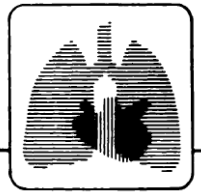
Choc septique

Cas particulier du choc septique

Etat hémodynamique
hyperdynamique



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:

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(Chest 1992; 101:1644-55)

Sepsis et sepsis sévère définition de 1992

- **SIRS** (syndrome de réponse inflammatoire systémique) : si deux ou plus des conditions suivantes sont remplies (1992)
  - température < 36°C ou > 38°C
  - fréquence cardiaque > 90/min
  - fréquence respiratoire > 20/min ou PaCO2 < 32 mm Hg
  - leucocytose > 12.000/mm3, < 4.000/mm3 ou présence de formes immatures circulantes (> 10 % des cellules)
- **Sepsis** : si le SIRS est dû à une infection: voir tableau 2003
- **Sepsis sévère** : si le sepsis est associé à une dysfonction organique, de l'hypoperfusion (acidose lactique, oligurie, troubles de conscience,...) ou de l'hypotension artérielle (TAs < 90 mmHg ou chute de > 40 mmHg de la valeur de base sans autre raison connue)
- **Choc septique** : sepsis avec hypotension, malgré un remplissage adéquat, avec des signes d'hypoperfusion
  - l'hypotension peut manquer si des agents vasopresseurs sont administrés

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

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

Table 1 Diagnostic criteria for sepsis

Infection[a]
Documented or suspected *and* some of the following[b]:
General parameters
Fever (core temperature >38.3°C)
Hypothermia (core temperature <36°C
Heart rate >90 bpm or >2 SD above the normal value for age
Tachypnea: >30 bpm
Altered mental status
Significant edema or positive fluid balance (>20 ml/kg over 24 h)
Hyperglycemia (plasma glucose >110 mg/dl or 7.7 mM/l) in the absence of diabetes
Inflammatory parameters
Leukocytosis (white blood cell count >12,000/µl)
Leukopenia (white blood cell count <4,000/µl)
Normal white blood cell count with >10% immature forms
Plasma C reactive protein >2 SD above the normal value
Plasma procalcitonin >2 SD above the normal value
Hemodynamic parameters
Arterial hypotension[b] (systolic blood pressure <90 mmHg, mean arterial pressure <70, or a systolic blood pressure decrease >40 mmHg in adults or <2 SD below normal for age)
Mixed venous oxygen saturation >70%[b]
Cardiac index >3.5 l min^{-1} m^{-2}[c,d]
Organ dysfunction parameters
Arterial hypoxemia (PaO_2/FIO2 <300)
Acute oliguria (urine output <0.5 ml kg^{-1} h^{-1} or 45 mM/l for at least 2 h)
Creatinine increase ≥0.5 mg/dl
Coagulation abnormalities (international normalized ratio >1.5 or activated partial thromboplastin time >60 s)
Ileus (absent bowel sounds)
Thrombocytopenia (platelet count <100,000/µl)
Hyperbilirubinemia (plasma total bilirubin >4 mg/dl or 70 mmol/l)
Tissue perfusion parameters
Hyperlactatemia (>3 mmol/l)
Decreased capillary refill or mottling

[a] Defined as a pathological process induced by a micro-organism

[b] Values above 70% are normal in children (normally 75–80%) and should therefore not be used as a sign of sepsis in newborns or children

[c] Values of 3.5–5.5 are normal in children and should therefore not be used as a sign of sepsis in newborns or children

[d] Diagnostic criteria for sepsis in the pediatric population is signs and symptoms of inflammation plus infection with hyper- or hypothermia (rectal temperature >38.5°C or <35°C), tachycardia (may be absent in hypothermic patients) and at least one of the following indications of altered organ function: altered mental status, hypoxemia, elevated serum lactate level, and bounding pulses

Table 2 Severe sepsis

Severe sepsis definition = sepsis-induced tissue hypoperfusion or organ dysfunction (any of the following thought to be due to the infection)
Sepsis-induced hypotension
Lactate above upper limits laboratory normal
Urine output <0.5 mL kg^{-1} h^{-1} for more than 2 h despite adequate fluid resuscitation
Acute lung injury with Pao_2/Fio_2 <250 in the absence of pneumonia as infection source
Acute lung injury with Pao_2/Fio_2 <200 in the presence of pneumonia as infection source
Creatinine >2.0 mg/dL (176.8 μmol/L)
Bilirubin >2 mg/dL (34.2 μmol/L)
Platelet count <100,000 μL
Coagulopathy (international normalized ratio >1.5)

Intensive Care Med (2013) 39:165–228
DOI 10.1007/s00134-012-2769-8

GUIDELINES

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Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock, 2012

Définition

Le sepsis sévère correspond à une insuffisance circulatoire reflétée par :

- une hypotension artérielle (PAS < 90 mm Hg – ou chute > 40 mm Hg ou PAM < 65 mm Hg)
- des signes d'altération de la perfusion tissulaire: oligurie, troubles de coagulation, troubles de l'état mental, troubles de la vascularisation cutanée
- une augmentation de la lactatémie (> 2 mEq/L)

... dans le contexte d'une source infectieuse et d'un agent infectieux identifiés

Evolution des concepts

- Le sepsis n'est plus considéré comme seulement une réaction inflammatoire systémique. Il y a également une réponse anti-inflammatoire et une réponse immunitaire à l'agression.
- Il est plutôt la conséquence d'une réaction « inadaptée » avec dysfonction d'un ou de plusieurs organes

Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Developing a New Definition and Assessing New Clinical Criteria for Septic Shock

For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

Manu Shankar-Hari, MD, MSc; Gary S. Phillips, MAS; Mitchell L. Levy, MD; Christopher W. Seymour, MD, MSc; Vincent X. Liu, MD, MSc; Clifford S. Deutschman, MD; Derek C. Angus, MD, MPh; Gordon D. Rubenfeld, MD, MSc; Mervyn Singer, MD, FRCP; for the Sepsis Definitions Task Force

JAMA. 2016;315(8):775-787. doi:10.1001/jama.2016.0289

PROCESS A task force (n = 19) with expertise in sepsis pathobiology, clinical trials, and epidemiology was convened by the Society of Critical Care Medicine and the European Society of Intensive Care Medicine. Definitions and clinical criteria were generated through meetings, Delphi processes, analysis of electronic health record databases, and voting, followed by circulation to international professional societies, requesting peer review and endorsement (by 31 societies listed in the Acknowledgment).

Définitions

Box 3. New Terms and Definitions

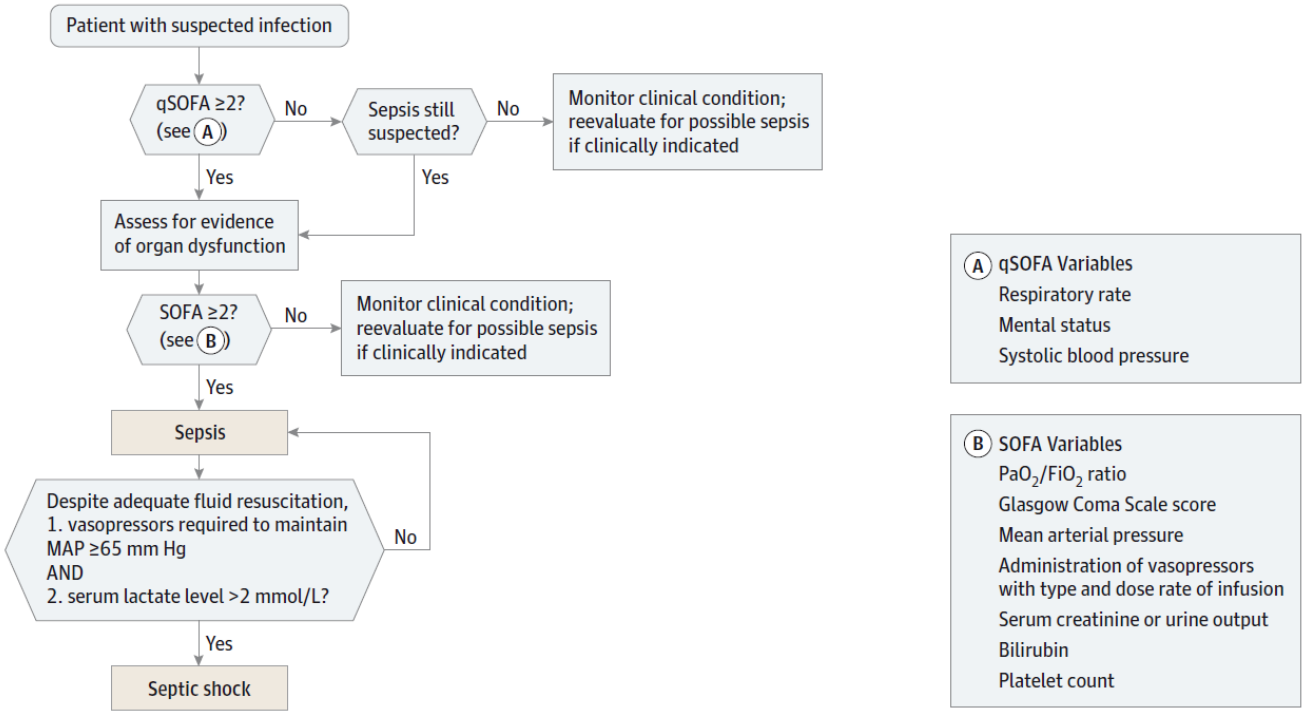
- Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.
- Organ dysfunction can be identified as an acute change in total SOFA score ≥2 points consequent to the infection.
  - The baseline SOFA score can be assumed to be zero in patients not known to have preexisting organ dysfunction.
  - A SOFA score ≥2 reflects an overall mortality risk of approximately 10% in a general hospital population with suspected infection. Even patients presenting with modest dysfunction can deteriorate further, emphasizing the seriousness of this condition and the need for prompt and appropriate intervention, if not already being instituted.
- In lay terms, sepsis is a life-threatening condition that arises when the body's response to an infection injures its own tissues and organs.
- Patients with suspected infection who are likely to have a prolonged ICU stay or to die in the hospital can be promptly identified at the bedside with qSOFA, ie, alteration in mental status, systolic blood pressure ≤100 mm Hg, or respiratory rate ≥22/min.
- Septic shock is a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality.
- Patients with septic shock can be identified with a clinical construct of sepsis with persisting hypotension requiring vasopressors to maintain MAP ≥65 mm Hg and having a serum lactate level >2 mmol/L (18 mg/dL) despite adequate volume resuscitation. With these criteria, hospital mortality is in excess of 40%.

Abbreviations: MAP, mean arterial pressure; qSOFA, quick SOFA; SOFA: Sequential [Sepsis-related] Organ Failure Assessment.

Table 2. Terminology and *International Classification of Diseases* Coding

Current Guidelines and Terminology	Sepsis	Septic Shock
1991 and 2001 consensus terminology[9,10]	Severe sepsis Sepsis-induced hypoperfusion	Septic shock[13]
2015 Definition	Sepsis is life-threatening organ dysfunction caused by a dysregulated host response to infection	Septic shock is a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality
2015 Clinical criteria	Suspected or documented infection and an acute increase of ≥2 SOFA points (a proxy for organ dysfunction)	Sepsis[a] and vasopressor therapy needed to elevate MAP ≥65 mm Hg and lactate >2 mmol/L (18 mg/dL) despite adequate fluid resuscitation[13]
Recommended primary *ICD* codes[a]		
ICD-9	995.92	785.52
ICD-10[a]	R65.20	R65.21
Framework for implementation for coding and research	Identify suspected infection by using concomitant orders for blood cultures and antibiotics (oral or parenteral) in a specified period[b] Within specified period around suspected infection[c]: 1. Identify sepsis by using a clinical criterion for life-threatening organ dysfunction 2. Assess for shock criteria, using administration of vasopressors, MAP <65 mm Hg, and lactate >2 mmol/L (18 mg/dL)[d]	

Figure. Operationalization of Clinical Criteria Identifying Patients With Sepsis and Septic Shock



The baseline Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score should be assumed to be zero unless the patient is known to have preexisting (acute or chronic) organ dysfunction before the onset of infection. qSOFA indicates quick SOFA; MAP, mean arterial pressure.

TABLEAU 1

Score SOFA (*Sequential Organ Failure Assessment*)

Organe/Système	Score				
	0	1	2	3	4
➥ Poumons					
PaO_2/FiO_2 mmHg (kPa)	● ⩾ 400 (53,3)	● < 400 (53,3)	● < 300 (40)	● < 200 (26,7) avec assistance respiratoire	● ⩽ 100 avec assistance respiratoire
➥ Coagulation					
Plaquettes, $\times 10^3$/uL	● ⩾ 150	● < 150	● < 100	● < 50	● < 20
➥ Foie					
Bilirubine, 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)
➥ Cardiovasculaire					
	● PAM ⩾ 70 mmHg	● PAM < 70 mmHg	● Dopamine < 5 *ou* ● Dobutamine	● Dopamine 5,1-15 ● *ou* Adrénaline ⩽ 0,1 ● *ou* Noradrénaline ⩽ 0,1	● Dopamine > 15 ● *ou* Adrénaline > 0,1 ● *ou* Noradrénaline > 0,1
➥ Système nerveux central					
Score de Glasgow	● 15	● 13-14	● 10-12	● 6-9	● < 6
➥ Rein					
Créatinine, mg/dL (umol/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)
Diurèse, mL/j				● < 500	● < 200

PaO_2 : pression artérielle en oxygène ; FiO_2 : fraction d'oxygène inspiré ; PAM : pression artérielle moyenne. La dose de catécholamines est donnée en µg/kg/min sur au moins 1 heure.

Échelle de coma de Glasgow

N 15; coma si < 9; coma grave si <5

TABLEAU 2

Échelle de Glasgow et de Liège

Ouverture des yeux (E)

- spontanée 4
- stimulation verbale 3
- stimulation douloureuse 2
- absente 1

Réponse motrice (M)

- sur commande 6
- réactivité aux stimuli douloureux
  - → localisateur 5
  - → retrait 4
  - → stéréotypé en flexion 3
  - → stéréotypé en extension 2
  - → absente 1

Réponse verbale (V)

- orientée 5
- confuse 4
- incohérente 3
- incompréhensible 2
- absente 1

Réflexes du tronc (Liège)

- fronto-orbiculaire 5
- oculo-céphalique vertical 4
- photomoteur 3
- oculo-céphalique horizontal 2
- oculo-cardiaque 1
- aucun 0

LA REVUE DU PRATICIEN VOL. 62
Janvier 2012

Les principaux foyers sources

- Cutanés
- Digestifs : angiocholite, diverticulite, entérite
- Respiratoires : pneumonie, pleurésie, abcès
- Urinaires : pyélonéphrite, prostatite, sonde
- Gynécologiques : salpingite, post-partum
- Veineux : cathéter
- Cardiaque : endocardite
- Cervico-facial : pharyngite, angine, otite, sinusite
- Neuro-méningé
- Ostéo-articulaire

Chez l'opéré récent

- Infection site opératoire
- Pneumopathie
- Infection urinaire
- Phlébite
- Infection sur cathéter

Signes cliniques du choc

- hypotension artérielle
- tachycardie (pouls filant)
- « choc chaud »: extrémités vasodilatées, rouges, chaudes, sèches
- hyperventilation (acidose métabolique)
- lipothymie, apathie, agitation
- oligurie, anurie

Prélèvements à réaliser

A. Microbiologiques:

- hémocultures : périphériques et par toutes les voies des cathéters en place (à mettre également en culture en cas de retrait)
- urines (avec EMU)
- si indiqué : expectorations, LCR, frottis de gorge ...

B. Biologiques:

- fonction rénale : ionogramme, urée, créatinine
- examen hématologique complet avec formule
- tests inflammatoires : CRP, fibrinogène
- tests hépatiques
- coagulation
- gazométrie artérielle et acide lactique

Traitement spécifique

- identifier le foyer infectieux :
  - pulmonaire (radiographie, expectorations)
  - urinaire (EMU, culture)
  - cutané (purpura, macropapules, pustules)
  - neuroméningé (PL)
  - abdominal (RX abdomen à blanc, échographie)
  - endocardite (échographie cardiaque)
  - ....
- toujours faire des hémocultures
- débuter l'antibiothérapie sur un pari bactériologique

Choix des antibiotiques

- sepsis sans foyer : une β-lactamine à large spectre (céphalosporine ou Tienam^{R} ou Méronem^{R} ou Tazocin^{R}) + aminoside (Amikacine-Amukin^{R}) : 15 mg/kg 1 x/j (DT 1,5 g/j)
- infections abdominales pelviennes (anaérobies) : Tienam^{R}/Méronem^{R} ou Tazocin^{R} + aminoside
- suspicion d'infection à staphylocoque : β-lactamine à large spectre + vancomycine (Vancocin^{R} 2 x 1 g i.v.)
- neutropénie fébrile : céphalosporine ou Tienam^{R}/Méronem^{R} ou Tazocin^{R} + amikacine

Le pronostic est lié à la durée de l'hypotension avant l'antibiothérapie

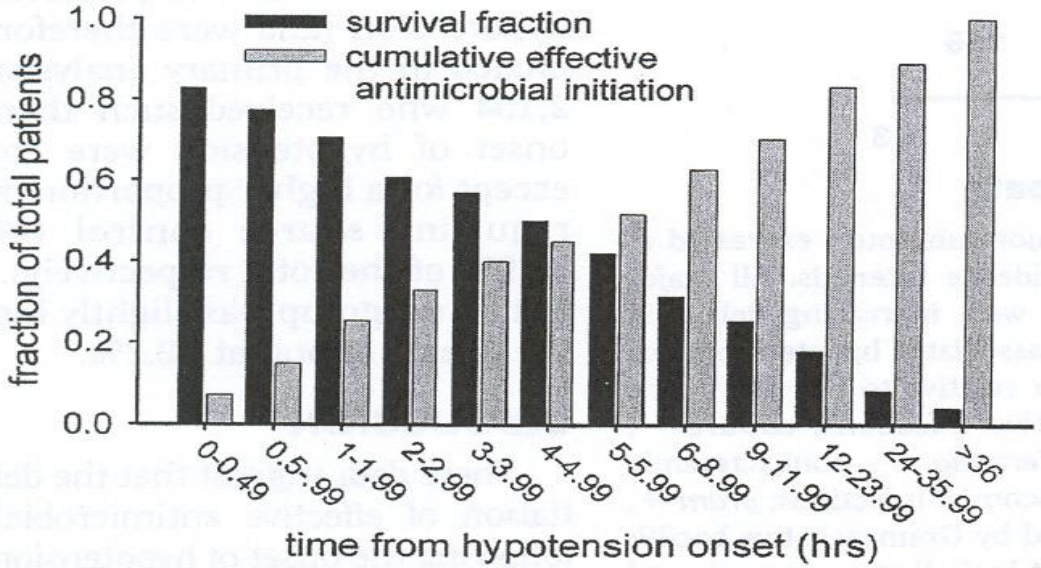


Figure 1. Cumulative effective antimicrobial initiation following onset of septic shock-associated hypotension and associated survival. The x-axis represents time (hrs) following first documentation of septic shock-associated hypotension. *Black bars* represent the fraction of patients surviving to hospital discharge for effective therapy initiated within the given time interval. The *gray bars* represent the cumulative fraction of patients having received effective antimicrobials at any given time point.

Kumar; 2006; 34 : 1589-96

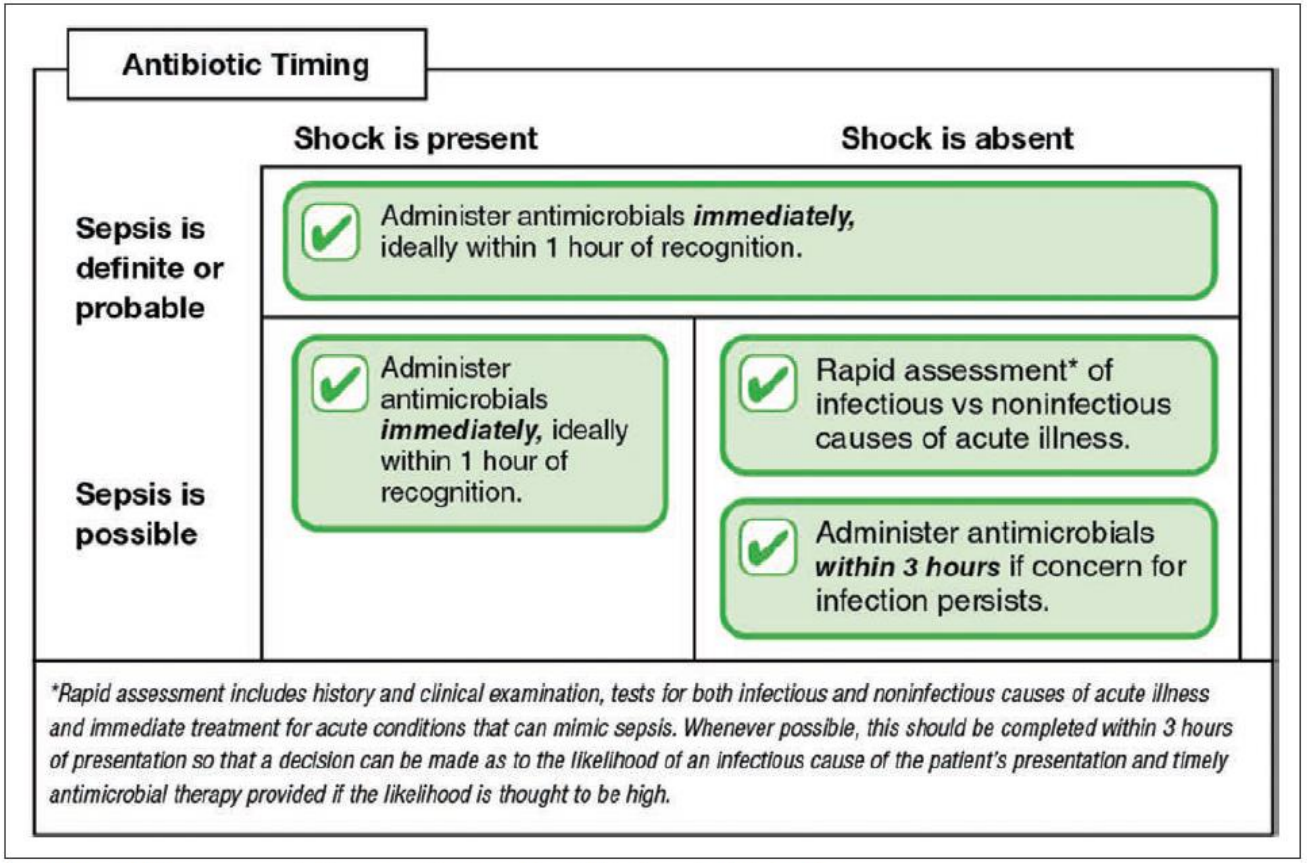


Figure 1. Recommendations on timing of antibiotic administration.

Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021

Traitement du choc

- monitorer la lactatémie : dosages réguliers (toutes les 2 h, selon la clinique)
- oxygénothérapie, éventuellement ventilation artificielle (pas de sédation avant instauration vasopresseurs)
- 4 phases successives :

1ère phase

remplissage adéquat

- par exemple 500 à 1000 ml d'un expanseur en 15-30 min
- maintenir l'hématocrite à au moins 25 à 30% (Hb > 7g/dl)

2ème phase

en cas de réponse non satisfaisante au remplissage adéquat : noradrénaline i.v. : 0,02 à 0,1 µg/kg/min

<u>objectifs</u> :

PAS > 90 mm Hg et/ou PAM > 60 mm Hg

lactatémie < 2 mEq/L

diurèse > 20 ml/h

3ème phase

en cas d'échec: échographie cardiaque et/ou un cathéterisme cardiaque droit:

- une hypovolémie (↓ PVC, ↓ PAPO, ↓ IC) : poursuivre le remplissage sous cathécolamines, en recherchant une cause à l'hypovolémie (ex. hémorragie)
- une dysfonction ventriculaire gauche (dilatation ventriculaire, hypokinésie globale ou segmentaire, ↓ IC avec ↑ PAPO) : associer dobutamine (5 à 20 γ/kg/min) et noradrénaline
- **un profil hémodynamique classique de choc septique après remplissage vasculaire** (hyperdynamique : IC > 4,5 L/min et RVS < 800 dynes. sec/cm^5.m^2) : augmenter la noradrénaline jusqu'à 10 µg/kg/min… ou **corticoïdes** (pour renverser l'insensibilité aux catécholamines) : Solucortef^R 300 mg en 24h en perfusion continue ou en 3-4 bolus (durée minimale : 5 jours)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Hydrocortisone plus Fludrocortisone for Adults with Septic Shock

D. Annane, A. Renault, C. Brun-Buisson, B. Megarbane, J.-P. Quenot, S. Siami, A. Cariou, X. Forceville, C. Schwebel, C. Martin, J.-F. Timsit, B. Misset, M. Ali Benali, G. Colin, B. Souweine, K. Asehnoune, E. Mercier, L. Chimot, C. Charpentier, B. François, T. Boulain, F. Petitpas, J.-M. Constantin, G. Dhonneur, F. Baudin, A. Combes, J. Bohé, J.-F. Loriferne, R. Amathieu, F. Cook, M. Slama, O. Leroy, G. Capellier, A. Dargent, T. Hissem, V. Maxime, and E. Bellissant, for the CRICS-TRIGGERSEP Network*

N Engl J Med 2018;378:809-18.
DOI: 10.1056/NEJMoa1705716

METHODS

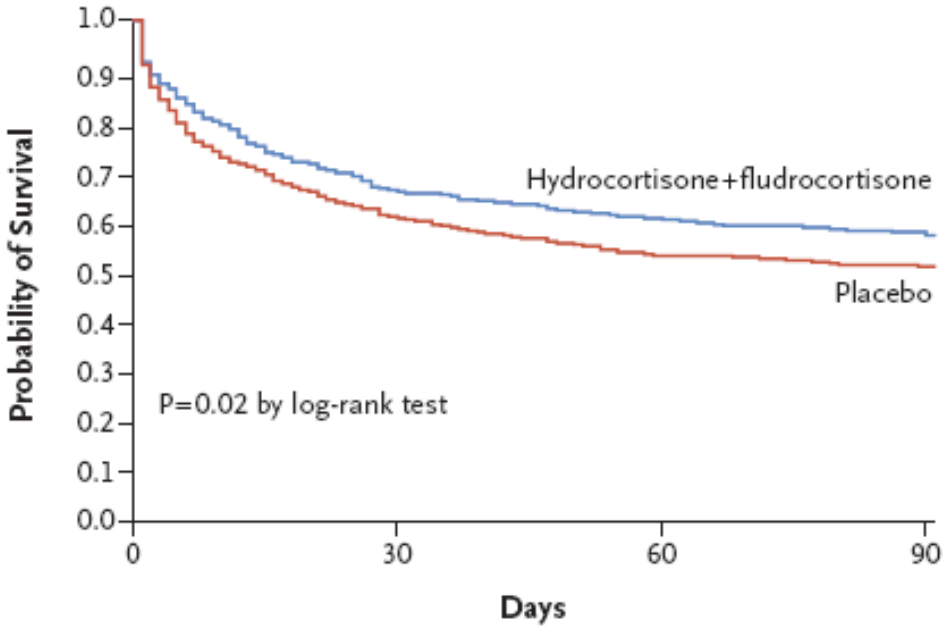
In this multicenter, double-blind, randomized trial with a 2-by-2 factorial design, we evaluated the effect of hydrocortisone-plus-fludrocortisone therapy, drotrecogin alfa (activated), the combination of the three drugs, or their respective placebos. The primary outcome was 90-day all-cause mortality. Secondary outcomes included mortality at intensive care unit (ICU) discharge and hospital discharge and at day 28 and day 180 and the number of days alive and free of vasopressors, mechanical ventilation, or organ failure. After drotrecogin alfa (activated) was withdrawn from the market, the trial continued with a two-group parallel design. The analysis compared patients who received hydrocortisone plus fludrocortisone with those who did not (placebo group).

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Placebo (N = 627)	Hydrocortisone plus Fludrocortisone (N = 614)	All Patients (N = 1241)
Male sex — no./total no. (%)	424/626 (67.7)	402/614 (65.5)	826/1240 (66.6)
Age — yr†	66±15	66±14	66±14
Admission from a medical ward — no./total no. (%)	499/616 (81.0)	495/601 (82.4)	994/1217 (81.7)
SAPS II‡	56±19	56±19	56±19
SOFA score§	11±3	12±3	12±3
Community-acquired infection — no./total no. (%)	459/608 (75.5)	468/602 (77.7)	927/1210 (76.6)
Site of infection — no./total no. (%)¶			
Unknown	18/626 (2.9)	11/614 (1.8)	29/1240 (2.3)
Lung	363/626 (58.0)	373/614 (60.7)	736/1240 (59.4)
Abdomen	68/626 (10.9)	74/614 (12.1)	142/1240 (11.5)
Urinary tract	118/626 (18.8)	102/614 (16.6)	220/1240 (17.7)
Positive blood culture — no./total no. (%)	229/626 (36.6)	225/614 (36.6)	454/1240 (36.6)
Documented pathogen — no./total no. (%)	441/626 (70.4)	450/614 (73.3)	891/1240 (71.9)
Gram-positive bacteria — no./total no. (%)	228/626 (36.4)	235/614 (38.3)	463/1240 (37.3)
Gram-negative bacteria — no./total no. (%)	264/626 (42.2)	261/614 (42.5)	525/1240 (42.3)
Adequate antimicrobial therapy — no./total no. (%)	602/626 (96.2)	595/614 (96.9)	1197/1240 (96.5)
Vasopressor administration			
Epinephrine			
No. of patients	58	53	111
Dose — μg/kg/min	1.74±2.41	2.31±6.62	2.01±4.88
Norepinephrine			
No. of patients	552	534	1086
Dose — μg/kg/min	1.14±1.66	1.02±1.61	1.08±1.63
Mechanical ventilation — no./total no. (%)	569/623 (91.3)	567/614 (92.3)	1136/1237 (91.8)
Renal-replacement therapy — no./total no. (%)	168/598 (28.1)	161/596 (27.0)	329/1194 (27.6)

Table 2. Trial Outcomes.*

Outcome	Placebo (N=627)	Hydrocortisone plus Fludrocortisone (N=614)	All Patients (N=1241)	Relative Risk (95% CI)†	P Value
Primary outcome: death from any cause at day 90 — no. (%)	308 (49.1)	264 (43.0)	572 (46.1)	0.88 (0.78–0.99)	0.03
Secondary outcomes					
Death from any cause					
At day 28 — no. (%)	244 (38.9)	207 (33.7)	451 (36.3)	0.87 (0.75–1.01)	0.06
At ICU discharge — no./total no. (%)	257/627 (41.0)	217/613 (35.4)	474/1240 (38.2)	0.86 (0.75–0.99)	0.04
At hospital discharge — no./total no. (%)	284/627 (45.3)	239/613 (39.0)	523/1240 (42.2)	0.86 (0.76–0.98)	0.02
At day 180 — no./total no. (%)	328/625 (52.5)	285/611 (46.6)	613/1236 (49.6)	0.89 (0.79–0.99)	0.04
Decision to withhold or withdraw active treatment by day 90 — no./total no. (%)	61/626 (9.7)	64/614 (10.4)	125/1240 (10.1)	1.07 (0.77–1.49)	0.69
Vasopressor-free days to day 28‡					
Mean	15±11	17±11	16±11	—	<0.001
Median (IQR)	19 (1–26)	23 (5–26)	21 (2–26)		
Ventilator-free days to day 28‡					
Mean	10±11	11±11	11±11	—	0.07
Median (IQR)	4 (0–21)	10 (0–22)	8 (0–21)		
Organ-failure–free days to day 28‡					
Mean	12±11	14±11	13±11	—	0.003
Median (IQR)	12 (0–24)	19 (0–25)	15 (0–24)		



No. at Risk				
Hydrocortisone+ fludrocortisone	614	405	372	353
Placebo	627	381	333	319

Figure 1. 90-Day Survival Distributions.

Shown are survival curves from randomization up to 90 days. The survival rate was significantly higher in the hydrocortisone-plus-fludrocortisone group than in the placebo group.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Adjunctive Glucocorticoid Therapy in Patients with Septic Shock

B. Venkatesh, S. Finfer, J. Cohen, D. Rajbhandari, Y. Arabi, R. Bellomo, L. Billot, M. Correa, P. Glass, M. Harward, C. Joyce, Q. Li, C. McArthur, A. Perner, A. Rhodes, K. Thompson, S. Webb, and J. Myburgh, for the ADRENAL Trial Investigators and the Australian–New Zealand Intensive Care Society Clinical Trials Group*

ABSTRACT

BACKGROUND

Whether hydrocortisone reduces mortality among patients with septic shock is unclear.

METHODS

We randomly assigned patients with septic shock who were undergoing mechanical ventilation to receive hydrocortisone (at a dose of 200 mg per day) or placebo for 7 days or until death or discharge from the intensive care unit (ICU), whichever came first. The primary outcome was death from any cause at 90 days.

RESULTS

From March 2013 through April 2017, a total of 3800 patients underwent randomization. Status with respect to the primary outcome was ascertained in 3658 patients (1832 of whom had been assigned to the hydrocortisone group and 1826 to the placebo group). At 90 days, 511 patients (27.9%) in the hydrocortisone group and 526 (28.8%) in the placebo group had died (odds ratio, 0.95; 95% confidence interval [CI],

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*A full list of investigators in the ADRENAL Trial is provided in the Supplementary Appendix, available at NEJM.org.

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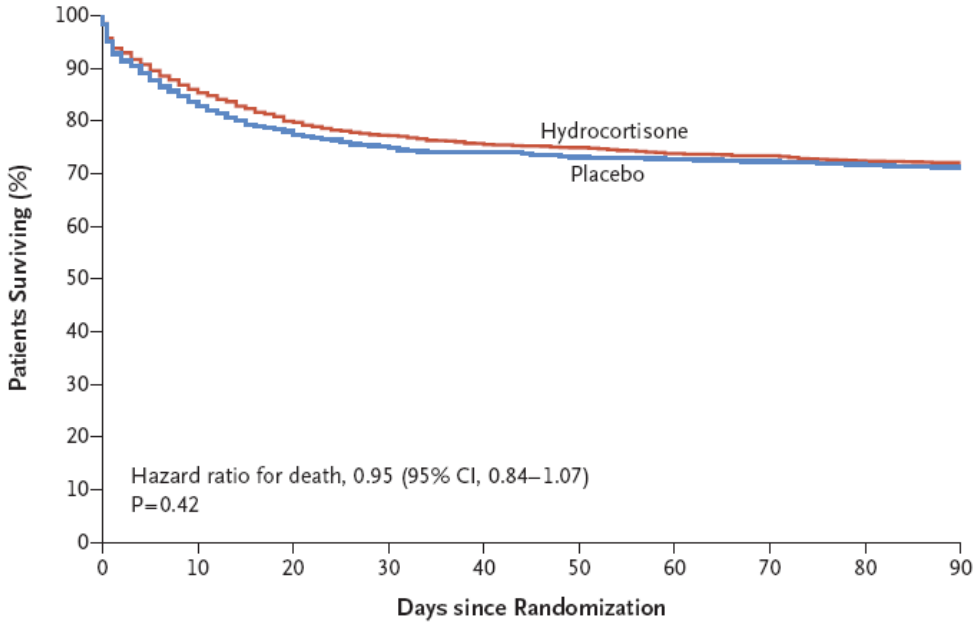
Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Hydrocortisone (N=1853)	Placebo (N=1860)
Age — yr	62.3±14.9	62.7±15.2
Male sex — no./total no. (%)	1119/1853 (60.4)	1140/1860 (61.3)
Weight — kg	85.8±26.6	85.6±26.3
Admission type — no./total no. (%)†		
Medical	1273/1849 (68.8)	1266/1857 (68.2)
Surgical	576/1849 (31.2)	591/1857 (31.8)
APACHE II score‡		
Median	24.0	23.0
Interquartile range	19.0–29.0	18.0–29.0
Therapy at baseline — no./total no. (%)§		
Mechanical ventilation	1845/1849 (99.8)	1855/1857 (99.9)
Inotropes or vasopressors	1843/1853 (99.5)	1854/1860 (99.7)
Norepinephrine	1823/1853 (98.4)	1821/1860 (97.9)
Vasopressin	280/1853 (15.1)	321/1860 (17.3)
Epinephrine	134/1853 (7.2)	113/1860 (6.1)
Other	157/1853 (8.5)	173/1860 (9.3)
Antimicrobial agent	1817/1848 (98.3)	1821/1857 (98.1)
Renal-replacement therapy	228/1849 (12.3)	242/1857 (13.0)

Table 2. Outcomes.*

Outcome	Hydrocortisone (N=1853)	Placebo (N=1860)	Odds Ratio, Hazard Ratio, or Absolute Difference (95% CI)	P Value
Primary outcome				
90-day mortality — no./total no. (%)	511/1832 (27.9)	526/1826 (28.8)	0.95 (0.82 to 1.10)†	0.50
Secondary outcomes				
28-day mortality — no./total no. (%)	410/1841 (22.3)	448/1840 (24.3)	0.89 (0.76 to 1.03)†	0.13
Median time to resolution of shock (IQR) — days	3 (2 to 5)	4 (2 to 9)	1.32 (1.23 to 1.41)‡	<0.001
Recurrence of shock — no. (%)	365 (19.7)	343 (18.4)	1.07 (0.94 to 1.22)†	0.32
Median time to discharge from the ICU (IQR) — days	10 (5 to 30)	12 (6 to 42)	1.14 (1.06 to 1.23)‡	<0.001
No. of days alive and out of the ICU	58.2±34.8	56.0±35.4	2.26 (0.04 to 4.49)§	0.047¶
Median time to discharge from the hospital (IQR) — days	39 (19 to NA)	43 (19 to NA)	1.06 (0.98 to 1.15)‡	0.13
No. of days alive and out of the hospital	40.0±32.0	38.6±32.4	1.45 (–0.59 to 3.49)§	0.16
Median time to cessation of initial mechanical ventilation (IQR) — days	6 (3 to 18)	7 (3 to 24)	1.13 (1.05 to 1.22)‡	<0.001
No. of days alive and free from mechanical ventilation	61.2±35.6	59.1±36.1	2.18 (–0.11 to 4.46)§	0.06
Recurrence of mechanical ventilation — no./total no. (%)	180/1842 (9.8)	154/1850 (8.3)	1.18 (0.96 to 1.45)†	0.11
No. of days alive and free from renal-replacement therapy	42.6±39.1	40.4±38.5	2.37 (–2.00 to 6.75)§	0.29
Use of renal-replacement therapy — no. (%)	567 (30.6)	609 (32.7)	0.94 (0.86 to 1.03)†	0.18
New-onset bacteremia or fungemia — no. (%)	262 (14.1)	262 (14.1)	1.00 (0.86 to 1.16)†	0.96
Blood transfusion — no./total no. (%)	683/1848 (37.0)	773/1855 (41.7)	0.82 (0.72 to 0.94)†	0.004

A Survival

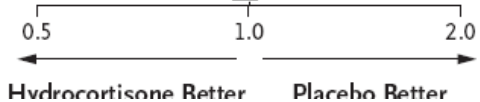


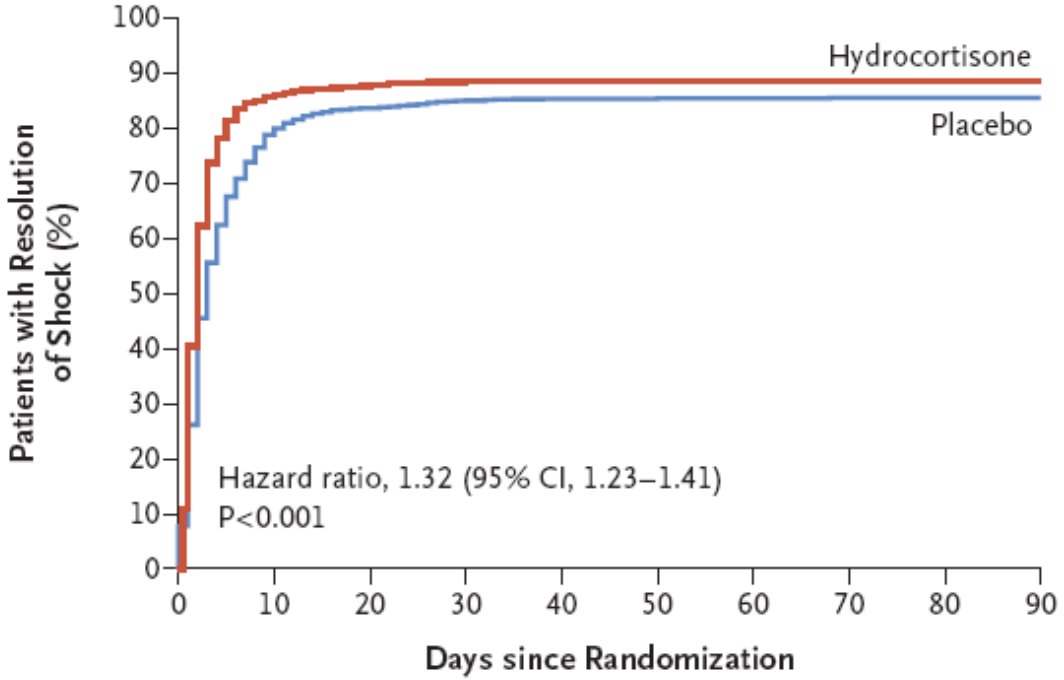
No. at Risk

Hydrocortisone	1832	1591	1481	1418	1388	1374	1356	1348	1328	1321
Placebo	1826	1546	1433	1376	1354	1337	1330	1322	1312	1300

B Subgroup Analysis of Death at 90 Days

Subgroup	Hydrocortisone	Placebo	Odds Ratio (95% CI)	P Value for Interaction
	no. of patients with event/total no. of patients (%)			
Sex				0.53
Male	312/1106 (28.2)	336/1122 (29.9)	0.92 (0.76–1.10)	
Female	199/726 (27.4)	190/704 (27.0)	1.01 (0.80–1.28)	
Admission type				0.73
Surgical	125/568 (22.0)	138/580 (23.8)	0.91 (0.69–1.21)	
Medical	386/1264 (30.5)	388/1245 (31.2)	0.97 (0.81–1.15)	
Catecholamine dose				0.25
≤15 μg/min	224/968 (23.1)	228/995 (22.9)	1.02 (0.82–1.26)	
>15 μg/min	281/849 (33.1)	291/805 (36.1)	0.86 (0.70–1.05)	
Site of sepsis				0.63
Pulmonary	243/799 (30.4)	250/828 (30.2)	0.99 (0.80–1.23)	
Other	268/1033 (25.9)	276/998 (27.7)	0.92 (0.76–1.12)	
APACHE II score				0.17
≥25	326/840 (38.8)	297/785 (37.8)	1.01 (0.83–1.24)	
<25	184/990 (18.6)	229/1039 (22.0)	0.82 (0.66–1.02)	
Time from shock onset to randomization				0.08
<6 hr	110/352 (31.2)	96/344 (27.9)	1.16 (0.83–1.61)	
6 to <12 hr	127/511 (24.9)	153/486 (31.5)	0.71 (0.54–0.94)	
12 to <18 hr	119/437 (27.2)	106/423 (25.1)	1.13 (0.83–1.54)	
≥18 hr	154/525 (29.3)	167/566 (29.5)	0.99 (0.76–1.29)	





No. at Risk

Hydrocortisone	1843	104	34	9	6	3	3	2	1	0
Placebo	1854	213	53	19	8	6	4	0	0	0

Figure 2. Cumulative Incidence Function of Time from Randomization to Resolution of Shock.

The cumulative incidence function plot was created by treating death as a competing risk.

dysfonction ventriculaire gauche

- la dysfonction cardiaque apparaît secondairement, nécessitant un support inotrope d'environ 48 h
- mécanisme : hypersécrétion NOS-2 dans les cavités cardiaques et autres muscles (diaphragme, grand droit) : NO se transforme en un dérivé peroxynitrite $ONOO^-$ réagissant avec les tyrosines des protéines musculaires avec formation de nitrotyrosine … et le muscle est bloqué
- BNP : taux très élevé non lié à la dépression myocardique mais à une diminution de son catabolisme par baisse de l'activité d'une endopeptidase vasculaire responsable de la destruction du BNP : donc rôle pronostic mais pas prédicteur de la dysfonction cardiaque
- détection : troponine circulante
- confirmation : échocardiographie (dilatation ventriculaire, hypokinésie globale ou segmentaire) ou hémodynamique invasive (baisse IC avec aaugmentation PAPO)

Penser à une étiologie infectieuse non couverte

- Abcès profond ou collection non drainée
- Fungémie ou autre infection non bactérienne
- Infection à staphylocoque
- Bactérie résistante aux antibiotiques prescrits

4ème phase

en cas d'insuffisance circulatoire persistante malgré la correction de l'hypovolémie et de la fonction ventriculaire gauche :

- passer à l'adrénaline
- sinon envisager :
  - augmentation les doses de catécholamines à niveaux très importants
  - associations de plusieurs catécholamines (ex. adrénaline, dopamine ...)
  - bleu de méthylène

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Early, Goal-Directed Therapy for Septic Shock — A Patient-Level Meta-Analysis

The PRISM Investigators*

N Engl J Med 2017;376:2223-34.
DOI: 10.1056/NEJMoa1701380

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

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

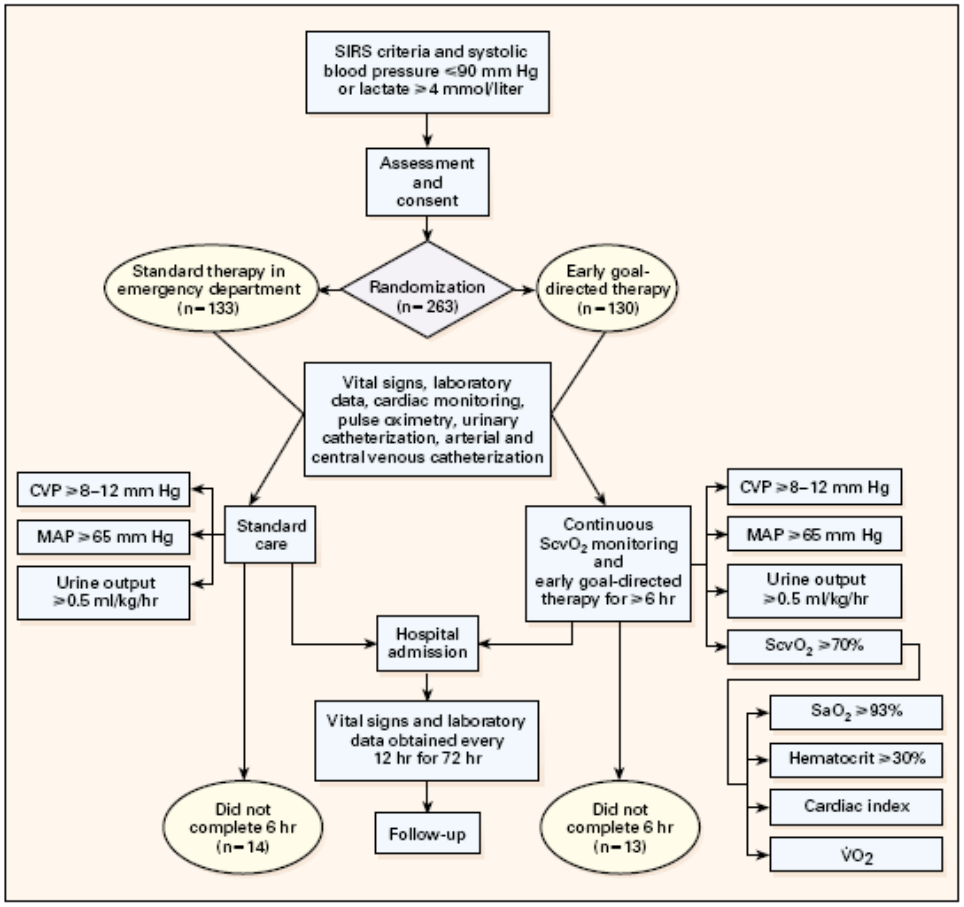
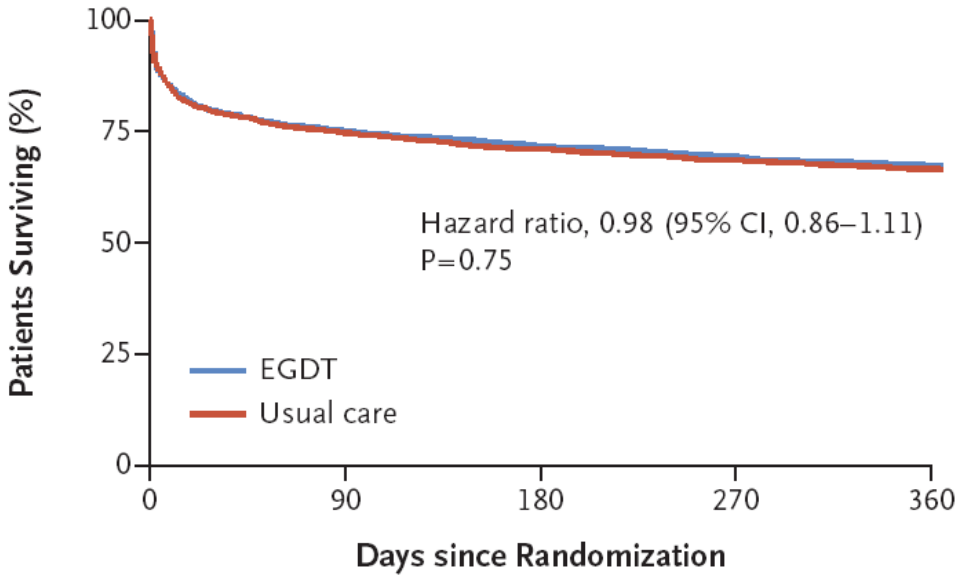


Figure 1. Overview of Patient Enrollment and Hemodynamic Support.

Table 2. Outcomes.*

Outcome	EGDT (N=1857)	Usual Care (N=1880)	Incremental Effect (95% CI)	P Value	
				Overall Comparison	Comparison among Trials
Primary outcome: death at 90 days — no./total no. (%)	462/1852 (24.9)	475/1871 (25.4)	0.97 (0.82 to 1.14)†‡	0.68	0.73
Secondary outcomes: mortality					
Death at hospital discharge — no./total no. (%)§	370/1857 (19.9)	365/1878 (19.4)	1.02 (0.85 to 1.21)†	0.86	0.42
Death at 28 days — no./total no. (%)	375/1854 (20.2)	385/1873 (20.6)	0.96 (0.81 to 1.15)†	0.68	0.57



No. at Risk					
EGDT	1857	1391	1287	1209	1119
Usual care	1880	1395	1295	1206	1110

Figure 1. Patient Survival over a Period of 1 Year.

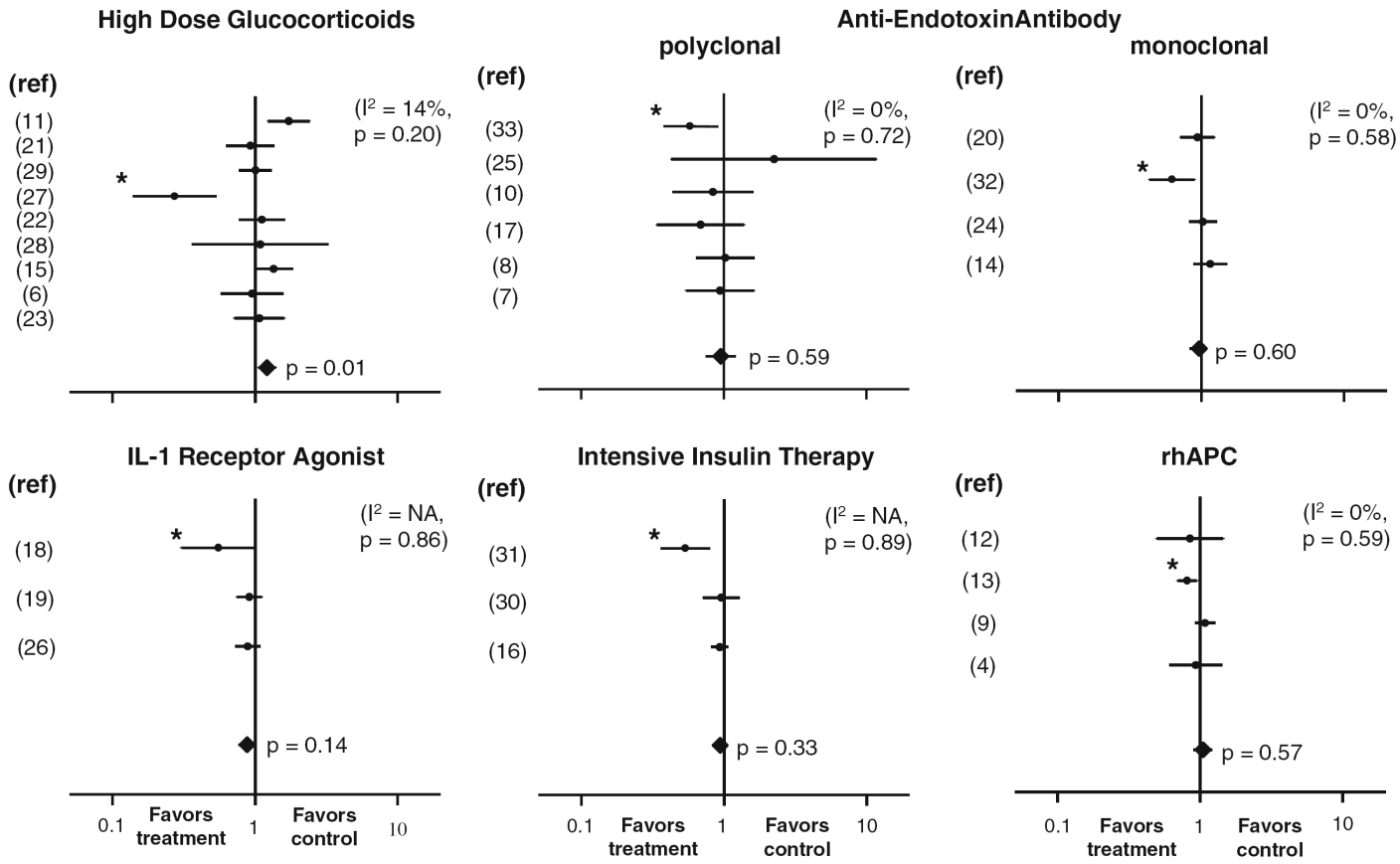
There was no significant difference in the duration of survival to 1 year between the group that received early, goal-directed therapy (EGDT) and the group that received usual care. Data with respect to survival were censored at the actual date that the patient was last known to be alive or at 365 days. CI denotes confidence interval.

Intensive Care Med (2008) 34:1955–1960
DOI 10.1007/s00134-008-1274-6

EDITORIAL

Daniel A. Sweeney
Robert L. Danner
Peter Q. Eichacker
Charles Natanson

Once is not enough: clinical trials in sepsis


High Dose Glucocorticoids
(ref)
(11)
(21)
(29)
(27)
(22)
(28)
(15)
(6)
(23)
*
(I² = 14%, p = 0.20)
p = 0.01
Anti-EndotoxinAntibody
polyclonal
(ref)
(33)
(25)
(10)
(17)
(8)
(7)
*
(I² = 0%, p = 0.72)
p = 0.59
monoclonal
(ref)
(20)
(32)
(24)
(14)
*
(I² = 0%, p = 0.58)
p = 0.60
IL-1 Receptor Agonist
(ref)
(18)
(19)
(26)
*
(I² = NA, p = 0.86)
p = 0.14
0.1
Favors treatment
1
Favors control
10
Intensive Insulin Therapy
(ref)
(31)
(30)
(16)
*
(I² = NA, p = 0.89)
p = 0.33
0.1
Favors treatment
1
Favors control
10
rhAPC
(ref)
(12)
(13)
(9)
(4)
*
(I² = 0%, p = 0.59)
p = 0.57
0.1
Favors treatment
1
Favors control
10
Relative Risk of Death (95% Confidence Interval)

Complication : syndrome de défaillance multiviscérale

- **= SDMV ou MOF (multiple organ failure)**
- Syndrome caractérisé par la défaillance d'au moins 2 organes, avec un pronostic d'autant plus sombre que le nombre d'organes atteints est élevé. Il n'y a pas à ce sujet consensus sur un système de score unique en réanimation.

défaillance	KNAUS	TRAN	FAGON
cardiovasculaire	(au moins 1 critère)		(au moins 1 critère)
	FC < 55/min PAM < 50 mmHg TV et/ou FV pH <7,25 avec PaCO2 > 50 mmHg	FC £ 50/min PAM £ 50 mmHg TV ou FV ou arrêt cardiaque ou infarctus nécessité expanseurs ou drogues vasoactives pour maintenir PAs > 100	PAs < 90 avec signes d'hypoperfusion périphérique drogues inotropes ou vasopressives pour maintenir PAs > 90
respiratoire	(au moins 1 critère) FR < 6 ou > 50/min PaCO2 > 50 mmHg AaDO2 > 350 mmHg VA au 4e jour	FR £ 5 ou ³ 50/min VA pdt ³ 3 j ou avec FiO2 >0,4 ou PEEP > 5 cm H2O	(au moins 1 critère) PaO2 < 60 avec FiO2 = 0,21 VA
rénale	(au moins 1 critère sans IRC) diurèse < 480 ml/24 h (ou < 160ml/8h) urée>100 mg/dl créatinine > 3,5 mg/dl	créatinine ³ 3,5 mg/dl épuration extrarénale	(au moins 1 critère) créatinine > 3,6 diurèse < 500 ml/24h (180 ml/8h) épuration extrarénale
hématologique	(au moins 1 critère) GB < 1000 plaquettes < 20.000 hématocrite < 20 %	GB £ 300 plaquettes £ 50.000 Ht £ 20 % CIVD	(au moins 1 critère) Ht £ 20 % GB < 2000 plaquettes < 40.000
neurologique	Glasgow < 6 (en l'absence de sédation)	idem	idem ou confusion brutale
hépatique		ictère clinique bilirubine $\geq$ 3 mg/dl sGPT > x 2 encéphalopathie hépatique	(au moins 1 critère) bilirubine > 6 mg/dl Ph Alc > x 3
gastrointestinale		ulcère aigu hémorragique pancréatite aiguë Hh cholécystite aiguë alithiasique entérocolite nécrosante perforation digestive	

ONLINE SPECIAL ARTICLE

Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021

KEY WORDS: adults; evidence-based medicine; guidelines; sepsis; septic shock

Laura Evans[1]
Andrew Rhodes[2]
Waleed Alhazzani[3]
Massimo Antonelli[4]

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