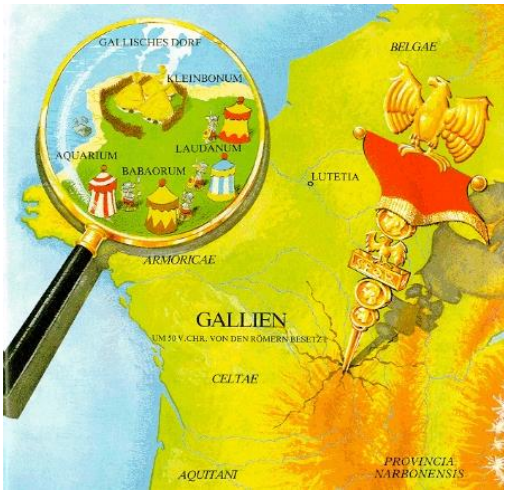
Leading Edge:

Gelatine im (Septischen) Schock

Dietmar Fries, Trauma ICU

Department for Anaesthesia and Critical Care Medicine
Medical University Innsbruck, Austria



Total body water: approx. 60%

Compartment	Glucose 5%	Crystalloid	Colloid
Intravascular (4%)	—	↑	↑↑↑
Interstitial (16%)	↑↑	↑↑	—
Intracellular (40%)	↑↑↑	—	—

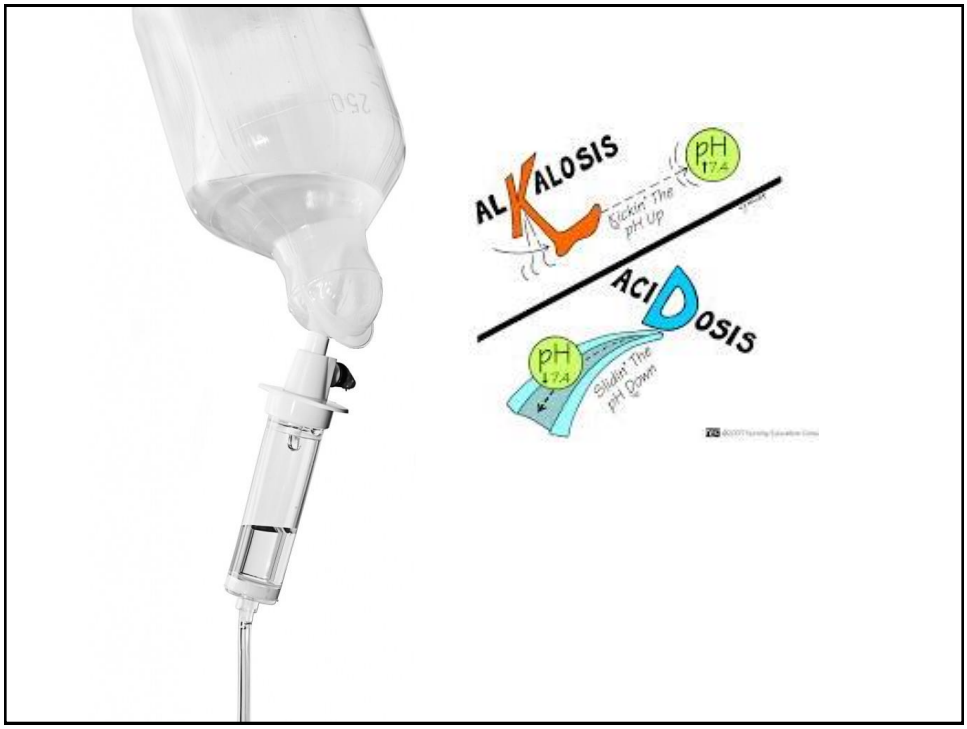
Crystalloids ...

Compartment	Glucose 5%	Crystalloid	Colloid
Intravascular (4%)	↑	↑	↑↑↑
Interstitial (16%)	↑↑	↑↑	—
Intracellular (40%)	↑↑↑	—	—

Gesamtkörperwasser ca. 60%

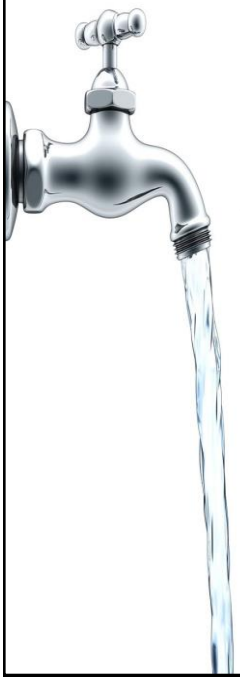
Kristalloide intravasal

Lösung	Ges.-Vol. (L)	Intravasal (L)	(%)	Literatur (Erstautor)
0,9 % NaCl	1,0	0,18	18	Lamke: Resuscitation 1976
	1,0	0,38	19	Lobo: Clin Sci 2001
	2,0	0,20	20	Drummer: Am J Physiol 1992
	3,2	0,77	24	Grathwohl: South Med 1996
	2,0	0,48	25	Reid: Clin Sci 2003
	3,5	1,09	31	Greenfield: Ann Emerg Med 1989
Ringer-Laktat	2,0	0,37	18	Reid: Clin Sci 2003
	1,0	0,19	19	Hauser: Surg Obstet 1980
Ringer-Azetat	1,5	0,23	15	Hahn: Br J Anaesth 1997
Mittelwert (n = 9)			21	



The „ideal“ fluid:

1. Minimal effect on acid base.
2. Physiological content of chloride.
3. Contains organic anion (precursors of $HCO3^-$).
4. Electrical neutralitlity (to avoid hypotonicity) with an SID between 24-30.



The „ideal fluid“: can not (co)-exist!

Two categories of i.v. crystalloid „balanced solutions“

1. **Minimal effect on acid base equilibrium (SID 24-29):**
2. **Chloride content equal or lower than 110 mEq**

	Na	K	Cl	SID	Osmol
Lactated Ringer	130	4	109	28	278
Ringer‘s Acetat	132	4	110	29	277
Sterofundin	145	4	127	29	309
Elomel	140	5	108	45	302
NaCl	154	0	154	0	309

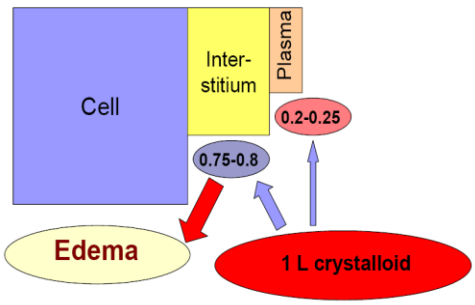
... the ideal fluid with minimal effects on acid base status, low chloride content and adequate tonicity is not available!

Colloids ...

Compartment	Glucose 5%	Crystalloid	Colloid
Intravascular (4%)	↑	↑	↑↑↑
Interstitial (16%)	↑↑	↑↑	—
Intracellular (40%)	↑↑↑	—	—

Gesamtkörperwasser ca. 60%

Volume Resuscitation and Crystalloids



The intravascular volume effect of **Ringer's lactate is below 20%**: a prospective study in humans . *Jacob M et al. Crit Care 2012*

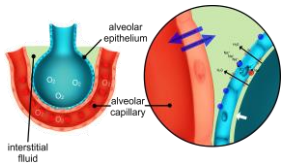
Exact Measurement of volume effect of 6% HES 130/0.4 during acute normovolemic hemodilution. *Jacob M et al. Anaesthesist 2012*.

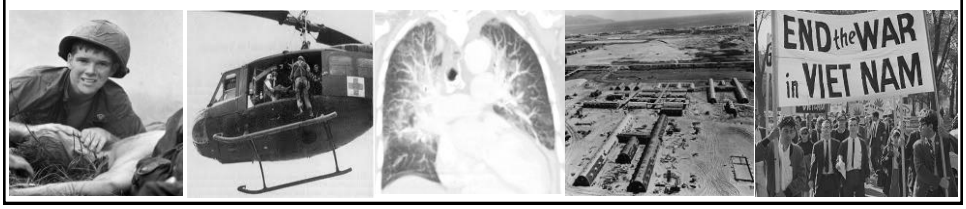
Fishman A.

Shock lung a distinctive nonentity. Circulation 1973

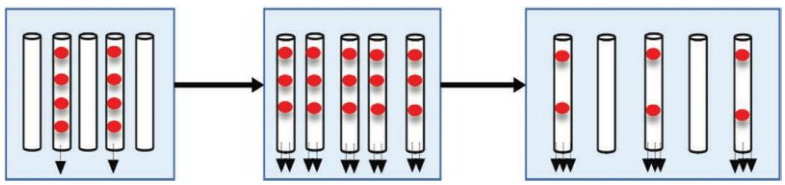
"wet lung" …"shock lung" …"Da Nang Lung"

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





Colloids and Microcirculation



A.Hypovolemia: decrease in convection flow and perfused capillary density

B.Expectation of fluid resuscitation: to increase convection flow and recruit the perfused capillary

C.Fluid overload: an increased diffusion distance caused by tissue edema and hemodilution

Huaiwu H, Can Ince. Anesth&Analg 2018; 126,5:1747-1754

MICROVASCULAR FLOW AND CAPILLARY PERFUSION AFTER EXTREME HEMODILUTION WITH GELATIN COMPARED TO NORMAL SALINE
STUDIES IN THE HAMSTER WINDOW MODEL

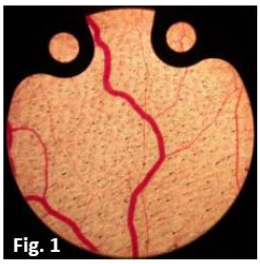
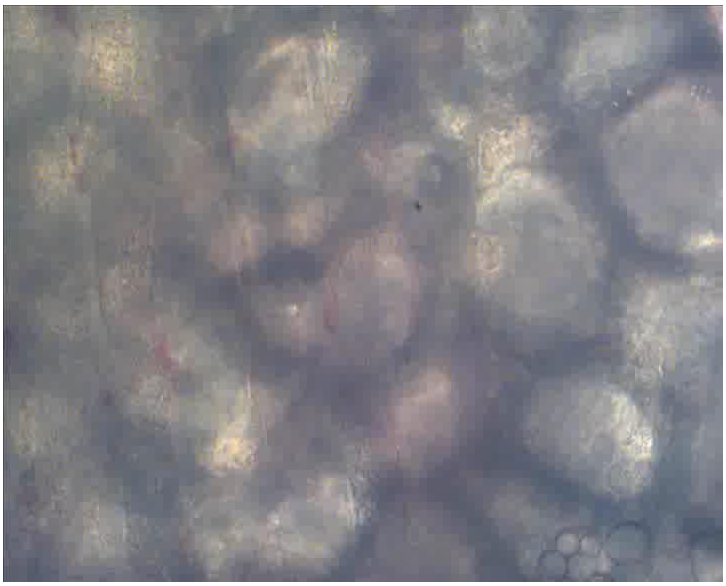
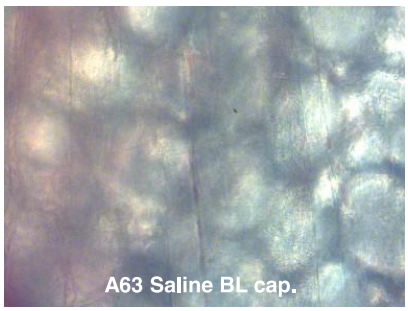
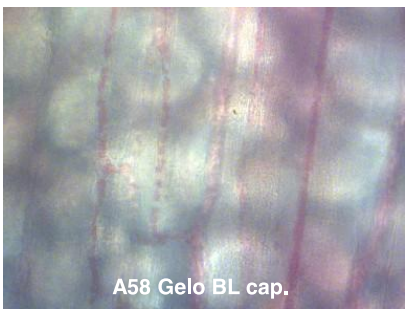


Fig. 1

"*Hamster skinfold window preparation*", a microcirculation model that allows for chronic and direct observation of microvessels by intravital microscopy.



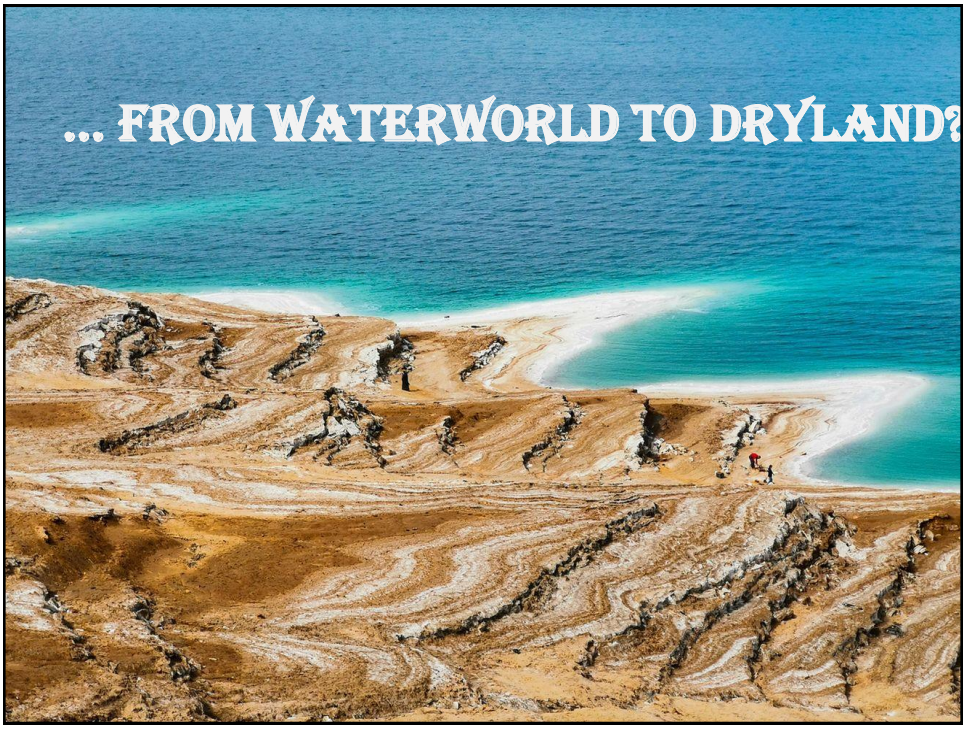


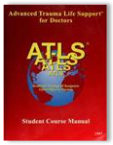


A63 (Saline)				
	Base	40%	35%	35%
Hct	48	34	25	16
Hb	14,3	8,5	6,9	5
pH	7,4	7,3	7,3	7,3
BE	9,3	-0,2	-3,9	-10,8

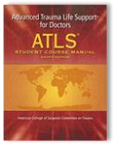
A58 (Gelofusin)				
	Base	40%	35%	35%
Hct	52	38	24	12
Hb	15,8	11,8	6,8	4,3
pH	7,3	7,3	7,3	7,5
BE	8,3	8,9	6,5	2,1


TRAUMA
MANAGEMENT
Fluid Resuscitation &
Permissive Hypotension

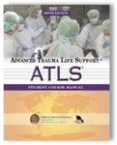

... FROM WATERWORLD TO DRYLAND?



1997: **8l colloids & crystalloids** (= 4,8l volume effect)



2004: **4l colloids & crystalloids** (= 2,4l volume effect)



2013: **2l crystalloids** (= 400 ml volume effect)

2019: **1l crystalloids** (= 200 ml volume effect)

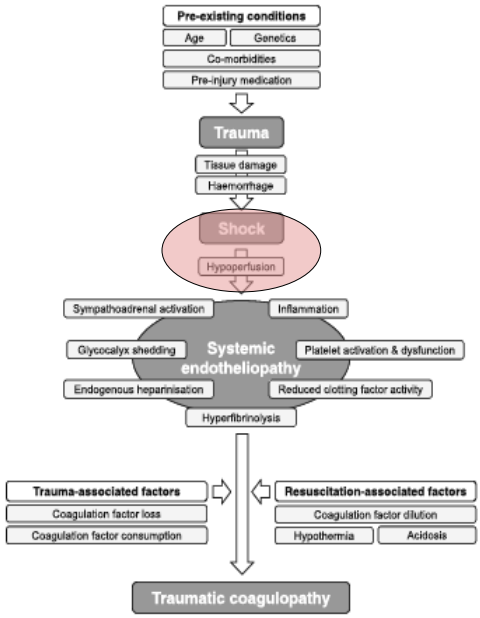
CRITICAL CARE

The European guideline on management of major bleeding and coagulopathy following trauma: sixth edition

Recommendation 15 We recommend that fluid therapy using **a 0.9% sodium chloride** or **balanced crystalloid** solution be initiated in the hypotensive bleeding trauma patient (Grade 1B).

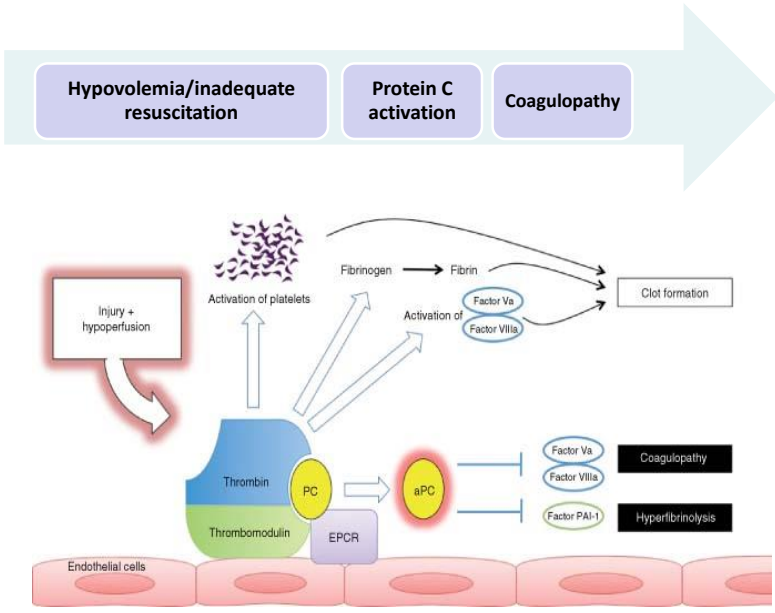
The concept of a restricted volume replacement and permissive hypotension. Tis strategy was mainly triggered by a RCT published in the 1990s demonstrating increased survival in penetrating trauma … (Bickell WH et al. 1994)

Rossaint R et al. Critical Care 2023; 27:80



„The lethal triad of hypothermia, acidosis and coagulopathy …“

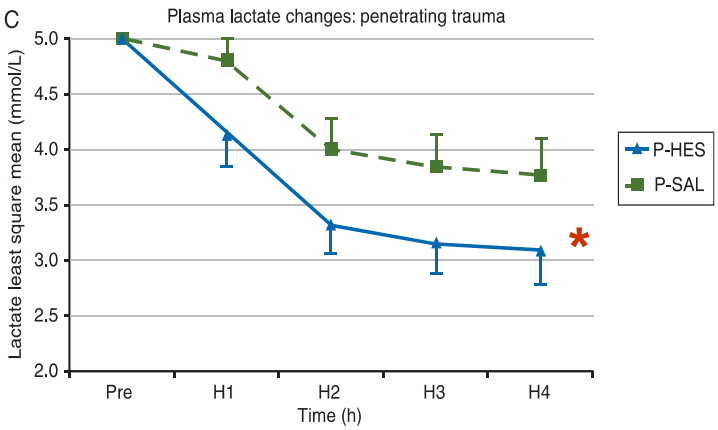
Coagulopathy



Thorsen K et al. 2011; British J of Surgery 98(7):894-907

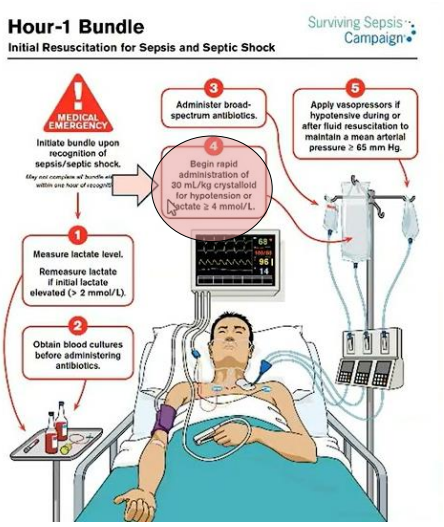
The FIRST Study:

Lactate/Lactate clearance in penetrating trauma



James. Br J Anaesth 2011;107:693

(Fluid)/volume resuscitation in sepsis/septic shock



Evans L et al. Critical Care Medicine 49(11): 1974-1982; Nov 2021

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

14 June 2013
EMA/349341/2013

PRAC recommends suspending marketing authorisations for infusion solutions containing hydroxyethyl-starch

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

19 December 2013
EMA/809470/2013

Hydroxyethyl-starch solutions (HES) no longer to be used in patients with sepsis or burn injuries or in critically ill patients

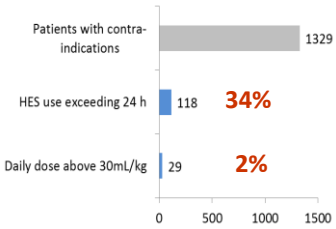
HES will be available in restricted patient populations

Major Flaws:

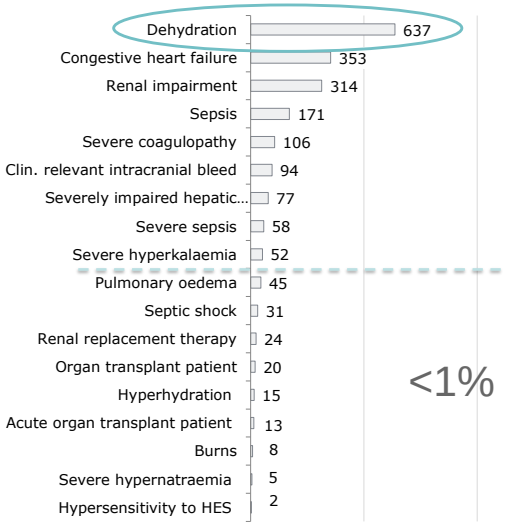
- **Both study groups received starches …**
- **Administartion of colloids AFTER hemodynamic stabilisation: …Fluid overload …!**
- **…**

2017: HES-DUS Studie: Non-Adherence zur Produktinformation

Patienten mit non-adherence zur SmPC



Patienten mit non-adherence zu Kontraindikationen



3.	Disturbed Fluid Status	◉ Yes	○ No
	Dehydration	○ Yes	◉ No
	Hyperhydration	○ Yes	◉ No

Query Information Panel:

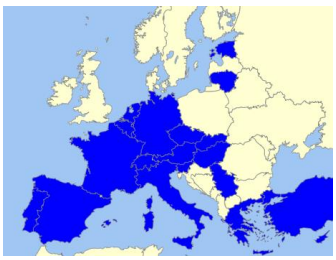
Disturbed Fluid Status

Edit Check:	
Text:	**Dehydration and Hyperhydration is 'No' but Disturbed Fluid Status is 'Yes'. Please check and correct.**
Status:	Open (high priority)

Add comment | Cancel

DGAI
Deutsche Gesellschaft für Anästhesiologie & Intensivmedizin

On behalf 19 European Societies of Anesthesiology*, we would like to express with this open letter our great concern about the current pharmacovigilance procedure for the volume replacement agent hydroxyethyl starch (HES) and ask you to stand up for obtaining marketing authorization from HES. At the same time, we agree with the statements of the Board of Directors of the European Society of Anaesthesiology (ESA) made in their letter from 5th of March 2018.



Austria Austrian Society of Anaesthesiology, Resuscitation and Intensive Care Medicine
Belgium Society of Anesthesia and Reanimation of Belgium
Czech Republic Czech Society of Anaesthesiology and Intensive Care Medicine
Estonia Estonian Society of Anaesthesiologists
France Société Française d'Anesthésie et de Réanimation
Germany German Society of Anaesthesiology and Intensive care Medicine
Greece Hellenic Society of Anaesthesiology
Hungary Hungarian Society of Anaesthesiology and Intensive Therapy
Italy S. I. A. A. R. T. I.
Israel Israel Society of Anaesthesiologists
Lithuania Lithuanian Society of Anaesthesiology and Intensive Care
Netherlands Nederlandse Vereniging voor Anesthesiologie
Portugal Portuguese Society of Anesthesiology
Serbia Serbian Association of Anaesthesiologists and Intensivists
Slovakia Slovak Society of Anaesthesiology and Intensive Medicine
Slovenia Slovenian Society of Anaesthesiology and Intensive Care Medicine
Spain Sociedad Espanola de Anestesiologia, Reanimacion y Terapeutica del Dolor
Switzerland Swiss Society for Anaesthesiology and Resuscitation
Turkey Turkish Society of Anesthesiology and Reanimation

PLOS ONE

Different effects of fluid loading with saline, gelatine, hydroxyethyl starch or albumin solutions on acid-base status in the critically ill

	NaCl 0.9% n = 28	Gelatine 4% n = 28	HES 6% n = 29	Albumin 5% n = 30
Age, years	61 (12)	61 (13)	60 (13)	60 (9)
Sex, female	5 (18%)	3 (11%)	10 (34%)	8 (27%)
Weight, kg	78 (12)	82 (13)	75 (11)	79 (16)
Height, m	1.75 (0.08)	1.77 (0.07)	1.72 (0.09)	1.71 (0.20)
APACHE II	10 (5)	11 (5)	11 (4)	11 (4)
Fluid infused, mL	1723 (209)	1509 (328)	1441 (295)	1553 (258)
Hb, mmol/L,				
T = 0	6.2 (1.2)	5.7 (0.9)	5.7 (1.1)	5.9 (1.2)
T = 90*,**	6.1 (0.9)	5.0 (0.7)[A]	5.0 (0.8)[A]	5.2 (0.9)[A]
Change in PV, %**	5 [18–24]	18 [-8-49][A]	21 [-11-50][A]	16 [2–61][A]

Values are mean (SD) or number (percentage), where appropriate. Abbreviations: PV, plasma volume; HES, hydroxyethyl starch.
* P<0.001 for decrease in whole group;
** P<0.001 between fluids;
[A] P<0.001 for change vs saline.

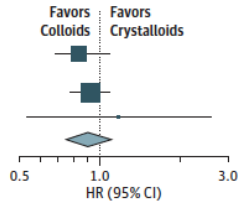
A. Spoelstra±de Man et al. PLoS ONE 2017 12(4): e0174507

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;

Reason for ICU Admission	Colloids Group (n = 1414) No. of Patients	Colloids Group (n = 1414) No. of Deaths	Crystalloids Group (n = 1443) No. of Patients	Crystalloids Group (n = 1443) No. of Deaths	HR (95% CI)
Other causes of hypovolemic shock	555	131	572	152	0.87 (0.69-1.10)
Sepsis	774	215	779	226	0.95 (0.78-1.10)
Trauma	85	13	92	12	1.19 (0.54-2.60)
All patients	1414	359	1443	390	0.93 (0.80-1.10)



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

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	No. (%) of Patients			
	Colloids (n = 1414)	Crystalloids (n = 1443)	RR (95% CI)	*P* Value[a]
Death				
Within 28 d	359 (25.4)	390 (27.0)	0.96 (0.88 to 1.04)	.26
Within 90 d	434 (30.7)	493 (34.2)	0.92 (0.86 to 0.99)	.03
In ICU	355 (25.1)	405 (28.1)	0.92 (0.85 to 1.00)	.06
In hospital	426 (30.1)	471 (32.6)	0.94 (0.87 to 1.02)	.07

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

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.journals.elsevier.com/journal-of-critical-care

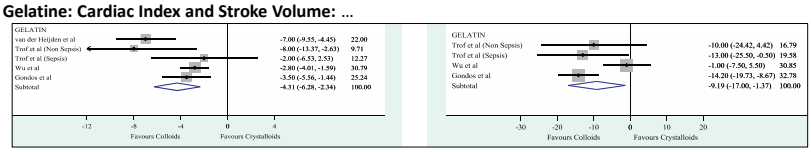
Crystalloids vs. colloids for fluid resuscitation in the Intensive Care Unit: A systematic review and meta-analysis

Metaanalyse: 55 RCTs (N = 27.036 patients)

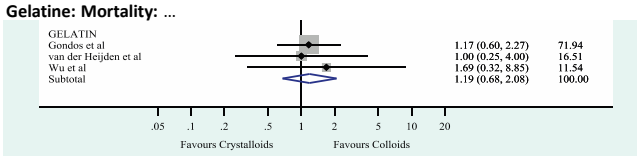
CVP: sig. lower with crystalloids than with Alb, HES or gelatin (p=0.001).

MAP: sig. lower with crystalloids vs. Alb (−3.5 mm Hg; p = .03) or gelatin (−9.2 mm Hg; p = .02).

Gelatine: Cardiac Index and Stroke Volume: …

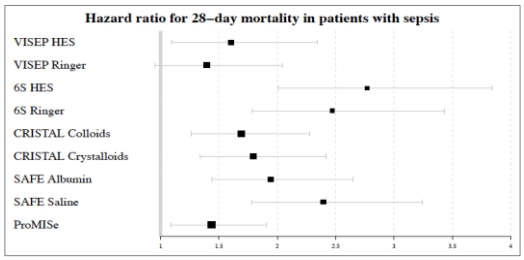


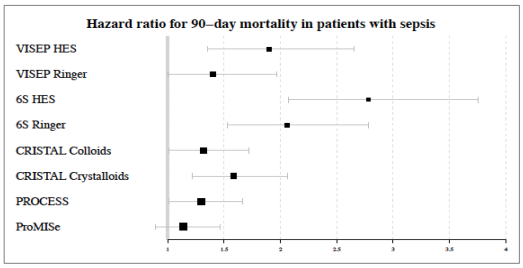
Gelatine: Mortality: …



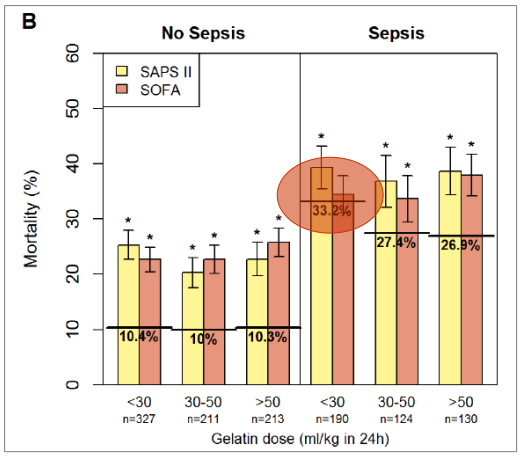
Greg S Martin and Paul Basset. Journal of Critical Care 50 (2019) 144–154.

Retrospective analysis of n = 1,216 ICU patients treated at the Department for General and Surgical Critical Care Medicine, Innsbruck. Volume therapy was exclusively performed with gelatin.





ICU mortality of gelatin treated ICU patients (n=1.259) in Innsbruck



In-hospital mortality (black line) and mortality predicted by SAPS II (yellow) and SOFA (red) for with and without Sepsis, respectively, stratified by gelatine dose in 24h.

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

- Prospective, controlled, randomized, double-blind, international, multicentric phase IV study.
- A total of 608 eligible patients will be randomly assigned to receive either a gelatine-crystalloid regime or a pure crystalloid regime
- The primary outcome is defined as the **time needed to achieve HDS**

Marx G et al. Trials 2021 Jun 2,22(1)376