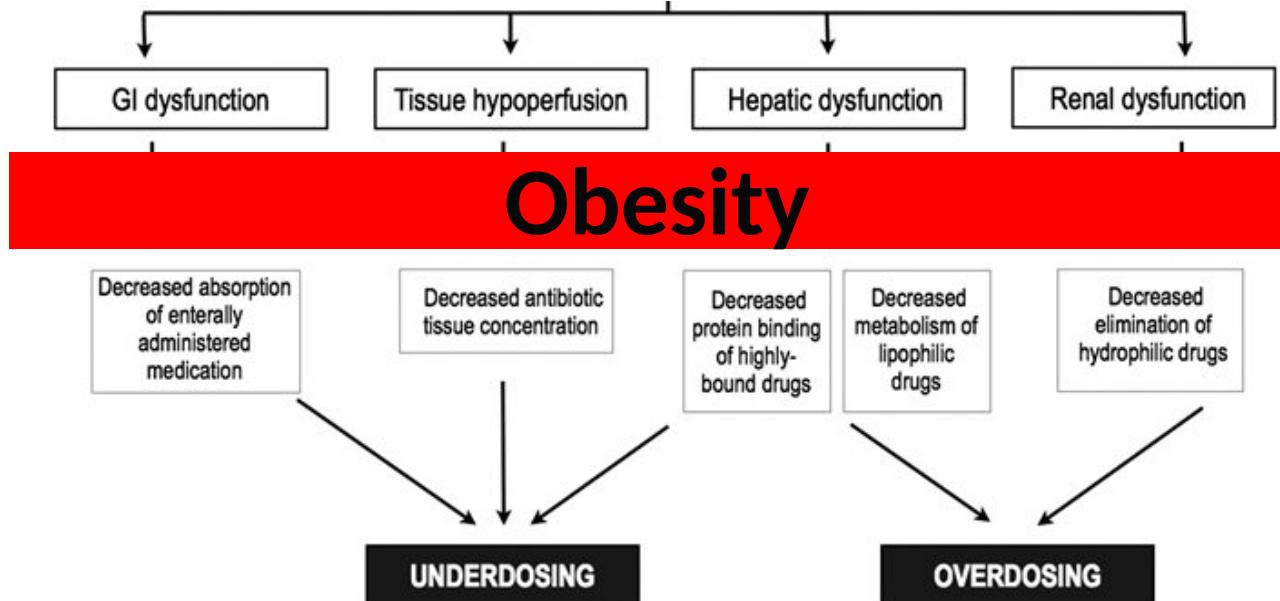
- Previous antibiotic therapy
- Recent hospitalization
- Local epidemiology
- Indwelling devices

Esposizione ottimale agli antibiotici: PARAMETRI PK/PD

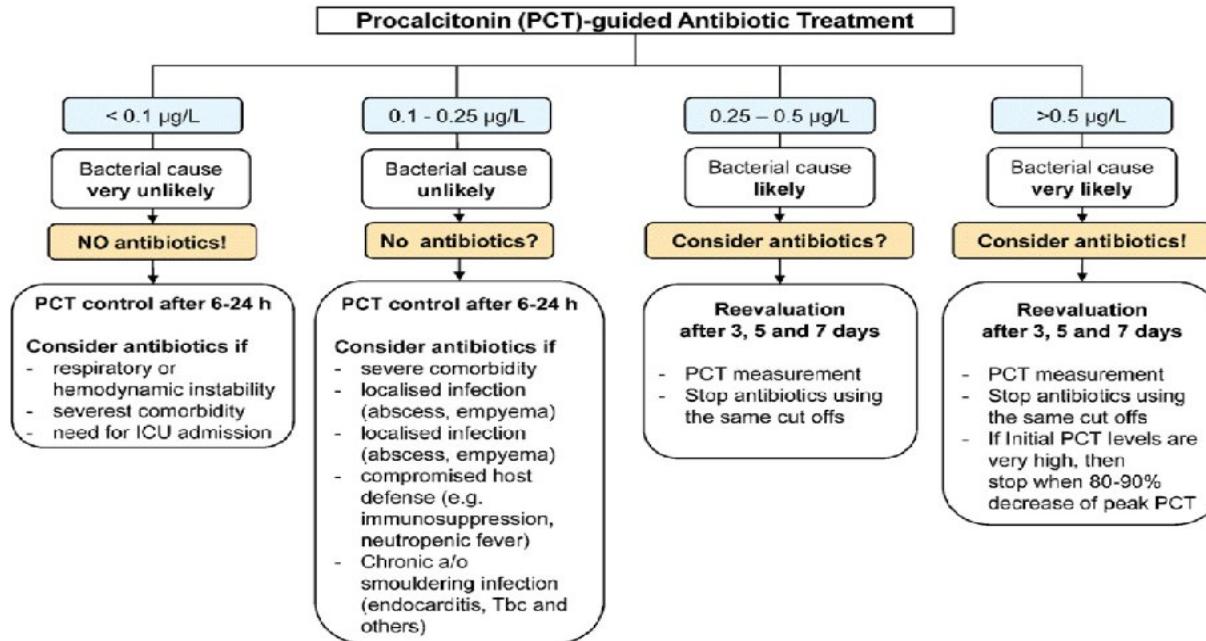


AUC, area under the concentration-time curve;
PAE, post-antibiotic effect..
Rybak MJ. Am J Med. 2006;119:S37-S44.

Implications of antibiotic PK



Procalcitonin

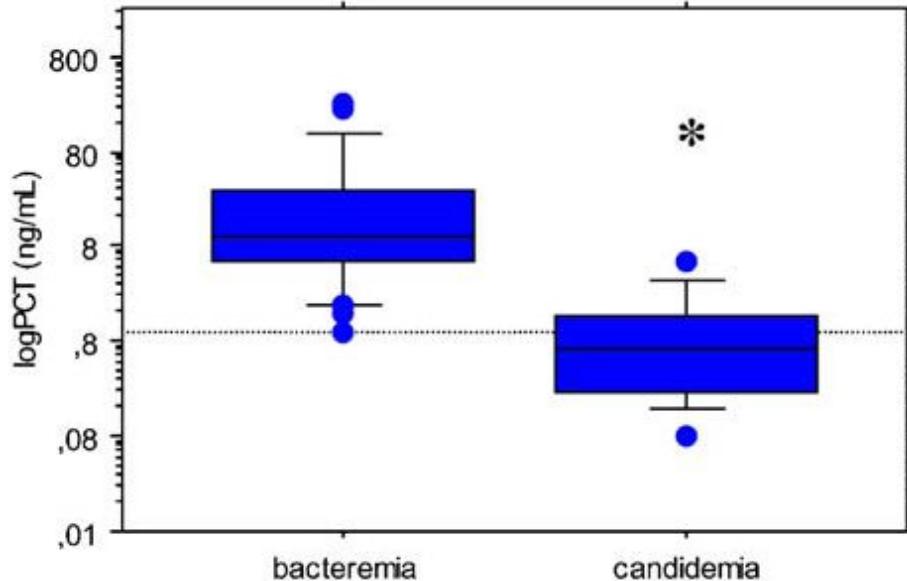


	Procalcitonin-guided group (n=761)	Standard-of-care group (n=785)	Between-group absolute difference in means (95% CI)	p value
Antibiotic consumption (days)				
Daily defined doses in first 28 days	7.5 (4.0 to 12.8)	9.3 (5.0 to 16.5)	2.69 (1.26 to 4.12)	<0.0001
Duration of treatment	5.0 (3.0 to 9.0)	7.0 (4.0 to 11.0)	1.22 (0.65 to 1.78)	<0.0001
Antibiotic-free days in first 28 days	7.0 (0.0 to 14.5)	5.0 (0 to 13.0)	1.31 (0.52 to 2.09)	0.0016
Mortality (%)				
28-day mortality	149 (19.6%)	196 (25.0%)	5.4% (1.2 to 9.5)	0.0122
1-year mortality	265 (34.8%)	321 (40.9%)	6.1% (1.2 to 10.9)	0.0158
Adverse events				
Reinfection	38 (5.0)	23 (2.9)	-2.1% (-4.1 to -0.1)	0.0492
Repeated course of antibiotics	175 (23.0)	173 (22.0)	-1.0% (-5.1 to 3.2)	0.67
Time (days) between stop and reinstitution of antibiotics	4.0 (2.0 to 8.0)	4.0 (2.0 to 8.0)	-0.22 (-1.31 to 0.88)	0.96
Costs				
Total cumulative costs of antibiotics	€150 082	€181 263	NA	NA
Median cumulative costs antibiotics per patient	€107 (51 to 229)	€129 (66 to 273)	€33.6 (2.5 to 64.8)	0.0006
Length of stay (days)				
On the intensive care unit	8.5 (5.0 to 17.0)	9.0 (4.0 to 17.0)	-0.21 (-0.92 to 1.60)	0.56
In hospital	22.0 (13.0 to 39.3)	22.0 (12.0 to 40.0)	0.39 (-2.69 to 3.46)	0.77

Data are median (IQR), n (%), or mean (95% CI). Between-group absolute differences were calculated using the mean values, percentage differences, and 95% CIs.
NA=not applicable.

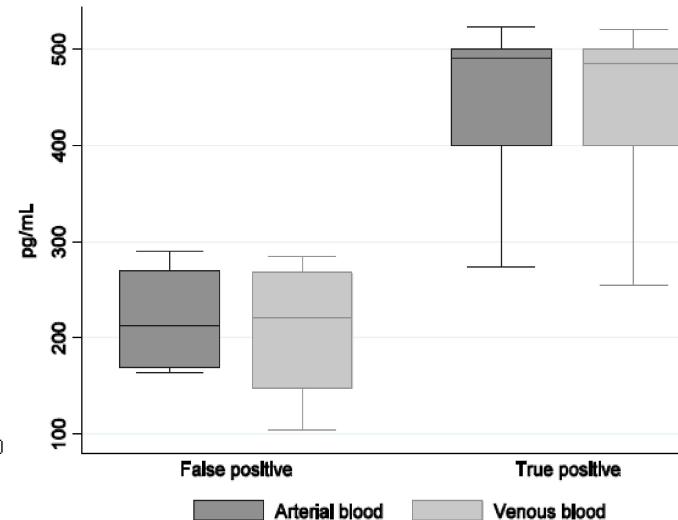
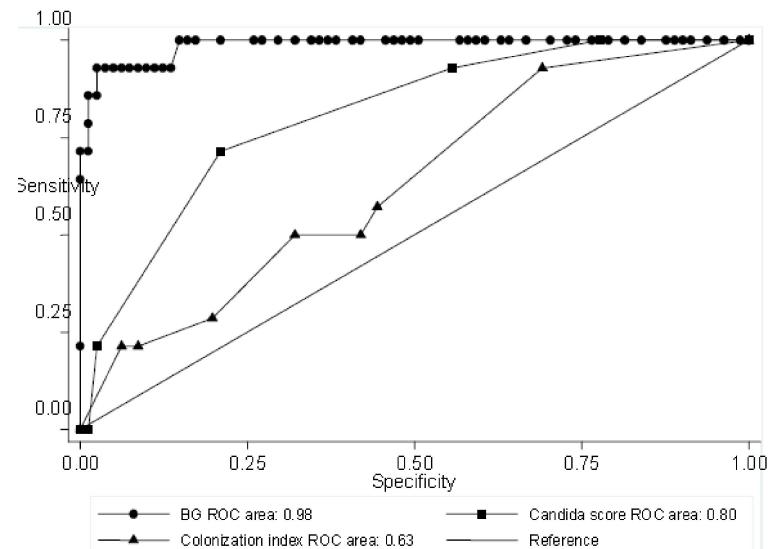
Serum procalcitonin measurement contribution to the early diagnosis of candidemia in critically ill patients

Charles E et al *Intensive Care Med* (2006) 32:1577–1583



Early diagnosis of candidemia in ICU patients with sepsis: a prospective comparison of (1[®] 3)-b-D-glucan assay, Candida score, and colonization index

Posteraro B, Antonelli M, Tumbarello M, ..& Sanguinetti M *Crit Care Med*, 2012



Early antibiotic therapy: the critical balance

Table 1 Rules for management of antibiotic therapy in patients with suspected or proven infection in emergency department

Restrict or avoid early antibiotic therapy, except for sepsis/septic shock and meningitis

Differentiate infection from colonization: request all adequate microbiological samples

Use non-culture-based diagnostics and biomarkers for early detection of infection

Call infectious diseases consultant for challenging clinical cases

Promote early antibiotic treatment only based on risk factors and biomarkers

Get treatment right the first time with appropriate drugs

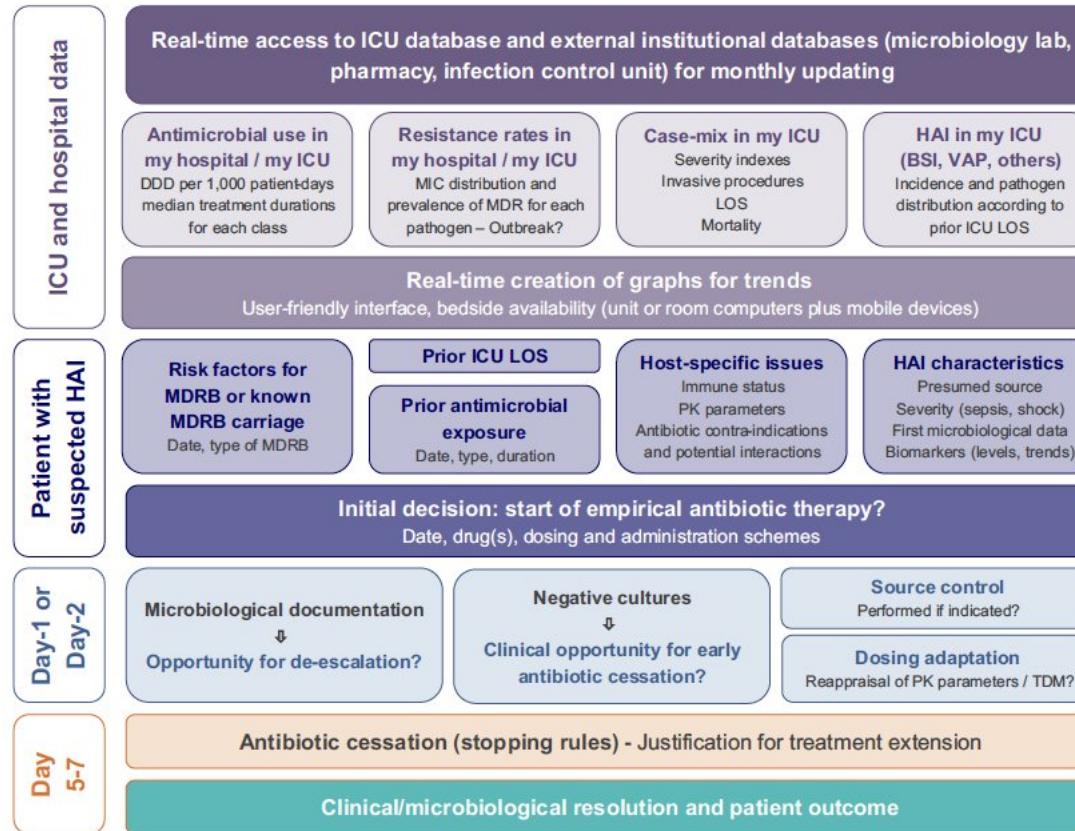
Provide adequate support of septic shock

Have adequate source control as soon as possible (i.e., catheter removal, appropriate drainage, surgical control)

Check for clinical improvement after 48–72 h: clinical stability, biomarkers, negative follow-up cultures

Stop early useless therapy and check duration of therapy

Personalized empiric antibiotic therapy



Not the least expensive drug
BUT
The best drug

KNOW YOUR
“MICROBIOLOGICAL” REALITY



How to manage septic shock?

- Cover most frequent pathogens
- Measure the risk for MDR
- Avoid induction/selection of antibiotic resistance
- Reduce the systemic inflammatory response to infection
- Reduce complications (i.e. cardiovascular)
- Therapeutic drug monitoring
- Early switch to oral therapy
- Decide the optimal duration of antibiotic therapy

Systemic approach for severe infections

- In the era of MDR pathogens an individualized approach to severe infection is mandatory
- Comorbidities, biomarkers and knowledge of genetic factors may allow transition from generalizing sepsis care bundles to a more tailored management in individual patients thereby reducing the risk for adverse treatment outcomes in patients who do not likely benefit from therapy.
- COVID-19 represents a model of systemic severe infection
- Autophagy and “precision medicine” are the new frontiers?

