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MI² Medical Infectious diseases Intensive care unit

Surviving sepsis campaign 2021: nouveautés

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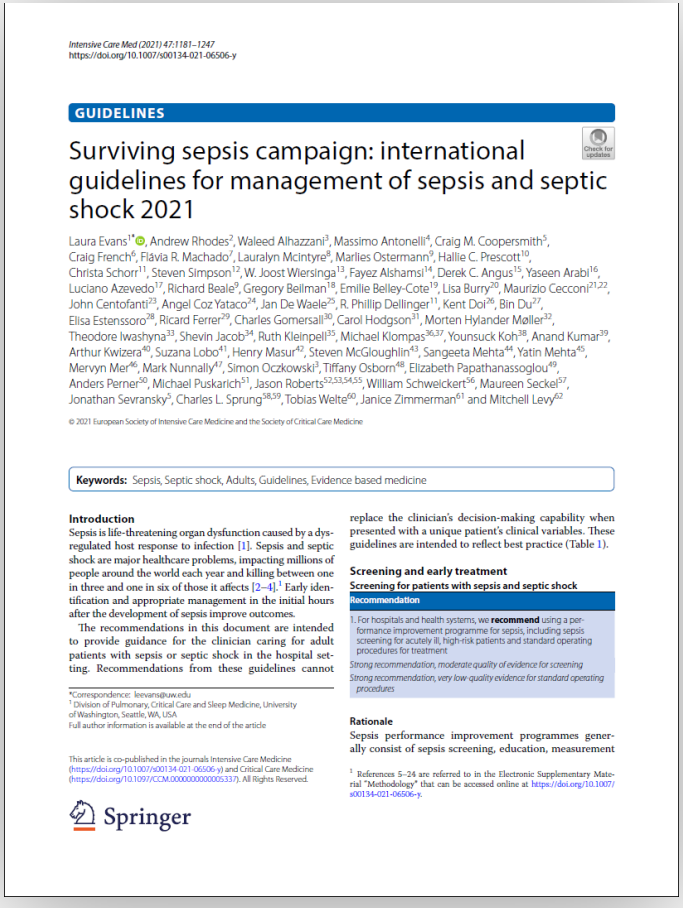

Intensive Care Med (2021) 47:1181–1247
https://doi.org/10.1007/s00134-021-06506-y

GUIDELINES

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

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Keywords: Sepsis, Septic shock, Adults, Guidelines, Evidence based medicine

Introduction

Sepsis is life-threatening organ dysfunction caused by a dysregulated host response to infection [1]. Sepsis and septic shock are major healthcare problems, impacting millions of people around the world each year and killing between one in three and one in six of those it affects [2–4].[1] Early identification and appropriate management in the initial hours after the development of sepsis improve outcomes.

The recommendations in this document are intended to provide guidance for the clinician caring for adult patients with sepsis or septic shock in the hospital setting. Recommendations from these guidelines cannot replace the clinician's decision-making capability when presented with a unique patient's clinical variables. These guidelines are intended to reflect best practice (Table 1).

Screening and early treatment

Screening for patients with sepsis and septic shock

Recommendation
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
Strong recommendation, moderate quality of evidence for screening
Strong recommendation, very low-quality evidence for standard operating procedures

Rationale

Sepsis performance improvement programmes generally consist of sepsis screening, education, measurement

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This article is co-published in the journals Intensive Care Medicine (https://doi.org/10.1007/s00134-021-06506-y) and Critical Care Medicine (https://doi.org/10.1097/CCM.0000000000005337).

[1] References 5–24 are referred to in the Electronic Supplementary Material "Methodology" that can be accessed online at https://doi.org/10.1007/s00134-021-06506-y.

Springer

- Declaration 2002 Barcelone
- Guidelines 2004, 2016, 2021
- Reprise de l'existant
- Elaboration des questions
- Identification des modifications
- Impact sur la connaissance du syndrome, l'identification des patients, la procédure de soins, le pronostic…

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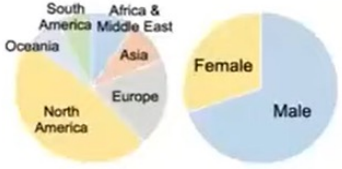
Surviving Sepsis Campaign



SSC Guideline Panel Leadership

Co-Chair: L. Evans
Co-Vice-Chair: H. Prescott

Co-Chair: A. Rhodes
Co-Vice-Chair: M. Ostermann

Society of Critical Care Medicine

Lead Methodologist: W. Alhazzani

ESICM

C. Coopersmith — **Conflict of Interest Management** — M. Atonelli

Public Panel
Group Heads:
M. Osterman
H. Prescott
11 Public Members

Screening & Initial Resuscitation
Group Head: S. Simpson
Methodologist: F. Alshamsi
M. Antonelli
P. Dellinger
Y. Koh
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T. Osborn
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A. Kumar
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Methodologist: E. Bellly-Cote
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L. Azevedo
R. Beale
G. Beilman
A. Coz
E. Estenssoro
S. Jacob
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Methodologist: J. Centrofanti
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S. Mehta
M. Seckel
W. Schweikert
T. Welte

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M. Cecconi
K. Doi
C. Gommersall
R. Kleinpell
Y. Mehta
A. Perer
R. Roca
C. Sprung

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Group Head: C. Shorr
Methodologist: S. Oczkowski
D. Angus
B. Du
S. Lobo
T. Iwashyna
E. Papathannassaglou
H.Prescott
J. Zimmermann

Endorsing Societies (24)
American Association of Critical Care Nurses
American College of Chest Physicians
American College of Emergency Physicians
American Thoracic Society
African Sepsis Alliance
Asia and Pacific Sepsis Alliance
Association De Medicina Intensiva Brasileira
Australian and New Zealand Intensive Care Society
Canadian Critical Care Society
Chinese Society of Critical Care Medicine
Chest
European Respiratory Society
European Society of Clinical Microbiology and Infectious Diseases
European Society of Intensive Care Medicine
Indian Society of Critical Care Medicine
Infectious Diseases Society of North America
Japanese Society of Intensive Care Medicine
Latin American Sepsis Institute
Society for Academic Emergency Medicine
Society of Critical Care Medicine
Scandinavian Critical Care Trials Group
Surgical Infection Society
World Federation of Critical Care Nurses
World Federation of Societies of Intensive and Critical Care Medicine

Surviving Sepsis Campaign

Types of Statements

Strong Ungraded (Best Practice Statement) "we recommend" 
Strong Graded "we recommend " 
Weak Graded "we suggest" 
No Recommendation (insufficient evidence) 

Strong (best practice statement or strong graded): All or almost all informed persons would choose the intervention (95%).
→ Should have widespread adoption, good for performance assessment

Weak: Most informed persons would choose the intervention (66%), but there are still important variation among informed persons.
→ Requires consideration and shared decision-making
→ Not optimal as a performance assessment

Recommendations are more likely to be weak when:

- Certainty of evidence is low
- There is close balance between desirable and undesirable effects
- There is substantial variation or uncertainty in patient values and preferences
- Interventions require considerable resources

DÉPISTAGE DU SEPSIS

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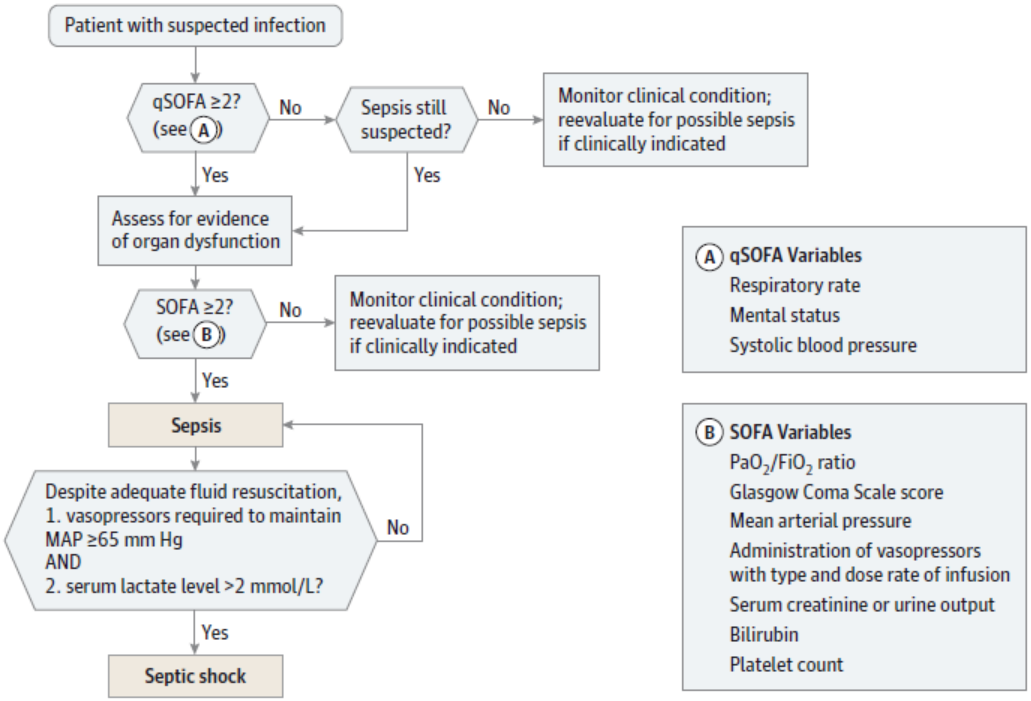
Définition: Sepsis 3.0 en 2016



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

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

Choc septique → sepsis + dysfonction métabolique + défaillance hémodynamique

Singer et al. – JAMA, 2016

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

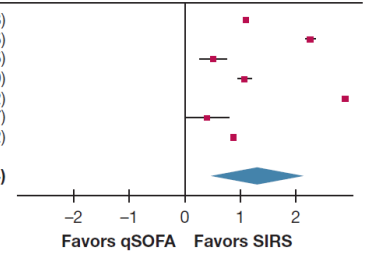
CHEST 2018; 153(3):646-655

- **SIRS predicts sepsis**
- **qSOFA predicts prognosis**

SEPSIS

Study or Subgroup	SIRS Mean	SIRS SD	SIRS Total	qSOFA Mean	qSOFA SD	qSOFA Total	Weight	Std. Mean Difference IV, Random, 95% CI
Churpek, 2017	0.88	0.45	30,677	0.38	0.45	30,677	14.4%	1.11 (1.09 to 1.13)
Donnelly, 2017	0.54	0.02	2,593	0.12	0.26	2,593	14.3%	2.28 (2.21 to 2.35)
Dorsett, 2017	0.39	0.5	152	0.16	0.38	152	14.2%	0.52 (0.29 to 0.75)
Freund, 2017	0.74	0.45	879	0.25	0.45	879	14.3%	1.09 (0.99 to 1.19)
Raith, 2017	0.86	0.11	184,875	0.54	0.11	184,875	14.4%	2.91 (2.90 to 2.92)
Siddiqui, 2017	0.62	0.47	58	0.42	0.51	58	14.0%	0.41 (0.04 to 0.77)
Williams, 2017	0.47	0.48	8,871	0.1	0.34	8,871	14.4%	0.89 (0.86 to 0.92)
Total (95% CI)			**228,105**			**228,105**	**100.0%**	**1.32 (0.40 to 2.24)**

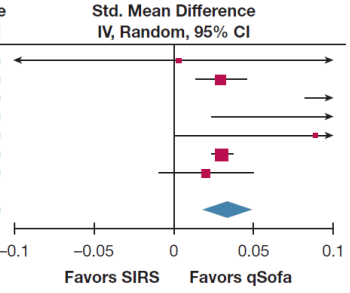
Heterogeneity: $Tau^2 = 1.53$; $Chi^2 = 43948.08$, df = 6 ($P < .00001$); $I^2 = 100\%$
Test for overall effect: Z = 2.81 ($P = .005$)



MORTALITY

Study or Subgroup	qSOFA Mean	qSOFA SD	qSOFA Total	SIRS Mean	SIRS SD	SIRS Total	Weight	Std. Mean Difference IV, Random, 95% CI
April, 2017	0.66	2.61	214	0.65	2.61	214	0.7%	0.00 (−0.19 to 0.19)
Churpek, 2017	0.69	1.34	30,677	0.65	1.34	30,677	31.9%	0.03 (0.01 to 0.05)
Finkelsztein, 2017	0.74	0.47	152	0.59	0.5	152	0.5%	0.31 (0.08 to 0.53)
Freund, 2017	0.8	1.59	879	0.65	0.83	879	2.8%	0.12 (0.02 to 0.21)
Park, 2017	0.733	1.54	1,009	0.599	1.46	1,009	3.2%	0.09 (0.00 to 0.18)
Raith, 2017	0.607	0.88	184,875	0.58	0.88	184,875	42.6%	0.03 (0.02 to 0.04)
Williams, 2017	0.73	0.48	8,871	0.72	0.48	8,871	18.3%	0.02 (−0.01 to 0.05)
Total (95% CI)			**226,677**			**226,677**	**100.0%**	**0.03 (0.02 to 0.05)**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 11.39$, df = 6 ($P = .08$); $I^2 = 47\%$
Test for overall effect: Z = 4.12 ($P < .0001$)



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

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

CHEST 2019; 156(2):289-297

qSOFA only a prognostic score

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

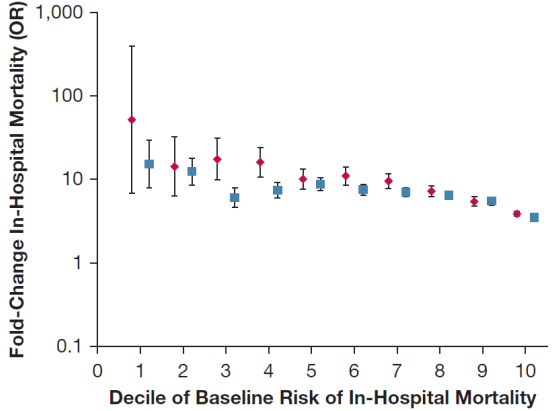
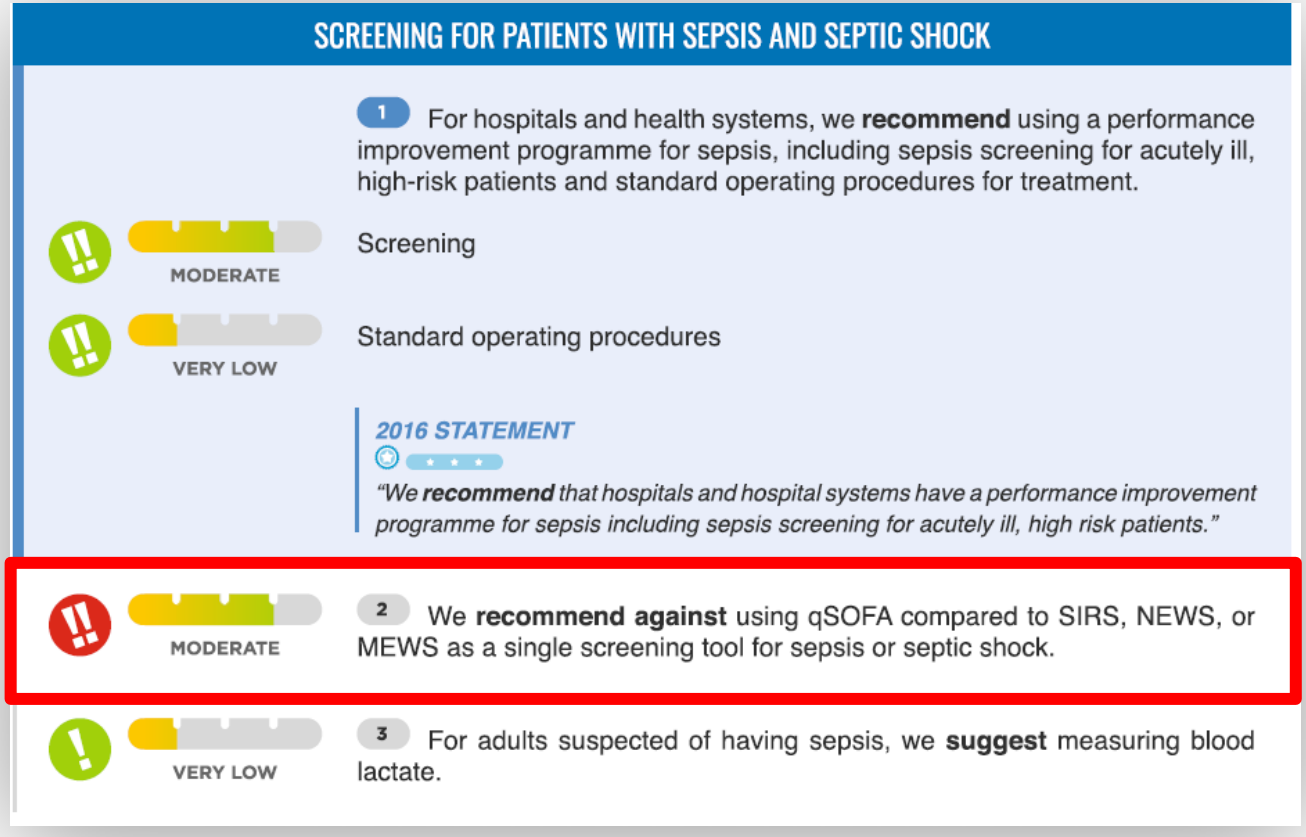


Figure 2 – *Fold change in rate of in-hospital mortality by deciles of baseline risk of death for ≥ 2 qSOFA criteria vs < 2 qSOFA criteria in patients with and without suspected infection on admission. The x axis*


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.

RÉANIMATION INITIALE

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Quels objectifs de perfusion ?

Evans L et al. 2021 ICM
SSC Guideline 2021

!! 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.

! 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.

NEW !

! LOW

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

Objectif de PAM ≥ 65 mmHg …

Lhypotension profonde et prolongée augmente la mortalité

Seuil variable ds la literature 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
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).

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.

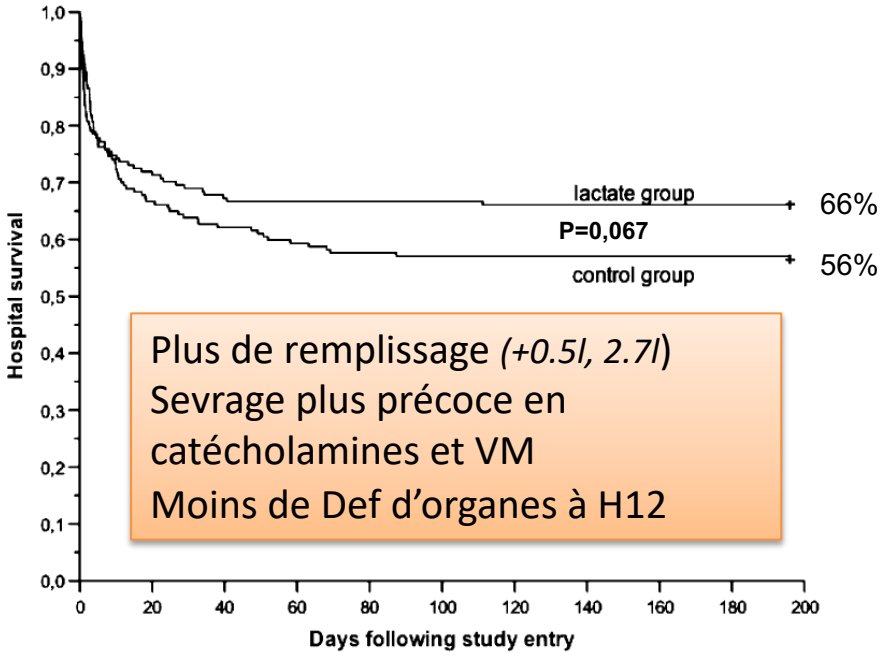
Early Lactate-Guided Therapy in Intensive Care Unit Patients

RCT multicentrique Hollande
348 patients Réanimation
2006 - 2008

Inclusion
ICU
Lactate≥3mmol/L

Intervention « open label »

Objectif ↓ ≥20% lactate /2h
Vs
Réanimation sans lactate
(excepté celui d'entrée)
Pendant 8 heures



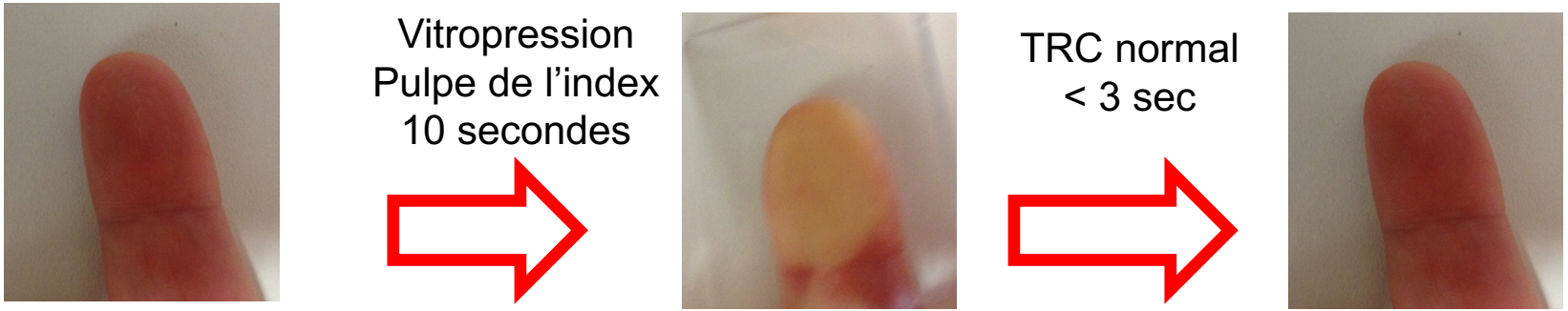
Plus de remplissage *(+0.5l, 2.7l)*
Sevrage plus précoce en catécholamines et VM
Moins de Def d'organes à H12

Après ajustement / facteurs de risque prédéfinis de mortalité

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

Jansen et al. Am J Respir Crit Care Med. 2010 Sep 15;182(6):752-61

Temps de recoloration cutanée



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; M... Manuel Jibaja, MD; Ronald Pairumani, MD; Paula Fern... Vladimir Granda-Luna, MD, PhD; Alexandre Biasi Caval... ANDROMEDA-SHOCK Investigators and the Latin Ame...

- Lactate level/2h

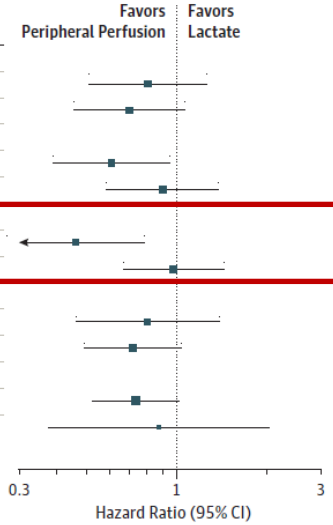
vs

- CRT/30 mn for 8 hours

Peripheral Lactate

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

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



JAMA. 2019;321(7):654

Research

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

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The ANDROMEDA-SHOCK Randomized Clinical Trial

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Lactate level/2h

vs

CRT/30 mn for 8 hours

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

JAMA. 2019;321(7):654

Surviving Sepsis Campaign

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

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."*

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.

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.

Society of Critical Care Medicine
The Intensive Care Professionals

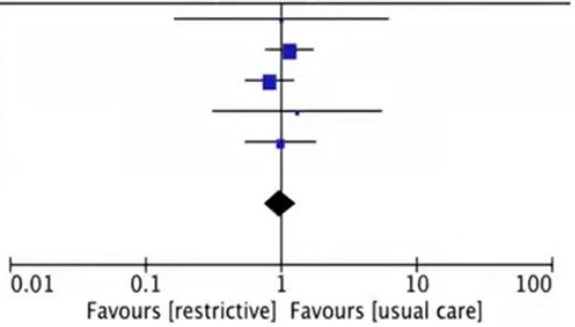
ESICM
The Intensive Connection

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.

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

Study or Subgroup	Restrictive Events	Restrictive Total	Usual care Events	Usual care Total	Weight	Risk Ratio M-H, Random, 95% CI
BALANCE	2	15	2	15	2.0%	1.00 [0.16, 6.20]
Chen 2015	23	41	20	41	38.9%	1.15 [0.76, 1.74]
CLASSIC	25	75	31	76	38.0%	0.82 [0.54, 1.24]
REFRESH	4	50	3	49	3.2%	1.31 [0.31, 5.54]
RIFTS	15	55	15	54	18.0%	0.98 [0.53, 1.81]
Total (95% CI)		**236**		**235**	**100.0%**	**0.98 [0.76, 1.27]**
Total events	69		71			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.45$, df = 4 (P = 0.83); $I^2 = 0\%$
Test for overall effect: Z = 0.13 (P = 0.90)



More data soon:
CLOVERS Trial
CLASSIC Trial

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.

JAMA Network Open 2018

Invited Commentary | Emergency Medicine

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

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

- Bayesian analysis of 37 EGDT studies (20 000 patients) suggested that the m… in the EGDT solely explained by earlier administration of appropriate antibiotics … fluids or any of the protocol's hemodynamic targets. Kalil et … *7-614*
- Time to IV 30 ml/kg bolus fluids is not related to m… r sepsis … *23):2235-2244*
- In a large US database of 35,135 pa… improves prognosis but, in patients receiving hi… ortality increases by 2.3% (95% CI 2.0, 2.5%; *p = 0.0002*) … *et al* - Intensive Care Med 2017; 43:625–632
- A multicen… the 3-hour antibiotic measure was associated with hi… ent bundle on any other component (including the 30-mL/kg fl… Rhee C et al - *Crit Care Med. 2018;46(10):1585-1591*
- Positive f… ight 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

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.

ANTIBIOTHERAPIE RÈGLES DE BASE ET RÈGLES D'ARRÊT

lame UMR 1137
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université PARIS DIDEROT PARIS 7

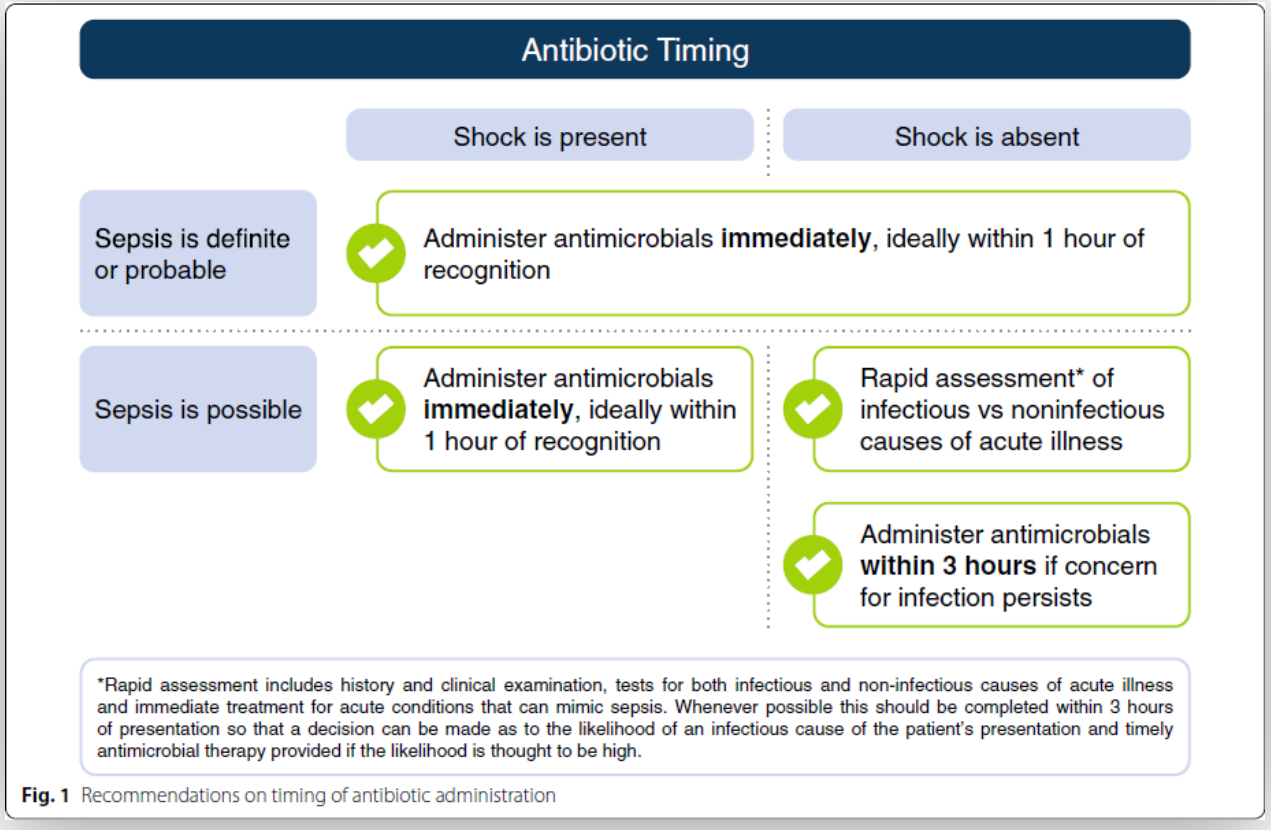
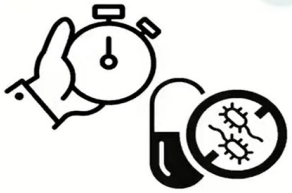


Fig. 1 Recommendations on timing of antibiotic administration



Time to antibiotics matters, particularly for sicker patients.

Diagnostic uncertainty is common in practice.

Treatment as soon as possible if shock with continuous reevaluation and watching of alternate diagnosis

Sepsis without shock: time-limited course of rapid investigation and ATB within 3 hours

If low likelihood of infection, suggestion for deferring antimicrobials

INFECTION

BEST PRACTICE

11 For adults with suspected sepsis or septic shock but unconfirmed infection, we **recommend** continuously re-evaluating and searching for alternative diagnoses and discontinuing empiric antimicrobials if an alternative cause of illness is demonstrated or strongly suspected.

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

LOW — Septic shock

VERY LOW — Sepsis without shock

2016 STATEMENT

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

BEST PRACTICE

13 For adults with possible sepsis without shock, we **recommend** rapid assessment of the likelihood of infectious versus non-infectious causes of acute illness.

VERY LOW

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

2016 STATEMENT

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

VERY LOW

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

2016 STATEMENT

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

VERY LOW

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.

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

Lancet Respir Med 2018; 6: 40–50

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

- RCT/regional ambulance service
- Pre hospital CRX 2g vs control
- 58% patients with (severe) sepsis
- Only 3% with septic shock
- 91% of « true » infections

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

(Table 1 continues in next column)

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

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

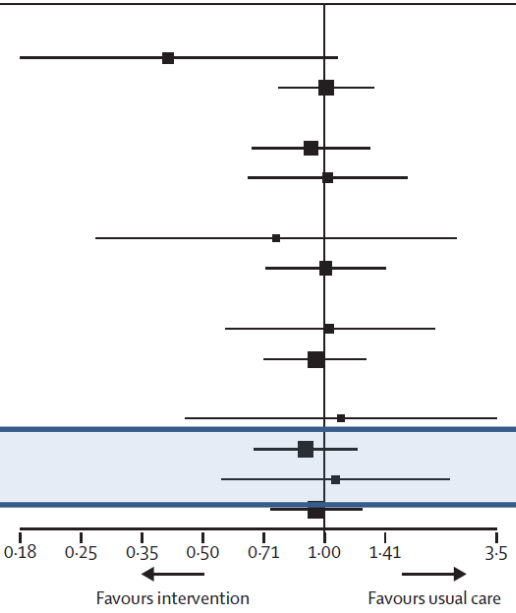
Alam – Lancet Resp Med 2018; 6: 40-50

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

Lancet Respir Med 2018; 6: 40–50

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

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



Les pistes pour les antibiothérapies

- 1- arrêt précoce en l'absence de documentation?
  - La mortalité des patients avec un LBA<10^4 cfu n'est pas augmentée par un arrêt de l'antibiothérapie précoce *Raman - Crit Care Med 2013; 41:1656–1663*
  - 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 clinque 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 expalined by patients severity**
  - higher eCURB (8.1% vs 5.0%)
  - Lower PaO2/FIO2 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 OR (95% CI)	p-value	IPTW-ATT 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#	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#	1.15 (0.97–1.36)	0.107	1.16 (0.97–1.38)	0.103
Pa_{O_2}/Fi_{O_2} ratio#	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#	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 e^{β} (95% CI)#	p-value	IPTW-ATT e^{β} (95% CI)#	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
Clostridioides difficile infection	3.85 (1.55–10.93)	0.006	5.79 (1.86–27.51)	0.008

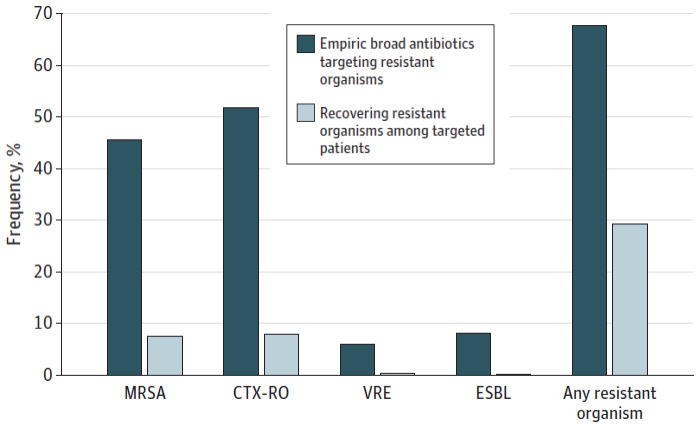
Webb BJ et al. Eur Respir J 2019; 54: 1900057

JAMA Network Open

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: unne**cessarily coverage of MRSA, VRE, CTX-R GNB when none of thes 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[a]

	Inadequate vs adequate empiric therapy						Unnecessarily broad vs not unnecessarily broad empiric therapy[b]					
	No./total No. (%)						No./total No. (%)					
Outcome	Inadequate	Adequate empiric therapy	Unadjusted OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value	Unnecessarily broad	Not unnecessarily broad	Unadjusted OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
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
Clostridioides difficile	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

JAMA Network Open. 2020;3(4):e202899

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."*

HEMODYNAMIQUE

MI²
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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)

Brown JS. Improving pulmonary immunity to bacterial pathogens through *Streptococcus pneumoniae* colonization of the nasopharynx. *Am J Respir Crit Care Med*. 2020 Feb 1;201(3):268-270.
Zampieri FG, Machado FR, Biondi RS, et al; BaSICS investigators and BRICNet members. Effect of slower vs faster intravenous fluid bolus rates on mortality in critically ill patients: the BaSICS randomized clinical trial. *JAMA*. 2021 Sep 7;326(9):830-838.

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."*

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.

ORIGINAL RESEARCH

Safety of peripheral administration of vasopressor medications: A systematic review

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

Emergency Medicine Australasia

Emergency Medicine Australasia (2020) **32**, 220–227

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[10]	506	8–16 mg in 250 mL N/S	32–64 μg/mL	49 ± 22	16 (2.3%)
Lewis[18]	146	4 mg in 250 mL N/S	16 μg/mL	11.2 ± 15‡	4 (2.7%)
Medlej[11]	50	8 mg in 250 mL D5W	32 μg/mL	16.9 ± 18.9‡	2 (4.0%)

EMA Emergency Medicine Australasia

Emergency Medicine Australasia (2020) 32, 210–219 doi: 10.1111/1742-6723.13394

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

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- Analyse post hoc de ARISE 937 patients
- 389 (42%) Vasopresseurs d'abord en periphérie 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

Inotropes/vasopresseurs

37 For adults with septic shock, we **recommend** using norepinephrine as the first-line agent over other vasopressors.

MODERATE

38 For adults with septic shock on norepinephrine with inadequate mean arterial pressure levels, we **suggest** adding vasopressin instead of escalating the dose of norepinephrine.

TRAITEMENTS ADJUVANTS

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ADDITIONAL THERAPIES

MODERATE

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

2016 STATEMENT

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

PRONOSTIC À LONG-TERME/ SEQUELLES

JAMA | Review

Enhancing Recovery From Sepsis
A Review

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

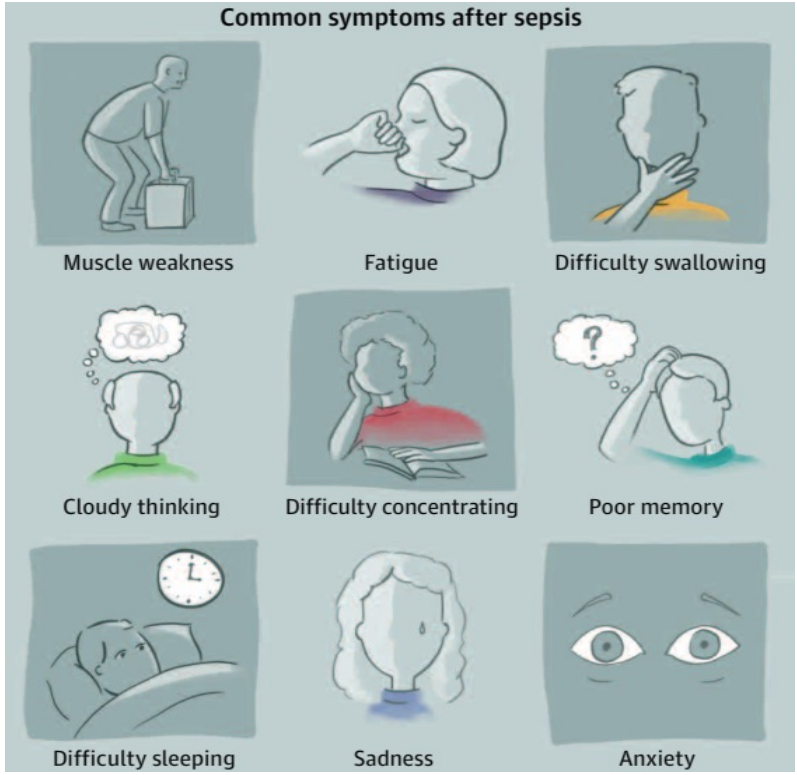
- Revue « systématique »: épidémiologie, physiopathologie, séquelles post sepsis

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

Séquelles post sepsis

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

Séquelles post sepsis



Séquelles post sepsis

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

Séquelles post sepsis

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

Nouveau: fortes recommandations/ faible niveau de preuves

- Discuter les objectifs des soins avec les patients et les familles
- Intégrer les soins palliatifs au projet thérapeutique au cas par cas
- Consultation de suivi: Evaluation physique cognitive et émotionnel après la sortie (avec ou sans programme spécifique de réhabilitation)
- Education des patients sur le sepsis
- Support socio-économique
- Directives anticipées pour les survivants incluant les patients, les familles

Vincent et al. Critical Care (2021) 25:397
https://doi.org/10.1186/s13054-021-03813-0

Critical Care

EDITORIAL Open Access

Equilibrating SSC guidelines with individualized care

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Recommandations

En moyenne: le traitement est le bon

Comment l'appliquer à mon malade?

INDIVIDUALISATION DU TRAITEMENT….

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