Sepsis
New Definitions & Recommendations

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COI Disclosures

Djillali Annane

No financial disclosure

Member of the Sepsis 3 Task Force

Member of the SSC panel for 2008; 2012 and 2016 updates

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

The Sepsis Definitions Task Force

SCCM/ESICM Task Force to Re-Define Sepsis

- Co-Chairs – Mervyn Singer, Cliff Deutschman

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Michael Bauer
Rinaldo Bellomo
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Mitchell Levy
John Marshall
Steve Opal
Gordon Rubenfeld
Tom van der Poll
Jean-Louis Vincent
Greg Martin
Manu Shankar-Hari
Chris Seymour

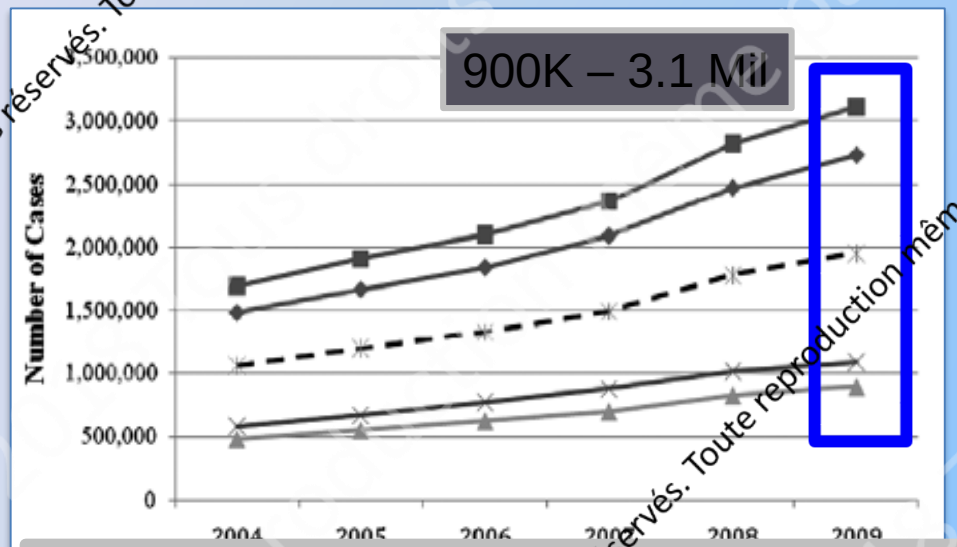
Limits of previous definition

Benchmarking the Incidence and Mortality of Severe Sepsis in the United States*

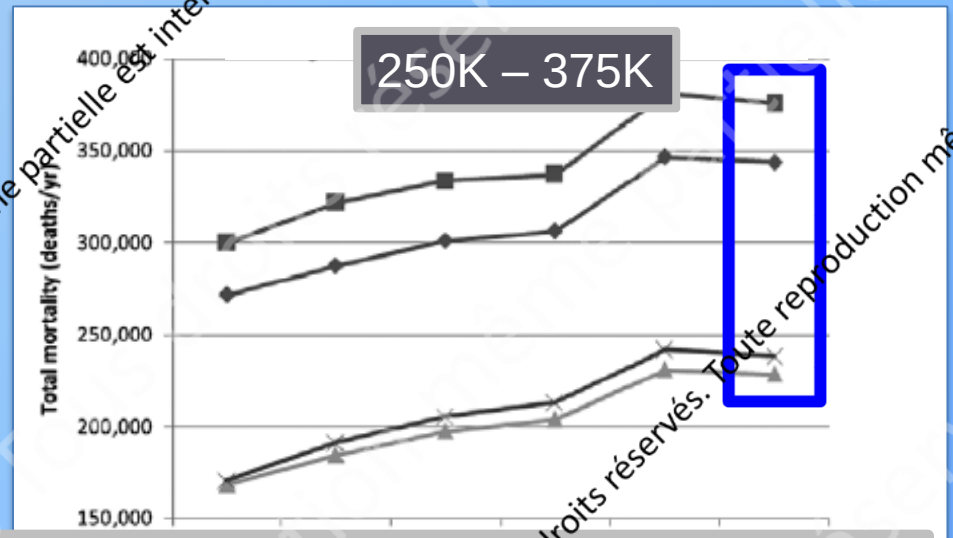
David F. Gaieski MD[1]; J. Matthew Edwards, MD[1]; Michael J. Kallan, MS[2]; Brendan G. Carr, MD, MA, MS[1–3]

Crit Care Med 2013; 41: 1167–1174

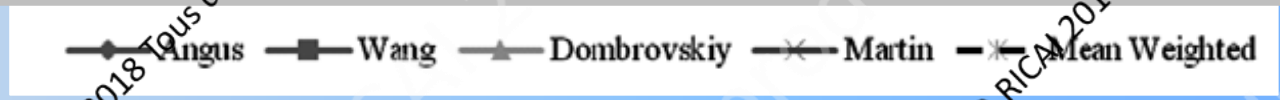
Number of cases



Total mortality



Four different ways to identify sepsis; four different sets of results



Task Force Decisions

CONSENSUS

1. Beyond the remit of the task force to define infection
2. Sepsis is not simply infection + two or more SIRS criteria
3. The host response is of key importance
4. **Sepsis represents** bad infection where

   bad = infection leading to organ dysfunction
5. "Severe sepsis" is not helpful and should be eliminated

The Definition of Sepsis

Key Distinctions

Sepsis is life-threatening *organ dysfunction* caused by a dysregulated host response to infection

So … “sepsis” now = the old “severe sepsis”

The Definition of Sepsis

Key Distinctions

Sepsis is life-threatening organ dysfunction caused by a *dysregulated host response* to infection

As opposed to the
"regulated host response"
that characterizes the non-septic response to infection

The Definition of Septic Shock

- What tangibly differentiates septic shock from sepsis ?
  - MORTALITY
    - Septic shock is “really bad” sepsis

Septic shock is a subset of sepsis in which profound circulatory, cellular and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone

The Need for Something Additional

- **Practitioners require something of value at the bedside**
  - **Preferably data-driven**
- **Clinical criteria**
  - **Existing**
  - **Newly derived and validated**

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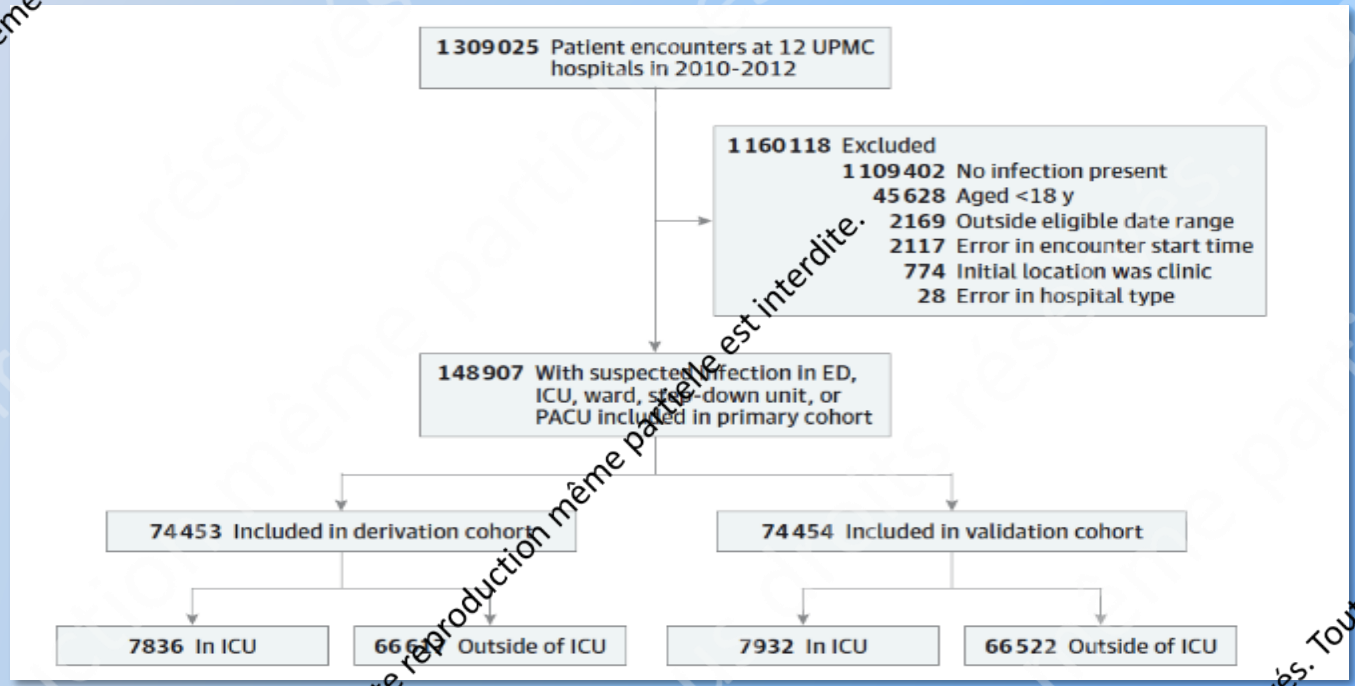
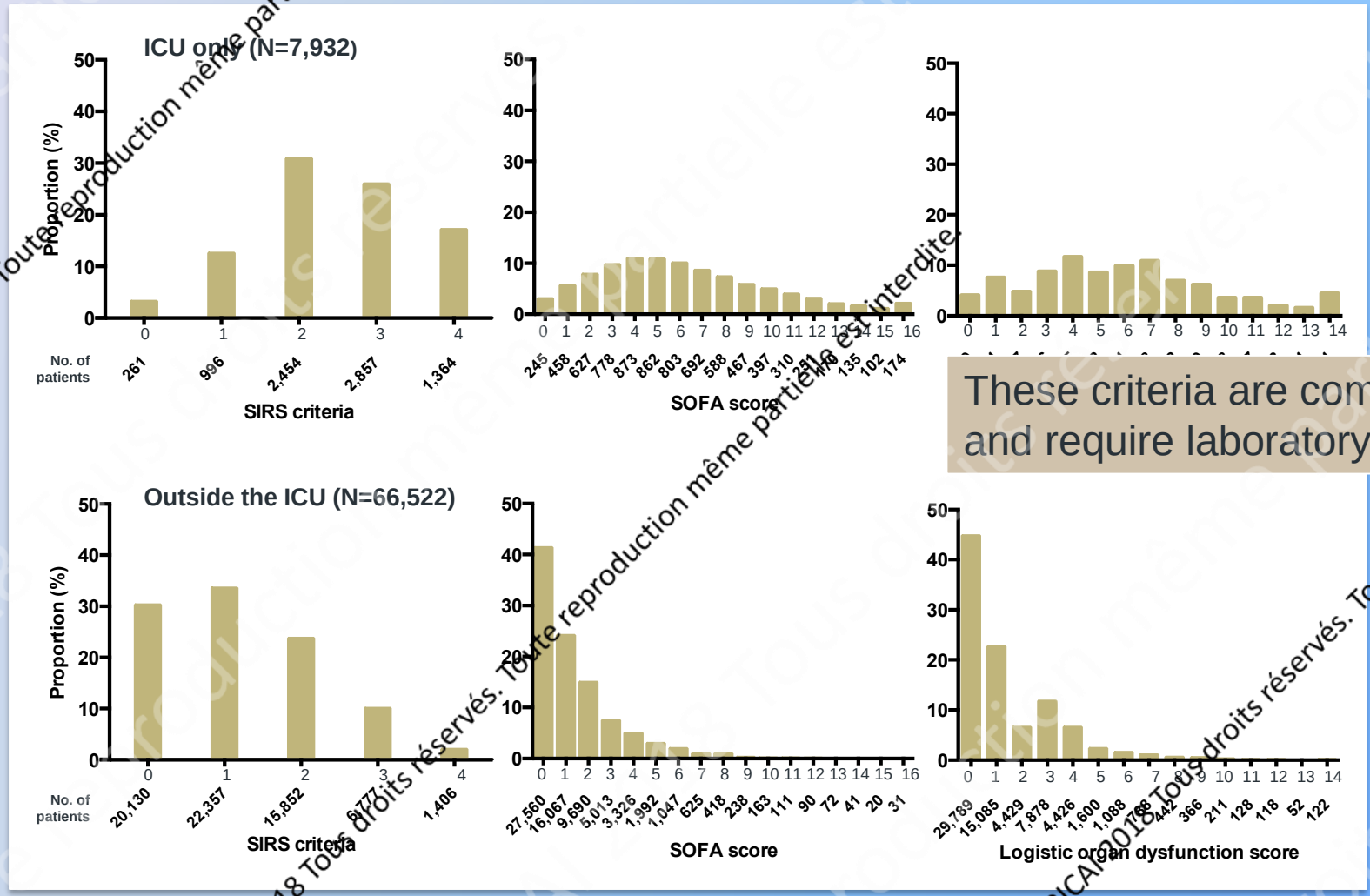
What data source to use?



Characteristics	KPNC	VA	ALERTS	KCEMS
Years of cohort	2009-2013	2008-2010	2011-2012	2009-2010
No. of hospitals	20	130	1	1
Total No. of encounters	1 847 165	1 640 543	38 098	950 727
Data source and study design	Retrospective study of EHRs	Retrospective study of EHRs	Prospective cohort study	Retrospective study of administrative records
Setting	Integrated health system in northern California	All hospitals in the US VA system	Single university hospital, Jena, Germany	Out-of-hospital records from integrated emergency medical services system in King County, Washington

Distribution of existing criteria



These criteria are complex and require laboratory tests

Developing new criteria

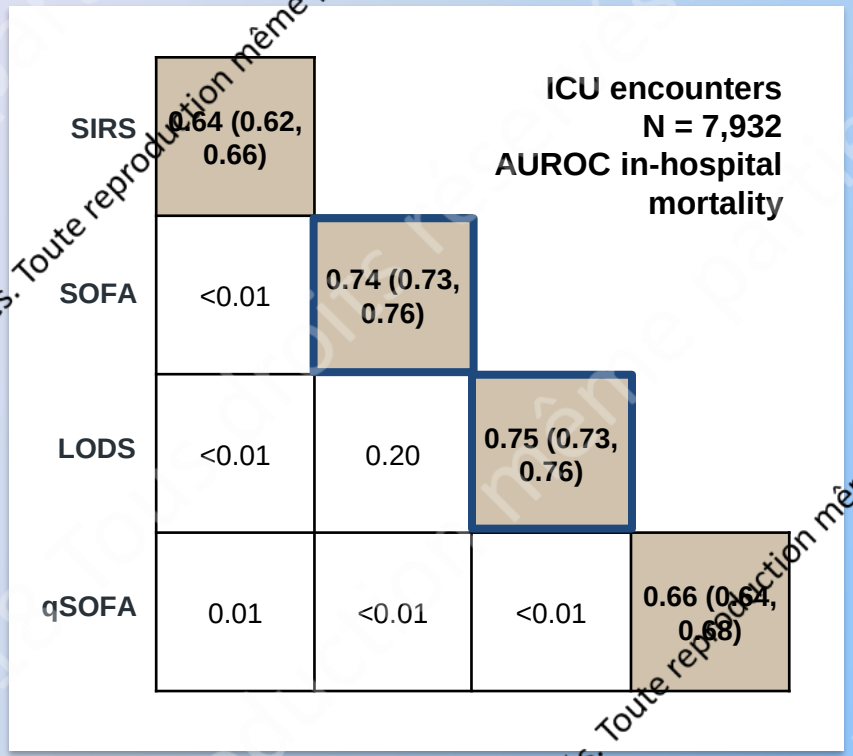
- Focus on timeliness, ease of use
- Studied 21 variables from Sepsis-2
- Multivariable logistic regression for in-hospital mortality

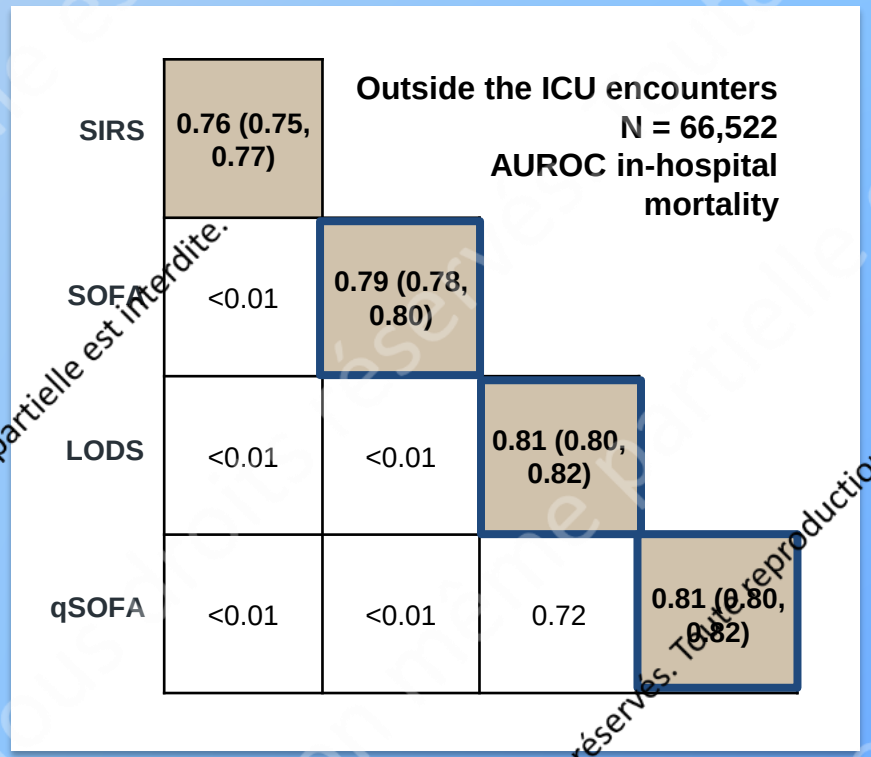
Respiratory rate ≥ 22 bpm

Altered mentation

Systolic blood pressure ≤ 100 mmHg

Assessment of Sepsis criteria





SOFA and LODS superior in the ICU

SEPSIS = INFECTION + SOFA ≥ 2

qSOFA similar to complex scores outside the ICU

At RISK for SEPSIS INFECTION + qSOFA≥2

SEPTIC SHOCK

- Definition

Septic shock is defined as a subset of sepsis where underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality

- Clinical criteria

Despite adequate fluid resuscitation, lactate >2 mmol/l and vasopressors needed to elevate MAP≥65 mmHg

n.b. if can't measure lactate use marker of poor perfusion, e.g. capillary refill

Why hypotension AND hyperlactatemia for septic shock?

	hospital mortality (%)
hypotension + lactate >2	42.3
hypotension alone	30.1
lactate >2 alone	25.7
no hypotension and lactate <2	18.7

Shankar-Hari et al. JAMA 2016

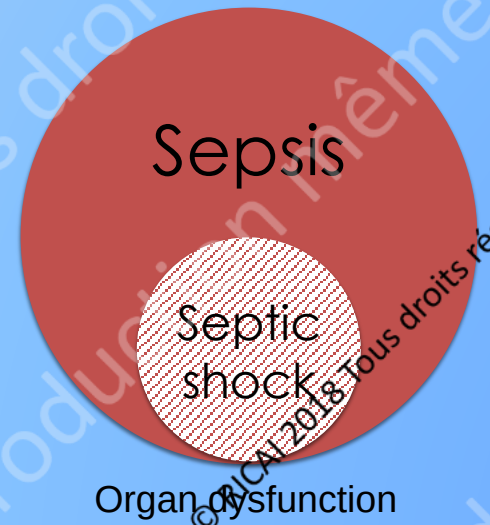
Conceptual changes

OLD

infection → sepsis (≥2 of 4 SIRS) → severe sepsis (organ dysfunction) → septic shock (CV collapse not responding to fluid)

NEW

infection → "Bad"



Special Communication | CARING FOR THE CRITICALLY ILL PATIENT

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

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

Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Assessment of Clinical Criteria for Sepsis For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

Christopher W. Seymour, MD, MSc; Vincent X. Liu, MD, MSc; Theodore J. Iwashyna, MD, PhD; Frank Brunkhorst, MD; Thomas D. Rea, MD, MPH; André Scherag, PhD; Manu Shankar-Hari, MD, MSc; Mervyn Singer, MD, FRCP; Clifford S. Deutschman, MD; Derek C. Angus, MD, MPH

Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

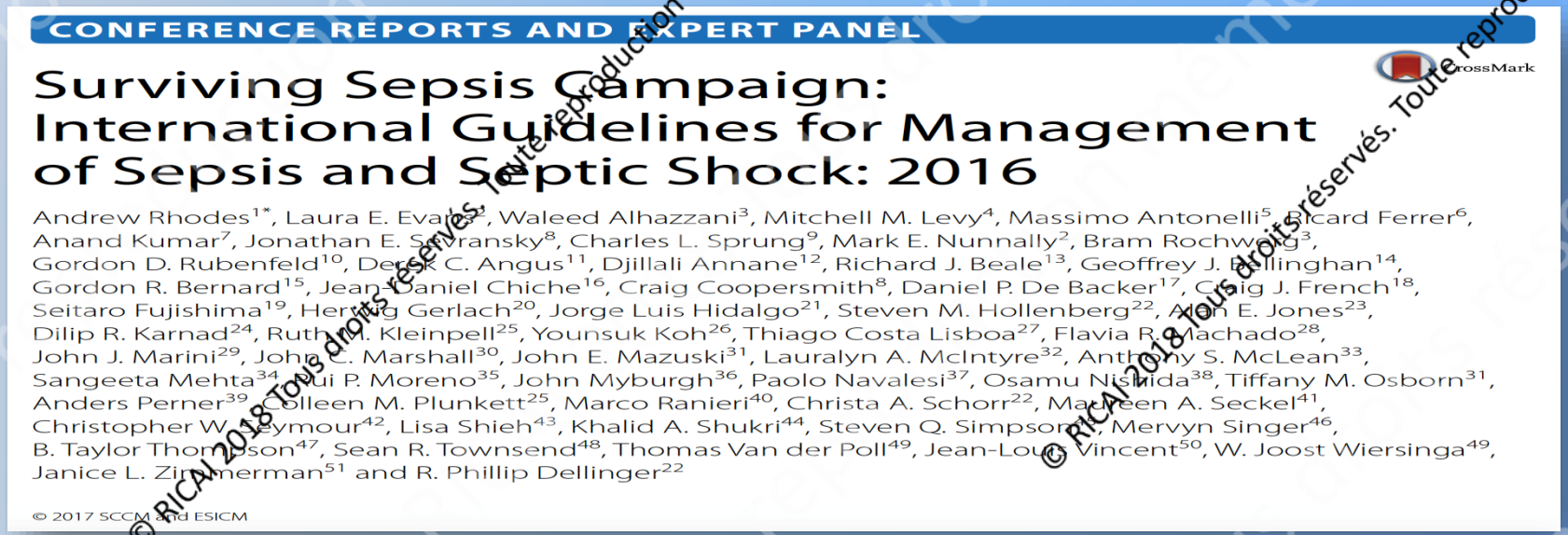
Developing a New Definition and Assessing New Clinical Criteria for Septic Shock For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

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

Timeline of the SSC Guidelines

- First edition in 2004
- Previous Revisions in 2008 and 2012

- Current revision started in 2014 published January 2017
- Jointly sponsored by ESICM and SCCM



CONFERENCE REPORTS AND EXPERT PANEL

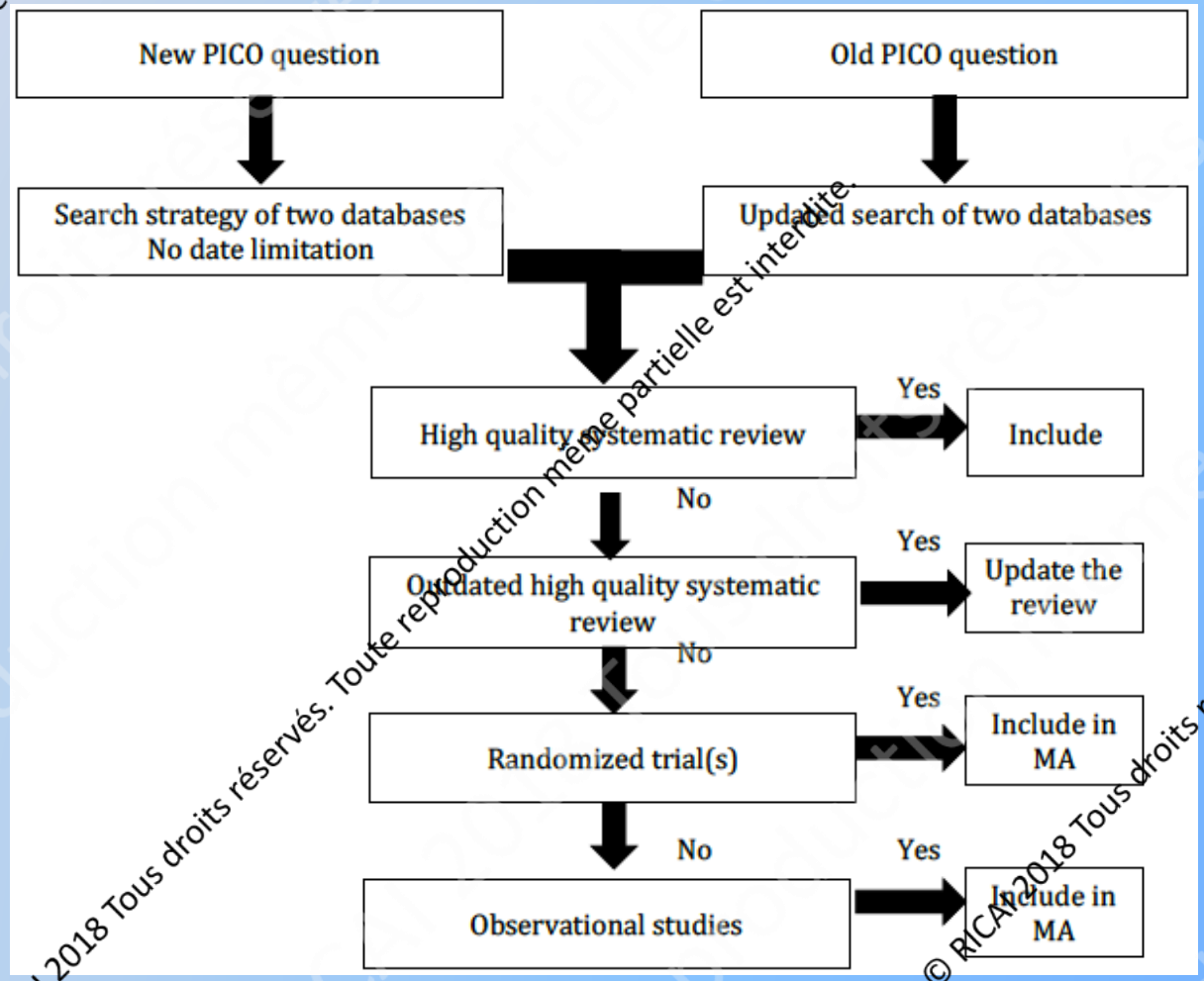
Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016

Andrew Rhodes[1*], Laura E. Evans[2], Waleed Alhazzani[3], Mitchell M. Levy[4], Massimo Antonelli[5], Ricard Ferrer[6], Anand Kumar[7], Jonathan E. Sevransky[8], Charles L. Sprung[9], Mark E. Nunnally[2], Bram Rochwerg[3], Gordon D. Rubenfeld[10], Derek C. Angus[11], Djillali Annane[12], Richard J. Beale[13], Geoffrey J. Bellinghan[14], Gordon R. Bernard[15], Jean-Daniel Chiche[16], Craig Coopersmith[8], Daniel P. De Backer[17], Craig J. French[18], Seitaro Fujishima[19], Herwig Gerlach[20], Jorge Luis Hidalgo[21], Steven M. Hollenberg[22], Alan E. Jones[23], Dilip R. Karnad[24], Ruth M. Kleinpell[25], Younsuk Koh[26], Thiago Costa Lisboa[27], Flavia R. Machado[28], John J. Marini[29], John C. Marshall[30], John E. Mazuski[31], Lauralyn A. McIntyre[32], Anthony S. McLean[33], Sangeeta Mehta[34], Rui P. Moreno[35], John Myburgh[36], Paolo Navalesi[37], Osamu Nishida[38], Tiffany M. Osborn[31], Anders Perner[39], Colleen M. Plunkett[25], Marco Ranieri[40], Christa A. Schorr[22], Maureen A. Seckel[41], Christopher W. Seymour[42], Lisa Shieh[43], Khalid A. Shukri[44], Steven Q. Simpson[45], Mervyn Singer[46], B. Taylor Thompson[47], Sean R. Townsend[48], Thomas Van der Poll[49], Jean-Louis Vincent[50], W. Joost Wiersinga[49], Janice L. Zimmerman[51] and R. Phillip Dellinger[22]

Management of Potential Conflict of Interest

- No industry input
- Panelists did not receive honoraria
- Personal disclosure of potential COI upon joining guidelines panel and annually
- Management of potential COI
  - Limited voting on topics pertinent to COI
  - Group reassignment

Study Selection



Recommendations

- 93 Recommendations
  - 32 **Strong** recommendations: ***"We recommend"***
  - 39 **Weak** recommendations: ***"We suggest"***
  - 18 Best Practice Statements
  - No recommendation provided for 4 PICO questions

One Hour Bundle

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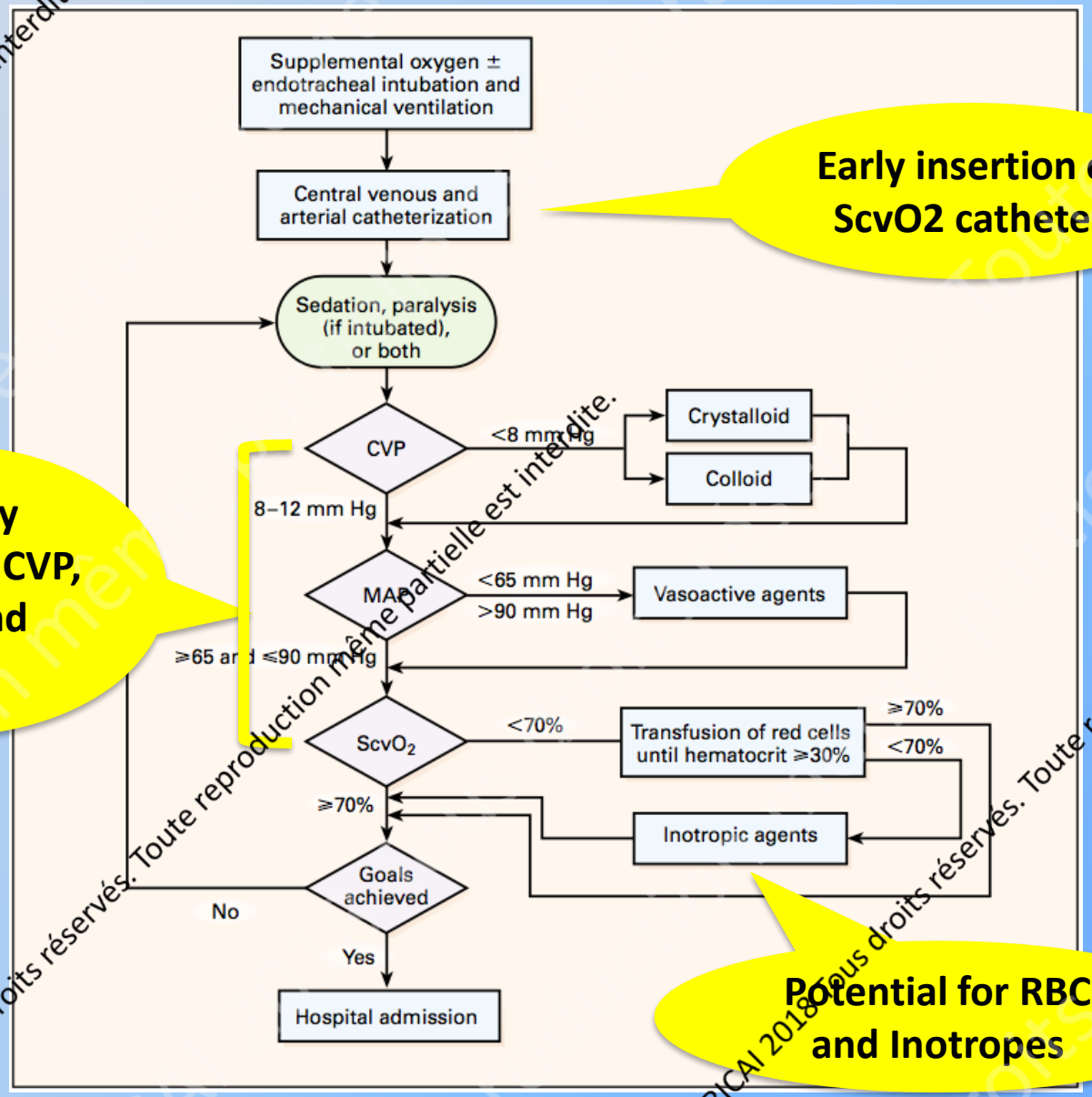
Initial Resuscitation

2012 Recommendation

We recommend the protocolized, quantitative resuscitation of patients with sepsis- induced tissue hypoperfusion. During the first 6 hours of resuscitation, the goals of initial resuscitation should include all of the following as a part of a treatment protocol:

a) CVP 8–12 mm Hg
b) MAP ≥ 65 mm Hg
c) Urine output ≥ 0.5 mL/kg/hr
d) Scvo2 ≥ 70%.



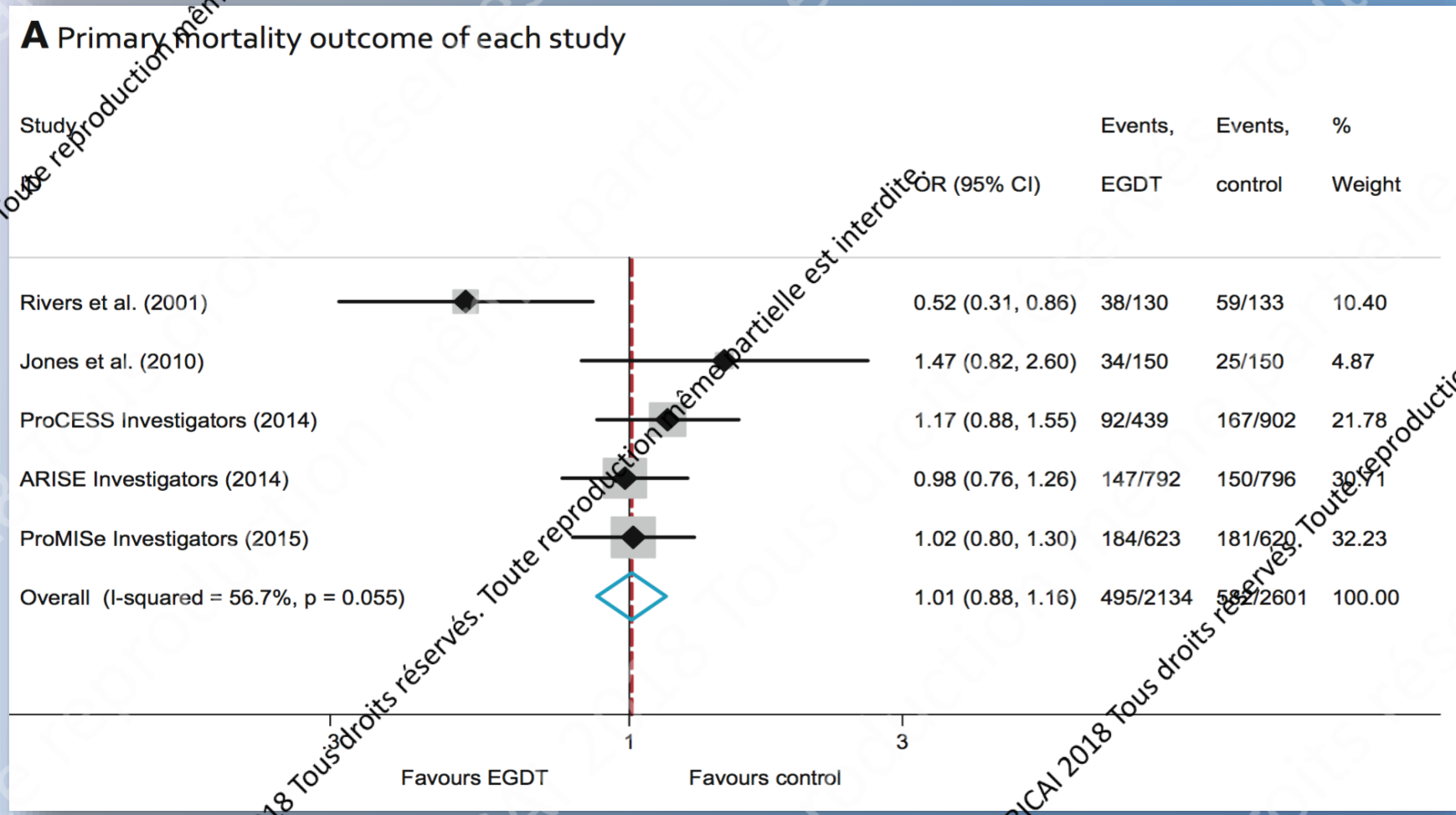
Early insertion of ScvO2 catheter

Therapy titrated to CVP, MAP and ScvO2

Potential for RBC and Inotropes

N Engl J Med, Vol. 345, No. 19 · November 8, 2001

A systematic review and meta-analysis of early goal-directed therapy for septic shock: the ARISE, ProCESS and ProMISe Investigators



Intensive Care Med (2015) 41:1549–1560
DOI 10.1007/s00134-015-3822-1

The River's work was useful….

- As it provided us a construct on how to understand resuscitation:
  - Start early- (give antibiotics)
  - Correct hypovolaemia
  - Restore perfusion pressure
  - And in some cases a little more may be required..!

- These concepts are as important today as they ever were.

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

Best Practice Statement

Source Control

We recommend that

1- a specific anatomic diagnosis of infection requiring emergent source control be identified or excluded as rapidly as possible in patients with sepsis or septic shock,

2- any required source control intervention be implemented as soon as medically and logistically practical after the diagnosis is made.

(Best Practice Statement).

Diagnosis

We recommend that appropriate routine microbiologic cultures (including blood) be obtained before starting antimicrobial therapy in patients with suspected sepsis and septic shock if doing so results in no substantial delay in the start of antimicrobials. (BPS)

- **Remarks: Appropriate routine microbiologic cultures always include at least two sets of blood cultures (aerobic and anaerobic).**

Antibiotics

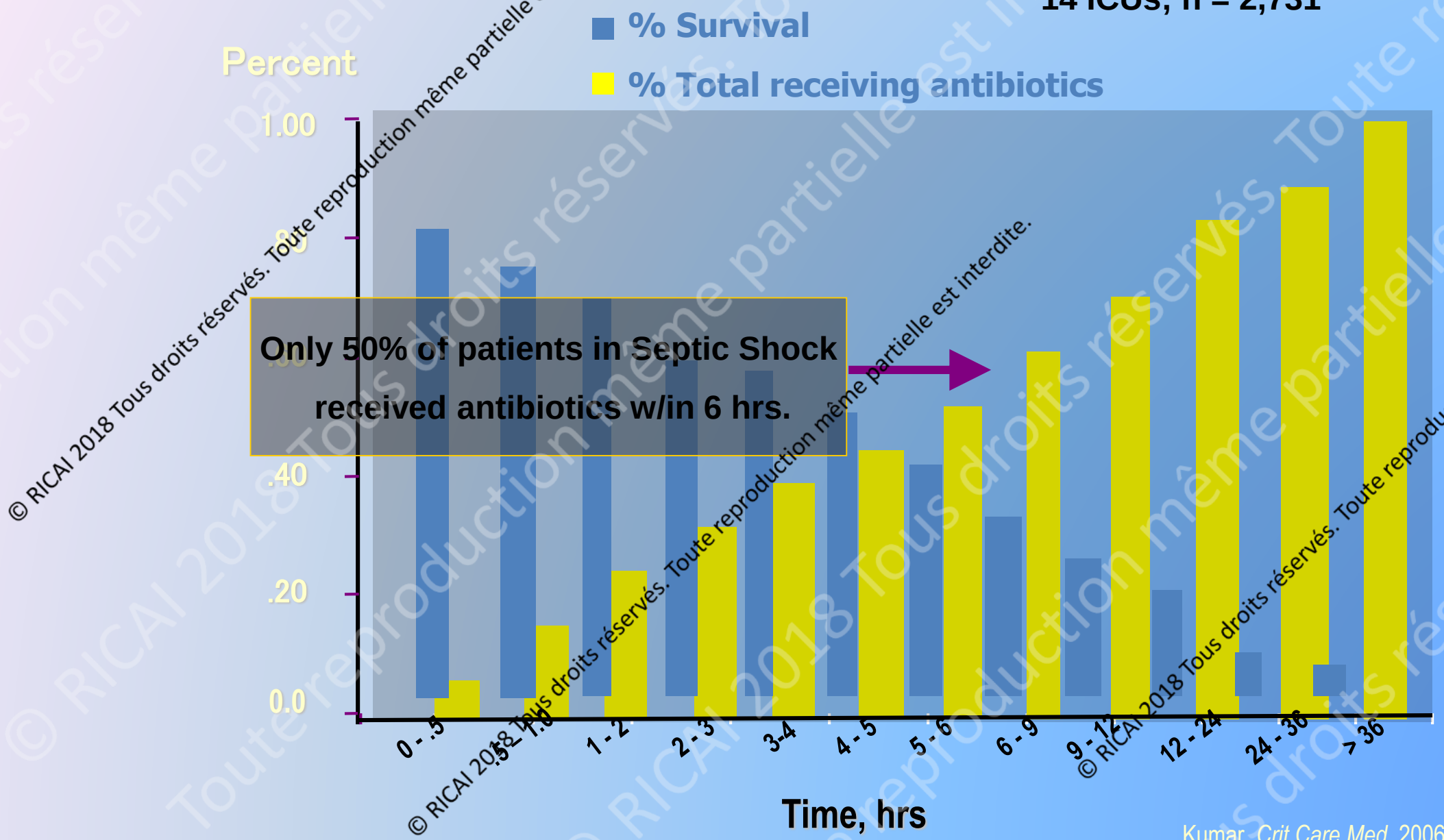
- **We recommend that administration of IV antimicrobials be initiated asap after recognition and within 1 h for both sepsis and septic shock.**

(strong recommendation, moderate quality of evidence).

- **We recommend empiric broad-spectrum therapy with one or more antimicrobials to cover all likely pathogens.**

(strong recommendation, moderate quality of evidence).

Septic Shock: Timing of Antibiotics



Kumar *Crit Care Med* 2006

Initial Hemodynamic Resuscitation

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

(Strong recommendation; low quality of evidence)

- **We recommend that following initial fluid resuscitation, additional fluids be guided by frequent reassessment of hemodynamic status.**

(Best Practice Statement)

Fluid Therapy

- **We recommend crystalloids as the fluid of choice for initial resuscitation and subsequent intravascular volume replacement in patients with sepsis and septic shock**

(Strong recommendation, moderate quality of evidence).

- **We suggest using albumin in addition to crystalloids when patients require substantial amounts of crystalloids**

(weak recommendation, low quality of evidence).

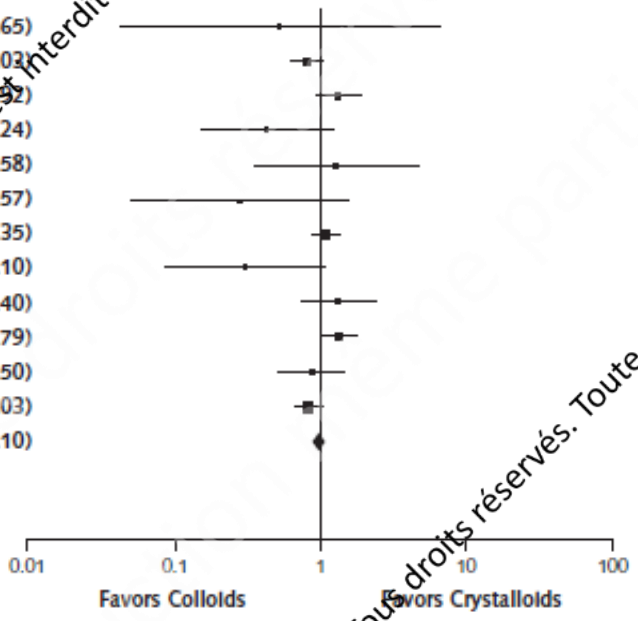
Mortality

Appendix Figure 3. **Forest plot for mortality in direct comparisons of all crystalloids vs. all colloids.**

Study, Year (Reference)	Events/Total, *n/N*		Weight, %	Odds Ratio: M–H, Fixed (95% CI)
	Colloids	Crystalloids		
Haupt and Rackow, 1982 (38)	8/13	3/4	0.2	0.53 (0.04–6.65)
Finfer et al, 2004 (2)	185/603	217/615	20.4	0.81 (0.64–1.03)
Brunkhorst et al, 2008 (1)	107/261	93/274	7.3	1.35 (0.95–1.92)
Li et al, 2008 (39)	14/30	20/30	1.5	0.44 (0.18–1.24)
McIntyre et al, 2008 (41)	9/21	7/19	0.6	1.29 (0.36–4.58)
Dubin et al, 2010 (37)	3/12	7/13	0.7	0.28 (0.05–1.57)
Myburgh et al, 2012 (3)	248/976	224/945	23.3	1.10 (0.89–1.35)
Lv et al, 2012 (40)	7/22	12/20	1.2	0.31 (0.09–1.10)
Guidet et al, 2012 (6)	40/99	32/95	2.7	1.33 (0.74–2.40)
Perner et al, 2012 (4)	202/398	173/400	17.6	1.35 (1.02–1.79)
Haase et al, 2013 (5)	44/117	50/124	4.2	0.89 (0.53–1.50)
Annane et al, 2013 (16)	252/774	286/779	26.4	0.83 (0.67–1.03)
Total	3326	3318	100.00	0.99 (0.89–1.10)
Total events	1119	1144		

Heterogeneity: chi-square = 23.20; I^2 = 53%

Test for overall effect: Z = 0.18 (P = 0.85)



M–H = Mantel–Haenszel.

Rochwerg et al Ann Intern Med 2014

Need for Renal Replacement Therapy

Table 3 Results of four-node network meta-analysis including confidence assessments

Comparison	Number of trials with direct comparisons	Direct estimate (95 % CI)	Indirect estimate (95 % CrI)	NMA estimate (95 % CrI) (higher of direct or indirect confidence)
Starch vs. crystalloid	7	1.39 (1.17, 1.66) H	–	1.39 (1.17–1.66) H
Albumin vs. crystalloid	1	1.04 (0.78, 1.38) M[a]	–	1.04 (0.78–1.38) M
Gelatin vs. crystalloid	0	–	1.05 (0.42, 2.56) VL[b]	1.05 (0.42–2.56) VL
Albumin vs. starch	0	–	0.74 (0.53, 1.04) L[b]	0.74 (0.53–1.04) L
Gelatin vs. starch	1	0.75 (0.31, 1.82) L[a,c]	–	0.75 (0.30–1.81) L
Gelatin vs. albumin	0	–	1.01 (0.38, 2.60) VL[b]	1.01 (0.38–2.60) VL

CI confidence interval, *CrI* credibility interval, *NMA* network meta-analysis, *H* high certainty, *M* moderate certainty, *L* low certainty, *VL* very low certainty

[a] Rated down for imprecision

[b] Rated down for imprecision and indirectness

[c] Rated down for risk of bias

Rochwerg et al Intensive Care Med 2015

We recommend an initial target mean arterial pressure of 65 mmHg in patients with septic shock requiring vasopressors.

(Strong recommendation; moderate quality of evidence)

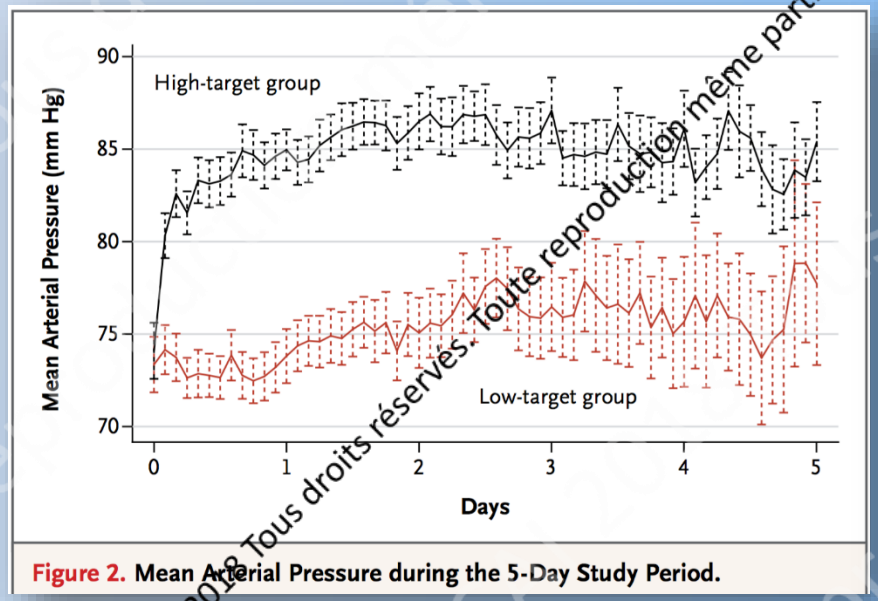


Figure 2. Mean Arterial Pressure during the 5-Day Study Period.

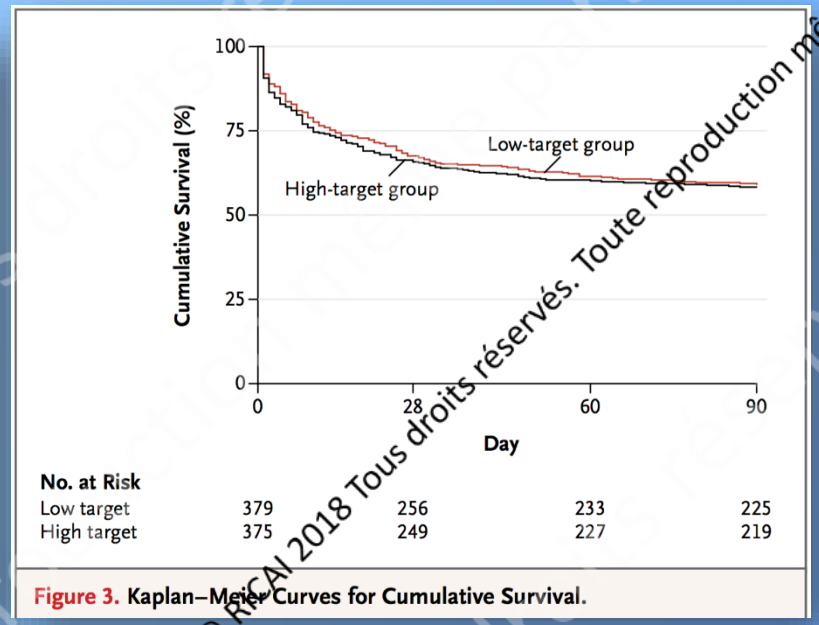


Figure 3. Kaplan–Meier Curves for Cumulative Survival.

DOI: 10.1056/NEJMoa1312173

High versus Low Blood-Pressure Target in Patients with Septic Shock

Vasoactive agents

- **We recommend norepinephrine as the first choice vasopressor**

(strong recommendation, moderate quality of evidence).

- **We suggest adding either vasopressin (up to 0.03 U/min) or epinephrine to norepinephrine with the intent of raising MAP to target, or adding vasopressin (up to 0.03 U/min) to decrease norepinephrine dosage.**

(weak recommendation, low quality of evidence)

[APHP1]Should be septic shock, shouldn't it?

Meta-analysis of Norepinephrine versus Dopamine

Outcomes	Illustrative comparative risks* (95% CI) Assumed risk Dopamine	Corresponding risk Norepinephrine	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
Short-term mortality	**Study population**		**RR 0.91** (0.83 to 0.99)	2043 (6 studies)	⊕⊕⊕⊖ **moderate**[1,2]
	530 per 1000	**482 per 1000** (440 to 524)			
Serious adverse events - Supraventricular arrhythmias	**Study population**		**RR 0.47** (0.38 to 0.58)	1931 (2 studies)	⊕⊕⊕⊖ **moderate**[1,2]
	229 per 1000	**82 per 1000** (34 to 195)			
Serious adverse events - Ventricular arrhythmias	**Study population**		**RR 0.35** (0.19 to 0.66)	1931 (2 studies)	⊕⊕⊕⊖ **moderate**[1,2]
	39 per 1000	**15 per 1000** (8 to 27)			

*The **assumed risk** is the median control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

[1] Strong heterogeneity in the results (I squared = 85%), however this reflects degree of effect, not direction of effect. We have decided not to lower the evidence quality.

[2] Effect results in part from hypovolemic and cardiogenic shock patients in De Backer, NEJM 2010. We have lowered the quality of evidence one level for indirectness.

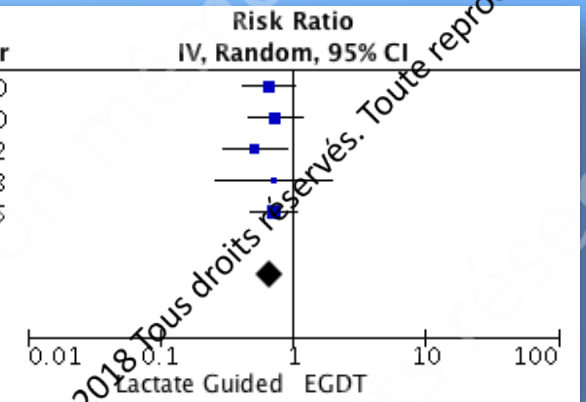
Annane for SSC 2015

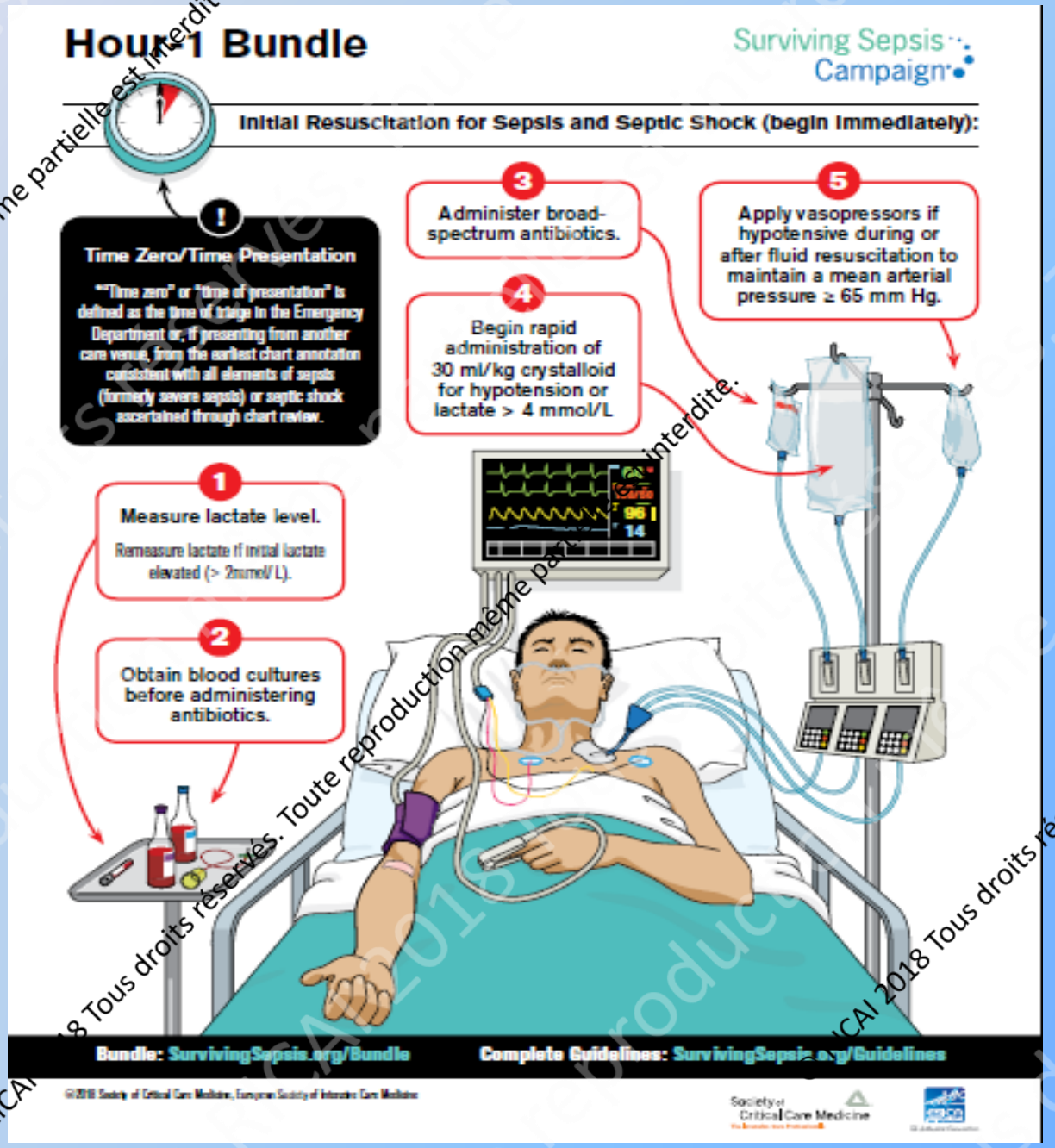
Lactate can help guide resuscitation

We suggest guiding resuscitation to normalize lactate in patients with elevated lactate levels as a marker of tissue hypoperfusion.
(Weak recommendation; low quality of evidence)

Study or Subgroup	Lactate Guided Events	Total	Standard Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Year
Jansen, 2010	20	68	30	67	24.9%	0.66 [0.42, 1.03]	2010
Jones, 2010	25	150	38	150	23.8%	0.74 [0.46, 1.17]	2010
Tian, 2012	14	43	12	19	16.9%	0.52 [0.30, 0.89]	2012
Yu, 2013	5	25	7	25	5.1%	0.71 [0.26, 1.95]	2013
Lyu 2015	20	50	28	50	29.2%	0.71 [0.47, 1.09]	2015
Total (95% CI)		**336**		**311**	**100.0%**	**0.67 [0.53, 0.84]**	
Total events	84		111				

Heterogeneity: Tau² = 0.00; Chi² = 1.14, df = 4 (P = 0.89); I² = 0%
Test for overall effect: Z = 3.51 (P = 0.0004)





SCREENING FOR SEPSIS AND PERFORMANCE IMPROVEMENT

We recommend that hospitals and hospital systems have a performance improvement program for sepsis including sepsis screening for acutely ill, high-risk patients. (BPS)

Sepsis Performance Improvement

- Performance improvement efforts for sepsis are associated with improved patient outcomes
- A recent meta-analysis of 50 observational studies:
  - Performance improvement programs associated with a significant increase in compliance with the SSC bundles and a reduction in mortality (OR 0.66; 95% CI 0.61-0.72).
- Mandated public reporting:
  - NYS, CMS, UK

Setting Goals of Care

- **We recommend that goals of care and prognosis be discussed with patients and families. (BPS)**
- **We recommend that the goals of care be incorporated into treatment and end-of-life care planning, utilizing palliative care principles where appropriate. (Strong recommendation; moderate quality of evidence)**
- **We suggest that goals of care be addressed as early as feasible, but no later than within 72 hours of ICU admission. (Weak recommendation; low quality of evidence)**