FLUID RESUSCITATION: TARGETS

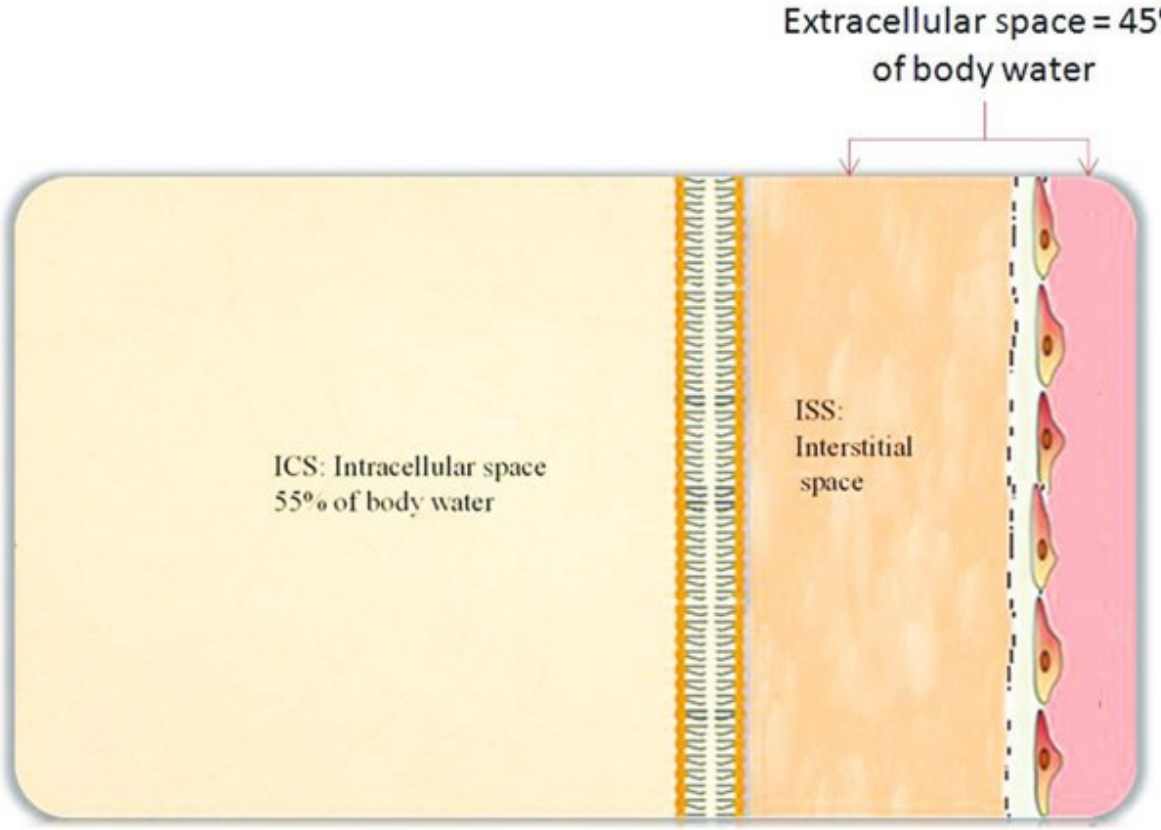
Management of both critically ill and elective surgery patients is mainly aimed at assuring adequate tissue perfusion and oxygenation. Physiologically adequate oxygen delivery (DO2) is assured by the cardiovascular and respiratory systems and it corresponds to the quantity (in mL) of oxygen per minute carried to the tissues.

$$DO2\ (mL/min) = (HR \times SV) \times [(1.34 \times Hb \times SaO2) + (0.003 \times paO2)]$$

PRELOAD : Frank and Starling LAW OF THE HEART

BODY FLUIDS MOVEMENTS

1. BODY FLUID COMPARTMENTS
2. INTERFACES SEPARATING THESE COMPARTMENTS
3. FORCES THAT GOVERN THE MOVEMENT OF FLUIDS



BODY FLUIDS MOVEMENTS

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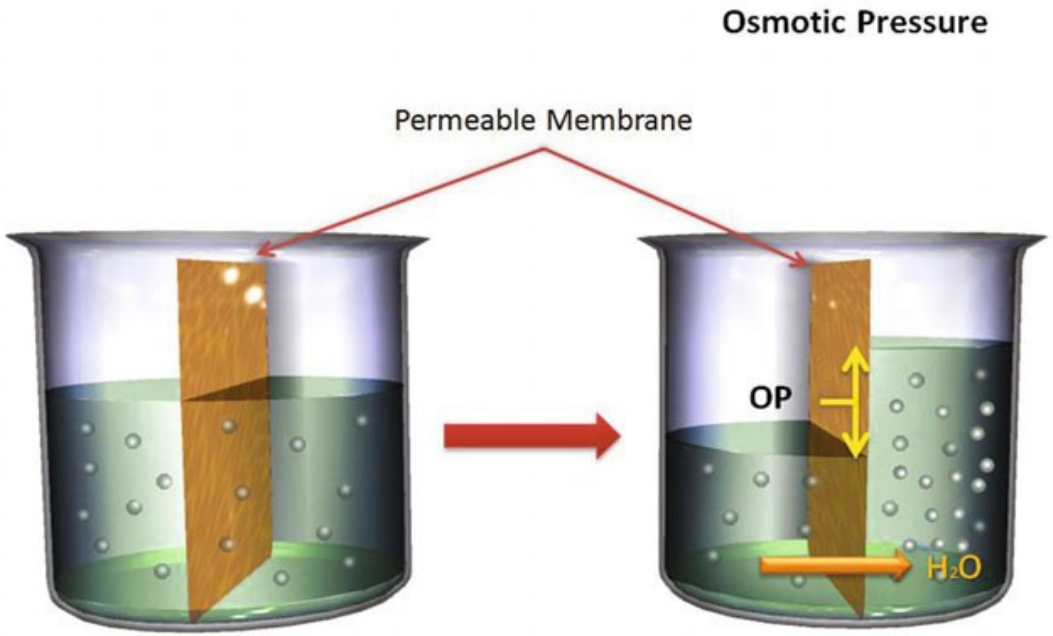
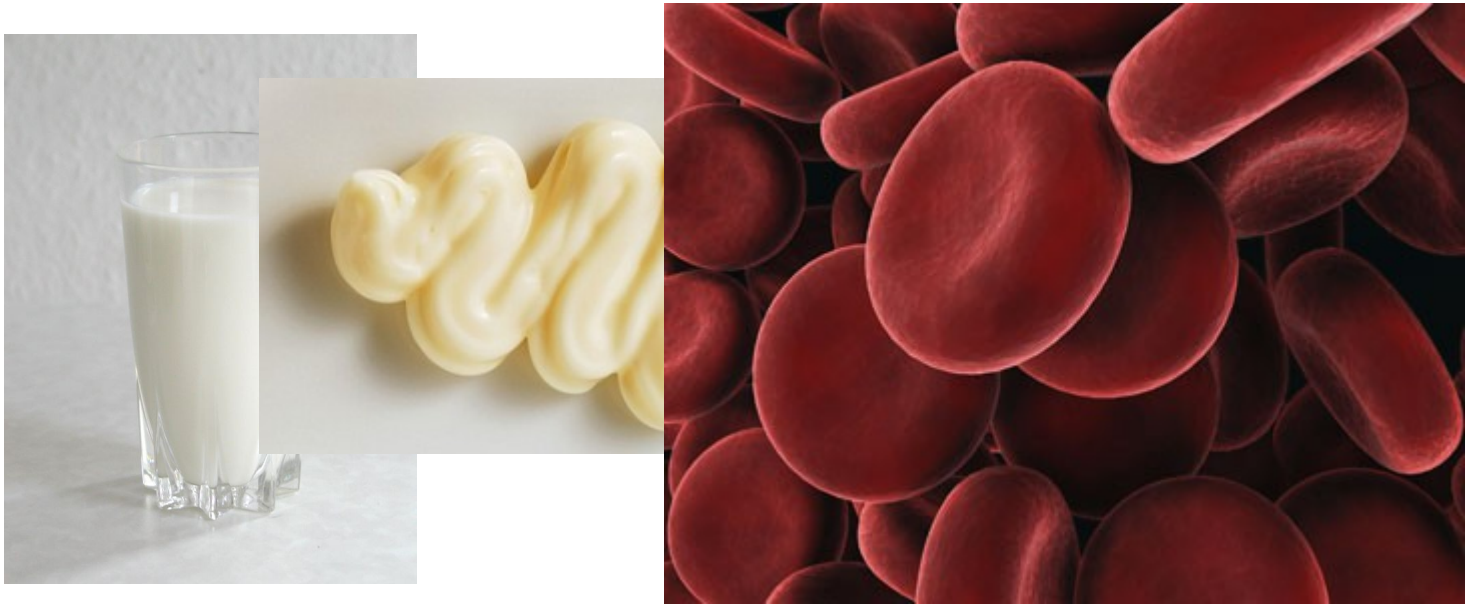


Osmolarity measure the concentration of a solution, expressed as the number of particles of solute per 1 L solution. Osmolarity is measured in milliosmoles per liter of solution (mOsm/L). It is calculated as the product of the molarity and the Van't Hoff coefficient, which considers the degree of dissociation of the solute present in the solution.

COLLOID-OSMOTIC PRESSURE

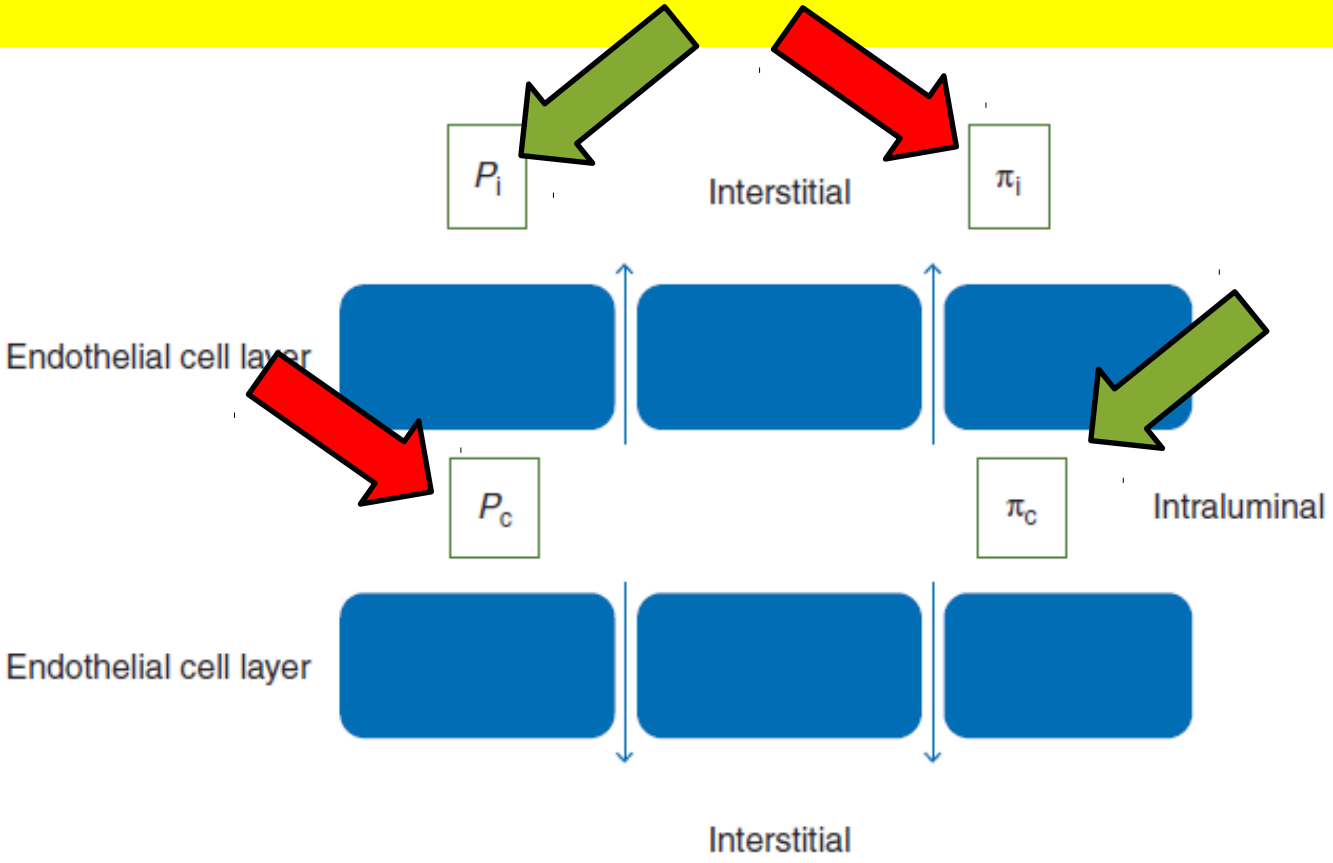
COLLOIDE: (o **sistema colloidale**) è una particolare miscela in cui una sostanza si trova in uno stato finemente disperso, intermedio tra la soluzione omogenea e la dispersione eterogenea. Questo stato "microeterogeneo" consiste quindi di due fasi: una fase costituita da una sostanza di **dimensioni microscopiche (diametro da 1 nm a 1 µm)** e una fase continua disperdente.



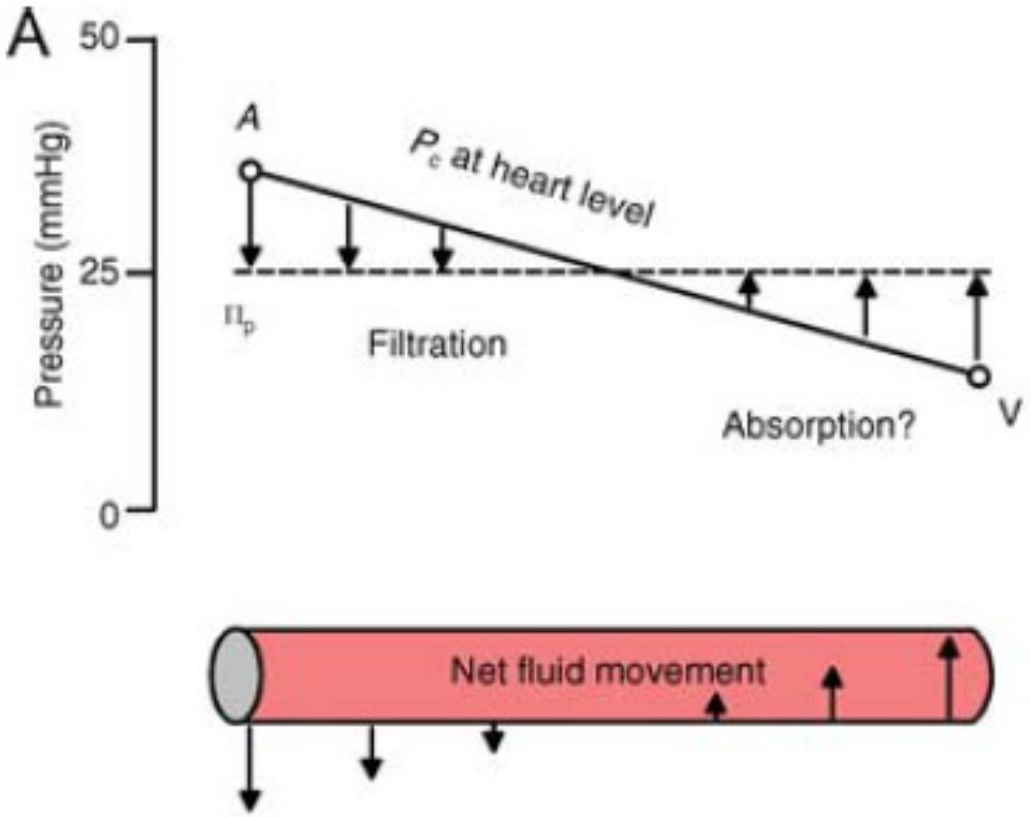
STARLING FORCES

STARLING FORCES

$$Jv = Kf \{(Pc - Pi) - \sigma (\Pi p - \Pi i)\}$$



STARLING FORCES



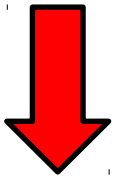
Interstitial forces considered small & negligible

$P_{c0} = \Pi_p = 25$ mmHg

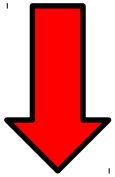
$P_v = 7.7 \pm 1.9$ mmHg (human arm, heart level)

CRYSTALLOIDS & COLLOIDS

Thomas Graham propone una classificazione delle sostanze in **cristalloidi** e **colloidi** in base alla loro capacità di diffondere o meno attraverso una membrana di pergamena.



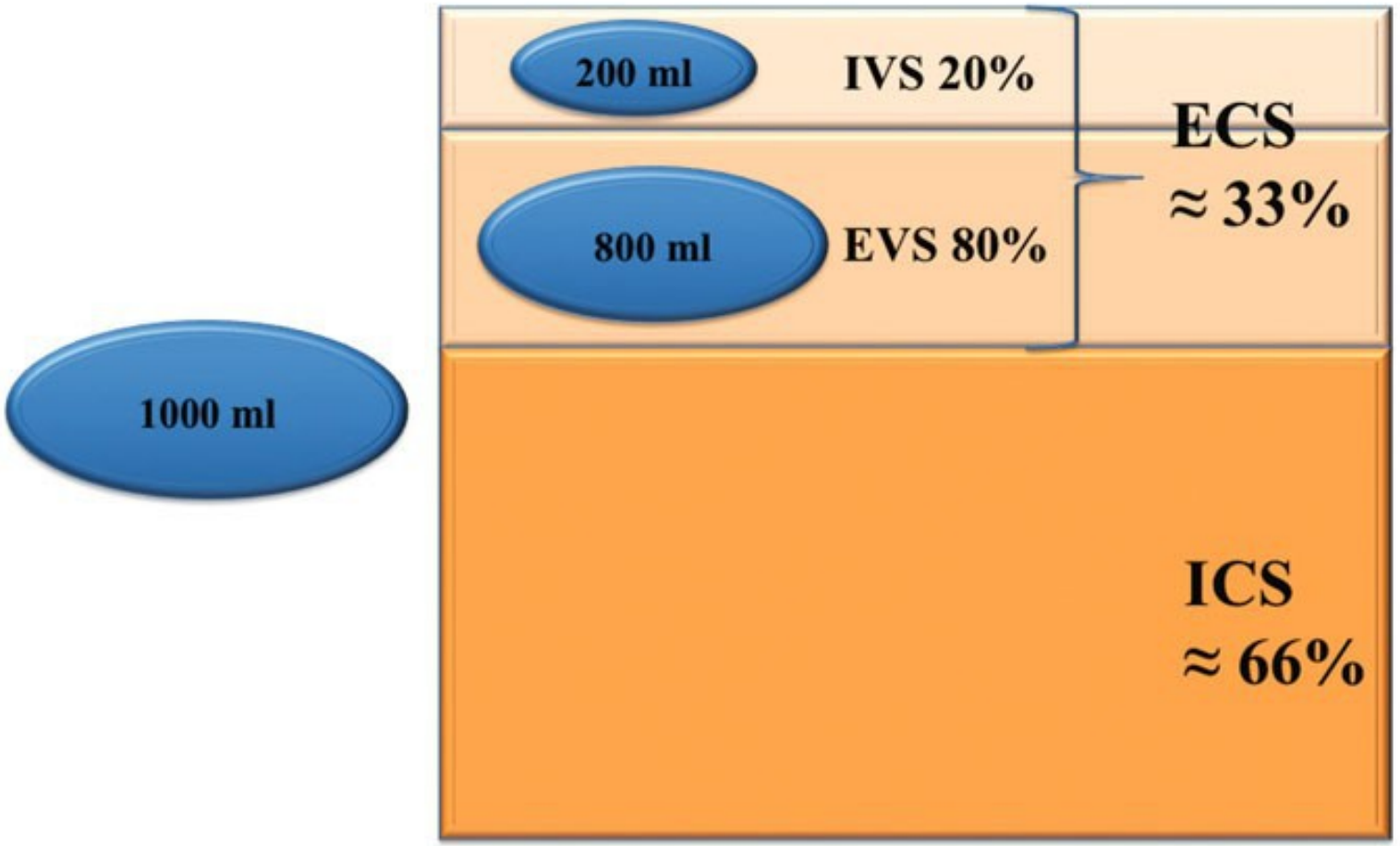
SOLUZIONE O SISTEMA COLLOIDALE



CAPACITA' DI PASSARE DAL COMPARTIMENTO INTRAVASCOLARE A QUELLO EXTRAVASCOLARE

CRYSTALLOIDS

Low-molecular weight salts, dissolved in water, constitute crystalloids. The salts pass freely from the IVS to the ISS and vice versa (membrane endoteliali permaeabili alla soluzione, principio di isoosmolarità).



CLASSIFICATION

Electrolyte or parameter	Plasma	0.9% NaCl	Ringer lactate	Ringer acetate	Sterofundin®
Colloid-osmotic pressure (mmHg)	25	-	-	-	-
Osmolality (mOsm/Kg)	287	308	277	256	291
Sodium (mEq/L)	142	154	131	130	145
Potassium (mEq/L)	4.5	-	5.4	5	4
Magnesium (mEq/L)	1.25	-	-	1	1
Chloride (mEq/L)	103	154	112	112	127
Calcium (mEq/L)	2.5	-	1.8	1	2.5
Lactate (mEq/L)	1	-	28	-	-
Bicarbonate (mEq/L)	24	-	-	-	-
Acetate/Malate (mEq/L)	-	-	-	27/-	24-5

NORMAL SALINE

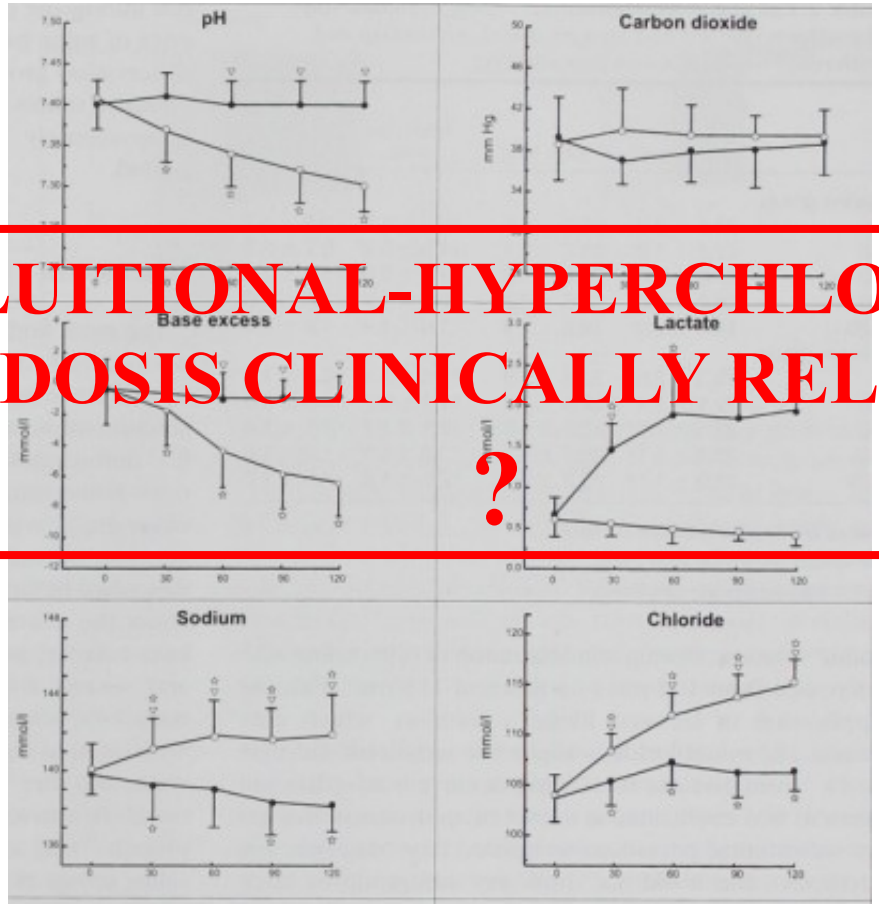
Neither normal nor physiological, however, saline solution is still a standard against which other solutions are measured.

Electrolyte or parameter	Plasma	0.9% NaCl
Colloid-osmotic pressure (mmHg)	25	-
Osmolality (mOsm/Kg)	287	308
Sodium (mEq/L)	142	154
Potassium (mEq/L)	4.5	-
Magnesium (mEq/L)	1.25	-
Chloride (mEq/L)	103	154
Calcium (mEq/L)	2.5	
Lactate (mEq/L)	1	-
Bicarbonate (mEq/L)	24	-
Acetate/Malate (mEq/L)	-	-

OSMOLALITY

CHLORIDE

Hyperchloraemic acidosis



IS DILUITIONAL-HYPERCHLORAEMIC ACIDOSIS CLINICALLY RELEVANT ?

Anesthesiology.1999 May;90(5):1265-70.
Rapid saline infusion produces hyperchloremic acidosis in patients undergoing gynecologic surgery. Scheingraber S, Rehm M, Sehmisch C, Finsterer U

RINGER LACTATE & RINGER ACETATE

Anaesthesia 1981 Dec;36(12):1115-21.

Sydney Ringer (1834-1910) and Alexis Hartmann (1898-1964). Lee JA.

Electrolyte or parameter	Plasma	Ringer lactate	Ringer acetate
Colloid-osmotic pressure (mmHg)	25	-	-
Osmolality (mOsm/Kg)	287	277	256
Sodium (mEq/L)	142	131	130
Potassium (mEq/L)	4.5	5.4	5
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Acetate/Malate (mEq/L)	-	-	27/-

OSMOLALITY

CHLORIDE

LACTATE

LATEST GENERATION CRYSTALLOIDS

Electrolyte or parameter	Plasma	Sterofundin®
Colloid-osmotic pressure (mmHg)	25	-
Osmolality (mOsm/Kg)	287	291
Sodium (mEq/L)	142	145
Potassium (mEq/L)	4.5	4
Magnesium (mEq/L)	1.25	1
Chloride (mEq/L)	103	127
Calcium (mEq/L)	2.5	2.5
Lactate (mEq/L)	1	-
Bicarbonate (mEq/L)	24	-
Acetate/Malate (mEq/L)	-	24-5

POTASSIUM, MAGNESIUM, PHOSPHATE

pH 7,4

COLLOIDS

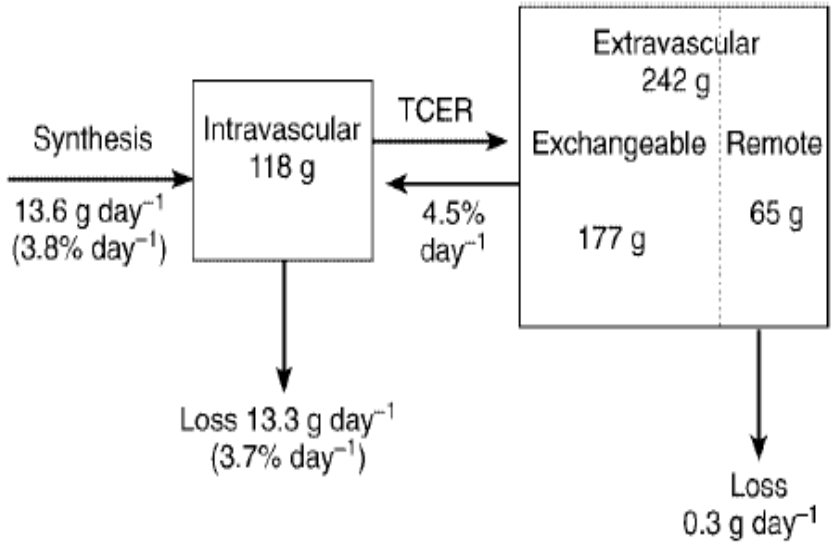
Colloids are homogenous noncrystalline substances consisting of large molecules or ultramicroscopic particles of one substance **dispersed** through a second substance.

NATURAL COLLOIDS

SEMISYNTHETIC COLLOIDS

ALBUMIN

Human Albumin is made up of 585 amino acids with a molecular mass of 69,000 Daltons. It is the main plasma protein (50–60%), accounting for 80% of normal oncotic pressure.



1- Maintenance of **oncotic pressure**
2- **Microvascular integrity**
3- **Transport**
- Fatty acids
- Bile salts
- Bilirubin
- Ca2+, Mg2+
- Drugs

4- **Metabolic**
- Acid–base
- Antioxidant
- Anticoagulant

ALBUMIN solutions

HA is prepared from pooled human plasma by alcoholic precipitation. On the basis of manufacturing process and the pathogen inactivation involved, albumin preparations are considered to carry **no risk of transmitting infections**.

Albumin solutions do not contain isoagglutinins or blood group substances and can thus be administered **independent of the recipient's blood group**.

Albumin solutions are dissolved in saline solution containing 154 mmol litre of sodium and 154 mmol litre of chloride.

Different concentrations of HA are commercially available: **20%** and **25%** HA (hyperoncotic), **5%** HA (iso-oncotic), **4%** HA (hypo-oncotic)

ALBUMIN pharmacokinetics

A 5% HA solution can be reasonably considered for volume replacement, leading to an 80% initial volume expansion, whereas HA 25% leads to a 200–400% volume increase within 30 min.

The decrease in plasma HA concentration is firstly due to passage from IVS to EVS and secondly to the fractional degradation rate.

ENDOTHELIAL INTEGRITY

?

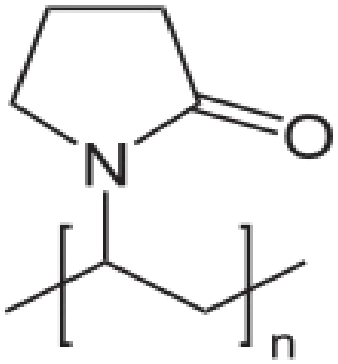
POTENTIAL RISKS

- Pulmonary Edema
- Coagulation and hemostasis
- Immunologic reactions

Synthetic colloids

UN PO' DI STORIA…

The development of **synthetic** colloids was markedly driven during times war to facilitate transport of wounded soldiers to medical centres.



POLYVINYLPYRROLIDONE
"PERISTON"

WAR IN PICTURES pictureshistory.blogspot.com

SYNTHETIC COLLOIDS

1- DEXTRANS

2- GELATINS

3- HYDROXYETHYL STARCHES

Classification

Colloid	Volemic effect		Side effect		
	Efficacy	Duration	AKI	Coag.	Anaf.
Dextrans	+++	+++	+++(40)	+++(70)	++
Gelatins	+	+	+	+	+++
HES high MW	+++	+++	++	+++	+
HES low MW	+++	++	+	++	+

+, mild; ++, moderate; +++, high; *MW*, molecular weight; *AKI*, acute kidney injury.

DEXTRANS

Dextrans are **glucose polymers** of different sizes, derived from Leconostoc mesenteroides, **a bacteria** originally isolated from contaminated sugar beets.

DEXTRANS

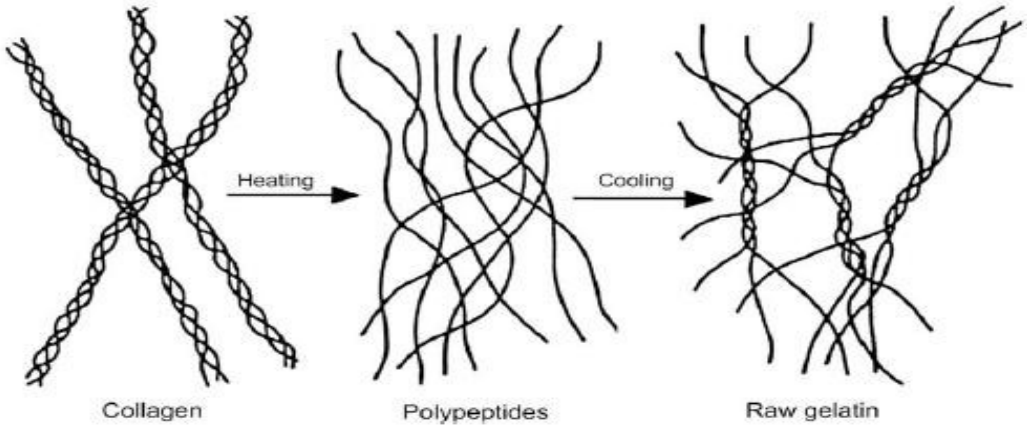
Characteristics of Dextran Solutions	6% Dextran 70	10% Dextran 40
Mean Molecular Weight (Dalton)	70,000	40,000
Volume efficacy (%) (approx.)	100	175-(200)
Volume effect (hours) (approx.)	5	3-4
Maximum Daily Dose (g/kg)	1.5	1.5

Dextran is no longer used because of its side effects: ANAPHYLAXIS, NEPHROTOXICITY, COAGULATION.

GELATINS

Gelatins are poydispersed peptides derived from bovine gelatin, a derivative of collagen.

STRUCTURE



Commercially available gelatin preparations contain either **oxypolygelatin**, **polygelin (urea cross-linked** polymerized polypeptides) or **gelatin polysuccinate**.

Succinylation induces spreading of the molecular structure that, in turn, increases the volume effect compared with equal molecular masses of non-succinylated gelatins

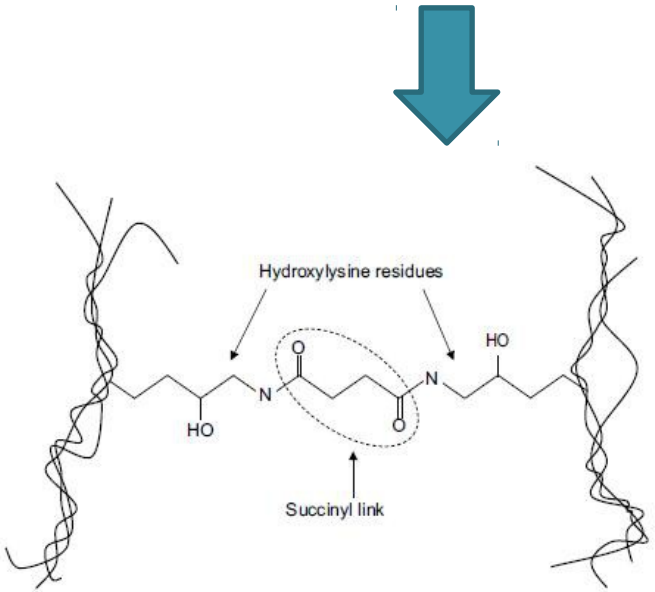


Fig. 6. Molecular characteristics of succinylated gelatin.

PHARMACOKINETICS

Characteristics of gelatin solutions	Succinylated gelatin	Cross-linked gelatin	Urea cross-linked gelatin
Concentration (%)	4.0	5.5	3.5
Mean Molecular Weight (Dalton)	30,000	30,000	35,000
Volume efficacy (%) (approx.)	80	80	80
Volume effect (hours) (approx.)	1-3	1-3	1-3
Osmolarity (mOsm/L)	274	296	301

-Polydispersed : **powerful initial osmotic effect**

- Approximately 50% of molecules are excreted into the urine during or shortly **after infusion**

- Osmotic diuretics

Br J Anaesthesia 2012 Aug;109(2):168-76. doi: 10.1093/bja/aes098. Epub 2012 Apr 16. **Effects of an intraoperative infusion of 4% succinylated gelatine (Gelofusine(R)) and 6% hydroxyethyl starch (Voluven(R)) on blood volume.** Awad S, Dharmavaram S, Wearn CS, Dube MG, Lobo DN.

POTENTIAL RISKS

- **Anaphylactic reactions** (severe reactions occur in 0,05-0,1%)
- Effects on **coagulation**
- Effects on **renal function**
- Osmotic **diuresis**

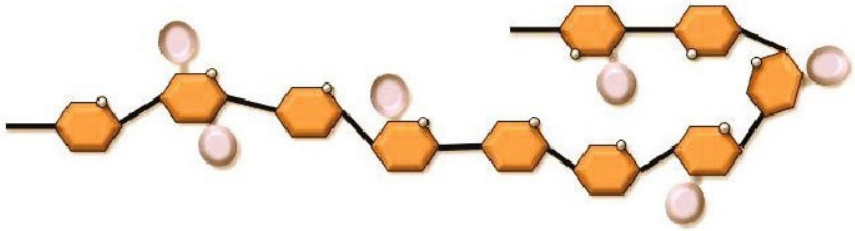
Hydroxyethil starches

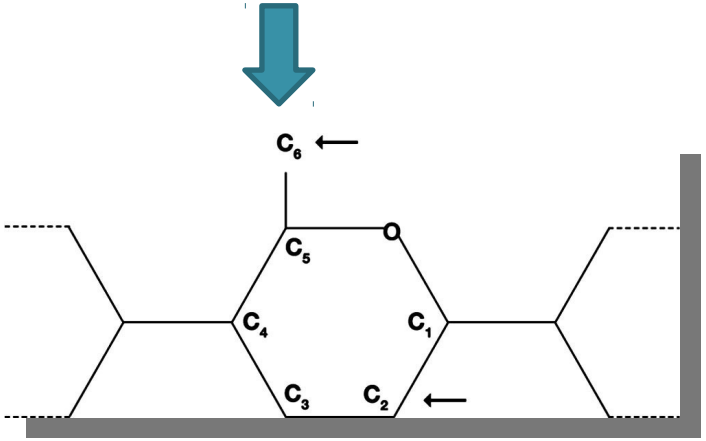
Hydroxyethyl starches (**HES**) are modified natural polysaccharides derived from amylopectin, a highly branched starch similar to glycogen that is found in maize or potatoes.

Hydroxyethil starches

Natural starches cannot be used in clinical routine since they are rapidly **hydrolyzed** by circulating amylase.

HES are obtained by replacing the hydroxyl groups of natural starches with hydroxyethyl groups at the **C2**, **C3**, and **C6** carbon positions of anhydroglucose residues. This results in greater solubility and less amylase degradation especially for hydroxyethylgroups at the **C2 position**.





Hydroxyethil starches

Starch (amylopectin)

Acid Hidrolysis

HYDROXYE THYLETION

Ultrafiltration

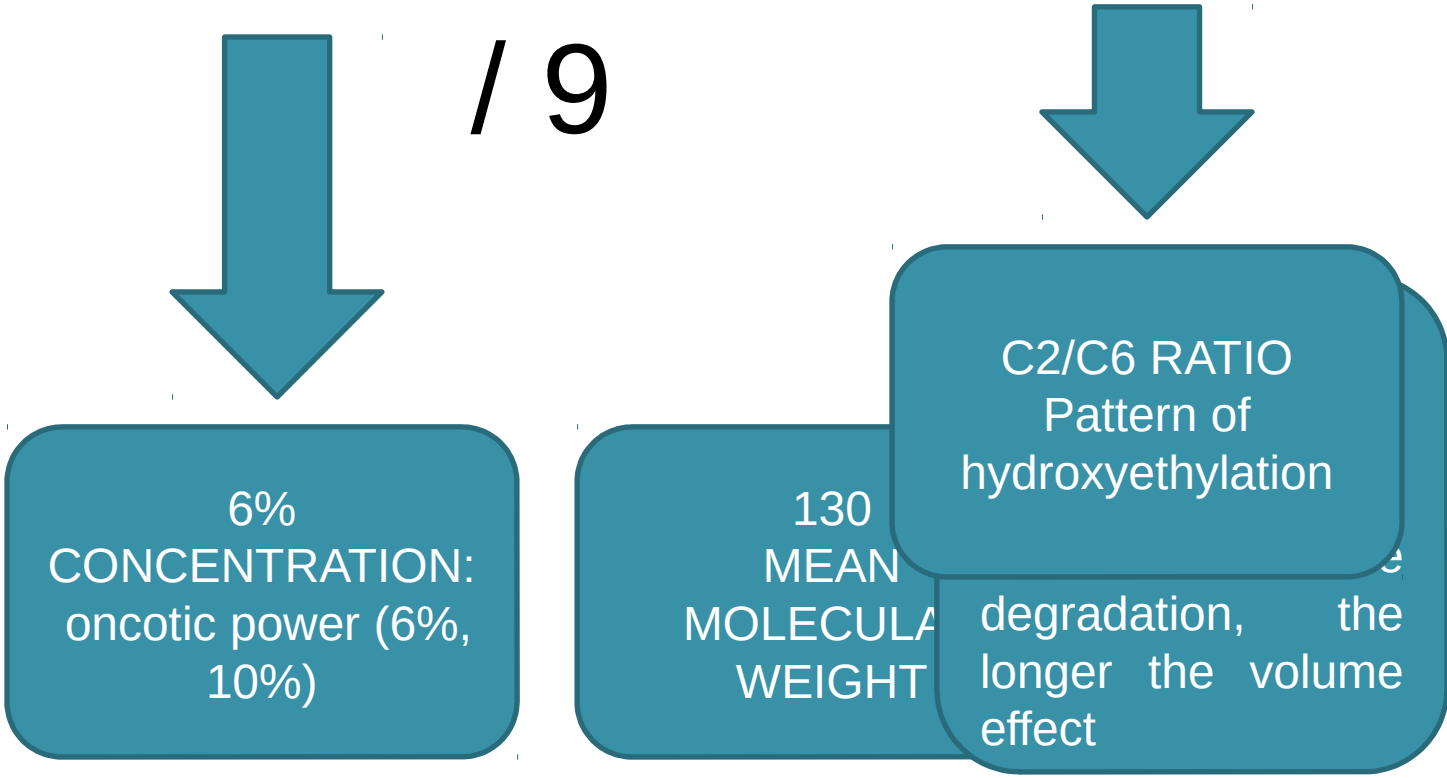
Determination of MOLECULAR WEIGHT (70000-670000 Da)

Determination of MOLAR SUBSTITUTION and C2/C6 RATIO

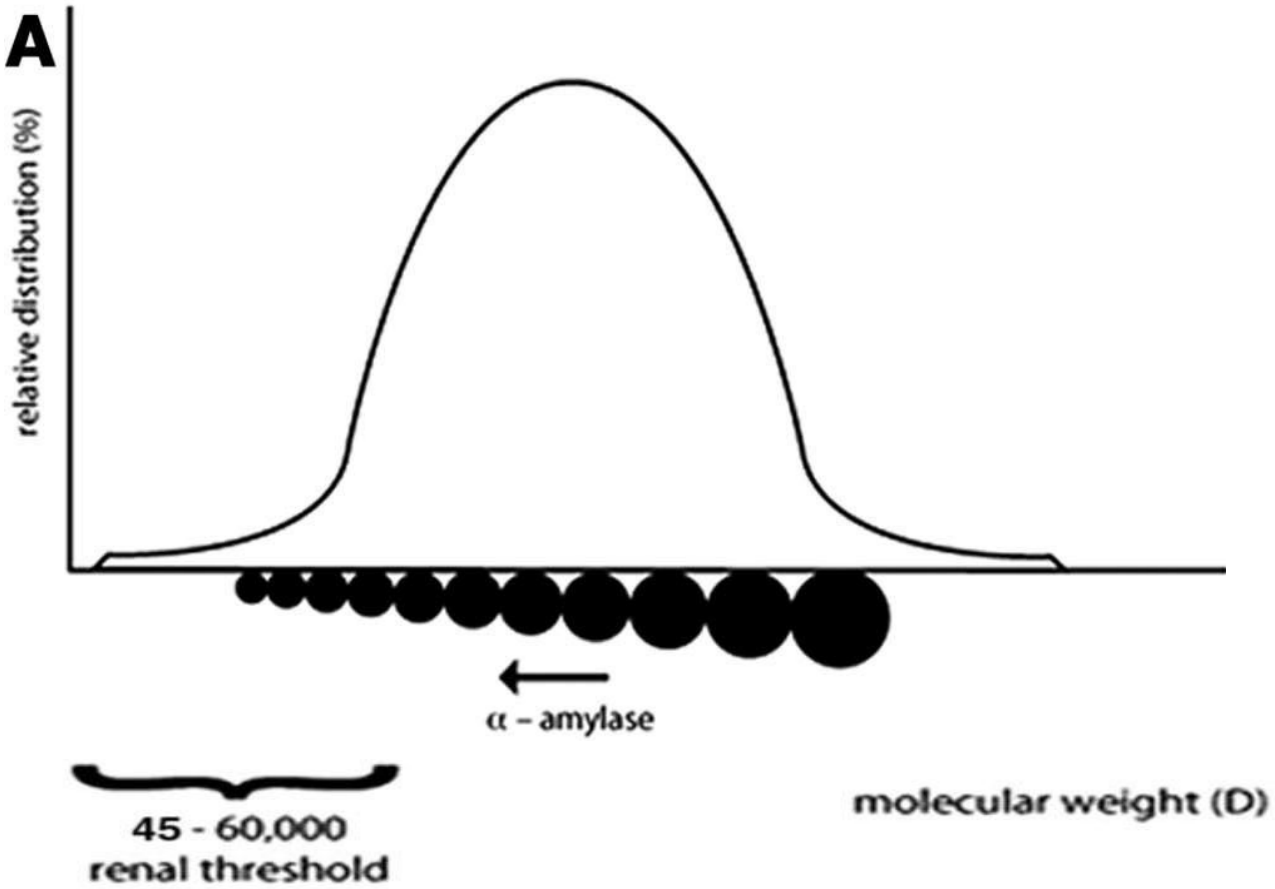
Classification

- HES are designated by a series of numeric parameters reflecting their pharmacokinetics.

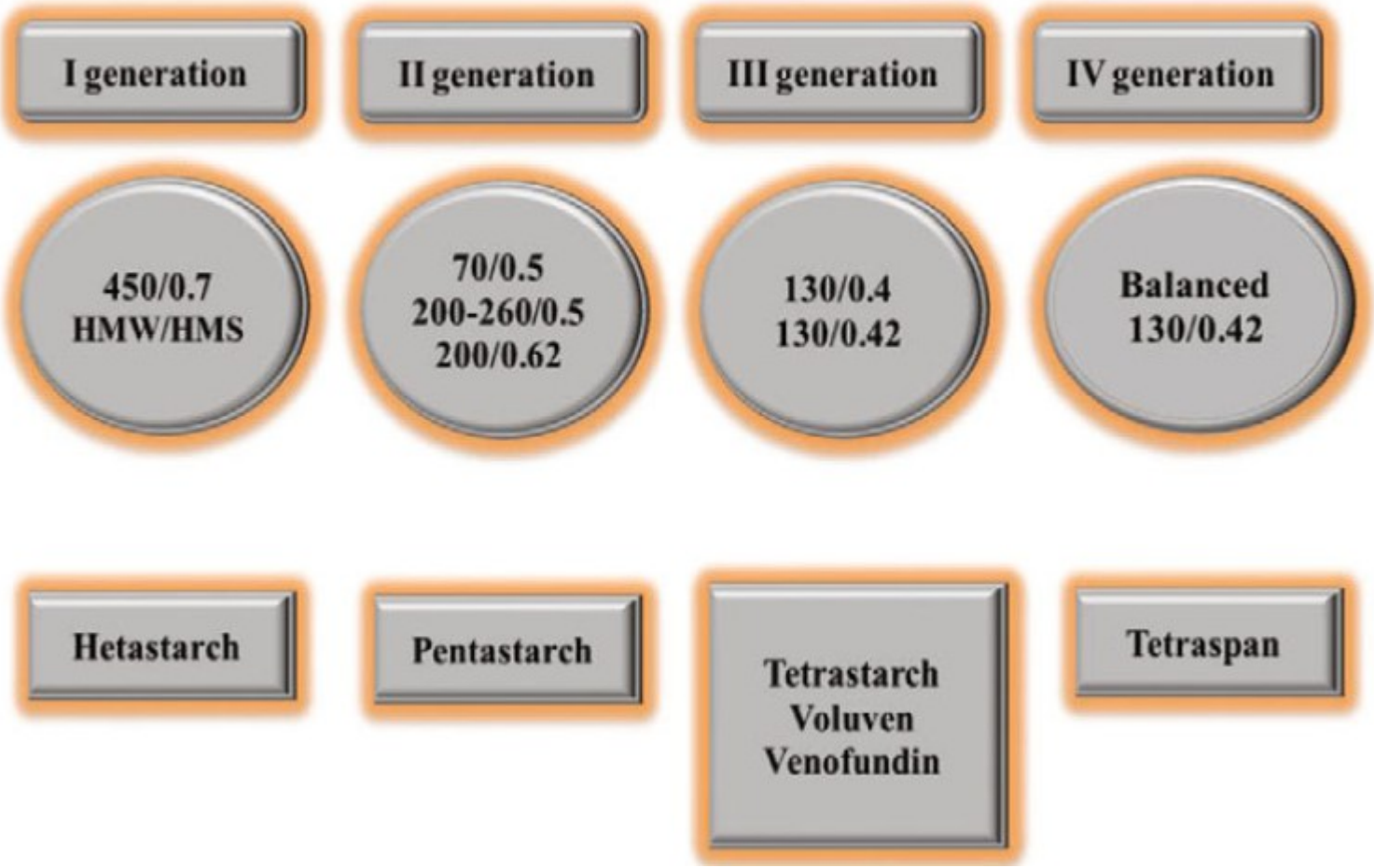
Voluven 6% HES 130 / 0,4 / 9



farmacokinetics

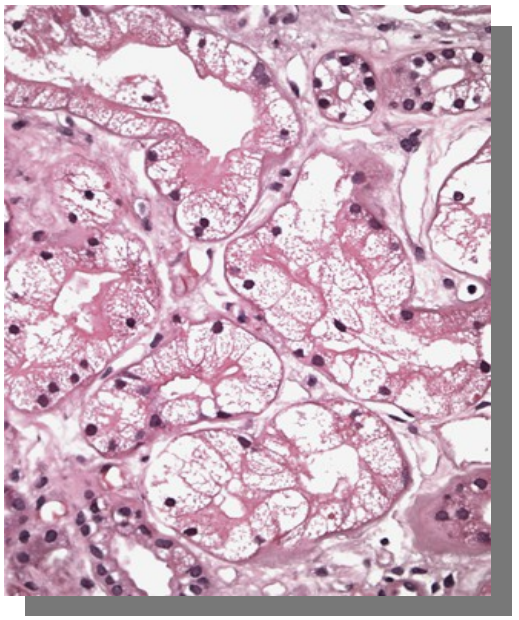


generations

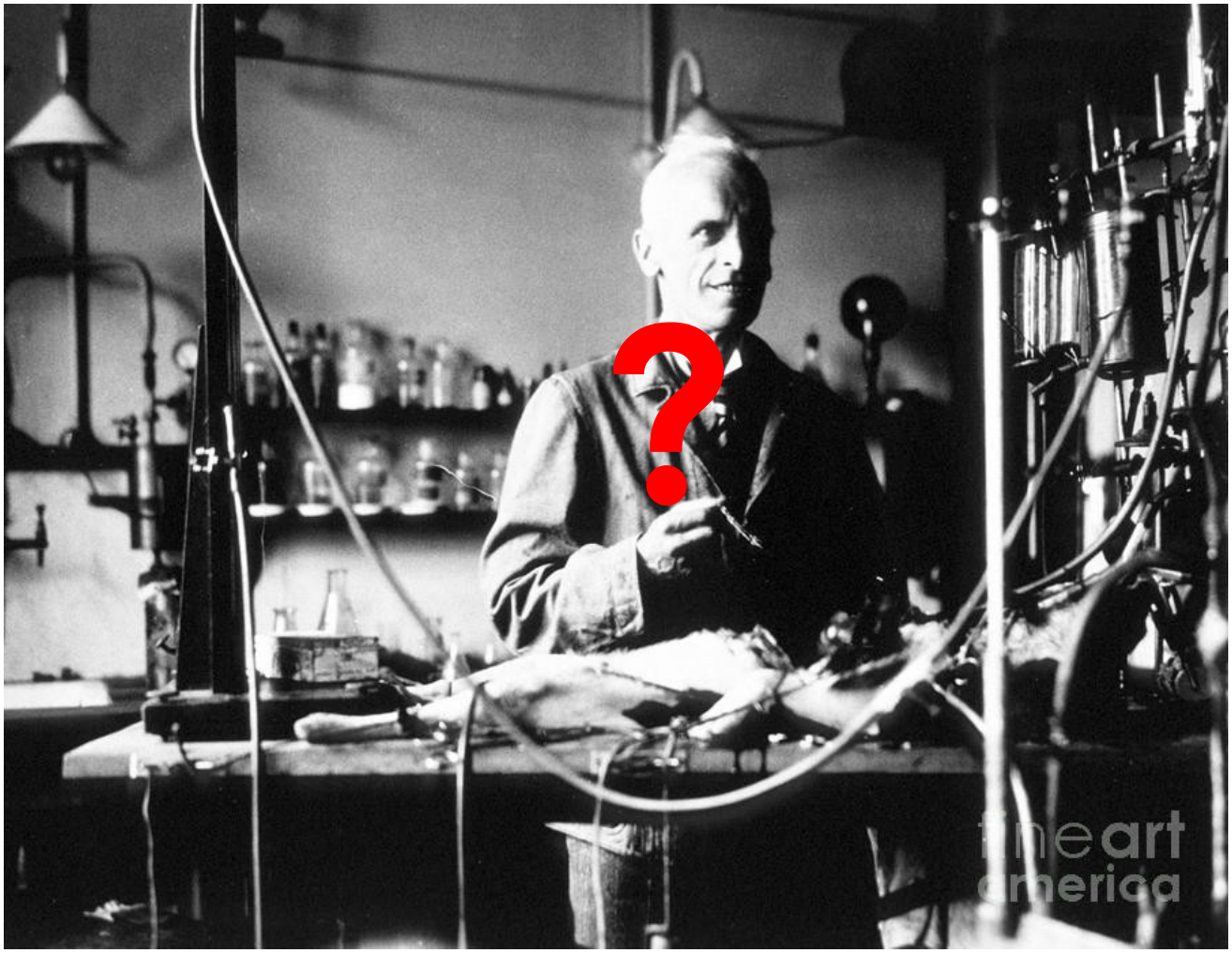


POTENTIAL RISKS

- Coagulation and hemostasis
- Nephrotoxicity
- Anaphylaxis
- Storage
- Itching
- Hyperglycemia



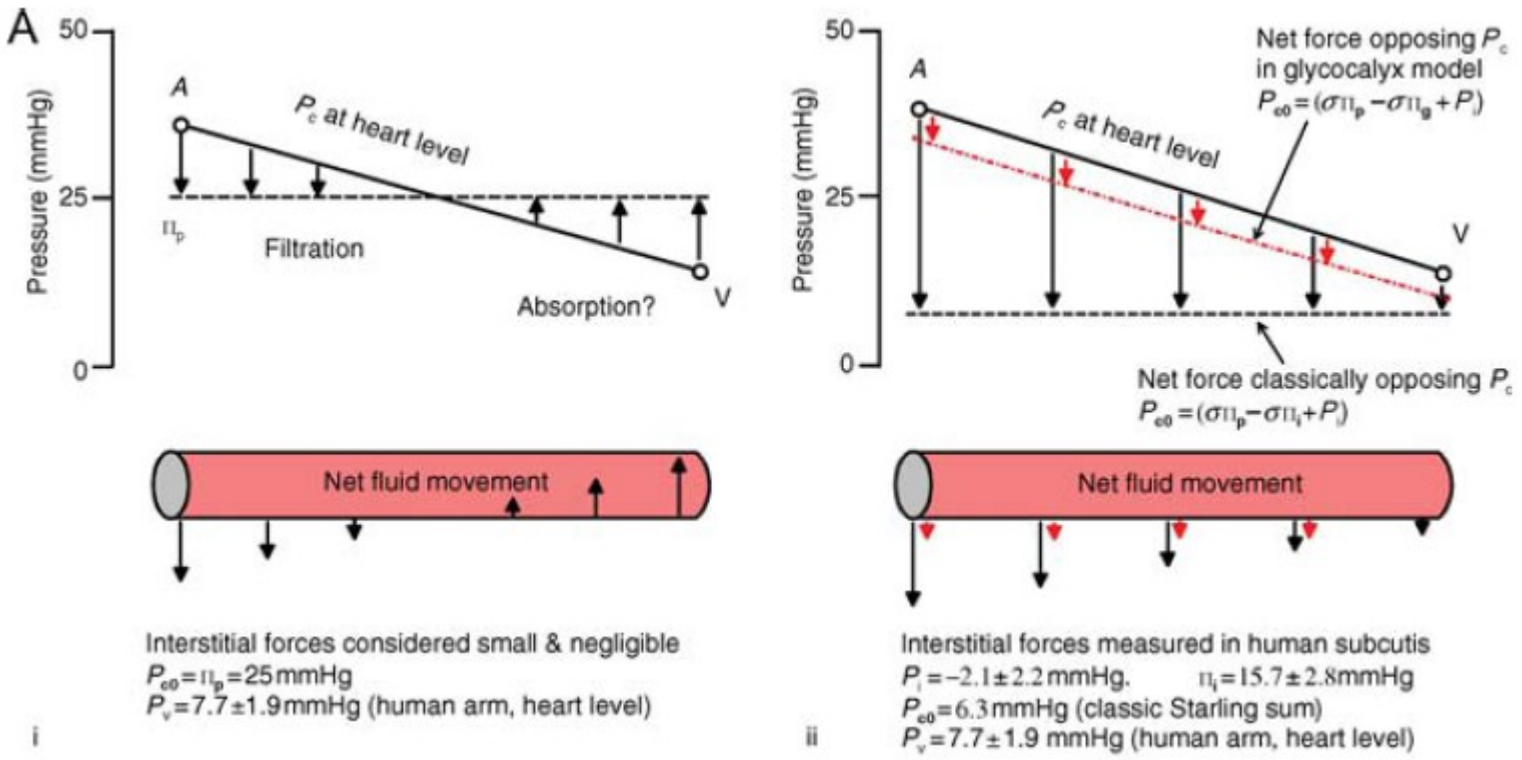
FLUID THERAPY MIGHT BE MORE DIFFICULT THAN YOU THINK



Cardiovasc Res. 2010 Jul 15;87(2):198-210.

Microvascular fluid exchange and the revised Starling principle.

Levick JR, Michel CC.



J Physiol. 2004 Jun 15;557(Pt 3):704.

Revision of the Starling principle: new views of tissue fluid balance.

Levick JR.

Cardiovasc Res. 2010 Jul 15;87(2):198-210.

Microvascular fluid exchange and the revised Starling principle.

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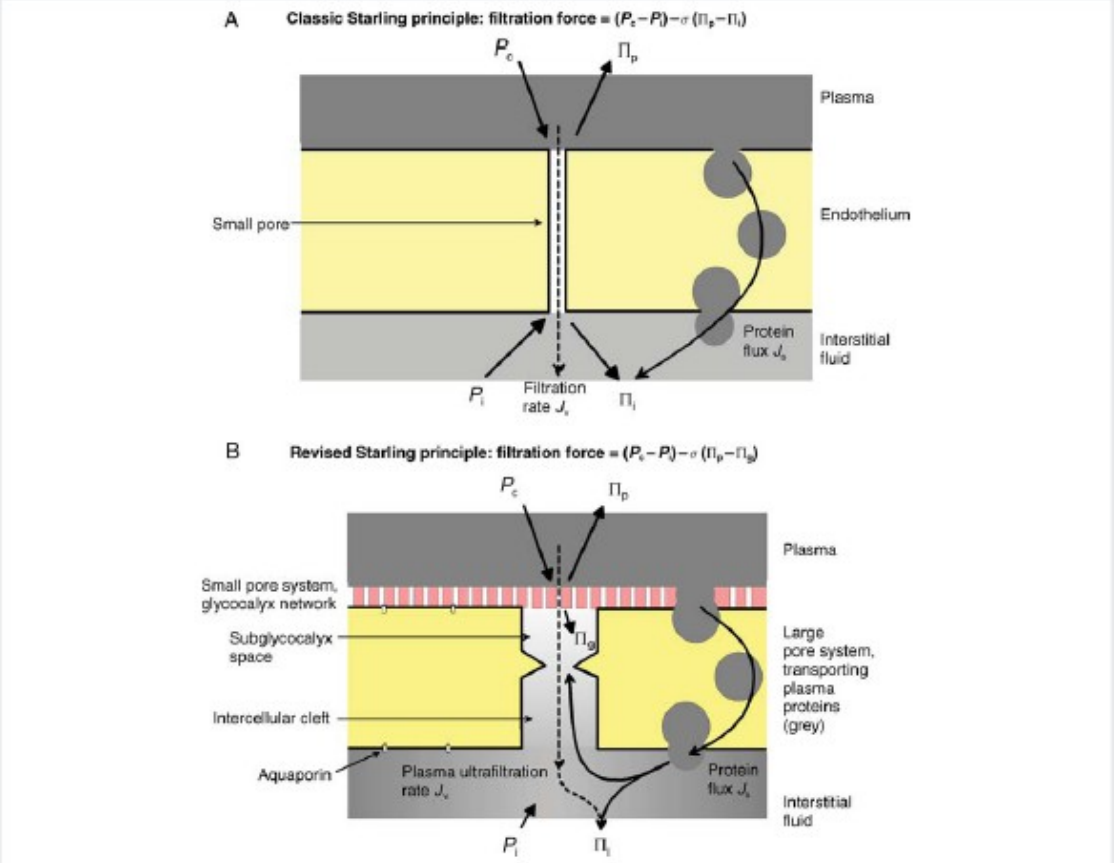

Figure 1 Comparison of traditional and revised views of the endothelial semipermeable membrane and the forces acting on it. (A) Traditional view of continuous endothelium as a semipermeable membrane. (B) The glycocalyx–cleft model identifies glycocalyx as a semipermeable layer. Its underside is subjected to the COP of fluid high inside the intercellular cleft rather than ISF, with important functional consequences.[80,82] Symbols defined in main text. Grey shade denotes concentration of plasma protein.

Br J Anaesth.2012 Mar;108(3):384-94.

Revised Starling equation and the glycocalyx model of transvascular fluid exchange: an improved paradigm for prescribing intravenous fluid therapy. Woodcock TE, Woodcock TM

Table 1 Comparison of the original and revised paradigms for prescribing fluid therapy

Original Starling principle	Revised Starling equation and glycocalyx model
Intravascular volume consists of plasma and cellular elements	Intravascular volume consists of glycocalyx volume, plasma volume, and red cell distribution volume
Capillaries separate plasma with high protein concentration from ISF with low protein concentration	Sinusoidal tissues (marrow, spleen, and liver) have discontinuous capillaries and their ISF is essentially part of the plasma volume Open fenestrated capillaries produce the renal glomerular filtrate Diaphragm fenestrated capillaries in specialized tissues can absorb ISF to plasma Continuous capillaries exhibit 'no absorption' The EGL is semi-permeable to anionic proteins and their concentration in the intercellular clefts below the glycocalyx is very low
The important Starling forces are the transendothelial pressure difference and the plasma–interstitial COP difference	The important Starling forces are the transendothelial pressure difference and the plasma–subglycocalyx COP difference. ISF COP is not a direct determinant of J_v
Fluid is filtered from the arterial end of capillaries and absorbed from the venous end. Small proportion returns to the circulation as lymph	J_v is much less than predicted by Starling's principle, and the major route for return to the circulation is as lymph
Raising plasma COP enhances absorption and shifts fluid from ISF to plasma	Raising plasma COP reduces J_v but does not cause absorption
At subnormal capillary pressure, net absorption increases plasma volume	At subnormal capillary pressure, J_v approaches zero. Auto transfusion is acute, transient, and limited to about 500 ml
At supranormal capillary pressure, net filtration increases ISF volume	At supranormal capillary pressure, when the COP difference is maximal, J_v is proportional to transendothelial pressure difference
Infused colloid solution is distributed through the plasma volume, and infused ISS through the extracellular volume	Infused colloid solution is initially distributed through the plasma volume, and infused ISS through the intravascular volume At supranormal capillary pressure, infusion of colloid solution preserves plasma COP, raises capillary pressure, and increases J_v At supranormal capillary pressure, infusion of ISS also raises capillary pressure, but it lowers COP and so increases J_v more than the same colloid solution volume At subnormal capillary pressure, infusion of colloid solution increases plasma volume and infusion of ISS increases intravascular volume, but J_v remains close to zero in both cases

Colloids *versus* Cristalloids for Fluid Resuscitation:

The CRISTAL Trial

Mercoledì 29/01 ore 14.30 – Auletta Didattica 2CR

Piva S. Ferrari D. Turin M. Zangrandi M.

Colloids *versus* Cristalloids

Once upon a time…

- Uno dei dibattiti più antichi in medicina
- Primo RCT colloidi vs. cristalloidi: **Surgery 1975**

Surgery. 1975 Sep; 78(3):291-303.

Randomized trial of albumin vs. electrolyte solutions during abdominal aortic operations.

Skillman JJ, Restall DS, Salzman EW.

P

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O

- 16 pazienti
- chirurgia ricostruttiva vascolare addominale (regime di elezione)
- albumina (n=7) vs. RL (n=9) (intra-operatori)
- outcomes surrogati: volume plasmatico, P oncotica plasmatica, albumina sierica e proteine totali; Δ tensione O2 alveolare - arteriosa (AaDO2, FIO2 = 1.0); clearance della creatinina, peso corporeo, intake di liquidi e sodio

Skillman. Surgery 1975

- risultati:

1. Control group:
   - maggiore assunzione di liquidi,
   - maggior aumento del peso corporeo,
   - MA **volume plasmatico** significativamente minore rispetto al pre-operatorio;
2. **clearance della creatinina** non significativamente diversa tra i due gruppi.

- conclusioni:

l' espansione del volume extracellulare può essere ridotta, senza effetti avversi sulla funzione renale, con la somministrazione di albumina.

Colloids *versus* Cristalloids

Show must go on…

- Altri 7 RCTs pubblicati negli anni ’70
  - 12 RCTs negli anni ’80
  - 26 RCTs negli anni ‘90

1998…

Human albumin administration in critically ill patients: systematic review of randomised controlled trials

Cochrane Injuries Group Albumin Reviewers

Human albumin administration in critically ill patients: systematic review of randomised controlled trials

Cochrane Injuries Group Albumin Reviewers

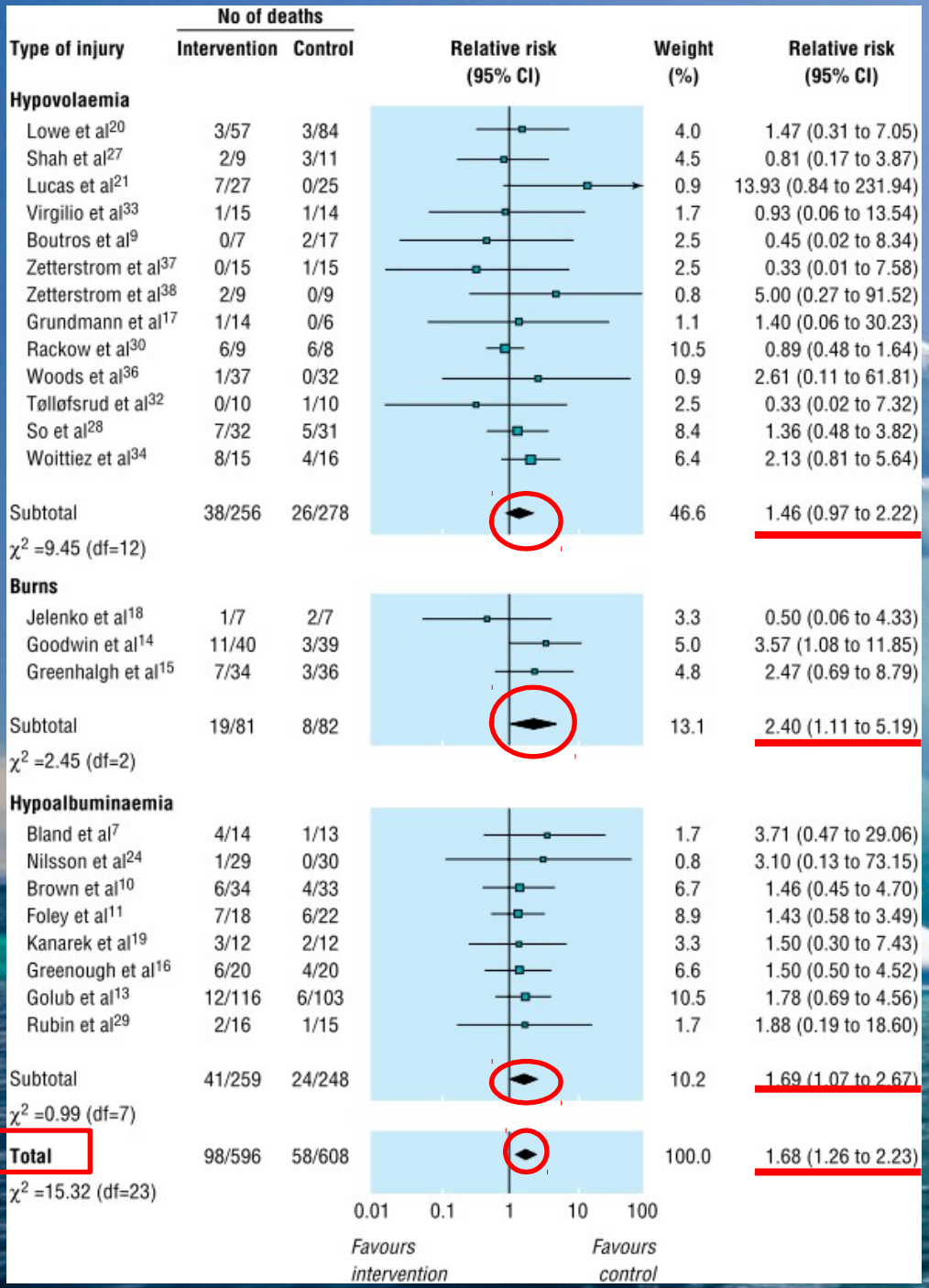
- Valutare l'effetto sulla mortalità della somministrazione di albumina in pazienti critici (ipovolemia - ustioni - ipoproteinemia)
- 30 RCTs (1419 pazienti)
  - Treatment group: Albumina o frazione proteica plasmatica
  - Control group: Cristalloidi o nessuna infusione

Human albumin administration in critically ill patients: systematic review of randomised controlled trials

Cochrane Injuries Group Albumin Reviewers

RISULTATI

- 32 RCTs
- 2 RCTs non riportavano i dati sulla mortalità
- In 6 trials: nessuna morte al follow-up nè nel gruppo trattamento nè nel gruppo controllo
- Nei restanti 24 RCTs:



RISULTATI:

- Suddivisi per tipo di pz
- La mortalità è maggiore nel gruppo trattato con albumina:

- Sia nei singoli sottogruppi di pz

- Sia complessivamente RR = 1.68 (95% CI 1.26 – 2.23)

RISULTATI

RR = 1.68

aumento del RA = 6%
(95% CI 3% al 9%)

6 morti aggiuntive per ogni 100 pz trattati

Human albumin administration in critically ill patients: systematic review of randomised controlled trials

Cochrane Injuries Group Albumin Reviewers

LIMITI

- Follow up: non specificato o a breve termine (prima settimana, dimissione dall'ospedale)
- Qualità di RCTs: scarsa (allocation concealment inadeguato o non chiaro in 11 RCTs), studi datati
- Dimensioni di RCTs: piccole
  - 22 RCTs → meno di 50 pz
  - 7 RCTs → 50-100 pz
  - 3 RCTs → più di 100 pz

Human albumin administration in critically ill patients: systematic review of randomised controlled trials

Cochrane Injuries Group Albumin Reviewers

CONCLUSIONI

Conclusions: There is no evidence that albumin administration reduces mortality in critically ill patients with hypovolaemia, burns, or hypoalbuminaemia and a strong suggestion that it may increase mortality. These data suggest that use of human albumin in critically ill patients should be urgently reviewed and that it should not be used outside the context of rigorously conducted, randomised controlled trials.

Colloids *versus* Cristalloids

Show must go on… II

- Questo risultato ha indotto l'avvio di altri numerosi RCTs: più grandi e di migliore qualità
- 30 RCTs dal 2000 al 2013
- Tra questi

N Engl J Med 2004: SAFE

*S*aline versus *A*lbumin *F*luid *E*valuation

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*

N Engl J Med 2004; 350:2247-56

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

The SAFE Study Investigators

P

- 6997 pazienti admitted to the closed, multidisciplinary ICUs of 16 academic tertiary hospitals in Australia and New Zealand (November 2001 – June 2003)
- con necessità di fluidotp per mantenere o aumentare il V intravascolare

I

C

- albumina 4% (n = 3499) vs. SF (n = 3501)
- primary outcome: mortalità a 28 giorni

O

- secondary outcomes: insorgenza di nuove insufficienze d'organo, durata di VAM, di tp renale sostitutiva, di ricovero in TI e in H

SAFE 2004

- risultati:

1. Baseline Characteristics:
   - i due gruppi di pz hanno caratteristiche di partenza simili,
     - unica differenza statisticamente significativa: PVC maggiore

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Albumin Group	Saline Group
Age — yr	58.6±19.1	58.5±18.7
Female sex — no. (%)	1424 (40.7)	1376 (39.3)
Reason for admission to ICU — no. (%)		
Surgical	1473 (43.0)	1465 (42.8)
Medical	1955 (57.0)	1958 (57.2)
Source of admission to ICU — no. (%)		
Emergency department	948 (27.7)	977 (28.5)
Hospital floor	614 (17.9)	573 (16.7)
Another ICU	63 (1.8)	66 (1.9)
Another hospital	323 (9.4)	341 (10.0)
Operating room (emergency surgery)	801 (23.4)	780 (22.8)
Operating room (elective surgery)	662 (19.3)	678 (19.8)
Same ICU (readmission)	17 (0.5)	8 (0.2)
Predefined subgroups — no. (%)		
Trauma	597 (17.4)	590 (17.2)
Severe sepsis	603 (18.1)	615 (18.4)
Acute respiratory distress syndrome	61 (1.8)	66 (1.9)
APACHE II score†	18.7±7.9	19.0±8.0
Physiological variables		
Heart rate — beats/min	91.4±23.5	92.3±23.5
Mean arterial pressure — mm Hg	77.8±16.4	78.2±16.3
Central venous pressure — mm Hg	9.0±4.7	8.6±4.6‡
Urine output — ml/hr	89.7±132.4	95.0±161.4
Serum albumin — g/liter	27.4±7.8	27.7±7.9
Organ failure— no. (%)§		
No failure	1962 (57.2)	1885 (55.1)
1 organ	1075 (31.4)	1148 (33.5)
2 organs	335 (9.8)	329 (9.6)
3 organs	50 (1.5)	57 (1.7)
4 organs	5 (0.1)	4 (0.1)
5 organs	1 (<0.1)	0
Mechanical ventilation — no. (%)	2186 (63.8)	2217 (64.8)
Renal-replacement therapy — no. (%)	45 (1.3)	41 (1.2)
Albumin in previous 72 hr — no. (%)	127 (3.7)	135 (3.9)

SAFE 2004

- risultati: 2. Nessuna differenza statisticamente significativa né per la **mortalità** né per **altri outcomes**

Table 3. Primary and Secondary Outcomes.*

Outcome	Albumin Group	Saline Group	Relative Risk (95% CI)	Absolute Difference (95% CI)	P Value
Status at 28 days — no./total no. (%)					
Dead	726/3473 (20.9)	729/3460 (21.1)	0.99 (0.91 to 1.09)		0.87
Alive in ICU	111/3473 (3.2)	87/3460 (2.5)	1.27 (0.96 to 1.68)		0.09
Alive in hospital†	793/3473 (22.8)	848/3460 (24.5)	0.93 (0.86 to 1.01)		0.10
Length of stay in ICU — days	6.5±6.6	6.2±6.2		0.24 (–0.06 to 0.54)	0.44
Length of stay in hospital — days†	15.3±9.6	15.6±9.6		–0.24 (–0.70 to 0.21)	0.30
Duration of mechanical ventilation — days	4.5±6.1	4.3±5.7		0.19 (–0.08 to 0.47)	0.74
Duration of renal-replacement therapy — days	0.48±2.28	0.39±2.0		0.09 (–0.0 to 0.19)	0.41
New organ failure — no. (%)‡					0.85§
No failure	1397 (52.7)	1424 (53.3)			
1 organ	795 (30.0)	796 (29.8)			
2 organs	369 (13.9)	361 (13.5)			
3 organs	68 (2.6)	75 (2.8)			
4 organs	18 (0.7)	17 (0.6)			
5 organs	2 (0.1)	0			

SAFE 2004

- conclusioni:

CONCLUSIONS

In patients in the ICU, use of either 4 percent albumin or normal saline for fluid resuscitation results in similar outcomes at 28 days.

Albumina e SF risultano clinicamente **equivalenti** per il trattamento dell' ipovolemia in una popolazione eterogenea di pz critici.

- subgroup analyses:

Sono necessari ulteriori studi per valutare se il riempimento volemico con albumina o soluzione salina conferisca un beneficio in popolazioni di pz critici più selezionate (trauma, sepsi severa, ARDS)

Colloids *versus* Cristalloids

RCTs su pz selezionati

- 6S: Scandinavian Starch for **Severe Sepsis /Septic Shock** – N Engl J Med 2012

- 804 pz con sepsi severa (26 TI scandinave)
- 6% HES 130/0.42 vs. Ringer acetato
- HES mortalità a 90 giorni e l' incidenza di danno renale

Colloids *versus* Cristalloids

RCTs su pz selezionati

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N Engl J Med 2012: CHEST

Crystalloid vs Hydroxyethyl Starch Trial

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; 367(20):1901-11

Hydroxyethyl Starch or Saline for Fluid Resuscitation in Intensive Care

John A. Myburgh et al.

P

- 7000 pazienti admitted to the adult medical-surgical ICUs of 32 hospitals in Australia and New Zealand
- judged to require fluid resuscitation

I

- 6% HES 130/0.4 (n=3500) vs. SF (n=3500) (Voluven)

C

- primary outcome: mortalità a 90 giorni
- secondary outcomes: insorgenza di danno renale acuto, di nuove insufficienze d'organo, durata di VAM, di tp renale sostitutiva, mortalità per specifiche cause

O

CHEST 2012

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	HES (N=3358)	Saline (N=3384)
Age — yr	63.1±17.0	62.9±16.9
Male sex — no./total no. (%)	2030/3356 (60.5)	2041/3384 (60.3)
Weight — kg	79.4±21.0	78.6±20.8
Source of admission to ICU — no./total no. (%)		
Emergency department	930/3353 (27.7)	931/3379 (27.6)
Hospital floor	659/3353 (19.7)	668/3379 (19.8)
Another ICU	53/3353 (1.6)	41/3379 (1.2)
Another hospital	315/3353 (9.4)	306/3379 (9.1)
Operating room		
After emergency surgery	625/3353 (18.6)	630/3379 (18.6)
After elective surgery	771/3353 (23.0)	803/3379 (23.8)
Diagnosis on admission — no./total no. (%)		
Surgical cases	1426/3353 (42.5)	1450/3379 (42.9)
Nonsurgical cases	1920/3353 (57.3)	1926/3379 (57.0)
APACHE II score — median (interquartile range)†	17.0 (12.0–22.0)	17.0 (12.0–23.0)
Time from ICU admission to randomization — hr	10.9±156.5	11.4±165.4
Physiological variables		
Heart rate — beats/min	89.3±23.6	88.8±23.3
Mean arterial pressure — mm Hg	74.0±14.9	73.7±14.6
Central venous pressure — mm Hg	9.5±5.4	8.9±5.1
Lactate — mmol/liter	2.1±2.0	2.0±1.5
Mechanical ventilation — no./total no. (%)	2131/3326 (64.1)	2177/3354 (64.9)
Use of vasopressor — no./total no. (%)	1520/3337 (45.5)	1551/3361 (46.1)
Serum creatinine — μmol/liter	101.5±57.1	100.1±58.0
Urine output 6 hr before randomization — ml	453.5±418.3	426.6±422.9
Predefined subgroups — no./total no. (%)		
RIFLE criteria for acute kidney injury‡	522/1449 (36.0)	511/1421 (36.0)
Sepsis	979/3355 (29.2)	958/3376 (28.4)
Trauma	267/3358 (8.0)	265/3384 (7.8)
Traumatic brain injury	28/3338 (0.8)	30/3365 (0.9)
APACHE II score ≥25	597/3335 (17.9)	624/3356 (18.6)
Receipt of HES before randomization	509/3347 (15.2)	508/3372 (15.1)

- risultati:

1. Baseline Characteristics:
   - i due gruppi di pz hanno caratteristiche di partenza simili,
     - Sottogruppi predefiniti

CHEST 2012

- risultati:

2. Nessuna differenza statisticamente significativa per la **mortalità** a 90 giorni

   - né nella popolazione complessiva
   - né nei sottogruppi analizzati

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

CHEST 2012

- risultati:

3. Renal-replacement therapy was used more in the HES group (RR 1.21; 95% CI, 1.00 to 1.45)

4. Incidenza di insufficienza cardiocircolatoria **minore** nel gruppo trattato con HES (RR=0.91; 95% CI 0.84 – 0.99)
5. Incidenza di insufficienza epatica **maggiore** nel gruppo trattato con HES (RR=1.56; 95% CI 1.03 – 2.36)

6. HES was associated with significantly more adverse events (5.3% vs. 2.8%, P<0.001)
   - prurito, rash cutaneo
   - Serious adverse events: P=0.98

CHEST 2012

- conclusioni:

CONCLUSIONS

In patients in the ICU, there was no significant difference in 90-day mortality between patients resuscitated with 6% HES (130/0.4) or saline. However, more patients who received resuscitation with HES were treated with renal-replacement therapy.

- **Nessuna differenza di mortalità**
- Maggior ricorso a tp renale sostitutiva nel gruppo trattato con HES

2013!

THE COCHRANE COLLABORATION®

Revisione Sistematica

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

Perel P, Roberts I, Ker K

[Intervention Review]

Colloids versus crystalloids for fluid resuscitation in critically ill patients

- **Valutare l'effetto sulla mortalità dei colloidi rispetto ai cristalloidi per il riempimento volemico dei pz critici**

- 78 RCTs (70 con dati relativi alla mortalità)
  - **56 RCTs:** Colloidi vs. Cristalloidi (isotonici)
  - **11 RCTs:** Colloidi in sol. Ipertoniche vs. Cristalloidi (isotonici)
  - **3 RCTs:** Colloidi vs. Sol. Ipertoniche

[Intervention Review]

Colloids versus crystalloids for fluid resuscitation in critically ill patients

1. COLLOIDI vs. CRISTALLOIDI_

- 56 RCTs

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

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Deaths	56		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	25	9147	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [1.02, 1.19]
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]

- Albumina, gelatine e destrani **NON** modificano significativamente la mortalità rispetto ai cristalloidi;
- La tp con HES **aumenta** la mortalità!

[Intervention Review]

Colloids versus crystalloids for fluid resuscitation in critically ill patients

2. **COLLOIDI** in soluzioni ipertoniche vs. **CRISTALLOIDI**_

- **11 RCTs**

Comparison 2. Colloid and hypertonic crystalloid versus isotonic crystalloid

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Deaths	11		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Albumin or plasma protein fraction	1	14	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.06, 4.33]
1.2 Hydroxyethyl starch	1	90	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.03, 2.15]
1.3 Modified gelatin	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.4 Dextran	9	1879	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.79, 1.06]

- I colloidi in soluzioni ipertoniche **NON** modificano significativamente la mortalità rispetto ai cristalloidi.

[Intervention Review]

Colloids versus crystalloids for fluid resuscitation in critically ill patients

3. COLLOIDI vs. SOLUZIONI IPERTONICHE_

- 3 RCTs
- In 2 RCTs: nessuna morte al follow-up nè nel gruppo trattamento nè nel gruppo controllo
- 1 RCT rimanente: solo 38 pz!

Sensitivity analysis

- **Esclusi RCTs di bassa qualità**

Risultati identici

- *"The editorial group is aware that a clinical trial by **Professor Joachim Boldt** has been found to have been fabricated (Boldt 2009)"…*

Sensitivity analysis

- **Esclusi RCTs di Boldt**

Risultati identici

*"When all trials authored by Professor Boldt (Boldt 1986; Boldt 1993; Boldt 2001; Lang 2001; Lang 2003) were excluded conclusions remain **unchanged**."*

CONCLUSIONI

Implications for practice

There is no evidence from randomised controlled trials that resuscitation using colloids compared with crystalloids reduces the risk of death in patients with trauma, burns or following surgery. The use of hydroxyethyl starch might even increase mortality. Since colloid use is not associated with improved survival and colloids are considerably more expensive than crystalloids, it is hard to see how their continued use in clinical practice can be justified.

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; Jean Charles Preiser, MD; Hervé Outin, MD; Gilles Trochú, MD; Claire Charpentier, MD; Jean Louis Trouillet, MD; Antoine Kimmoun, MD; Xavier Forceville, MD, PhD; Michael Darmon, MD; Olivier Lesur, MD, PhD; Jean Reignier, MD; Fékri Abroug, MD; Philippe Berger, MD; Christophe Clec'h, MD, PhD; Joël Cousson, MD; Laure Thibault, MD; Sylvie Chevret, MD, PhD; for the CRISTAL Investigators

Mercoledì 29/1/2014
Piva S., Ferrari D., Turin M., Zangrandi M.

TRIAL DESIGN

- **Multinational**: 57 ICUs (France, Belgium, Canada, North Africa)
- ICUs in university and non university hospitals
- **PRAGMATIC** trial
- **Randomized** 1:1, stratified by centre and case mix (sepsis/trauma/others)
- Allocation was concealed (sealed envelopes), but open-labeled drugs were used

TREATMENT

- **CONTROL ARM**: Cristalloids only
- **EXPERIMENTAL ARM**: Colloids only

- **Molecule and dose** were left at the physicians' discretion, with the restriction of following marketing raccomandations (HES < 30 ml/kg/die)

- **EXCEPTIONS:** maintenance fluids, which were isotonic crystalloids, regardless of treatment group; and hypoalbuminemia

INCLUSION CRITERIA

- Aged 18 or older, admitted in the ICU and **requiring fluid resuscitation for acute hypovolemia** (no prior fluid resuscitation)
- **Waiver of consent** (patients underresuscitated, had to be randomized as soon as possible)

- February 2003 - August 2012

- **ACUTE HYPOVOLEMIA (defined by the combination of):**
- (1) hypotension: SBP < 90 mm Hg, MBP < 60 mm Hg, orthostatic hypotension, or a delta PP of 13% or higher;
- (2) evidence for low filling pressures and low cardiac index
- **SIGNS OF TISSUE HYPOPERFUSION/HYPOXIA**
- (1) Including at least 2 of the following: GCS <12, mottled skin, urinary output < 25 mL/h, or capillary refilling time > 3 seconds;
- (2) increased arterial lactate levels, blood urea nitrogen; or a fractional excretion of sodium <1%.

INDICATION OF FLUID THERAPY FOR HYPOVOLEMIA/SHOCK

EXCLUSION CRITERIA

- Pregnancy
- DNR order
- Brain death/organ donor
- Burns >20% of body surface
- Chronic renal failure
- Advanced cronic liver disease
- Known inherited coagulation disorders
- Any known allergy to study drugs/ acute anaphylaxis
- Dehydration
- Anesthestetic drugs related hypovolemia/hypotension

TRIAL ENDPOINTS

- **PRIMARY OUTCOME:**
- 28-day all cause mortality
- **SECONDARY OUTCOME:**
- death rates at 90 days
- number of days alive and not receiving renal replacement therapy, mechanical ventilation, or vasopressor therapy
- days without organ system failure
- hospital lenght of stay

HYPOTESIS & STOPPING RULE

- **CRISTAL was designed to: test an absolute increase in mortality with colloids of 5% when compared with cristalloids, with a baseline risk of death of 20% (Cochrane review 1998**: increased mortality in patients receiving colloids)
- **1504 patients per arm**

- For safety concern, sequential triangular test (every 100 deaths) allowed to inform the DSMB about any eccess in the risk of death in any arm : **INFERIORITY TRIAL**

Recruitment into the trial was stopped in August 2012

Table 1. Baseline Characteristics

	Colloids Group (n = 1414)	Crystalloids Group (n = 1443)
Age, median (IQR), y	63 (50-76)	63 (50-75)
Male sex, No. (%)	880 (62.2)	902 (62.5)
Weight, median (IQR), kg	70 (60-81)	70 (61-81)
Height, median (IQR), cm	170 (161-175)	169 (162-175)
Source of admission to ICU, No. (%)		
Community	674 (48.2)	745 (52.0)
Hospital ward	617 (44.1)	575 (40.1)
Other ICU	57 (4.1)	65 (4.5)
Long-term care facility	50 (3.6)	48 (3.3)
Type of ICU admission, No. (%)	(n = 1399)	(n = 1432)
Medical	991 (70.8)	1040 (72.6)
Emergency surgery	276 (19.7)	267 (18.6)
Scheduled surgery	109 (7.8)	89 (6.2)
Trauma	23 (1.6)	36 (2.5)
McCabe class, No. (%)		
No underlying disease or no fatal disease	903 (63.9)	913 (63.3)
Underlying ultimately fatal disease (>5 y)	429 (30.3)	469 (32.5)
Underlying rapidly fatal disease (<1 y)	82 (5.8)	61 (4.2)
Knaus disability scale, No. (%)		
Prior good health, no functional limitations	342 (24.5)	375 (26.3)
Mild to moderate limitation of activity because of chronic medical problem	439 (31.5)	446 (31.3)
Chronic disease producing serious but not incapacitating restriction of activity	323 (23.2)	325 (22.8)
Severe restriction of activity due to disease, includes persons bedridden or institutionalized due to illness	289 (20.8)	278 (19.5)
Physiology score, median (IQR)		
SAPS II[a]	48 (35-64)	50 (36-65)
SOFA[b]	8 (5-11)	8 (5-11)
Injury Severity[c]	(n = 79) 21 (14-27)	(n = 88) 22 (14-34)
Glasgow Coma Scale score, median (IQR)	(n = 1326) 11 (3-15)	(n = 1353) 11 (3-15)
Systolic blood pressure, median (IQR), mm Hg	(n = 1337) 92 (80-112)	(n = 1372) 94 (80-113)
Heart rate, median (IQR), beats/min	(n = 1335) 105 (86-123)	(n = 1366) 105 (88-21)
Urinary output, median (IQR), mL/h	(n = 1245) 40 (20-70)	(n = 1259) 40 (20-60)
Lactate levels, median (IQR), mmol/L	(n = 1151) 2.3 (1.3-3.8)	(n = 1176) 2.4 (1.4-4.5)
Fluid administration prior ICU admission (within the past 12 h)		
Crystalloids, No. (%)	526 (37.2)	402 (27.9)
Dose, median (IQR), mL	1000 (500-1000)	650 (500-1000)
Colloids, No. (%)	585 (41.4)	685 (47.5)
Dose, median (IQR), mL	1000 (500-2000)	1000 (500-2000)
Mechanical ventilation, No. (%)	1007 (71.2)	1061 (73.5)
Renal replacement therapy, No. (%)	67 (4.7)	73 (5.1)
Predefined strata, No. (%)		
Sepsis	774 (54.7)	779 (54.0)
Trauma	85 (6.0)	92 (6.4)
Hypovolemic shock (without sepsis or trauma)	555 (39.3)	572 (39.6)

Abbreviations: ICU, intensive care unit; IQR, interquartile range; SAPS II, Simplified Acute Physiology Score II; SOFA, Sequential Organ Failure Assessment.

[a] Score range from 0 to 163 with higher scores indicating more severe organ dysfunction.

[b] Score range from 0 to 24 with higher scores indicating more severe organ dysfunction.

[c] Score range from 0 to 75 with higher scores indicating more severe injuries.

		Colloids N=1414	Crystalloids N=1443
Isotonic saline			
	— no (%)	252 (17.82)	1236 (85.65)
	volume - ml	1000 [500;2500]	2500 [1500;4500]
	Duration - days	1 [1;2]	2 [1;3]
Ringers lactate	— no (%)	88 (6.22)	255 (17.67)
	volume - ml	3000 [1000;7000]	2000 [1000;4500]
	Duration - days	2 [1;5]	2 [1;3]
Hypertonic saline	— no (%)	19 (1.34)	61 (4.23)
	volume - ml	500 [265;869]	1500 [500;2250]
	Duration - days	1 [1;3]	2 [1;2]
Gelatins	— no (%)	494 (34.94)	24 (1.66)
	volume - ml	1500 [1000;3000]	1000 [500;2000]
	Duration - days	2 [1;3]	1 [1;1]
Hydroxyethyl starch	— no (%)	973 (68.81)	69 (4.78)
	volume - ml	1500 [1000;2000]	500 [500;1000]
	Duration - days	2 [1;2]	1 [1;1]
Albumin 4%	— no (%)	87 (6.15)	60 (4.16)
	volume - ml	1000 [500;1500]	1000 [500;1500]
	Duration - days	1 [0;3]	1 [0;2]
Albumin 20%	— no (%)	201 (14.21)	177 (12.27)
	volume - ml	300 [200;600]	300 [200;500]
	Duration - days	0 [0;1]	0 [0;0]
Dextrans	— no (%)	5 (0.35)	0 (0)
	volume - ml	500 [500;1000]	
	Duration - days	1 [1;1]	

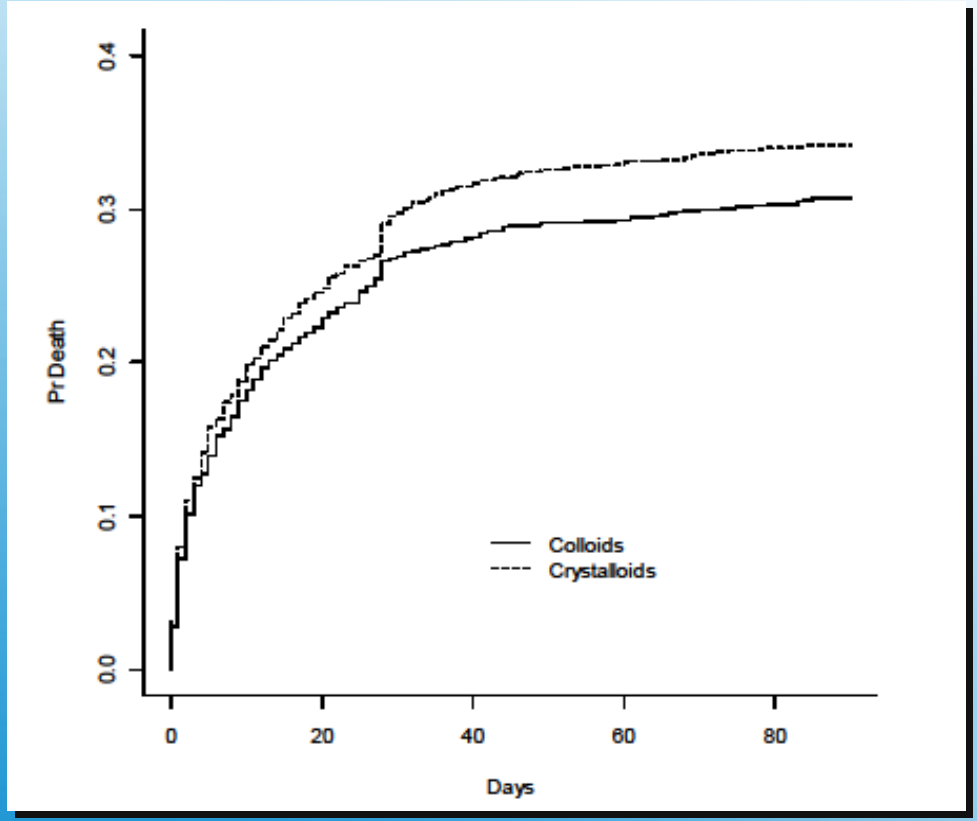
Continuous data are expressed as median and [interquartile range], and categorical variables as percentage.

FLUID THERAPY & TREATMENT EFFECTS

	Colloids N=1414	Crystalloids N=1443	Mean difference (95%CI)	P value
AUC for mean blood pressure during the first 24 hours	1606 (898-1822)	1598 (1058-1821)	17.9 (-1746;+1782)	0.85
Weight at 72 hours	0.5 (0;+2.0)	0.5 (0;+2.4)	-0.23 (-0.61;+0.15)	0.23
Chest X Ray score at 72 hours	0 (0-0)	0 (0-0)	-0.04 (-0.24;+0.16)	0.86

SHORT TERM TREATMENTS' EFFECT

- D-28: **749** deaths (26,3%)
- D-90: **927** deaths (32,5%)



CUMULATIVE MORTALITY

Table 2. Study Outcomes by Treatment Group

	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
No. of days alive and without the following treatment or condition	**Mean (SD)**		**Mean Difference (95% CI)**	
Mechanical ventilation within the first 7 d	2.1 (2.4)	1.8 (2.3)	0.30 (0.09 to 0.48)	.01
Mechanical ventilation within the first 28 d	14.6 (11.4)	13.5 (11.5)	1.10 (0.14 to 2.06)	.01
Renal replacement therapy within the first 7 d	4.8 (2.9)	4.6 (2.9)	0.2 (−0.4 to 0.8)	.38
Renal replacement therapy within the first 28 d	13.9 (11.3)	13.1 (11.4)	0.8 (−1.6 to 3.3)	.90
Organ failure (SOFA score <6) within the first 7 d	6.2 (1.8)	6.1 (1.8)	0.06 (−0.10 to 0.20)	.31
Organ failure (SOFA score <6) within the first 28 d	21.4 (10.3)	20.9 (10.6)	0.6 (−0.4 to 1.5)	.16
Vasopressor therapy within the first 7 d	5.0 (3.0)	4.7 (3.1)	0.30 (−0.03 to 0.50)	.04
Vasopressor therapy within the first 28 d	16.2 (11.5)	15.2 (11.7)	1.04 (−0.04 to 2.10)	.03
ICU stay within the first 28 d	8.3 (9.0)	8.1 (9.2)	0.2 (−0.5 to 0.9)	.59
Hospital stay within the first 28 d	11.9 (11.1)	11.6 (11.4)	0.3 (−0.5 to 1.1)	.37

Abbreviations: ICU, intensive care unit; RR, relative risk; SOFA, Sequential Organ Failure Assessment.

[a] For mortality end points, the analysis was performed using the Mantel-Haenszel test stratified based on admission diagnosis (ie, sepsis, trauma, or other causes ofh ypovolemic shock). The number of days alive and not receiving mechanical ventilation, vasopressor therapy, and renal replacement therapy and days alive without organ system failure were compared between randomized groups using the nonparametric Wilcoxon rank sum test.

STUDY OUTCOMES

In critically ill patients with hypovolemia/shock, **fluid therapy with colloids:**

- did **not change** the **28 day mortality**
- was associated with
  - - **more days alive** andfree of MV e VP
  - - **Fewer deaths at 90 days**

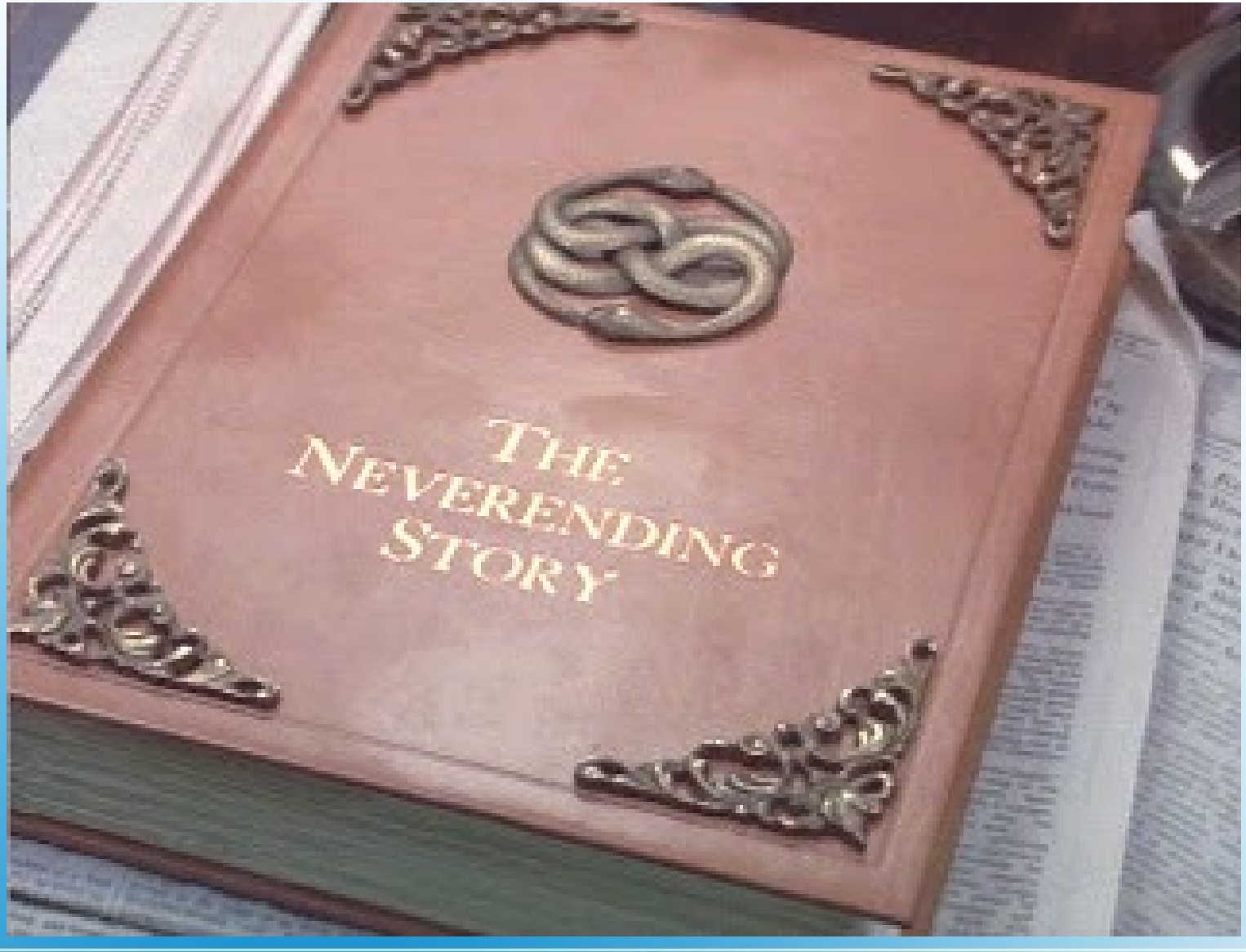
CONCLUSIONS

- How should we consider this results??
- What comes next??

“Colloids: it's hard to see how their use in clinical practice can be justified”

Cochrane review 2013

WHAT NOW??



..grazie per l’attenzione!!