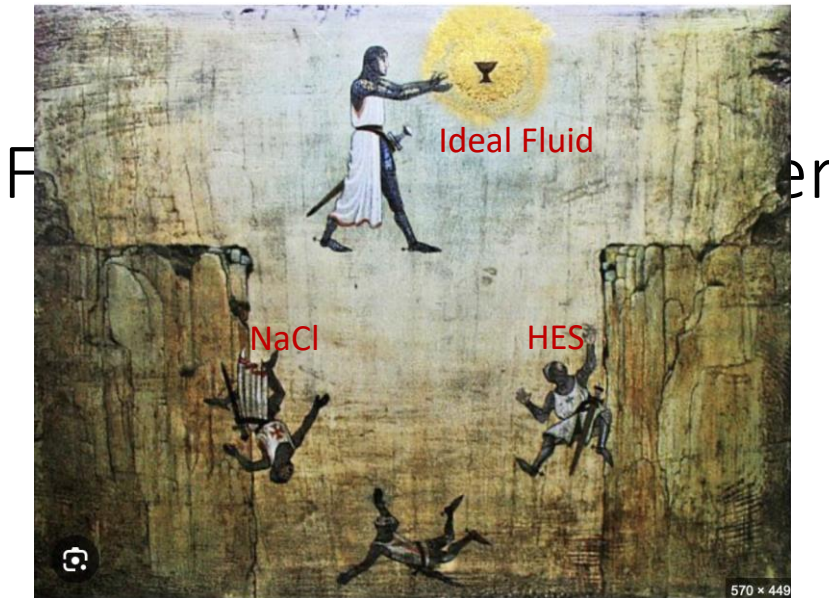


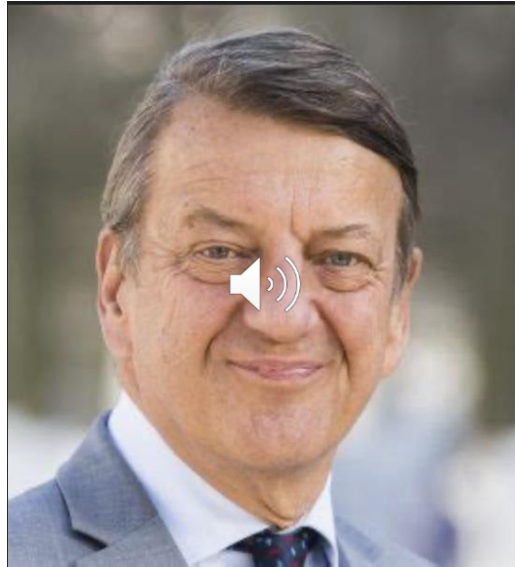


Andreas Markl-Le Levé

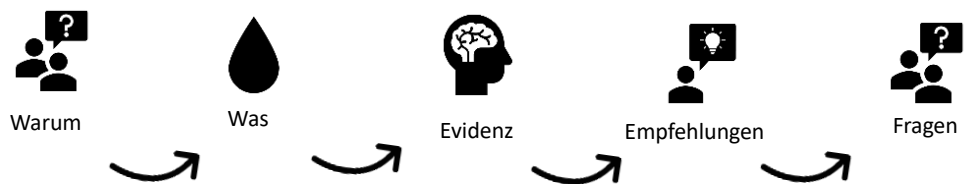
Interessenskonflikte

- Keine im Zusammenhang mit diesem Vortrag
- Reisekostenerstattung – Pfizer
- Reisekostenerstattung – Menarini

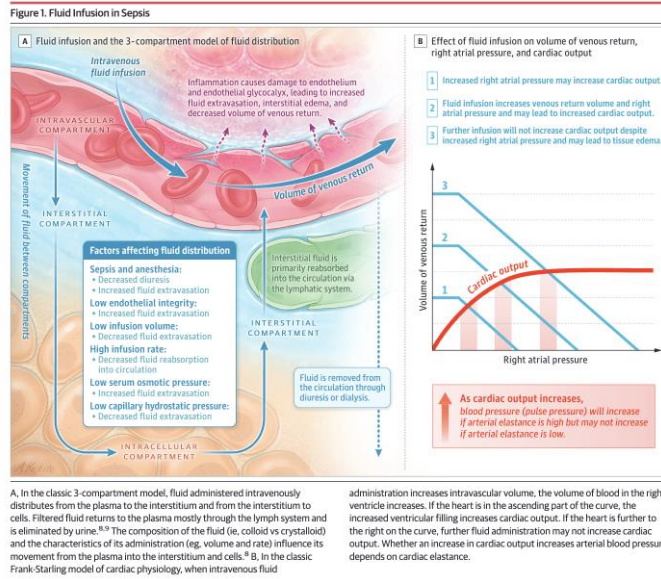




Inhalte

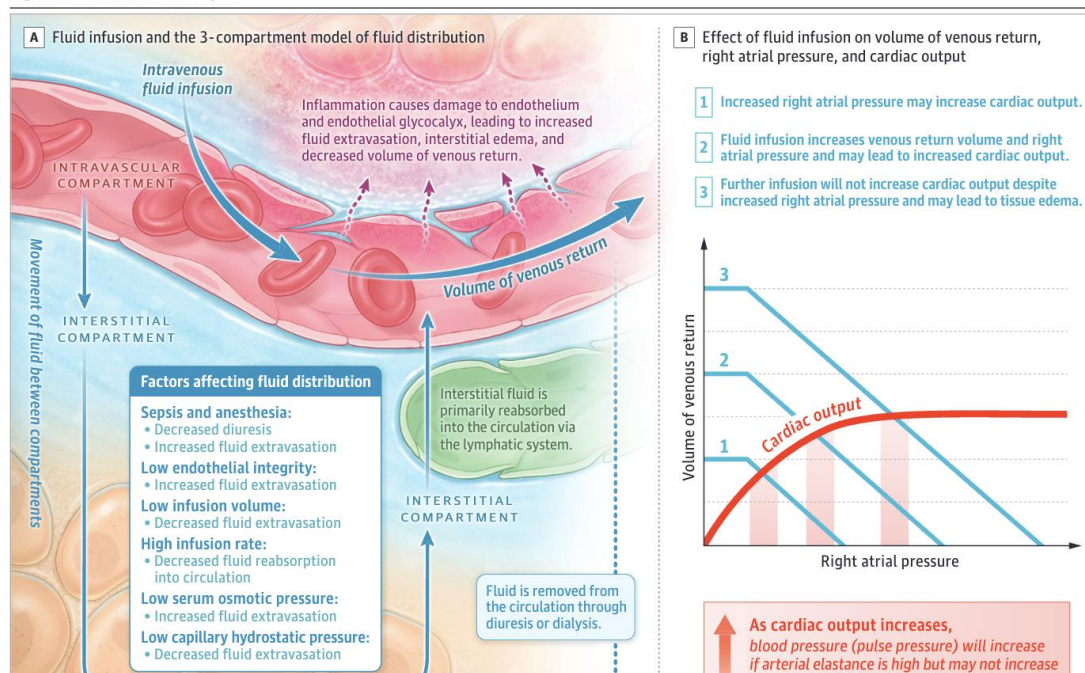


Warum / Pathophysiologie



Zampieri, F. G., Bagshaw, S. M. & Semler, M. W. Fluid Therapy for Critically Ill Adults With Sepsis: A Review. *Jama* **329**, 1967–1980 (2023).

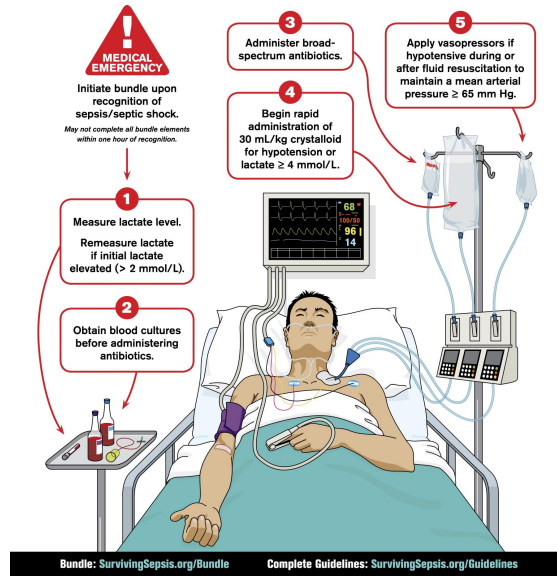
Figure 1. Fluid Infusion in Sepsis



Hour-1 Bundle

Initial Resuscitation for Sepsis and Septic Shock

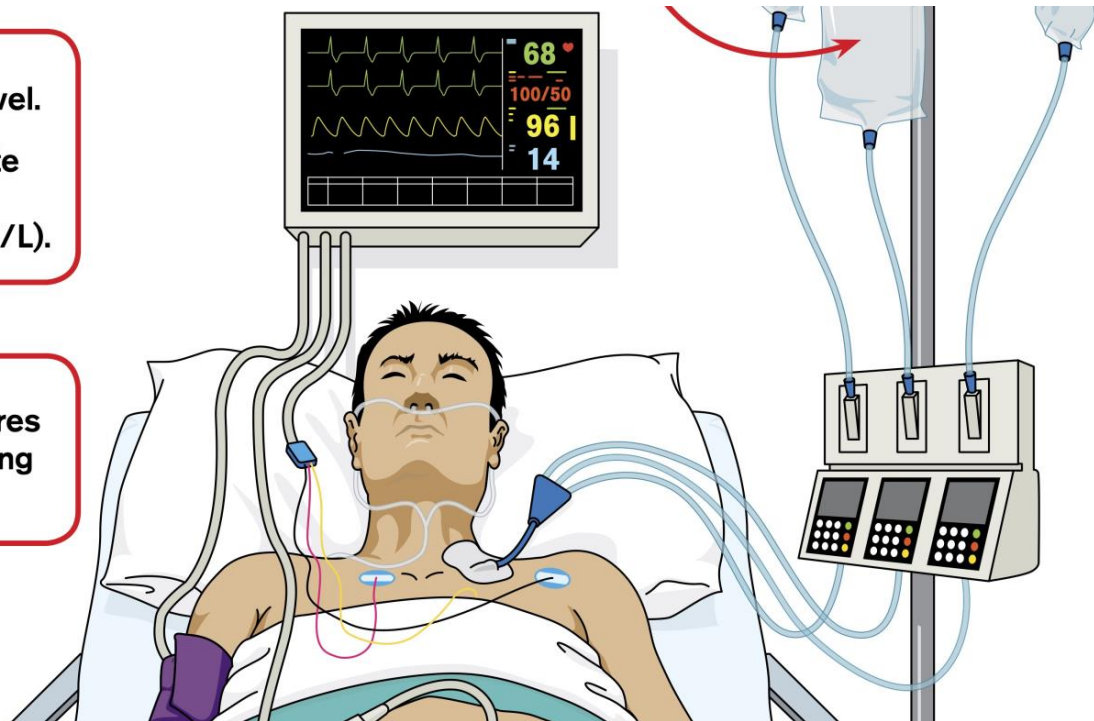
Surviving Sepsis
Campaign



ate level.

lactate
lactate
mmol/L).

l cultures
nistering
ics.





Bundle upon
initiation of
septic shock.

all bundle elements
are of recognition.

lactate level.

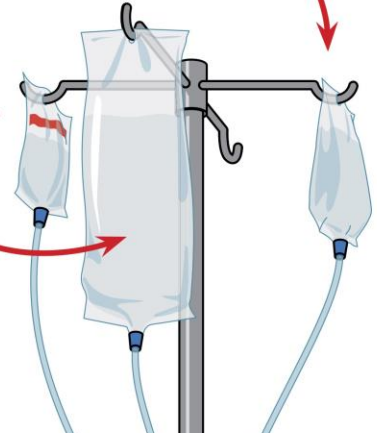
measure lactate
lactate

Administer broad-
spectrum antibiotics.

4

Begin rapid
administration of
30 mL/kg crystalloid
for hypotension or
lactate ≥ 4 mmol/L.

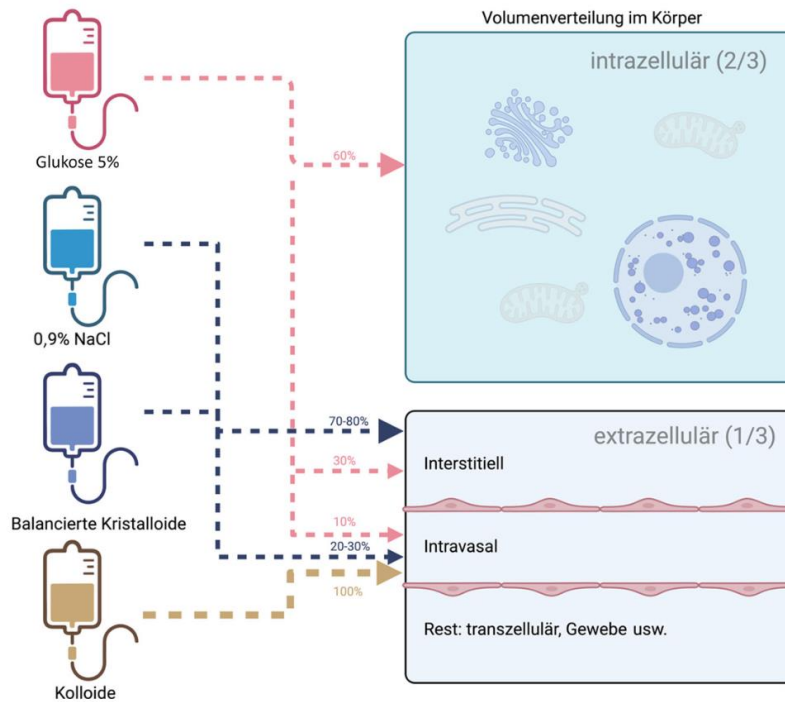
Apply vasopressors if
hypotensive during or
after fluid resuscitation to
maintain a mean arterial
pressure ≥ 65 mm Hg.



Welche Flüssigkeiten?

- Kristalloide
 - NaCl 0,9%
 - Balancierte Lösungen
- Kolloide
 - Albumin
 - Gelatine
 - HES
- FFP

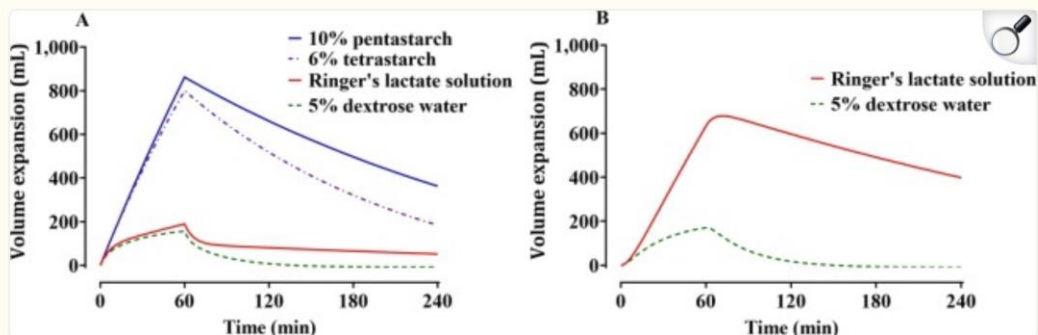




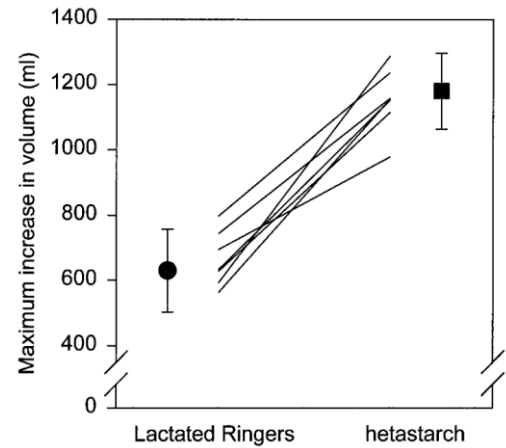
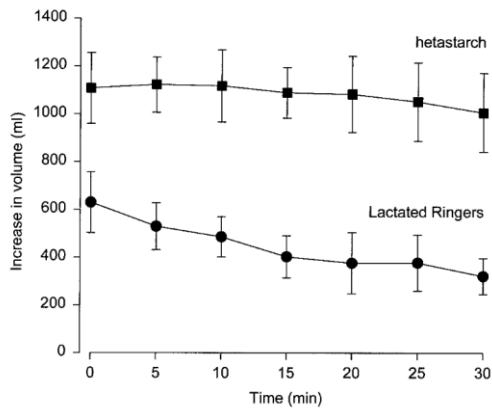
Mayerhöfer, T., Lehner, G. F. & Joannidis, M. Volumentherapie – welches Präparat in welcher Situation? *Med. Klin. - Intensiv. Notfallmedizin* **119**, 640–649 (2024).

Abb. 1 ◀ Theoretische (ungefähre) Verteilung intravenöser Flüssigkeiten bei gesunden Menschen. (Modifiziert nach [2]; erstellt mit BioRender.com)

Figure 5.



Yi, J.-M. *et al.* Population-based volume kinetics of crystalloids and colloids in healthy volunteers. *Sci. Rep.* **9**, 18638 (2019).



McIlroy, D. R. & Kharasch, E. D. Acute Intravascular Volume Expansion with Rapidly Administered Crystalloid or Colloid in the Setting of Moderate Hypovolemia. *Anesthesia Analg.* **96**, 1572–1577 (2003).

Kristalloide – Pharmakologische Probleme

- Elektroneutralität ist eine gegebene Größe
 - > Summe der Kationen entspricht der Summe der Anionen
 - > Kompromiss bei Elektrolyten
 - > Kompromiss bei Osmolarität
 - > Zusatz von metabolisierbaren Anionen (Laktat, Azetat, Malat...)

	Plasma	NaCl 0,9%	Elo-Mel	Ringer-Laktat
Kationen				
Na+	142	154	140	130
K	4,5	-	5	5
Ca	2,5	-	2,5	1
Mg	1,25	-	1,5	1
Anionen				-
Cl-	103	154	108	112
HCO ₃	24	-		-
Laktat	1,5	-		27
Acetat	-	-	45	-
Malat	-	-		-
Proteinat	20	-	-	-
Osmolarität mosmol/l	291mosmol/l	308	302	276
Osmolalität mosmol/H ₂ O	287mosmol/H ₂ O	286	288	258
BE	0	-24	-24	-24
Bepot	0	-24	0	+3

	4,5	-	5	5
	2,5	-	2,5	1
	1,25	-	1,5	1
				-
	103	154	108	112
	24	-		-
	1,5	-		27
	-	-	45	-
	-	-		-
	20	-	-	-
ol/l	291mosmol/l	308	302	276
ol/H ₂ O	287mosmol/H ₂ O	286	288	258
	0	-24	-24	-24
	0	-24	0	+3

Erhöhter Sauerstoffverbrauch?

Infusionslösungen: Metabolisierbare Anionen			
Anion	HCO_3^- / mol	mol O_2 / mol	mol O_2 / mol HCO_3^-
Malat ²⁻	2	3	1,5
Zitrat ³⁻	3	4,5	1,5
Azetat ⁻	1	2	2
Laktat ⁻	1	3	3
Glukonat ⁻	1	5,5	5,5

Die therapeutisch erwünschte, metabolische Wirkung der Anionen, d. h. wieviel mol HCO_3^- werden pro mol Anion freigesetzt (HCO_3^- / mol), unterscheidet sich vom metabolisch erforderlichen O_2 -Verbrauch (mol O_2 / mol) und damit vom therapeutisch erforderlichen O_2 -Verbrauch pro mol freigesetztem HCO_3^- (mol O_2 / mol HCO_3^-).

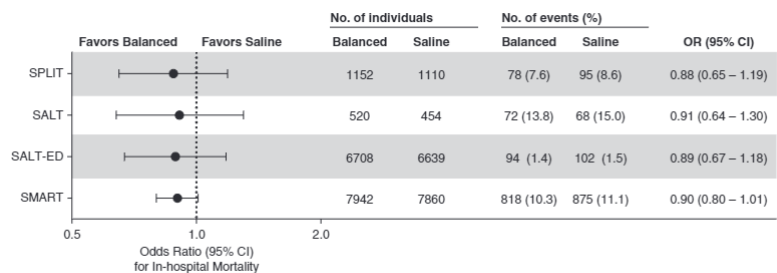
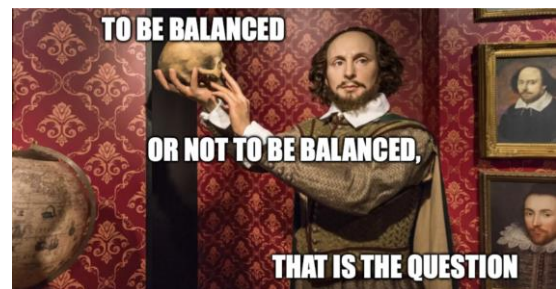
1l Elo-Mel = 45mmol Acetat -> 90mmol O_2 = 2l O_2 Mehrverbrauch

	Plasma	NaCl 0,9%	Elo-Mel	Ringer-Laktat
Kationen				
Na ⁺	142	154	140	130
K	4,5	-	5	5
Ca	2,5	-	2,5	1
Mg	1,25	-	1,5	1
Anionen				-
Cl ⁻	103	154	108	112
HCO_3	24	-		-
Laktat	1,5	-		27
Acetat	-	-	45	-
Malat	-	-		-
Proteinat	20	-	-	-
Osmolarität mosmol/l	291mosmol/l	308	302	276
Osmolalität mosmol/H ₂ O	287mosmol/H ₂ O	286	288	258
BE	0	-24	-24	-24
Bepot	0	-24	0	+3

	142	154	140	130
	4,5	-	5	5
	2,5	-	2,5	1
	1,25	-	1,5	1
ien				-
	103	154	108	112
i	24	-		-
t	1,5	-		27
it	-	-	45	-
t	-	-		-
inat	20	-	-	-
olarität mosmol/l	291mosmol/l	308	302	276
olarität mol/H2O	287mosmol/H2O	286	288	258
	0	-24	-24	-24
t	0	-24	0	+3

Kristalloide

- NaCl 0,9% vs Balancierte
- Mortalität kein Unterschied
- Tendenziell mehr AKI



Semler, M. W. & Kellum, J. A. Balanced Crystalloid Solutions. *Am. J. Respir. Crit. Care Med.* **199**, 952–960 (2018).

Figure 2. Effect of balanced crystalloids versus saline on mortality among critically ill adults. The odds ratios (ORs) and 95% confidence intervals (CIs) for in-hospital mortality with balanced crystalloids compared with saline are displayed for the four large randomized trials among critically ill adults (56–59).

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 Mehrrens, RN; John Myburgh, PhD; Alex Psirides, FCICM; Sumeet Reddy, MBChB; Rinaldo Bellomo, FCICM; for the SPLIT Investigators and the ANZICS CTG

- 2278 Patienten
- NaCl 0,9% vs. Plasmalyte
- **Primärer Endpunkt AKI – kein Unterschied**
- Sekundäre Endpunkte:
 - **Mortalität, RRT, Beatmungsdauer – kein Unterschied**
- Einschränkungen:
 - Wenig Sepsispatienten (4%)
 - Niedriger APACHE II -14
 - 2 Liter pro Patient

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Balanced Crystalloids versus Saline in Noncritically Ill Adults

Wesley H. Self, M.D., M.P.H., Matthew W. Semler, M.D.,
Jonathan P. Wanderer, M.D., Li Wang, M.S., Daniel W. Byrne, M.S.,
Sean P. Collins, M.D., Corey M. Slovis, M.D., Christopher J. Lindsell, Ph.D.,
Jesse M. Ehrenfeld, M.D., M.P.H., Edward D. Siew, M.D.,
Andrew D. Shaw, M.B., Gordon R. Bernard, M.D.,
and Todd W. Rice, M.D., for the SALT-ED Investigators*

- Ringer-Laktat vs. NaCl 0,9%
- 13.347 Patienten
- **Primärer Endpunkt: Krankenhausfreie Tage – kein Unterschied**
- **Sekundäre Endpunkte: MAKE30 (Major kidney events) – 4,7vs 5,6% (p=0,01)**
- Single-Center Design
- Nicht kritisch Krank
- MAKE30 – kombinierter Endpunkt (Tod, RRT, persistierende Nierendysfunktion)

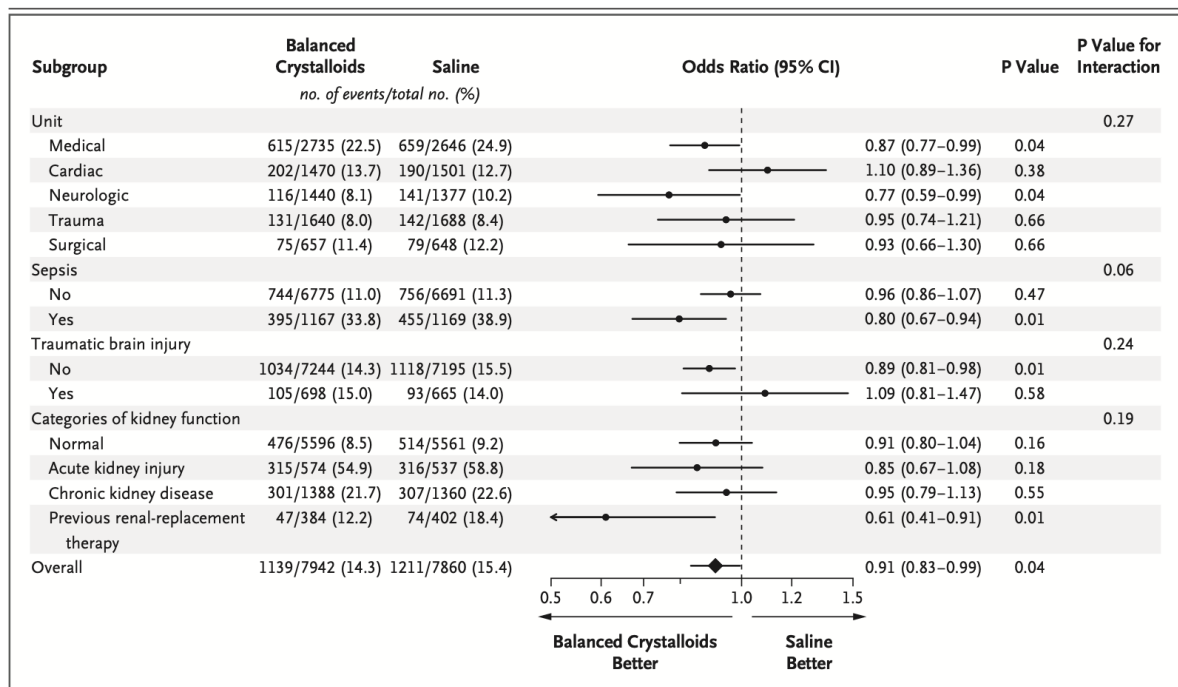
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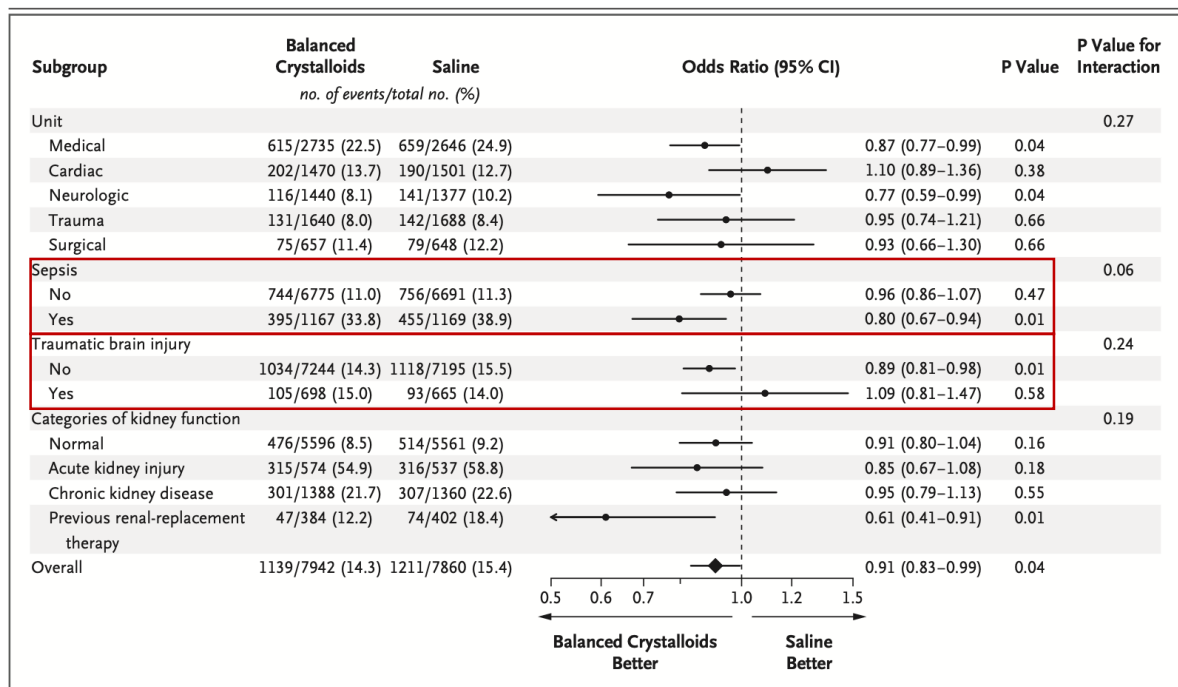
ORIGINAL ARTICLE

Balanced Crystalloids versus Saline
in Critically Ill Adults

Matthew W. Semler, M.D., Wesley H. Self, M.D., M.P.H.,
Jonathan P. Wanderer, M.D., Jesse M. Ehrenfeld, M.D., M.P.H.,
Li Wang, M.S., Daniel W. Byrne, M.S., Joanna L. Stollings, Pharm.D.,
Avinash B. Kumar, M.D., Christopher G. Hughes, M.D.,
Antonio Hernandez, M.D., Oscar D. Guillaumondegui, M.D., M.P.H.,
Addison K. May, M.D., Liza Weavind, M.B., B.Ch., Jonathan D. Casey, M.D.,
Edward D. Siew, M.D., Andrew D. Shaw, M.B., Gordon R. Bernard, M.D.,
and Todd W. Rice, M.D., for the SMART Investigators
and the Pragmatic Critical Care Research Group*

- 15802 Patienten
- Ringer-Laktat/Plasmalyt vs NaCl 0,9%
- **Primärer Endpunkt: MAKE30 – 14,3% vs 15,4% (p=0,04)**
 - **Sepsis-Subgruppe: Mortalitätssenkung – 30,7% vs 35,4% (p=0,01)**
- Single-Center
- Mediane Menge ~1000ml





JAMA | Original Investigation

Effect of Intravenous Fluid Treatment With a Balanced Solution vs 0.9% Saline Solution on Mortality in Critically Ill Patients The BaSICS Randomized Clinical Trial

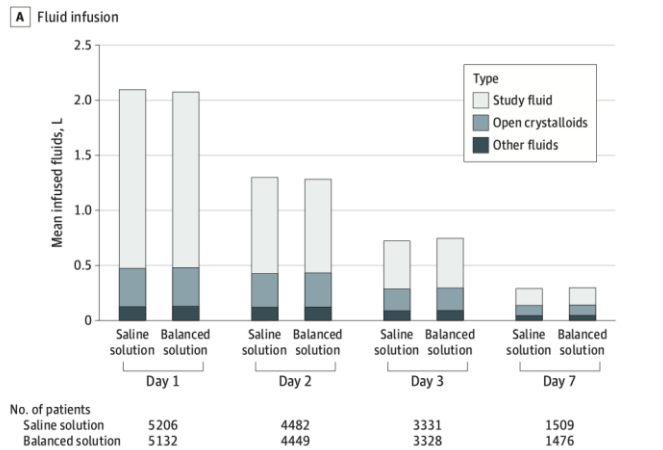
Fernando G. Zampieri, MD, PhD; Flávia R. Machado, MD, PhD; Rodrigo S. Biondi, MD; Flávio G. R. Freitas, MD, PhD; Viviane C. Veiga, MD, PhD; Rodrigo C. Figueiredo, MD; Wilson J. Lovato, MD; Cristina P. Amêndola, MD, PhD; Ary Serpa-Neto, MD, PhD; Jorge L. R. Paranhos, MD; Marco A. V. Guedes, MD, PhD; Eraldo A. Lúcio, MD, PhD; Lúcio C. Oliveira-Junior, MD; Thiago C. Lisboa, MD, PhD; Fábio H. Lacerda, MD; Israel S. Maia, MD; Cintia M. C. Grion, MD, PhD; Murillo S. C. Assunção, MD, PhD; Anton L. O. Manoel, MD, PhD; João M. Silva-Junior, MD, PhD; Péricles Duarte, MD; Rafael M. Soares, PhD; Tamiris A. Miranda, MSc; Lucas M. de Lima, IT; Rodrigo M. Gurgel, Biomed Sci; Denise M. Paisani, PhD; Thiago D. Corrêa, MD, PhD; Luciano C. P. Azevedo, MD, PhD; John A. Kellum, MD; Lucas P. Damiani, MSc; Nilton Brandão da Silva, MD, PhD; Alexandre B. Cavalcanti, MD, PhD; for the BaSICS investigators and the BRICNet members

- 10520 Patienten
- Balanciert (Plasmalyte vs NaCl 0,9%)
- **90-Tage-Mortalität: Kein Unterschied (26,4% vs. 27,2%, $p = 0,47$).**
- Subgruppen: Möglicher Benefit bei Sepsis-Patienten mit vorheriger Balanciert-Gabe (OR 0,70, 89% CrI 0,50–0,97).
- 60% vor Beginn bereits andere Flüssigkeiten

JAMA | Original Investigation

Effect of Intravenous Fluid Treatment With a Balanced Solution vs 0.9% Saline Solution on Mortality in Critically Ill Patients The BaSICS Randomized Clinical Trial

Figure 2. Volume of Infused Fluids at Days 1, 2, 3, and 7 and Boxplot of Serum Chloride Levels



ORIGINAL ARTICLE

Balanced Crystalloids versus Saline in Critically Ill Adults — A Systematic Review with Meta-Analysis

Naomi E. Hammond, Ph.D.^{1,2}, Fernando G. Zampieri, Ph.D.^{3,4}, Gian Luca Di Tanna, Ph.D.⁵, Tessa Garside, Ph.D.^{1,2}, Derick Adigbli, Ph.D.^{1,2}, Alexandre B. Cavalcanti, M.D. Ph.D.³, Flavia R. Machado, M.D., Ph.D.⁵, Sharon Micallef, B.N.¹, John Myburgh, Ph.D.^{1,7}, Mahesh Ramanan, M.Med.^{8,9}, Todd W. Rice, M.D.¹⁰, Matthew W. Semler, M.D.¹⁰, Paul J. Young, Ph.D.^{11,12}, Balasubramanian Venkatesh, M.D.^{1,13}, Simon Finfer, M.D.^{1,14}, and Anthony Delaney, Ph.D.^{1,2}

Drs. Hammond and Zampieri, as well as Drs. Finfer and Delaney, contributed equally to this article.

- Kein „harter“ Mortalitätsvorteil aber Wahrscheinlich positiver Effekt von balancierten Lösungen

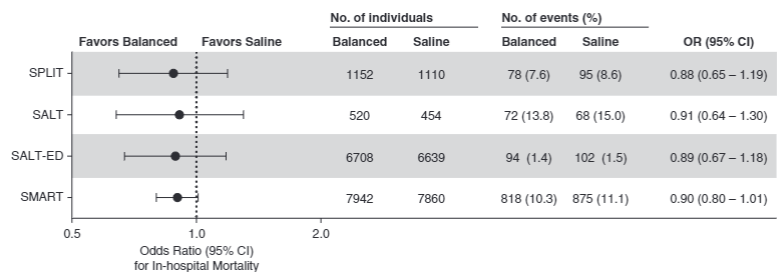


Figure 2. Effect of balanced crystalloids versus saline on mortality among critically ill adults. The odds ratios (ORs) and 95% confidence intervals (CIs) for in-hospital mortality with balanced crystalloids compared with saline are displayed for the four large randomized trials among critically ill adults (56–59).

Semler, M. W. & Kellum, J. A. Balanced Crystalloid Solutions.
Am. J. Respir. Crit. Care Med. **199**, 952–960 (2018).

Fishman A.

Shock lung a distinctive nonentity. Circulation 1973

“Thus, on the battlefield, overzealous
administration of liquids, particularly of
crystalloidal solutions, predisposes to pulmonary
congestion and edema”

“wet lung” ... “shock lung” ... “Da Nang Lung”



Kristalloide Zusammenfassung

- Balancierte Lösung wahrscheinlich günstig
- Cave: schweres SHT
- In den Leitlinien als Erstliniensubstanz empfohlen
- Studien alle mit geringen Flüssigkeitsmengen

Kolloide

- Albumin
- HES
- Gelatine



Albumin

- 67 000 Dalton, negativ geladen, Transportprotein, HWZ bis 19 Tage
- Seit Pearl Harbor in Verwendung
- Sicherheitsprofil – seit SAFE Study evaluiert
- 4% vs 20%
- Hypoalbuminämie als Mortalitätsmarker



Name.	Concentration Albumin (g/L)	Sodium Content (mmol/L)	Company
Human Albumin "CSL Behring" 20% Infusionslösung	200	125	CSL Behring, Hattersheim, Germany
Alburex 5/20	50/200	140	CSL Behring, Hattersheim, Germany
Human Albumin "Octapharma" 25%—Infusionsflasche	250		Octapharma Pharmazeutika, Wien, Austria
Human Albumin Takeda 50 g/L; 200 g/L; 250 g/L Infusionslösung	50/200/250	130–160/100–130/130–160	Takeda Manufacturing Austria AG, Wien, Austria
Humanalbumin Kedrion 200 g/L Infusionslösung	200	123–136	Kedrion SpA, Barga (LU), Italy
Humanalbumin Kedrion 250 g/L Infusionslösung	250	123–136	
Humanalbumin Octapharma 50 g/L Infusionslösung	50	143–157	Octapharma Pharmazeutika, Wien, Austria
Humanalbumin Octapharma 200 g/L Infusionslösung	200	143–157	
Albutein 50 g/L/200 g/L	50/200	130–160	Grifols GmbH, Frankfurt, Germany
Plasbumin 20/25	200/250 g	145	Grifols GmbH, Frankfurt, Germany
Crealb 40 g/L; Crealb 200 g/L	40/200	140	Sanquin Plasma Products B.V., Amsterdam, The Netherlands

Source: Office for healthcare safety in Germany (Bundesamt für Sicherheit im Gesundheitswesen) (14 March 2023): https://aspreghister.basg.gv.at/aspreghister/faces/aspreghister.jspx?_afrcid=ROvgVvp6ibNQN7mKwgKJ0uV6-J6QTAeGWHZIJZl4OpLGGl6lMnm1-345026110. Paul-Ehrlich Institut: <https://www.pei.de/DE/arzneimittel/blutprodukte/albumine/albumine-node.html> (accessed on 20 February 2023).

Name.	Concentration Albumin (g/L)	Sodium Content (mmol/L)	Company
Human Albumin "CSL Behring" 20% Infusionslösung	200	125	CSL Behring, Hattersheim, Germany
Alburex 5/20	50/200	140	CSL Behring, Hattersheim, Germany
Human Albumin "Octapharma" 25%—Infusionsflasche	250		Octapharma Pharmazeutika, Wien, Austria
Human Albumin Takeda 50 g/L; 200 g/L; 250 g/L Infusionslösung	50/200/250	130–160/100–130/130–160	Takeda Manufacturing Austria AG, Wien, Austria
Humanalbumin Kedrion 200 g/L Infusionslösung	200	123–136	Kedrion SpA, Barga (LU), Italy
Humanalbumin Kedrion 250 g/L Infusionslösung	250	123–136	
Humanalbumin Octapharma 50 g/L Infusionslösung	50	143–157	Octapharma Pharmazeutika, Wien, Austria
Humanalbumin Octapharma 200 g/L Infusionslösung	200	143–157	
Albutein 50 g/L/200 g/L	50/200	130–160	Grifols GmbH, Frankfurt, Germany
Plasbumin 20/25	200/250 g	145	Grifols GmbH, Frankfurt, Germany
Crealb 40 g/L; Crealb 200 g/L	40/200	140	Sanquin Plasma Products B.V., Amsterdam, The Netherlands

Source: Office for healthcare safety in Germany (Bundesamt für Sicherheit im Gesundheitswesen) (14 March 2023): https://aspreghister.basg.gv.at/aspreghister/faces/aspreghister.jspx?_afrcid=ROvgVvp6ibNQN7mKwgKJ0uV6-J6QTAeGWHZIJZl4OpLGGl6lMnm1-345026110. Paul-Ehrlich Institut: <https://www.pei.de/DE/arzneimittel/blutprodukte/albumine/albumine-node.html> (accessed on 20 February 2023).

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Comparison of Albumin and Saline for Fluid Resuscitation in the Intensive Care Unit

The SAFE Study Investigators*

- 4% Albumin vs NaCl 0,9%
- **28-Tage-Mortalität: -Kein Unterschied** zwischen Albumin (20,9%) und NaCl (21,1%) – *RR 0,99 (95%-KI 0,91–1,09)*.
- Subgruppen:
 - Trauma mit Schädel-Hirn-Trauma (**SHT**): **Höhere Mortalität unter Albumin** (24,5% vs. 15,1%; *RR 1,62*).
 - **Sepsis: Trend zu geringerer Mortalität** mit Albumin (30,7% vs. 35,3%; *RR 0,87, p=0,09*).
- Sekundäre Endpunkte:
Keine Unterschiede in ICU/Krankenhausaufenthalt, Beatmungstagen oder Nierenersatztherapie
- **Albumin 40-80x Kostenintensiver**

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., Mariela 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*

- 1.818 Patienten; Albumin 20% + Kristalloide vs Kristalloide allein
- **Mortalität: 28 Tage: 31,8% (Albumin) vs. 32,0% (Kristalloide);
90 Tage: 41,1% vs. 43,6%; *RR 0,94 (95%-KI 0,85–1,05)*.**
- Höherer mittlerer arterieller Druck und schnellere Vasopressoren-Absetzung in der Albumin-Gruppe (*Median 3 vs. 4 Tage*).
- Subgruppen:
- Bei **septischem Schock** (ältere Sepsis-2-Definition) **möglicher Überlebensvorteil** (*RR 0,87; 95%-KI 0,77–0,99*), nicht bestätigt mit Sepsis-3-Kriterien

Albumin -Zusammenfassung

- Derzeit geringe Sicherheitsbedenken – Cave Trauma (insbesondere SHT)
- Beste Daten für: Zirrhose, Spontan bakterielle Peritonitis, Large-Volume-Paracentesis
- Sepsis, ARDS, ECMO derzeit keine hart belastbaren Daten – erwägen bei anhaltender Instabilität unter Kristalloiden
- Kosten

Saner, F. H., Stueben, B.-O., Hoyer, D. P., Broering, D. C. & Bezinover, D. Use or Misuse of Albumin in Critical Ill Patients. *Diseases* **11**, 68 (2023).

Hydroxyethylstarch



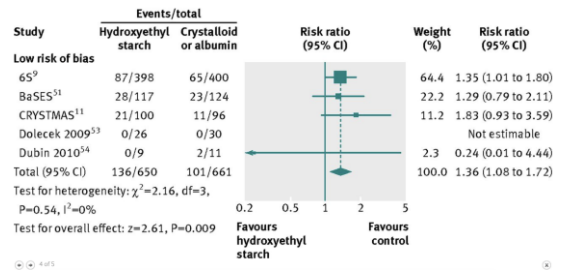
HES



11 October 2013
EMA/606303/2013

PRAC confirms that hydroxyethyl-starch solutions (HES) should no longer be used in patients with sepsis or burn injuries or in critically ill patients

HES will be available in restricted patient populations



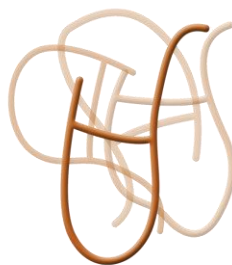
Haase, N. *et al.* Hydroxyethyl starch 130/0.38-0.45 versus crystalloid or albumin in patients with sepsis: systematic review with meta-analysis and trial sequential analysis. *BMJ : Br. Med. J.* **346**, f839 (2013).

Gelatine



Succinylated gelatin

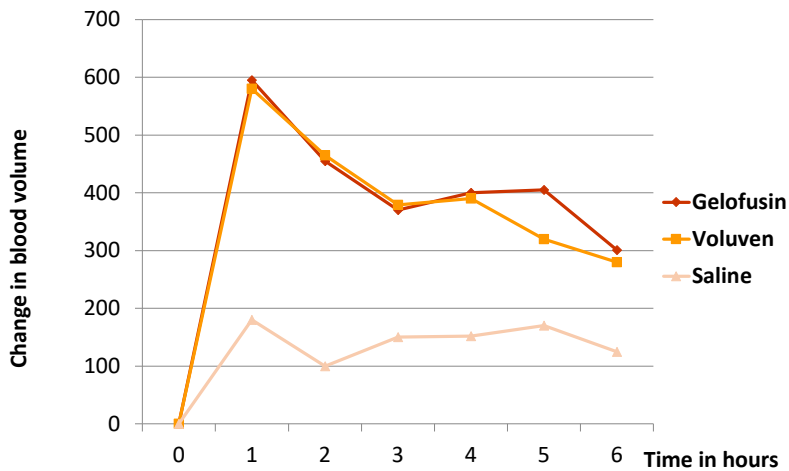
- Gelofusin®
- 154 mmol Natrium, 120 mmol Chlorid
- **Anaphylaxie 0,1%**



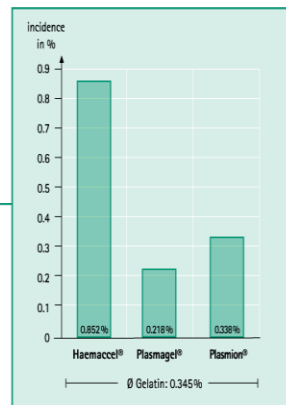
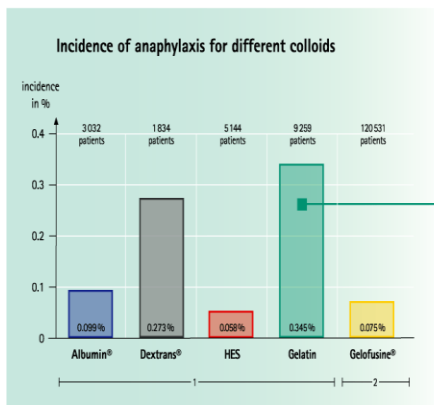
Urea- cross linked gelatin

- Haemacel®
- **Anaphylaxie 1%**





Effect of volume loading with 1 liter of 0.9% saline, 4% gelatine and 6% hydroxyethyl starch on blood volume and endocrine responses.
Lobo DN et al. Crit Care 2010



- 1) Laxenaire, M. C. et al. Ann Fr Aesth Réanim 13 (1994) 301-310
- 2) Lundsgaard-Hansen P. et al. Dev Biol Stand 48 (1980) 251-256

Reviews

Benefits and risks of using gelatin solution as a plasma expander for perioperative and critically ill patients: a meta-analysis

M. M. SAW*, B. CHANDLER†, K. M. HO‡

Intensive Care Department, Royal Perth Hospital, Perth, Western Australia, Australia

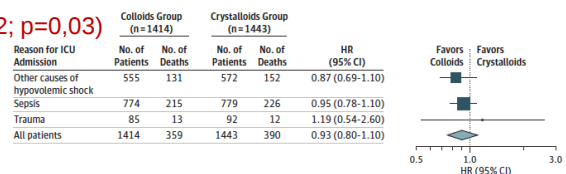
- **Meta-Analyse 2.709 patients**
- **Weniger AKI vs HES (odds ratio 0.43, 95% confidence interval 0.20 to 0.92; P=0.03).**
- **Kein Unterschied zu Kristalloiden**

Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effects of Fluid Resuscitation With Colloids vs Crystalloids on Mortality in Critically Ill Patients Presenting With Hypovolemic Shock The CRISTAL Randomized Trial

Djillali Annane, MD, PhD; Shidasp Siami, MD; Samir Jaber, MD, PhD; Claude Martin, MD, PhD; Souheil Elatrous, MD; Adrien Descorps Declère, MD;

- 2857 Patienten, Kolloid (HES/Gelatine vs Kristalloid)
- 28-Tage Mortalität – kein Unterschied
- 90-Tage Mortalität - (30,7 % vs. 34,2 %, RR=0,92; p=0,03)
- Weniger Volumenbedarf



Annane D et al; JAMA 2013 Nov 6;310(17):1809-17

STUDY PROTOCOL

Open Access

Efficacy and safety of early target-controlled plasma volume replacement with a balanced gelatine solution versus a balanced electrolyte solution in patients with severe sepsis/septic shock: study protocol, design, and rationale of a prospective, randomized, controlled, double-blind, multicentric, international clinical trial



GENIUS—Gelatine use in ICU and sepsis

Gernot Marx^{1*}, Kai Zacharowski², Carole Ichai³, Karim Asehnoune⁴, Vladimir Cerny⁵, Rolf Dembinski⁶, Ricard Ferrer Roca⁷, Dietmar Fries⁸, Zsolt Molnar^{9,10}, Peter Rosenberger¹¹, Manuel Sanchez-Sanchez¹², Tobias Schürholz¹³, Tamara Dehnhardt¹⁴, Sonja Schmier¹⁵, Elke von Kleist¹⁶, Ute Brauer¹⁸ and Tim-Philipp Simon¹

Abstract

Background: Sepsis is associated with capillary leakage and vasodilatation and leads to hypotension and tissue hypoperfusion. Early plasma volume replacement is required to achieve haemodynamic stability (HDS) and maintain adequate tissue oxygenation. The right choice of fluids to be used for plasma volume replacement (colloid or crystalloid solutions) is still a matter of debate, and large trials investigating the use of colloid solutions containing gelatine are missing. This study aims to investigate the efficacy and safety of plasma volume replacement using either a combined gelatine-crystalloid regime (1:1 ratio) or a pure crystalloid regime.

Marx et al. *Trials* (2021) 22:376
https://doi.org/10.1186/s13063-021-05311-8

Trials

STUDY PROTOCOL

Open Access

Efficacy and safety of early target-controlled plasma volume replacement with a balanced gelatine solution versus a balanced electrolyte solution in patients with severe sepsis/septic shock: study protocol, design, and rationale of a prospective, randomized, controlled, double-blind, multicentric, international clinical trial

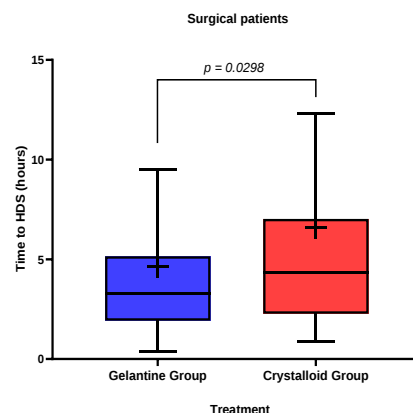
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- 167 Patienten
- HDS: 4.7 h Gelatine vs 5.8 h in the Kristalloidgruppe ($p = 0,3716$).
- Subgruppen – Chirurgische Patienten:
HDS 4,6h Gelatine vs 6,6h Kristalloide ($p=0,0298$)
- Gelatine Gruppe: Vorteilhafter Flüssigkeitsstatus nach 24 h (medians: 3.463 ml vs. 4.164; $p = 0.0395$) und **weniger fluid overload** (medians: 4.296 vs 5.218 %; $p = 0.0217$).
- **Kein Unterschied** in Adverse Events und Mortalität



A63 (Saline)				
	Base	40%	35%	35%
Hct	48	34	25	16
Hb	14,3	8,5	6,9	5
pH	7,4	7,3	7,3	7,3
BE	9,3	-0,2	-3,9	-10,8
A58 (Gelofusin)				
	Base	40%	35%	35%
Hct	52	38	24	12
Hb	15,8	11,8	6,8	4,3
pH	7,3	7,3	7,3	7,5
BE	8,3	8,9	6,5	2,1

Zusammenfassung Gelatine

- Insgesamt noch wenig Daten
- Succinylierte Gelatine sicherer
- GENIUS Trial ausständig (Sepsispatienten)
- Sicherer als HES, gleich sicher wie Kristalloide?
- Kosten



FFP

RECOMMENDATIONS

Recommendations for the use of albumin and immunoglobulins

Giancarlo Liunbruno¹, Francesco Bennardello², Angela Lattanzio³, Pierluigi Piccoli⁴, Gina Rossetti⁵ as Italian Society of Transfusion Medicine and Immunohaematology (SIMIT) Working Party

¹U.U.O.C.C. di Immunematologia e Medicina Trasfusionale e Patologia Clinica, Ospedale "San Giovanni Calibita" Fatebenefratelli, Roma; ²Servizio di Immunematologia e Medicina Trasfusionale, Azienda Ospedaliera "Civile-Maria Paternò-Arezzo", Ragusa; ³Servizio di Immunematologia e Medicina Trasfusionale, Azienda Ospedaliera di Carbonara di Bari; ⁴Servizio di Immunematologia e Medicina Trasfusionale, Azienda Ospedaliera di Verona; ⁵Servizio di Immunematologia e Medicina Trasfusionale, Azienda Ospedaliera di Trento, Italy

- Volumenersatzmittel in der Sepsis?
- Volumenersatzmittel bei septischen Patienten mit Gerinnungsstörungen?
- Für einen Albuminanstieg um 1g/dl benötigt man ~45ml/kg Plasma

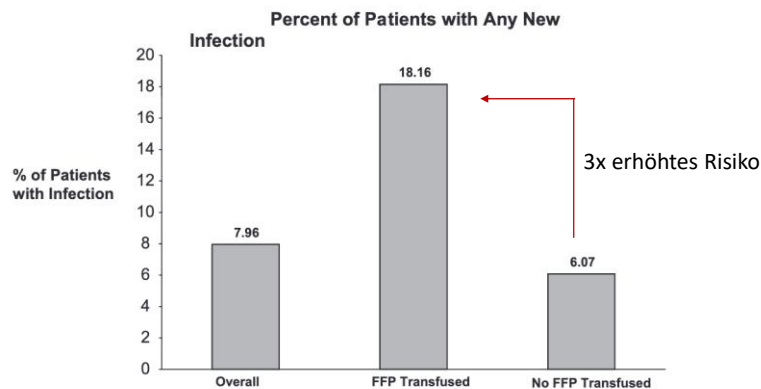


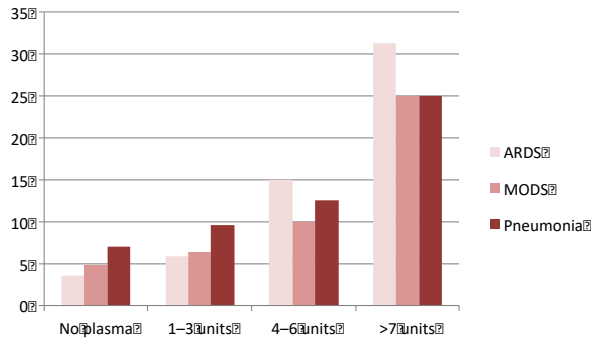
Figure 1. Patients who received fresh frozen plasma (FFP) were significantly more likely to develop an infection than those who did not receive FFP in a univariate model ($p < .01$).

FFP Transfusion assoziiert mit:

- VAP mit (RR 5.42) und ohne Schock (RR 1.97)
- Septischer Schock mit + BK (RR 3.35)
- Non-specified septic shock (RR 3.22)
- RR für FFP Gabe und Infektionen: 2.99

Sarani, B. *et al.* Transfusion of fresh frozen plasma in critically ill surgical patients is associated with an increased risk of infection. *Crit. Care Med.* **36**, 1114–1118 (2008).

FFP und Komplikationen: Dosis abhängiger Effekt

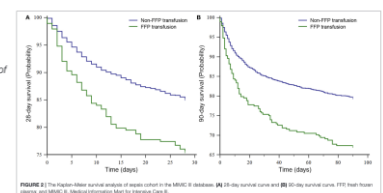


Inaba K, et al. Impact of plasma transfusion in trauma patients who do not require massive transfusion. *J Am Coll Surg* 2010;210:957-65.

Early Fresh Frozen Plasma Transfusion: Is It Associated With Improved Outcomes of Patients With Sepsis?

Xiaoyi Qin^{1†}, Wei Zhang^{2†}, Xiaodan Zhu³, Xiang Hu⁴ and Wei Zhou^{3*}

¹ Department of Hematology, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China, ² Department of Thoracic Surgery, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China, ³ Department of Intensive Care Unit, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China, ⁴ Department of Endocrine and Metabolic Diseases, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China



- Anstieg der 28 und 90 Tage Mortalität mit Zunahme der **FFP Volumenmenge**
- Andere Arbeiten ebenfalls mit Zunahme von MOF, Mortalität, Krankenhausaufenthalt, etc

Church GD, Matthay MA, Liu K, Milet M, Flori HR. Blood product transfusions and clinical outcomes in pediatric patients with acute lung injury. *Pediatr Crit Care Med*. (2009) 10:297-302.

Karam O, Lacroix J, Robitaille N, Rimensberger PC, Tucci M. Association between plasma transfusions and clinical outcome in critically ill children: a prospective observational study. *Vox Sang*. (2013) 104:342-9.

ASSOCIATION BETWEEN PLASMA TRANSFUSION AND IN-HOSPITAL MORTALITY IN CRITICALLY ILL PATIENTS WITH SEPSIS-INDUCED COAGULOPATHY

Renli Wang,* Rongjun Liu,[†] and Zhaojun Xu*

*Department of Intensive Care Unit, Ningbo No. 2 Hospital, Ningbo, Zhejiang, China; and [†]Department of Anesthesiology, Ningbo No. 2 Hospital, Ningbo, Zhejiang, China

- **Erhöhte Mortalität** bei septischen Patienten und Koagulopathie bei FFP Gabe
- Erhöhte Interaktion mit pTF als mögliche Ursache

TABLE 5. The relationship between the start time of plasma transfusion and in-hospital mortality

Model	No. patients	OR (95% CI)	P	
Unmatched	Model 1	1,874	0.5461 (0.4493–0.6635)	<0.05
	Model 2		0.5528 (0.4433–0.6887)	<0.05
	Model 3		0.5449 (0.4348–0.6821)	<0.05
	Model 4		0.5426 (0.4398–0.6844)	<0.05
PSM	1,320	0.5747 (0.4563–0.7225)	<0.05	
IPTW	3,742.5	0.6290 (0.5490–0.7203)	<0.05	

FFP in der Sepsis

- Surviving Sepsis Campaign 2021 – **keine Empfehlung** für FFP Gabe
- Erhöhtes Infektionsrisiko und Risiko für Sepsis und septischen Schock
- Keine Verbesserung bei septischen Patienten mit Koagulopathie
- Offene Studien:
 - EXCHANGE 2 Trial
 - PROPHECY 2 Trial

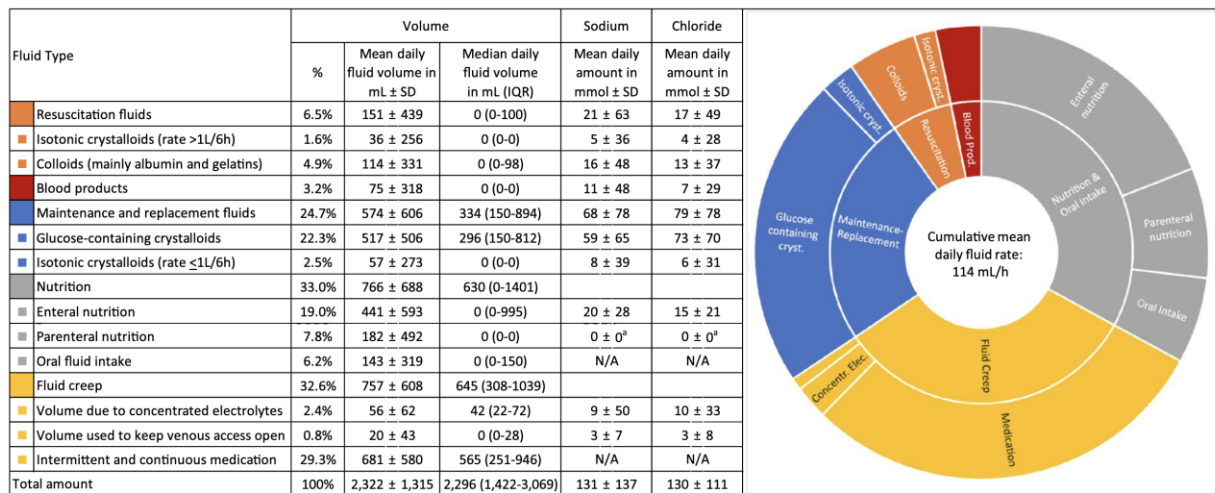
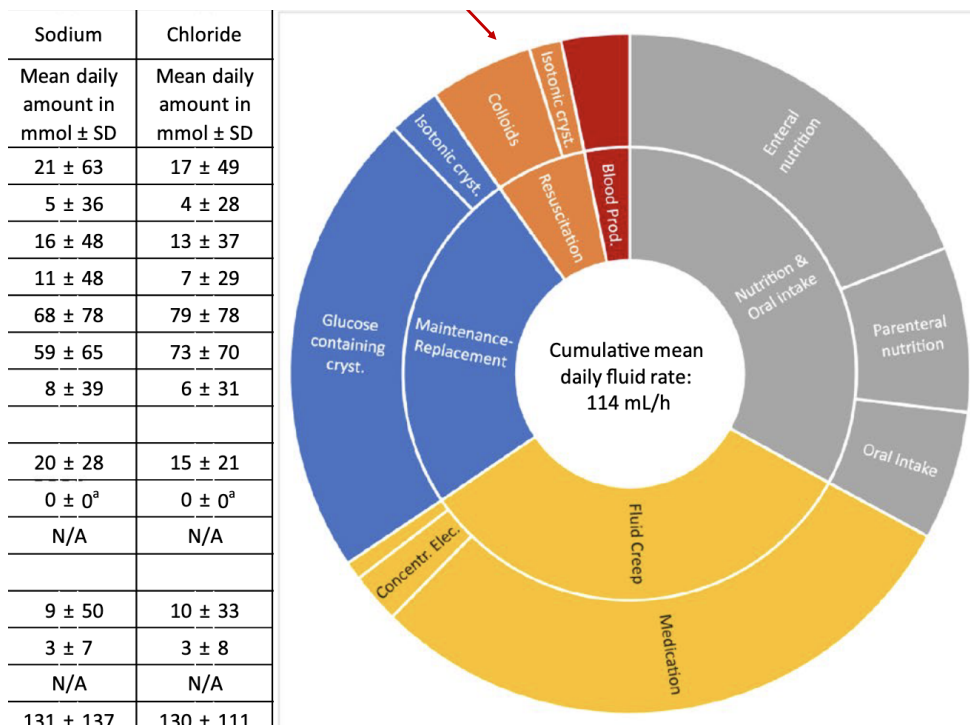


Fig. 1 Proportion, mean, and median fluid volumes, and mean sodium and chloride burdens of the different fluid types (average of 14,654 patients on their cumulative 103,098 days of ICU stay), including a graphic representation of the distribution of the different mean daily fluid volumes. Mean duration of one ICU day, 20.3 ± 6.7 h. SD standard deviation, IQR interquartile range, N/A data not available. ^aTo ensure optimal electrolyte management in our ICU, only electrolyte-free formulas of parenteral nutrition are prescribed, with separate administration of electrolytes

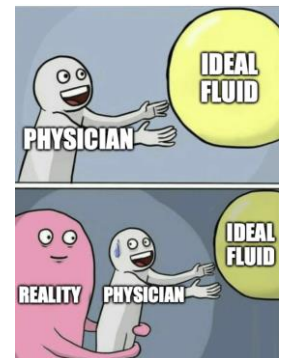


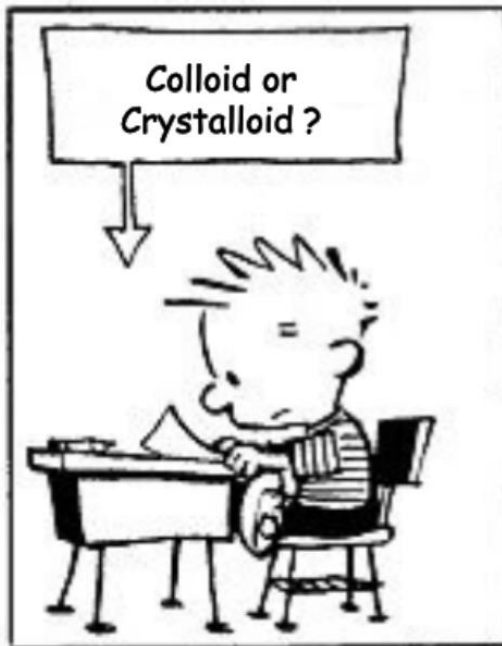
Überlegungen zu Flüssigkeiten

- Möglicherweise gesteigerter Sauerstoffverbrauch je nach Zusatz
- Menge der Resuscitation Fluid wirklich relevant?
- Theoretische Überlegungen vs Real Life...

Evidenzbasiert Empfehlungen 2025?

- Primum non nocere
- 1st Line Balancierte Kristalloide – cave SHT
- Gelatine als synthetische Alternative – GENIUS Trial
- Albumin als Alternative bei anhaltender Volumendepletion?





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I cannot answer this question, as it is against my religious principles.

