



UFR
SCIENCES
DE SANTÉ
DIJON



Prise en charge initiale du sepsis

DES Maladies Infectieuses

Avril 2021

PE CHARLES

Médecine Intensive Réanimation - C.H.U. Dijon

U.M.R. U1231 – I.N.S.E.R.M.

- Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.

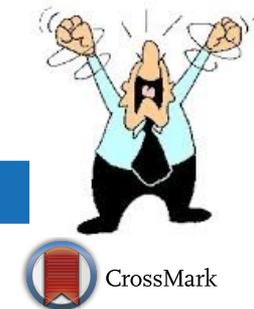


Diagnosis of
infection

QUICK!



Severity
assessment



The Surviving Sepsis Campaign Bundle: 2018 update

- Measure **lactate level**. Remeasure if initial lactate is >2 mmol/L.
- Obtain **blood cultures** prior to administration of antibiotics.
- Administer **broad-spectrum** antibiotics.
- Begin rapid administration of **30ml/kg crystalloid** for hypotension or lactate ≥ 4 mmol/L.
- Apply **vasopressors** if patient is hypotensive during or after fluid resuscitation to maintain MAP ≥ 65 mm Hg.



**“Time zero” or “time of presentation” is defined as the time of triage in the Emergency Department or, if presenting from another care venue, from the earliest chart and documentation of the clinical elements of sepsis (formerly severe sepsis) or septic shock ascertainment.*

Fig. 1 Hour-1 Surviving Sepsis Campaign Bundle of Care

**Dans
l’heure!!!**

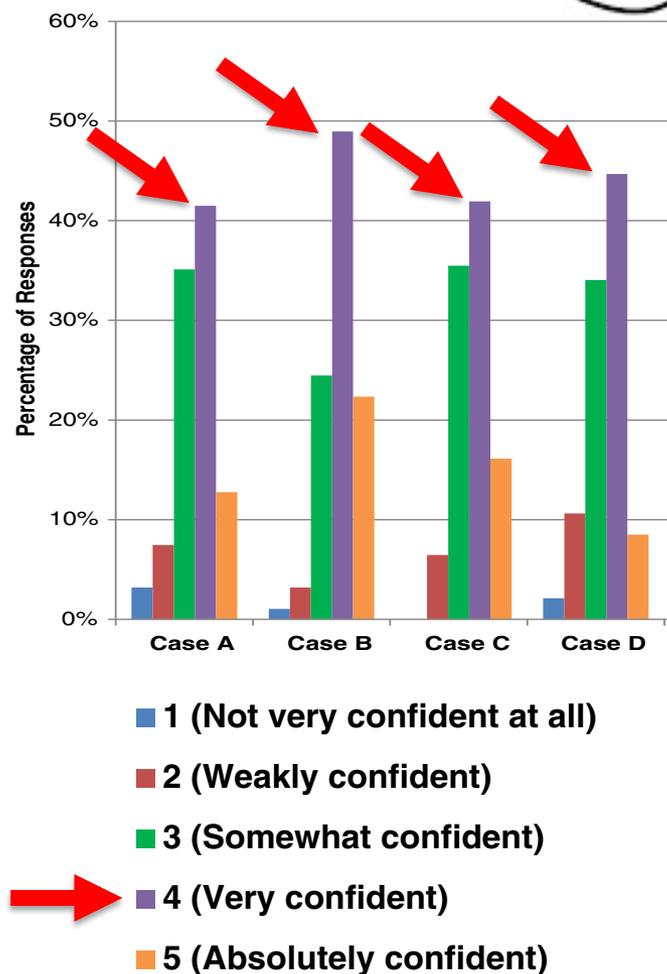
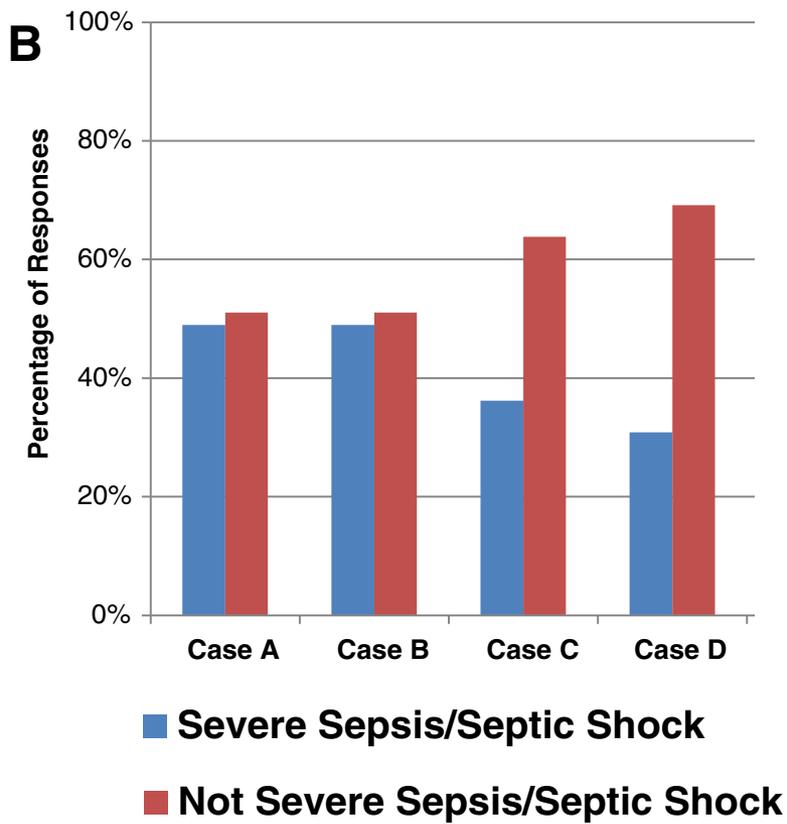
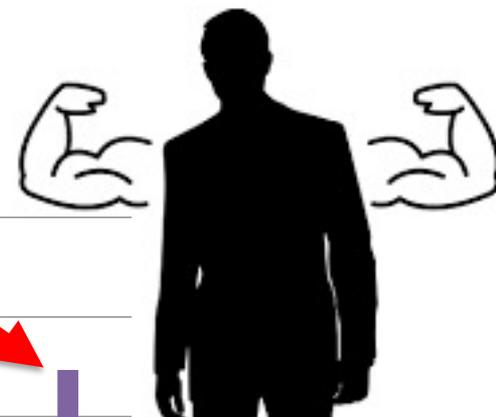


*Sepsis early
recognition?*

Hard job in the
ED setting!



Diagnosing sepsis is **subjective** and highly variable: a survey of intensivists using case vignettes



Special Communication | CARING FOR THE CRITICALLY ILL PATIENT

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



Box 4. qSOFA (Quick SOFA) Criteria

Respiratory rate ≥ 22 /min

Altered mentation

Systolic blood pressure ≤ 100 mm Hg



→ Patient with suspected infection

subjectif...

qSOFA ≥ 2 ?
(see **A**)

No

Sepsis still
suspected?

No

Monitor clinical condition;
reevaluate for possible sepsis
if clinically indicated

Yes

Assess for evidence
of organ dysfunction

Yes

SOFA ≥ 2 ?
(see **B**)

No

Monitor clinical condition;
reevaluate for possible sepsis
if clinically indicated

Yes

Sepsis

Despite adequate fluid resuscitation,
1. vasopressors required to maintain
MAP ≥ 65 mm Hg
AND
2. serum lactate level > 2 mmol/L?

No

Yes

Septic shock

A qSOFA Variables

Respiratory rate

Mental status

Systolic blood pressure

B SOFA Variables

PaO₂/FiO₂ ratio

Glasgow Coma Scale score

Mean arterial pressure

Administration of vasopressors
with type and dose rate of infusion

Serum creatinine or urine output

Bilirubin

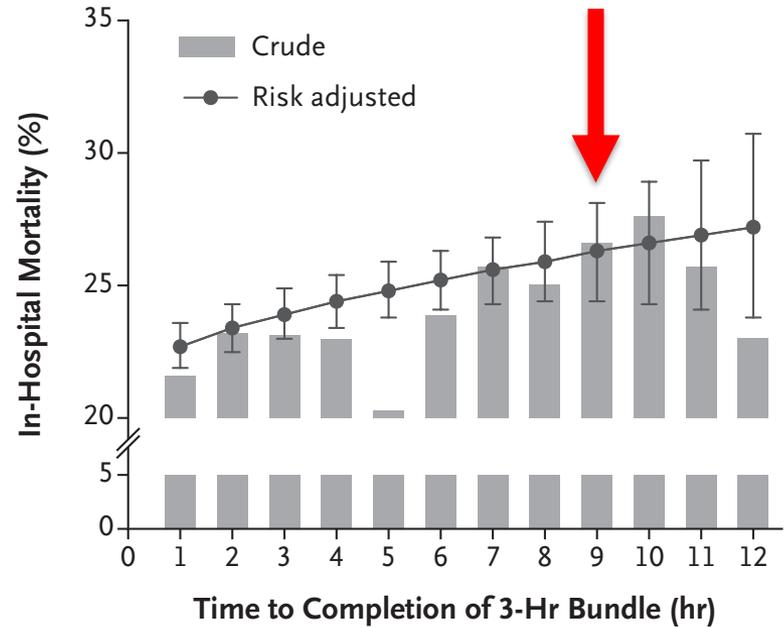
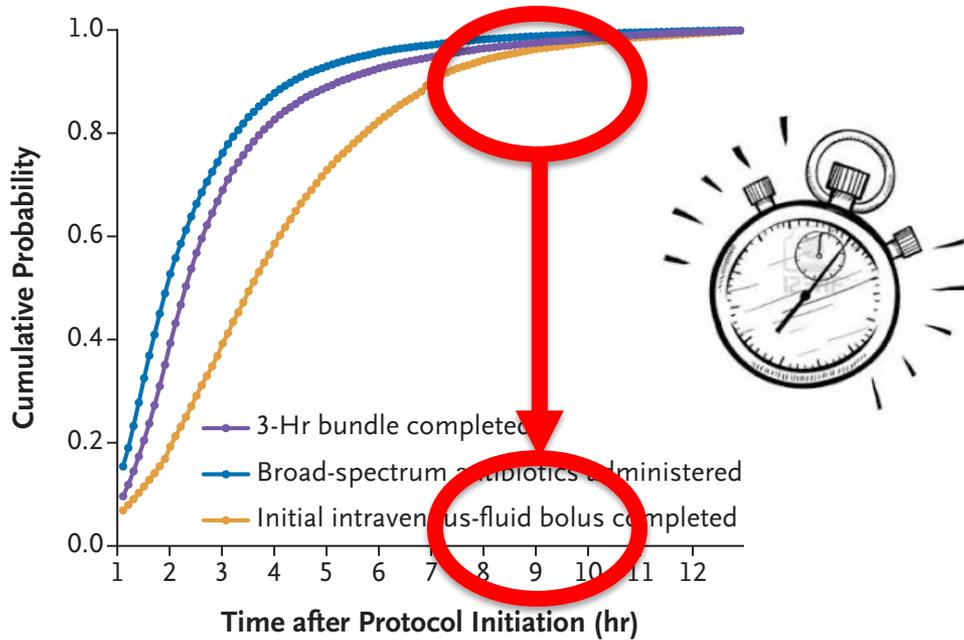
Platelet count

ORIGINAL ARTICLE

3-Hrs Bundle:

- Broad spectrum ATB
- Blood culture collection
- Lactate measurement

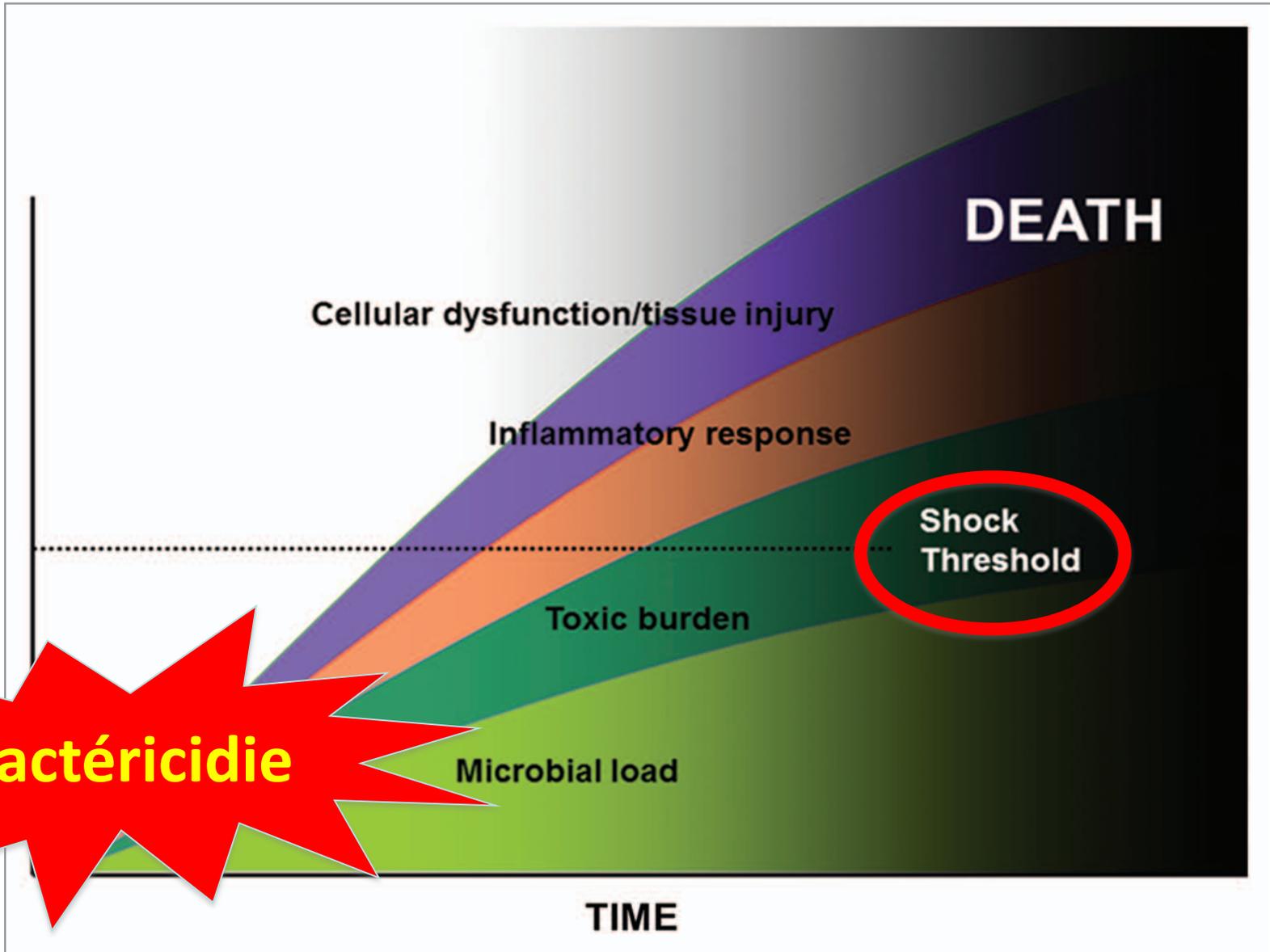
Time to Treatment and Mortality during Mandated Emergency Care for Sepsis





Prise en charge initiale du sepsis

ANTIBIOTHÉRAPIE EMPIRIQUE ADAPTÉE



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

D. ANTIMICROBIAL THERAPY

1. We recommend that administration of IV antimicrobials be initiated as soon as possible after recognition and **within 1 h for both sepsis and septic shock** (strong recommendation, moderate quality of evidence; grade applies to both conditions).



**Broad-spectrum
is tantalizing!**

In addition, the clinician must assess risk factors for infection with multidrug-resistant pathogens including prolonged hospital/chronic facility stay, recent antimicrobial use, prior hospitalization, and prior colonization or infection with multidrug-resistant organisms. The occurrence of more severe illness (e.g., septic shock) may be intrinsically associated with a higher probability of resistant isolates due to selection in failure to respond to earlier antimicrobials.



CrossMark

Strategies to reduce curative in intensive care

**Carbapenems should
be avoided except...**

Cédric Bretonnière
Marc Leone
Christophe Milési
Bernard Allaouchiche
Laurence Armand-Lefevre
Olivier Baldesi
Lila Bouadma
Dominique Decré
Samy Figueiredo
Rémy Gauzit
Benoît Guery
Nicolas Joram
Boris Jung
Sigismond Lasocki
Alain Lepape
Fabrice Lesage
Olivier Pajot
François Philippart
Bertrand Souweine
Pierre Tattevin
Jean-François Timsit
Renaud Vialet
Jean Ralph Zahar
Benoît Misset
Jean-Pierre Bedos

In terms of empirical antimicrobial treatment, when hospital-acquired severe bacterial infection is suspected, we recommend not prescribing carbapenem solely on the basis of the nosocomial nature of the infection, but rather considering the presence of at least two of the following criteria:

- Previous treatment with a third-generation cephalosporin, fluoroquinolones (including a single dose) or a piperacillin-tazobactam combination in the last 3 months,
- Carriage of extended-spectrum β -lactamase-producing *Enterobacteriaceae* or of ceftazidime-resistant *P. aeruginosa*, determined within the last 3 months, whatever the sampling site,
- Hospitalization during the last 12 months,
- Patient living in a nursing facility or in a long-term care facility for elderly and carrying an indwelling catheter and/or a gastrostomy tube,
- Ongoing epidemic episode of multidrug-resistant bacteria in the healthcare institution for which the only treatment option is carbapenem

Optimisation des doses!

Long-established antibiotics

Piperacillin/tazobactam	4.5 g every 6 h CI	BSI, HAP, VAP, UTI, cIAI
Ceftazidime	6 g every 24 h CI	BSI, HAP, VAP, UTI
Cefepime	2 g every 8 h or CI	BSI, HAP, VAP, UTI
Aztreonam	1 g (2 g) every 8 h	BSI, HAP, VAP, UTI, SSTI
Imipenem/cilastatin	500 mg (1 g) every 6 h	BSI, HAP, VAP, UTI, cIAI
Meropenem	1 g (2 g) every 8 h or CI	BSI, HAP, VAP, UTI, cIAI
Tigecycline	100–200 mg loading those, then 50–100 mg every 12 h	cIAI

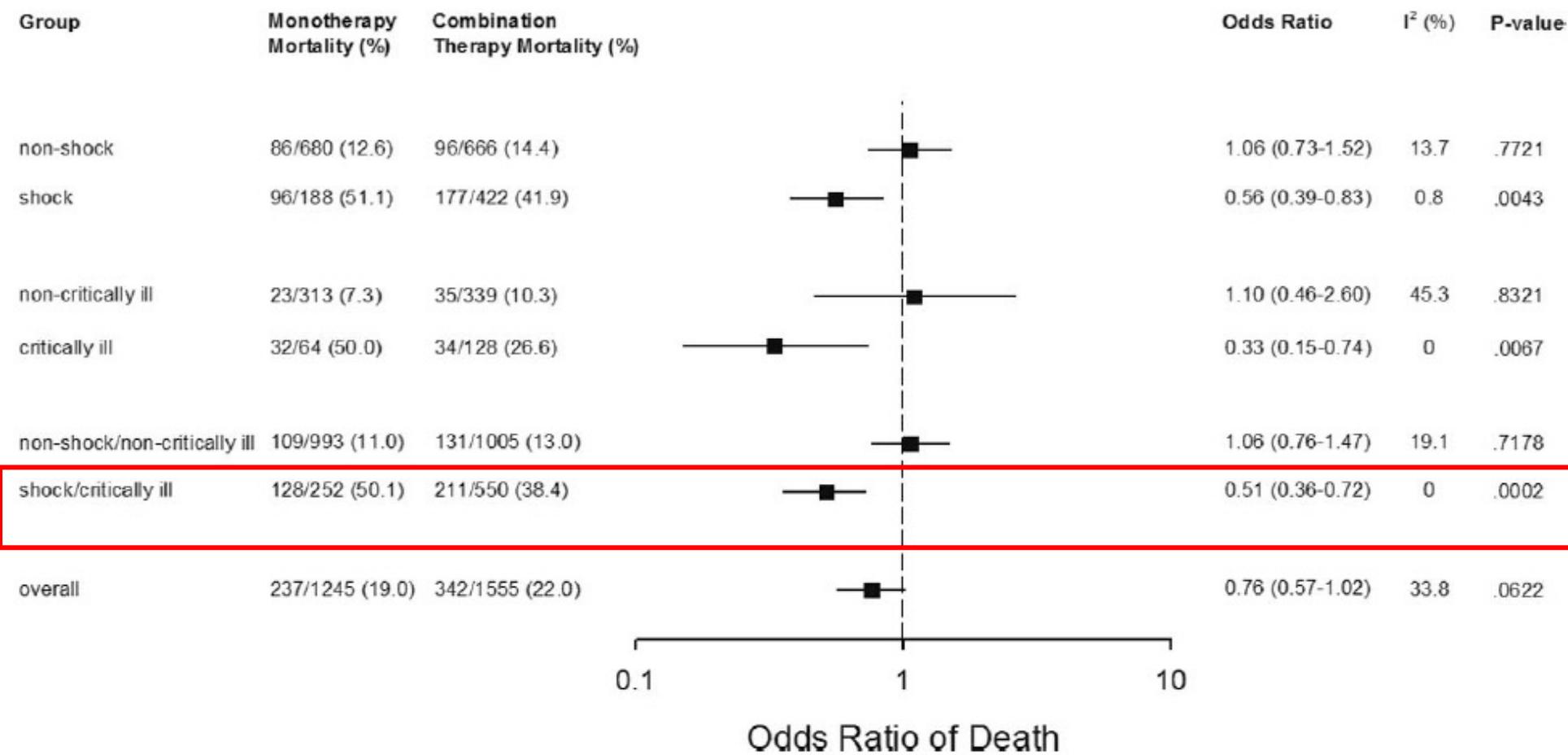
"Old" antibiotics

Gentamicin	7 mg/kg/day every 24 h	In combination for BSI, UTI, cHAP, cIAI, VAP
Amikacin	25–30 mg/kg/day every 24 h	In combination for BSI, UTI, cHAP, cIAI, VAP
Colistin	9 MU loading dose, 4.5 MU every 8–12 h	In combination for BSI, UTI, cHAP, cIAI, VAP
Fosfomycin	4–6 g every 6 h CI	In combination for BSI, UTI, cHAP, cIAI, VAP
Vancomycin	15–30 mg/kg loading dose, 30–60 mg/ kg every 12 h, 6 h or CI	BSI, HAP, VAP, SSTI
Linezolid	600 mg every 12 h	BSI, HAP, VAP, SSTI



bolus!

Bithérapie?



Chez les immunodéprimés...

Type of immune deficiency	Infection risk to guide antimicrobial rationale	Antimicrobial empirical coverage
Solid organ transplant	Timing from transplant surgery 0–2 months: high risk of HAI 2–6 months: high risk of both HAI and CAI 6–12 months: low risk of HAI, moderate risk of HAI and OI > 12 months: low risk of HAI, moderate risk of CAI and OI	<i>Pseudomonas</i> spp., <i>S. aureus</i> , <i>Candida</i> spp., <i>Aspergillus</i> spp., <i>Cryptococcus</i> spp. <i>Nocardia</i> spp., endemic mycoses, CMV PCP, tuberculosis, <i>S. pneumoniae</i>
Neutropenia	Absolute neutrophil count, duration, and comorbidities > 500 cells/μL, anticipated to last < 7 days < 100 cells/μL, anticipated to last > 7 days Shock, mucositis, diarrhea, central line	Low risk <i>Pseudomonas</i> spp., <i>S. aureus</i> , <i>S. viridans</i> , molds <i>Pseudomonas</i> spp., <i>S. aureus</i> , <i>S. viridans</i> , <i>Candida</i> spp.
HIV	CD4 cell count 200–500 cells/μL: low risk of OI 50–200 cells/μL: high risk of OI < 50 cells/μL: very high risk of OI HIV-induced humoral immunodeficiency at any CD4 level HIV and intravenous drug abuse	Tuberculosis Tuberculosis, PCP Cryptococcosis, toxoplasmosis, CMV <i>S. pneumoniae</i> <i>S. aureus</i>
Immunoglobulin deficiency	Common variable immunodeficiency Chronic lymphocytic leukemia Multiple myeloma Chronic granulomatous disease	Encapsulated bacteria ^a Encapsulated bacteria ^a , <i>S. aureus</i> Encapsulated bacteria ^a <i>S. aureus</i> , <i>Burkholderia cepacia</i> , <i>Aspergillus</i> spp.
Iatrogenic immunosuppression	Steroids (prednisone > 20 mg/day) Inhibitors of TNF, IL-1, IL-6, IL-17, IL-12/23 Anti-CD20 monoclonal antibodies Anti-CD52 monoclonal antibodies	<i>Candida</i> spp., PCP, <i>Nocardia</i> spp. Tuberculosis, <i>S. aureus</i> , <i>Listeria</i> spp., <i>Legionella</i> Low risk <i>Aspergillus</i> spp., <i>Mucor</i> , <i>Listeria</i> spp.

Source control in the management of severe sepsis and septic shock: An evidence-based review



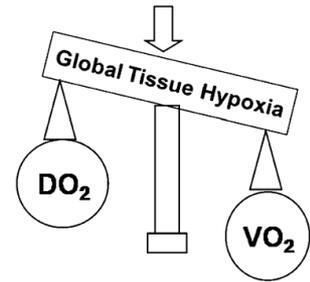


Prise en charge initiale du sepsis

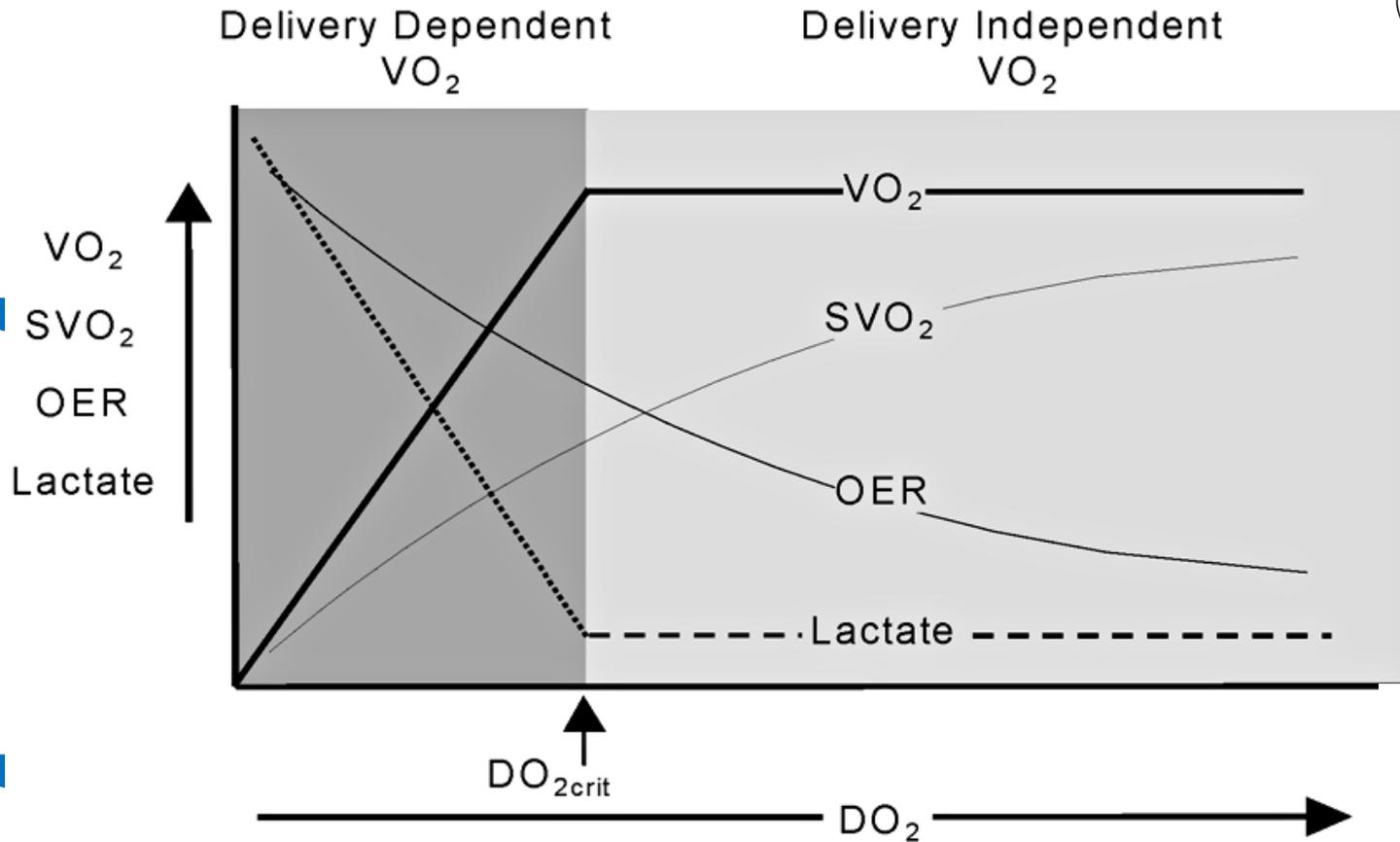
REMPLEISSAGE VASCULAIRE ADAPTÉ

Insuffisance circulatoire **aiguë**:

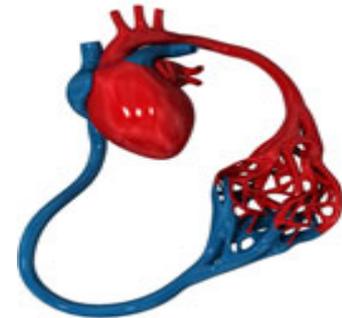
inadéquation VO_2/DO_2

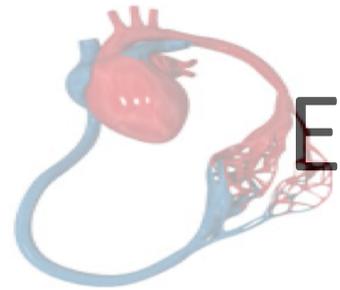


$$SvO_2 \approx SaO_2 - VO_2 / (Qc \times Hb)$$



$$DO_2 = Hb \times 1.36 \times SaO_2 \times Qc$$

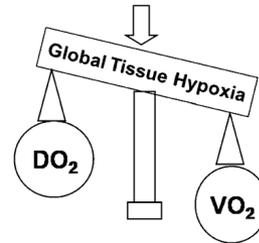




Evaluation hémodynamique

MACROCIRCULATION

- Pression artérielle
- Fréquence cardiaque
- Débit cardiaque
- *Pression veineuse centrale*



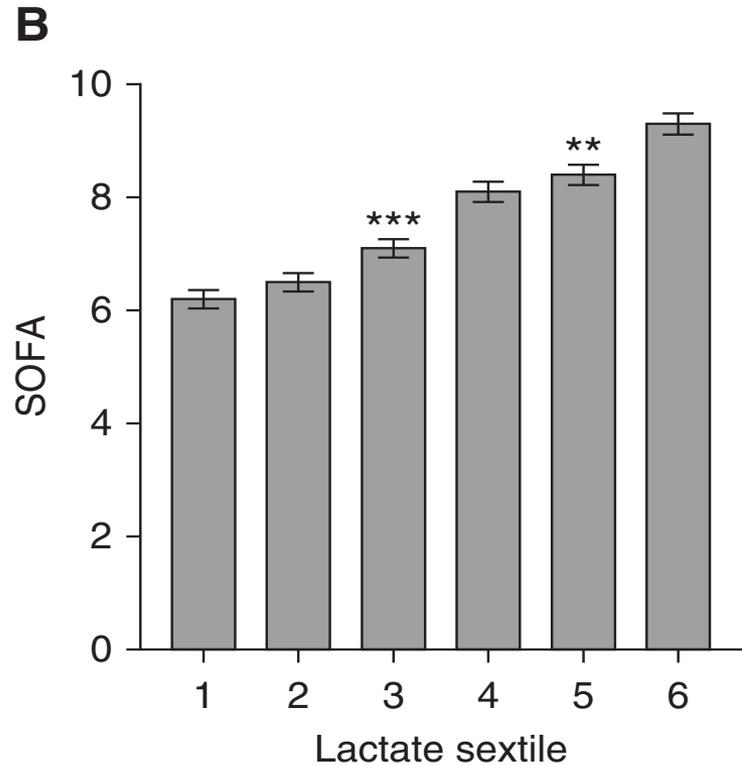
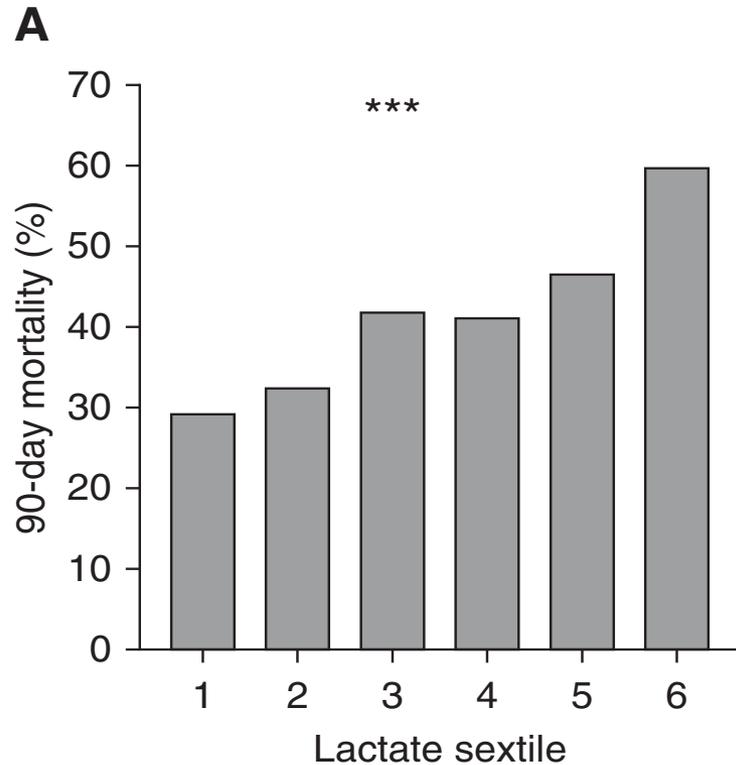
PERFUSION TISSULAIRE MICROCIRCULATION

- Réfugements
- Diurèse
- **Lactate**
- $ScvO_2$



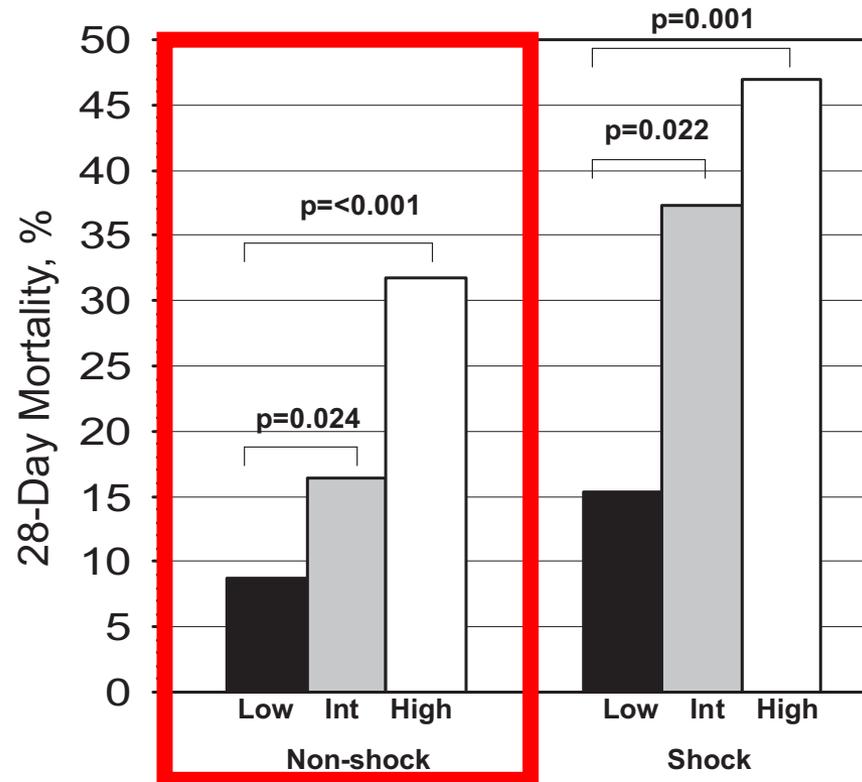
***Discordances et
manque de cohérence
dans le sepsis...***

Hyperlactatémie et **sévérité** clinique

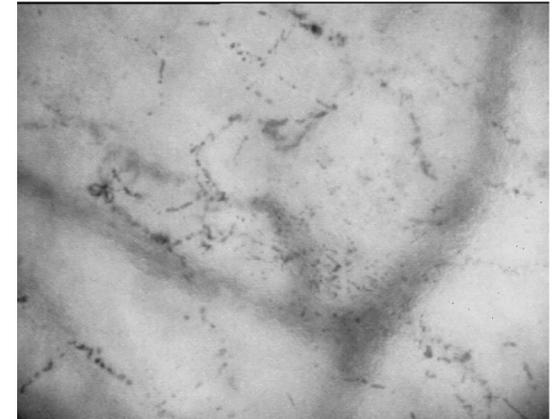
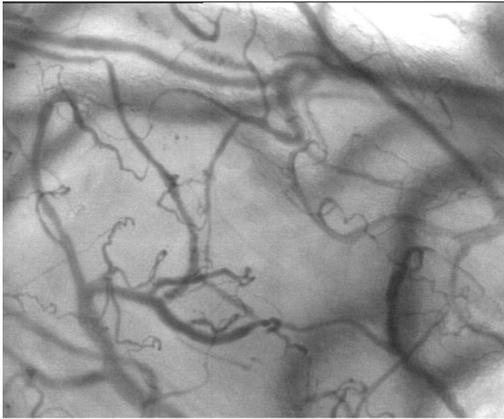


Lactate elevation ...risk stratification

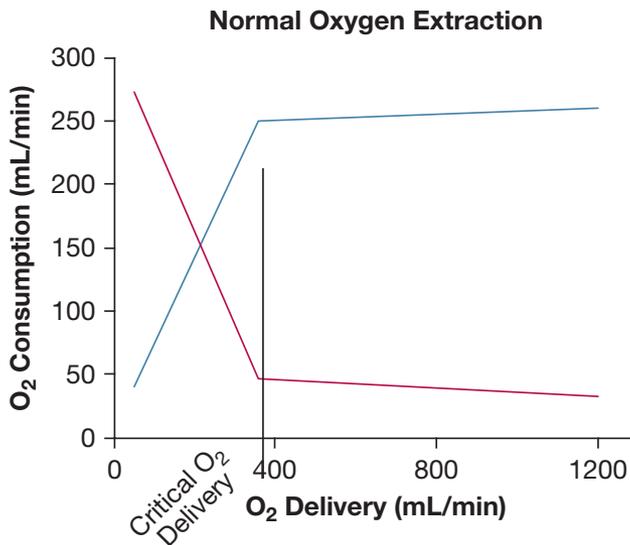
Même si tension conservée!!!



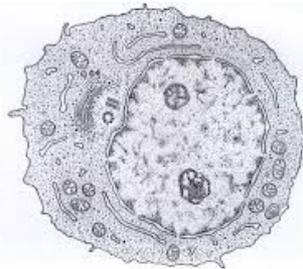
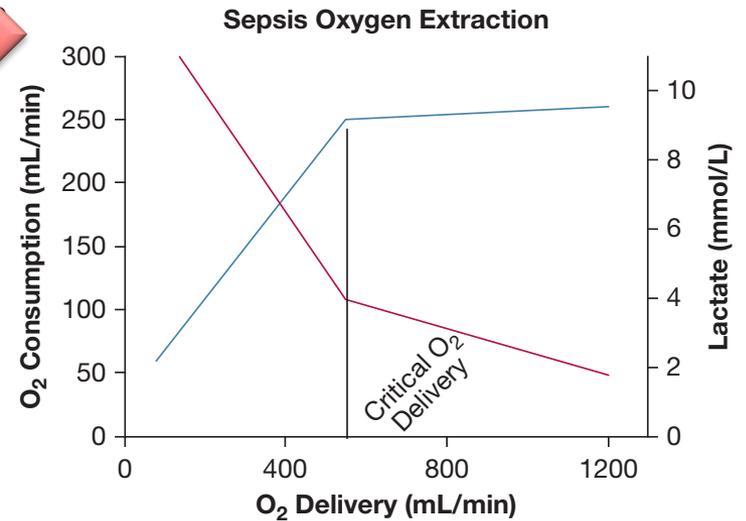
Baisse extraction O_2 ...



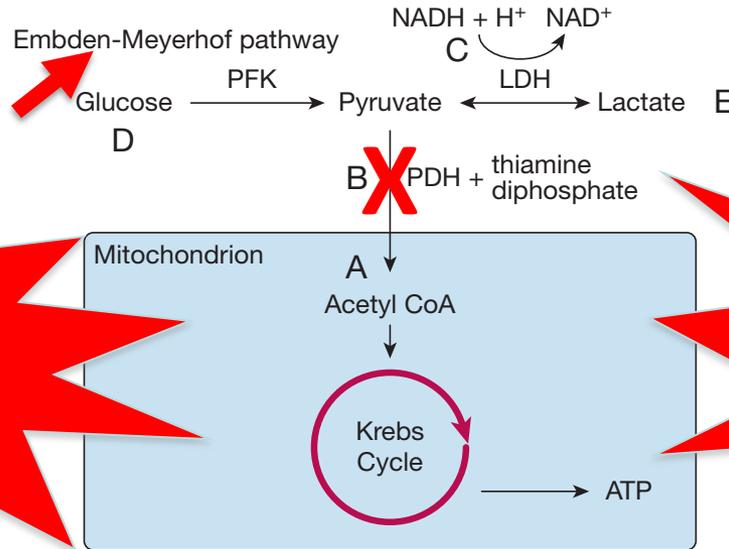
A



SEPSIS



Baisse extraction O₂...

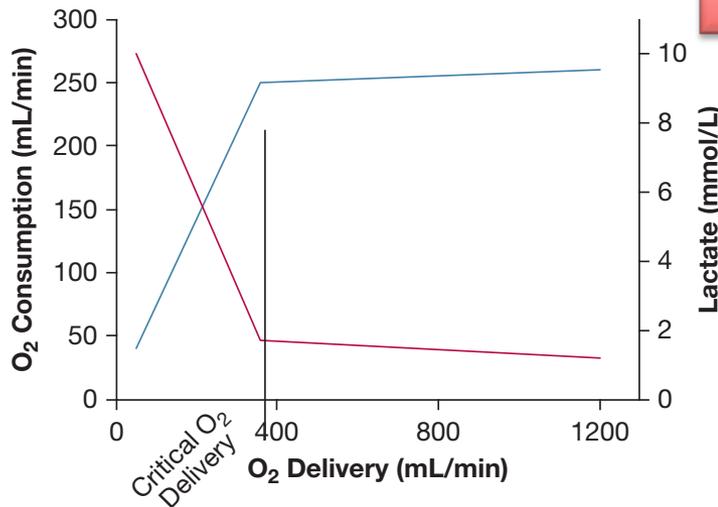


Glycolyse
+++

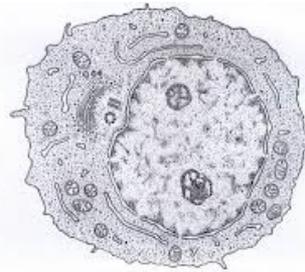
Warburg effect

A

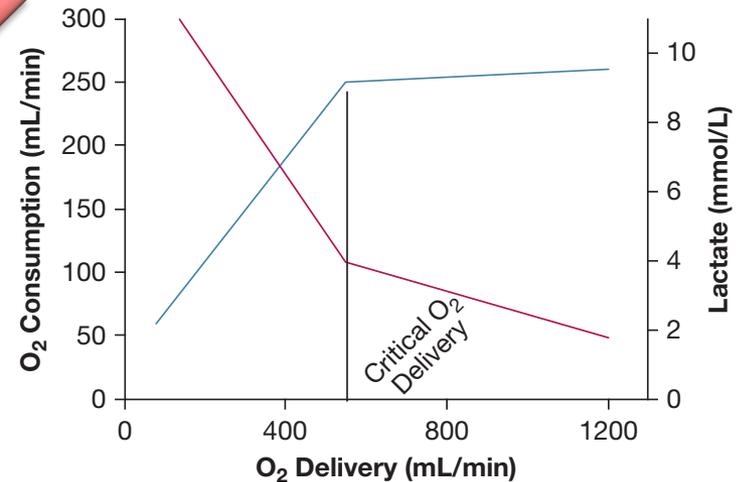
Normal Oxygen Extraction



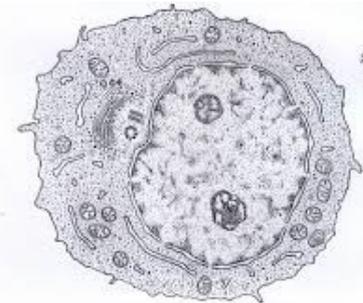
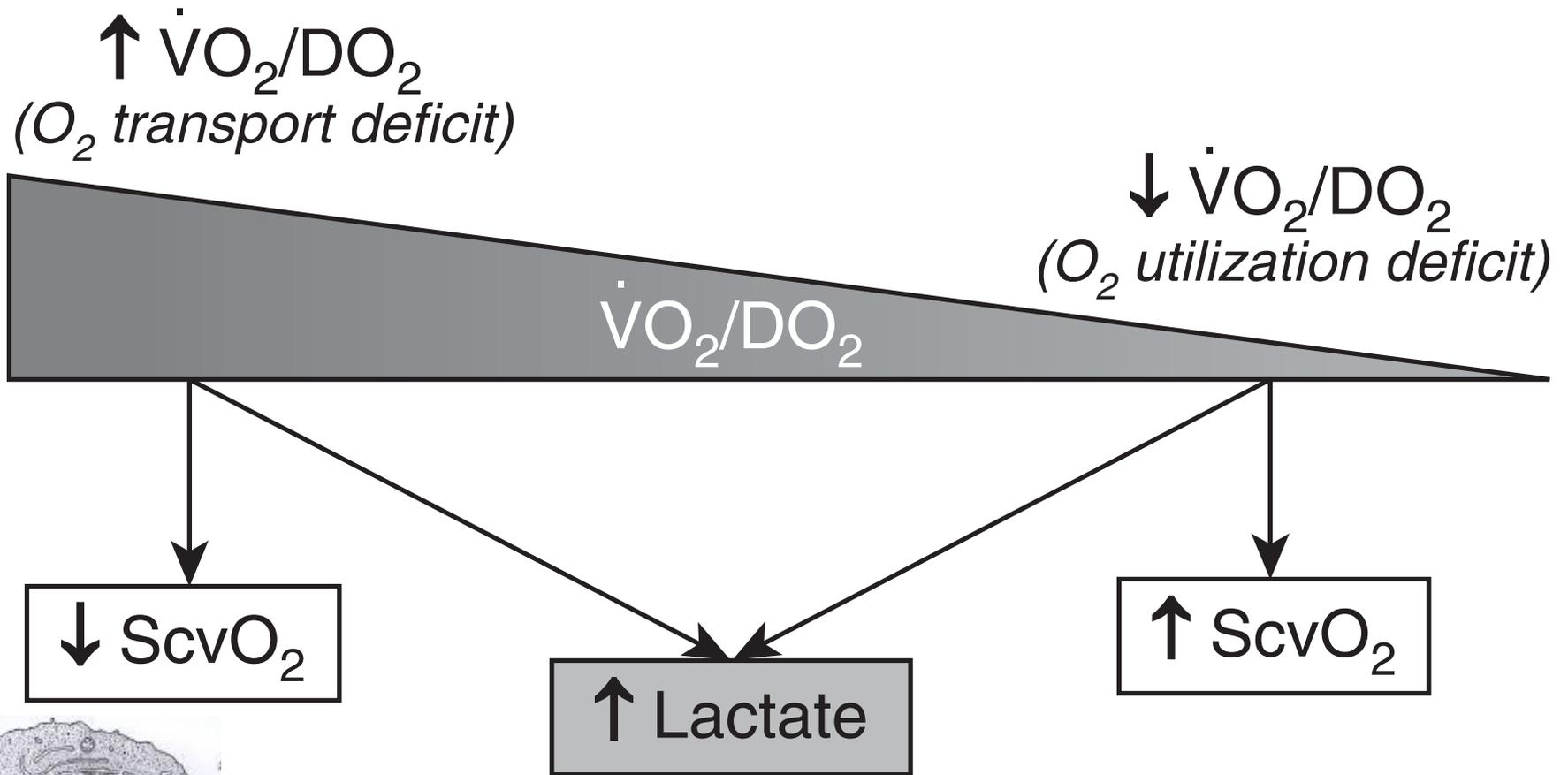
SEPSIS



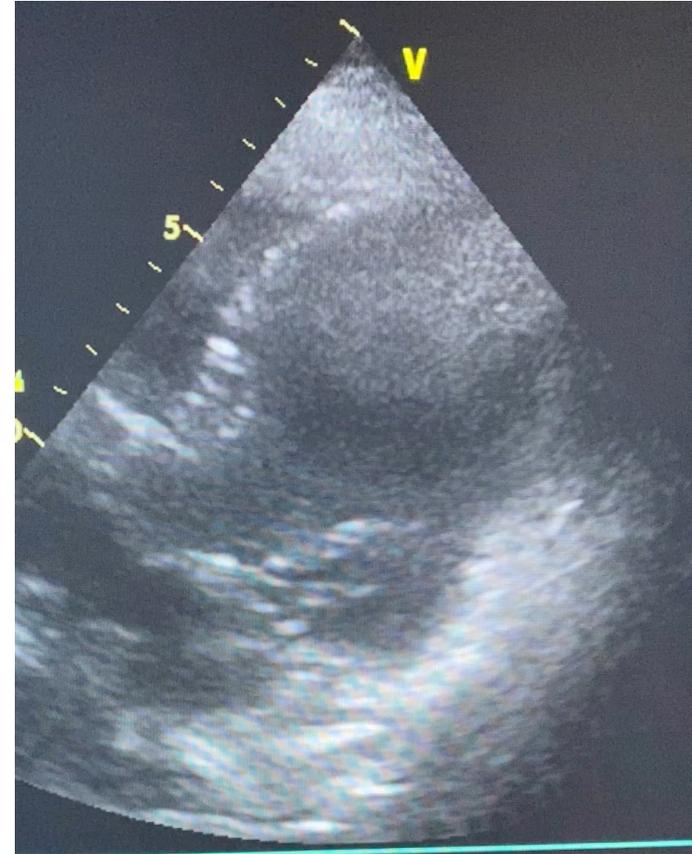
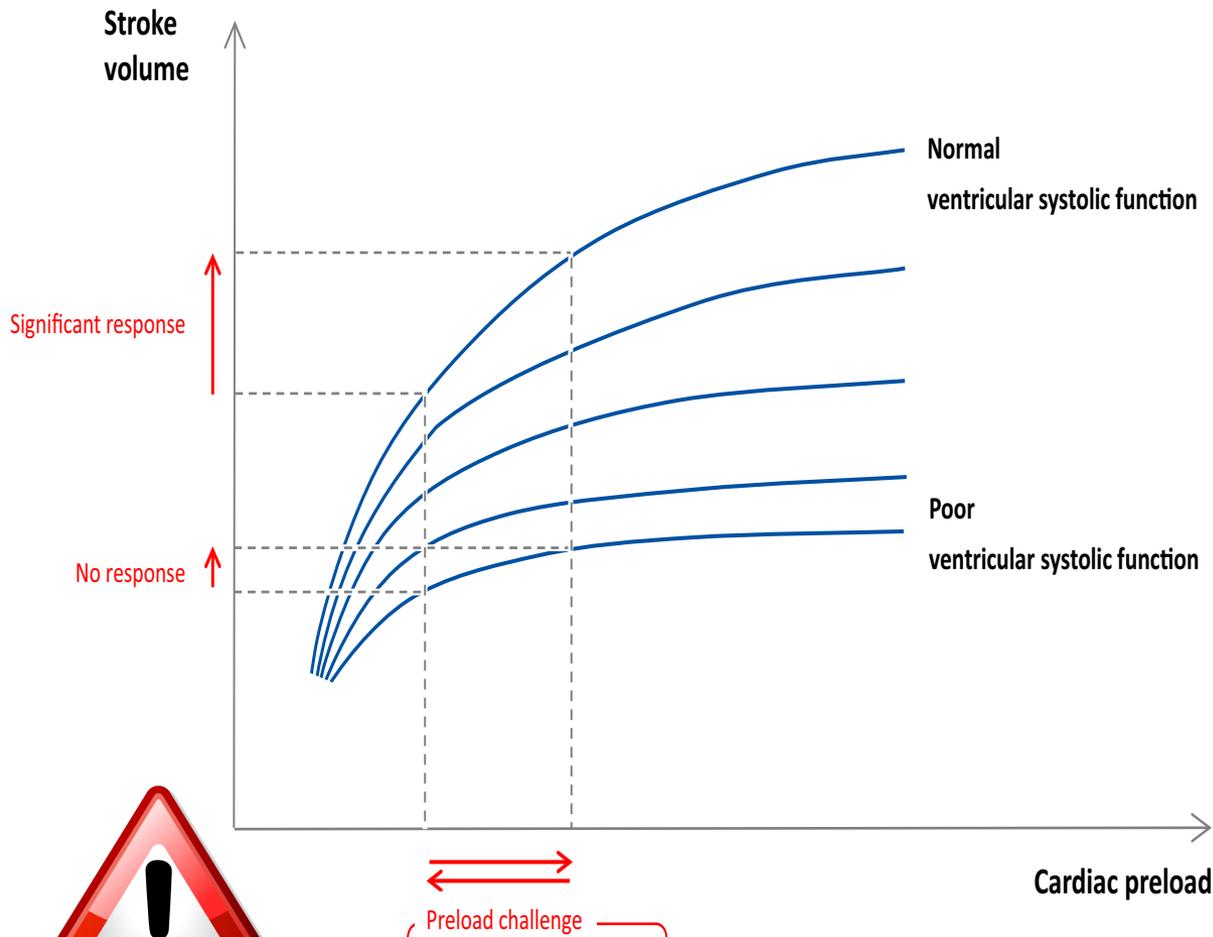
Sepsis Oxygen Extraction



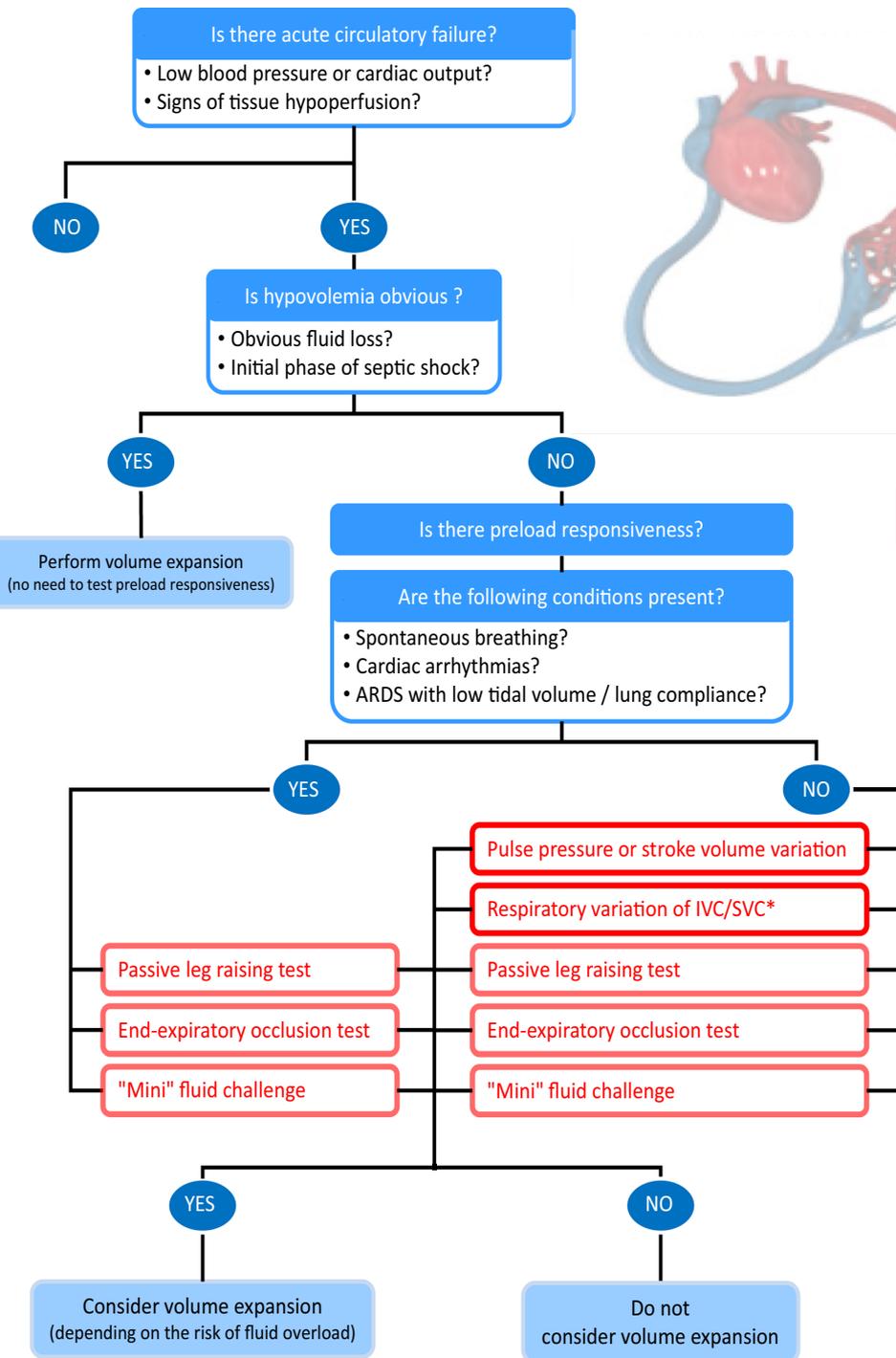
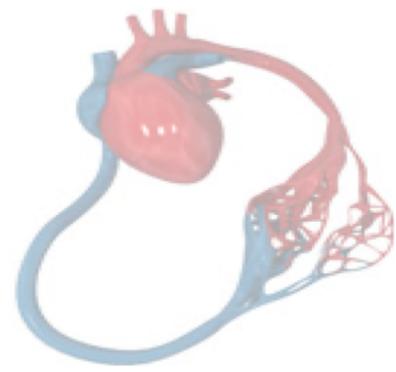
Lactatémie et ScvO₂



Amélioration DO_2 : *Précharge*-dépendance?



$$DO_2 = Hb \times 1.36 \times SaO_2 \times Q_c$$



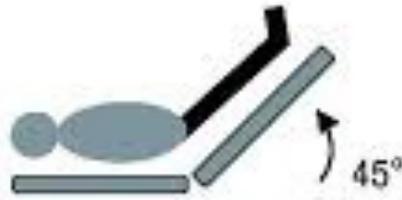
Patient en ventilation spontanée...

Method	Threshold	Main limitations
Pulse pressure/stroke volume variations [22]	12%	Cannot be used in case of spontaneous breathing, cardiac arrhythmias, low tidal volume/ lung compliance
Inferior vena cava diameter variations [44]	12%	Cannot be used in case of spontaneous breathing, low tidal volume/lung compliance
Superior vena caval diameter variations [44]	36%*	Requires performing transesophageal Doppler Cannot be used in case of spontaneous breathing, low tidal volume/lung compliance
Passive leg raising [55]	10%	Requires a direct measurement of cardiac output
End-expiratory occlusion test [75]	5%	Cannot be used in non-intubated patients Cannot be used in patients who interrupt a 15-s respiratory hold
"Mini"-fluid challenge (100 mL) [84]	6%**	Requires a precise technique for measuring cardiac output
"Conventional" fluid challenge (500 mL) [81]	15%	Requires a direct measurement of cardiac output Induces fluid overload if repeated

Prédire la précharge-dépendance: levé de jambes passif



Semi-recumbent position

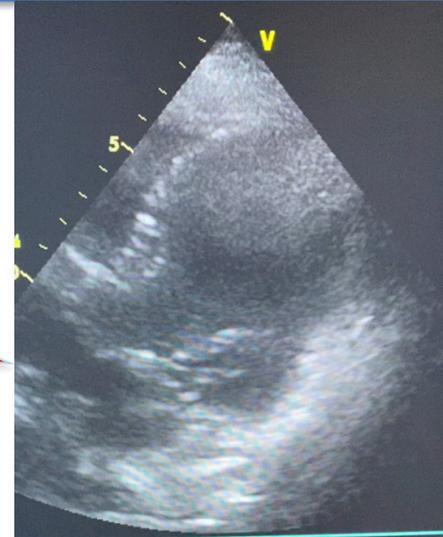


Passive leg raising

« *auto-remplissage* »
250 mL



débit
cardiaque?

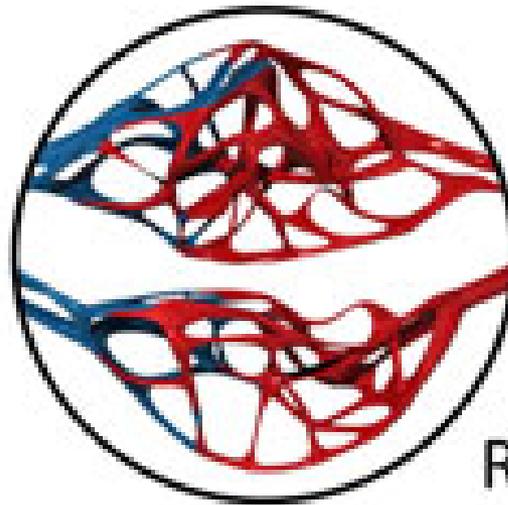




Jusqu'où faut-il remplir les patients **septiques**?

The Good

Stroke volume
Tissue oxygenation
Perfusion
Viscosity

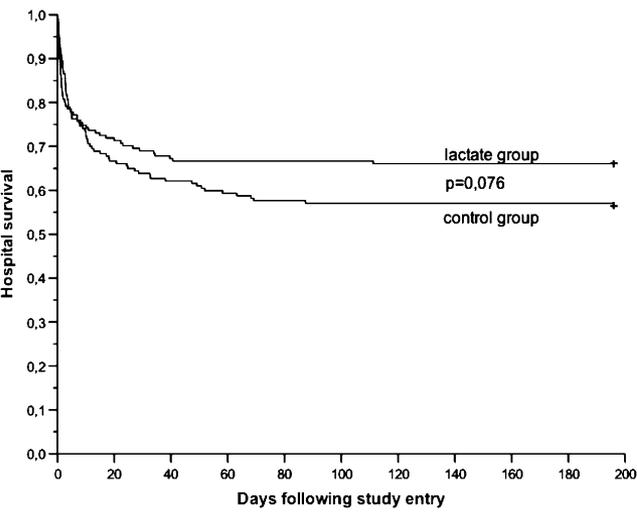
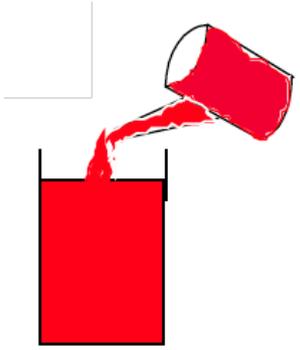


The Bad

Venous congestion
Edema
Reactive oxygen species
Coagulation
Anemia-hypoxemia
Glycocalyx-endothelium
Acidosis

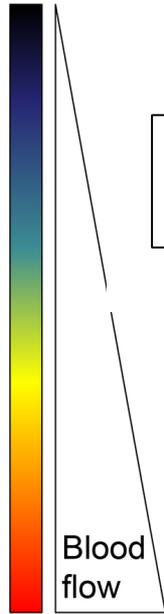
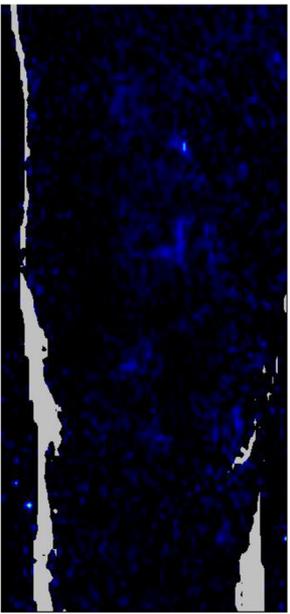
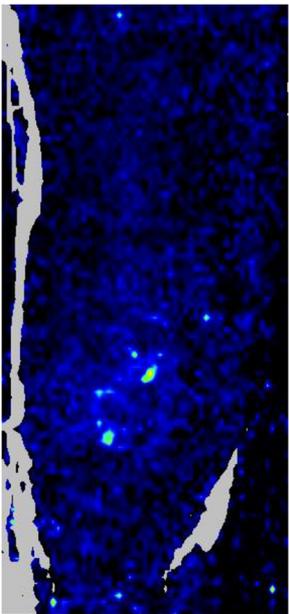
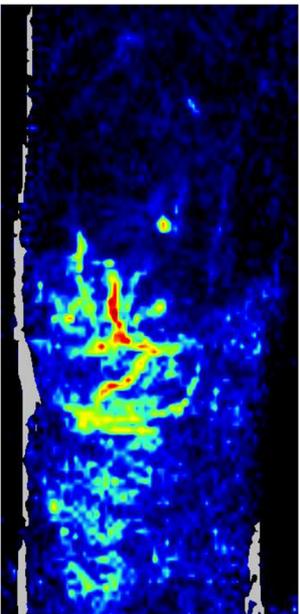
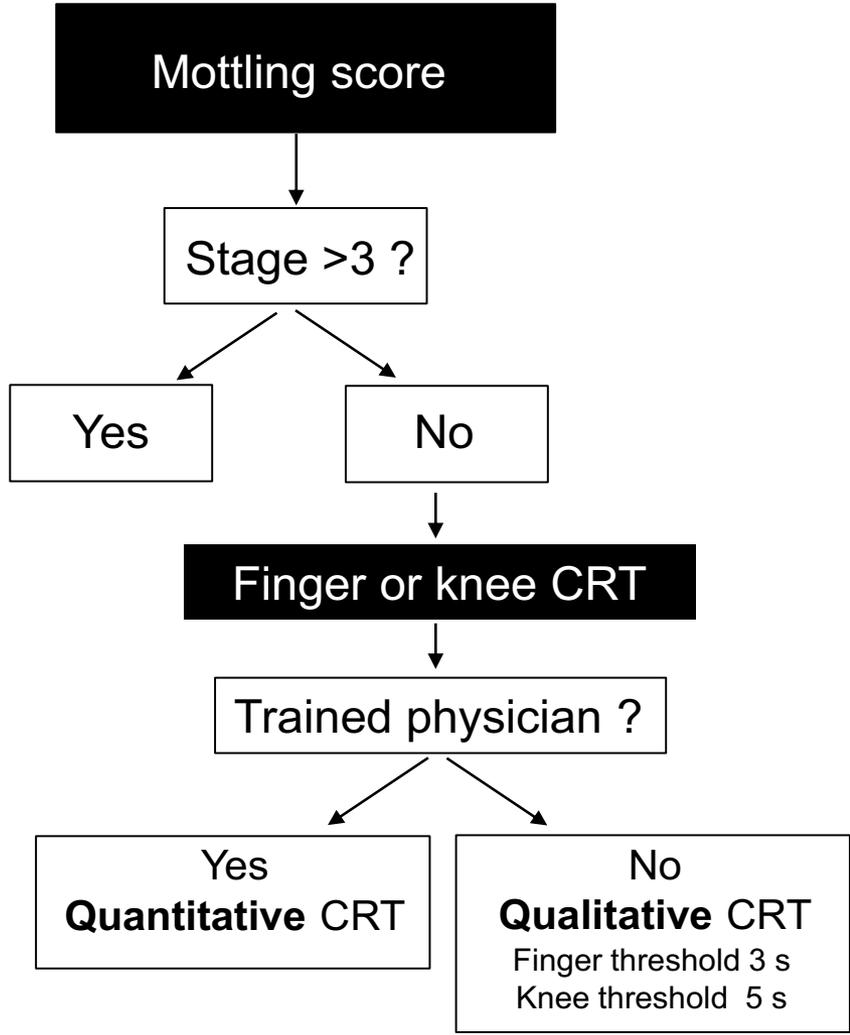
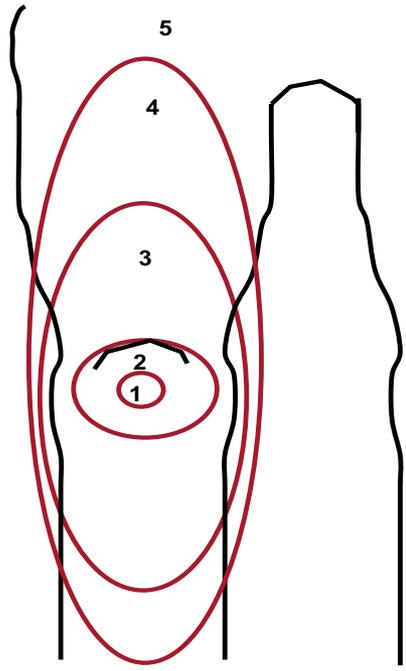
Early Lactate-Guided Therapy in Intensive Care Unit Patients

A Multicenter, Open-Label, Randomized Controlled Trial



Treatment	Control Group	Lactate Group	P Value
Fluids, ml*			
0-8 h [†]	2,194 ± 1,669	2,697 ± 1,965	0.011
9-72 h [‡]	10,043 ± 6,141	8,515 ± 4,987	0.055
Red blood cell transfusion, ml			
0-8 h [†]	196 ± 495	322 ± 1037	0.15
9-72 h [‡]	345 ± 667	423 ± 1300	0.59
Any inotropic, %§			
0-8 h [†]			0.17
9-72 h [‡]			0.12
Any vasodilator, %			
0-8 h [†]			<0.001
9-72 h [‡]			0.005
Any vasopressor, %**			
0-8 h [†]	63.6	69.5	0.25
9-72 h [‡]	63.7	71.4	0.16

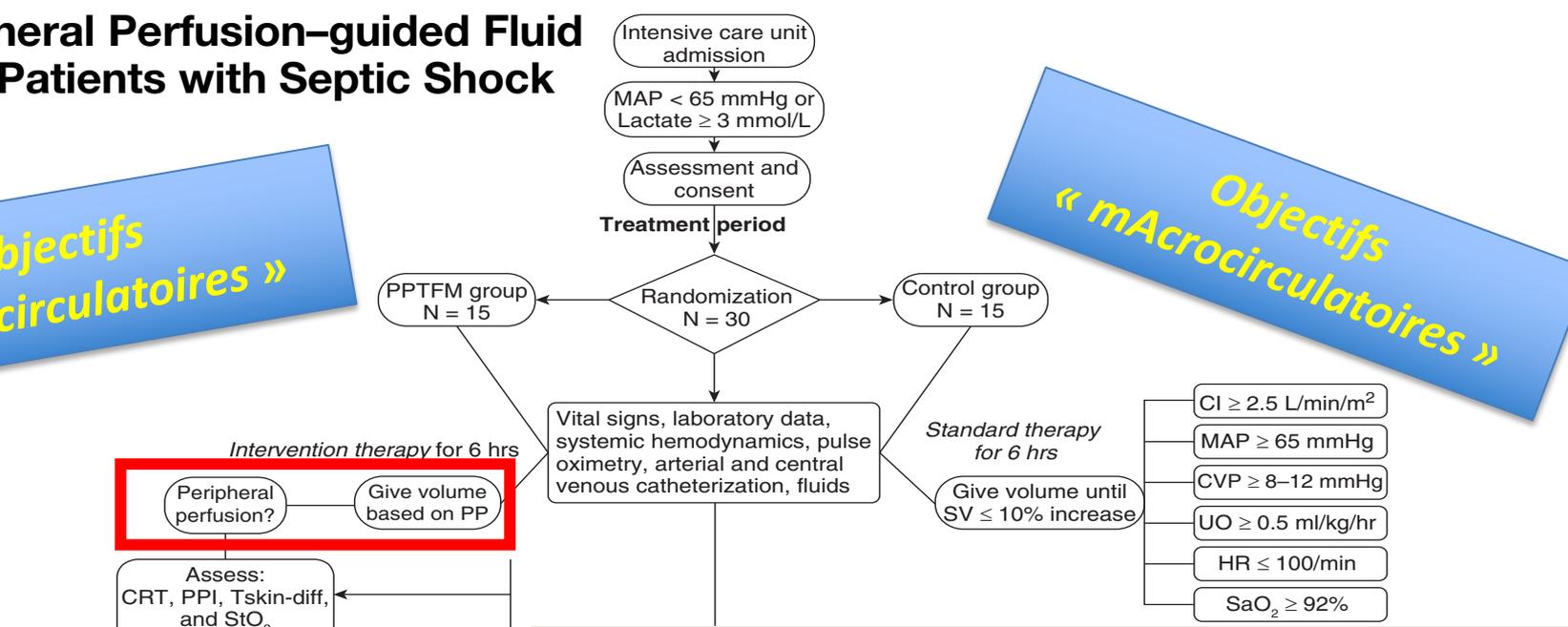
**Remplissage
+rapide/-abondant**



Early Peripheral Perfusion-guided Fluid Therapy in Patients with Septic Shock

Objectifs « microcirculatoires »

Objectifs « mAcrocirculatoires »



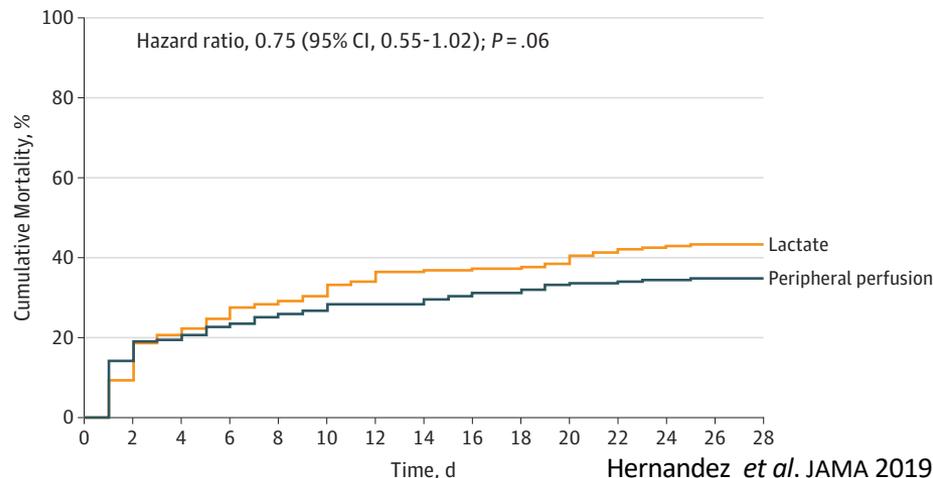
Variables and Groups	Study Period	
	0–6 h	7–72 h
Cumulative fluids, ml		
Control	6,069 (1,715)	10,028 (941)
PPTFM	4,227 (1,081)	7,565 (982)
Urine output, ml		
Control	520 (160)	2,469 (542)
PPTFM	332 (84)	1,680 (527)
SOFA _{total}		
Control	12.8 (10.0–16.8)	11.0 (5.3–15.3)
PPTFM	11.5* (8.0–13.0)	8.3 (5.5–13.1)
Mechanical ventilation free days, d		
Control	2 (2–6)	
PPTFM	2 (1–5)	
Intensive care unit mortality, n (%)		
Control	6 (40)	
PPTFM	7 (47)	
Intensive care unit stay, d		
Control	8 (3–8)	
PPTFM	10 (2–10)	
Hospital stay, d		
Control	43 (8–45)	
PPTFM	16 (5–28)*	



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

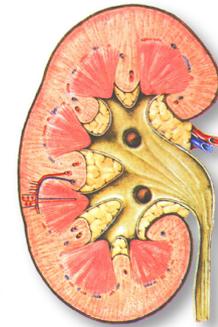
Outcome	Peripheral Perfusion-Targeted Resuscitation (n = 212)	Lactate Level-Targeted Resuscitation (n = 212)	Unadjusted Absolute Difference (95% CI)	Adjusted Relative Measure (95% CI)	P Value
SOFA at 72 h, No. ^d	165	166			.045
Mean (SD)	5.6 (4.3)	6.6 (4.7)	-1.00 (-1.97 to -0.02)		
ICU length of stay, mean (SD), d ^e	9.1 (9.8)	9.0 (9.6)	0.1 (-1.7 to 2.0)		.91
Hospital length of stay, mean (SD), d ^f	22.9 (28.8)	18.3 (19.0)	4.6 (0.0 to 9.1)		.05
Amount of resuscitation fluids within the first 8 h, No.	206	209			
Mean (SD), mL	2359 (1344)	2767 (1749)	-408 (-705 to -110)		.01





Prise en charge initiale du sepsis

**QUEL(S) SOLUTÉ(S) DE
REEMPLISSAGE UTILISER?**



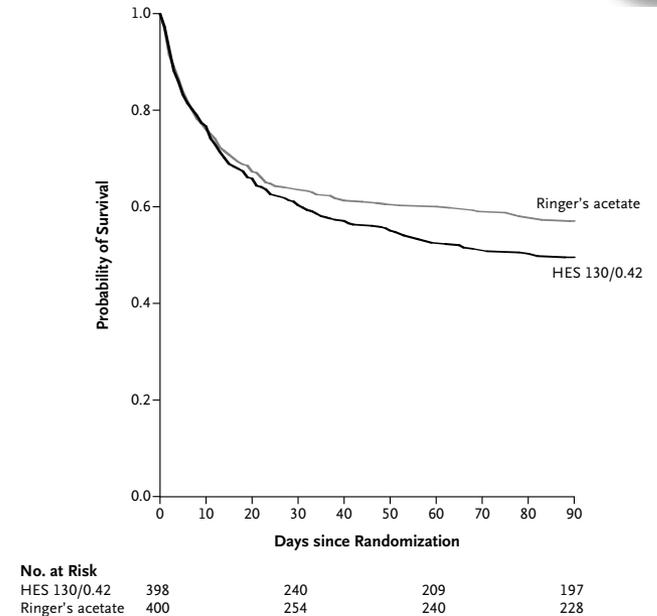
ORIGINAL ARTICLE

Hydroxyethyl Starch 130/0.42 versus Ringer's Acetate in Severe Sepsis

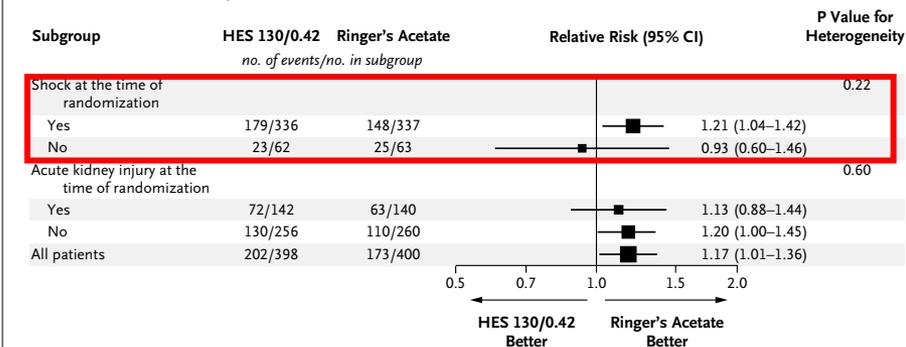
Table 1. Baseline Characteristics of the Patients.*

Characteristic	HES 130/0.42 (N=398)	Ringer's Acetate (N=400)
Age — yr		
Median	66	67
Interquartile range	56–75	56–76
Male sex — no. (%)	239 (60)	244 (61)
Ideal body weight — kg†		
Median	72	72
Interquartile range	60–80	60–80
Admitted to university hospital — no. (%)	194 (49)	188 (47)
Surgery — no. (%)‡		
Emergency	114 (29)	116 (29)
Elective	34 (9)	48 (12)
Source of ICU admission — no. (%)		
Emergency department	109 (27)	94 (24)
General ward	177 (44)	196 (49)
Operating or recovery room	59 (15)	54 (14)
Other ICU in the same hospital	21 (5)	14 (4)
Other hospital	32 (8)	42 (10)
Source of sepsis — no. (%)§		
Lungs	212 (53)	229 (57)
Abdomen	130 (33)	133 (33)
Urinary tract	56 (14)	50 (12)
Soft tissue	38 (10)	46 (12)
Other	43 (11)	33 (8)
SAPS II — median (interquartile range)¶	50 (40–60)	51 (39–62)
SOFA score — median (interquartile range)¶	7 (5–9)	7 (5–9)
Shock — no. (%)**	336 (84)	337 (84)
Acute kidney injury — no. (%)††	142 (36)	140 (35)
Mechanical ventilation — no. (%)	240 (60)	245 (61)

A Time to Death

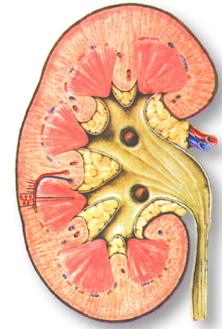


B Relative Risk of the Primary Outcome



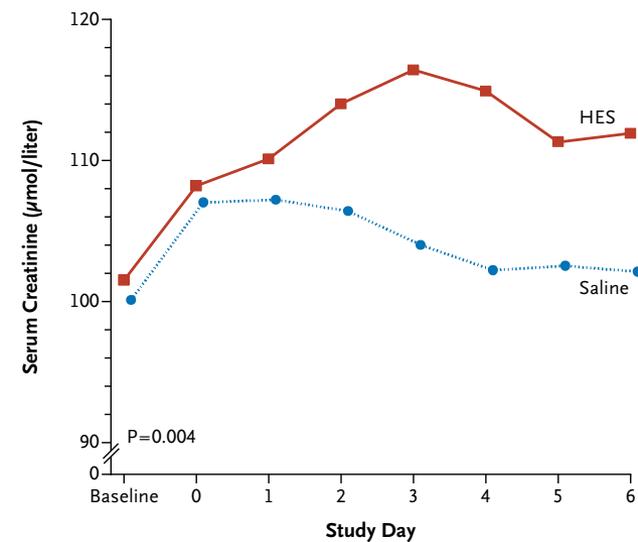
Secondary outcomes — no./total no. (%)

Renal outcomes				
RIFLE-R	1788/3309 (54.0)	1912/3335 (57.3)	0.94 (0.90 to 0.98)	0.007
RIFLE-I	1130/3265 (34.6)	1253/3300 (38.0)	0.91 (0.85 to 0.97)	0.005
RIFLE-F	336/3243 (10.4)	301/3263 (9.2)	1.12 (0.97 to 1.30)	0.12
Use of renal-replacement therapy	235/3352 (7.0)	196/3375 (5.8)	1.21 (1.00 to 1.45)	0.04
New organ failure†				
Respiratory	540/2062 (26.2)	524/2094 (25.0)	1.05 (0.94 to 1.16)	0.39
Cardiovascular	663/1815 (36.5)	722/1808 (39.9)	0.91 (0.84 to 0.99)	0.03
Coagulation	142/2987 (4.8)	119/3010 (4.0)	1.20 (0.95 to 1.53)	0.13
Hepatic	55/2830 (1.9)	36/2887 (1.2)	1.56 (1.03 to 2.36)	0.03



Néphrose osmotique?

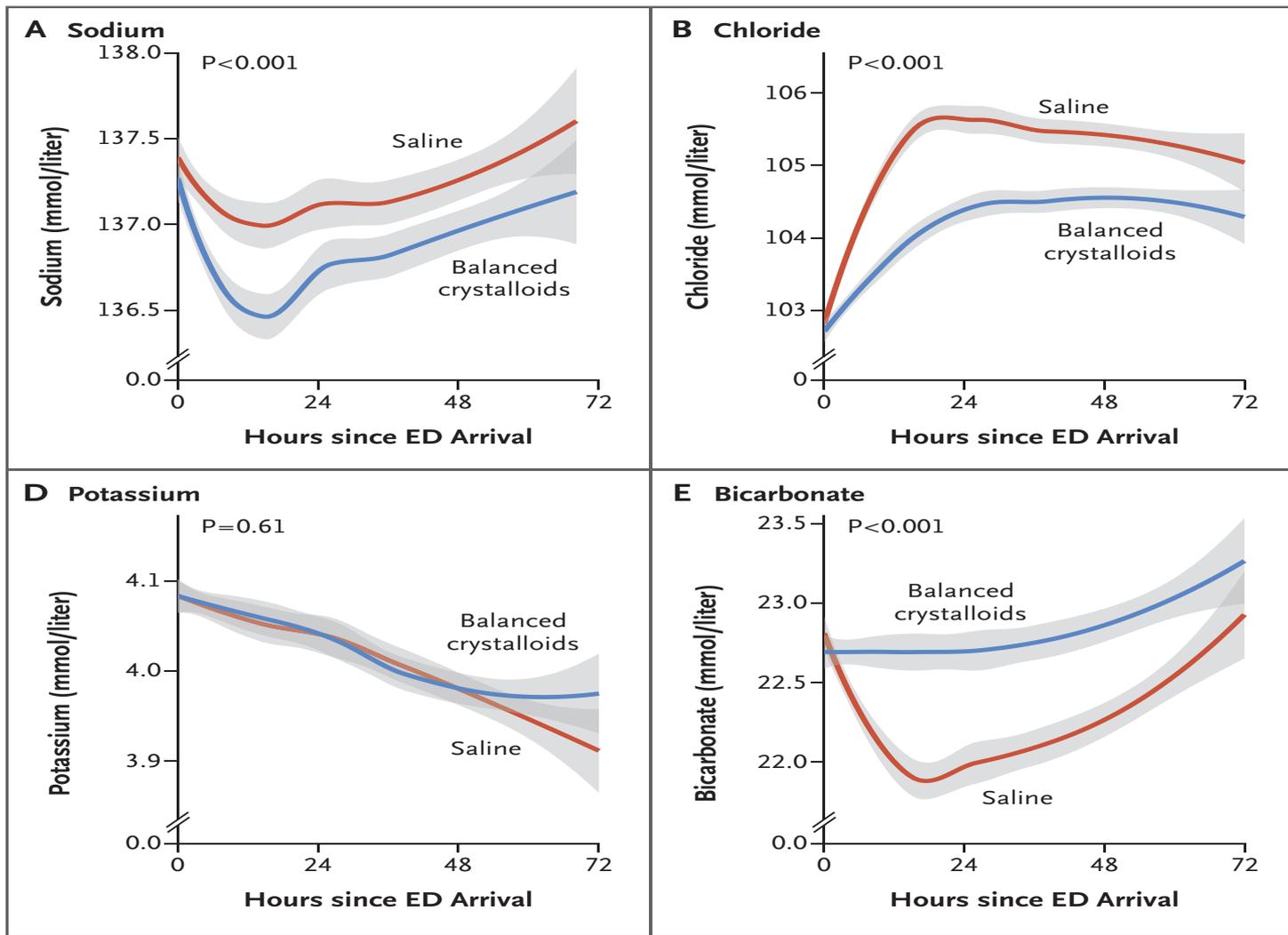
A Serum Creatinine



No. at Risk	Baseline	0	1	2	3	4	5	6
HES	3260	2197	2899	2111	1576	1238	998	851
Saline	3283	2253	2916	2196	1614	1291	1026	857

ORIGINAL ARTICLE

Balanced Crystalloids versus Saline in Noncritically Ill Adults

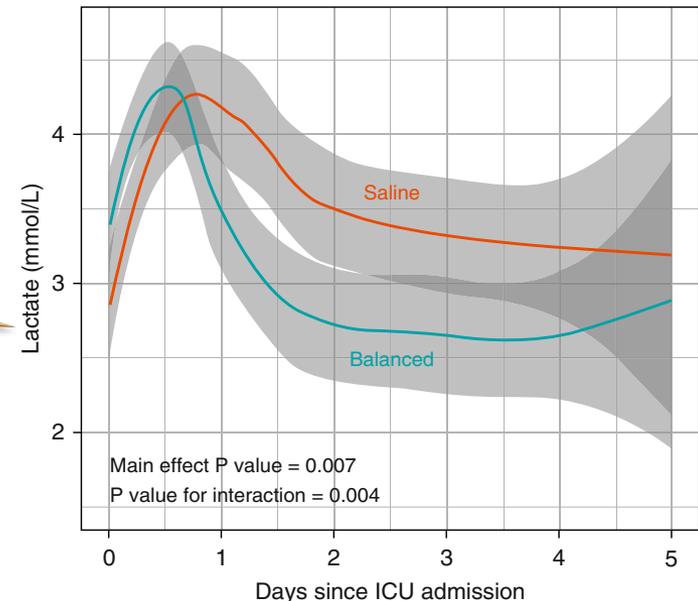


Balanced Crystalloids versus Saline in Sepsis

A Secondary Analysis of the SMART Clinical Trial

Outcome*	n	Balanced Crystalloids (n = 824)	Saline (n = 817)	Adjusted OR (95% CI) [†]
Primary outcome				
30-d in-hospital mortality, n (%)	1,641	217 (26.3)	255 (31.2)	0.74 (0.59 to 0.93)
Additional renal outcomes [§]				
Major adverse kidney event within 30 d, n (%)	1,641	292 (35.4)	328 (40.1)	0.78 (0.63 to 0.97)

Clearance lactate plus rapide



Sodium bicarbonate therapy for patients with severe metabolic acidaemia in the intensive care unit (BICAR-ICU): a multicentre, open-label, randomised controlled, phase 3 trial



pH ≤ 7.20
HCO₃ ≤ 20 mmol/L
PaCO₂ ≤ 45 mmHg
≤ 48H ICU

	Control group (n=194)	Bicarbonate group (n=195)
(Continued from previous page)		
Physiological support†		
Invasive mechanical ventilation	160 (82%)	164 (84%)
Vasopressor support	156 (80%)	154 (79%)
Laboratory results		
Arterial pH	7.15 (7.11–7.18)	7.15 (7.09–7.18)
PaO ₂ -to-FiO ₂ ratio (mm Hg)	229 (142–355)	264 (144–403)
PaCO ₂ (mm Hg)	37 (32–42)	38 (33–42)
Serum bicarbonate (mmol/L)	13 (10–15)	13 (10–15)
Serum lactate (mmol/L)	5.3 (3.4–9.0)	6.3 (3.6–9.7)
Serum lactate ≥ 2 mmol/L at enrolment	152 (78%)	168 (86%)
Serum creatinine (mg/dL)	1.76 (1.21–2.48)	1.67 (1.11–2.33)
Blood urea nitrogen (mg/dL)	31 (20–48)	28 (20–45)

	Control group (n=194)	Bicarbonate group (n=195)	Absolute difference estimate (95% CI)	p value
Primary outcome				
Overall population (n=389)				
Composite outcome	138 (71%)	128 (66%)	-5.5 (-15.2 to 4.2)	0.24
Day 28 mortality	104 (54%)	87 (45%)	-9.0 (-19.4 to 1.4)	0.07
At least one organ failure at day 7	134 (69%)	121 (62%)	-2.8 (-15.4 to 9.8)	0.15
Patients with AKIN scores of 2–3* (n=182)				
Composite outcome	74/90 (82%)	64/92 (70%)	-12.3 (-26.0 to -0.1)	0.0462
Day 28 mortality	57/90 (63%)	42/92 (46%)	-17.7 (-33.0 to -2.3)	0.0166
At least one organ failure at day 7	74/90 (82%)	61/92 (66%)	-15.9 (-28.4 to -3.4)	0.0142
Secondary outcomes				
Renal replacement therapy				
Overall population (n=389)				
Use of renal replacement therapy during ICU stay	100 (52%)	68 (35%)	-16.7 (-26.4 to -7.0)	0.0009

Patient with suspected infection

qSOFA ≥ 2 ?
(see **A**)

No

Sepsis still suspected?

No

Monitor clinical condition;
reevaluate for possible sepsis
if clinically indicated

Yes

Assess for evidence
of organ dysfunction

Yes

SOFA ≥ 2 ?
(see **B**)

No

Monitor clinical condition;
reevaluate for possible sepsis
if clinically indicated

Yes

Sepsis

Despite adequate fluid resuscitation,
1. vasopressors required to maintain
MAP ≥ 65 mm Hg
AND
2. serum lactate level > 2 mmol/L?

No

Yes

Septic shock

- A** qSOFA Variables
- Respiratory rate
 - Mental status
 - Systolic blood pressure

- B** SOFA Variables
- PaO₂/FiO₂ ratio
 - Glasgow Coma Scale score
 - Mean arterial pressure
 - Administration of vasopressors with type and dose rate of infusion
 - Serum creatinine or urine output
 - Bilirubin
 - Platelet count

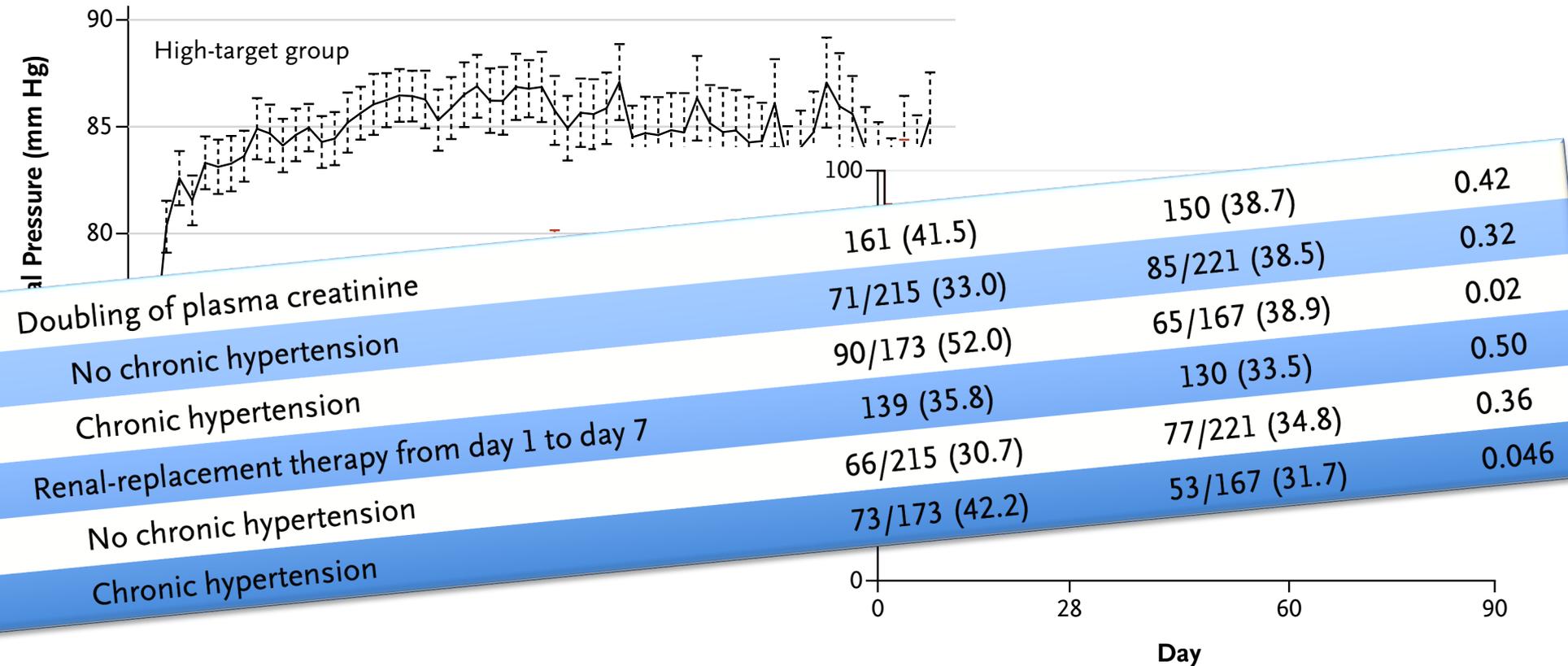
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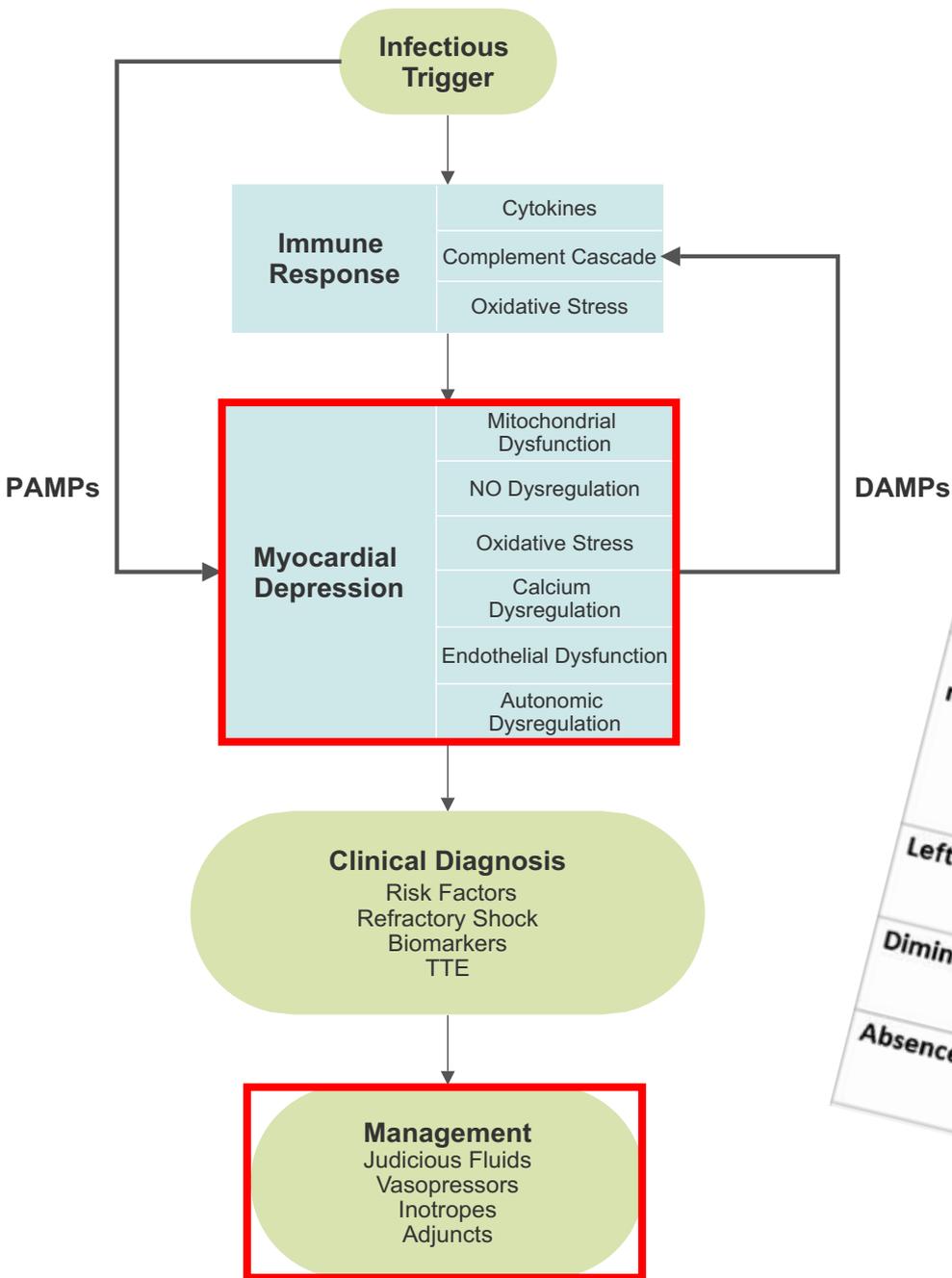
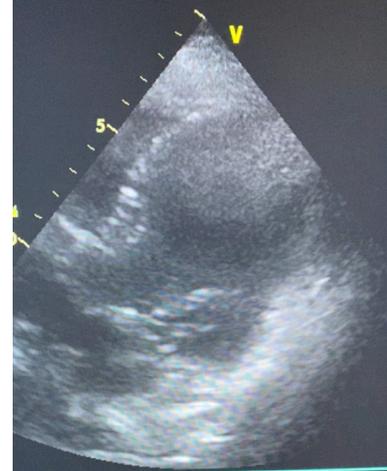
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High versus Low Blood-Pressure Target in Patients with Septic Shock



No. at Risk

	Day 0	Day 28	Day 60	Day 90
Low target	379	256	233	225
High target	375	249	227	219



Proposed Diagnostic Criteria for Sepsis-Induced Cardiomyopathy

Acute and reversible, within 7-10 days
Global, biventricular dysfunction (systolic and/or diastolic) with reduced contractility
Left ventricular dilation
Diminished response to fluid resuscitation and catecholamines
Absence of acute coronary syndrome as etiology

Prise en charge du patient septique

- Remplissage précoce du patient septique
- Solutés **crystalloïdes** (sol. balancés+++)
- **Simultanément avec** l'antibiothérapie
- La précocité impacte fortement sur le **devenir** des patients
- Nécessité d'**endpoints**: clinique, **lactate**, $SvcO_2$