Hémoperfusion dans le sepsis

VASSEUR ANNE-SOPHIE
DESC RÉANIMATION 3ÈME ANNÉE
TUTEUR : PR NSEIR

Introduction

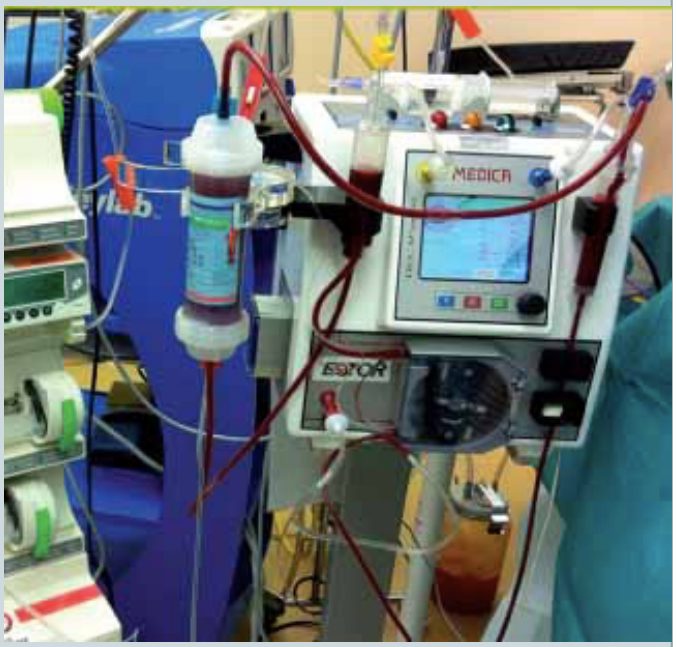
MISE AU POINT

Hémoperfusion en toxicologie

Hemoperfusion in poisoning

F. Saulnier*, T. Onimus, R. Lubret, S. Ledoux, A. Durocher

Circulation extra-corporelle
Colonne permettant de fixer l'endotoxine circulante



Rationnel

Mortalité élevée

56% à 28 jours en 1995

JAMA. 1995, Brun-Buisson, Incidence, risk factors, and outcome of severe sepsis and septic shock in adults.

Surviving Sepsis Campaign

35% en 2014 : 274/776 patients

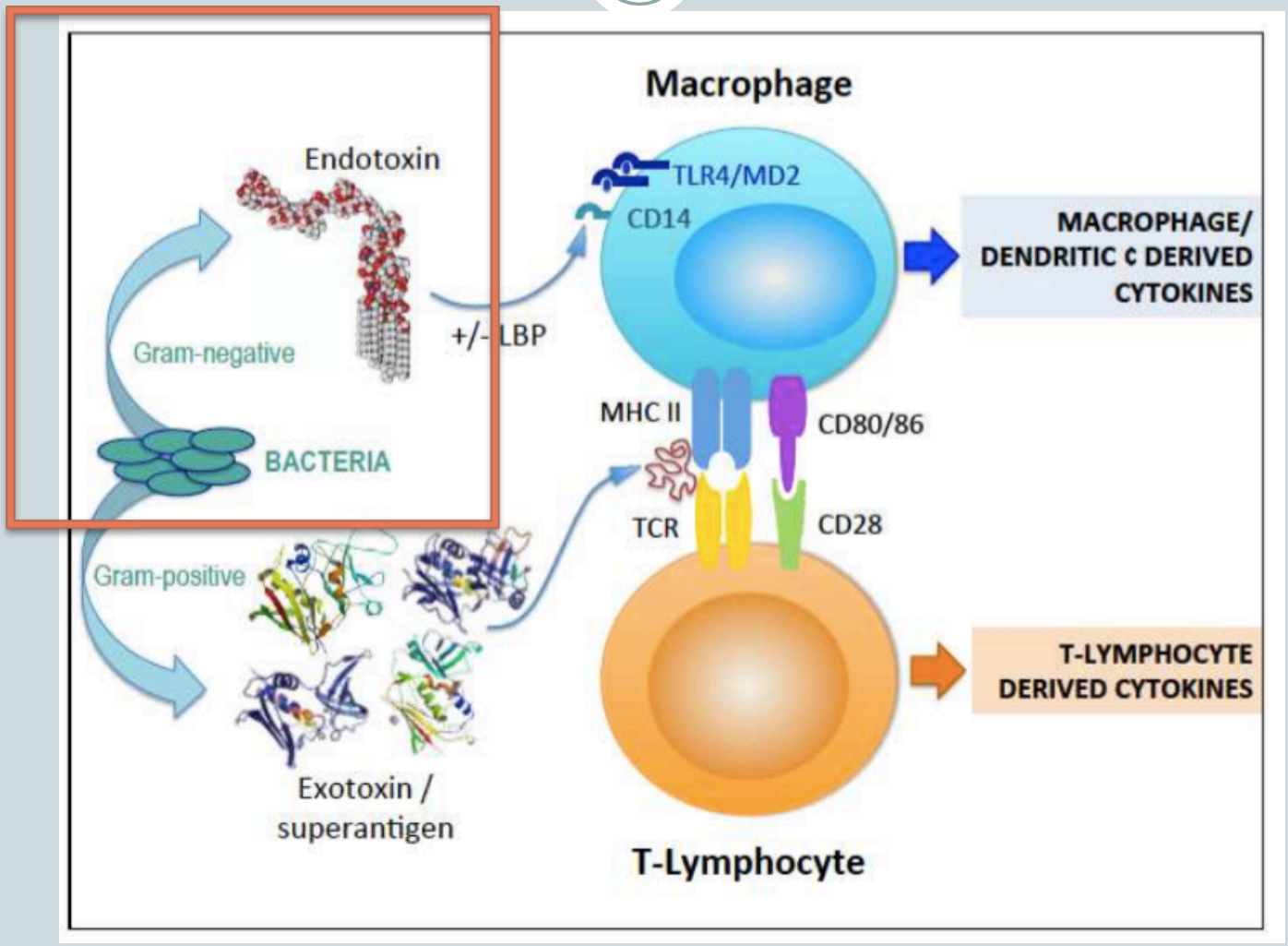
NEJM, 2014, Asfar, High versus low blood pressure in patients with sepstic choc

K. BLOOD PURIFICATION

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

International Surviving Sepsis Campaign guidelines 2016: the perspective from low-income and middle-income countries, Shrestha GS, Lancet Infect Dis. 2017

Endotoxines



Toxicon, Cavaillon, 2017, Exotoxins and endotoxins: Inducers of inflammatory cytokines

Endotoxemia in Human Septic Shock*

Robert L. Danner, M.D.; Ronald J. Elin, M.D., Ph.D.; Jeanette M. Hosseini, B.S.; Robert A. Wesley, Ph.D.; Joseph M. Reilly, M.D.; and Joseph E. Parillo, M.D.

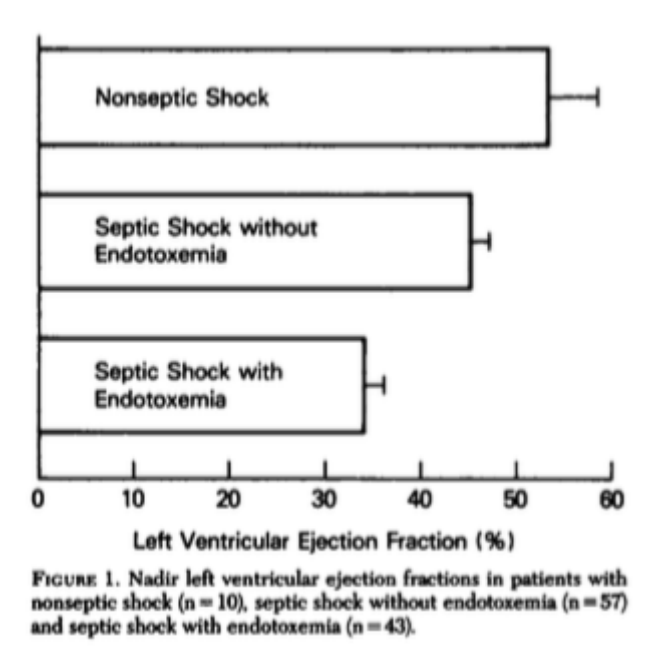


FIGURE 1. Nadir left ventricular ejection fractions in patients with nonseptic shock (n = 10), septic shock without endotoxemia (n = 57) and septic shock with endotoxemia (n = 43).

Médiateur pro-inflammatoire : Associée à la survenue de dysfonction d'organe et au risque de décès en réanimation

Table 2—*Characteristics of 100 Patients with Septic Shock Evaluated for Endotoxemia*

Characteristics	Endotoxemia Present	Endotoxemia Absent	p Value*
No. of patients (%)	43 (43)	57 (57)	. . .
Age (yr)†	49 ± 2.3	44 ± 2.3	NS
Underlying disease (%)			
Hematologic malignancy	24 (56)	26 (46)	NS
Solid tumor	13 (30)	16 (28)	NS
AIDS	1 (2.3)	8 (14)	NS (0.08)
Liver disease	2 (5)	0 (0)	NS
Aplastic anemia	2 (5)	0 (0)	NS
Other	1 (2.3)	7 (12)	. . .
Laboratory findings			
Positive blood culture (%)	23 (53)	14 (25)	0.003
Lactate (mmol/L)	5.5 ± 0.8	3.0 ± 0.3	0.002
C_{5a}-like activity (units of deflection)	0.5 ± 0.06	0.36 ± 0.03	0.017
Bilirubin (μmol/L)	68 ± 12	53 ± 12	NS
Fibrongen (g/L)	2.8 ± 0.2	3.5 ± 0.2	0.018
Cardiovascular Evaluation			
Systemic vascular resistance (dynes·s·cm^{-5})	456 ± 30	582 ± 33	0.013
Left ventricular ejection fraction (%)	34 ± 2	45 ± 2	0.0001
Clinical Outcomes			
Vasopressor therapy required (%)	28 (65)	27 (47)	NS (0.08)
Renal insufficiency	19 (44)	9 (16)	0.002
ARDS	22 (51)	15 (26)	0.01
Both renal insufficiency and ARDS	16 (37)	3 (5)	0.0006
Mortality	12 (28)	12 (21)	NS

*Two-tailed chi square or *t* test as appropriate. NS denotes p≥0.05.
†Continuous variables are expressed as means ± SEM.

Diagnostic and Prognostic Implications of Endotoxemia in Critical Illness: Results of the MEDIC Study

John C. Marshall,[1] Debra Foster,[4] Jean-Louis Vincent,[6] Deborah J. Cook,[5] Jonathan Cohen,[11] R. Phillip Dellinger,[9,a] Steven Opal,[7] Edward Abraham,[8] Stephen J. Brett,[10] Terry Smith,[2] Sangeeta Mehta,[3] Anastasia Derzko,[4] and Alex Romaschin[1,4]

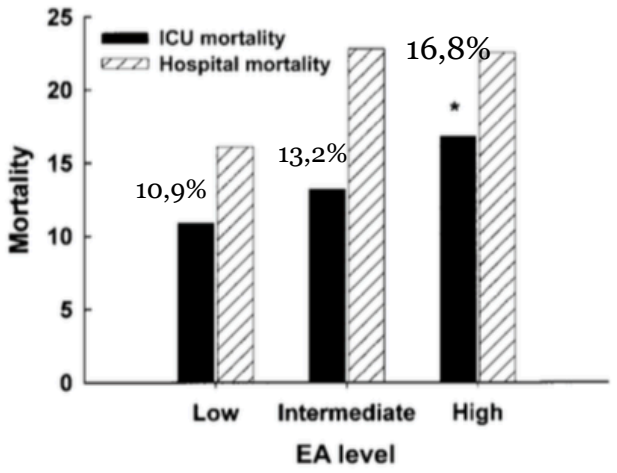


Figure 2. Increasing intensive care unit (ICU) and hospital mortality with increasing levels of endotoxin activity at the time of ICU admission. ICU mortality, $\chi^2 = 4.229$, $P = .04$ (Mantel-Haenzel); hospital mortality, $\chi^2 = 4.343$, $P = .04$ (Mantel-Haenzel).

Table 4. Endotoxin activity (EA) level and risk of severe sepsis.

EA level	Risk of severe sepsis in first 24 h of ICU admission, % (no./total)	OR (95% CI)[a]	*P*
Low (<0.40)	4.9 (18/367)	…	…
Intermediate (0.40–0.60)	9.2 (21/228)	2.0 (1.0–3.8)	<.05
High (>0.60)	13.4 (35/262)	3.0 (1.7–0.5)	<.001

NOTE. CI, confidence interval; ICU, intensive-care unit; OR, odds ratio.
[a] Mantel-Haenzel $\chi^2 = 13.962$, $P = .0002$.

Probable lien entre le taux d'endotoxines et le devenir des patients

Variable dans le temps, peut rester élevé pendant plusieurs jours

MISE AU POINT

Hémoperfusion au cours du sepsis sévère

Hemoperfusion during severe sepsis

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[b] *Département d'anesthésie—réanimation, CHU Lariboisière, 75475 Paris cedex 10, France*

Tableau 1 Les différentes possibilités théoriques de s'opposer à l'endotoxine produite au cours du sepsis.

Neutralisation immunologique de l'ET	Inhibiteurs de synthèse du lipide-A Vaccination anti-ET Anticorps anti-ET
Inhibition du complexe LPS/CD14/LBP	Antagonistes de la protéine LBP
Inhibition de la signalisation	Anticorps anti-CD14 Anticorps anti-TLR4 Blocage des récepteurs TLR Inhibition de NF-KB
Épuration de ET (ou d'autres composés bactériens) à partir du sang ou d'autres milieux de l'organisme	Neutralisation et élimination de ET ou d'autres composants bactériens par filtration ou adsorption

ET : endotoxine ; LPS : lipopolysaccharide ; TLR : *toll-like* recepteurs ; LBP : *lipopolysaccharide binding protein*.

Décevant

Hémoperfusion

Hémoperfusion

TABLE 1: Devices designed to remove endotoxin and cytokines in patients with septic shock.

Device	Company	Composition	Mechanism	Substance eliminated
Toraymyxin 20R	Toray Industries, Japan	Polymyxin B covalently bound to polypropylene-polystyrene fibers fabric	Adsorption	Endotoxin
LPS adsorber	Alteco Medical, Sweden	Synthetic polypeptide bound to porous polyethylene discs	Adsorption	Endotoxin
oXiris	Gambro-Hospal, France	AN69-based membrane, surface treated with a polyethyleneimine (PEI) and grafted with heparin	Adsorption Convection	Endotoxin Cytokines
MATISSE	Fresenius SE, Germany	Human serum albumin immobilised on polymethacrylate beads	Adsorption	Endotoxin
CPFA	Bellco, Italy	Polyethersulfone Plasma filter with adsorption on an unselective hydrophobicresin cartridge, and a synthetic high-permeability polyethersulfone hemofilter for continuous hemofiltration	Adsorption Plasma filtration	Cytokines
Cytosorb	Cytosorbents, USA	Polystyrenedivinyl benzene copolymer beads with a biocompatible polyvinylpyrrolidone coating.	Adsorption Convection	Cytokines

- Hémoperfusion:
  - Réalisée avec les machines d'hémofiltration continue
  - Débit 80 à 120 mL/min
  - Traitement anti coagulant
  - Séance de 2 heures, 2 séances /24h
  - Bonne tolérance (éruption cutanée)

Mediators Inflamm, 2014, Esteban, Immunomodulation in sepsis : the role of endotoxin removal by polymixin B –immobilized cartridge

Mécanisme d'action

Mécanisme principal

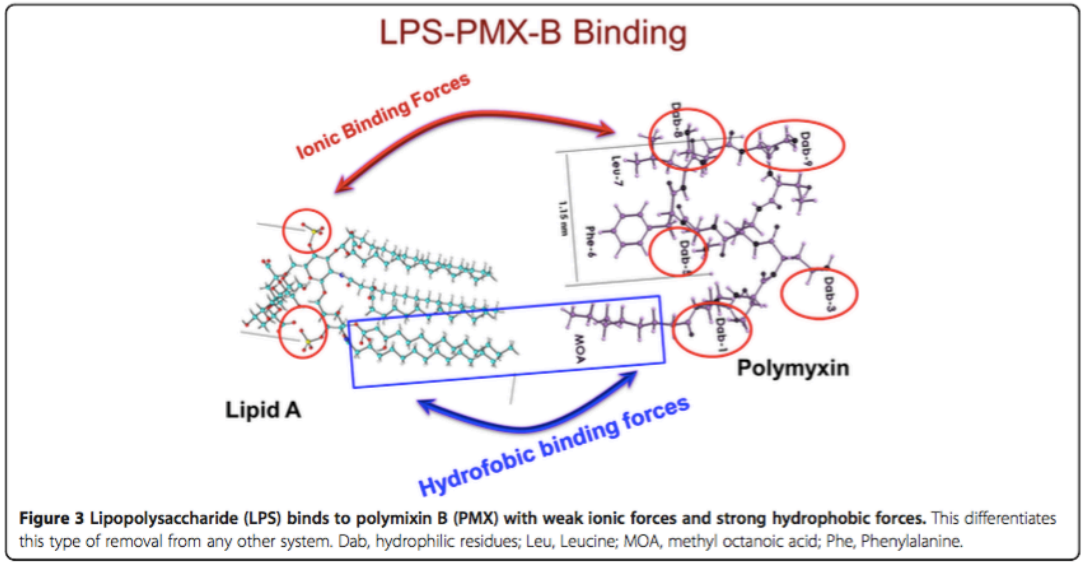


Figure 3 Lipopolysaccharide (LPS) binds to polymixin B (PMX) with weak ionic forces and strong hydrophobic forces. This differentiates this type of removal from any other system. Dab, hydrophilic residues; Leu, Leucine; MOA, methyl octanoic acid; Phe, Phenylalanine.

adsorption directe du LPS circulant

Mécanisme secondaire

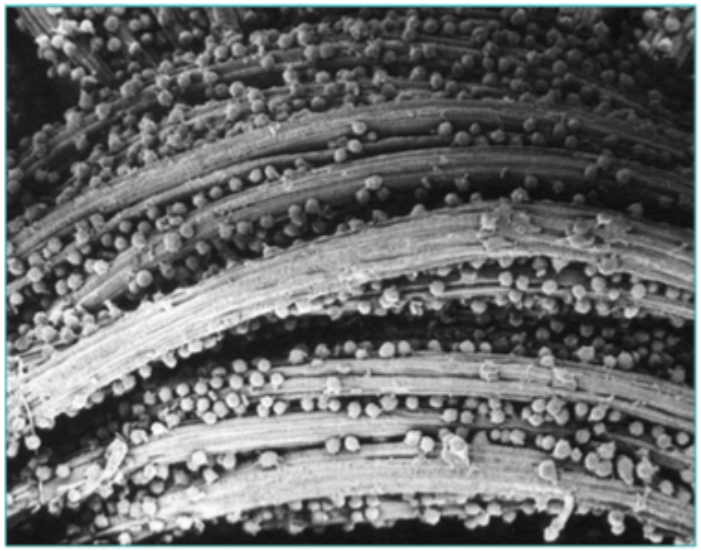


Figure 4 Pictorial view of activated cells adsorbed by the fibers.

Élimination des cellules inflammatoires
Réduction des médiateurs inflammatoires
Diminution des facteurs apoptotiques circulants

Therapeutic Apheresis and Dialysis, 2003, Extracorporeal Endotoxin Removal For The Treatment of Sepsis: Endotoxin Adsorption Cartridge (Toraymyxin) Hisataka Shoji

Etudes chez l'animal

Inocuité ?

Sato T, et al: Experimental study of extracorporeal perfusion for septic shock. ASAIO J 1993

capacité du PMX-DHP à réduire les taux d'endotoxines circulantes
à améliorer la pression artérielle
à réduire la mortalité chez les animaux traités

Confirmé dans d'autres études : Amélioration de l'état hémodynamique d'animaux septiques

Aoki H, Hanasawa K, Tani T, et al. Comparative study between PMX-F and other adsorbents for treatment of septic shock. Ther Plasmapheresis 1988;312:345—50

Available online at www.sciencedirect.com
ScienceDirect
journal homepage: www.JournalofSurgicalResearch.com

Effects of endotoxin absorber hemoperfusion on microcirculation in septic pigs

Yu-Chang Yeh,[a] Linda Chia-Hui Yu,[b] Chun-Yu Wu,[a] Ya-Jung Cheng,[a] Chen-Tse Lee,[a] Wei-Zen Sun,[a] Jui-Chang Tsai,[c,d] and Tzu-Yu Lin,[e,] on behalf of the NTUH Center of Microcirculation Medical Research (NCMMR)*

Table 3 – Microvascular flow index and heterogeneity index.

	Sham	Sepsis	Sepsis + PMX-HP
Ileum mucosa			
MFI 0 h	3.0 (3.0-3.0)	2.7 (2.1-3.0)*	2.7 (1.9-3.0)*
HI 0 h	0.00 (0.00-0.00)	0.20 (0.00-0.60)	0.18 (0.00-0.45)
MFI 6 h	3.0 (3.0-3.0)	1.7 (1.0-2.7)*	2.7 (2.4-3.0)*
HI 6 h	0.00 (0.00-0.00)	0.32 (0.19-1.39)*	0.38 (0.05-0.49)*

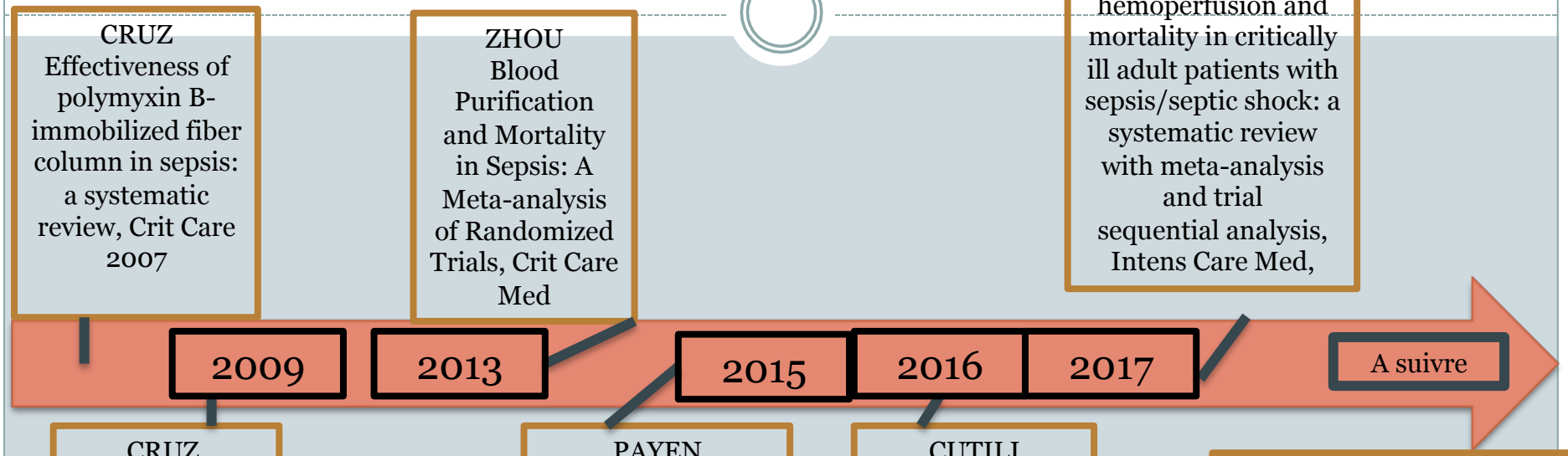
Action sur la microcirculation et sur l'oxygénation tissulaire

Table 4 – Tissue oxygen saturation obtained using a superficial tissue oxygenation monitor with the light reflectance spectroscopy technique.

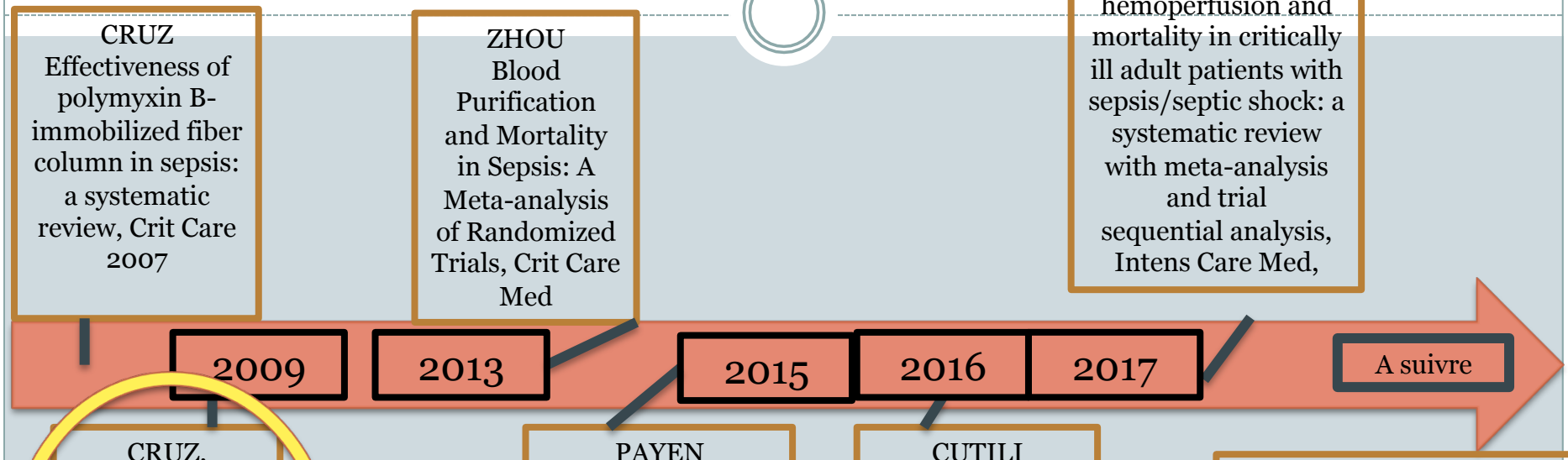
StO_2 (%)	Sham	Sepsis	Sepsis + PMX-HP
Ileum mucosa			
0 h	51.6 (10.8)	45.5 (16.7)	49.5 (17.9)
6 h	60.9 (8.5)	40.6 (11.7)*,†	54.9 (8.9)
Colon mucosa			
0 h	60.8 (12.4)	46.2 (14.4)	41.1 (13.5)
6 h	59.3 (5.1)	36.5 (20.3)*	51.6 (9.8)
Kidney surface			
0 h (left)	73.2 (10.3)	57.8 (14.0)	65.8 (10.0)
6 h (right)	76.5 (6.4)	58.7 (14.1)*	63.9 (9.3)

PMX-HP = polymyxin B hemoperfusion; StO_2 = tissue oxygen saturation; ANOVA = analysis of variance.
Data are represented as the mean (standard deviation). $n = 12$ for each group in ileum mucosa (two segments from each rat); $n = 6$ for each group in colon mucosa and kidney surface).
*$P < 0.05$ *versus* the sham group, as determined using one-way ANOVA with the Tukey test.
†$P < 0.05$ *versus* the sepsis + PMX-HP group, as determined using one-way ANOVA with the Tukey test.

Etudes cliniques



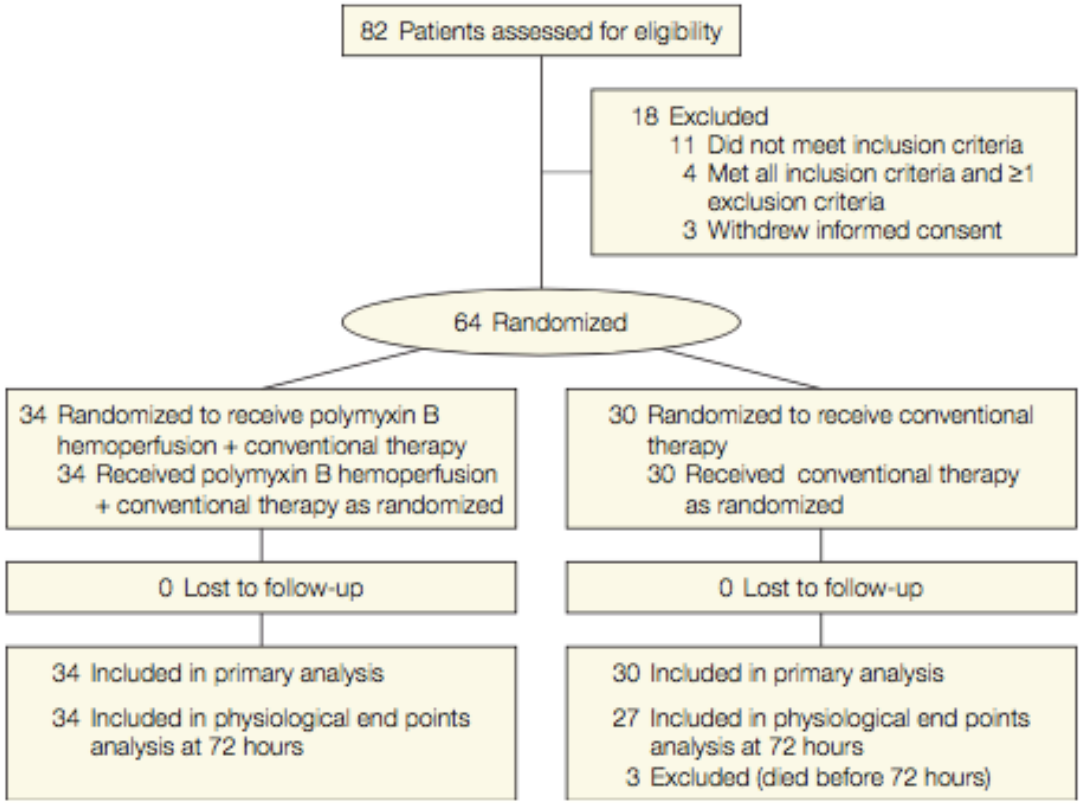
Etudes cliniques



Early Use of Polymyxin B Hemoperfusion in Abdominal Septic Shock

The EUPHAS Randomized Controlled Trial

Figure 1. Patient Flow Diagram of EUPHAS Trial



EUPHAS indicates Early Use of Polymyxin B Hemoperfusion in Abdominal Sepsis. Patients in the polymyxin B hemoperfusion group were treated with 2 sessions of direct hemoperfusion with polymyxin B in addition to standard conventional therapy.

CJP:
Amélioration de la PAM et modification des besoins en vasopresseurs

CJS:
Ratio PaO2/FiO2
Score SOFA
Mortalité à 28 jours

Table 1. Baseline Characteristics of the Treatment Groups[a]

Characteristics	Mean (95% Confidence Interval)		*P* Value
	Polymyxin B Hemoperfusion (n = 34)	Conventional Therapy (n = 30)	
Age, y	61 (57-66)	67 (61-72)	.09
Male sex, No. (%)	24 (71)	18 (60)	.53
APACHE II score	21 (19-23)	20 (18-23)	.86
SOFA score	11 (10-12)	9 (8-11)	.07
Mean arterial pressure, mm Hg	76 (72-80)	74 (70-78)	.40
Noradrenaline, µg/kg/min	0.27 (0.17-0.36)	0.24 (0.13-0.36)	.70
Dopamine, µg/kg/min	3.1 (1.7-4.4)	4.6 (2.9-5.6)	.13
Inotropic score	29.9 (20.4-39.4)	28.6 (16.6-40.7)	.85
Vasopressor dependency index, $mm\ Hg^{-1}$	4.3 (2.7-5.9)	4.1 (2.3-6.0)	.87
White blood cell count, 1000/µL	13.7 (11.4-16.0)	11.4 (9.0-13.8)	.12
Pa_{O_2}/Fi_{O_2}	235 (206-265)	217 (188-247)	.53
Diuresis, mL/h	66 (50-90)	87 (59-116)	.22
Creatinine, mg/dL	2.3 (1.7-2.9)	1.7 (1.3-2.2)	.18
Renal replacement therapy, No. (%)	13 (38)	6 (20)	.17

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; Fi_{O_2}, fraction of inspired oxygen; SOFA, Sequential Organ Failure Assessment.

SI conversion: To convert creatinine to µmol/L, multiply by 88.4.

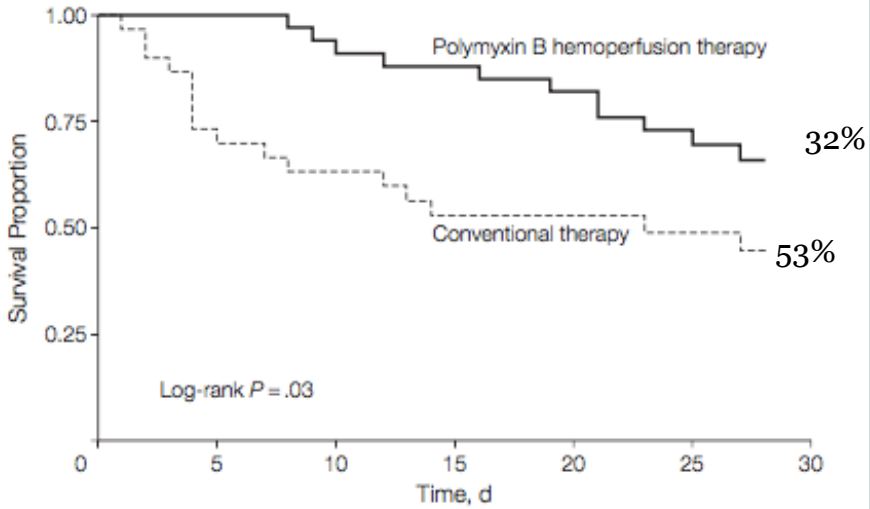
[a] Patients in the polymyxin B hemoperfusion group were treated with 2 sessions of direct hemoperfusion with polymyxin B in addition to standard conventional therapy. Range of APACHE II score was 0 to 71, with lower scores indicating better organ function. Range of SOFA score was 0 to 24, with lower scores indicating better organ function. See "Methods" section for formulas for inotropic score and vasopressor dependency index.

Table 3. Physiological End Points by Treatment Group at Baseline and 72 Hours[a]

Physiological End Points	Polymyxin B Hemoperfusion Mean (95% CI) Baseline (n = 34)	72 Hours (n = 34)	*P* Value	Conventional Therapy Mean (95% CI) Baseline (n = 30)	72 Hours (n = 27)	*P* Value
Mean arterial pressure, mm Hg	76 (72-80)	84 (80-88)	.001	74 (70-78)	77 (72-82)	.37
Inotropic score	29.9 (20.4-39.4)	6.8 (2.9-10.7)	<.001	28.6 (16.6-40.7)	22.4 (9.3-35.5)	.14
Vasopressor dependency index, $mm\ Hg^{-1}$	4.3 (2.7-5.9)	0.9 (0.3-1.5)	<.001	4.1 (2.3-6.0)	3.3 (1.3-5.3)	.26
PaO_2/FIO_2	235 (206-265)	264 (236-292)	.049	217 (188-247)	228 (199-258)	.79
Renal replacement therapy, No. (%)	13 (38)	15 (44)	.50	6 (20)	8 (30)	.50

Abbreviations: CI, confidence interval; FIO_2, fraction of inspired oxygen.
[a]See "Methods" section for formulas for inotropic score and vasopressor dependency index. In the conventional therapy group, 3 patients died before 72 hours (n=27).

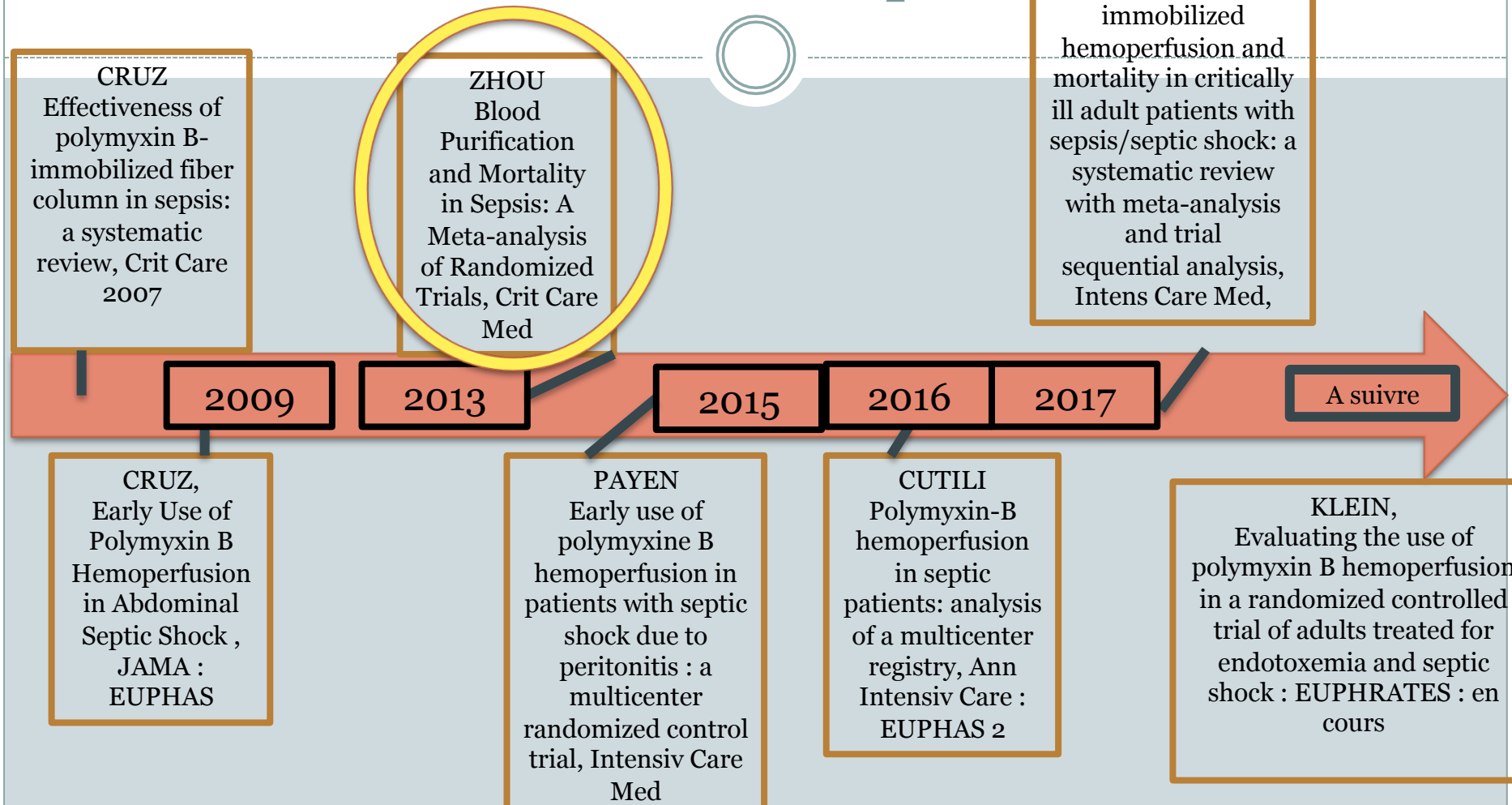
Figure 3. Estimation of Survival Rate According to Treatment Group



Patients in the polymyxin B hemoperfusion group were treated with 2 sessions of direct hemoperfusion with polymyxin B in addition to standard conventional therapy.

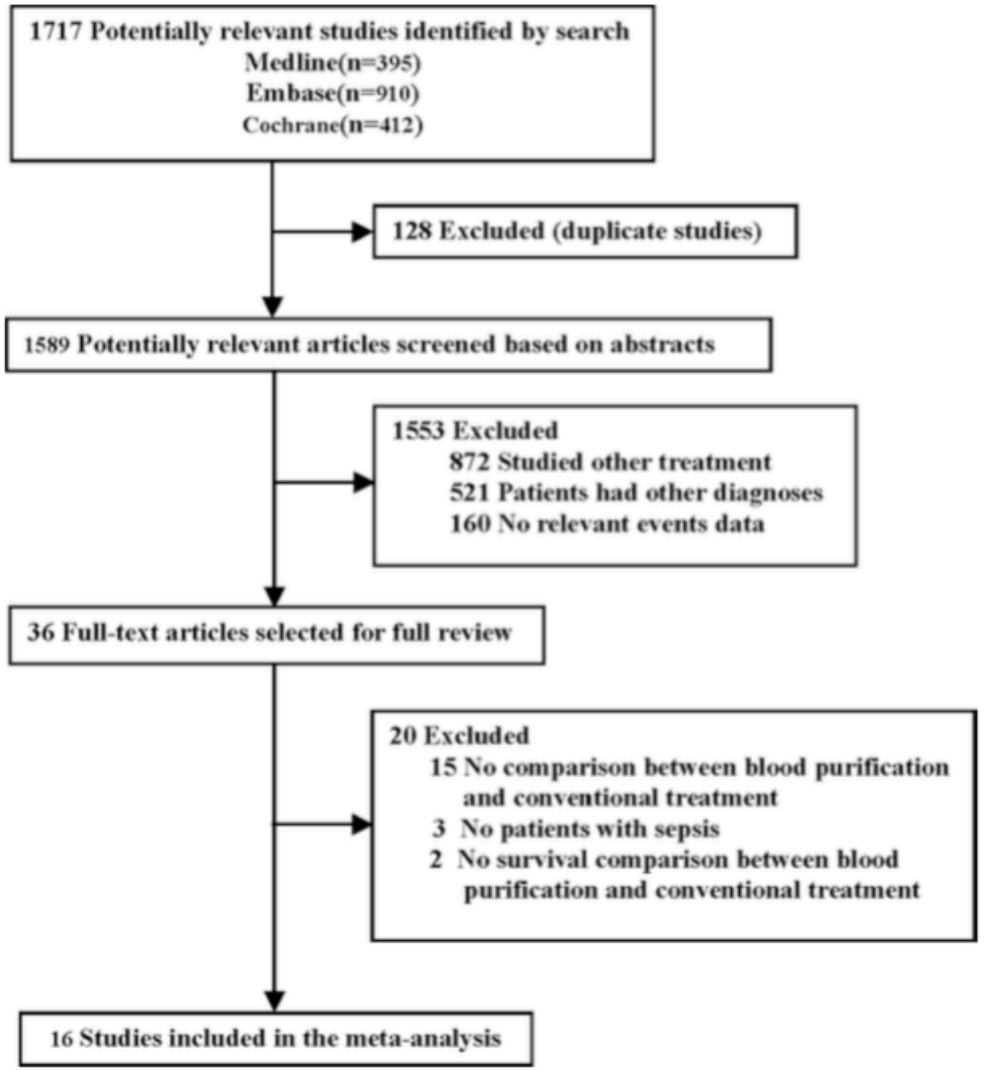
Limites :
- Arrêt précoce
- Pas d'aveugle
- Pas de mesure de l'endotoxémie

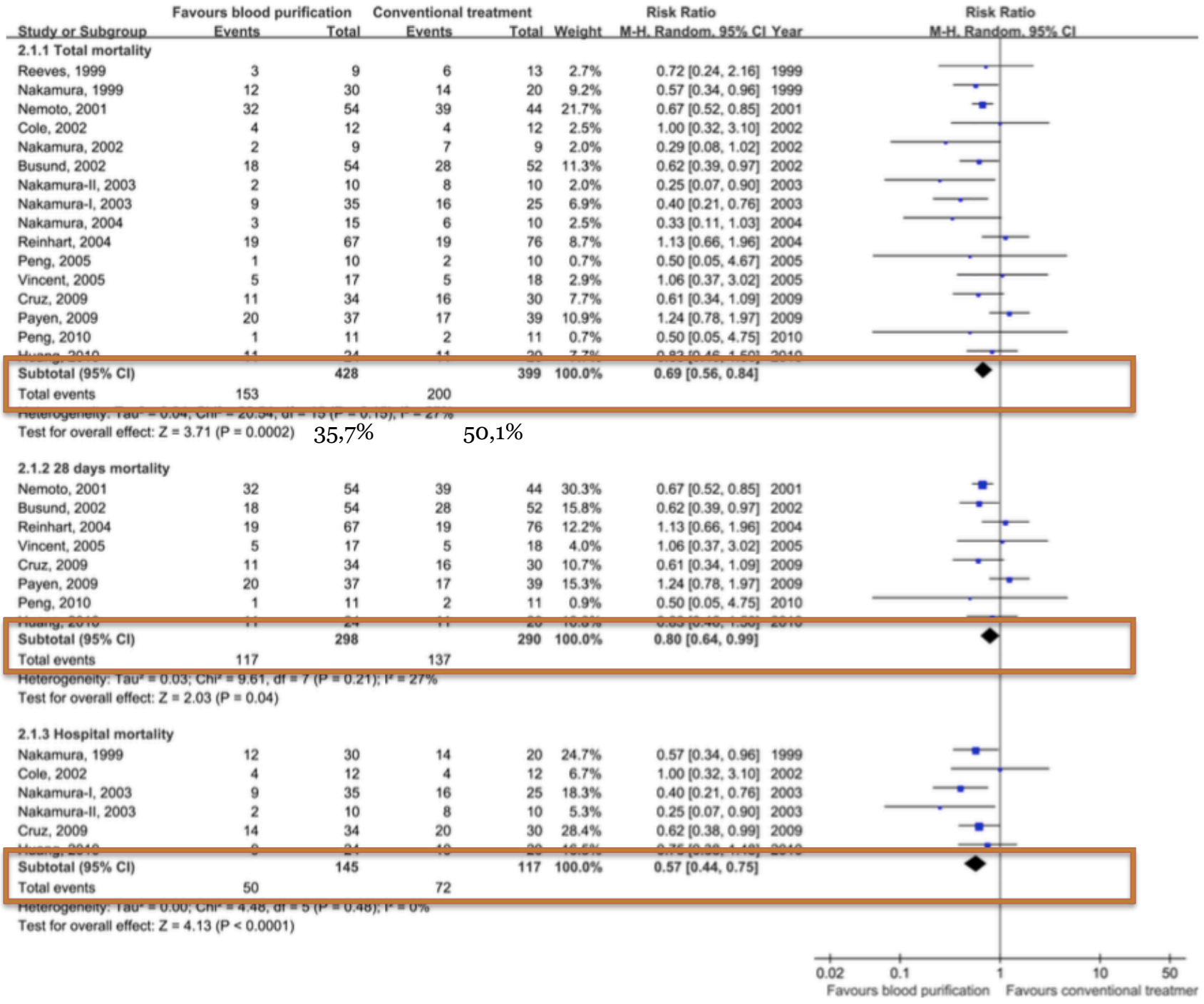
Etudes cliniques



Blood Purification and Mortality in Sepsis: A Meta-analysis of Randomized Trials

Feihu Zhou, MD, PhD[1,2], Zhiyong Peng, MD, PhD[1], Raghavan Murugan, MD, MS, FRCP[1], and John A. Kellum, MD, FCCM[1]




Favours blood purification
Conventional treatment
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI Year
M-H, Random, 95% CI
2.1.1 Total mortality
Reeves, 1999 3 9 6 13 2.7% 0.72 [0.24, 2.16] 1999
Nakamura, 1999 12 30 14 20 9.2% 0.57 [0.34, 0.96] 1999
Nemoto, 2001 32 54 39 44 21.7% 0.67 [0.52, 0.85] 2001
Cole, 2002 4 12 4 12 2.5% 1.00 [0.32, 3.10] 2002
Nakamura, 2002 2 9 7 9 2.0% 0.29 [0.08, 1.02] 2002
Busund, 2002 18 54 28 52 11.3% 0.62 [0.39, 0.97] 2002
Nakamura-II, 2003 2 10 8 10 2.0% 0.25 [0.07, 0.90] 2003
Nakamura-I, 2003 9 35 16 25 6.9% 0.40 [0.21, 0.76] 2003
Nakamura, 2004 3 15 6 10 2.5% 0.33 [0.11, 1.03] 2004
Reinhart, 2004 19 67 19 76 8.7% 1.13 [0.66, 1.96] 2004
Peng, 2005 1 10 2 10 0.7% 0.50 [0.05, 4.67] 2005
Vincent, 2005 5 17 5 18 2.9% 1.06 [0.37, 3.02] 2005
Cruz, 2009 11 34 16 30 7.7% 0.61 [0.34, 1.09] 2009
Payen, 2009 20 37 17 39 10.9% 1.24 [0.78, 1.97] 2009
Peng, 2010 1 11 2 11 0.7% 0.50 [0.05, 4.75] 2010
Subtotal (95% CI) 428 399 100.0% 0.69 [0.56, 0.84]
Total events 153 200
Test for overall effect: Z = 3.71 (P = 0.0002)
35,7%
50,1%
2.1.2 28 days mortality
Nemoto, 2001 32 54 39 44 30.3% 0.67 [0.52, 0.85] 2001
Busund, 2002 18 54 28 52 15.8% 0.62 [0.39, 0.97] 2002
Reinhart, 2004 19 67 19 76 12.2% 1.13 [0.66, 1.96] 2004
Vincent, 2005 5 17 5 18 4.0% 1.06 [0.37, 3.02] 2005
Cruz, 2009 11 34 16 30 10.7% 0.61 [0.34, 1.09] 2009
Payen, 2009 20 37 17 39 15.3% 1.24 [0.78, 1.97] 2009
Peng, 2010 1 11 2 11 0.9% 0.50 [0.05, 4.75] 2010
Subtotal (95% CI) 298 290 100.0% 0.80 [0.64, 0.99]
Total events 117 137
Heterogeneity: Tau² = 0.03; Chi² = 9.61, df = 7 (P = 0.21); I² = 27%
Test for overall effect: Z = 2.03 (P = 0.04)
2.1.3 Hospital mortality
Nakamura, 1999 12 30 14 20 24.7% 0.57 [0.34, 0.96] 1999
Cole, 2002 4 12 4 12 6.7% 1.00 [0.32, 3.10] 2002
Nakamura-I, 2003 9 35 16 25 18.3% 0.40 [0.21, 0.76] 2003
Nakamura-II, 2003 2 10 8 10 5.3% 0.25 [0.07, 0.90] 2003
Cruz, 2009 14 34 20 30 28.4% 0.62 [0.38, 0.99] 2009
Subtotal (95% CI) 145 117 100.0% 0.57 [0.44, 0.75]
Total events 50 72
Heterogeneity: Tau² = 0.00; Chi² = 4.48, df = 5 (P = 0.48); I² = 0%
Test for overall effect: Z = 4.13 (P < 0.0001)
0.02 0.1 1 10 50
Favours blood purification
Favours conventional treatmer

Study or Subgroup	Blood purification Events	Total	Conventional treatment Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
3.1.1 Hemoperfusion							
Nakamura, 1999	12	30	14	20	13.2%	0.57 [0.34, 0.96]	1999
Nemoto, 2001	32	54	39	44	27.6%	0.67 [0.52, 0.85]	2001
Nakamura, 2002	2	9	7	9	3.1%	0.29 [0.08, 1.02]	2002
Nakamura-II, 2003	2	10	8	10	3.1%	0.25 [0.07, 0.90]	2003
Nakamura-I, 2003	9	35	16	25	10.0%	0.40 [0.21, 0.76]	2003
Reinhart, 2004	19	67	19	76	12.5%	1.13 [0.66, 1.96]	2004
Nakamura, 2004	3	15	6	10	3.8%	0.33 [0.11, 1.03]	2004
Vincent, 2005	5	17	5	18	4.4%	1.06 [0.37, 3.02]	2005
Cruz, 2009	11	34	16	30	11.2%	0.61 [0.34, 1.09]	2009
Huang, 2010	11	24	11	20	11.2%	0.83 [0.46, 1.50]	2010
Subtotal (95% CI)		**295**		**262**	**100.0%**	**0.63 [0.50, 0.80]**	
Total events	106		141				

Heterogeneity: Tau² = 0.04; Chi² = 13.19, df = 9 (P = 0.15); I² = 32%

Test for overall effect: Z = 3.75 (P = 0.0002)

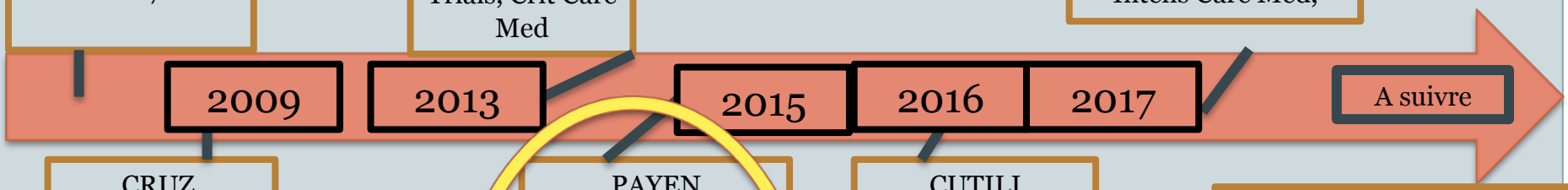
Dépend de la modalité

3.1.3 Plasma exchange							
Reeves, 1999	3	9	6	13	20.4%	0.72 [0.24, 2.16]	1999
Busund, 2002	18	54	28	52	79.6%	0.62 [0.39, 0.97]	2002
Subtotal (95% CI)		**63**		**65**	**100.0%**	**0.63 [0.42, 0.96]**	
Total events	21		34				

Heterogeneity: Tau² = 0.00; Chi² = 0.07, df = 1 (P = 0.80); I² = 0%

Test for overall effect: Z = 2.14 (P = 0.03)

Etudes cliniques



CRUZ
Effectiveness of polymyxin B-immobilized fiber column in sepsis: a systematic review, Crit Care 2007

ZHOU
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Early Use of Polymyxin B Hemoperfusion in Abdominal Septic Shock , JAMA : EUPHAS

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Early use of polymyxine B hemoperfusion in patients with septic shock due to peritonitis : a multicenter randomized control trial, Intensiv Care Med

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Polymyxin-B hemoperfusion in septic patients: analysis of a multicenter registry, Ann Intensiv Care : EUPHAS 2

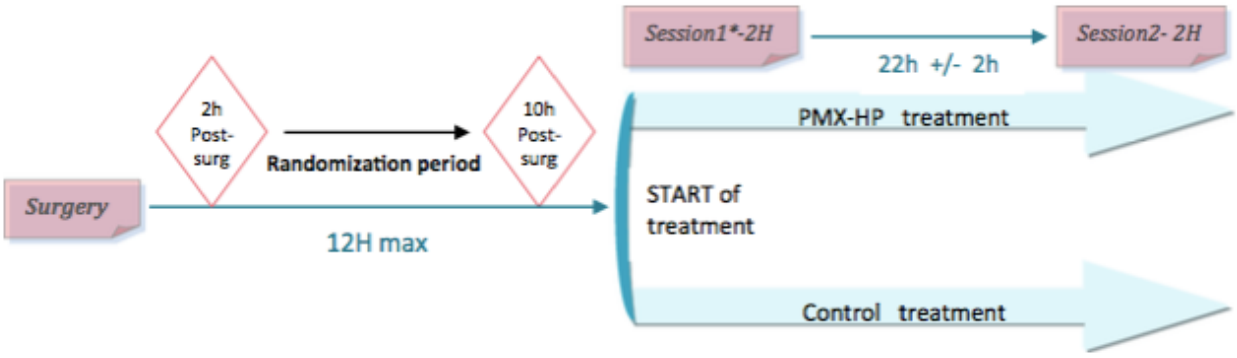
KLEIN,
Evaluating the use of polymyxin B hemoperfusion in a randomized controlled trial of adults treated for endotoxemia and septic shock : EUPHRATES : en cours

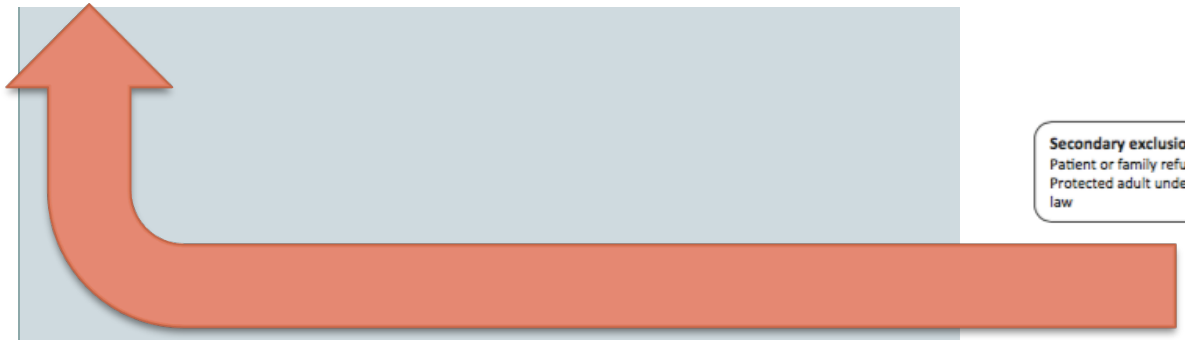
Intensive Care Med (2015) 41:975–984
DOI 10.1007/s00134-015-3751-z

SEVEN-DAY PROFILE PUBLICATION

Didier M. Payen
Joelle Guilhot
Yoann Launey
Anne Claire Lukaszewicz
Mahmoud Kaaki

Early use of polymyxin B hemoperfusion in patients with septic shock due to peritonitis: a multicenter randomized control trial





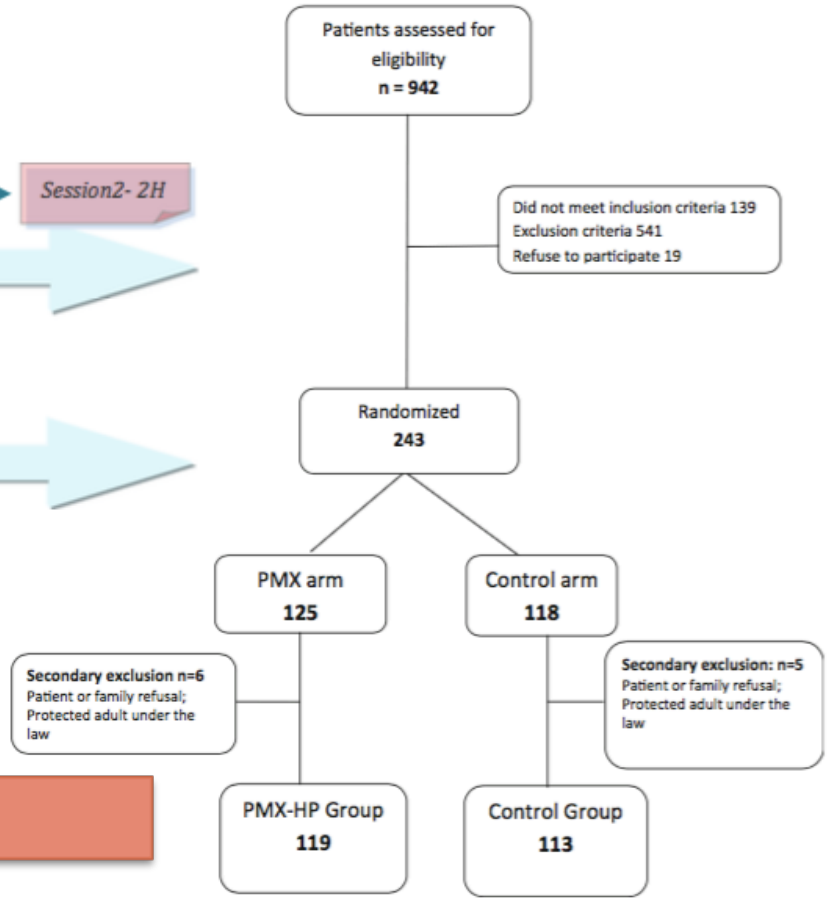


Table 1 Patient characteristics at baseline (before randomization)

	PMX-treated group ($n = 119$)	Standard treatment ($n = 113$)
Age (years)	71.5 (19–90)	72 (39–94)
Male–female ratio, no. (%)	72 (60)–47 (40)	62 (55)–51 (45)
SAPS2	57 (25–107)	59 (21–116)
SOFA score	10 (3–15)	10 (5–14)
McCabe 1, no. (%)	73 (61)	71 (63)
McCabe 2, no. (%)	45 (38)	38 (34)
McCabe 3, no. (%)	1 (1)	4 (4)
Body weight (kg)	74 (43–185)	78 (40–137)
Pre-existing conditions, no. (%)		
Hypertension	69 (58)	63 (56)
Cardiac failure	13 (11)	13 (12)
Diabetes	24 (20)	20 (18)
Chronic renal disorders	2	3
Cancer or hematological malignancy		
Remission	21 (18)	23 (20)
Evolutive	14 (12)	10 (9)
Heart rate (beat/min)	112 (61–177)	105 (60–168)
Systolic arterial pressure (mmHg)	90 (45–150)	93 (45–183)
Diastolic arterial pressure (mmHg)	50 (26–80)	50 (15–95)
Mean arterial pressure (mmHg)	64 (31–93)	65 (28–96)
Leukocytes count (10^3/mL)	8.9 (0.5–43.3)	8.9 (0.3–39.6)
Platelets count (10^3/mL)	216 (35–931)	217 (30–700)
INR	1.64 (1.10–4.90)	1.70 (1.10–3.10)
Plasma creatinine (μmol/L)	133 (38–570)	133 (30–464)
Bilirubin (μmol/L)	15 (2–142)	15 (2–132)
Lactates (mmol/L)	2.9 (0.7–13.0)	3.1 (0.5–13.0)
Plasma IL-6 (pg/mL)	2,146 (107–9,717)	1,927 (540–9,757)
Mechanical ventilation, no. (%)	117 (98)	110 (97)
pH	7.29 (6.91–7.50)	7.28 (6.86–7.47)
PaO_2/FiO_2	219 (46–573)	197 (63–659)
Norepinephrine infusion, no. (%)	119 (100)	113 (100)
Norepinephrine infusion rate (μg/kg/min)	0.44 (0.04–5.00)	0.41 (0.30–11.40)
Epinephrine infusion, no. (%)	1 (1)	7 (6)
Dobutamine infusion, no. (%)	6 (3)	2 (2)
Fluid therapy before randomization (mL)	4,497 (354–14,723)	4,000 (500–13,232)

Values expressed as median with minimum–maximum (min–max) or in number and percentage (%). Numerical values are expressed as median (min–max) except for IL-6 median (interquartile range)

SAPS simplified acute physiologic score, *INR* international normalized ratio

Fig. 3 Cumulative incidence of death overtime in the two arms: HP-PMX (*continuous line*) and standard treatment (*hashed line*). No significant difference was observed ($p = 0.1067$)

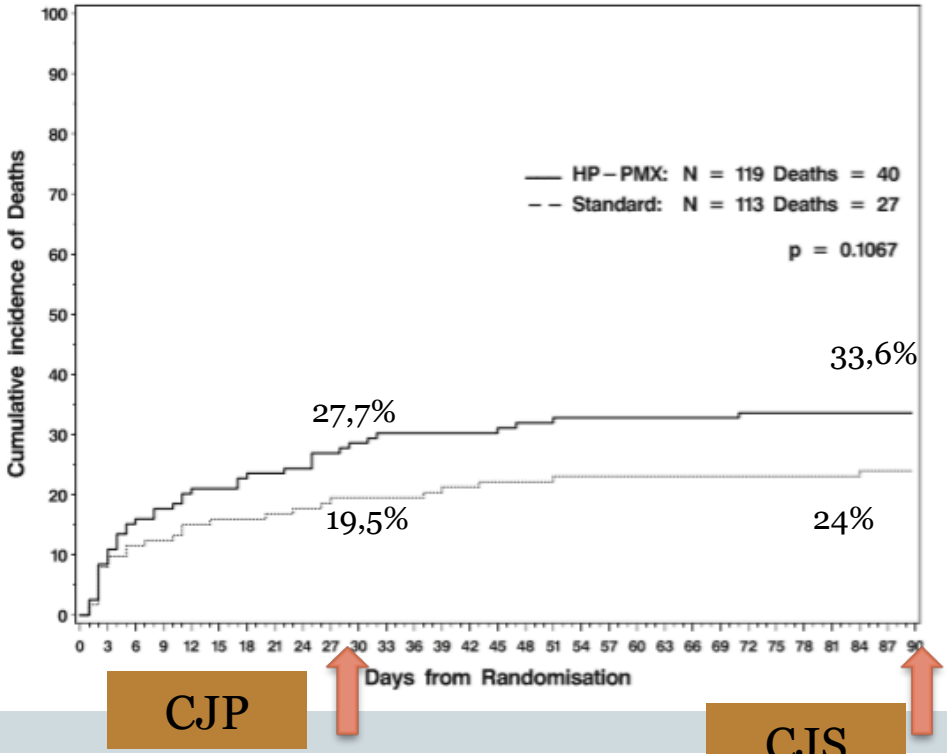


Table 3 SOFA variation between baseline and day 3

	PMX-HP group		Control group	
	Baseline ($n = 119$)	Day 3 ($n = 107$)	Baseline ($n = 113$)	Day 3 ($n = 103$)
SOFA[a]	10 (3–15)	8 (0–16)	10 (5–14)	7 (0–16)
SOFA cardiovascular	4 (3–4)	4 (0–4)	4 (3–4)	4 (0–4)
SOFA renal	3 (0–4)	1 (0–4)	4 (0–4)	1 (0–4)
SOFA hematological	0 (0–3)	2 (0–4)	0 (0–3)	0 (0–4)[b]
SOFA respiratory	2 (0–4)	2 (0–4)	2 (0–4)	2 (0–4)
SOFA liver	0 (0–3)	0 (0–2)	0 (0–3)	0 (0–2)

[a] SOFA score excluding the neurological alteration (see "Methods")
[b] $p < 0.01$, day 3, PMX-HP versus control group

LIMITES

① Taux de mortalité attendu de 37 % dans le groupe témoin > aux 23% observés

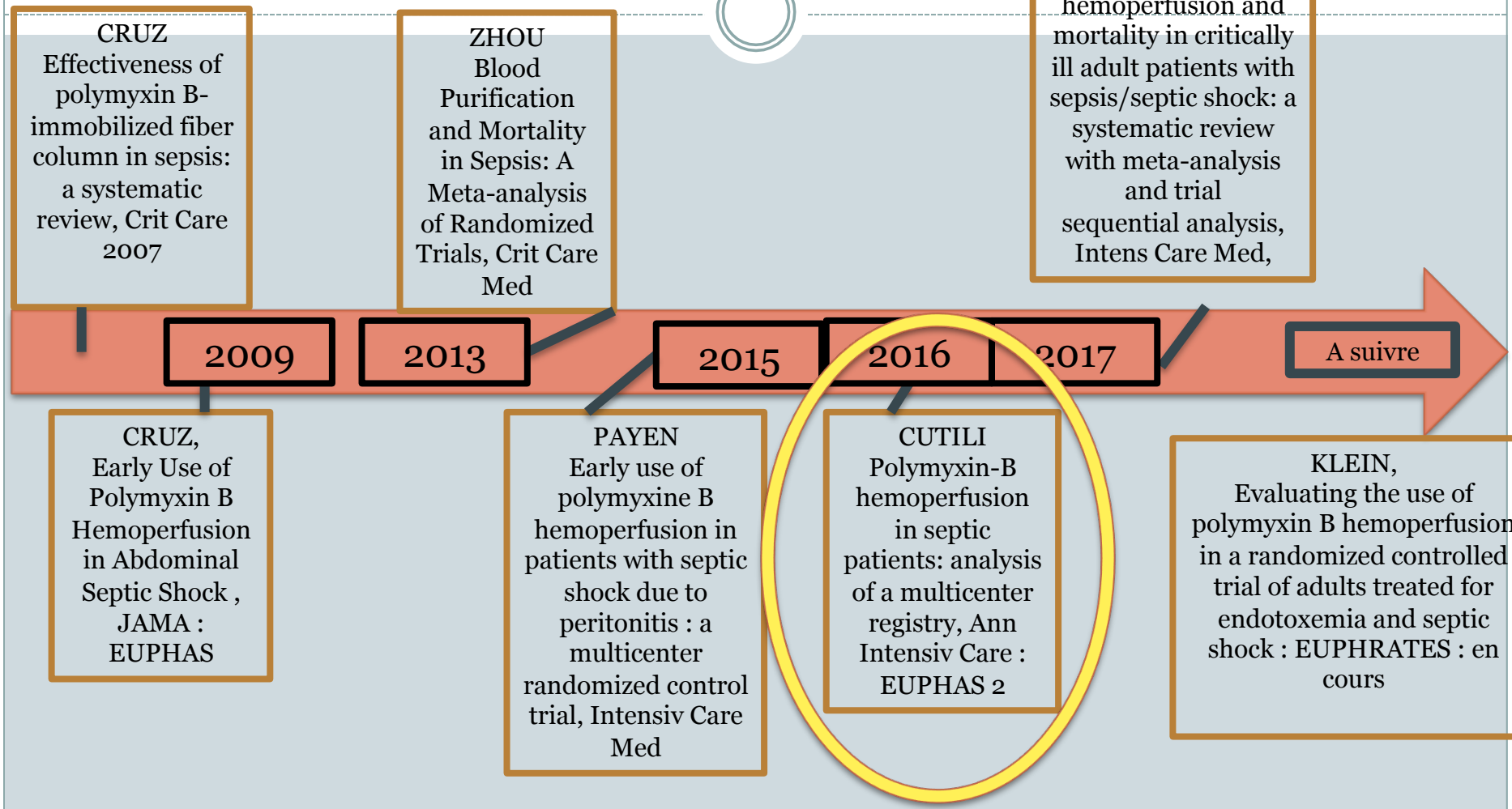
② Réduction de 20% de la mortalité attendue dans le groupe PMX => optimiste mais traitement lourd devant comporter un bénéfice

③ Incidence élevée du traitement incomplet avec les séances de PMX (38%) : décès précoce, instabilité hémodynamique, coagulopathie…

④ Pas de bénéfice dans l'analyse uniquement des traitements complets

⑤ Pas de mesure du taux d'endotoxines

Etudes cliniques



Cutuli et al. Ann. Intensive Care (2016) 6:77
DOI 10.1186/s13613-016-0178-9

Annals of Intensive Care

RESEARCH Open Access

Polymyxin-B hemoperfusion in septic patients: analysis of a multicenter registry

Salvatore Lucio Cutuli[1*], Antonio Artigas[2], Roberto Fumagalli[3], Gianpaola Monti[3], Vito Marco Ranieri[4], Claudio Ronco[5], Massimo Antonelli[1] and The EUPHAS 2 Collaborative Group

Table 1 Demographic characteristics of patients treated with PMX-HP

Demographic characteristics	N 357
Age, years, mean ± SD	63 (51–72)
Gender, male	240 (67.2)
SAPS II at admission, mean ± SD	50.3 ± 19.2
APACHE II at admission, mean ± SD	21.8 ± 7.2
SOFA at admission, mean ± SD	10.9 ± 3.5
Incidence of shock	305 (85.4)
Source of sepsis	
Abdominal	157 (44)
Pulmonary	63 (17.6)
Urinary	16 (4.5)
Cardiac	23 (6.4)
Trauma	19 (5.3)
Other[a]	79 (22)
Patients without microbiological cultures *N* (%)	139 (38.9)
Patients with microbiological cultures	218 (61.1)
Negative microbiological cultures	41 (18.8)
Positive microbiological cultures	177 (81.1)
Gram positive only	17 (7.8)
Gram negative only	81 (37.2)
Fungi only	13 (6.0)
Mixed including gram negatives	51 (23.4)
Mixed not including gram negatives	8 (3.7)
Patients with endotoxin activity assay, *N* (%)	132 (37)
Abdominal	47 (35.6)
Non-abdominal	85 (64.4)
Without microbiology data	33 (25)
Negative cultures	12 (9)
Gram positive only	7 (5.3)
Gram negative only	43 (32.6)
Fungi only	14 (10.6)
Mixed including gram negatives	21 (15.9)
Mixed not including gram negatives	3 (2.2)
Patients with 2 treatments, *N* (%)	219 (61)
Patients with 1 treatment, *N* (%)	138 (39)
28 days survival	180 (54.5)
ICU survival	192 (55.2)
Hospital survival	172 (50)

Data are expressed as *N* (%) apart from otherwise indicated

[a] Other includes soft tissue infections, CVC-related infections, meningitides

Table 2 Variables changes 72 h after PMX-HP

Patients	t_0 $N = 357$	t_{72} $N = 299$	p (Wilcoxon)
SOFA score	12.4 ± 4.2	10.5 ± 5.3	*<0.001*
Cardiovascular SOFA	3.32 ± 1.29	2.16 ± 1.77	*<0.001*
Renal SOFA	2.23 ± 1.62	1.84 ± 1.77	*0.013*
Hepatic SOFA	1.22 ± 1.28	1.19 ± 1.30	0.80
Respiratory SOFA	2.40 ± 1.06	1.95 ± 0.95	*<0.001*
Coagulation SOFA	1.33 ± 1.29	1.67 ± 1.38	*0.004*
Inotropic score	30 (11.9–72.5)	6.0 (0.0–22)	*<0.001*
Lactate, mmol/L	3.4 (1.9–6.0)	1.9 (1.3–2.9)	*<0.001*
Platelets, 10^3/μL	117 (56–220)	86 (40–163)	*<0.001*

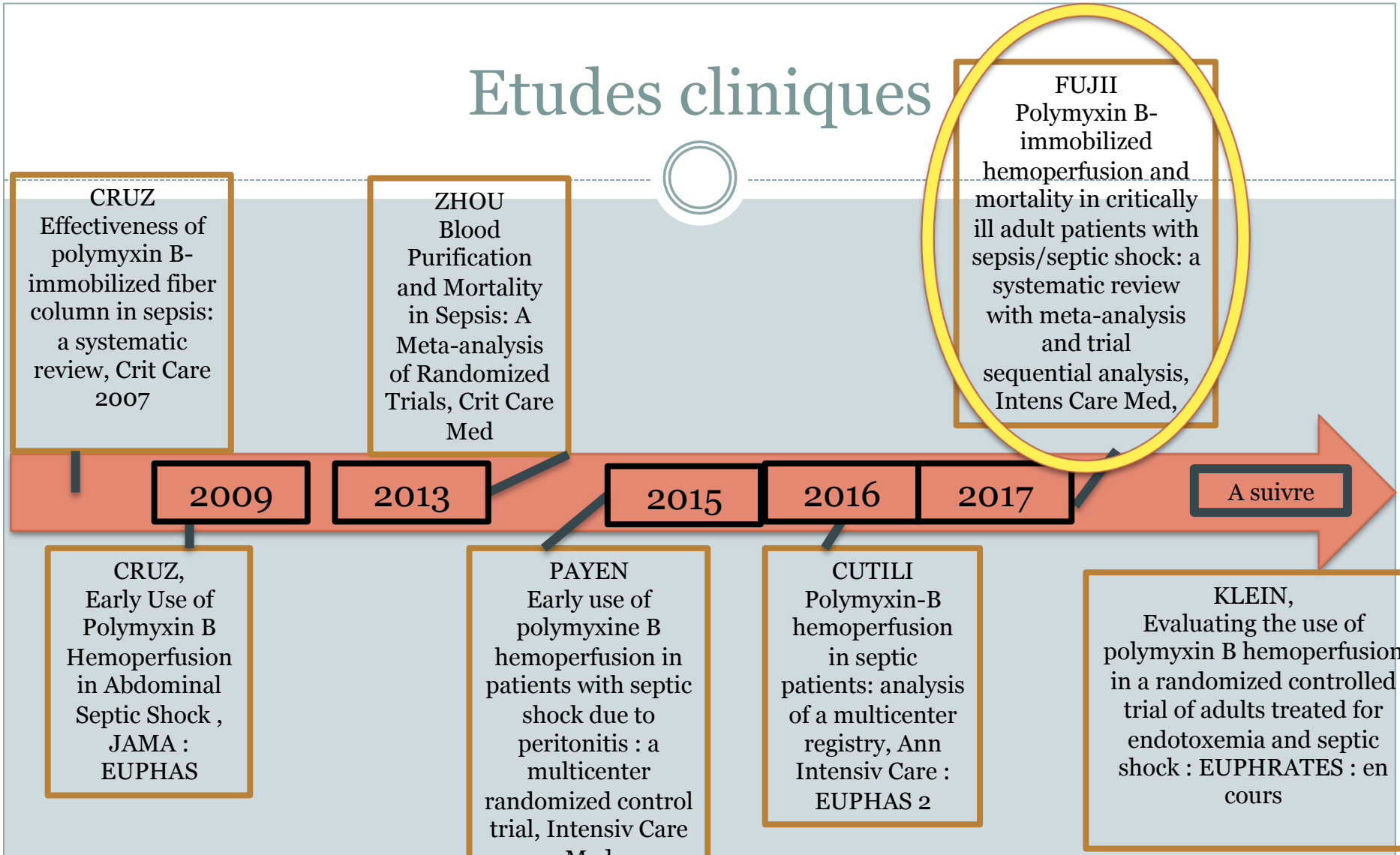
Normally distributed data are expressed as mean ± SD and non-normally distributed data as median (interquartile range)

Italics indicates significant *p* values

- infection abdominale + PMX-HP dans les 24 h => survie à 28 jours de 64,5%.
- Amélioration de de l'activité cardiovasculaire après PMX-HP => survie de 75% par rapport à la survie de 39% des patients sans PMX (p <0,001).

Conclusion: The EUPHAS 2 is the largest registry conducted outside Japan on the clinical use of PMX-HP in septic patients. Data analysis confirmed the feasibility of PMX-HP to treat septic patients in daily clinical practice, showing clinical benefits associated with endotoxin removal without significant adverse events related to the extracorporeal technique.

Etudes cliniques



SYSTEMATIC REVIEW

Polymyxin B-immobilized hemoperfusion and mortality in critically ill adult patients with sepsis/septic shock: a systematic review with meta-analysis and trial sequential analysis

Tomoko Fujii[1,2], Riki Ganeko[3], Yuki Kataoka[4], Toshi A. Furukawa[5], Robin Featherstone[6], Kent Doi[7], Jean-Louis Vincent[8], Daniela Pasero[9], René Robert[10], Claudio Ronco[11] and Sean M. Bagshaw[12*]

Table 1 Characteristics of the trials included in the meta-analysis

Source	Country	Study cites	Funding	Total no. of patients	Exclusion from ITT analysis	Age, mean (SD), years	Sex, male, female, *n*	Patient status	Duration, no. of sessions	Primary outcome
Nakamura 2003 [32]	Japan	NA	Investigator-initiated	60	0	56 (NA)	40, 20	Culture-positive sepsis	2 h, twice	Unclear[b]
Vincent 2005 [14]	Six countries in Europe	Multicenter	Industry-sponsored	35	0	57.7 (15.6)[a]	22, 13	Abdominal sepsis, surgical	2 h, once	The SOFA score
Cantaluppi 2008 [31]	Italy	Two centers	Investigator-initiated	16	0	60 (11.3)	12, 4	Confirmed gram-negative sepsis	2 h, twice	Viability of renal cell cultures
Cruz 2009 [15], Berto 2011 [33]	Italy	Multicenter	Industry-sponsored	64	0	63.8 (14.2)[a]	42, 22	Abdominal sepsis, surgical	2 h, twice	MAP and vasopressor requirement
Payen 2015 [17]	France	Multicenter	Industry-sponsored	243	11	69.7 (11.6)	134, 98	Abdominal sepsis, surgical, septic shock	2 h, twice	28-day mortality
EUPHRATES 2017 [18], Klein 2014 [34]	USA, Canada	Multicenter	Industry-sponsored	450	0	59.8 (14.9)[a]	273, 177[a]	Septic shock, high endotoxin activity assay	2 h, twice	28-day mortality

Table 2 Outcome measures

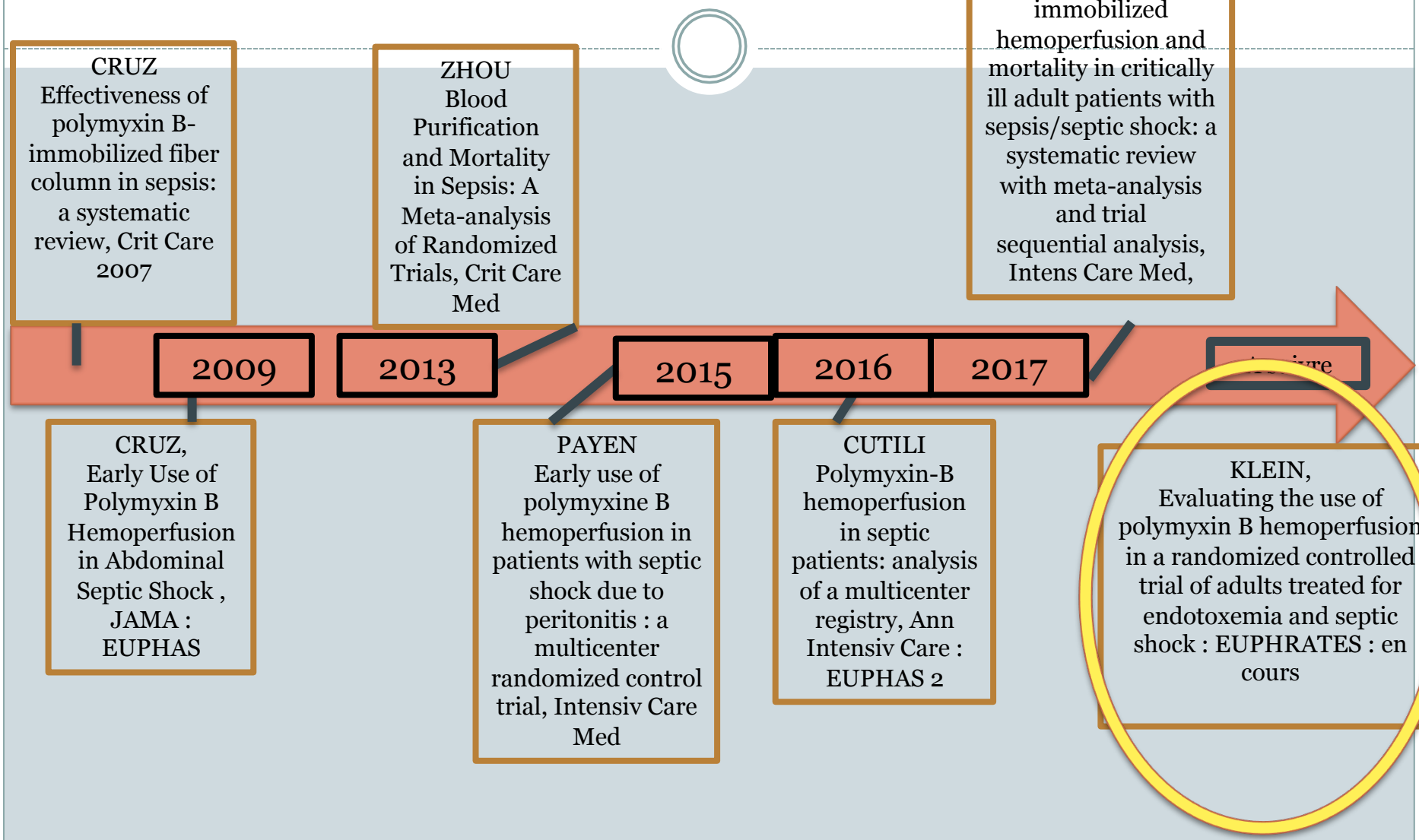
	Studies	Study reference no.	PMX-HP	Standard	Effect estimate (95% CI)	I^2 (%)
Primary outcomes						
28-day mortality	5[a]	14, 15, 17, 18, 31	135/402	124/395	Pooled RR, 1.03 (0.78, 1.36)	25
Number of patients with at least one serious adverse event	3[a]	14, 17, 18	8/360	3/357	Pooled RR, 2.17 (0.68, 6.94)	0
Change in organ dysfunction scores over 24–72 h after treatment	5[a]	14, 15, 17, 18, 31			SMD, − 0.26 (− 0.64, 0.12)	78
Secondary outcomes						
90-day all-cause mortality	1	17	40/119	27/113	RR, 1.41 (0.93, 2.13)	NA
Change in mean arterial blood pressure over 24–72 h after the treatment	4[a]	14, 15, 18, 31			MD, 5.23 (2.75, 7.72)	0
Endotoxin levels measured by LAL assay over 24–72 h after the treatment	3[a]	14, 31, 32			MD, − 40.77 (− 118.53, 36.99)	96
28-day vasopressor-free days	3[a]	14, 17, 31			MD, − 1.10 (− 4.05, 1.85)	10
ICU length of stay	4[a]	14, 15, 17, 31			MD, − 1.95 (− 7.91, 4.00)	70
The need for RRT	4[a]	14, 15, 18, 31			Pooled RR, 0.76 (0.33, 1.71)	61
Mortality at 28 days or any follow-up duration	6[a]	14, 15, 17, 18, 31, 32	144/436	140/420	Pooled RR, 0.85 (0.58, 1.26)	64

CI Confidence interval, *RR* risk ratio, *NA* not available, *SMD* standardized mean difference, *MD* mean difference, *ICU* intensive care unit

[a] Includes data provided from the study authors

Conclusions: There is currently insufficient evidence to support the routine use of PMX-HP to treat patients with sepsis or septic shock.

Etudes cliniques



STUDY PROTOCOL Open Access

The EUPHRATES trial (Evaluating the Use of Polymyxin B Hemoperfusion in a Randomized controlled trial of Adults Treated for Endotoxemia and Septic shock): study protocol for a randomized controlled trial

David J Klein[1*], Debra Foster[2], Christa A Schorr[3], Kazem Kazempour[4], Paul M Walker[2] and R Phillip Dellinger[3]

Inclusion criteria

Subjects who meet the following criteria (and have a signed informed consent) will be allowed into the study:

1. Age ≥18 years of age

2. Hypotension requiring vasopressor support: Requirement for at least one of the vasopressors listed below, at the dose shown below, for at least 2 continuous hours and no more than 30 hours

a. Norepinephrine >0.05 µg/kg/minute

b. Dopamine >10 µg/kg/minute

c. Phenylephrine >0.4 µg/kg/minute

d. Epinephrine >0.05 µg/kg/minute

e. Vasopressin >0.03 units/minute

f. Vasopressin (any dose) in combination with another vasopressor listed above

3. The subject must have received intravenous fluid resuscitation of a minimum 30 mL/kg administered within 24 hours of eligibility

4. Documented or suspected infection defined as definitive or empiric intravenous antibiotic administration

5. Endotoxin activity assay ≥0.60

6. Evidence of at least one of the following criteria for new onset organ dysfunction that is considered to be due to the acute illness

a. Requirement for positive pressure ventilation via an endotracheal tube or tracheostomy tube

b. Thrombocytopenia defined as acute onset of platelet count <150,000 µ/L or a reduction of 50% from prior known levels

c. Acute oliguria defined as urine output <0.5 ml/kg/hour for at least 6 hours despite adequate fluid resuscitation

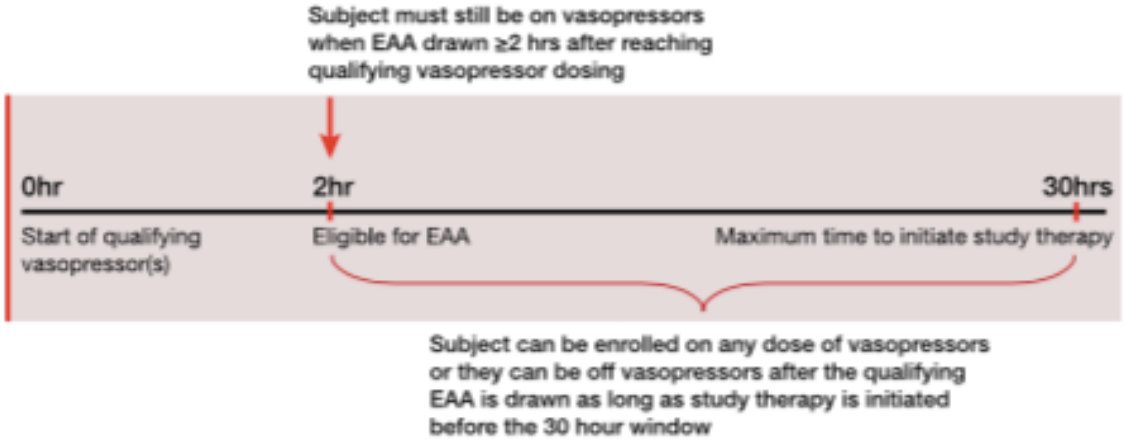


Figure 2 Timing for patient identification and enrollment. EAA, endotoxin activity assay.

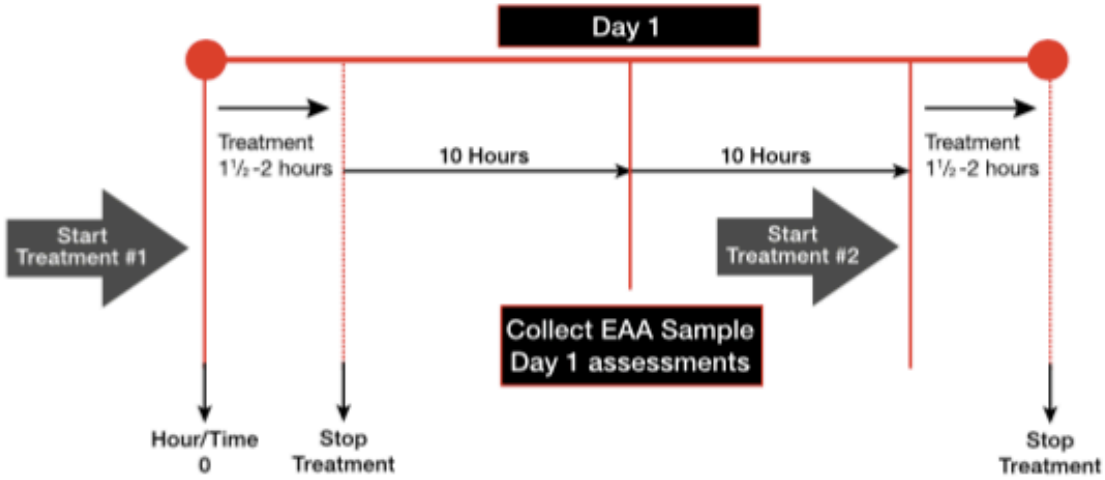


Figure 3 Timeline for initiation of intervention. EAA, endotoxin activity assay.

Etude complète, pas de résultats publiés…

To be continued…

Conclusion

Ronco and Klein *Critical Care* 2014, 18:309
http://ccforum.com/content/18/3/309

CRITICAL CARE

VIEWPOINT

Polymyxin B hemoperfusion: a mechanistic perspective

Conclusion

PMX-DHP is a well-tolerated and safe treatment for septic shock with a long history of clinical experience and both clinical and basic science data to support efficacy in endotoxemia. Its principle mechanism of action is through the removal of circulating endotoxin, although its effects are likely pleiotropic. In an era of numerous failed clinical trials in sepsis, it is easy to be cynical. However, this personalized, targeted approach to a

disease with unacceptable mortality, with a treatment with a long history of clinical use and strong supporte around the globe truly may represent a step forwa improving patient care.

K. BLOOD PURIFICATION

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

MERCI POUR VOTRE ATTENTION