Le choc

Définition

Le choc est une altération de la circulation (déficit hémodynamique) où la perfusion tissulaire est insuffisante pour assurer le métabolisme cellulaire

Sémiologie

- hypotension artérielle
- tachycardie (pouls filant)
- lipothymie, apathie, agitation
- pâleur, froideur, moiteur
- marbrures cutanées, cyanose
- oligurie, anurie
- hyperventilation (acidose métabolique)
- « choc chaud »: extrémités vasodilatées, rouges, chaudes, sèches

Classification

- choc hypovolémique
- choc cardiogénique
- choc obstructif
- choc distributif

Traitement du choc : 3 grands axes

- Augmenter le transport de l ’oxygène

  $DO_2 = Ca\ O_2 \times DC$

- Diminuer la demande en oxygène

  $VO_2 = Ca\text{-}v\ O_2 \times DC$

- Traitement étiologique

Paramètres d'évaluation

- Pression artérielle : **PAS > 90 mm Hg et/ou PAM > 65 mm Hg**
- Diurèse : **> 20 ml/h**
- Lactatémie: **< 2 mEq/L**

Intensive Care Med (2014) 40:1795–1815
DOI 10.1007/s00134-014-3525-z

CONFERENCE REPORTS AND EXPERT PANEL

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Consensus on circulatory shock and hemodynamic monitoring. Task force of the European Society of Intensive Care Medicine

Table 1 Main differences between the 2006 and 2014 consensus papers in terms of definition of shock, blood pressure statements and fluid responsiveness statements

Topic	ICM Antonelli 2007	ICM Cecconi 2014
Definition	We recommend that shock be defined as a life-threatening, generalized maldistribution of blood flow resulting in failure to deliver and/or utilize adequate amounts of oxygen, leading to tissue dysoxia. Level 1; QoE moderate (B)	We define circulatory as a life-threatening, generalized form of acute circulatory failure associated with inadequate oxygen utilization by the cells. *Ungraded*
Blood pressure statements	–We recommend a target blood pressure during initial shock resuscitation of: –For uncontrolled hemorrhage due to trauma: MAP of 40 mmHg until bleeding is surgically controlled. Level 1; QoE moderate (B) –For TBI without systemic hemorrhage: MAP of 90 mmHg. Level 1; QoE low (C) –For all other shock states: MAP >65 mmHg. Level 1; QoE moderate (B)	–We recommend individualizing the target blood pressure during shock resuscitation. Level 1; QoE moderate (B) –We recommend to initially target a MAP of ≥65 mmHg. Level 1; QoE low (C) –We suggest to tolerate a lower level of blood pressure in patients with uncontrolled bleeding (i.e. in patients with trauma) without severe head injury. Level 2; QoE low (C) –We suggest a higher MAP in septic patients with history of hypertension and in patients that show clinical improvement with higher blood pressure. Level 2; QoE moderate (B)
Fluid responsiveness statements	–We do not recommend the routine use of dynamic measures of fluid responsiveness (including but not limited to pulse pressure variation, aortic flow changes, systolic pressure variation, respiratory systolic variation test and collapse of vena cava). Level 1; QoE high (A) –There may be some advantage to these measurements in highly selected patients. Level 1; QoE moderate (B)	–We recommend using dynamic over static variables to predict fluid responsiveness, when applicable. Level 1; QoE moderate (B) –When the decision for fluid administration is made we recommend to perform a fluid challenge, unless in cases of obvious hypovolemia (such as overt bleeding in a ruptured aneurysm). Level 1; QoE low (C) –We recommend that even in the context of fluid-responsive patients, fluid management should be titrated carefully, especially in the presence of elevated intravascular filling pressures or extravascular lung water. *Ungraded best practice*

ICM, Intensive Care Medicine; QoE, Quality of experience, MAP, mean arterial pressure; TBI, traumatic brain injury

Table 2 Main differences between the 2006 and 2014 consensus papers in terms of hemodynamic monitoring

Topic	ICM Antonelli 2007	ICM Cecconi 2014
Hemodynamic monitoring	–We do not recommend routine measurement of CO for patients with shock. Level 1; QoE moderate (B) –We suggest considering echocardiography or measurement of CO for diagnosis in patients with clinical evidence of ventricular failure and persistent shock with adequate fluid resuscitation. Level 2 (weak); QoE moderate (B) –We do not recommend the routine use of the pulmonary artery catheter for patients in shock. Level 1; QoE high (A)	–We recommend further hemodynamic assessment (such as assessing cardiac function) to determine the type of shock if the clinical examination does not lead to a clear diagnosis. *Ungraded best practice* –We suggest that, when further hemodynamic assessment is needed, echocardiography is the preferred modality to initially evaluate the type of shock as opposed to more invasive technologies. Level 2; QoE moderate (B) –In complex patients we suggest to additionally use pulmonary artery catheterization or transpulmonary thermodilution to determine the type of shock. Level 2; QoE low (C) –We do not recommend routine measurement of cardiac output for patients with shock responding to the initial therapy. Level 1; QoE low (C) –We recommend measurements of cardiac output and stroke volume to evaluate the response to fluids or inotropes in patients that are not responding to initial therapy. Level 1; QoE low (C) –We suggest sequential evaluation of hemodynamic status during shock. Level 1; QoE low (C) –Echocardiography can be used for the sequential evaluation of cardiac function in shock. *Statement of fact* –We do not recommend the routine use of the pulmonary artery catheter for patients in shock. Level 1; QoE high (A) –We suggest pulmonary artery catheterization in patients with refractory shock and right ventricular dysfunction. Level 2; QoE low (C) –We suggest the use of transpulmonary thermodilution or pulmonary artery catheterization in patients with severe shock especially in the case of associated acute respiratory distress syndrome. Level 2; QoE low (C) –We recommend that less invasive devices are used, instead of more invasive devices, only when they have been validated in the context of patients with shock. *Ungraded best practice*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Early, Goal-Directed Therapy for Septic Shock — A Patient-Level Meta-Analysis

The PRISM Investigators*

N Engl J Med 2017;376:2223-34.
DOI: 10.1056/NEJMoa1701380

EARLY GOAL-DIRECTED THERAPY IN THE TREATMENT OF SEVERE SEPSIS AND SEPTIC SHOCK

EMANUEL RIVERS, M.D., M.P.H., BRYANT NGUYEN, M.D., SUZANNE HAVSTAD, M.A., JULIE RESSLER, B.S., ALEXANDRIA MUZZIN, B.S., BERNHARD KNOBLICH, M.D., EDWARD PETERSON, PH.D., AND MICHAEL TOMLANOVICH, M.D., FOR THE EARLY GOAL-DIRECTED THERAPY COLLABORATIVE GROUP*

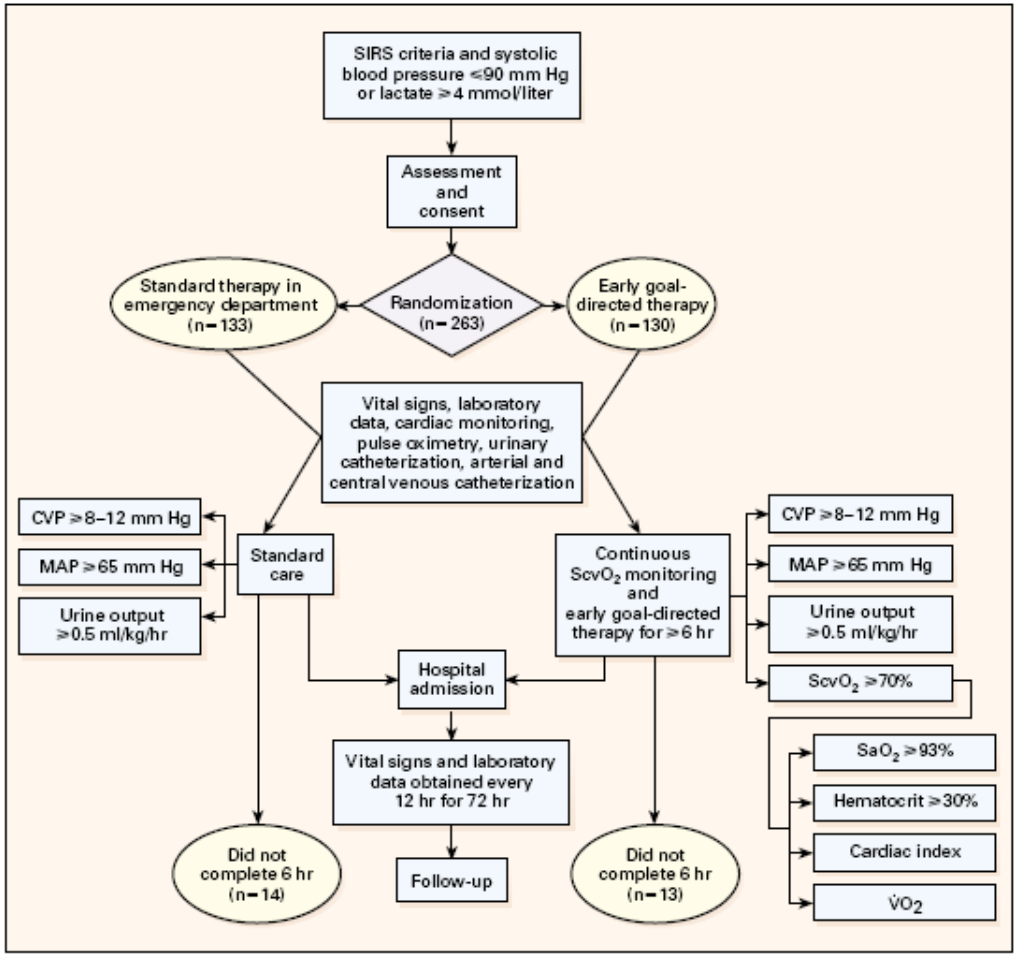
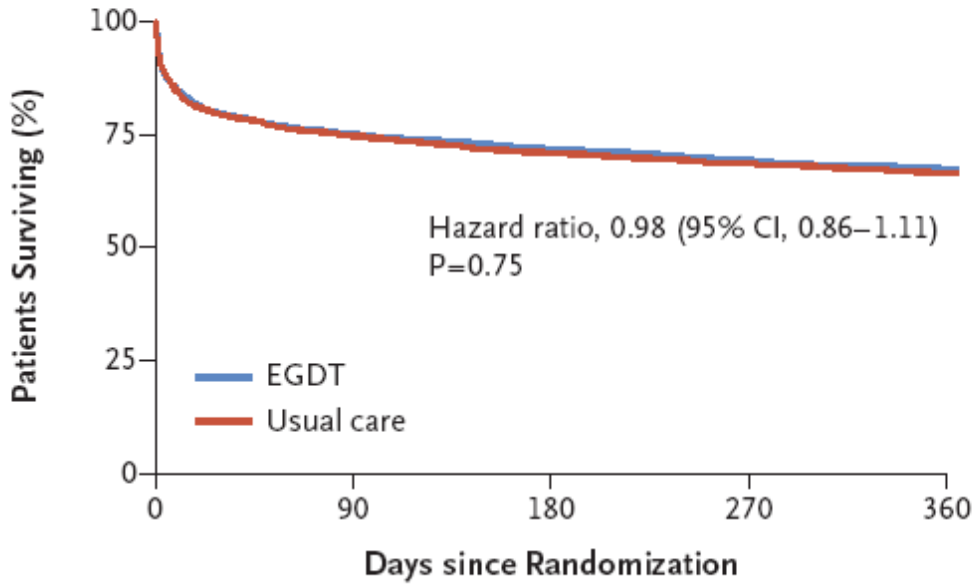


Figure 1. Overview of Patient Enrollment and Hemodynamic Support.

Table 2. Outcomes.*

Outcome	EGDT (N=1857)	Usual Care (N=1880)	Incremental Effect (95% CI)	P Value	
				Overall Comparison	Comparison among Trials
Primary outcome: death at 90 days — no./total no. (%)	462/1852 (24.9)	475/1871 (25.4)	0.97 (0.82 to 1.14)†‡	0.68	0.73
Secondary outcomes: mortality					
Death at hospital discharge — no./total no. (%)§	370/1857 (19.9)	365/1878 (19.4)	1.02 (0.85 to 1.21)†	0.86	0.42
Death at 28 days — no./total no. (%)	375/1854 (20.2)	385/1873 (20.6)	0.96 (0.81 to 1.15)†	0.68	0.57
Secondary outcomes: duration of stay from randomization					



No. at Risk					
EGDT	1857	1391	1287	1209	1119
Usual care	1880	1395	1295	1206	1110

Figure 1. Patient Survival over a Period of 1 Year.

There was no significant difference in the duration of survival to 1 year between the group that received early, goal-directed therapy (EGDT) and the group that received usual care. Data with respect to survival were censored at the actual date that the patient was last known to be alive or at 365 days. CI denotes confidence interval.

Augmenter le transport en oxygène

A. le débit cardiaque:

- expanseurs
- sympathomimétiques

B. la concentration en hémoglobine (anémie)

C. la Fi O_2 (oxygénothérapie)

Les expanseurs

- Cristalloïdes
- Colloïdes artificielles
- Colloïdes naturelles (dérivés plasmatiques)

Table 1. Types and Compositions of Resuscitation Fluids.*

Variable	Human Plasma	Colloids									Crystalloids		
		4% Albumin	Hydroxyethyl Starch						4% Succinylated Modified Fluid Gelatin	3.5% Urea-Linked Gelatin	0.9% Saline	Compounded Sodium Lactate	Balanced Salt Solution
			10% (200/0.5)	6% (450/0.7)	6% (130/0.4)		6% (130/0.42)						
Trade name		Albumex	Hemohes	Hextend	Voluven	Volulyte	Venofundin	Tetraspan	Gelofusine	Haemaccel	Normal saline	Hartmann's or Ringer's lactate	PlasmaLyte
Colloid source		Human donor	Potato starch	Maize starch	Maize starch	Maize starch	Potato starch	Potato starch	Bovine gelatin	Bovine gelatin			
Osmolarity (mOsm/liter)	291	250	308	304	308	286	308	296	274	301	308	280.6	294
Sodium (mmol/liter)	135–145	148	154	143	154	137	154	140	154	145	154	131	140
Potassium (mmol/liter)	4.5–5.0			3.0		4.0		4.0		5.1		5.4	5.0
Calcium (mmol/liter)	2.2–2.6			5.0				2.5		6.25		2.0	
Magnesium (mmol/liter)	0.8–1.0			0.9		1.5		1.0					3.0
Chloride (mmol/liter)	94–111	128	154	124	154	110	154	118	120	145	154	111	98
Acetate (mmol/liter)						34		24					27
Lactate (mmol/liter)	1–2			28								29	
Malate (mmol/liter)								5					
Gluconate (mmol/liter)													23
Bicarbonate (mmol/liter)	23–27												
Octanoate (mmol/liter)		6.4											

* To convert the values for potassium to milligrams per deciliter, divide by 0.2558. To convert the values for calcium to milligrams per deciliter, divide by 0.250. To convert the values for magnesium to milligrams per deciliter, divide by 0.4114.

Cristalloïdes

Sérum physiologique

- 9 g de NaCl/L d'eau
- 154 mmol/L sodium
- 154 mmol/L chlorure
- Osmolalité = 308 mosm/L
- pH = 5,0

Solution de Ringer

- Sodium: 147 mmol/l
- Potassium: 4 mmol/l
- Calcium: 2,25 mmol
- Chlorures: 155,5 mmol/l
- Osmolarité approximative: 309 mOsm/L
- pH: 5 – 7,5

Solution de Lactate Ringer

Un litre de liquide de Ringer contient :

- 130 mEq d'ion sodium = 130 mmol/l
- 109 mEq d'ion chlorure = 109 mmol/l
- 28 mEq de lactate = 28 mmol/l
- 4 mEq d'ion potassium = 4 mmol/l
- 3 mEq d'ion calcium = 1,5 mmol/l
- pH = 5,0

Solution de Hartmann

- Un litre de liquide de Hartmann contient:
- 131 mEq d'ion sodium = 131 mmol/L.
- 111 mEq d'ion chlorure = 111 mmol/L.
- 29 mEq de lactate = 29 mmol/L.
- 5 mEq d'ion potassium = 5 mmol/L.
- 4 mEq d'ion calcium = 2 mmol/L.
- pH = 6,5
- Osmolarité = 279 mosm/L

Plasmalyte A

- Composition (en mmole/l) :
  - sodium 140
  - chlore 98
  - lactate 28
  - potassium 5
  - magnésium 1,5
  - acétate 27
  - gluconate 23
- pH 7,4

Colloïdes

- Gélatines
- Amidons

Gélatines

- Gélofusine^{R} : flacon de 500 ml à 4 %, contenant 154 mEq Na/l et de PM moyen de 30000
- autre spécialité : Geloplasma^{R}, Plasmion^{R}
- expansion volémique = volume perfusé
- effets secondaires : rarement réaction allergique

Hydroxyéthylamidons (HEA)

- Haes-steril^{R}, Plasmasteril^{R}, Voluven^{R}: solution à 6 % en NaCl isotonique
- expansion volémique supérieure au volume perfusé (550 à 750 ml pour 500 ml perfusé)
- effets secondaires : rarement réaction allergique et surtout troubles de l'hémostase à doses totales élevées ou si forme à longue durée d'action (Elohès); risque accru d'insuffisance rénale; prurit au long terme

Dérivés plasmatiques

- *Plasma frais congelé*
  risque de transmission de maladies virales (hépatite, SIDA) : à ne plus utiliser comme expanseur
- *SSPP* (solution stable de protéines plasmatiques): Albumine à 4%
  - 40 g protéines/l en solution isotonique et avec > 95 % d'albumine (correspond en fait à de l'albumine à 4%); flacon de 400 ml
  - volume injecté = expansion volumique
  - très peu de risque
  - *! critères restreints de remboursement en Belgique !* prescription limitée au choc distributif et anaphylactique et au choc associé à pancréatite; ascite réfractaire du cirrhotique avec hypoprotéinémie et ponctions itératives; syndrome néphrotique avec hypoprotéinémie; plasmaphérèse itérative; cirrhose décompensée avec ponction d'ascite de > 5l ou péritonite bactérienne spontanée
- *Albumine humaine à 20%*
  - flacon de 100 ml à 20 % (=20 g d'albumine)
  - expansion volumique importante (400 ml pour un flacon)
  - intérêt : œdème interstitiel important (notamment pulmonaire)

Que prescrire?

Colloids versus crystalloids for fluid resuscitation in critically ill patients (Review)

Perel P, Roberts I

THE COCHRANE COLLABORATION®

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2012, Issue 11

http://www.thecochranelibrary.com

Comparison 1. Colloid versus crystalloid (add-on colloid)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Deaths	52		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Albumin or plasma protein fraction	24	9920	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.93, 1.10]
1.2 Hydroxyethyl starch	21	1385	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.91, 1.32]
1.3 Modified gelatin	11	506	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.49, 1.72]
1.4 Dextran	9	834	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [0.94, 1.65]

Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of a Buffered Crystalloid Solution vs Saline on Acute Kidney Injury Among Patients in the Intensive Care Unit
The SPLIT Randomized Clinical Trial

Paul Young, FCICM; Michael Bailey, PhD; Richard Beasley, DSc; Seton Henderson, FCICM; Diane Mackle, MN; Colin McArthur, FCICM; Shay McGuinness, FANZCA; Jan Mehrtens, RN; John Myburgh, PhD; Alex Psirides, FCICM; Sumeet Reddy, MBChB; Rinaldo Bellomo, FCICM; for the SPLIT Investigators and the ANZICS CTG

IMPORTANCE Saline (0.9% sodium chloride) is the most commonly administered intravenous fluid; however, its use may be associated with acute kidney injury (AKI) and increased mortality.

OBJECTIVE To determine the effect of a buffered crystalloid compared with saline on renal complications in patients admitted to the intensive care unit (ICU).

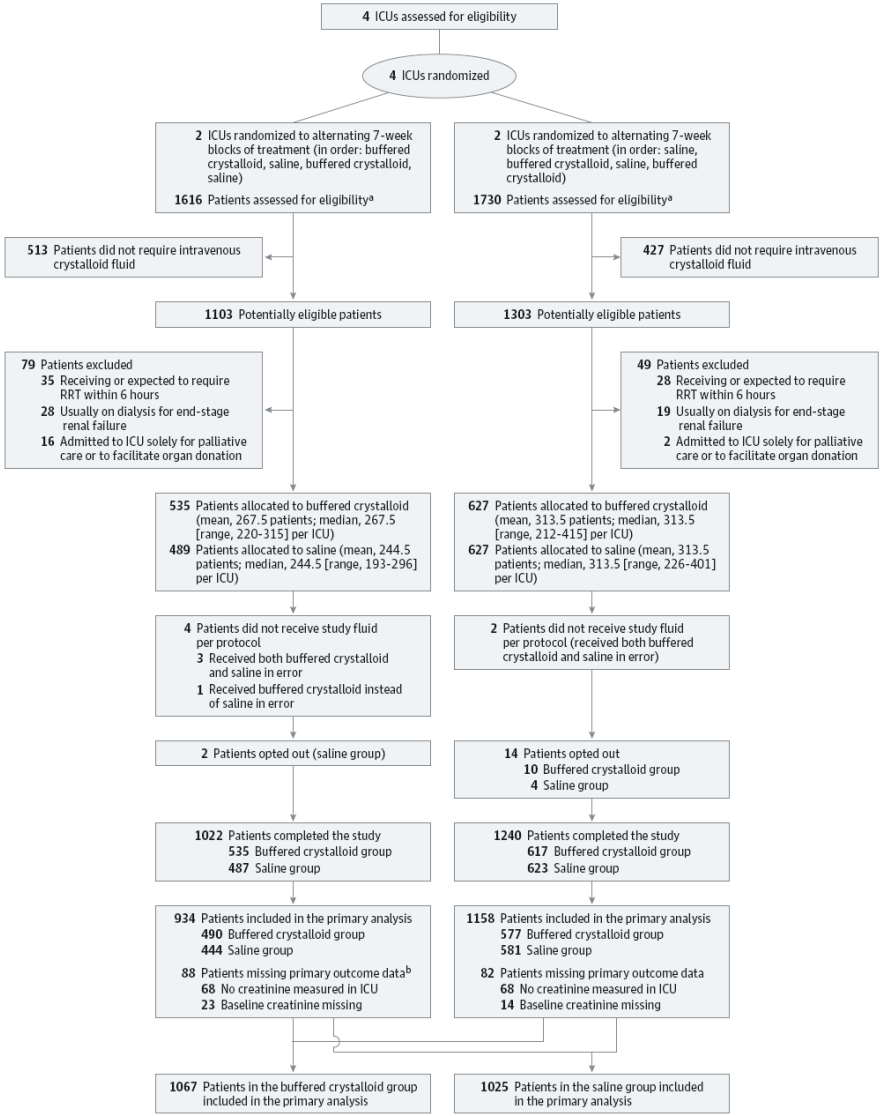
Editorial page 1695

Supplemental content at jama.com

Plasma-Lyte 148 (PL-148)

JAMA. 2015;314(16):1701-1710. doi:10.1001/jama.2015.12334
Published online October 7, 2015.

Figure 1. Flow of Clusters and Participants Through the SPLIT Trial



ICU indicates intensive care unit; RRT, renal replacement therapy; SPLIT, 0.9% Saline vs Plasma-Lyte 148 for Intensive Care Unit Fluid Therapy.

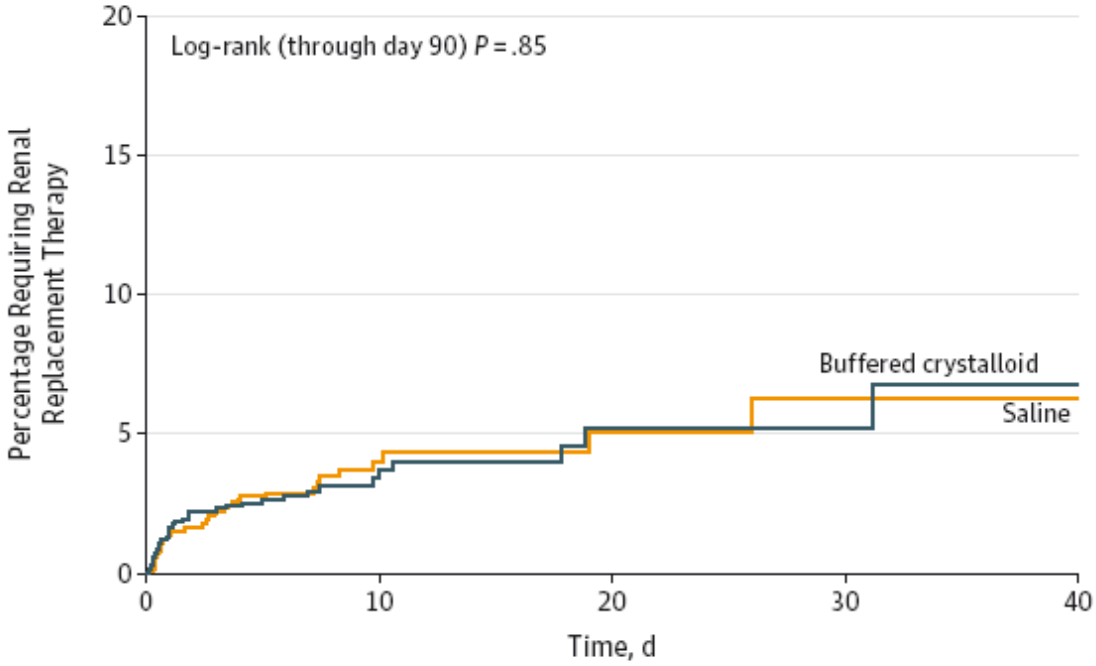
[a] All patients admitted to 1 of the study ICUs during the 28 weeks of recruitment were screened for study enrollment except for 2 patients who decided not to participate in the study prior to ICU admission.

[b] Patients could have both types of missing data

Table 2. Outcomes for Patients in the Intensive Care Unit Receiving Buffered Crystalloid vs Saline Fluid Therapy

Variable	No./Total No. (%)		Absolute Difference (95% CI)	Relative Risk (95% CI)	*P* Value
	Buffered Crystalloid	Saline			
Primary Outcome					
Acute kidney injury or failure[a]	102/1067 (9.6)	94/1025 (9.2)	0.4 (−2.1 to 2.9)	1.04 (0.80 to 1.36)	.77
Secondary Outcomes (Renal Outcomes)					
RIFLE[b]					
Risk	123/1067 (11.5)	107/1025 (10.4)	1.1 (−1.6 to 3.8)	1.10 (0.86 to 1.41)	.44
Injury	46/1067 (4.3)	57/1025 (5.6)	−1.2 (−3.1 to 0.6)	0.78 (0.53 to 1.13)	.19
Failure	54/1067 (5.1)	36/1025 (3.5)	1.5 (−0.2 to 3.3)	1.44 (0.95 to 2.18)	.09
Loss	2/1067 (0.2)	1/1025 (0.1)	0	1.92 (0.17 to 21.16)	>.99
End-stage renal failure	0/1067 (0)	0/1025 (0)			
KDIGO stage[c]					
1	194/1067 (18.2)	194/1025 (18.9)	−0.7 (−4.1 to 2.6)	0.96 (0.80 to 1.15)	.69
2	43/1067 (4.0)	46/1025 (4.5)	−0.5 (−2.2 to 1.3)	0.90 (0.60 to 1.4)	.67
3	62/1067 (5.8)	58/1025 (5.7)	0.2 (−1.8 to 2.1)	1.03 (0.73 to 1.45)	.93
RRT use and indications for RRT initiation					
RRT use	38/1152 (3.3)	38/1110 (3.4)	−0.1 (−1.6 to 1.4)	0.96 (0.62 to 1.50)	.91
Oliguria	10/1152 (0.9)	11/1110 (1.0)	−0.1 (−0.9 to 0.7)	0.88 (0.37 to 2.05)	.83

Figure 2. Cumulative Incidence of Patients Requiring Renal Replacement Therapy Until Day 90 After Enrollment in the SPLIT Trial



No. at risk					
Buffered crystalloid	1152	341	134	62	36
Saline	1110	310	124	64	28

Colloid solutions for fluid resuscitation (Review)

Bunn F, Trivedi D

THE COCHRANE COLLABORATION®

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2012, Issue 11

http://www.thecochranelibrary.com

Society of Critical Care Anesthesiologists

Section Editor: **Michael J. Murray**

Fluid Resuscitation with 6% Hydroxyethyl Starch (130/0.4) in Acutely Ill Patients: An Updated Systematic Review and Meta-Analysis

David J. Gattas, MBBS, MMed, FCICM,*† Arina Dan, MBBS, FCICM,*‡
John Myburgh, MBBCh, PhD, FCICM,*‖ Laurent Billot, MSc, DEA, AStat,¶ Serigne Lo, PhD, AStat,¶
Simon Finfer, MBBS, FRCP, FRCA, FCICM,*# and The CHEST Management Committee

Table 3. Renal Outcomes Reported by Trials Comparing 6% HES 130/0.4 with Crystalloid and Other Types of Colloid

Author and year	Control fluid(s)	Need for RRT *n/N* in HES 130/0.4 group	Need for RRT *n/N* in control group
Reports RIFLE criteria, or data allowing its calculation			
No studies			
Reports need for RRT			
Compares HES 130/0.4 with crystalloid			
No studies			
Compares HES 130/0.4 with a non-HES colloid			
Ooi,[50] 2009	4% gelatin	0/45	0/45
Godet,[51] 2008	3% gelatin	0/33	1/34
Mahmood,[52] 2007	4% gelatin	1/21	3/20
Mukhtar,[54] 2009	5% albumin	1/20	1/20
	Total	2/119	5/119
Retracted studies			
Boldt,[21] 2008	4% gelatin	1/30	1/33
Boldt,[22] 2007	5% albumin	0/25	0/25
Boldt,[23] 2007	5% albumin	0/25	0/25
Boldt,[24] 2008	5% albumin	0/25	0/25
Boldt,[27] 2003	4% gelatin	0/20	0/20
	Total	1/125	1/128

Reports comparing 6% hydroxyethyl starch (HES) 130/0.4 with other forms of HES have been excluded.

RRT = renal replacement therapy; *n* = number of RRT cases; *N* = number of RRT events; RIFLE = classification system for acute kidney injury (Risk, Injury, Failure, Loss, End-stage kidney disease).[10]

Hydroxyethyl starch (HES) versus other fluid therapies: effects on kidney function (Review)

Dart AB, Mutter TC, Ruth CA, Taback SP

THE COCHRANE COLLABORATION®

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2011, Issue 5

http://www.thecochranelibrary.com

Comparison 1. HES versus other fluid

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Renal replacement therapy	12	1236	Risk Ratio (M-H, Random, 95% CI)	1.38 [0.89, 2.16]
1.1 Non-sepsis	8	487	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.14, 1.38]
1.2 Sepsis	3	702	Risk Ratio (M-H, Random, 95% CI)	1.59 [1.20, 2.10]
1.3 Deceased organ donor	1	47	Risk Ratio (M-H, Random, 95% CI)	6.67 [0.92, 48.45]
2 RIFLE (Risk or worse)	4	325	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.81, 1.80]
2.1 Non-sepsis	2	185	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.27, 2.85]
2.2 Sepsis	2	140	Risk Ratio (M-H, Random, 95% CI)	1.28 [0.81, 2.02]
3 RIFLE (Injury or worse)	4	325	Risk Ratio (M-H, Random, 95% CI)	1.34 [0.83, 2.15]
3.1 Non-sepsis	2	185	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.12, 5.40]
3.2 Sepsis	2	140	Risk Ratio (M-H, Random, 95% CI)	1.39 [0.84, 2.30]
4 RIFLE (Failure)	4	325	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.75, 2.36]
4.1 Non-sepsis	2	185	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.07, 3.73]
4.2 Sepsis	2	140	Risk Ratio (M-H, Random, 95% CI)	1.45 [0.80, 2.64]
5 Kidney failure (author defined)	8	1199	Risk Ratio (M-H, Random, 95% CI)	1.50 [1.20, 1.87]
5.1 Non-sepsis	5	367	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.57, 2.25]
5.2 Sepsis	4	832	Risk Ratio (M-H, Random, 95% CI)	1.55 [1.22, 1.96]
6 Creatinine clearance	3	199	Mean Difference (IV, Random, 95% CI)	2.33 [-6.01, 10.67]
7 Creatinine at postoperative day 1 or 24 hours (by fluid type)	15	1084	Mean Difference (IV, Random, 95% CI)	-2.29 [-6.64, 2.07]
7.1 HES versus albumin	8	646	Mean Difference (IV, Random, 95% CI)	-2.82 [-8.38, 2.74]
7.2 HES versus gelatin	6	418	Mean Difference (IV, Random, 95% CI)	-3.28 [-10.88, 4.31]
7.3 HES versus crystalloid	1	20	Mean Difference (IV, Random, 95% CI)	19.0 [-3.86, 41.86]
8 Creatinine at postoperative day 1 or 24 hours (by patient population)	15	1084	Mean Difference (IV, Random, 95% CI)	-2.29 [-6.64, 2.07]
8.1 Non-sepsis	14	914	Mean Difference (IV, Random, 95% CI)	-2.06 [-6.58, 2.47]
8.2 Sepsis	2	170	Mean Difference (IV, Random, 95% CI)	-5.73 [-21.95, 10.49]
9 Creatinine at day 3	6	500	Mean Difference (IV, Random, 95% CI)	-3.77 [-15.67, 8.12]
10 Creatinine at days 5-8	5	461	Mean Difference (IV, Random, 95% CI)	-13.96 [-30.60, 2.68]

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Hydroxyethyl Starch or Saline for Fluid Resuscitation in Intensive Care

John A. Myburgh, M.D., Ph.D., Simon Finfer, M.D., Rinaldo Bellomo, M.D., Laurent Billot, M.Sc., Alan Cass, M.D., Ph.D., David Gattas, M.D., Parisa Glass, Ph.D., Jeffrey Lipman, M.D., Bette Liu, Ph.D., Colin McArthur, M.D., Shay McGuinness, M.D., Dorrilyn Rajbhandari, R.N., Colman B. Taylor, M.N.D., and Steven A.R. Webb, M.D., Ph.D., for the CHEST Investigators and the Australian and New Zealand Intensive Care Society Clinical Trials Group*

N Engl J Med 2012.
DOI: 10.1056/NEJMoa1209759

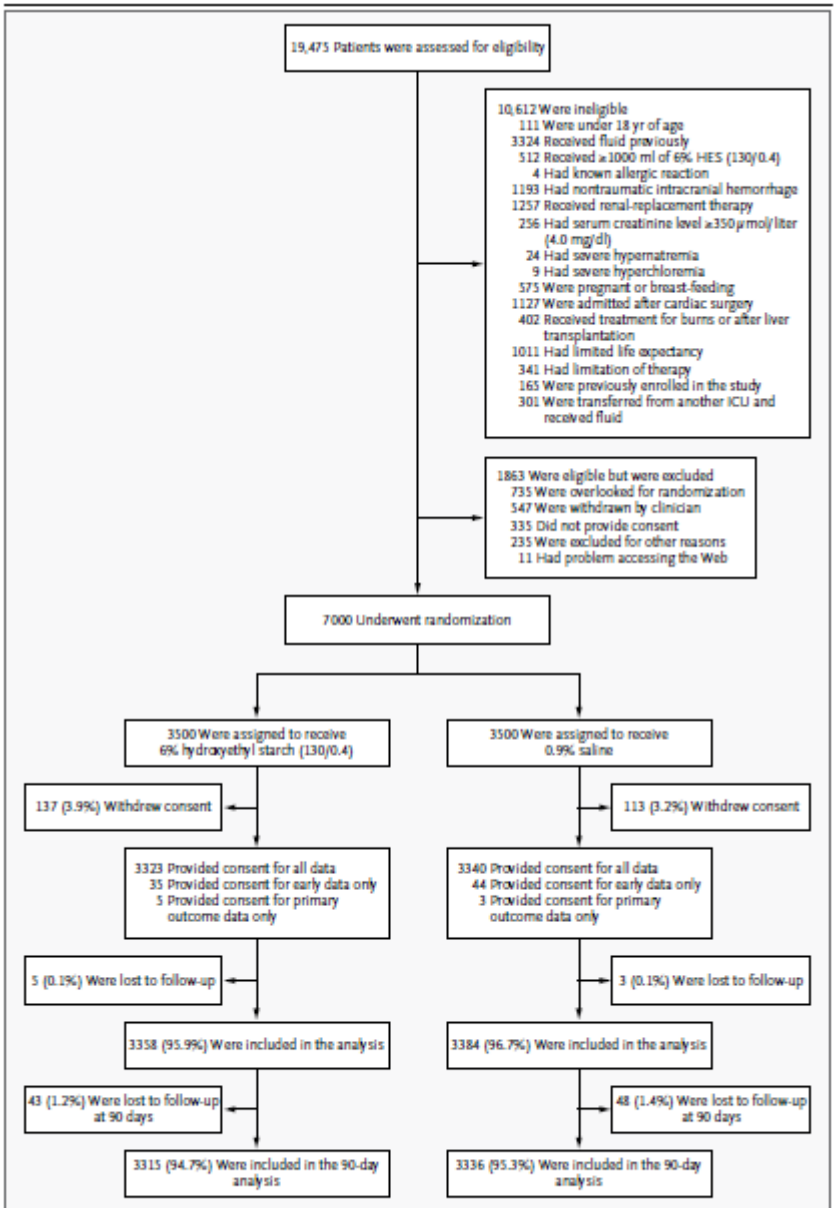


Figure 1. Assessment, Randomization, and Follow-up of the Patients.

Table 2. Outcomes and Adverse Events.*

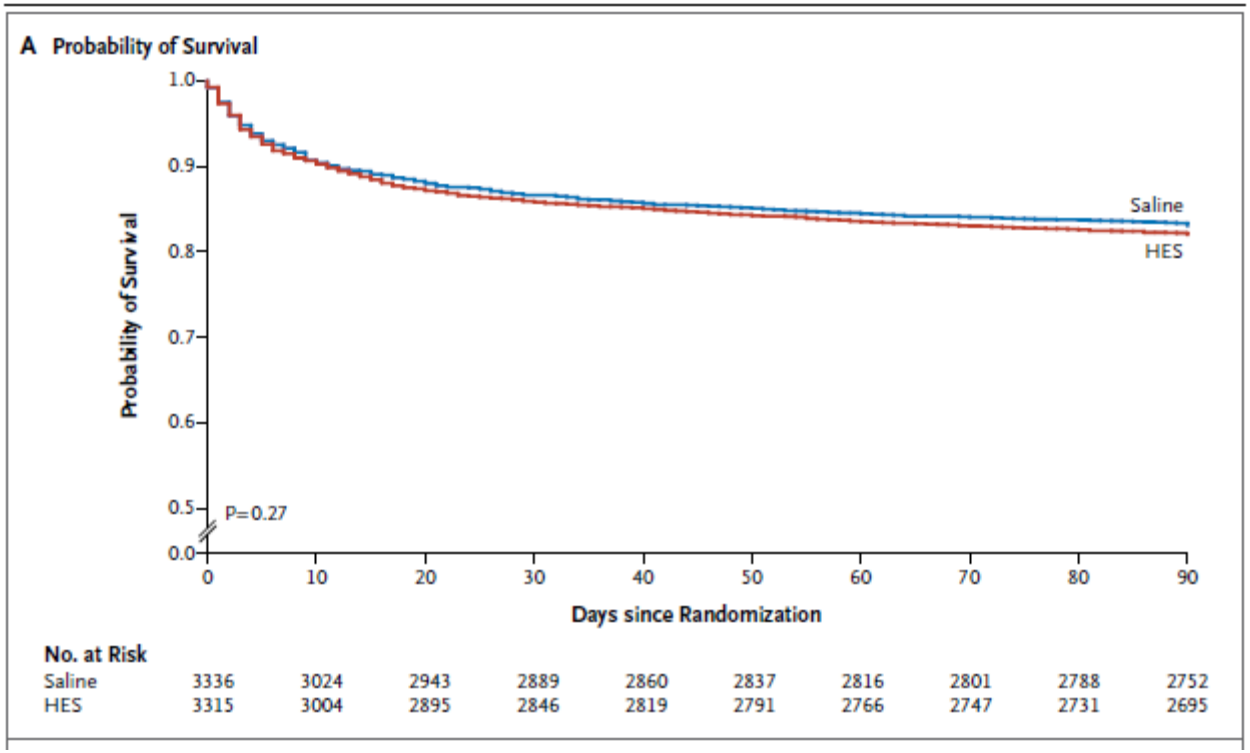
Variable	HES	Saline	Relative Risk (95% CI)	P Value
Outcome				
Primary outcome of death at day 90 — no./total no. (%)	597/3315 (18.0)	566/3336 (17.0)	1.06 (0.96 to 1.18)	0.26
Secondary outcomes — no./total no. (%)				
Renal outcomes				
RIFLE-R	1788/3309 (54.0)	1912/3335 (57.3)	0.94 (0.90 to 0.98)	0.007
RIFLE-I	1130/3265 (34.6)	1253/3300 (38.0)	0.91 (0.85 to 0.97)	0.005
RIFLE-F	336/3243 (10.4)	301/3263 (9.2)	1.12 (0.97 to 1.30)	0.12
Use of renal-replacement therapy	235/3352 (7.0)	196/3375 (5.8)	1.21 (1.00 to 1.45)	0.04
New organ failure†				
Respiratory	540/2062 (26.2)	524/2094 (25.0)	1.05 (0.94 to 1.16)	0.39
Cardiovascular	663/1815 (36.5)	722/1808 (39.9)	0.91 (0.84 to 0.99)	0.03
Coagulation	142/2987 (4.8)	119/3010 (4.0)	1.20 (0.95 to 1.53)	0.13
Hepatic	55/2830 (1.9)	36/2887 (1.2)	1.56 (1.03 to 2.36)	0.03
Tertiary outcomes — no./total no. (%)				
Death in ICU	364/3313 (11.0)	360/3331 (10.8)	1.02 (0.89 to 1.17)	0.81
Death within 28 days	458/3313 (13.8)	437/3331 (13.1)	1.05 (0.93 to 1.19)	0.40
Death in hospital	483/3307 (14.6)	456/3324 (13.7)	1.06 (0.95 to 1.20)	0.30
			Mean Difference (95% CI)	
Service utilization — no.				
Days in ICU	7.3±0.2	6.9±0.2	0.4 (0.0 to 0.9)	0.07
Days in hospital	19.3±0.3	19.1±0.3	0.2 (−0.8 to 1.1)	0.72
Days receiving mechanical ventilation	6.0±0.2	5.7±0.2	0.4 (−0.1 to 0.8)	0.12
Days receiving renal-replacement therapy	5.6±0.4	5.5±0.4	0.1 (−0.1 to 1.2)	0.86
Treatment-related adverse events‡				
Any event — no./total no. (%)	180/3416 (5.3)	95/3358 (2.8)		<0.001
Pruritus	137/3416 (4.0)	73/3358 (2.2)		
Skin rash	34/3416 (1.0)	16/3358 (0.5)		
Other	9/3416 (0.3)	6/3358 (0.2)		
Serious adverse events — no./total no. (%)§	2/3416 (0.1)	2/3358 (0.1)		0.98

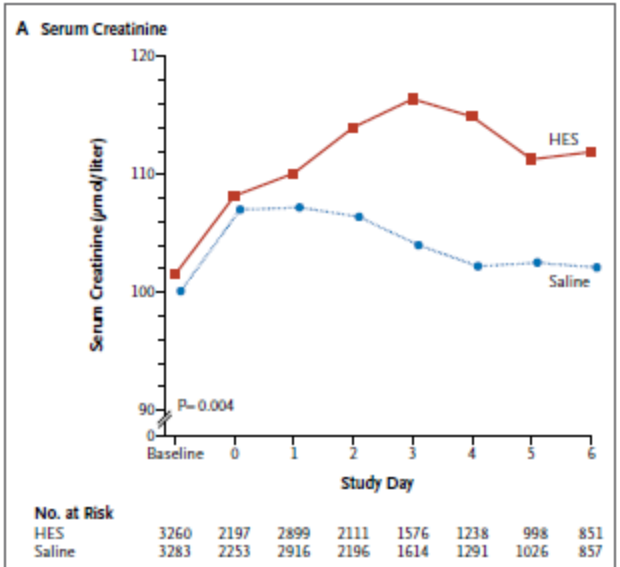
* Plus–minus values are means ±SE.

† New organ failure was defined as a Sequential Organ Failure Assessment (SOFA) score[12] of at least 3 for each category in patients who did not have such organ failure at baseline.

‡ Adverse events in the HES group include those in patients who received HES both before and after randomization.

§ Among the serious (nonfatal) treatment-related adverse events were one case each of anaphylactic shock and extravasation of fluid causing airway obstruction in the HES group and one case each of toxic epidermal necrolysis requiring unblinding of the study-group assignment and unexplained severe hypotension in the saline group.


A Probability of Survival
Probability of Survival
1.0
0.9
0.8
0.7
0.6
0.5
0.0
P=0.27
Saline
HES
0
10
20
30
40
50
60
70
80
90
Days since Randomization
No. at Risk
Saline 3336 3024 2943 2889 2860 2837 2816 2801 2788 2752
HES 3315 3004 2895 2846 2819 2791 2766 2747 2731 2695



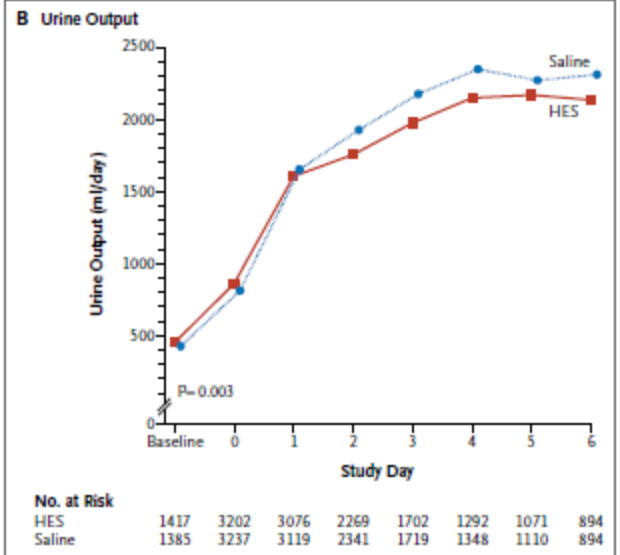


Figure 3. Serum Creatinine Levels and Urine Output through Day 6.
Day 0 was defined as the day of randomization to the end of that day, which averaged 12 hours in the two study groups. P values are for the between-group comparisons of means of the individual daily averages for 7 days, including day 0. To convert the values for creatinine to milligrams per deciliter, divide by 88.4.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Hydroxyethyl Starch 130/0.4 versus Ringer's Acetate in Severe Sepsis

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Anne B. Guttormsen, M.D., Ph.D., Jyrki Tenhunen, M.D., Ph.D.,
Gudmundur Klemenzson, M.D., Anders Åneman, M.D., Ph.D.,
Kristian R. Madsen, M.D., Morten H. Møller, M.D., Ph.D., Jeanie M. Elkjær, M.D.,
Lone M. Poulsen, M.D., Asger Bendtsen, M.D., M.P.H., Robert Winding, M.D.,
Morten Steensen, M.D., Pawel Berezowicz, M.D., Ph.D., Peter Søe-Jensen, M.D.,
Morten Bestle, M.D., Ph.D., Kristian Strand, M.D., Ph.D., Jørgen Wiis, M.D.,
Jonathan O. White, M.D., Klaus J. Thornberg, M.D., Lars Quist, M.D.,
Jonas Nielsen, M.D., Ph.D., Lasse H. Andersen, M.D., Lars B. Holst, M.D.,
Katrin Thormar, M.D., Anne-Lene Kjældgaard, M.D., Maria L. Fabritius, M.D.,
Frederik Mondrup, M.D., Frank C. Pott, M.D., D.M.Sci., Thea P. Møller, M.D.,
Per Winkel, M.D., D.M.Sci., and Jørn Wetterslev, M.D., Ph.D.,
for the 6S Trial Group and the Scandinavian Critical Care Trials Group*

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DOI: 10.1056/NEJMoa1204242

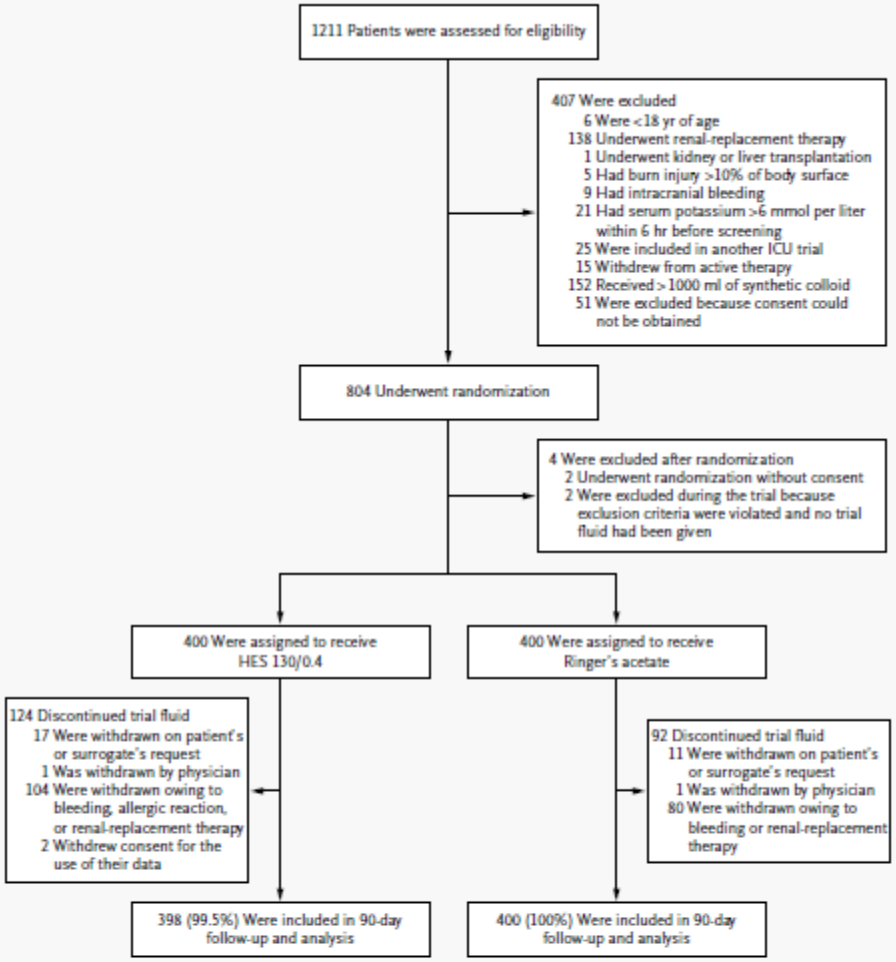


Figure 1. Randomization and Follow-up of Study Patients.

Patients were excluded for medical reasons or if they had previously undergone randomization; if they had received more than 1000 ml of synthetic colloid in the previous 24 hours; if they were enrolled in another intensive care unit (ICU) trial of drugs with effects on circulation, renal function, or coagulation; or if consent could not be obtained. Sixteen patients met two exclusion criteria. Two patients were excluded after they had been randomly assigned to a treatment group because consent had not been obtained before randomization. Another two patients were excluded, as specified by the statistical analysis plan, because subsequent assessment showed that they met exclusion criteria and they never received trial fluid. Thus, four additional patients were randomly assigned to a study group to obtain the full sample size. Two patients withdrew consent for the use of their data after the end of the trial. HES denotes hydroxyethyl starch.

Table 3. Primary and Secondary Outcomes.*

Outcome	HES 130/0.4 (N = 398)	Ringer's Acetate (N = 400)	Relative Risk (95% CI)	P Value
Primary outcome				
Dead or dependent on dialysis at day 90 — no. (%)	202 (51)	173 (43)	1.17 (1.01–1.36)	0.03
Dead at day 90 — no. (%)	201 (51)	172 (43)	1.17 (1.01–1.36)	0.03
Dependent on dialysis at day 90 — no. (%)	1 (0.25)	1 (0.25)	—	1.00
Secondary outcome measures				
Dead at day 28 — no. (%)	154 (39)	144 (36)	1.08 (0.90–1.28)	0.43
Severe bleeding — no. (%)†	38 (10)	25 (6)	1.52 (0.94–2.48)	0.09
Severe allergic reaction — no. (%)†	1 (0.25)	0	—	0.32
SOFA score at day 5 — median (interquartile range)	6 (2–11)	6 (0–10)	—	0.64
Use of renal-replacement therapy — no. (%)‡	87 (22)	65 (16)	1.35 (1.01–1.80)	0.04
Use of renal-replacement therapy or renal SOFA score ≥3 — no. (%)§	129 (32)	108 (27)	1.20 (0.97–1.48)	0.10
Doubling of plasma creatinine level — no. (%)†	148 (41)	127 (35)	1.18 (0.98–1.43)	0.08
Acidosis — no. (%)†¶	307 (77)	312 (78)	0.99 (0.92–1.06)	0.72
Alive without renal-replacement therapy — mean % of days‖	91	93	—	0.048
Use of mechanical ventilation — no. (%)†	325 (82)	321 (80)	1.02 (0.95–1.09)	0.61
Alive without mechanical ventilation — mean % of days‖	62	65	—	0.28
Alive and out of hospital — mean % of days‖	29	34	—	0.048

* For severe bleeding and severe allergic reaction, data were missing for 1 patient in the Ringer's acetate group. For doubling of the plasma creatinine level, data were missing for 38 patients in the HES 130/0.4 group and 34 patients in the Ringer's acetate group. For alive without mechanical ventilation, data were missing for 1 patient in the Ringer's acetate group. CI denotes confidence interval.

† Outcomes are for patients in the ICU during the 90-day trial period.

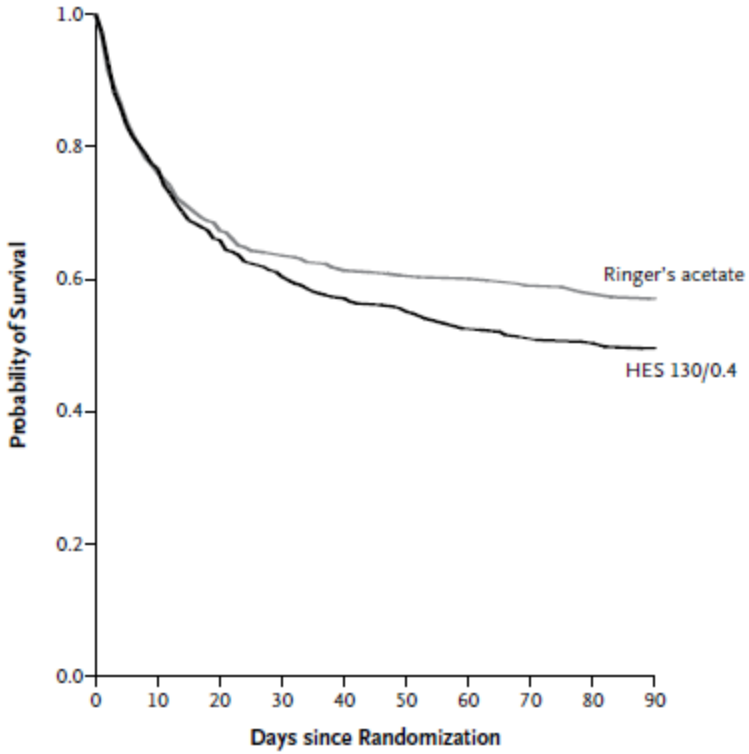
‡ Outcomes are for patients with any form of renal-replacement therapy during the 90-day trial period.

§ Outcomes are for patients with any form of renal-replacement therapy during the 90-day trial period or with a renal SOFA score of 3 or higher after the patient had a renal SOFA score of 2 or lower at randomization.

¶ Acidosis was defined as an arterial pH of less than 7.35.

‖ The mean percentage of days was calculated as the number of days without renal-replacement therapy or mechanical ventilation or the number of days out of the hospital divided by the number of days alive in the 90-day follow-up period.

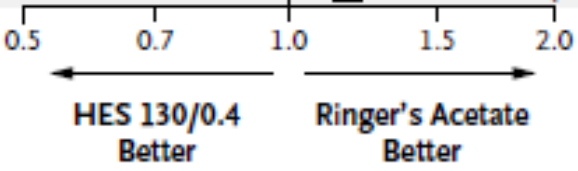
A Time to Death



No. at Risk				
HES 130/0.4	398	240	209	197
Ringer's acetate	400	254	240	228

B Relative Risk of the Primary Outcome

Subgroup	HES 130/0.4	Ringer's Acetate	Relative Risk (95% CI)	P Value for Heterogeneity
	no. of events/no. in subgroup			
Shock at the time of randomization				0.22
Yes	179/336	148/337	1.21 (1.04–1.42)	
No	23/62	25/63	0.93 (0.60–1.46)	
Acute kidney injury at the time of randomization				0.60
Yes	72/142	63/140	1.13 (0.88–1.44)	
No	130/256	110/260	1.20 (1.00–1.45)	
All patients	202/398	173/400	1.17 (1.01–1.36)	



Association of Hydroxyethyl Starch Administration With Mortality and Acute Kidney Injury in Critically Ill Patients Requiring Volume Resuscitation

A Systematic Review and Meta-analysis

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Ahmed M. Abou-Setta, MD, PhD
Alexis F. Turgeon, MD, MSc
Brett L. Houston, BSc
Lauralyn McIntyre, MD, MSc
John C. Marshall, MD
Dean A. Fergusson, PhD, MHA

Importance Hydroxyethyl starch is commonly used for volume resuscitation yet has been associated with serious adverse events, including acute kidney injury and death. Clinical trials of hydroxyethyl starch are conflicting. Moreover, multiple trials from one investigator have been retracted because of scientific misconduct.

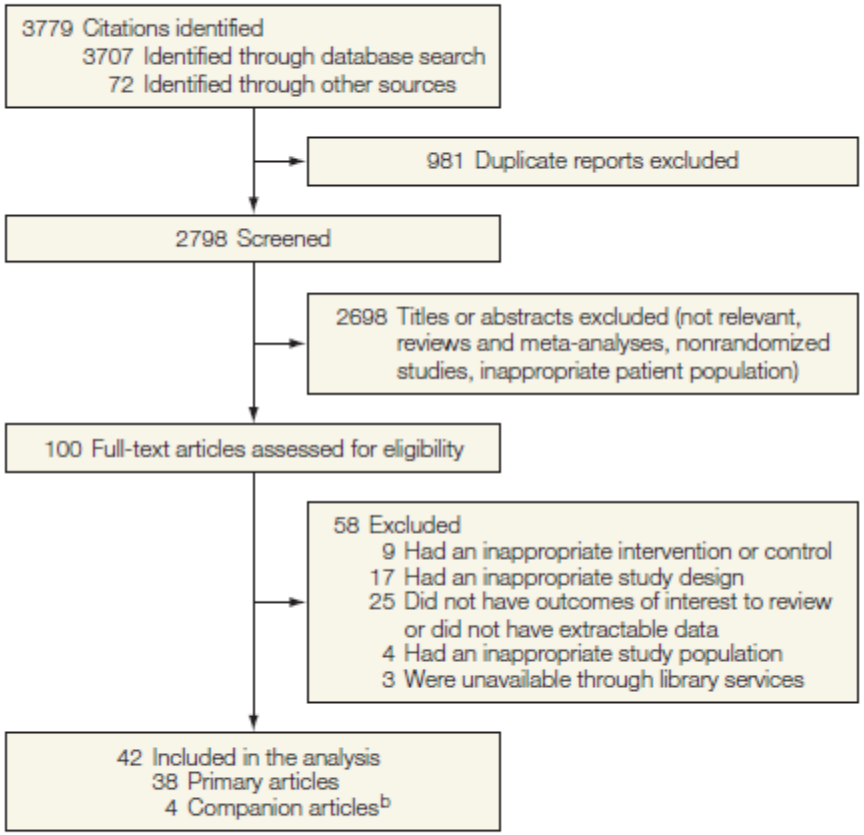
Objectives To evaluate the association of hydroxyethyl starch use with mortality and acute kidney injury.

Data Sources Randomized controlled trials from MEDLINE, EMBASE, CENTRAL, Global Health, HealthStar, Scopus, Web of Science, the International Clinical Trials Registry Platform (inception to October 2012), reference lists of relevant articles, and gray literature.

FLUIDS ARE A CORE ELEMENT IN

JAMA. 2013;309(7):678-688

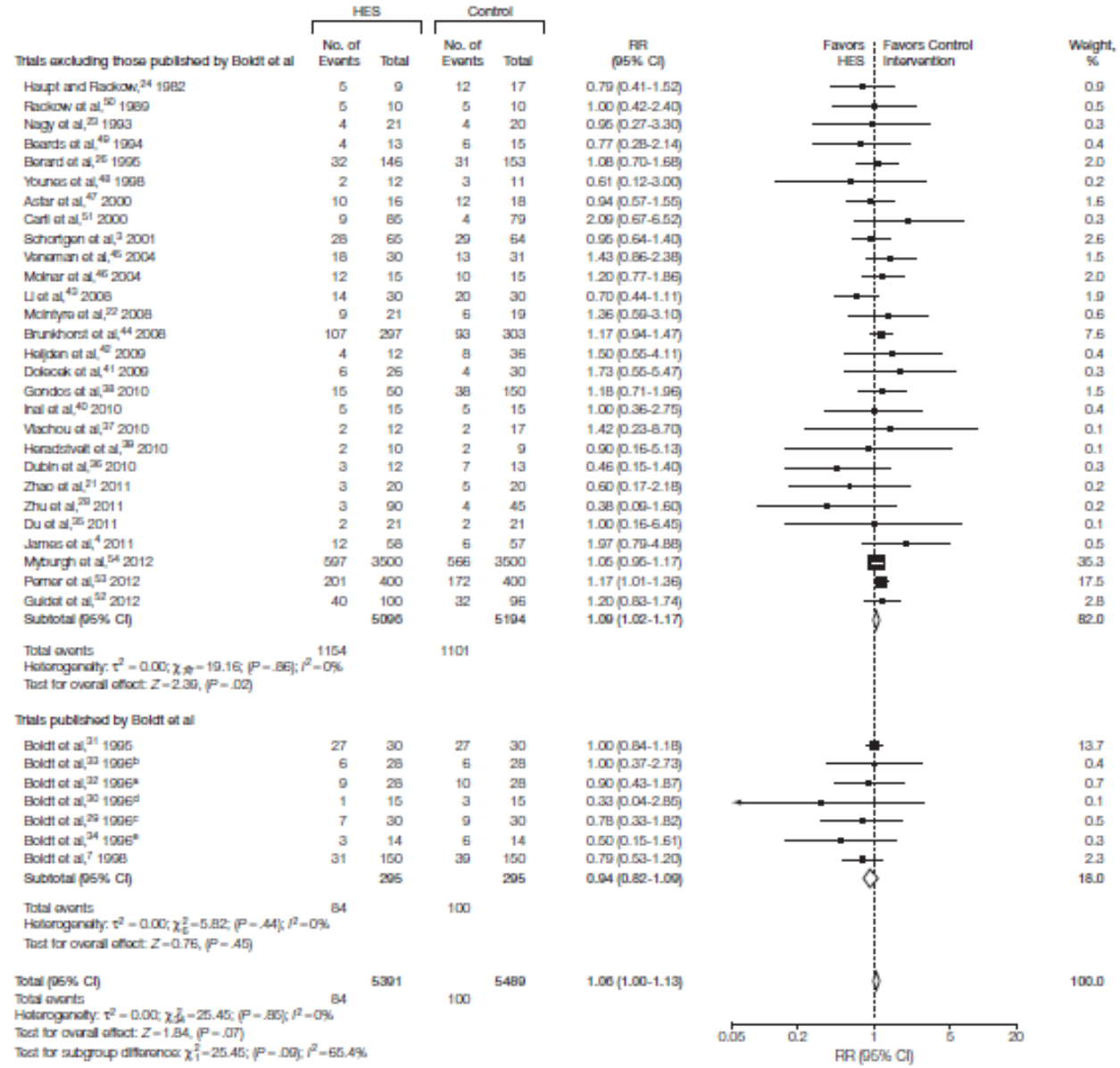
Figure 1. Study Flow Diagram[a]



[a] This flow diagram follows the Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA)[14] with modifications.

[b] Companion articles represent reports of previously published analyses involving the same study population.

Figure 2. Mortality and Hydroxyethyl Starch



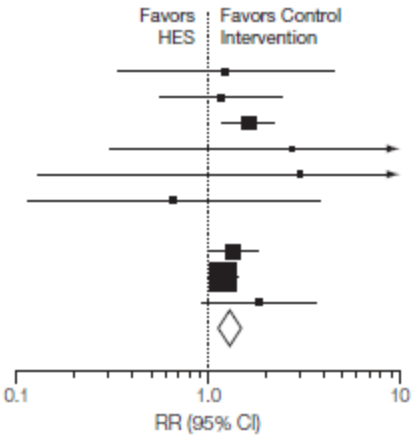
The varying sizes of the boxes represent the weight in the analysis. HES indicates hydroxyethyl starch. Risk ratios (RRs) are derived by a random-effects model using Mantel-Haenszel tests.

Figure 3. Renal Replacement Therapy and Hydroxyethyl Starch

Source	HES No. of Events	HES Total	Control No. of Events	Control Total	RR (95% CI)	Weight, %
Berard et al,[26] 1995	5	155	4	152	1.23 (0.34-4.48)	1.0
Schortgen et al,[3] 2001	13	65	11	64	1.16 (0.56-2.40)	3.3
Brunkhorst et al,[44] 2008	81	297	51	303	1.62 (1.19-2.21)	18.0
McIntyre et al,[22] 2008	3	21	1	19	2.71 (0.31-23.93)	0.4
Du et al,[35] 2011	1	21	0	21	3.00 (0.13-69.70)	0.2
James et al,[4] 2011	2	58	3	57	0.66 (0.11-3.78)	0.6
Viachou et al,[37] 2010	0	12	0	17	Not estimable	
Perner al,[53] 2012	87	400	65	400	1.34 (1.00-1.79)	20.8
Myburgh et al,[54] 2012	235	3500	196	3500	1.20 (1.00-1.44)	51.8
Guidet et al,[52] 2012	21	100	11	96	1.83 (0.93-3.59)	3.9
Total (95% CI)		**4629**		**4629**	**1.32 (1.15-1.50)**	**100.00**
Total events	448		342			

Heterogeneity: $\tau^2 = 0.00$; $\chi^2_8 = 5.07$; ($P = .75$); $I^2 = 0\%$

Test for overall effect: $Z = 4.08$, ($P < .001$)



The varying sizes of the boxes represent the weight in the analysis. HES indicates hydroxyethyl starch. Risk ratios (RRs) are derived by a random-effects model using Mantel-Haenszel tests.

EDITORIAL

Hydroxyethyl Starch for Intravenous Volume Replacement

More Harm Than Benefit

Massimo Antonelli, MD

Claudio Sandroni, MD

In addition, this meta-analysis[4] included 3 additional randomized trials published in 2012—the Crystalloid Versus Hydroxyethyl Starch Trials (CHEST),[2] the Scandinavian

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DOI 10.1007/s00134-012-2614-0

SYSTEMATIC REVIEW

Christiane S. Hartog
Helga Skupin
Charles Natanson
Junfeng Sun
Konrad Reinhart

Systematic analysis of hydroxyethyl starch (HES) reviews: proliferation of low-quality reviews overwhelms the results of well-performed meta-analyses

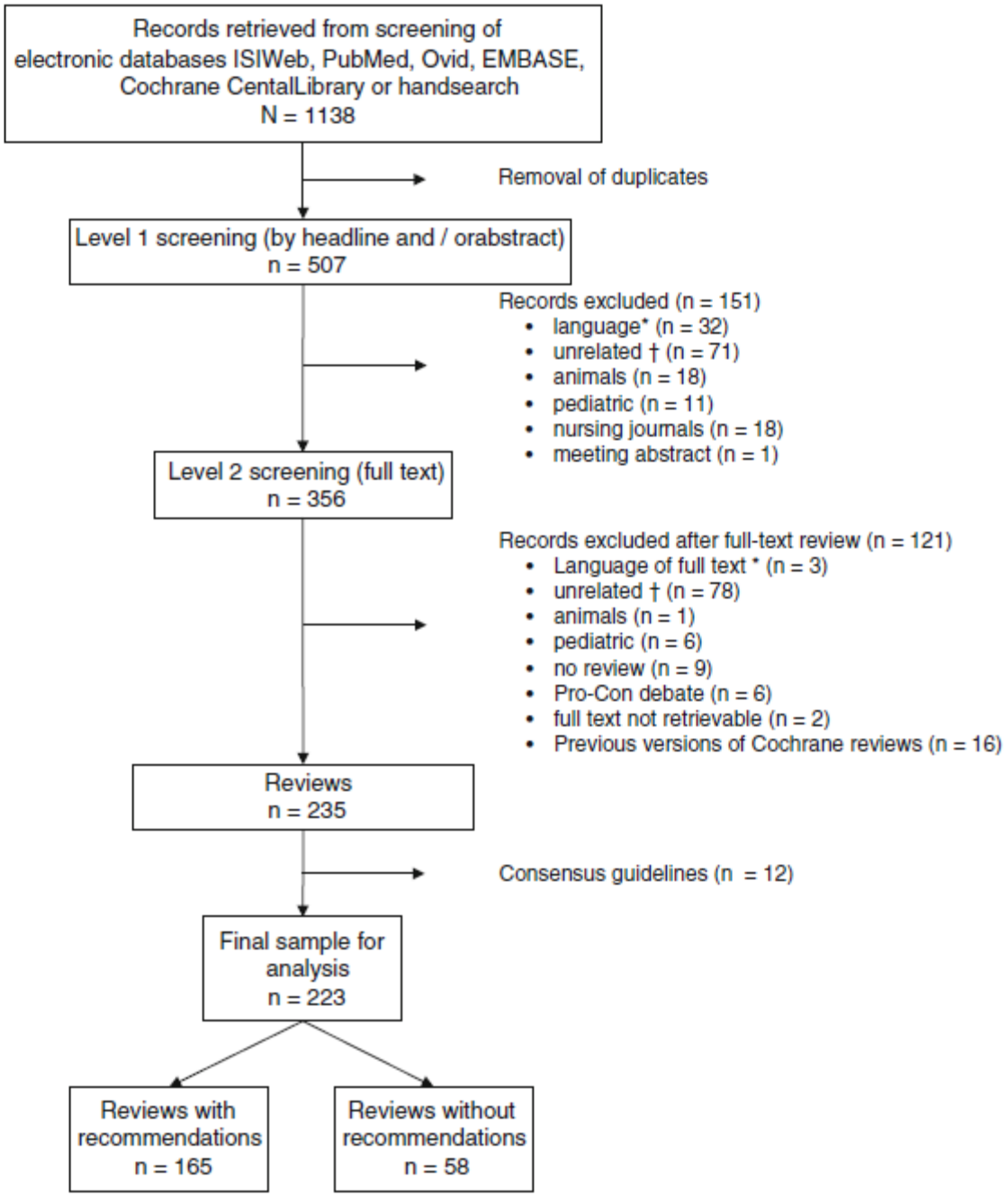


Fig. 1 Study flow. *Excluded languages: Japanese, Russian, Serbocroatian, Polish, Danish, Swedish, Spanish, Portuguese, Chinese, Lithuanian, Czech, Italian. †Unrelated conditions: ovarian hyperstimulation syndrome, retinal vein occlusion, small-volume resuscitation, idiopathic sensorineural hearing loss, eclampsia, diabetic ketoacidosis, chronic obstructive lung disease, polymer science, pharmacokinetics, apheresis, cell harvest, blood component harvest and organ preservation

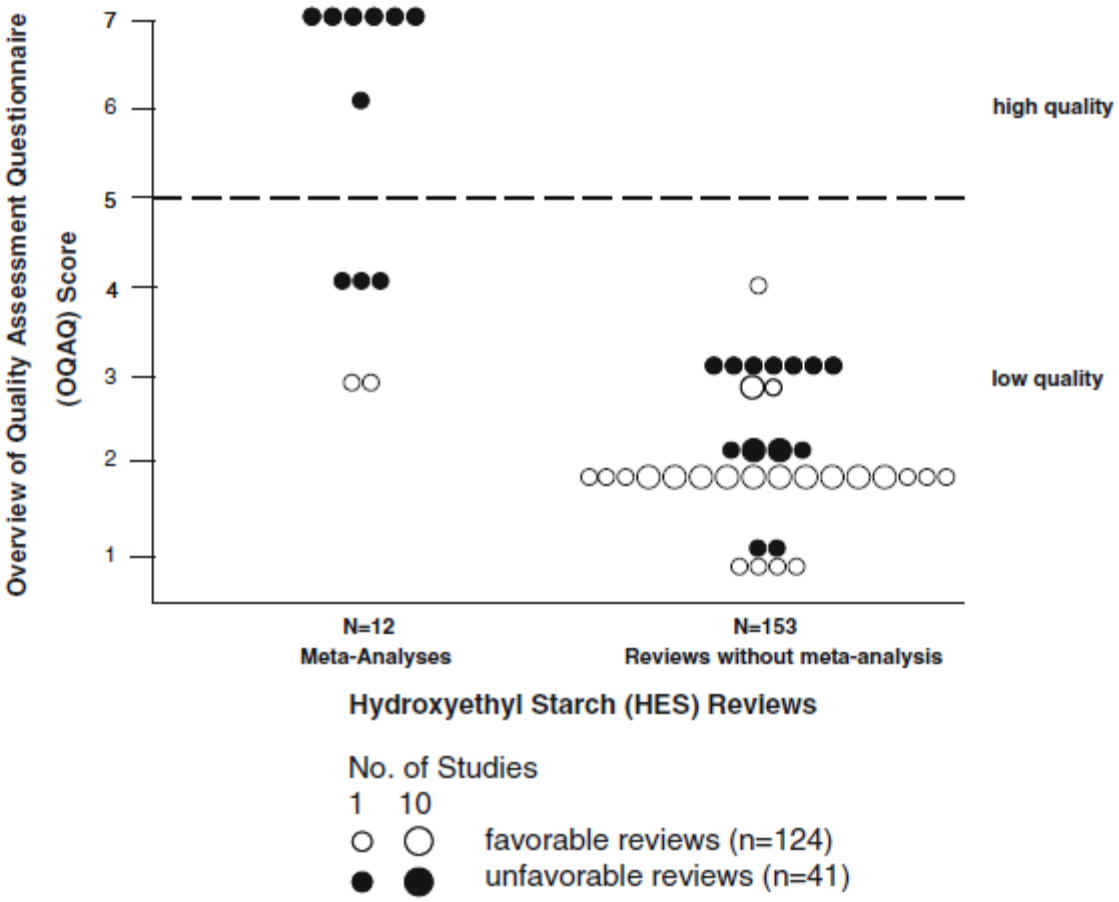
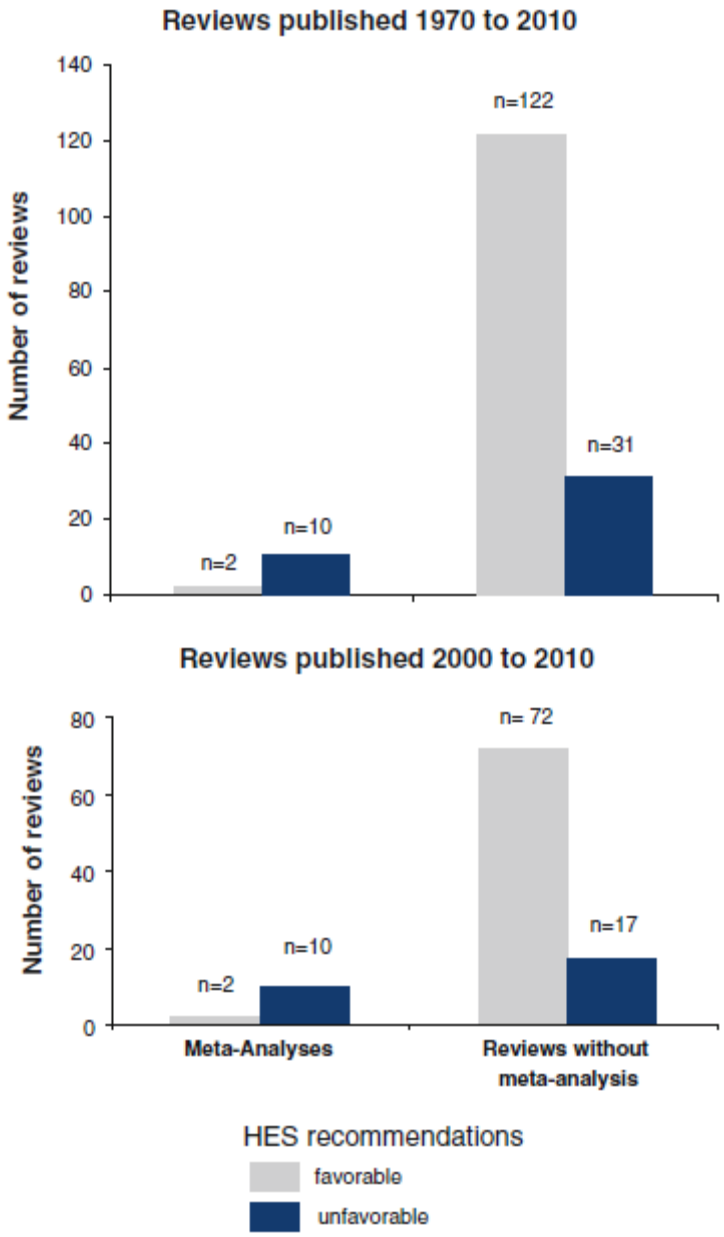


Fig. 2 Quality assessment of hydroxyethyl starch (*HES*) reviews by *OQAQ* score. Reviews with an overall Overview of Quality Assessment Questionnaire (OQAQ) score of ≥5 are regarded as having minor or minimal flaws, i.e., being of high quality. HES meta-analyses achieved significantly higher OQAQ scores [$n = 12$; median (range) 6.5 (3–7)] than HES reviews without a meta-analysis [$n = 153$; 2 (1–4); $p < 0.0001$]. Meta-analyses that were not in favor of HES use achieved significantly higher OQAQ scores [$n = 10$, 7 (4–7)] than favorable meta-analyses [$n = 2$, 3 (3–3); $p = 0.02$]


Reviews published 1970 to 2010
Number of reviews
140
120
100
80
60
40
20
0
n=122
n=31
n=10
n=2
Reviews published 2000 to 2010
Number of reviews
80
60
40
20
0
n= 72
n=17
n=10
n=2
Meta-Analyses
Reviews without meta-analysis
HES recommendations
favorable
unfavorable

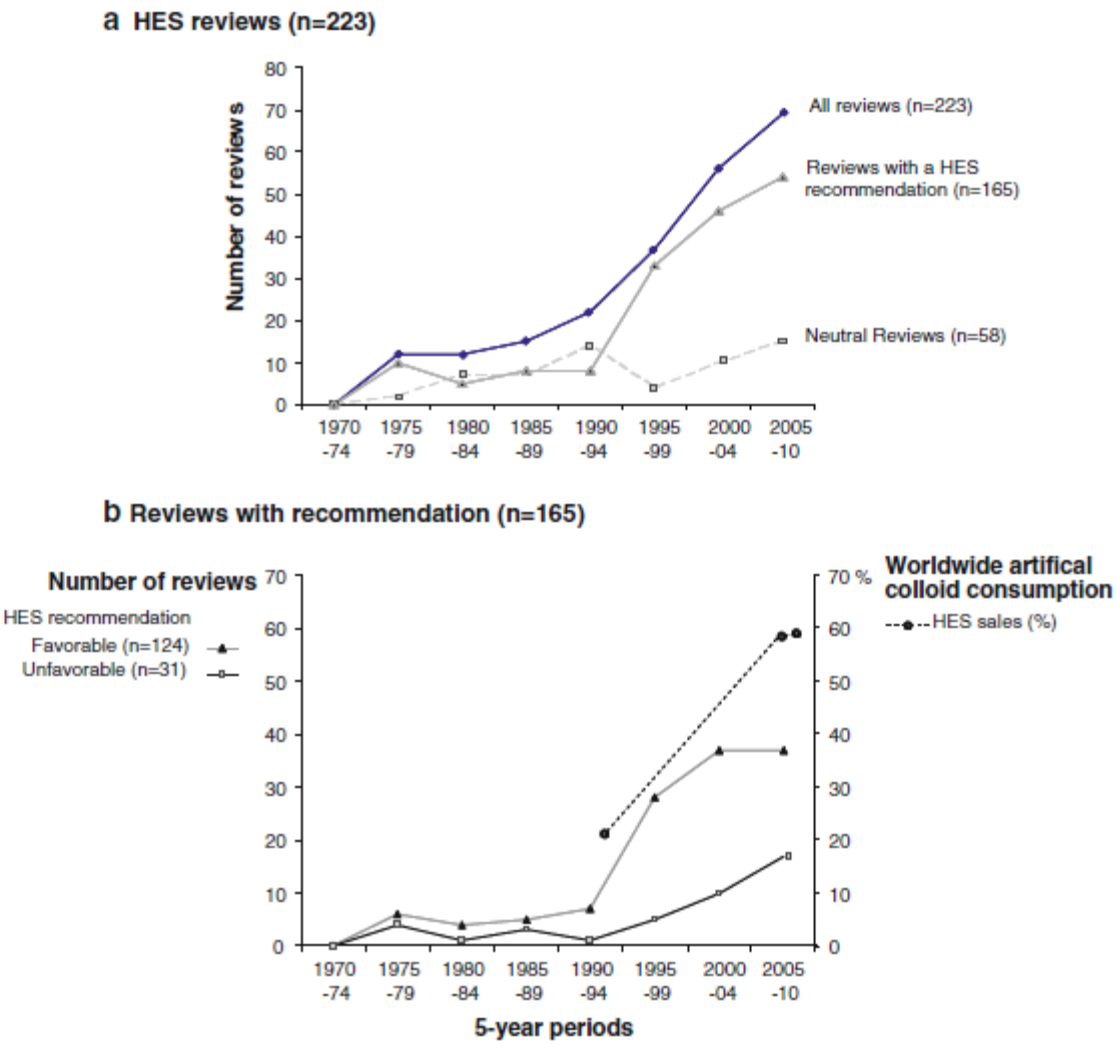


Fig. 4 Hydroxyethyl starch reviews and HES consumption. The number of HES reviews increased after 1990, and most of these contained a recommendation (**a**). Favorable reviews in particular increased dramatically during this period in which the HES market share of worldwide artificial colloid consumption tripled from approx. 20 % [43] to approx. 60 % [44] (**b**)

Table 2 The 14 most prolific authors of 124 favorable HES reviews and their potential conflict of interest with fluid manufacturers

Author	pCOI declared/ HES reviews by this author (*n*)	Years in which HES reviews were published	Years in which a pCOI related to a fluid manufacturer was declared by the author
1	1/21	1998–2009	2009 ("past research activities were funded by…") [19]
2	1/5	2005, 2007–2009	2008 (lead author of a meta-analysis funded by and co-authored by a salaried employee of a fluid manufacturer) [70]; 2010 ("has received honoraria as a speaker and research support from…") [86]
3	0/5	1997–2000	2003 ("unrestricted grant by fluid manufacturer") [87]
4	0/4	1998, 2001, 2003	2006 ("received honoraria from …") [88]
5	1/4	2007–2009	2008 ("recipient of travel grants" and an "unrestricted educational grant") [89]
6	0/4	1993, 2003–2005	2008 ("honoraria and unrestricted grants from… ") [54]
7	0/4	1991, 2000, 2004	2006 ("has received unrestricted grants") [90]; see correction published [Br Med J 2006; 333 doi:10.1136/bmj.39041.739479.68]
8	0/3	1998, 2000, 2002	2002 (recipient of salary from fluid manufacturer) [91]
9	0/3	2008, 2009	2011 (recipient of salary from fluid manufacturer) [92]
10	3/3	2005, 2007–2008	2002–2008 (recipient of salary from fluid manufacturer) [70, 92]
11	0/4	1993, 1998, 2007, 2009	No pCOI identified
12	0/4	1982, 1986, 1996, 2002	No pCOI identified
13	0/3	1986, 1996, 2007	No pCOI identified
14	0/3	2004–2006	No pCOI identified

A potential conflict of interest (pCOI) was declared by four authors in six of these reviews. A pCOI with a fluid manufacturer was declared by additional six authors in other publications at the time or up to 3 years after their last HES review was published. Three authors (9/124 reviews) served as salaried Medical Officers for a fluid manufacturing company at the time of writing or soon thereafter

Fourteen authors wrote 56 % (70/124) of all favorable reviews. The three most prolific authors (authors 1, 2 and 3) wrote 25 % (31/124) of these reviews; the remaining 11 authors wrote 31 % (39/124)

Intensive Care Med (2012) 38:1134–1142
DOI 10.1007/s00134-012-2560-x

ORIGINAL

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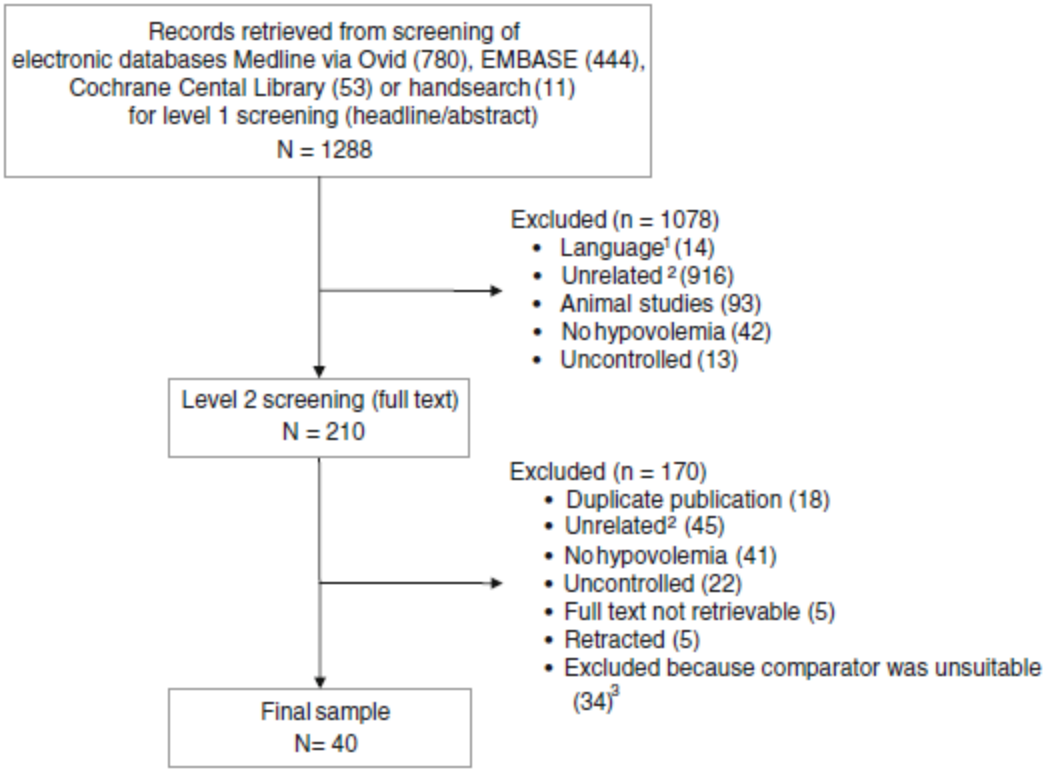
V. Vlasakov
K. Reinhart
R. Jaeschke
H. Rueddel
R. Hutagalung
A. Stacke
C. S. Hartog

Safety of gelatin for volume resuscitation—a systematic review and meta-analysis

Fig. 1 Study flow



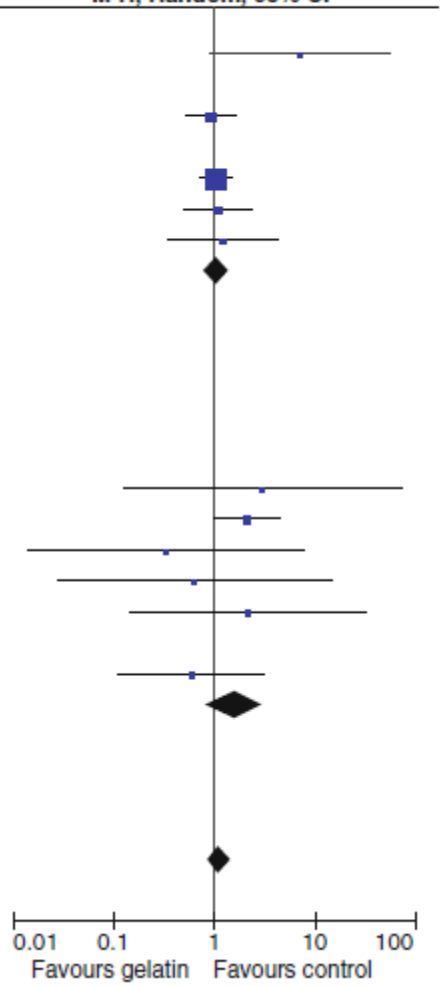
[1] Russian (9), Chinese (2), Portuguese (1), Danish (1), Turkish (1)

[2] reviews, letters, case reports, in-vitro studies

[3] non-protein colloids were defined as unsuitable comparators

A *Mortality*

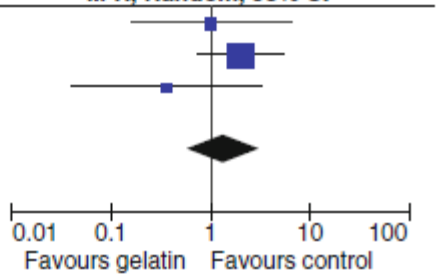
Study or Subgroup	Gelatin Events	Gelatin Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
2.1.1 Critically ill adults and children						
Akech 2006	7	44	1	44	1.5%	7.00 [0.90, 54.55]
Dung 1999	0	13	0	37		Not estimable
Gondos 2010	12	50	26	100	18.2%	0.92 [0.51, 1.67]
Ngo 2001	0	56	0	166		Not estimable
Stockwell 1992	50	249	45	229	49.4%	1.02 [0.71, 1.47]
Upadhay 2005	9	29	9	31	10.7%	1.07 [0.49, 2.32]
van der Heijden 2009	3	12	5	24	4.1%	1.20 [0.34, 4.20]
Subtotal (95% CI)		**453**		**631**	**84.0%**	**1.05 [0.80, 1.38]**
Total events	81		86			
Heterogeneity: Tau² = 0.00; Chi² = 3.60, df = 4 (P = 0.46); I² = 0%						
Test for overall effect: Z = 0.34 (P = 0.73)						
2.1.2 Trauma, Emergency and Elective Surgery						
Boldt 1992	0	14	0	28		Not estimable
Himpe 1991	1	35	0	35	0.6%	3.00 [0.13, 71.22]
Parker 2004	19	198	9	198	10.9%	2.11 [0.98, 4.55]
Soares 2009	0	20	1	20	0.6%	0.33 [0.01, 7.72]
Tollofsrud 1995	0	10	1	20	0.7%	0.64 [0.03, 14.36]
Verheij 2006	1	16	1	34	0.9%	2.13 [0.14, 31.85]
Wahba 1996b	0	10	0	10		Not estimable
Wu 2001	2	18	3	16	2.3%	0.59 [0.11, 3.11]
Subtotal (95% CI)		**321**		**361**	**16.0%**	**1.57 [0.84, 2.96]**
Total events	23		15			
Heterogeneity: Tau² = 0.00; Chi² = 3.36, df = 5 (P = 0.64); I² = 0%						
Test for overall effect: Z = 1.40 (P = 0.16)						
Total (95% CI)		**774**		**992**	**100.0%**	**1.12 [0.87, 1.44]**
Total events	104		101			
Heterogeneity: Tau² = 0.00; Chi² = 8.33, df = 10 (P = 0.60); I² = 0%						
Test for overall effect: Z = 0.87 (P = 0.38)						
Test for sub group differences: Chi² = 1.32, df = 1 (P = 0.25), I² = 24.1%						



C *Acute kidney injury*[1]

Study or Subgroup	Gelatin Events	Gelatin Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Soares 2009	2	20	2	20	20.0%	1.00 [0.16, 6.42]
Stockwell 1992	11	59	5	53	65.7%	1.98 [0.73, 5.32]
Upadhay 2005	1	29	3	31	14.3%	0.36 [0.04, 3.23]
Total (95% CI)		**108**		**104**	**100.0%**	**1.35 [0.58, 3.14]**
Total events	14		10			

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 2.08$, df = 2 (P = 0.35); $I^2 = 4\%$
Test for overall effect: Z = 0.70 (P = 0.49)



[1] AKI defined as serum urea > 30 mmol/L, or requirement for renal replacement therapy [29] or abnormal serum creatinine and urinary spot sodium of >40 mmol/L, or an increase in serum creatinine by 2.0mg/dL (176 µmol/L) [25] or elevation of creatinine above 1.5 mg/dL [30].

Table 2 Subgroup outcomes

Subgroup	Outcome	Studies	Patients	No. of events/ no. of patients		Effect estimate[a]
				Gelatin	Control	
High dose[b]	Mortality	4	623	66/322	55/301	1.19 (0.66, 2.13)
	Exposure to allogeneic transfusions	1	41	8/21	1/20	7.62 (1.05, 55.55)
>24 h	Mortality	6	1,213	69/558	55/655	1.27 (0.72, 2.22)
	Exposure to allogeneic transfusions	2	420	32/210	22/210	1.44 (0.87, 2.38)

[a] Statistical method: risk ratio (M-H, random, 95 % CI); <1 favors gelatin, >1 favors control
[b] Gelatin dose ≥30 ml/kg

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

Objective: To assess whether resuscitation with albumin-containing solutions, compared with other fluids, is associated with lower mortality in patients with sepsis.

Data Sources: MEDLINE, Embase, and Cochrane Central Register of Controlled Trials databases, the metaRegister of Controlled Trials, and the Medical Editors Trial Amnesty Register.

Study Selection: Prospective randomized clinical trials of fluid resuscitation with albumin-containing solutions compared with other fluid resuscitation regimens, which included a population or subgroup of participants with sepsis, were included.

Data Extraction: Assessment of the validity of included studies and data extraction were conducted independently by two authors.

Data Synthesis: For the primary analysis, the effect of albumin-containing solutions on all-cause mortality was assessed by using a fixed-effect meta-analysis.

Results: Seventeen studies that randomized 1977 participants were included in the meta-analysis. There were eight studies that included only patients with sepsis and nine where patients with sepsis were a subgroup of the study population. There was no evidence of heterogeneity, $I^2 = 0\%$. The use of albumin for resuscitation of patients with sepsis was associated with a reduction in mortality with the pooled estimate of the odds ratio of 0.82 (95% confidence limits 0.67–1.0, $p = .047$).

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)

KEY WORDS: sepsis; resuscitation; albumin-containing solutions; meta-analysis

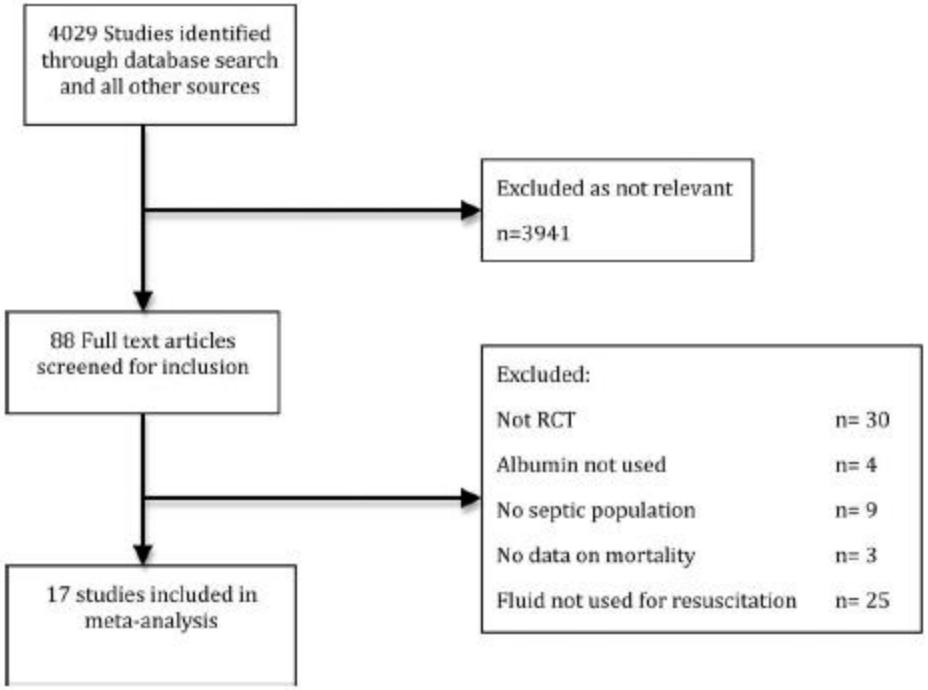


Figure 1. Flow diagram showing results of search and reasons for exclusion of studies. *RCT*, randomized controlled trial.

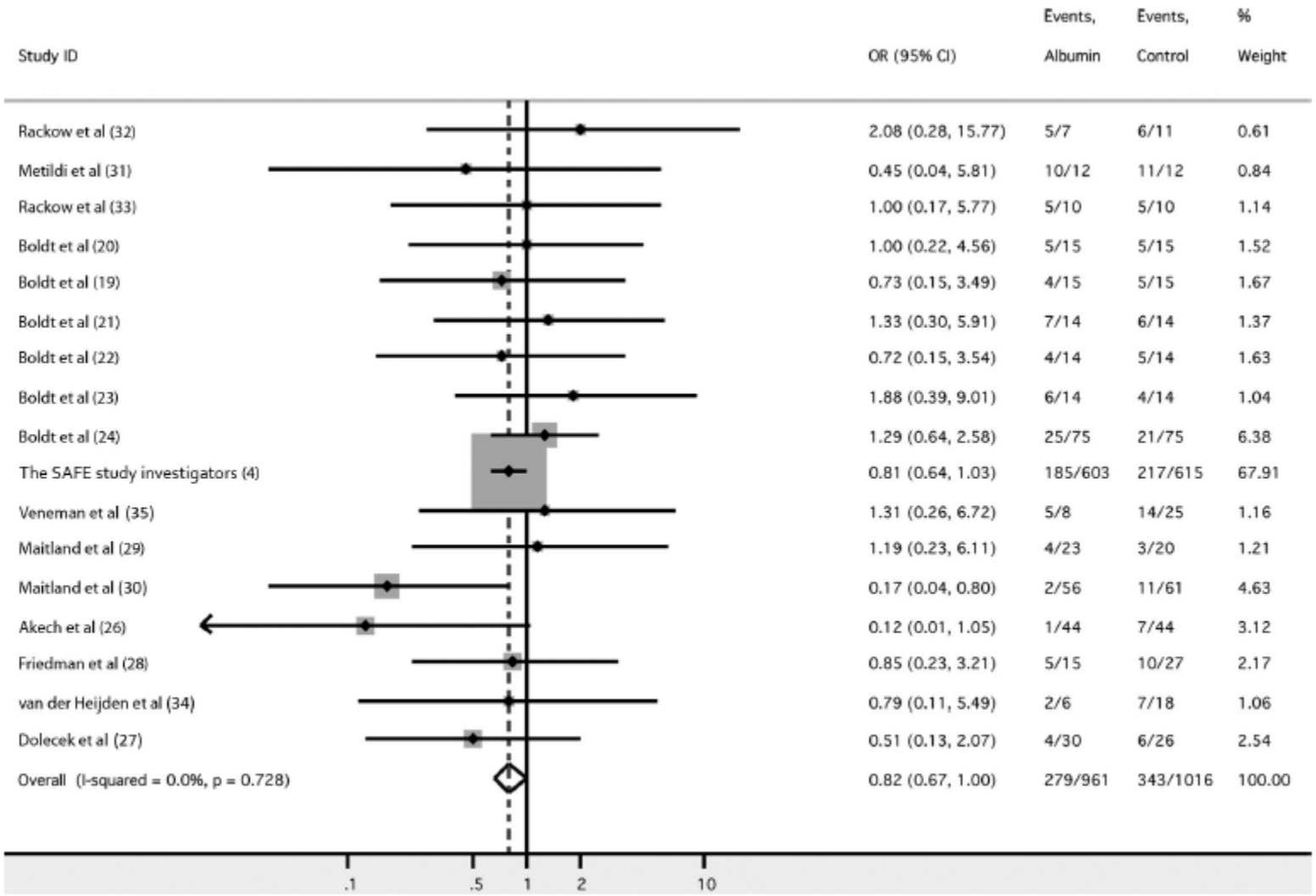


Figure 2. Forrest plot showing the pooled estimate of the effect of resuscitation with albumin-containing solutions on mortality for patients with sepsis. *OR*, odds ratio; *CI*, confidence limit.

Table 3. Pooled estimates of the effect of resuscitation fluid regimens compared with albumin in patients with sepsis

Fluid	Number of Studies	Total Participants	I^2	Estimate of Odds Ratio	95% Confidence Limits	p
Crystalloid	7	1441	0%	0.78	0.62–0.99	.04
Starch	12	463	0%	1.04	0.7–1.54	.84
Gelofusine	2	100	40.1%	0.27	0.06–1.14	.08

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Albumin Replacement in Patients with Severe Sepsis or Septic Shock

Pietro Caironi, M.D., Gianni Tognoni, M.D., Serge Masson, Ph.D., Roberto Fumagalli, M.D., Antonio Pesenti, M.D., Marilena Romero, Ph.D., Caterina Fanizza, M.Stat., Luisa Caspani, M.D., Stefano Faenza, M.D., Giacomo Grasselli, M.D., Gaetano Iapichino, M.D., Massimo Antonelli, M.D., Vieri Parrini, M.D., Gilberto Fiore, M.D., Roberto Latini, M.D., and Luciano Gattinoni, M.D., for the ALBIOS Study Investigators*

N Engl J Med 2014;370:1412-21.
DOI: 10.1056/NEJMoa1305727

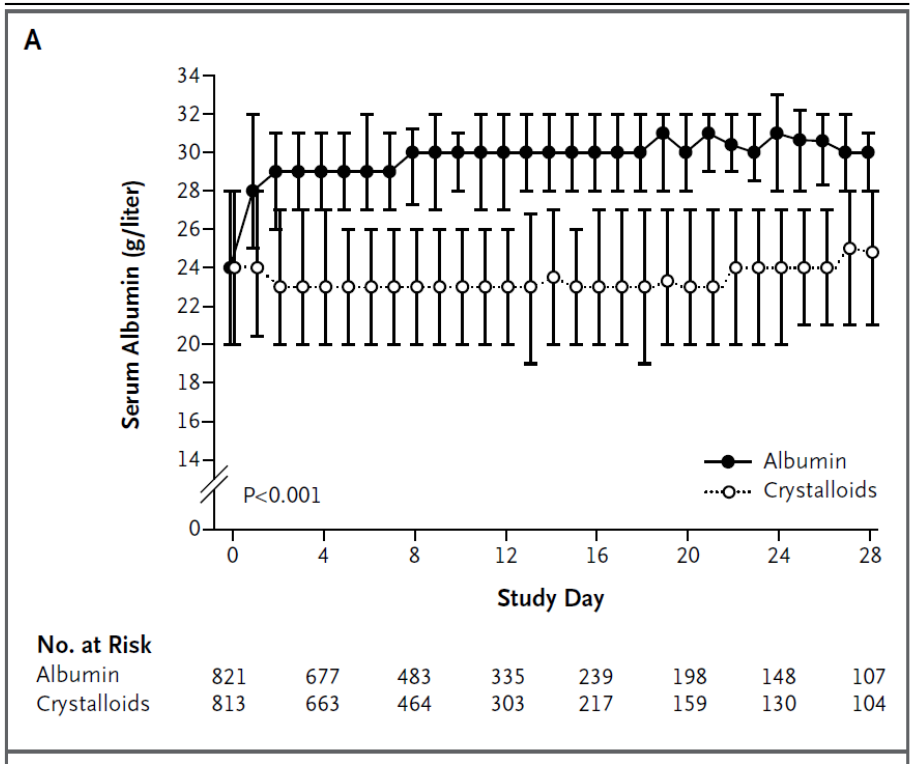
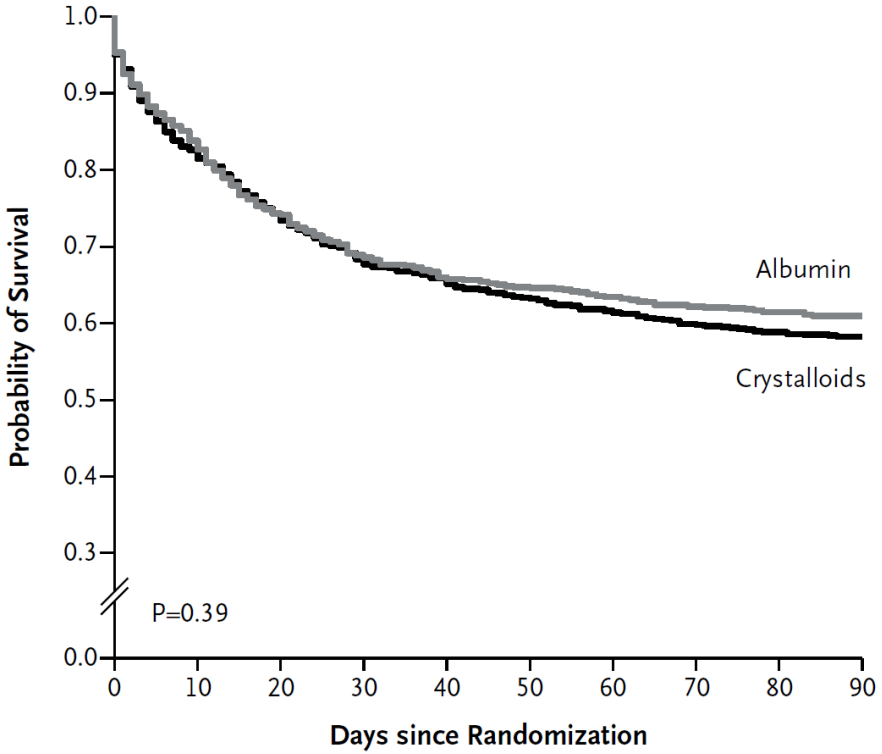


Figure 1. Serum Albumin Levels through Day 28 and Net Fluid Balance through Day 7.

Panel A shows the serum albumin concentration through day 28 in patients receiving albumin and crystalloids or crystalloids alone. Day 0 was defined as the time of randomization. Data are medians, with I bars indicating interquartile ranges. The P value is for the between-group comparison performed with the use of a two-factor analysis of variance for repeated measurements to test time (29 days for serum albumin, including day 0) and group effects. Panel B shows the net fluid balance through day 7 for patients receiving albumin and crystalloids or crystalloids alone. The daily net fluid balance was calculated as the difference between the total amount of administered fluid (including 20% albumin; crystalloids; other blood products, such as packed red cells, fresh-frozen plasma, or platelets; and other fluids) and the total amount of excreted fluid each day (including urinary output and other fluid losses, such as fluids potentially removed with continuous renal-replacement therapy, fluids lost as feces, aspirated gastric content, drainage fluids,

Table 2. Outcomes.

Outcome	Albumin Group	Crystalloid Group	Relative Risk (95% CI)	P Value
Primary outcome: death at 28 days — no./total no. (%)	285/895 (31.8)	288/900 (32.0)	1.00 (0.87–1.14)	0.94
Secondary outcomes				
Death at 90 days — no./total no. (%)	365/888 (41.1)	389/893 (43.6)	0.94 (0.85–1.05)	0.29
New organ failures — no./total no. (%)*				0.99
None	372/836 (44.5)	383/841 (45.5)		
1 organ	283/836 (33.9)	287/841 (34.1)		
2 organs	130/836 (15.6)	123/841 (14.6)		
3 organs	40/836 (4.8)	36/841 (4.3)		
4 organs	10/836 (1.2)	11/841 (1.3)		
5 organs	1/836 (0.1)	1/841 (0.1)		



No. at Risk

Albumin	903	733	647	597	567	556	545	535	529	523
Crystalloids	907	729	652	598	676	551	538	521	511	504

Figure 2. Probability of Survival from Randomization through Day 90.

The graph shows the Kaplan–Meier estimates for the probability of survival among patients receiving albumin and crystalloids and among those receiving crystalloids alone. The P value was calculated with the use of the log-rank test.

Conclusions

Les solutions recommandées sont:

- Cristalloïdes
- Gélatines (à éviter en cas de risque ou présence d'insuffisance rénale)

Les amidons ne doivent plus être utilisés.

Les catécholamines

Les médicaments

- Dopamine (problème de commercialisation en Belgique)
- Adrénaline
- Noradrénaline
- Dobutamine

Tableau 2 Propriétés pharmacologiques des différents vasopresseurs

Vasopressine et analogues	Action sur les récepteurs V1a-R (membrane des cellules musculaires lisses) Améliore la réponse aux amines α-stimulantes (diminue les besoins en noradrénaline) [109] À fortes doses, diminution des débits (cardiaque, hépatosplanchnique) par vasoconstriction extrême [68]
Terlipressine	Action principale sur les récepteurs V1(>>V2) [110,111]
Amines sympathomimétiques	
Noradrénaline	Stimulation α-adrénergique Vasoconstriction artérielle puissante et augmentation de la précharge (et donc du débit cardiaque si celui-ci est dépendant de la précharge) [27,112-114]
Dopamine	Vasodilatation à faibles doses (< 5 µg/kg/mn) [115] Inotrope positif (5-10 µg/kg/mn) Effet α-adrénergique prédominant d'où vasoconstriction artérielle (> 10µg/kg/mn)
Adrénaline	Effets chronotrope, bathmotrope et inotrope positifs, vasoconstriction puissante
Phényléphrine	α1-agoniste pur, augmente la PAM sans modifier le débit ni les pressions de remplissage cardiaques [28,78]

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Comparison of Dopamine and Norepinephrine in the Treatment of Shock

Daniel De Backer, M.D., Ph.D., Patrick Biston, M.D., Jacques Devriendt, M.D., Christian Madl, M.D., Didier Chochrad, M.D., Cesar Aldecoa, M.D., Alexandre Brasseur, M.D., Pierre Defrance, M.D., Philippe Gottignies, M.D., and Jean-Louis Vincent, M.D., Ph.D., for the SOAP II Investigators*

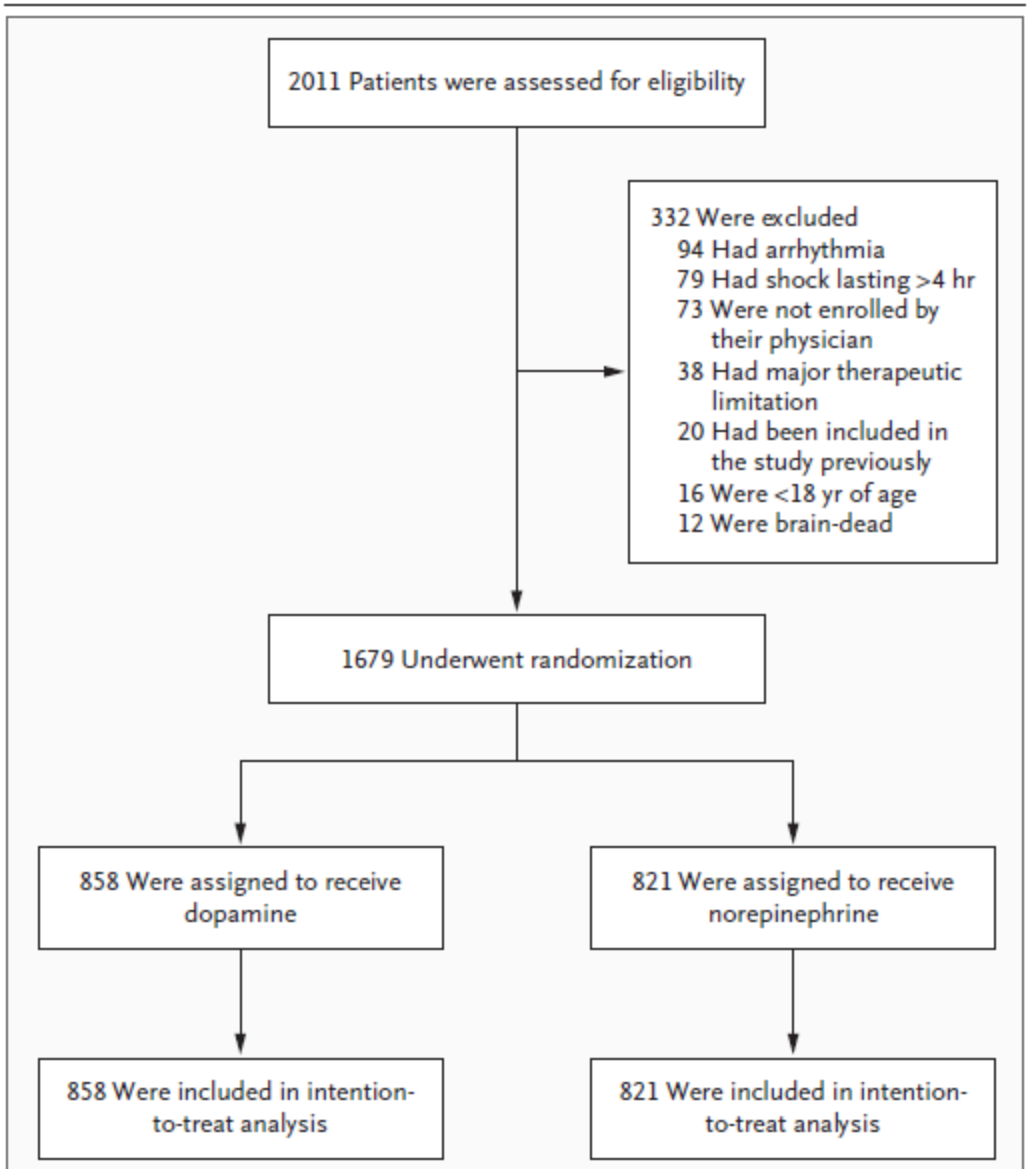
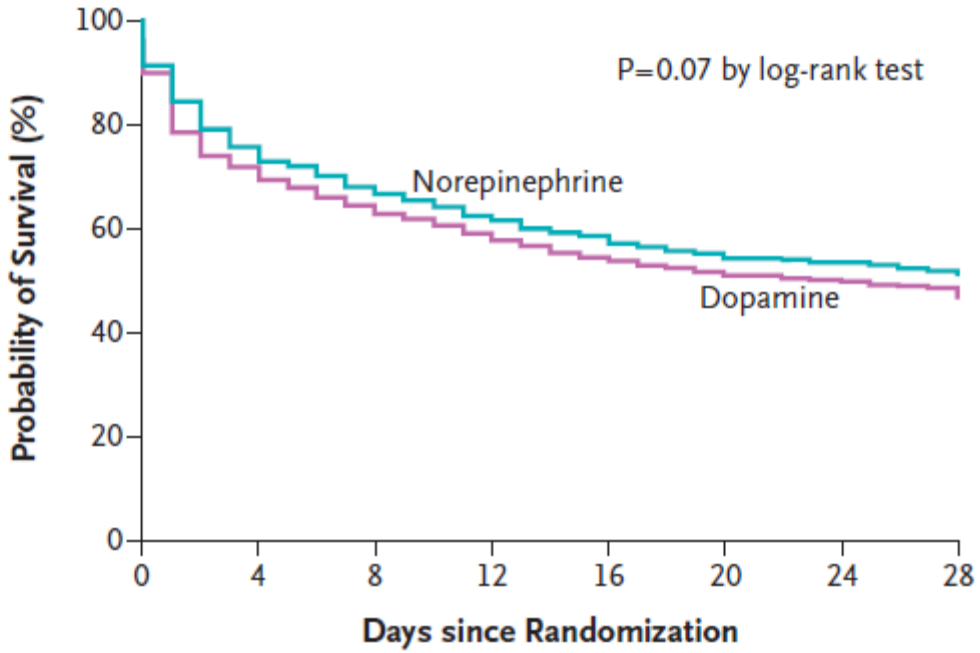


Figure 1. Screening and Enrollment.

Table 2. Mortality Rates.*

Time Period	Dopamine	Norepinephrine	Odds Ratio (95% CI)†	P Value
	percent mortality			
During stay in intensive care unit	50.2	45.9	1.19 (0.98–1.44)	0.07
During hospital stay	59.4	56.6	1.12 (0.92–1.37)	0.24
At 28 days	52.5	48.5	1.17 (0.97–1.42)	0.10
At 6 mo	63.8	62.9	1.06 (0.86–1.31)	0.71
At 12 mo	65.9	63.0	1.15 (0.91–1.46)	0.34

* Data were available for 1656 patients in the intensive care unit, in the hospital, and at 28 days; for 1443 patients at 6 months; and for 1036 patients at 12 months.
† Odds ratios for death are for the comparison of the dopamine group with the norepinephrine group.



No. at Risk								
Norepinephrine	821	617	553	504	467	432	412	394
Dopamine	858	611	546	494	452	426	407	386

Figure 2. Kaplan–Meier Curves for 28-Day Survival in the Intention-to-Treat Population.

Table 1. Baseline Characteristics of the Patients and Major Therapeutic Interventions at Baseline.*

Variable	Dopamine (N = 858)	Norepinephrine (N = 821)
Age — yr		
Median	68	67
Interquartile range	55–76	56–76
Male sex — no. (%)	507 (59.1)	449 (54.7)
APACHE II score†		
Median	20	20
Interquartile range	15–28	14–27
SOFA score‡		
Median	9	9
Interquartile range	7–12	6–12
Reason for admission — no. (%)		
Medical	565 (65.9)	532 (64.8)
Scheduled surgery	168 (19.6)	161 (19.6)
Emergency surgery	125 (14.6)	128 (15.6)
Cause of shock — no. (%)		
Sepsis	542 (63.2)	502 (61.1)
Lungs	278 (32.4)	246 (30.0)
Abdomen	138 (16.1)	135 (16.4)
Urine	51 (5.9)	42 (5.1)
Catheter	14 (1.6)	10 (1.2)
Endocardium	9 (1.0)	11 (1.3)
Mediastinum	10 (1.2)	15 (1.8)
Soft tissues	11 (1.3)	13 (1.6)
Other	15 (1.7)	20 (2.4)
Cardiogenic source	135 (15.7)	145 (17.6)
Myocardial infarction	75 (8.7)	86 (10.5)
Dilated cardiomyopathy	25 (2.9)	19 (2.3)
Tamponade	2 (0.2)	7 (0.9)
Pulmonary embolism	10 (1.2)	8 (1.0)
Valvular disease	4 (0.5)	5 (0.6)
After cardiopulmonary bypass	19 (2.2)	20 (2.4)
Other		
Hypovolemia	138 (16.1)	125 (15.2)
Hemorrhage	130 (15.2)	116 (14.1)
Trauma	17 (2.0)	23 (2.8)
Gastrointestinal bleeding	31 (3.6)	22 (2.7)
Bleeding at surgical site	64 (7.5)	57 (6.9)
Other	18 (2.1)	14 (1.7)
Dehydration	8 (0.9)	9 (1.1)
Other	48 (5.9)	44 (5.0)
Spinal	6 (0.7)	8 (1.0)
Peridural§	13 (1.5)	4 (0.5)
Intoxication-related¶	7 (0.8)	4 (0.5)
Anaphylactic	3 (0.3)	4 (0.5)
Miscellaneous	13 (1.5)	29 (3.5)
Hemodynamic, respiratory, and biologic variables		

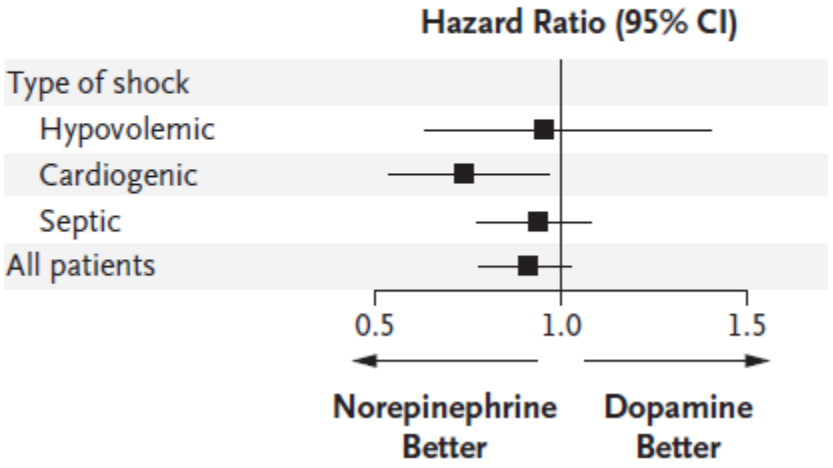


Figure 3. Forest Plot for Predefined Subgroup Analysis According to Type of Shock.

A total of 1044 patients were in septic shock (542 in the dopamine group and 502 in the norepinephrine group), 280 were in cardiogenic shock (135 in the dopamine group and 145 in the norepinephrine group), and 263 were in hypovolemic shock (138 in the dopamine group and 125 in the norepinephrine group). The P value for interaction was 0.87.

Dopamine versus norepinephrine in the treatment of septic shock: A meta-analysis*

Daniel De Backer, MD, PhD; Cesar Aldecoa, MD; Hassane Njimi, MSc, PhD; Jean-Louis Vincent, MD, PhD, FCCM

Objectives: There has long-been controversy about the possible superiority of norepinephrine compared to dopamine in the treatment of shock. The objective was to evaluate the effects of norepinephrine and dopamine on outcome and adverse events in patients with septic shock.

Data Sources: A systematic search of the MEDLINE, Embase, Scopus, and CENTRAL databases, and of Google Scholar, up to June 30, 2011.

Study Selection and Data Extraction: All studies providing information on the outcome of patients with septic shock treated with dopamine compared to norepinephrine were included. Observational and randomized trials were analyzed separately. Because time of outcome assessment varied among trials, we evaluated 28-day mortality or closest estimate. Heterogeneity among trials was assessed using the Cochrane Q homogeneity test. A Forest plot was constructed and the aggregate relative risk of death was computed. Potential publication bias was evaluated using funnel plots.

Methods and Main Results: We retrieved five observational (1,360 patients) and six randomized (1,408 patients) trials, totaling 2,768 patients (1,474 who received norepinephrine and 1,294 who received dopamine). In observational studies, among which there was significant heterogeneity ($p < .001$), there was no difference in mortality (relative risk, 1.09; confidence interval, 0.84–1.41; $p = .72$). A sensitivity analysis identified one trial as being responsible for the heterogeneity; after exclusion of that trial, no heterogeneity was observed and dopamine administration was associated with an increased risk of death (relative risk, 1.23; confidence interval, 1.05–1.43; $p < .01$). In randomized trials, for which no heterogeneity or publication bias was detected ($p = .77$), dopamine was associated with an increased risk of death (relative risk, 1.12; confidence interval, 1.01–1.20; $p = .035$). In the two trials that reported arrhythmias, these were more frequent with dopamine than with norepinephrine (relative risk, 2.34; confidence interval, 1.46–3.77; $p = .001$).

Conclusions: In patients with septic shock, dopamine administration is associated with greater mortality and a higher incidence of arrhythmic events compared to norepinephrine administration. (Crit Care Med 2012; 40:725–730)

Key Words: adrenergic agents; adverse effects; mortality; outcome; vasopressor

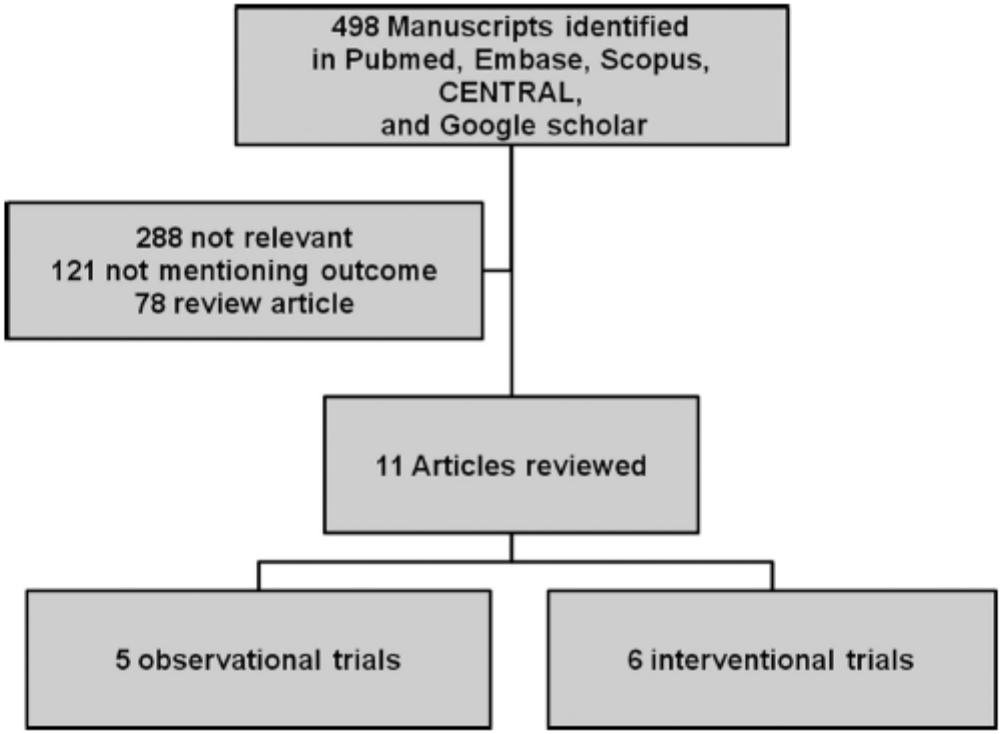


Figure 1. Flow chart of systematic search.

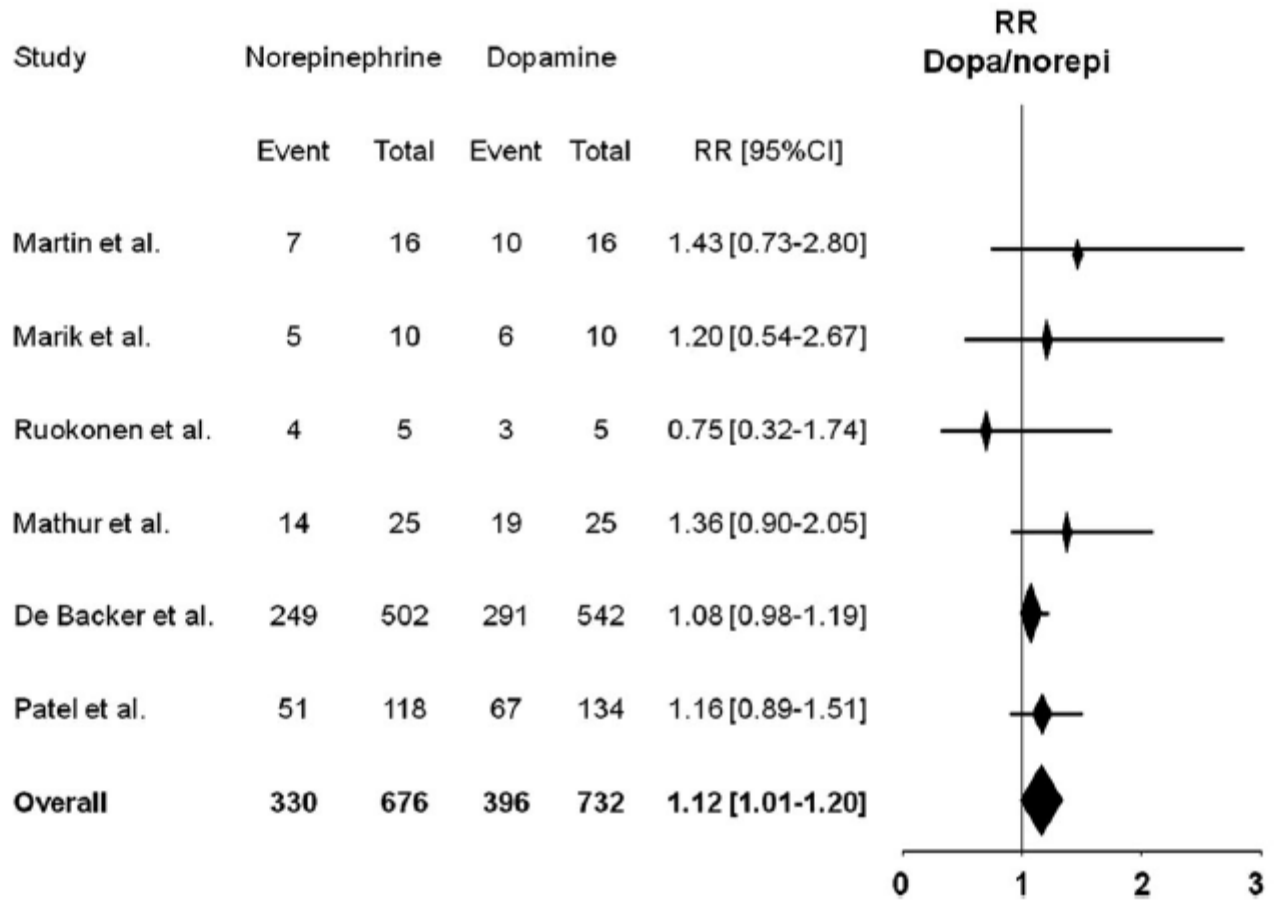


Figure 3. Forest plot of risk ratio (*RR*) of death (28 days or nearest estimate) in interventional trials. The *p* value for aggregate RR of dopamine (*dopa*) compared to norepinephrine (*norepi*) in interventional studies was .035. Relative weights of the different trials in the analysis: Martin et al (27) 2%; Marik et al (30) 1%; Ruokonen et al (29) 1%; Mathur et al (25) 4%; De Backer et al (15) 81%; and Patel et al (16) 10%. No heterogeneity was observed ($p = .77$; $I^2 = 0$; confidence interval, 0%–25%).

Norepinephrine plus dobutamine versus epinephrine alone for management of septic shock: a randomised trial

*Djillali Annane, Philippe Vignon, Alain Renault, Pierre-Edouard Bollaert, Claire Charpentier, Claude Martin, Gilles Troché, Jean-Damien Ricard, Gérard Nitenberg, Laurent Papazian, Elie Azoulay, Eric Bellissant, for the CATS Study Group**

Lancet 2007; 370: 676–84

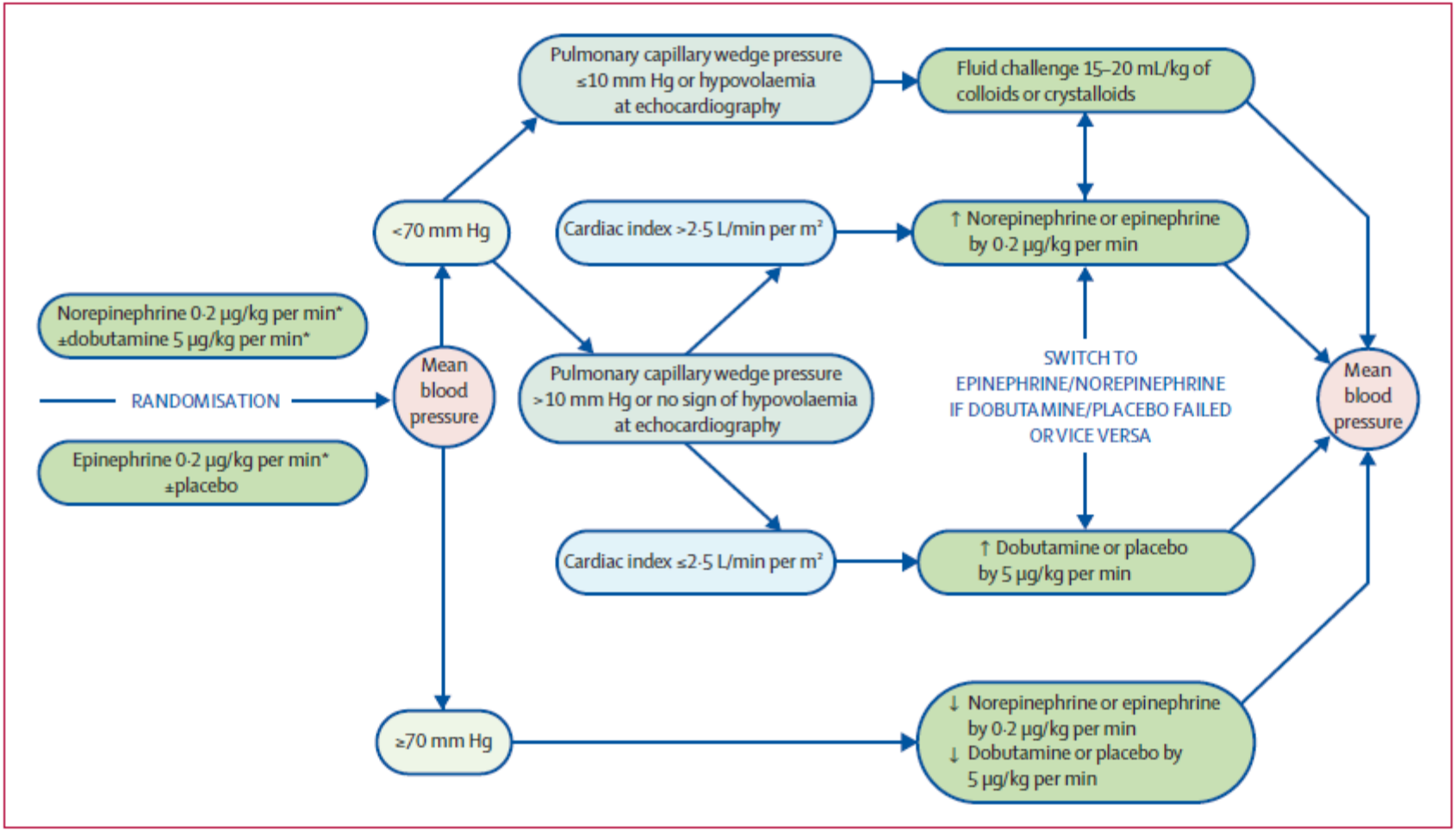
See Comment page 636

*Listed at end of report

Raymond Poincaré Hospital

Summary

Background International guidelines for management of septic shock recommend that dopamine or norepinephrine are preferable to epinephrine. However, no large comparative trial has yet been done. We aimed to compare the efficacy and safety of norepinephrine plus dobutamine (whenever needed) with those of epinephrine alone in septic shock.


Pulmonary capillary wedge pressure ≤10 mm Hg or hypovolaemia at echocardiography
Fluid challenge 15–20 mL/kg of colloids or crystalloids
<70 mm Hg
Cardiac index >2·5 L/min per m²
↑ Norepinephrine or epinephrine by 0·2 µg/kg per min
Norepinephrine 0·2 µg/kg per min* ±dobutamine 5 µg/kg per min*
RANDOMISATION
Epinephrine 0·2 µg/kg per min* ±placebo
Mean blood pressure
Pulmonary capillary wedge pressure >10 mm Hg or no sign of hypovolaemia at echocardiography
SWITCH TO EPINEPHRINE/NOREPINEPHRINE IF DOBUTAMINE/PLACEBO FAILED OR VICE VERSA
Mean blood pressure
Cardiac index ≤2·5 L/min per m²
↑ Dobutamine or placebo by 5 µg/kg per min
≥70 mm Hg
↓ Norepinephrine or epinephrine by 0·2 µg/kg per min
↓ Dobutamine or placebo by 5 µg/kg per min

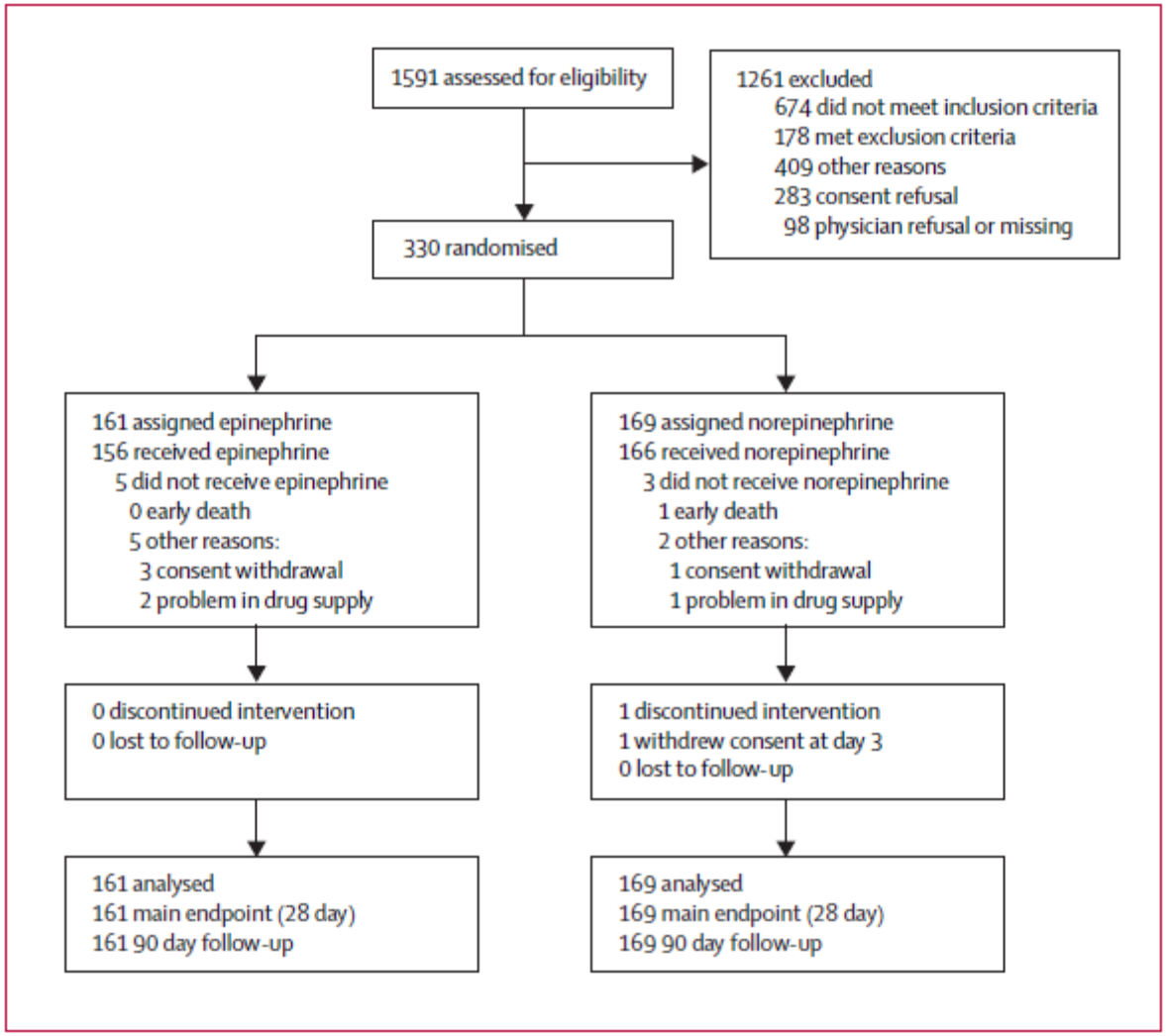


Figure 2: **Trial profile**

	Epinephrine (n=161)	Norepinephrine plus dobutamine (n=169)	p
At day 7	40 (25%)	34 (20%)	0·30
At day 14	56 (35%)	44 (26%)	0·08
At day 28	64 (40%)	58 (34%)	0·31
At discharge from intensive care	75 (47%)	75 (44%)	0·69
At discharge from hospital	84 (52%)	82 (49%)	0·51
At day 90	84 (52%)	85 (50%)	0·73

Data are number of deaths (%).

Table 3: **All-cause mortality rates**

	OR (logistic regression)	HR (Cox regression)
All covariates (n=308)	0·90 (0·54–1·49); p=0·67	0·87 (0·59–1·28); p=0·47
All covariates except appropriateness of antibiotic treatment (n=319)	0·82 (0·51–1·34); p=0·44	0·84 (0·58–1·22); p=0·36
All covariates except blood lactate concentration and appropriateness of antibiotic treatment (n=330)	0·82 (0·51–1·31); p=0·40	0·87 (0·61–1·24); p=0·43

Data are risk estimate (95% CI); p value.

Table 4: **Adjusted treatment effects on mortality rates at day 28**

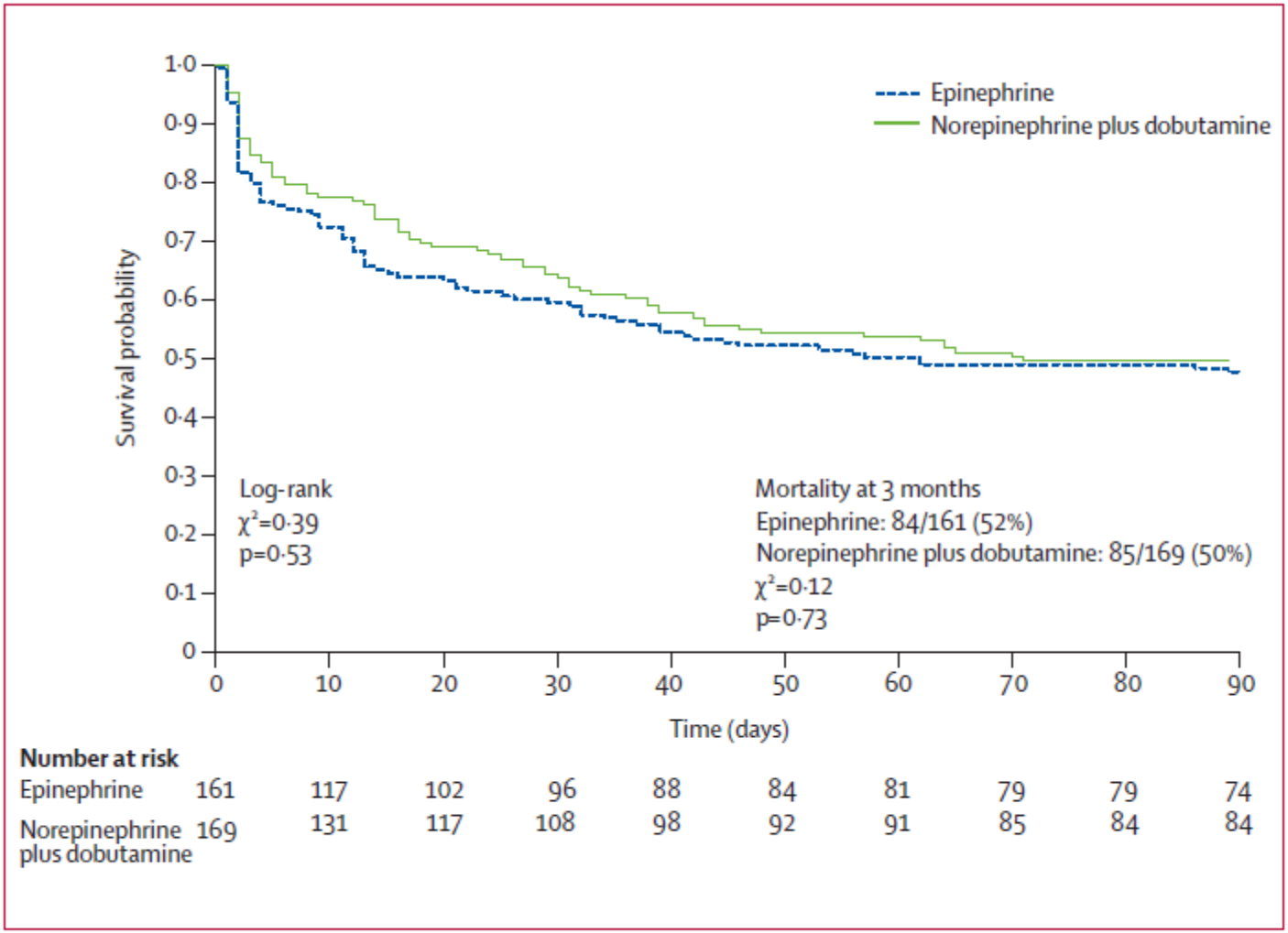


Figure 3: Survival from randomisation to day 90

	Overall (n=330)	Epinephrine (n=161)	Norepinephrine plus dobutamine (n=169)
During catecholamine infusion			
Supraventricular tachycardia >150 bpm	41 (12%)	19 (12%)	22 (13%)
Ventricular arrhythmias	20 (6%)	12 (7%)	8 (5%)
Acute coronary event	8 (2%)	5 (3%)	3 (2%)
Limb ischaemia	8 (2%)	2 (1%)	6 (4%)
Stroke	4 (1%)	2 (1%)	2 (1%)
Central nervous system bleeding	3 (0·9%)	3 (2%)	0 (0%)
After catecholamine infusion			
Arrhythmias	13 (4%)	6 (4%)	7 (4%)
Stroke	4 (1%)	2 (1%)	2 (1%)
Other neurological sequelae	2 (0·6%)	1 (0·6%)	1 (0·6%)
Others	6 (2%)	3 (2%)	3 (2%)

Data are n (%).

Table 6: **Serious adverse events**

Diminuer la demande en oxygène

A. Ventilation artificielle (travail respiratoire)

B. Sédatifs et narcotiques

C. Réduire les stimulations adrénergiques

Traitement étiologique

- Choc septique : antibiothérapie empirique
- Tamponnade péricardique
- Choc hémorragique
  - Corriger troubles de coagulation
- Choc anaphylactique
- Tachyarythmies