DESC de Médecine d'Urgence Inter-région Paris IDF
Séminaire « Urgence en pathologie infectieuse » – Paris, 13 juin 2008

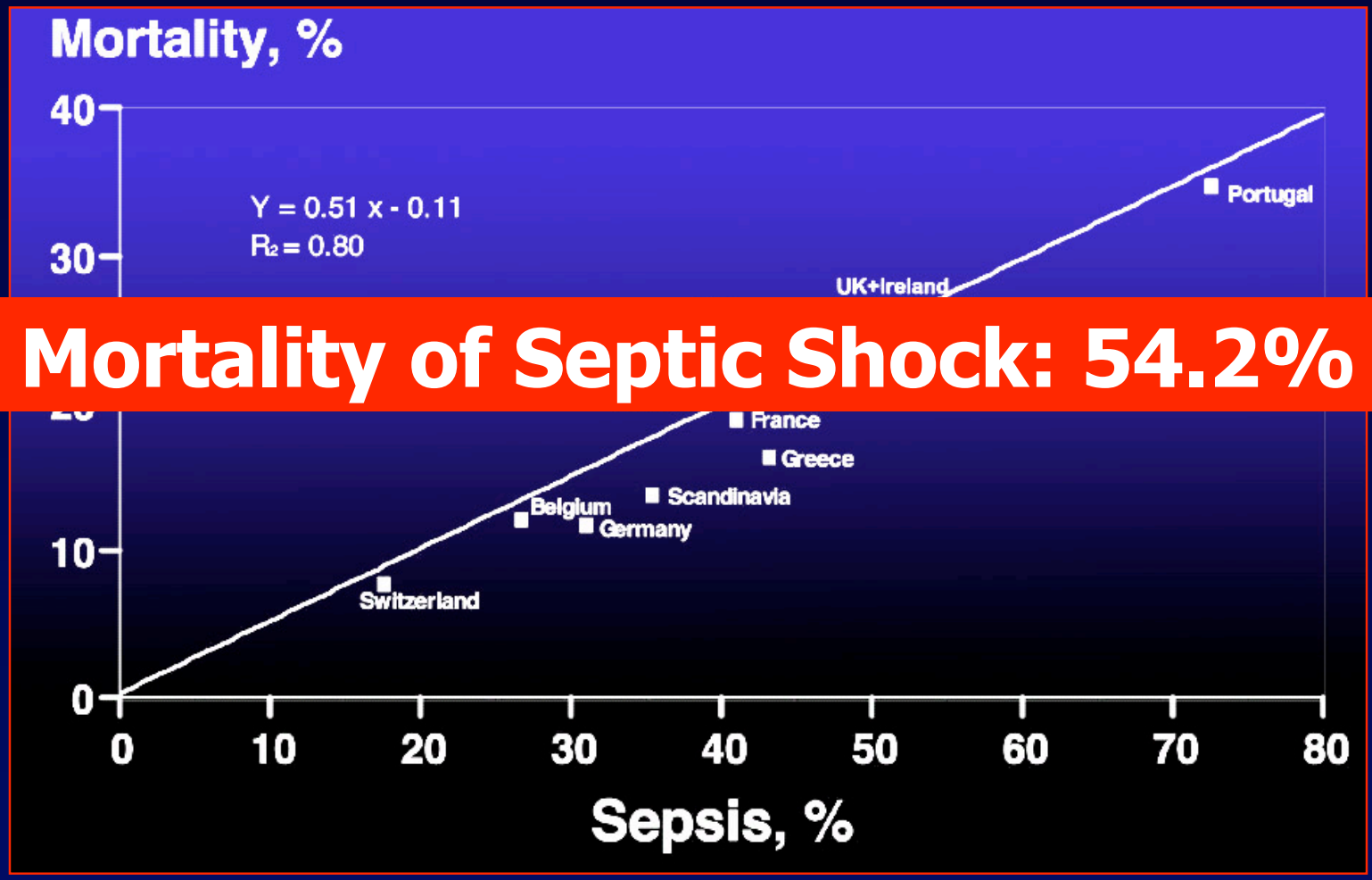
# Sepsis et « Early-Goal Directed Therapy »

## … à propos des dernières recommandations

Alain Cariou
Pôle Réanimations – Urgences : Hôpital Cochin
Université Paris Descartes

# Mortality of Septic Shock

**SOAP study: 3,147 pts**



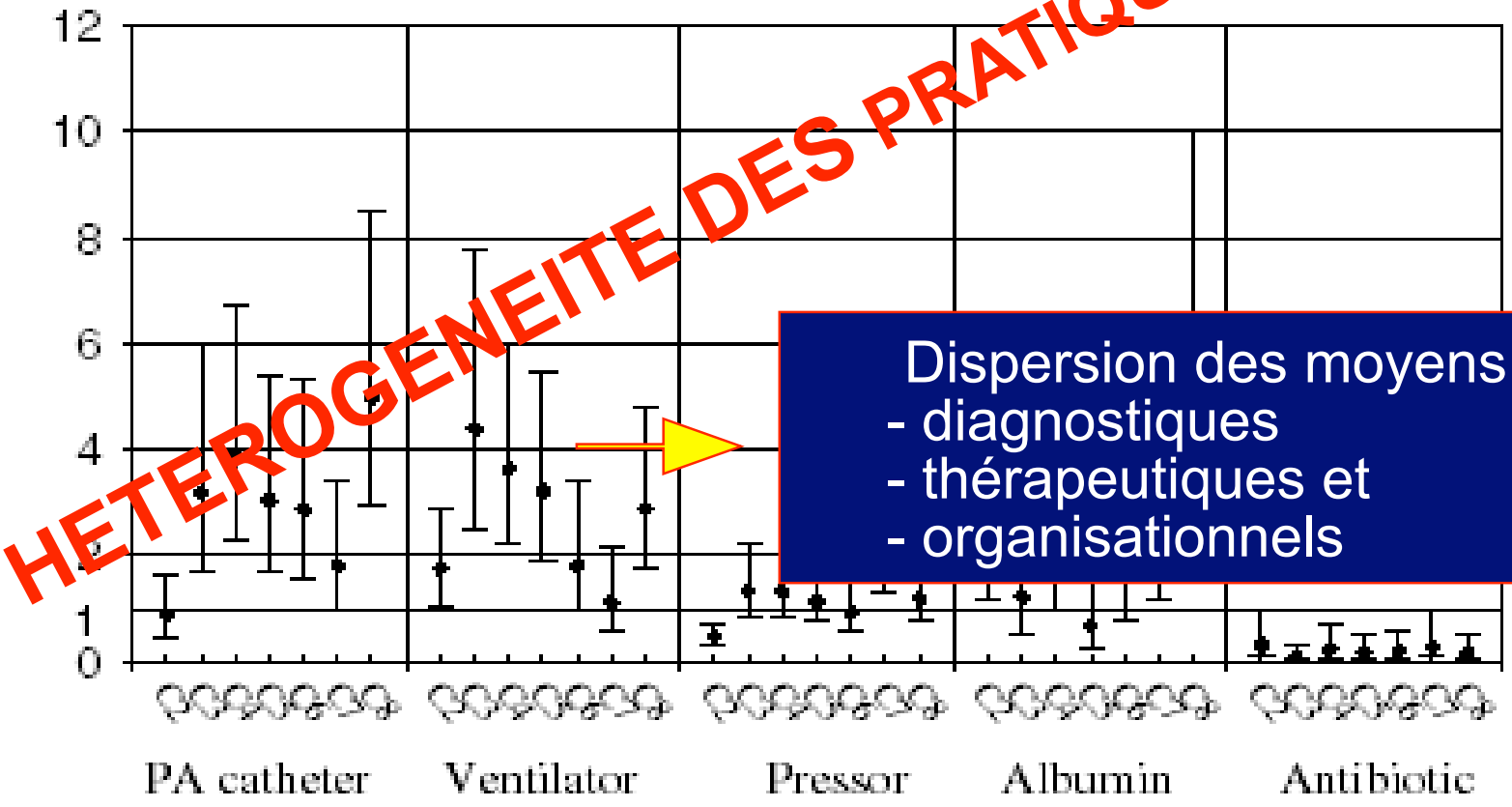

**Mortality of Septic Shock: 54.2%**

Vincent JL Crit Care Med 2006;34:943

# Severe sepsis: variation in resource and therapeutic modality use among academic centers

D Tony Yu[1], Edgar Black[2], Kenneth E Sands[3], J Sanford Schwartz[4], Patricia L Hibberd[5], Paul S Graman[6], Paul N Lanken[7], Katherine L Kahn[8], David R Snydman[9], Jeffrey Parsonnet[10], Richard Moore[11], Richard Platt[12] and David W Bates[13], for the Academic Medical Center Consortium Sepsis Project Working Group

HETEROGENEITE DES PRATIQUES




Dispersion des moyens
- diagnostiques
- thérapeutiques et
- organisationnels

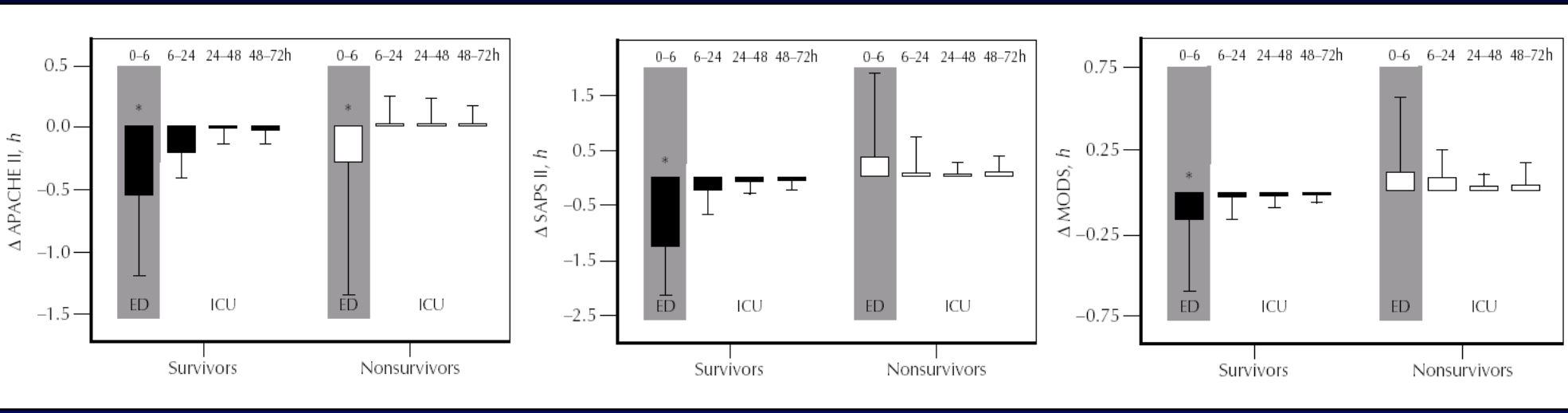
Yu et al. Crit Care 2003

# Optimiser la prise en charge des états septiques graves en 2008

1. Diagnostic rapide + évaluation sévérité
2. Procédures formalisées
3. Objectifs clairs
4. Thérapeutiques adaptées
5. Place des traitements « adjuvants » ?

# Critical care in the ED: a physiologic assessment and outcome evaluation

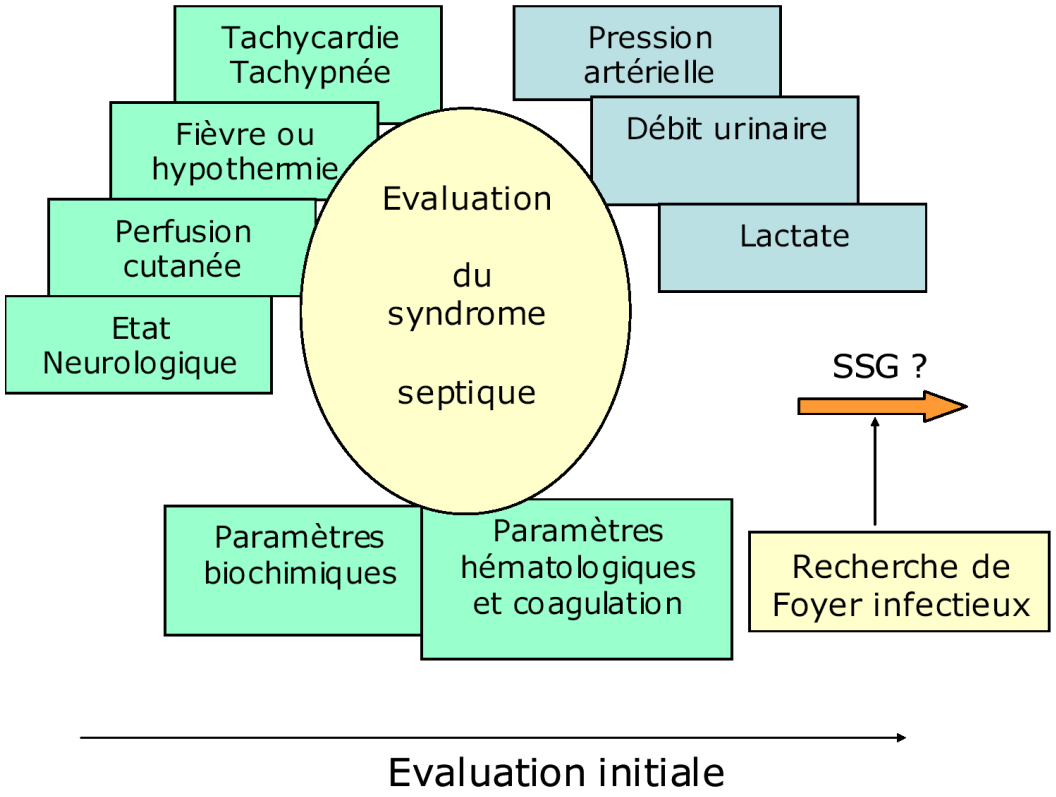
Nguyen et al. Acad Emerg Med 2000; 7: 1354-1361




- Care provided in the ED significantly impacts the progression of OF and mortality
- Physiologic determinants of outcome may be established before ICU admission
- Unique physiologic assessment methodologies should be developed
  - ✓ to examine the quality of patient care
  - ✓ to improve the accuracy of prognostic decisions
  - ✓ to objectively measure the impact of clinical interventions and pathways

**Groupe Transversal Sepsis**
**« Prise en charge initiale des états septiques graves de l'adulte et de l'enfant »**

ADARPEF
GFRUP
SAMU de France
SFAR
SFMU
SPILF
SRLF




# 1. Diagnostic rapide


***Coordination :***

Christian BRUN-BUISSON (SRLF) & Claude MARTIN (SFAR)

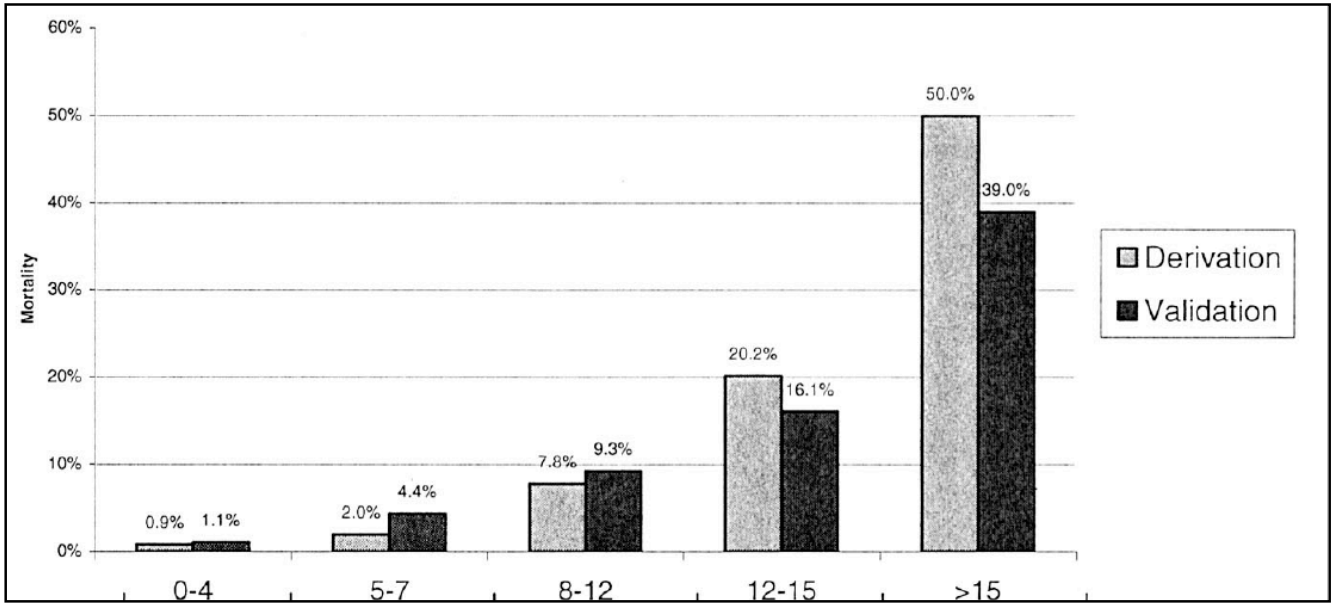
Feature Articles

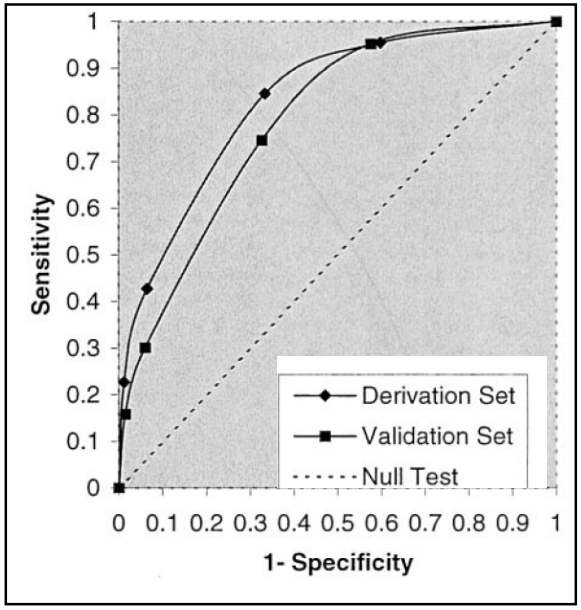
# Mortality in Emergency Department Sepsis (MEDS) score: A prospectively derived and validated clinical prediction rule*

Nathan I. Shapiro, MD; Richard E. Wolfe, MD; Richard B. Moore, MD; Eric Smith, BA; Elizabeth Burdick, PhD; David W. Bates, MD, MSc

Crit Care Med 2003

| Characteristic | Points Assigned |
|---|---|
| Predisposition | |
| Age > 65 year | 3 |
| Nursing home resident | 2 |
| Rapidly terminal comorbid illness | 6 |
| Infection | |
| Lower respiratory infection | 2 |
| Response | |
| Bands > 5% | 3 |
| Organ dysfunction | |
| Tachypnea or hypoxemia | 3 |
| Septic shock | 3 |
| Platelet count <150,000/mm$^3$ | 3 |
| Altered mental status | 2 |



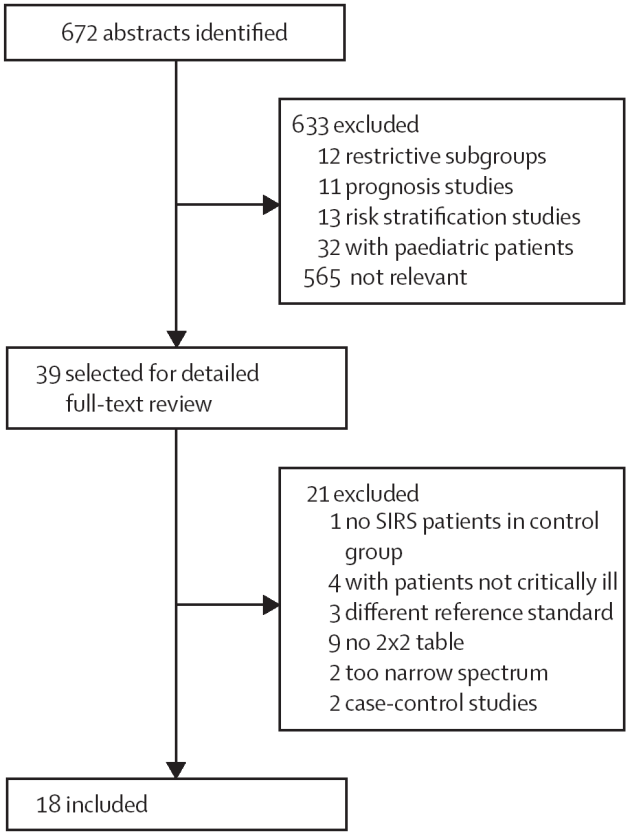



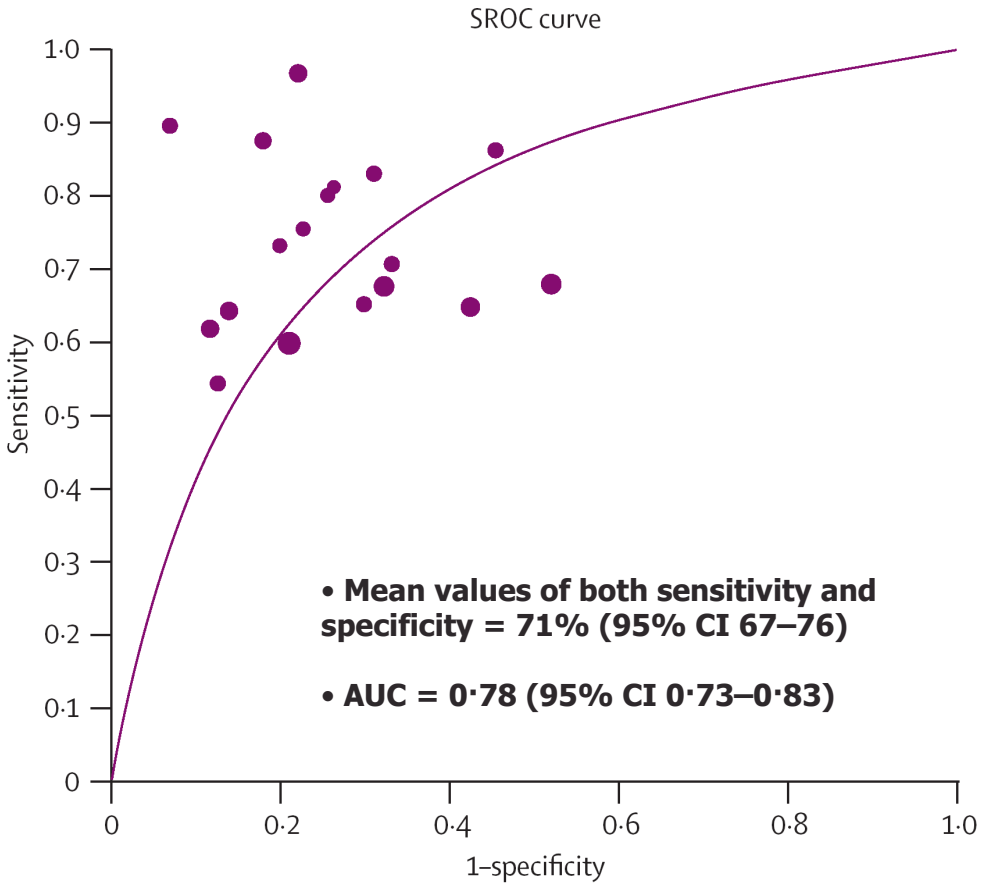

« In patients with suspected infection, this model identifies significant correlates of death and allows stratification of patients according to mortality risk »

# Accuracy of procalcitonin for sepsis diagnosis in critically ill patients: systematic review and meta-analysis

Benjamin M P Tang, Guy D Eslick, Jonathan C Craig, Anthony S McLean

**Lancet Infectious Disease 2007**

The New England
Journal of Medicine



Volume 345 November 8, 2001 Number 19

# 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*

## High-Risk Patients:

**2 Signs of SIRS**

- Temp °C < 36° or ≥ 38°C
- HR > 90 beats per/min
- Resp > 20 breaths per/min or $PaCO_2$ < 32mm Hg
- WBC > 12,000 per $mm^3$ or < 4,000 per $mm^3$ or > 10% immature bands

+

**Sign of Global Tissue Hypoxia**

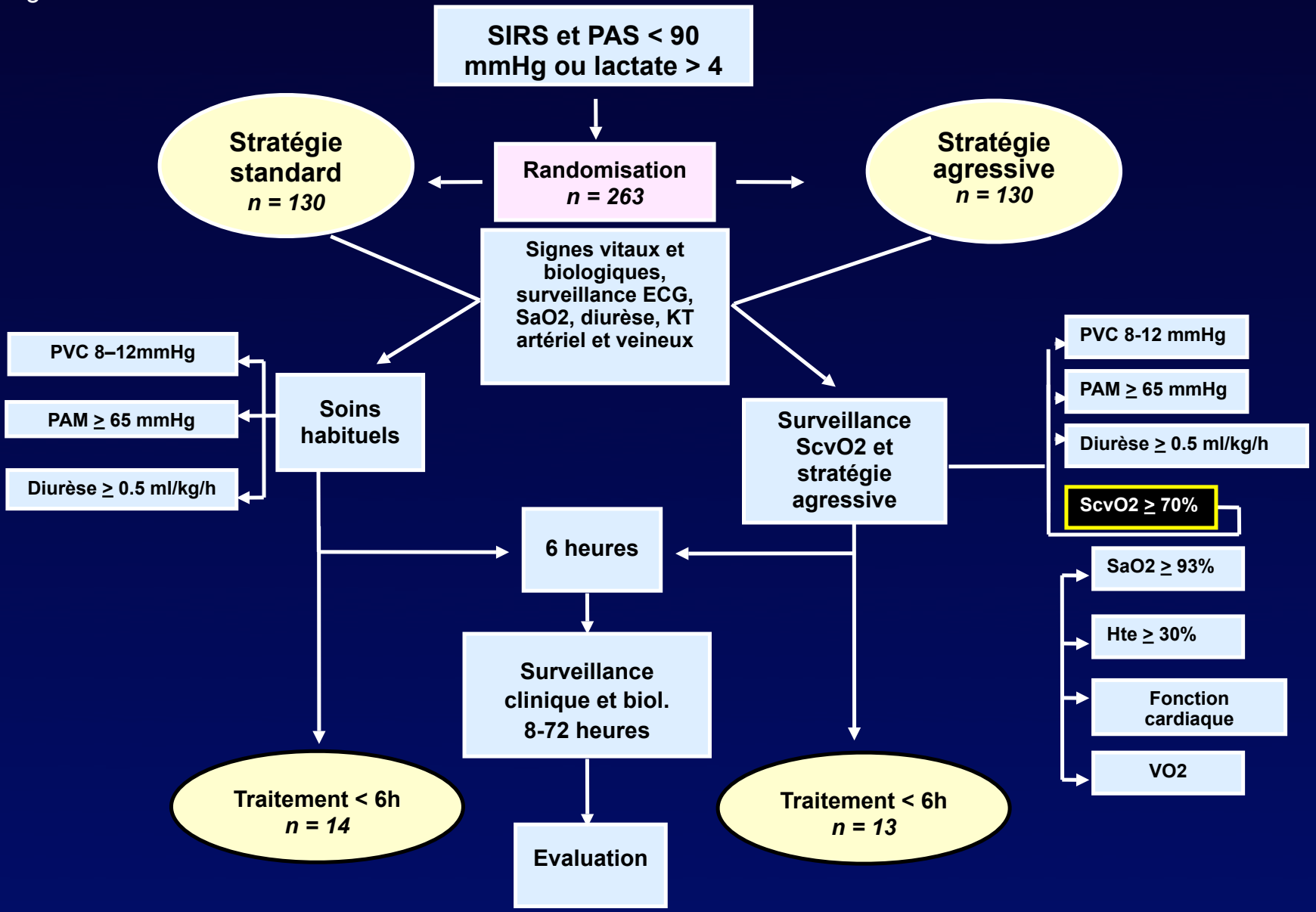
- Systolic BP ≤ 90 mm Hg

or

- Lactate ≥ 4 mmol/L

# Patient enrollment and hemodynamic support

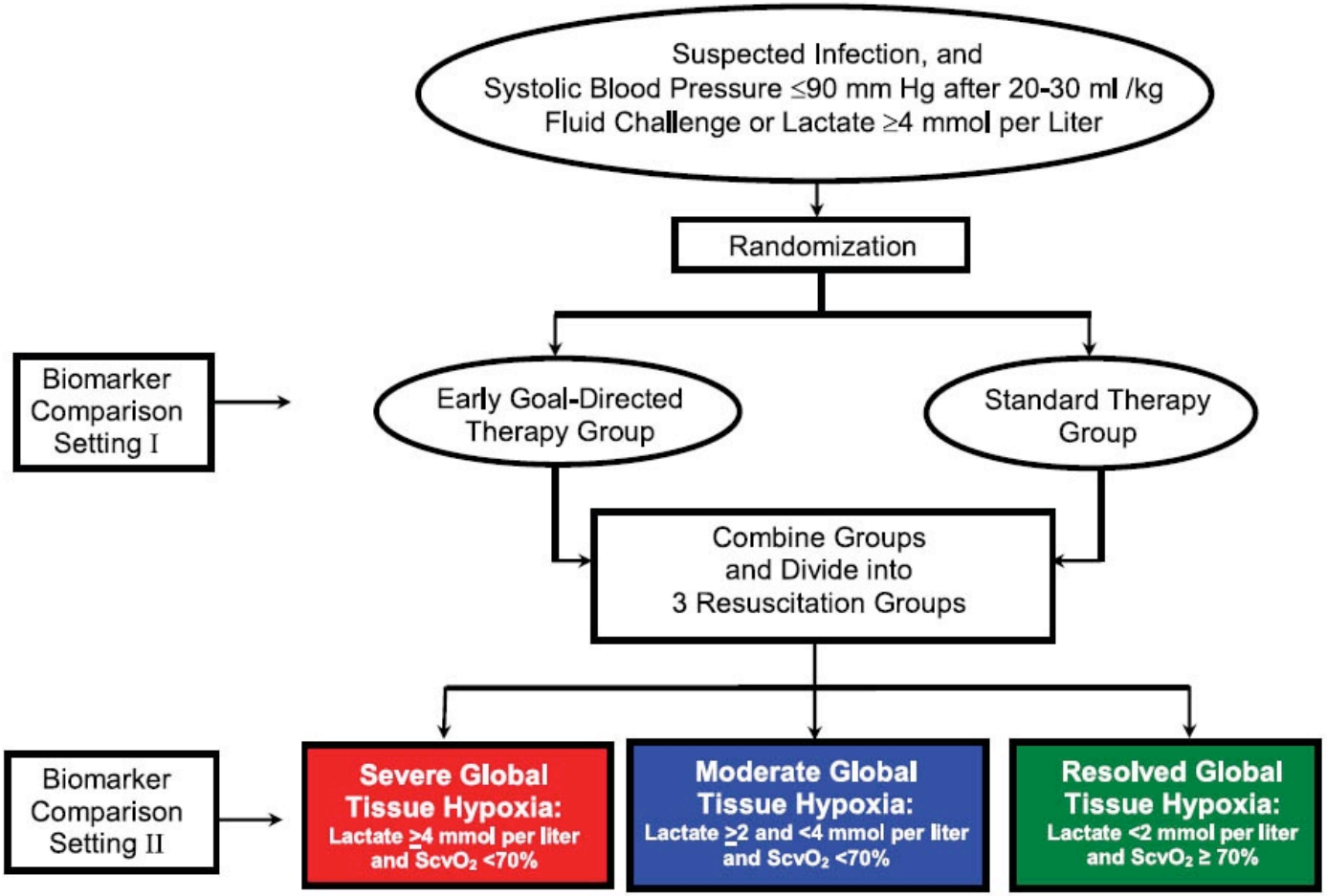
Rivers et al. N Engl J Med 2001



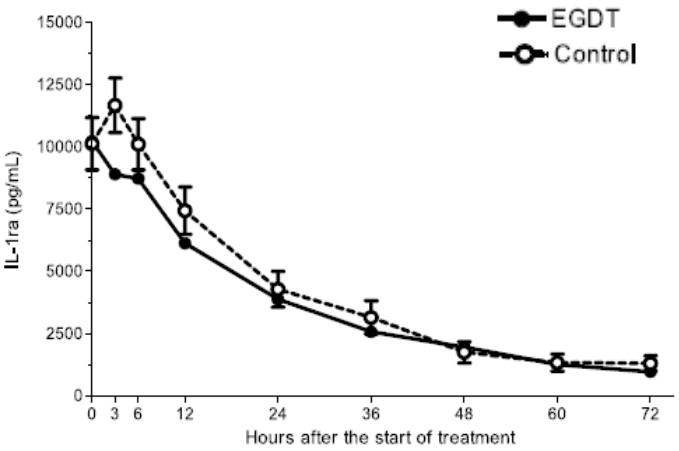
# The influence of early hemodynamic optimization on biomarker patterns of severe sepsis and septic shock*

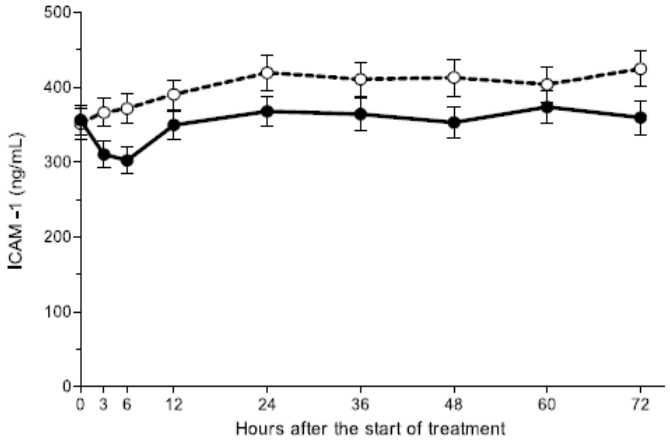
Emanuel P. Rivers, MD, MPH; James A. Kruse, MD; Gordon Jacobsen, MS; Kant Shah, MD; Manisha Loomba, MD; Ronny Otero, MD; Ed W. Childs, MD

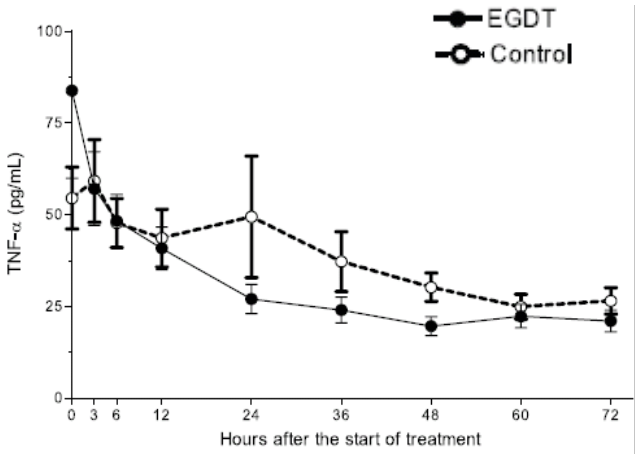
Crit Care Med 2007 Vol. 35, No. 9

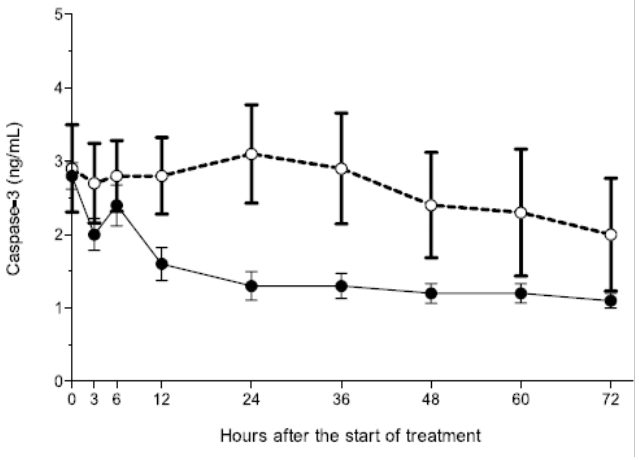


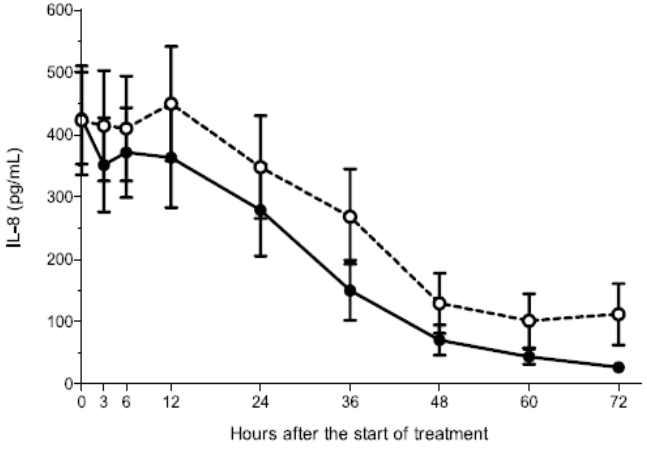
# EGDT in Severe Sepsis and Biomarkers




***Rivers E. Crit Care Med 2007:35:2016***

# Implementation of a bundle of quality indicators for the early management of severe sepsis and septic shock is associated with decreased mortality*

Critical Care Medicine 2007

H. Bryant Nguyen, MD, MS; Stephen W. Corbett, MD, PhD; Robert Steele, MD; Jim Banta, PhD, MPH; Robin T. Clark, BS; Sean R. Hayes; Jeremy Edwards; Thomas Cho, MD; William A. Wittlake, MD

6-hr emergency department severe sepsis bundle

1. Initiate CVP/$Scvo_2$ monitoring within 2 hrs of meeting bundle criteria
2. Give broad-spectrum antibiotics within 4 hrs of meeting bundle criteria
3. Complete early goal-directed therapy (CVP $\geq$8 mm Hg, SBP $\geq$90 mm Hg or MAP $\geq$65 mm Hg, and $Scvo_2$ $\geq$70%) at 6 hrs of meeting bundle criteria
4. Give steroid if patient is on vasopressor or if adrenal insufficiency is suspected
5. Monitor for lactate clearance

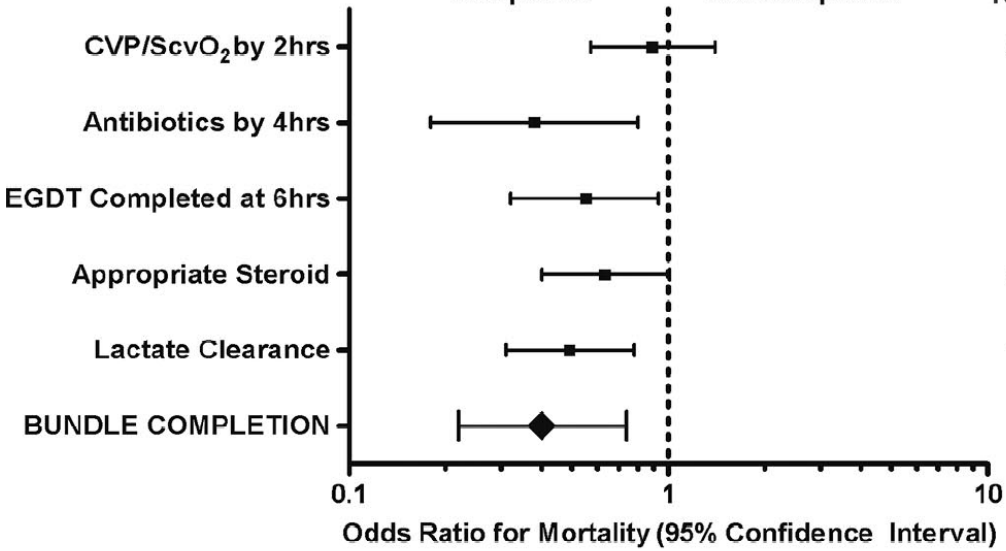
Completion of the bundle is defined as completion of quality indicators 1, 2, and 3 and one or more of items 4 and 5

The criteria to initiate the bundle are the following

1. Two of the following four items
   a. Temperature >38.3°C or <36.0°C
   b. Heart rate >90 beats/min
   c. Respiration >20 breaths/min
   d. White blood cell count >12,000 or <4000/$mm^3$, or >10% bandemia
2. A suspected infection
3. SBP <90 mm Hg after 20-mL/kg fluid bolus or lactate $\geq$4 mmol/L

# Implementation of a bundle of quality indicators for the early management of severe sepsis and septic shock is associated with decreased mortality*

H. Bryant Nguyen, MD, MS; Stephen W. Corbett, MD, PhD; Robert Steele, MD; Jim Banta, PhD, MPH; Robin T. Clark, BS; Sean R. Hayes; Jeremy Edwards; Thomas Cho, MD; William A. Wittlake, MD




| | | In-Hospital Mortality (%) | | |
|---|---|---|---|---|
| | No. Patients* | Completed | Not Completed | P-value |
| CVP/ScvO2 by 2hrs | 208 vs. 122 | 33.8 | 36.4 | 0.65 |
| Antibiotics by 4hrs | 298 vs. 32 | 32.9 | 56.0 | 0.03 |
| EGDT Completed at 6hrs | 93 vs. 237 | 25.8 | 38.8 | 0.03 |
| Appropriate Steroid | 208 vs. 122 | 31.3 | 41.8 | 0.06 |
| Lactate Clearance | 160 vs. 170 | 26.9 | 42.9 | <0.01 |
| **BUNDLE COMPLETION** | **77 vs. 253** | **20.8** | **39.5** | **<0.01** |

H. Bryant N'Guyen et al. Crit Care Med 2007

# Barriers to implementing protocol-based sepsis resuscitation in the emergency department—Results of a national survey*

David J. Carlbom, MD; Gordon D. Rubenfeld, MD, MSc

**Critical Care Med 2008**

***Objective:*** **To identify barriers to implementation of a written protocol for early goal-directed therapy for severe sepsis in the busiest emergency departments in the United States.**
***Design:*** **Telephone survey with both quantitative and qualitative analysis.**
***Setting:*** **Two busiest teaching and two busiest nonteaching emergency departments in each of the 25 most densely populated combined statistical areas in the United States.**
***Subjects:*** **24 physician directors and 40 nursing managers representing 53% of the 100 emergency departments surveyed**

Barriers to implementing protocol-based sepsis resuscitation in the emergency department—Results of a national survey*

David J. Carlbom, MD; Gordon D. Rubenfeld, MD, MSc

Critical Care Med 2008

***Main barriers identified:***

- **Lack of available nursing staff to perform the procedure**
- **Inability to monitor CVP in the ED**
- **Challenges in identifying septic patients**

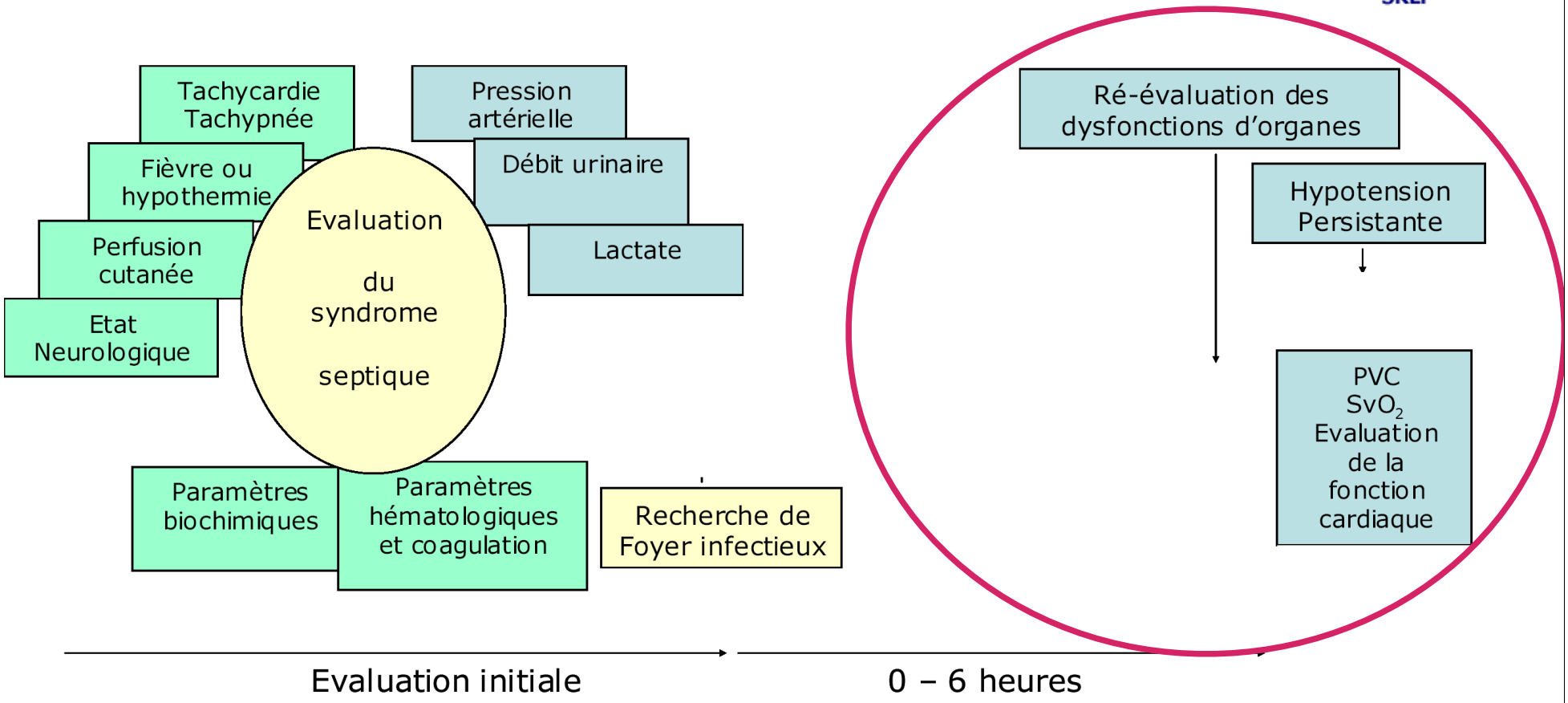
***Differences between nurse managers and physicians*:**

- **CVP insertion (38% vs. 5%; *p* .01)**
- **Lack of agreement with the EGDT protocol (16% vs. 0%; *p* .03)**

# Quels objectifs pour apprécier l'effet des traitements ?

**Groupe Transversal Sepsis**
**« Prise en charge initiale des états septiques graves de l'adulte et de l'enfant »**

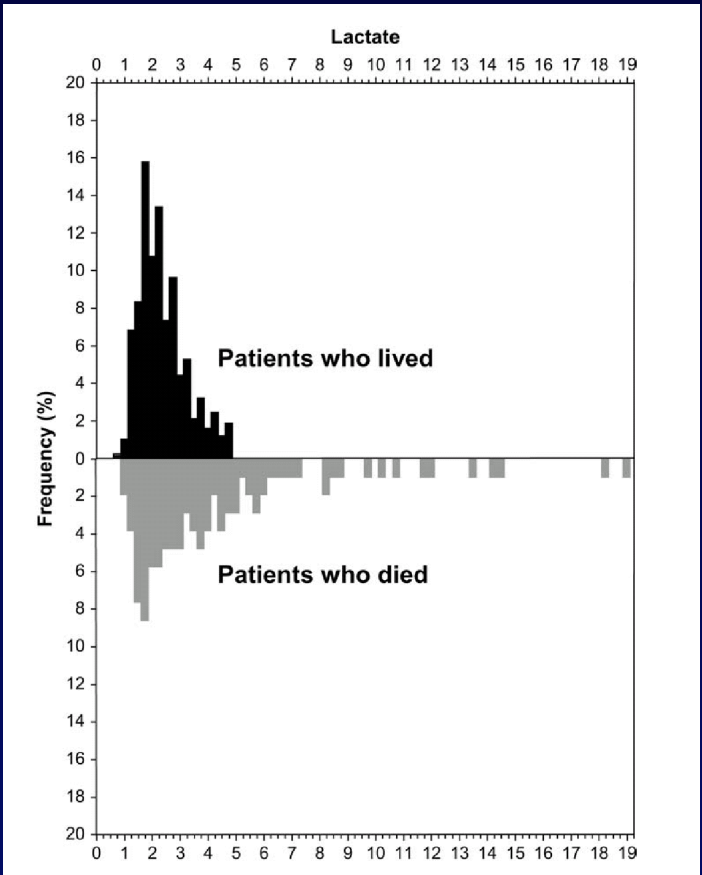
**ADARPEF**
**GFRUP**
**SAMU de France**
**SFAR**
**SFMU**
**SPILF**
**SRLF**



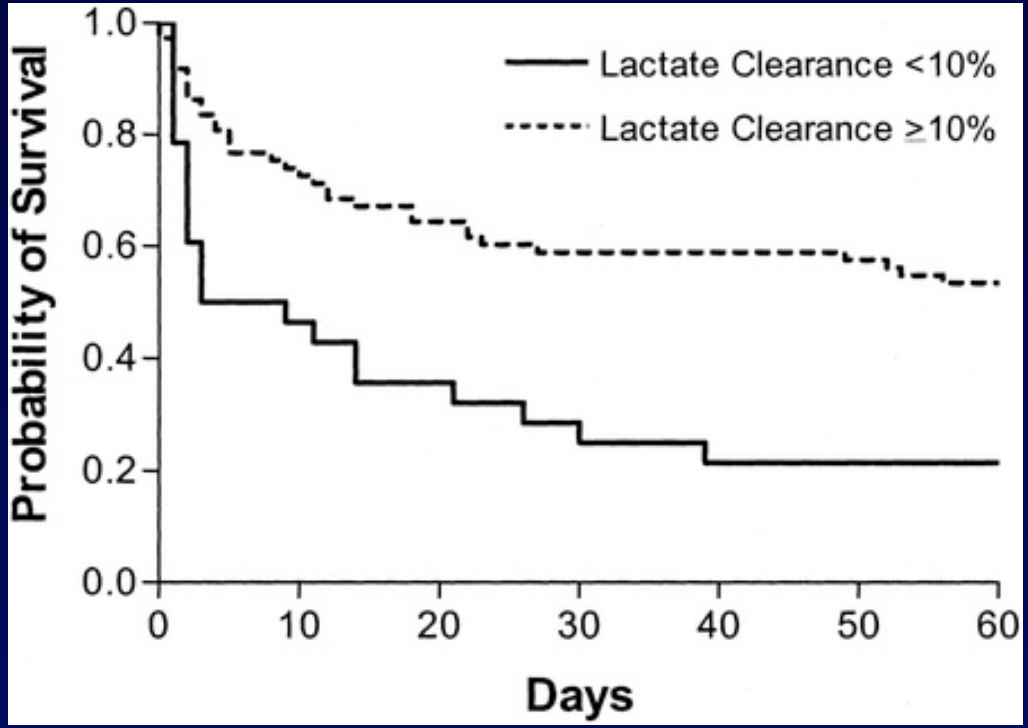

***Coordination*** **:**

Christian BRUN-BUISSON (SRLF) & Claude MARTIN (SFAR)

# Serum Lactate as a Predictor of Mortality in Emergency Department Patients With Infection




Shapiro et al. AEM 2005



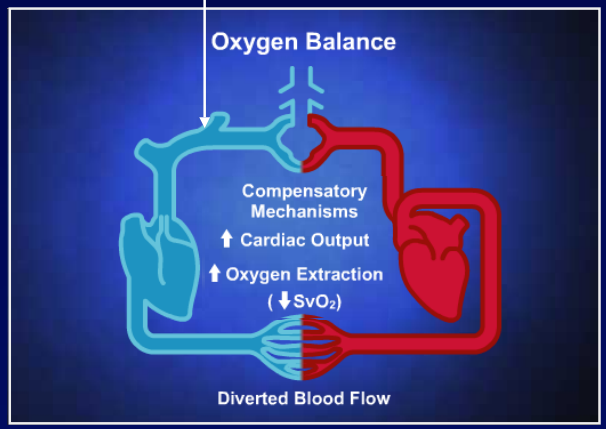

Nguyen et al. CCM 2004

## Combination of variables of global and regional perfusion ?

- Global perfusion end-points
  - Oxygen delivery
  - Base deficit
  - Lactate
- Regional perfusion end-points
  - Gastric tonometry
  - Sublingual capnography
  - Near-infrared spectrometry (NIRS)
  - OPS imaging
- Mitochondrial function

# Saturation en $O_2$ du sang veineux mêlé ($SvO_2$)

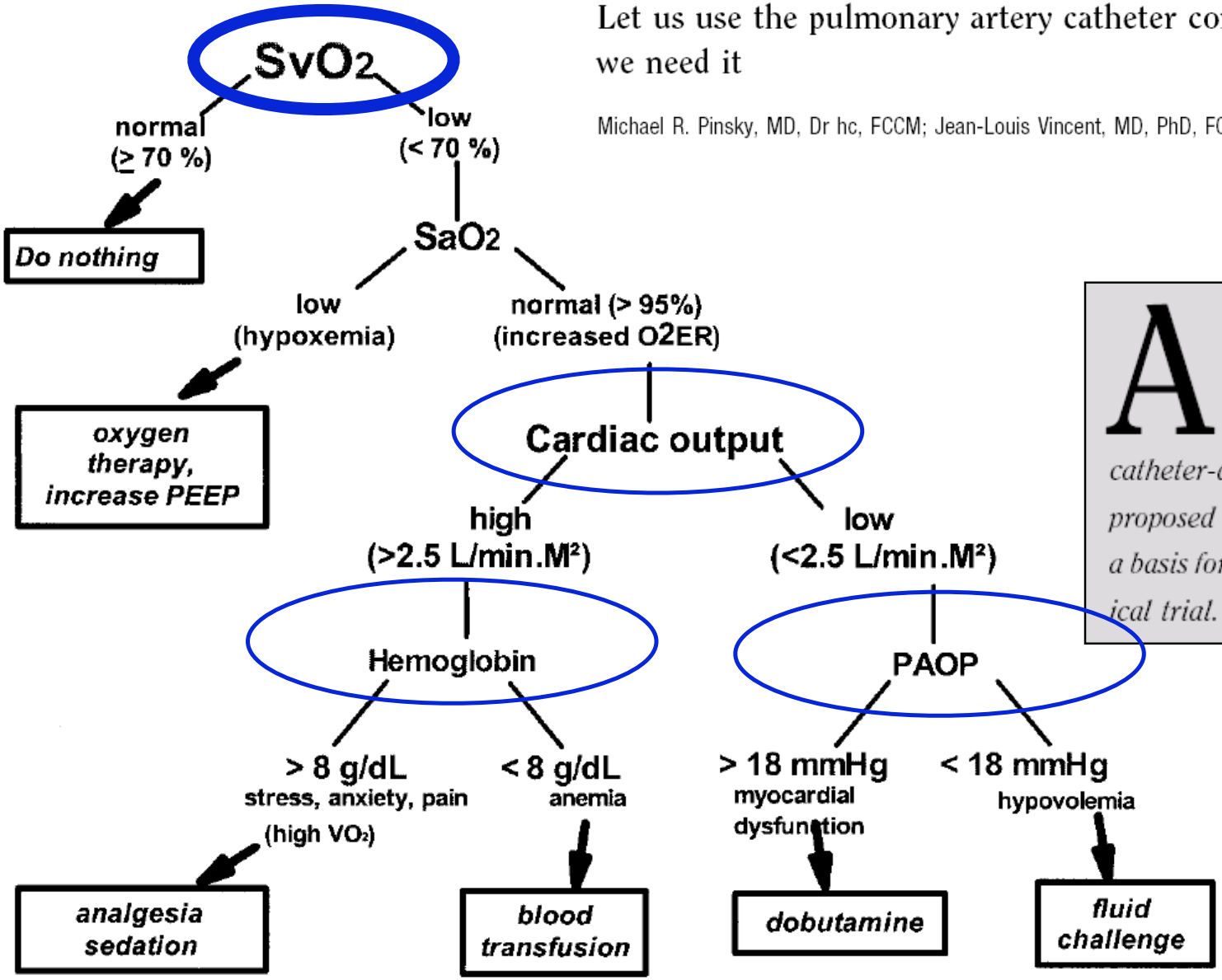
- Reflet de la balance entre $TaO_2$ et $VO_2$ tisssulaire
- **$SvO_2 = SaO_2 – [VO_2 (Qc \times Hb \times 1.34)]$**
  - 4 déterminants interdépendants
  - tous potentiellement altérés a cours du sepsis
  - variations rarement imputables à un seul mécanisme
- Valeurs normales
  - sujet « sain » au repos : 70-75 %
  - sujet « sain » à l'exercice : 45%
  - $SvO_2$ critique ?
- Interprétation prudente dans 2 situations
  - lorsque la $SvO_2$ critique est atteinte
  - altération de l'extraction (au cours du choc septique)



Let us use the pulmonary artery catheter correctly and only when we need it

Michael R. Pinsky, MD, Dr hc, FCCM; Jean-Louis Vincent, MD, PhD, FCCM

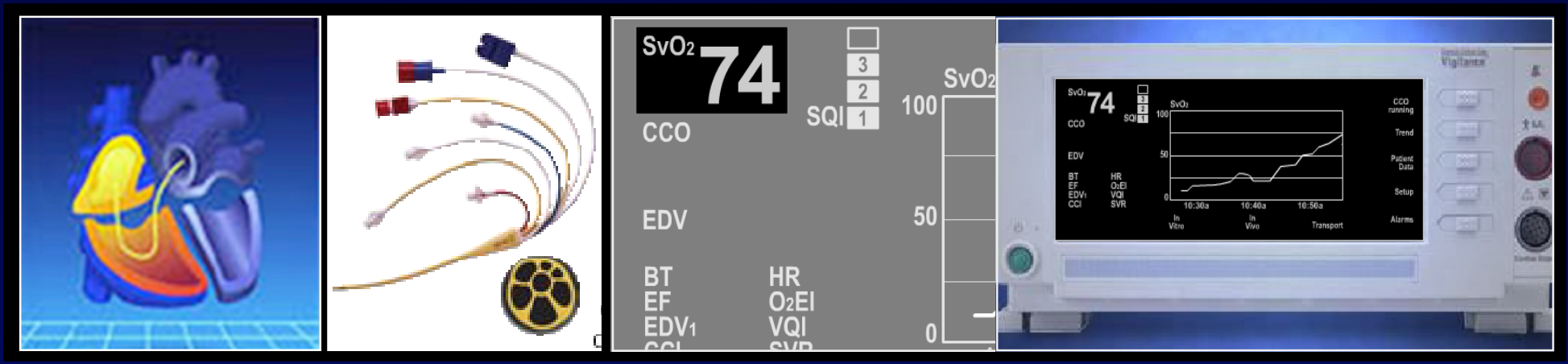
Crit Care Med 2005




*A treatment protocol for the use of pulmonary artery catheter-derived variables is proposed that could serve as a basis for a prospective clinical trial.*

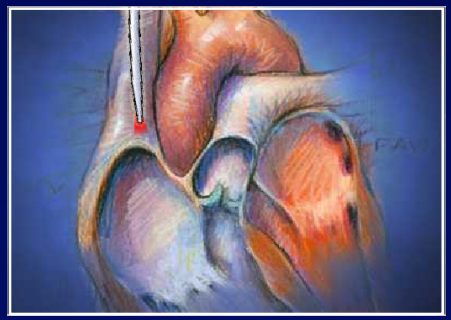
# Continuous measurement of $SvO_2$:
## *Two methods*

- Pulmonary artery $SvO_2$ : Modified PAC (optical fibers)



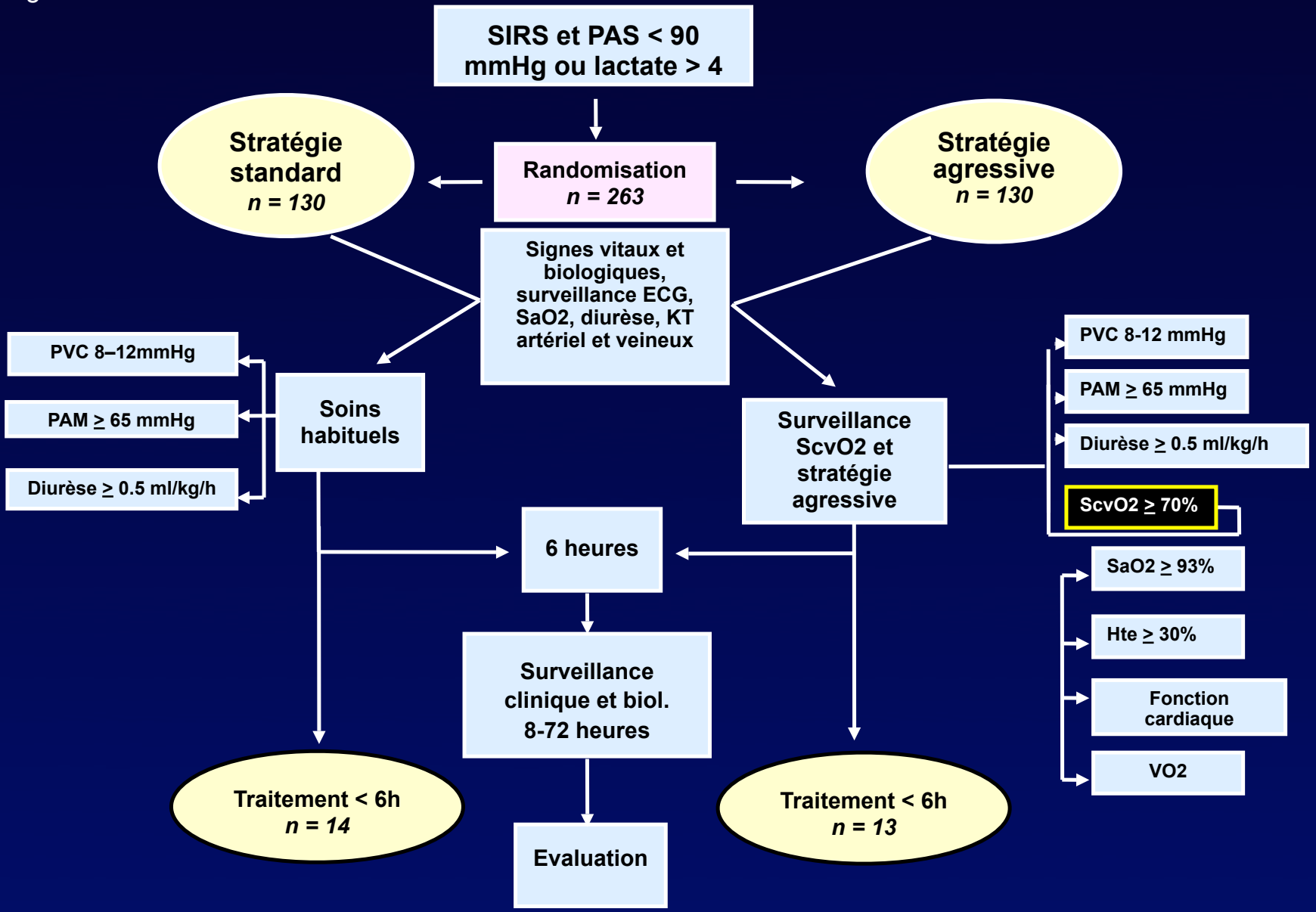

- Central venous $SvO_2$ = $ScvO_2$ :

  ➔ Modified CVC by adjunction of optical fibers



# Patient enrollment and hemodynamic support

Rivers et al. N Engl J Med 2001



# Prise en charge initiale du sepsis sévère et du choc septique

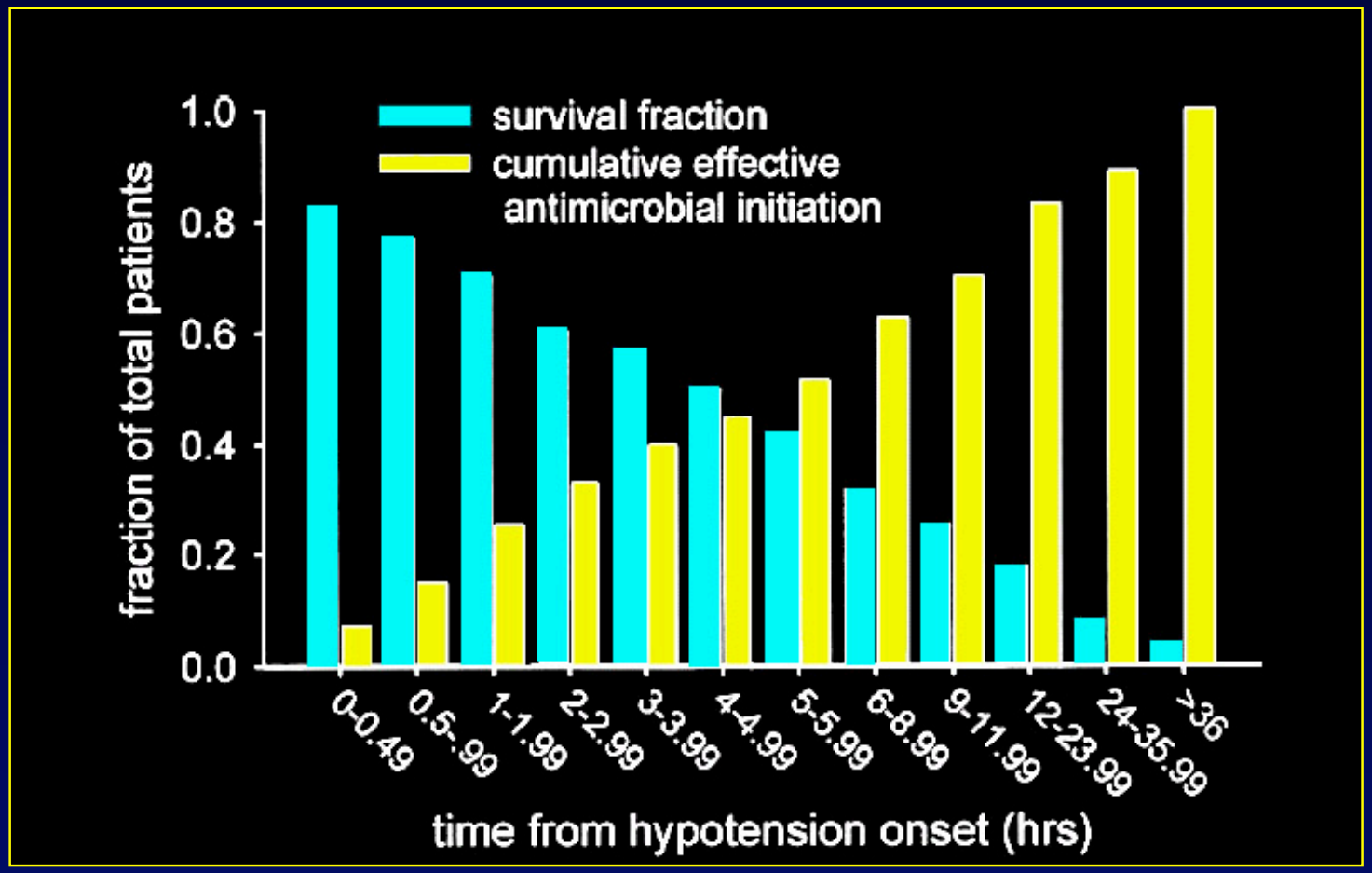
## Deux aspects majeurs

Traitement anti-infectieux précoce
- Antibiothérapie
- Contrôle de la source

Contrôle rapide des désordres hémodynamiques

## Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock*

Anand Kumar, MD; Daniel Roberts, MD; Kenneth E. Wood, DO; Bruce Light, MD; Joseph E. Parrillo, MD; Satendra Sharma, MD; Robert Suppes, BSc; Daniel Feinstein, MD; Sergio Zanotti, MD; Leo Taiberg, MD; David Gurka, MD; Aseem Kumar, PhD; Mary Cheang, MSc





Kumar A et al. Crit Care Med 2006;34:1589

# Delays in Antimicrobial Treatment and Mortality Rate of Meningitis

Detrimental role of delayed antibiotic administration and penicillin-nonsusceptible strains in adult intensive care unit patients with pneumococcal meningitis: The PNEUMOREA prospective multicenter study*

Marc Auburtin, MD; Michel Wolff, MD; Julien Charpentier, MD; Emmanuelle Varon, MD; Yves Le Tulzo, MD, PhD; Christophe Girault, MD; Ismaël Mohammedi, MD; Benoît Renard, MD; Bruno Mourvillier, MD; Fabrice Bruneel, MD; Jean-Damien Ricard, MD; Jean-François Timsit, MD, PhD

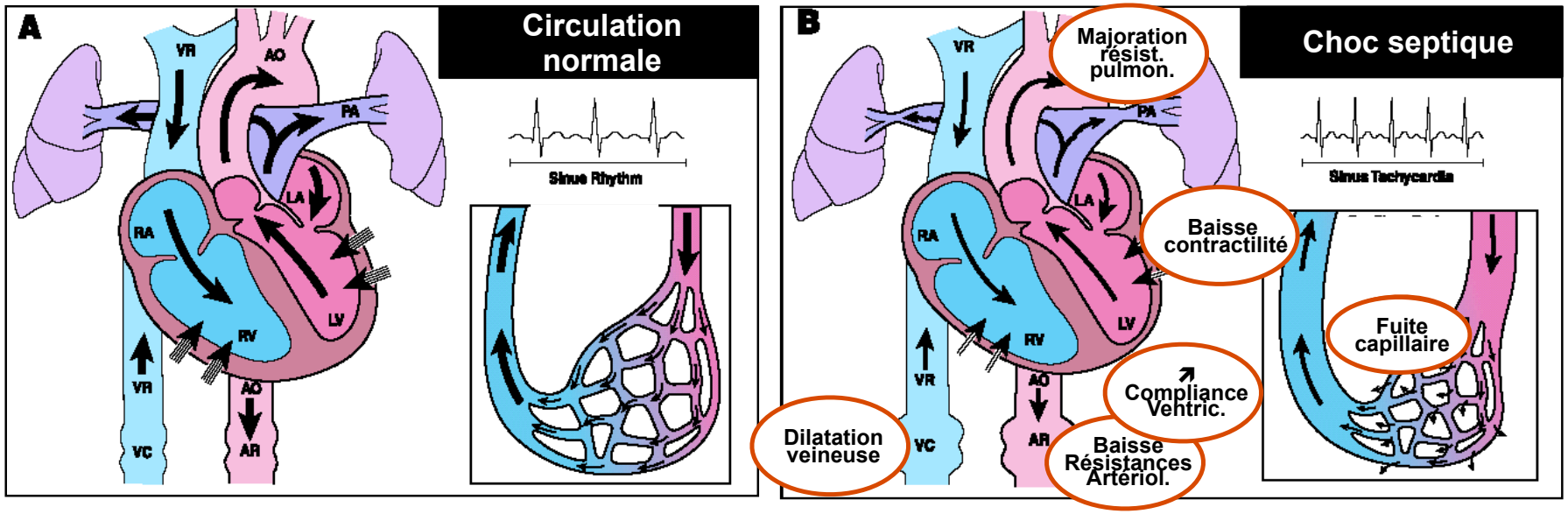
## French multicenter study
## Multivariate analysis for risk factors of mortality at 3 months

| Variable | Odds Ratio | 95% Confidence Interval | *p* Value |
|---|---|---|---|
| SAPS II[a] | 1.12 | 1.072–1.153 | .002 |
| Penicillin-nonsusceptible *Streptococcus pneumoniae* | 6.83 | 2.94–20.8 | $<10^{-4}$ |
| Interval >3 hrs between hospital admission and antibiotic treatment | 14.12 | 3.93–50.9 | $<10^{-4}$ |
| CSF leukocyte count $>10^3/\mu L$ | 0.30 | 0.10–0.944 | .04 |

Aubertin, Crit Care Med 2006

# Physiopathologie des anomalies cardio-circulatoires observées au cours du sepsis.

Dellinger RP. **Crit Care Med**
**2003**




Tachycardie, hypotension artérielle
Signes de mauvaise perfusion tissulaire

**Diagnostic de sepsis grave**

**Détresse vitale menaçante ?**

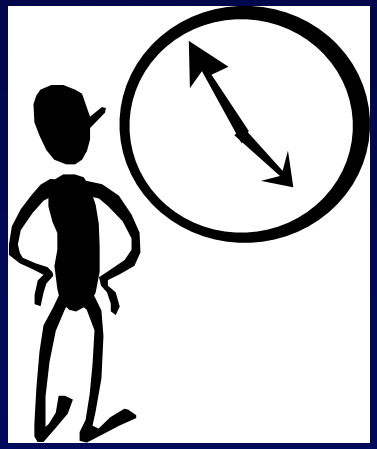
**Oui**

**Non**

- **Monitorage : scope, PA, FR, diurèse**
- **Oxygénothérapie pour SpO2 > 95%**
- **Bilan sanguin (lactates) et bactériologique**
- **Cristalloïdes : 500 ml/15 mn (PAM > 65)**
- **Appel référent**

organisée conjointement par
la Sfar et la SRLF

Prise en charge hémodynamique du sepsis sévère (nouveau-né exclu)

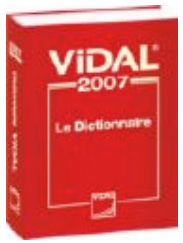


**90 minutes …**

**Admission en réanimation**

# Remplissage vasculaire
## *Produits disponibles ?*

- **Cristalloïdes isotoniques**
  - Solutions « standards »
    - Chlorure de sodium 0,9%
    - Ringer lactate
  - Solutions « balancées » Isofundine®

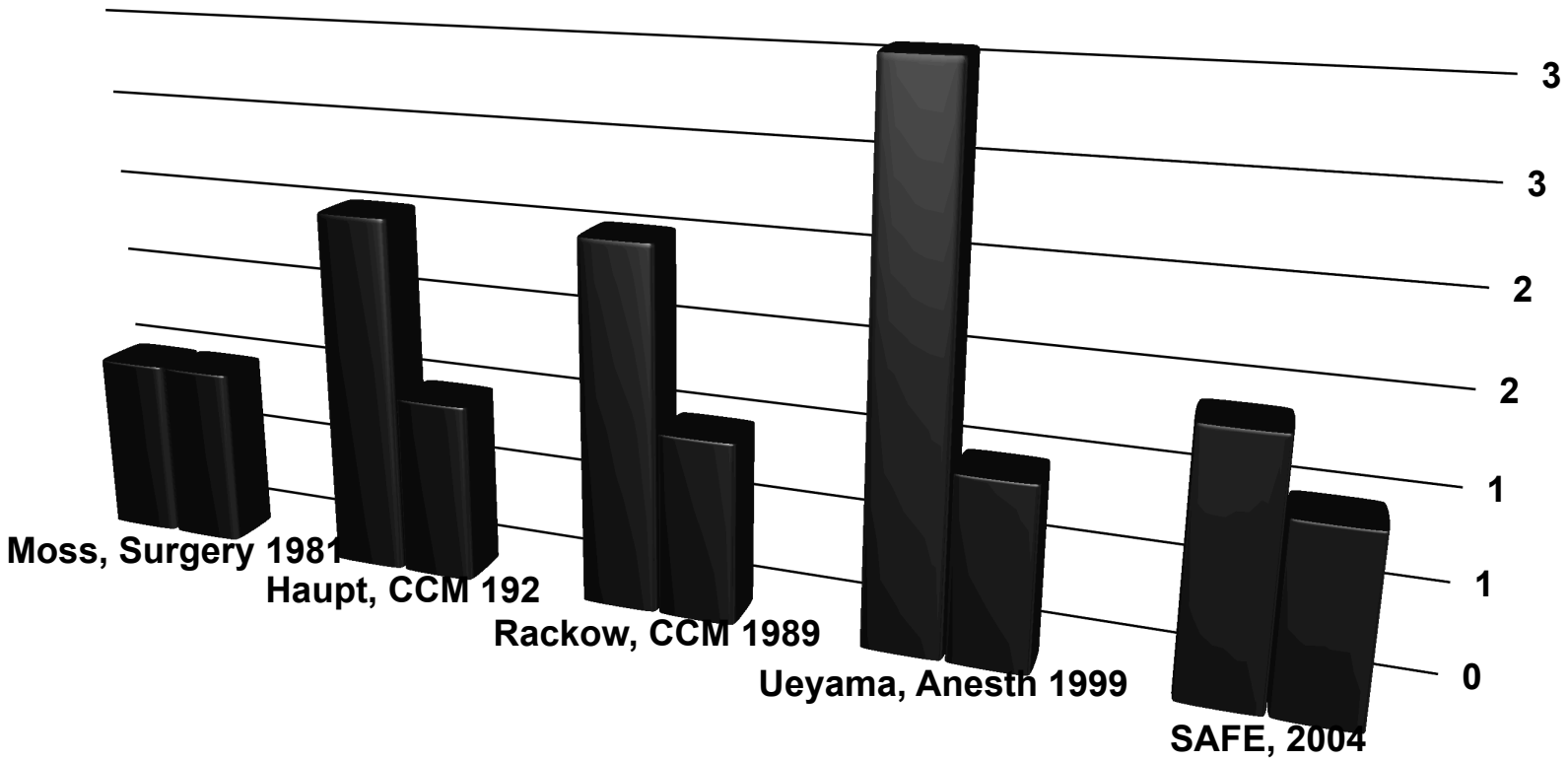



- **Colloïdes de synthèse**
  - Gélatines fluides modifiées
    - 3% (Plasmion®)
    - 4% (Gelofusine®)
  - Hydroxyéthylamidons
    - 240 kDa/0,5 (HEAfusine®, Hesteril®
    - 130 kDa/0,4 (Restorvol®, Voluven®)

- **Solutions salées hypertoniques**
  - Avec hydroxyéthylamidon 200 kDa/0,5 (HyperHES®)
  - Avec dextran 70 (Rescuflow®)

# Volume nécessaire pour obtenir le même effet ?

*ratio cristalloïde / colloïde



# Produits de remplissage

1. Les produits sanguins stables ou labiles, les dextrans et les amidons de poids moléculaire > à 150 KDa ne doivent pas être employés comme des solutés de remplissage
2. Les cristalloïdes et les autres colloïdes, quand ils sont titrés pour un même objectif hémodynamique, ont une efficacité équivalente.
3. Compte tenu d'un coût bien moindre et de leur innocuité, on peut recommander les cristalloïdes isotoniques, surtout à la phase initiale du choc.

**Grade B**

# Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2008

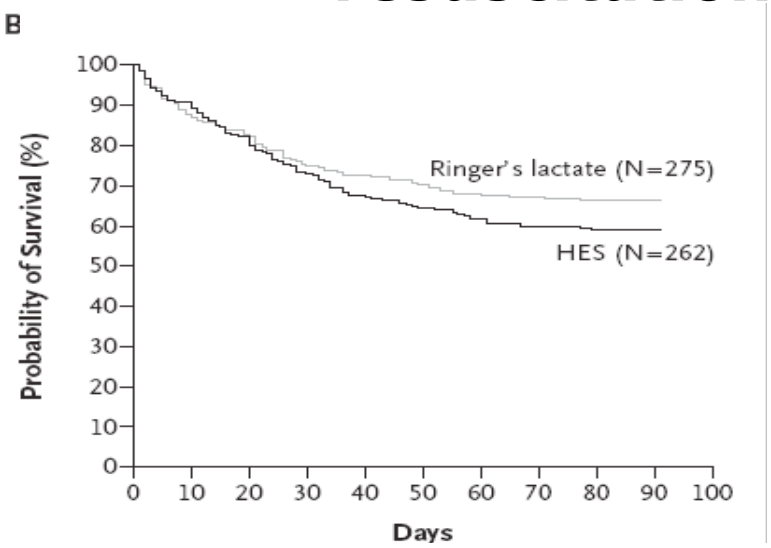
## *Fluid therapy*

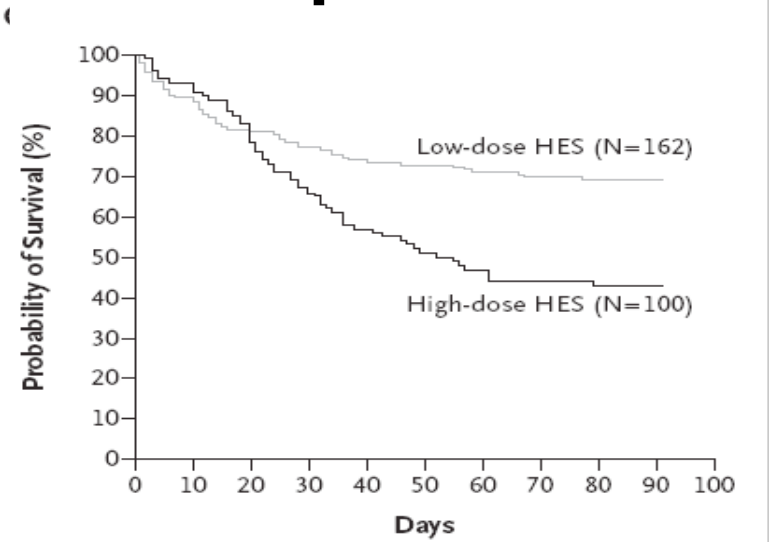
- Fluid-resuscitate using crystalloids or colloids (1B)
- Target a CVP of 8 mm Hg (12 mm Hg if mechanically ventilated) (1C)
- Use a fluid challenge technique while associated with a hemodynamic improvement (1D)
- Give fluid challenges of 1000 mL of crystalloids or 300–500 mL of colloids over 30 mins. More rapid and larger volumes may be required in sepsis-induced tissue hypoperfusion (1D)
- Rate of fluid administration should be reduced if cardiac filling pressures increase without concurrent hemodynamic improvement (1D)

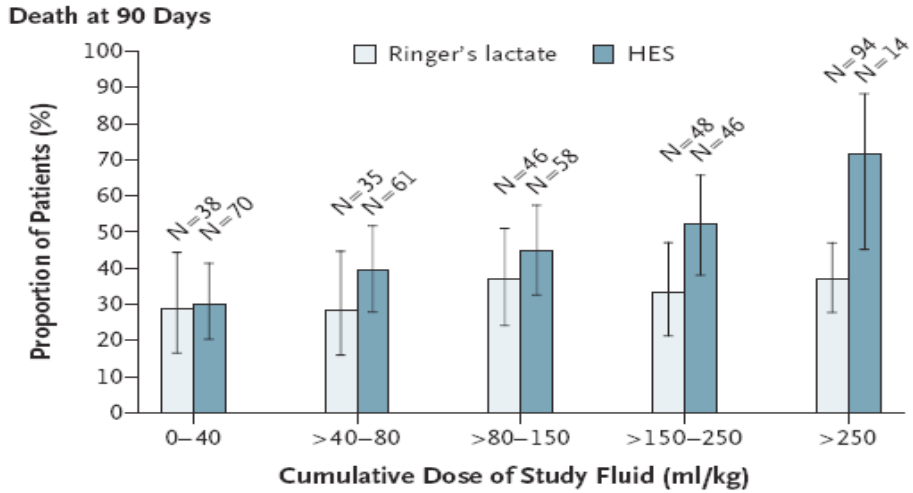
Crit Care Med 2008
Intensive Care Med 2008

# Intensive insulin therapy and pentastarch resuscitation in severe sepsis

Brunkhorst FM et al. NEJM 2008




« Low-dose » ≤ 22 ml/kg/j

Dose cumulée 48.3 ml/kg [21.9-96.2]

« High-dose » > 22 ml/kg/j

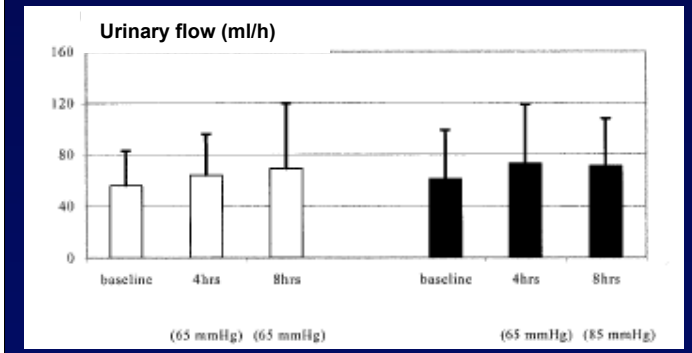
Dose cumulée 136.0 ml/kg [79-180]

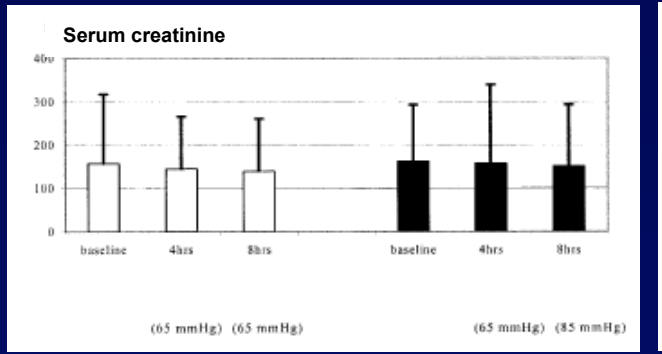
# Increasing mean arterial pressure in patients with septic shock: Effects on oxygen variables and renal function

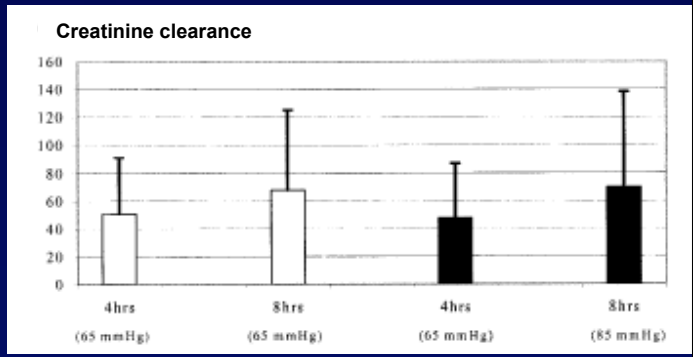
Bourgoin et al. Crit Care Med 2005 ; 33 : 780-6

Table 3. Biochemical variables, median (range)

| | Group 1 (n = 14) MAP, 65 mm Hg | | Group 2 (n = 14) MAP, 85 mm Hg | |
|---|---|---|---|---|
| | Baseline | 8 Hrs | Baseline | 8 Hrs |
| Arterial pH | 7.39 (7.21–7.46) | 7.40 (7.20–7.47) | 7.39 (7.23–7.45) | 7.42 (7.21–7.46) |
| Arterial $Pa_{O_2}$, mm Hg | 70 (57–115) | 75 (54–117) | 75 (53–119) | 72 (57–121) |
| Arterial $Pc_{O_2}$, mm Hg | 35 (30–42) | 35 (31–44) | 37 (32–45) | 37 (31–45) |
| Hemoglobin, g · 100 $mL^{-1}$ | 10.0 (7.9–13.4) | 9.8 (7.7–13.1) | 10.0 (7.6–13.4) | 9.9 (7.5–13.1) |

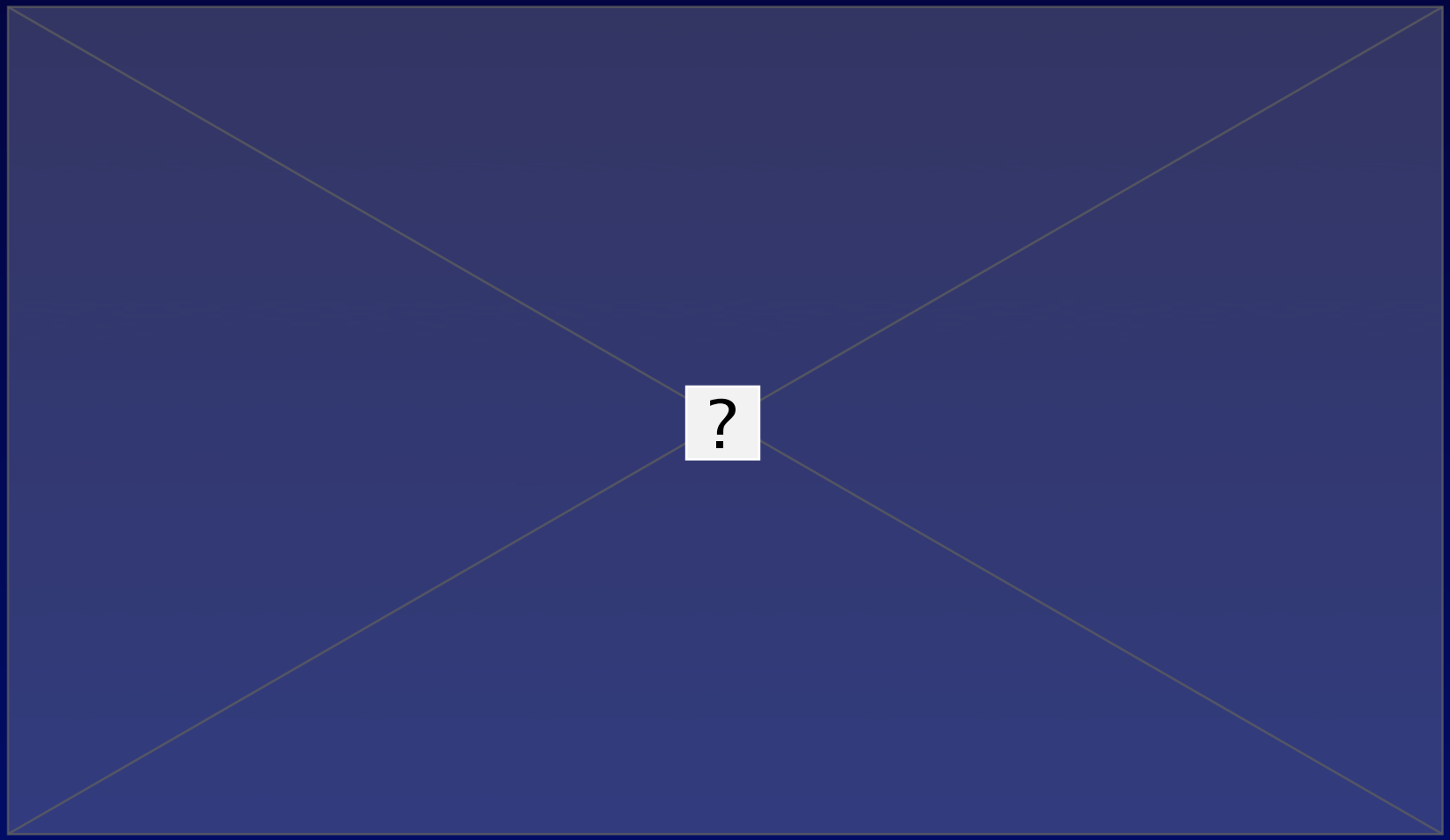


# Norepinephrine plus dobutamine versus epinephrine alone for management of septic shock: a randomised trial

Annane D, Vignon P, Renault A, Bollaert PE, Charpentier C, Martin C, Troché G, Ricard JD, Nitenberg G, Papazian L, Azoulay E, Bellissant E; CATS Study Group. **Lancet 2007**



# Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2008

## *Vasopressors*

- Maintain MAP 65 mm Hg (1C)
- Norepinephrine and dopamine centrally administered are the initial vasopressors of choice (1C)

o Epinephrine, phenylephrine, or vasopressin should not be administered as the initial vasopressor in septic shock (2C). Vasopressin 0.03 units/min may be subsequently added to norepinephrine with anticipation of an effect equivalent to norepinephrine alone

o Use epinephrine as the first alternative agent in septic shock when blood pressure is poorly responsive to norepinephrine or dopamine (2B).

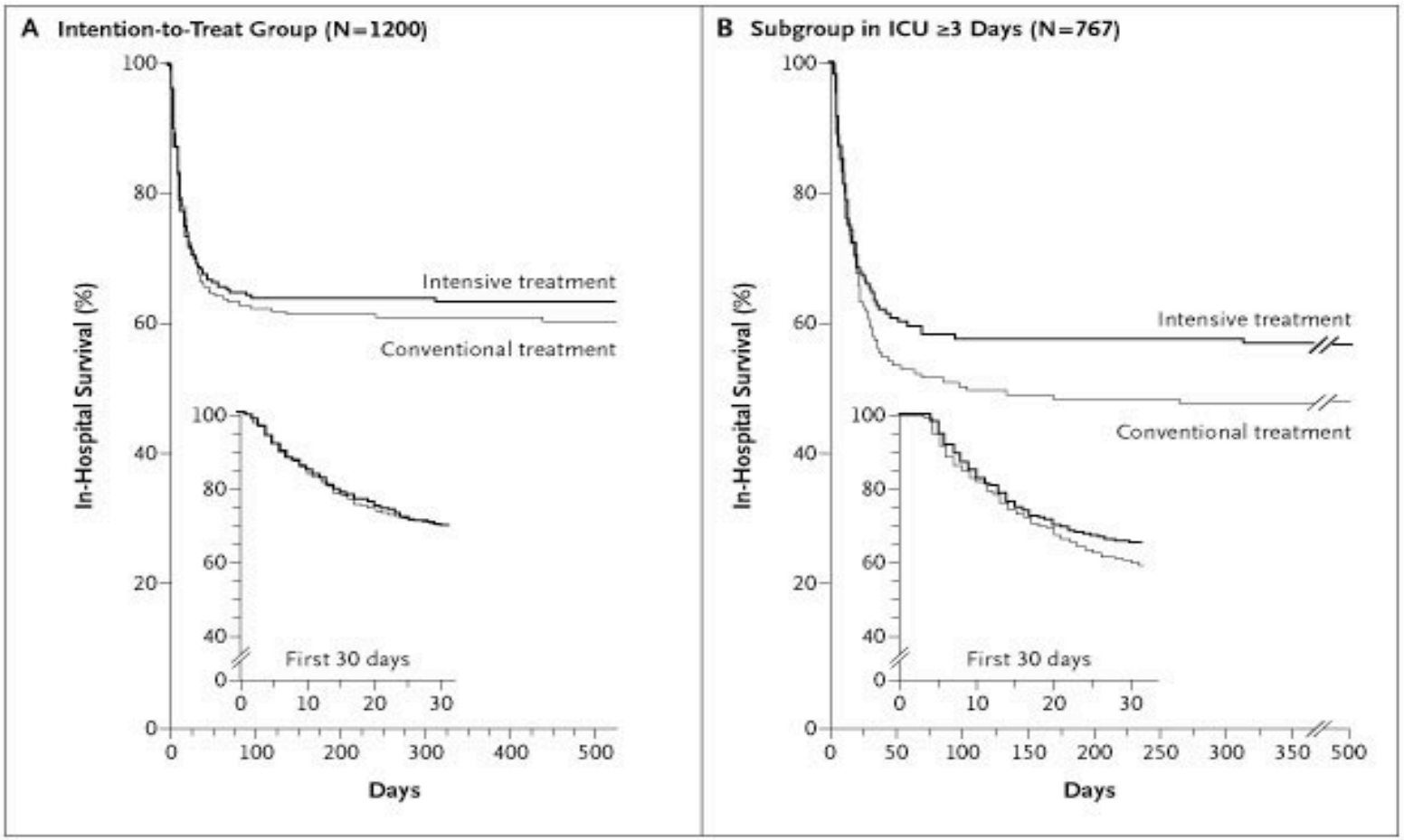
- Do not use low-dose dopamine for renal protection (1A)
- In patients requiring vasopressors, insert an arterial catheter

Crit Care Med 2008
Intensive Care Med 2008

# Traitements « adjuvants »

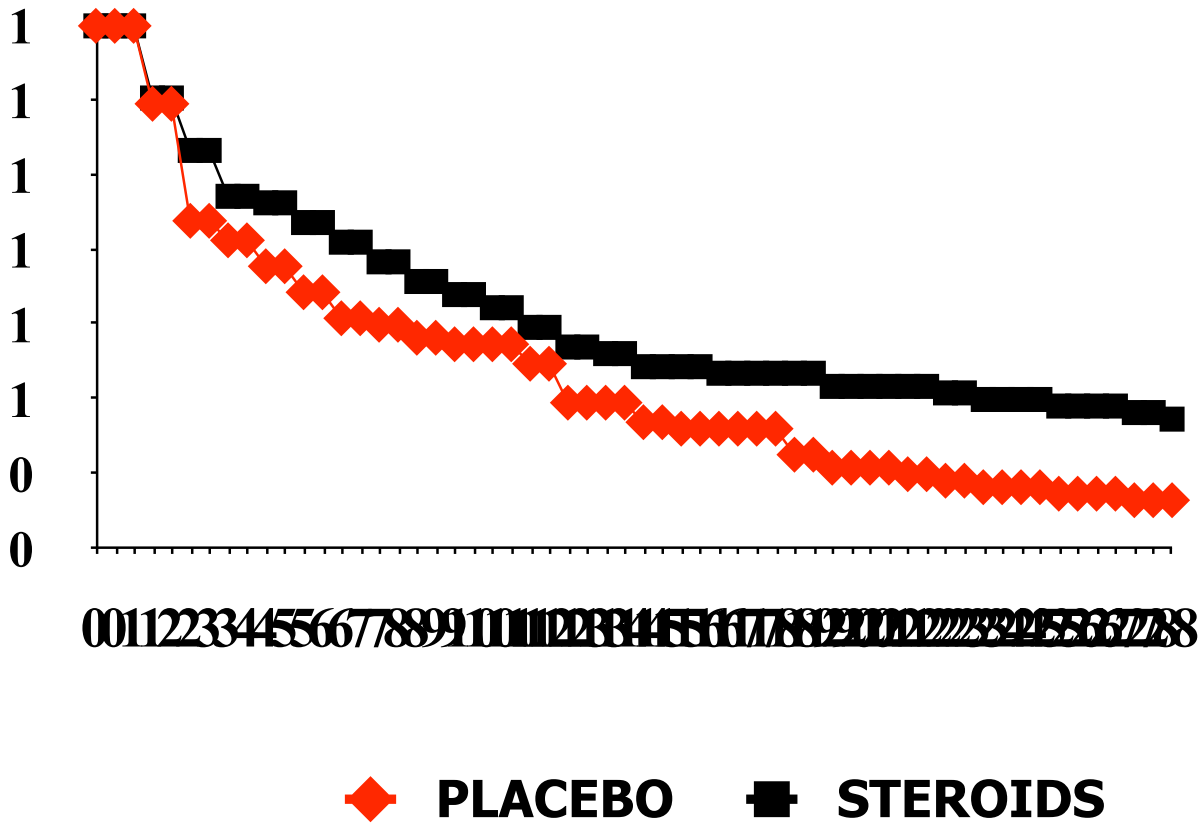
- Insuline ?
- Corticostéroides ?
- Nouveaux « anticoagulants » ?

# Intensive insulin therapy in the medical ICU




Van den Berghe, NEJM 2006

# 28-DAY SURVIVAL IN NON RESPONDERS

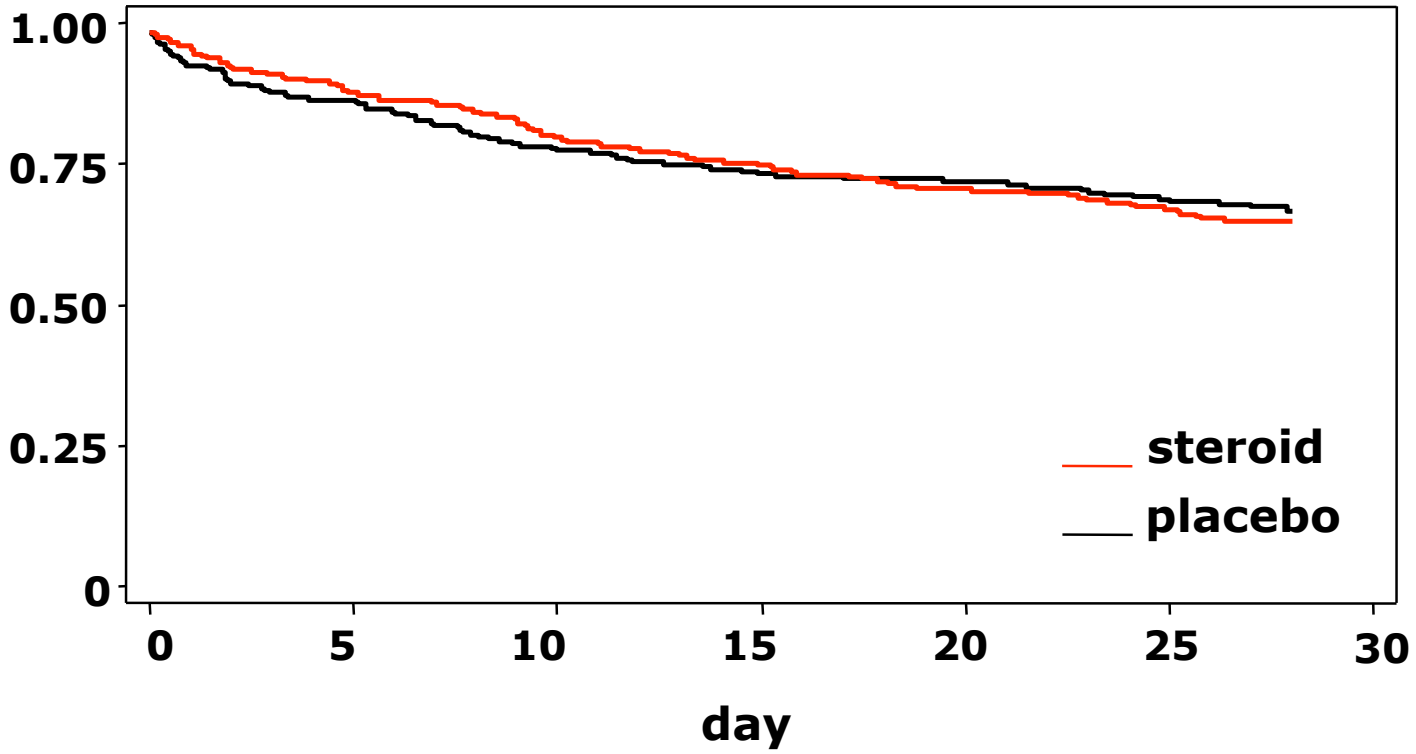



Annane, JAMA 2002

# Hydrocortisone therapy for patients with septic shock

Sprung CL, Annane D, Keh D, Moreno R, Singer M, Freivogel K, Weiss YG, Benbenishty J, Kalenka A, Forst H, Laterre PF, Reinhart K, Cuthbertson BH, Payen D, Briegel J; CORTICUS Study Group. **N Engl J Med 2008**

**Kaplan-Meier 28 day survival curves - all patients**



# Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2008

## *Steroids*

o Consider iv HC for adult septic shock when hypotension responds poorly to adequate fluid resuscitation and vasopressors (2C)

o ACTH stimulation test is not recommended to identify the subset of adults with septic shock who should receive HC (2B)

o HC is preferred to dexamethasone (2B)

o Fludrocortisone (50 g orally once a day) may be included if an alternative to HC is being used that lacks significant mineralocorticoid

Crit Care Med 2008
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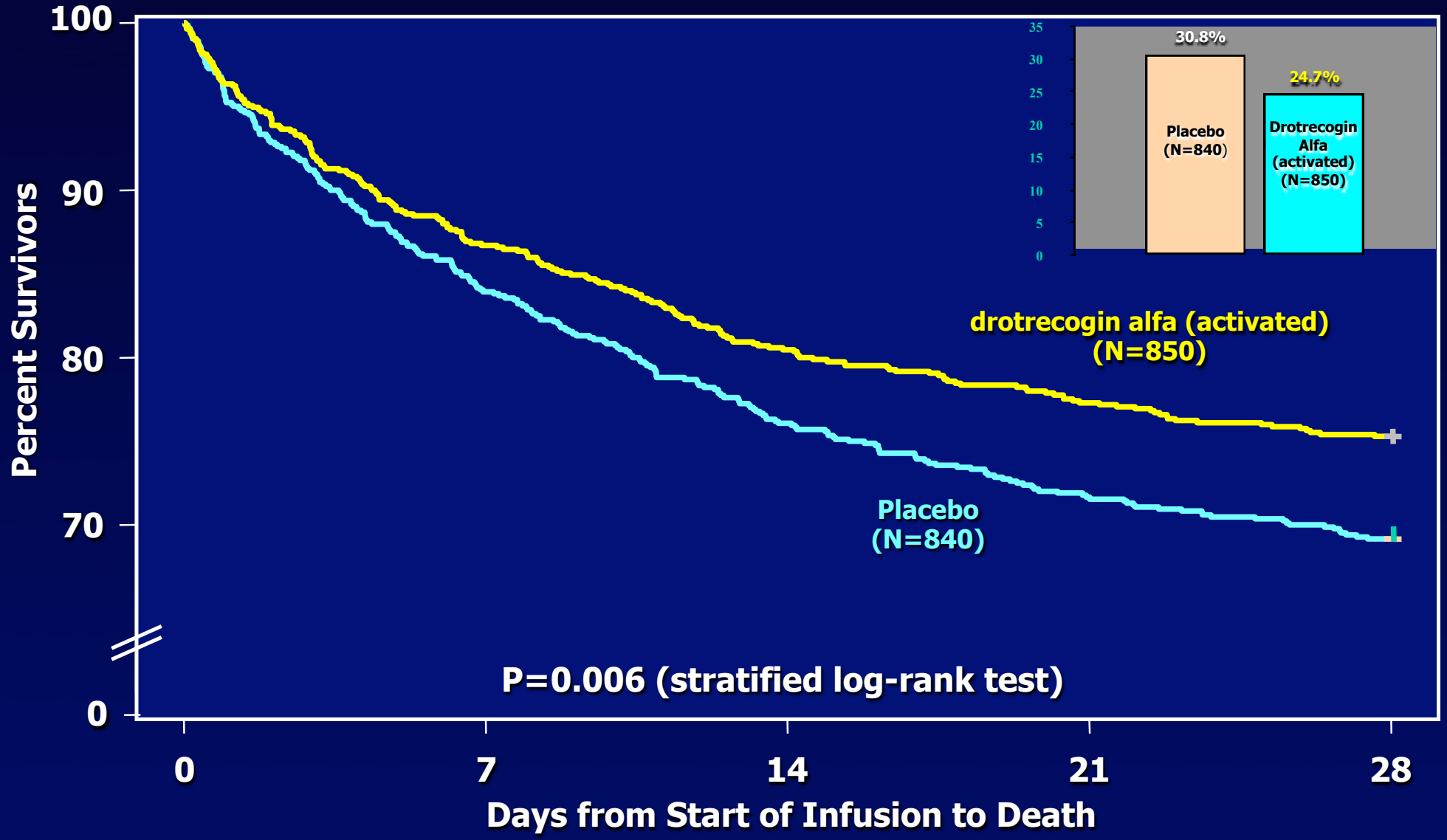
# Sepsis and new anticoagulants

- Tissue Factor Pathway Inhibitor (TFPI)
- Antithrombin (AT)
- Activated Protein C (APC)

# PROWESS : Summary of 28-Day All Cause Mortality




Bernard G et al, NEJM 2001 (PROWESS Study)

# Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2008

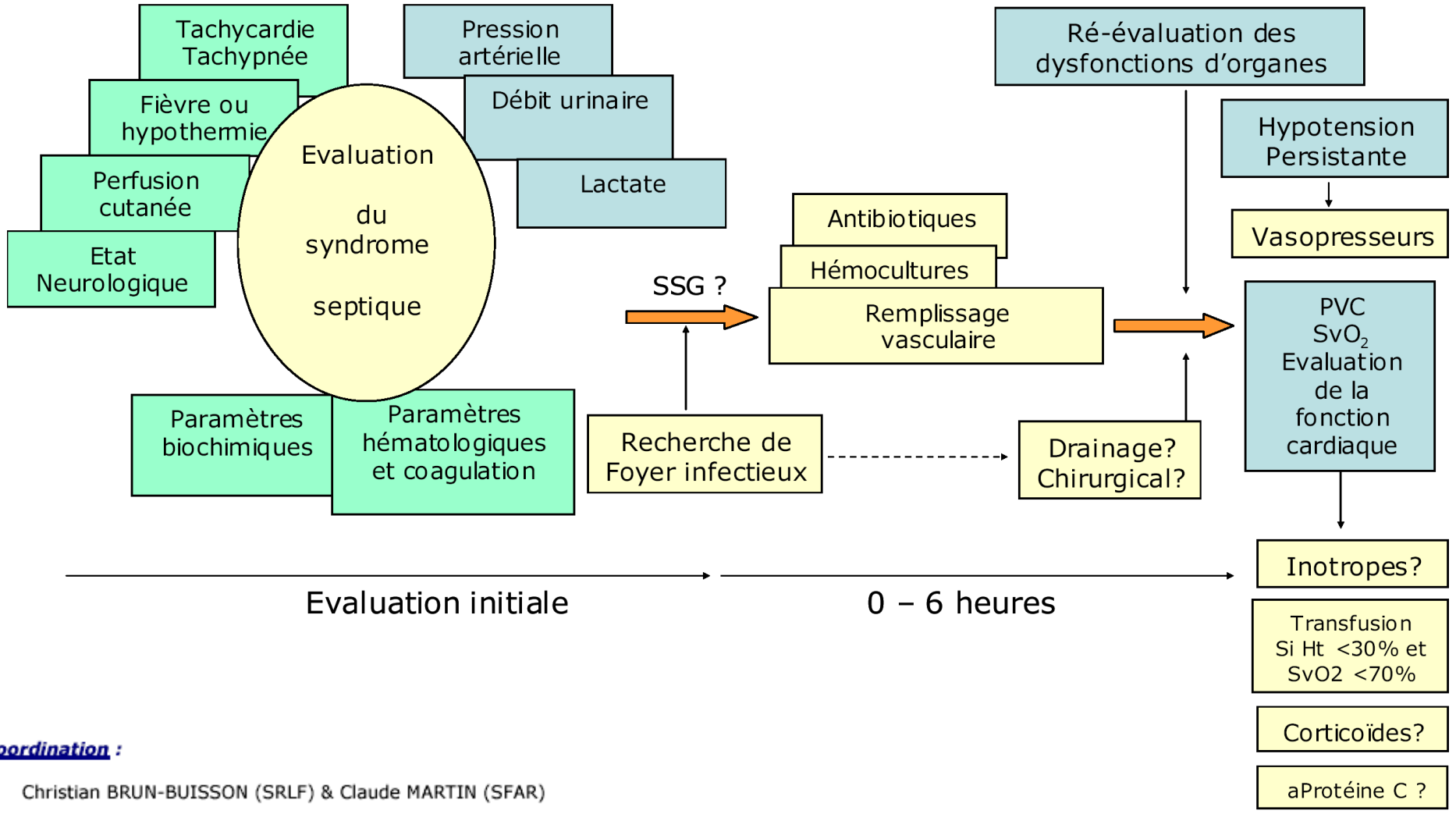
*Recombinant human activated protein C*

- ○ Consider rhAPC in adult patients with sepsis-induced organ dysfunction with clinical assessment of high risk of death (typically APACHE II ≥25 or multiple organ failure) if there are no contraindications (2B, 2C for postoperative patients).
- ● Adult patients with severe sepsis and low risk of death (typically, APACHE II <20 or one organ failure) should not receive rhAPC (1A)

Crit Care Med 2008
Intensive Care Med 2008

**Groupe Transversal Sepsis**
**« Prise en charge initiale des états septiques graves de l'adulte et de l'enfant »**

**ADARPEF**
**GFRUP**
**SAMU de France**
**SFAR**
**SFMU**
**SPILF**
**SRLF**




***Coordination*** **:**

Christian BRUN-BUISSON (SRLF) & Claude MARTIN (SFAR)

## Sur quels éléments serons-nous jugés ?

EPP « Prise en charge du sepsis sévère » SRLF - SFAR

Audit clinique ciblé

- Heure du diagnostic noté dans le dossier
- Remplissage vasculaire débuté (>500 mL)
- Dosage du lactate
- Hémocultures prélevées
- Antibiothérapie à spectre adapté