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Service
de médecine
intensive adulte

Extracorporeal Treatment in Sepsis and the Place of CRRT

PD MER Antoine G. Schneider MD, PhD

Tabriz, Iran, 20.11.2019

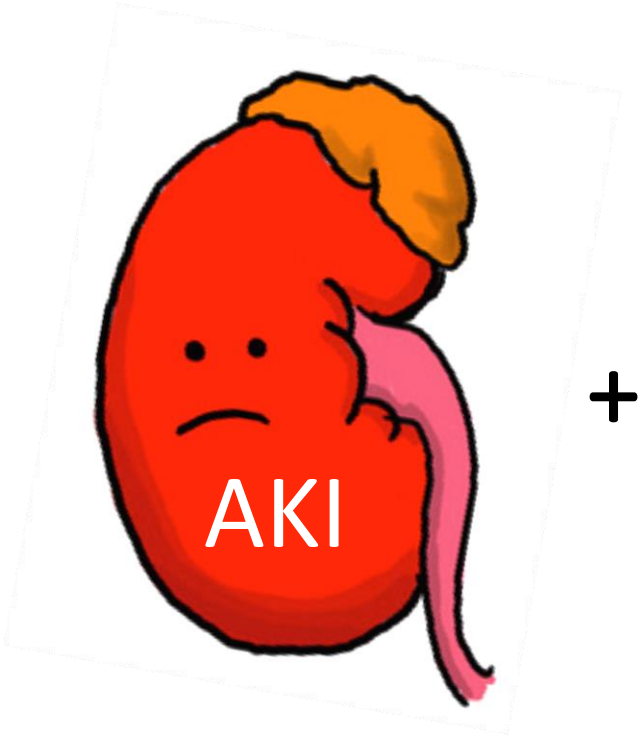
Disclosures

- Salary support by Canton de Vaud
- Grant support from the Leenaards Foundation, Switzerland
- Speaking / Consulting / Travel support from
  - Fresenius Medical Care
  - B. Braun Melsungen AG
  - Cytosorbents

REVIEW

Acute kidney injury in sepsis

Rinaldo Bellomo[1,2*], John A. Kellum[3], Claudio Ronco[4,5], Ron Wald[6,7], Johan Martensson[8], Matthew Maiden[9,10], Sean M. Bagshaw[11], Neil J. Glassford[12,13], Yugeesh Lankadeva[14], Suvi T. Vaara[15] and Antoine Schneider[16]



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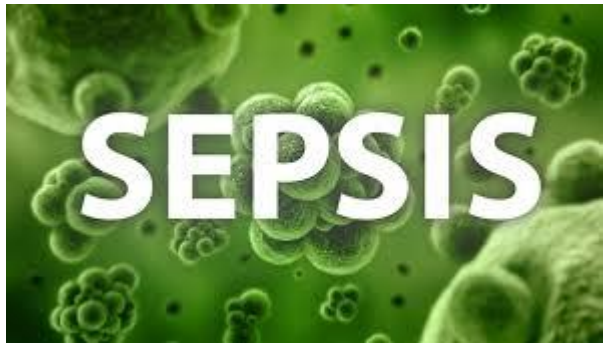

- Common
- Associated with ↑mortality
- Important issue in ICU

Intensive Care Medicine 2017

and when it is too severe…

Renal Replacement Therapy in Septic AKI:

When to Start?

What Modality?

What Dose?

Associated Therapies?

Renal Replacement Therapy in Septic AKI:

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Criteria for RRT Initiation

5.1.1: **Initiate RRT emergently when life-threatening changes in fluid, electrolyte, and acid-base balance exist. (*Not Graded*)**

5.1.2: **Consider the broader clinical context, the presence of conditions that can be modified with RRT, and trends of laboratory tests—rather than single BUN and creatinine thresholds alone—when making the decision to start RRT. (*Not Graded*)**

KDIGO Kidney International 2012: 2 (1)

No clear consensus regarding clinical criteria

“Early” RRT

Pros:

- Facilitates fluid balance control
- Improves acid-base status
- Corrects electrolytes abnormalities
- Early removal of kidney removed toxins?
- Removal of cytokines in early phases of sepsis?

Cons:

- Potential removal of salutary substances (antibiotics)
- Potential harm (catheter, hypotension, other complications)
- Higher cost

Effect of Early vs Delayed Initiation of Renal Replacement Therapy on Mortality in Critically Ill Patients With Acute Kidney Injury
The ELAIN Randomized Clinical Trial

ORIGINAL ARTICLE

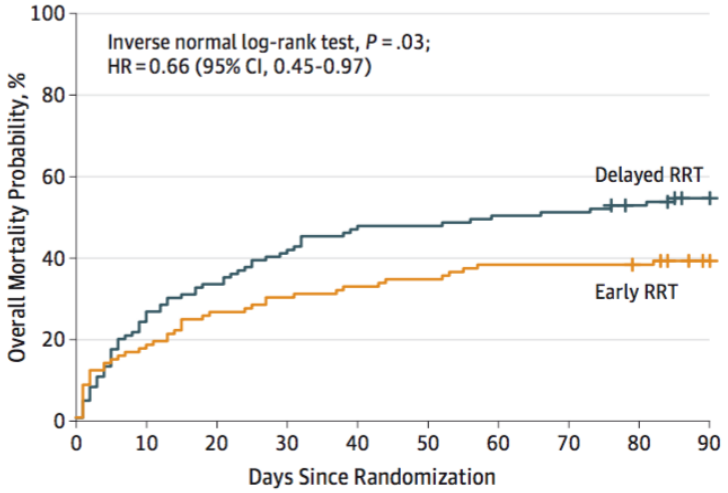
Initiation Strategies for Renal-Replacement Therapy in the Intensive Care Unit

ORIGINAL ARTICLE

Timing of Renal-Replacement Therapy in Patients with Acute Kidney Injury and Sepsis

	ELAIN	AKIKI	IDEAL ICU
Nb of centers	1 (Germany)	31 (France)	29 (France)
Number of patients	231	620	488
Main inclusion criteria	KDIGO Stage 2 ↑NGAL + sepsis, pressors, FO or ↑SOFA	KDIGO stage 3 + MV and/or pressors	RIFLE F + early septic shock
Definition of Early	8 hr of KDIGO St. 2	6 hr of KDIGO St. 3	12 hr of RIFLE F
Definition of Late	12 hr of KDIGO St. 3	AKI complications	Emergency indication
	Zarbock et al JAMA 2016	Gaudry et al NEJM 2016	Barbar et al NEJM 2018

Effect of Early vs Delayed Initiation of Renal Replacement Therapy on Mortality in Critically Ill Patients With Acute Kidney Injury
The ELAIN Randomized Clinical Trial



Zarbock et al JAMA 2016

Interpretation

Altogether the burden of evidence seems to point toward the absence of benefit for early RRT initiation

However:

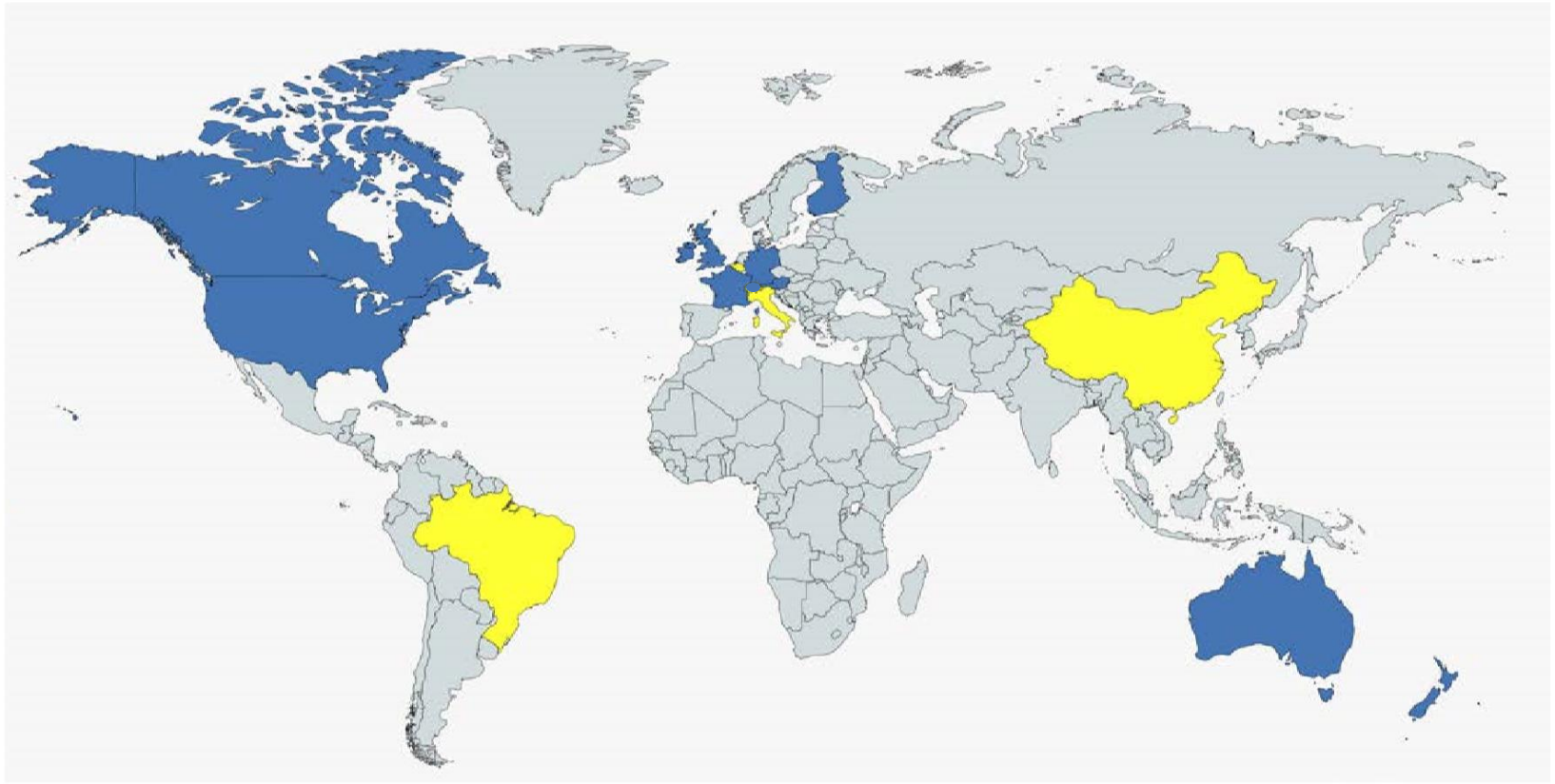
- This trial have not REALLY assessed RRT initiation timing (>50% of patients never received the therapy in AKIKI and IDEAL-ICU)

They demonstrate that:

- KDIGO criteria are not good predictors of the need for RRT
- *Early initiation based on KDIGO criteria* is not associated with a mortality benefit

We need better biomarkers predicting the need for RRT and… more trials

STARRT AKI



Enrollment for August 9th, 2019

Enrollment to date: 3000

Total target enrollment: 3000

Percentage of target recruitment: 100%

Current enrollment by country:

- Australia: 401
- Austria: 53
- Belgium: 46
- Brazil: 8
- Canada: 885
- China: 255
- Finland: 53
- France: 761
- Germany: 29
- Ireland: 3
- Italy: 4
- New Zealand: 165
- Switzerland: 40
- United Kingdom: 171
- United States: 126

So, When to Start RRT?

- Current evidence inconclusive, and both approaches can be accepted.
- Later initiation associated with lower short term costs…
- (many) new data coming… stay tuned

Renal Replacement Therapy in Septic AKI:

When to Start?

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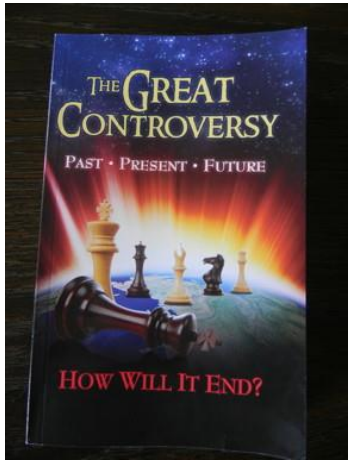
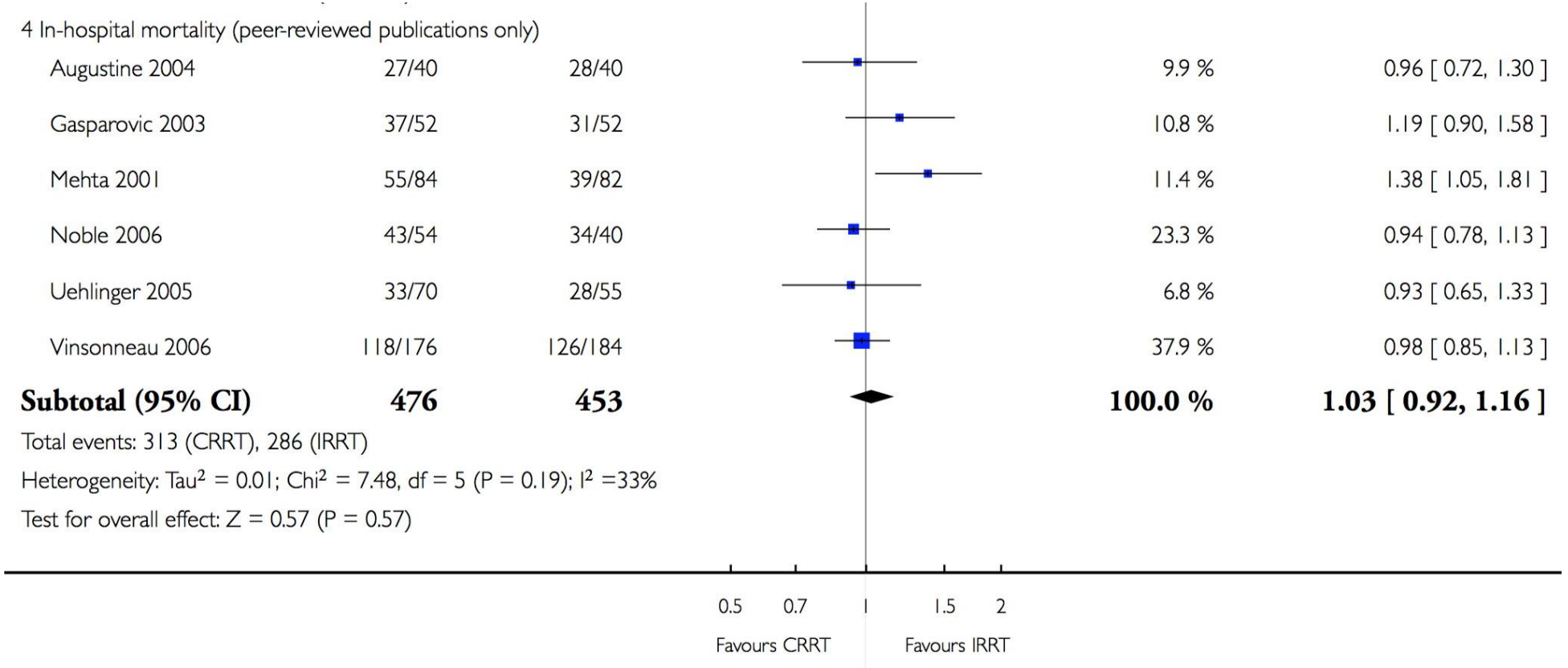
Associated Therapies?



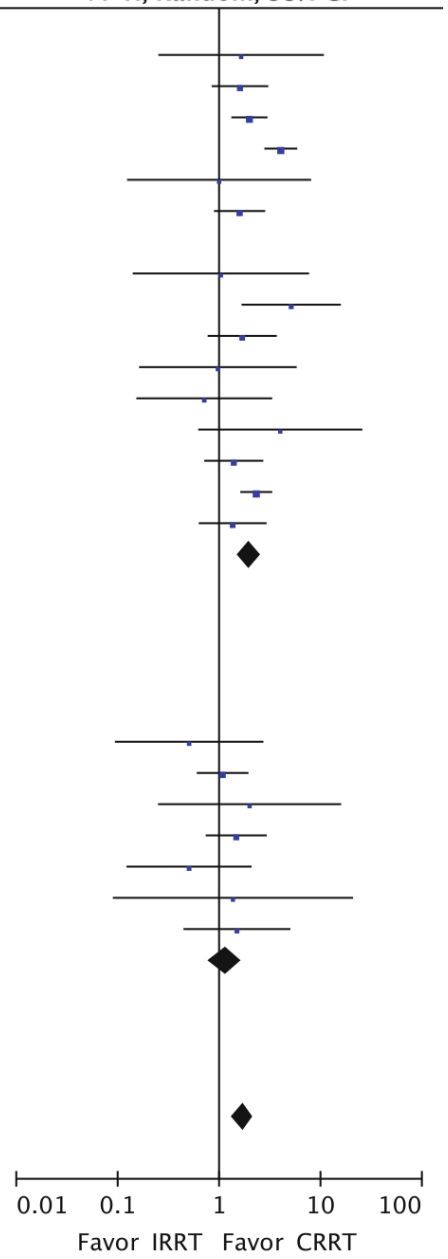
CRRT vs IRRT: Mortality



Rabindranath Cochrane Database Syst Rev 2007 Issue 3

Renal Recovery

Study or Subgroup	IRRT Events	IRRT Total	CRRT Events	CRRT Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Observational						
Andrikos 2009	1	4	5	33	1.5%	1.65 [0.25, 10.81]
Bagshaw 2006	15	42	12	54	7.0%	1.61 [0.84, 3.06]
Bell 2007	26	158	78	944	9.8%	1.99 [1.32, 3.00]
CartinCeba 2009	256	555	26	229	10.3%	4.06 [2.80, 5.90]
Chang 2004	4	44	1	11	1.3%	1.00 [0.12, 8.08]
Elsevier 2010	37	175	13	98	7.7%	1.59 [0.89, 2.85]
Garcia-Fernandes 2011	0	16	0	55		Not estimable
Gonwa 2001	1	6	4	25	1.4%	1.04 [0.14, 7.71]
Jacka 2005	9	14	3	24	3.5%	5.14 [1.66, 15.89]
Lin 2009	11	54	10	83	5.7%	1.69 [0.77, 3.71]
Lins 2006	9	37	1	4	1.6%	0.97 [0.16, 5.83]
Marshall 2012	5	56	2	16	2.1%	0.71 [0.15, 3.34]
Park 2005	37	83	1	9	1.5%	4.01 [0.62, 25.86]
Swartz 2005	24	110	10	64	6.7%	1.40 [0.71, 2.73]
Uchino 2007	37	110	52	360	10.5%	2.33 [1.62, 3.35]
Waldrop 2005	7	12	6	14	5.8%	1.36 [0.63, 2.94]
Subtotal (95% CI)		**1476**		**2023**	**76.4%**	**1.99 [1.53, 2.59]**
Total events	479		224			
Heterogeneity: $Tau^2 = 0.09$; $Chi^2 = 24.14$, df = 14 (P = 0.04); $I^2 = 42\%$						
Test for overall effect: Z = 5.14 (P < 0.00001)						
1.1.2 RCT						
Abe 2010	2	25	3	19	1.8%	0.51 [0.09, 2.74]
Augustine 2004	8	12	8	13	7.6%	1.08 [0.60, 1.95]
Kumar 2004	3	12	1	8	1.3%	2.00 [0.25, 15.99]
Lins 2009	15	60	11	65	6.5%	1.48 [0.74, 2.96]
Mehta 2001	3	43	4	29	2.4%	0.51 [0.12, 2.09]
Uehlinger 2005	1	27	1	37	0.8%	1.37 [0.09, 20.95]
Vinsonneau 2006	6	61	4	61	3.1%	1.50 [0.45, 5.05]
Subtotal (95% CI)		**240**		**232**	**23.6%**	**1.15 [0.78, 1.68]**
Total events	38		32			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.20$, df = 6 (P = 0.78); $I^2 = 0\%$						
Test for overall effect: Z = 0.71 (P = 0.48)						
Total (95% CI)		**1716**		**2255**	**100.0%**	**1.73 [1.35, 2.20]**
Total events	517		256			
Heterogeneity: $Tau^2 = 0.12$; $Chi^2 = 37.19$, df = 21 (P = 0.02); $I^2 = 44\%$						
Test for overall effect: Z = 4.36 (P < 0.0001)						
Test for subgroup differences: $Chi^2 = 5.45$, df = 1 (P = 0.02), $I^2 = 81.7\%$						



Schneider et al ICM 2013

Intradialytic complications during hemodialysis

Andrew DAVENPORT
University College London Centre for Nephrology, Royal Free Hospital, London, UK

Hypotension is the most common intradialytic problem encountered in routine clinical practice.[1] Its incidence has been reported from <5% to 40% of all treatments. In

Intensity of Renal Support in Critically Ill Patients with Acute Kidney Injury

The VA/NIH Acute Renal Failure Trial Network*

Event	Intensive Strategy (N=563)	Less-Intensive Strategy (N=561)	P Value
	no. of patients (%)		
Any serious adverse event†	287 (51.0)	280 (49.9)	0.72
Not related to study therapy	207 (72.1)	202 (72.1)	
Possibly or probably related to study therapy	48 (16.7)	51 (18.2)	
Definitely related to study therapy	32 (11.1)	27 (9.6)	
Nonfatal only‡	137 (47.7)	128 (45.7)	
Catheter-related complications			
Insertion-related complications	28 (5.0)	31 (5.5)	0.68
Late catheter-related complications	48 (8.5)	38 (6.8)	0.27
Hypotension			
Requiring vasopressor support	81 (14.4)	56 (10.0)	0.02
Requiring discontinuation of treatment	55 (9.8)	49 (8.7)	0.55
Requiring other intervention	212 (37.7)	168 (29.9)	0.006
Other treatment-related complications			
Any nonhypotensive complication	216 (38.4)	194 (34.6)	0.19

Intermittent vs Continuous?

Unstable Septic Patients

IRRT

CRRT

CRRT vs IRRT

CRRT

easier to use

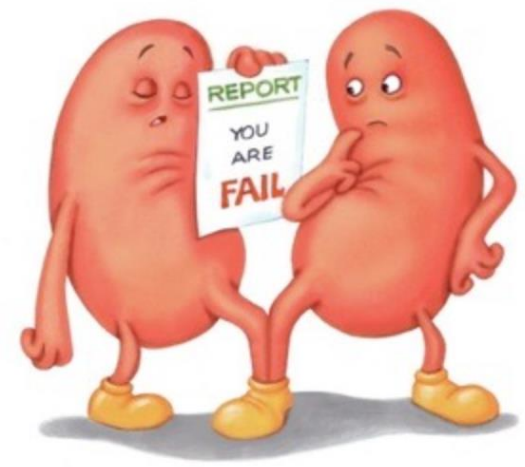
less hypotensive episodes

better renal recovery

lower costs (accounting for long term costs)

Outside specific indications IRRT should probably not be used in septic AKI

Renal Replacement Therapy in Septic AKI:

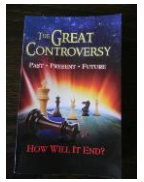


When to Start?

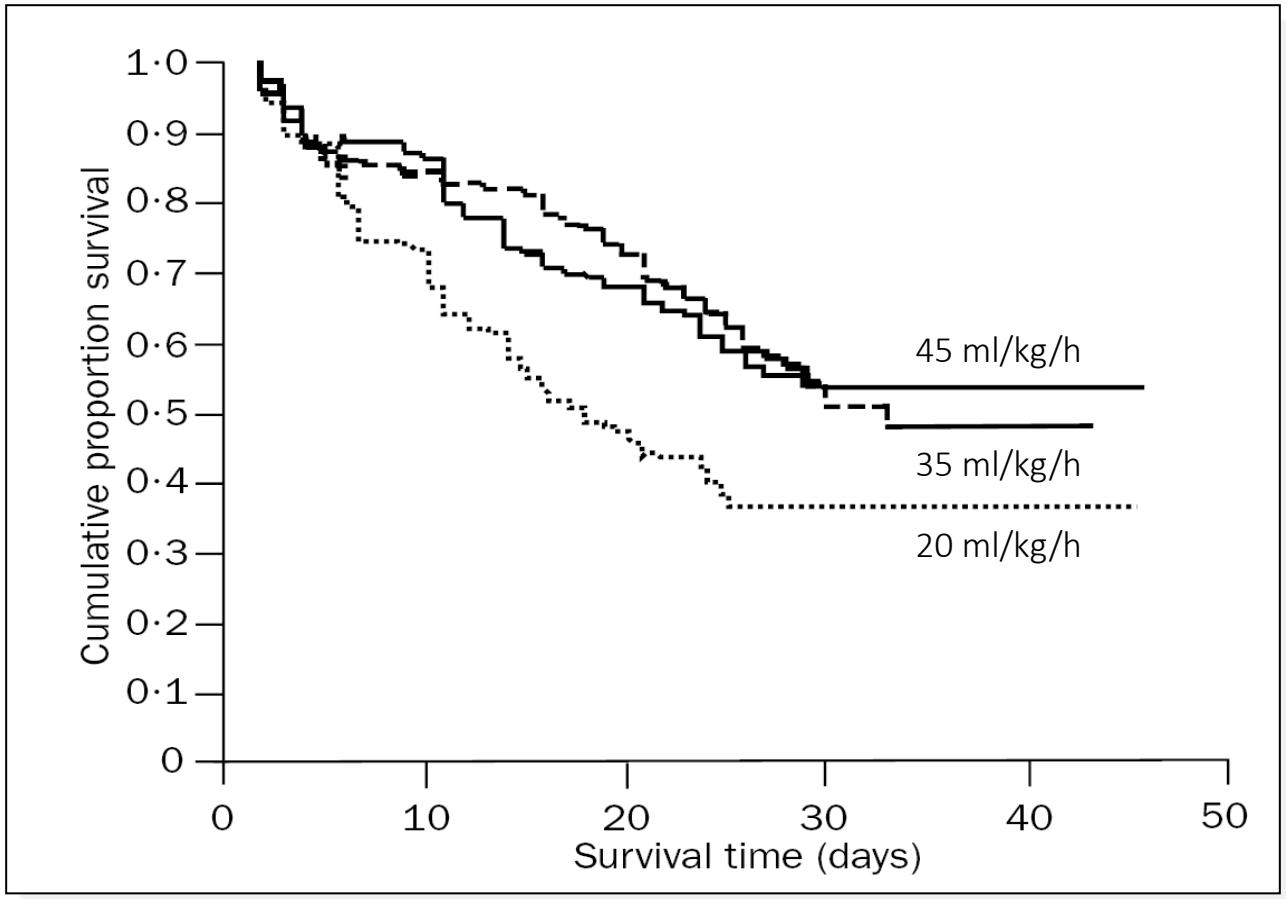
What Modality?

What Dose?

Associated Therapies?



RRT Dose



RRT Dose

=

Effluent Volume

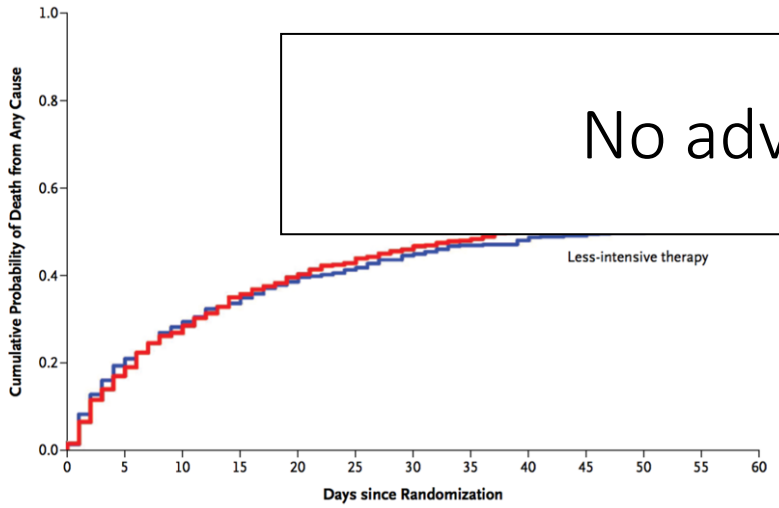
Ronco Lancet 2000

Two Large RRT RCTs

The NEW ENGLAND JOURNAL of MEDICINE

Intensity of Renal Support in Critically Ill Patients with Acute Kidney Injury

The VA/NIH Acute Renal Failure Trial Network*

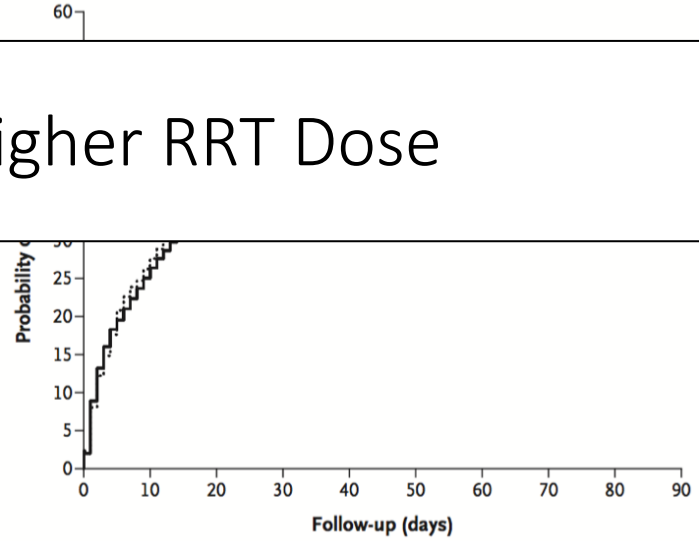


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 22, 2009 VOL. 361 NO. 17

Intensity of Continuous Renal-Replacement Therapy in Critically Ill Patients

The RENAL Replacement Therapy Study Investigators*



No advantage for higher RRT Dose

Palevsky NEJM 2008;359(1):7-20

Bellomo NEJM 2009; 361(17):1627-1638

Practical Approach

- TARGET: 20-25 ml/kg/h of delivered effluent flow
- However, we need to compensate for DOWNTIME
  - Alarms
  - Radiology examinations (CT MR…)
  - Circuit clotting
  - Surgery

Might represent 3 to 8 hrs per day: 25% of the time

Prescribe: 25 to 30 ml/kg/h

Renal Replacement Therapy in Septic AKI:

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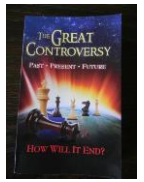
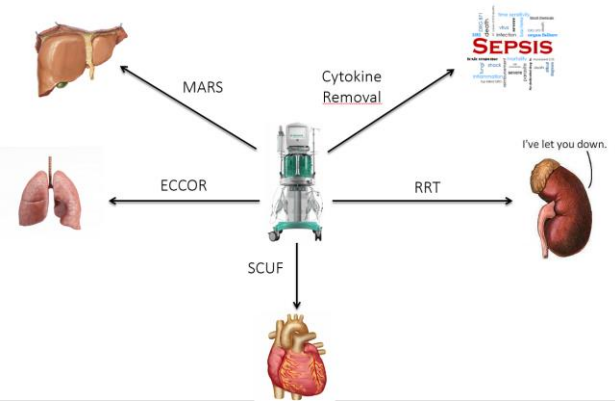
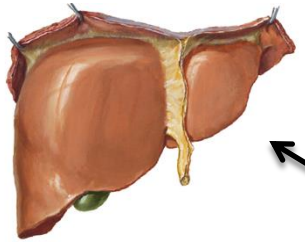




Beyond Renal Replacement Therapy…

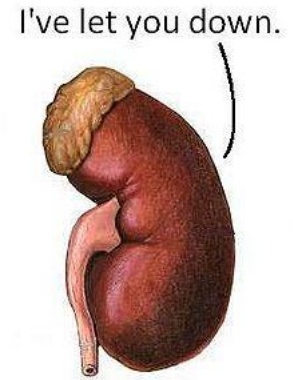


MARS

Cytokine Removal

ECCOR

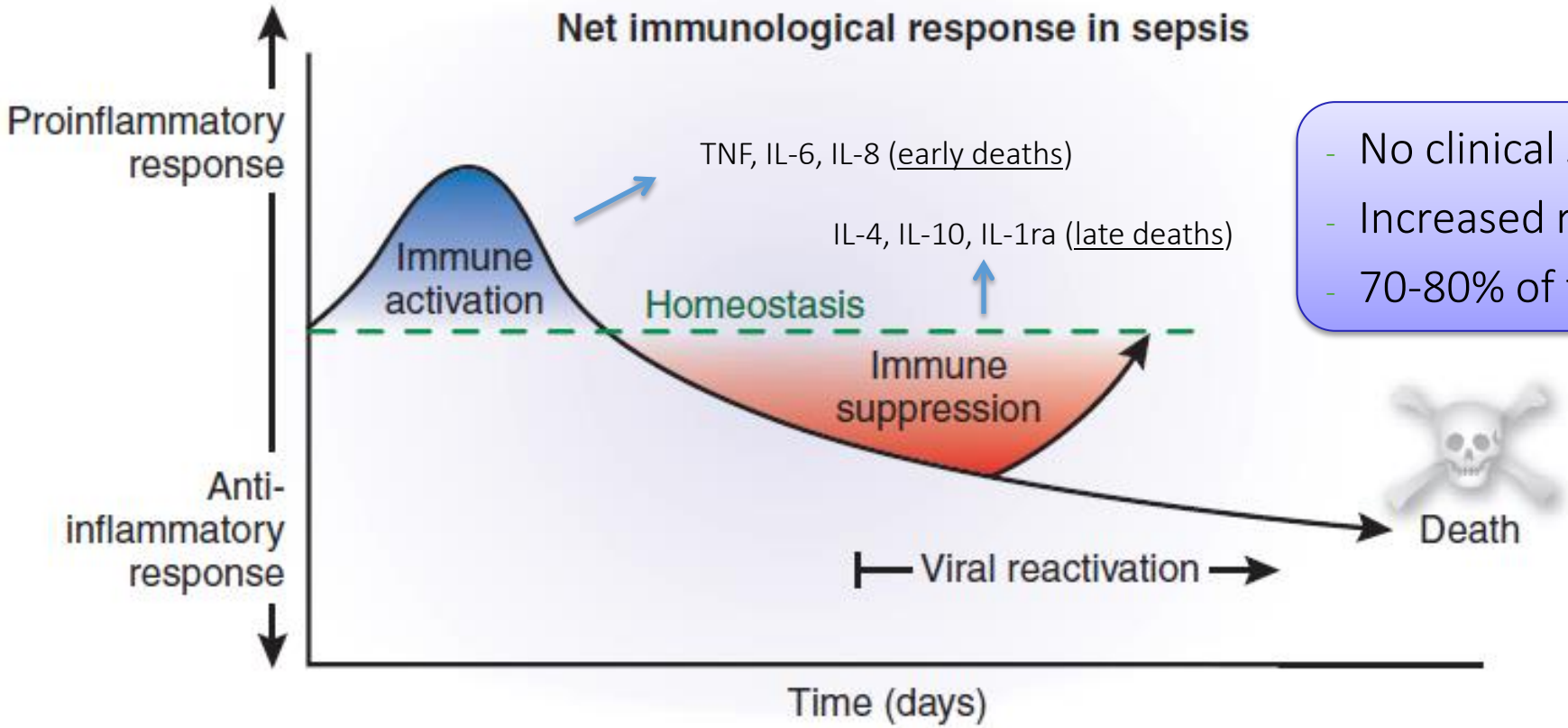
RRT



SCUF

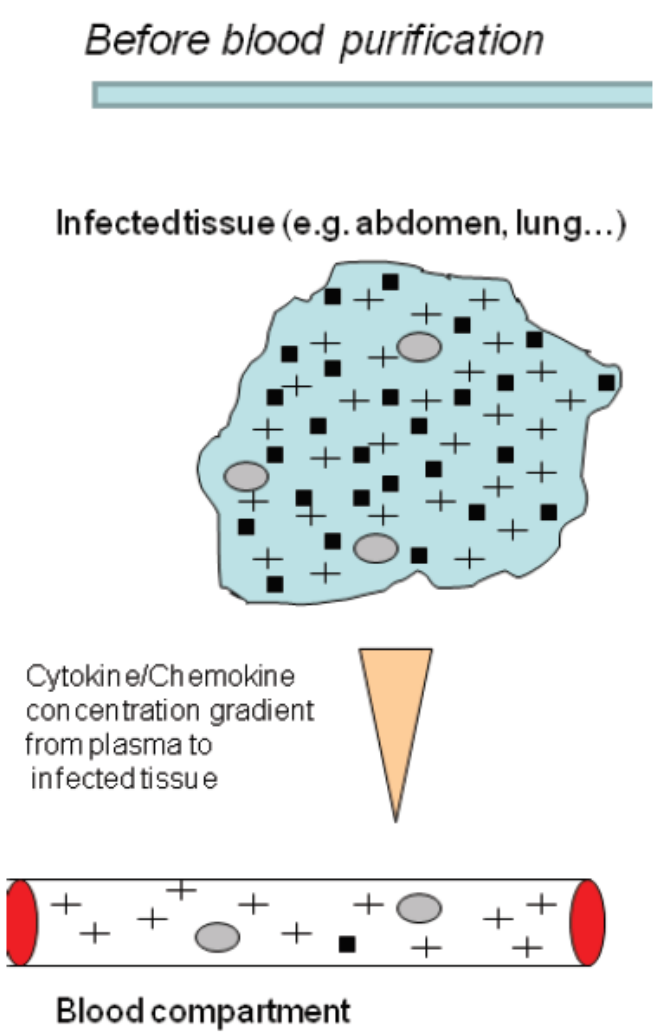
Multiple Organ Support

Sepsis: a Dysregulated Host Response to Infection



- No clinical signs
- Increased risk of HAI
- 70-80% of total mortality

Singer et al. JAMA 2016;315(8):801-810.
Hotchkiss et al. *Nat Med* 2009;15(5):496-497.



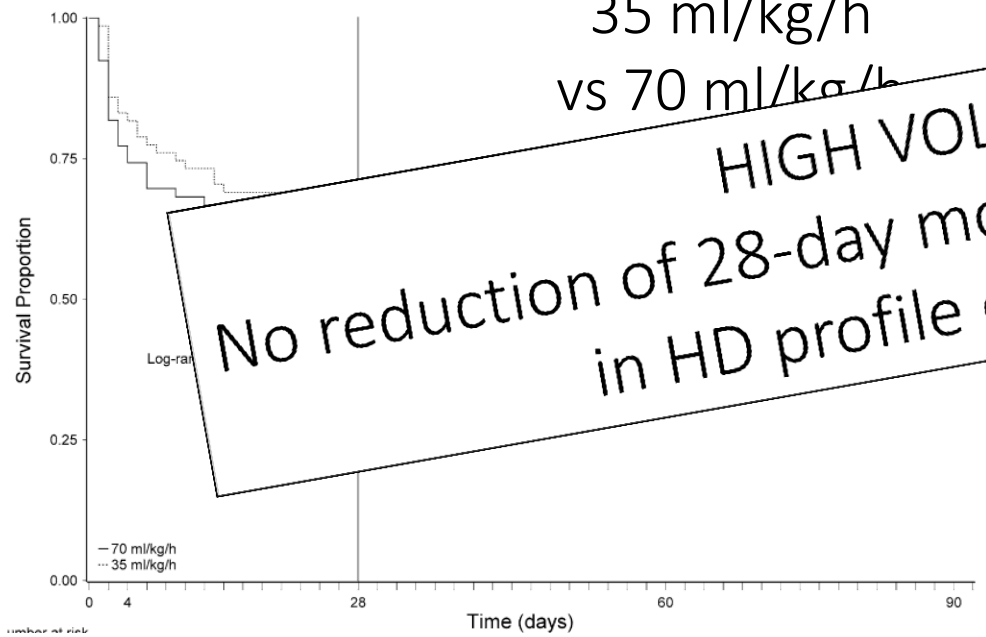
Rimmele T. Kellum J. Critical Care 2011,15:205

Intensive Care Med (2013) 39:1535–1546
DOI 10.1007/s00134-013-2967-z

ORIGINAL

Olivier Joannes-Boyau
Patrick M. Honoré
Paul Perez
Sean M. Bagshaw
Hubert Grand
Jean-Luc Canivet
Antoine Dewitte
Claire Flamens
Wilfried Pujol
Anne-Sophie Grandoulier
Catherine Fleureau
Rita Jacobs
Christophe Broux
Hervé Floch
Olivier Branchard
Stephane Franck
Hadrien Rozé
Vincent Collin
Willem Boer
Joachim Calderon
Bernard Gauche
Herbert D. Spapen
Gérard Janvier
Alexandre Ouattara

High-volume versus standard-volume haemofiltration for septic shock patients with acute kidney injury (IVOIRE study): a multicentre randomized controlled trial



35 ml/kg/h
vs 70 ml/kg/h

HIGH VOLUME CVVH
No reduction of 28-day mortality or early improvement in HD profile or organ function

B and NL)
ial of high volume HF
ry low feasibility (technical difficulties)

- Very high work load for nursing staff

Joannes-Boyau et al ICM 2013

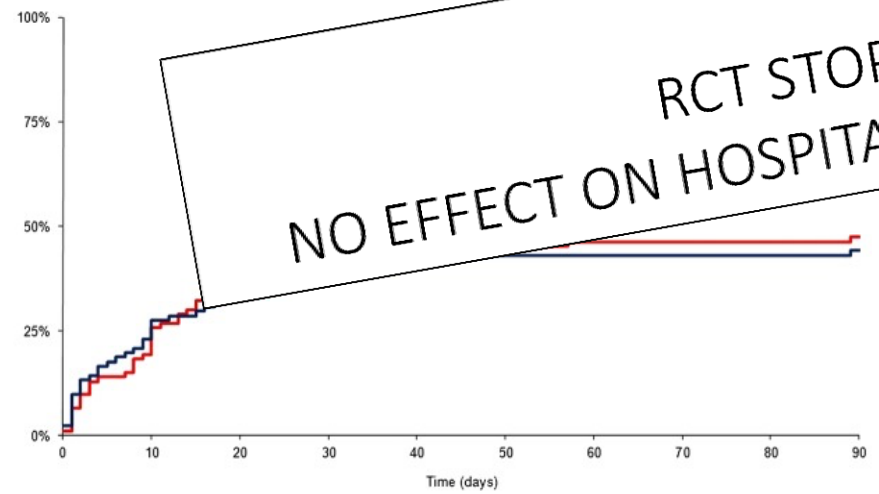
Efficacy of coupled plasma filtration adsorption (CPFA) in patients with septic shock: A multicenter randomised controlled clinical trial

Sergio Livigni,[1] Guido Bertolini,[2] Carlotta Rossi,[2] Fiorenza Ferrari,[1] Michele Giardino,[2] Marco Pozzato,[3] Giuseppe Remuzzi,[2] GiViTI: Gruppo Italiano per la Valutazione degli Interventi in Terapia Intensiva (Italian Group for the Evaluation of Interventions in Intensive Care Medicine) is an independent collaboration network of Italian Intensive Care units

CPFA

RCT STOPPED EARLY FOR FUTILITY

NO EFFECT ON HOSPITAL MORTALITY OR NEW ORGAN FAILURES



- terminated for futility)
- (min 10hrs) for 5 days vs standard of care
- No difference in hospital mortality (primary), new organ failures or free-ICU days during the first 30 days
- Lower mortality in patients who received "full" CPFA dose >0.18 L/kg/d (OR 0.36, 95% CI 0.13 to 0.99)

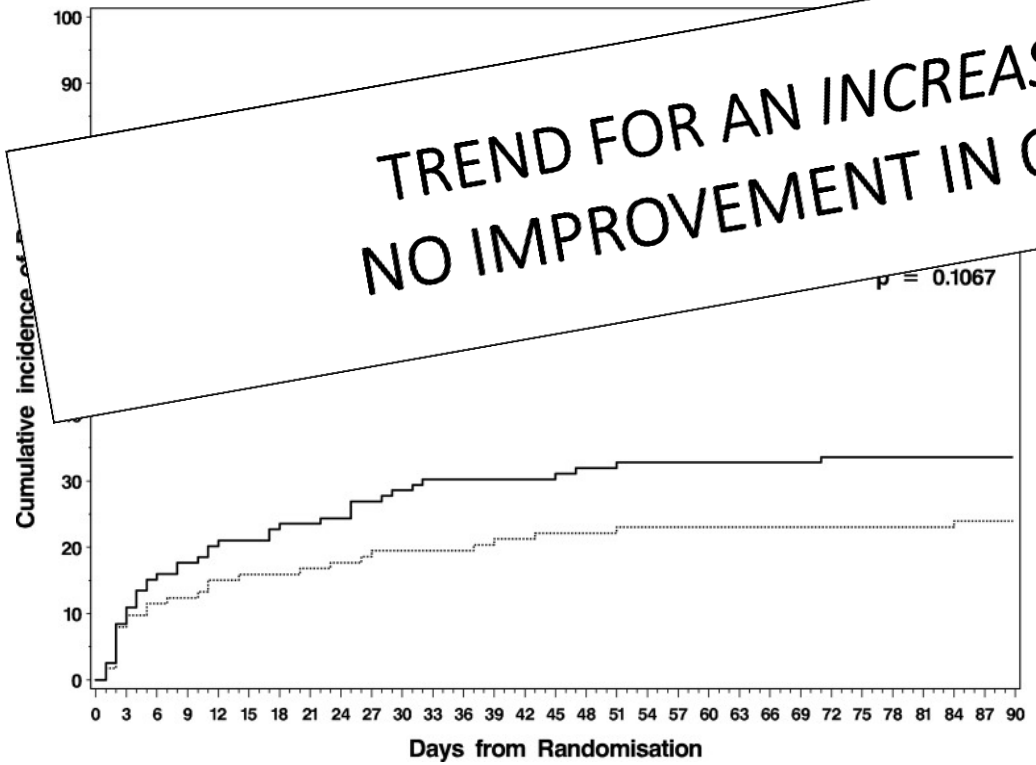
Livigny et al BMJ Open 2014;4:e003536

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
Benoit Veber
Julien Pottecher
Olivier Joannes-Boyau
Laurent Martin-Lefevre
Matthieu Jabaudon
Olivier Mimoz
Rémi Coudroy
Martine Ferrandière
Eric Kipnis
Carlos Vela
Stéphanie Chevallier
Jihad Mallat
René Robert
The ABDOMIX Group

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

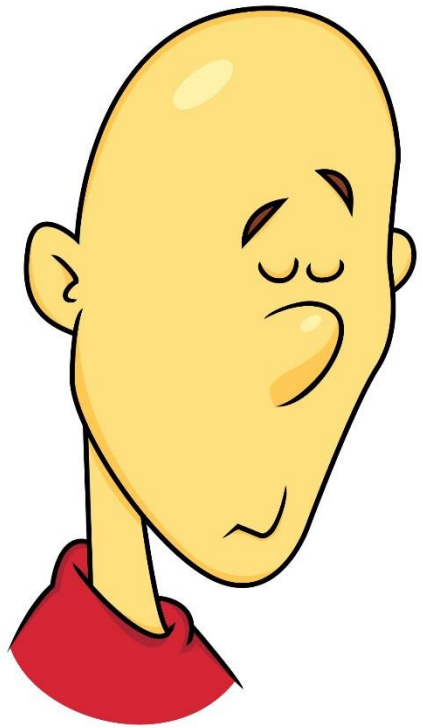


TREND FOR AN *INCREASED* MORTALITY
NO IMPROVEMENT IN ORGAN FAILURES

- RCT PMX HP (2 sessions) vsh conventional Tx
- 243 septic shock Pts within 12 hrs of emergency surgery for peritonitis related to organ perforation

Livigny et al BMJ Open 2014;4:e003536

Should we just Forget about it?



CONFERENCE REPORTS AND EXPERT PANEL

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

K. BLOOD PURIFICATION

1. 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.

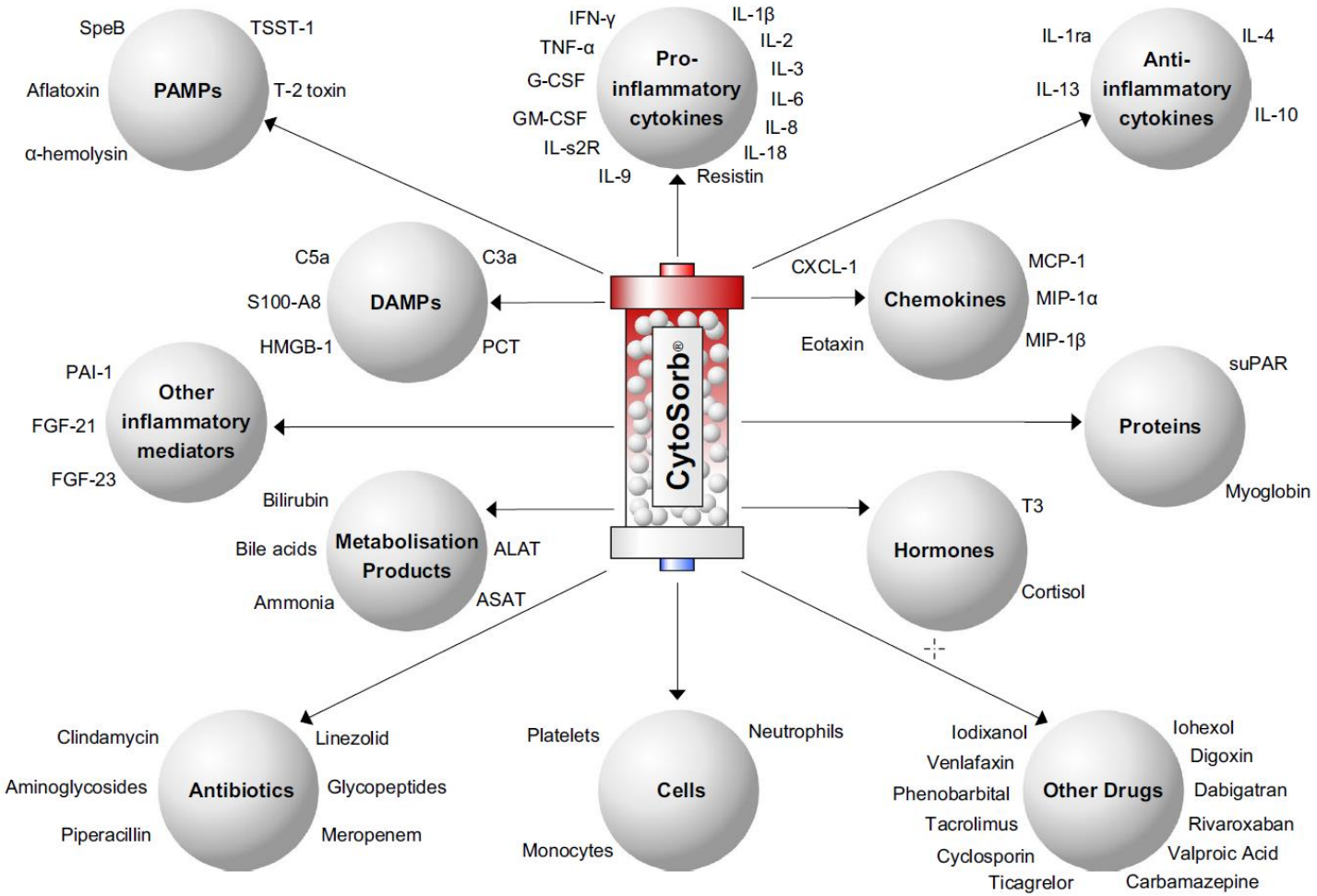
Rhodes et al. *Intensive Care Med* 2017;43:304-377.

Hemoadsorption Devices

Device	Company	Composition	Substance Removed
PMX	Toray, Japan	PMX covalently bound to polypropylene-polystyrene fiber	Endotoxin
HA330	Jafron, China	Neutral resin	Cytokines
MG350	Biosun, China	Neutral resin	Cytokines
Cytosorb	Cytosorbents, USA	Polystyrenedivinyl benzene copolymer beads with biocompatible polyvinylpyrrolidone coating	Cytokines
LPS adsorber	Alteco, Sweden	Synthetic polypeptide bound to porous polyethylene discs	Endotoxin

Hemoadsorption with CytoSorb®

Elettra C. Poli[1], Thomas Rimmelé[2,3] and Antoine G. Schneider[1*]



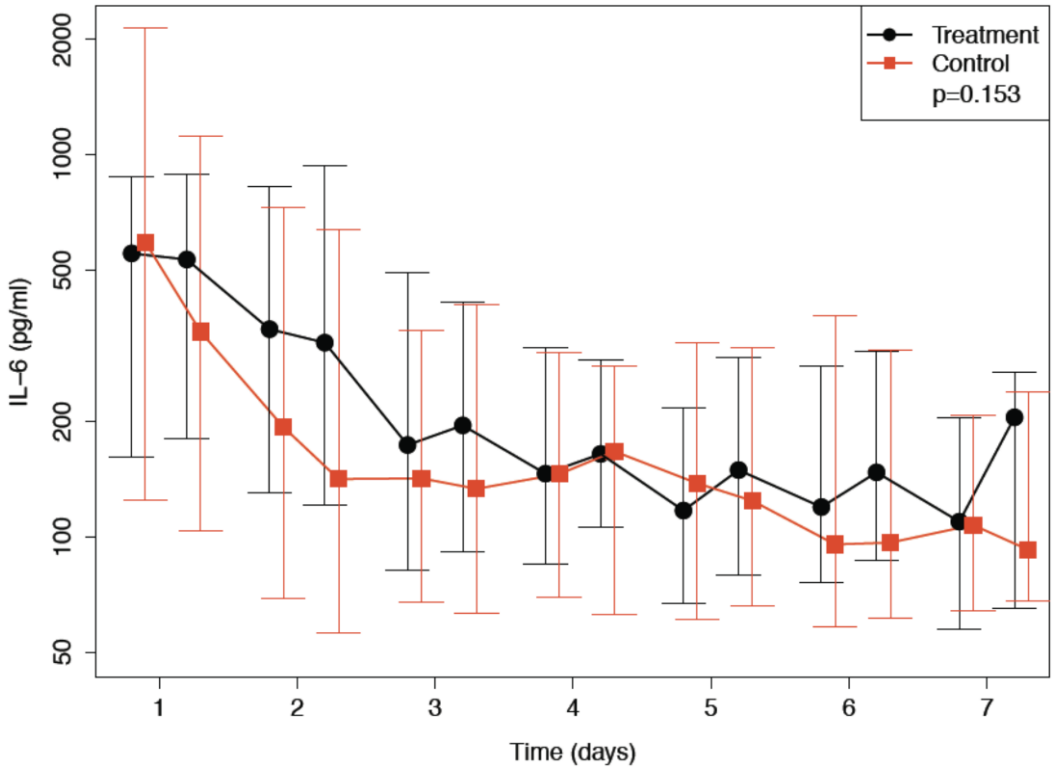
Poli et al Intensive Care Medicine 2018

PLOS ONE

RESEARCH ARTICLE

The effect of a novel extracorporeal cytokine hemoadsorption device on IL-6 elimination in septic patients: A randomized controlled trial

Dirk Schädler[1☯*], Christine Pausch[2☯], Daniel Heise[3], Andreas Meier-Hellmann[4], Jörg Brederlau[5], Norbert Weiler[1], Gernot Marx[6], Christian Putensen[7], Claudia Spies[8], Achim Jörres[9], Michael Quintel[3], Christoph Engel[2], John A. Kellum[10], Martin K. Kuhlmann[11]



- 100 Mechanically ventilated patients with severe sepsis or septic shock and ALI
- Randomized controlled Trial
- Cytosorb for 6hrs per day up to 7 days
- Primary Outcome IL-6 serum concentrations
- No difference in secondary outcomes multiple organ dysfunction score, ventilation time and time course of oxygenation

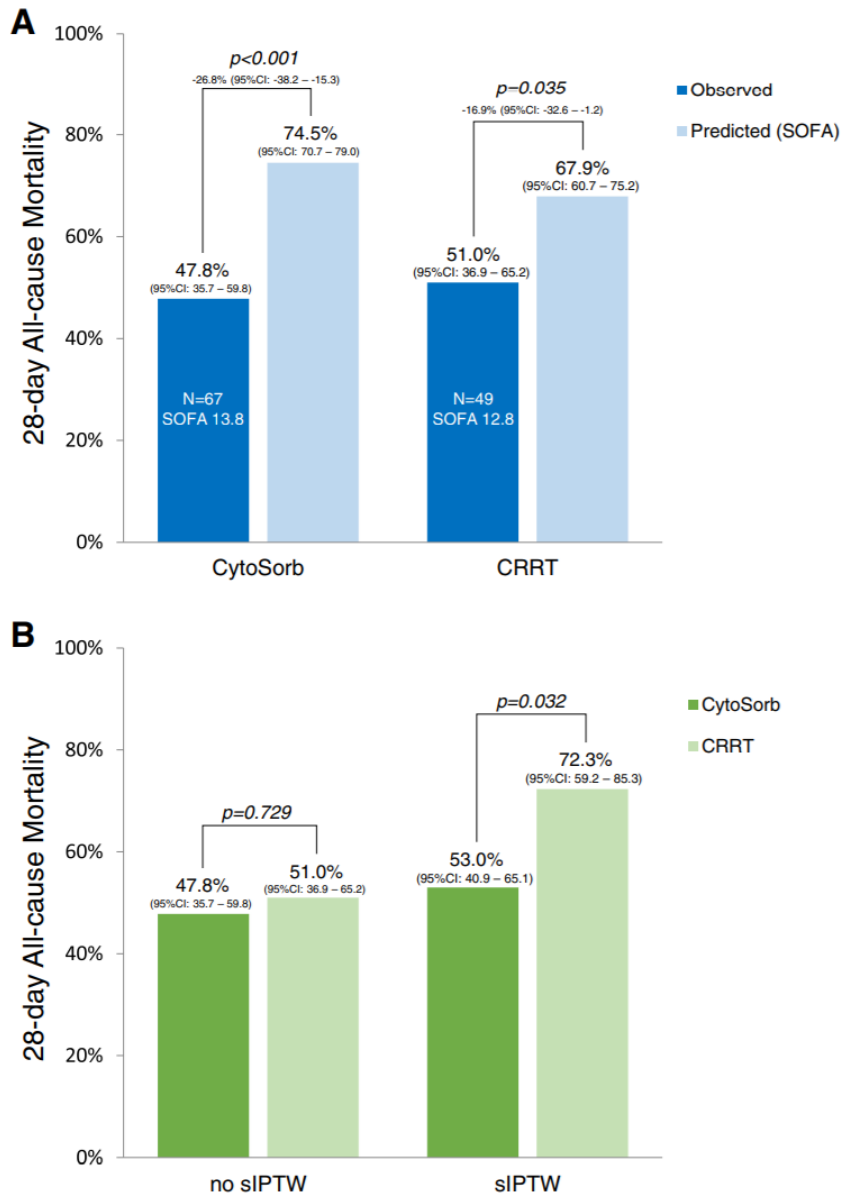
Schädler et al PLOS One 2017 Oct 30;12(10:

RESEARCH Open Access

Hemoadsorption with CytoSorb shows a decreased observed versus expected 28-day all-cause mortality in ICU patients with septic shock: a propensity-score-weighted retrospective study

Willem Pieter Brouwer[1,2*], Servet Duran[3], Martijn Kuijper[4] and Can Ince[5]

- Retrospective observational study
- 67 patients treated with CytoSorb vs 49 matched controls treated with CRRT only
- Decreased observed versus expected 28-day all-cause mortality.
- IPTW analysis: CytoSorb associated with a decreased all-cause mortality at 28 days compared to CRRT alone



Brouwer et al Critical Care 2019

Better Patients Selection?

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Targeted Polymyxin B Hemoperfusion on 28-Day Mortality in Patients With Septic Shock and Elevated Endotoxin Level

The EUPHRATES Randomized Clinical Trial

R. Phillip Dellinger, MD, MSc; Sean M. Bagshaw, MD, MSc; Massimo Antonelli, MD; Debra M. Foster, BSc; David J. Klein, MD, MBA; John C. Marshall, MD; Paul M. Palevsky, MD; Lawrence S. Weisberg, MD; Christa A. Schorr, DNP, MSN, RN; Stephen Trzeciak, MD, MPH; Paul M. Walker, MD, PhD; for the EUPHRATES Trial Investigators

- Multicenter RCT in 55 centers in North America
- 450 patients with septic shock and elevated endotoxin activity essay (>0.6)
- Intervention: 2PMX hemoperfusion session (90-120 min) or sham hemoperfusion

Table 2. Summary of the Primary End Point of 28-Day Mortality for All Participants and for Patients With MODS of More Than 9

	No./Total (%)		(95% CI)		
	Polymyxin-B Hemoperfusion	Sham	Risk Difference	Risk Ratio	*P* Value[a]
All Participants	84/223 (37.7)	78/226 (34.5)	3.15 (−5.73 to 12.04)	1.09 (0.85 to 1.39)	.49
>9 MODS[b]	65/146 (44.5)	65/148 (43.9)	0.60 (−10.75 to 11.97)	1.01 (0.78 to 1.31)	.92

Table 3. Per-Protocol (Each Group Received 2 Treatments) 28-Day Mortality

	No./Total (%)			
Population	Polymyxin-B Hemoperfusion	Sham	Difference, % (95% CI)	*P* Value[a]
All participants	50/173 (28.9)	59/202 (29.2)	−0.3 (−9.5 to 8.9)	.94
>9 MODS	38/115 (33.0)	47/129 (36.4)	−3.1 (−15.2 to 9.0)	.58

ORIGINAL

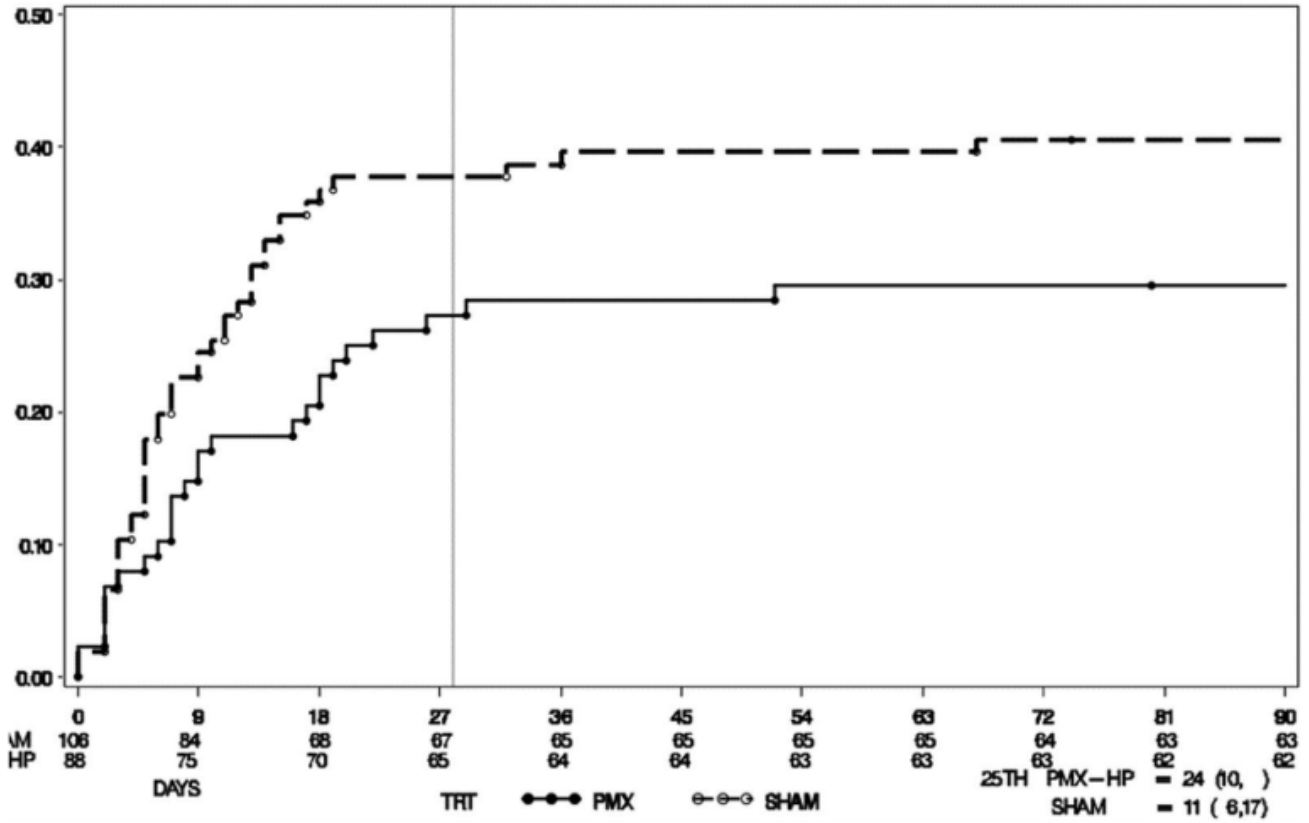
Polymyxin B hemoperfusion in endotoxemic septic shock patients without extreme endotoxemia: a post hoc analysis of the EUPHRATES trial

D. J. Klein[1*], D. Foster[2], P. M. Walker[2], S. M. Bagshaw[3], H. Mekonnen[4] and M. Antonelli[5]

Post-hoc analysis of the EUPHRATES trial

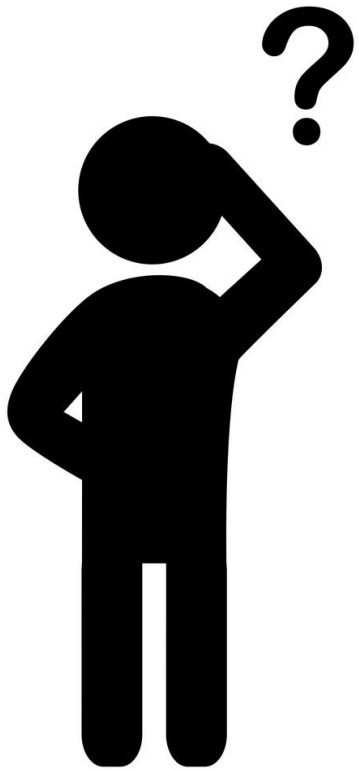
Restricted to the 194 patients with EAA ≥0.6–0.89 who completed two treatments (PMX or sham).

Hypothesis generating
Future study planned to validate this result.



Klein et al ICM (2018) 44:2205-2212

More Research is Required…



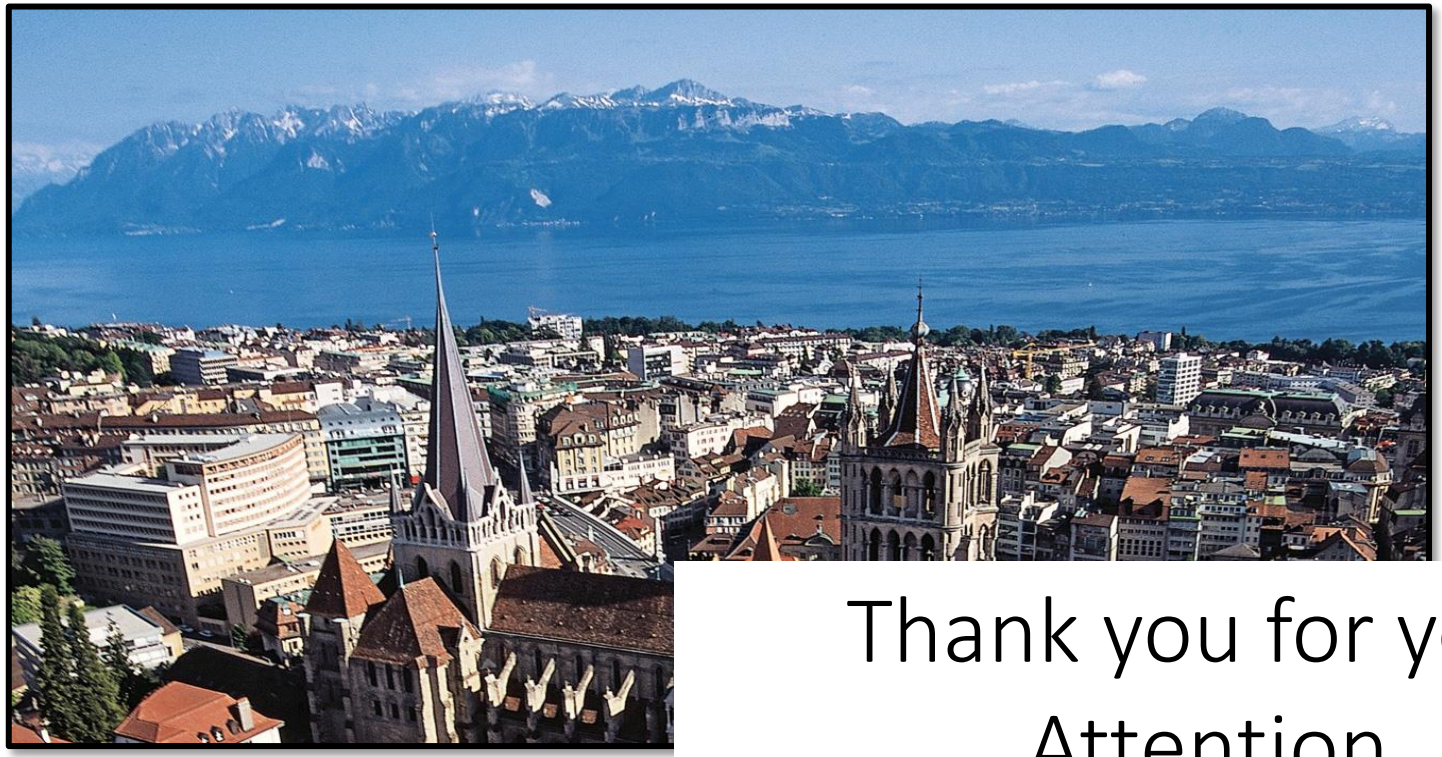
Conclusions

- Septic AKI is common and associated with increased mortality
- When severe, RRT might be required however the ideal timing for initiation remains to be determined
- CRRT is the preferred method of blood puriification during sepsis
- A prescribed dose of 25 ml/kg/h should be *delivered* (prescription of higher dose often necessary)

Conclusions

- Currently published data have failed to demonstrate a benefit of blood purification in sepsis or sepsis like syndromes

- Further research is required to identify patients or clinical situations who could benefit from such interventions



Lausanne

Thank you for your Attention

CHUV