AER 2019

25ème AER : 19 & 20 novembre 2020

Université de Paris

HÔPITAUX UNIVERSITAIRES PARIS NORD VAL DE SEINE
Bichat - Claude Bernard

MI² Medical Infectious diseases Intensive care unit

Sepsis: Actualités

Pr Jean-François Timsit

APHP:Hôpital Bichat - Médecine Intensive et Infection (MI²)

IAME U 1137- Université de Paris

F 75018- Paris, France

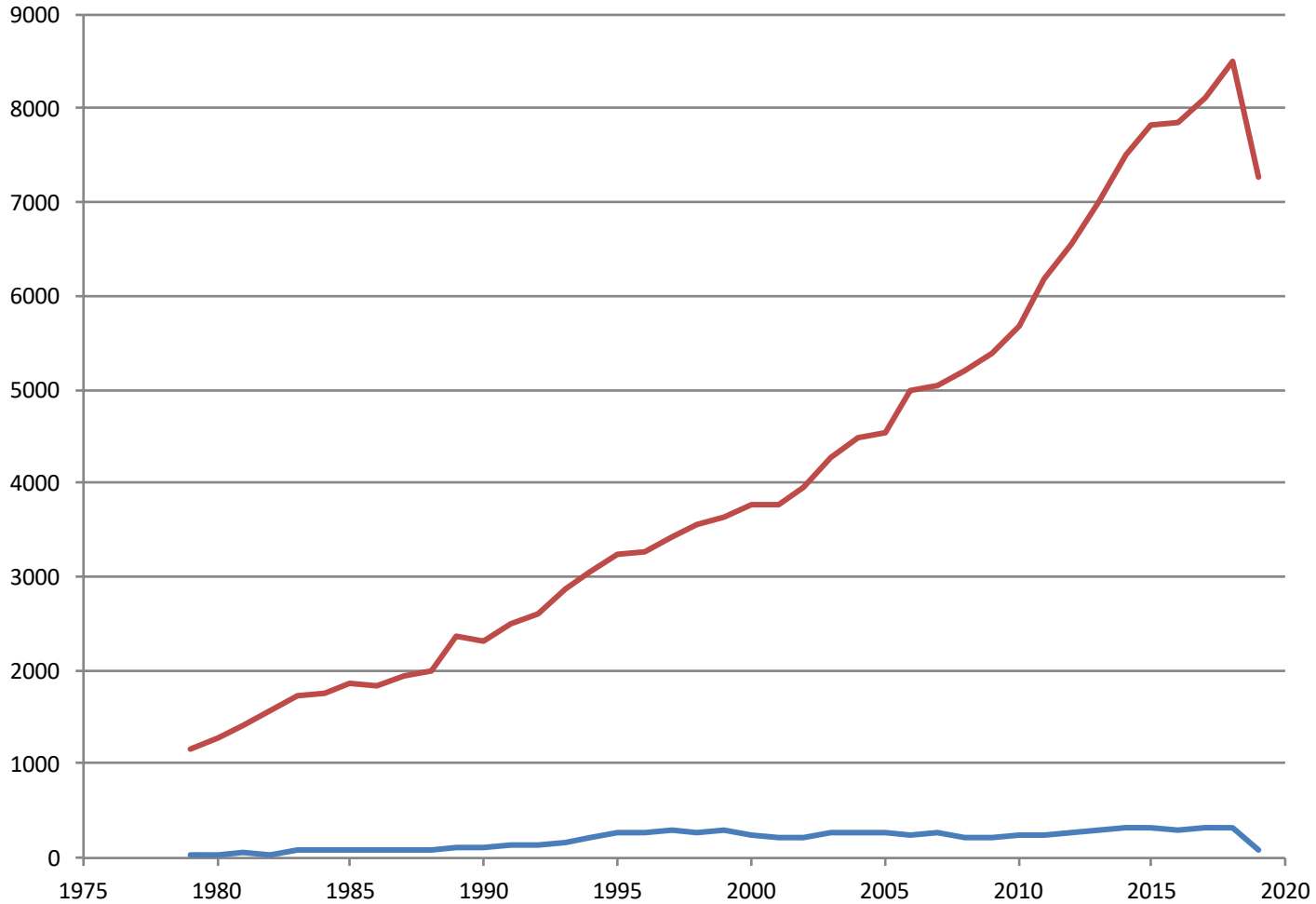
IAME UMR 1137

Infection • Antimicrobiens • Modélisation • Evolution

Liens d'intérêt

- Lectures: Biomerieux, Pfizer, Nabriva, Gilead, Merck
- Grant: Merck, Pfizer, 3M
- Board scientifique: Merck, Paratez, Bayer, Nabriva, Gilead

Sepsis or septic shock (Pubmed)



>8,000 per year

>300 per year

Focus on sepsis: new concepts and findings in sepsis care

Table 1 Uncertainties in sepsis

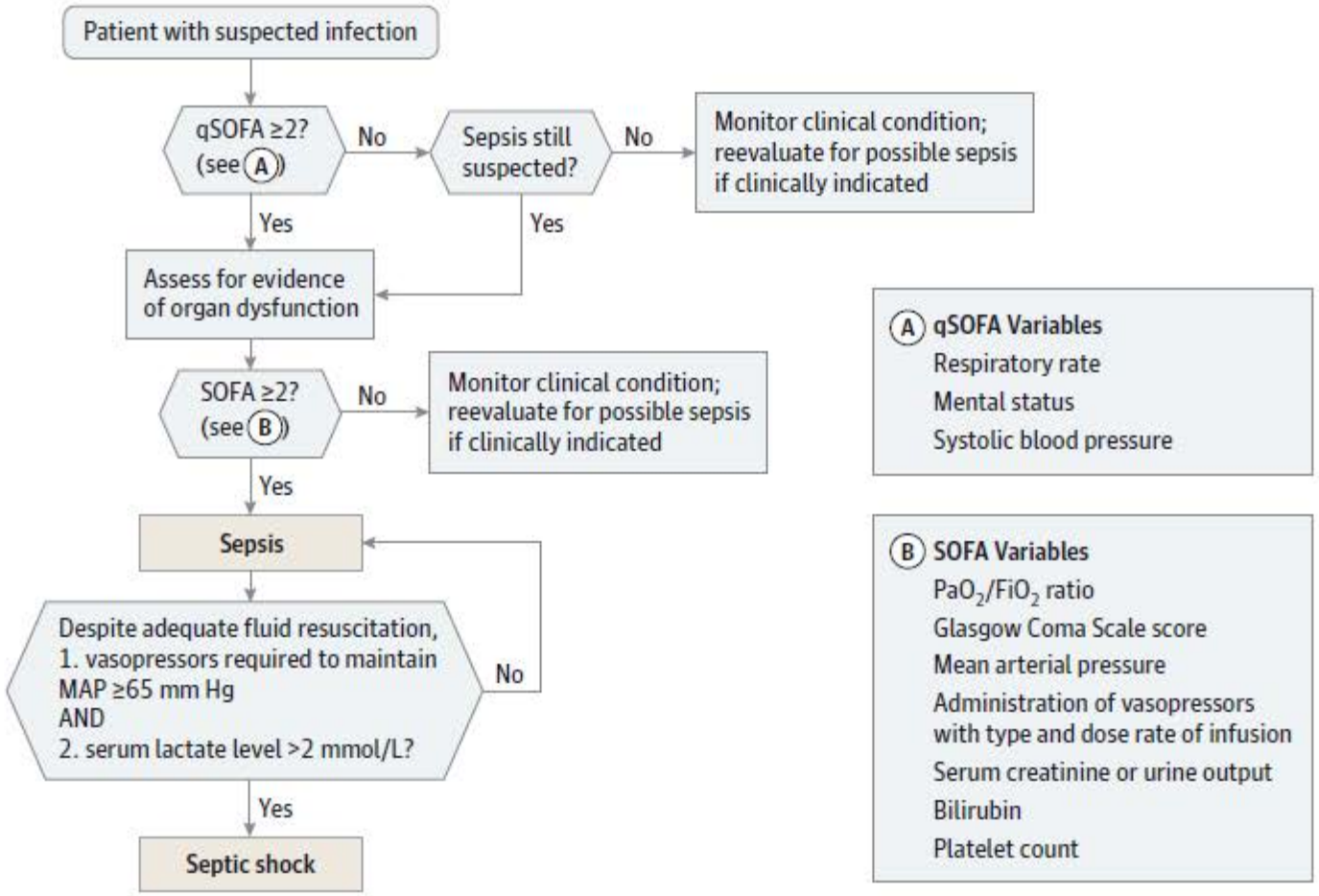
1.	Optimal amount of initial fluids in sepsis-induced hypoperfusion
2.	Ideal clinical parameters and endpoints for volume resuscitation
3.	Time-to-initiation of empirical antibiotics in patients with sepsis without shock
4.	Role of rapid microbiological diagnostic tests in the management of sepsis
5.	Selection of patients for treatment with adjunctive therapies
6.	Efficacy and feasibility of treatment recommendations in resource-limited countries

Intensive Care Med (2018) 44:1997–1999

Agenda

- **Epidémiologie**
  - **Changements?**
  - **Hétérogénéité et intelligence artificielle**
  - **Impact à long terme → traitements non limités à la phase initiale**
- Etudes pivot
  - Défaillances d'organes
  - Approches inflammatoire
- Domaines d'intérêt pour le futur

Définition: Sepsis 3.0 en 2016



La défaillance d'organe est au premier plan pour identifier les patients avec une « infection pathologique »

Sepsis
→ Réponse anormale de l'hôte à l'infection
→ Infection aboutissant à une défaillance d'organe

Choc septique → sepsis + dysfonction métabolique + défaillance hémodynamique

Singer et al. – JAMA, 2016

Epidemiology of Quick Sequential Organ Failure Assessment Criteria in Undifferentiated Patients and Association With Suspected Infection and Sepsis

Vijay Anand, DO; Zilu Zhang, MS; Sameer S. Kadri, MD; Michael Klompas, MD, MPH; and Chanu Rhee, MD, MPH; for the CDC Prevention Epicenters Program

CHEST 2019; 156(2):289-297

qSOFA only a prognostic score

- 1,004,347 hospitalized patients, **271,500 (27.0%) were qSOFA-positive**
- **qSOFA-positive patients** were older (median age, 65 vs 58 years), required ICU admission more often (28.5% vs 6.5%), and had **higher mortality** (6.7% vs 0.8%)
- **Sensitivities** of qSOFA for suspected infection and **sepsis** were 41.3% (95% CI, 41.1%-41.5%) and **62.8%** (95% CI, 62.4%-63.1%), respectively
- **AUC-ROC for prognosis of qSOFA was higher for patients WITHOUT infections**

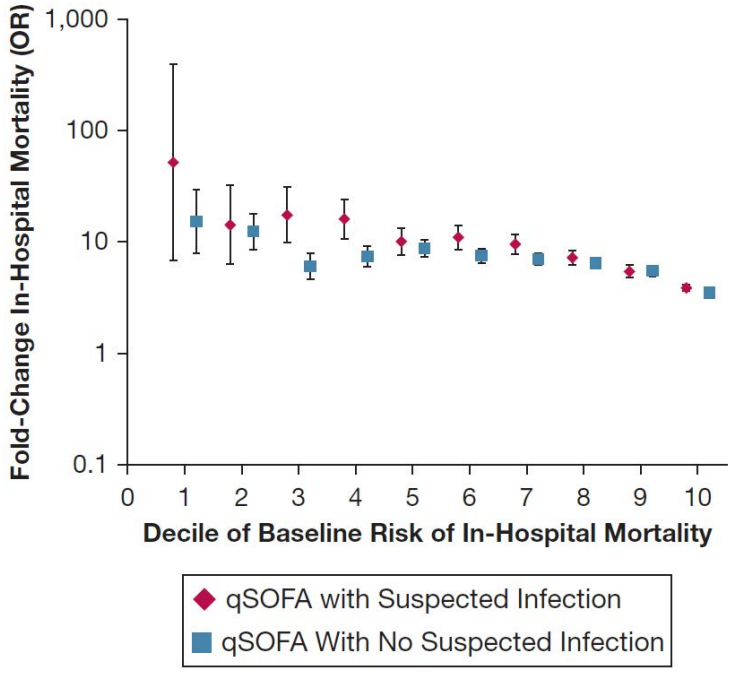


Figure 2 – *Fold change in rate of in-hospital mortality by deciles of baseline risk of death for ≥ 2 qSOFA criteria vs < 2 qSOFA criteria in patients with and without suspected infection on admission. The x axis*

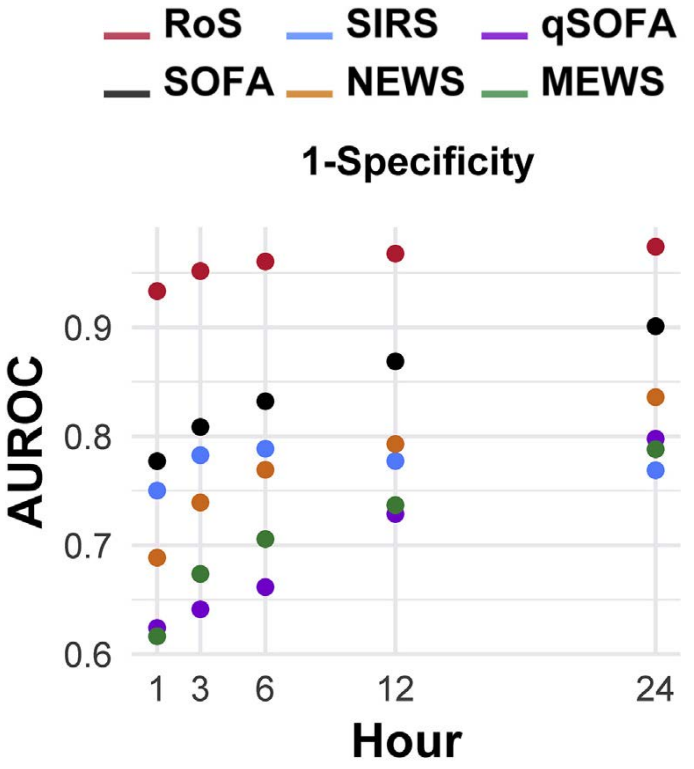
Development and Evaluation of a Machine Learning Model for the Early Identification of Patients at Risk for Sepsis

Ryan J. Delahanty, PhD; JoAnn Alvarez, MS; Lisa M. Flynn, MD; Robert L. Sherwin, MD; Spencer S. Jones, PhD*

*Corresponding Author. E-mail: ssj1364@gmail.com, Twitter: @ssj1364.

- 2,729,529 patients (49 ED)
- Sepsis defined according to Rhee's criterias
  - 2% sepsis (ICU admission 53.0% versus 3.4%; P<.00
  - a selected comorbid diagnoses (20.4% versus 3.0%)
  - Hospital death (11.9% versus 0.4%;P<.001).
- 56 potential major inputs (vital signs demographics lab results medication prescribed..)
- supervised machine learning called gradient boosting (local decision trees
- Multiple Internal cross validation
- Tested in a derivation cohort

Feature	Median (Interquartile Range)	Relative Influence, %*	Unobserved, %†
Lactic acid (max), mmol/L	1.5 (1.1 to 2.4)	52.4	90.7
Shock index‡×age (last)	27.4 (19.5 to 37.1)	6.5	0.6
WBC count (max), 10^9/L	8.5 (6.6 to 11.1)	5.4	46.4
Lactic acid (change), mmol/L	−0.8 (−1.6 to −0.2)	4.4	90.7
Neutrophils (max), %	68 (58.6 to 77.7)	4.2	49.6
Glucose (max), mg/dL	110 (96 to 142)	4.2	48.0
Blood urea nitrogen (max), mg/dL	14 (10.2 to 20)	3.9	49.7
Shock index‡×age (first)	27.6 (19.7 to 37.5)	3.9	0.6
Respiratory rate (max), breaths/min	18 (18 to 20)	3.8	0.7
Albumin (last), g/dL	4 (3.6 to 4.3)	3.4	58.5
Systolic blood pressure (min), mm Hg	128 (114 to 142)	3.1	0.4
Serum creatinine (max), mg/dL	0.8 (0.7 to 1.1)	2.5	49.7
Temperature (max), °F	98.3 (98 to 98.6)	2.5	2.8



=PPV

Model	Screening Threshold	Alert Rate, %	Sensitivity, %	Specificity, %	Precision, %*	AUROC
RoS	≥8.6%	4.9	67.7	96.4	27.6	0.93
qSOFA	≥2	0.2	3.7	99.8	31.3	0.62
SOFA	≥2	8.0	49.2	92.9	12.2	0.78
SIRS	≥2	7.1	40.4	93.6	11.2	0.75
MEWS	≥5	1.1	11.5	99.1	21.2	0.62
NEWS	≥7	1.7	18.2	98.6	20.7	0.69

Ann Emerg Med Volume 73, no. 4 : April 2019

Hétérogénéité du sepsis

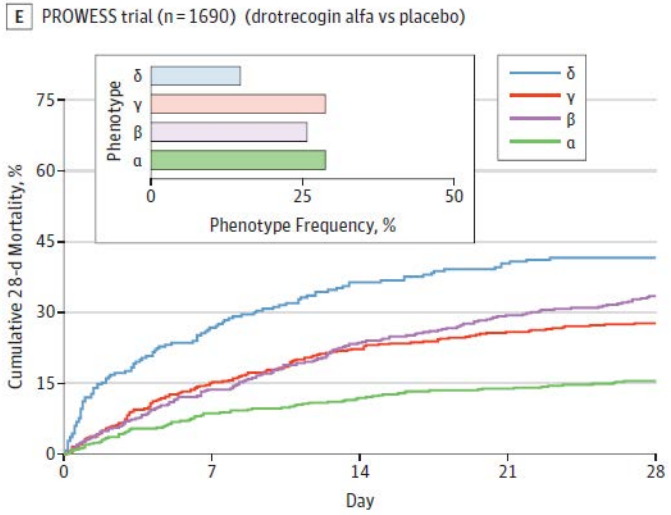
Classification non supervisée

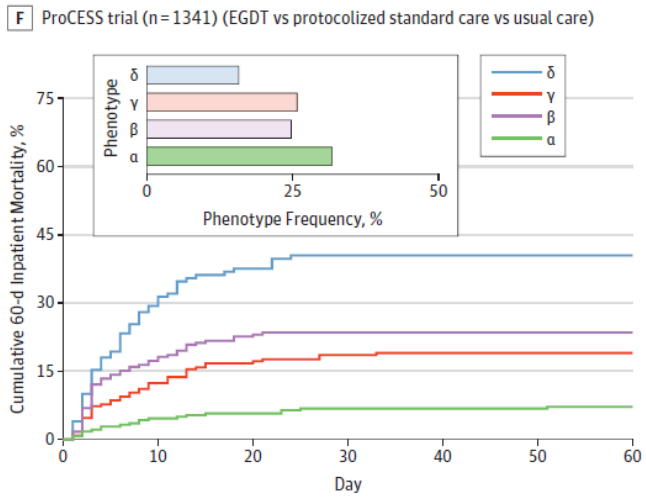
JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

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

Christopher W. Seymour, MD, MSc; Jason N. Kennedy, MS; Shu Wang, MS; Chung-Chou H. Chang, PhD; Corrine F. Elliott, MS; Zhongying Xu, MS; Scott Berry, PhD; Gilles Clermont, MD, MSc; Gregory Cooper, MD, PhD; Hernando Gomez, MD, MPH; David T. Huang, MD, MPH; John A. Kellum, MD, FACP, MCCM; Qi Mi, PhD; Steven M. Opal, MD; Victor Talisa, MS; Tom van der Poll, MD, PhD; Shyam Visweswaran, MD, PhD; Yoram Vodovotz, PhD; Jeremy C. Weiss, MD, PhD; Donald M. Yealy, MD, FACEP; Sachin Yende, MD, MS; Derek C. Angus, MD, MPH

- Data from 3 cohorts and 3 RCTs (1998-2014)
- Variables: vital signs comorbidities severity scores biological parameters (incl. Lactates and albumin)
- K-clustering
- 4 clusters with very different inflammatory pattersns and prognosis
  - **α phenotype**: fewer abnormal laboratory values and less organ dysfunction
  - **β phenotype** older, greater chronic illness, and more renal dysfunction
  - **γ phenotype** elevated measures of inflammation (eg,white blood cell count,premature neutrophil count [bands], erythrocyte sedimentation rate, or C-reactive protein), lower albumin level, and higher temperature;
  - **δ phenotype** elevated serum lactate levels, elevated levels of transaminases, and hypotension





JAMA. 2019;321(20):2003-2017.

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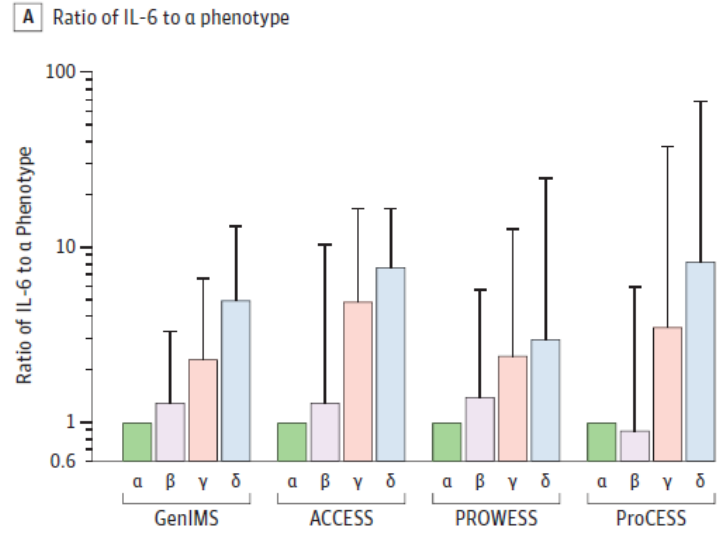
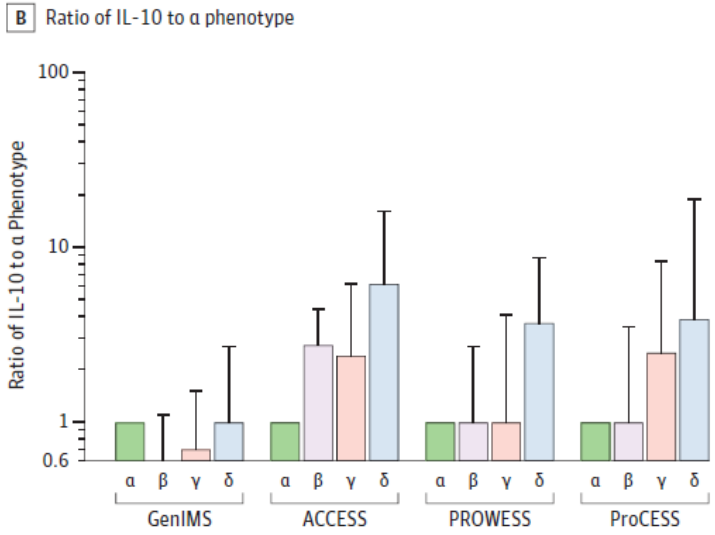
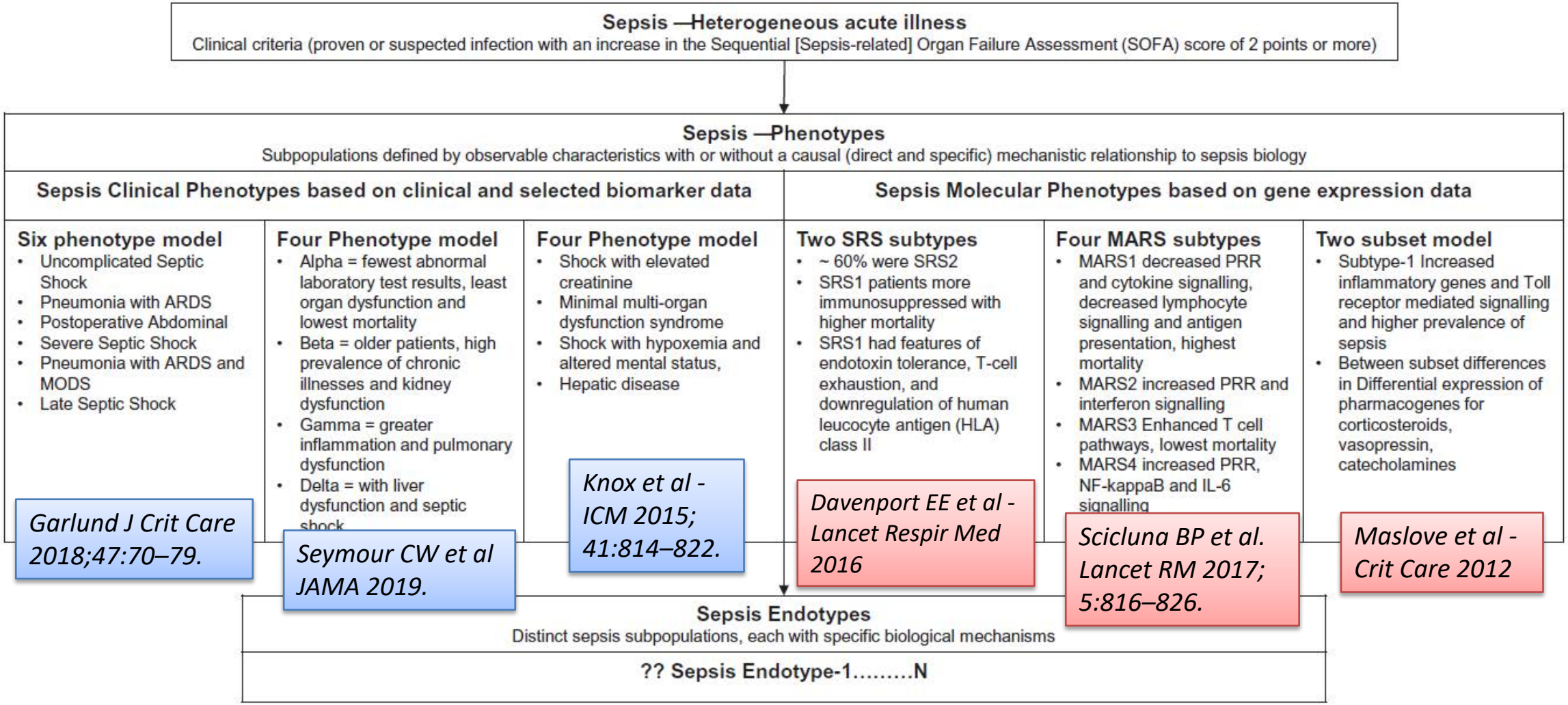




JAMA. 2019;321(20):2003-2017.

Sepsis phenotypes



Shankar-hari - Curr Opin Crit Care 2019, 25:000–000

Sepsis heterogeneity: What for?

« intelligence artificielle ou bêtise naturelle »

- **Phenotype** resulted from interactions of the genotype and the environment
- **Endotype** is defined as a phenotype with a specific biological pathway that explains the observable properties of that phenotype.

“Unsupervised artificial intelligence is not unbiased because only the data available within the database can be explored, and only the data that are known or thought to be important are entered**.**

Because knowledge of the underlying pathophysiological mechanisms associated with multiple organ failure **in patients with sepsis** is still **limited, the data** that are **directly related to the cause** or mechanisms **of organ failure cannot be registered.**

This creates the **danger that the next clinical trial** will be performed **in patient subgroups without a common underlying pathophysiology of multiple organ failure, <u>leading to off-target effects and another unsuccessful trial”</u>**

Mosers J et al – Jama 2019 (letter)

Intensive Care Med (2019) 45:1599–1607
https://doi.org/10.1007/s00134-019-05790-z

ORIGINAL

ICU staffing feature phenotypes and their relationship with patients' outcomes: an unsupervised machine learning analysis

Fernando G. Zampieri[1,2], Jorge I. F. Salluh[1,3], Luciano C. P. Azevedo[4], Jeremy M. Kahn[5,6], Lucas P. Damiani[2], Lunna P. Borges[3], William N. Viana[7], Roberto Costa[8], Thiago D. Corrêa[9], Dieter E. S. Araya[10], Marcelo O. Maia[11], Marcus A. Ferez[12], Alexandre G. R. Carvalho[13], Marcos F. Knibel[14], Ulisses O. Melo[15], Marcelo S. Santino[16], Thiago Lisboa[17], Eliana B. Caser[18], Bruno A. M. P. Besen[19], Fernando A. Bozza[1,20], Derek C. Angus[5,6], Marcio Soares[1*] and the ORCHESTRA Study Investigators

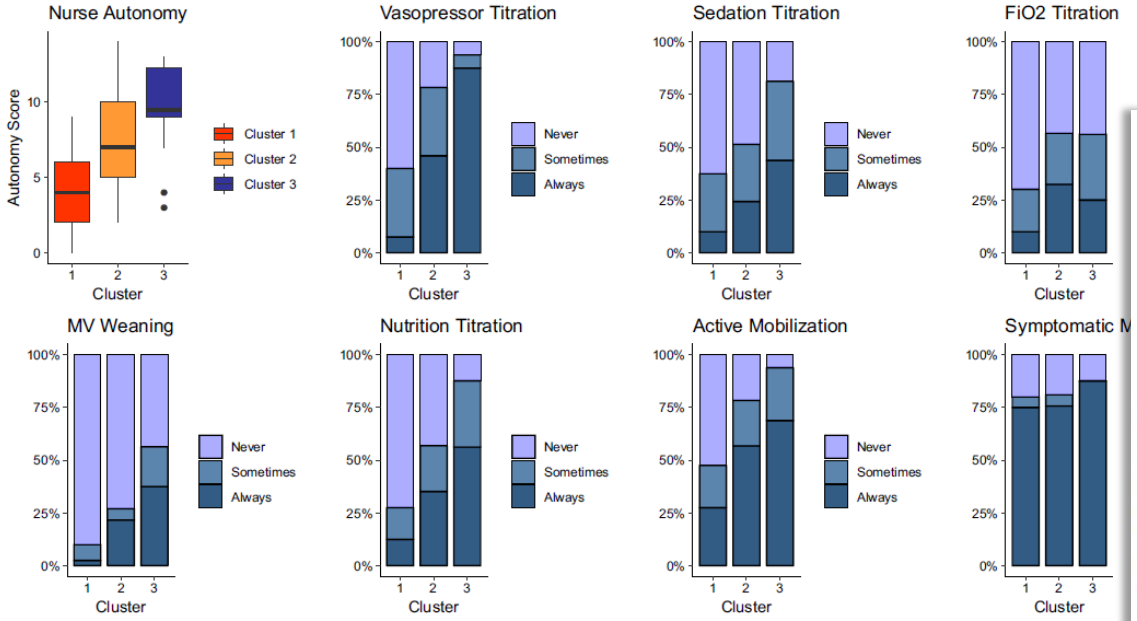
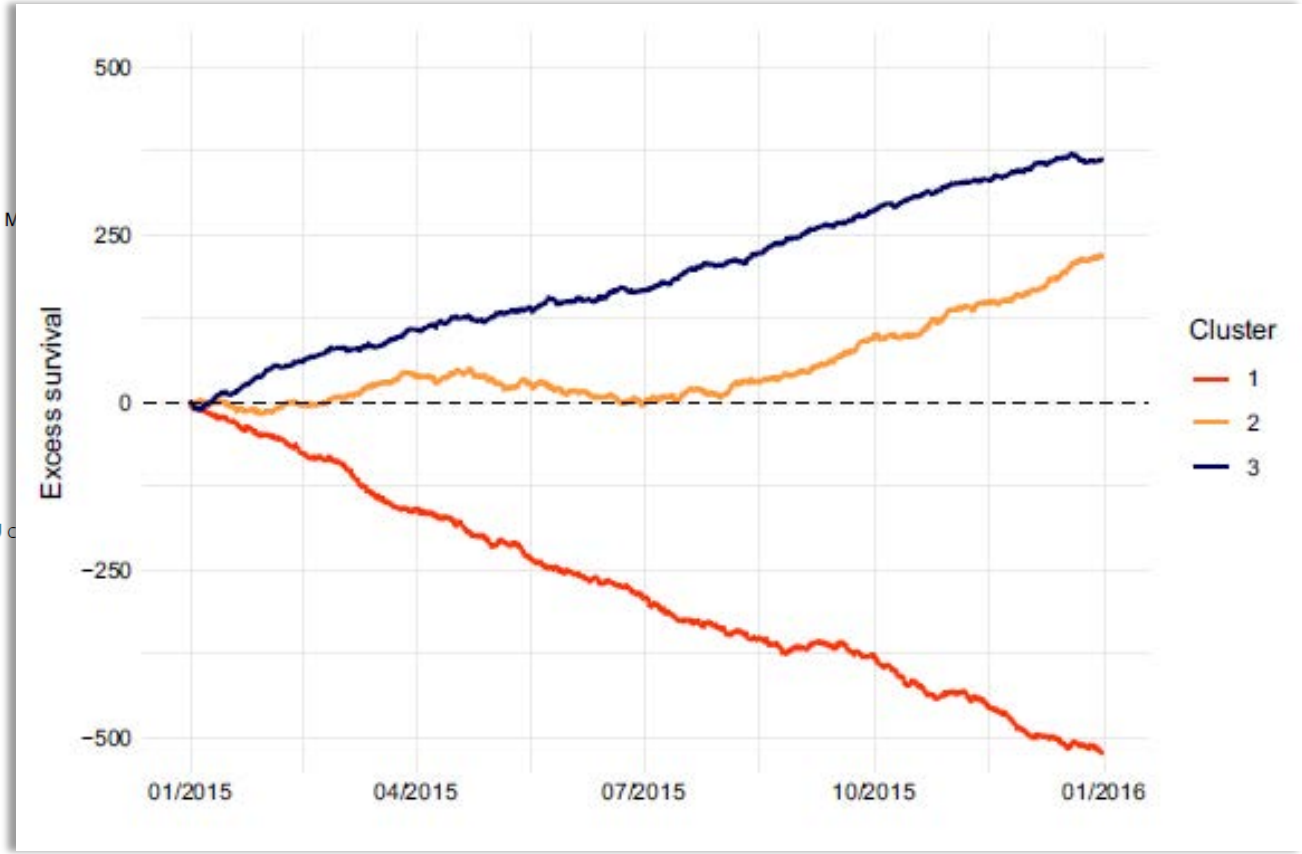


Fig. 2 Top left: nurse autonomy score according to cluster. Each following panel represents the autonomy level of nurses in each ICU c
regarding each autonomy component of nurse autonomy score

Board-certified intensivists in the ICU 24/7 (present in Cluster 3)

Dedicated pharmacists (present in Clusters 2 and 3)

Extent of nurse autonomy (which increased from Clusters 1 to 3)



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The Development of Chronic Critical Illness Determines Physical Function, Quality of Life, and Long-Term Survival Among Early Survivors of Sepsis in Surgical ICUs*

Anna K. Gardner, PhD[1,2]; Gabriela L. Ghita, MPH[3]; Zhongkai Wang, MS[3]; Tezcan Ozrazgat-Baslanti, PhD[4]; Steven L. Raymond, MD[2]; Robert T. Mankowski, PhD[1]; Babette A. Brumback, PhD[3]; Philip A. Efron, MD[2]; Azra Bihorac, MD[4]; Frederick A. Moore, MD[2]; Stephen D. Anton, PhD[1]; Scott C. Brakenridge, MD[2]

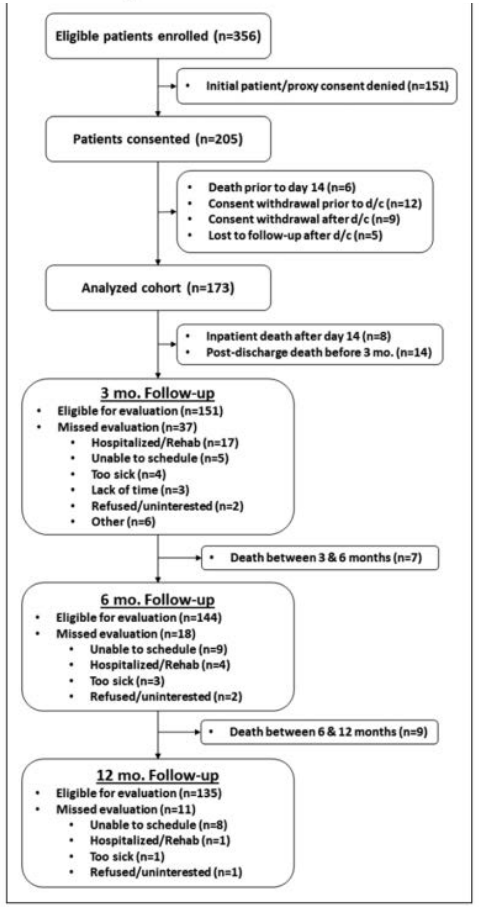


Figure 1. Consolidated Standards of Reporting Trials diagram and retention rates of 12-month follow-up. d/c = index hospitalization discharge.

2 réanimations

Survivants à J14

173 patients avec sepsis

63 (36%) “chronic critical illness: >14 j avec des DO”

≠ survie à 12 mois (54% vs 92%; $p < 0.01$).

≠ capacité fonctionelle

≠ qualité de vie.

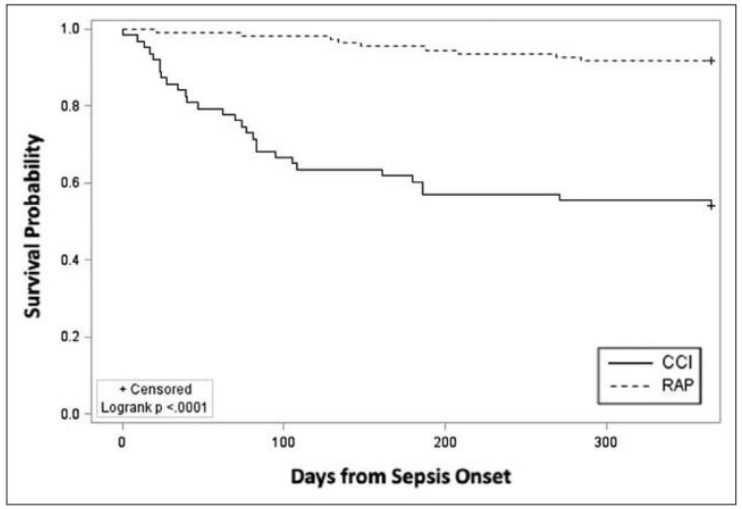


Figure 2. Twelve-month survival among chronic critical illness (CCI) versus rapid recovery (RAP) patients.

CCI: chronic chritical illness
RAP: rapide recovery

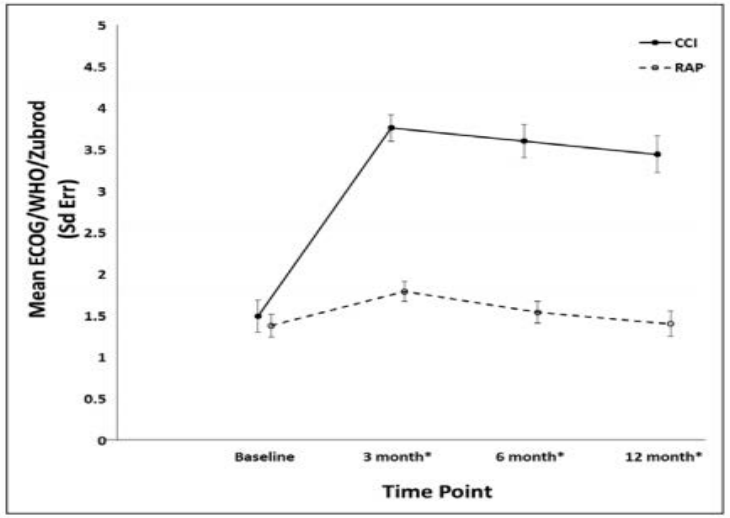


Figure 3. Twelve-month performance status differences in chronic critical illness (CCI) versus rapid recovery (RAP) patients. Zubrod Score: 0, asymptomatic (fully active, able to carry out all pre-disease activities without restriction); 1, symptomatic but completely ambulatory (restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature); 2, symptomatic, less than 50% in bed during the day (ambulatory and capable of all self-care but unable to carry out any work activities); 3, symptomatic, greater than 50% in bed, but not bedbound (capable of only limited self-care, confined to bed or chair 50% or more of waking hours); 4, bedbound (completely disabled. Cannot carry on any self-care. Totally confined to bed or chair); and 5, death. *$p < 0.05$. ECOG = Eastern Cooperative Oncology Group, WHO = World Health Organization.

DEVENIR DES PATIENTS

JAMA | Review

Enhancing Recovery From Sepsis
A Review

Hallie C. Prescott, MD, MSc; Derek C. Angus, MD, MPH

- Revue « systématique »: épidémiologie, physiopathologie, séquelles post sepsis

- Plus de 19 Millions de sepsis par an dans le monde
- Baisse de la mortalité de 35% en 2000 à 18% en 2012
- Nouvelles données tendent à dire que les survivants présentent:
  - Plus de plaintes fonctionnelles
  - Plus de comorbidités
  - En perte d'autonomie
  - plus de recours aux soins
- Besoin d'organiser la prise en charge (« management ») post hospitalisation.

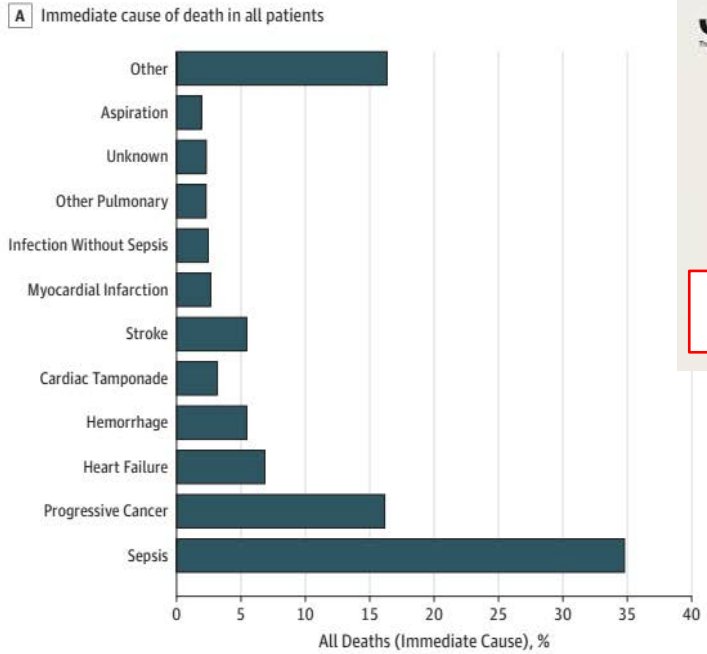
JAMA. 2018 Jan 2;319(1):62-75

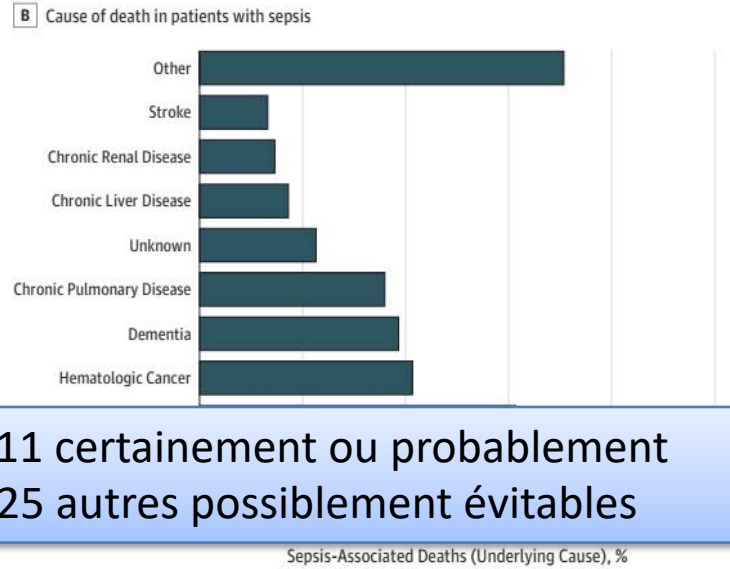
Original Investigation | Critical Care Medicine

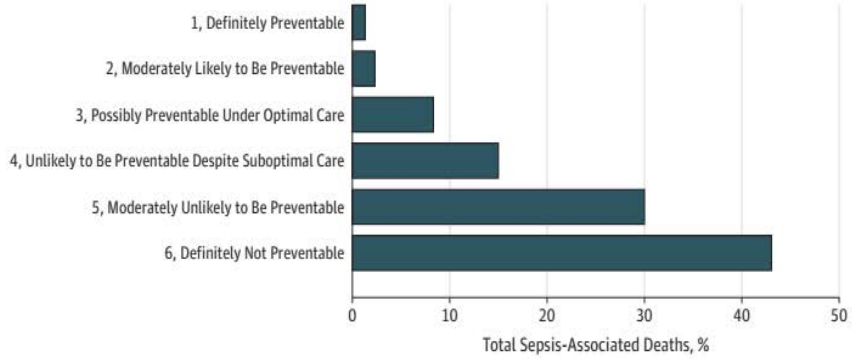
Prevalence, Underlying Causes, and Preventability of Sepsis-Associated Mortality in US Acute Care Hospitals

Chanu Rhee, MD, MPH; Travis M. Jones, PharmD; Yasir Hamad, MD; Anupam Pande, MD, MPH; Jack Varon, MD; Cara O'Brien, MD; Deverick J. Anderson, MD, MPH; David K. Warren, MD, MPH; Raymund B. Dantes, MD, MPH; Lauren Epstein, MD, MS; Michael Klompas, MD, MPH; for the Centers for Disease Control and Prevention (CDC) Prevention Epicenters Program

- 6 US academic and community hospitals from January 1, 2014, to December 31, 2015
- Rétrospectif, 568 dossiers en 2014/2015 aux USA de patients décédés à l'hôpital ou admis en long-séjour
- **Sepsis pour 52.8% d'entre eux.**
- **Sepsis comme causes immédiate de décès pour 198 cas.**







MAIS Uniquement 11 certainement ou probablement évitables (3.7%) et 25 autres possiblement évitables

Séquelles post sepsis

- Au USA en 2014, post sepsis
  - 1/2 récupération complète
  - 1/6 perte d'autonomie importante
  - 1/3 décèdent dans l'année (½ récidive de sepsis; ½ comorbidités/âge).

JAMA. 2018 Jan 2;319(1):62-75

Séquelles post sepsis

- Sociales
  - 35% maisons médicalisés
  - 43% de retour au travail dans l'année pour les patients travaillant
  - 33% des patients vivant à domicile avant récupèrent une autonomie à 6 mois

Séquelles post sepsis

- Somatiques
  - Récurrence infection et sepsis:
    - 40% de réadmission dans les 90 jours
      - 12% pour sepsis, infection/8% pour âge et comorbidités,
    - 9 fois plus de risque de sepsis que dans une population similaire sans ATCD de sepsis
  - Exacerbation d'une pathologie chronique

Epidemiology and Predictors of 30-Day Readmission in Patients With Sepsis

Shruti K. Gadre, MD; Mahek Shah, MD; Eduardo Mireles-Cabodevila, MD; Brijesh Patel, DO; and Abhijit Duggal, MD

CHEST

2019

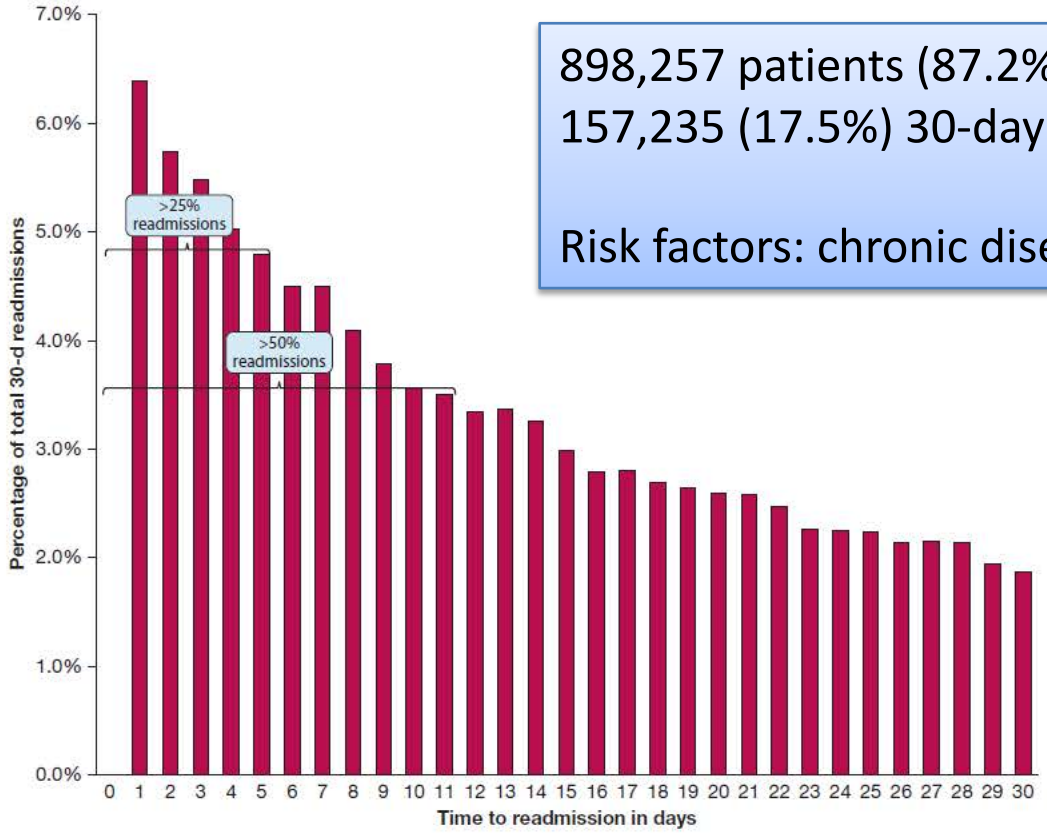


Figure 1 – *Time to first 30-d readmission following a sepsis admission.*

898,257 patients (87.2%) survivors
157,235 (17.5%) 30-day readmission;

Risk factors: chronic diseases

TABLE 2] Etiologies for 30-d Readmission Following Primary Admission for Sepsis

Etiology for Readmission	No. (%)
Infectious etiologies	**75,433 (42.16)**
Sepsis	35,944 (22.86)
Unspecified septicemia	32,779 (18.38)
Staphylococcal septicemia	2,601 (1.45)
Escherichia coli septicemia	1,908 (1.16)
Pseudomonas septicemia	758 (0.42)
Other gram-negative septicemia	1,923 (1.07)
Anaerobic septicemia	692 (0.38)
Pneumonia/pneumonitis	12,107 (6.75)
UTI or pyelonephritis	5,281 (2.94)
Infections of skin and subcutaneous tissue	4,050 (2.25)
UTI from indwelling catheter	1,485 (0.82)
Central venous catheter-related infection	1,249 (0.69)
Clostridium difficile colitis	3,189 (1.77)
Intestinal infections	365 (0.2)
Acute and subacute bacterial endocarditis	609 (0.33)
Meningitis	94 (0.05)
Central nervous system abscess	240 (0.13)
Gastrointestinal/hepatic and pancreatic etiologies	**17,252 (9.6)**
Cardiovascular etiologies	**15,737 (8.73)**
Heart failure[a]	7,571 (4.22)
Respiratory etiologies	**14,063 (7.82)**
Respiratory failure	5,268 (2.94)
Obstructive lung disease	3,358 (1.87)
Kidney/genitourinary etiologies	**8,958 (4.99)**
Acute or acute on chronic kidney failure	6,249 (3.48)

All percentages were rounded off to the closest second decimal point; total may not equal 100%. Boldface type indicates broad subcategories of etiology of readmission.
[a]Includes systolic, diastolic, combined, acute, chronic, unspecified, and volume overload.

The mean cost per readmission was $16,852; annual cost was > $3.5 billion within the United States

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RESEARCH LETTER

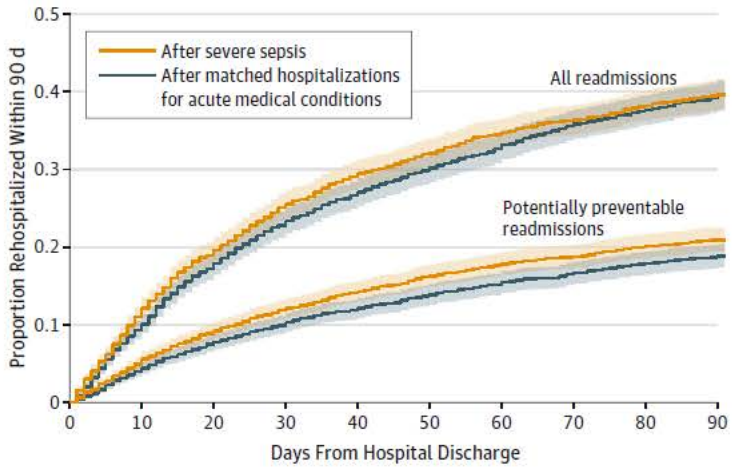
Readmission Diagnoses After Hospitalization for Severe Sepsis and Other Acute Medical Conditions

Hallie C. Prescott, MD, MSc
Kenneth M. Langa, MD, PhD
Theodore J. Iwashyna, MD, PhD

Table. Most Frequent Readmission Diagnoses After Hospitalization for Severe Sepsis

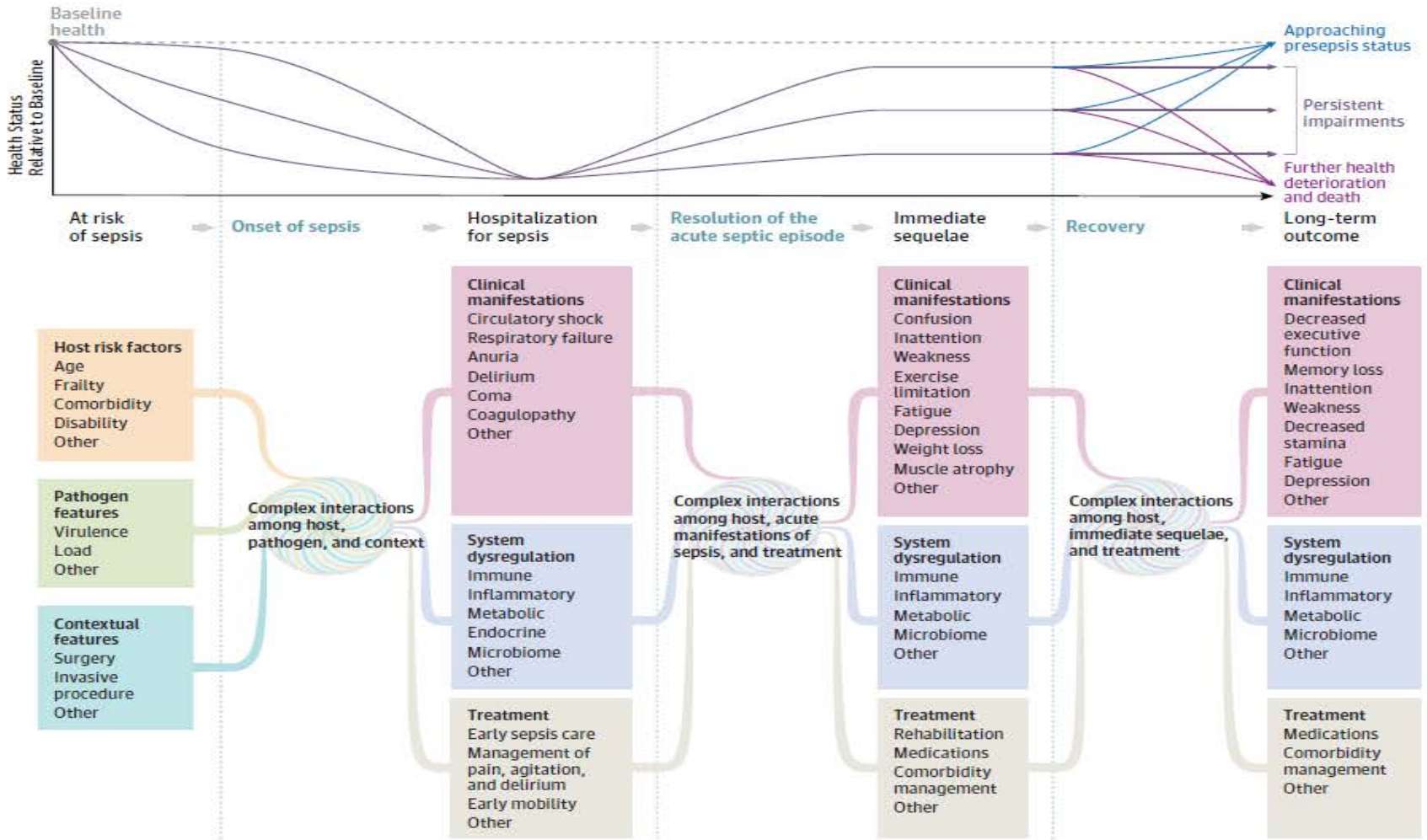
Diagnosis[a]	Severe Sepsis (n = 2617)		Matched Hospitalizations for Other Acute Medical Conditions (n = 2617)[b]		*P* Value[c]
	No. of Survivors	% (95% CI)	No. of Survivors	% (95% CI)	
Sepsis	167	6.4 (5.4-7.3)	73	2.8 (2.2-3.4)	<.001
Congestive heart failure	144	5.5 (4.6-6.4)	204	7.8 (6.8-8.8)	.001
Pneumonia	92	3.5 (2.8-4.2)	85	3.3 (2.6-3.9)	.58
Acute renal failure	87	3.3 (2.6-4.0)	30	1.2 (0.7-1.6)	<.001
Rehabilitation	74	2.8 (2.2-3.5)	120	4.6 (3.8-5.4)	.001
Respiratory failure	65	2.5 (1.9-3.1)	38	1.5 (1.0-1.9)	.007
Complication of device, implant, or graft	52	2.0 (1.5-2.5)	59	2.3 (1.7-2.8)	.50
COPD exacerbation	49	1.9 (1.4-2.4)	41	1.6 (1.1-2.0)	.40
Aspiration pneumonitis	47	1.8 (1.3-2.3)	31	1.2 (0.8-1.6)	.06
Urinary tract infection	44	1.7 (1.2-2.2)	47	1.8 (1.3-2.3)	.75

Figure. Total and Potentially Preventable 90-Day Readmissions Among Survivors of Severe Sepsis and Matched Hospitalizations for Acute Medical Conditions



Potentially preventable readmission diagnoses include pneumonia, hypertension, dehydration, asthma, urinary tract infection, chronic obstructive pulmonary disease exacerbation, perforated appendix, diabetes, angina, congestive heart failure, sepsis, acute renal failure, skin or soft tissue infection, and aspiration pneumonitis. The shaded areas indicate 95% confidence intervals.

Figure 2. A Conceptual Model of the Potential Network of Factors and Interactions Important to Determining a Patient's Clinical Course and Long-term Outcome After Sepsis



There are many potential clinical courses that a patient may experience after a hospitalization for sepsis, from rapid complete recovery to recurrent complications and death. This figure depicts examples of common clinical trajectories and presents a conceptual model of factors important to shaping a patient's clinical course and long-term outcome. This figure draws from the Wilson-Cleary model,[18] which links underlying biological factors to physical function and quality of life, but extends the representation of the biological factors to demonstrate their complex and unmeasurable interactions.

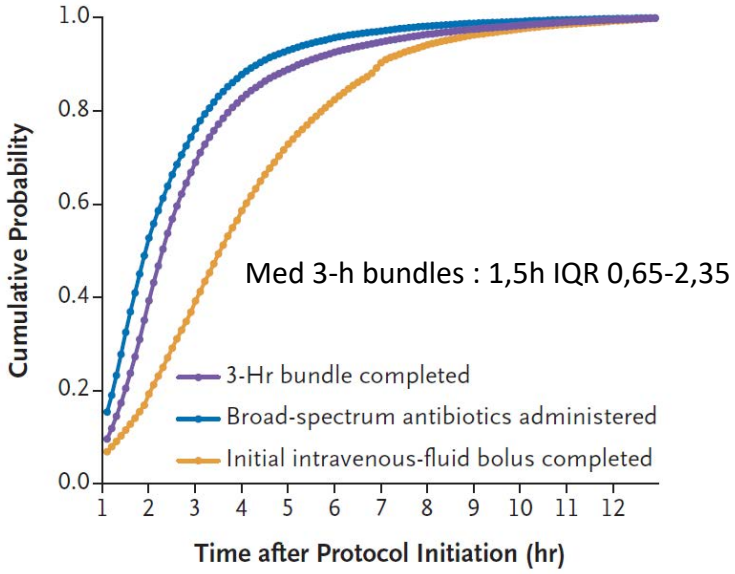
JAMA. 2018 Jan 2;319(1):62-75

Agenda

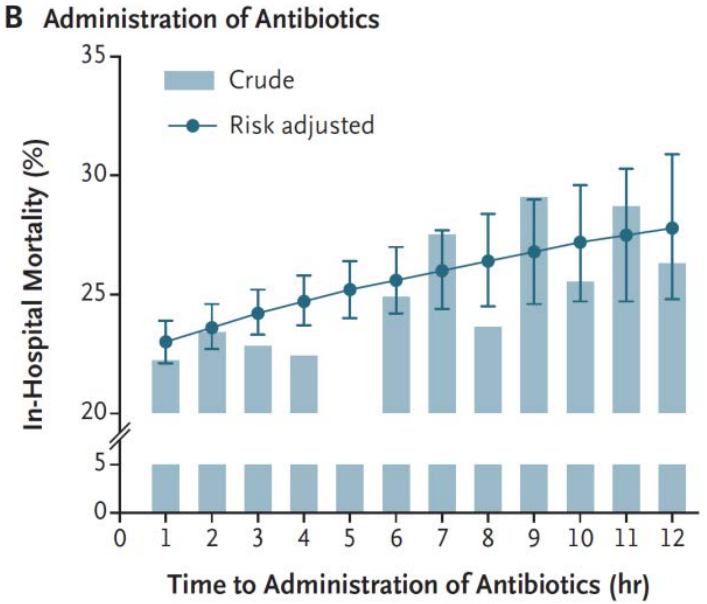
- Epidémiologie
  - Changements?
  - Hétérogénéité et intelligence artificielle
  - Impact à long terme
- **Etudes pivot**
  - **Antibiotiques et Défaillances d'organes**
  - **Approches « inflammatoire »**
- Domaines d'intérêt pour le futur

3-h bundle and prognosis

49331 patients ; sepsis and septic shock in 149 hospitals
Administrative data
82,5% respect of the 3-h bundles
Hospital mortality 22,8%

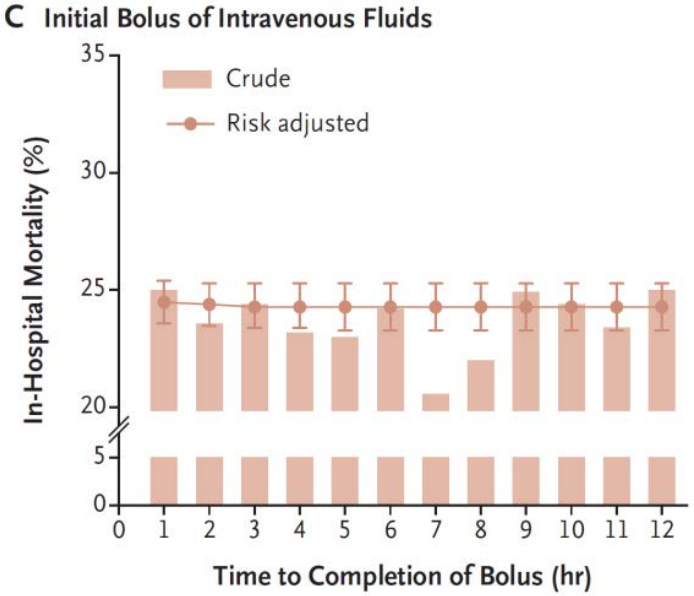


Med 3-h bundles : 1,5h IQR 0,65-2,35



Median ABx: 0.95h IQR 0,35-1,95

OR 1.04 per hour, p<0.001



Median fluids : 2,56 IQR 1,33-4,20

Seymour et *al.* – NEJM 2017

JAMA Network Open

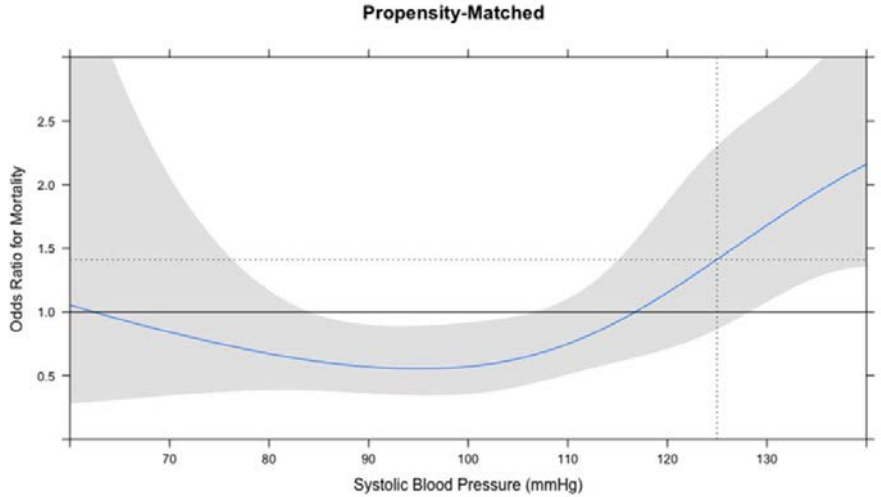
Original Investigation | Emergency Medicine

Association Between Early Intravenous Fluids Provided by Paramedics and Subsequent In-Hospital Mortality Among Patients With Sepsis

Daniel J. Lane, PhD; Hannah Wunsch, MD, MSc; Refik Saskin, MS; Sheldon Cheskes, MD; Steve Lin, MDCM, MSc; Laurie J. Morrison, MD, MSc; Damon C. Scales, MD, PhD

- 1871 patients in Canada: Early administration of intravenous fluids provided by paramedics and in-hospital mortality
- Early IV fluids (400ml in median) to patients presenting with a low initial SABP was associated with reduced OR of mortality but not among patients with a higher initial SABP

eFigure 2: Changes in odds of mortality for IV fluid treatment at different initial systolic blood pressures, with 95% confidence bands, in propensity matched model



NB: Adjusted on:

- baseline characteristics
- initial physiological measures
- documented symptoms,
- Physical examination findings
- paramedics' suspicion of sepsis in the patient,
- total prehospital time
- transportation priority

CAUTION: Antibiotics given by doctors only / prehospital time shorter for severe cases

JAMA Network Open. 2018;1(8):e185845. doi:10.100

JAMA Network | Open 2018

Invited Commentary | Emergency Medicine

Toward a More Nuanced Approach to the Early Administration of Intravenous Fluids in Patients With Sepsis

Chanu Rhee, MD, MPH; Andre C. Kalil, MD, MPH

- Bayesian analysis of 37 EGDT studies (20 000 patients) suggested that the mortality **benefit in the EGDT solely** explained by **earlier administration of appropriate antibiotics**, **rather than intravenous fluids** or any of the protocol's hemodynamic targets. Kalil et al – *Crit Care Med. 2017;45(4):607-614*
- **Time to IV 30 ml/kg bolus fluids** is **not related to mortality** during mandated emergency care for sepsis Seymour et al - *NEJM. 2017;376(23):2235-2244*
- In a large US database of 35,135 patients a low volume resuscitation (1–4.99 L) improved prognosis but, in patients receiving **high volume resuscitation (5 to ≥ 9 L), the mortality increased** by 2.3% (95% CI 2.0, 2.5%; *p = 0.0003) for each additional liter.* *Marik et al* - Intensive Care Med 2017; 43:625–632
- A multicenter analysis (SEP-1) suggested that failing on the 3-hour antibiotic measure was associated with higher mortality, while failing the treatment **bundle** on any other component (including **the 30-mL/kg fluid requirement**) **was not**. Rhee C et al - *Crit Care Med. 2018;46(10):1585-1591*
- **Positive fluid balance** and weight gain are associated with a **poorer outcome** in sepsis

Sakr Y- *Crit Care Med. 2017;45(3):386-394.*

Andrews B (RCT). *JAMA. 2017;318(13):1233-1240.*

Gros A - Crit Care Med. 2018 Oct;46(10):e981-e987

Research

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of a Resuscitation Strategy Targeting Peripheral Perfusion Status vs Serum Lactate Levels on 28-Day Mortality Among Patients With Septic Shock

The ANDROMEDA-SHOCK Randomized Clinical Trial

Glenn Hernández, MD, PhD; Gustavo A. Ospina-Tascón, MD, PhD; Lucas Petri Damiani, MSc; Elisa Estenssoro, MD; Arnaldo Dubin, MD, PhD; Javier Hurtado, MD; Gilberto Friedman, MD, PhD; Ricardo Castro, MD, MPH; Leyla Alegría, RN, MSc; Jean-Louis Teboul, MD, PhD; Maurizio Cecconi, MD, FFICM; Giorgio Ferri, MD; Manuel Jibaja, MD; Ronald Pairumani, MD; Paula Fernández, MD; Vladimir Granda-Luna, MD, PhD; Alexandre Biasi Cavalcanti, MD, PhD; ANDROMEDA-SHOCK Investigators and the Latin American Intensive Care Network (LIVEN)

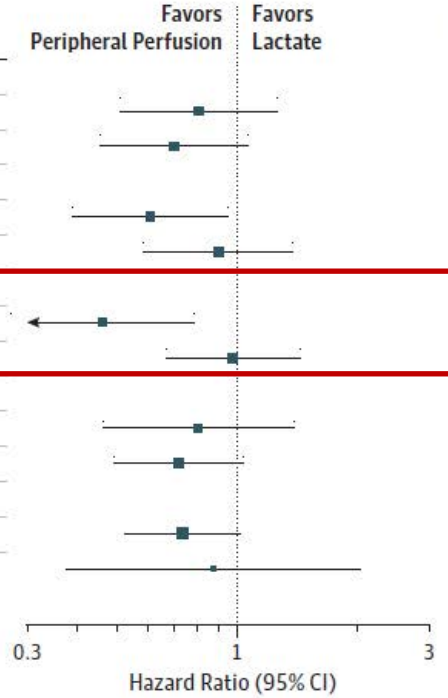
- Lactate level/2h

vs

- CRT/30 mn for 8 hours

Figure 3. Risk of Death Within 28 Days in the Prespecified Subgroups Among Patients Treated With Peripheral Perfusion–Targeted Resuscitation vs Lactate Level–Targeted Resuscitation

Subgroup	No. of Events/Total (%) Peripheral Perfusion–Targeted Resuscitation	No. of Events/Total (%) Lactate Level–Targeted Resuscitation	Hazard Ratio (95% CI)	P for Interaction
Baseline lactate, mmol/L				
>4	37/85 (43.5)	41/88 (46.6)	0.82 (0.52-1.28)	.61
≤4	37/127 (29.1)	51/124 (41.1)	0.70 (0.46-1.07)	
APACHE II				
<25	32/130 (24.6)	49/135 (36.3)	0.61 (0.39-0.96)	.23
≥25	42/82 (51.2)	43/77 (55.8)	0.90 (0.59-1.38)	
SOFA				
<10	21/103 (20.4)	42/107 (39.3)	0.46 (0.27-0.78)	.03
≥10	53/109 (48.6)	50/105 (47.6)	0.98 (0.67-1.45)	
Confirmed source of infection				
No	25/61 (41)	26/59 (44.1)	0.84 (0.48-1.45)	.63
Yes	49/151 (32.5)	66/153 (43.1)	0.71 (0.49-1.03)	
Lactate decrease from admission to baseline measurement, %				
≤10	64/181 (35.4)	80/171 (46.8)	0.73 (0.53-1.02)	.70
>10	10/31 (32.3)	12/41 (29.3)	0.87 (0.38-2.04)	



Infection • Antimicrobiens • Modélisation • Evolution

Université de Paris

JAMA. 2019;321(7):654-664.

Research

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

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Lactate level/2h

vs

CRT/30 mn for 8 hours

Outcome	Peripheral Perfusion-Targeted Resuscitation (n = 212)	Lactate Level-Targeted Resuscitation (n = 212)	Unadjusted Absolute Difference (95% CI)	Adjusted Relative Measure (95% CI)	*P* Value
Primary Outcome					
Death within 28 d, No. (%)	74 (34.9)	92 (43.4)	−8.5 (−18.2 to 1.2)[b]	HR, 0.75 (0.55 to 1.02)[a]	.06[a]
Amount of resuscitation fluids within the first 8 h, No.	206	209			
Mean (SD), mL	2359 (1344)	2767 (1749)	−408 (−705 to −110)		.01
Total fluid balance, mL[g]					
Within 8 h, No.	198	205			
Mean (SD)	1587 (1388)	1874 (1756)	−288 (−598 to 22.0)		.07
Within 24 h, No.	176	185			
Mean (SD)	2025 (2181)	2343 (2336)	−318 (−785 to 149)		.18
Within 48 h, No.	153	160			
Mean (SD)	992 (1810)	1224 (3336)	−233 (−831 to 366)		.45
Within 72 h, No.	157	162			
Mean (SD)	1389 (2809)	1601 (3069)	−212 (−858 to 434)		.52

JAMA. 2019;321(7):654-664.

Research

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

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Lactate level/2h

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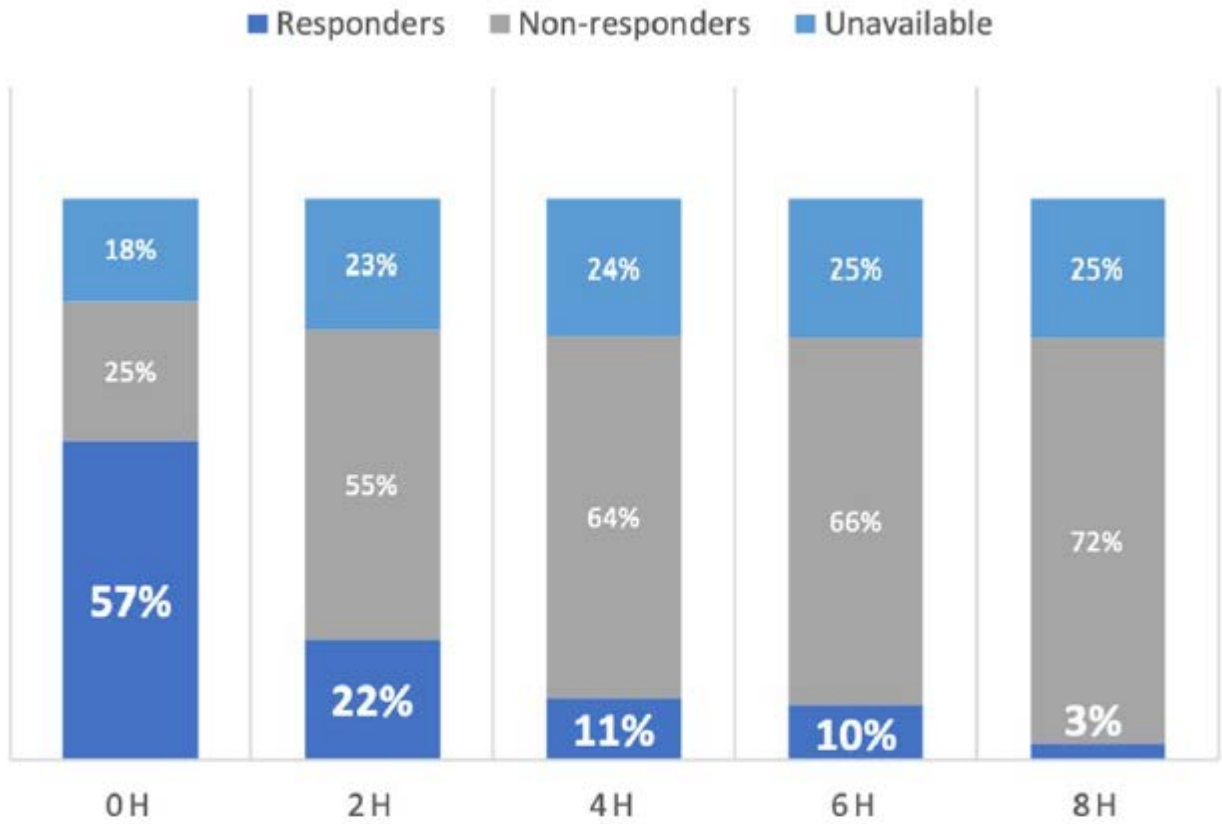


Fig. 1 Fluid responsiveness (in %) over time in 424 patients with sepsis Adapted with permission from Hernandez et al. [5]

Sylversides et al - Intensive Care Med (2019) 45:1440–1442

Intensive Care Med (2019) 45:1503–1517
https://doi.org/10.1007/s00134-019-05801-z

STATE-OF-THE-ART REVIEW

Vasopressor therapy in critically ill patients with shock

James A. Russell*

Take-home message

Vasopressors are administered to critically ill patients with vasodilatory shock not responsive to volume resuscitation, and less commonly cardiogenic shock and hypovolemic shock. Norepinephrine as first choice may be followed by vasopressin or epinephrine. Angiotensin II and dopamine have limited indications. In future, predictive biomarkers may guide vasopressor selection and novel vasopressors may emerge.

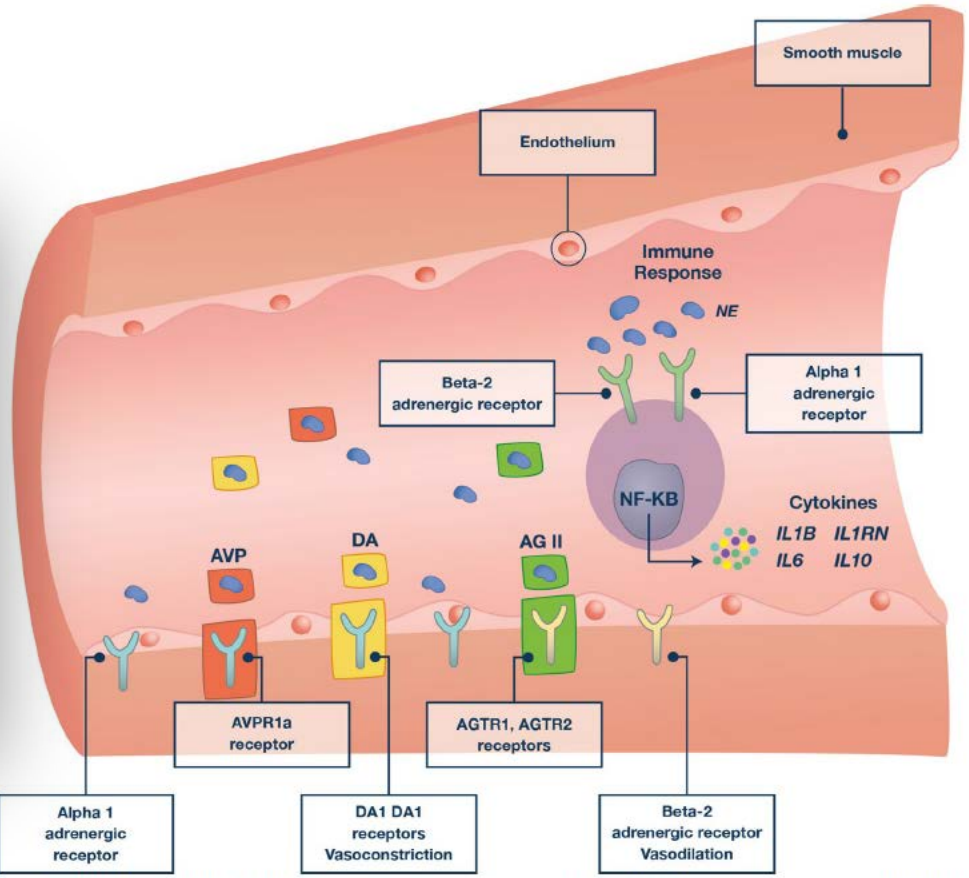


Fig. 1 Norepinephrine (NE) binds to alpha-1 adrenergic receptors of vascular smooth muscle to induce vasoconstriction, binds to beta-1 and beta-2 receptors causing vasodilation, and binds to alpha-1 and beta-2 adrenergic receptors on leukocytes to differentially modulate immune response in sepsis. Exposure to NE also down-regulates alpha-1 and beta-2 receptor density and that could alter sensitivity to NE, thereby leading to increased doses of norepinephrine and greater risk of adverse vascular and immune effects. Vasopressin (AVP) binds to the AVPR1a receptor, dopamine (DA) binds to DA1 and DA2 receptors, and angiotensin II (AG) binds to angiotensin II receptors (AGTR1, AGTR2), all causing vasoconstriction

Early antimicrobial therapy: « as soon as possible »

this can become problematic when guideline recommendations are overly rigid [12]. The Surviving Sepsis Campaign Guidelines recommend "that administration of IV antimicrobials be initiated as soon as possible after recognition and within 1 hour for both sepsis and septic shock (strong recommendation, moderate quality of evidence; grade applies to both conditions)."

IDSA agrees that antimicrobials should be initiated as soon as possible to patients with severe infections. We are fearful,

CID 2018:66 (15 May) • IDSA Sepsis Task Force

Prehospital antibiotics in the ambulance for sepsis: a multicentre, open label, randomised trial

Lancet Respir Med 2018; 6: 40–50

Nadia Alam, Erick Oskam, Patricia M Stassen, Pieternel van Exter, Peter M van de Ven, Harm R Haak, Frits Holleman, Arthur van Zanten, Hien van Leeuwen-Nguyen, Victor Bon, Bart A M Duineveld, Rishi S Nannan Panday, Mark H H Kramer, Prabath W B Nanayakkara, on behalf of the PHANTASi Trial Investigators and the ORCA (Onderzoeks Consortium Acute Geneeskunde) Research Consortium the Netherlands*

- RCT/regional ambulance service
- Training for early recognition of sepsis
- Pre hospital CRX 2g vs control
- Only 3% with septic shock
- 91% of « true » infections

	Usual care group (n=1137)	Intervention group (n=1535)
Age (years)	72·5 (14·1)	73·0 (13·6)
Sex		
Male	650 (57%)	885 (58%)
Female	487 (43%)	650 (42%)
Charlson comorbidity score	1 (1–3)	1 (1–3)
Patients already on oral antibiotics before randomisation	255 (22%)	322 (21%)
National Early Warning Score (in the ambulance)*		
0	1 (<1%)	0
1–4	145 (19%)	192 (19%)
5–6	241 (31%)	306 (30%)
≥7	382 (50%)	521 (51%)
qSOFA score (in the ambulance)†		
<2	872 (83%)	1132 (78%)
≥2	181 (17%)	318 (22%)
DNR policy in place at admission	437 (38%)	609 (40%)
Severity of sepsis		
Non-severe sepsis	424 (37%)	579 (38%)
Severe sepsis	657 (58%)	868 (57%)
Septic shock	37 (3%)	66 (4%)
Other diagnosis	19 (2%)	22 (1%)

(Table 1 continues in next column)

	Usual care group (n=1137)	Intervention group (n=1535)
(Continued from previous column)		
Organ dysfunction		
Respiratory	378 (34%)	540 (35%)
Tissue perfusion	280 (25%)	276 (18%)
Neurological	239 (21%)	340 (22%)
Cardiovascular	119 (11%)	180 (12%)
Renal	79 (7%)	119 (8%)
Haematological	15 (1%)	25 (2%)
TTA before arriving at the ED (min)	..	26 (19–34)
Intravenous fluids administered prehospital		
n (%)	418 (37%)	986 (64%)
Median total (mL)	500 (500–500)	500 (300–500)
Mean total (mL)	450·7 (185·8)	447·1 (247·9)
Intravenous fluids administered at ED		
n (%)	495 (44%)	629 (41%)
Median total (mL)	1000 (500–1000)	1000 (500–1500)
Mean total (mL)	1026·3 (813·3)	1019·2 (687·0)

	Usual care group (n=1137)	Intervention group (n=1535)	Relative risk (95% CI)	Risk difference (%, 95% CI)	p value
28 day mortality	93 (8%)*	120 (8%)	0·95 (0·74 to 1·24)	−0·37 (−2·5 to 1·7)	0·78
90 day mortality	134 (12%)*	178 (12%)	0·98 (0·80 to 1·21)	−0·20 (−2·7 to 2·3)	0·87
Median TTA in the ED (min)	70 (36–128)	..	..	..	..
TTA in the ED (min)					
0–60	410 (42%)	..	..	..	..
61–120	254 (26%)	..	..	..	..
121–180	125 (13%)	..	..	..	..
181–240	78 (8%)	..	..	..	..
>240	56 (6%)	..	..	..	..
Missing	50 (5%)	..	..	..	..
No antibiotics in the ED	164 (14%)	..	..	..	..
Intensive care unit admission	98 (9%)	155 (10%)	1·17 (0·92 to 1·49)	1·5 (−0·73 to 3·7)	0·19
28 day re-admission	119 (10%)	102 (7%)	..	..	0·0004
Median length of stay (days)					
Intensive care unit	3 (2–8)	4 (2–10)	..	..	0·28
Hospital	6 (3–9)	6 (4–10)	..	..	0·12

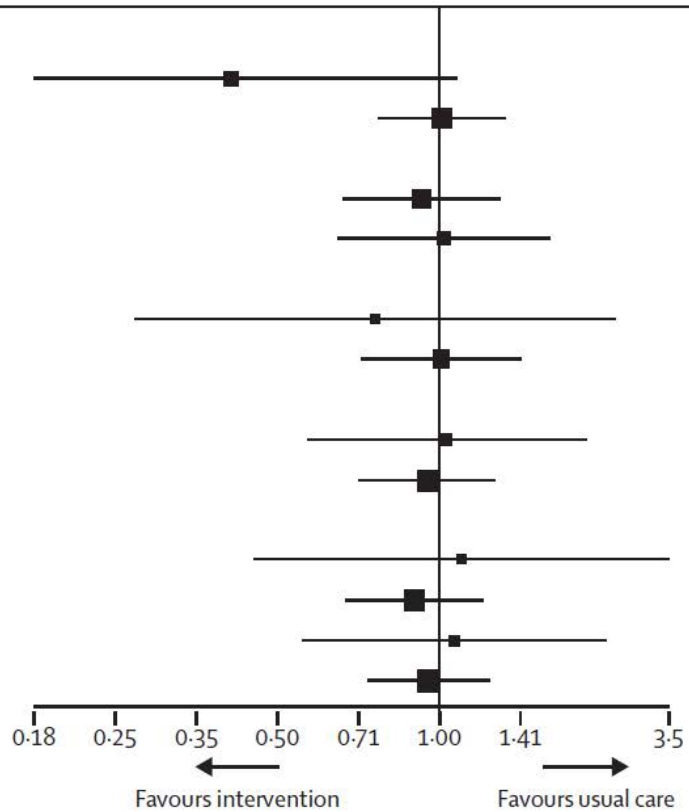
Alam – Lancet Resp Med 2018; 6: 40-50

Prehospital antibiotics in the ambulance for sepsis: a multicentre, open label, randomised trial

Lancet Respir Med 2018; 6: 40–50

*Nadia Alam, Erick Oskam, Patricia M Stassen, Pieternel van Exter, Peter M van de Ven, Harm R Haak, Frits Holleman, Arthur van Zanten, Hien van Leeuwen-Nguyen, Victor Bon, Bart A M Duineveld, Rishi S Nannan Panday, Mark H H Kramer, Prabath W B Nanayakkara, on behalf of the PHANTASi Trial Investigators and the ORCA (Onderzoeks Consortium Acute Geneeskunde) Research Consortium the Netherlands**

	Usual care group (n=1137)	Intervention group (n=1535)	Relative risk (95% CI)	p value
Age (years)				
<65	12/276 (4%)	6/336 (2%)	0·41 (0·16–1·08)	0·10
≥65	81/860 (9%)	114/1199 (10%)	1·01 (0·77–1·32)	1·00
qSOFA (prehospital)				
<2	59/872 (7%)	71/1132 (6%)	0·93 (0·66–1·29)	0·72
2	25/180 (14%)	45/318 (14%)	1·02 (0·65–1·60)	1·00
NEWS (prehospital)				
<5	7/146 (5%)	7/192 (4%)	0·76 (0·27–2·12)	0·80
≥5	53/622 (9%)	71/827 (9%)	1·01 (0·72–1·42)	1·00
SBP (prehospital)				
≤100	15/112 (13%)	25/181 (14%)	1·03 (0·57–1·87)	1·00
>100	75/1001 (7%)	95/1337 (7%)	0·95 (0·71–1·27)	0·78
Severity of sepsis				
Sepsis	8/424 (2%)	12/579 (2%)	1·10 (0·45–2·66)	1·00
Severe sepsis	74/656 (11%)	88/868 (10%)	0·90 (0·67–1·20)	0·53
Septic shock	10/37 (27%)	19/66 (29%)	1·07 (0·56–2·04)	0·85
Overall	**93/1136 (8%)**	**120/1535 (8%)**	**0·95 (0·74–1·24)**	**0·78**



Les pistes pour les antibiothérapies

- 1- Identification ultra précoce
  - Oui mais avec l'aide d'experts…
- 2- Optimisation de la PK?
  - Une fT> 6XCMI semble être l'objectif le plus associé au succès clinque pour les betalactamines

    Wong G et al - J Antimicrob Chemother. 2019 in press
- 3- arrêt précoce en l'absence de documentation?
  - Sur 1047 survivants d'un sepsis non documenté la durée médiane d'antibiothérapie est de 6 jours *Lockhart Open Forum Infect Dis. 2019 Oct 9;6(10):ofz397.*
  - L'arrêt précoce des anti-SARM ne modifie pas le pronostic des PAVM est associes à moins de DC et mois d'IRA *Labelle AJ et al - Chest 2010; 137:1130–7.; Cowley MC - Chest. 2019 Jan;155(1):53-59*
  - La mortalité des patients avec un LBA<10^4 cfu n'est pas augmentée par un arrêt de l'antibiothérapie précoce *Raman - Crit Care Med 2013; 41:1656–1663*

The NEW ENGLAND JOURNAL of MEDICINE

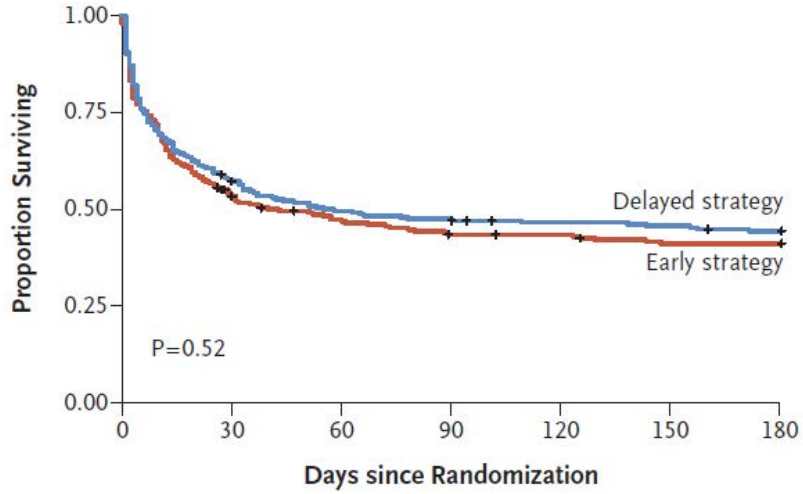
ORIGINAL ARTICLE

Timing of Renal-Replacement Therapy in Patients with Acute Kidney Injury and Sepsis

S.D. Barbar, R. Clere-Jehl, A. Bourredjem, R. Hernu, F. Montini, R. Bruyère, C. Lebert, J. Bohé, J. Badie, J.-P. Eraldi, J.-P. Rigaud, B. Levy, S. Siami, G. Louis, L. Bouadma, J.-M. Constantin, E. Mercier, K. Klouche, D. du Cheyron, G. Piton, D. Annane, S. Jaber, T. van der Linden, G. Blasco, J.-P. Mira, C. Schwebel, L. Chimot, P. Guiot, M.-A. Nay, F. Meziani, J. Helms, C. Roger, B. Louart, R. Trusson, A. Dargent, C. Binquet, and J.-P. Quenot, for the IDEAL-ICU Trial Investigators and the CRICS TRIGGERSEP Network*

Table 2. Primary and Secondary Outcomes.*

Variable	Early Strategy (N=246)	Delayed Strategy (N=242)	P Value
Primary outcome			
Death at 90 days — no./total no. (%)	138/239 (58)	128/238 (54)	0.38
Secondary outcomes			
Death at 28 days — no. (%)	111 (45)	102 (42)	0.48
Death at 180 days — no./total no. (%)	143/236 (61)	134/235 (57)	0.37
Median time from diagnosis of failure-stage acute kidney injury to initiation of renal-replacement therapy (IQR) — hr†	7.6 (4.4–11.5)	51.5 (34.6–59.5)	<0.001
Patients who received renal-replacement therapy — no. (%)	239 (97)	149 (62)	<0.001
Patients in the delayed-strategy group who received emergency renal-replacement therapy before 48 hr, according to criterion — no. (%)‡		41 (17)	



No. at Risk

Delayed strategy	242	137	117	112	107	105	101
Early strategy	246	127	109	99	98	92	92

N Engl J Med 2018;379:1431-42.

ORIGINAL ARTICLE

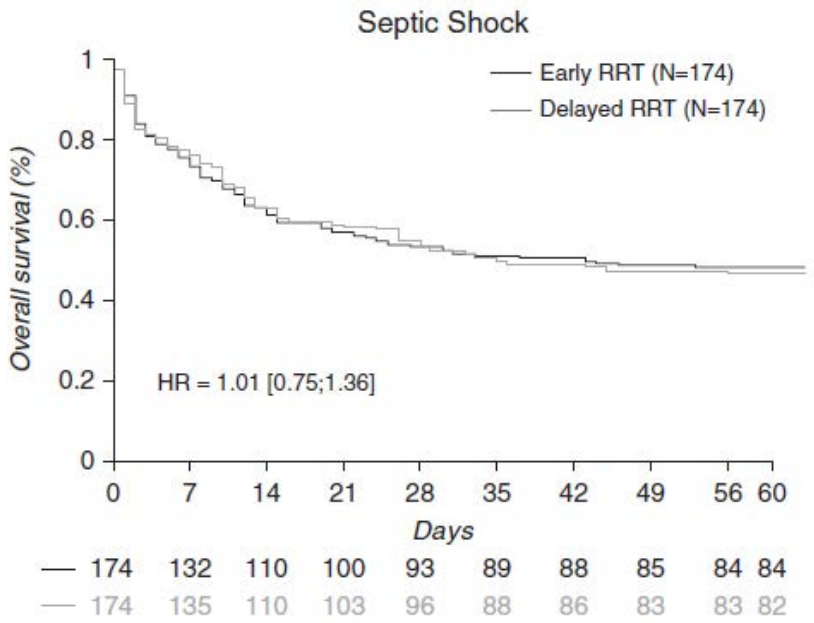
Timing of Renal Support and Outcome of Septic Shock and Acute Respiratory Distress Syndrome

A *Post Hoc* Analysis of the AKIKI Randomized Clinical Trial

Stéphane Gaudry[1,2], David Hajage[3,4,5], Frédérique Schortgen[6], Laurent Martin-Lefevre[7], Charles Verney[1], Bertrand Pons[8,9], Eric Boulet[10], Alexandre Boyer[11], Guillaume Chevrel[12], Nicolas Lerolle[13], Dorothée Carpentier[14], Nicolas de Prost[15,16], Alexandre Lautrette[17], Anne Bretagnol[18], Julien Mayaux[19], Saad Nseir[20,21], Bruno Megarbane[22], Marina Thirion[23], Jean-Marie Forel[24], Julien Maizel[25], Hodane Yonis[26], Philippe Markowicz[27], Guillaume Thiery[8,9], Florence Tubach[3,5,28], Jean-Damien Ricard[1,29,30], and Didier Dreyfuss[1,29,30]

Post hoc: 348 septic shock

Saps3 incl: 75; SOFA 11.5



Outcomes	Septic Shock		
	Early RRT Strategy (*n* = 174)	Delayed RRT Strategy (*n* = 174)	*P* Value
Patients who actually received RRT, *n* (%)	173 (99)	95 (55)	<0.001
RRT-free days, median (IQR)	11 (1–25)	16 (4–29)	<0.001
Ventilator-free days, median (IQR)	4 (0–21)	4 (0–19)	0.83
Vasopressor-free days, median (IQR)	16 (0–25)	18 (0–25)	0.89
Length of ICU stay, median (IQR)			
Survivors	13 (9–24)	13 (8–25)	0.74
Nonsurvivors	6 (2–12)	7 (2–13)	0.94
Length of hospital stay, median (IQR)			
Survivors	28 (18–51)	37 (21–25)	0.43
Nonsurvivors	6 (2–12)	8 (2–13)	0.89
RRT dependence*, *n*/subtotal (%)			
At Day 28	12/102 (12)	8/105 (8)	0.31
At Day 60	1/90 (3)	3/94 (3)	0.62

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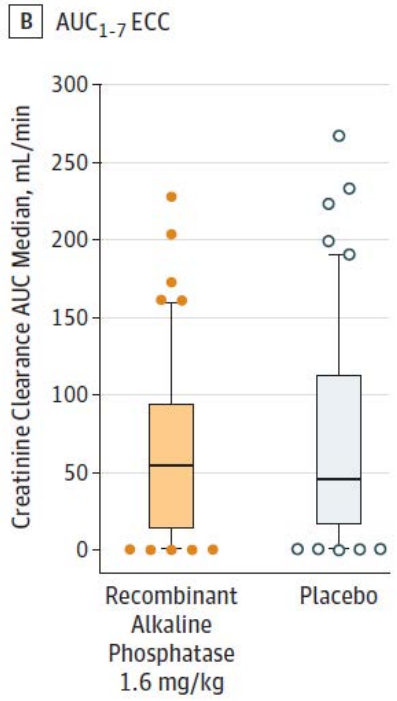
Effect of Human Recombinant Alkaline Phosphatase on 7-Day Creatinine Clearance in Patients With Sepsis-Associated Acute Kidney Injury
A Randomized Clinical Trial

Peter Pickkers, MD, PhD; Ravindra L. Mehta, MD; Patrick T. Murray, MD; Michael Joannidis, MD; Bruce A. Molitoris, MD; John A. Kellum, MD; Mirjam Bachler, PhD; Eric A. J. Hoste, MD, PhD; Oscar Hoiting, MD; Kenneth Krell, MD; Marlies Ostermann, MD, PhD; Wim Rozendaal, MD; Miia Valkonen, MD, PhD; David Brealey, MD, PhD; Albertus Beishuizen, MD, PhD; Ferhat Meziani, MD, PhD; Raghavan Murugan, MD, MS, FRCP; Hilde de Geus, MD, PhD; Didier Payen, MD, PhD; Erik van den Berg, MSc; Jacques Arend, MD; for the STOP-AKI Investigators

- Background:
  - Endogenous enzyme that exerts detoxifying effects through dephosphorylation of bacterial endotoxins and proinflammatory mediators such as extracellular ADP
  - In animal sepsis models, treatment with alkaline phosphatase attenuated systemic inflammation and organ dysfunction and improved survival rates
  - administration of bovine alkaline phosphatase significantly improved kidney function in patients with sepsis.



- Adaptative design:
  - Dose ranging and efficacy
    - End-point: AUC Cr Cl at day 1 to 7.
    - Hierarchical analyses of secondary end-points
    - Delta clairance, mortality, MAKE

NS

JAMA. 2018;320(19):1998-2009

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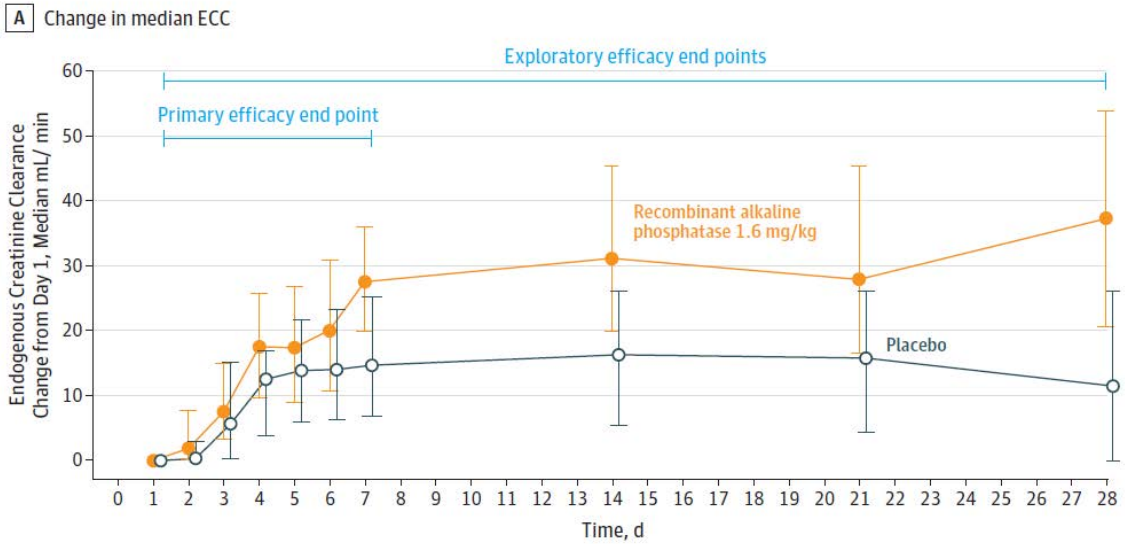
Post-hoc exploratory analyses:

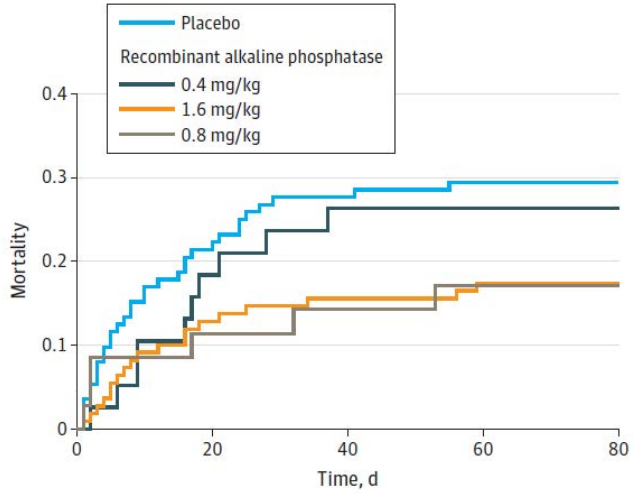


No. of patients

Recombinant alkaline phosphatase																											
1.6 mg/kg	111	102	95	92	92	86	82	82																	64	47	38
Placebo	116	102	92	95	90	86	83	81																	63	46	30

Day 21 (mean difference, 16.3 mL/min [95% CI, 3.07 to 29.5]; P = .02

Figure 3. Cumulative Incidence of Fatal Events From Baseline to 90 Days for All Treatment Groups in the Safety Data Population of Patients Who Were Critically Ill With Sepsis-Associated Acute Kidney Infection



No. at risk

Recombinant alkaline phosphatase					
Placebo	112	88	81	79	79
0.4 mg/kg	38	31	28	28	28
0.8 mg/kg	35	31	30	29	29
1.6 mg/kg	109	95	92	90	90

Day 28 death: 1.6 mg/kg 14.4% vs PB: 26.3%, p=0.02 (persisting at D90)

No effect on MAKE 30 but…
Significant effect on MAKE 60 and MAKE 90…

JAMA. 2018;320(19):1998-2009

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Effect of a Recombinant Human Soluble Thrombomodulin on Mortality in Patients With Sepsis-Associated Coagulopathy
The SCARLET Randomized Clinical Trial

Jean-Louis Vincent, MD, PhD; Bruno Francois, MD; Igor Zabolotskikh, MD, PhD; Mradul Kumar Daga, MD; Jean-Baptiste Lascarrou, MD; Mikhail Y. Kirov, MD; Ville Pettilä, MD; Xavier Wittebole, MD; Ferhat Meziani, MD, PhD; Emmanuelle Mercier, MD; Suzana M. Lobo, MD, PhD; Philip S. Barie, MD, MBA; Mark Crowther, MD; Charles T. Esmon, PhD; Jawed Fareed, PhD; Satoshi Gando, MD, PhD; Kenneth J. Gorelick, MD, PhD; Marcel Levi, MD, PhD; Jean-Paul Mira, MD, PhD; Steven M. Opal, MD; Joseph Parrillo, MD, PhD; James A. Russell, MD; Hidehiko Saito, MD, PhD; Kazuhisa Tsuruta, PhD; Takumi Sakai; David Fineberg, MD; for the SCARLET Trial Group

- ART-123 is a recombinant human soluble thrombomodulin.
- The primary mechanism of is derived from its capacity to bind circulating thrombin molecules and serve as an activation complex to convert protein C to activated protein C.
- In addition,ART-123 inhibits inflammation and organ injury caused by DAMP, such as HMGB1 and histones
- **Phase 2b: best effect if infection and at least 1 sepsis-associated organ dysfunction (cardiovascular and/or respiratory),and coagulopathy indicated by prolongation of the INR and reduction of platelet count**

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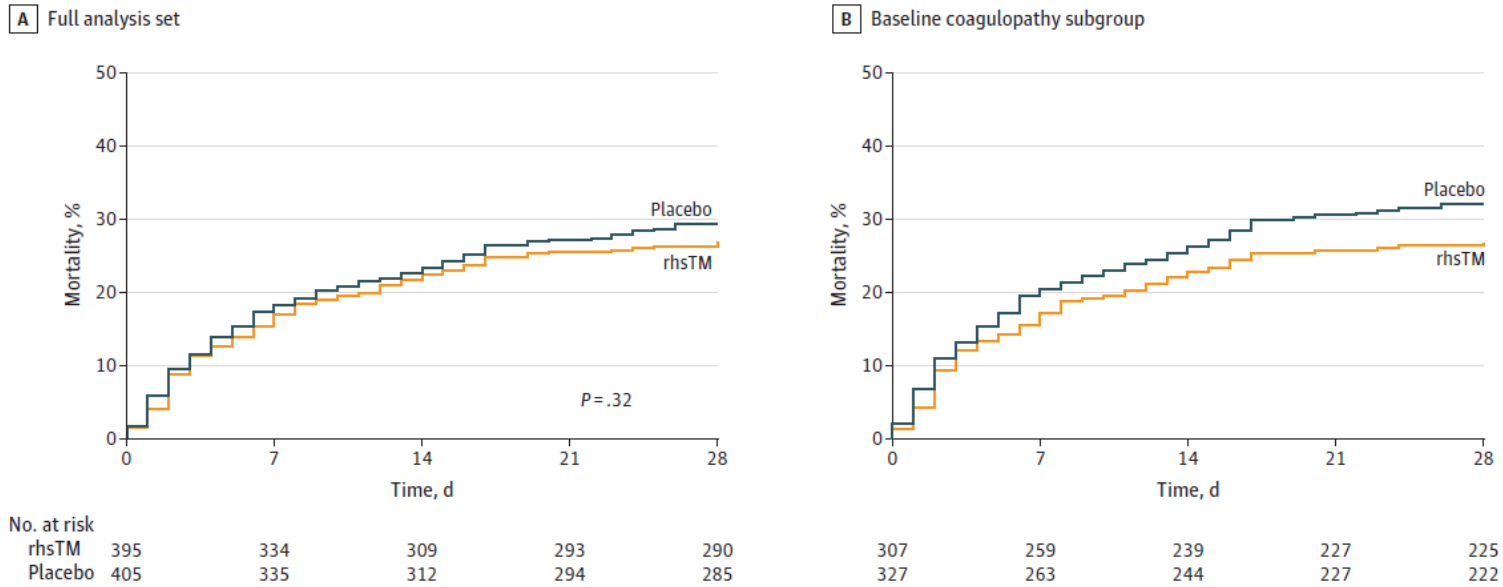
Time window for ART 123 administration 40 hours



JAMA. 2019;321(20):1993-2002

Agenda

- Epidémiologie
  - Changements?
  - Hétérogénéité et intelligence artificielle
  - Impact à long terme
- Etudes pivot
  - Antibiotiques et Défaillances d'organes
  - Approches « inflammatoire »
- **Domaines d'intérêt pour le futur**

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Effect of Vitamin C Infusion on Organ Failure and Biomarkers of Inflammation and Vascular Injury in Patients With Sepsis and Severe Acute Respiratory Failure
The CITRIS-ALI Randomized Clinical Trial

Alpha A. Fowler III, MD; Jonathon D. Truwit, MD; R. Duncan Hite, MD; Peter E. Morris, MD; Christine DeWilde, RN, PhD; Anna Priday, BS, MS; Bernard Fisher, BS, MS; Leroy R. Thacker II, PhD; Ramesh Natarajan, PhD; Donald F. Brophy, PharmD; Robin Sculthorpe, RPh; Rahul Nanchal, MD; Aamer Syed, MD; Jamie Sturgill, PhD; Greg S. Martin, MD, MSc; Jonathan Sevransky, MD, MHS; Markos Kashiouris, MD, MPH; Stella Hamman, RN, MSN; Katherine F. Egan, BSN, RN, CCRC; Andrei Hastings, MD; Wendy Spencer, RN, CPN; Shawnda Tench, BBA, CCRP; Omar Mehkri, MD; James Bindas, MBA; Abhijit Duggal, MD; Jeanette Graf, BS, CCRP; Stephanie Zellner, MS, CCRC; Lynda Yanny, RN, BSN, CCRC; Catherine McPolin, RN, BSN, CCRP; Tonya Hollrith, RT, MR; David Kramer, MD; Charles Ojielo, MD; Tessa Damm, DO; Evan Cassity, MS; Aleksandra Wieliczko, RN; Matthew Halquist, PhD

- Vitamin C attenuates systemic inflammation, corrects sepsis-induced coagulopathy, and attenuates vascular injury
- Double blind RCT/ 7 centers
- Inclusion:
  - SEPSIS + Inv MV + PaO2 to FiO2 ratio < 300 mm Hg + bilateral opacities < 1 week + no eidence of left atrial hypertension
  - Suspected or proven infection + > 2 SIRS criteria
  - All criteria had to be met within a 24-hour period.
- Exclusion:
  - known allergy to vitamin C
  - no ability to obtain informed consent;
  - Age< 18 years
  - more than 48 hours had elapsed since they met ARDS criteria (
  - Moribund status
  - Home mechanical ventilation (via tracheostomy or noninvasively) or home oxygen> 2 L/min; or interstitial lung disease, diffuse alveolar hemorrhage,
  - Diabetic ketoacidosis, or an active kidney stone.

Intervention: 50 mg/kg actual body weight every 6 hours for 96 hours vs Placebo

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The primary outcomes:

- modified SOFA scores at 96 hours (without bilirubin??? For missing values…)
- Plasma biomarker levels (C-reactive protein and thrombomodulin) at 168 hou

- NNT: complex simulations 85 patients per arm
- 46 prespecified secondary outcomes!!!
  - Mortality
  - Respiratory, neuro, cardiac and kidney failures
  - Biomarkers

Variable	Vitamin C (n = 84)	Placebo (n = 83)
Demographic data, No. (%)		
Age, median (IQR), y	54 (39-67)	57 (44-70)
Men	45 (54)	45 (54)
Women	39 (46)	38 (46)
Non-Hispanic white	68 (81)	60 (72)
Non-Hispanic black	13 (15)	19 (23)
Hispanic/Asian/ Pacific Islander	3 (4)	4 (5)
Sepsis etiology, No. (%)		
Thorax	69 (82)	58 (70)
Abdomen	6 (7)	13 (16)
Urinary tract	3 (4)	2 (2)
Central nervous system	1 (1)	3 (4)
Central venous catheter	0	1 (1)
Unknown/other	5 (6)	6 (7)
Admission source, No. (%)		
Emergency department	39 (46)	36 (43)
Outside hospital transfer	26 (31)	28 (34)
Inpatient ward transfer	17 (20)	18 (22)
Operating room	1 (1)	1 (1)
Direct admission	1 (1)	0
Kidney failure, No. (%)		
Acute kidney failure, No. (%)	21 (25)	26 (31)
Chronic kidney failure/ dialysis, No. (%)	7 (8)	8 (10)
Respiratory, mean (SD)		
Tidal volume, mL	423.7 (88.4)	418.3 (85.5)
Pao_2/Fio_2 ratio at baseline	189.3 (95.9)	214.5 (182.8)
PEEP, cm H_2O	9.9 (4.0)	9.6 (4.0)
Oxygenation index,[a] mean (SD)	10.7 (7.4)	10.1 (6.3)
Incidence of shock, No. (%)		
At baseline, vasopressor in use	57 (68)	60 (72)
mSOFA scores,[b] mean (SD)		
At randomization	9.8 (3.2)	10.3 (3.1)
At 96 h	8.02 (4.2)	6.96 (3.5)
Corticosteroid use during study, No. (%)	56 (67)	54 (65)
IV fluids, mL/kg/24 h		
Day 1, mean (SD)	40 (28.5)	42.6 (35.5)
Day 7, mean (SD)	32.8 (19.6)	33.9 (16.8)
Day 1, median (IQR)	35.1 (21.2-50.3)	33.9 (20.2-55.3)
Day 7, median (IQR)	26.5 (19.7-40.9)	26.8 (16.7-38.3)
Urine output, mL/kg/24 h		
Day 1, mean (SD)	14.1 (14.5)	10.5 (11.7)
Day 7, mean (SD)	24.4 (24.9)	24.6 (22.9)
Day 1, median (IQR)	9.9 (3.9-20)	6.7 (1.7-15)
Day 7, median (IQR)	18.2 (1.5-36)	20.9 (6.1-34.4)

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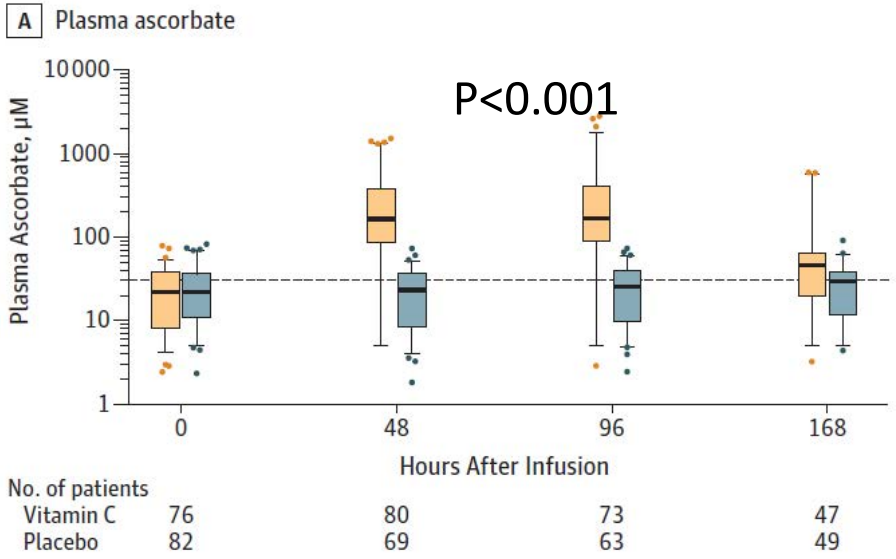

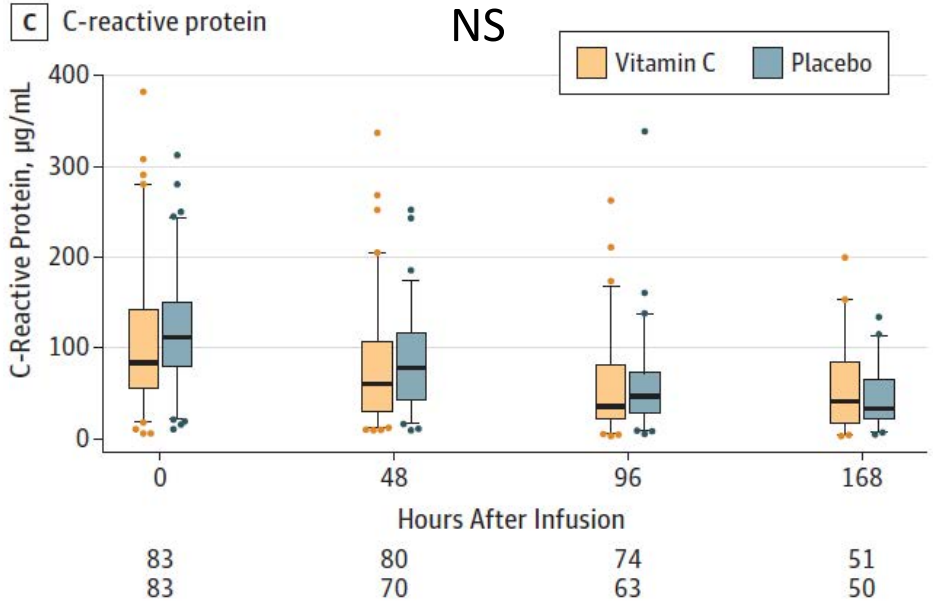

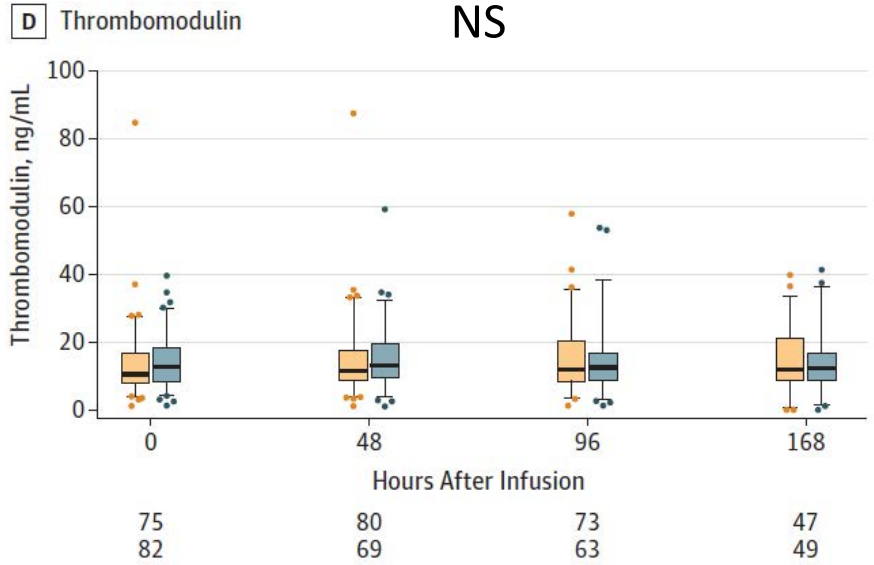

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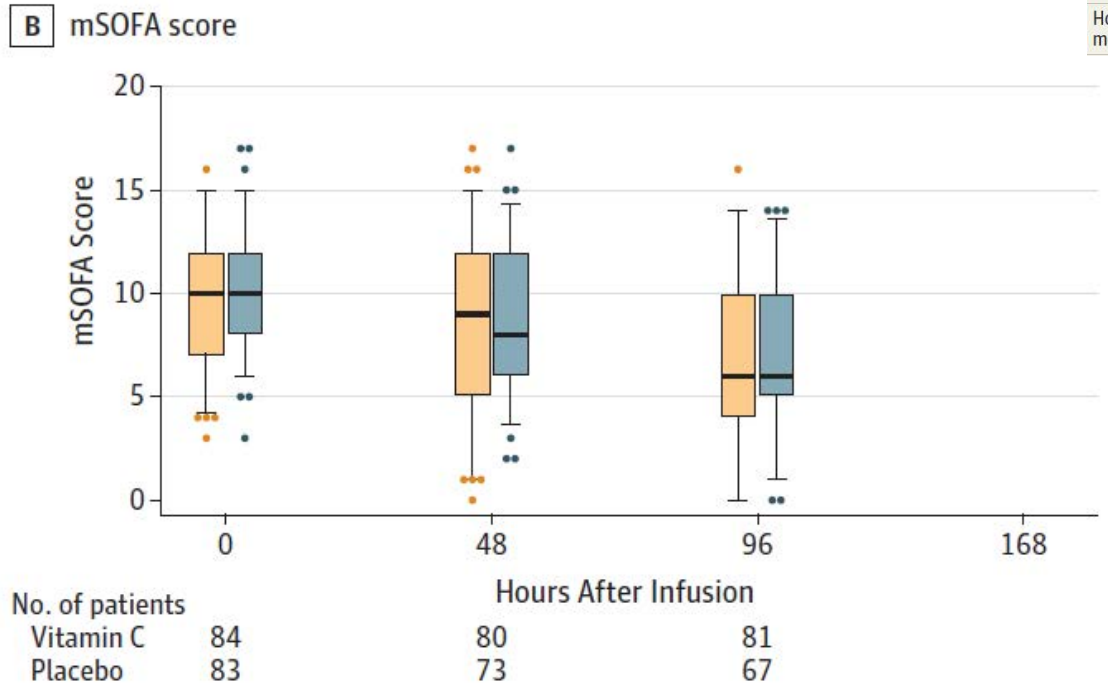
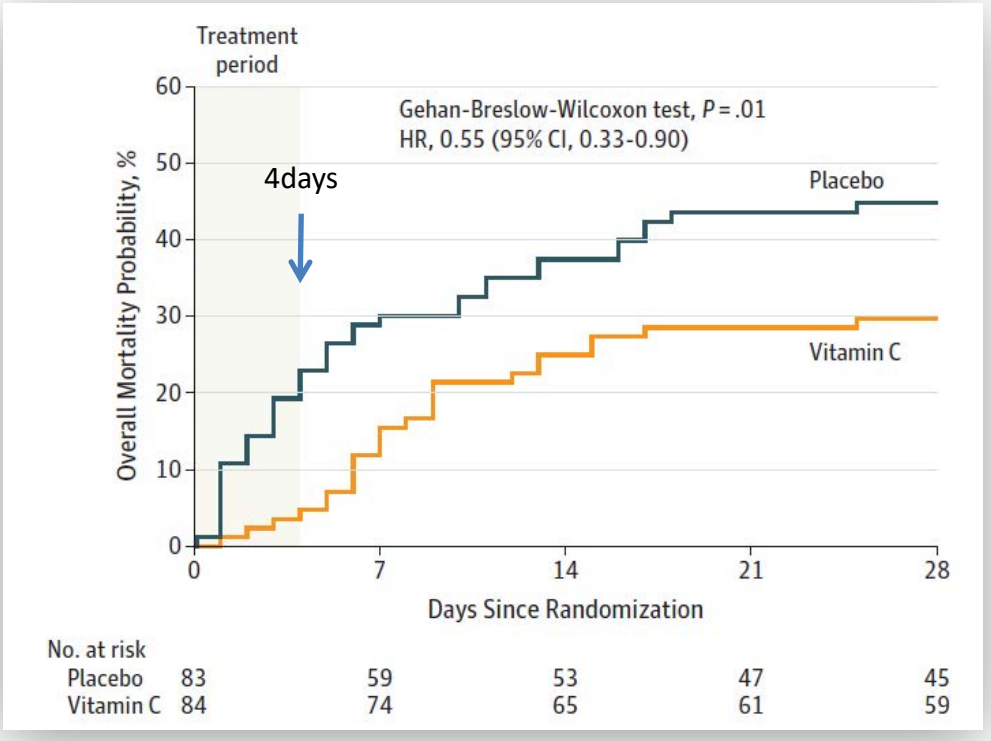
But Impressive exploratory analysis on mortality data

Variable	Hour	Vitamin C No.	Vitamin C Median or %	Vitamin C IQR	Placebo No.	Placebo Median or %	Placebo IQR	Difference, Coefficient (95% CI)	*P* Value
All-cause mortality to day 28, %			84	29.8	38	82	46.3	−0.17	.03
Ventilator-free days to day 28, median (IQR), d		84	17	24	82	8	22	2.5 (−0.9 to 5.9)	.15
ICU-free days to day 28, median (IQR), d		83	11	21	82	0	18	3.2 (0.3 to 6.0)	.03
Hospital-free days, to day 60, median (IQR), d		82	22	46	80	0	39	7.0 (0.3 to 13.8)	.04

NS but only alive patients were taken into account





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A before after study : anti-oxydant cocktail (VitC+thiamine+HSHC)

- The propensity adjusted odds of mortality in patients treated with the vitamin C protocol was 0.13 (95% CI, 0.04-0.48; P < 0.002)

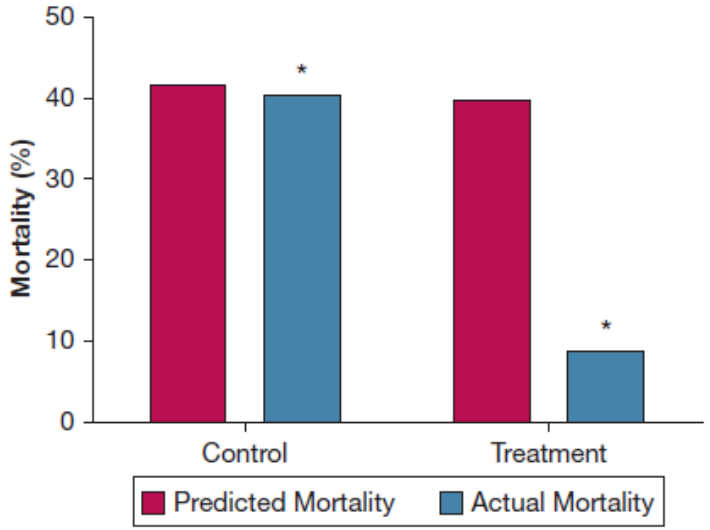


Figure 1 – *Predicted and actual mortality in the treatment and control groups. Predicted mortality was derived from APACHE IV scoring system results. *P < .001 for comparison of treatment group vs control group (see text). APACHE = Acute Physiology and Chronic Health Evaluation.*

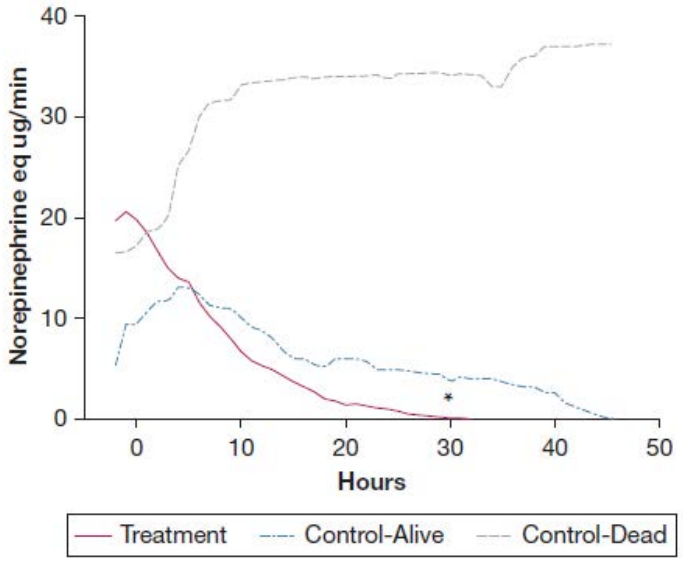


Figure 2 – *Time course of vasopressor dose (in norepinephrine equivalents) in the treatment group and in the control group survivors and nonsurvivors. *P < .001 for comparison of treatment group vs control group (see text).*

Marik et al - CHEST 2017; 151(6):1229-1238

Hager et al. Trials (2019) 20:197
https://doi.org/10.1186/s13063-019-3254-2

Trials

STUDY PROTOCOL Open Access

The Vitamin C, Thiamine and Steroids in Sepsis (VICTAS) Protocol: a prospective, multi-center, double-blind, adaptive sample size, randomized, placebo-controlled, clinical trial

David N. Hager[1*], Michael H. Hooper[2], Gordon R. Bernard[3], Laurence W. Busse[4], E. Wesley Ely[5,6,7], Alpha A. Fowler[8], David F. Gaieski[9], Alex Hall[10,11], Jeremiah S. Hinson[12], James C. Jackson[5,6,7,13], Gabor D. Kelen[12], Mark Levine[14], Christopher J. Lindsell[15], Richard E. Malone[16], Anna McGlothlin[17], Richard E. Rothman[12], Kert Viele[17], David W. Wright[10,11], Jonathan E. Sevransky[4] and Greg S. Martin[4,11]

RCT double blind 1:1 PB controlled study, 40 US ICUs

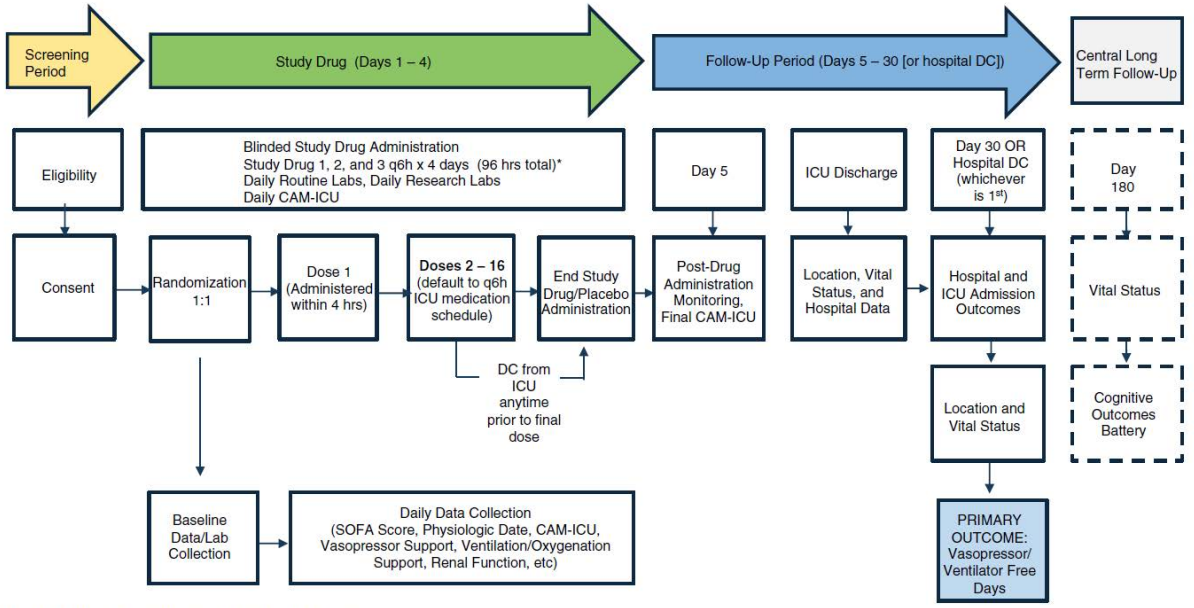
Intervention for 4 days

Primary outcome: Consecutive days free of ventilator and vasopressor support (VVFDs) in the 30 days

The key secondary outcome is mortality at 30 days.

Adaptative design for NNT with pre-stated stopping rules to allow the early recognition of a large mortality benefit if one exist and to refocus on the more sensitive outcome of VVFDs if a early large mortality benefit is not observed.

→ 2000 patients



*Note: 96h can occur over 5 calendar days

Fig. 2 Overview of study progression. Abbreviations: *CAM-ICU* Confusion Assessment Method for the Intensive Care Unit, *DC* discharge, *ICU* intensive care unit, *SOFA* Sequential Organ Failure Assessment.

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Early documented therapy for the future

- Before (n=163) after (n=166) study, monocenter
- ICU patients with positive BC:
- Maldi-tof alone vs maldi-Tof + filmarray biofire
- FA-BCID testing identified 96.2% of all on panel strains covering 85.2% of all microorganisms

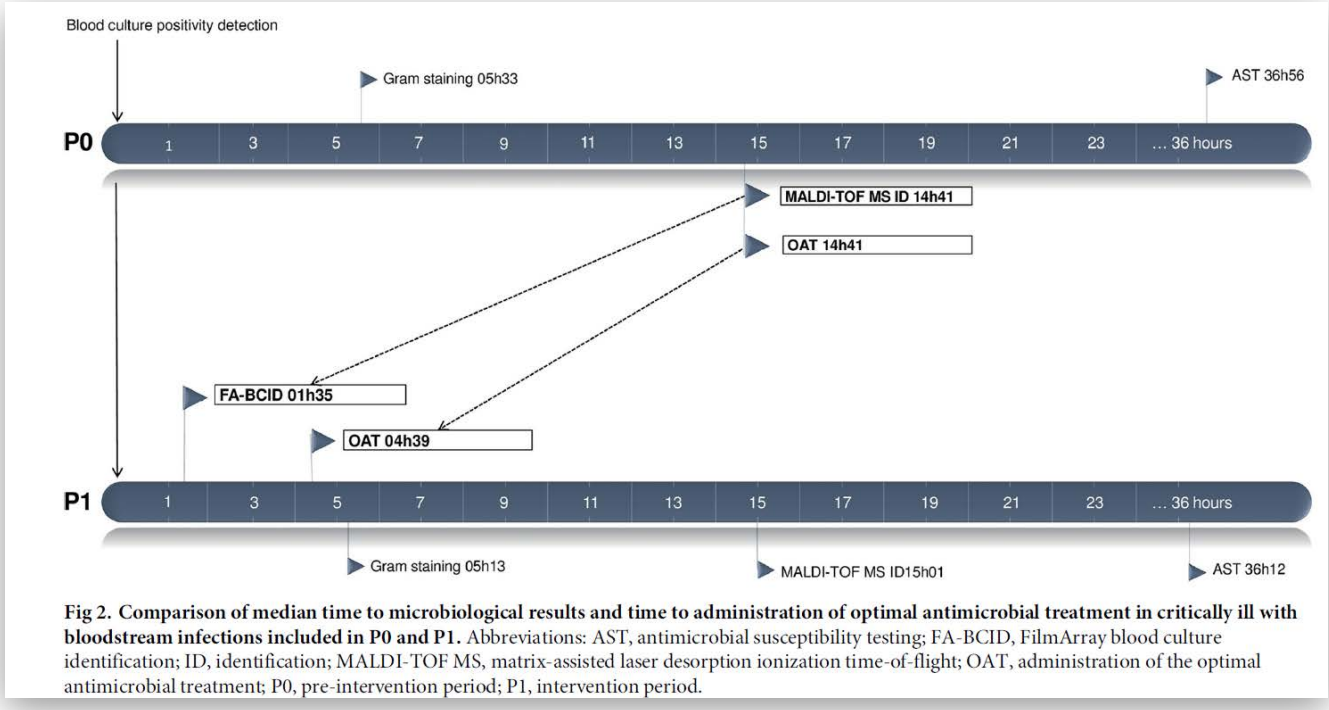


Fig 2. Comparison of median time to microbiological results and time to administration of optimal antimicrobial treatment in critically ill with bloodstream infections included in P0 and P1. Abbreviations: AST, antimicrobial susceptibility testing; FA-BCID, FilmArray blood culture identification; ID, identification; MALDI-TOF MS, matrix-assisted laser desorption ionization time-of-flight; OAT, administration of the optimal antimicrobial treatment; P0, pre-intervention period; P1, intervention period.

Verroken A et al - PLoS ONE 14(9): e0223122

Clinical Effect of Expedited Pathogen Identification and Susceptibility Testing for Gram-Negative Bacteremia and Candidemia by Use of the Accelerate Pheno™ System

JALM
Jan 2019

Jason P. Burnham,[1*] Meghan A. Wallace,[2] Brian M. Fuller,[3] Angela Shupe,[2] Carey-Ann D. Burnham,[2] and Marin H. Kollef[4]

- 153 meeting inclusion criteria: 110 on-panel GNB, 10 *Candida glabrata, and 5 Candida albicans from ED or ICUs. (Gram Pos not included)*
- 15 assay failures (12%), including 3 instrument technical failures, 2 failed ID, and 10 failed AST.
- 74/153 (48.4%) possible positive change
  - ADE (56/74, 75.7%)
  - change to appropriate (24/74, 32.4%).
- Of patients with on panel organisms, 30 (24.0%) received IIAT. Patients with *C. albicans or C. glabrata were not on empiric* antifungal therapy in 11 cases (91.7%) and could have been deecalated in the other case

Table 2. Timing of ID and AST for SOC and AXDX for all organisms.

Time parameter	SOC	AXDX	Difference, h
Time from blood culture positivity to AXDX initiation, mean ± SD[a]	NA	4.6 ± 1.8	—
Time from blood culture positivity to ID[b] (h [IQR])	28.6 [26.1–31.5]	6.4 [4.7–8.2]	22.2
Time from AXDX initiation to ID[c] (h [IQR])	NA	1.37 [1.37–1.38]	—
Time from blood culture positivity to AST[b] (h [IQR])	52.2 [49.5–55.1]	11.4 [10.0–13.3]	40.8
Time from AXDX initiation to AST[b] (hours [IQR])	NA	6.7 [6.65–6.73]	—

[a] All times reported as ±1 SD.
[b] For organisms not on panel, time to ID and AST for SOC were substituted.
[c] Only calculated for on panel organisms.

Table 3. Coverage, sensitivity, specificity, and positive and negative predictive values for AXDX as compared to SOC for GNB or yeast ID.

	Full cohort[a]		On-panel organisms only	
Parameter	GNB or yeast ID (95% CI)	Calculation	GNB or yeast ID (95% CI)	Calculation
Coverage or sensitivity	75.3 (67.8–81.8)	119/158 [TP/(TP + FN)]	91.5 (85.0–95.5)	119/130 [TP/(TP + FN)]
Specificity	99.7 (99.3–99.9)	1575/1580 [TN/(TN + FP)]	99.6 (98.9–99.8)	1115/1120 [TN/(TN + FP)]
PPV	96.0 (90.8–98.3)	119/124 [TP/(TP + FP)]	96.0 (90.4–98.5)	119/124 [TP/(TP + FP)]
NPV	97.6 (96.9–98.2)	1575/1614 [TN/(TN + FN)]	99.0 (98.2–99.5)	1115/1126 [TN/(TN + FN)]

[a] Full cohort: includes all on-panel and off-panel organisms.

Major errors: 21/1030
CA was lowest for ampicillin-sulbactam (71.8%), ceftazidime (78.7%), cefazolin (85.2%), piperacillin-tazobactam (85.6%), and tobramycin (87.6%).

Randomized Clinical Trial Evaluating Clinical Impact of RAPid IDentification and Antimicrobial Susceptibility Testing for Gram-Negative Bacteremia (RAPIDS-GN) – Banerjee R et al IDWEEK Oct 19 Abs 640

- 500 pa
- Rando
- Prima

Plus de questions que de réponse…

Différence entre la rapidité de l'examen et la vitesse de rendu du résultat?

Point-of-care?

Trou de spectre? Raisonnement rapide difficile

Nécessité d'une **expertise** pour être efficace? **Refonte de l'enseignement** de l'infectiologie urgente

Comment mesurer l'impact? BMR?/consommation/end-points pour les patients

Characteristic
Male
Mean (S.D.) age years
Mean (S.D.) Pitt Bacteremia Score
ICU at randomization
Neutropenic at randomization
Escherichia coli blood culture
Urinary source of bacteremia

Significant impact of duration of broad spectrum antimicrobials (Pearson et al Abs 2137)

Mebazaa *et al. Critical Care* (2018) 22:354
https://doi.org/10.1186/s13054-018-2243-2

Critical Care

RESEARCH Open Access

Circulating adrenomedullin estimates survival and reversibility of organ failure in sepsis: the prospective observational multinational Adrenomedullin and Outcome in Sepsis and Septic Shock-1 (AdrenOSS-1) study

Alexandre Mebazaa[1,2,3], Christopher Geven[4†], Alexa Hollinger[1,2,5*†], Xavier Wittebole[6], Benjamin Glen Chousterman[1,3], Alice Blet[1,2], Etienne Gayat[1,2,3], Oliver Hartmann[7], Paul Scigalla[8], Joachim Struck[7], Andreas Bergmann[7], Massimo Antonelli[9], Albertus Beishuizen[10], Jean-Michel Constantin[11], Charles Damoisel[1], Nicolas Deye[2,20], Salvatore Di Somma[12], Thierry Dugernier[13], Bruno François[14,15], Stephane Gaudry[16], Vincent Huberlant[17], Jean-Baptiste Lascarrou[18], Gernot Marx[19], Emmanuelle Mercier[20], Haikel Oueslati[1], Peter Pickkers[4], Romain Sonneville[21], Matthieu Legrand[1,2,3], Pierre-François Laterre[22] and AdrenOSS-1 study investigators

- 583 patients with sepsis or septic shock
- inactive midregional pro-ADM, or recently by direct measurement of the bioactive form of ADM (bio-ADM)

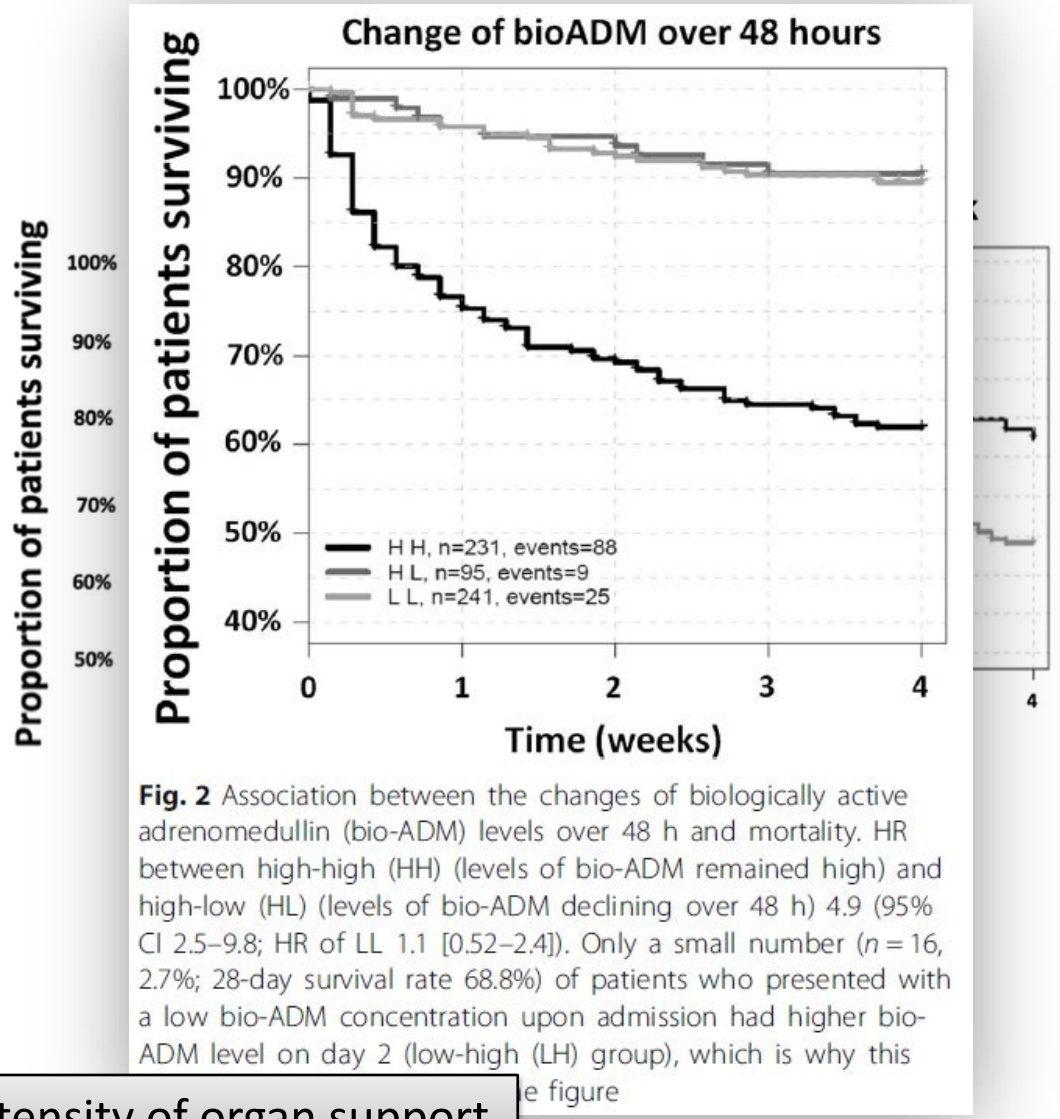


Fig. 2 Association between the changes of biologically active adrenomedullin (bio-ADM) levels over 48 h and mortality. HR between high-high (HH) (levels of bio-ADM remained high) and high-low (HL) (levels of bio-ADM declining over 48 h) 4.9 (95% CI 2.5–9.8; HR of LL 1.1 [0.52–2.4]). Only a small number ($n = 16$, 2.7%; 28-day survival rate 68.8%) of patients who presented with a low bio-ADM concentration upon admission had higher bio-ADM level on day 2 (low-high (LH) group), which is why this

...e figure

Also associated with intensity of organ support

Similar results with the FROG6ICU DB
(Lemasle et al *Crit Care Med 2019; in press)*

lame UMR 1137
Infection • Antimicrobiens • Modélisation • Evolution

Université de Paris

BMJ Open

A double-blind, placebo-controlled, randomised, multicentre, proof-of-concept and dose-finding phase II clinical trial to investigate the safety, tolerability and efficacy of adrecizumab in patients with septic shock and elevated adrenomedullin concentration (AdrenOSS-2)

Christopher Geven,[1] Alice Blet,[2,3,4] Matthijs Kox,[1] Oliver Hartmann,[5] Paul Scigalla,[5] Jens Zimmermann,[5] Gernot Marx,[6] Pierre-François Laterre,[7] Alexandre Mebazaa,[2,3,4] Peter Pickkers[1]

- Adrenomedullin (ADM) is a vasoactive peptide. High plasma concentrations of ADM correlate with worse outcome in sepsis patients
- ADM-binding antibody adrecizumab showed promising effects in animal models of septic shock
- Phase II biomarker-guided by measurement of circulating biologically active ADM concentration at admission.
- Primary endpoint is safety and tolerability of adrecizumab over a 90-day period.
- Key secondary endpoint is the Sepsis Severity Index over a 14-day period.

Geven C, *et al. BMJ Open 2019;9:e024475*

Immunosuppression in Patients Who Die of Sepsis and Multiple Organ Failure

Table 1. Immune System Analysis

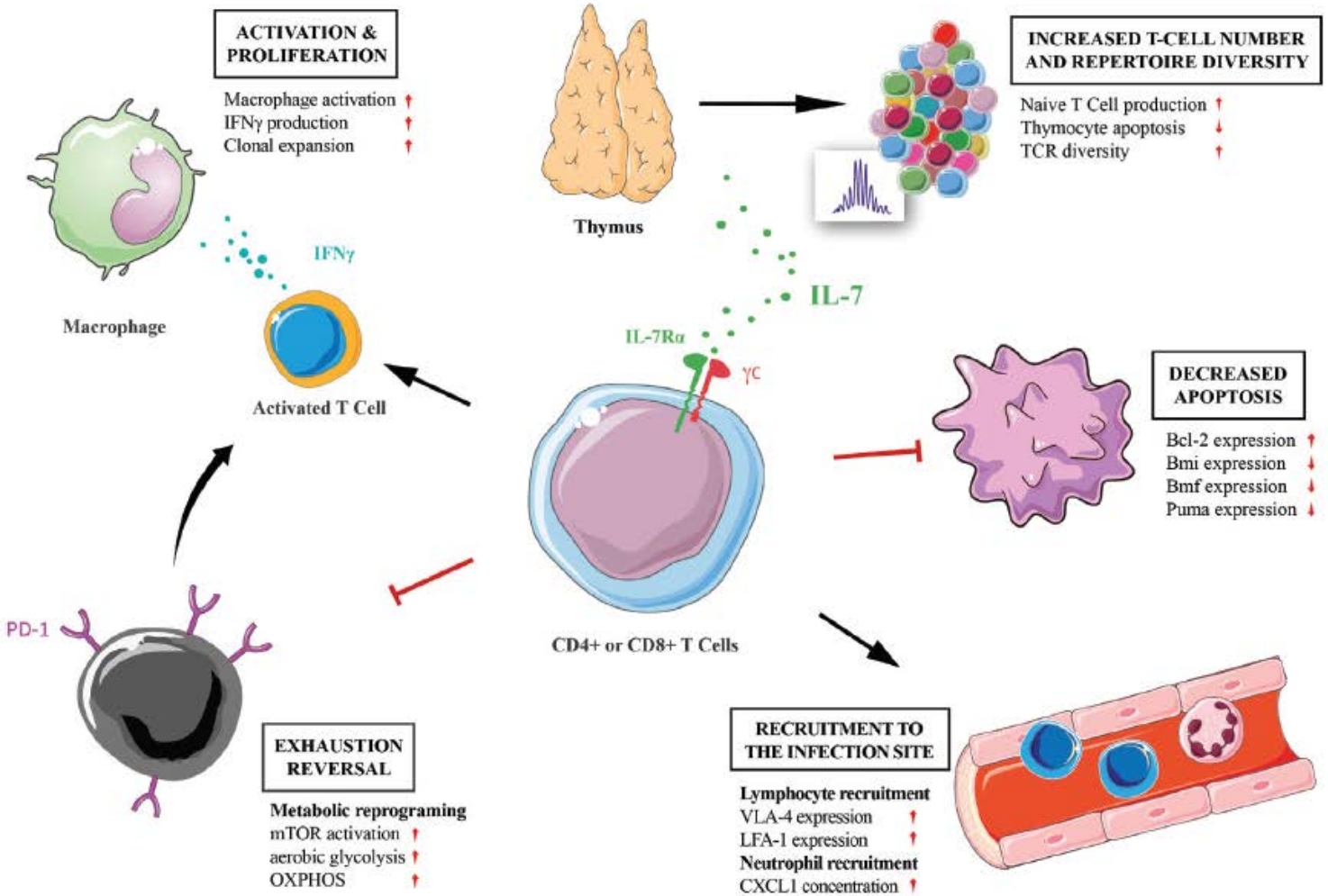
Immune Function	Analysis of Cell Populations	Assay Methods	Organ/Tissue	Results
Immune effector cells				
Innate	Dendritic cells, macrophages, natural killer cells, monocytes	Flow cytometry, immunohistochemistry	Spleen and splenocytes Lung and lung cells	Splenocytes: Figure 1, Figure 2, Figure 3 Lung cells: Figure 4 Spleen: Figure 5 Lung: Figure 6, Figure 7
Adaptive	T cells (CD4 and CD8)			
Immune supressor cells	Regulatory T cells, myeloid-derived suppressor cells	Flow cytometry	Splenocytes: regulatory T cell Lung cells: regulatory T cells and myeloid-derived suppressor cells	Results section of text
Immune cell receptor expression				
Expression of molecules associated with antigen presentation	HLA-DR expression	Flow cytometry, immunohistochemistry	Splenocytes, spleen	Splenocytes: Figure 3 Spleen: Figure 5
Expression of molecules that enhance immune responses	Receptors: CD28, CD69, IL-2α, IL-7Rα Ligands: CD86	Flow cytometry, immunohistochemistry	Splenocytes Lung cells	Splenocytes: Figure 2, Figure 3, Figure 5 Lung cells: Figure 4
Expression of molecules that suppress immune responses	Receptors: BTLA, PD-1, CTLA-4 Ligands: PD-L1, PD-L2, HVEM	Flow cytometry, immunohistochemistry	Splenocytes or lung cells Spleen or lung	Splenocytes: Figure 2, Figure 3 Lung cells: Figure 4 Lung: Figure 6, Figure 7
Immune cell effector function				
Cytokine secretion				
Innate immune response: lipopolysaccharide	Natural killer cells, dendritic cells, macrophages, monocytes	Enzyme-linked immunosorbent assay	Splenocytes	Figure 1
Adaptive immune response: anti-CD3/anti-CD28	T cells			

Abbreviations: BTLA, B- and T-lymphocyte attenuator; CTLA, cytotoxic T-lymphocyte antigen; HVEM, herpes virus entry mediator; IL, interleukin; PD, programmed cell death.

Altered cytokine secretion

Boomer et al - JAMA. 2011;306(23):2594-2605

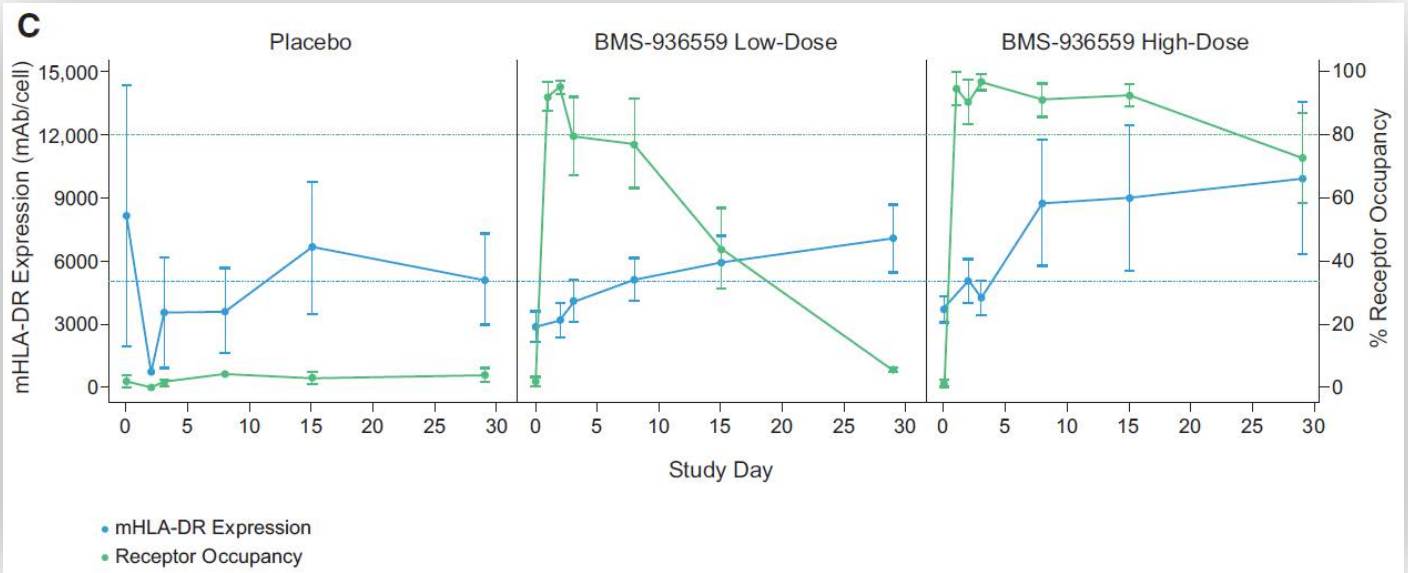
Effects of rhIL-7



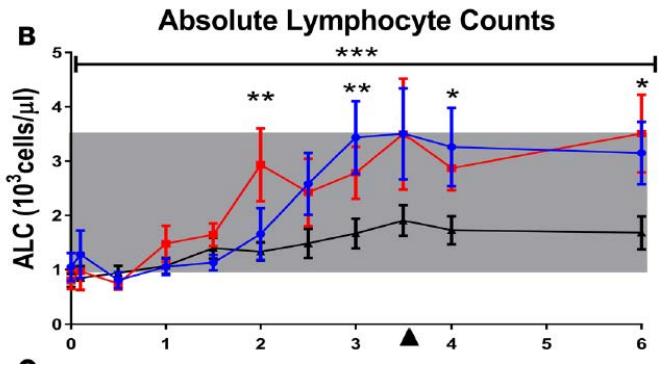
De Roquetaillade - *Critical Reviews™ in Immunology, 38(6):433–451 (2018)*

Immune Checkpoint Inhibition in Sepsis: A Phase 1b Randomized, Placebo-Controlled, Single Ascending Dose Study of Antiprogrammed Cell Death-Ligand 1 Antibody (BMS-936559)*

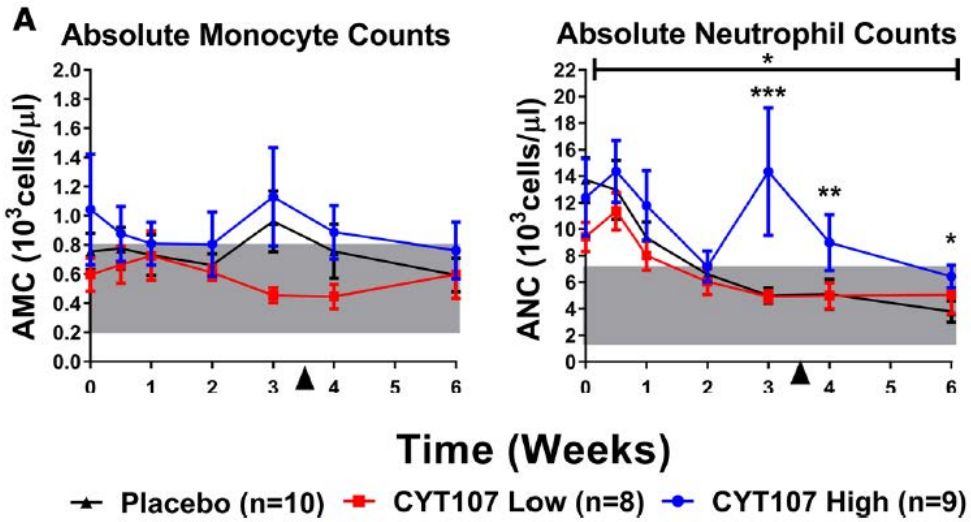
- PD1-PDL1 binding trigger T-cell « inactivation »
- 24 patients sepsis or septic shock and lymphocyte count<1,100 cells/µL.
- A single-dose BMS-936559 (10–900 mg; *n = 20) or placebo (n = 4)*
- *The 2 highest doses result in HLA-DR > 5000 mab/c*



Hotchkiss et al - Crit Care Med 2019; 47:632–642)



- 27 septic shock and severe lymphopenia of 900 lymphocytes/µl or lower
- CYT107 was well tolerated
- No induced cytokine storm or worsening inflammation organ dysfunction.
- CYT107 caused a 3- to 4-fold increase in absolute lymphocyte counts and in circulating CD4+ and CD8+ T cells that persisted for weeks after drug administration.
- CYT107 also increased T cell proliferation and activation



JCI Insight. 2018;3(5):e98960.

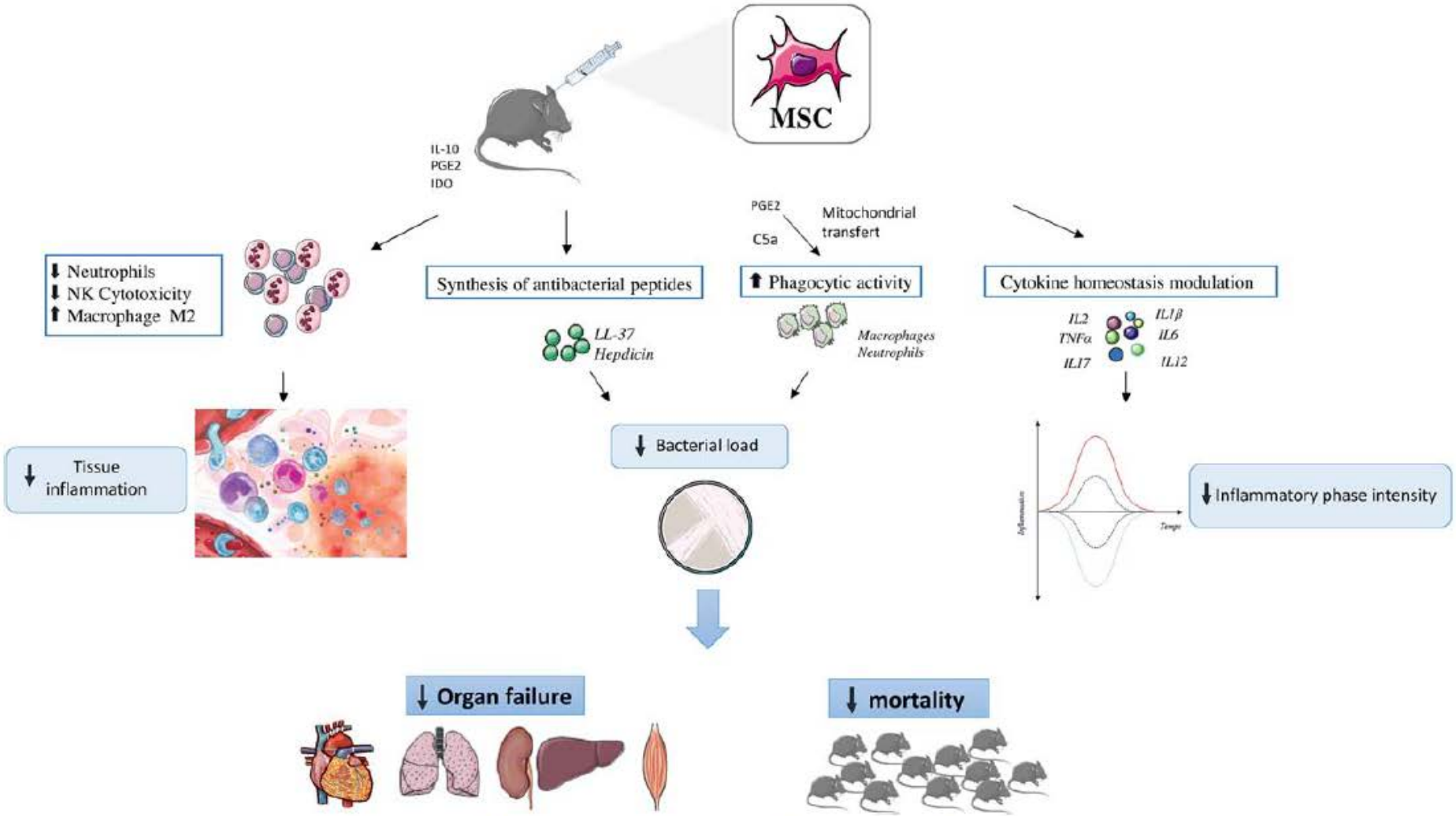


Figure 1. Mesenchymal stromal/stem cell (MSC) action during sepsis and septic shock. The action of MSCs during sepsis and septic shock is extensive. Their immunomodulatory capacity decreases tissue inflammation by regulating cytokine homeostasis and decreasing the traffic of immune cells into organs. Their antibacterial capacities are mediated by direct action on the bacterial load through secreting antibacterial peptides and by indirect action through increasing the phagocytic activity of macrophages and neutrophils. These properties allow MSCs to reduce organ failure and mortality associated with sepsis and septic shock. Abbreviations: IL, interleukin; LL-37, Cathelicidin LL-37; IDO, Indoleamine 2, 3-dioxygenase; NK, natural killer; PGE, prostaglandin; TNF, tumor necrosis factor.

Laroye et al - STEM CELLS 2017;35:2331–2339

ORIGINAL ARTICLE

Cellular Immunotherapy for Septic Shock

A Phase I Clinical Trial

Lauralyn A. McIntyre[1,2,3], Duncan J. Stewart[2,4], Shirley H. J. Mei[2,5], David Courtman[2,5], Irene Watpool[2], John Granton[6], John Marshall[7], Claudia dos Santos[7], Keith R. Walley[8], Brent W. Winston[9], Kenny Schlosser[2,5], and Dean A. Fergusson[2,3]; for the Canadian Critical Care Trials Group and the Canadian Critical Care Translational Biology Group

[1]Division of Critical Care, Department of Medicine; [3]Department of Epidemiology and Community Medicine, and [4]Department of Cell and Molecular Medicine, University of Ottawa, Ottawa, Ontario, Canada; [2]Ottawa Hospital Research Institute, Ottawa, Ontario, Canada; [5]Department of Regenerative Medicine, Ottawa Hospital Research Institute, Ottawa, Ontario, Canada; [6]Department of Medicine and [7]Department of Surgery and Critical Care Medicine, Keenan Research Centre of the Li Ka Shing Knowledge Institute, St. Michael's Hospital, University of Toronto, Toronto, Ontario, Canada; [8]Centre for Heart Lung Innovation, University of British Columbia, Vancouver, British Columbia, Canada; and [9]Department of Critical Care Medicine, Biochemistry and Molecular Biology, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada

- Preclinical sepsis studies suggest that mesenchymal stem (stromal) cells (MSCs) may modulate inflammation, enhance pathogen clearance and tissue repair, and reduce death
- Phase I safety of 250 million cells allogenenic freshly cultured bone marrow–derived MSCs for the treatment of septic shock.
- 9 intervention group vs 21 control group. No adverse events

American Journal of Respiratory and Critical Care Medicine Volume 197 Number 3 | February 1 2018

STEM CELLS

Intravenous Infusion of Human Adipose Mesenchymal Stem Cells Modifies the Host Response to Lipopolysaccharide in Humans: A Randomized, Single-Blind, Parallel Group, Placebo Controlled Trial

Desiree Perlee,[aa] Lonneke A. van Vught,[a] Brendon P. Scicluna,[a,b] Anja Maag,[a] René Lutter,[c] Elles M. Kemper,[d] Cornelis van 't Veer,[a] Marie A. Punchard,[e] Jesús González,[e] Marie Paule Richard,[e] Wilfried Dalemans,[f] Eleuterio Lombardo,[e] Alex F. de Vos,[a] Tom van der Poll[a,g]

SEPCELL STEM CELLS FOR SEPSIS

- 32 healthy subjects placebo or allogeneic adipose MSCs (ASCs) intravenously at either 0.25×10^6, 1×10^6, or 4×10^6 cells/kg (H1)
- LPS stimulation (H0)

1 - Adipose MSC cells was safe

2- High dose increased the febrile response

3- mixed pro-inflammatory (enhanced interleukin-8 and nucleosome release) and anti-inflammatory effects (increased interleukin-10 and transforming growth factor-β release)

4- Enhanced coagulation activation and reduced the fibrinolytic response.

5- Blood leukocyte transcriptome at 2 hours post LPS, ASC-infused subjects displayed higher expression of genes involved in innate immune pathways, whereas at 4 hours post LPS these subjects had lower expression of innate immune pathway genes

6- Early enhancement (2 hours post-LPS) and later suppression (4 hours post-LPS) of NF-κB signaling in blood leukocytes

SEPCELL/ Phase II PB controlled study - Severe CAP 180 patients

STEM CELLS 2018;36:1778–1788 www.StemCells.com

Université de Paris

HÔPITAUX UNIVERSITAIRES PARIS NORD VAL DE SEINE
Bichat - Claude Bernard

MI² Medical Infectious diseases Intensive care unit

Jean-francois.timsit@aphp.fr

@JF_Timsit

Iame UMR 1137
Infection • Antimicrobiens • Modélisation • Evolution