

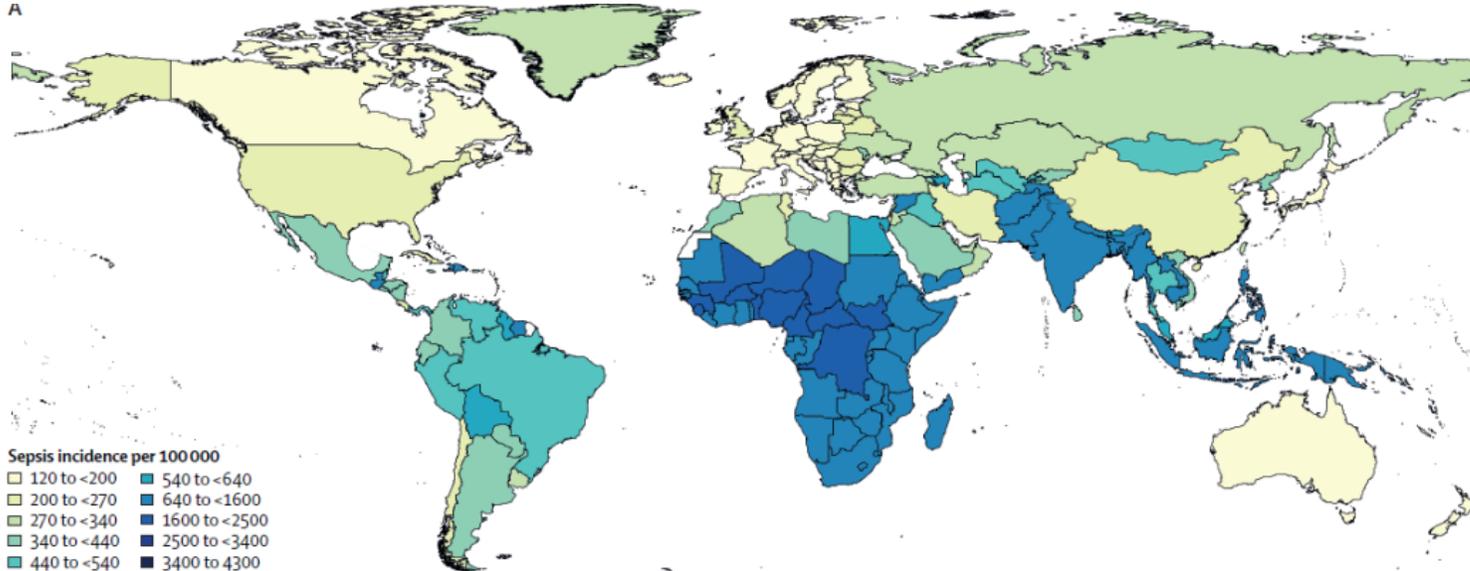
Actualités dans le sepsis

Pr Carole Schwebel
Médecine Intensive - Réanimation
CHU Grenoble-Alpes



Pas de conflit d'intérêt

Sepsis : un enjeu de santé publique



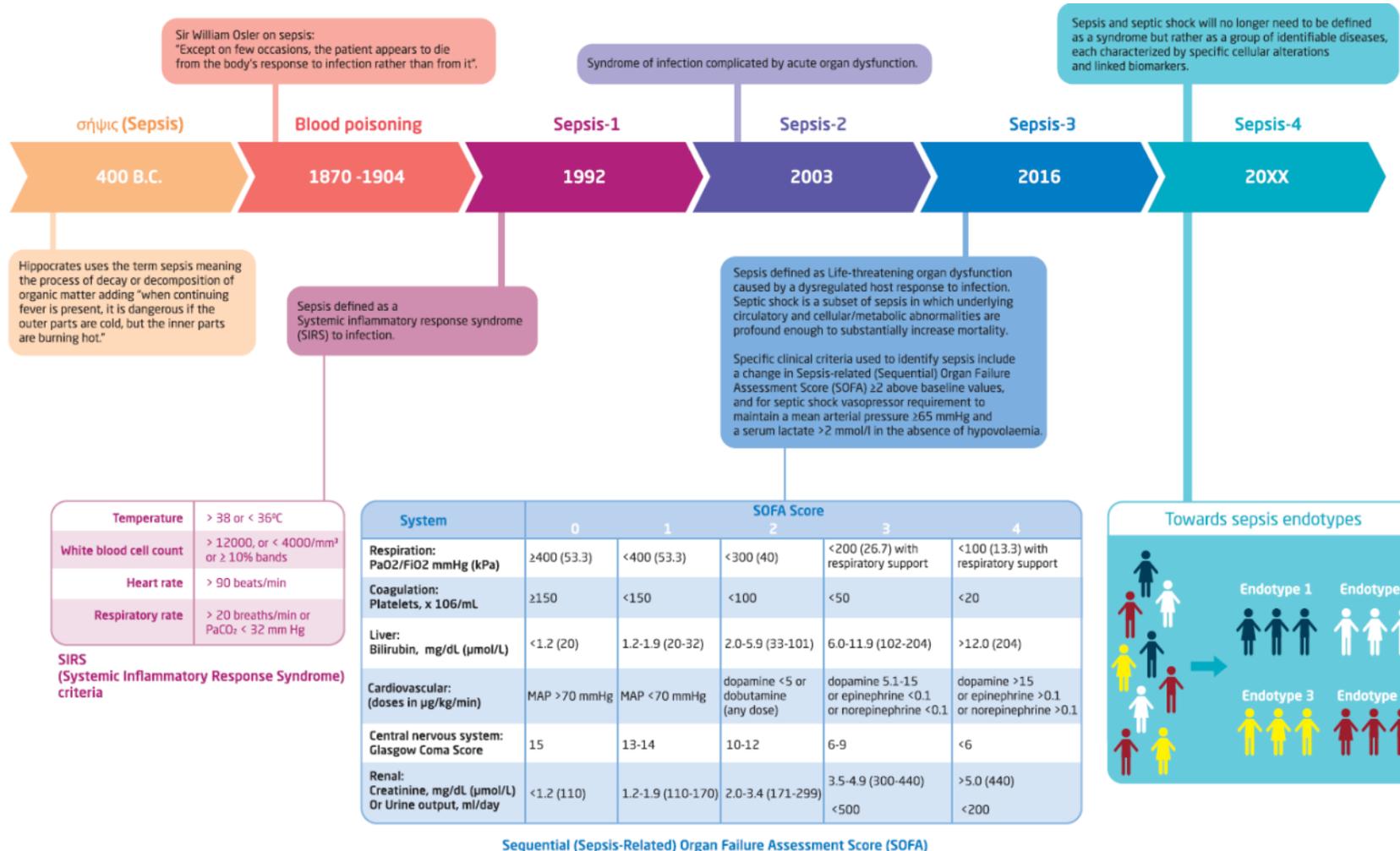
- 300000 cas/an
- 57000 décès /an



- 700000 décès /an

- Près de 50 millions de sepsis / an dans le monde
- Incidence de > 350/100000 hbts
- 11 millions de décès /an - 1 décès sur 5
- 50% sont des enfants dont 40% de moins de 5 ans

Sepsis: l'évolution des concepts et définition



le qSOFA : à bon escient !

Indicateur d'alerte vs outil de screening

- Introduit par SSC 2016
- qSOFA vs SIRS
 - Moins sensible
 - Plus spécifique
- Rappel historique
 - 24% qSOFA ≥ 2
 - Impact pronostique pour 70%
- Enjeux de diagnostic par excès

qSOFA : Une infection et...



Trouble des
fonctions supérieures



Fréquence respiratoire
 $\geq 22/\text{min}$



Pression artérielle
 $\leq 100 \text{ mmHg}$

2 critères ou plus identifie un patient
ayant un risque de mortalité par sepsis $\geq 10\%$

Sepsis : un nouvel indicateur ???

Incidence and mortality of hospital- and ICU-treated sepsis: results from an updated and expanded systematic review and meta-analysis

C. Fleischmann-Struzek¹, L. Mellhammar², N. Rose¹, A. Cassini³, K. E. Rudd⁴, P. Schlattmann⁵, B. Allegranzi³ and K. Reinhart^{6,7,8*} 

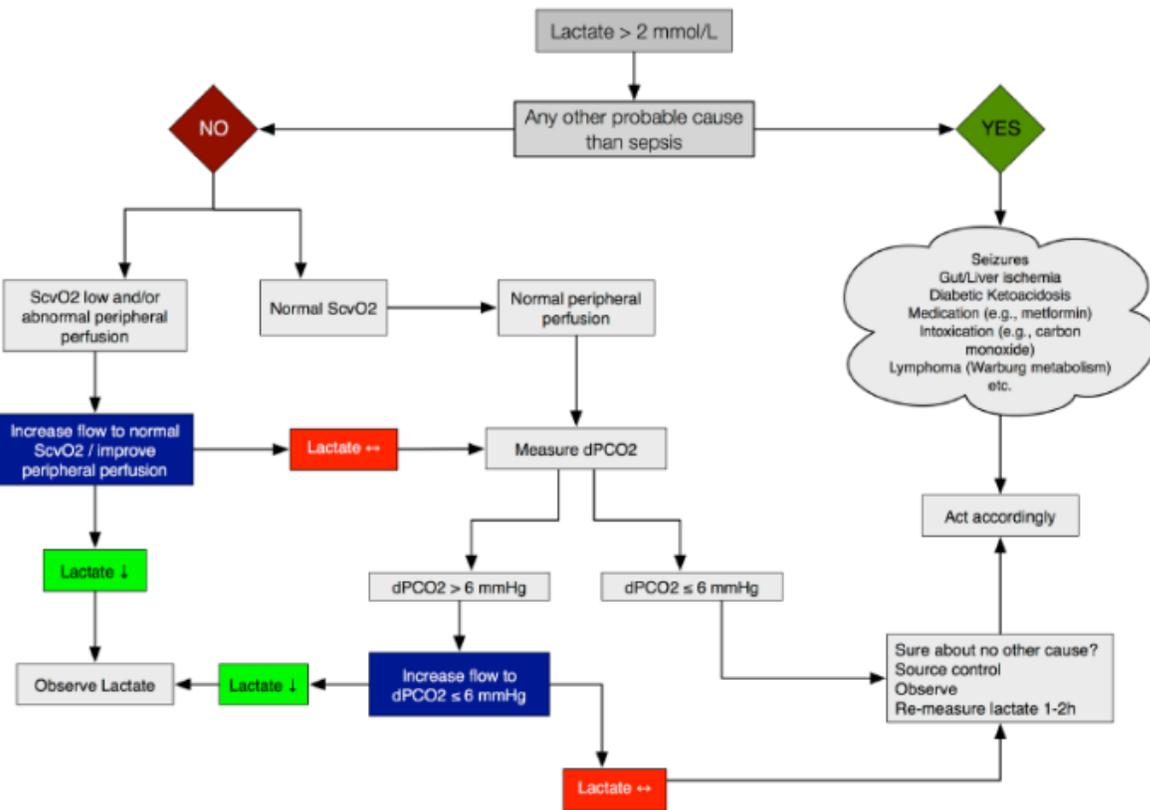
Study setting	Sepsis type	Number of studies	Pooled estimate (95% CI)	Inter-study heterogeneity (I^2 statistics)	Range of individual study estimates
Incidence of hospital-acquired sepsis per 1000 hospitalized patients					
Hospital patients	Hospital-acquired sepsis	4	15.4 (9.2–25.7)	$I^2 = 99\%$	7.4–29.5
	Hospital-acquired sepsis with organ dysfunction	5	9.3 (7.3–11.9)	$I^2 = 100\%$	2–20.6
	Hospital-acquired septic shock	1	–	–	1
ICU patients	ICU-acquired sepsis	7	44.8 (25.5–77.4)	$I^2 = 99\%$	8–90.4
	Hospital-acquired sepsis	1	–	–	59.7
	ICU-acquired sepsis with organ dysfunction	12	35.8 (19.1–66.3)	$I^2 = 100\%$	5–373.2
	Hospital-acquired sepsis with organ dysfunction	11	56.5 (35–90.2)	$I^2 = 99\%$	9.2–254.4
	ICU-acquired septic shock	2	20.3 (0.9–317.1)	$I^2 = 100\%$	4.2–91.8
	Hospital-acquired septic shock	1	–	–	23.2
Neonates in NICUs	Hospital-acquired neonatal sepsis	9	112.9 (64.2–191.1)	$I^2 = 99\%$	18.4–368.2
	Blood culture-proven hospital-acquired neonatal sepsis	5	45.7 (26–79.2)	$I^2 = 96\%$	20.5–75.6

SSC 2016 : le lactate ciblé mais

- Hyperlactatémie pas synonyme d'hypoperfusion - autres causes d'hyperlactatémie
- Hyperlactatémie marqueur de sévérité et gravité
- Lactate guided resuscitation (*Hernandez et al. JAMA 2019, ANDROMEDA Shock trial*)

	CRT normal	CRT abnormal	p value
Number of patients	25 (108)	75 (316)	
Age (years)	65 [48-75]	66 [53-76]	0.13
Sex (female)	51 (55)	45 (143)	0.7
APACHE score	19 [13-24]	23 [18-29]	0.001
SOFA score	8 [6-10]	10 [7-12]	0.001
Charlson index	3 [0-5]	3 [1-5]	0.3
Randomization arm	CRT-T: 44.4 (48) LT: 55.6 (60)	CRT-T: 51.8 (164) LT: 48.2 (152)	0.2
Sepsis origin	Abdominal 28 (30) Pulmonary 34 (37) Urinary 21 (23) Other 17 (18)	Abdominal: 38 (119) Pulmonary: 29 (91) Urinary: 20 (64) Other: 13 (42)	0.1
MAP (mmHg)	68 [64-77]	65 [57-76]	0.015
CVP (mmHg)	8 [5-12]	9 [6-13]	0.5
Fluids administered before ICU admission (ml)	2000 [1500-2907]	2000 [1196-2747]	0.18
Fluid responsiveness positive state	42 (45)	62 (197)	0.001
Fluid administered in boluses between 0-8 h (ml)	500 [0-1100]	1000 [500-2250]	0.001
Fluid balance at 8-h (ml)	929 [260-1740]	1700 [855-2772]	0.001
Norepinephrine dose (mcg/kg/min)	0.13 [0.08-0.24]	0.25 [0.12-0.42]	0.001
Lactate (mmol/L)	3.0 [2.5-4.2]	3.8 [2.8-5.8]	0.001
CRT (sec)	2 [2, 3]	5 [4-7]	0.001
ScvO2 (%)	75 [69-81]	71 [62-78]	0.001
Delta pCO2(v-a)	7 [4-9]	7 [5-10]	0.06
SOFA at 24-hours	7 [4-10]	9 [6-12]	0.001
Renal replacement therapy	10 (11)	19 (61)	0.013
Mechanical ventilation	62 (67)	80 (255)	0.001
ICU length of stay (days)	5 [3-12]	6 [1-8]	0.26
28-day mortality	27 (29)	43 (137)	0.001

Intensive Care Med (2020) 46:816-818



Intensive Care Med (2019) 45:82-85

REA / soins critiques : the place to be

Sepsis et choc septique

- Admission différée facteur de mortalité
- Retard à l'application des recommandations
- Durée de ventilation
- Durée de séjour en réa et hospitalière
- **Le bon timing : avant H6**
 - +1,5% de décès par heure de retard

Sepsis : une dynamique de recherche

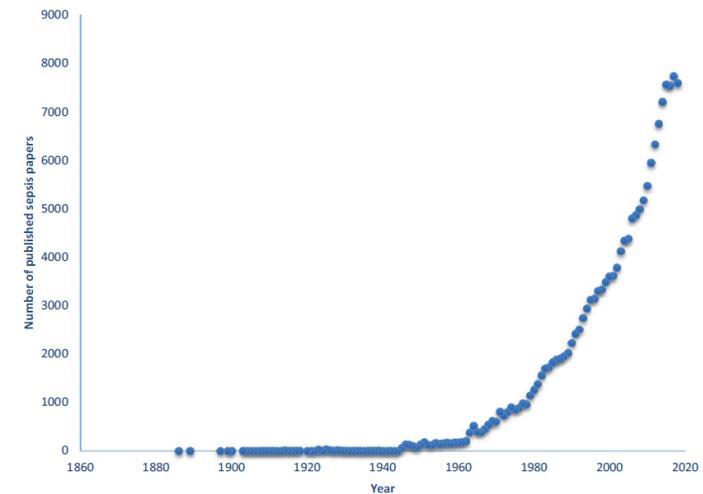
The image shows two screenshots of search results. The top screenshot is from PubMed.gov, displaying a search for 'sepsis' with 44,185 results. The bottom screenshot is from ClinicalTrials.gov, displaying 2603 studies found for 'sepsis'.

PubMed.gov Search Results:

- Search term: sepsis
- Results: 44,185 results
- Sorted by: Best match
- Options: Save, Email, Send to, Display options

ClinicalTrials.gov Search Results:

- Search term: sepsis
- Results: 2603 Studies found for: sepsis



Le questionnement post SSC 2018

CONFERENCE REPORTS AND EXPERT PANEL

Surviving sepsis campaign: research priorities for sepsis and septic shock



Can targeted/personalized/precision medicine approaches determine which therapies will work for which patients at which times?

What are ideal endpoints for volume resuscitation and how should volume resuscitation be titrated?

Should rapid diagnostic tests be implemented in clinical practice?

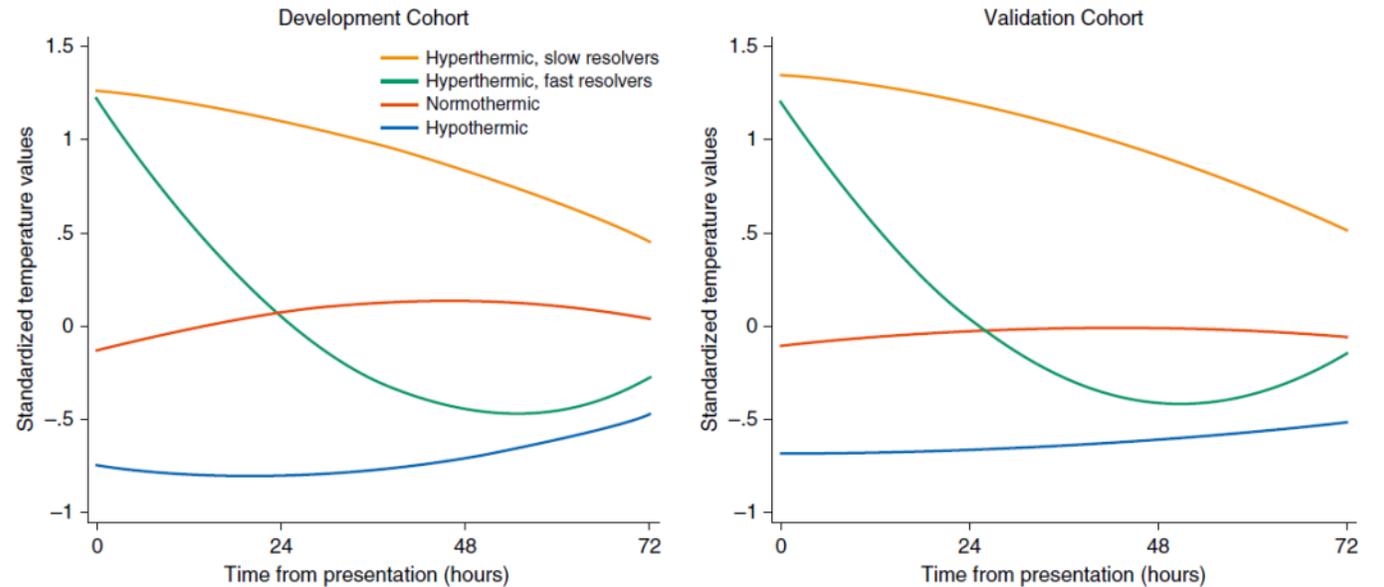
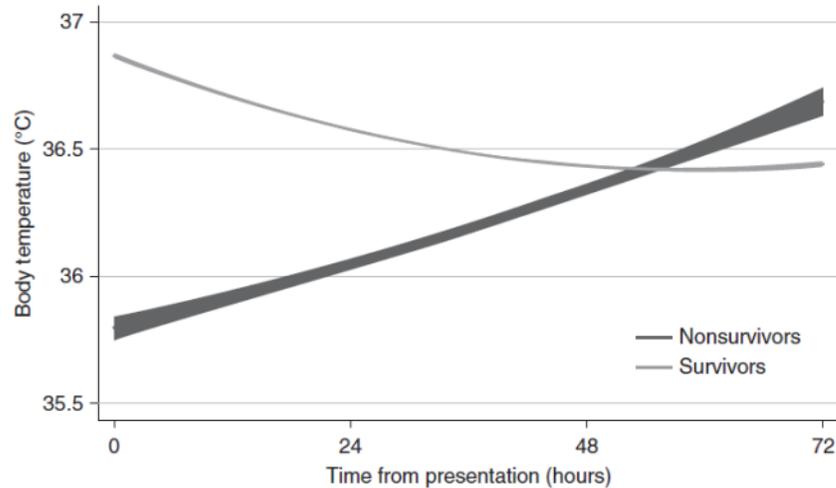
Should empiric antibiotic combination therapy be used in sepsis or septic shock?

What are the predictors of sepsis long-term morbidity and mortality?

What information identifies organ dysfunction?

Cinétique de la température

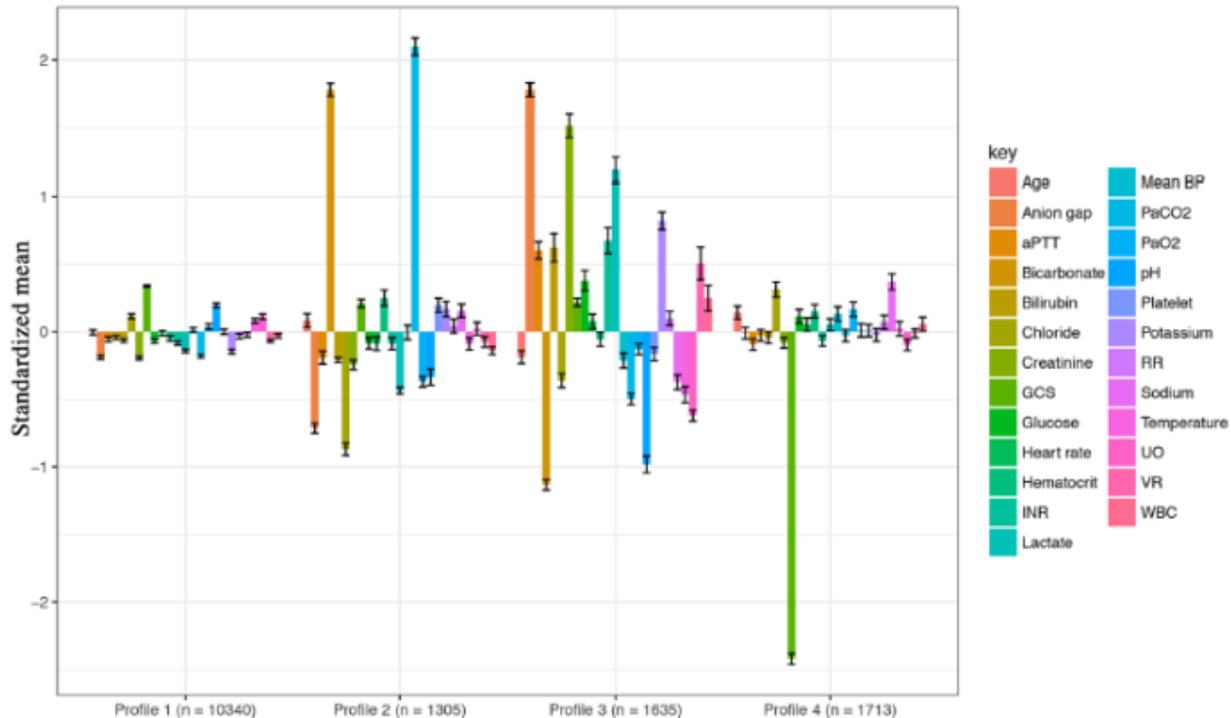
Cohorte rétrospective de 14000 patients, urgences, sepsis- AB thérapie 24



Impact de mortalité significatif HT > NT > HTSR > HTFR

réponse thérapeutique et pronostic variable selon profil de patients

Analysis rétrospective monocentrique- 14993 patients – association mortalité et réponse remplissage



4 groupes identifiés

Gr 1 : mortalité la plus basse

Gr2 : dysfonction respiratoire

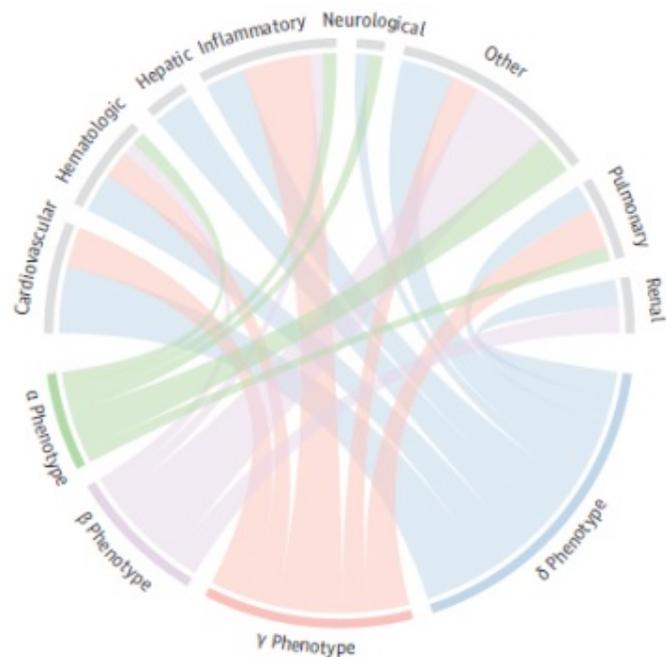
Gr3 : défaillance pluriviscérale

Gr4 : défaillance neurologique

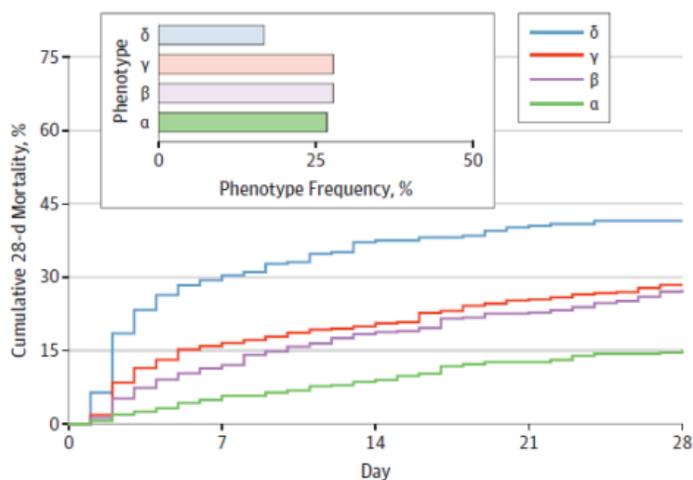
Mortalité hospitalière GR 3 >4 >2

Phénotypage et pronostic

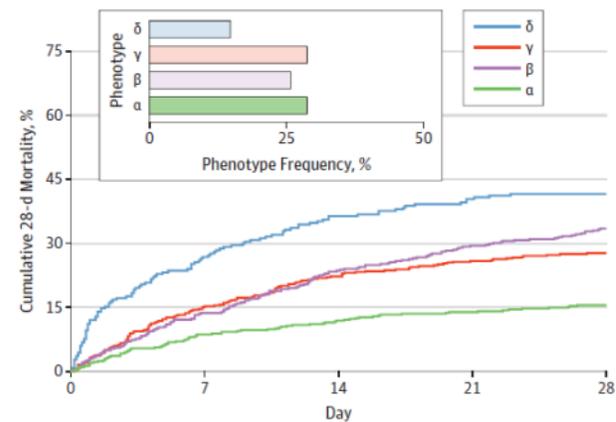
Rétrospectif multicentrique- plus de 20000 patients-



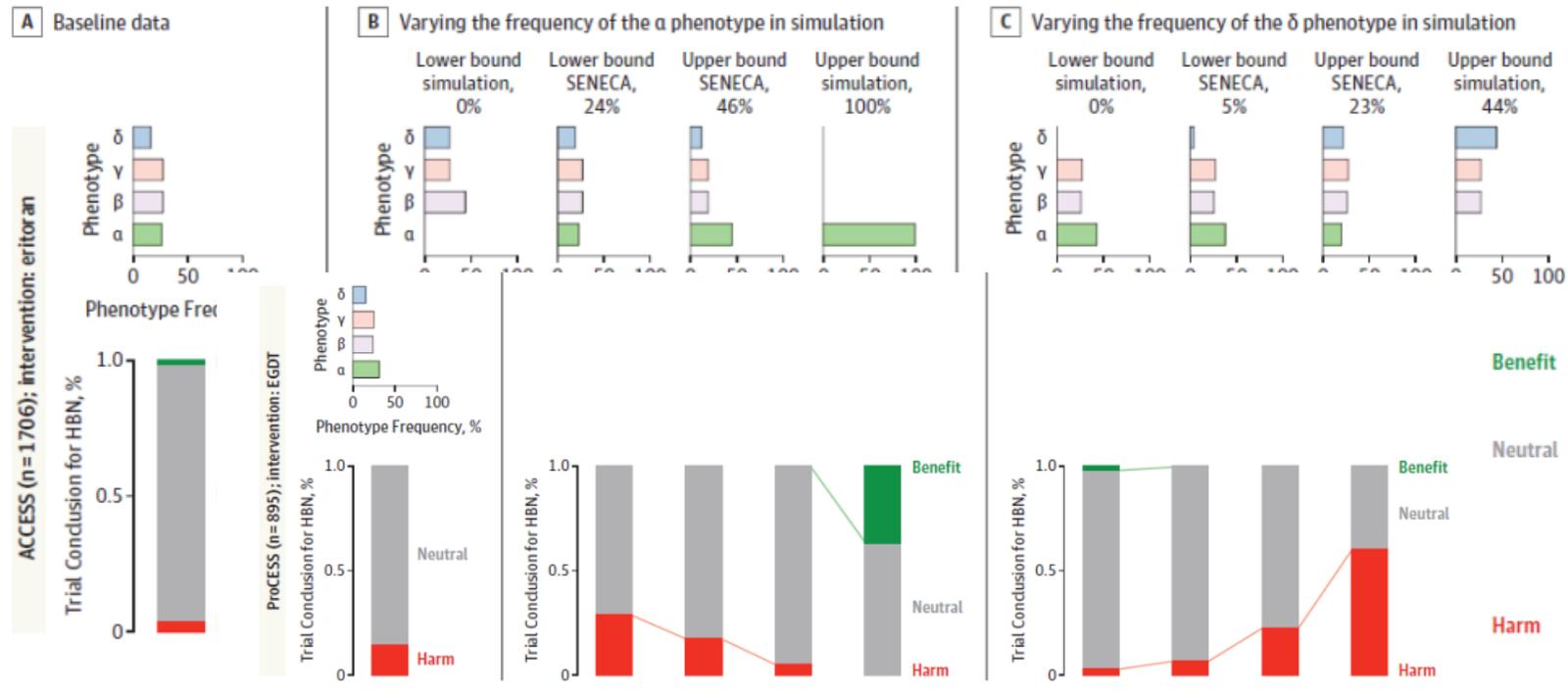
D ACCESS trial (n=1706) (eritoran vs placebo)



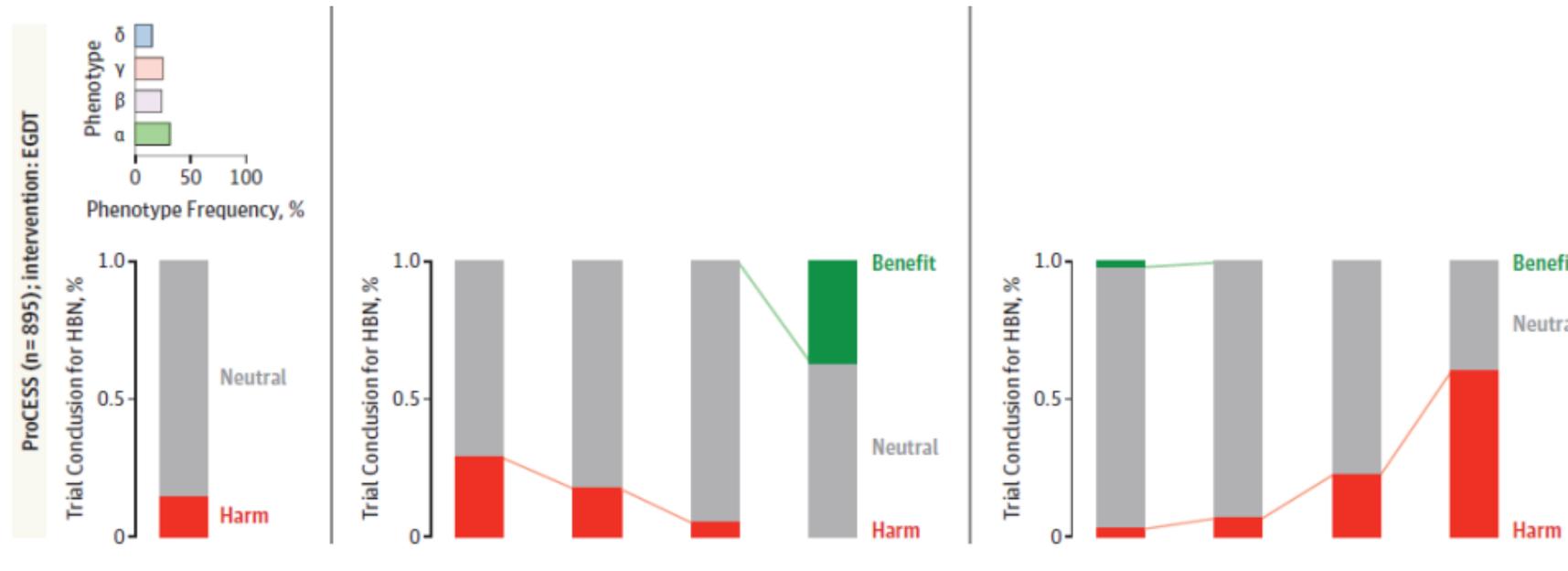
E PROWESS trial (n=1690) (drotrecogin alfa vs placebo)



Effets thérapeutiques revisités



Effets thérapeutiques revisités

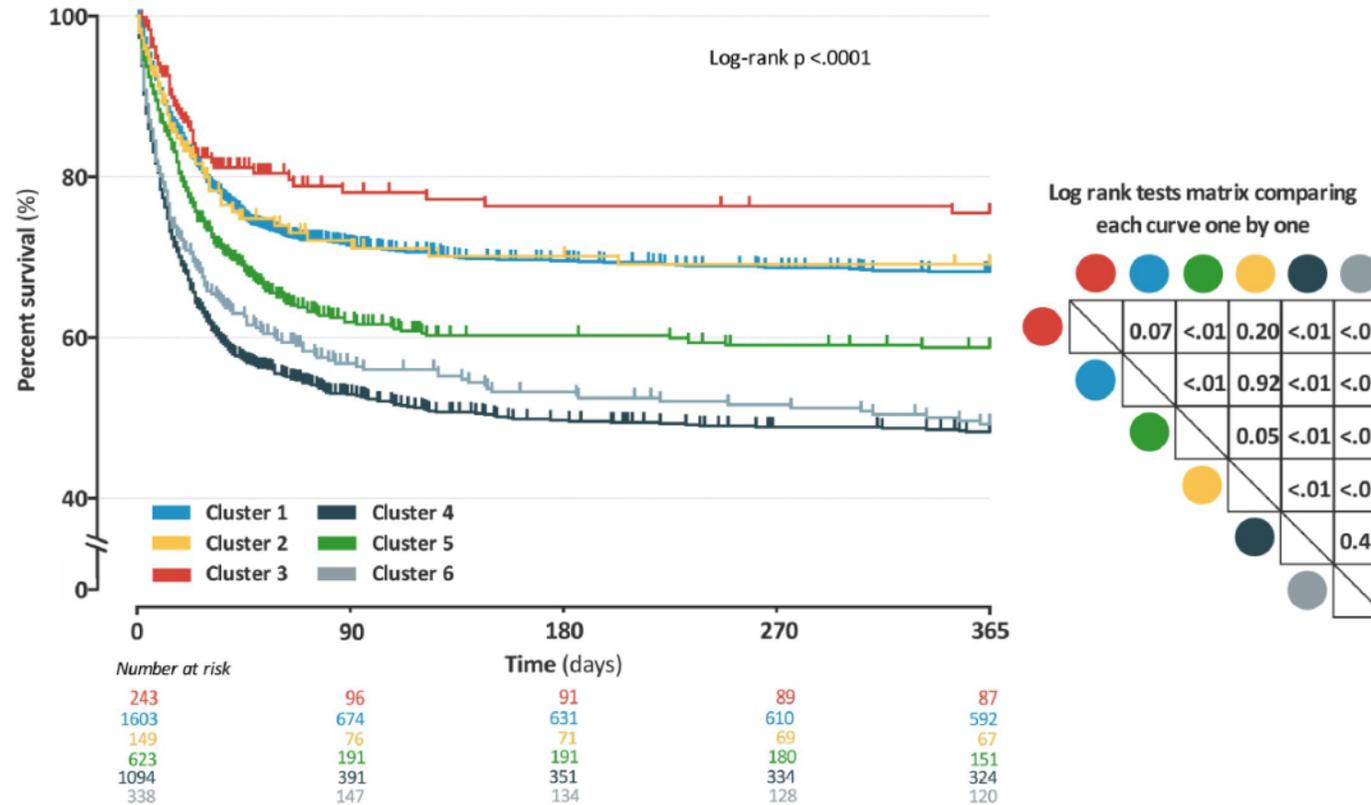


Comorbidités et site infecté : marqueurs d'hétérogénéité

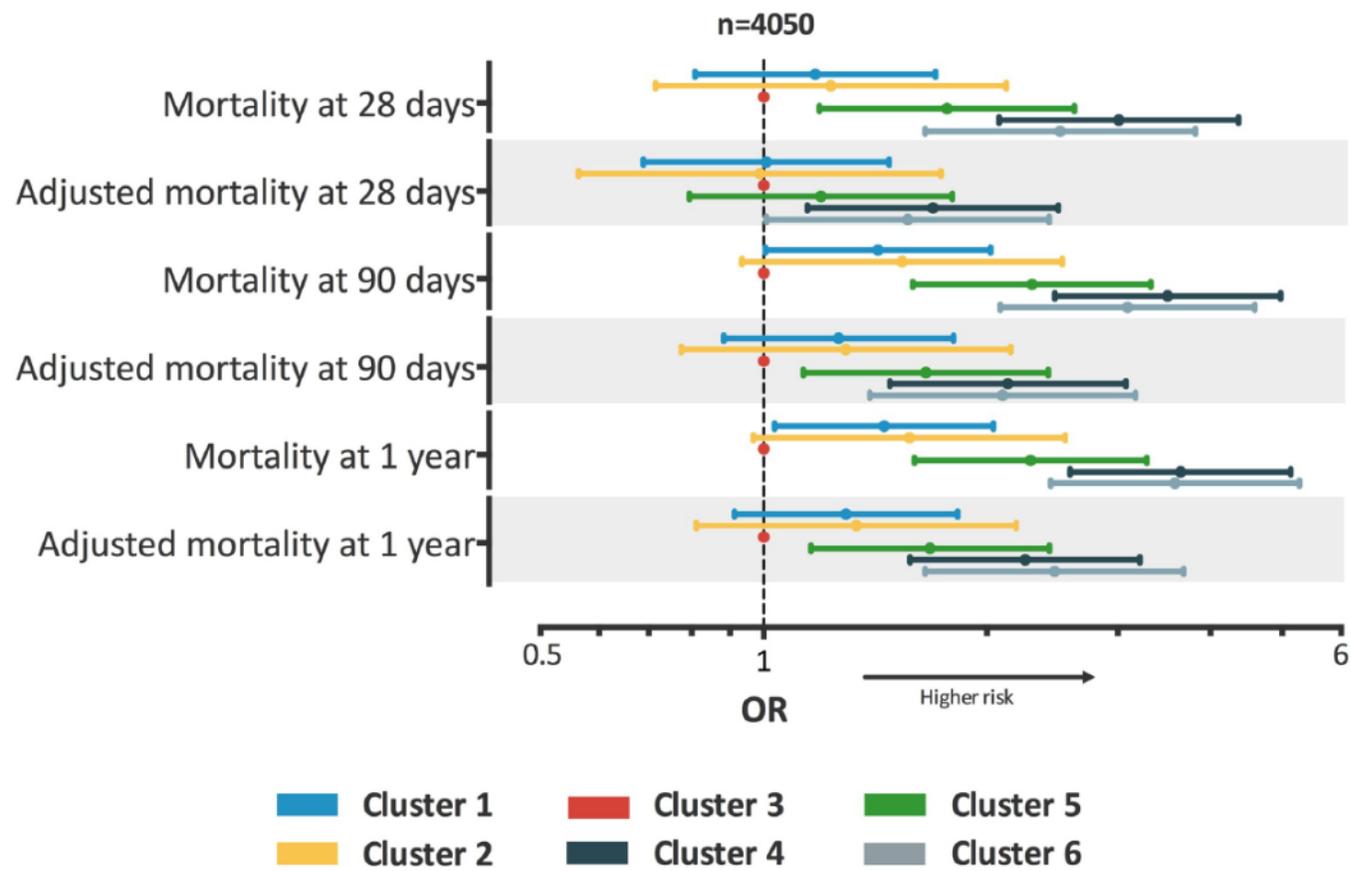
Cohorte multicentrique prospective **OutcomeRea** - sepsis ou choc septique - n= 4650 patients
Hierarchical Clustering

-  **Cluster 1** Jeunes sans comorbidité - PNP communautaire - **40%** des patients
-  **Cluster 2** Jeunes sans comorbidité - PNP communautaire - **4%** des patients
-  **Cluster 3** Agés - BPCO- infection bronchique- peu défaillants - **6%** des patients
-  **Cluster 4** Les plus âgés - comorbidités chroniques- défaillances d'organes - **27%** des patients
-  **Cluster 5** Post-opératoires- infections nosocomiales - **15%** des patients
-  **Cluster 6** Jeunes - immunodéprimés- VIH- corticothérapie- hémato maligne - **8%** des patients

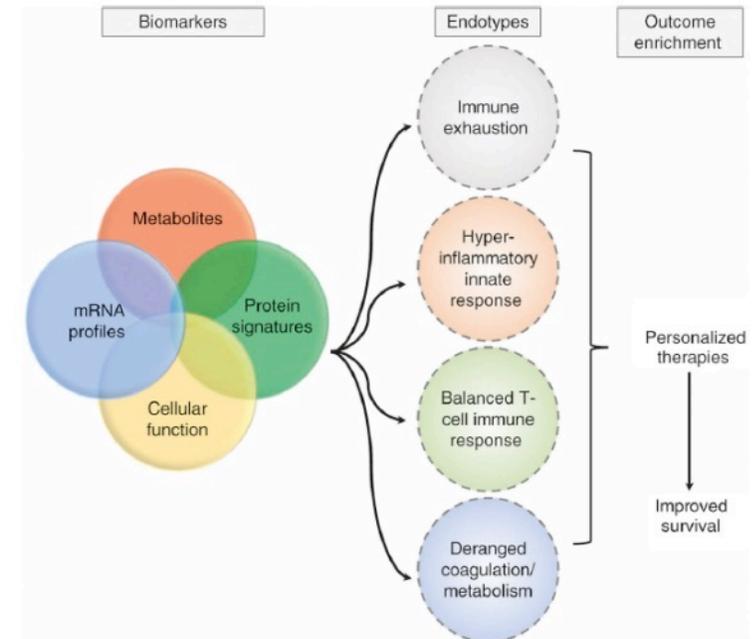
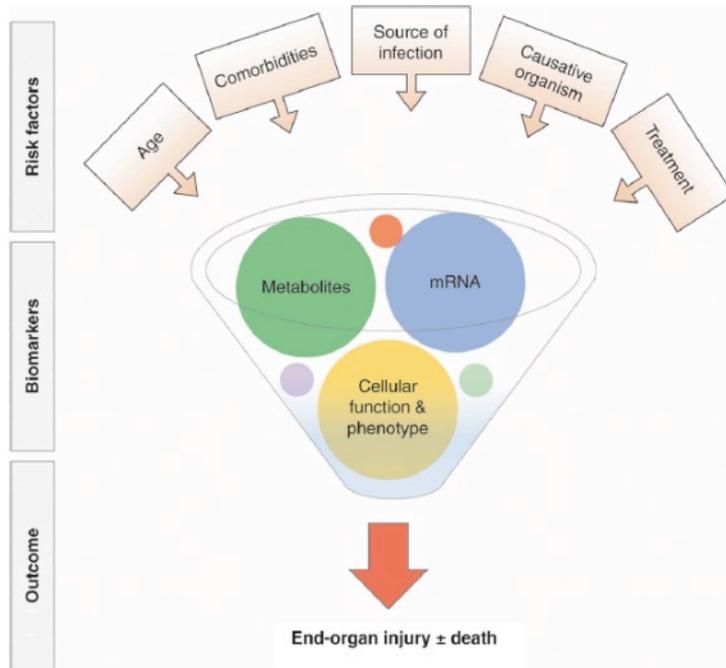
Impact pronostique de la typologie des patients



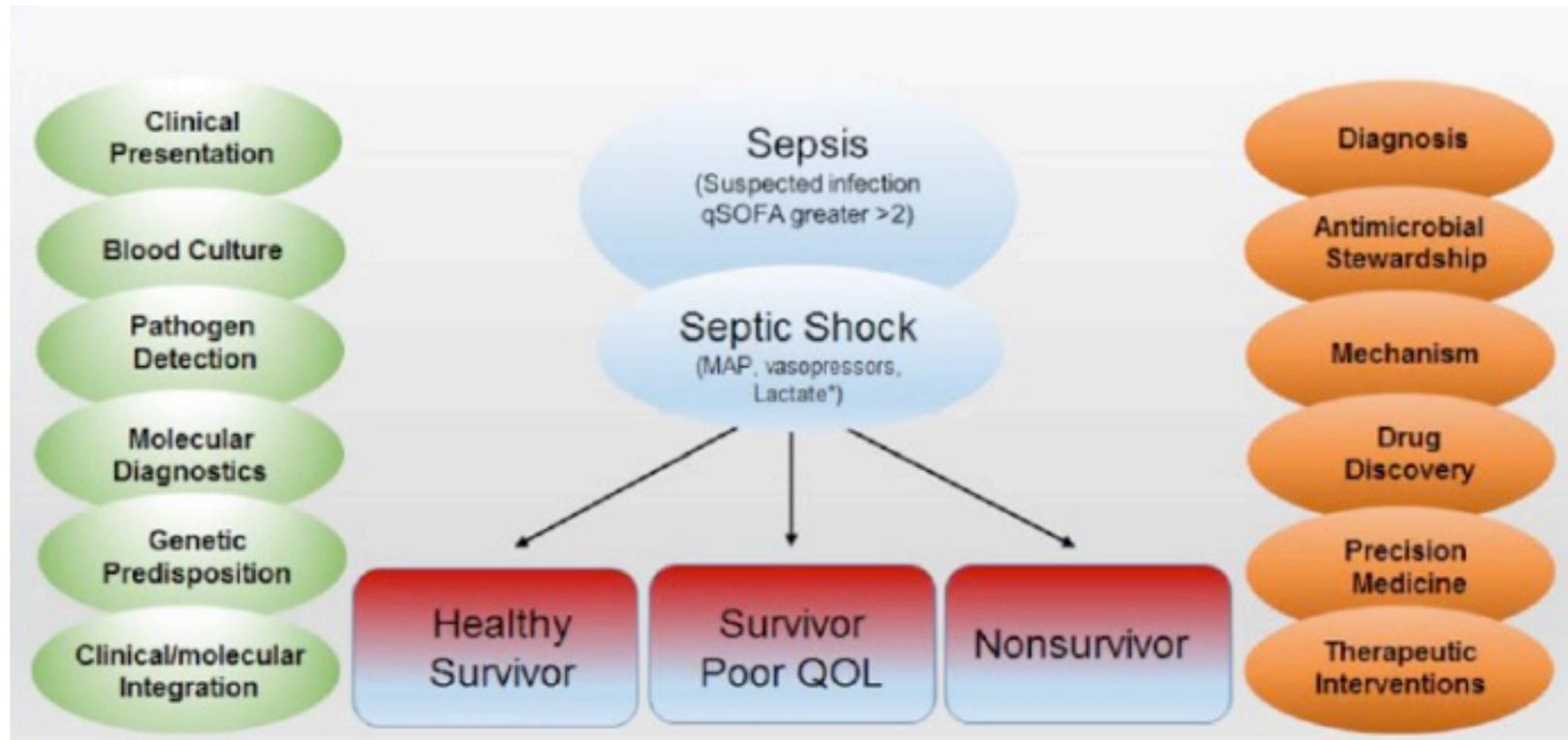
Impact sur la mortalité précoce et tardive



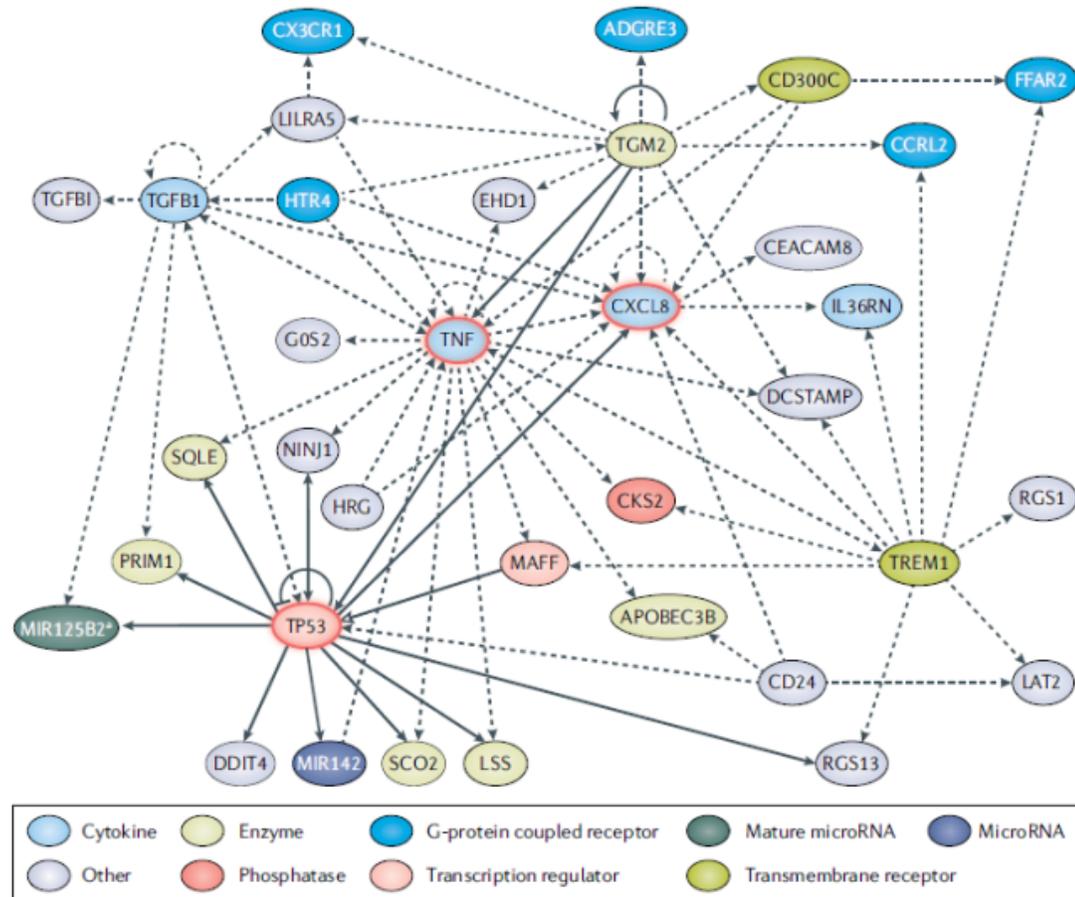
Sepsis : hétérogénéité multifactorielle et pluridimensionnelle



Les outils de biologie moléculaire

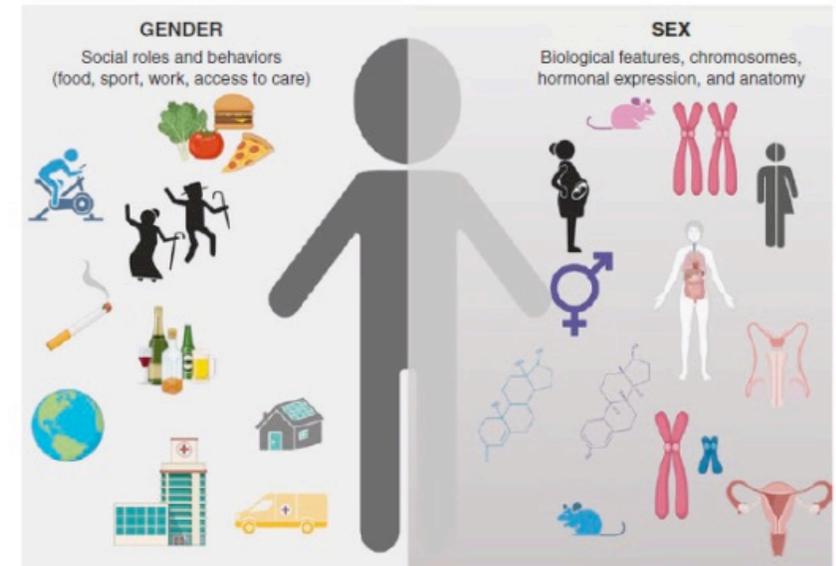
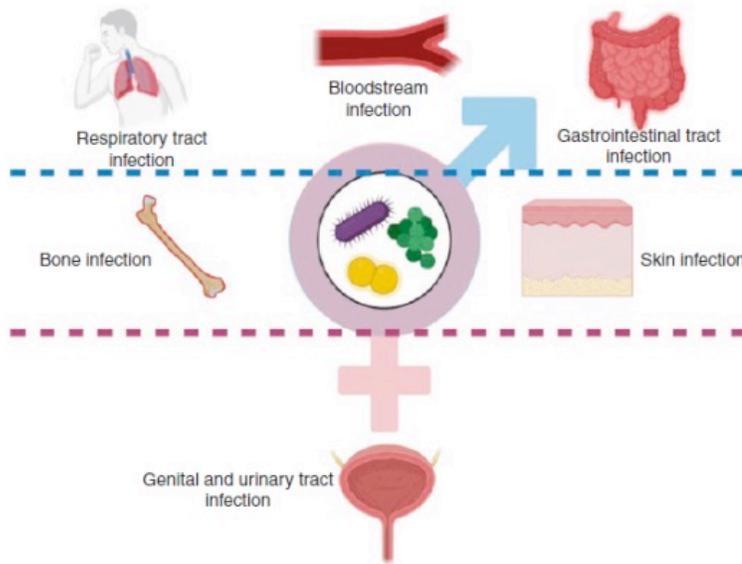


Les omics pour identifier les cibles

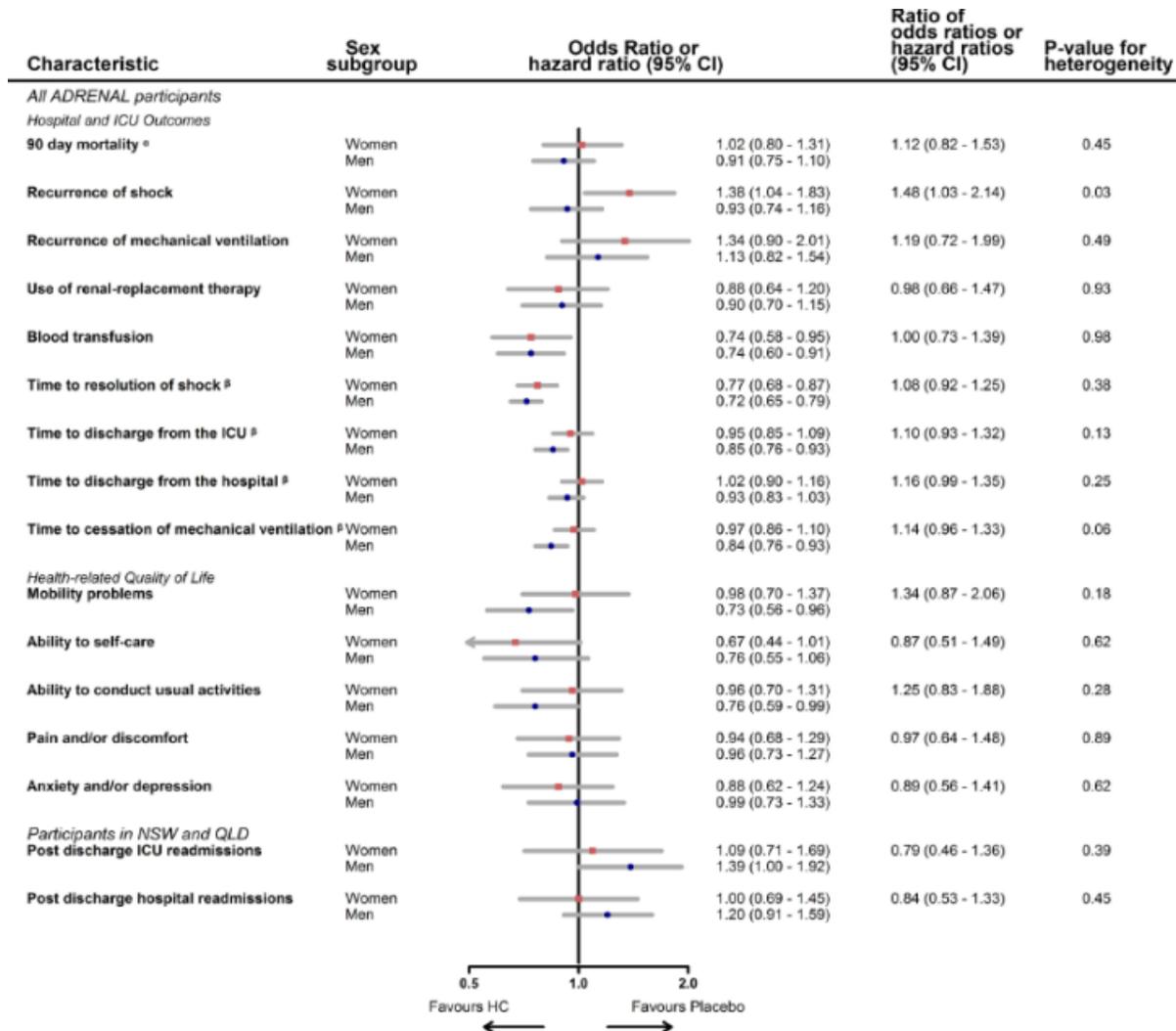


Dimorphisme sexuel et sepsis

- 54-61% des sepsis mâles
- Influence selon âge et statut hormonal
- Rôle chromosome X
 - hormones
 - réponse immunitaire
- Exemple du Sars-Cov2



Sexe: une (1^{ère}?) étape d'approche personnalisée?



Intensive Care Med (2021) 47:246–248
<https://doi.org/10.1007/s00134-020-06325-7>

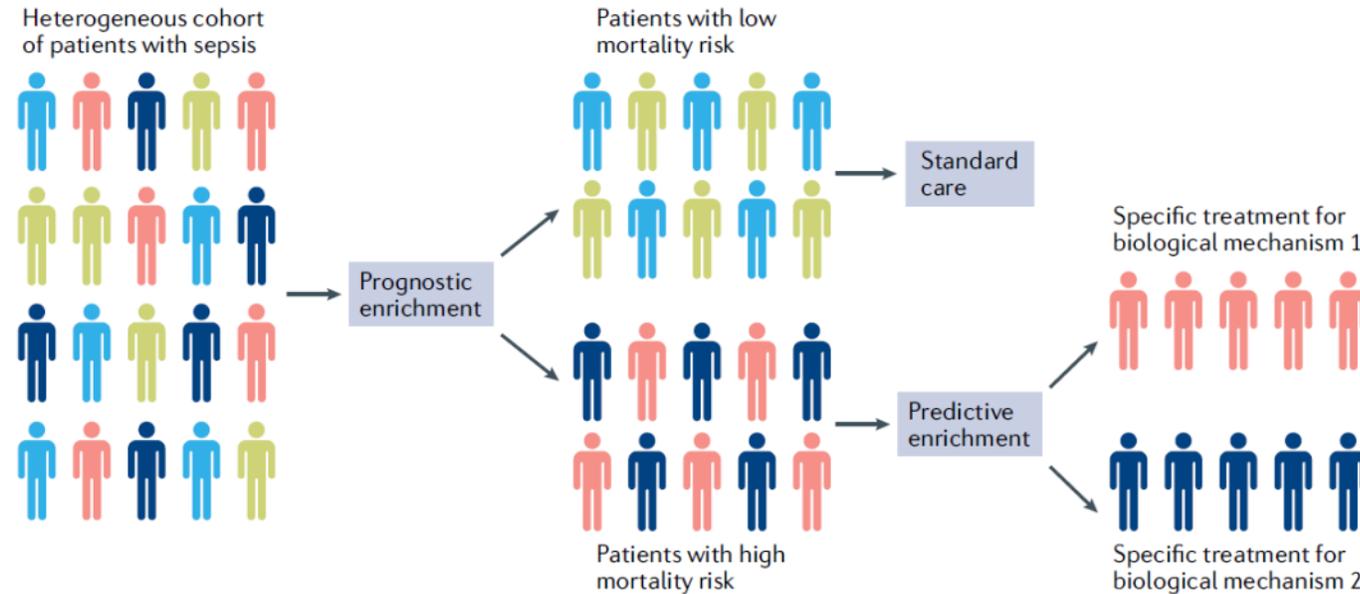
LETTER

Sex differences in response to adjunctive corticosteroid treatment for patients with septic shock



Kelly Thompson^{1,2*}, Balasubramanian Venkatesh^{1,2,3,4}, Naomi Hammond^{1,2,5,6}, Colman Taylor^{1,2} and Simon Finfer^{1,2,6} on behalf of the ADRENAL Investigators, sex-disaggregated analysis Steering Committee

sepsis à l'heure des 4 P : possible et pertinent



ORIGINAL



JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Targeted Polymyxin B Hemoperfusion on 28-Day Mortality in Patients With Septic Shock and Elevated Endotoxin Level

The EUPHRATES Randomized Clinical Trial

R. Phillip Dellinger, MD, MSc; Sean M. Bagshaw, MD, MSc; Massimo Antonelli, MD; Debra M. Foster, BSc; David J. Klein, MD, MBA; John C. Marshall, MD; Paul M. Palevsky, MD; Lawrence S. Weisberg, MD; Christa A. Schorr, DNP, MSN, RN; Stephen Trzeciak, MD, MPH; Paul M. Walker, MD, PhD; for the EUPHRATES Trial Investigators

Polymyxin B hemoperfusion in endotoxemic septic shock patients without extreme endotoxemia: a post hoc analysis of the EUPHRATES trial

D. J. Klein^{1*}, D. Foster², P. M. Walker², S. M. Bagshaw³, H. Mekonnen⁴ and M. Antonelli⁵

Table 2. Summary of the Primary End Point of 28-Day Mortality for All Participants and for Patients With MODS of More Than 9

	No./Total (%)		95% CI		
	Polymyxin-B Hemoperfusion	Sham	Risk Difference	Risk Ratio	P Value ^a
All Participants	84/223 (37.7)	78/226 (34.5)	3.15 (−5.73 to 12.04)	1.09 (0.85 to 1.39)	.49
>9 MODS ^b	65/146 (44.5)	65/148 (43.9)	0.60 (−10.75 to 11.97)	1.01 (0.78 to 1.31)	.92

JAMA. 2018;320(14):1455-1463.

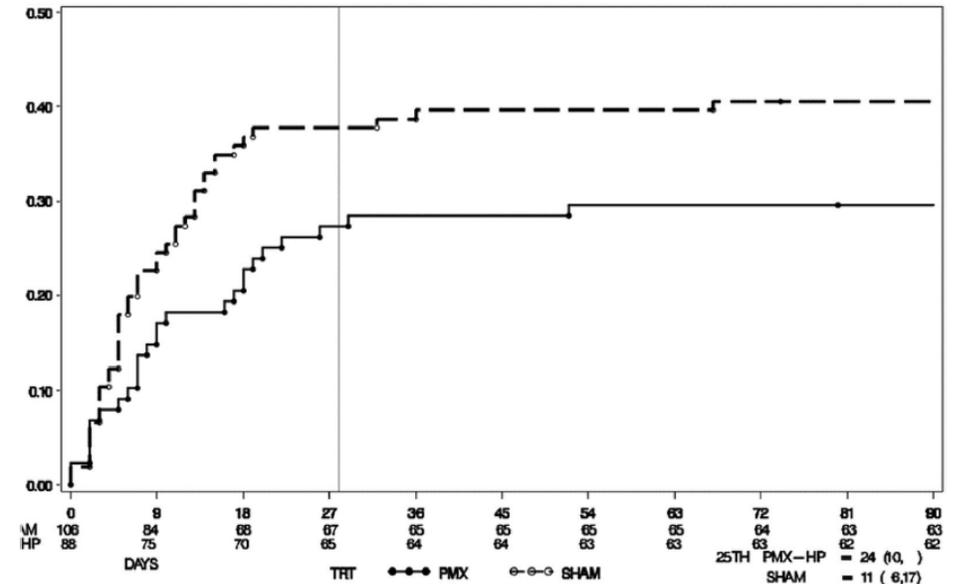
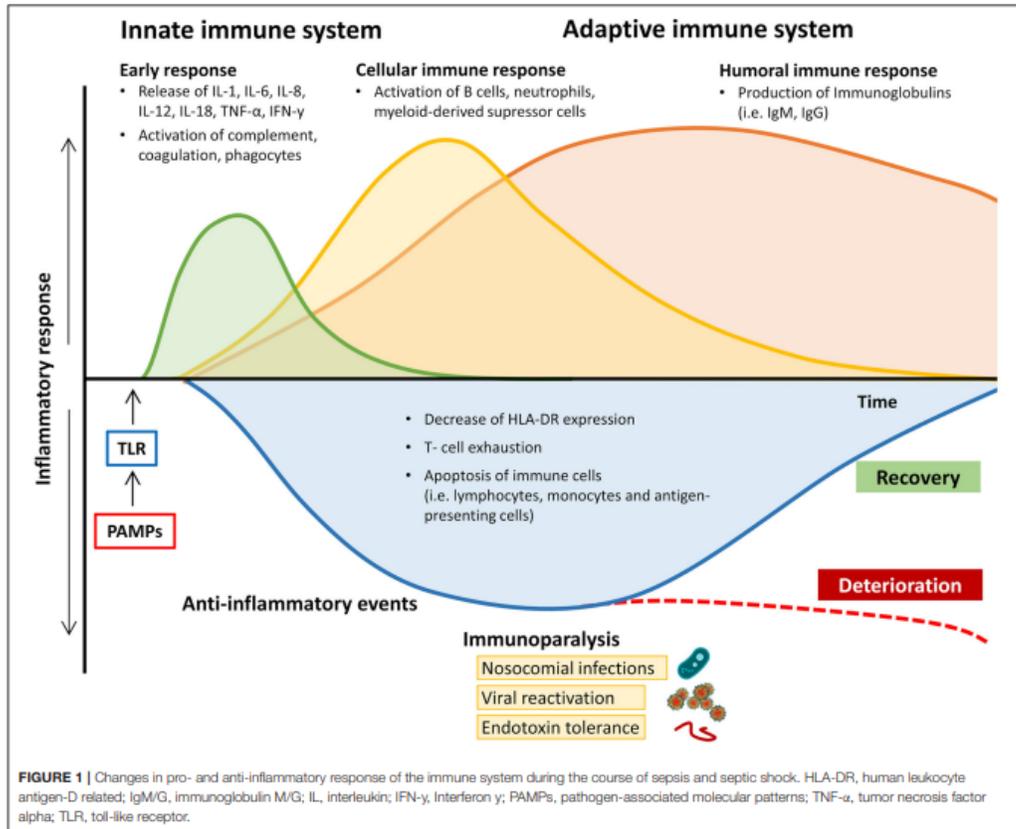


Fig. 2 Time to death within 90 days for PMX versus sham. Kaplan-Meier estimates of the probability of survival to day 90 among 194 per-protocol patients with MODS > 9 and EAA between 0.6 and 0.89, by treatment groups. The 90-day results of Cox proportional hazards adjusted for baseline MAP and APACHE II score are the hazard ratio [0.57, 95% CI (0.35, 0.93), P value = 0.02]. The vertical line represents the 28-day interval. The 28-day adjusted Cox proportional hazard ratio for death in the PMX group compared with the sham group is 0.58 (95% CI, 0.35 to 0.98; P = 0.04). TRT treatment, 25th 25th percentile at 90 days

La fonction immunitaire : la cible?



- Un rationnel
- Quelle(s) cible(s)?
- Des perspectives
 - Anti-PD-1 - PD-L1?
 - Nivolumab
 - Hotchkiss et al. Intensive Care Med 2019
 - Hotchkiss et al. Crit Care Med 2019
 - Il-7 recombinant
 - François et al. JCI 2018

Sepsis / choc septique : et après?

Le fardeau

SYSTEMATIC REVIEW

Rate and risk factors for rehospitalisation in sepsis survivors: systematic review and meta-analysis

Manu Shankar-Hari^{1,2,3*}, Rohit Saha², Julie Wilson¹, Hallie C. Prescott^{4,5}, David Harrison³, Kathryn Rowan³, Gordon D. Rubenfeld^{6,7} and Neill K. J. Adhikari^{6,7}



- Réhospitalisations : 50 % des patients entre J 7 et J 365 post-réa
 - 1 patient sur 5 dans les 30j
 - 40 % des patients à 1 an
 - Motif infectieux ++ : 1 à 2/3 des hospitalisations
- Facteurs de risque
 - Génériques : âge- sexe masculin- pré-réa- comorbidités
 - Aval post-réa (RAD ou non) - durée séjour
 - D'ordre infectieux : sepsis digestif - BLSE-sévérité- DMS hospitalière
 - Divers : Hte- recours nutrition parentérale- trachéotomie - socio-économique

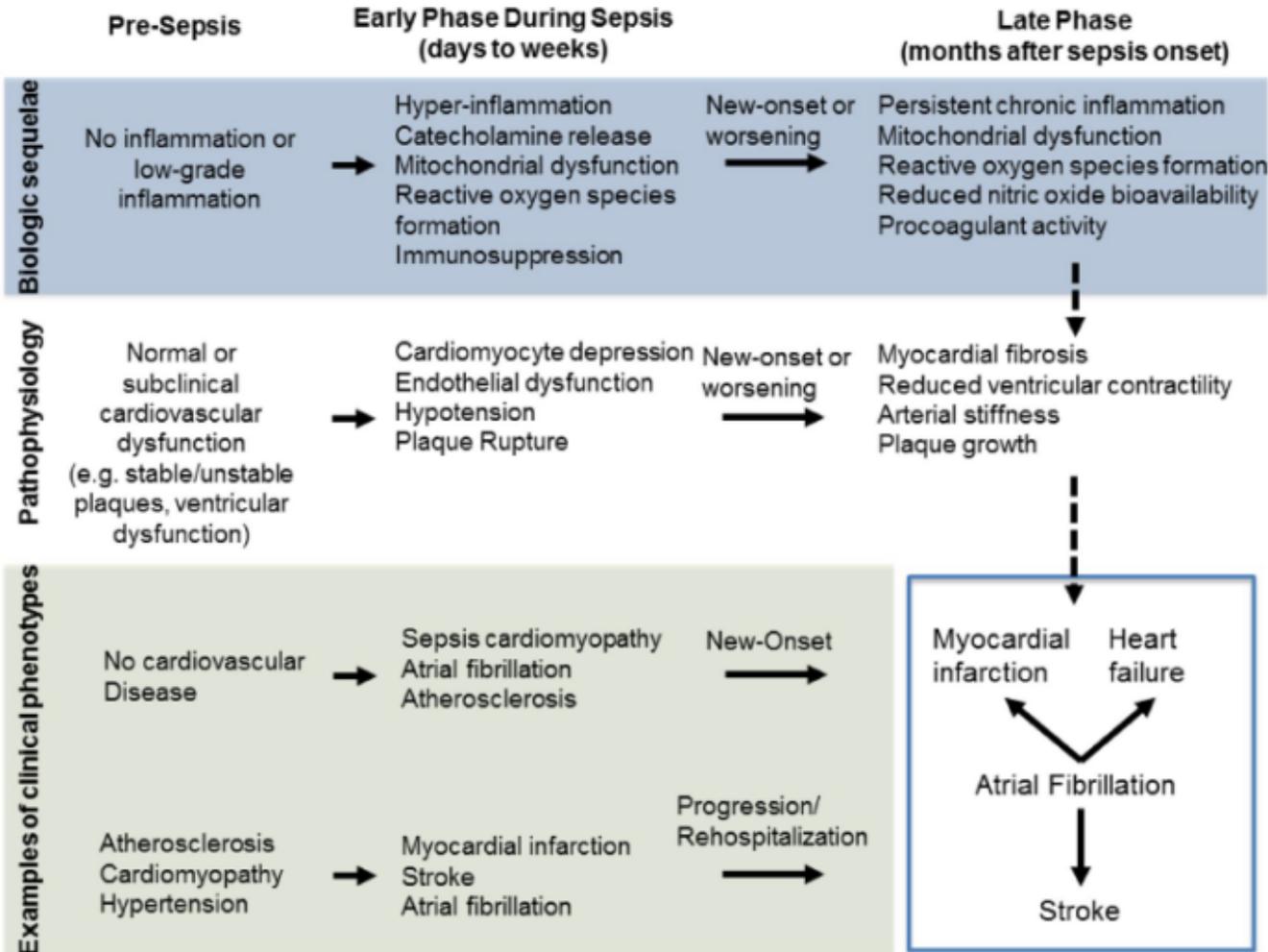
Focus cardiovasculaire post- sepsis

Intensive Care Med (2019) 45:78–81
<https://doi.org/10.1007/s00134-018-5173-1>

WHAT'S NEW IN INTENSIVE CARE

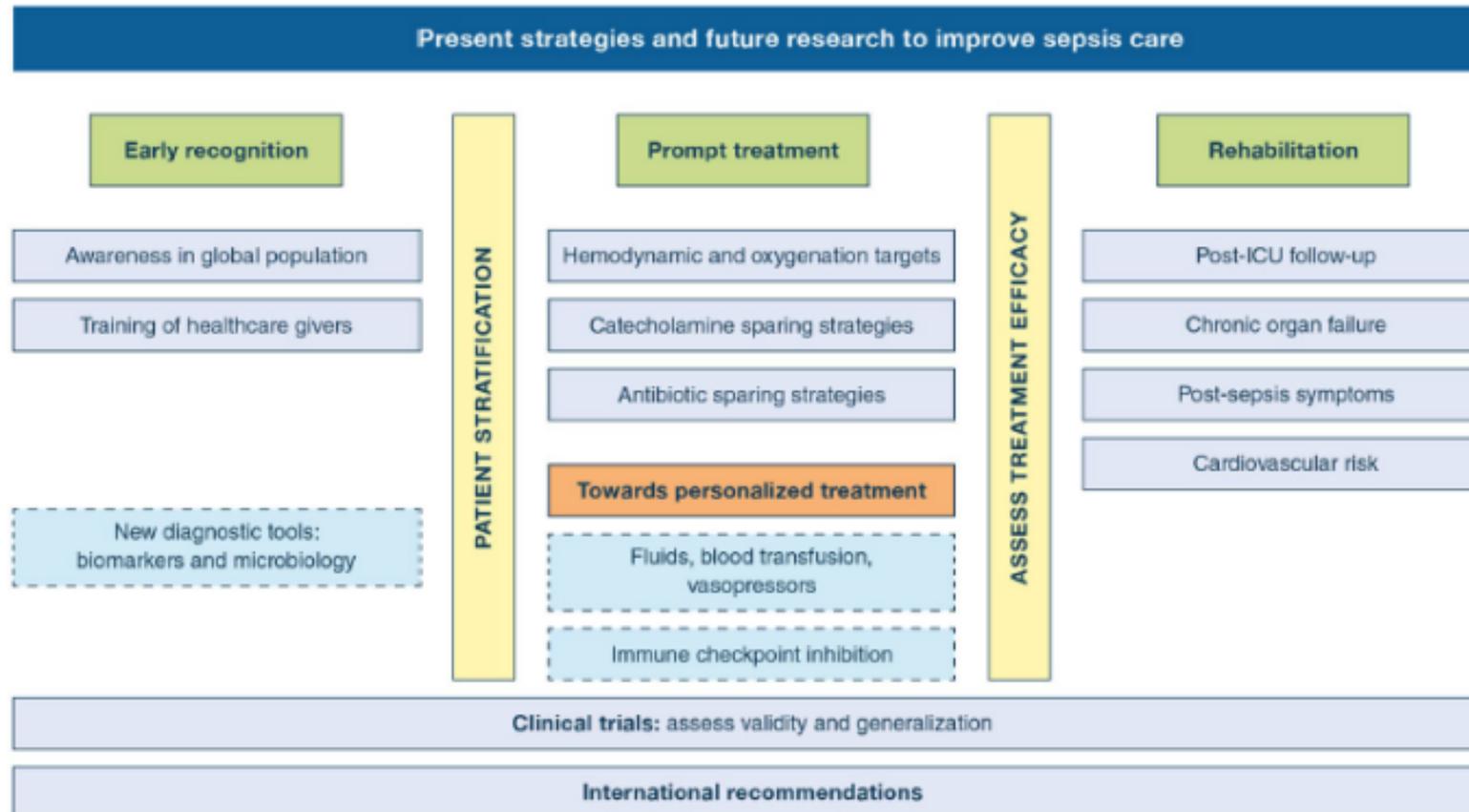
Long-term impact of sepsis on cardiovascular health

R. T. Mankowski¹, S. Yende^{2,3} and D. C. Angus^{2*}



- Trajectoires post sepsis
 - Récupération complète ou partielle
 - aggravation
- Sepsis facteur précipitant
 - 18% AVC - IDM 7% - 8,6% IC - FA 7%
- Impact utilisation ressources
 - Réadmissions-réhospitalisations- poussés
 - QOL

Sepsis 2021: en pratique



GUIDELINES

Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021



- 21 recommandations nouvelles ou modifiées - 9 champs
- Prise en charge infectieuse
- Prise en charge hémodynamique
- Traitements adjuvants

Sepsis 2021: resuscitation vs de-resuscitation

INITIAL RESUSCITATION

 **BEST PRACTICE** 

4 Sepsis and septic shock are medical emergencies, and we **recommend** that treatment and resuscitation begin immediately.

 **LOW** 

5 For patients with sepsis induced hypoperfusion or septic shock we **suggest** that at least 30 mL/kg of intravenous (IV) crystalloid fluid should be given within the first 3 hours of resuscitation.

2016 STATEMENT
↓  

"We **recommend** that in the initial resuscitation from sepsis-induced hypoperfusion, at least 30ml/kg of intravenous crystalloid fluid be given within the first 3 hours."

 **LOW** 

8 For adults with septic shock, we **suggest** using capillary refill time to guide resuscitation as an adjunct to other measures of perfusion.

Antibiothérapie : les nuances et timing en 2021

12 For adults with possible septic shock or a high likelihood for sepsis, we **recommend** administering antimicrobials immediately, ideally within one hour of recognition.

  **LOW** Septic shock

  **VERY LOW** Sepsis without shock

2016 STATEMENT
 
"We **recommend** that administration of intravenous antimicrobials should be initiated as soon as possible after recognition and within one hour for both a) septic shock and b) sepsis without shock."

  **VERY LOW**

14 For adults with possible sepsis without shock, we **suggest** a time-limited course of rapid investigation and if concern for infection persists, the administration of antimicrobials within 3 hours from the time when sepsis was first recognized.

2016 STATEMENT
 
"We **recommend** that administration of intravenous antimicrobials should be initiated as soon as possible after recognition and within one hour for both a) septic shock and b) sepsis without shock."

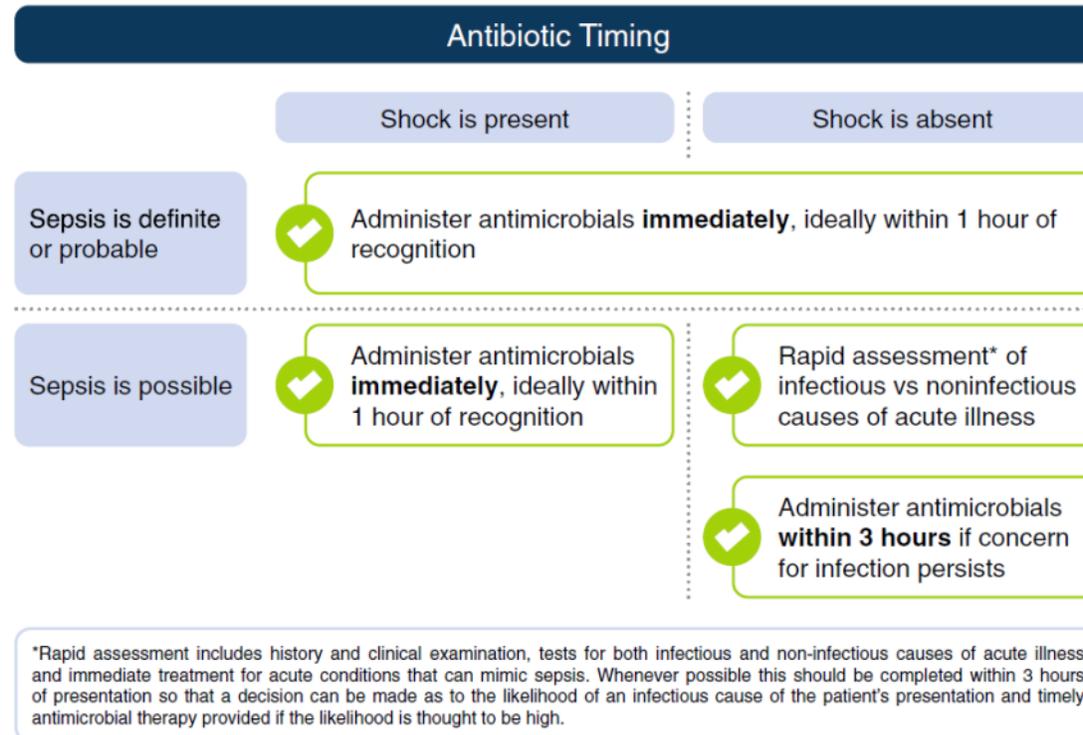
  **VERY LOW**

15 For adults with a low likelihood of infection and without shock, we **suggest** deferring antimicrobials while continuing to closely monitor the patient.

2016 STATEMENT
 
"We **recommend** that administration of intravenous antimicrobials should be initiated as soon as possible after recognition and within one hour for both a) septic shock and b) sepsis without shock."

2021 TABLE OF RECOMMENDATIONS

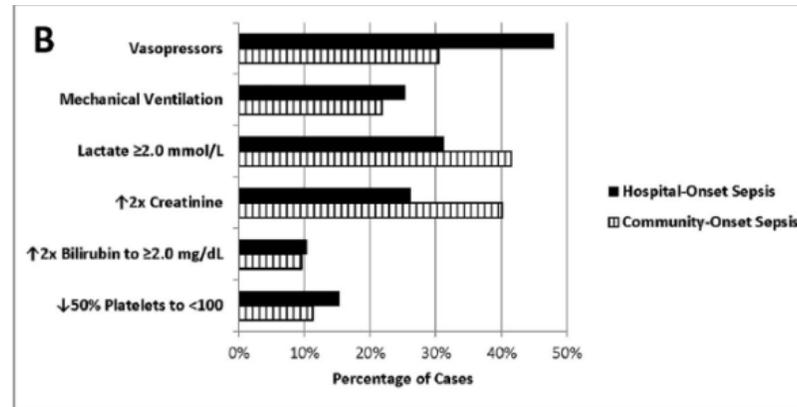
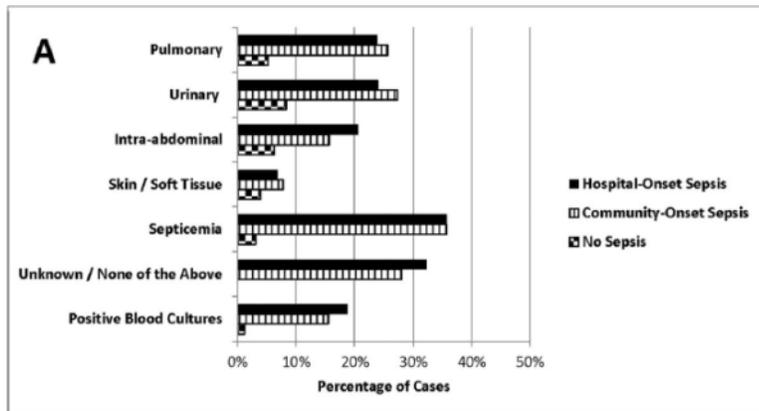
NEW and UPDATED recommendations are highlighted with a blue background



2021 TABLE OF RECOMMENDATIONS

NEW and UPDATED recommendations are highlighted with a blue background

Sepsis communautaire vs nosocomial



Rank	Community-Onset Sepsis (n=12951)	Hospital-Onset Sepsis (n=2,163)
1	Escherichia – 2,876 (22.2%)	Staphylococcus aureus - 514 (23.8%)
2	Staphylococcus aureus - 2,592 (20.0%)	Enterococcus - 243 (11.2%)
3	Streptococcus – 2,283 (17.6%)	Candida - 240 (11.1%)
4	Klebsiella – 1,090 (8.4%)	Escherichia - 236 (10.9%)
5	Enterococcus – 806 (6.2%)	Klebsiella - 220 (10.2%)
6	Candida - 566 (4.4%)	Streptococcus - 160 (7.4%)
7	Proteus - 476 (3.7%)	Pseudomonas – 133 (6.1%)
8	Pseudomonas – 454 (3.6%)	Enterobacter – 73 (3.4%)
9	Enterobacter – 290 (2.2%)	Acinetobacter – 43 (2.0%)
10	Serratia – 139 (1.1%)	Bacteroides – 36 (1.7%)

Sepsis 2021 : cristalloides balancés

HEMODYNAMIC MANAGEMENT



MODERATE

32 For adults with sepsis or septic shock, we **recommend** using crystalloids as first-line fluid for resuscitation.



LOW

33 For adults with sepsis or septic shock, we **suggest** using balanced crystalloids instead of normal saline for resuscitation.

2016 STATEMENT



*"We **suggest** using either balanced crystalloids or saline for fluid resuscitation of patients with sepsis or septic shock"*



MODERATE

36 For adults with sepsis and septic shock, we **suggest against** using gelatin for resuscitation.

2016 STATEMENT



*"We **suggest** using crystalloids over gelatins when resuscitating patients with sepsis or septic shock."*

Sepsis 2021 : vasopresseur sur VVC ou pas



LOW

42 For adults with septic shock and cardiac dysfunction with persistent hypoperfusion despite adequate volume status and arterial blood pressure, we **suggest against** using levosimendan.



VERY LOW

44 For adults with septic shock, we **suggest** starting vasopressors peripherally to restore mean arterial pressure rather than delaying initiation until a central venous access is secured.



45 There is insufficient evidence to make a recommendation on the use of restrictive versus liberal fluid strategies in the first 24 hours of resuscitation in patients with sepsis and septic shock who still have signs of hypoperfusion and volume depletion after the initial resuscitation.

2016 STATEMENT



*"We **suggest** using either balanced crystalloids or saline for fluid resuscitation of patients with sepsis or septic shock."*



*"We **suggest** using crystalloids over gelatins when resuscitating patients with sepsis or septic shock."*

Sepsis 2021 : corticoïdes adjuvants, seuls ciblés

ADDITIONAL THERAPIES

  MODERATE

58 For adults with septic shock and an ongoing requirement for vasopressor therapy we **suggest** using IV corticosteroids.

2016 STATEMENT
  

*"We **suggest against** using intravenous hydrocortisone to treat septic shock patients if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability (see goals for Initial Resuscitation). If this is not achievable, we **suggest** intravenous hydrocortisone at a dose of 200 mg per day."*

  LOW

59 For adults with sepsis or septic shock we **suggest against** using polymyxin B hemoperfusion.

2016 STATEMENT
"We make no recommendation regarding the use of blood purification techniques."

  LOW

70 For adults with sepsis or septic shock we **suggest against** using IV vitamin C.

Aujourd'hui et demain

- Le sepsis reste un enjeu de santé publique majeur
- Le sepsis reste notre challenge quotidien de réanimateur (rice)
- L'hétérogénéité phénotypique multifactorielle et pluri-dimensionnelle impacte le pronostic
- Les big datas et les outils de biologie moléculaire apparaissent pertinents pour identifier les sous-groupes
- Les stratégies « personnalisées » semblent prometteuses