Salt, Albumin and Water: The Physiology of Fluid Management
Fluid Management: An important clinical issue

Introduction

- **Under- / Over-hydration** cause significant morbidity and mortality (e.g. pulmonary oedema, AKI). The problem is widely recognised by healthcare professionals.

- **Extent**: difficult to quantify because it is often multifactorial + under-reported.

- **Mortality**: ~9000 deaths/yr due to poor fluid management in the USA.

- **Morbidity**: fluid-related complications occur in 17-54% of post-operative patients (↑ length of stay 3-14 days).

Why is fluid management so poor?

Potential causes

• **Education**: many errors due to inadequate knowledge in junior medical staff (e.g. N/Saline sodium content). Senior clinicians not much better!

• **Poor supervision / low priority**: >80% post-operative fluid prescriptions by junior clinicians (with no senior reviews).

• **Poor documentation**: <50% fluid charts adequate (NCEPOD). Fluid administration rate considered unimportant in one study!
How competent are YOU?

a. How much sodium is in a litre of normal saline (in mmol)?
   a. 74   b. 104   c. 124   d. 134   e. 154

b. How much sodium does a normal person require daily (in mmol)?
   a. 10-60   b. 70-120   c. 130-180   d. 190-240   e. 250-300

c. What is the maximum urine concentration that can be generated by normal kidneys (mOsm/L)?
   a. 300   b. 500   c. 1000   d. 1500   e. 2000

d. 4 hours after administration of 1L of 5% dextrose fluid, how much is left in the vascular compartment (in mls)?
   a. ~70mls   b. ~150mls   c. ~225mls   d. ~300mls   e. ~350mls

e. How much water is bound to 1 gram of albumin (in mls)?
   a. ~6   b. ~12   c. ~18   d. ~24   e. ~30
What are we assessing in the previous questions?

- What is in the fluid administered?
- What are the normal daily fluid + electrolyte requirements?
- How is the fluid (electrolyte) given, subsequently excreted?
- Where does the fluid administered go (i.e. what is the volume of distribution and the destination)?
- How is the intravascular volume maintained in health and during pathophysiological insults?
So how do we do?

“Well, it’s not a good sign, that’s for sure ...”
# Basic Physiology: Fluid distribution

## Total Body water
42 litres (~42kg)

### Extracellular fluid (ECF) ~ 17 litres
Composition (in mmol/L): \( \text{Na}^+ 140, \text{chloride} 105, \text{K}^+ 3.7, \text{phosphate} 1 \)

<table>
<thead>
<tr>
<th>Vascular Space (5 litres)</th>
<th>Interstitial Space</th>
<th>Intracellular fluid (ICF) ~ 25 litres</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma (non cellular blood) 3 litres</td>
<td>Interstitial Fluid (ISF) ~14 litres</td>
<td>Composition (in mmol/L): Na+ 10, chloride 3, ( \text{K}^+ 155, \text{phosphate} 105 )</td>
</tr>
</tbody>
</table>

### Colloids (i.e proteins + haemaglobin) pull water into blood vessels

Water distributes through the ICF and ECF

Sodium pumped out of cells

- \( \text{Na}^+ \) = Sodium
- \( \text{K}^+ \) = Potassium
- \( \text{H}_2\text{O} \) = Water
- Albumin molecule
- Collagen+hyaluronic fibres

Repulsion of albumin by negative charges
**Crystalloid Fluid Distribution**

Distribution of body water

- **Total Body water**
  - 42 litres (~42kg)

- **Extracellular fluid** (ECF) ~17 litres
- **Intracellular fluid** (ICF) ~25 litres
- **Interstitial Fluid** (bathes cells) (ISF) ~14 litres
- **Plasma** (non cellular component of blood) ~3 litres

Sodium pumped out of cells (i.e. smaller volume of distribution)

Water distributes in both ICF + ECF (bigger volume of distribution)

Colloids (i.e proteins + blood) pull H₂O into the intravascular compartment
**Crystalloid Fluid Distribution**

Normal person given 1L of:

<table>
<thead>
<tr>
<th>Fluid</th>
<th>Amount in circulation (4hrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5% Dextrose</td>
<td>( \frac{3}{42} \times 1L = 71 \text{ mls} )</td>
</tr>
<tr>
<td>N/saline</td>
<td>( \frac{3}{17} \times 1L = 176 \text{ mls} )</td>
</tr>
</tbody>
</table>
Normal Daily Fluid + Electrolyte Requirements

**Fluid + electrolyte losses**

Urine water (70mls/hr = 70 x 24) = ~ 1500mls water/day
Urine electrolyte losses = Na⁺ ~70-120mmol; K⁺ ~40-70mmol
Insensible fluid losses: breathing = ~ 400mls/day (pure water)
Sweat = ~ 100mls/day (water + some salts)

**Daily water requirement**

= 1500mls (urine) + 500mls (breathing/sweat) = ~2000 mls/day (30mls/kg)

**Daily electrolyte requirements**

= 70-120mmol Na⁺ + 40-70mmol K⁺

**Possible fluid regime**

= 1L N/saline (or BPS) + 1L 5% dextrose (+20mmol KCl per 1L bag)
Normal Fluid + Electrolyte Output

Normal
(renal concentrating ability: max ~1000 mOsmol/L)

<table>
<thead>
<tr>
<th>Fluid + Solute LOAD (24hrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
</tr>
<tr>
<td>Solute mmol</td>
</tr>
<tr>
<td>NaCl</td>
</tr>
<tr>
<td>KCl</td>
</tr>
<tr>
<td>N₂ urea waste</td>
</tr>
<tr>
<td>Total Solute Load</td>
</tr>
</tbody>
</table>

During illness + after 6L iv N/saline with impaired renal concentrating ability (max ~500 mOsmol/L)

<table>
<thead>
<tr>
<th>Fluid + Solute LOAD (24 hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N Saline (Water)</td>
</tr>
<tr>
<td>Solute mmol</td>
</tr>
<tr>
<td>NaCl (6L)</td>
</tr>
<tr>
<td>N₂ urea waste</td>
</tr>
<tr>
<td>Total Solute Load</td>
</tr>
</tbody>
</table>

All the daily solute load excreted + fluid balanced

Fluid + Solute OUTPUT (24hrs)
1. Urine 1.0L (impaired renal function):
   - max urine conc 500 mOsmol/L
   - can only excrete 500 mOsmol waste
   - 2348 mOsmol load retained in body

2. Insensible Loss 1.5L

2348 mOsmol waste and 3.5L of water retained
Assessment

Requirements:
- replace normal fluid + electrolyte losses
- adjust for additional losses/gains depending on pathology

Assessment of fluid + electrolytes
- take account of
  - clinical features, pathology, ECF status
  - electrolytes: Na\(^+\), urea, HCO\(_3\), Cl\(-\)
  - fluid losses, renal function

- adjustments required for failure of feeding
- patients on CVVH do not need maintenance fluids
Assessing Fluid Requirements: Vomiting/NG tube losses

Normal/postoperative patient: vomits (or NG tube output) 2L/day
Vomit contains $\text{Na}^+ + \text{H}^+ + \text{Cl}^-$ → causes hypokalaemic alkalosis

**Fluid Replacement/day**

$= 1500\text{mls urine} + 500\text{mls breathing/sweat}$

$= 4000\text{mls of water daily}$

**Electrolyte Replacement/day**

$= 400\text{mmol Na}^+ (\text{vomit/urine/sweat}) + \sim 200\text{mmol K}^-$

Kidney corrects alkalosis

A fall in serum $\text{K}^+$ of 0.5

**Possible fluid regime**

$= 2.0\text{L Normal Saline} +$
Assessing Complex Fluid Requirements: Equilibration

e.g. severe dehydration

Normal patient in the desert for 3 days
Insensible loss in breath = 2-3L/day (= pure water)
U+Es: Na+ = 173mmol/L, Urea 26.7mmol/L, Creat 240umol/L

What Fluid would you give?
= water loss 9-10L = ? How much water

Electrolyte Replacement

= electrolyte conservation…How much electrolyte?

Time has allowed equilibration between extra- and intracellular fluids
Give Normal Saline to prevent central pontine demyelination!!
Basic Physiology: Albumin Cycle

**ALBUMIN CYCLE**

120g of albumin returns to the blood via the lymphatics daily

120g / day albumin (○) leaks into ICF.

**VASCULAR POOL 120g**

**EXTRA VASCULAR POOL 150g**

Surgery + Sepsis
Increase leakage to 300-700g/day

Severe illness = Acute phase protein production instead of albumin

Half life of albumin 21 days = 15g loss of albumin day

120g of albumin synthesised by liver

15g / day albumin leaks into ICF.

Gosling P. Care of the Critically ill 1995;11:57
Maintaining Intravascular Volume

Intravascular volume = 5L
(haematocrit 0.4 = 2L red blood cells + 3L plasma)

- 1g albumin binds 18mls water
- 120g albumin in circulation
  \[= 120 \times 18 \text{mls} = 2160 \text{mls} \text{ water bound in intravascular space}\]

About 750mls water bound by haemoglobin / globulins
The relationship between cardiac output and venous return.

Right Atrial Pressure

STROKE VOLUME (SV)
depends on venous return, ventricular EDV and contractility

STRESSED VOLUME (↔) increases Venous return by up to 30%

UNSTRESSED VOLUME (↔) is a physiological reservoir

VENOUS BLOOD = 70% blood volume

CARDIAC OUTPUT (mls/min) =
HR (beats/min) x SV (mls)

Mean systemic pressure
Mean arterial pressure
Perfusion pressure

ARTERIAL BLOOD = 20% blood volume
Resuscitation
What type of fluid + how much?

Type of fluid

- 5% Dextrose vs N/saline vs Balanced Physiological solutions
- Normotonic vs hypotonic vs hypertonic
- Crystalloid vs Colloid

How much depends on:

- Disease process
- Volume of resuscitation
- Timing
- Comorbid conditions etc
Type of fluid

**Hyperchloreaemic acidosis (HCMA)**

- Excessive Cl⁻ ion administration causes HCMA
- Accounts for up to 1/3<sup>rd</sup> of the acid load (e.g. sepsis)
- HMCA increased in all studies (e.g. postoperative) comparing N.Saline vs Balanced Physiological Solutions (e.g. Hartmann’s)

**Does this make a difference?**

HCMA causes:

- Decreased mental acuity
- Abdominal discomfort, nausea & vomiting
- Reduced urine flow

Kellum JA et al. *Crit Care* 2004; 8: 331-336
Crystalloids vs. colloids in fluid resuscitation: A systematic review.

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>#Pts</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lowe</td>
<td>1977</td>
<td>141</td>
<td>0.68 (0.14 - 3.24)</td>
</tr>
<tr>
<td>Lucas</td>
<td>1978</td>
<td>52</td>
<td>0.07 (0.00 - 1.20)</td>
</tr>
<tr>
<td>Boutros</td>
<td>1979</td>
<td>24</td>
<td>2.22 (0.12 - 41.20)</td>
</tr>
<tr>
<td>Virgilio</td>
<td>1979</td>
<td>29</td>
<td>1.07 (0.07 - 15.54)</td>
</tr>
<tr>
<td>Moss</td>
<td>1981</td>
<td>36</td>
<td>2.43 (0.11 - 55.89)</td>
</tr>
<tr>
<td>Goodwin</td>
<td>1983</td>
<td>50</td>
<td>0.27 (0.09 - 0.86)</td>
</tr>
<tr>
<td>Modig</td>
<td>1983</td>
<td>23</td>
<td>1.08 (0.02 - 50.43)</td>
</tr>
<tr>
<td>Rackow</td>
<td>1983</td>
<td>26</td>
<td>1.23 (0.71 - 2.11)</td>
</tr>
<tr>
<td>Shires</td>
<td>1983</td>
<td>18</td>
<td>1.00 (0.02 - 45.63)</td>
</tr>
<tr>
<td>Metlici</td>
<td>1984</td>
<td>32</td>
<td>0.82 (0.52 - 1.29)</td>
</tr>
<tr>
<td>Sade</td>
<td>1985</td>
<td>83</td>
<td>1.83 (0.04 - 90.08)</td>
</tr>
<tr>
<td>Karanko</td>
<td>1987</td>
<td>32</td>
<td>2.37 (0.10 - 54.06)</td>
</tr>
<tr>
<td>Dawidson</td>
<td>1991</td>
<td>20</td>
<td>1.00 (0.07 - 13.87)</td>
</tr>
<tr>
<td>London</td>
<td>1992</td>
<td>90</td>
<td>0.22 (0.01 - 3.93)</td>
</tr>
<tr>
<td>Pockaj</td>
<td>1994</td>
<td>76</td>
<td>0.90 (0.02 - 44.34)</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>732</td>
<td>0.86 (0.63 - 1.17)</td>
</tr>
</tbody>
</table>

Favors Crystalloids

Favors Colloids

# VISEP Trial (Hemohes vs. Crystalloid) Morbidity

<table>
<thead>
<tr>
<th></th>
<th>Crystalloid</th>
<th>HES</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVVH</td>
<td>19%</td>
<td>31%</td>
<td>0.001</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>23%</td>
<td>35%</td>
<td>0.003</td>
</tr>
<tr>
<td>Transfusion</td>
<td>69%</td>
<td>76%</td>
<td>0.07</td>
</tr>
<tr>
<td>Bleeding events</td>
<td>3.6%</td>
<td>5%</td>
<td>0.52</td>
</tr>
<tr>
<td>Transfused RBC’s</td>
<td>4</td>
<td>6</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
VISEP Trial (HES vs. Crystalloid)

- Subgroup HES survival -

HES ≤ 22 ml/kg BW/day n=162

HES > 22 ml/kg BW/day * n=99

P < 0.0001

* on at least one study day
How much fluid?

Trauma: Iatrogenic damage due to fluids

Permissive hypotension

Cannon W, Fraser J, Cowell E.
The Preventative Treatment of Wound Shock. JAMA 1918

Bickell WH et al. 'Immediate vs. delayed fluid for hypotensive patients with penetrating torso injuries' N Engl J Med 1994
How much fluid? Sepsis

- Capillary permeability causes fluid and albumin leakage.
- Fluid loss: into ECF = tissue oedema; alveoli = hypoxaemia
- Reduced intravascular albumin (40g/dl→10g/dl reduces bound water from 2.2L to 0.6L) causes hypovolaemia
- Vasodilation + intravascular hypovolaemia cause hypotension
- Assessment of this hypovolaemia can be difficult: Complex cases require invasive monitoring

Best survival outcome
But associated morbidity cost
= tissue oedema
= alveolar oedema, increased shunt and hypoxaemia
# How much fluid? Outcome of AAA repair

<table>
<thead>
<tr>
<th></th>
<th>Hospital 1</th>
<th>Hospital 2</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n=89</strong></td>
<td><strong>18</strong></td>
<td><strong>96</strong></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Use of PAC - %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crystalloid - 1st 24 hrs</td>
<td>2300</td>
<td>3000</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>mls, med</td>
<td>med</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colloid - 1st 24 hrs mls</td>
<td>1500</td>
<td>4775</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>med</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine - 1st 24 hrs mls</td>
<td>2000</td>
<td>2410</td>
<td>ns</td>
</tr>
<tr>
<td>med</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal Failure - %</td>
<td>6</td>
<td>28</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mortality - %</td>
<td>9</td>
<td>28</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

How much fluid? Comparison of 2 Fluid-Management strategies (liberal vs conservative) in ALI

- 1,000 patients
- 71% Pneumonia or Sepsis
- 14% Aspiration
- >1/3rd still in shock on entry into study

Figure 3. Probability of Survival to Hospital Discharge and of Breathing without Assistance during the First 60 Days after Randomization.
Conclusions

• Fluid therapy is a powerful intervention and timing is key
• Maintenance requirements are corrected for additional losses or gains
• The use of more ‘physiologically balanced’ intravenous fluids may be associated with an improved outcome
• Colloids may be associated with worse outcome
Fluid Replacement

OR