



# Choc septique : Diagnostic et points- clé de prise en charge

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# Il est 2 heures du matin...

Vous êtes appelé par votre collègue urgentiste au sujet de M. M., 56 ans, en raison d'une hypotension persistante.

Son principal antécédent est une maladie lithiasique urinaire. Il présente des infections urinaires à répétition et est porteur de sondes JJ depuis trois ans.

Il se plaint depuis trois jours de douleurs lombaires gauches, accompagnées d'asthénie. Il frissonne depuis cet après-midi. Il a pris de lui-même de l'Augmentin et des AINS.

Les constantes sont les suivantes :

- GCS : 13
- Pression artérielle systolique : 70 mmHg
- Fréquence cardiaque : 110 bpm

# Épidémiologie

# Concernant l'épidémiologie du sepsis

- A. 30% des patients de réanimation présente un sepsis à leur admission en réanimation
- B. Le taux de mortalité lié au choc septique est de 40%
- C. L'incidence du choc septique augmente depuis ces 20 dernières années
- D. Le taux de mortalité lié au sepsis baisse de 2% par an
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## Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the Global Burden of Disease Study



Kristina E Rudd, Sarah Charlotte Johnson, Kareha M Agesa, Katya Anne Shackelford, Derrick Tsoi, Daniel Rhodes Kievlan, Danny V Colombara, Kevin S Ikuta, Niranjana Kissoon, Simon Finfer, Carolin Fleischmann-Struzek, Flavia R Machado, Konrad K Reinhart, Kathryn Rowan, Christopher W Seymour, R Scott Watson, T Eoin West, Fatima Marinho, Simon I Hay, Rafael Lozano, Alan D Lopez, Derek C Angus, Christopher J L Murray, Mohsen Naghavi

## Global burden of Disease (GBD) Study

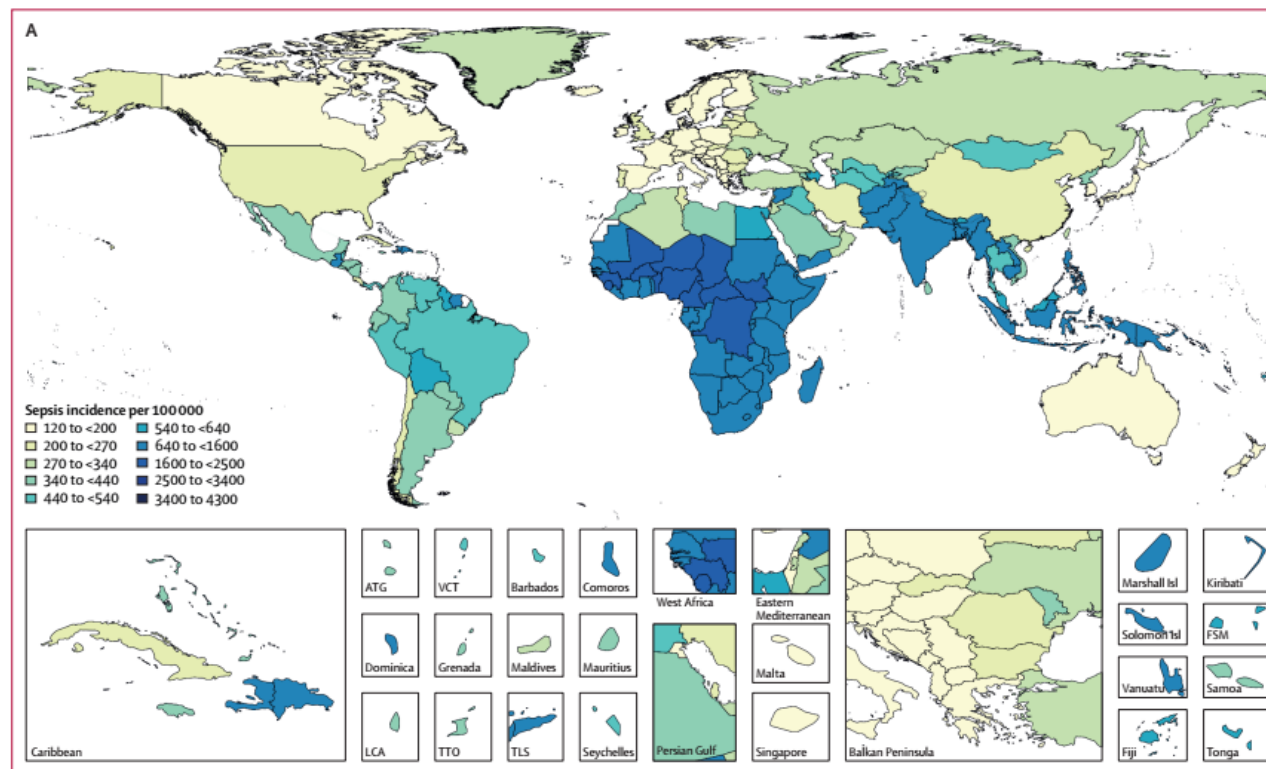
Institute for Health Metrics and Evaluation (IHME)

### « Global burden of sepsis » en 2017

-  **Nombre estimé de nouveaux cas de sepsis :**  
48,9 millions (IC 95 % : 38,9 – 62,9 millions)
-  **Incidence mondiale du sepsis :**  
677,5 cas pour 100 000 habitants (IC 95 % : 535,7 – 876,1)
-  **Baisse de l'incidence (standardisée selon l'âge) entre 1990 et 2017 : –37,0 % (IC 95 % : 11,8 – 54,5)**

# Incidence hétérogène à travers le monde

- Incidence sepsis plus important dans les “low- and middle-income countries (LMICs)” (sub-Saharan Africa, Oceania, south Asia, east Asia, and southeast Asia).
- Causes:
  - Accès limités aux soins, retard de diagnostic et prise en charge,
  - Une prévalence plus élevée de maladies infectieuses
  - Le vieillissement des populations
  - Augmentation du taux de chirurgies invasives
  - Émergence de bactéries multirésistantes





## Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the Global Burden of Disease Study

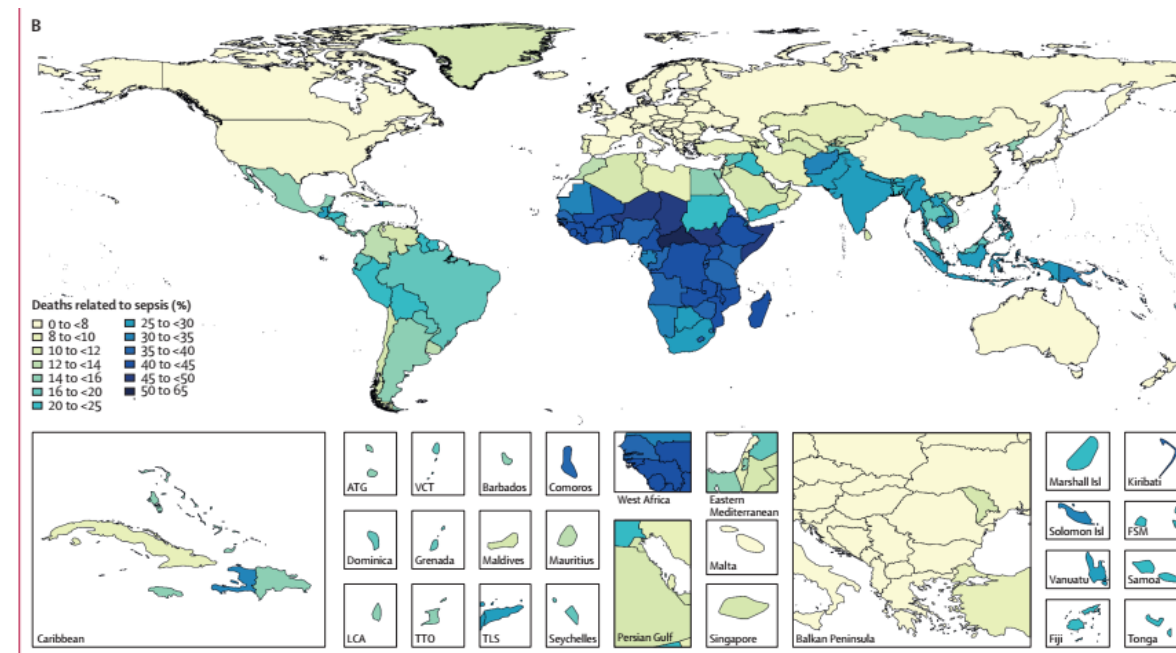


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## Global burden of Disease (GBD) Study

### Mortalité liée au sepsis en 2017

-  Décès liés au sepsis : **11,0 millions** (IC 95 % : 10,1 – 12,0)  
→ soit **19,7 %** de l'ensemble des décès mondiaux (IC 95 % : 18,2 – 21,4)
-  Diminution de la mortalité (standardisée selon l'âge) entre 1990 et 2017 : **–52,8 %** (IC 95 % : 47,7 – 57,5)
-  Régions les plus touchées : Afrique subsaharienne, Océanie, Asie du Sud, Asie de l'Est et Asie du Sud-Est





# Et les séquelles à long terme?



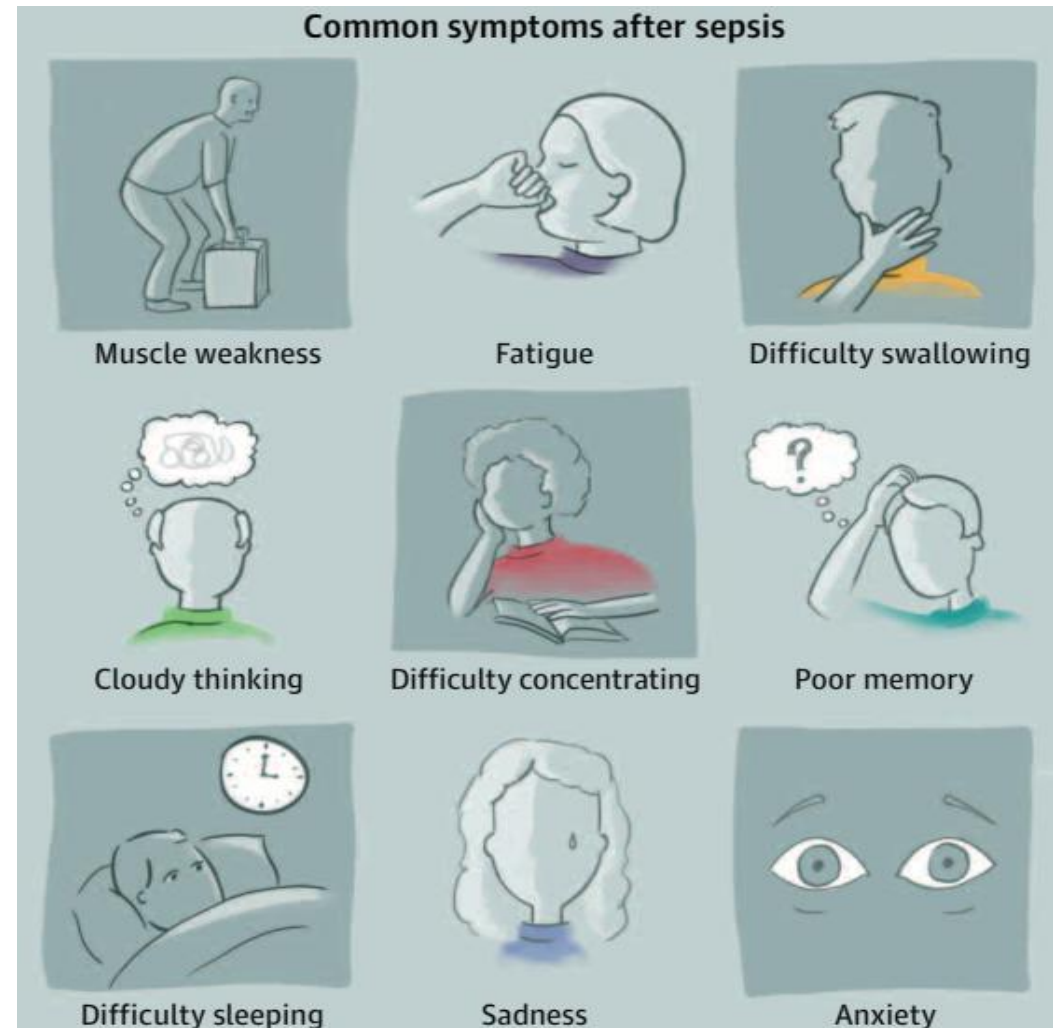
2018

JAMA | Review

## Enhancing Recovery From Sepsis A Review

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

- Jusqu'à 50% des survivants du sepsis vont présenter un syndrome post sepsis = syndrome post réanimation = persistance de séquelles physiques, cognitives ou psychologiques.
- Les survivants présentent:
  - Plus de plaintes fonctionnelles
  - Plus de comorbidités
  - Une perte d'autonomie
  - Plus de recours aux soins



# Dépistage du sepsis

# Quels sont les arguments pour un choc septique.

- A. Un score **qSOFA**  $\geq 2$  suggère un risque élevé de sepsis.
- B. Un score **SOFA**  $\geq 2$  définit un **choc septique**
- C. La présence d'une **hypotension réfractaire au remplissage** définit un **choc septique**.
- D. Un **lactate**  $> 2 \text{ mmol/L}$  est un critère de gravité nécessaire à la définition du choc septique.
- E. Un **choc septique réfractaire** se définit par la nécessité d'une **dose de noradrénaline**  $> 0,5 \text{ à } 1 \mu\text{g/kg/min}$ , malgré un remplissage adéquat.

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# Une histoire qui dure depuis 30 ans

Intensive Care Med (2003) 29:530–538  
DOI 10.1007/s00134-003-1662-x

EXPERT PANEL

Mitchell M. Levy  
Mitchell P. Fink  
John C. Marshall  
Edward Abraham  
Derek Angus  
Deborah Cook  
Jonathan Cohen  
Steven M. Opal  
Jean-Louis Vincent  
Graham Ramsay  
for the International Sepsis  
Definitions Conference

**2001 SCCM/ESICM/ACCP/ATS/SIS  
International Sepsis Definitions Conference**



**accp/sccm consensus conference**

**Definitions for Sepsis and Organ Failure and  
Guidelines for the Use of Innovative Therapies in  
Sepsis**

THE ACCP/SCCM CONSENSUS CONFERENCE COMMITTEE:

*Roger C. Bone, M.D., F.C.C.P., Chairman*  
*Robert A. Balk, M.D., F.C.C.P.*  
*Frank B. Cerra, M.D.*  
*R. Phillip Dellinger, M.D., F.C.C.P.*

*Alan M. Fein, M.D., F.C.C.P.*  
*William A. Knaus, M.D.*  
*Roland M. H. Schein, M.D.*  
*William J. Sibbald, M.D., F.C.C.P.*

1991

**Sepsis - 1**

2001

**Sepsis - 2**

2016

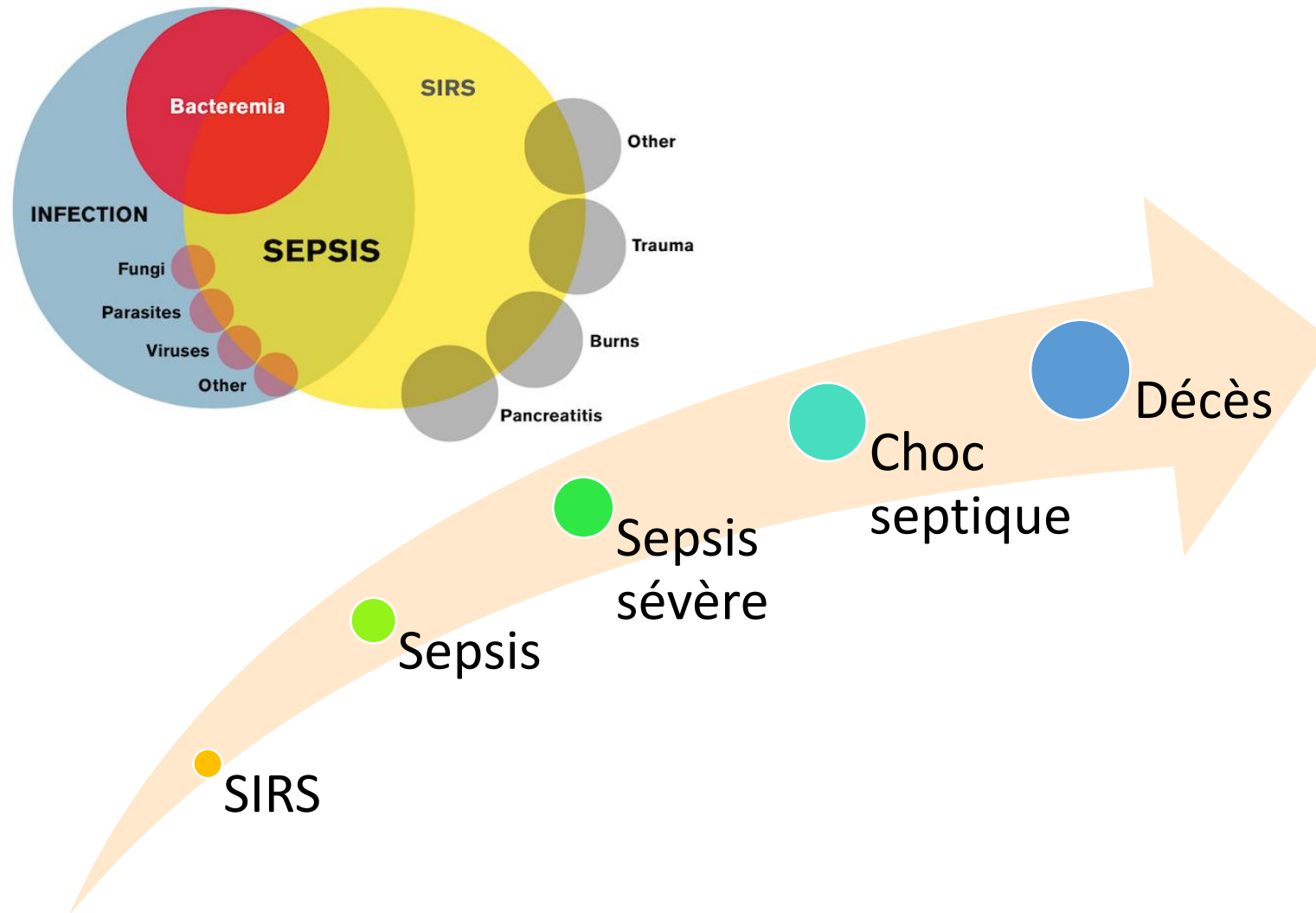
**Sepsis - 3**

Special Communication | **CARING FOR THE CRITICALLY ILL PATIENT**

**The Third International Consensus Definitions  
for Sepsis and Septic Shock (Sepsis-3)**

Mervyn Singer, MD, FRCP; Clifford S. Deutschman, MD, MS; Christopher Warren Seymour, MD, MSc; Manu Shankar-Hari, MSc, MD, FFICM;  
Djillali Annane, MD, PhD; Michael Bauer, MD; Rinaldo Bellomo, MD; Gordon R. Bernard, MD; Jean-Daniel Chiche, MD, PhD;  
Craig M. Coopersmith, MD; Richard S. Hotchkiss, MD; Mitchell M. Levy, MD; John C. Marshall, MD; Greg S. Martin, MD, MSc;  
Steven M. Opal, MD; Gordon D. Rubenfeld, MD, MS; Tom van der Poll, MD, PhD; Jean-Louis Vincent, MD, PhD; Derek C. Angus, MD, MPH

# SEPSIS – 1.0



**Table 1 – Definitions**

**Infection** = microbial phenomenon characterized by an inflammatory response to the presence of microorganisms or the invasion of normally sterile host tissue by those organisms.

**Bacteremia** = the presence of viable bacteria in the blood.

**Systemic inflammatory response syndrome (SIRS)** = the systemic inflammatory response to a variety of severe clinical insults. The response is manifested by two or more of the following conditions: (1) temperature  $>38^{\circ}\text{C}$  or  $<36^{\circ}\text{C}$ ; (2) heart rate  $>90$  beats per minute; (3) respiratory rate  $>20$  breaths per minute or  $\text{PaCO}_2 <32$  mm Hg; and (4) white blood cell count  $>12,000/\text{cu mm}$ ,  $<4,000/\text{cu mm}$ , or  $>10\%$  immature (band) forms

**Sepsis** = the systemic response to infection, manifested by two or more of the following conditions as a result of infection: (1) temperature  $>38^{\circ}\text{C}$  or  $<36^{\circ}\text{C}$ ; (2) heart rate  $>90$  beats per minute; (3) respiratory rate  $>20$  breaths per minute or  $\text{PaCO}_2 <32$  mm Hg; and white blood cell count  $>12,000/\text{cu mm}$ ,  $<4,000/\text{cu mm}$ , or  $>10\%$  immature (band) forms.

**Severe sepsis** = sepsis associated with organ dysfunction, hypoperfusion, or hypotension. Hypoperfusion and perfusion abnormalities may include, but are not limited to lactic acidosis, oliguria, or an acute alteration in mental status.

**Septic shock** = sepsis-induced with hypotension despite adequate fluid resuscitation along with the presence of perfusion abnormalities that may include, but are not limited to, lactic acidosis, oliguria, or an acute alteration in mental status. Patients who are receiving inotropic or vasopressor agents may not be hypotensive at the time that perfusion abnormalities are measured.

**Sepsis-induced hypotension** = a systolic blood pressure  $<90$  mm Hg or a reduction of  $\geq 40$  mm Hg from baseline in the absence of other causes for hypotension.

**Multiple organ dysfunction syndrome (MODS)** = presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention.

# SEPSIS – 2.0

Sepsis

=

Infection

+

Sepsis sévère

=

Sepsis

+

La gravité du sepsis est définie par l'existence de dysfonctions d'organe associées.

Choc septique

=

Sepsis sévère

+

## Paramètres généraux

- Température  $> 38,3$  ou  $< 36$  °C
- Tachycardie  $> 90$  bpm ou  $> 2$  DS au-delà de la valeur normale haute pour l'âge
- Tachypnée
- Altération de l'état de conscience
- Œdèmes ou balance hydrique positive ( $> 20$  mL/kg de poids corporel sur 24 h)
- Hyperglycémie  $> 1,2$  g/L (6,7 mmol/L) en l'absence de diabète

SIRS

## Paramètres inflammatoires

- Hyperleucocytose  $> 12$  G/L ou leucopénie 10 % de formes immatures
- CRP (C-reactive protein)  $> 2$  DS au-delà de la valeur normale haute
- Procalcitonine  $> 2$  DS au-delà de la valeur normale haute

## Paramètres hémodynamiques

- Hypotension artérielle (PAS  $< 40$  mmHg ou  $> 2$  DS au-dessous de la valeur normale basse pour l'âge ; PAM  $< 70$  mmHg)
- Élévation de la saturation en  $O_2$  du sang veineux mêlé ( $SvO_2 > 70$  %)
- Augmentation de l'index cardiaque ( $> 3,5$  L/min/m<sup>2</sup>)

## Dysfonctions d'organe

- Hypoxémie artérielle ( $PaO_2/FiO_2 < 300$ )
- Oligurie aiguë  $< 0,5$  mL/kg/h ou  $< 45$  mL/h pendant au moins 2 h
- Augmentation du taux de créatinine  $> 5$  mg/L ( $> 44$  µmol/L)
- Anomalies de la coagulation (INR  $> 1,5$  ; TCA  $> 60$  s)
- Iléus paralytique (absence de bruits hydro-aériques)
- Thrombocytopénie  $< 100\,000/mm^3$
- Hyperbilirubinémie  $> 40$  mg/L (68 µmol/L)

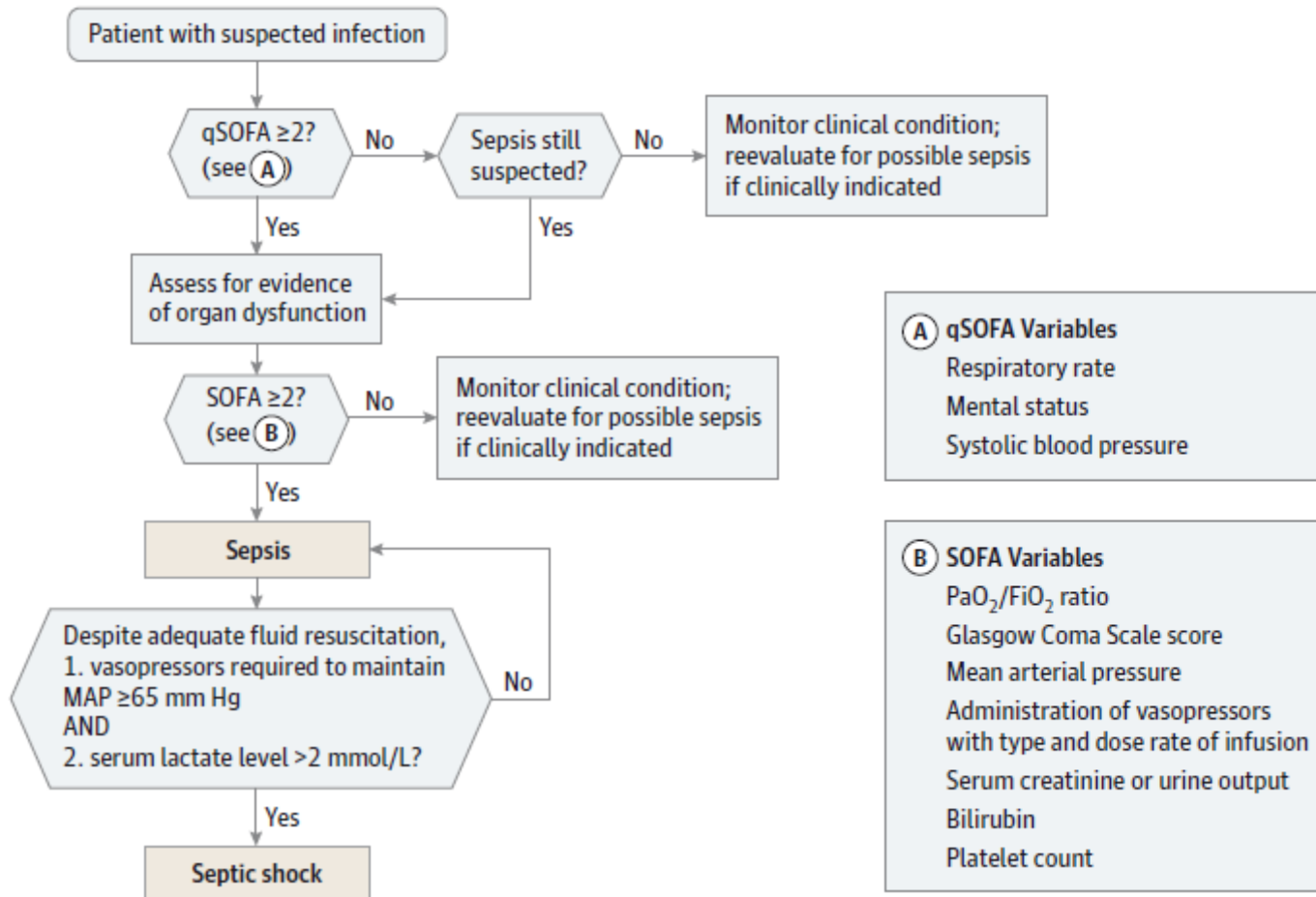
→ de la perfusion tissulaire avec

- Hyperlactatémie ou
- augmentation du temps de recoloration cutanée ou
- présence de marbrures

→ Hypotension réfractaire au remplissage vasculaire



# SEPSIS – 3.0



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



ALTERED  
MENTAL STATUS

Encéphalopathie  
GCS < 13



FAST RESPIRATORY  
RATE

FR > 22



LOW BLOOD  
PRESSURE

PAS < 100 mmHg



# A Comparison of the Quick-SOFA and Systemic Inflammatory Response Syndrome Criteria for the Diagnosis of Sepsis and Prediction of Mortality

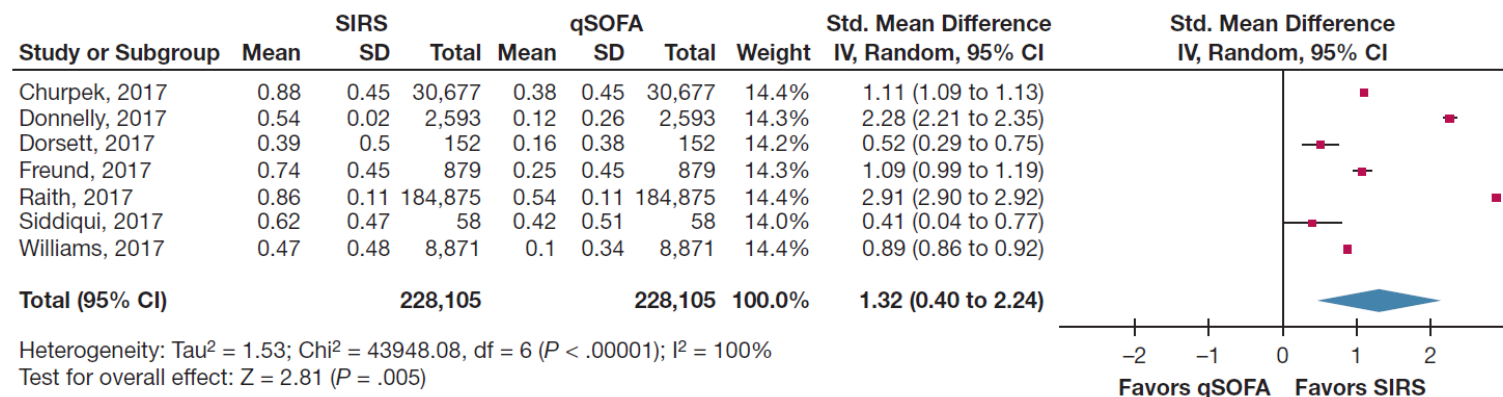
## A Systematic Review and Meta-Analysis

Rodrigo Serafim, MD; José Andrade Gomes, MD; Jorge Salluh, MD, PhD; and Pedro Póvoa, MD, PhD

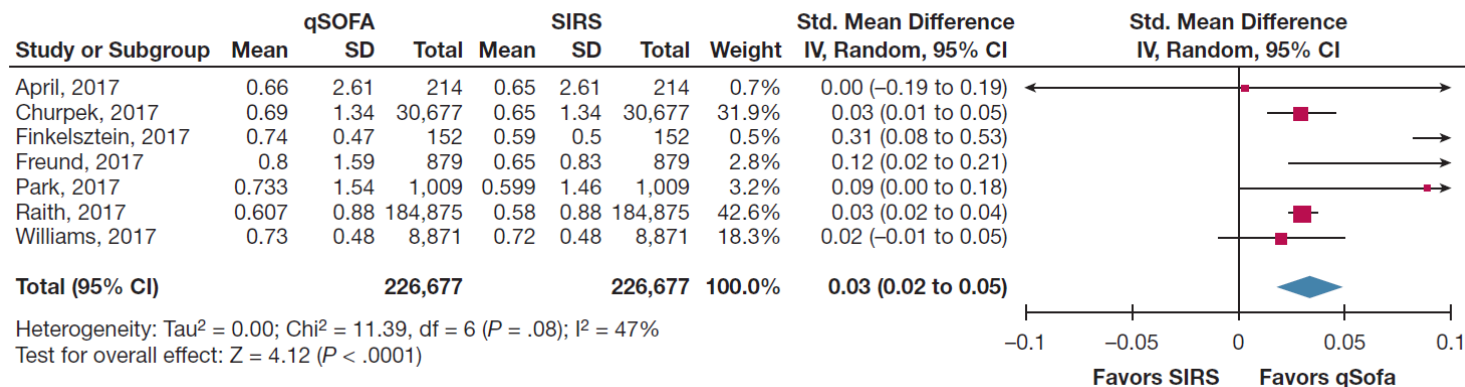
CHEST 2018; 153(3):646-655

- SIRS prédit le sepsis
- qSOFA est associé au pronostic

### SEPSIS



### MORTALITY



# 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

## 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**

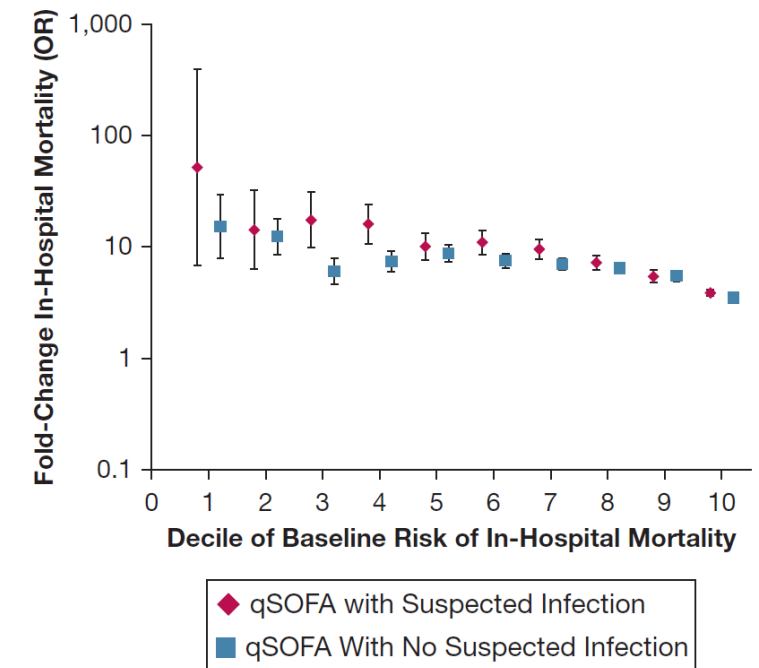


Figure 2 – Fold change in rate of in-hospital mortality by deciles of baseline risk of death for  $\geq 2$  qSOFA criteria vs  $< 2$  qSOFA criteria in patients with and without suspected infection on admission. The x axis

## SCREENING FOR PATIENTS WITH SEPSIS AND SEPTIC SHOCK

**1** For hospitals and health systems, we **recommend** using a performance improvement programme for sepsis, including sepsis screening for acutely ill, high-risk patients and standard operating procedures for treatment.



MODERATE

Screening



VERY LOW

Standard operating procedures

**2016 STATEMENT**

*"We **recommend** that hospitals and hospital systems have a performance improvement programme for sepsis including sepsis screening for acutely ill, high risk patients."*



MODERATE

**2** We **recommend against** using qSOFA compared to SIRS, NEWS, or MEWS as a single screening tool for sepsis or septic shock.



VERY LOW

**3** For adults suspected of having sepsis, we **suggest** measuring blood lactate.

# Choc septique réfractaire

- Pas de définition dans SEPSIS 3.0
- Grande hétérogénéité des définitions
- Le plus souvent:
  - noradrénaline  $\geq 1 \mu\text{g/kg/min}$
  - Et/ou 2ème ligne agent vasopresseur (vasopressine, angiotensine II ...)



Refractory septic shock and alternative wordings: A systematic review of literature

Elio Antonucci<sup>a</sup>, Tania Polo<sup>a</sup>, Manuela Giovini<sup>a</sup>, Massimo Girardis<sup>b</sup>, Ignacio Martin-Loeches<sup>c</sup>,

## Shock Definitions & Reported Norepinephrine Dosages.

| Authors                       | Shock Definition                                                                                                | Norepinephrine Dosage ( $\mu\text{g/kg/min}$ ) |
|-------------------------------|-----------------------------------------------------------------------------------------------------------------|------------------------------------------------|
| Martin et al. (2015) [4]      | Sepsis with the need for vasopressor administration                                                             | Maximum: $0.79 \pm 1.03 \mu\text{g/kg/min}$    |
| Albanese et al. (2005) [10]   | Septic shock with hemodynamic instability and two or more organ dysfunctions                                    | Maximum: $1.7 \pm 0.9 \mu\text{g/kg/min}$      |
| Auchet et al. (2017) [16]     | Septic shock with the need for HDV (NE dose $\geq 1 \mu\text{g/kg/min}$ for $\geq 1$ h)                         | Maximum: $3.28 \pm 2.41 \mu\text{g/kg/min}$    |
| O'Brien et al. (2002) [14]    | Septic shock and high CO with the need for high-dose norepinephrine infusion                                    | Mean: $0.59 \mu\text{g/kg/min}$                |
| Tsuneyoshi et al. (2001) [15] | Septic shock and persistent hypotension, with the need for NE with or without infusions of other catecholamines | Maximum: $0.3 \mu\text{g/kg/min}$              |
| Dunser et al. (2003) [11]     | Vasodilatory shock with and without sepsis, with the need for NE infusions exceeding $0.5 \mu\text{g/kg/min}$   | Mean: $0.84 \pm 0.41 \mu\text{g/kg/min}$       |
| Lauzier et al. (2006) [12]    | Septic shock with the need for vasopressors for $<12$ h before randomization                                    | Mean: $0.20 (0.17-0.46) \mu\text{g/kg/min}$    |
| Leone et al. (2004) [13]      | Hemodynamic instability with the need for HDV                                                                   | Maximum: $3.8 \pm 1.3 \mu\text{g/kg/min}$      |

Abbreviations: NE norepinephrine, CO cardiac output, HDV high-dose of vasopressors.

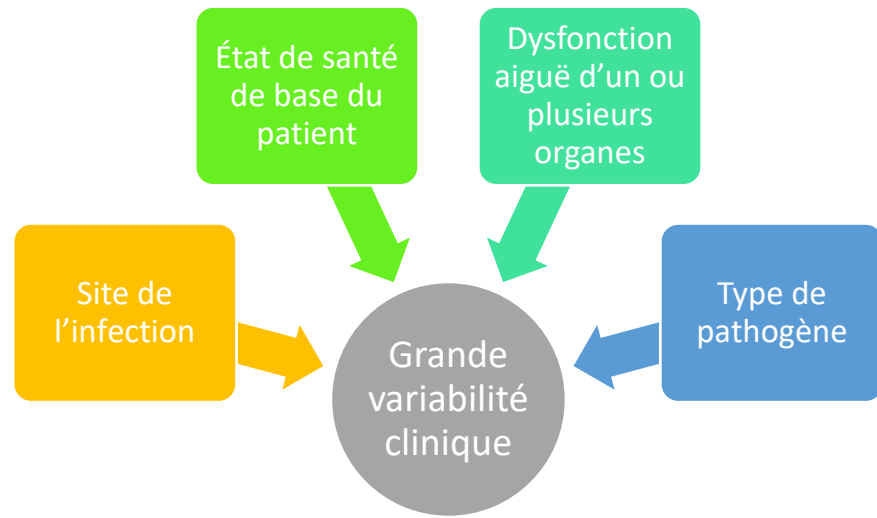
# Quels examens complémentaires allez vous demander à ce stade de la prise en charge

- A. Procalcitonine
- B. CRP
- C. Ionogramme sanguin, urée créatinine
- D. NFS plaquette
- E. Bilan hépatique
- F. Gaz du sang, lactate
- G. Scanner abdominal
- H. Hémocultures
- I. ECBU

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## Diagnostic



### signes généraux d'infection

- Fièvre ou hypothermie, malaise

### Signes spécifiques au site infectieux

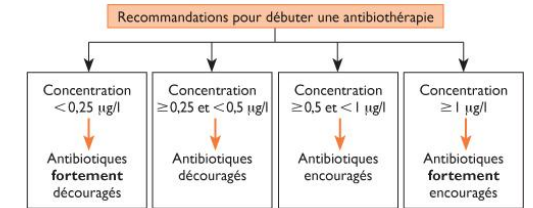
- Toux, dysurie, érythème

### Signes de dysfonction aiguë d'organe

- Confusion, oligurie, dyspnée

## Reconnaissance précoce pouvant être difficile

- qSOFA
- SIRS
- **Biomarqueurs (CRP – PCT)**



Bouadma, Lancet, 2010

## Identifier site et cause de l'infection

- Respiratoire
- Abdominale
- Voies urinaires
- Peau
- Cathéters

## Évaluer la fonction des organes et la perfusion

- SOFA
- Lactate

| System                                           | Score | 0             | 1                 | 2                                                 | 3                                                                       | 4                                                                    |
|--------------------------------------------------|-------|---------------|-------------------|---------------------------------------------------|-------------------------------------------------------------------------|----------------------------------------------------------------------|
| Respiration                                      |       |               |                   |                                                   |                                                                         |                                                                      |
| Pao <sub>2</sub> /Fio <sub>2</sub> , mm Hg (kPa) |       | ≥400 (53.3)   | <400 (53.3)       | <300 (40)                                         | <200 (26.7) with respiratory support                                    | <100 (13.3) with respiratory support                                 |
| Coagulation                                      |       |               |                   |                                                   |                                                                         |                                                                      |
| Platelets, ×10 <sup>3</sup> /µL                  |       | ≥150          | <150              | <100                                              | <50                                                                     | <20                                                                  |
| Liver                                            |       |               |                   |                                                   |                                                                         |                                                                      |
| Bilirubin, mg/dL (µmol/L)                        |       | <1.2 (20)     | 1.2-1.9 (20-32)   | 2.0-5.9 (33-101)                                  | 6.0-11.9 (102-204)                                                      | >12.0 (204)                                                          |
| Cardiovascular                                   |       |               |                   |                                                   |                                                                         |                                                                      |
| MAP ≥70 mm Hg                                    |       | MAP ≥70 mm Hg | MAP <70 mm Hg     | Dopamine <5 or dobutamine (any dose) <sup>b</sup> | Dopamine 5.1-15 or epinephrine ≤0.1 or norepinephrine ≤0.1 <sup>b</sup> | Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1 <sup>b</sup> |
| Central nervous system                           |       |               |                   |                                                   |                                                                         |                                                                      |
| Glasgow Coma Scale score <sup>c</sup>            |       | 15            | 13-14             | 10-12                                             | 6-9                                                                     | <6                                                                   |
| Renal                                            |       |               |                   |                                                   |                                                                         |                                                                      |
| Creatinine, mg/dL (µmol/L)                       |       | <1.2 (110)    | 1.2-1.9 (110-170) | 2.0-3.4 (171-299)                                 | 3.5-4.9 (300-440)                                                       | >5.0 (440)                                                           |
| Urine output, mL/d                               |       |               |                   |                                                   | <500                                                                    | <200                                                                 |



## Biomarkers to Start Antibiotics

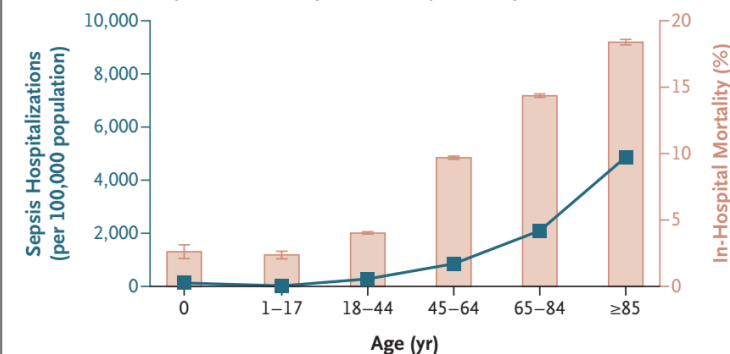
### Recommendation

16. For adults with suspected sepsis or septic shock, we **suggest against** using procalcitonin plus clinical evaluation to decide when to start antimicrobials, as compared to clinical evaluation alone.

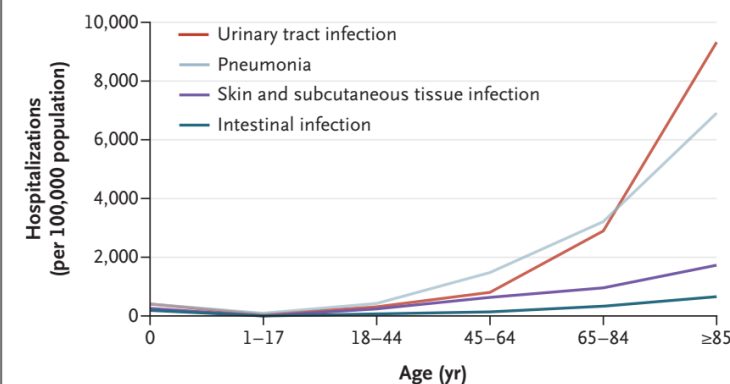
*Weak recommendation, very low quality of evidence.*

- Au mieux sur identification du germe ou à défaut sur une forte suspicion clinique
- Sites d'infection
  - Pulmonaire (40 à 60 % des cas),
  - Abdomen (15 à 30 %),
  - Système génito-urinaire (15 à 30 %),
  - Sang,
  - Peau ou les tissus mous.
- Un agent pathogène est identifié dans environ 60 à 70 % des cas.
  - Antibiothérapie préalable
  - Techniques de prélèvement inadéquates
  - Anomalies pré-analytiques
- Germes en cause: bactérie avec gram positif ou Gram négatif, suivie par une infection fongique ou virale.

A Incidence of Sepsis and In-Hospital Mortality from Sepsis



B Hospitalization According to Infection Site



C Hospitalization According to Pathogen Type

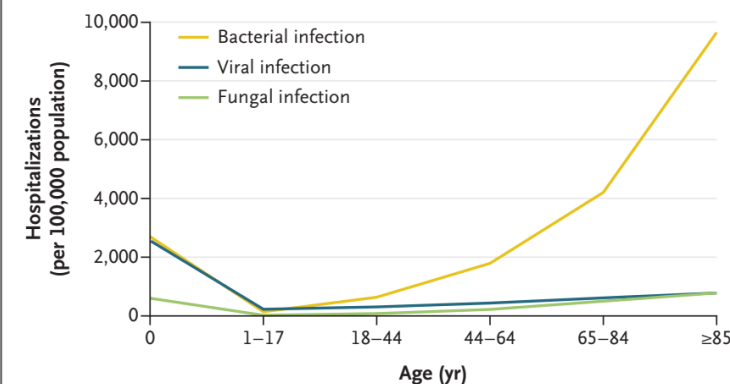


Figure 1. Epidemiologic Features of Sepsis in the United States According to Age Group.

# Techniques

- Gold standard
  - culture microbiologique
  - puis antibiogramme (48H00)



- PCR (Polymerase Chain Reaction)
  - Grippe
  - PCR multiplex spécifiques d'organe

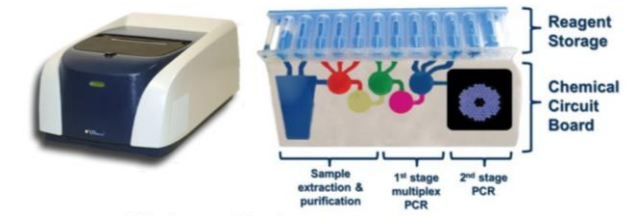
## ePlex® Respiratory Pathogen Panel

- influenza viruses A–H1, A-H1N1, A-H3, and B;
- respiratory syncytial viruses [RSV] A and B;
- parainfluenza viruses [PIV] types 1, 2, 3, and 4;
- human metapneumovirus [hMPV];
- rhinovirus and/or enterovirus; coronaviruses 229E, HKU1, NL63, OC43, and MERS;
- adenovirus, and
- bocavirus) and
- four bacteria (*Bordetella pertussis*, *Chlamydomphila pneumoniae*, *Legionella pneumophila*, and *Mycoplasma pneumoniae*).



Diagnostic intégré  
Biofire FilmArray® – Diagnostic tous virus  
respiratoires

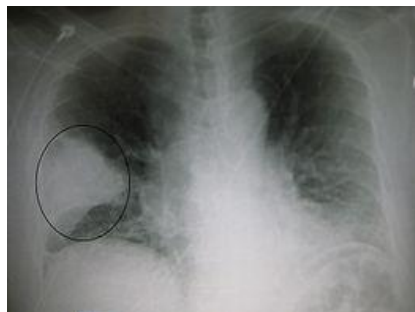
RT-PCR multiplex unitaire permettant  
la détection simultanée de 18 virus et de 3 bactéries



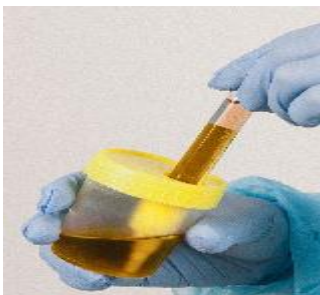
Résultats en 75 minutes

# En pratique

Pour tous → PCT et hémocultures  
Radiographie thoracique



Urines



Neuro



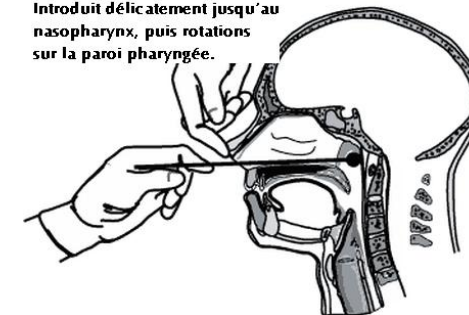
Pneumopathie



ECBC + Ag U L et P



Ecouvillon Viroclut (vert)  
Introduit délicatement jusqu'au  
nasopharynx, puis rotations  
sur la paroi pharyngée.



Abdomen



- Le patient a finalement reçu aux urgences 1000 mL de sérum physiologique.
- Sa Pam reste à 60 mmHg, FC 110 bpm, sat 98% en AA.
- Gaz du sang: pH=7.25; PaCO<sub>2</sub> = 28 mmHg; HCO<sub>3</sub><sup>-</sup>= 13 mmol/L; lactate 10 mmol/L.
- Pq 110 G/L; Hb 12.7 g/dL; GB 15 G/L; créat 350 µmol/L; bili 10 µmol/L; TP 70%; Fg 2.5 G/L.



# Prise en charge du choc septique

Surviving sepsis campaign 2021

# Quels sont les premiers éléments de votre prise en charge?

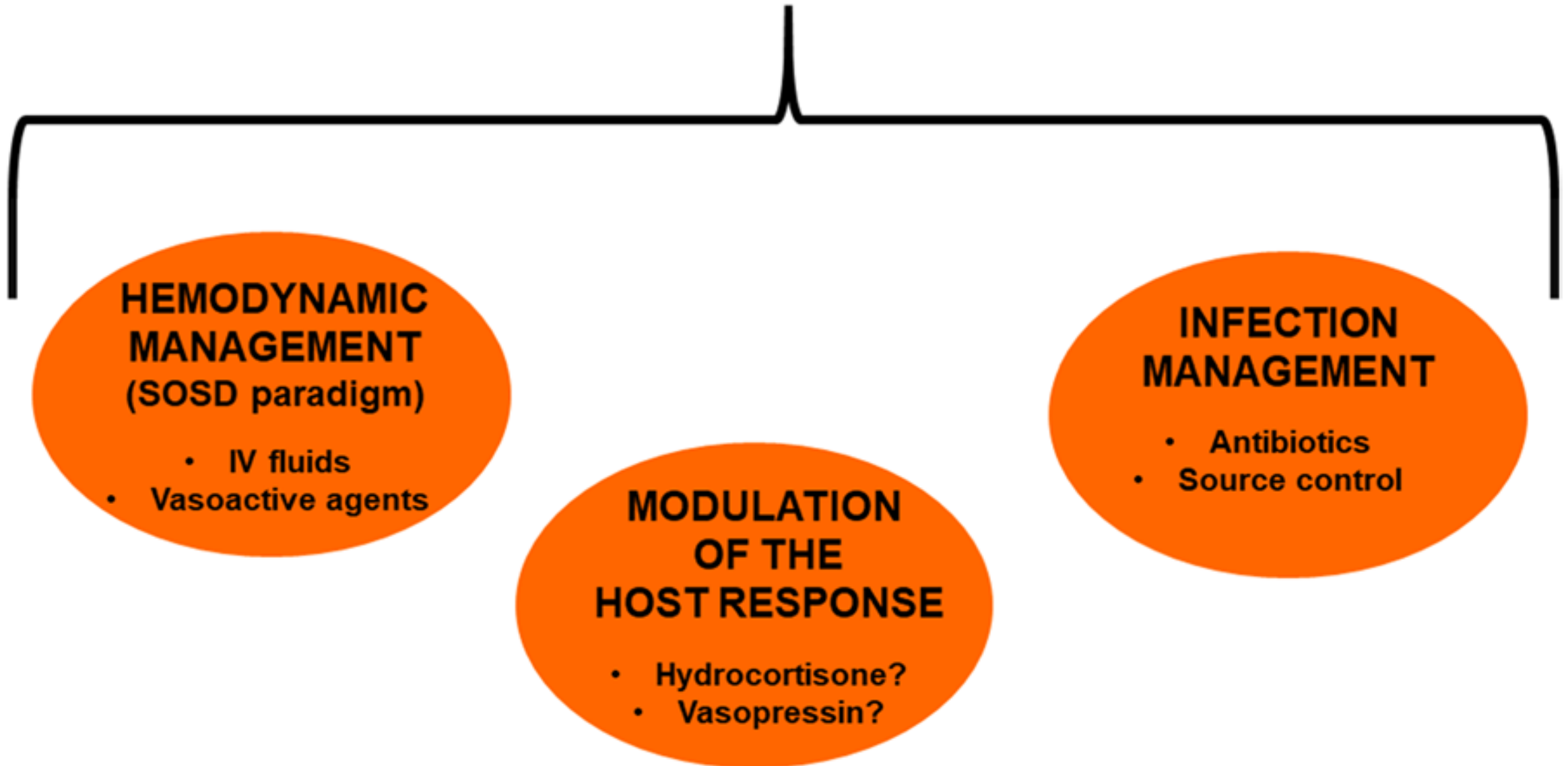
- A. Admission en soins intensifs
- B. Mise en place d'un **cathéter artériel**.
- C. Objectif hémodynamique : **PAM  $\geq$  70 mmHg**
- D. Introduction de la **noradrénaline**, après mise en place d'une **voie veineuse centrale**.
- E. **Antibiothérapie probabiliste à large spectre** débutée sans délai, après hémocultures, sans attendre les résultats microbiologiques.



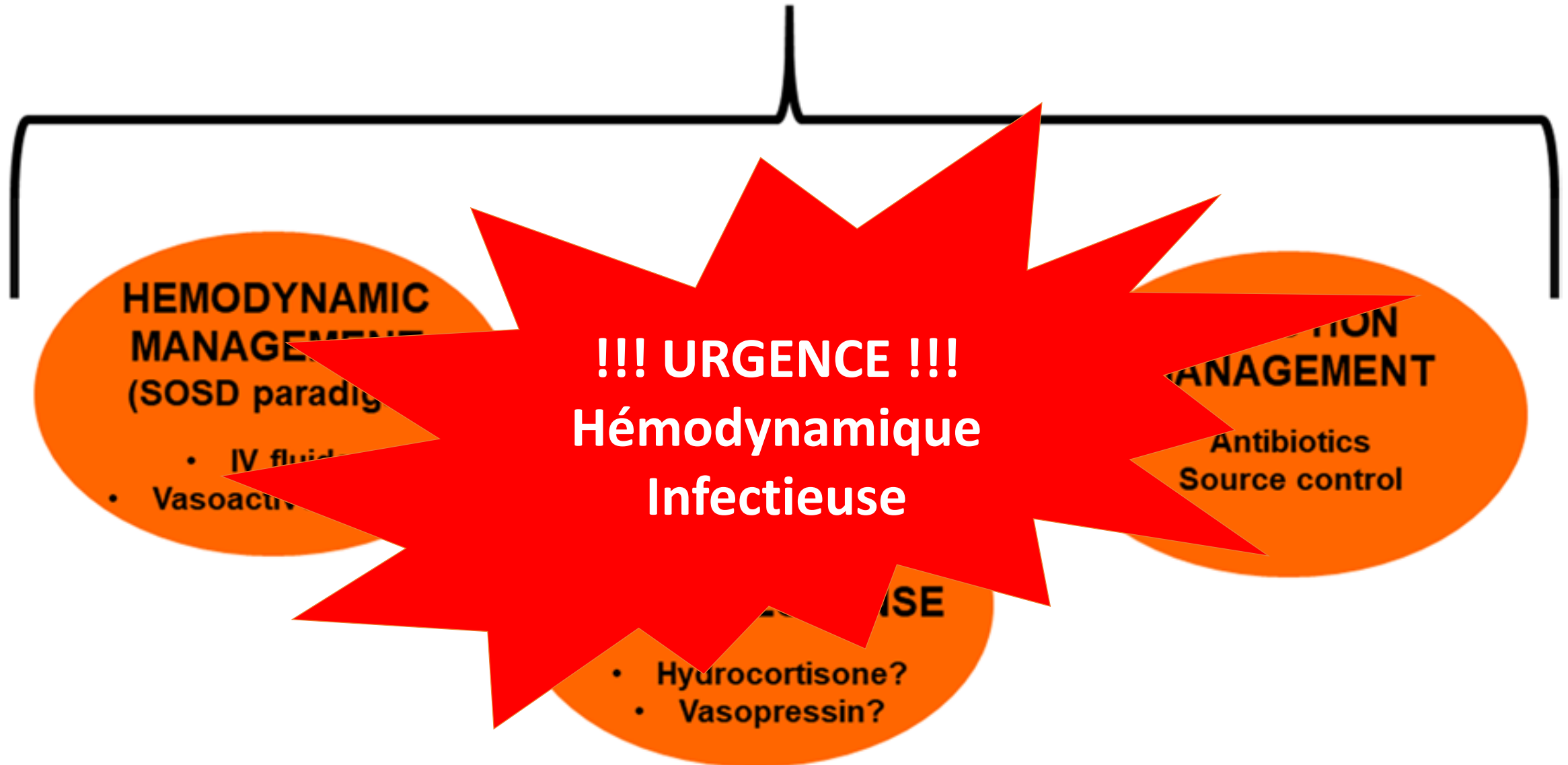
# Quels sont les premiers éléments de votre prise en charge?

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# SEPSIS MANAGEMENT



# SEPSIS MANAGEMENT



# Protocoles de prise en charge

- **AGIR VITE**

- détection, prélèvements, traitements

- Pour restaurer hémodynamique

- Pour contrôler la source

- Protocoliser les soins +++

- Avec une médecine plus « personnalisée »



BUNDLES

3 à 5 mesures

Mise en œuvre

Pronostic du patient

# Orientation précoce du patient

- Appel rapide du réanimateur
- Prise en charge au déchocage si sepsis confirmé= défaillance d'organe
- Transfert en réanimation, USI
- Fait partie des déterminants du pronostic

# Quels objectifs de Pam ?



MODERATE

9

For adults with septic shock on vasopressors, we **recommend** an initial target mean arterial pressure (MAP) of 65 mm Hg over higher MAP targets.

Evans L et al. 2021 ICM  
*SSC Guideline 2021*



# Objectif de PAM $\geq 65$ mmHg ...

Une hypotension profonde et prolongée augmente la mortalité

Seuils variables dans la littérature entre 60 et 85 mmHg

*Varpula et al. 2005 ICM (65 mmHg); Dünser et al. 2009 ICM (60-75 mmHg); Dunser et al. 2009 Crit Care; Vincent et al. 2018 AIC; Maheshwari et al. 2018 ICM*

Quel objectif de perfusion?  
Quel seuil!!!



## Asfar et al. 2014 NEJM - SEPSIS-PAM

N=776 65±14 ans

**Pas de différence entre 65-70 et 80-85 mmHg**

MAIS:

cible haute favorise la FA

Cible haute diminue le risque d'insuffisance rénale chez les hypertendus chroniques

## Lamontagne et al. JAMA 2020 – 65 trial

N=2600 >65 ans (75±7 ans)

**Pas de différence entre hypoTA permissive (60-65) et SoC**

DC90 41.0% (perm.) vs 43.8%(soC), RR 0.93; 95% CI, 0.85-1.03).

Après ajustement (post hoc): RR=0.82 (95% CI, 0.68 to 0.98). ( en faveur Pam plus basse)

## Endo et al. ICM 2025 – OPTPRESS

N=518 >65 ans (75±7 ans) choc septique

**Surrisque décès pour PAM haute (80-85 mmHg) vs SOC (PAM 65-70 )**

By 90 days after randomisation, 101 patients (39.3%) in the high-target group and 74 (28.6%) in the control group had died from any cause (risk difference = 10.7; 95% confidence interval, 2.6–18.9).





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.

## Safety of peripheral administration of vasopressor medications: A systematic review

David H TIAN,<sup>1</sup> Claire SMYTH,<sup>1</sup> Gerben KEIJZERS,<sup>2,3,4</sup> Stephen PJ MACDONALD <sup>5,6</sup>  
Sandra PEAKE,<sup>7,8,9</sup> Andrew UDY <sup>8,10</sup> and Anthony DELANEY <sup>1,8,11,12</sup>

### VASOPRESSEURS?

- Revue systématique
- 7 études/ 1382 patients
- Durée moyenne de perfusion 22 heures
- Extravasation 3.4% 95% CI 2.5-4.7%
- Aucune complication grave (nécroses, ischémies)

|                               | Number of infusions | Dilution              | Effective dose/mL | Duration (h) | Extravasation |
|-------------------------------|---------------------|-----------------------|-------------------|--------------|---------------|
| Noradrenaline                 |                     |                       |                   |              |               |
| Cardenas-Garcia <sup>10</sup> | 506                 | 8–16 mg in 250 mL N/S | 32–64 µg/mL       | 49 ± 22      | 16 (2.3%)     |
| Lewis <sup>18</sup>           | 146                 | 4 mg in 250 mL N/S    | 16 µg/mL          | 11.2 ± 15‡   | 4 (2.7%)      |
| Medlej <sup>11</sup>          | 50                  | 8 mg in 250 mL D5W    | 32 µg/mL          | 16.9 ± 18.9‡ | 2 (4.0%)      |

## Initiation of vasopressor infusions via peripheral *versus* central access in patients with early septic shock: A retrospective cohort study

Anthony DELANEY <sup>1,2,3</sup> Mark FINNIS,<sup>3,4</sup> Rinaldo BELLOMO,<sup>3,5</sup> Andrew UDY <sup>3,6</sup> Daryl JONES,<sup>3,5</sup>  
Gerben KEIJZERS,<sup>7,8,9</sup> Stephen MACDONALD <sup>10,11</sup> and Sandra PEAKE<sup>3,12</sup>



- Analyse post hoc de ARISE 937 patients
- 389 (42% ) Vasopresseurs d'abord en périphérie vs 548 (58%) après abord central

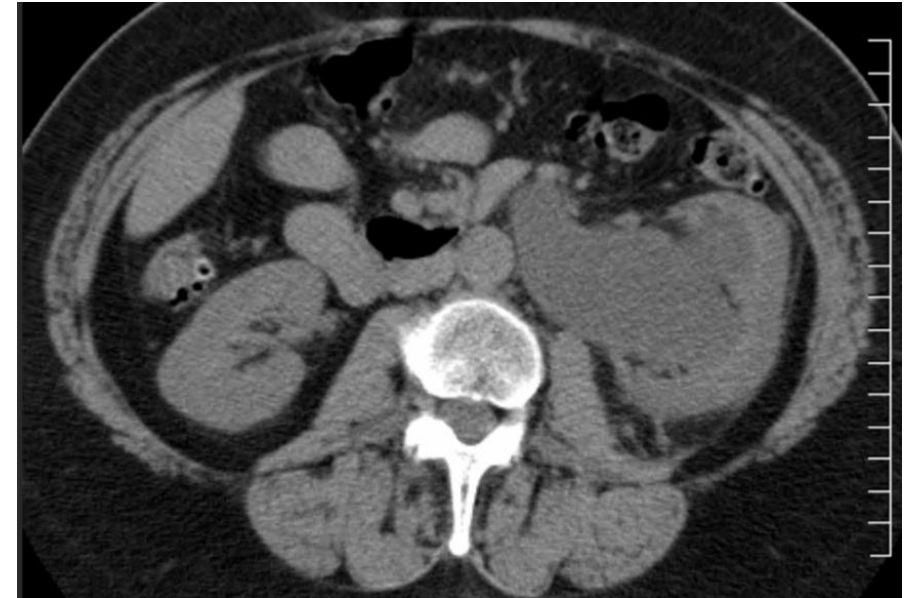
| Mortalité (ajustée)           | RR=1.26 (0.95-1.67; p=0.11)         |
|-------------------------------|-------------------------------------|
| Arrivée aux SAU-Antibiotiques | PV: 55 min vs CVC 71.5 min, p<0.001 |
| Arrivée au SAU-Vasopresseurs  | PV 2.4 h vs CVC 4.9 h, p<0.001      |

### Prise en charge initiale aux urgences :

- **Remplissage vasculaire** par 2 L de **Ringer lactate**.
- **Introduction de la noradrénaline** en périphérie (VVP), à visée de soutien vasopresseur.
- **Antibiothérapie probabiliste à large spectre** initiée en urgence.
- Admission en soins intensifs

### État clinique post-prise en charge initiale :

- **PAM à 65 mmHg** sous **noradrénaline 0,5 µg/kg/min**.
- Lactatémie à 5 mmol/L, pH à 7.36; PaCO<sub>2</sub> à 28 mmHg.
- Absence de défaillance **respiratoire, neurologique et hépatique**.
- Présence d'une **insuffisance rénale aiguë** :
  - **Créatininémie** à 350 µmol/L.
  - **Oligurie** persistante.
- **Thrombopénie modérée** avec **plaquettes à 100 G/L**.



**Vous réévaluez votre patient qui vient d'arriver en réanimation. Quels sont les éléments qui vous rassurent?**

- A. Le taux de lactate est à 5 mmol/L
- B. Le pH est à 7.36
- C. Un temps de recoloration cutané est à 4 secondes
- D. Les marbrures sont toujours présentes mais n'ont pas augmentées
- E. La Pam est contrôlée sous 0.5 µg/kg/min de noradrénaline

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# Quels objectifs de perfusion ?



MODERATE

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For adults with septic shock on vasopressors, we **recommend** an initial target mean arterial pressure (MAP) of 65 mm Hg over higher MAP targets.

Evans L et al. 2021 ICM  
SSC Guideline 2021



LOW

7

For adults with sepsis or septic shock, we **suggest** guiding resuscitation to decrease serum lactate in patients with elevated lactate level, over not using serum lactate.



LOW

8

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

**NEW !**



# Baisse du lactate



LOW

7

For adults with sepsis or septic shock, we **suggest** guiding resuscitation to decrease serum lactate in patients with elevated lactate level, over not using serum lactate.



LOW

8

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

## Early Goal-Directed and Lactate-Guided Therapy in Adult Patients With Severe Sepsis and Septic Shock: A Meta-Analysis of Randomized Controlled Trials

Mortality benefit associated with lactate-guided resuscitation

## 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

34.9% vs. 43.4% mortality,  $P = 0.06$

Gu WJ, Zhang Z, Bakker J. Early lactate clearance-guided therapy in patients with sepsis: a meta-analysis with trial sequential analysis of randomized controlled trials. *Intensive Care Med*. 2015 Oct;41(10):1862-1863.

Ding XF, Yang ZY, Xu Z, et al. Early goal-directed and lactate-guided therapy in adult patients with severe sepsis and septic shock: a meta-analysis of randomized controlled trials. *J Transl Med*. 2018 Nov 29;16(1):331.

Hernandez G, Ospina-Tascon GA, Damiani LP, et al. 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. *JAMA*. 2019 Feb 19;321(7):654-664.



# Early Lactate-Guided Therapy in Intensive Care Unit Patients

RCT multicentrique Hollande  
348 patients Réanimation  
2006 - 2008

## Inclusion

ICU

Lactate  $\geq 3$  mmol/L

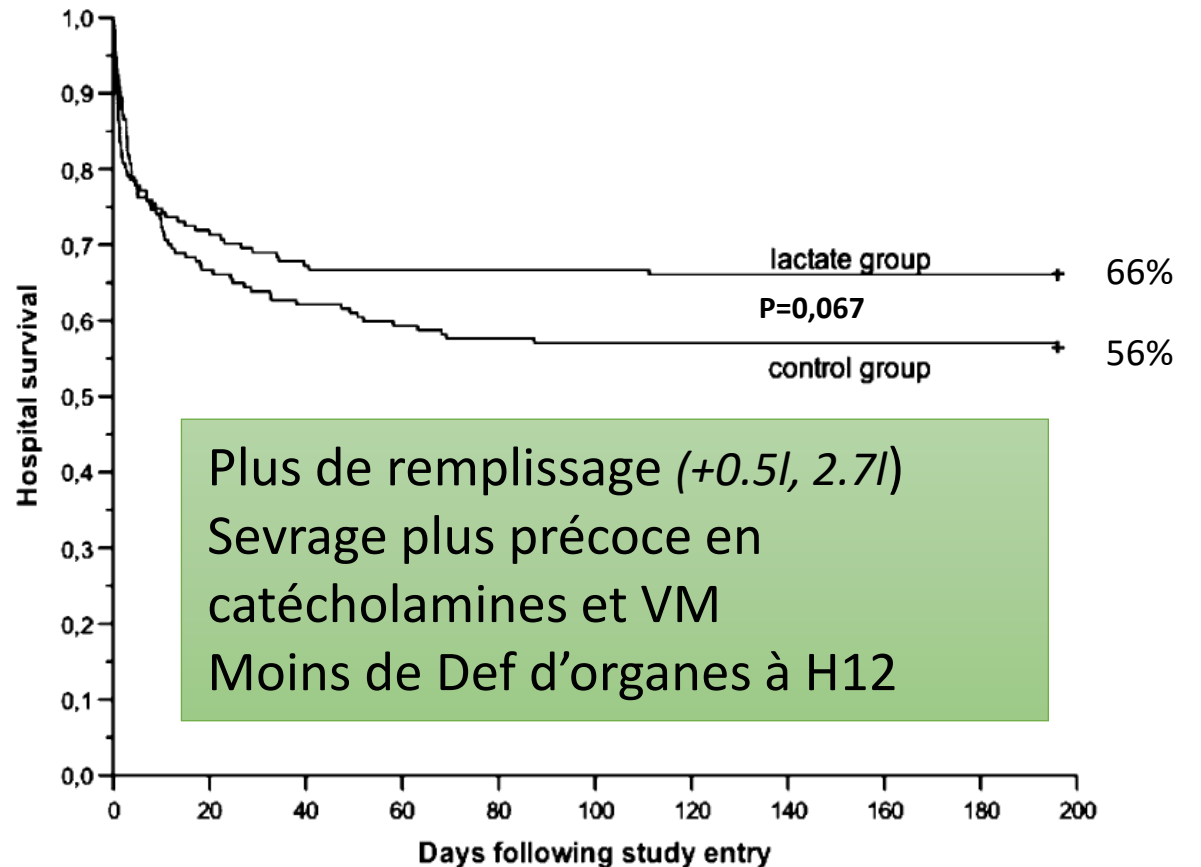
## Intervention « open label »

Objectif  $\downarrow \geq 20\%$  lactate /2h

**Vs**

Réanimation sans lactate  
(excepté celui d'entrée)

**Pendant 8 heures**



Plus de remplissage (+0.5l, 2.7l)  
Sevrage plus précoce en  
catécholamines et VM  
Moins de Def d'organes à H12

Après ajustement / facteurs de risque  
prédéfinis de mortalité

**HR 0,61 (IC 95% 0,43 – 0,87 ; p=0,006)**

# Temps de recoloration cutanée



LOW

8

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

# Temps de recoloration cutanée



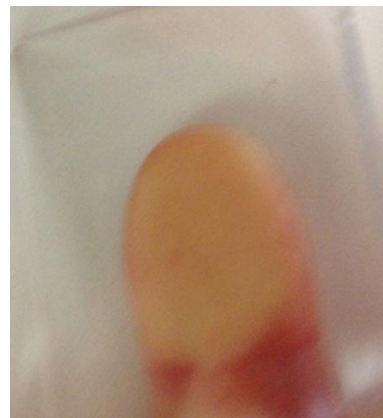
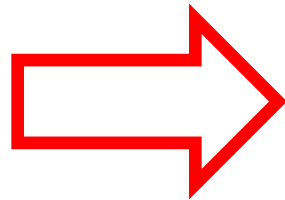
LOW



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



Vitropression  
Pulpe de l'index  
10 secondes



# Temps de recoloration cutanée



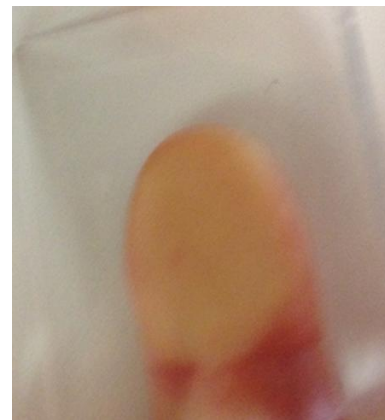
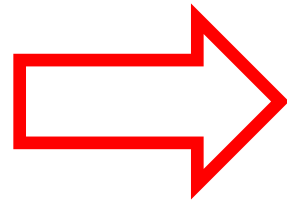
LOW



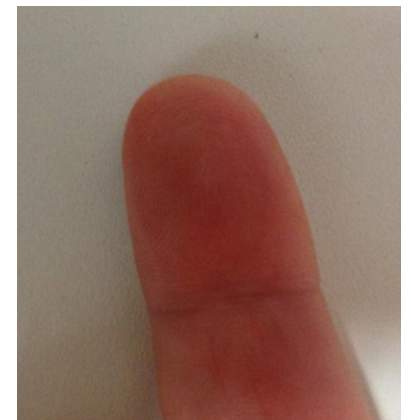
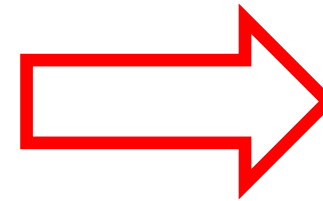
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Vitropression  
Pulpe de l'index  
10 secondes



TRC normal  
< 3 sec



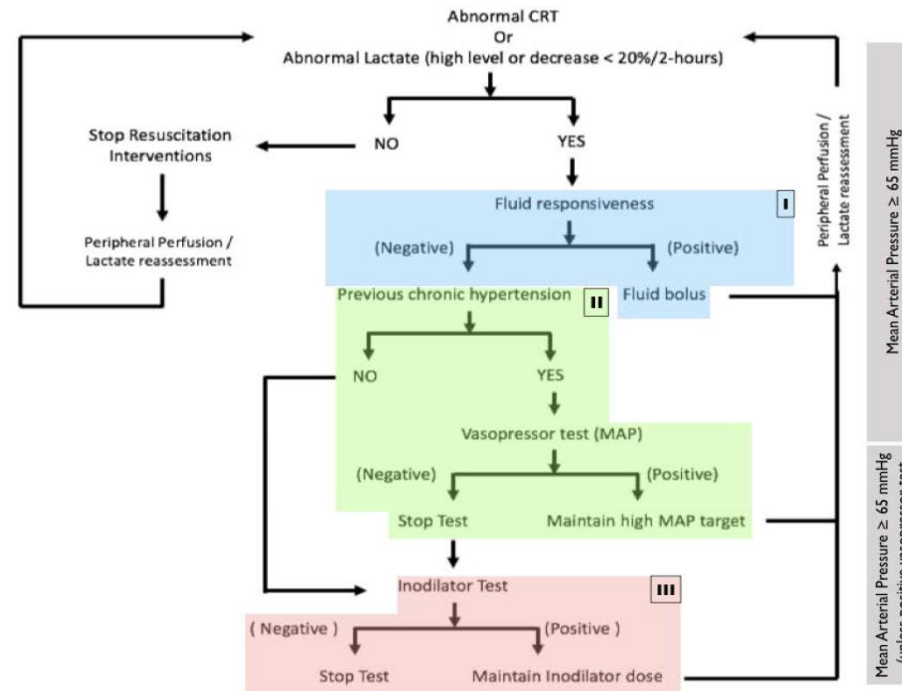
JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

# 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; Diego Barahona, MD; Vladimir Granda-Luna, MD, PhD; Alexandre Biasi Cavalcanti, MD, PhD; Jan Bakker, MD, PhD; for the ANDROMEDA-SHOCK Investigators and the Latin America Intensive Care Network (LIVEN)

- Lactate level/2h
- vs
- CRT/30 mn for 8 hours



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) <sup>b</sup>        | HR, 0.75 (0.55 to 1.02) <sup>a</sup> | .06 <sup>a</sup> |
| Secondary Outcomes                                                      |                                                       |                                                |                                         |                                      |                  |
| Death within 90 d, No. (%)                                              | 87 (41.0)                                             | 99 (46.7)                                      | −5.7 (−15.6 to 4.2) <sup>b</sup>        | HR, 0.82 (0.61 to 1.09) <sup>a</sup> | .17 <sup>a</sup> |
| Mechanical ventilation-free days within 28 d, mean (SD) <sup>c</sup>    | 14.6 (12.1)                                           | 12.7 (12.2)                                    | 1.9 (−0.6 to 4.3)                       |                                      | .14              |
| Renal replacement therapy-free days within 28 d, mean (SD) <sup>c</sup> | 18.5 (12.1)                                           | 16.9 (12.1)                                    | 1.7 (−1.5 to 4.8)                       |                                      | .31              |
| Vasopressor-free days within 28 d, mean (SD) <sup>c</sup>               | 16.7 (12.0)                                           | 15.1 (12.3)                                    | 1.6 (−0.7 to 3.9)                       |                                      | .18              |
| SOFA at 72 h, No. <sup>d</sup>                                          | 165                                                   | 166                                            |                                         |                                      | .045             |
| Mean (SD)                                                               | 5.6 (4.3)                                             | 6.6 (4.7)                                      | −1.00 (−1.97 to −0.02)                  |                                      |                  |
| ICU length of stay, mean (SD), d <sup>e</sup>                           | 9.1 (9.8)                                             | 9.0 (9.6)                                      | 0.1 (−1.7 to 2.0)                       |                                      | .91              |
| Hospital length of stay, mean (SD), d <sup>f</sup>                      | 22.9 (28.8)                                           | 18.3 (19.0)                                    | 4.6 (0.0 to 9.1)                        |                                      | .05              |
| Exploratory Outcomes                                                    |                                                       |                                                |                                         |                                      |                  |
| Amount of resuscitation fluids within the first 8 h, No.                | 206                                                   | 209                                            |                                         |                                      |                  |
| Mean (SD), mL                                                           | 2359 (1344)                                           | 2767 (1749)                                    | −408 (−705 to −110)                     |                                      | .01              |

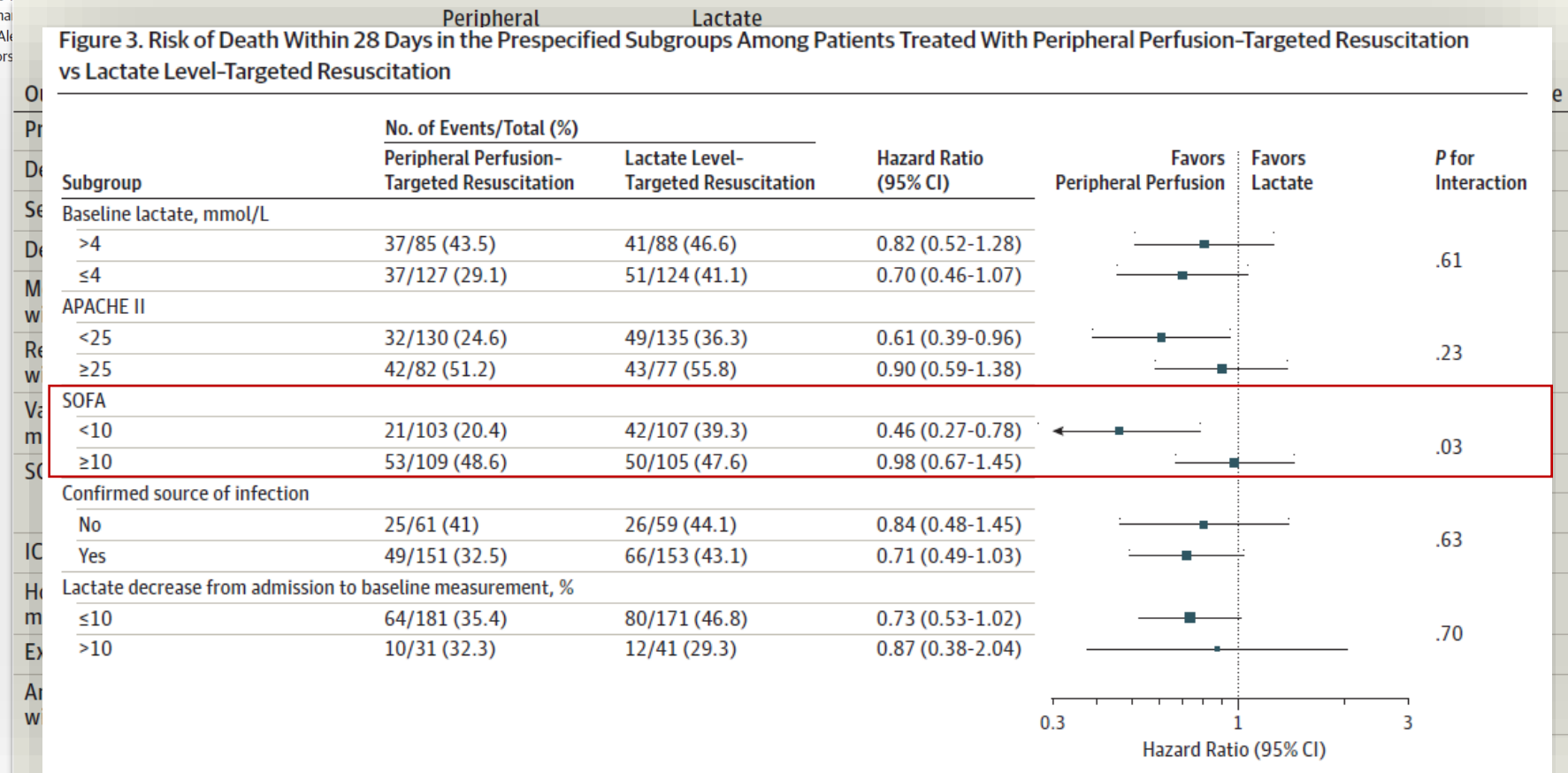
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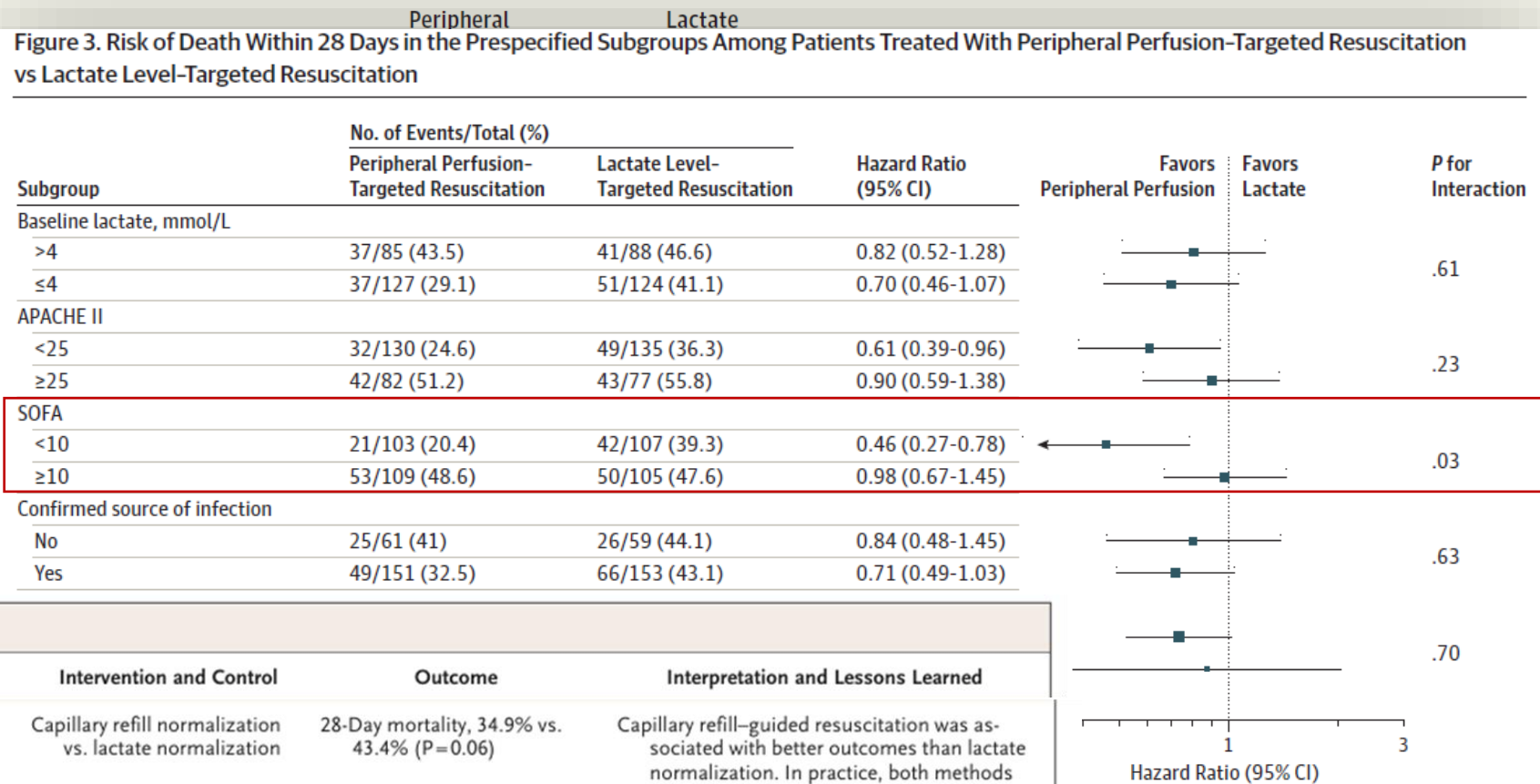


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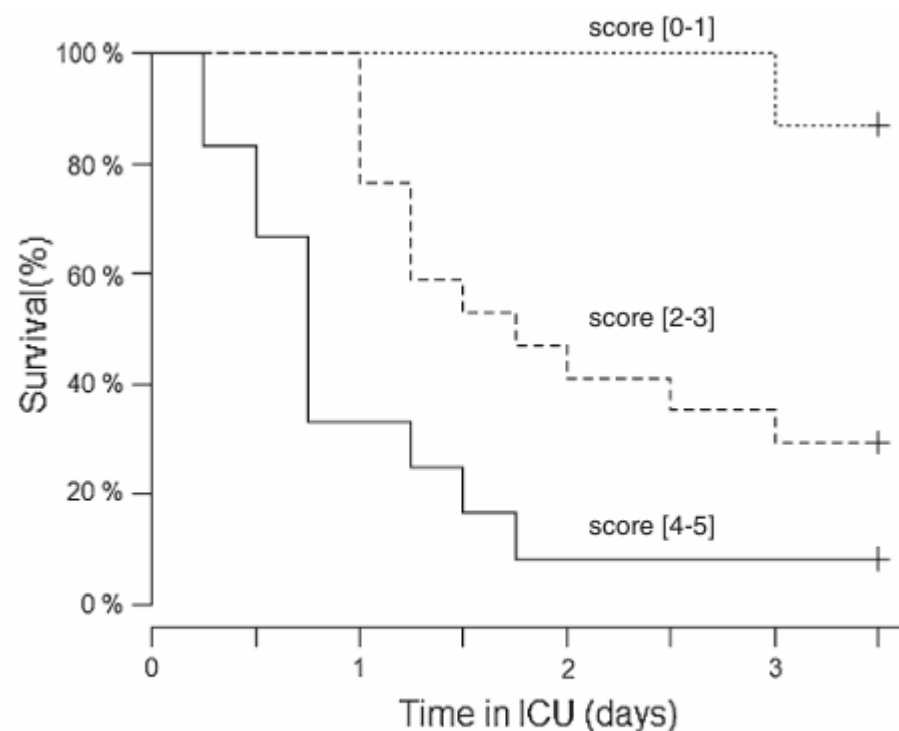
**Table 2. Landmark Sepsis Clinical Trials since 2015.\***

| Trial or Trials                  | Patients                                                                                                                         | Intervention and Control                                 | Outcome                                    | Interpretation and Lessons Learned                                                                                                           |
|----------------------------------|----------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------|--------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------|
| ANDROMEDA-SHOCK <sup>70,71</sup> | 424 Patients with septic shock and lactate level ≥2.0 mmol/liter at 28 sites in Argentina, Chile, Colombia, Ecuador, and Uruguay | Capillary refill normalization vs. lactate normalization | 28-Day mortality, 34.9% vs. 43.4% (P=0.06) | Capillary refill-guided resuscitation was associated with better outcomes than lactate normalization. In practice, both methods can be used. |

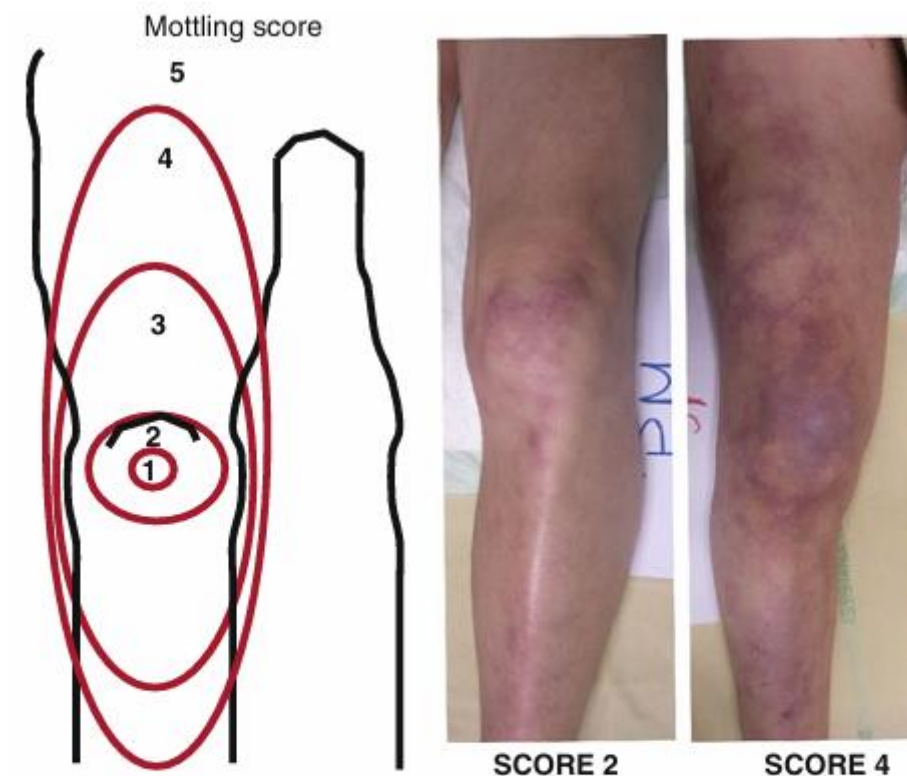


H. Ait-Oufella  
S. Lemoine  
P. Y. Boelle  
A. Galbois  
J. L. Baudel  
J. Lemant  
J. Joffre  
D. Margetis  
B. Guidet  
E. Maury  
G. Offenstadt

## Mottling score predicts survival in septic shock



**Fig. 2** Kaplan-Meier survival estimates according to the H6 mottling score. Larger mottling scores were associated with earlier death ( $p < 0.0001$ )



**Fig. 1** *Left:* the mottling score is based on a mottling area extension on the legs. Score 0 indicates no mottling; score 1, a modest mottling area (coin size) localized to the center of the knee; score 2, a moderate mottling area that does not exceed the superior edge of the kneecap; score 3, a mild mottling area that does not exceed the middle thigh; score 4, a severe mottling area that does not go beyond the fold of the groin; score 5, an extremely severe mottling area that goes beyond the fold of the groin. *Right:* Examples of the mottling score

Depuis une heure en soins intensifs, malgré encore 1.5 L de remplissage par Ringer Lactate, vous arrivez à peine à obtenir une Pam > 65 mmHg avec une noradrénaline à 0.75 µg/kg/min.

## Quel est alors la suite de votre prise en charge

- A. Introduction de vasopressine
- B. Vous poursuivez le remplissage avec du ringer lactate
- C. Drainage urinaire en urgence
- D. Administration d'hémisuccinate d'hydrocortisone
- E. Mise en place d'une voie veineuse centrale

Depuis une heure en soins intensifs, malgré encore 1.5 L de remplissage par Ringer Lactate, vous arrivez à peine à obtenir une Pam > 65 mmHg avec une noradrénaline à 0.75 µg/kg/min.

## Quel est alors la suite de votre prise en charge

- A. Introduction de vasopressine
- B. Vous poursuivez le remplissage avec du ringer lactate
- C. Drainage urinaire en urgence
- D. Administration d'hémisuccinate d'hydrocortisone
- E. Mise en place d'une voie veineuse centrale

# Quelle expansion volémique?



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.

Earlier SSC guidelines (2004, 2008, 2012) recommended EGDT.  
Based on PROMISE, PROCESS, and ARISE, this was simplified to 30 mL/kg in 2016.  
There are no trials testing fluid volume.

PRISM meta-analysis fluid pre-randomization

|        | EGDT       | Usual Care |
|--------|------------|------------|
| Median | 27.5 ml/kg | 27.7ml/hr  |

## Multicenter Implementation of a Treatment Bundle for Patients With Sepsis and Intermediate Lactate Values

Mortality decline was mediated by increased fluid and decreased mortality among patients with history of heart failure and/or kidney disease.

### 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."

PRISM Investigators, Rowan KM, Angus DC, et al. Early, goal-directed therapy for septic shock: a patient-level meta-analysis. *N Engl J Med*. 2017 Jun 8;376(23):2223-2234.  
Liu VX, Morehouse JW, Marelich GP, et al. Multicenter implementation of a treatment bundle for patients with sepsis and intermediate lactate values. *Am J Respir Crit Care Med*. 2016 Jun 1;193(11):1264-1270.

Table 2. Landmark Sepsis Clinical Trials since 2015.\*

| Trial or Trials                                                       | Patients                                                                                                                                                                                                  | Intervention and Control                                                                                                         | Outcome                                                                                                                                                                               | Interpretation and Lessons Learned                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|-----------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| ARISE, <sup>57</sup> ProCESS, <sup>58</sup> and ProMISe <sup>59</sup> | ARISE: 1600 patients with septic shock at 51 sites in Australia and New Zealand<br>ProCESS: 1341 patients with septic shock at 31 U.S. sites<br>ProMISe: 1260 patients with septic shock at 56 U.K. sites | ARISE: EGDT vs. usual care<br>ProCESS: EGDT vs. protocol-based "standard" therapy vs. usual care<br>ProMISe: EGDT vs. usual care | ARISE: 90-day mortality, 18.6% vs. 18.8% (P=0.90)<br>ProCESS: 60-day in-hospital mortality, 21.8% vs. 18.2% vs. 18.9% (P=0.83)<br>ProMISe: 90-day mortality, 29.5% vs. 29.2% (P=0.90) | These trials showed that outcomes were similar with EGDT and usual care. Patients in these trials were less sick than those in the Rivers et al. trial (e.g., baseline ScvO <sub>2</sub> 70% vs. 49%). <sup>60</sup> However, there was no indication of benefit with EGDT across any subgroups examined in a meta-analysis of data from individual patients, including more severely ill patients. <sup>61</sup> Although these trials suggest that EGDT and usual care yield equivalent outcomes, EGDT is more labor-intensive, and standard care has evolved away from it. |

# Balance bénéfice/risque du remplissage

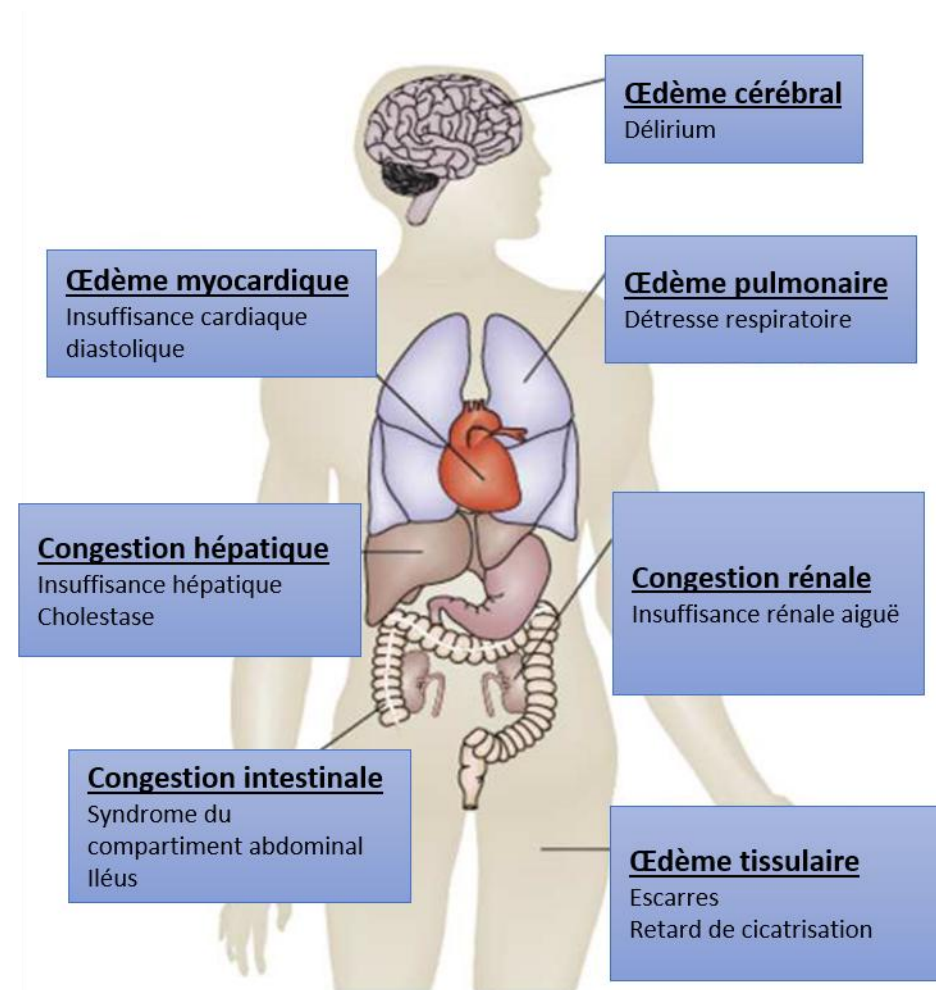
## Bénéfices

- ↑ du DC et du TaO<sub>2</sub>
- Éviter les défaillances d'organes



## Risques

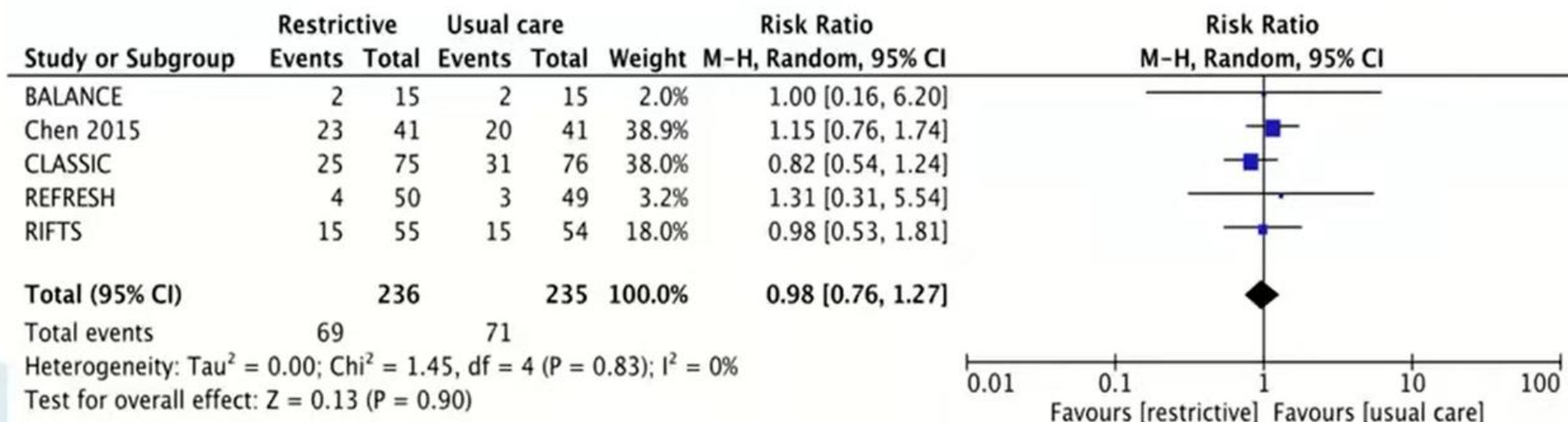
- Congestion
- Défaillances d'organes





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.

5 pilot RCTs: no signal, wide heterogeneity in definitions of conservative vs. liberal fluid approach.



Semler MW, Janz DR, Casey JD, Self WH, Rice TW. Conservative fluid management after sepsis resuscitation: a pilot randomized trial. *J Intensive Care Med*. 2020 Dec;35(12):1374-1382.

Chen C, Kollef MH. Targeted fluid minimization following initial resuscitation in septic shock: a pilot study. *Chest*. 2015 Dec;148(6):1462-1469.

Hjortrup PB, Haase N, Bundgaard H, et al; CLASSIC Trial Group; Scandinavian Critical Care Trials Group. Restricting volumes of resuscitation fluid in adults with septic shock after initial management: the CLASSIC randomised, parallel-group, multicentre feasibility trial. *Intensive Care Med*. 2016 Nov;42(11):1695-1705.

Macdonald SPJ, Keijzers G, Taylor DM, et al; REFRESH trial investigators. Restricted fluid resuscitation in suspected sepsis associated hypotension (REFRESH): a pilot randomised controlled trial. *Intensive Care Med*. 2018 Dec;44(12):2070-2078.

Corl KA, Prodromou M, Merchant RC, et al. The Restrictive IV Fluid Trial in Severe Sepsis and Septic Shock (RIFTS): a randomized pilot study. *Crit Care Med*. 2019 Jul;47(7):951-959.

**Table 2.** Landmark Sepsis Clinical Trials since 2015.\*

| Trial or Trials                                 | Patients                                                                                                                 | Intervention and Control                                                                                              | Outcome                                                                                                                                                                       | Interpretation and Lessons Learned                                                                                                                                                                                                                                                                                                     |
|-------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| CLASSIC <sup>74</sup> and CLOVERS <sup>75</sup> | CLASSIC: 1554 patients with septic shock at 31 sites in Europe<br>CLOVERS: 1563 patients with sepsis-induced hypotension | CLASSIC: fluid-restrictive resuscitation vs. usual care<br>CLOVERS: fluid-restrictive vs. fluid-liberal resuscitation | CLASSIC: 90-day mortality, 42.3% vs. 42.1% (P=0.46)<br>CLOVERS: 90-day mortality, 14.0% vs. 14.9%; estimated difference, -0.9 percentage points; 95% CI, -4.4 to 2.6 (P=0.61) | Fluid-restrictive and fluid-liberal resuscitation yielded similar outcomes in the overall trial populations, which suggests that more personalized approaches may be needed. Nearly all patients received $\geq 30$ ml of fluids per kilogram, so these trials provide no data on the safety of limiting resuscitation to $<30$ ml/kg. |

\* ADRENAL denotes Adjunctive Corticosteroid Treatment in Critically Ill Patients with Septic Shock, APROCCHSS Activated Protein C and Corticosteroids for Human Septic Shock, ARISE Australasian Resuscitation in Sepsis Evaluation, BaSICS Balanced Solution versus Saline in Intensive Care Study, CLASSIC Conservative versus Liberal Approach to Fluid Therapy of Septic Shock in Intensive Care, CLOVERS Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis, EGDT early goal-directed therapy, FRESH Fluid Response Evaluation in Sepsis Hypotension and Shock, IV intravenous, JVP jugular venous pressure, PHANTASi Prehospital Antibiotics Against Sepsis Trial, ProCESS Protocolized Care for Early Septic Shock, ProMiSe Protocolised Management in Sepsis, ScvO<sub>2</sub> central venous oxygen saturation, SMART Isotonic Solutions and Major Adverse Renal Events Trial, and SSSP-2 Simplified Severe Sepsis Protocol 2.

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) improves prognosis but, in patients receiving high volume resuscitation (5 to  $\geq 9$  L), the mortality increases 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](#)



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- Time to IV 30 ml/kg bolus fluids is not related to mortality. [Seymour et al - Am J Respir Crit Care Med. 2017; 195:1618-1625](#)
- In a large US database of 35,135 patients with sepsis, patients receiving high volume resuscitation had higher mortality (OR 1.02; 95% CI 1.01, 1.03;  $p = 0.0003$ ) for each additional liter of fluid received. [Seymour et al - Crit Care Med. 2017; 45:1585-1591](#)
- A multicenter analysis of 10,000 patients with sepsis found that early administration of fluids improves prognosis but, in patients receiving high volume resuscitation, mortality increases by 2.3% (95% CI 2.0, 2.5%;  $p = 0.0003$ ) for each additional liter of fluid received. [Seymour et al - Crit Care Med. 2017; 45:1585-1591](#)
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- Positive fluid balance and volume depletion after the initial resuscitation 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](#)

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.



LOW

33

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

## Balanced Crystalloids Versus Saline in Sepsis: A Secondary Analysis of the SMART Clinical Trial

Sepsis subgroup from SMART:  
26.3% vs. 31.2% mortality  
aOR 0.74 (0.59, 0.93)

## Effect of Intravenous Fluid Treatment With a Balanced Solution vs 0.9% Saline Solution on Mortality in Critically Ill Patients: The BaSICS Randomized Clinical Trial

Sepsis subgroup:  
46.7% vs. 49.0% mortality  
aOR 0.93 (0.82, 1.06)

### Interpretation and Lessons Learned

These trials showed that resuscitation with balanced solutions is associated with better outcomes than resuscitation with normal saline, particularly among patients with sepsis and when used from the onset of resuscitation.



MODERATE

36

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

#### 2016 STATEMENT

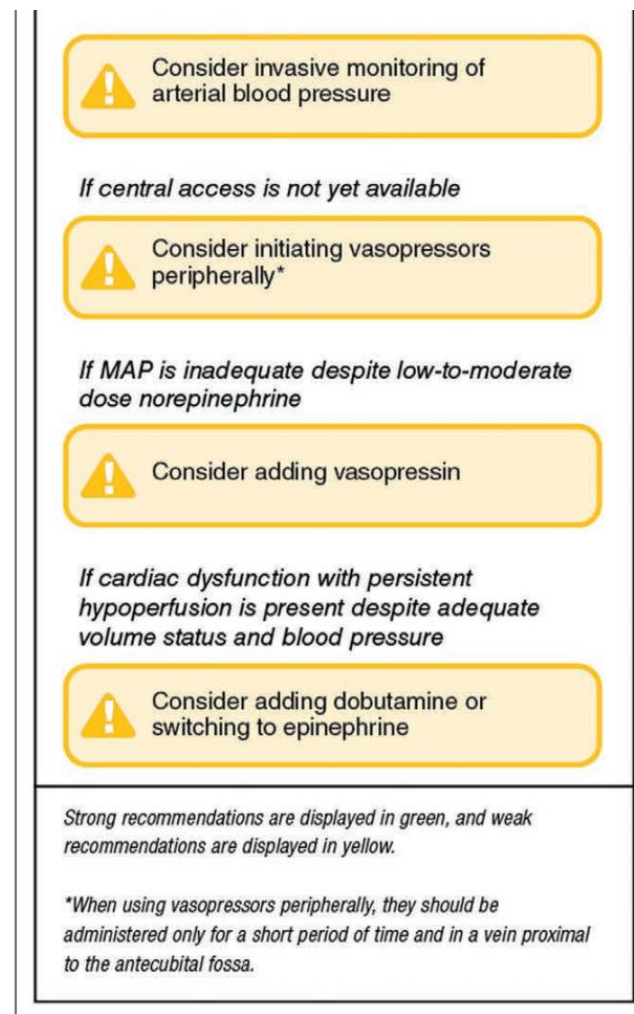
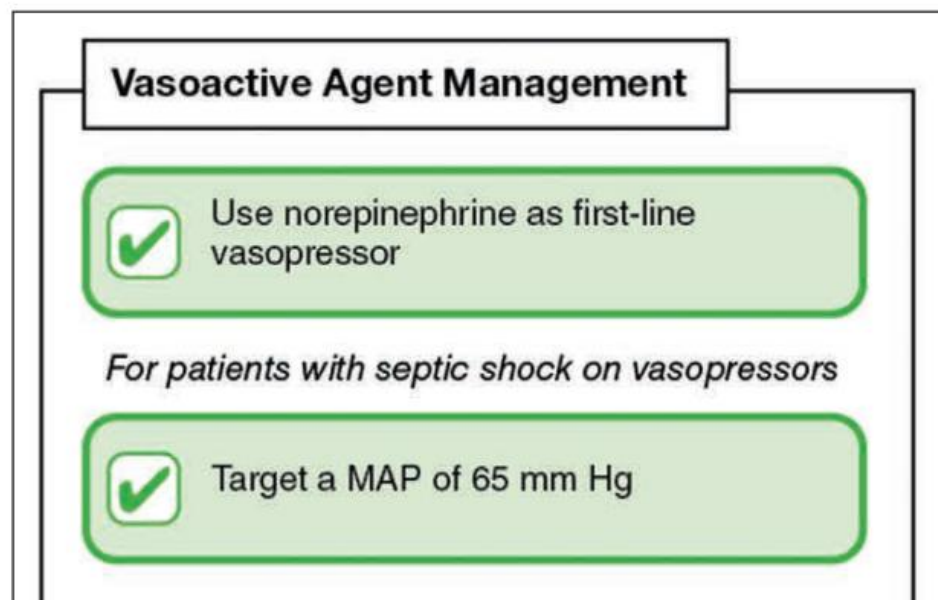


*"We **suggest** using crystalloids over gelatins when resuscitating patients with sepsis or septic shock."*

# Amines et autres traitements cardiovasculaires

1. Si persistance hypotension malgré remplissage → amines vasopressives.
2. Noradrénaline +++ →  $\nearrow$  PA, ainsi que des débits régionaux, sans augmentation de la FC.
3. Objectifs de Pam  $\geq 65$  mmHg; plus haut chez les patients hypertendus??<sup>1</sup>  
Introduction précoce
4. Si échec noradrénaline
  1. Ajout de Vasopressine (0,03 unité/minute)<sup>2</sup> ,  
Quand NaD > 0.25 – 0.5  $\mu\text{g/kg/min}$
5. Dobutamine est l'inotrope recommandé en première intention.
  1. Indication non clairement définie
  2. SSC: si dysfonction cardiaque
  3. 2.5 à 5  $\mu\text{g/kg/min}$

# Vasoactive Agent Management



**Figure 2.** Summary of vasoactive agents recommendations.

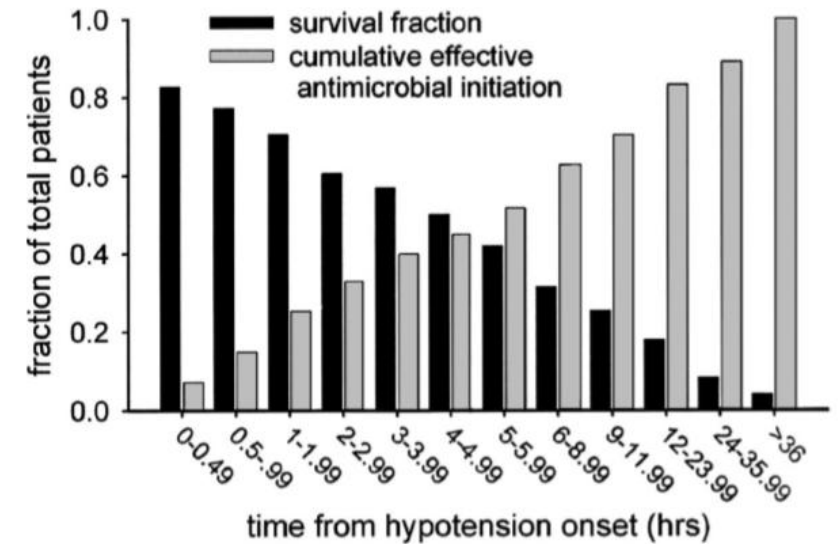
# Management de l'infection

| Recommendations          |                                                                                                                                                    | Strength |
|--------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------|----------|
| <b>Infection Control</b> |                                                                                                                                                    |          |
|                          | For possible septic shock or a high likelihood of sepsis, administer antimicrobials immediately.                                                   | Strong   |
|                          | For possible sepsis without shock, complete a time-limited evaluation, administer antimicrobials within 3 hours if concern for infection persists. | Strong   |
|                          | For sepsis or septic shock, evaluate whether source control is needed.                                                                             | Strong   |
|                          | For sepsis or septic shock, remove of intravascular access devices that are a possible source once other vascular access is established.           | Strong   |
|                          | For sepsis or septic shock, assess daily for de-escalation of antimicrobials.                                                                      | Weak     |
|                          | For sepsis or septic shock, use shorter over longer duration of antimicrobial therapy.                                                             | Weak     |
|                          | When optimal duration of antimicrobial therapy is unclear, use procalcitonin and clinical evaluation to decide when to discontinue antimicrobials. | Weak     |

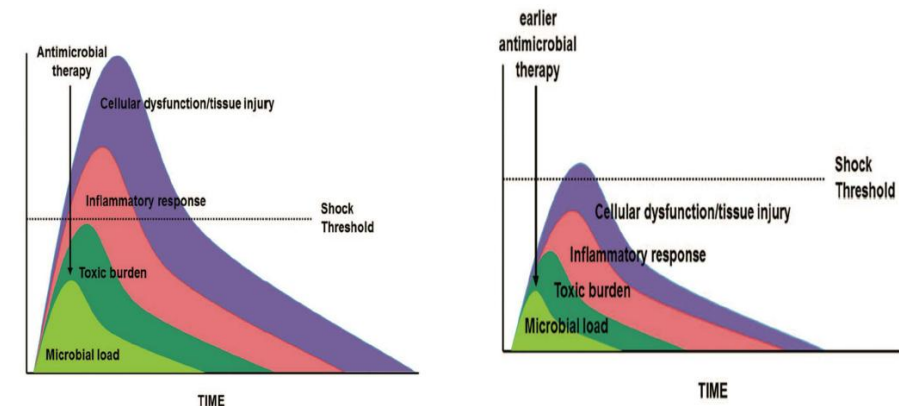


# Antibiothérapie

- Retard d'administration et aggravation du pronostic
  - ↗ mortalité de 7.6% par heure de retard au traitement antibiotique
  - Dans l'heure de la reconnaissance du choc septique faire: prélèvements bactériologiques, hémocultures et antibiothérapie.



## Rationnel du traitement anti-infectieux



A Kumar; Virulence, 2014; 5:1, 80–97.



**Antibiotic Timing**

|                                | Shock is present                                                                                                                                                       | Shock is absent                                                                                                                                                                                                                                                                                                                             |
|--------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Sepsis is definite or probable |  Administer antimicrobials <b>immediately</b> , ideally within 1 hour of recognition. |                                                                                                                                                                                                                                                                                                                                             |
| Sepsis is possible             |  Administer antimicrobials <b>immediately</b> , ideally within 1 hour of recognition. |  Rapid assessment* of infectious vs noninfectious causes of acute illness.<br><br> Administer antimicrobials <b>within 3 hours</b> if concern for infection persists. |

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

- Traitement probabiliste la plupart du temps
- Choix antibiothérapie
  - Site présumé infection
  - Sévérité infection
  - Épidémiologie locale
  - Facteurs de risque de germes atypiques ou résistants
  - Colonisation
  - Historique antibiothérapie préalable

- Initiation dans l'heure
- Antibiothérapie IV
- Association d'antibiotiques
  - bactéricidie et élargir le spectre
  - ➔  $\beta$ -lactamine/aminosides.
    - Si choc septique
    - Non recommandé pour les bactériémies et les sepsis sans choc
    - Non recommandé pour le neutropénique sans choc
  - ➔ PAC grave:  $\beta$ -lactamine/macrolide
- Adapter le traitement aux particularités PK/PD des patients septiques
- Désescalade après documentation
  - En spectre
  - En nombre
  - En durée, si la source est contrôlée
  - Réévaluation quotidienne
- PCT peut être utilisée pour guider l'arrêt



BEST PRACTICE

17 For adults with sepsis or septic shock at high risk of MRSA, we **recommend** using empiric antimicrobials with MRSA coverage over using antimicrobials without MRSA coverage.

## 2016 STATEMENT

"We **recommend** empiric broad-spectrum therapy with one or more antimicrobials for patients presenting with sepsis or septic shock to cover all likely pathogens (including bacterial and potentially fungal or viral coverage)."



LOW

18 For adults with sepsis or septic shock at low risk of MRSA, we **suggest against** using empiric antimicrobials with MRSA coverage, as compared with using antimicrobials without MRSA coverage.

## 2016 STATEMENT

"We **recommend** empiric broad-spectrum therapy with one or more antimicrobials for patients presenting with sepsis or septic shock to cover all likely pathogens (including bacterial and potentially fungal or viral coverage)."



VERY LOW

19 For adults with sepsis or septic shock and high risk for multidrug resistant (MDR) organisms, we **suggest** using two antimicrobials with gram-negative coverage for empiric treatment over one gram-negative agent.



VERY LOW

20 For adults with sepsis or septic shock and low risk for multidrug resistant (MDR) organisms, we **suggest against** using two gram-negative agents for empiric treatment, as compared to one gram-negative agent.



VERY LOW

21 For adults with sepsis or septic shock, we **suggest against** using double gram-negative coverage once the causative pathogen and the susceptibilities are known.



LOW

22 For adults with sepsis or septic shock at high risk of fungal infection, we **suggest** using empiric antifungal therapy over no antifungal therapy.

## 2016 STATEMENT

"We **recommend** empiric broad-spectrum therapy with one or more antimicrobials for patients presenting with sepsis or septic shock to cover all likely pathogens (including bacterial and potentially fungal or viral coverage)."



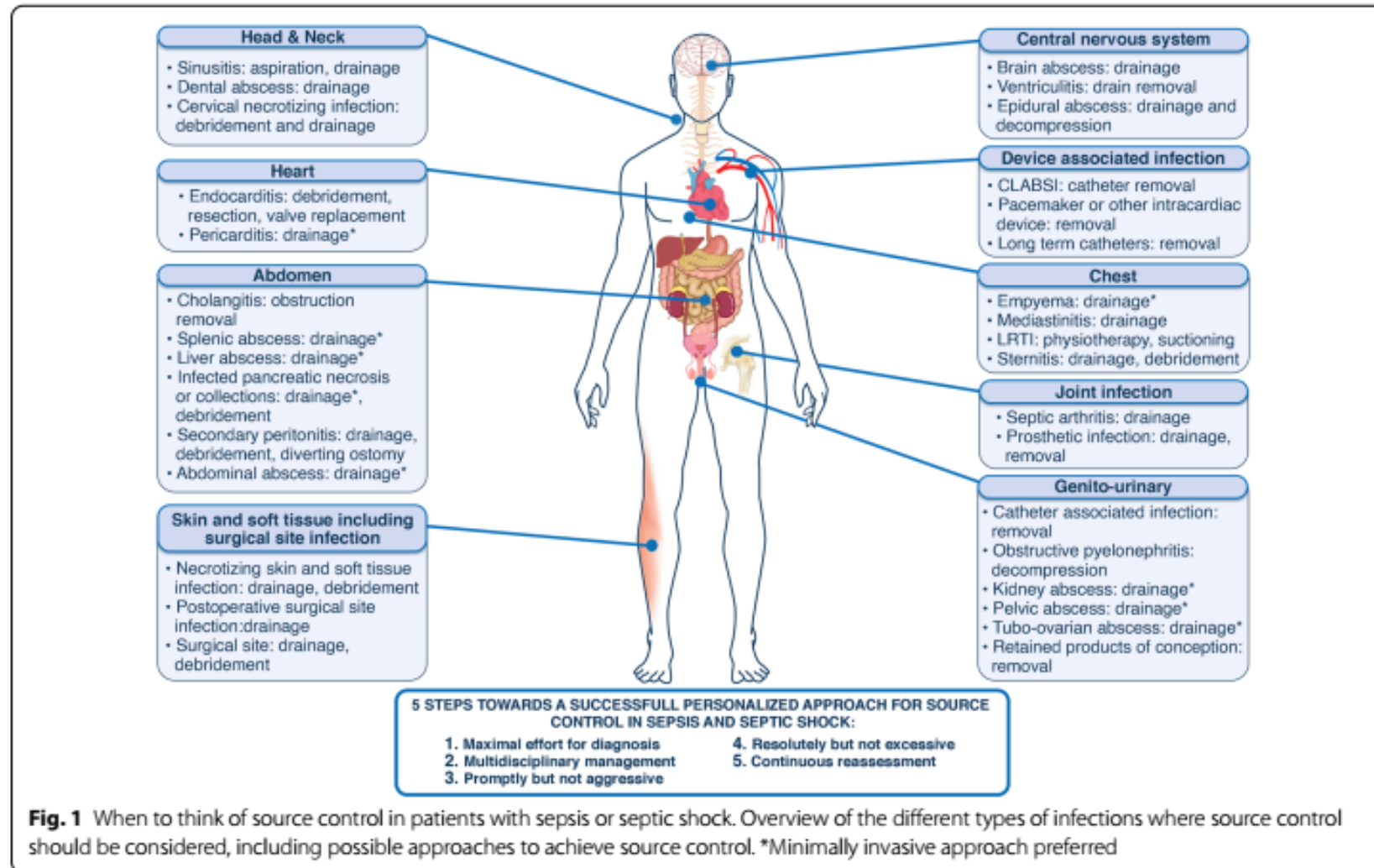
LOW

23 For adults with sepsis or septic shock at low risk of fungal infection, we **suggest against** empiric use of antifungal therapy.

## 2016 STATEMENT

"We **recommend** empiric broad-spectrum therapy with one or more antimicrobials for patients presenting with sepsis or septic shock to cover all likely pathogens (including bacterial and potentially fungal or viral coverage)."

# Contrôle de la source





# 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, Pieter 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
- Pre hospital CRX 2g vs control
- 58% patients with (severe) sepsis
- Only 3% with septic shock
- 91% of « true » infections

|                                                           | Usual care group<br>(n=1137) | Intervention<br>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<br>(n=1137) | Intervention<br>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<br>(n=1137) | Intervention group<br>(n=1535) | Relative risk<br>(95% CI) | Risk difference<br>(%, 95% CI) | p value |
|-------------------------------|------------------------------|--------------------------------|---------------------------|--------------------------------|---------|
| 28 day mortality              | 93 (8%)*                     | 120 (8%)                       | 0.95<br>(0.74 to 1.24)    | -0.37<br>(-2.5 to 1.7)         | 0.78    |
| 90 day mortality              | 134 (12%)*                   | 178 (12%)                      | 0.98<br>(0.80 to 1.21)    | -0.20<br>(-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<br>(0.92 to 1.49)    | 1.5<br>(-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    |

**Table 2.** Landmark Sepsis Clinical Trials since 2015.\*

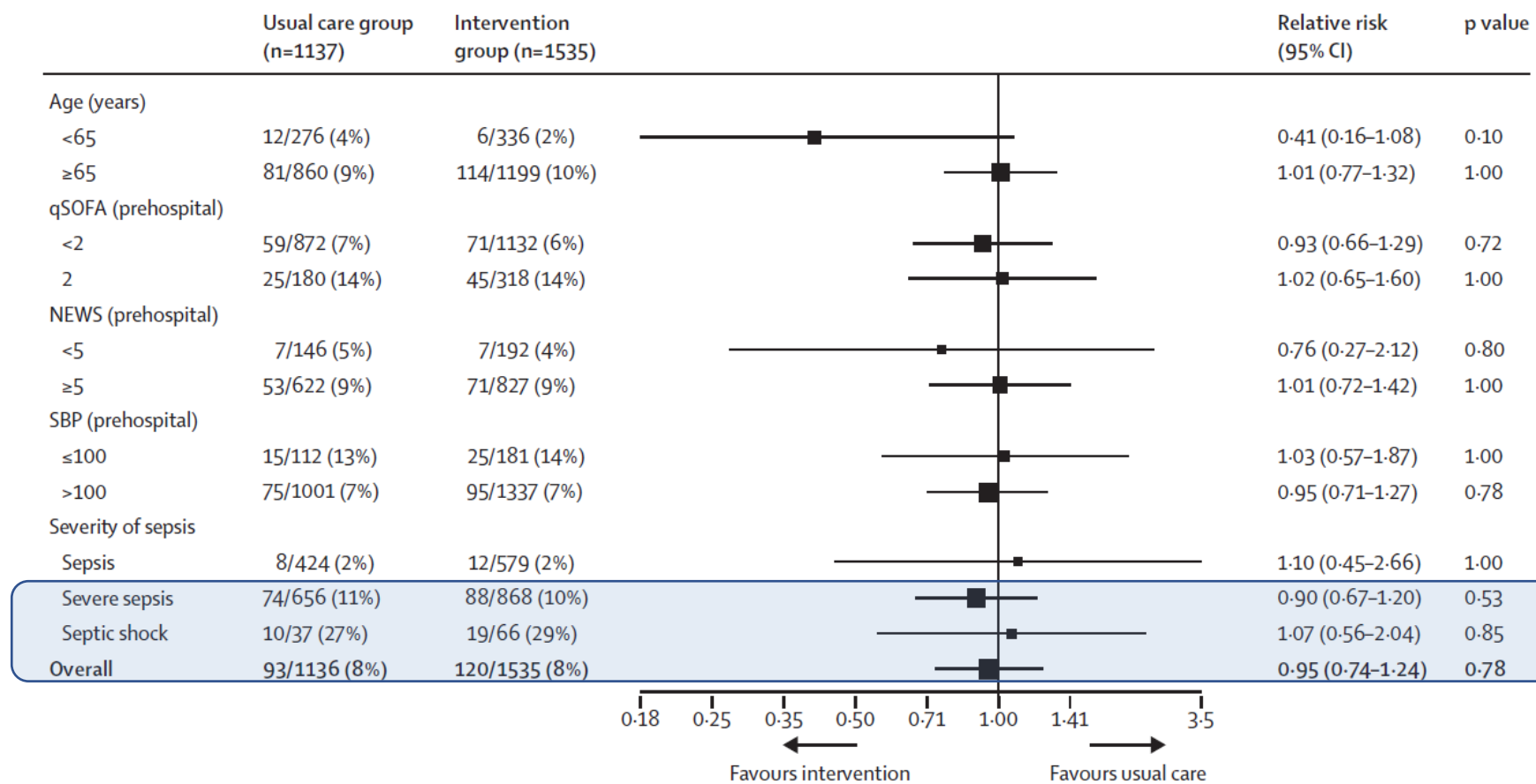
| Trial or Trials        | Patients                                                                           | Intervention and Control                                             | Outcome                         | Interpretation and Lessons Learned                                                                                                                                                                                                                      |
|------------------------|------------------------------------------------------------------------------------|----------------------------------------------------------------------|---------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| PHANTASi <sup>65</sup> | 2689 Patients with sepsis, identified in ambulance, at 34 sites in the Netherlands | Antibiotic administration before arrival at hospital vs. in hospital | 28-Day mortality, 7.8% vs. 8.2% | In-ambulance antibiotic therapy yielded numerically but not significantly lower mortality. However, the difference of 0.4 percentage points is consistent with effect sizes in observational studies adjusted for less severely ill trial participants. |



# 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, Pieter 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\*



# Les pistes pour les antibiothérapies

- 1- Arrêt précoce en l'absence de documentation?
  - La mortalité des patients avec un LBA < 10<sup>4</sup> cfu n'est pas augmentée par un arrêt de l'antibiothérapie précoce  
*Raman - Crit Care Med 2013; 41:1656–1663*
  - 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 associé à moins de DC et moins d'IRA  
*Labelle AJ et al - Chest 2010; 137:1130–7.; Cowley MC - Chest. 2019 Jan;155(1):53-59*
- 2- Identification ultra précoce
  - Oui!! mais avec l'aide d'experts...  
*Banerjee R et al - Clin Infect Dis 2015;61(7):1071-80*
- 3- Optimisation de la PK?
  - Une fT > 6XCMI semble être l'objectif le plus associé au succès clinique pour les betalactamines  
*Wong G et al - J Antimicrob Chemother. 2019 in press*



# Broad-spectrum antibiotic use and poor outcomes in community-onset pneumonia

- **731/2198 Broad spectrum AB (39.7%)**
- **Drug-resistant pathogens 3%!!**
- **Broad spectrum prescription is mainly explained by patients severity**
  - higher eCURB (8.1% vs 5.0%)
  - Lower PaO<sub>2</sub>/FIO<sub>2</sub> ratio (248.2 vs 269.5) and more sCAP criteria (2 versus 1).
  - Intubation (13.3% vs 2.8%)
  - vasopressor use (13% vs 1.7%) were more common in the broad-spectrum group.
- Observed 30-day mortality was 18.3% versus 4.4%.
- 2 analyses:
  - Multivariate regression
  - IPTW adjusted on the probability of Broad-spectrum AB
- **Antibiotic-associated events were found in 17.5% of mortality cases in the broad-spectrum group**

TABLE 2 Unweighted and inverse-probability treatment weighting (IPTW) multivariable regression effects of broad-spectrum antibiotics on 30-day mortality

|                                                       | Primary regression<br>OR (95% CI) | p-value | IPTW-ATT<br>OR (95% CI) | p-value |
|-------------------------------------------------------|-----------------------------------|---------|-------------------------|---------|
| (Intercept)                                           | 0.04 [0–0.38]                     | 0.012   | 0.01 [0–0.27]           | 0.008   |
| Broad-spectrum antibiotics                            | 3.82 [2.48–5.92]                  | <0.001  | 4.61 [2.92–7.46]        | <0.001  |
| Age <sup>#</sup>                                      | 2.16 [1.68–2.82]                  | <0.001  | 2.51 [1.9–3.38]         | <0.001  |
| Female                                                | 1.13 [0.78–1.63]                  | 0.522   | 1.11 [0.74–1.67]        | 0.608   |
| eCURB <sup>#</sup>                                    | 1.15 [0.97–1.36]                  | 0.107   | 1.16 [0.97–1.38]        | 0.103   |
| PaO <sub>2</sub> /FIO <sub>2</sub> ratio <sup>#</sup> | 0.99 [0.79–1.22]                  | 0.902   | 1.02 [0.8–1.28]         | 0.889   |
| sCAP                                                  | 1.7 [1.41–2.05]                   | <0.001  | 1.74 [1.42–2.14]        | <0.001  |
| Intubation                                            | 1.22 [0.62–2.37]                  | 0.559   | 1.4 [0.7–2.75]          | 0.335   |
| Vasopressors                                          | 2.53 [1.29–5.01]                  | 0.007   | 2.55 [1.31–5]           | 0.006   |
| Inadequate antibiotic therapy                         | 5.34 [1.1–23.19]                  | 0.03    | 5.56 [1.11–24.92]       | 0.029   |
| Bacteraemia                                           | 1.53 [0.68–3.27]                  | 0.291   | 1.54 [0.68–3.34]        | 0.282   |
| Length of stay <sup>#</sup>                           | 0.82 [0.66–0.99]                  | 0.045   | 0.7 [0.56–0.86]         | 0.001   |
| Charlson Comorbidity Index                            | 0.99 [0.91–1.09]                  | 0.91    | 0.92 [0.83–1.01]        | 0.088   |
| HCAP                                                  | 1.19 [0.76–1.85]                  | 0.449   | 1.24 [0.8–1.93]         | 0.332   |

TABLE 3 Unweighted and inverse-probability treatment weighting (IPTW) multivariable regression effects of broad-spectrum antibiotics on secondary outcomes

| Outcome                                   | Unweighted regression<br>e <sup>b</sup> [95% CI] <sup>#</sup> | p-value | IPTW-ATT<br>e <sup>b</sup> [95% CI] <sup>#</sup> | p-value |
|-------------------------------------------|---------------------------------------------------------------|---------|--------------------------------------------------|---------|
| Length of stay                            | 1.66 [1.53–1.8]                                               | <0.001  | 1.52 [1.41–1.63]                                 | <0.001  |
| Cost                                      | 1.83 [1.68–2.01]                                              | <0.001  | 1.7 [1.57–1.84]                                  | <0.001  |
| <i>Clostridioides difficile</i> infection | 3.85 [1.55–10.93]                                             | 0.006   | 5.79 [1.86–27.51]                                | 0.008   |

Original Investigation | Infectious Diseases

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

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

- 17 430 adults/104 US hospitals
- Community-onset sepsis and positive clinical cultures within 2 days of admission.
- **Unnecessary: unnecessarily coverage of MRSA, VRE, CTX-R GNB when none of these were isolated)**
- 15 183 cases with ST → **12 398 [81.6%]) received adequate empiric AB**
- Empiric coverage of resistant organisms 11 683/17 430 cases (67.0%)
- **Resistant organisms were uncommon** (MRSA, 2045 [11.7%]; CTX-RO, 2278 [13.1%]; VRE, 360 [2.1%]; ESBLs, 133 [0.8%])

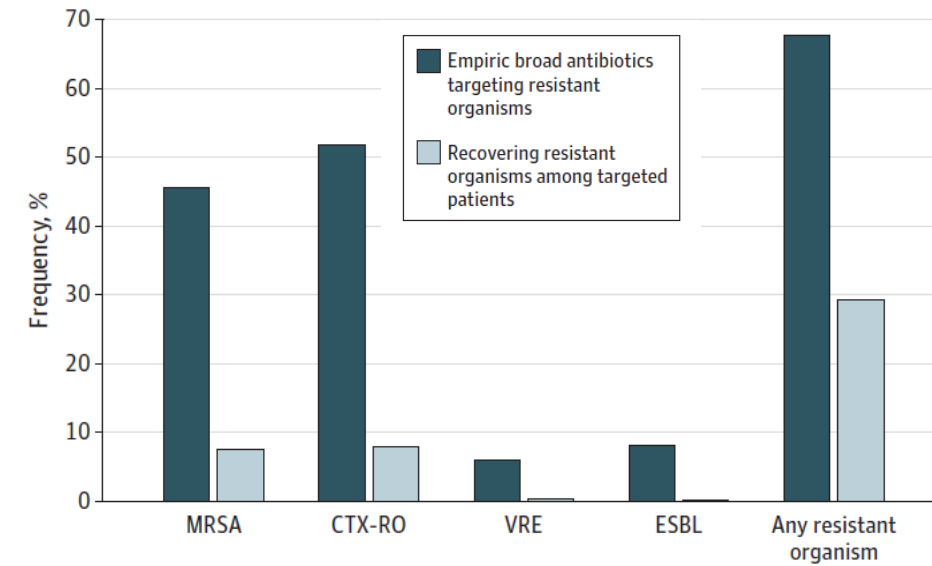


Table 2. Outcomes Associated With Inadequate and Unnecessarily Broad Empiric Antibiotic Therapy<sup>a</sup>

| Outcome                            | Inadequate vs adequate empiric therapy |                          |                        |         |                      |         | Unnecessarily broad vs not unnecessarily broad empiric therapy <sup>b</sup> |                         |                        |         |                      |         |
|------------------------------------|----------------------------------------|--------------------------|------------------------|---------|----------------------|---------|-----------------------------------------------------------------------------|-------------------------|------------------------|---------|----------------------|---------|
|                                    | No./total No. (%)                      |                          | Unadjusted OR (95% CI) | P value | Adjusted OR (95% CI) | P value | No./total No. (%)                                                           |                         | Unadjusted OR (95% CI) | P value | Adjusted OR (95% CI) | P value |
|                                    | Inadequate                             | Adequate empiric therapy |                        |         |                      |         | Unnecessarily broad                                                         | Not unnecessarily broad |                        |         |                      |         |
| In-hospital death                  | 488/2785 (17.5)                        | 2011/12 388 (16.3)       | 1.10 (0.98-1.22)       | .09     | 1.19 (1.03-1.37)     | .02     | 1575/8405 (18.7)                                                            | 436/3993 (10.9)         | 1.88 (1.68-2.11)       | <.001   | 1.22 (1.06-1.40)     | .007    |
| Hospital-onset acute kidney injury | 486/2785 (17.5)                        | 2196/12 398 (17.7)       | 0.98 (0.88-1.09)       | .74     | 1.02 (0.90-1.16)     | .72     | 1641/8405 (19.5)                                                            | 555/3993 (13.9)         | 1.50 (1.35-1.67)       | <.001   | 1.12 (1.00-1.26)     | .05     |
| <i>Clostridioides difficile</i>    | 207/2785 (7.4)                         | 498/12 398 (4.0)         | 1.92 (1.63-2.27)       | <.001   | 1.19 (0.98-1.45)     | .09     | 367/8405 (4.4)                                                              | 131/3993 (3.3)          | 1.34 (1.10-1.65)       | .004    | 1.26 (1.01-1.57)     | .04     |

# Autres

## Red Blood Cell (RBC) Transfusion Targets

### Recommendation

61. For adults with sepsis or septic shock, we **recommend** using a restrictive (over liberal) transfusion strategy.

*Strong recommendation; moderate quality of evidence.*

### Remarks:

A restrictive transfusion strategy typically includes a hemoglobin concentration transfusion trigger of 70 g/L; however, RBC transfusion should not be guided by hemoglobin concentration alone. Assessment of a patient's overall clinical status and consideration of extenuating circumstances such as acute myocardial ischemia, severe hypoxemia or acute hemorrhage is required.

## Vitamin C

### Recommendation

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

*Weak recommendation, low quality of evidence.*

# Corticoïdes et choc septique

## Recommendation

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

*Weak recommendation; moderate quality of evidence.*

### Remarks:

The typical corticosteroid used in adults with septic shock is IV hydrocortisone at a dose of 200 mg/d given as 50 mg intravenously every 6 hours or as a continuous infusion. It is suggested that this is commenced at a dose of norepinephrine or epinephrine  $\geq 0.25$  mcg/kg/min at least 4 hours after initiation.

**Table 2.** Landmark Sepsis Clinical Trials since 2015.\*

| Trial or Trials                                   | Patients                                                                                                                                                                                                             | Intervention and Control                                                                                                                | Outcome                                                                                                      | Interpretation and Lessons Learned                                                                                                                                                                                                                                                                                                                                                                  |
|---------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| ADRENAL and <sup>62</sup> APROCCHSS <sup>63</sup> | ADRENAL: 3800 patients with septic shock at 69 sites in Australia, United Kingdom, New Zealand, Saudi Arabia, and Denmark<br>APROCCHSS: 1241 patients with multiorgan failure and septic shock at 34 sites in France | ADRENAL: hydrocortisone vs. placebo<br>APROCCHSS: hydrocortisone plus fludrocortisone vs. placebo (and activated protein C vs. placebo) | ADRENAL: 90-day mortality, 27.9% vs. 28.8% (P=0.50)<br>APROCCHSS: 90-day mortality, 43.0% vs. 49.1% (P=0.03) | Glucocorticoids were associated with reduced mortality in APROCCHSS but not in ADRENAL, although secondary outcomes in ADRENAL favored glucocorticoids. After these trials, guidelines were updated to include a weak recommendation to use glucocorticoids for persistent septic shock. <sup>53</sup> However, the benefit varies among patients, so treatment decisions should be individualized. |



REVIEW

# Management of adult sepsis in resource-limited settings: global expert consensus statements using a Delphi metho

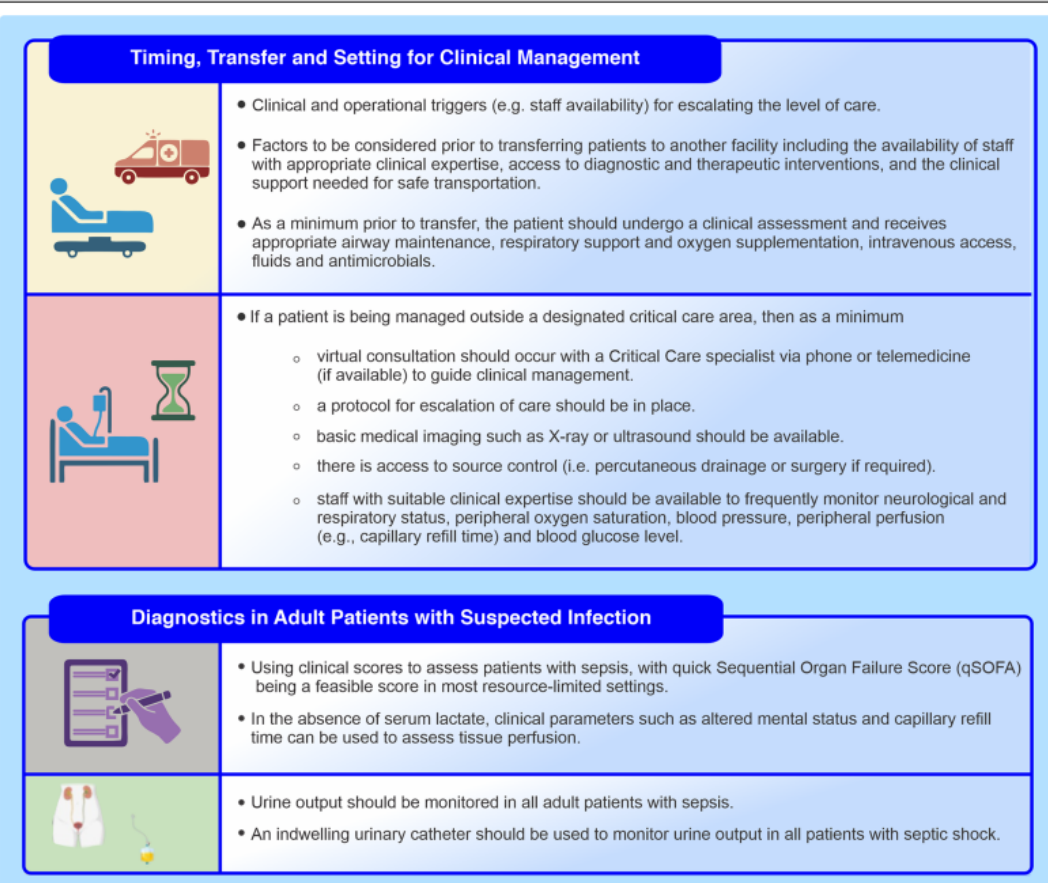


Fig. 2 Clinical practice statements on timing, location and diagnostic interventions for sepsis management in resource-limited settings

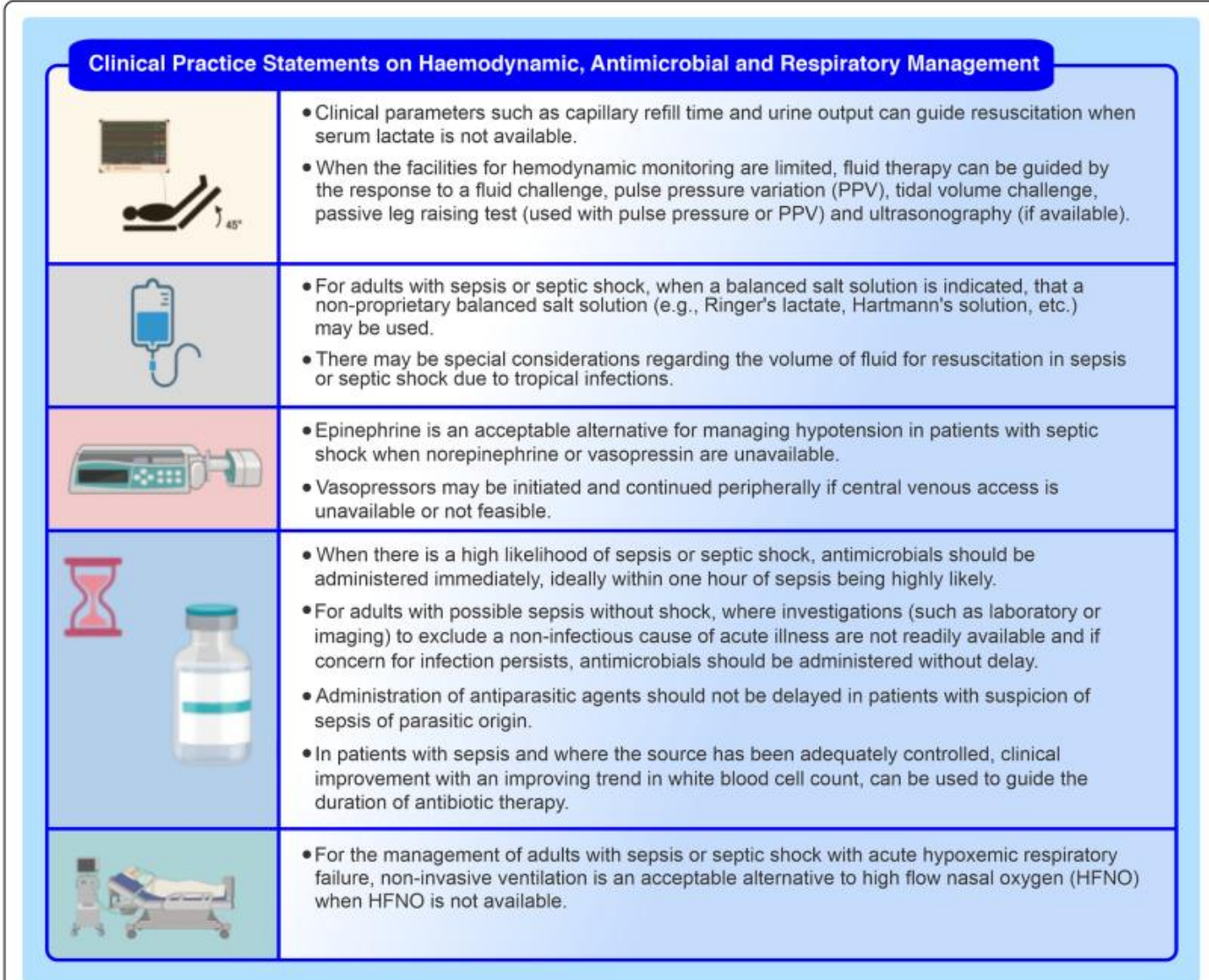


Fig. 3 Clinical practice statements on haemodynamic, antimicrobial and respiratory management for sepsis management in resource-limited settings

# Messages à retenir

- Maladie fréquente, grave, hétérogène
- Pronostic en fonction de la rapidité de prise en charge
- Reconnaissance précoce
- Prise en charge précoce
  - Hémodynamique
    - Remplissage avec cristalloïde balancé
    - Introduction précoce Noradrénaline sur vvp
    - Monitoring en fonction rapidité résolution du choc
    - Introduction vasopressine si noradrénaline  $> 0.5 \mu\text{g/kg/min}$
    - Dobutamine si dysfonction cardiaque
  - Infection
    - Antibiothérapie probabiliste précoce
    - Contrôle de la source
  - Pour inflammation:
    - Corticoïdes



# Merci pour votre attention

