My talk today:

- The Swollen Witness
- A little Physiology (goes a long way)
- Reflections on a rat cremaster
- RSE&GM
- The Great Fluid Debate
- The Boldt Debacle
- African Lesson
- The Forgotten Ion
THE SWOLLEN WITNESS
Week-end.

21 years old, student, Jehovah Witness
Admitted for Pneumonia.
Syncope, hypotensive
BP 85/60 HR 110 RR 20 Tt 38 SpO$_2$ aa 92%
(A-a)O$_2$ 20 HCO$_3$ 25 GB 17400
Admitted in ICU (severe sepsis??)
Day 2

Not MV, BGA ok.

Transferred to Intermediate Care.

Parents very angry.

She is not my daughter, she is swollen!


Creat 0.6 mg %, Na 135 mEq/L Alb↓

BW gain >11 Kg. Any idea?

The astute clinician count...
## Fluid balance 36 hrs

<table>
<thead>
<tr>
<th></th>
<th>IN</th>
<th>OUT</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>saline</td>
<td>6750</td>
<td></td>
<td></td>
</tr>
<tr>
<td>colloids</td>
<td>2000</td>
<td>2400</td>
<td>diuresis</td>
</tr>
<tr>
<td>Gluc.5%</td>
<td>1500</td>
<td>1200</td>
<td>Persp.</td>
</tr>
<tr>
<td>NaHCO₃ 1M</td>
<td>200</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NaCl 3%</td>
<td>200</td>
<td></td>
<td></td>
</tr>
<tr>
<td>os</td>
<td>2400</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>13050</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
“Drink plenty of fluids”:
a systematic review of evidence for this recommendation in acute respiratory infections

Guppy PB et al   BMJ 2004;328:499
Intravenous fluid therapy
Intravenous fluid therapy in adults in hospital

Clinical Guideline <CG174>
Methods, evidence and recommendations
December 2013

Commissioned by the National Institute for Health and Care Excellence
Determine **whether an intravenous fluid is necessary at all**, a basic question that needs to be asked as oral or nasogastric fluids are usually always preferable.

*NICE Intravenous Fluid therapy, dec 2013*
Intravenous fluid administration is indicated in patients who are:

- **acutely unwell** and requiring large quantities of fluid for resuscitation
- **unable to drink** (e.g. unconscious, unsafe swallow (e.g. following strokes, facio-maxillary injury))
- **unable to absorb adequate quantities of water** (e.g. vomiting, paralytic ileus, diarrhoea)
- **losing excessive quantities of fluid** (e.g. diarrhoea, haemorrhage, burns)

NICE Intravenous Fluid therapy, dec 2013
Routine maintenance

If patients need IV fluids for routine maintenance alone, restrict the initial prescription to:

- 25–30 ml/kg/day of water and
- approximately 1 mmol/kg/day of K, Na and Cl and
- approximately 50–100 g/day of glucose to limit starvation ketosis. (This quantity will not address patients’ nutritional needs)

Consider prescribing less fluid (for example, 20–25 ml/kg/day fluid) for patients who:

- are older or frail
- have renal impairment or cardiac failure
- are malnourished and at risk of refeeding syndrome

NICE Intravenous Fluid therapy, dec 2013
Osmolality is a physical property dependent on the total *number of solute particles present in a solution*

Tonicity is a physiological process dependent upon the selectively permeable characteristics of a membrane
Water moves from solution with the lower concentration to the solution with the higher concentration: this is OSMOSIS.
• Too much sodium
  EDEMA

• Too little sodium
  VOLUME DEPLETION (ECF)
Water Balance

- Water intake regulated by **thirst**
- Water balance **affects cell volume**
- Cell volume regulates **thirst** and urine water losses (ADH)
From the lower to the higher 

ECF

High [Na⁺]

H₂O

ICF

CELL SHRINKAGE
From the lower to the higher

Low $[\text{Na}^+]$

$\text{ECF}$

$\text{H}_2\text{O}$

$\text{ICF}$

CELL SWELLING
TBW
(Total Body Water)
60% of body weight

2/3 ICF

1/3 ECF

H₂O

Na

3/4 INT

1/4 PL
EABV is an unmeasured entity that reflects tissue perfusion. EABV usually varies directly with the ECF volume.
Both of these parameters are *normally proportional to total body sodium stores*, since sodium salts are the primary extracellular solutes that act to hold water within the extracellular space.
EABV

Tissues Perfusion

1/3 ECF

3/4 INTERSTITIUM (extravascular)

1/4 PLASMA (ECV) (intravascular)

H2O ⇌ H2O
Na ⇌ Na

* large molecules

TBW (Total Body Water) 60% of body weight

2/3 ICF

1/3 ECF

EABV (700 ml)
The primary function of the cardiovascular system.
Delivery oxygen for utilization by the parenchymal cells for their metabolic needs to sustain organ function.
myocardial contractility
preload
afterload

Stoke Volume

Heart Rate

SVR  CO  x  Hb  O₂

PERFUSION

DO₂
Perfusion, $\text{DO}_2$....

The \textit{microcirculation} may be the right target.
Microcirculatory Responses to Hypovolemic Shock

Szopinski J et al. Journal of Trauma: Injury, Infection, and Critical Care
Vol 71(6), December 2011, pp 1779-1788

The A1, A2, and A3 arterioles and corresponding venules in the rat cremaster model of the microcirculation network.
Microcirculatory alterations have been repeatedly observed in patients with severe sepsis, but also occur in patients with severe heart failure and in those submitted to high-risk surgery. More severe and more persistent alterations are observed in patients with a poor outcome.
As *microcirculation is the place where oxygen exchanges take place,* its *dysfunction, which happens in *septic shock* and *other shock states,* can contribute to *cellular hypoxia even when global DO₂ is preserved.*

In the setting of sepsis, the endothelium and vasculature are under assault by activated leukocytes, inflammatory mediators, and reactive oxygen species that cause microcirculatory dysfunction in advance of organ failure.

A compromised microcirculation is no longer able to regulate blood flow distribution, resulting in functional shunting where the oxygen need of the parenchymal cells is not met by adequate delivery.

Ince C Critical Care 2013, 17(Suppl 1):S9
**Too little volume** is defined as low microcirculatory blood flow and **too much volume** as a *dilution of the capillaries*, resulting in increased diffusion distances.
Interstitium:
The next diagnostic and therapeutic platform in critical illness.

Venkatesh B et al  Crit Care Med 2010; 38[Suppl.]:S630–S636
Pathophysiologic Alterations in the ISF Associated with Critical Illness

In **sepsis** there are well-documented **increases in the** extracellular body water during the acute phase of the inflammatory response.

**Elderly** patients with sepsis demonstrate increases in extracellular water compared with younger patients, and **increasing** extracellular water are associated with worse outcome.

Patients with **major blunt trauma** display similar pathophysiologic changes.
RSE&GM

Revised Starling equation (RSE) and the glycocalyx model (GM) of transvascular fluid exchange: an improved paradigm for prescribing intravenous fluid therapy

Woodcock TE, Woodcock TM

Levick R, Michel CC
Cardiovascular Research (2010) 87, 198–210
Driving pressure across capillary wall

\[ J = K_f \left( \left[ P_c - P_i \right] - \sigma \left[ \Pi_c + \Pi_i \right] \right) \]

\[ K_f(P_{HS \, capillary} - P_{HS \, interst}) - \sigma(P_{o \, capillary} - P_{o \, interst}) \]

- \( P_c \): Hydrostatic capillary pressure
- \( P_i \): Hydrostatic interstitial pressure
- \( \Pi_c \): Oncotic capillary pressure
- \( \Pi_i \): Oncotic interstitial pressure
- \( K_f \): Filtration co-efficient
- \( \sigma \): Reflection co-efficient
There are **three intravascular volumes**:

- plasma volume
- red cell volume
- glycocalix

*1.5 litres of the intravascular volume in health*

from Woodcock, modified
endothelial glycocalyx layer, a web of membrane-bound glycoproteins and proteoglycans on endothelial cells, key determinant of membrane permeability in various vascular organ systems.
Compaction of the glycocalyx layer increases plasma volume and the red cell dilution volume independently of changes in intravascular volume.
Sinusoidal
*(liver, spleen, marrow)*

Non-fenestrated
*(CNS, muscle, connective, lung)*

Fenestrated
*(endocrine, choroid plexus, gut mucosa)*

Fenestrated
*(glomerular)*

- **nonfenestrated capillaries** normally **filter fluid** to the ISF throughout their length.

- **absorption** through venous capillaries and venules **does not occur**.

- **COP** opposes, but does not reverse, filtration.

- **most of the filtered fluid returns to the circulation as lymph.**
Liver has primitive ‘sinusoidal’ capillaries which are freely permeable to larger molecules, making the interstitial fluid of these tissues an extension of the plasma volume.

In resuscitated septic shock patients, as much as 50% of the cardiac output goes to this very leaky microcirculation.
Plasma proteins, including albumin, escape to the interstitial space by a relatively small number of large pores, which are responsible for the increased transcapillary flow \((J_v)\) observed in the early stage of inflammation.
It appears, on the evidence from human studies to date, that the **EGL is compromised in systemic inflammatory states** such as diabetes, hyperglycaemia, surgery, trauma, and **sepsis**

SIRS → Increased capillary permeability → Interstitial edema → impaired DO₂ → MODS → Membrane dysfunction
The Thirty Years War
The end of the crystalloid era?


Is it the end of the road for synthetic starches in critical illness?

Prowler & Pearse, Editorial, BMJ 2013;346:f1805
**crystalloids**

Solutions that contain *sodium* as their major osmotically active particle (saline, Ringer)

**colloids**

*Large molecular weight* substances, dispersed most usually in *normal saline*, that do not pass readily across capillary walls, as albumin, gelatine or HES
### Crystalloid solution

<table>
<thead>
<tr>
<th>Crystalloid solution</th>
<th>Components (mEq in 1,000 ml)</th>
<th>pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactated Ringer's / Hartmann's solution</td>
<td>Sodium 130, chlorine 109, potassium 4, calcium 3, lactate 28</td>
<td>6 to 7.5</td>
</tr>
<tr>
<td>Ringer's acetate</td>
<td>Sodium 130, chlorine 112, potassium 5.4, calcium 0.9,</td>
<td>5.1 to 5.9</td>
</tr>
<tr>
<td></td>
<td>magnesium 1, acetate 27</td>
<td></td>
</tr>
<tr>
<td>Normal saline</td>
<td>Sodium 154, chlorine 154</td>
<td>4.5 to 7</td>
</tr>
<tr>
<td>NormoSol-R, Plasma-Lyte A</td>
<td>Sodium 140, chlorine 98, potassium 5, magnesium 3,</td>
<td>7.4 (other pH formulations available)</td>
</tr>
<tr>
<td></td>
<td>acetate 27, gluconate 23</td>
<td></td>
</tr>
</tbody>
</table>

### Colloid solution

<table>
<thead>
<tr>
<th>Colloid solution</th>
<th>Components (per liter)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin 25%</td>
<td>12.5 g/50 ml human albumin</td>
<td>Human</td>
</tr>
<tr>
<td>Plasma protein fraction 5%</td>
<td>50 g/l selected plasma proteins (88% albumin, 12% α-globulins and β-globulins, 1% γ-globulins), sodium 154 mEq, potassium 0.25 mEq, chlorine 100 mEq</td>
<td>Human</td>
</tr>
<tr>
<td>Hydroxyethylstarch 130/0.4</td>
<td>Hydroxyethylstarch 130/0.4, 6% in 500 ml normal saline (other base solutions available)</td>
<td>Synthesized from amylopectin</td>
</tr>
<tr>
<td>Hydroxyethylstarch 600/0.75</td>
<td>Hydroxyethylstarch 600/0.75, 6% in 500 ml normal saline (other base solutions are available)</td>
<td>Synthesized from amylopectin</td>
</tr>
<tr>
<td>Gelatin 4%</td>
<td>40 g gelatinpolysuccinate</td>
<td>Bovine collagen</td>
</tr>
</tbody>
</table>
FLUID THERAPY

preload

myocardial contractility

Stroke Volume

Heart Rate

Rhythm

afterload

SVR

CO

Hb

O₂

PERFUSION

DO₂

inotropes

vasopressors
By raising oncotic pressures, recruit fluids into the circulation from the ISF.
However, this model is not consistent with the observed effects.

The preferred use of colloidal solutions is based on **rationales that are not supported by clinical evidence**.

Hartog CS et al  Anesth Analg 2011;112:156 –64

The **common belief** that **3 to 4 times more crystalloids than colloids are needed** to achieve similar hemodynamic effects is **not supported by this clinical observation**.

Schortgen F, Brochard L  Crit Care Med 2012 40;9:2709-10
Evidence that colloids provide better survival is lacking

Consensus statement of the ESICM task force on colloid volume therapy in critically ill patients

Intensive Care Med 2012; 38:368–383
The great tragedy of Science, the slaying of a beautiful hypothesis by an ugly fact.

Thomas Huxley
Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP) trial *(HES 200/0.5-0.6)*

....*stopped early for safety reasons.*


...from 6% *HES 130/0.4* to 4% *gelatins* to *crystalloids* only

Fluid resuscitation with *only crystalloids* was *equally effective*, resulted in a more positive fluid balance only on the first 2 days, and was associated with a *lesser incidence of acute kidney injury*.

Patients with severe sepsis assigned to fluid resuscitation with **HES 130/0.42** 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**.

7000 patients who had been admitted to an ICU in a 1:1 ratio to receive either 6% HES (130/0.4, Voluven) in 0.9% NaCl or 0.9% NaCl (saline) for all fluid resuscitation until ICU discharge, death, or 90 days after randomization.
In conclusion, our study does not provide evidence that resuscitation with 6% HES (130/0.4), as compared with saline, in the ICU provides any clinical benefit to the patient. Indeed, the use of HES resulted in an increased rate of renal replacement therapy.
We recommend **not to use HES** with molecular weight $>200$ kDa and/or degree of substitution 0.4 in patients with **severe sepsis or risk of acute kidney injury** and suggest **not to use 6% HES 130/0.4 or gelatin** in these populations.

...not to use colloids in patients with **head injury** and not to administer gelatins and HES in organ donors.
There is **no evidence** from RCTs that resuscitation with **colloids reduces the risk of death**, compared to resuscitation with crystalloids...

......Furthermore, the use of **HES might increase mortality**.

As colloids are not associated with an improvement in survival and are considerably more expensive than crystalloids, **it is hard to see how their continued use in clinical practice can be justified**.

*Cochrane Database of Systematic Reviews, 28 feb 2013, Issue 2.*
\textit{...unlikely therefore that HES provides overall clinical benefit for patients with sepsis.}

Haase N, Perner A et al. BMJ 2013;346:1839

In acutely ill surgical and intensive care patients, fluid resuscitation with \textit{6 \% HES 130 increased the use of renal replacement therapy and mortality.}


Clinical use of HES for acute volume resuscitation is not warranted due to \textit{serious safety concerns.}

Zarychanski R et al. JAMA. 2013;309(7):678-688
...no data from high-quality trials showing that 6 % HES 130 improves any patient-important outcome, and there are clear signals of harm.


6 % HES as part of initial fluid resuscitation for severe sepsis was associated with harm and, as alternatives exist, in our view should be avoided.


Fluid resuscitation practice with HES is associated with an increase in AKI incidence, need of RRT, RBC transfusion, and 90-day mortality in patients with sepsis.

The Boldt debacle

Cardiopulmonary Bypass Priming Using a High Dose of a Balanced Hydroxyethyl Starch Versus an Albumin-Based Priming Strategy

Joachim Boldt, MD
Stephan Suttner, MD
Christian Bornh, MD
Andreas Lehmann, MD
Kerstin Ruhn, MD
Andreas Menges, MD

MATERIALS AND METHODS: The optimal priming solution for cardiopulmonary bypass (CPB) is unclear. In this study, we evaluated the influence of high-volume priming with a crystalloid balanced hydroxyethyl starch (HES) preparation on coagulation, inflammation, and organ function compared with an albumin-based CPB priming regimen. METHODS: In 2 groups undergoing coronary artery bypass grafting, the CPB circuit was proactively and randomly primed with either 1300 mL of 6% HES 130/0.42 in a balanced electrolyte solution (Na⁺ 140 mmol/L, Ca²⁺ 2.5 mmol/L, Mg²⁺ 1 mmol/L, acetate-24 mmol/L, lactate 3 mmol/L, or with 330 mL of 7% human albumin plus 1030 mL 0.9% saline solution (n = 20). RESULTS: Total volume of crystalloid priming fluid was lower in the albumin-based priming group than in the HES priming group (42 ± 1.2 mmol/L vs 42 ± 2.2 mmol/L, P < 0.001). Plasma levels of IL-6, IL-10, and macrophage inflammatory protein-1 were higher after CPB in the albumin-based priming group compared with the HES priming group (P = 0.0032). Urinary excretion of albuminuria, neutrophil gelatinase-associated lipocalin, and cardiac troponin I. CONCLUSIONS: High-volume priming of the CPB circuit with a crystalloid balanced HES solution resulted in reduced inflammation, less endothelial damage, and fewer alterations in renal tubular integrity compared with an albumin-based priming. Coagulation including platelet function was better preserved with high-dose balanced HES CPB priming compared with albumin-based CPB priming.
With the **exclusion of trials conducted by Boldt**

HES administration was significantly associated with **increased mortality and severe kidney injury** (acute renal failure and RRT).

Zarychanski R et al JAMA. 2013;309(7):678-688
The CRISTAL Randomized Trial
Effects of Fluid Resuscitation With Colloids vs Crystalloids on Mortality in Critically Ill Patients Presenting With Hypovolemic Shock

open-labeled fluids
recruitment period of 9 years

Among ICU patients with hypovolemia, the use of colloids compared with crystalloids did not result in a significant difference in 28-day mortality.

Annane D et al.  JAMA 2013;310:1809-17
The Committee confirmed that HES solutions must no longer be used to treat patients with sepsis or burn injuries or critically ill patients, because of an increased risk of kidney injury and mortality.

However the PRAC agreed that HES could continue to be used in patients with hypovolaemia caused by acute blood loss where treatment with alternative infusions solutions known as ‘crystalloids’ alone are not considered to be sufficient.

11.11.2013
HES solutions should not be used for more than 24 hours and patients’ kidney function should be monitored for at least 90 days.

In addition, the PRAC requested that further studies be carried out on the use of these medicines in elective surgery and trauma patients.

EMA 11.11.2013
To the Executive Director of the European Medicines Agency

We are concerned that the European Medicines Agency’s (EMA) Pharmacovigilance Risk Assessment Committee’s (PRAC) recent conclusions on the use of hydroxyethyl starch (HES) will result in harm to patients.

R. Bellomo
J. Bion
S. Finfer
J. Myburgh
A. Perner
K. Reinhart
on behalf of all co-signatories
Retrospective analyses in observational studies found the use of gelatin to be associated with increased renal impairment and the need for transfusion products in patients with severe sepsis and cardiac surgery. Considering that the use of non-protein colloids is not associated with improved clinical outcomes, potentially harmful effects of gelatins should be carefully explored.

All of the evidence was of very low quality.


NICE Intravenous Fluid therapy, dec 2013
Albumin

... if the *oncotic, antiinflammatory, and nitric oxide-scavenging properties of albumin* are of clinical importance, these may be maximally exploited in the conditions that are the most severe, such as cardiovascular dysfunction.
...in view of the **absence of evidence of a mortality benefit** from albumin and the **increased cost** compared to alternatives such as saline, it would seem reasonable that albumin should **only be used within the context of well concealed and adequately powered RCT.**

Cochrane Database of Systematic Reviews. 11, 2012
In patients in the ICU, use of either 4% albumin or normal saline for fluid resuscitation results in similar outcomes at 28 days.
<table>
<thead>
<tr>
<th>Patients</th>
<th>Albumin Group</th>
<th>Saline Group</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>726/3473</td>
<td>729/3460</td>
<td>0.99 (0.91–1.09)</td>
</tr>
<tr>
<td>Trauma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>81/596</td>
<td>59/590</td>
<td>1.36 (0.99–1.86)</td>
</tr>
<tr>
<td>No</td>
<td>641/2831</td>
<td>666/2830</td>
<td>0.96 (0.88–1.06)</td>
</tr>
<tr>
<td>Severe sepsis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>185/603</td>
<td>217/615</td>
<td>0.87 (0.74–1.02)</td>
</tr>
<tr>
<td>No</td>
<td>518/2734</td>
<td>492/2720</td>
<td>1.05 (0.94–1.17)</td>
</tr>
<tr>
<td>ARDS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>24/61</td>
<td>28/66</td>
<td>0.93 (0.61–1.41)</td>
</tr>
<tr>
<td>No</td>
<td>697/3365</td>
<td>697/3354</td>
<td>1.00 (0.91–1.09)</td>
</tr>
</tbody>
</table>

**Figure 2. Relative Risk of Death from Any Cause among All the Patients and among the Patients in the Six Predefined Subgroups.**

The size of each symbol indicates the relative number of events in the given group. The horizontal bars represent the confidence intervals (CI). ARDS denotes the acute respiratory distress syndrome.
Neither of these differences in these subgroups reached statistically significance even without correction for multiple testing.
Until the results of ongoing randomized controlled trials are known, clinicians should consider the use of albumin-containing solutions for the resuscitation of patients with sepsis.


Although a beneficial effect of HAS resuscitation in sepsis is biologically plausible, and this is supported by the post-hoc analysis from the SAFE study, no work has yet dissected out the different facets of the problem in order to convincingly demonstrate its superiority.

Leitch A et al  JICS Volume 14, Number 1, January 2013
In patients with severe sepsis, albumin replacement in addition to crystalloids, as compared with crystalloids alone, did not improve the rate of survival at 28 and 90 days.
Post hoc univariate and multivariate analyses of data from the 1121 patients with septic shock showed significantly lower mortality at 90 days in the albumin group.

Conversely, in the subgroup of patients with severe sepsis without shock, mortality appeared to be higher among those who were treated with albumin.
Dry and die, wet and survive.

J. Boldt
Fluid resuscitation in septic shock: a positive fluid balance and elevated CVP are associated with increased mortality

Emerging data from basic and clinical science have challenged the dogma of large-volume fluid resuscitation in trauma.

Douzinas EE Crit Care Med 2012 Vol. 40, No. 4

Current evidence indicates that initial liberal fluid resuscitation strategies may be associated with higher mortality in injured patients.

An African Lesson

Fluid Expansion as Supportive Therapy (FEAST) trial

the trial was stopped after the recruitment of 3141 patients when bolus-fluid resuscitation with albumin or saline was shown to increase the absolute risk of death at 48 hours by 3.3 % and the risk of death, neurologic sequelae, or both at 4 weeks by 4%.
Excess mortality from boluses occurred in all subgroups of children.

Contrary to expectation, cardiovascular collapse rather than fluid overload appeared to contribute most to excess deaths with rapid fluid resuscitation.

Maitland et al. BMC Medicine 2013, 11:68
The cause of excess deaths was primarily refractory shock and not fluid overload.

These features are consistent with a potential cardiotoxic or ischemia-reperfusion injury following resuscitation with boluses of intravenous fluid.
... interruption of genetically determined catecholamine-mediated host defense responses by the rapid increase in plasma volume, which might result in a reperfusion injury.

..... transient hypervolemia or hyperosmolality might exacerbate capillary leak in patients who are susceptible to intracranial hypertension or pulmonary edema, with fatal consequences.
The pathophysiology of the host response to stress includes activation of the neurohumoral system that is targeted at conserving both sodium and water.

The amount and type of fluid administered by clinicians to critically ill patients affects this acute adaptative response and, through this, may affect subsequent survival and recovery.

Saxena MK Crit Care Res 2013 15; 2:75-76
...discontinuation of the practice of bolus- fluid resuscitation in patients with febrile illness due to medical causes and impaired perfusion or compensated shock must be recommended.
Rapid crystalloid infusion in volunteers results in elevated plasma levels of hyaluronic acid and may therefore be injurious


Acute myocardial infarction is associated with endothelial glycocalyx and cell damage and a parallel increase in circulating catecholamines

A critique of fluid bolus resuscitation in severe sepsis

Hilton and Bellomo  Critical Care 2012, 16:302

.... recommendations are only based on expert opinion and lack adequate experimental or controlled human evidence.
Saline is not “physiologic”

The forgotten ion: chloride
The end of saline solutions?

Lactated Ringer’s solution is perfectly reasonable as an alternative, and if clinicians were to make that change, one would expect to see a drop in the rate of AKI and dialysis.

J. Kellum
Infusion of normal saline, with its supraphysiological chloride content, is associated with higher serum chloride concentrations and metabolic acidosis, as well as renal vasoconstriction in animal and human models. Infusion of 'balanced' crystalloids is not linked to such changes. Although data on clinical outcomes associated with crystalloid infusion are heterogeneous, advantages of balanced salt solutions might include a lower need of blood products, and lower incidence of renal replacement therapy, hyperkalaemia and postoperative infections. Taken together, a critical appraisal of the data suggests that balanced salt solutions deserve consideration as infusates of first choice.

Humans evolved as long distance persistence hunters on the arid savannahs of south and east Africa.

....we are delayed drinkers ....

.....there is no need to completely replace any fluid deficit as it develops either at rest or during exercise.

Instead people optimise their hydration status by drinking according to the dictates of thirst.

Noakes TD  BMJ 2012;344:e4171
Administration of resuscitation fluid requires as much thought and care as the administration of any other potentially lethal drug.
...if the ideal randomized, controlled trial definitively reported the truth, would clinical practice change?

Han J, Martin GS  Critical Care 2010, 14:1006
Figure 2 Percentage of fluid resuscitation episodes given as crystalloid, colloid or blood product according to country*. Crystalloid; Colloid; Blood. *Difference in proportions given crystalloid, colloid or blood between countries, respectively $P < 0.001$, $P < 0.001$, $P < 0.001$
<table>
<thead>
<tr>
<th></th>
<th>ml</th>
<th>€</th>
</tr>
</thead>
<tbody>
<tr>
<td>NaCl 0,9%</td>
<td>1000</td>
<td>0.72</td>
</tr>
<tr>
<td>NaCl 0,9%</td>
<td>500</td>
<td>0.43</td>
</tr>
<tr>
<td>Ringer Ac</td>
<td>500</td>
<td>0.48</td>
</tr>
<tr>
<td>Voluven 500 ml</td>
<td>500</td>
<td>6.27</td>
</tr>
<tr>
<td>Alb 20% 50 ml</td>
<td>20</td>
<td>15.20</td>
</tr>
<tr>
<td>Emagel 500 ml</td>
<td>500</td>
<td>3.69</td>
</tr>
</tbody>
</table>

AOU, Udine, Italy 2012
The difficulty lies, not in new ideas, but in escaping old ones, which ramify, for those brought up with them, as most of us have been, into every corner of our minds.

John Maynard Keynes
Averceli, i clorioni
Tradizionalisti → Omeostasi
Modernisti
Post-modernisti → Allostasi
The allostatic concept emphasizes that the brain predicts the most likely demand during a stress response, and therefore modifies physiological variables to values that match anticipated demand.

Healthy physiological values routinely targeted in the critically ill are not related to these anticipatory demands and are thus likely to be inappropriate.

Cuesta JM, Singer M Crit Care Med 2012; 40:1-7
“Should we just carry on doing *what we have always done*, which is essentially giving *too much fluid*?”

“Or should we make some effort to be a bit more thoughtful in what we are doing and *reduce the amount of fluid*?”
Quantitative toxicity (fluid overload) is associated with adverse outcomes and can be mitigated when fluid therapy based on functional hemodynamic parameters that predict volume responsiveness and minimization of non-essential fluid. Qualitative toxicity (fluid type),

Fluid Therapy Might Be
More Difficult Than You Think

Hydration at 1 L per day did not improve symptoms, quality of life, or survival compared with placebo.
Relatively small increases in total body water can be fatal.

A 2% increase in total body water produces generalised oedema that can impair athletic and mental performance; greater levels of overhydration result in hyponatraemic encephalopathy—severe cerebral oedema that produces confusion, seizures, coma, and ultimately death from respiratory arrest.
Issues influencing IV fluid prescriptions

Cardiac dysfunction
Increased vulnerability to fluid and sodium overload with consequent congestive failure. Potential for hypokalaemia from diuretics and renin/angiotensin/aldosterone activation, or hyperkalemia from potassium sparing diuretics. Severe cardiac patients may also have consequent renal or liver impairment.

Renal disease
Impaired clearance or excessive losses of both fluids and electrolytes in both acute and chronic kidney disease. Disordered calcium and phosphate handling in chronic renal failure.

Gastrointestinal problems
High losses of both fluid and electrolytes are seen in many GI problems, and patients with ileus can sequester large volumes of electrolyte rich fluid.

Liver disease
Very abnormal fluid and electrolyte handling with a tendency for marked sodium and water retention due to complex pathophysiological changes including hyper-aldosteronism. Moderate to severe renal impairment is seen in many patients – the hepato-renal syndrome).

Respiratory disease
High respiratory fluid losses but many patients are vulnerable to fluid overload. SIADH common. Cor-pulmonale makes patients vulnerable to venous circulatory overload, sometimes with hepatic congestion and dysfunction.

Neurology
Hypothalamic or pituitary disease can severely damage fluid regulatory mechanisms. High concentration IV saline is sometime administered to try to reduce intracranial pressure.

Dermatology
Burns and other extensive skin inflammatory problems can lead to very high fluid/plasma loss.

Endocrine
Problems including diabetes mellitus, Addison’s disease and SIADH can markedly alter fluid and electrolyte handling.
For every complex problem there is a simple solution... and it is wrong.
Less SAFE than presumed?

In this post hoc study of critically ill patients with traumatic brain injury, fluid resuscitation with albumin was associated with higher mortality rates than was resuscitation with saline.

Our findings show no clinical benefit of 25% albumin in patients with ischaemic stroke; however, they should not discourage further efforts to identify effective strategies to protect the ischaemic brain, especially because of preclinical literature showing convincing proof-of-principle for the possibility of this outcome.