



XIII congresso nazionale

simeu

GENOVA 30 MAG - 1 GIU 2024



SEPS

I
Hot
Topics

Mario Calci

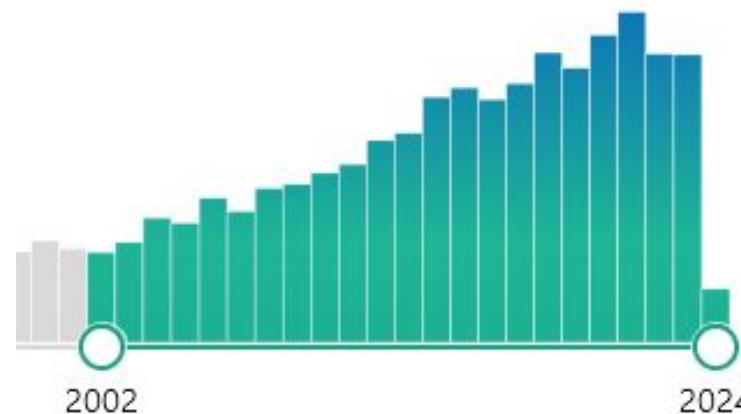
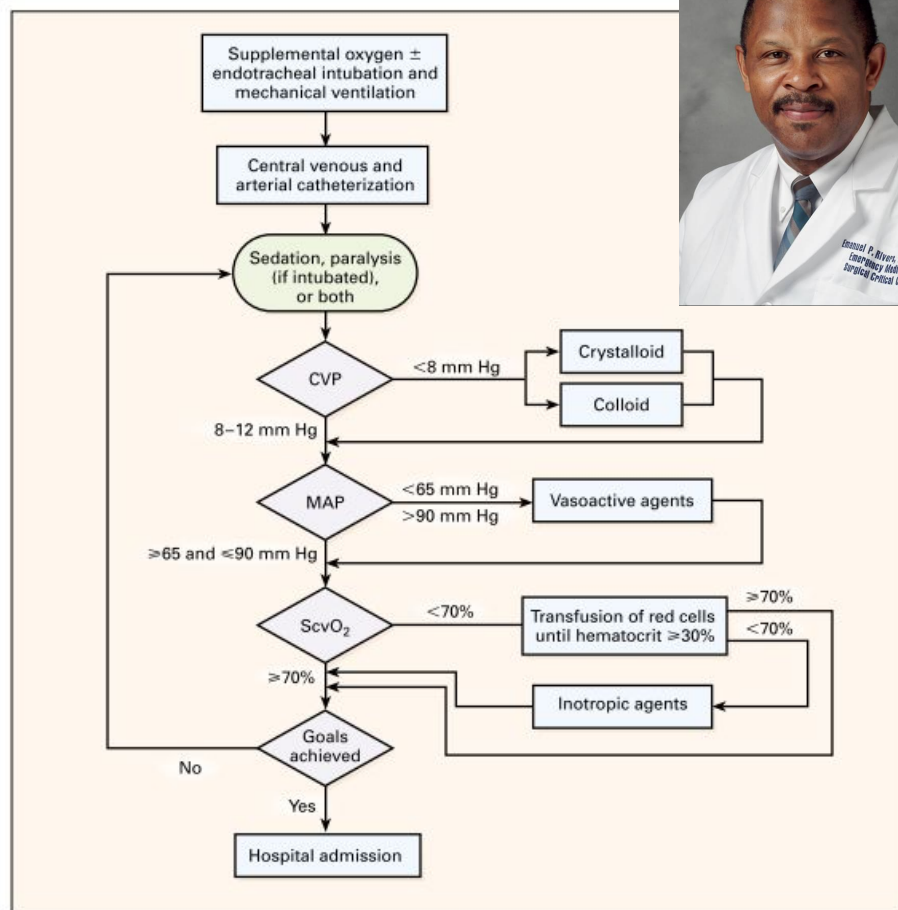
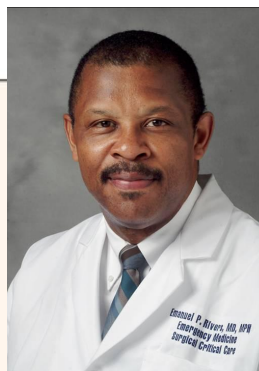


COLD CASE



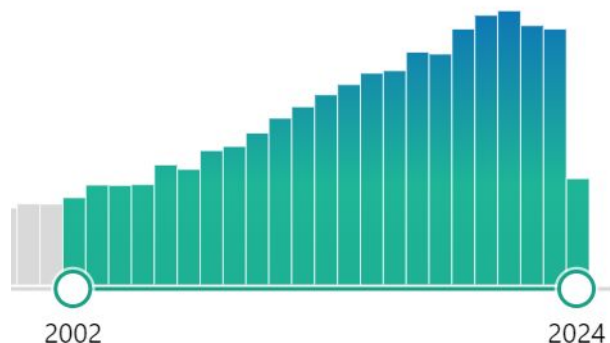
EARLY GOAL-DIRECTED THERAPY IN THE TREATMENT OF SEVERE SEPSIS AND SEPTIC SHOCK

EMANUEL RIVERS, M.D., M.P.H., BRYANT NGUYEN, M.D., SUZANNE HAVSTAD, M.A., JULIE RESSLER, B.S.,
ALEXANDRIA MUZZIN, B.S., BERNHARD KNOBLICH, M.D., EDWARD PETERSON, PH.D., AND MICHAEL TOMLANOVICH, M.D.,
FOR THE EARLY GOAL-DIRECTED THERAPY COLLABORATIVE GROUP*



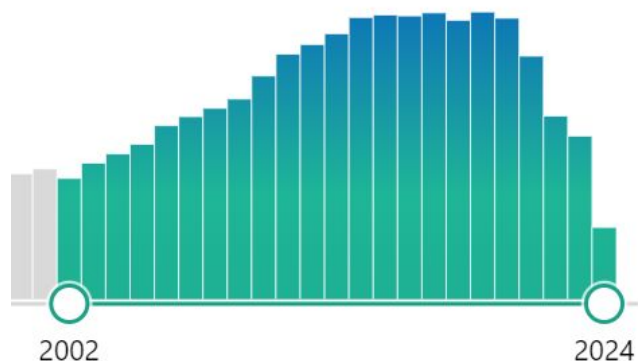
((Sepsis) OR (septic shock)) AND
fluid

**9.970
articoli**



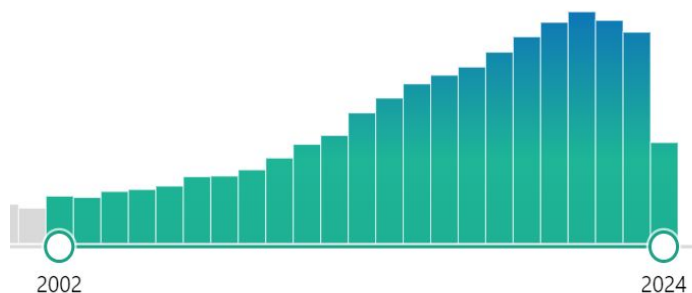
((SEPSIS) OR (SEPTIC SHOCK)) AND
(ANTIBIOTIC)

31.077
articoli



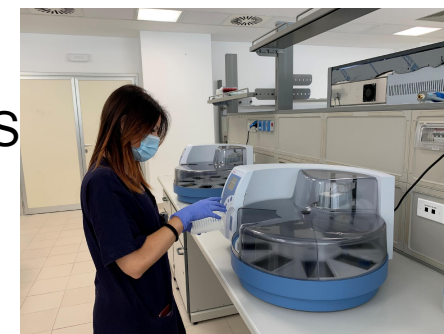
((SEPSIS) OR (SEPTIC SHOCK)) AND
(MICROBIOLOGY)

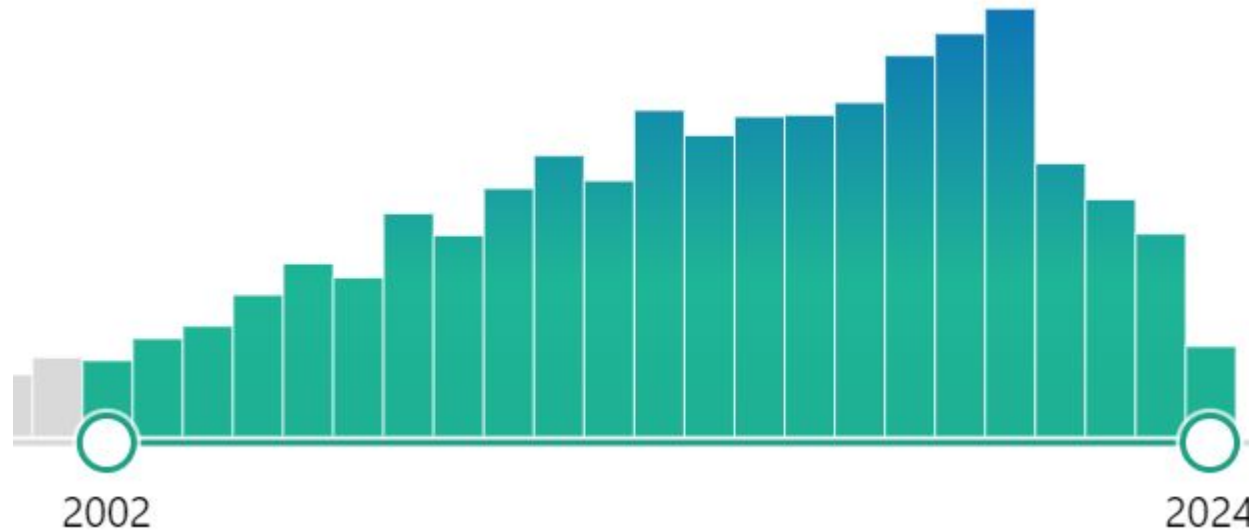
40.602
articoli



((SEPSIS) OR (SEPTIC SHOCK)) AND (BIOMARKERS)

12.478 articoli



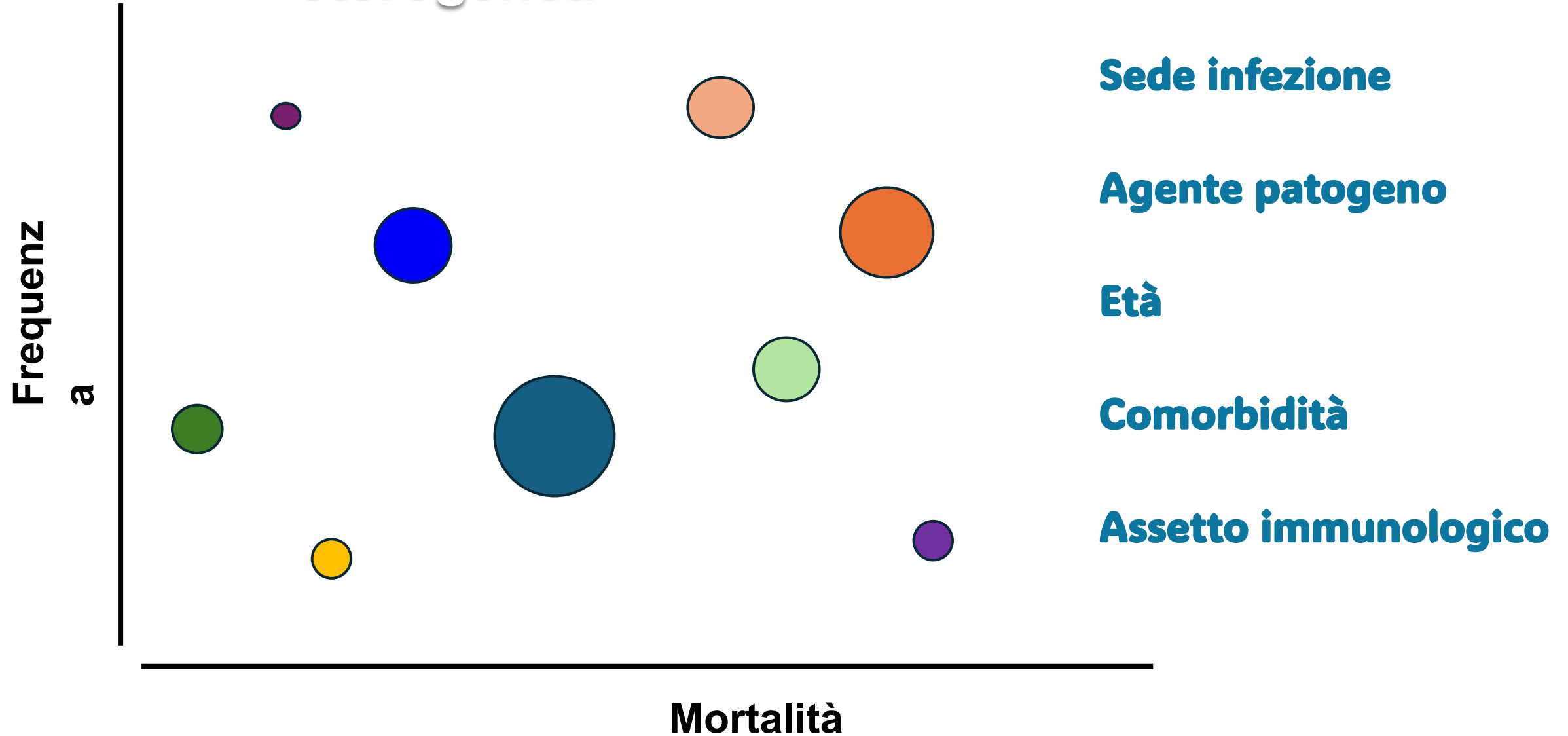


((SEPSIS) OR (SEPTIC SHOCK)) AND
GUIDELINES

3.101
articoli

La sepsi è una sindrome

eterogenea



Evidence based medicine: what it is and what it isn't

It's about integrating individual clinical expertise and the best external evidence

D L
Sackett

BMJ VOLUME 312 13 JANUARY 1996

Singer *Critical Care* 2019, **23**(Suppl 1):127
<https://doi.org/10.1186/s13054-019-2398-5>

Critical Care

REVIEW

Open Access

Sepsis: personalization v protocolization?

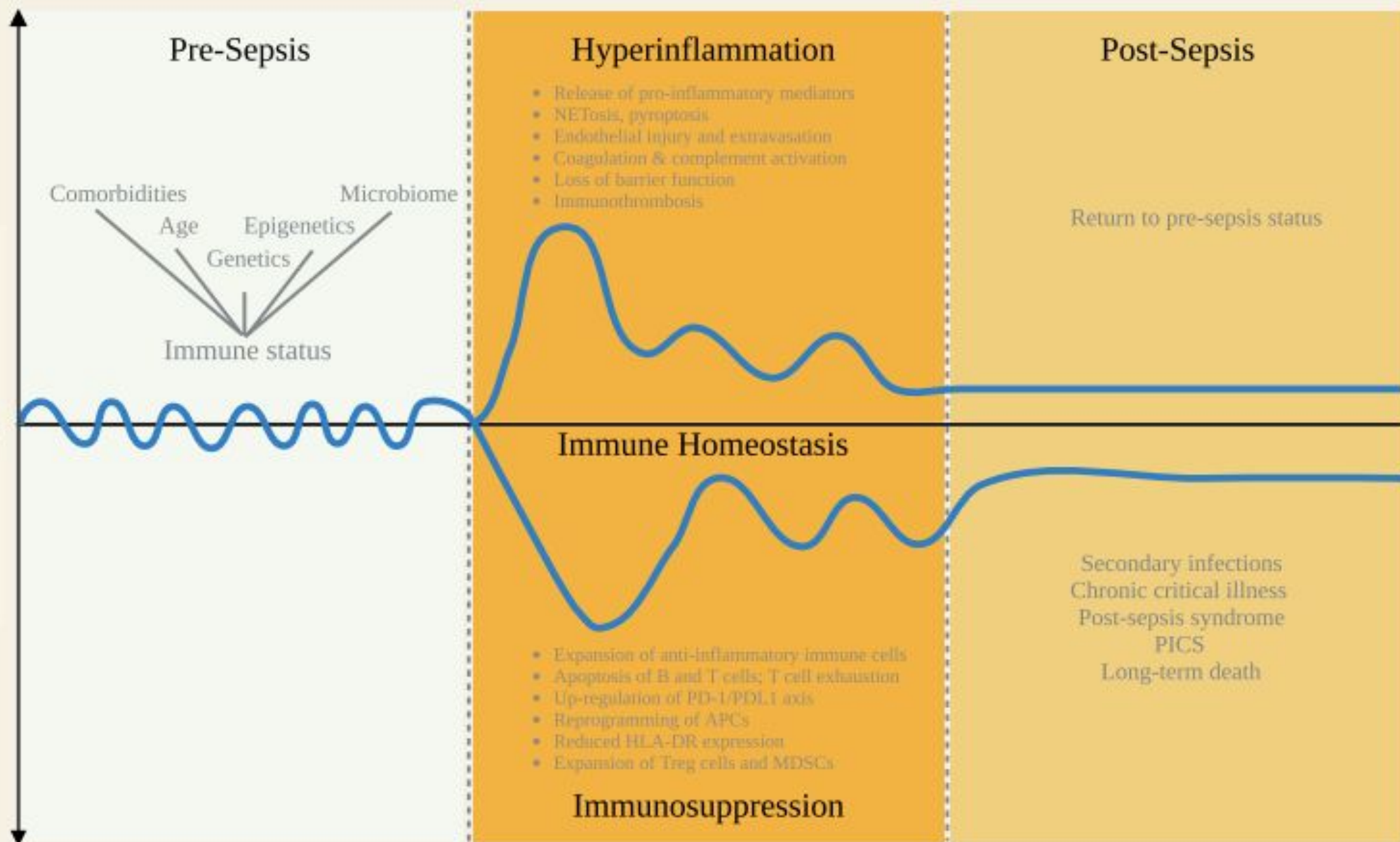
Mervyn Singer 



We must acknowledge there is still no 'right' way to manage all the complexities of a septic patient

**Le
sfide....**

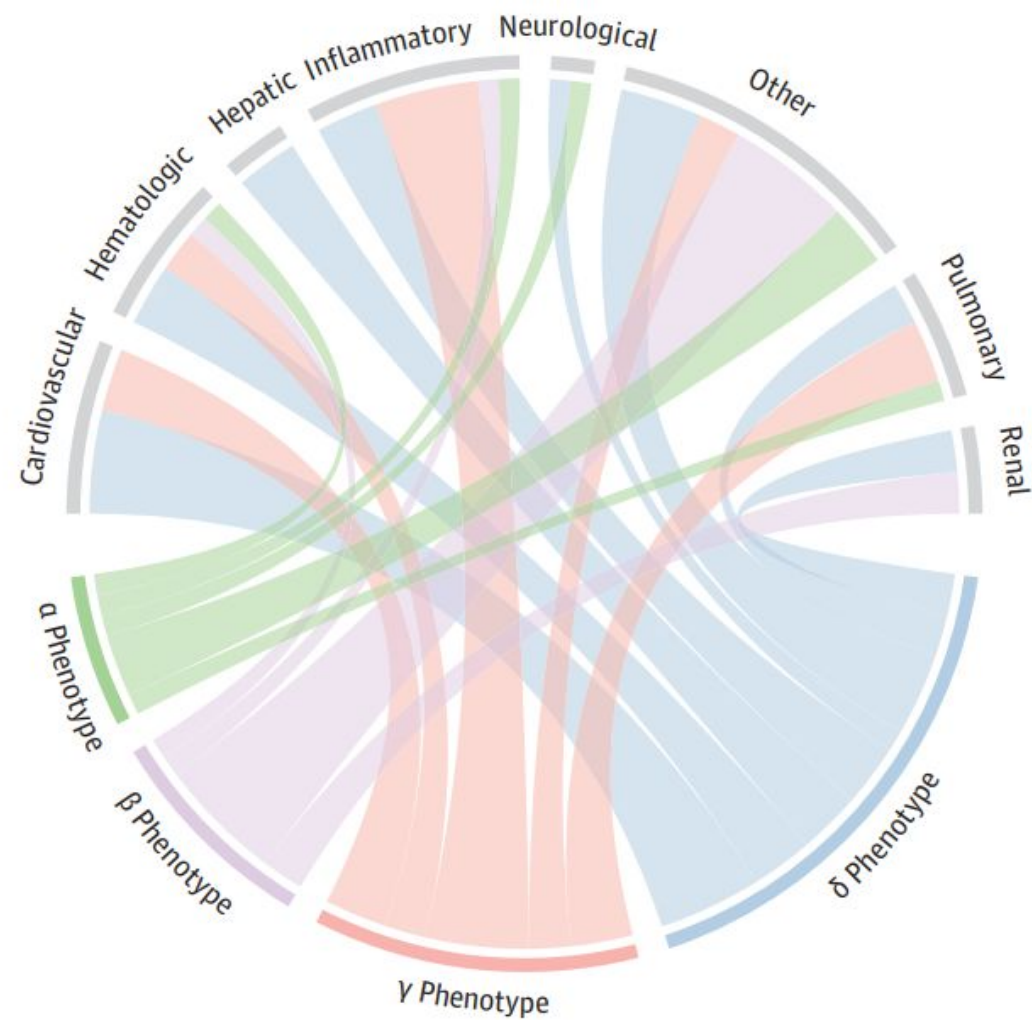
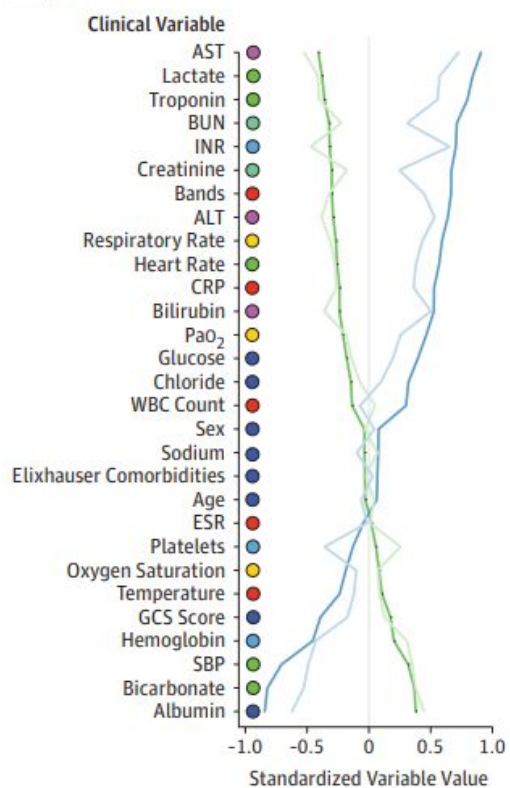
1. Identificare il tipo di paziente



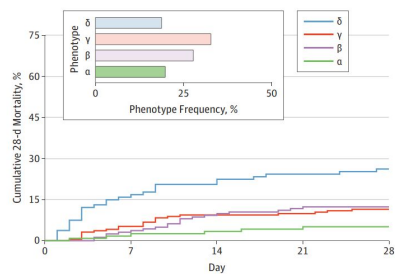
Derivation, Validation, and Potential Treatment Implications of Novel Clinical Phenotypes for Sepsis

Seymour,

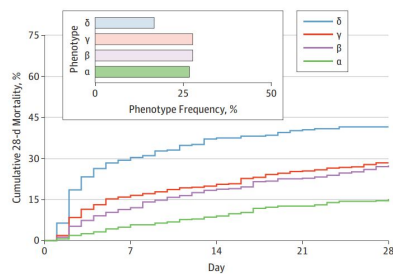
JAMA. 2019;321(20):2003-2017. doi:10.1001/jama.2019.5791

C δ vs α phenotype

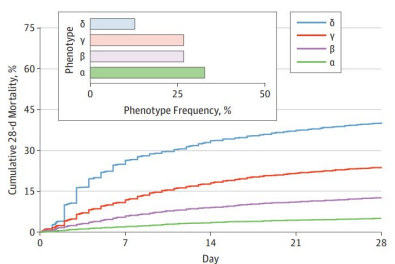
C GenIMS cohort (n = 583)



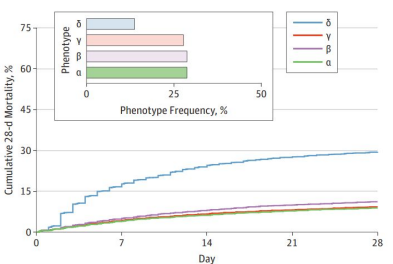
D ACCESS trial (n = 1706) (eritoran vs placebo)



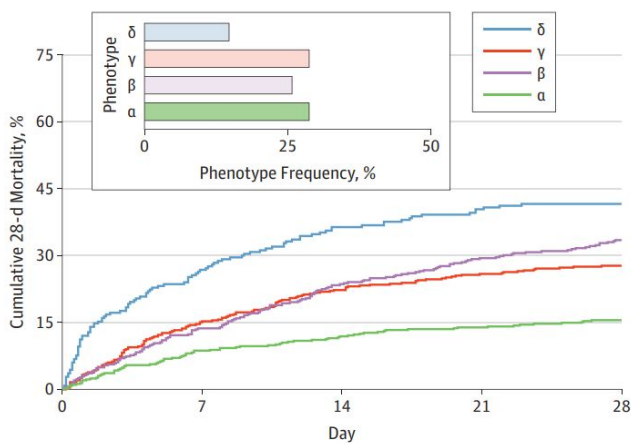
A SENECA derivation cohort (n = 16 652)^a



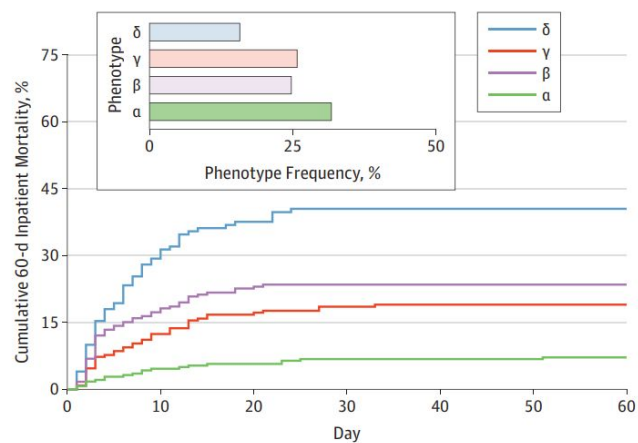
B SENECA validation cohort (n = 31 160)^a



E PROWESS trial (n = 1690) (drotrecogin alfa vs placebo)



F ProCESS trial (n = 1341) (EGDT vs protocolized standard care vs usual care)



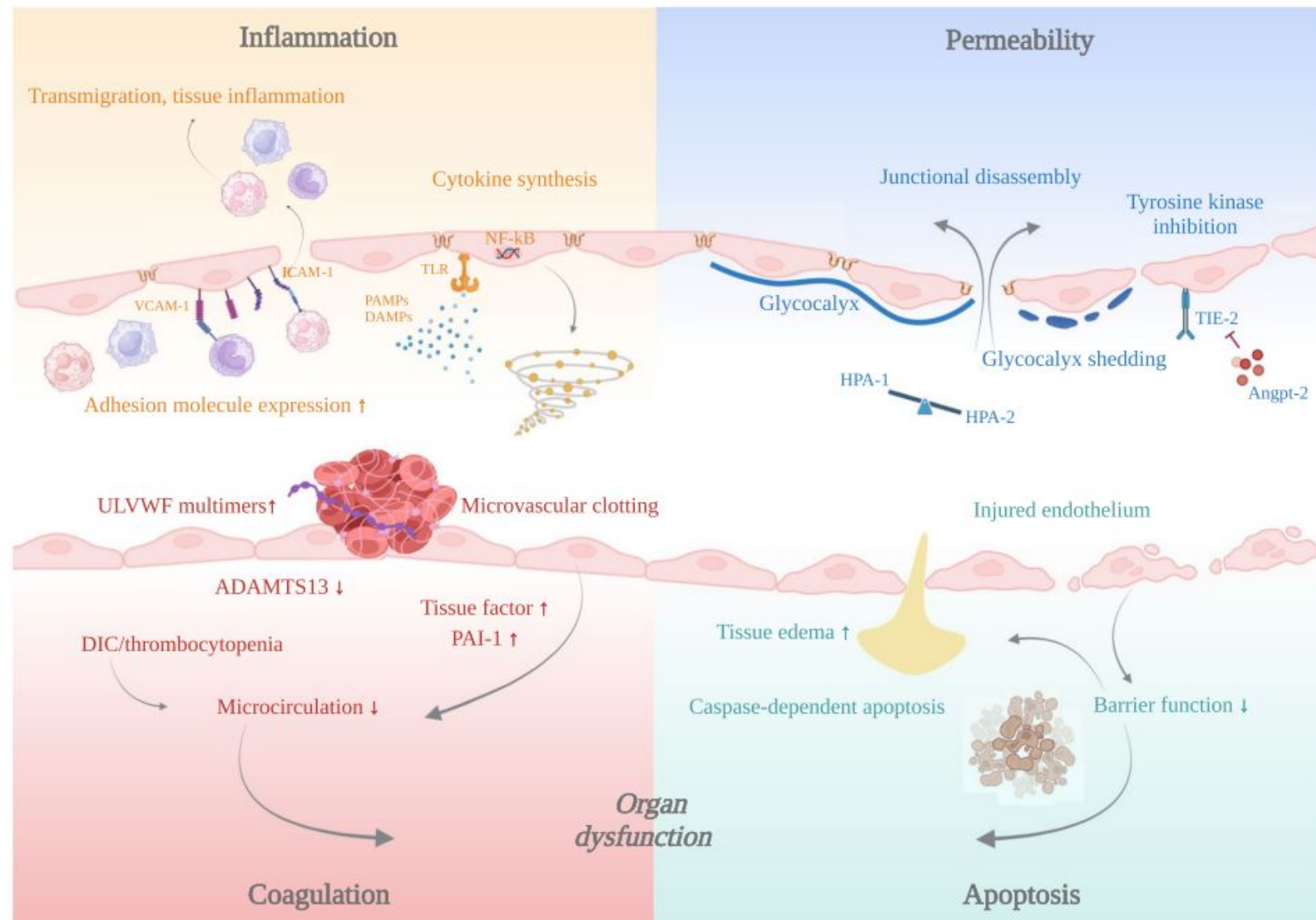
REVIEW

Open Access

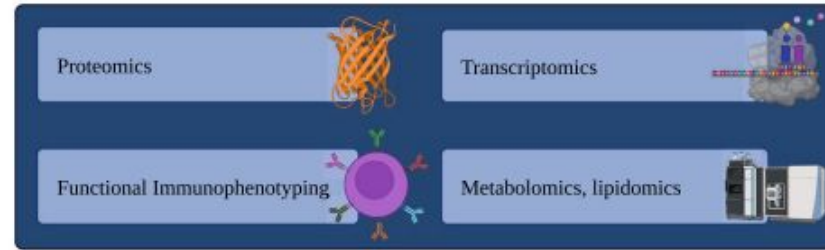


Targeting the host response in sepsis: current approaches and future evidence

Christian Bode^{1*}, Sebastian Weis^{2,3,4}, Andrea Sauer¹, Pedro Wendel-Garcia⁵ and Sascha David⁵



Large Retrospective and
Prospective Cohorts



Targeting hyperinflammation

Selective immunomodulators

Tumor necrosis factor anti-TNF

Interleukin-1 receptor Anakinra

Complement inhibition (anti-C5a) anti-C5a

Non-selective immunomodulators

Corticosteroids hydrocortisone

Vitamin C Vitamin C

Antibiotics with anti-inflammatory properties tetracyclines

macrolides

(Activated) protein C and thrombomodulin

Bioactive adrenomedullin

Extracorporeal blood purification

Immune augmentation strategies

Immunostimulatory cytokines and growth factors

Granulocyte–macrophage colony-stimulating factor

Interferon gamma

Thymosin alpha 1

Immunoglobulins

Mesenchymal stem cells

Immune checkpoint inhibitors

anti-PD-1

nivolumab

Biological Phenotyping in Sepsis and ARDS

Pratik Sinha¹, Nuala J. Meyer², Carolyn S. Calfee³

Challenges to Clinical Implementation of Phenotypes

Utility

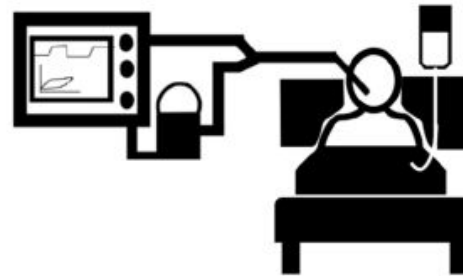
How does it help my patients?

Currently Experimental
Lacking Prospective Data

Feasibility

Can phenotyping be part of clinical workflow?

Biomarkers processing
Clinician skepticism



Stability

What are the implications of changing phenotypes?

Most schema use cross-sectional data

Unstable measurement system

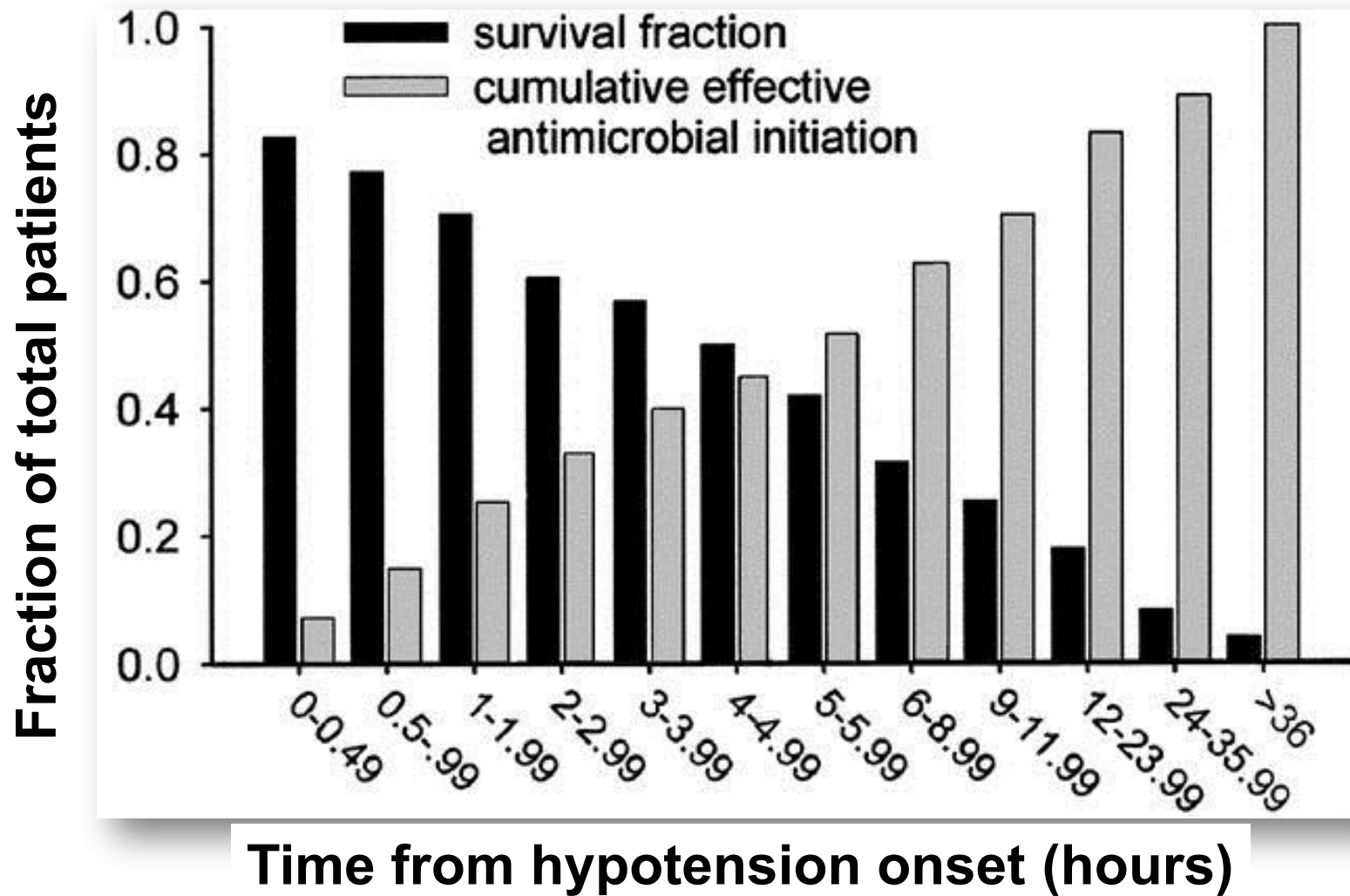
Rudimentary

Do we understand the biology sufficiently?

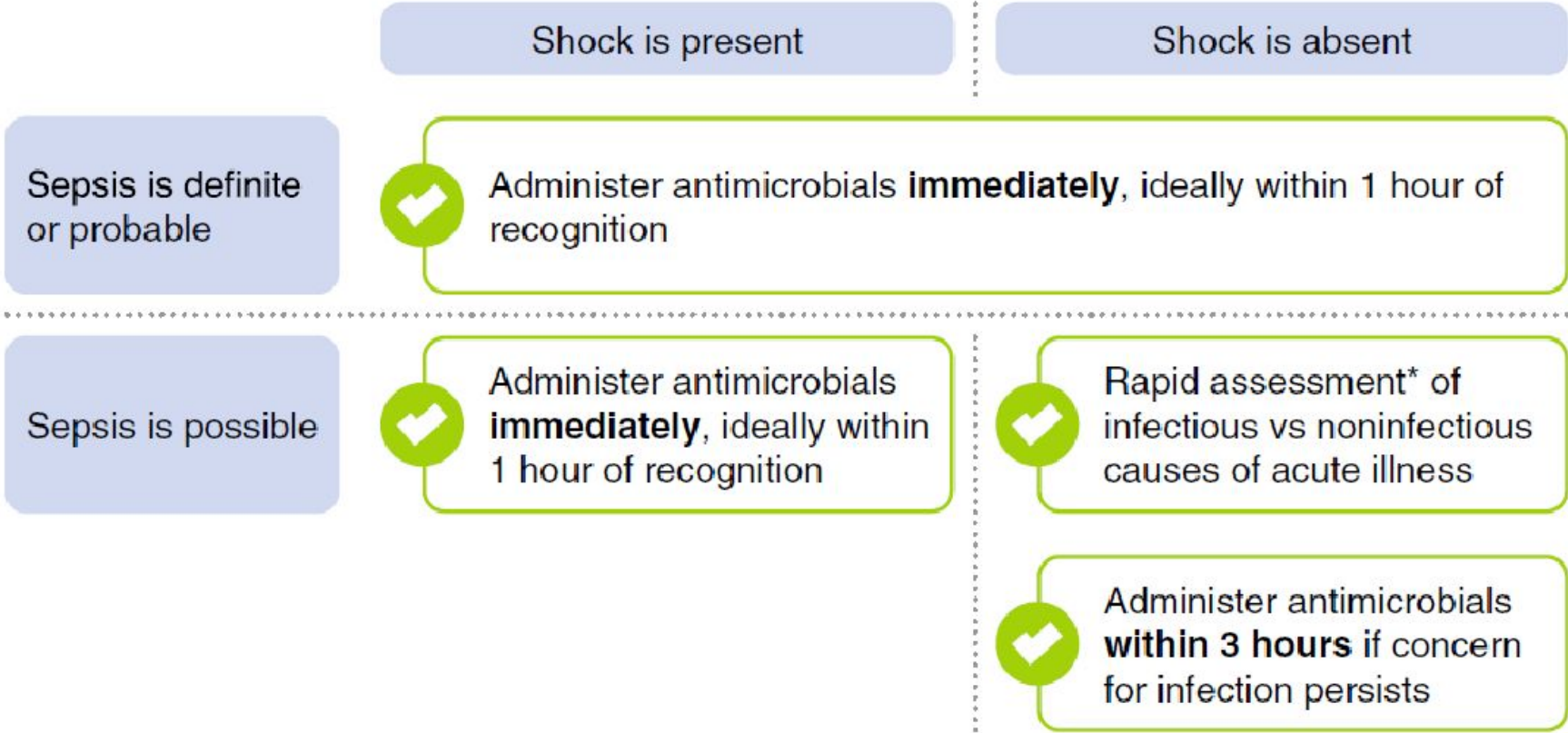
Phenotypes may be too simplistic for ICU

Optimal therapies unknown

2. Ottimizzare la terapia antibiotica



Antibiotic Timing



*Rapid assessment includes history and clinical examination, tests for both infectious and non-infectious causes of acute illness and immediate treatment for acute conditions that can mimic sepsis. Whenever possible this should be completed within 3 hours of presentation so that a decision can be made as to the likelihood of an infectious cause of the patient's presentation and timely antimicrobial therapy provided if the likelihood is thought to be high.

Fig. 1 Recommendations on timing of antibiotic administration

Risk of Misleading Conclusions in Observational Studies of Time-to-Antibiotics and Mortality in Suspected Sepsis

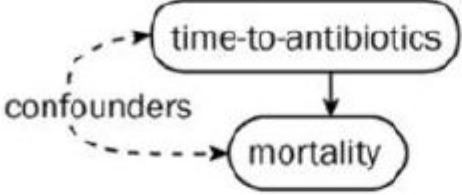
Theodore R. Pak,^{1,2,●} Jessica Young,¹ Caroline S. McKenna,¹ Anna Agan,¹ Laura DelloStritto,¹ Michael R. Filbin,³ Sayon Dutta,^{3,●} Sameer S. Kadri,⁴ Edward J. Septimus,¹ Chanu Rhee,^{1,5,a,●} and Michael Klompas^{1,5,a}

Clinical Infectious Diseases

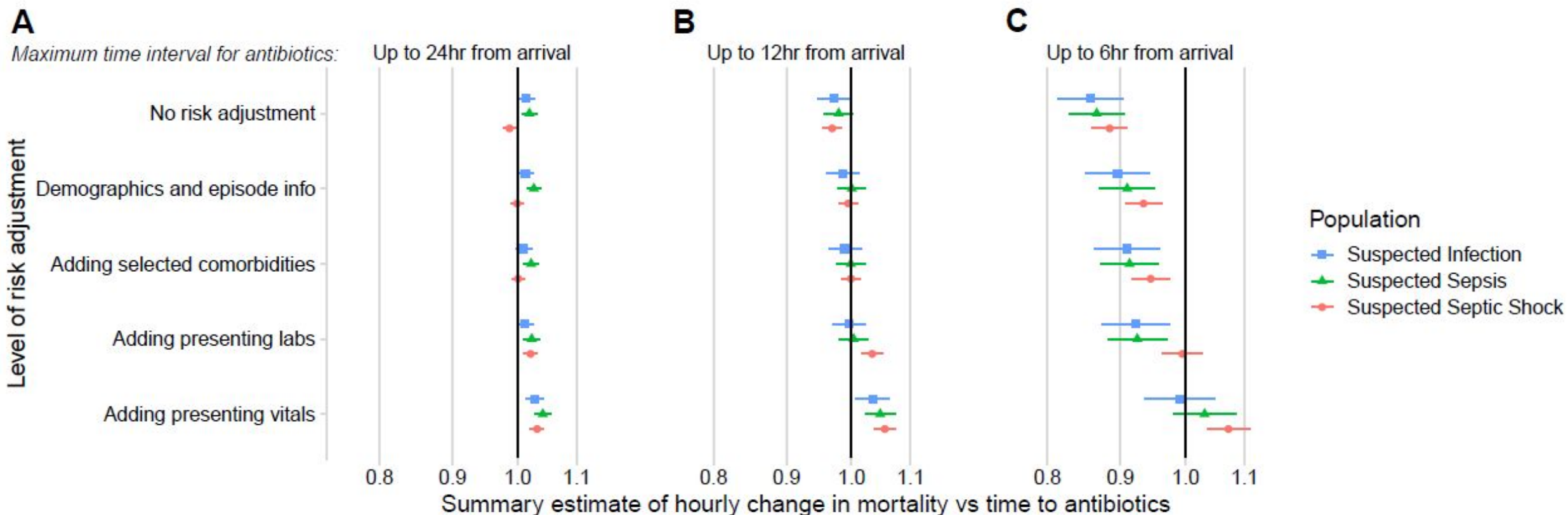
MAJOR ARTICLE

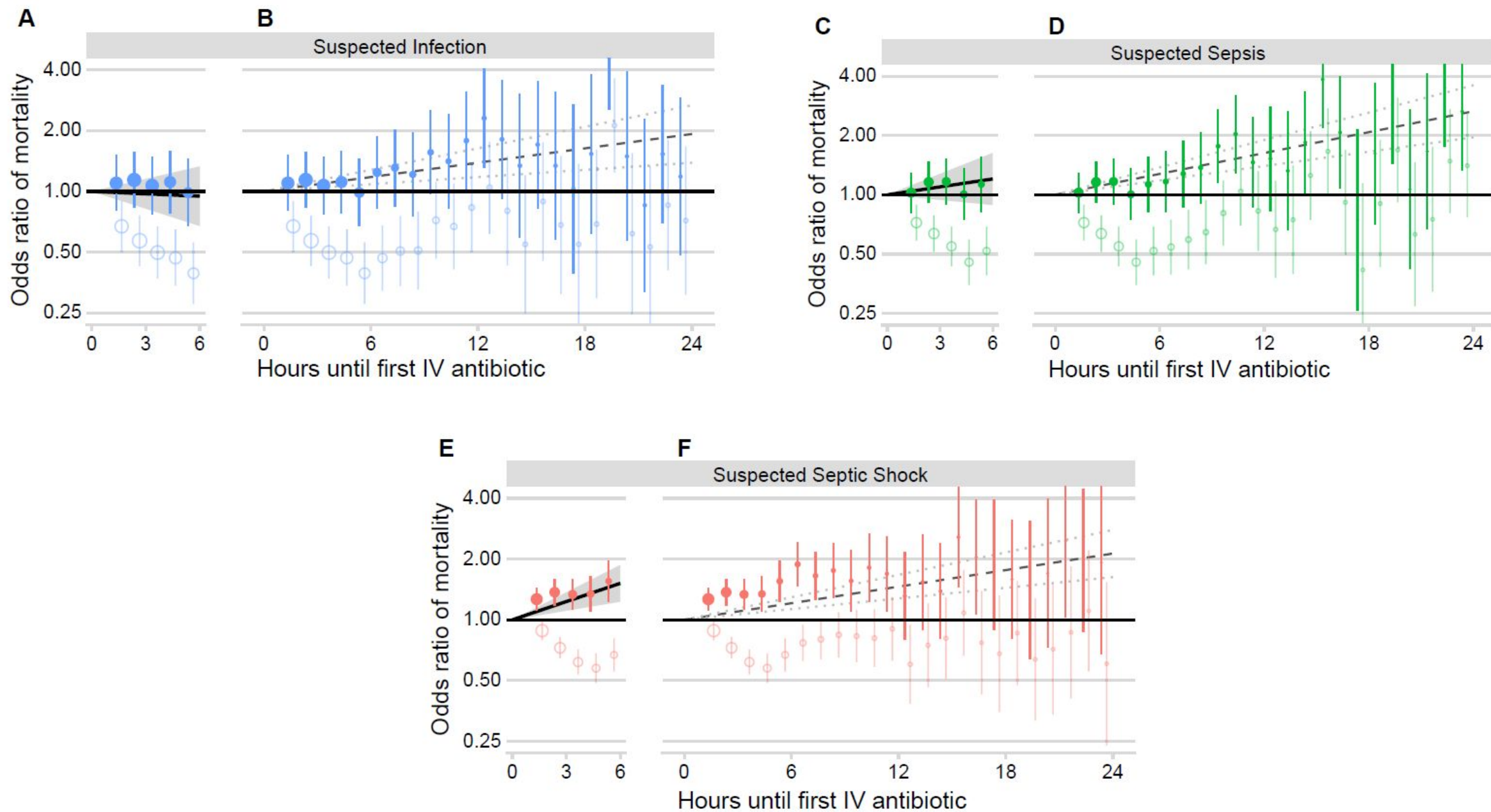
Clinical Infectious Diseases®

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<https://doi.org/10.1093/cid/ciad450>

ANALYTICAL CONCERN	TEST	RESULTS
Insufficient confounding adjustment 	Add progressively more detailed covariates: basics → + comorbidities → + labs → + vitals	 Changed
Including time-to-antibiotics outliers 	Pts treated >6h are rare & different. Lower max time-to-antibiotics: 24h → 12h → 6h	 Changed
Equating sepsis & septic shock 	Separate analyses for: • suspected infection • suspected sepsis • suspected septic shock	 Changed
Linearizing non-linearity 	Remove the assumption of a linear relationship between time-to-antibiotics ↔ log odds of mortality	 Changed

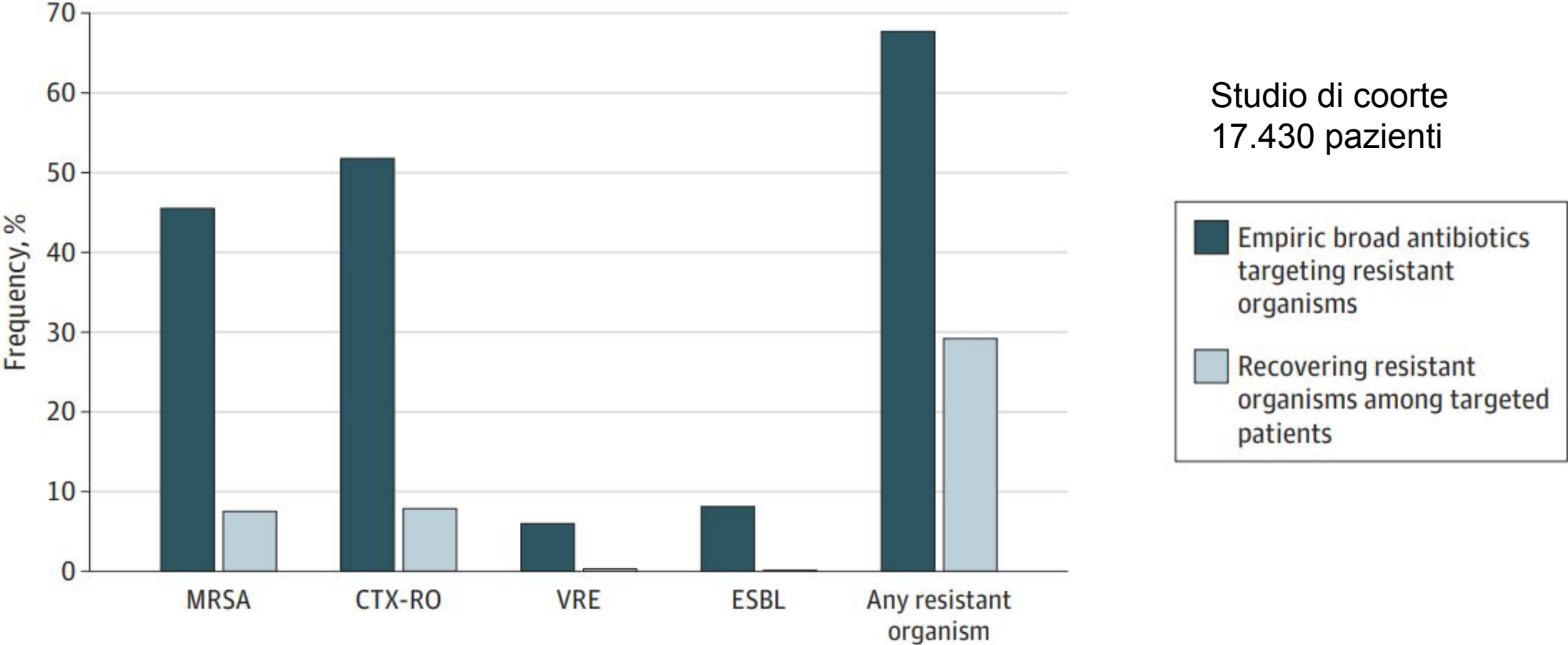
	Cohort		
	Suspected Infection (N = 54 639)	Suspected Sepsis (N = 23 619)	Suspected Septic Shock (N = 25 990)
Decessi	1049 (1.9%)	1423 (6.0%)	3484 (13%)



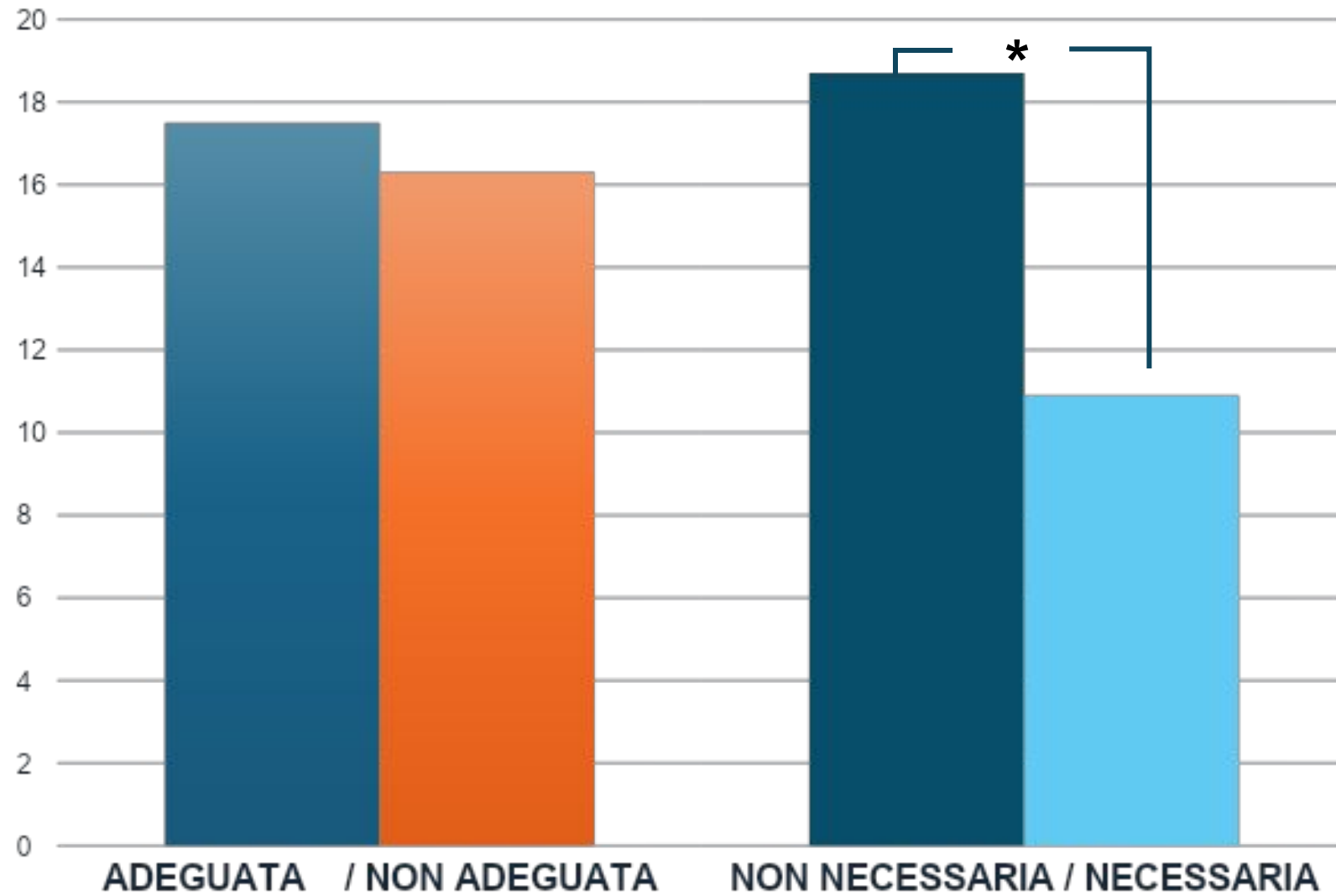


Prevalence of Antibiotic-Resistant Pathogens in Culture-Proven Sepsis and Outcomes Associated With Inadequate and Broad-Spectrum Empiric Antibiotic Use

Chanu Rhee, MD, MPH; Sameer S. Kadri, MD, MSc; John P. Dekker, MD, PhD; Robert L. Danner, MD; Huai-Chun Chen, PhD; David Fram, BA; Fang Zhang, PhD; Rui Wang, PhD; Michael Klompas, MD, MPH; for the CDC Prevention Epicenters Program



Mortalità ospedaliera in relazione alla terapia antibiotica empirica



* = $p < 0,001$

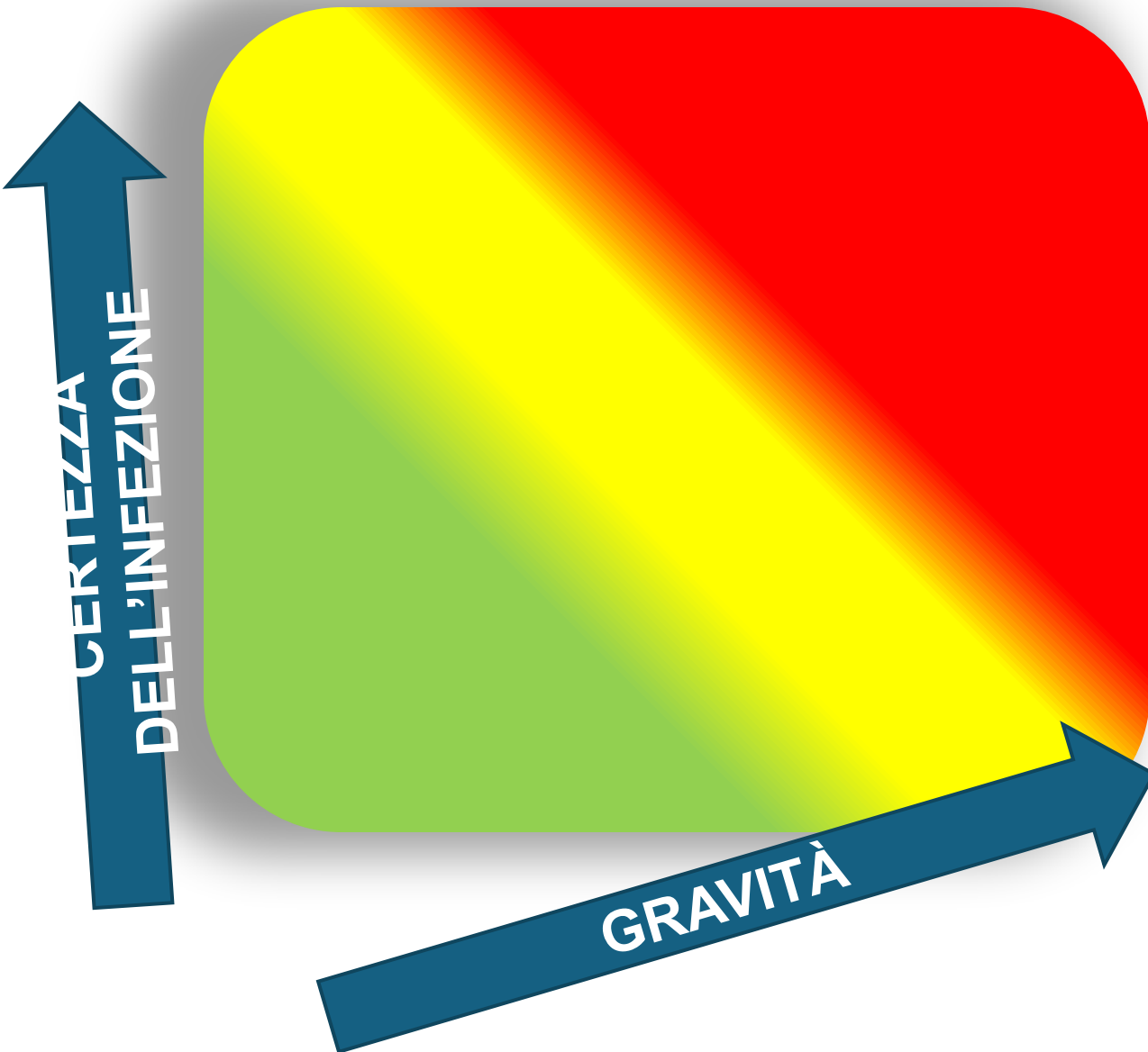
VERSO UN RAGIONEVOLE EQUILIBRIO

SHOCK SETTICO

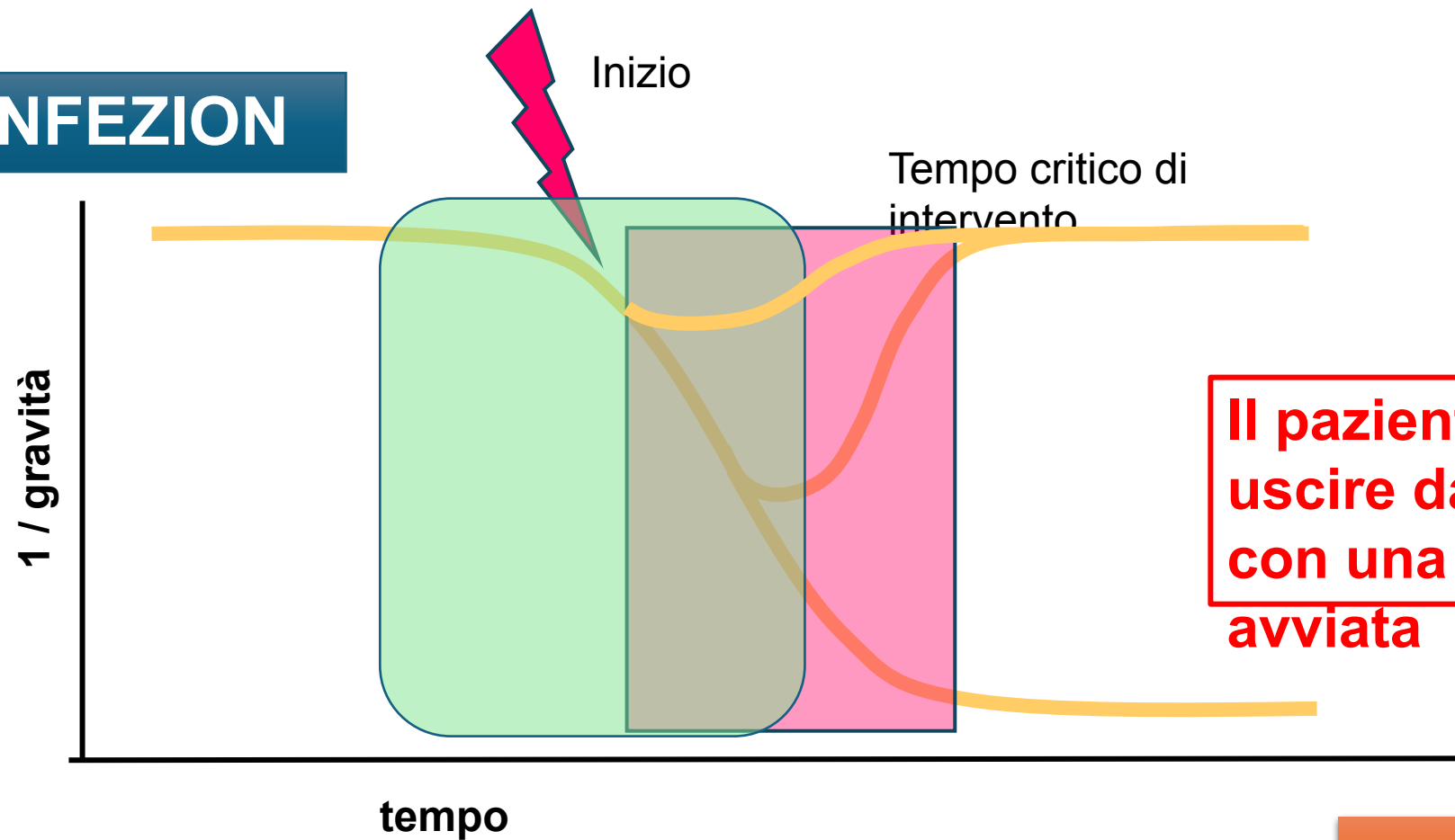
antibiotico ad ampio spettro subito,
eventuale deescalation

SEPSI ED INFEZIONE

Ci diamo il tempo di riflettere per
una terapia mirata



INFEZION



**Il paziente deve SEMPRE
uscire dal Pronto Soccorso
con una terapia antibiotica
avviata**

SEPS

BAD BUGS, NO DRUGS

As Antibiotic Discovery Stagnates ...
A Public Health Crisis Brews



E **SCHERICHIA**
COLI

NORMAL
FLORA



environment

INFECT



S **TAPHYLOCOCCUS**

S. pseudintermedius

NORMAL
FLORA



SKIN



S. schleiferi

NORMAL
FLORA



SKIN



S. aureus

NORMAL
FLORA



SKIN



K **LEBSIELLA**
PNEUMONIAE

NORMAL
FLORA



INFECT



A **CINETOBACTER**
BAUMANNII

NORMAL
FLORA



environment

INFECT



P **SEUDOMONAS**
AERUGINOSA

NORMAL
FLORA



environment

INFECT



E **NTEROCOCCUS**
FAECALIS **AND** **FAECIUM**

NORMAL
FLORA

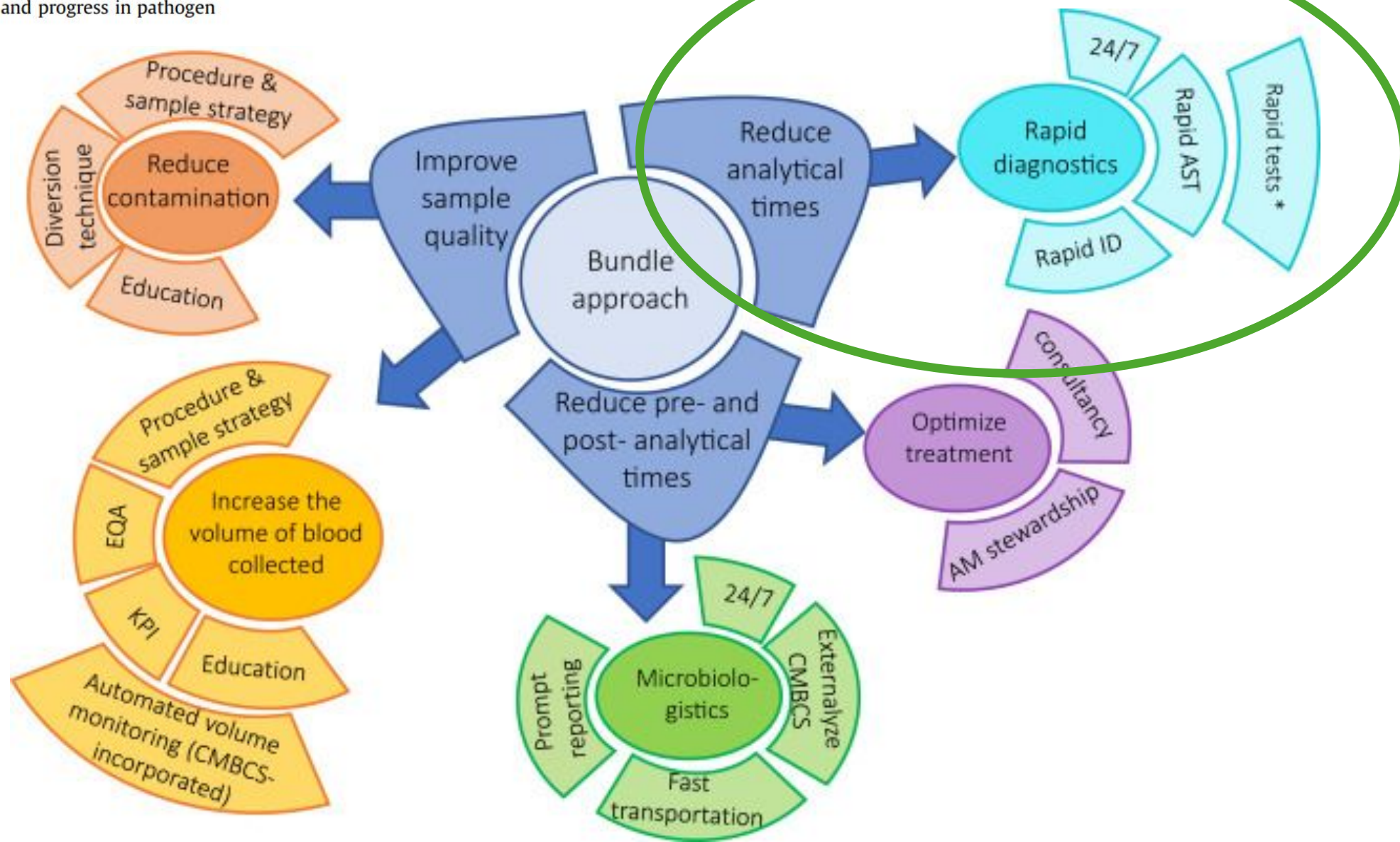


INFECT



Narrative review

Bloodstream infections – Standard and progress in pathogen diagnostics



I pannelli molecolari multiplex

vantaggi

- ❖ tempi di analisi
- ❖ simultanea identificazione di più agenti patogeni
- ❖ scelte più precise
- ❖ decisioni più rapide

sfide

- ❖ Costi
- ❖ strategie di utilizzo condivise
- ❖ interpretazione del risultato



Test fenotipici
(spettrometria
di massa)



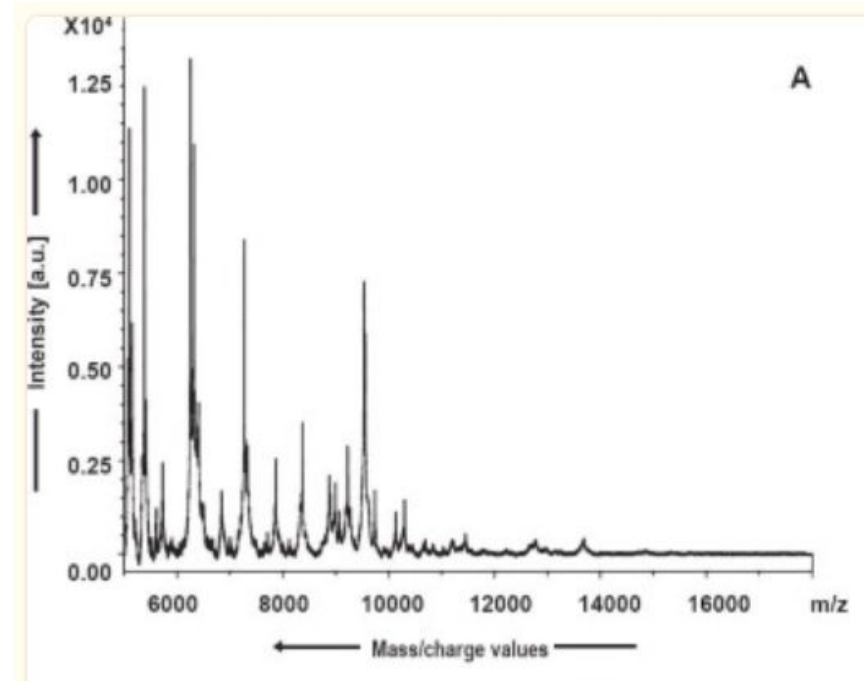
Test genomici
Film Array



T2RM

Spettrometria di massa MALDI-TOF

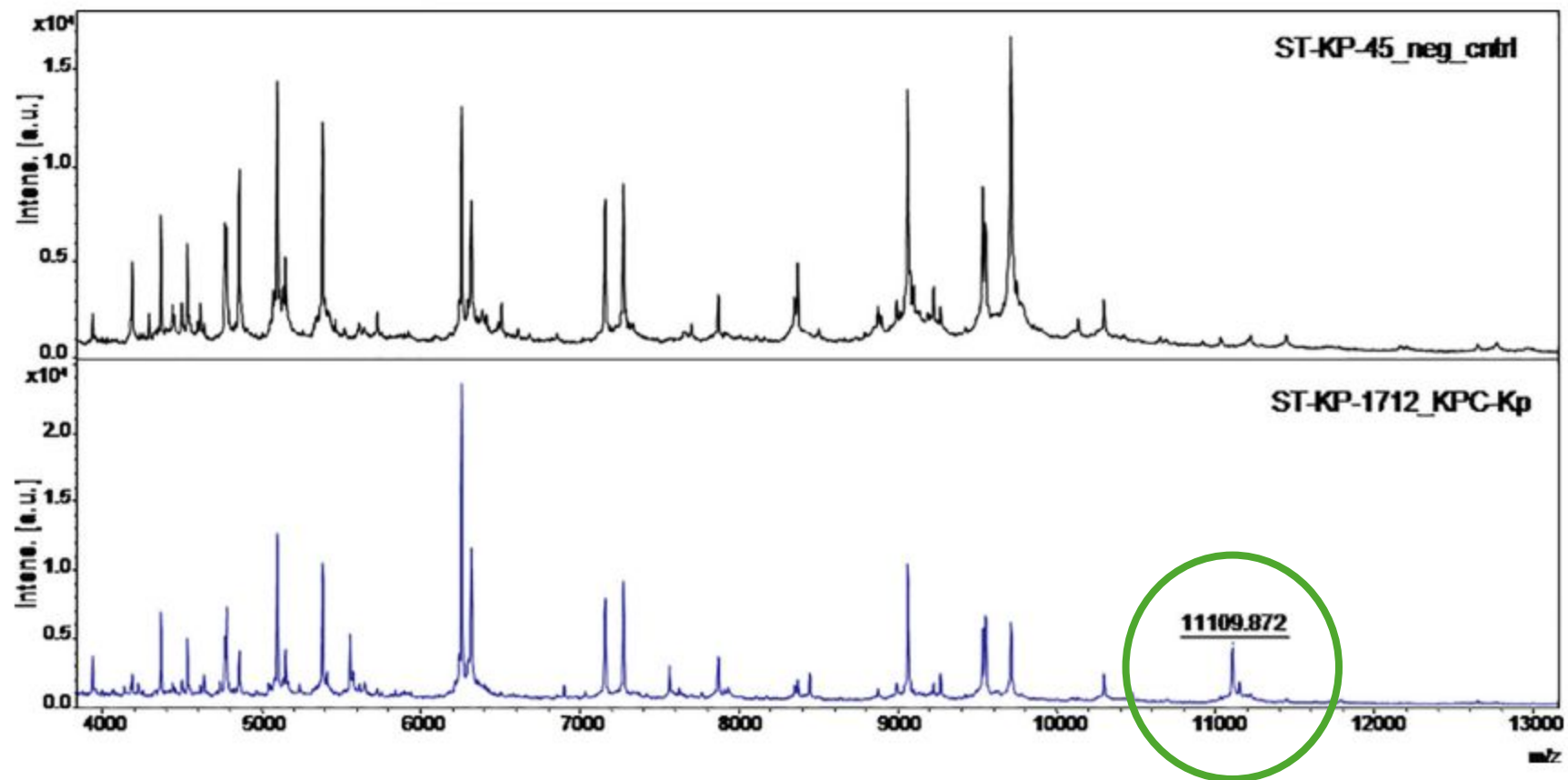
“Matrix-Assisted Laser Desorption/Ionization – Time of Flight”,



23 min **vs** 24-48 h

after culture positivity

il MALDI-TOF attualmente non è in grado di differenziare *E. coli* da *Shigella*.



Identificazione dei profili di resistenza



FilmArray: Approccio Sindromico



1. Approccio Sindromico

Capacità di **testare completamente un ampio spettro di patogeni** quando il paziente presenta un insieme di segni e sintomi aspecifici



L'approccio sindromico massimizza le probabilità di produrre una risposta **accurata in un tempo clinicamente rilevante**



2. Risultato rapido



3. Sinergia tra il laboratorio ed il clinico



Respiratory 2.1 (RP2.1) Panel*

Respiratory 2.1 *plus* (RP2.1*plus*) Panel*



Pneumonia *plus* (PN*plus*) Panel*



Blood Culture Identification (BCID) Panel*

Blood Culture Identification 2 (BCID2) Panel*

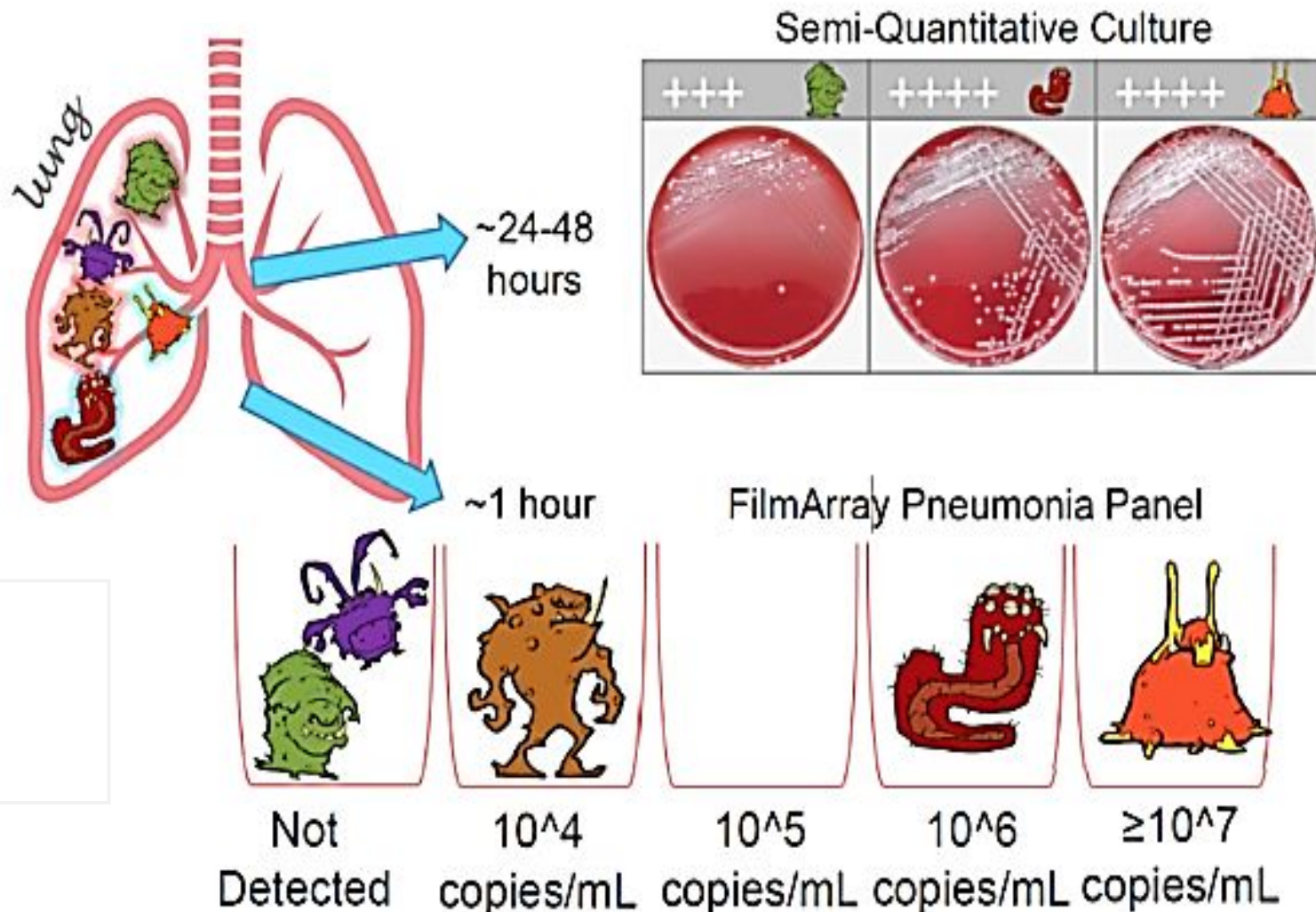


Gastrointestinal (GI) Panel*



Meningitis/Encephalitis (ME) Panel*

Una coltura standard conta gli organismi vitali Il FilmArray misura la presenza di acidi nucleici.



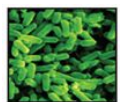
La coltura può richiedere dalle 24 alle 48 ore.

L'esame colturale può non essere sensibile, in particolare per i batteri esigenti o se il prelievo è stato fatto dopo l'inizio della terapia empirica

I risultati relativi ai batteri comuni sono di tipo semi-quantitativo, con refertazione in log 10^4 , 10^5 , 10^6 , $>10^7$ di copie genomiche/mL di campione.

La refertazione in copie/mL dei livelli degli acidi nucleici è stata disegnata per essere analoga alle tecniche di coltura standard.

The BioFire[®] FilmArray[®] BCID2 Panel emocoltura



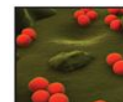
Gram-Negative Bacteria

Acinetobacter calcoaceticus-baumannii complex
*Bacterioides fragilis**
Haemophilus influenzae
Neisseria meningitidis
Pseudomonas aeruginosa
*Stenotrophomonas maltophilia**
Enteric Bacteria
Enterobacter cloacae complex
Escherichia coli
*Klebsiella aerogenes**
Klebsiella oxytoca
Klebsiella pneumoniae group
Proteus
*Salmonella**
Serratia marcescens



Gram-Positive Bacteria

*Enterococcus faecalis**
*Enterococcus faecium**
Listeria monocytogenes
Staphylococcus
Staphylococcus aureus
*Staphylococcus epidermidis**
*Staphylococcus lugdunensis**
Streptococcus
Streptococcus agalactiae
Streptococcus pneumoniae
Streptococcus pyogenes



Resistance Markers

Carbapenemases
*IMP**
KPC
*Oxa-48-like**
*NDM**
*VIM**
ESBL
*CTX-M**
Methicillin resistance
mecA/C
mecA/C and *MREJ** (MRSA)
Vancomycin resistance
vanA/B
Colistin resistance
*Mcr-1**



Yeast

Candida albicans
*Candida auris**
Candida glabrata
Candida krusei
Candida parapsilosis
Candida tropicalis
*Cryptococcus neoformans/gattii**

(43 Targets)

CASO 1 F. 21

anni

Diabete insipido a seguito di asportazione di faringioma a 6 anni. In terapia con desmopressina.

- Esordio improvviso con gastralgia
- Vomito incoercibile (>10 episodi) e diarrea (> 10 episodi)
- Temperatura fino 39,1 °C
- Impossibilità ad assumere la desmopressina, altri farmaci, liquidi

BATTERIOLOGIA

Materiale: Feci

Ricerca diretta molecolare multiplex pannello gastroenterico

BATTERI

- Campylobacter spp
- Clostridium difficile toxin A/B
- Plesiomonas shigelloides
- Salmonella spp
- Vibrio spp
- Vibrio cholerae
- Yersinia enterocolitica
- E.coli patogeni / Shigella
- EAEC (aggR)
- EPEC (eaeA)
- ETEC (It / st)
- STEC (stx 1 / 2)
- Shigella/Enteroinvasive E.coli (EIEC)

	Negativa
	Negativa
	Negativa
	Negativa
	Negativa
	Negativa
	Negativa
	Negativa
	Negativa
	Negativa
	Negativa
	Negativa

Alla c.a. Dott.CALCI

BATTERIOLOGIA

Materiale: Feci

Ricerca diretta molecolare multiplex - Virus

Norovirus G 1	Positiva
Norovirus G 2	Positiva
Rotavirus	Negativa
Adenovirus	Negativa
Astrovirus	Negativa
Sapovirus	Negativa

Alla c.a. Dott.CALCI

CASO 2 F 35

anni

Tossicodipendenza.

Dolore anca destra

In PS anemia severa, febbre,
ipotensione

Sig.ra MELCHIOR SARITA
Data Nascita: 15/10/1986 Età: 36 Anni Sesso: F
Richiesta: 55346030 del: 06/12/2022 Ore: 09:36
(UD)-Seminterrato, Pad. 1

raggi: 1 di 1

Esame	Esito	U.M.	Intervalli di riferimento
-------	-------	------	---------------------------

BATTERIOLOGIA

Materiale: Sangue
Flacone culturale aerobi

Sviluppo di

Ceppo 1	Streptococcus dysgalactiae		
---------	----------------------------	--	--

Sede del prelievo non specificata.

Flacone culturale anaerobi

Sviluppo di

Ceppo 1	Streptococcus dysgalactiae		
---------	----------------------------	--	--

Flacone culturale aerobi 2° set

Sviluppo di

Ceppo 1	Streptococcus dysgalactiae		
---------	----------------------------	--	--

Sede del prelievo non specificata.

Flacone culturale anaerobi 2° set

Sviluppo di

Ceppo 1	Streptococcus dysgalactiae		
---------	----------------------------	--	--

Antibiogramma

ANTIBIOTICO	Ceppo 1
	MIC
Clindamicina	S 0.0625
Eritromicina	S 0.125
Penicillina G	S <=0.0078

< R = Resistente, S = Sensibile, I = Intermedio >

Esito esame microscopico: si osserva la presenza di cocci Gram positivi. Dato comunicato il 06/12/2022 alle ore 17:50, mediante modalità read back.

Sig.ra MELCHIOR SARITA

Data Nascita: 15/10/1986 Età: 36 Anni Sesso: F

Richiesta: 55346030 del: 06/12/2022 Ore: 09:36

(UD)-Seminterrato, Pad. 1

Esame	Esito	U.M.	Intervalli di riferimento
-------	-------	------	---------------------------

Note 2° set emocultura

Esito esame microscopico: si osserva la presenza di cocci Gram positivi. Dato comunicato il 06/12/2022 alle ore 17:50, mediante modalità read back.

Ricerca diretta molecolare multiplex

GRAM POSITIVI

Enterococcus faecalis	Negativa
Enterococcus faecium	Negativa
Listeria monocytogenes	Negativa
Staphylococcus spp	Negativa
Staphylococcus aureus	Negativa
Staphylococcus epidermidis	Negativa
Staphylococcus lugdunensis	Negativa
Streptococcus spp	Positiva
Streptococcus agalactiae	Negativa
Streptococcus pneumoniae	Negativa
Streptococcus pyogenes	Negativa

Ricerca diretta molecolare multiplex

GRAM NEGATIVI

Acinetobacter calcoaceticus-baumannii complex	Negativa
Bacteroides fragilis	Negativa
Enterobacterales	Negativa
Enterobacter cloacae complex	Negativa
Escherichia coli K1	Negativa
Klebsiella aerogenes	Negativa
Klebsiella oxytoca	Negativa
Klebsiella pneumoniae group	Negativa
Proteus spp.	Negativa
Salmonella spp	Negativa
Serratia marcescens	Negativa
Haemophilus influenzae	Negativa
Neisseria meningitidis	Negativa
Pseudomonas aeruginosa	Negativa
Stenotrophomonas maltophilia	Negativa

Ecocardiografia:
endocardite

CASO 3 F 59
anni

Recidiva di fistola rino-liquorale
Lamenta congestione nasale e
cefalea
T.C. 40,2°C
Presenza di rigor

Sig.ra RUTIGLIANI GRAZIELLA
Data Nascita: 03/11/1963 Età: 59 Anni Sesso: F
Richiesta: 55420044 del: 20/12/2022 Ore: 14:00
(UD)-Seminterrato, Pad. 1

Pag.: 2 di

Esame Esito U.M Intervalli di riferimento

Ciprofloxacina	S	0.006
Levofloxacina	S	0.016
Meropenem	S	0.125

< R = Resistente, S = Sensibile, I = Intermedio >

Esame culturale batteri anaerobi
Esame culturale miceti

Nessuno sviluppo
Nessuno sviluppo

Richiedente Referto: (UD)-Pronto Soccorso Generale

Pag.: 1 di 2

Sig.ra RUTIGLIANI GRAZIELLA
Data Nascita: 03/11/1963 Età: 59 Anni Sesso: F
Richiesta: 55420044 del: 20/12/2022 Ore: 14:00
(UD)-Seminterrato, Pad. 1

Esame Esito U.M Intervalli di riferimento

BATTERIOLOGIA

Materiale: Liquor
Ricerca diretta molecolare multiplex
BATTERI
Escherichia coli K1
Haemophilus influenzae
Listeria monocytogenes
Neisseria meningitidis
Streptococcus agalactiae
Streptococcus pneumoniae
VIRUS
Citomegalovirus (CMV)
Enterovirus
Herpes simplex virus 1 (HSV-1)
Herpes simplex virus 2 (HSV-2)
Human herpes virus 6 (HHV-6)
Human parechovirus
Varicella zoster virus (VZV)
LIEVITI
Cryptococcus neoformans/gattii

Negativa
Positiva
Negativa
Negativa
Negativa
Negativa
Negativa
Negativa
Negativa
Negativa
Positiva
Negativa
Negativa
Negativa
Negativa
Negativa

Dato comunicato il 20/12/2022 alle ore 17:56, mediante modalità read back.

Esame culturale batteri aerobi Sviluppo di

Ceppo 1 Haemophilus influenzae Numerose colonie

Antibiogramma

ANTIBIOTICO	Ceppo 1	MIC
Amoxicillina-clavulanato	S	1
Ampicillina	S	0.5
Cefotaxime	S	0.047
Ceftazidime	S	0.19
Ceftriaxone	S	0.016

CASO 4 M 19 anni

Tosse secca e febbre da 3
gg

All'ecografia

Addensamento apicale
destro ed interstiziopatia a
destra

Microbiologia

Materiale: Tamp. faringeo

Multiplex Respiratory plus

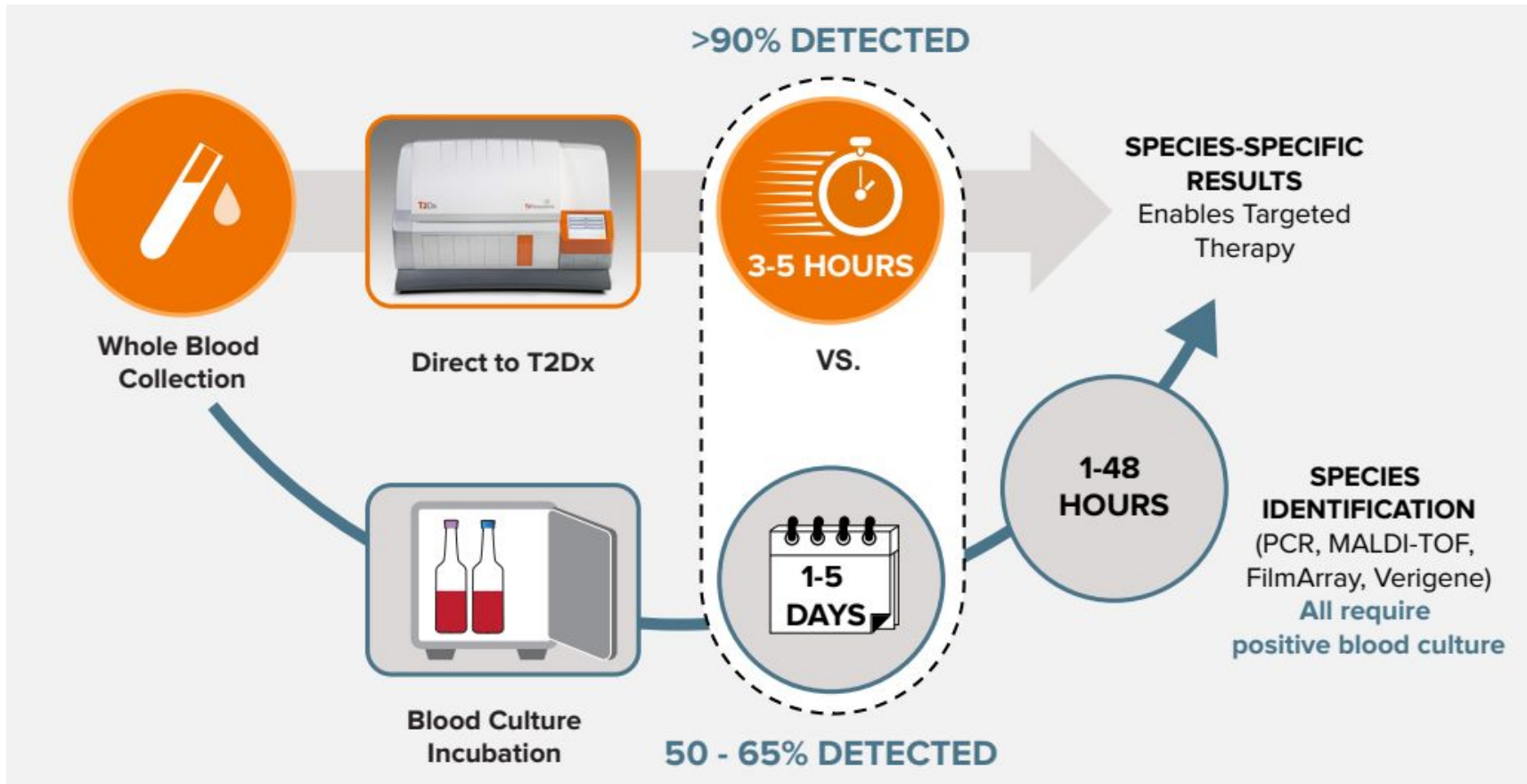
Bordetella pertussis	Negativo
Bordetella parapertussis	Negativo
Chlamydia pneumoniae	Negativo
Mycoplasma pneumoniae	Positivo
Adenovirus	Negativo
Coronavirus 229E	Negativo
Coronavirus HKU1	Negativo
Coronavirus OC43	Negativo
Coronavirus NL63	Negativo
H. Metapneumovirus	Negativo
H. Rhinovirus/Enterovirus	Negativo
Influenza A	Negativo
Influenza B	Negativo
MERS-CoV	Negativo
Parainfluenza 1	Negativo
Parainfluenza 2	Negativo
Parainfluenza 3	Negativo
Parainfluenza 4	Negativo
Virus Respiratorio Sinciziale (RSV)	Negativo
SARS-CoV 2	Negativo



Grazie ad un approccio molecolare in **Multiplex PCR**, unito ad un sistema di rilevazione in **risonanza magnetica** ora è possibile per il microbiologo definire la **terapia antibiotica** più appropriata e concorrere all'applicazione dei protocolli di **stewardship**, per il controllo dei fenomeni di **resistenza farmacologica**, in solo 3.5 ore dall'inizio del test.

Powered by CARB-X			
T2Candida®	T2Bacteria®	T2Resistance™	T2Candida® auris
Sensibilità: 91,1% ² Specificità: 99,4% ²	Sensibilità: 95,4% ¹ Specificità: 98,0% ²	FDA in corso CE fine 2019	Sensibilità: ≥89% Specificità: 98%
<i>C. albicans</i> <i>C. tropicalis</i> <i>C. parapsilosis</i> <i>C. krusei</i> <i>C. glabrata</i>	<i>E. faecium</i> <i>S. aureus</i> <i>K. pneumoniae</i> <i>A. baumannii</i> <i>P. aeruginosa</i> <i>E. coli</i>	<i>mec A/C</i> <i>van A/B</i> CTXM-14/15 KPC OXA-48 Group NDM, VIM, IMP AmpC (CMY/DHA)	<i>C. auris</i> <i>C. duobushaemulonii</i> <i>C. haemulonii</i>
Approvato FDA 1-3 CFU/mL LoD	Approvato FDA 2-11 CFU/mL LoD	Pannello RUO 2-5 CFU/mL LoD	RUO, validazione CDC su tamponi, prestazioni su sangue dimostrate; ≤5 CFU/mL LoD

The T2MR-powered **T2Dx[®] Instrument** can detect organisms as low as 1 CFU/mL, enabling it to be the only FDA-cleared technology that can detect low levels of pathogens in whole blood.



T2Bacteria[®] Panel*

95.8% Sensitivity | 98.1% Specificity¹

- *Enterococcus faecium*
- *Staphylococcus aureus*
- *Klebsiella pneumoniae*
- *Acinetobacter baumannii*
- *Pseudomonas aeruginosa*
- *Escherichia coli*

T2Candida[®] Panel

91.1% Sensitivity | 99.4% Specificity²

- *Candida albicans*
- *Candida tropicalis*
- *Candida krusei*
- *Candida glabrata*
- *Candida parapsilosis*

T2 batteri da sangue intero

Escherichia coli
Klebsiella pneumoniae
Pseudomonas aeruginosa
Acinetobacter baumannii

Batteri Gram positivi

Staphylococcus aureus
Enterococcus faecium

Sensibilità: 95,4%
Specificità: 98,0%

su batteri E.S.K.A.P.E.
Sensibilità e specificità sono calcolate tramite
il criterio di vera infezione

LoD compreso fra 2 – 11 CFU/mL

KPC
OXA-48
NDM / VIM / IMP
CTX-M 15/14
AmpC (CMY/DHA)
van A/B
mec A/C

Studi microbiologici di validazione hanno già dimostrato

LoD 2 CFU/mL
FDA Breakthrough Device*

CE IVD

Flusso di lavoro T2Dx[®]

T2Dx_FlussoLavoro



3 - 5 ore

Diagnosis and management of infections caused by multidrug-resistant bacteria: guideline endorsed by the Italian Society of Infection and Tropical Diseases (SIMIT), the Italian Society of Anti-Infective Therapy (SITA), the Italian Group for Antimicrobial Stewardship (GISA), the Italian Association of Clinical Microbiologists (AMCLI) and the Italian Society of Microbiology (SIM)



[International Journal of Antimicrobial Agents 60 \(2022\) 106611](#)

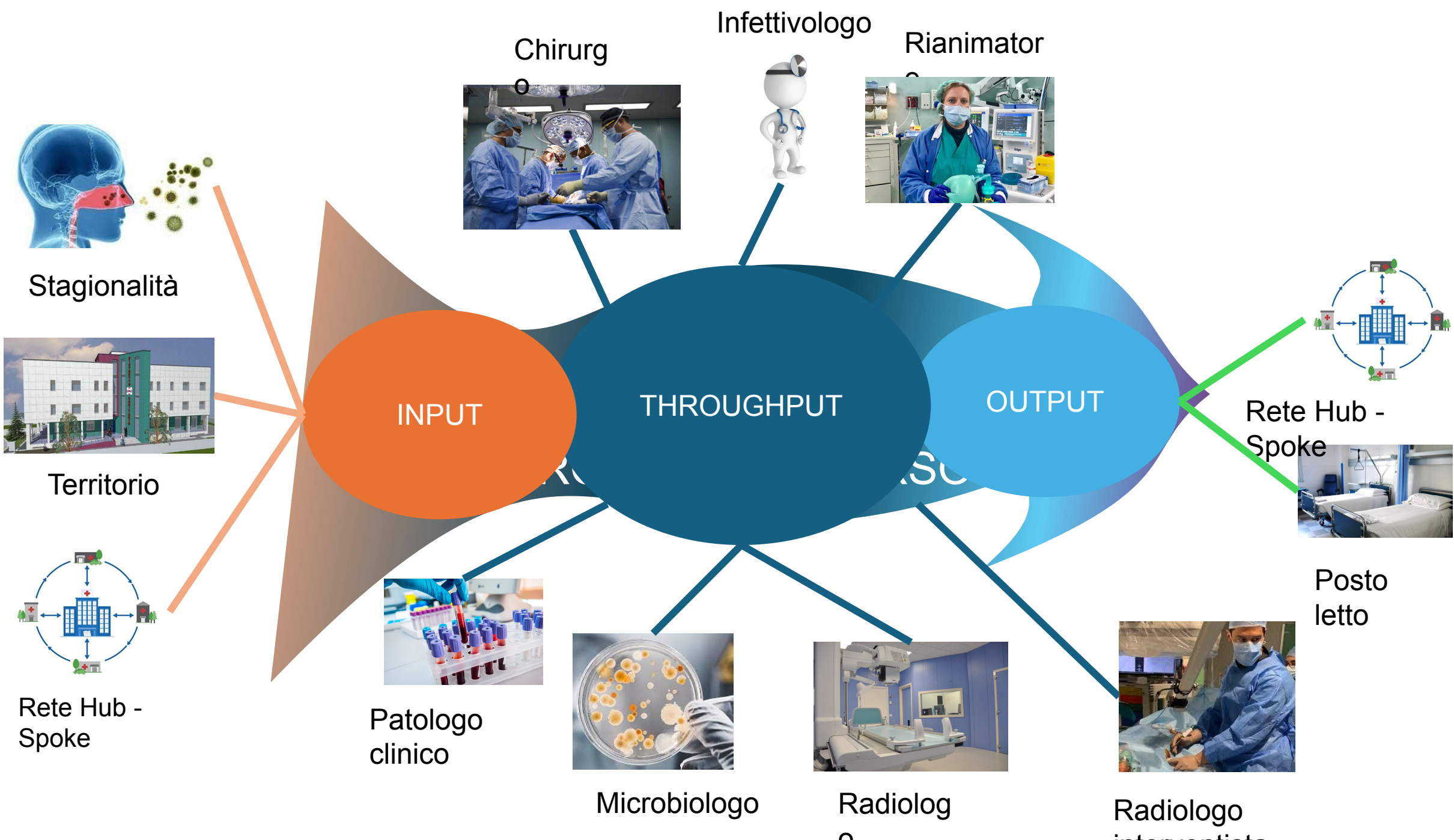
QUESTION #1: Do rapid microbiological diagnostics impact on the management and clinical outcome of critically ill/septic patients?

Recommendation 1.1:

In critically ill patients, the use of rapid diagnostic microbiological tests (RDTs) should be adopted since they have the potential to improve the timing to initiate appropriate therapy and possibly improve the patient outcome.

Strength of recommendations:	STRONG	Certainty of evidence:	LOW
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3. Lavorare in rete





INTENSITA'

alta

media

bassa

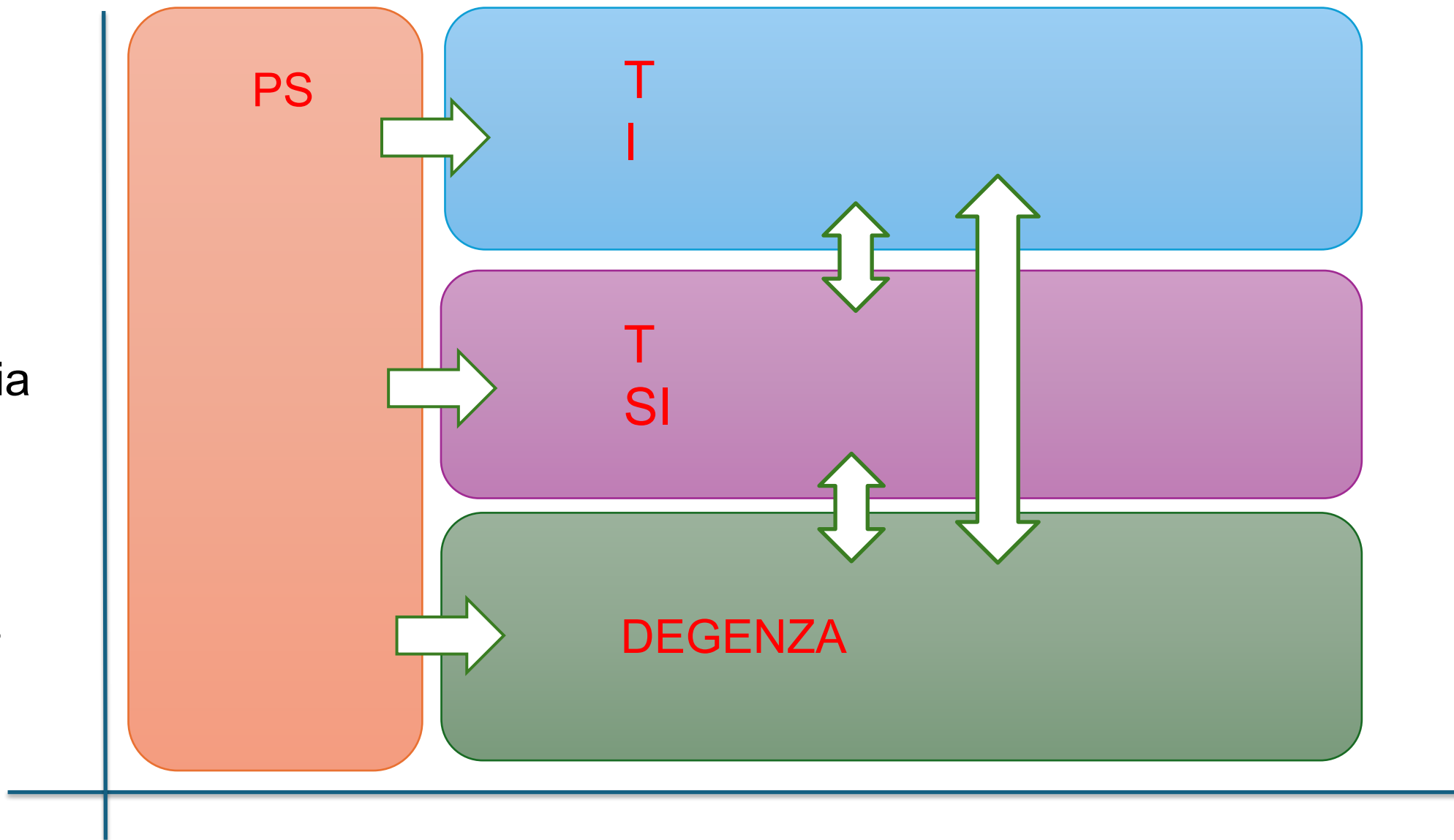
PS

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DEGENZA

TEMPO





Grazie per l'attenzione