Les Hôpitaux Universitaires de STRASBOURG

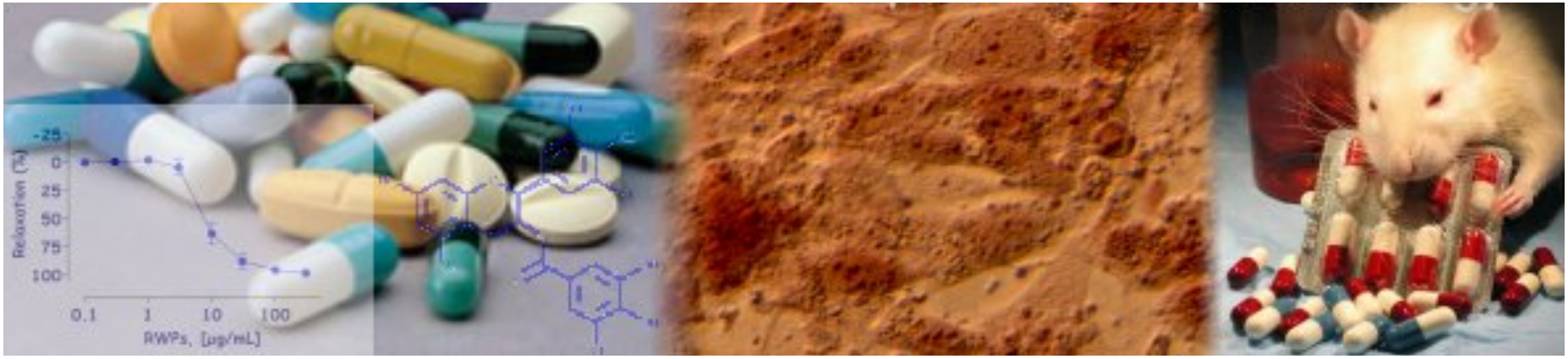
UNIVERSITÉ DE STRASBOURG

Insuffisance rénale aiguë du sepsis

DESC juin 2018

Julie Helms – MCU-PH

Réanimation Médicale – NHC Strasbourg



SEPSIS ET CHOC SEPTIQUE

Clinical Review & Education

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

(Singer, JAMA 2016)

SEPSIS

INFECTION

+

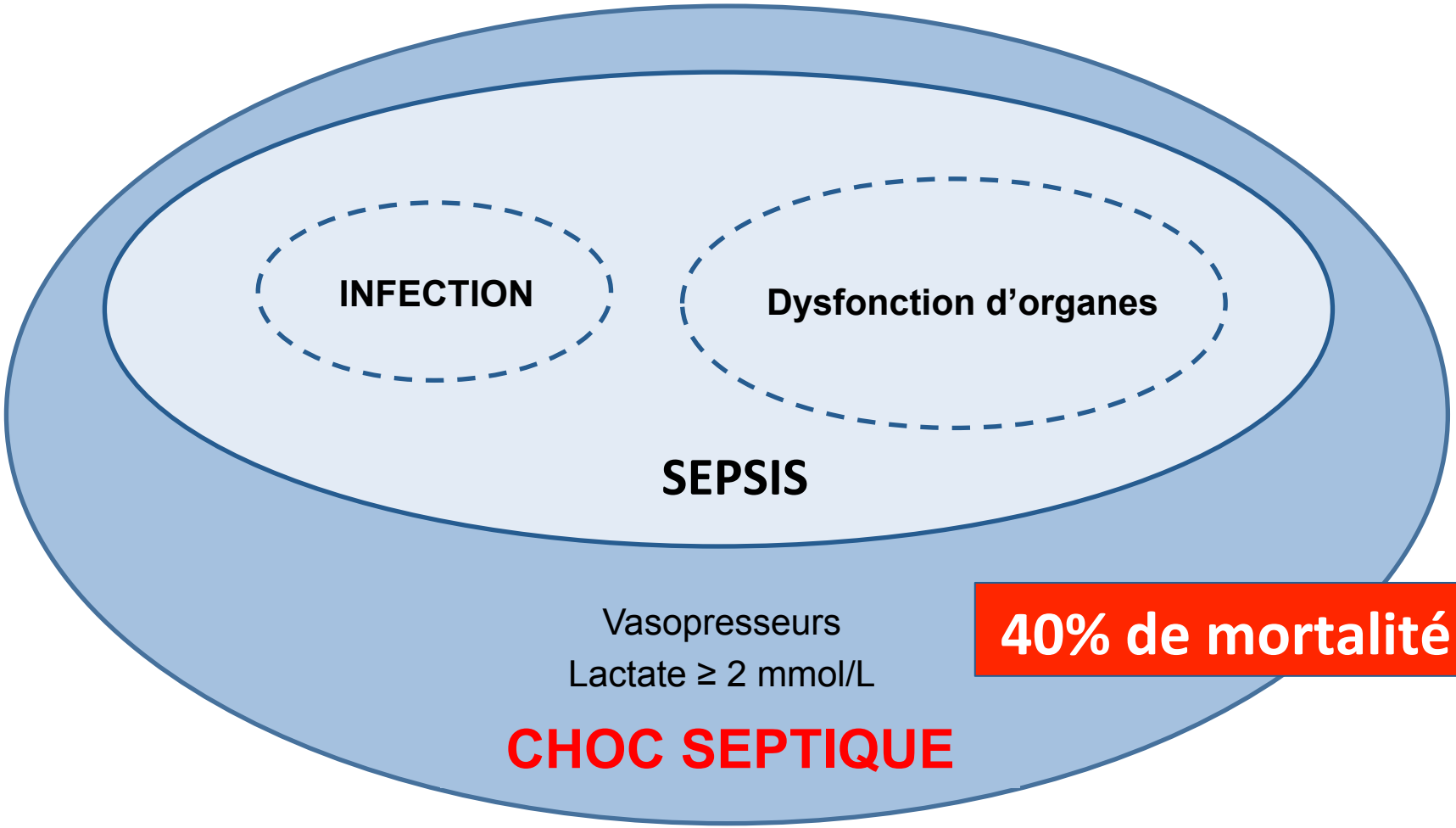
Sepsis-related
Organ
Failure
Assessment

- PaO_2/FiO_2
- Hypotension
- Glasgow coma scale
- Platelets
- Bilirubinemia
- Oliguria / Creatinine

≥2

(Singer, JAMA 2016)

LE SEPSIS ET LE CHOC SEPTIQUE



(Singer, JAMA 2016)

TRAITEMENT DU CHOC SEPTIQUE

ANTI-INFECTIEUX

- état circulatoire et ventilatoire
- réduire dette O_2

SYMPTOMATIQUE

CHOC SEPTIQUE

Immunomodulateurs

Immunonutrition :
glutamine, arginine, lipides, antioxydants, oligo-éléments

Nutrition
Insuline

Insuffisance surrénalienne :
hydrocortisone

Epuration sanguine
(cytokine, endotoxine)

Coagulopathie :
PCa, AT, sTM, Héparine

(Parrillo, N Engl J Med 1993 ; Taylor, J Crit Care 1995 ; Annane, Lancet 2005 ; Angus, N Engl J Med 2013)

REMPLISSAGE VASCULAIRE

Surviving Sepsis Campaign

We recommend that, in the resuscitation from sepsis-induced hypoperfusion, at least 30 mL/kg of IV crystalloid fluid be given within the first 3 h (strong recommendation, low quality of evidence).

We suggest using either balanced crystalloids or saline for fluid resuscitation of patients with sepsis or septic shock (weak recommendation, low quality of evidence).

(Rhodes, ICM 2017)

REMPLISSAGE VASCULAIRE

Surviving Sepsis Campaign

We suggest using albumin in addition to crystalloids for initial resuscitation and subsequent intravascular volume replacement in patients with sepsis and septic shock when patients require substantial amounts of crystalloids (weak recommendation, low quality of evidence).

→ **We recommend against using hydroxyethyl starches (HESs)**

→ **crystalloids over gelatins**

(Rhodes, ICM 2017)

CATÉCHOLAMINES

Surviving Sepsis Campaign

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) (weak recommendation, moderate quality of evidence) or epinephrine (weak recommendation, low quality of evidence)

→ **We recommend against using low-dose dopamine for renal protection (strong recommendation, high quality of evidence).**

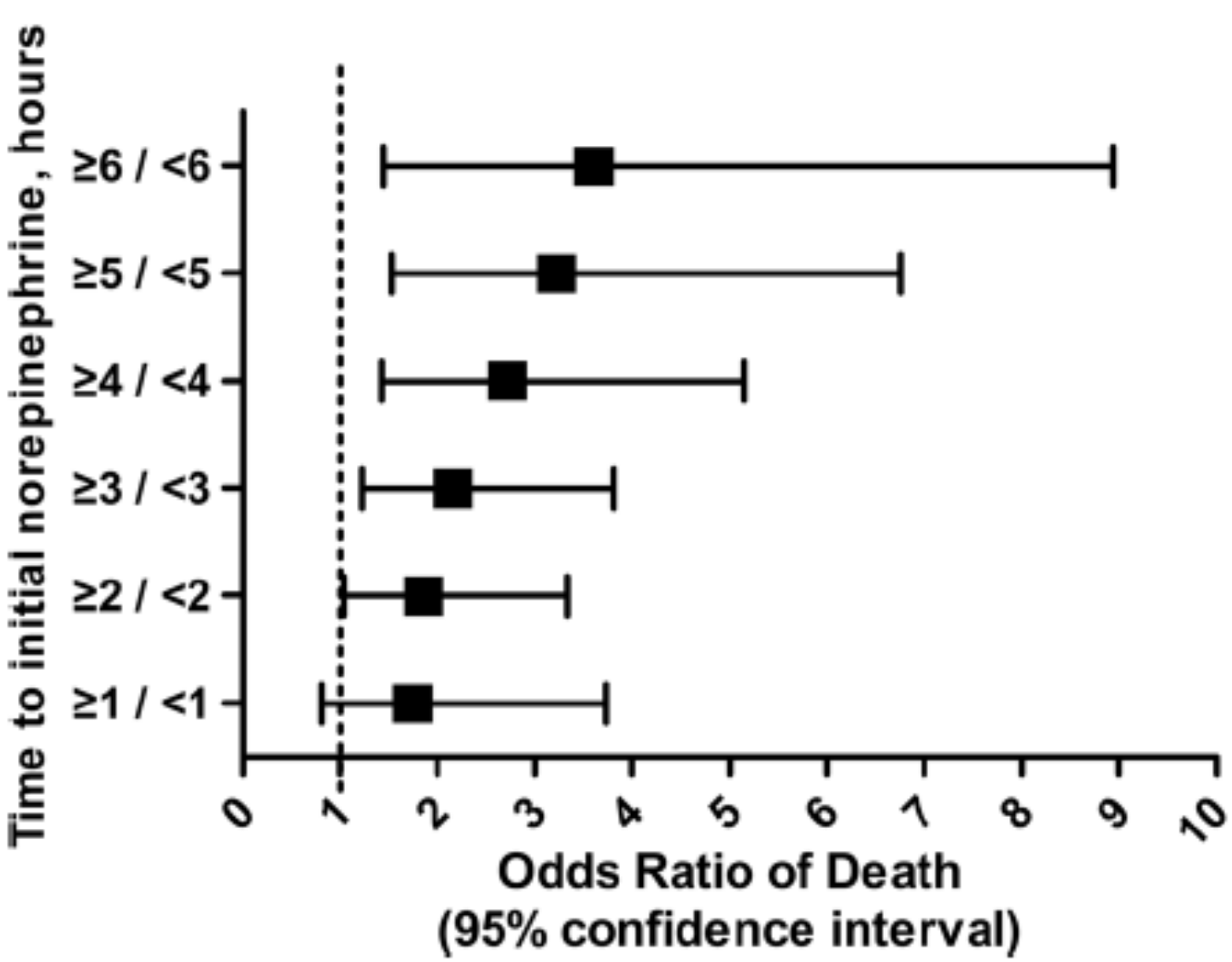
(Rhodes, ICM 2017)

Surviving Sepsis Campaign

We suggest using dobutamine in patients who show evidence of persistent hypoperfusion despite adequate fluid loading and the use of vasopressor agents (weak recommendation, low quality of evidence).

(Rhodes, ICM 2017)
(Rhodes, ICM 2017)

LE TEMPS EST PRÉCIEUX…



(Bai, Crit care 2014)

OBJECTIFS PAM

Surviving Sepsis Campaign

We recommend an initial target mean arterial pressure (MAP) of 65 mm Hg in patients with septic shock requiring vasopressors (strong recommendation, moderate quality of evidence).

(Rhodes, ICM 2017)

OBJECTIFS PAM

894 patients

- **SEPSISPAM :** PAM 65-70 mmHg *vs.* 80-85 mmHg, CS <6h
- **OVATION :** PAM 65-70 mmHg *vs.* 75-80 mmHg, choc <24h

Outcome	Subgroup	Higher MAP arm event/*n* (%)	Lower MAP arm event/*n* (%)	Odds ratio (95% CI)	*p* value
28-day mortality	≤ 6 h	137/390 (35%)	134/379(35%)	1.01 (0.75–1.36)	0.97
				.33–6.74)	< 0.01
90-day				.71–1.27)	0.74
				.34–6.42)	< 0.01

Take-home message:

In this individual patient-data meta-analysis, higher blood-pressure targets–i.e. more aggressive use of vasopressors - were associated with an increased risk of death in patients enrolled >6 h after initiation of vasopressors. Lower blood-pressure targets were not associated with patient-important adverse events in any subgroup, including chronically hypertensive patients.

(Lamontagne, ICM 2018)

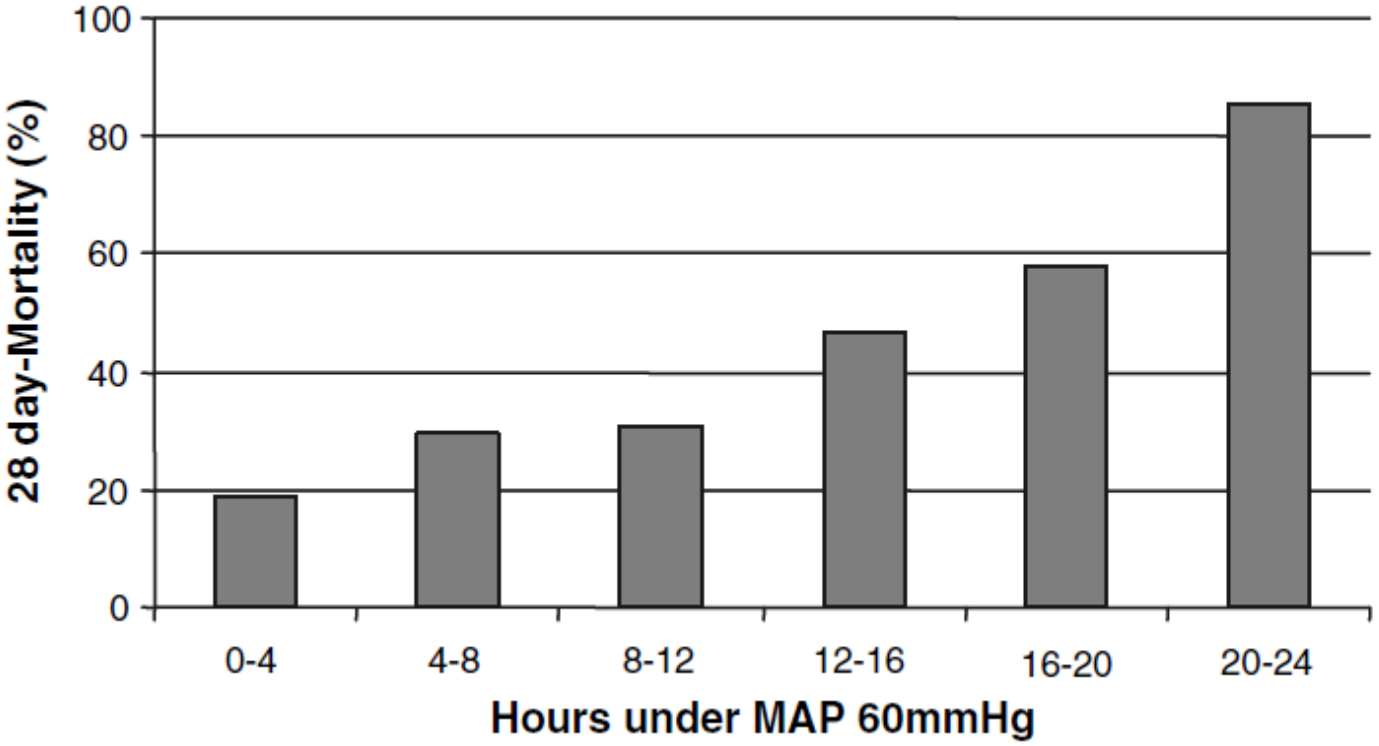
Intensive Care Med (2009) 35:1225–1233
DOI 10.1007/s00134-009-1427-2

ORIGINAL

Martin W. Dünser
Jukka Takala
Hanno Ulmer
Viktoria D. Mayr
Günter Luckner
Stefan Jochberger
Fritz Daudel
Philipp Lepper
Walter R. Hasibeder
Stephan M. Jakob

Arterial blood pressure during early sepsis and outcome

274 patients



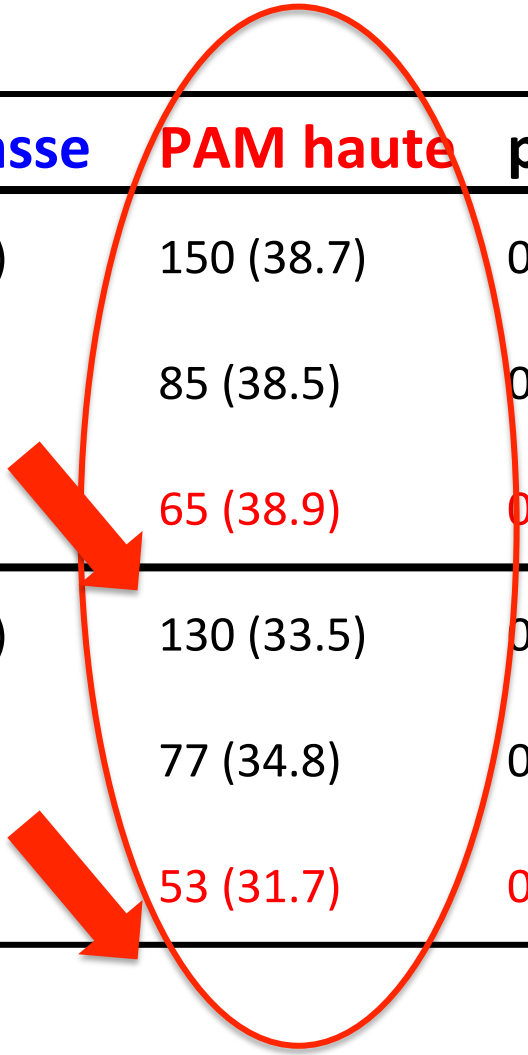
No. of periods ⇑ MAP < 60 mm Hg ⇒ mortality ⇑

MAP ⇑ ⇒ improved kidney function?

OBJECTIFS PAM

SEPSISPAM : 776 CS ; PAM 65-70 mmHg *vs.* 80-85 mmHg, CS <6h

n (%)	PAM basse	PAM haute	p
Doublement créatinine	161 (41.5)	150 (38.7)	0.42
pas d'HTA	71 (33.0)	85 (38.5)	0.32
HTA	90 (52.0)	65 (38.9)	0.02
EER J1 - J7	139 (35.8)	130 (33.5)	0.5
pas d'HTA	66 (30.7)	77 (34.8)	0.36
HTA	73 (42.2)	53 (31.7)	0.046



(Asfar, NEJM 2014)

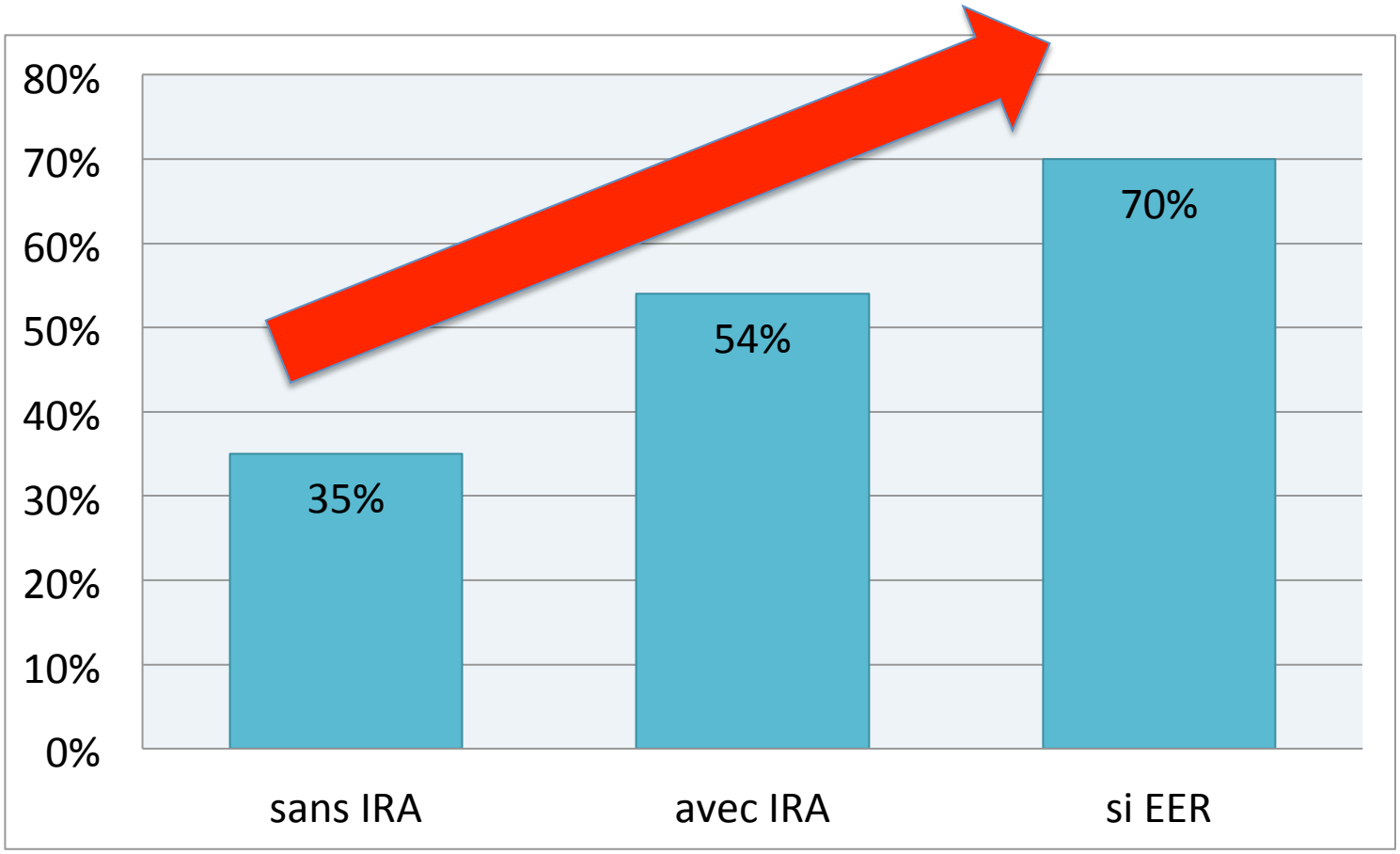
INSUFFISANCE RÉNALE AIGUË DU SEPSIS

ÉPIDÉMIOLOGIE : IRA / SEPSIS

- Sepsis sévère : 20% d'IRA
- Choc septique :
  - 50% d'IRA
  - 20% d'EER
- IRA : 48% sepsis sévère

(Rangel-Frausto, JAMA 1995 ; Annane D, AJRCCM 2003 ; Uchino JAMA 2005)

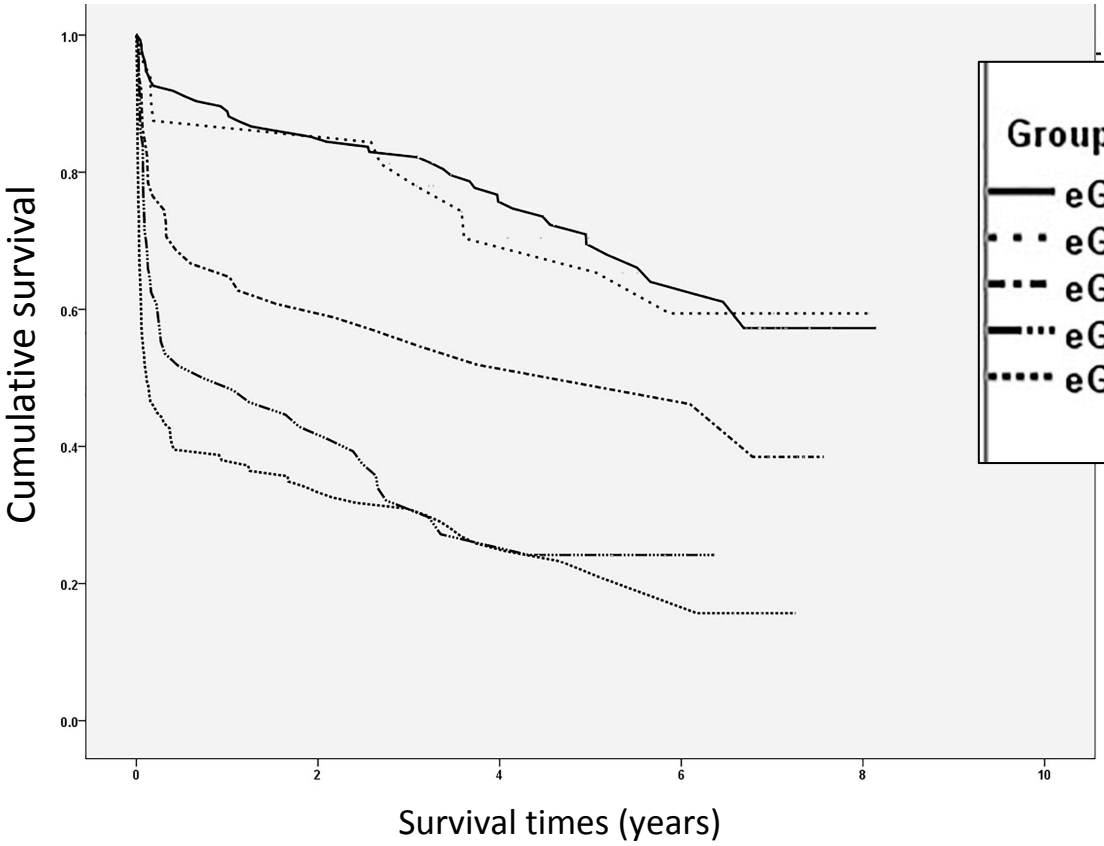
Mortalité sepsis sévère :



(Hoste A, JASN 2003 ; Fagon JY, Int Care Med 1993 ; Bashaw S, CJASN 2007)

IRA : SURMORTALITÉ ET ÉVOLUTION VERS EER CHRONIQUE

Rétrospectif, monocentrique (Chine) : 403 patients de réa avec EER



Évolution vers EER chronique :

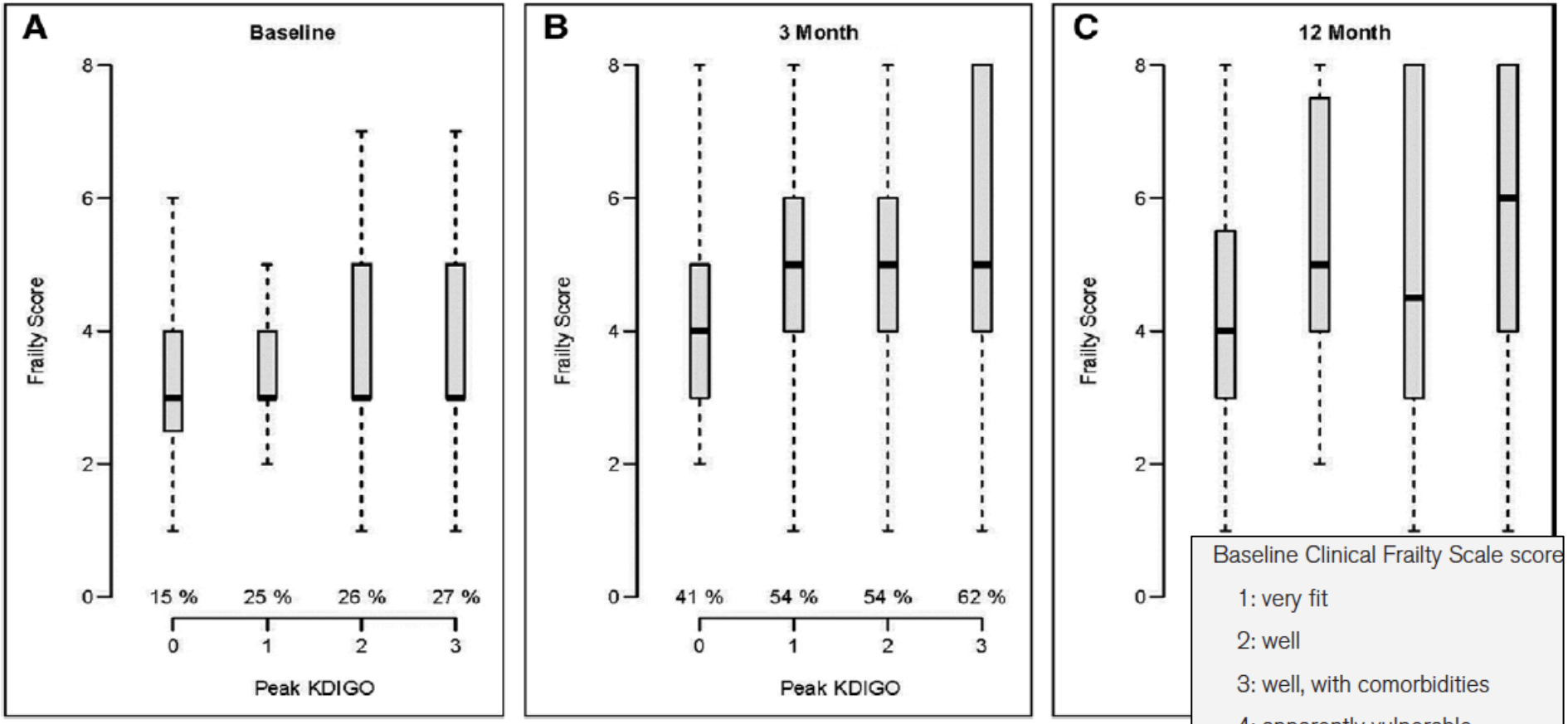
- IRA : 7%
- IRA sur IRC : 24%

Conclusions: This study showed that impaired kidney function at discharge was shown to be an important risk factor affecting the long-term renal survival rates of critically ill patients with AKI. An eGFR <45 mL/min/1.73 m^2 was an independent risk factor for decreased overall survival and renal survival.

(Wu, Ren fail 2017)

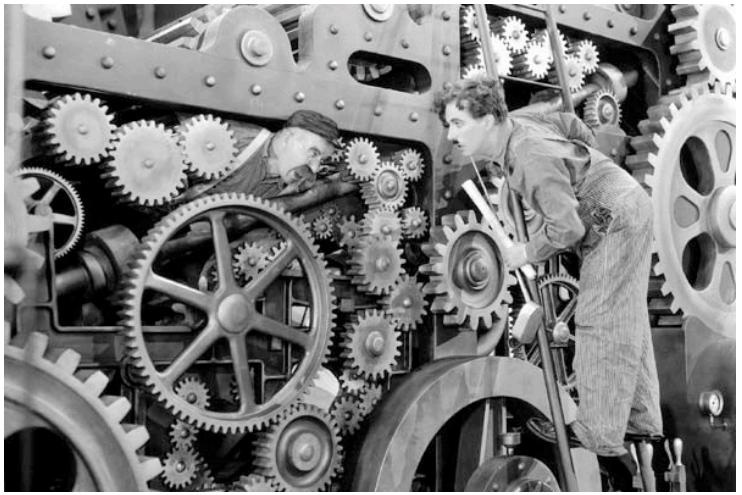
EER ET MORBIDITÉ

317 patients, défaillance respiratoire/hémodynamique

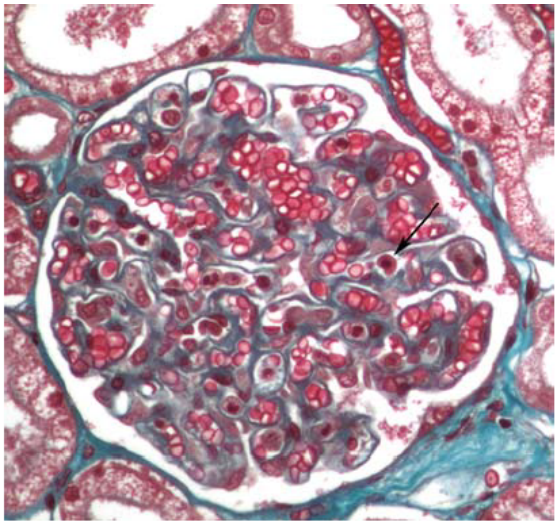


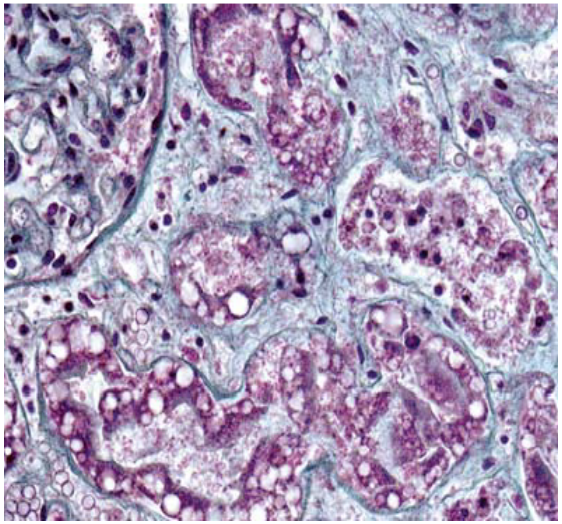
(Abdel-Kader, CCM 2018)

PHYSIOPATHOLOGIE

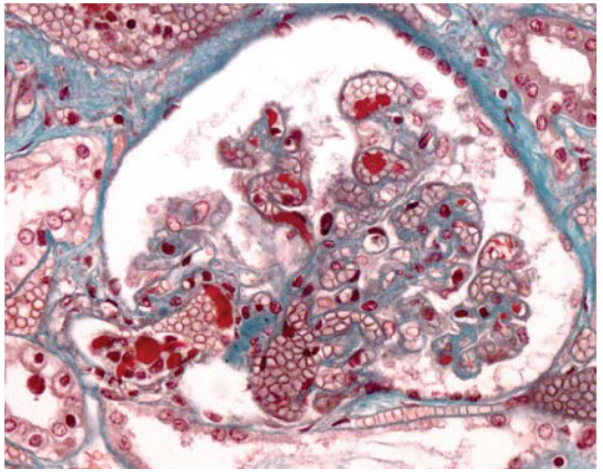


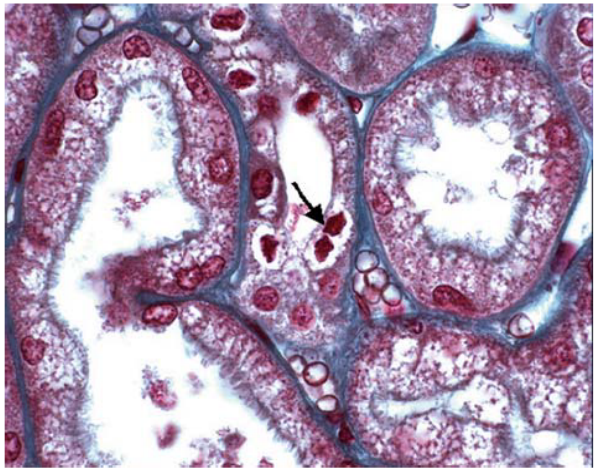
BIOPSIES RÉNALES DE PATIENTS DÉCÉDÉS





- **Lésions tubulaire aiguës** (perte bordure en brosse, aplatissement épithélium, débris cellulaires, nécrose)
- **Infiltration leucocytaire** vasculaire et glomérulaire
- Intense **apoptose**
- Dépôts capillaires de **fibrine et thrombi**

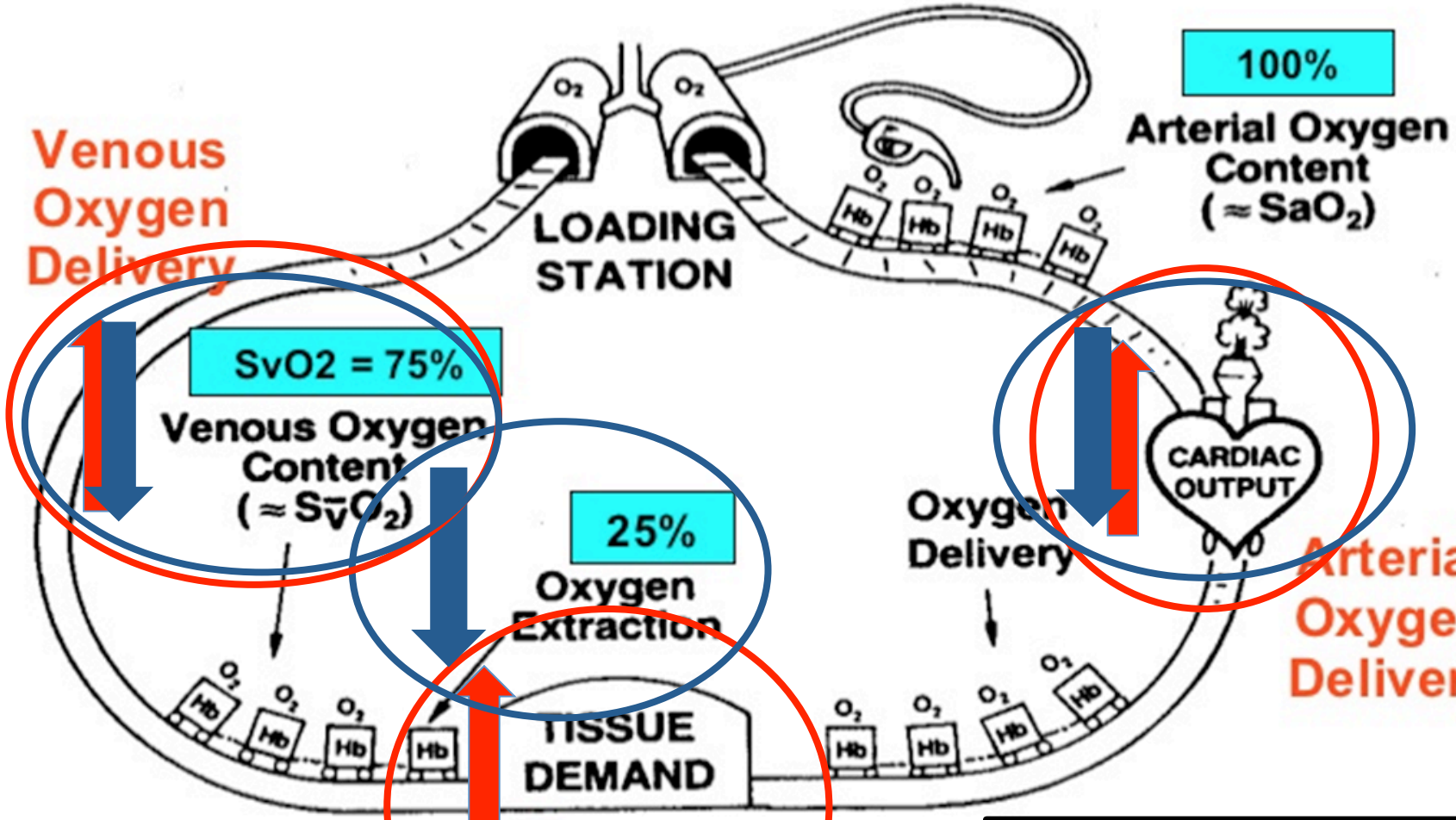




(Lerolle, Int Care Med. 2010)

ASPECTS HÉMODYNAMIQUES : DYSFONCTION CARDIO-CIRCULATOIRE

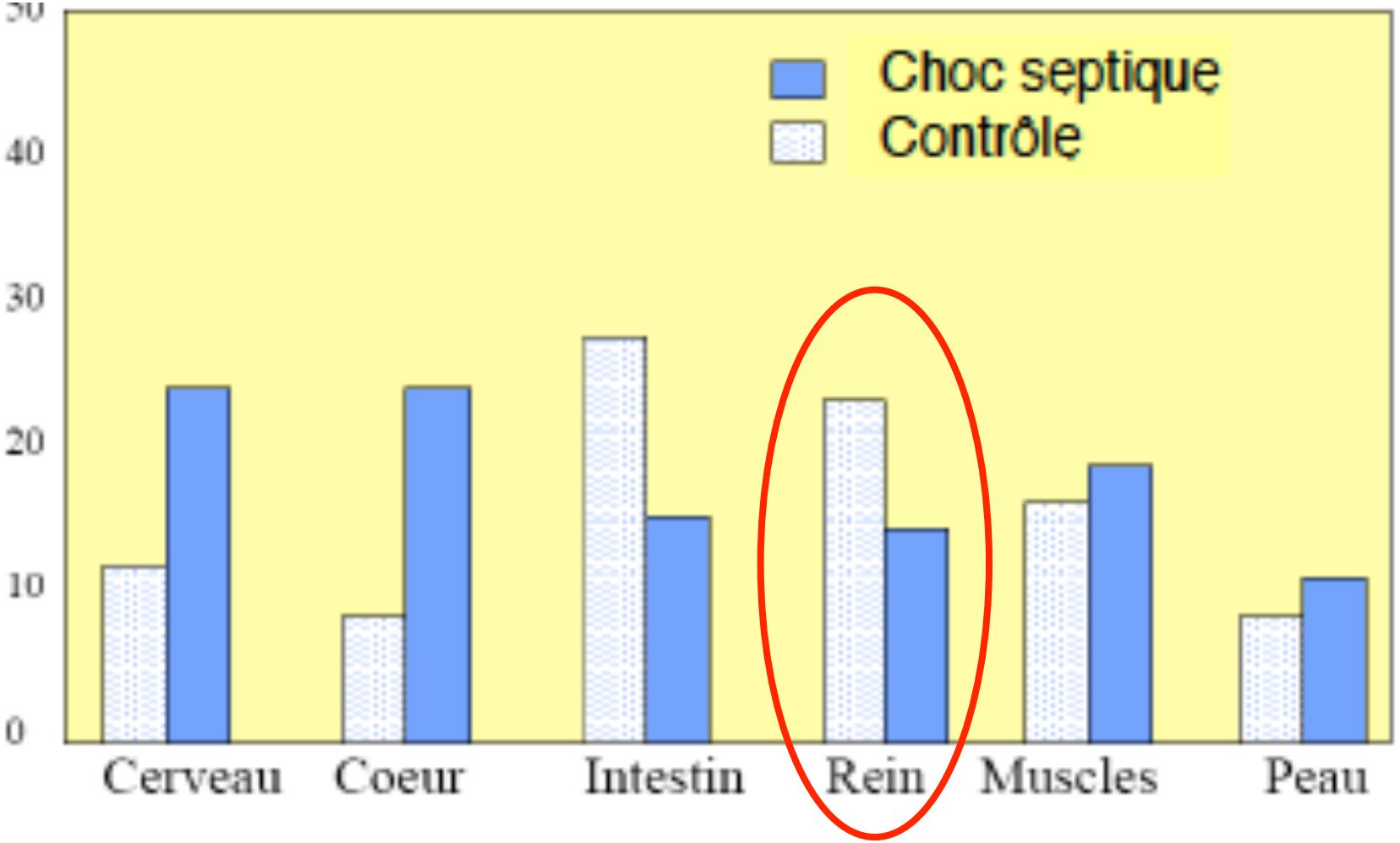
Hypovolémie (vraie et relative)



Dysfonction cardio-circulatoire

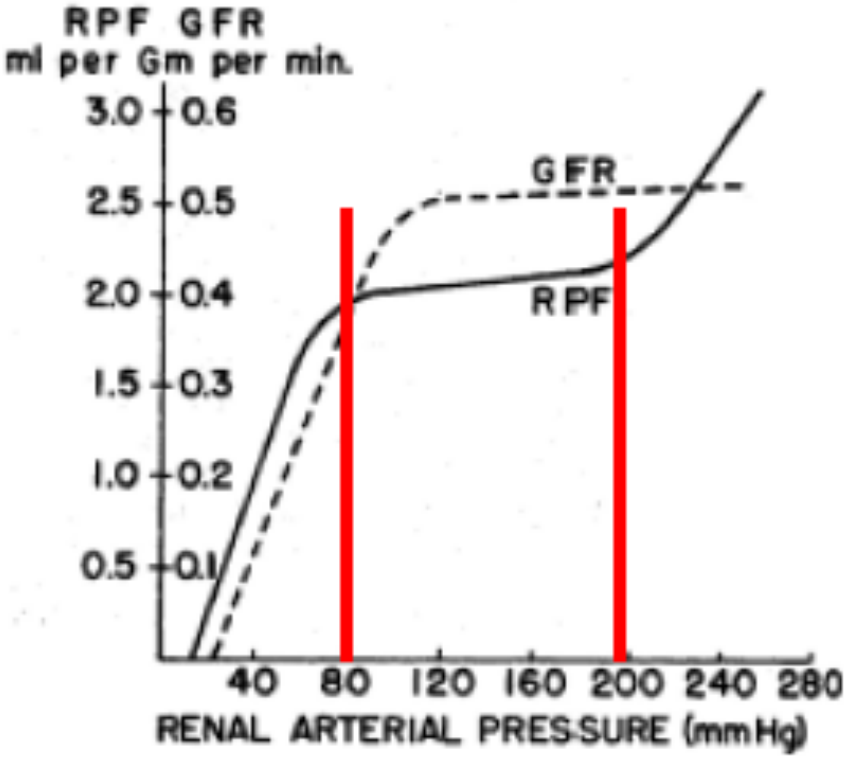
COMPOSANTE HÉMODYNAMIQUE DE LA DÉFAILLANCE RÉNALE

Répartition des débits sanguins régionaux (% du DC)



Perte de l'autorégulation du débit sanguin rénal

$$Jv = Kf\,[(P_{capillary} - P_{Bowman}) - \sigma\,(\Pi_{capillary} - \Pi_{Bowman})] = Kf\,[(DP) - (D\Pi)]$$



- Augmentation résistances vasculaires intra-rénales
- Diminution coefficient d'ultrafiltration Kf
- Obstruction tubules par cellules tubulaires nécrosées

Vasoconstriction intra-rénale

- …pas de données chez l'homme

- Rats-LPS réanimés : maintien PA, DC, DSR et RVR… avec IRA et lésions rénales
- Modèle cochon-LPS : DSR conservé jq H12, alors que IRA et lésions histo rénales dès H6

⇒ **Lésions rénales avant l'apparition des anomalies hémodynamiques**

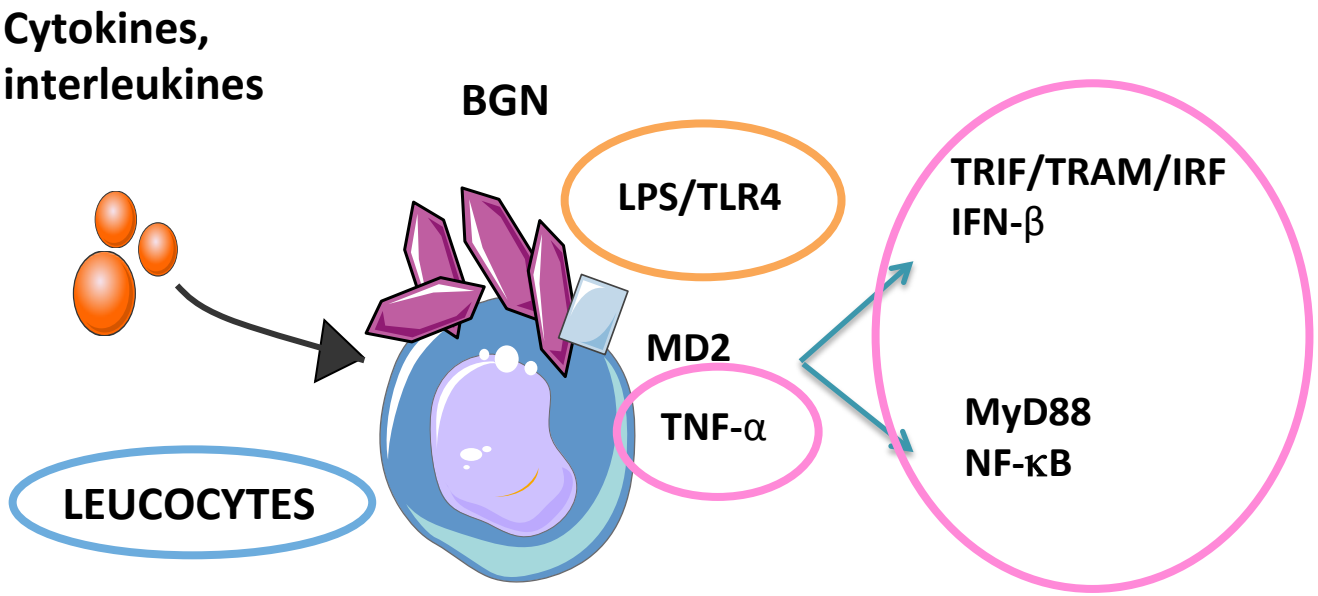
⇒ **implication d'autres mécanismes.**

(Langenberg, Crit Care Med 2005 ; Bellomo AJRCCM 1999)

RÔLE DE L'IMMUNITÉ ET DE L'INFLAMMATION

INFLAMMATION → SIRS

IMMUNITÉ INNÉE



Rôle du TNF-α sécrété par macrophages :

- KO TNF-R + LPS => Ø lésions rénales

TLR2, TLR9, MyD88, NLR, Caspase-1, IL-18…

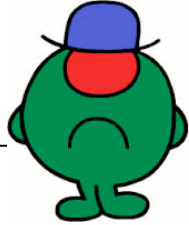
(Haberstroh, Kindey Int 2002 ; Cunnigham, J immunol 2003 ; Li, Semin Nephrol 2010)

PRÉVENTION / TRAITEMENT

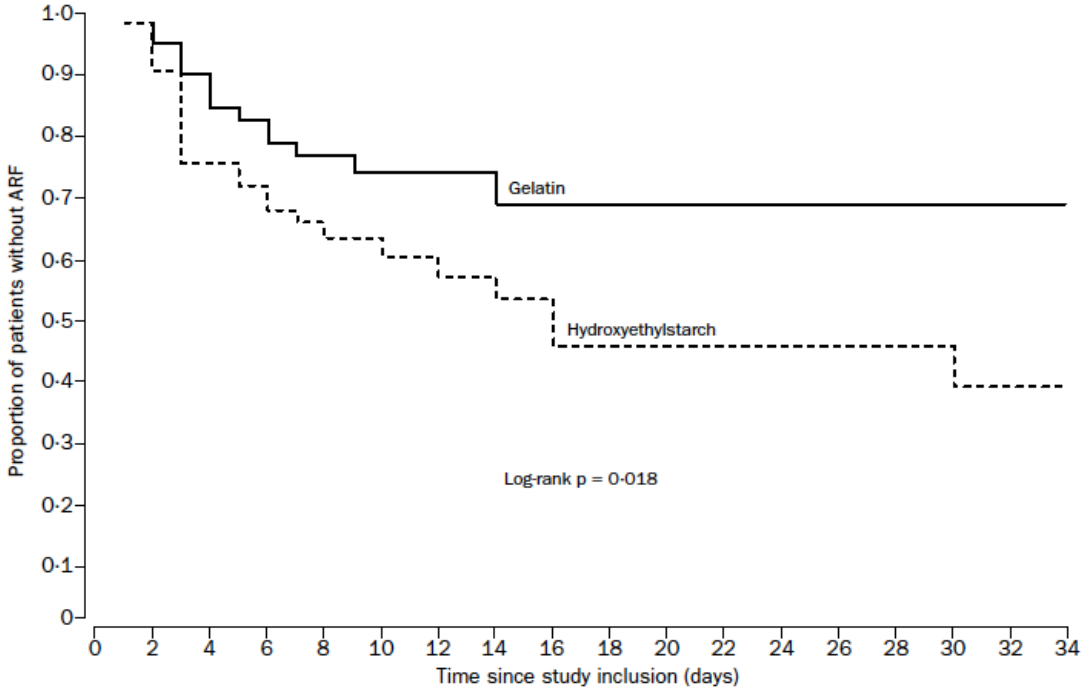
RESTAURER LA PERFUSION RÉNALE

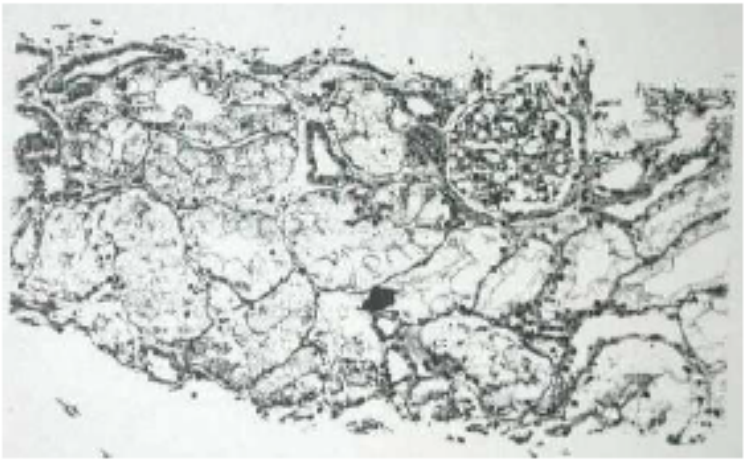
- Restaurer l'hémodynamique :
  - Remplissage vasculaire
  - Catécholamines
  - Objectifs PAM 65 mmHg

LIMITER LA IATROGÉNIE

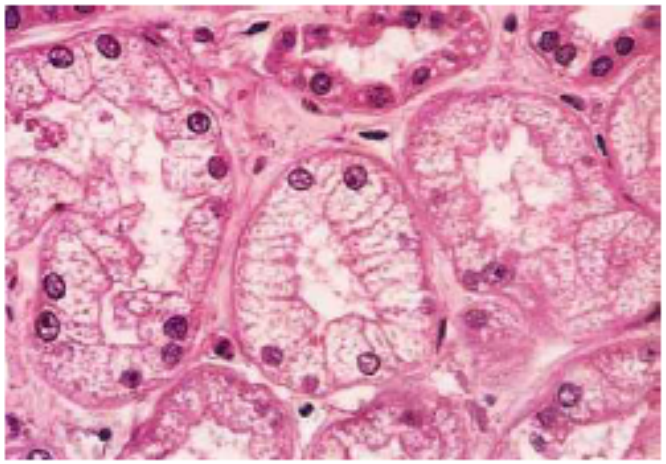


Recommandations ANSM 2013 :
HEA contre-indiqués dans le sepsis





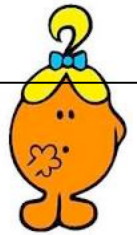
Dextran 40
Drumi et al. NEJM 1988



Starch (200/0.6)
Cittanova et al. Lancet, 1996

(Marshall, J Infect Dis. 2004)

PURIFICATION DU SANG



Surviving Sepsis Campaign

We make no recommendation regarding the use of blood purification techniques.

In consideration of all these limitations, our confidence in the evidence is very low either in favor of or against blood purification techniques; therefore, we do not provide a recommendation. Further research is needed to clarify the clinical benefit of blood purification techniques.

(Rhodes, ICM 2017)

EER ET SEPSIS

LES PROBLÉMATIQUES DANS LE SEPSIS

1. Quand débuter l'EER ?
2. Quelle technique ?
3. Quelle dose ?

QUAND DÉBUTER L'EER ?

RATIONNEL

- EER précoce : pour maintenir l'homéostasie ?

- EER tardive : pour éviter les complications additionnelles de l'EER ?

QUAND DÉBUTER, EN RÉANIMATION ?

- Nombreuses études
  - Méthodologie douteuse
  - et/ou faibles effectifs

- Méta-analyse 2012 : 15 études (10 rétrospectives, 3 RCT) incluant 2955 patients de réanimation avec IRA

(Wang, Renal Failure 2012)

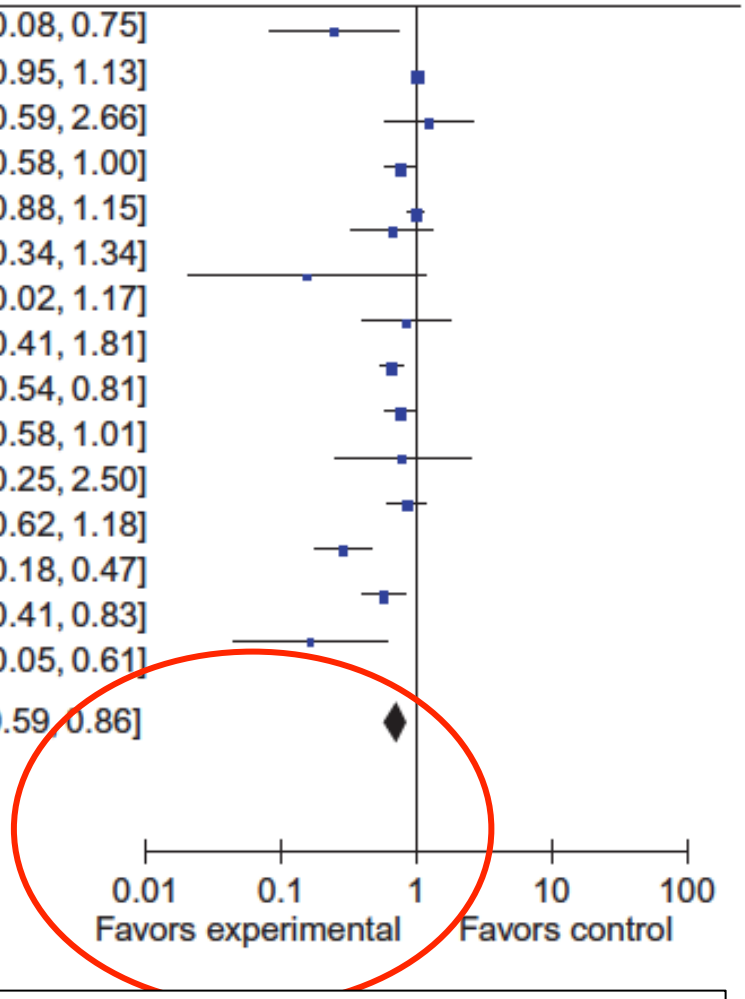
DÉFINITION : TÔT VERSUS TARD ?

First author	Year	Modality	Population	Definitions of early and late	
				Early	Late
Bouman[2]	2002	CVVH	Cardiac surgery/medical	RRT within 12 h if urine output <30 mL/h	Urea >40 mmol/L or K >6.5 mmol/L
Durmaz[10]	2003	IHD	Cardiac surgery (CABG)	Postoperative sCr increased by 10%	Postoperative sCr increased by 50% or urine output was <400 mL/24 h
Sugahara[3]	2004	CVVH	Cardiac surgery	Urine output <30 mL/h	Urine Output <20 cc/h
Liu[11]	2006	CRRT/IHD	Medical, surgery	Urea <27.1 mmol/L	Urea >27.1 mmol/L
Bagshaw[12]	2009	CRRT/IHS	Medical, surgical	Urea <24.2 mmol/L	Urea >24.2 mmol/L
Gettings[13]	1999	CRRT	Trauma	Urea <21.4 mmol/L	Urea >21.4 mmol/L
Elahi[14]	2004	CVVH	Cardiac surgery	Urine output <100 cc in 8 h	K >6 mmol/L, Cr >250 mmol/L
Dermirkilic[15]	2004	CVVHDF	Cardiac surgery	Cr >400 µmol/L, K >5.5 mmol/L	Oliguria
Andrade[16]	2007	IHD/SLED	Medical (ARDS/sepsis)	On admission	At 24 h
Manche[17]	2008	IHD	Cardiac surgery	Hyperkalemia	Urine output <0.5mL/kg/h
Iyem[18]	2009	CVVH	Cardiac surgery	RRT on admission	After 48 h when anuric
Shiao[19]	2009	CVVH	Surgery/trauma	RIFLE criteria (risk)	RIFLE injury (failure)
Carl[20]	2010	CRRT/IHD	Medical (sepsis)	Urea <35.7 mmol/L	Urea >35.7 mmol/L
Chou[21]	2011	CRRT/SLED	Sepsis	RIFLE criteria (risk)	RIFLE injury (failure)
García-Fernández[22]	2011	CRRT/IHD	Cardiac surgery	≤3 days after cardiac surgery	>3 days after cardiac surgery

MORTALITÉ

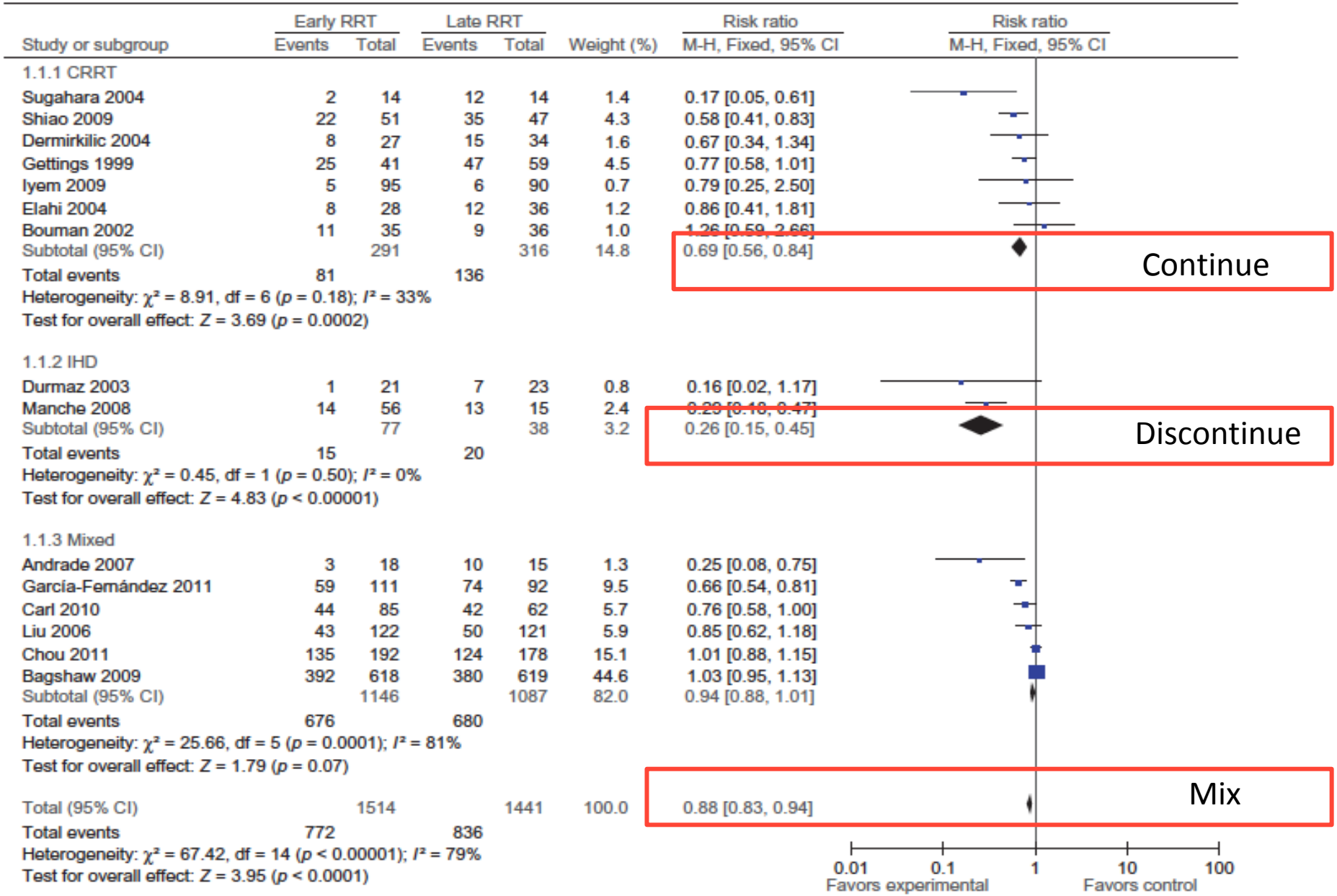
Study or subgroup	Early RRT Events	Early RRT Total	Late RRT Events	Late RRT Total	Weight (%)	Risk ratio M-H, Random, 95% CI
Andrade 2007	3	18	10	15	2.4	0.25 [0.08, 0.75]
Bagshaw 2009	392	618	380	619	12.3	1.03 [0.95, 1.13]
Bouman 2002	11	35	9	36	4.2	1.26 [0.59, 2.66]
Carl 2010	44	85	42	62	10.0	0.76 [0.58, 1.00]
Chou 2011	135	192	124	178	11.8	1.01 [0.88, 1.15]
Dermirkilic 2004	8	27	15	34	4.7	0.67 [0.34, 1.34]
Durmaz 2003	1	21	7	23	0.8	0.16 [0.02, 1.17]
Elahi 2004	8	28	12	36	4.2	0.86 [0.41, 1.81]
García-Fernández 2011	59	111	74	92	11.0	0.66 [0.54, 0.81]
Gettings 1999	25	41	47	59	9.9	0.77 [0.58, 1.01]
Iyem 2009	5	95	6	90	2.2	0.79 [0.25, 2.50]
Liu 2006	43	122	50	121	9.2	0.85 [0.62, 1.18]
Manche 2008	14	56	13	15	6.7	0.29 [0.18, 0.47]
Shiao 2009	22	51	35	47	8.7	0.58 [0.41, 0.83]
Sugahara 2004	2	14	12	14	1.8	0.17 [0.05, 0.61]
Total (95% CI)		1514		1441	100.0%	0.71 [0.59, 0.86]
Total events	772		836			

Heterogeneity: $\tau^2 = 0.07$; $\chi^2 = 67.42$, df = 14 ($p < 0.00001$); $I^2 = 79\%$
Test for overall effect: $Z = 3.55$ ($p = 0\ .0004$)



Tôt 51% *vs.* tard 58%, IC95 [0,59 ; 0,86]

TÔT, QUELLE QUE SOIT LA TECHNIQUE ?

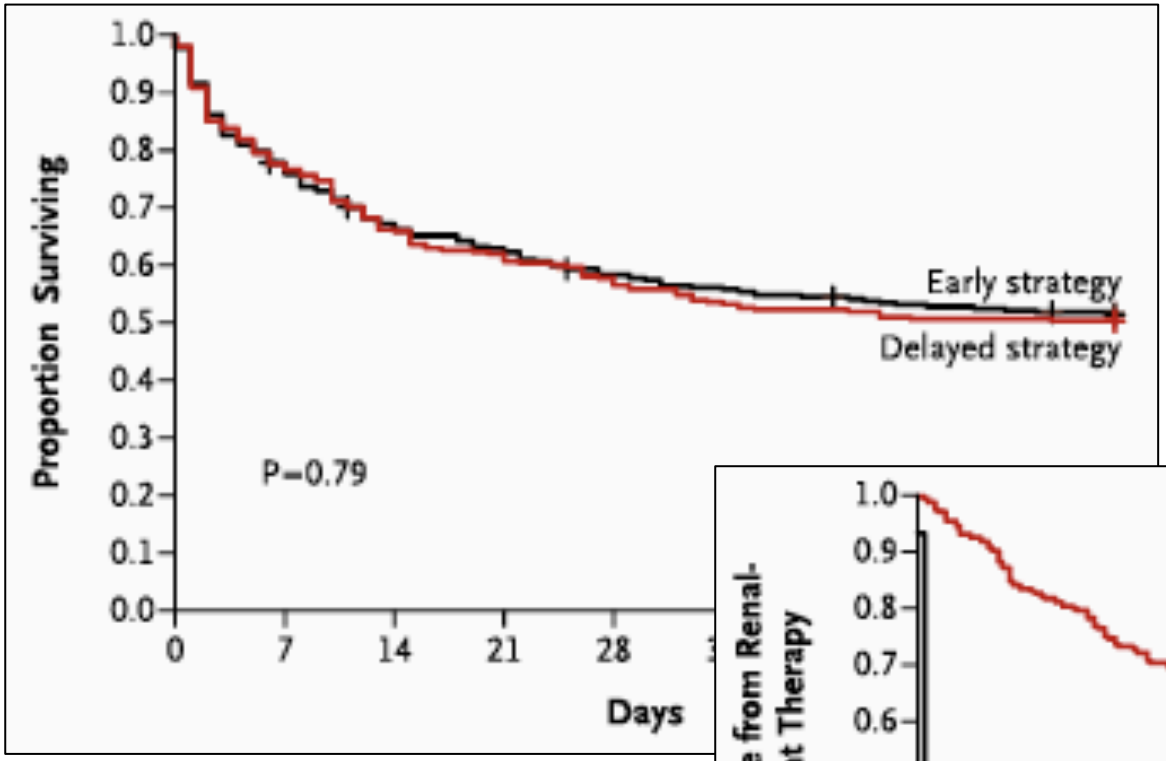


AKIKI

- KDIGO 3
- Bras précoce : EER < 6h
- Bras tardif : EER si anomalies biologiques et/ou oligo-anurie > 72h

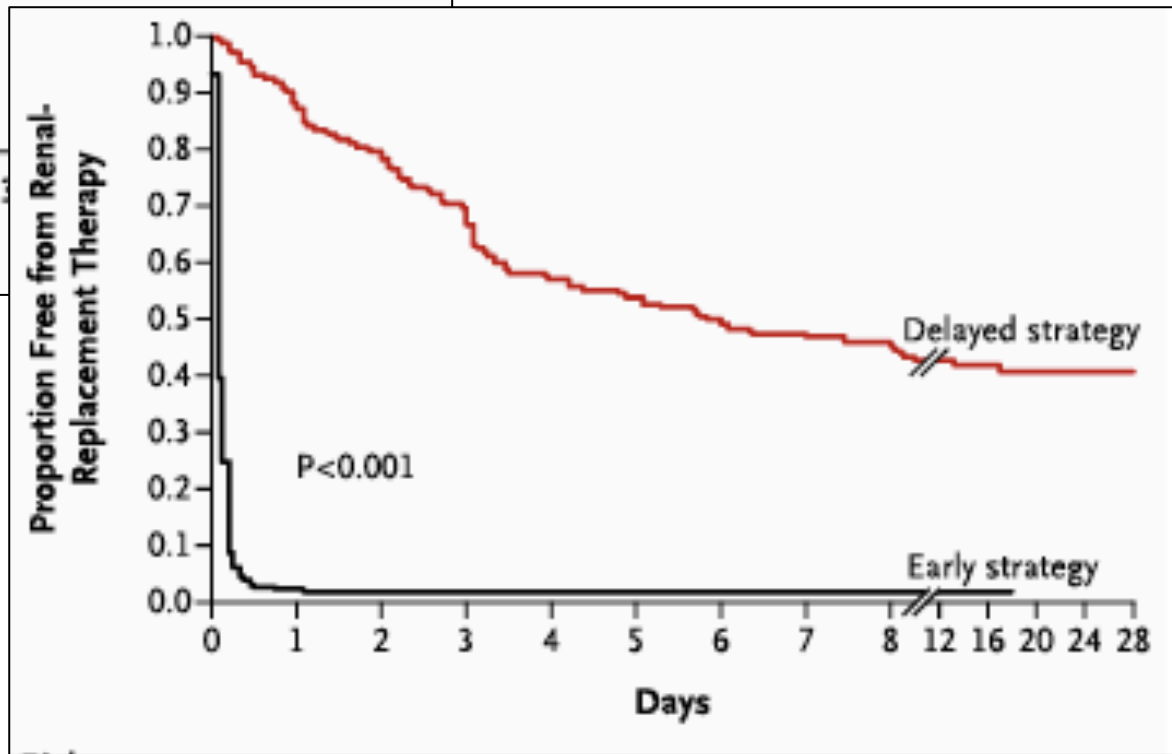
(Gaudry, NEJM 2016)

QUAND DÉBUTER, EN RÉANIMATION ?



Survie J60 : NS

RRT-free days : p<0,001



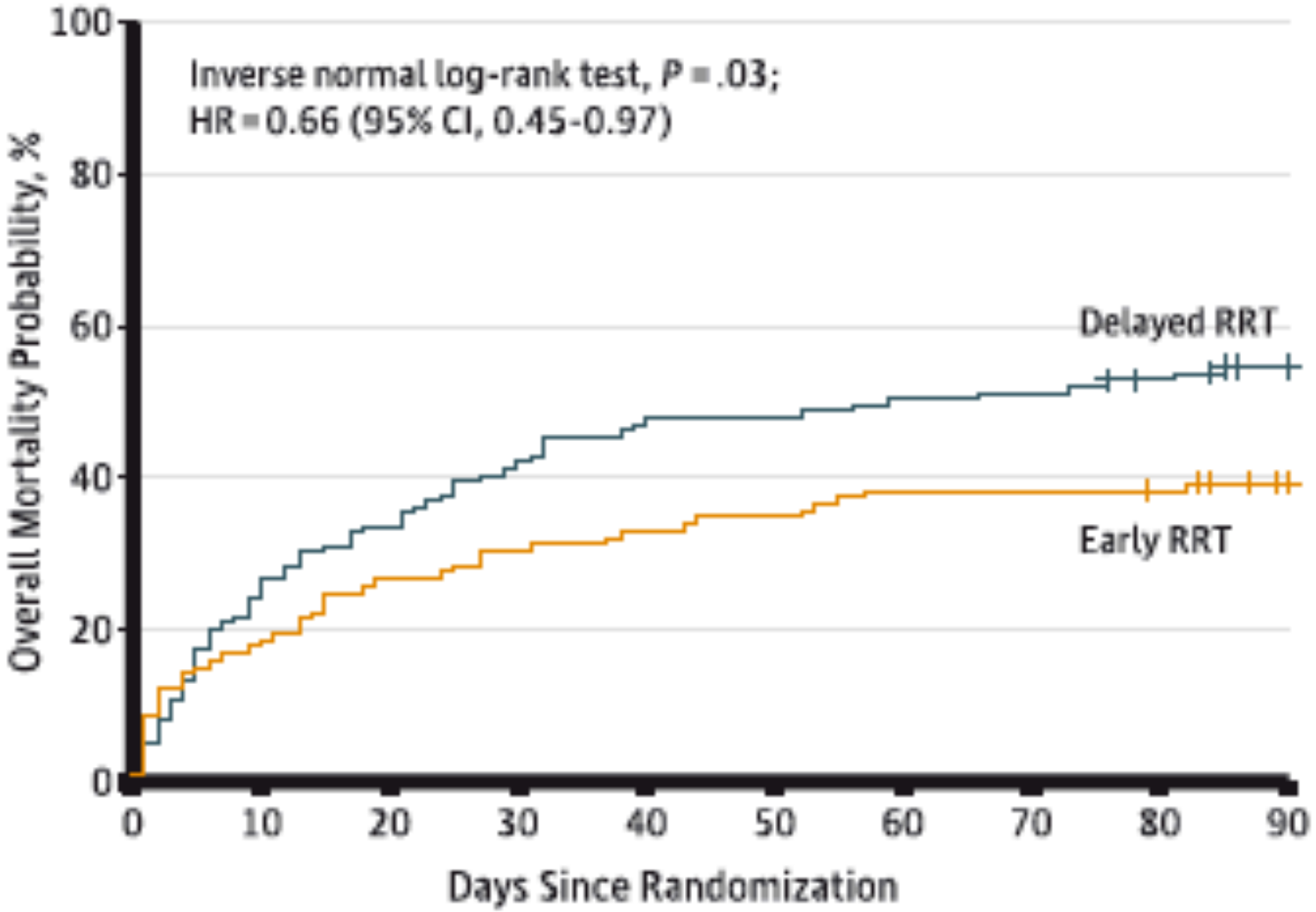
(Gaudry, NEJM 2016)

ELAIN

- KDIGO 2
- Bras précoce : EER < 8h
- Bras tardif : EER si
  - >12h de KDIGO 3
  - Indication absolue : hyperK, oligo-anurie > 12h, OAP

(Zarbock, JAMA 2016)

QUAND DÉBUTER, EN RÉANIMATION ?



(Zarbock, JAMA 2016)

QUAND DÉBUTER, DANS LE CHOC SEPTIQUE ?

- Hémofiltration prophylactique :
- RCT dans 12 réanimations françaises, incluant 80 patients en choc septique
  - HF précoce (<24h) pendant 96h, 25 ml/kg/h
  - vs gp conventionnel

⇒ SOFA gp HF > gp conventionnel

⇒ Dosages de cytokines plasmatiques : NS

(Payen, Crit Care Med 2009)

QUAND DÉBUTER, DANS LE CHOC SEPTIQUE ?

- IDEAL-ICU :
  - RCT
  - Patients en phase précoce de CS
  - EER <H12 ou H48-60 suivant le diagnostic d'IRA au stade FAILURE (RIFLE)
  - Critère de jugement : mortalité à J90.

  - … article soumis !

(Clinicaltrials.gov, NCT01682590)

CRITÈRES D'EER

Surviving Sepsis Campaign

→ **We suggest against the use of RRT in patients with sepsis and acute kidney injury for increase in creatinine or oliguria without other definitive indications for dialysis (weak recommendation, low quality of evidence).**

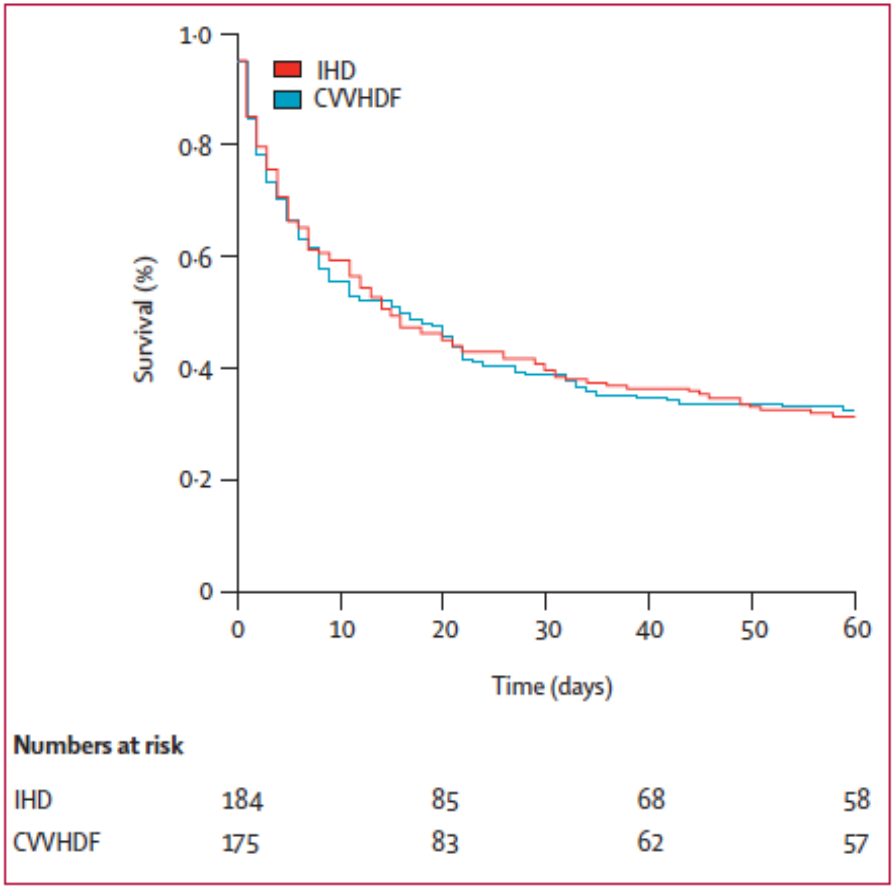
(Rhodes, ICM 2017)

QUELLE TECHNIQUE ?

Etude Hémodiafe :

- Patients médicaux-chir. avec IRA et SDMV (2 X 180 patients)
- CVVHDF *vs.* HDI
- Changement de technique possible

- Mortalié J60 : NS

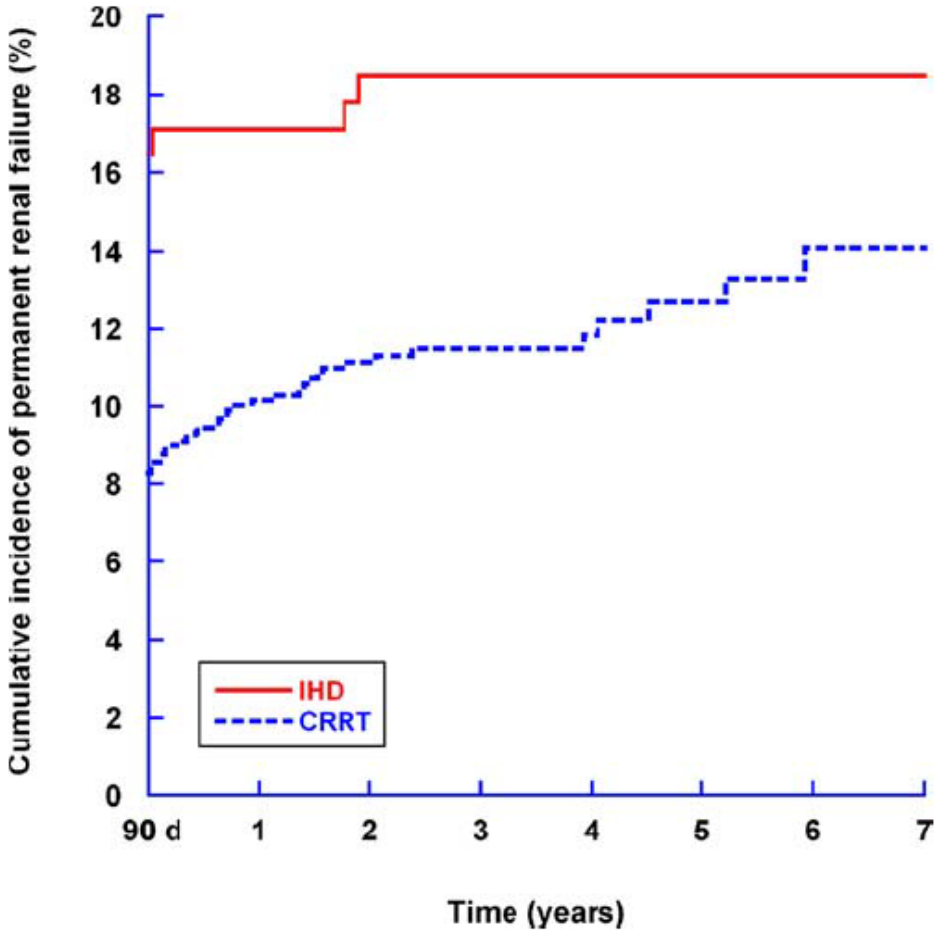


(Vinsionneau, Lancet 2007)

QUELLE TECHNIQUE ?

- Cohorte rétrospective, 2002 patients de réanimation, dont 16% sepsis

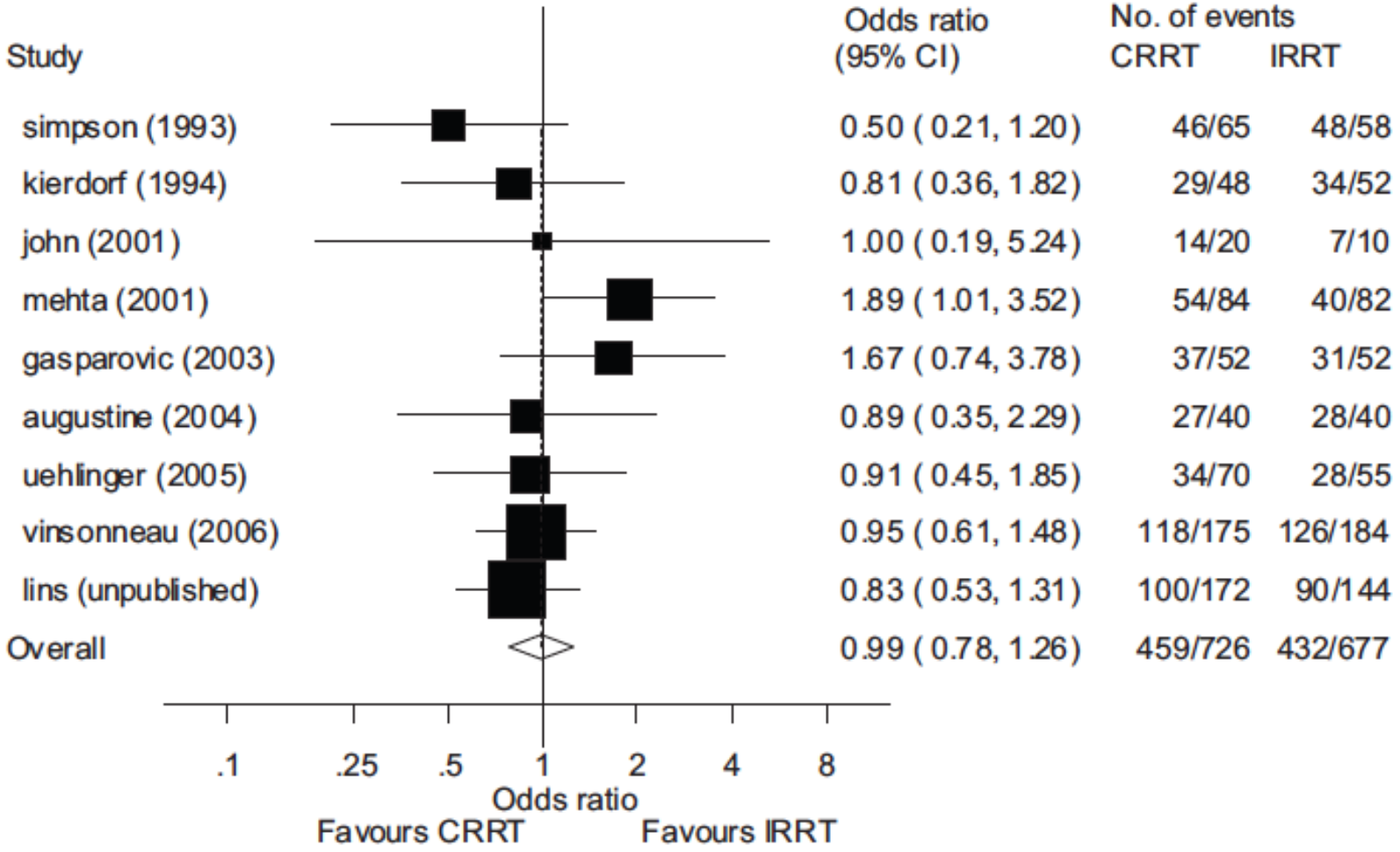
- Mortalité : NS
- Moins d'IRC lq EER continue



(Bell, Int Care Med 2007)

QUELLE TECHNIQUE ?

Méta-analyse : 9 RCT, 1403 patients, mortalité ?



(Bagshaw, Crit Care Med 2008)

Surviving Sepsis Campaign

We suggest that either continuous RRT (CRRT) or intermittent RRT be used in patients with sepsis and acute kidney injury (weak recommendation, moderate quality of evidence).

→ **We suggest using CRRT to facilitate management of fluid balance in hemodynamically unstable septic patients (weak recommendation, very low quality of evidence).**

(Rhodes, ICM 2017)

QUELLE DOSE ?

QUELLE DOSE, EN RÉANIMATION ?

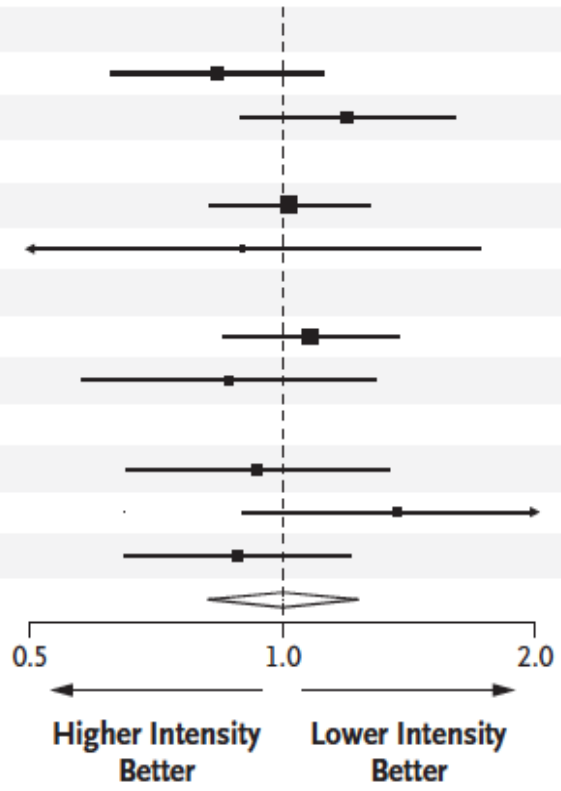
- Etude RENAL : 1508 patients de réanimation avec ≥ 2 défaillances, dont IRA ; incluant notamment 723 chocs septiques
  - CVVHDF 40 ml/kg/h (post filtre)
  - *vs.* CVVHDF 25 ml/kg/h (post filtre)

=> Mortalité à J90 : NS

(NEJM 2009; 361:1627)

QUELLE DOSE, DANS LE CHOC SEPTIQUE ?

Prespecified Subgroup	Higher Intensity (N=721)	Lower Intensity (N=743)	Odds Ratio (95% CI)
	no. of deaths/no. of patients (%)		
Patients with criteria for sepsis			
Yes	168/359 (46.8)	186/363 (51.2)	0.84 (0.62–1.12)
No	154/362 (42.5)	145/379 (38.3)	1.19 (0.89–1.60)
Patients with at least one nonrenal organ failure			
Yes	299/628 (47.6)	306/649 (47.2)	1.02 (0.82–1.27)
No	23/93 (24.7)	25/93 (26.9)	0.89 (0.46–1.72)
Patients with SOFA cardiovascular score of 3 or 4			
Yes	247/510 (48.4)	254/546 (46.5)	1.08 (0.85–1.37)
No	74/210 (35.2)	75/194 (38.7)	0.86(0.58–1.29)
Patients with eGFR <60 ml/min			
Yes	114/250 (45.6)	105/222 (47.3)	0.93 (0.65–1.34)
No	81/157 (51.6)	81/185 (43.8)	1.37 (0.89–2.10)
Missing	127/314 (40.5)	146/336 (43.5)	0.88 (0.65–1.21)
Death from any cause by day 90	322/721 (44.7)	332/743 (44.7)	1.00 (0.81–1.23)



(NEJM 2009; 361:1627)

QUELLE DOSE, DANS LE CHOC SEPTIQUE ?

IVOIRE : RCT

- 140 patients en choc septique et IRA < 24h
- 70 mL/kg/h vs 35 mL/kg/h pendant 96

⇒ Mortalité à J28 : NS

⇒ Arrêt prématuré après 140 patients : plus de fonds…

(Joannes-Boyau, Int Care Med 2013)

QUELLE DOSE, DANS LE CHOC SEPTIQUE ?

- Méta-analyse 2013 de 3 études
  - 64 patients en choc septique
  - 25-35 ml/kg/h vs >35 ml/kg/h

⇒ Mortalité J28 : NS

- Revue et méta-analyse 2014 de 4 RCT :
  - 470 patients en choc septique
  - >50 ml/kg/h vs <50 ml/kg/h

⇒ Mortalité J28 : NS

(Borthwick, Cochrane 2013 ; Clark, Crit Care 2014)

KHA-CARI : Guidelines for AKI

- Effluent : 20-25 ml/kg/h lq EER continue
- Kt/V = 3,9 / semaine lq HDI
- Cible urée <25 mmol/L lq HDI ou SLED

(Langham, Nephrology 2014)

Recommandations SRLF 2014

- **3.3.2 En EER continue, il faut probablement que la dose de dialyse minimale délivrée soit de 20 - 25 ml/kg/h d'effluent, obtenus par filtration et/ou diffusion**. Accord fort

CONCLUSION

- Diagnostic précoce et réanimation
- Limiter la iatrogénie…
- Quand débuter l'épuration ?
- Comment ? HDI = CVVHD/F
- Répercussions hémodynamiques ? Optimiser la prescription !