BODY FLUIDS AND COMPARTMENTS

FLUIDS

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with special thanks to Peter Gosling
A few basic principles
- Fluid compartments
- Fluids
- Fluids and fluid compartments
- Clinical use and abuse of fluids
- It’s not as simple as that
- Key papers and guidelines
- Some more basic principles by way of a summary
- mmm…beer
The most commonly described model is one with three compartments: the vascular, (approximately 3 L in adults), the interstitial (12 L) and the intracellular (25L).

- Blood cells and large molecular weight proteins are retained in the vascular compartment by the vascular endothelium, but
- Water, electrolytes and small molecules such as glucose pass freely from the vascular compartment to the interstitial compartment.
The cell membrane of the cellular compartment has two energy consuming pumps which actively exclude sodium from the cell and retain potassium within the cell.

So large molecules will tend to remain in the vascular space, sodium will equilibrate across the vascular and interstitial compartments and only water can move across all three spaces.
The pharmacology of different intravenous fluids depends on the physiology of the fluid compartments of the body and how this changes in illness.

In most conditions requiring intravenous fluid therapy, the distribution of fluid between the three compartments changes, depending on the nature of the illness.
BODY FLUIDS AND COMPARTMENTS

- Inflammation: the vascular endothelium allows passage of larger molecules with their attendant fluid to pass into the interstitial space.

- Intracellular energy deficit: compromises the action of the membrane sodium potassium pumps -> movement of sodium into the cell and potassium out of the cell
FLUIDS

- ASSESSMENT
  - History
  - Thirst
  - skin turgor
  - Mucosa
  - Oedema
  - CVS
  - JVP
  - Urine output
  - CVP
  - Dynamic CVS monitoring
  - PAC/PCWP
FLUIDS

• REQUIREMENTS
  – NORMAL
    • fluids
    • electrolytes
  – ABNORMAL
    • pre-op fasting
    • evaporation
    • bleeding
    • GIT/fistulae

Input:
- 1500 liquid
- 750ml food
- 250ml metabolism

Output:
- 1800ml urine
- 100ml faeces
- 600ml insensible
## Body composition

<table>
<thead>
<tr>
<th></th>
<th>PLASMA</th>
<th>INTERSTITIAL</th>
<th>INTRACELLULAR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na+</td>
<td>140</td>
<td>140</td>
<td>10</td>
</tr>
<tr>
<td>K+</td>
<td>4</td>
<td>4</td>
<td>150</td>
</tr>
<tr>
<td>Cl-</td>
<td>110</td>
<td>110</td>
<td>3</td>
</tr>
<tr>
<td>Mg++</td>
<td>3</td>
<td>3</td>
<td>30</td>
</tr>
</tbody>
</table>
**FLUIDS**

**Normal 24 hr fluid and electrolyte balance**

<table>
<thead>
<tr>
<th></th>
<th>Input</th>
<th>Output</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>2500 mL</td>
<td>2500ml (1800ml urine)</td>
</tr>
<tr>
<td>Sodium</td>
<td>100 mmol</td>
<td>100 mmol</td>
</tr>
<tr>
<td>Nitrogen</td>
<td>500 mmol</td>
<td>500 mmol</td>
</tr>
<tr>
<td>Other</td>
<td>100 mmol</td>
<td>100 mmol</td>
</tr>
<tr>
<td>Total</td>
<td>800 mosmols</td>
<td>800 mosmols</td>
</tr>
</tbody>
</table>

Urine osmolality 800/1800 = 450 mosm/L
Urine 40% maximally concentrated
FLUIDS

- CRYSTALLOIDS
  - REPLACEMENT
  - THERAPEUTIC

- COLLOIDS
  - GELATINS
  - DEXTRANS
  - STARCHES: 1st, 2nd, 3rd and 4th generation
  - BLOOD
  - BLOOD PRODUCTS
  - BLOOD SUBSTITUTES
Distribution of Infused Solutions

- Plasma
- Interstitial fluid
- Intracellular fluid

- Colloids
- 0.9% NaCl
- 5% Dextrose

0% 20% 40% 60% 80% 100%
CRYSTALLOIDS

- Definition: crystalloids are salt solutions containing electrolytes or easily metabolised small molecules such as glucose
- Primary Uses:
  1. To provide free water (glucose)
  2. To replace lost electrolytes (salt solutions)
  3. To provide a vehicle for i.v. delivery of drugs
CRYSTALLOIDS

- Definition: crystalloids are salt solutions containing electrolytes or easily metabolised small molecules such as glucose
- Primary Uses:
  1. Poor man’s volume expander (10-20% stays in vasc. space)
  2. An i.v. fluid for the unthinking e.g. ‘normal’ saline must be safe
FLUIDS

- CRYSTALLOIDS
  - REPLACEMENT
    - saline
    - glucose
    - combinations
    - balanced salt solutions
Concerns about fluid and electrolyte prescribing

Hyponatraemia after orthopaedic surgery  BMJ 1999;318:1363-64

‘Appropriateness of fluid regimes’


‘Concern about variability in perioperative fluid administration’

Sherry et al: Extremes of age: The 1999 report of the National Confidential Enquiry into Perioperative Deaths 1999

‘Fluid regimes highlighted’
Concerns about fluid and electrolyte prescribing

Hypernatraemia in the ICU: an indicator of quality of care?

Poldermann et al. Crit Care Med 1999;27:1;105-8

‘Hospital acquired hypernataemia versus admission hypernataemia was associated with higher mortality rate’

Changes in weight, fluid balance and serum albumin in patients referred for nutritional support


‘12L mean fluid overload in oedematous patients referred for nutritional support’
SALINE

- Evans GH. The Abuse of Normal Salt Solution: American Medical Association 1911.
FLUIDS

• SALINE

 observes the utter recklessness with which salt solution is frequently prescribed, particularly in the postoperative period, without previous knowledge of the condition of the blood-pressure, the ability of the heart to handle large amounts of fluid successfully, or the functional capacity of the kidneys to excrete successfully the large amount of chlorid thus forced on them.

Prehistoric dietary sodium intake was low

Human ability to conserve sodium is powerful

Human ability excrete sodium is weak
## Chemical and Physical Properties of Crystalloids

<table>
<thead>
<tr>
<th>Fluid</th>
<th>Sodium mmol/L</th>
<th>Chloride mmol/L</th>
<th>Potassium mmol/L</th>
<th>Osmolarity mosm/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal plasma</td>
<td>140</td>
<td>95</td>
<td>4</td>
<td>295</td>
</tr>
<tr>
<td>0.9% saline</td>
<td>154</td>
<td>154</td>
<td>0</td>
<td>308</td>
</tr>
<tr>
<td>Ringers lactate</td>
<td>130</td>
<td>109</td>
<td>4</td>
<td>273</td>
</tr>
<tr>
<td>Hartmanns</td>
<td>131</td>
<td>111</td>
<td>5</td>
<td>275</td>
</tr>
<tr>
<td>Plasmalyte</td>
<td>140</td>
<td>98</td>
<td>5</td>
<td>294</td>
</tr>
<tr>
<td>7.5% saline</td>
<td>1283</td>
<td>1283</td>
<td>0</td>
<td>2566</td>
</tr>
</tbody>
</table>
FLUIDS

- **SALINE**
  - Evans GH. The Abuse of Normal Salt Solution: American Medical Association 1911.
The Strong Ion Difference (SID) is the difference between the sums of concentrations of the strong cations and strong ions:

\[
\text{[SID]} = [Na^+] + [K^+] + [Ca^{2+}] + [Mg^{2+}] \text{ minus } [Cl^-] + \text{[Other Strong Anions]}
\]

\[
140 + 4 + 1 + 1 = 146 \quad \quad 100 + 6 = 106
\]

With normal protein levels SID is about 40mmol/L.

Base Excess = 0 mmol/L
<table>
<thead>
<tr>
<th>Independent</th>
<th>Dependent</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Pa CO2</td>
<td>• HCO3</td>
</tr>
<tr>
<td>• strong ions</td>
<td></td>
</tr>
<tr>
<td>• weak acids</td>
<td></td>
</tr>
</tbody>
</table>

\[ \text{SID} = [\text{Na}+\text{K}+\text{Ca}+\text{Mg}] - [\text{Cl-lactate}] \]
The Strong Ion Difference (SID) is the difference between the sums of concentrations of the strong cations and strong ions:

$$[\text{SID}] = [\text{Na}^+] + [\text{K}^+] + [\text{Ca}^{2+}] + [\text{Mg}^{2+}] \text{ minus } [\text{Cl}^-] + [\text{Other Strong Anions}]$$

$$140 + 4 + 1 + 1 = 146$$

$$100 + 1 = 101$$

Measured SID = 45 mmol/L

Base Excess = + 5 mmol/L
Strong Ion Difference

\[ [\text{SID}] = [\text{Na}^+] + [\text{K}^+] + [\text{Ca}^{2+}] + [\text{Mg}^{2+}] \quad \text{minus} \quad [\text{Cl}^{-}] - [\text{Other Strong Anions}] \]

\[
140 + 4 + 1 + 1 = 146
\]

\[
120 + 6 = 126
\]

Hyperchloraemia SID now 26 mmol/L.

Base Excess about – 5 to -10 mmol/L

Anion Gap normal because chloride ions included in calculation
Effects of 2000 mL acute fluid loading in 10 volunteers. Blind cross over trial
(Lobo et al Br J Surg 2001)
Weight gain following 2L Saline or Dextrose in normal subjects

% Wt change

Hours

1 2 3 4 5 6

Saline Dextrose
Serum sodium following 2L Saline or Dextrose in normal subjects

- **Saline**
- **Dextrose**

![Graph showing serum sodium levels over time for Saline and Dextrose.](image)
Serum chloride following 2L Saline or Dextrose in normal subjects

[Graph showing serum chloride levels over time for Saline and Dextrose]

- Saline
- Dextrose
Assume blood volume about 3000 mL

\[0.08 \text{Hct} \times 3000 = 240 \text{mL}\]

\[
\frac{240}{2000} = 12\% \text{ saline in vasc. space}
\]
FLUIDS

- Balanced vs. saline

Williams EL et al. The Effect of Intravenous Lactated Ringer’s Solution Versus 0.9% Sodium Chloride Solution on Serum Osmolality in Human Volunteers. Anesthesia & Analgesia. 1999;88(5):999-1003.
FLUIDS

- **SALINE**
  - Hyperchloraemic metabolic acidosis
  - Hyperosmolar states
  - Stimulation of ADH - fluid retention
  - Chloride causes renal vasoconstriction – fluid retention
  - Nausea, vomiting, abdo pain, hyperventilation, thirst
  - Impaired cognitive ability, headaches

Hartmann AF, Senn MJE 1932 J Clin Invest 11:337-44
Waters JH et al Anesthesiology 2000:93:1184-7
Williams EL et al Anesthesia & Analgesia 1999;88:999-1003
Healey MA et al J Trauma;45:894-9
REPLACEMENT CRYSTALLOIDS
- Saline
- Glucose
- Mixtures
- Balanced salt solutions
**FLUIDS**

- **HARTMANN’S SOLUTION**

![Chemical structure of lactic acid and lactate](image)

FLUIDS

- HARTMANN’S SOLUTION

Other solutions

7.5% Saline

Other solutions

0.45% Saline + 5% glucose

- The low sodium content of sodium chloride 0.18% with glucose 4% infusion increases the risk of the patient developing hyponatraemia, particularly in the absence of individualised prescribing and robust on-going monitoring.

- The majority of children may be safely administered sodium chloride 0.45% with glucose 5% (hypotonic solution), or sodium chloride 0.45% with glucose 2.5% (hypotonic solution). There is currently little evidence to recommend a particular strength of glucose.

BNFC update December 2012

Risk of fatal hyponatraemia with hypotonic intravenous infusions

The use of hypotonic intravenous infusion fluids in children has been associated with fatal hyponatraemia. The guidance in BNFC section 9.2.2.1 has been updated to reflect recent recommendations from the MHRA/CHM (Drug Safety Update, October 2012). Sodium chloride 0.18% and glucose 4% intravenous infusion is now contra-indicated in children aged 16 years or less, except when initiated and maintained under expert medical supervision in paediatric specialist settings.
COLLOIDS

Definition: A colloid solution contains molecules which are large enough to be retained by the vascular endothelium

The ability of a colloid solution to remain in the vascular space depends upon:
1. Molecular size
2. Rate of degradation
3. Permeability of the endothelium

Primary use: To fill the depleted vascular compartment
FLUIDS

- COLLOIDS
  - **Definition:** A *colloid solution contains molecules which are large enough to be retained by the vascular endothelium*

  - **FOR:**
    - greater intravascular retention
    - lower overall infusion volumes
    - viscosity
  - **AGAINST:**
    - anaphylaxis
    - acid-base
    - renal function
    - coagulation
FLUIDS

- DEXTRANS
FLUIDS

- STARCHES
  - Molecular weight
  - Substitution ratio
  - Substitution pattern
  - Carrier solution

- STARCHES
  - 1st generation
  - 2nd generation
  - 3rd generation
  - 4th generation
**FLUIDS**

- **STARCHES**
  - Molecular weight
  - Mean molecular weight
    - \( \text{Mn} = \frac{\text{total wt}}{\text{total no. of molecules}} \)
      - \( \Rightarrow \) oncotic pressure
  - \( \text{Mw} = \text{weight average} \) <-> bigger molecules contain more of the total mass
    - \(-\) no of molecules at a given weight x molecular wt/total weight of molecules in the solution
    - \(-\) repeat for all and add together
      - \( \Rightarrow \) viscosity
FLUIDS

- STARCHES
  - Viscosity
    - Poiseuille’s Law

FLUIDS

- **STARCHES**
  - Viscosity
    - Poiseuille’s Law
    - Blood viscosity (Hct 40) = 3cp
    - Hartmann’s = 0.8cp
    - Gelofusine = 1.9cp
    - HES (130/0.4) = 2.7-3.5cp

cP=centipoise
• **STARCHES**
  - Substitution ratio

![Diagram of Hydroxyethyl Starches](image)
**STARCHES**

- substitution pattern

![Starch Structure](attachment:starch_structure.png)

- Amylase action on starch molecule
## Characteristics of different hydroxyethyl starch preparations

Adapted from Anesthesiology: 2005; 103:654-660

<table>
<thead>
<tr>
<th>Degradation rate</th>
<th>Molar Subst.</th>
<th>Mol Wt kDa</th>
<th>C2/C6 ratio</th>
<th>Conc. %</th>
<th>Volume effect</th>
<th>Max dose mL/kg/24h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetra</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Penta</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heta</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heta</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>‘Hepta’</td>
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<td></td>
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</tr>
<tr>
<td>‘Hepta’</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
STARCHES:
- Maize starch contains 95% amylopectin + 5% amylose, in contrast to potato starch containing 20-30% amylose. The MW of the amylose part is lower than MW of amylopectin.
- Higher MS in potato (0.45) derived HES compared to corn derived HES (0.41).
- Higher C2/C6 ratio in corn derived HES compared to potato derived HES.
- Potato starch is eliminated slightly faster than maize starch: i.e. the higher MS of potato derived HES does not fully compensate for the lower C2/C6 ratio.
- Significantly higher degree of esterification with phosphoric acid with potato starch.
- Potato starch derived HES compromises *in vitro* blood coagulation to a stronger extent than corn starch derived HES.
Acute blood loss

Reduced blood volume
Reduced interstitial volume
Reduced intracellular volume

THERAPY

To fill vascular space:
Balanced electrolyte solution
Red blood cells

To fill interstitial space & cells
Balanced electrolyte solution

Haemostasis
**Fluid and electrolyte balance  24 hr post major surgery**

<table>
<thead>
<tr>
<th>Input</th>
<th>Output</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluid</td>
<td>8000 mL</td>
</tr>
<tr>
<td></td>
<td>1000 mL Urine</td>
</tr>
<tr>
<td>Sodium</td>
<td>1200 mmol</td>
</tr>
<tr>
<td></td>
<td>25 mmol</td>
</tr>
<tr>
<td>Nitrogen</td>
<td>600 (catabolism)</td>
</tr>
<tr>
<td></td>
<td>400 mmol</td>
</tr>
<tr>
<td>Other</td>
<td>500 mmol</td>
</tr>
<tr>
<td></td>
<td>50 mmol</td>
</tr>
<tr>
<td>mosmoles</td>
<td>3500</td>
</tr>
<tr>
<td></td>
<td>500</td>
</tr>
</tbody>
</table>

**6000 mL positive fluid balance**

**3000 mosmoles positive balance**

**Requires 6 litres of urine to clear sodium + N$_2$**

**(500 mosm/L maximum concentration)**
BODY FLUIDS AND COMPARTMENTS

- Saline/kidneys
  - Hyperchloraemic metabolic acidosis
  - Hyperosmolar states
  - Stimulation of ADH - fluid retention
  - Renal vasoconstriction – fluid retention
  - Nausea, vomiting, abdo pain, hyperventilation, headaches, thirst

Hartmann AF, Senn MJE 1932 J Clin Invest 11:337-44
Waters JH et al Anesthesiology 2000:93:1184-7
Williams EL et al Anesthesia & Analgesia 1999;88:999-1003
Healey MA et al J Trauma;45:894-9
Post resuscitation +6000mL Na Cl positive
+ 3000mosm positive
Hypovolaemia with ++ interstitial oedema

Hypernatraemia, uraemia, hyperosmolar, more ADH

Renin, aldosterone, ADH
Salt and water retention

Catabolic N₂ competes with Na Cl excretion hypernatraemia,

KIDNEY
Reduced concentrating ability (<500mmosm/L) needs 6000mL urine!
Renal oedema reduced perfusion
Low UO

Intractable oedema

URINE

Stress and hypovolaemia

Low UO misinterpreted so more fluid given!
Crystalloids and Colloids: is there really a debate?

Colloids
Definition: A colloid solution contains molecules which are large enough to be retained by the vascular endothelium.

Properties: A colloid has the property of trapping water: e.g. 1 gram of albumin binds 18 grams of water.

The ability of a colloid solution to remain in the vascular space depends upon:
1. Molecular size
2. Rate of degradation
3. Permeability of the endothelium

Primary use: To fill the depleted vascular compartment.
Crystalloids and Colloids: is there really a debate?

Crystalloids

Definition: crystalloids are salt solutions containing electrolytes or easily metabolised small molecules such as glucose.

Properties: Crystalloid solutions are isotonic with plasma at the time of intravenous administration, but in the case of glucose solutions, they become hypotonic in vivo as the glucose is metabolised.

Ad hoc uses for salt solutions:

- Poor man's volume expander (10-20% stays in vasc. space)
- An i.v. fluid for the unthinking e.g. ‘normal saline’ must be safe

The glucose is metabolised.

Primary Uses:

1. To provide free water (dextrose)
2. To replace lost electrolytes (salt solutions)
3. To provide a vehicle for i.v. delivery of drugs
Advantages of HES for fluid resuscitation

- Better vascular retention than gelatins, albumin or crystalloid only: lower sodium and water load
- Less extravascular Na\(^+\) & water - less oedema
- Better kidney and lung function
- Reduction of cytokine inflammation
FLUIDS

Volume Effect of HES and Gelatins 2 hours after infusion

End of Infusion | 30 min | 60 min | 120 min
--- | --- | --- | ---
HES 200/0.5, 6% | 650 | 660 | 640
Gelatin 3.5% | 570 | 580 | 40
Ringers's Lactate | 400 | 400 | 120

HES 200/0.5, 6% | Gelatin 3.5% | Ringers's Lactate
Lobo DN, Stanga Z, Aloysius MM, Wicks C, Nunes QM, Ingram KL, et al. Effect of volume loading with 1 liter intravenous infusions of 0.9% saline, 4% succinylated gelatine (Gelofusine) and 6% hydroxyethyl starch (Voluven) on blood volume and endocrine responses: a randomized, three-way crossover study in healthy volunteers. Critical care medicine. 2010;38(2):464-70.
FLUIDS

Volume Effect of HES and Gelatins 2 hours after infusion

Awad S, Dharmavaram S, Wearn CS, Dube MG, Lobo DN. Effects of an intraoperative infusion of 4% succinylated gelatine (Gelofusine®) and 6% hydroxyethyl starch (Voluven®) on blood volume. British journal of anaesthesia. 2012;109(2):168-76
Advantages of HES for fluid resuscitation

- Better vascular retention than gelatins, albumin or crystalloid only: lower sodium and water load
- Less extravascular Na$^+$ & water - less oedema
- Better kidney and lung function
- Reduction of cytokine inflammation
The vascular endothelium is an organ

$10^{13}$ Endothelial Cells

1 kilogram

4000 to 7000 m$^2$

Is endothelium the first organ to fail?
Is endothelium the first organ to fail?

Glomerular permeability to FITC-Dextran in control and laparotomy hamsters

- Laparotomy n = 11
- Control n = 11

Capillary leak predicts lung dysfunction in surgery and trauma

Aortic Surgery
A = 10 patients with lung dys. at 24hrs
B = 30 patients with no lung complications

![Graph showing microlbuminuria mg/mmol creatinine over hours post start of surgery with A and B groups compared.](image)
Urine albumin on admission to ICU predicts mortality

Median urine ACR on admission and after 4-6 hours

Median ACR 4-6 h post ICU admission

Survivors n = 341   Non survivors n = 90

Gosling et al Crit Care Med 2006;34:2158-5166
Anti-inflammatory

Hydroxyethyl Starch (130 kD), but Not Crystalloid Volume Support, Improves Microcirculation during Normotensive Endotoxemia

Johannes N. Hoffmann, M.D., Brigitte Vollmar, M.D., Matthias W. Laschka, M.D., Dietrich Inthorn, M.D., Friedrich W. Schildberg, M.D., Michael D. Menger, M.D.
When compared with gelatin or dextran solutions, hydroxyethyl starch provided a therapeutic advantage in this setting by exerting an inhibitory effect on the ischemia-reperfusion-induced local and systemic leukocyte reactions and the postischemic periosteal microvascular dysfunction.

In this issue of Critical Care Medicine, Varga et al. compare the effects of three commonly used volume expanding colloids on microvascular hemodynamics and the inflammatory response to ischemia reperfusion injury.

They elegantly show that, compared with dextran (6% 60 kD) or gelatin (4% 35 kD), resuscitation with hydroxyethyl starch (HES) (6% 130 kD/0.4) is associated with a reduction in local and systemic leukocyte activation and improved microvascular blood flow.
Side effects of HES administration

• Osmotic like nephrosis after high dose
• Retention in reticuloendothelial system
• Pruritis after chronic administration
• Coagulopathy
Colloids and Acute Renal Failure

• Any colloid given in sufficient amounts to raise plasma colloid osmotic pressure to level sufficient to effectively counteract the opposing hydraulic filtration pressure in the glomerulus.

• The critical value of COP is around 27 - 29 mmHg but may be lower in patients with sepsis

• Hyperoncotic acute renal failure has been reported with Dextrans, HES, Gelatins and 20% Albumin
Effects of hydroxyethylstarch and gelatin on renal function in severe sepsis: a multicentre randomised study

Frederique Schortgen, Jean-Claude Lacherade, Fabrice Bruneel, Isabelle Cattaneo, Francois Hemery, Francois Lemaire

Summary
Over 18 months 129 adult patients with severe sepsis or septic shock were randomised to hydroxyethylstarch or gelatin for plasma volume expansion. Severity of illness and serum creatinine (median 143 (IQR 88-203) vs 114 (91-175) umol/L) were similar at baseline between the hydroxyethylstarch and gelatin groups. The frequency of acute renal failure (27/65 [42%] vs 15/64 [23%], p=0.028) and oliguria (35/62[56%] vs 23/63 [37%], p=0.025) and peak serum creatinine (225 [130-339] vs 169 [108-273]) concentrations were significantly higher in the hydroxyethylstarch group than in the gelatin group. In a multivariate analysis, risk factors for ARF include mechanical ventilation (odds ratio 4.02 [95%CI 1.37-11.8, p=0.013) and the use of hydroxyethylstarch (2.57 [1.13-5.83] p=0.026)

The use of this preparation of hydroxyethylstarch as a plasma volume expander is an independent risk factor for ARF in patients with severe sepsis or septic shock.
Colloids and Acute Renal Failure

HES 6% (200,000 Mol Wt) up to 33ml/Kg/day until maximum dose only then crystalloids given

Gelatine 3% (30,000 Mol Wt) unlimited administration

Result - hyperoncotic state in HES group

Insufficient free water given in HES group
Intensive Insulin Therapy and Pentastarch Resuscitation in Severe Sepsis

Frank M. Brunkhorst, M.D., Christoph Engel, M.D., Frank Bloos, M.D., Ph.D., Andreas Meier-Hellmann, M.D., Max Ragaller, M.D., Norbert Weiler, M.D., Onnen Moerer, M.D., Matthias Gruendling, M.D., Michael Oppert, M.D., Stefan Grond, M.D., Derk Olthoff, M.D., Ulrich Jaschinski, M.D., Stefan John, M.D., Rolf Rossaint, M.D., Tobias Welte, M.D., Martin Schaefer, M.D., Peter Kern, M.D., Evelyn Kuhnt, M.Sc., Michael Kiehntopf, M.D., Christiane Hartog, M.D., Charles Natanson, M.D., Markus Loeffler, M.D., Ph.D., and Konrad Reinhart, M.D., for the German Competence Network Sepsis (SepNet)
VISEP Study: Amount of HES infusions

38% Patients overdosed

HES 10% 200 kD: high risk of hyperoncotic acute renal failure

<table>
<thead>
<tr>
<th>Overdose</th>
<th>HES (n = 262)</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>At least at one day</td>
<td>38.2</td>
</tr>
<tr>
<td>Within first 24 h</td>
<td>28.2</td>
</tr>
</tbody>
</table>

ml HemoHes / kg BW/day

22 ml/kg BW

0 - 24h 24 - 24h
VISEP Study: Reasons for renal impairment

- Study design: Ringers versus HES in 0.9% saline – chloride nephrotoxicity
- Volume therapy with HES 10% (HES 200/0.5) with insufficient free water in some patients
- HES 200/0.5 administered in some patients with contraindication – renal impairment
- HES 200/0.5 has been overdosed in 38% patients
The effects of hydroxyethyl starch solution in critically ill patients.

PATIENTS
Critically ill with sepsis

INTERVENTION
Hydroxyethyl starch 6% (130/0.4) n=10
Albumin 20% n = 10
To maintain PCWP 15 - 18 mmHg

RESULTS:
Compared with 20% albumin group, HES treated patients showed increased cardiac index (CI), right ventricular ejection fraction (RVEF), oxygen consumption index (VO(2)I), oxygen delivery index (DO(2)I), PaO2/FiO2 ratio (P<0.05). APACHE II score decreased significantly only in HES treated group (P<0.05),

Safety of HES 130/0.4 in patients with preoperative renal dysfunction undergoing abdominal aortic surgery

PATIENTS
AAA elective surgery pre op creatinine clearance < 80 mL min-1.
Perioperative volume expansion

INTERVENTION
6% hydroxyethyl starch (Voluven(R); n = 32
3% gelatin (Plasmion(R); n = 33.

OUTCOME MEASURE
peak serum creatinine up to post op day 6

RESULTS
No adverse effects of hydroxyethyl starch on renal function.

Conclusions.

- Both ROTEMTM and SONOCLOTTTM are sensitive tests for the detection of impaired blood coagulation due to haemodilution.
- There are fewer effects on blood coagulation using crystalloids compared with colloids.
- The effects of GEL and HES are similar. There is no difference between balanced HES 130/0.42 and non-balanced HES 130/0.4.

Casutt M, Kristoffy A, Schuepfer G, Spahn DR, Konrad C. Effects on coagulation of balanced (130/0.42) and non-balanced (130/0.4) hydroxyethyl starch or gelatin compared with balanced Ringer’s solution: an in vitro study using two different viscoelastic coagulation tests ROTEM® and SONOCLOT®. British journal of anaesthesia. 2010;105:273-81.
Conclusions. In cardiac surgery patients aged .80 years, volume therapy with HES 130/0.4 6% was associated with less marked changes in kidney function and a less marked endothelial inflammatory response than gelatin 4%.

• **Background:** Hydroxyethyl starch (HES) 130/0.4 is widely used for fluid resuscitation in intensive care units (ICUs), but its safety and efficacy have not been established in patients with severe sepsis.

• **Methods:** In this multicenter, parallel-group, blinded trial, we randomly assigned patients with severe sepsis to fluid resuscitation in the ICU with either 6% HES 130/0.4 or Ringer’s acetate at a dose of up to 33 ml per kilogram of ideal body weight per day.

• The primary outcome measure was either death or end-stage kidney failure (dependence on dialysis) at 90 days after randomization.

• **Results:** Patients with severe sepsis assigned to fluid resuscitation with HES 130/0.4 had an increased risk of death at day 90 and were more likely to require renal-replacement therapy, as compared with those receiving Ringer’s acetate.

We randomly assigned 7000 patients who had been admitted to an intensive care unit (ICU) in a 1:1 ratio to receive either 6% HES with a molecular weight of 130 kDa and a molar substitution ratio of 0.4 (130/0.4, Voluven) in 0.9% sodium chloride or 0.9% sodium chloride (saline) for all fluid resuscitation until ICU discharge, death, or 90 days after randomization.

The primary outcome was death within 90 days.

Secondary outcomes included acute kidney injury and failure and treatment with renal-replacement therapy.

<table>
<thead>
<tr>
<th>Predefined subgroups — no./total no. (%)</th>
<th>HES (n=1449)</th>
<th>Saline (n=1421)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RIFLE criteria for acute kidney injury‡</td>
<td>522/1449 (36.0)</td>
<td>511/1421 (36.0)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>979/3355 (29.2)</td>
<td>958/3376 (28.4)</td>
</tr>
<tr>
<td>Trauma</td>
<td>267/3358 (8.0)</td>
<td>265/3384 (7.8)</td>
</tr>
<tr>
<td>Traumatic brain injury</td>
<td>28/3338 (0.8)</td>
<td>30/3365 (0.9)</td>
</tr>
<tr>
<td>APACHE II score ≥25</td>
<td>597/3335 (17.9)</td>
<td>624/3356 (18.6)</td>
</tr>
<tr>
<td>Receipt of HES before randomization</td>
<td>509/3347 (15.2)</td>
<td>508/3372 (15.1)</td>
</tr>
</tbody>
</table>
There was no significant difference in mortality in six predefined subgroups.

Renal-replacement therapy was used in 235 of 3352 patients (7.0%) in the HES group and 196 of 3375 (5.8%) in the saline group (relative risk, 1.21; 95% CI, 1.00 to 1.45; P=0.04).

In the HES and saline groups, renal injury occurred in 34.6% and 38.0% of patients, respectively (P=0.005)

Renal failure occurred in 10.4% and 9.2% of patients, respectively (P=0.12).

HES was associated with significantly more adverse events (5.3% vs. 2.8%, P<0.001).

• Renal-replacement therapy was used in 235 of 3352 patients (7.0%) in the HES group and 196 of 3375 (5.8%) in the saline group (relative risk, 1.21; 95% CI, 1.00 to 1.45; P=0.04).
• In the HES and saline groups, renal injury occurred in 34.6% and 38.0% of patients, respectively (P=0.005)
• Renal failure occurred in 10.4% and 9.2% of patients, respectively (P=0.12).
The FIRST trial

- **Background:**
  - The role of fluids in trauma resuscitation is controversial. We compared resuscitation with 0.9% saline vs hydroxyethyl starch, HES 130/0.4, in severe trauma with respect to resuscitation, fluid volume, gastrointestinal recovery, renal function, and blood product requirements.

- **Conclusions:**
  - In penetrating trauma, HES provided significantly better lactate clearance and less renal injury than saline.
  - No firm conclusions could be drawn for blunt trauma.

Renal function following AAA

Capillary leak predicts lung dysfunction in surgery and trauma

Capillary leak in AAA patients

Anti-inflammatory effects of HES

Anti-inflammatory effects of HES

Clinical studies show reduced expression of pro-inflammatory cytokines and adhesion molecules.

In vitro and animal studies suggest attenuation of neutrophil-endothelial cell interaction.
When using Hydroxyethyl starch

- Do not exceed maximum dose (possible exceptions massive blood loss burns)
- Reduce HES dose or avoid in renal impairment
- Always give sufficient free water (e.g. 1 part HES to 2 parts crystalloid)
FLUIDS

- COLLOIDS
  - BLOOD
  - BLOOD PRODUCTS
  - BLOOD SUBSTITUTES
Infection risk of imported blood 'known in 70s'

- 'Lost' documents emerge, public inquiry told
- Health department set to release more information

Sarah Boseley, health editor
guardian.co.uk, Saturday May 26 2007 23:59 BST

### Table 1. Noninfectious Serious Hazards of Transfusion (NISHOTs)\(^a\)

<table>
<thead>
<tr>
<th>Immune mediated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemolytic transfusion reactions</td>
</tr>
<tr>
<td>Febrile nonhemolytic transfusion reactions</td>
</tr>
<tr>
<td>Allergic/urticarial/anaphylactic transfusion reactions</td>
</tr>
<tr>
<td>Transfusion-related acute lung injury (TRALI)</td>
</tr>
<tr>
<td>Posttransfusion purpura (PTP)</td>
</tr>
<tr>
<td>Transfusion-associated graft versus host disease (TA-GVHD)</td>
</tr>
<tr>
<td>Microchimerism</td>
</tr>
<tr>
<td>Transfusion-related immunomodulation (TRIM)</td>
</tr>
<tr>
<td>Alloimmunization</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nonimmune mediated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Septic transfusion reactions</td>
</tr>
<tr>
<td>Nonimmune hemolysis</td>
</tr>
<tr>
<td>Mistransfusion</td>
</tr>
<tr>
<td>Transfusion-associated circulatory overload (TACO)</td>
</tr>
<tr>
<td>Metabolic derangements</td>
</tr>
<tr>
<td>Coagulopathic complications from massive transfusion</td>
</tr>
<tr>
<td>Complications from red cell storage lesions</td>
</tr>
<tr>
<td>Over/undertransfusion</td>
</tr>
<tr>
<td>Iron overload</td>
</tr>
</tbody>
</table>
FLUIDS

- COLLOIDS
  - BLOOD


FLUIDS

- COLLOIDS
  - ALBUMIN
FLUIDS

♦ COLLOID
  – BLOOD SUBSTITUTES
Distinction is made (a) between fluid and electrolytes required for normal existence (daily maintenance) and (b) for resuscitation or replacement of abnormal losses. No intravenous infusion should be continued simply because it is a “routine” component of clinical care. Food and fluids should be provided orally or enteraly and intravenous infusions discontinued as soon as possible. Prescribers need to understand the effects of surgical and metabolic stress on the renin-angiotensin-aldosterone system and on vasopressin elaboration. They must take care to assess the patient’s sodium, chloride, potassium, and water requirements from a knowledge of the stress response and any current deficit or excess; they must take into consideration normal maintenance requirements and the expected composition of intestinal or other losses. Requirements thus calculated are to be met based on a quantitative knowledge of the sodium, chloride and potassium contents of the fluids prescribed. Prescription should not be made without such knowledge and no intravenous fluid should be regarded as intrinsically safe. Nutrition should be assessed and cautiously maintained. The oedematous patient should be managed with particular care, in order to achieve successful negative sodium and water balance.
Joachim Boldt is at the centre of a criminal investigation amid allegations that he may have forged up to 90 crucial studies on the treatment. He has been stripped of his professorship and sacked from a German hospital following allegations about his research into drugs known as colloids.

Experts described Mr Boldt's alleged forgeries as possibly the biggest medical research scandal since Andrew Wakefield was struck off last year for falsely claiming to have proved a link between the MMR vaccine and autism. Guidelines for British anaesthetists regarding colloids – used to boost blood volume in patients undergoing surgery – are being revised after it emerged that four of the key studies on which they were based are to be formally retracted.

Mr Boldt, 57, was regarded as a leading specialist in intravenous fluid management, and his work was published widely in British medical journals. He claimed to have proved that colloids were as safe as other, similar treatments despite earlier studies showing them to be more dangerous. Mr Boldt's alleged forgeries date back up to a decade.

Millions of surgery patients at risk in drug research fraud scandal

Millions of NHS patients have been treated with controversial drugs on the basis of "fraudulent research" by one of the world's leading anaesthetists, The Daily Telegraph can disclose.
These guidelines were first published in 2008, in response to concern about the high incidence of postoperative sodium and water overload and evidence to suggest that preventing or treating this, by more accurate fluid therapy, would improve outcome.

They were then revised in 2011, when the authors learnt that Professor Joachim Boldt is under investigation following allegations of research fraud. Whilst remaining open minded as to whether these allegations would prove to be true or false, they felt that since the guidelines used six of his references there was a need to review them to see if any changes were needed after removing these six references.

The text and recommendations remained exactly as before and one review reference was added to replace the Boldt references removed. Removal of his references from these Guidelines therefore has had absolutely no impact on the recommendations for patient care.
FLUIDS
Give fluids for a reason:

To correct hypovolaemia

- Effective colloid to fill vascular space
- Red blood cells
- Clotting factors/platelets for haemostasis
- Minimum water, Na\(^+\) and Cl\(^-\)
FLUIDS
Give fluids for a reason:

To replace electrolyte losses

- For resuscitation or replacement use balanced electrolyte solution
- Avoid 0.9% saline except for specific Na⁺ Cl⁻ losses (e.g. DKA resuscitation, Addisons, D&V)
- Enough water to excrete urea and sodium and replace insensible losses
- STOP when resuscitation or replacement completed
Five messages for fluids in major surgery

1. Use cardiac index and stroke volume to guide vascular filling and optimise oxygen delivery.

2. Volume expand with a colloid which is well retained in the leaky circulation and gives the maximum volume expansion with the minimum sodium and water load. Avoid colloid overload!

3. Replace electrolyte losses with balanced crystalloid, allowing for the sodium and chloride given with the colloid.

4. Allow the patient to off load ‘resuscitation’ sodium and water. This may require haemodynamic monitoring, further volume expansion with colloid and inotropic support

5. Post op maintenance fluid should be 5% dextrose or enteral water plus feed and potassium until the sodium load has been excreted. Only then should sodium be included in maintenance fluids. More refractory fluid retention will require diuretics.
Optimal fluid therapy is that which maintains vascular filling and oxygen delivery with the minimum of interstitial oedema despite leaky endothelium.

Patient to patient endothelial response to the same ‘insult’ is very variable, so fluid therapy must be matched to the individual patient’s overall response.
Before a patient can recover they have to excrete all the fluid and electrolytes we give them.
• Borunda MSC. La Cerveza Como Bebida Rehidratante Después Del Ejercicio. 2011.

The dehydration protocol (race) was effective as shown by various parameters such as changes in weight, urea, creatinine, lean mass and so on. The protocol also was a high intensity and wear as shown by changes in insulin and growth hormone. Furthermore, rehydrated with a moderate amount of beer with alcohol (660 ml) and water to retrieve adequately the losses produced by dehydration in the same post-exercise as drinking water is achieved, even in certain parameters such as volume of water extracellular seems to be a better recovery with the protocol of beer + water. So if adequate rehydration is accomplished with both beverages, in the case of beer, we also achieved an extra contribution of nutrients derived from their composition.
Beer after sport 'is good for the body'

By Nic Fleming, Science Correspondent

A beer after playing a game of football, a long run, or a strenuous round of golf can be good for the body, scientists say.

In a rare piece of good news for those who like a pint, Spanish researchers say beer can help someone who is dehydrated retain liquid better than water.

Prof Manuel Garzon, of Granada University, also claimed the bubbles in beer help to quench the thirst and that its carbohydrate content can help to replace lost calories.

Prof Garzon asked a group of students to do strenuous exercise in temperatures of around 40°C (104°F). Half were given a pint of beer, while the others received the same volume of water.

Prof Garzon, who announced the results at a press conference in Granada beneath a banner declaring "Beer, Sport, Health", said the hydration effect in those who drank beer was "slightly better".

Juan Antonio Corbalan, a cardiologist who worked formerly with Real Madrid football players and Spain’s national basketball team, said beer had the perfect profile for re-hydration after sport.

He added that he had long recommended barley drinks to professional sportsmen after exercise.

Dr James Betts, an expert on nutrition and metabolism at Bath University, said a moderate amount of beer might be just as good as water at helping the body retain liquid, but that he doubted it could be any better.

Dr Betts said: "If you are dehydrated to start with following exercise, a beer, as opposed to a spirit, probably does not have a high enough concentration of alcohol to induce a diuretic effect."

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