Recommendations ESICM Task Force on Colloid Volume Therapy in Critically Ill Patients

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European Society of Intensive Care Medicine
and
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ESICM Task Force on Colloids - Members

- Richard Beale, London, UK
- Johan Groeneveld, Amsterdam, Netherlands
- Christiane Hartog, Jena, Germany
- Roman Jaeschke, Hamilton, Canada
- Anders Perner, Copenhagen, Denmark
- Konrad Reinhart, Jena, Germany
- Frederique Schortgen, Paris, France
- Charles L. Sprung, Jerusalem, Israel

Background and purpose

- Colloids are administered to more patients than crystalloids and the use is increasing
- Recent evidence suggests that colloids may possibly be harmful in some patients
- Compile consensus recommendations based on the current best evidence for the safety and efficacy of the most frequently used colloids :
  - hydroxyethyl starches (HES)
  - gelatins
  - human albumin

Methods

- Data sources:
  - Meta-analyses, systematic reviews and clinical studies of colloid use for fluid resuscitation
- Populations:
  - Mixed ICU, cardiac surgery, head injury, sepsis, and organ donor patients.
- Clinical endpoints
  - Mortality, kidney function, bleeding, other
- Publications from 1960 until May 2011 were included
- GRADE system used
  - Grades of Recommendation, Assessment, Development and Evaluation (GRADE) system

Grading of evidence

- A strong recommendation is worded as “we recommend” and a weak recommendation as “we suggest.”
- In order to issue a recommendation preferring one option over an alternative option at least 5 out of 8 votes were required.
- To have a strong recommendation *(we recommend)*, at least 6 out of 8 votes would need to indicate preference for a strong recommendation; otherwise the recommendation was weak *(we suggest).*

General findings and principles

- Weigh benefits against risks
- For most indications there is no evidence for the superiority of one type of fluid over another in terms of mortality
- Lack of evidence of efficacy or safety, combined with the presence of alternatives with known safety give greater weight to potential side effects and adverse events

Systematic reviews consistently failed to find evidence for the superiority of colloids over crystalloids

THE COCHRANE COLLABORATION®

"[t]here is no evidence from RCTs that resuscitation with colloids reduces the risk of death, compared to resuscitation with crystalloids, in patients with trauma, burns or following surgery. As colloids are not associated with an improvement in survival, and as they are more expensive than crystalloids, it is hard to see how their continued use in these patients can be justified outside the context of RCTs."

Perel: Cochrane Collaboration 2009

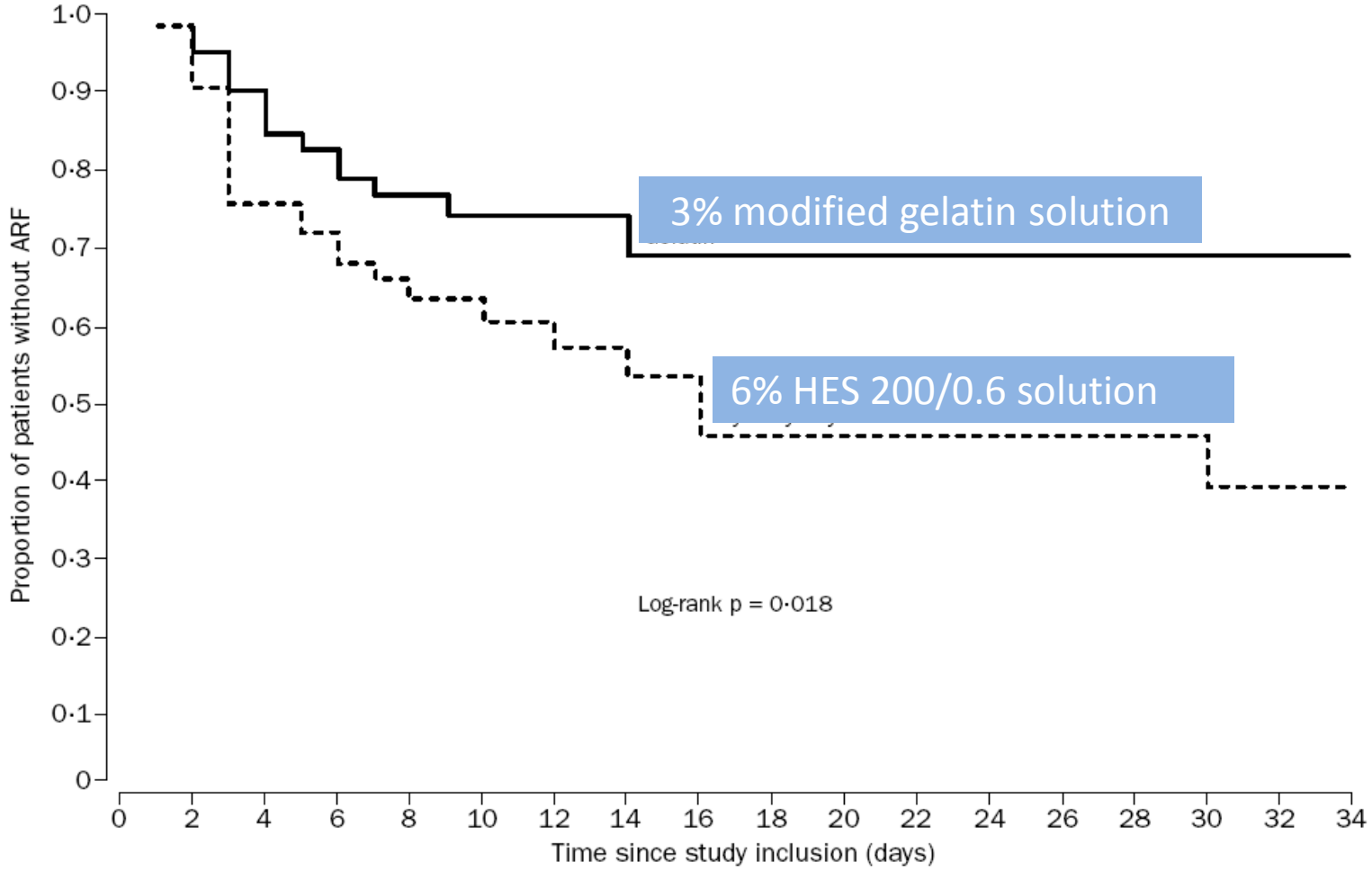
Recommendation 1

I. We recommend not to use HES with molecular weight $\geq$ 200 kDa and/or a degree of substitution > 0.4 in patients with severe sepsis (Grade 1B) and recommend not to use these HES solutions in other intensive care patients with increased risk for AKI (Grade 1C).

8 (8 strong)

increased risk of AKI was defined by a recent consensus conference as advanced age, sepsis, cardiovascular surgery, contrast nephropathy.

Acute renal failure in severe sepsis



Number at risk

Gelatin	64	54	45	38	26	20	15	14	12	11	11	11	9	9	9	9	7	6
Hydroxyethylstarch	65	54	40	31	22	18	16	14	12	10	10	10	9	9	9	7	6	6

Figure 2: **Proportion of patients without ARF as assessed by Kaplan-Meier curves**

Schortgen F et al, Lancet 2001

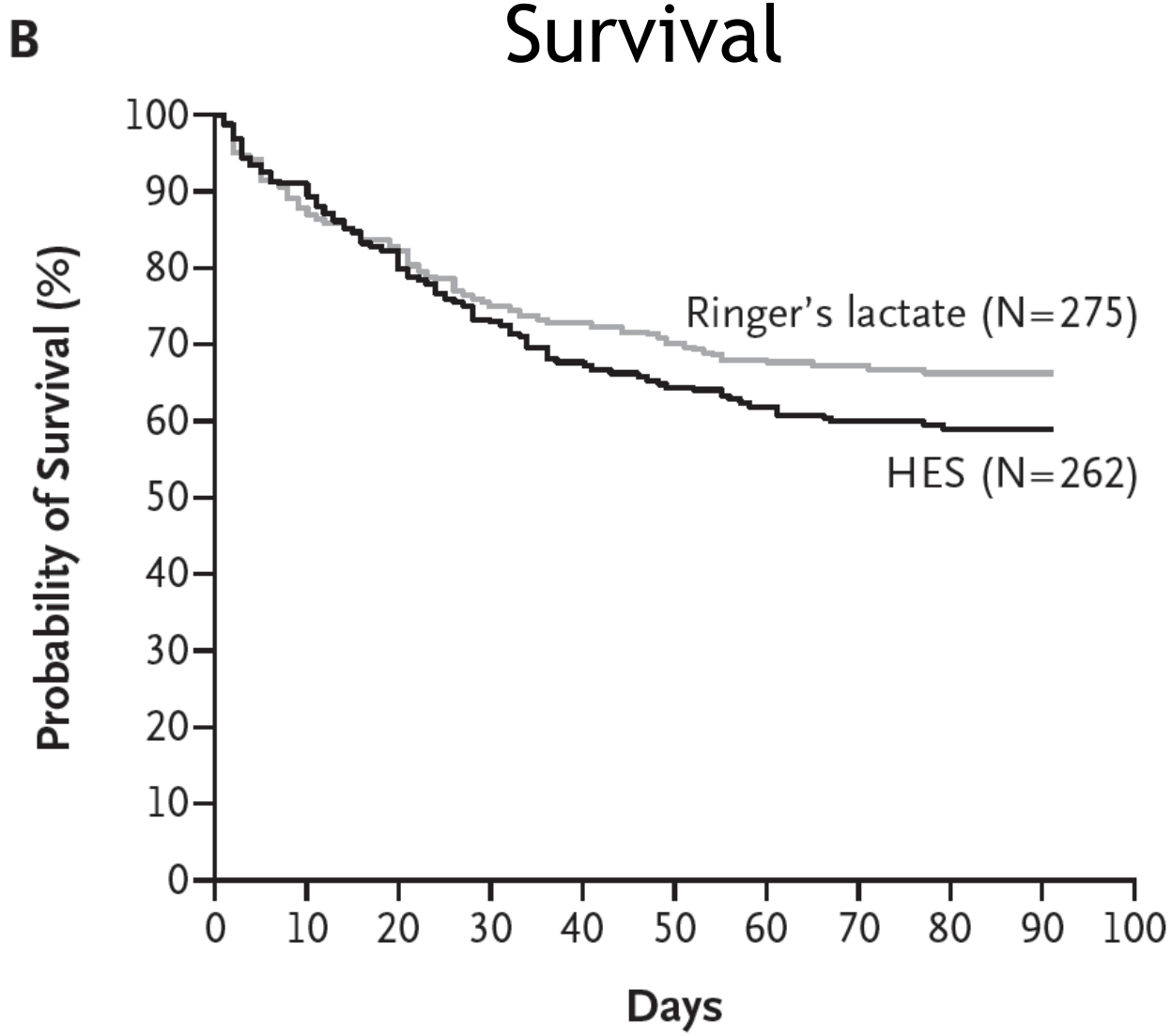
VISEP Trial (HES vs. Ringer's lactate)

- Morbidity -

	Ringer's Lactate			HES			
	n	N	%	n	N	%	p
Hemofiltration (HF)	51	272	18.6	81	261	31.0	0.001
Days with HF	321	3471	9.3	650	3554	18.3	
Acute renal failure	63	272	23.2	91	261	34.9	0.003
Transfusion	189	275	68.7	199	262	76.0	0.07
Bleeding events	10	275	3.6	13	262	5.0	0.52
Transfusion RBC (nos.)	6.6	7.2	4.0	8.7	9.9	6.0	<0.001

Brunkhorst FM et al. NEJM, 2008

HES vs. Ringer's for fluid therapy in sepsis: Survival



Brunkhorst FM et al. NEJM, 2008

Study	Studies *n*	No. of events / No. of participants: HES	Control	Odds ratio (95% CI)
All studies				
Brunkhorst[18]		81/261	51/272	1.95 (1.30–2.91)
McIntyre[19]		3/21	1/19	3.00 (0.28–31.63)
Schortgen[7]		13/65	11/64	1.20 (0.49–2.93)
Cittanova[8]		9/27	1/20	9.50 (1.09–82.72)
Overall	4	106/374	64/375	1.90 (1.22–2.96)
Subgroup analyses				
Patient population				
Severe sepsis/septic shock	3	97/347	53/355	1.82 (1.27–2.61)
Organ	1	9/27	1/20	9.50 (1.09–82.72)
Type of comparator				
Gelatin	2	22/92	12/84	2.64 (0.37–18.96)
Crystalloid	2	84/282	52/291	1.98 (1.33–2.94)

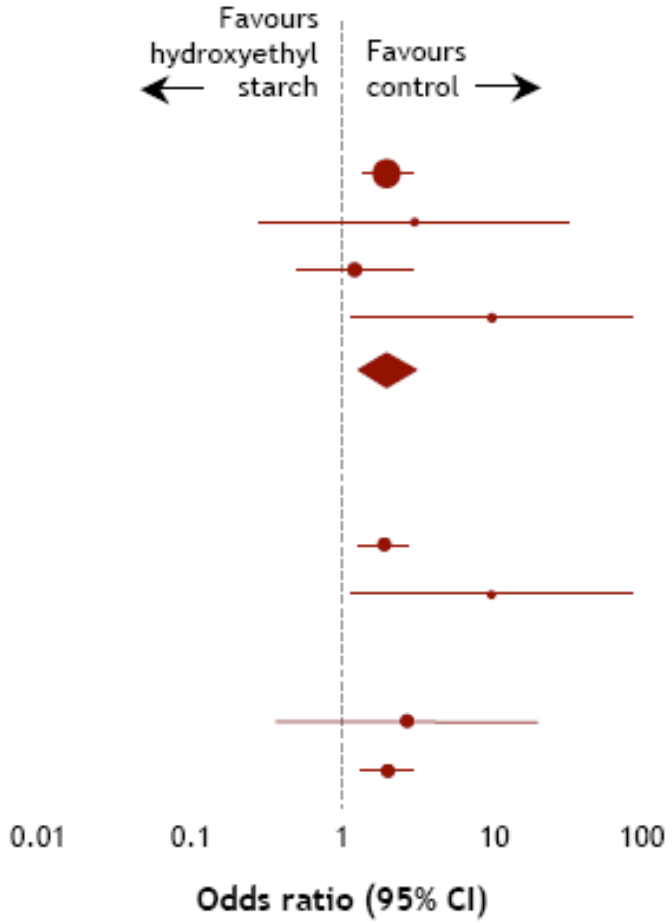
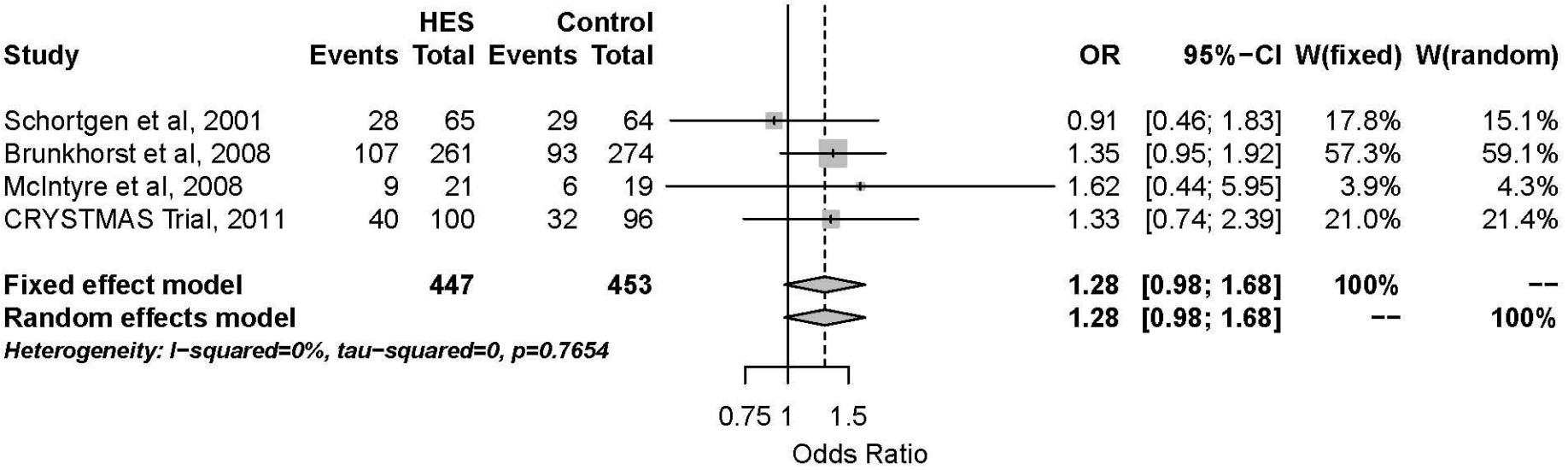


Figure 2: Renal replacement therapy associated with hydroxyethyl starch (HES)

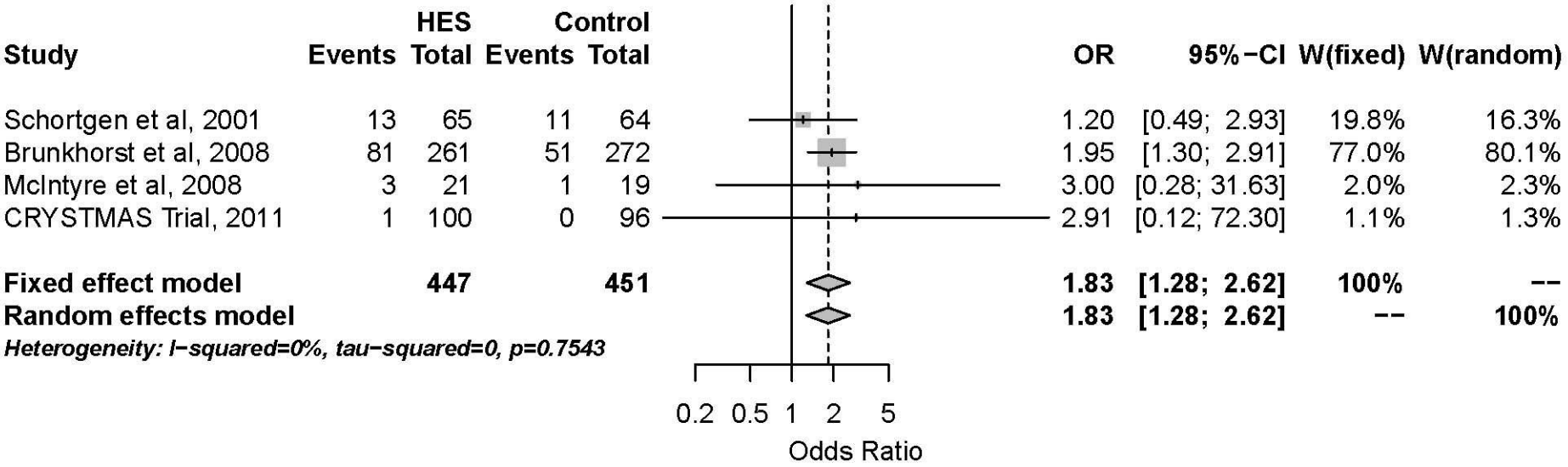
Mortality in Severe Sepsis/Septic Shock

Meta-Analysis of Randomized Trials



Renal Replacement Therapy in Severe Sepsis/Septic Shock

Meta-Analysis of Randomized Trials



Recommendation 2

II. We suggest that HES 130/0.4 is used in severe sepsis and other ICU patients with increased risk for AKI or bleeding only in the context of clinical trials rather than in routine clinical practice (Grade 2C).

8 (8 strong)

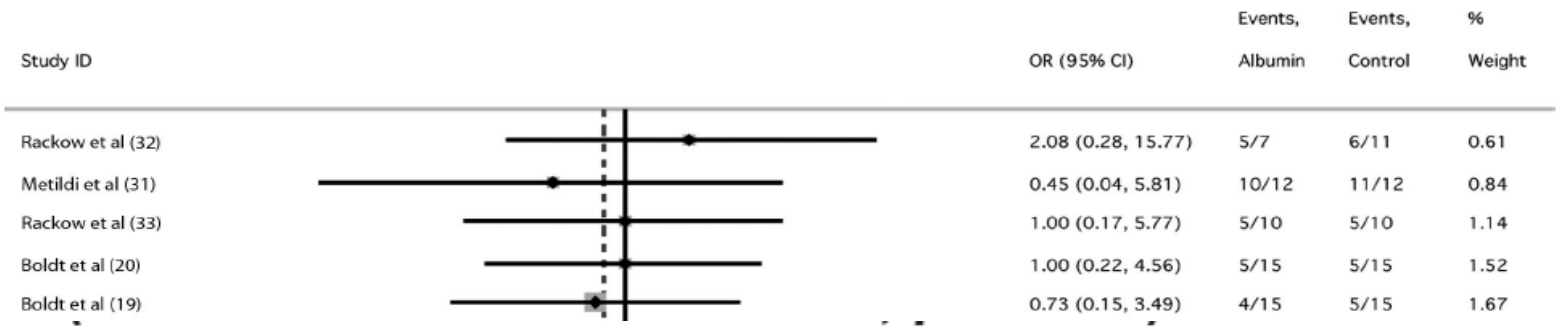
Recommendation 3

III. We suggest that albumin may be included in the resuscitation of severe sepsis patients (Grade 2 B).

8 (1 strong, 7 weak)

The role of albumin as a resuscitation fluid for patients with sepsis: A systematic review and meta-analysis*

Anthony P. Delaney, MD, FCICM; Arina Dan, MD, FCICM; John McCaffrey, MD, FCICM; Simon Finfer, MD, FCICM



Conclusions: **In this meta-analysis, the use of albumin-containing solutions for the resuscitation of patients with sepsis was associated with lower mortality compared with other fluid resuscitation regimens. Until the results of ongoing randomized controlled trials are known, clinicians should consider the use of albumin-containing solutions for the resuscitation of patients with sepsis. (Crit Care Med 2011; 39:386–391)**

Figure 2. Forrest plot showing the pooled estimate of the effect of resuscitation with albumin-containing solutions on mortality for patients with sepsis. *OR*, odds ratio; *CI*, confidence limit.

Recommendation 4

IV. We recommend that solutions other than albumin be used in patients with head injury (Grade 1C).

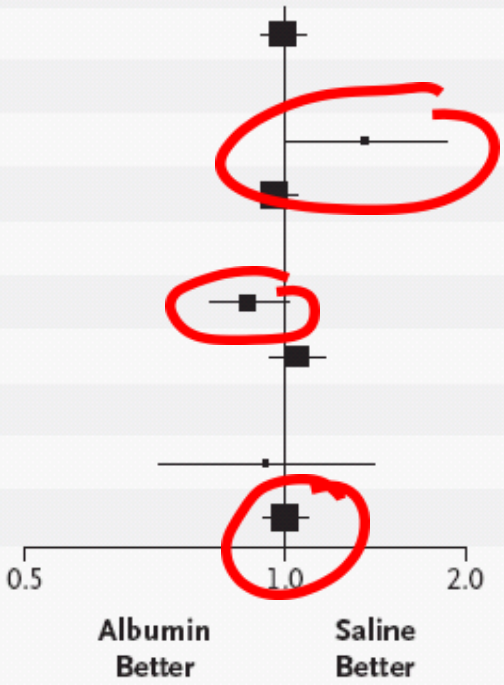
8 (8 strong)

We recommend not to use synthetic colloid in patients with head injury or intracranial bleeding (Grade 1C).

8 (8 strong)

Outcomes

Patients	Albumin Group	Saline Group	Relative Risk (95% CI)
	no. of deaths/total no.		
Overall	726/3473	729/3460	0.99 (0.91–1.09)
Trauma			
Yes	81/596	59/590	1.36 (0.99–1.86)
No	641/2831	666/2830	0.96 (0.88–1.06)
Severe sepsis			
Yes	185/603	217/615	0.87 (0.74–1.02)
No	518/2734	492/2720	1.05 (0.94–1.17)
ARDS			
Yes	24/61	28/66	0.93 (0.61–1.41)
No	697/3365	697/3354	1.00 (0.91–1.09)



SAFE Investigators: NEJM 2004

SAFE-TBI

The NEW ENGLAND JOURNAL of MEDICINE

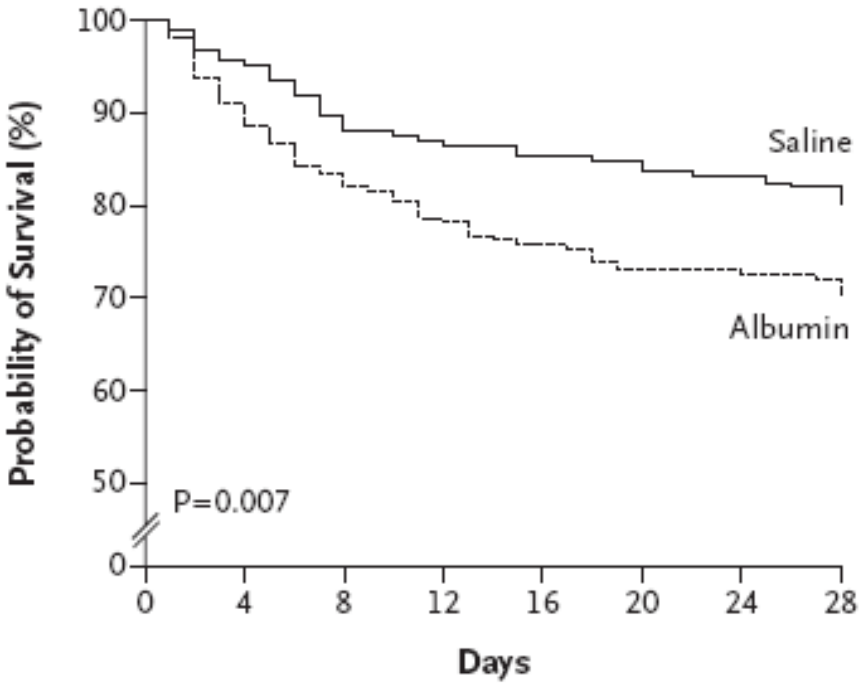
ORIGINAL ARTICLE

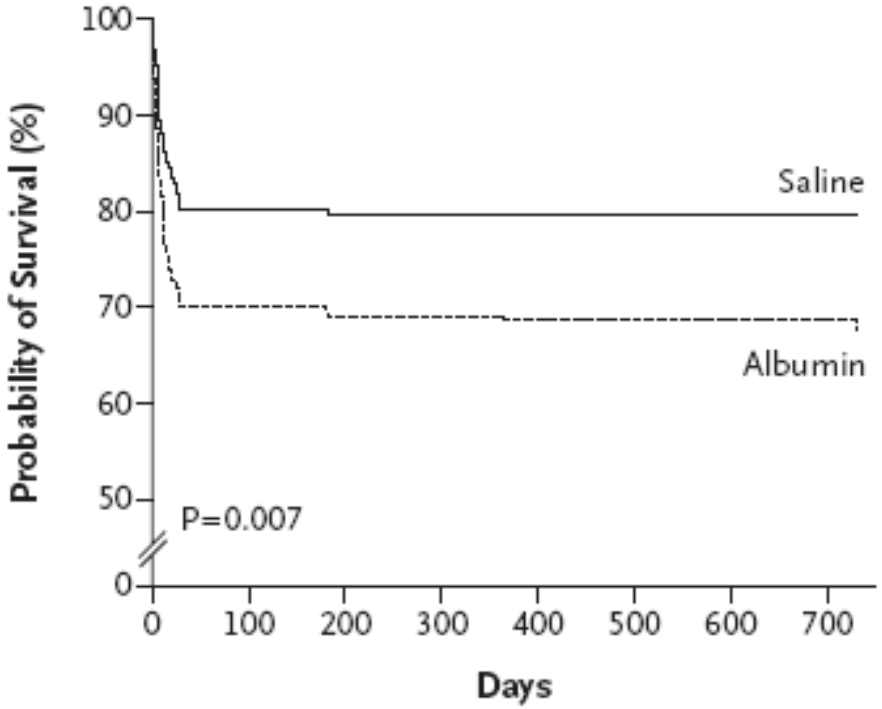
Saline or Albumin for Fluid Resuscitation in Patients with Traumatic Brain Injury

The SAFE Study Investigators*

New Eng J Med: 2007: 357: 874-884

SAFE-TBI





Safe Investigators: NEJM 2007

Lissauer ME, Chi A, Kramer ME, Scalea TM, Johnson SB (2011) Association of 6% hetastarch resuscitation with adverse outcomes in critically ill trauma patients. Am J Surg

Use of hetastarch, in comparison to not receiving this solution was associated with a greater risk of death in patients with brain injury in a retrospective review of 2,225 adult trauma patients (OR 2.5, 95% CI, 1.77-3.54)

Tseng MY, Hutchinson PJ, Kirkpatrick PJ (2008) Effects of fluid therapy following aneurysmal subarachnoid haemorrhage: a prospective clinical study. Br J Neurosurg 22: 257-268

Cohort study in patients with aneurysmal intracerebral haemorrhage suggested that gelatin or HES was dose-dependently associated with more requirements for blood transfusions ($P = 0.003$) and unfavourable neurological outcome at 6 months (OR 4.45, 95% CI 1.11-17.77)

Neff TA, Doelberg M, Jungheinrich C, Sauerland A, Spahn DR, Stocker R (2003) Repetitive large-dose infusion of the novel hydroxyethyl starch 130/0.4 in patients with severe head injury. Anesth Analg 96: 1453-1459

- RCT of 31 head injury patients, the rate of bleeding complications was similar after HES 200/0.5 or HES 130/0.4.
- Intracranial bleeding complications (5 of 16 6% HES 130/0.4 versus 5 of 15 patients 6% HES 200/0,5)
- The study was stopped by the IRB after the interim analysis because of safety concerns.

Recommendation 5

V. We suggest not to use gelatin in ICU patients who are at increased risk for renal failure or bleeding outside the context of clinical trials (Grade 2 C).

6 (2 strong, 4 weak)

2 weak against the direction of recommendation

Recommendation 6

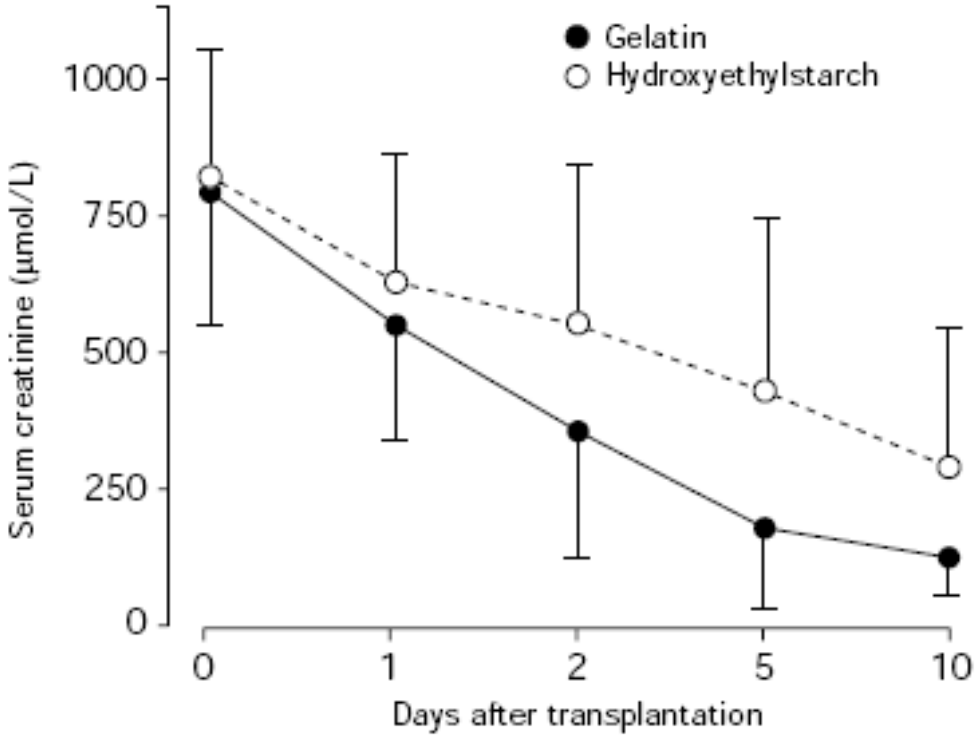
VI. We recommend not to use HES or gelatin in organ donors outside the context of clinical trials (Grade 1C).

8 (6 strong, 2 weak)

Starch and nephrotoxicity

Effect of hydroxyethylstarch in brain-dead kidney donors on renal function in kidney-transplant recipients

6% hydroxyethyl starch (200/0.62) vs 4% gelatin



Increased incidence of post-graft azotaemia and dialysis

Cittanova: Lancet 1996

Subsequent non-randomized cohort studies confirmed that HES was a risk factor for delayed graft function in these patients

Robert R et alJ Crit Care 25: 582-590

Giral MTransplantation 83: 1174-1181

or found no difference in comparison to fluid therapy with only crystalloids or other colloids

Hokema F et a. Nephrol Dial Transplant 2011

Deman A, Peeters P, Sennesael J (1999) Nephrol Dial Transplant 14: 1517-1520

Recommendation 7

VII. We recommend that any new colloid should be introduced into clinical practice only after its patient-important safety parameters are established, rather than introduced on the basis of small ‘bridging’ studies based mostly on haemodynamic parameters (Grade 1C).

8 (8 strong)

History…

Year	Crystalloids	Colloids	Author
1883	Ringer's solution		S. Ringer
1885	Normal saline		H.J. Hamburger
1915		Gum acacia	W. Bayliss
1934	Lactated Ringer's		A. Hartmann
1940		Polyvinylpyrrolidone	H. Weese, G. Hecht
1940		Human Albumin	E. Cohn
1947		Dextran	A. Grönwall, B. Ingelman
1951		Oxypolygelatin	D.H. Campbell
1952		Modified fluid gelatin	D. Tourtelotte
1957		Oxyethyl starch	M. Wiedersheim
1962		Succinylated gelatin	J. Schmidt-Thomé
1962		Hydroxyethyl starch	W.L. Thompson

Statement of the German Regulatory Agency BfArM on approval process for HES preparations

....”all recent HES authorisations are indeed based on references to old authorisations, with the old data having been linked to the more recent products by smaller pharmacokinetics, pharmacodynamics and bioequivalence bridging studies as well as by smaller efficacy and safety studies”.

Recommendation 8

VIII. We suggest not to use hyperoncotic solutions for fluid resuscitation outside the context of clinical trials (Grade 2 C).

6 (2 strong, 4 weak)

2 (2 weak) against the direction of the recommendation

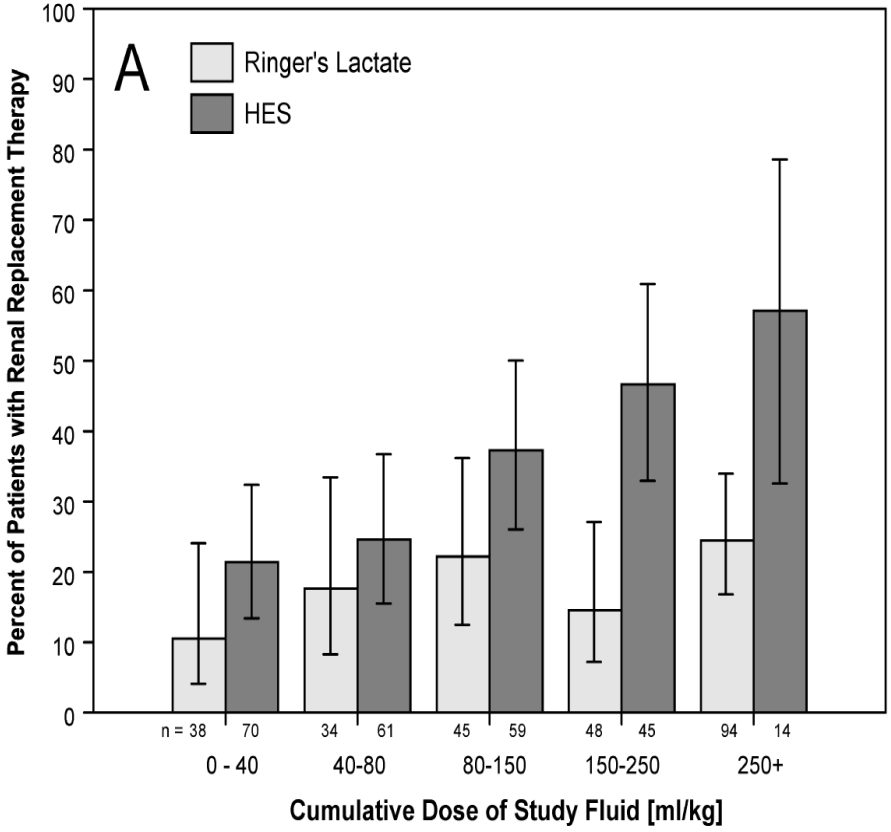
Recommendation 9

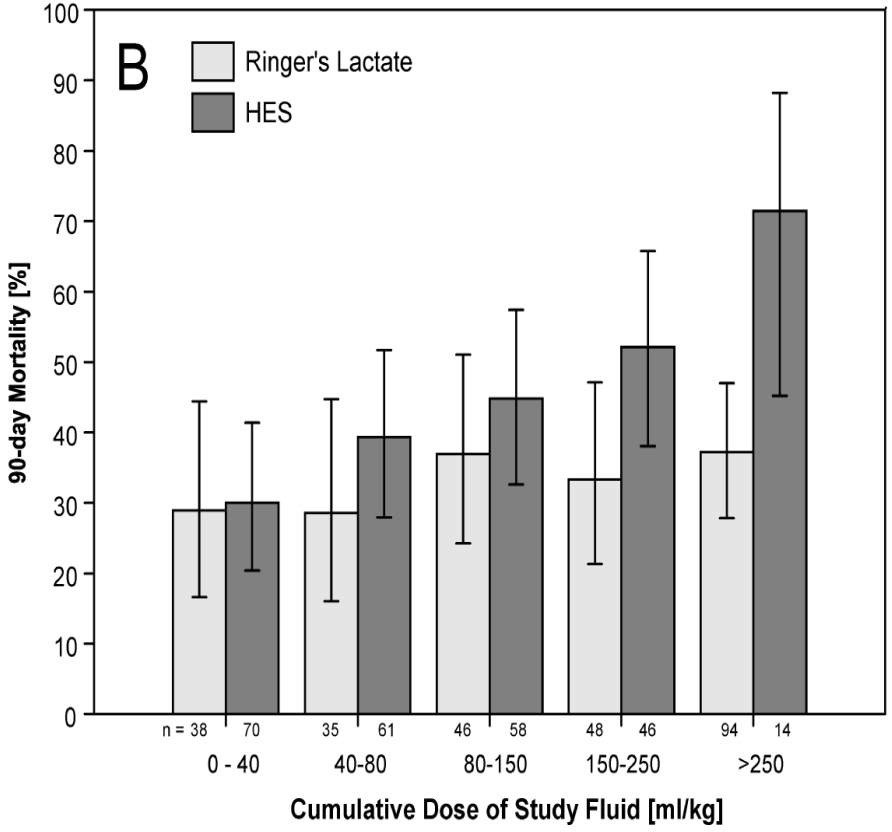
IX. We recommend reassessment of existing dose limits for HES and an assessment of whether dose limitations should apply for gelatins (Grade 1B).

8 (7 strong, 1 weak)

Cumulative dose:

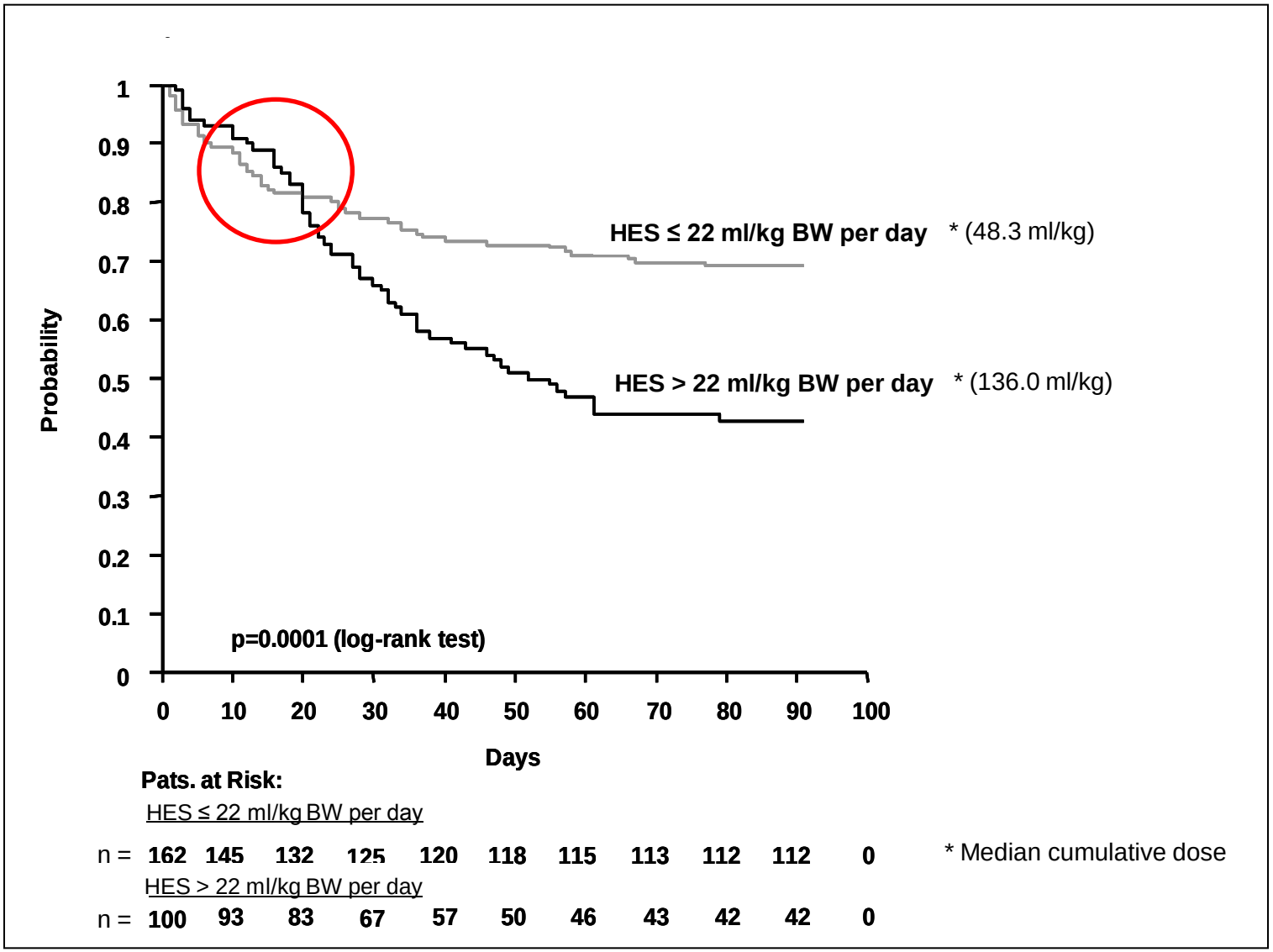
Renal replacement therapy and 90-day mortality





Brunkhorst FM et al. NEJM, 2008

VISEP: Survival by dosage subgroups



Brunkhorst FM et al. NEJM, 2008

Synthetic colloids in CPB patients (n=6478) before and after design

	6%HES 130/0.4	p	Gelatin 4%	p	Crystalloids
Patients, n	**2137**		**2324**		**2017**
Cum. Dose - ml/kg (median, IQR)	30 (19-49)		14 (7-25)		111 (77-169)
Total fluid (ml/kg)	161 (111-281)	< .001	205 (145-322)	< .001	222 (156-351)
RIFLE Failure, n (%)	196 (9.2)	< .001	205 (8.8)	< .001	115 (5.7)
RRT, n (%)	149 (7.0)	.003	171 (7.4)	.001	97 (4.8)

RRT as dependent binary variable	6%HES 130/0.4	p	Gelatin 4%	p	Crystalloids
Odds Ratio (95% CI)	2.6 (1.6-4.2)	< .001	2.9 (1.8-4.4)	< .001	Reference

Bayer O. et al ICM 2011 Vol 37 Suppl.1 0786

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Patients, n	**2137**		**2324**		**2017**
Cum. Dose (median, IQ					111 (77-169)
Total fluid (ml/kg)					222 (156-351)
RIFLE Failu (%)					115 (5.7)
RRT, n (%)					97 (4.8)

Ratio day 0-1, HES vs. crystalloids: 1 : 1.41

Ratio day 0-2, HES vs. crystalloids: 1 : 1.39

RRT as dependent binary variable	6%HES 130/0.4	p	Gelatin 4%	p	Crystalloids
Odds Ratio (95% CI)	2.6 (1.6-4.2)	< .001	2.9 (1.8-4.4)	< .001	Reference

Bayer O. et al ICM 2011 Vol 37 Suppl.1 0786

Recommendation 10

X. Acknowledging the likelihood that despite our recommendation or suggestion to the contrary clinicians will continue to use HES, we discussed the possibility of issuing a statement describing cumulative threshold doses. Given the differences of opinions among members of the task force, we conducted a formal vote on preferences and the results are as follows: Six of 8 panel members preferred not to issue such a statement (using as a rationale that we do not know if such a ‘safe’ dose exists);