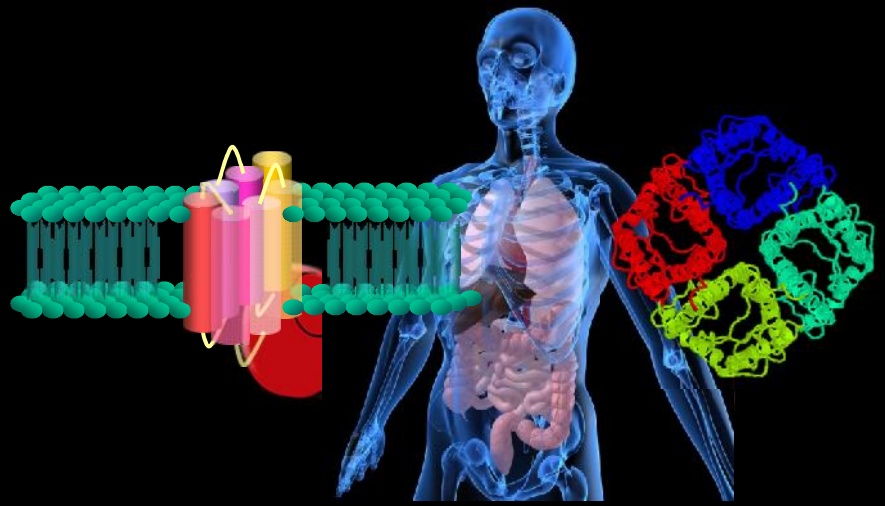
ABCD Meeting, Manchester, April 2016

Hyponatraemia

.....for Homer Simpson



Steve Ball

Central Manchester University Hospitals NHS Trust &
Manchester Academic Health Science Centre, UK

Manchester Academic Health Science Centre

MANCHESTER 1824 The University of Manchester

NHS

Manchester Academic Health Science Centre

MANCHESTER 1824 The University of Manchester

NHS

Hyponatraemia

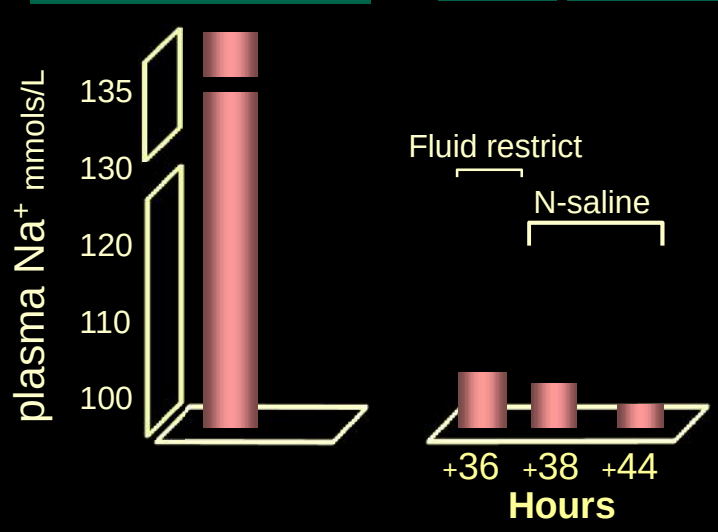
everybody's problem…….

- The clinical context
- Guidance
- Approaches to management
- Moving forward

Manchester Academic Health Science Centre
The University of Manchester

What best to do?

Susan's story



Manchester Academic Health Science Centre
The University of Manchester

When we aren't sure
why we struggle with guidance

- Too complex
  - more information than need
- Too simple
- It doesn't say anything useful
- Contradictory
- …..Evidence-based?

Hyponatraemia
guidance on diagnosis & management

The Intensive Connection

European Society of Endocrinology
the European hormone society

Clinical practice guideline on diagnosis and treatment of hyponatraemia

Goce Spasovski, Raymond Vanholder, Bruno Allolio, Djillali Annane, Steve Ball,
Daniel Bichet, Guy Decaux, Wiebke Fenske, Ewout Hoorn, Carole Ichai, Michael Joannidis,
Alain Soupart, Robert Zietse, Maria Haller, Sabine van der Veer, Wim Van Biesen and Evi Nagler
on behalf of the Hyponatraemia Guideline Development Group

European Journal of Endocrinology (2014) 170, G1–G47

Manchester Academic Health Science Centre

The University of Manchester

Guidance methodology

grade system for recommendations

Recommendation

Strength of recommendation	**1**	Strong
	2	Weak

Quality of evidence	A	High
	B	Moderate
	C	Low
	D	Very low

BMJ **Guyatt GH *et al*. 2008.**
GRADE: an emerging consensus on rating quality of evidence & strength of recommendations
British Medical Journal 336: 924-926.

ERBP

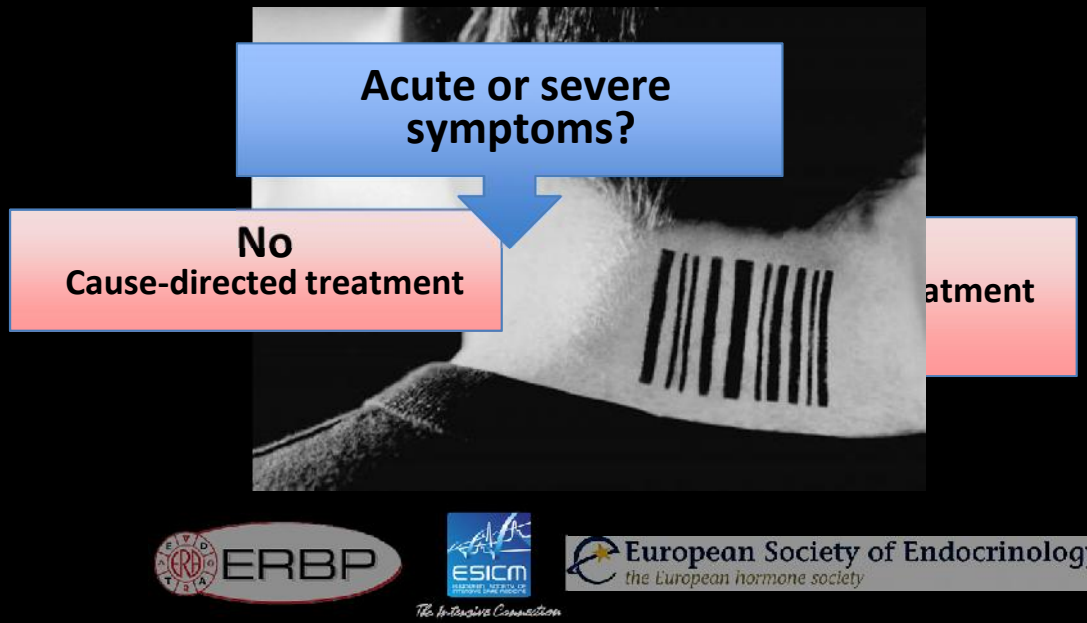
ESICM
The Intensive Connection

European Society of Endocrinology
the European hormone society

Manchester Academic Health Science Centre
MANCHESTER 1824
The University of Manchester
NHS

Recommendations

management pathway



ERBP

ESICM
The Intensive Connection

European Society of Endocrinology
the European hormone society

Treatment recommendations
hyponatraemia with severe symptoms

***iv* infusion 150 mL** … **…aline or equivalent** (1D)

Close m… …t (not graded)

***iv* infusion 150 mL** … **…aline or equivalent** (2D)

Repeat twice or until 5mmol/L increase in Na^+ (2D)

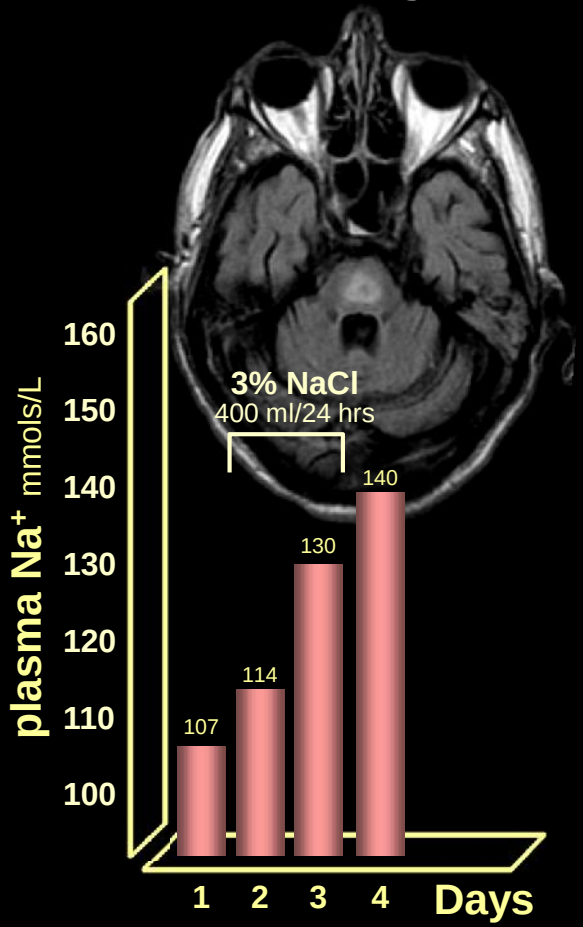
Follow up management after 5 mmol/L rise Na^+
Stop infusion hypertonic saline (1D)
Keep *iv* line open minimum volume 0.9% saline (1D)
Start diagnosis-specific treatment (1D)
Limit increase Na^+ to 10 mmol/L first 24 hours (1D)
Limit increase Na^+ to additional 8 mmol/L every 24 hours thereafter until Na^+ 130 mmol/L (1D)
Check Na^+ 6 hours, 12 hours & daily until stable under stable treatment (1D)

ERBP ESICM The Intensive Connection European Society of Endocrinology the European hormone society

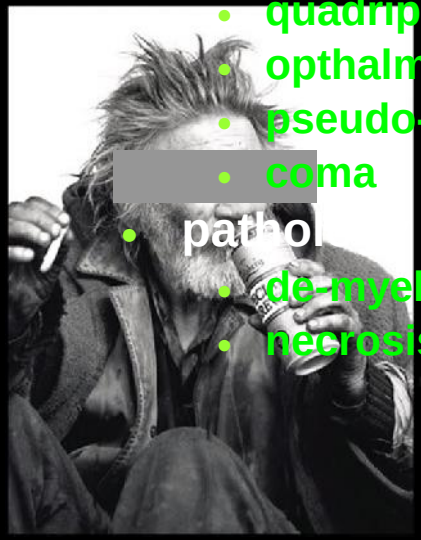
Manchester Academic Health Science Centre
MANCHESTER 1824 The University of Manchester NHS

Correcting the Na^+....

John's story

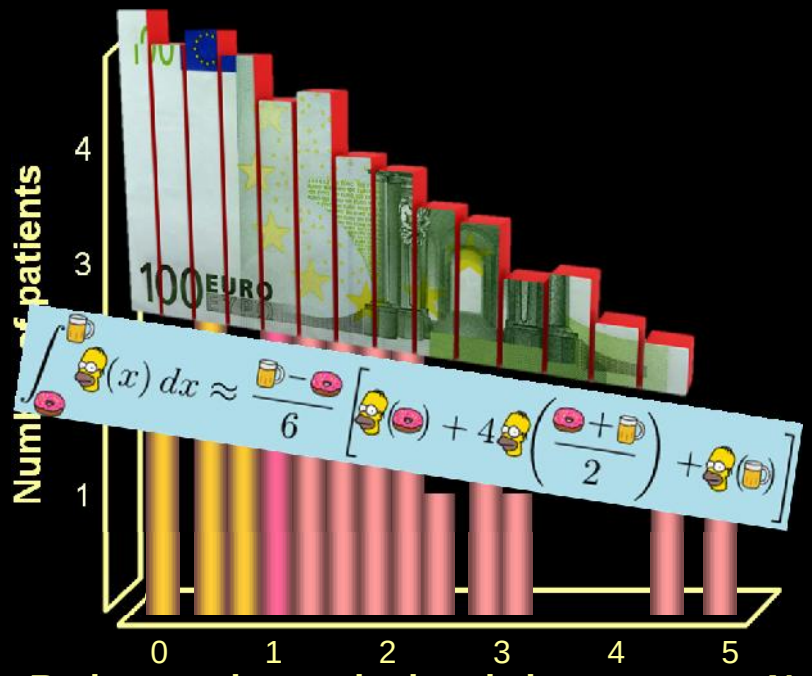


- **Osmotic demyelination syndrome**
  - neurology
    - quadriplegia
    - opthalmoplegia
    - pseudo-bulbar palsy
    - coma
  - pathology
    - de-myelination
    - necrosis

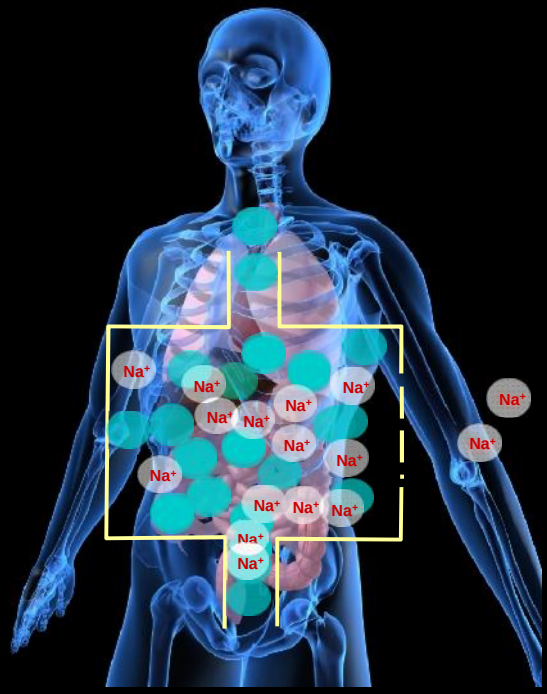


The Androgue-Madias formula

static models don't fit dynamic situations



Ratio actual *vs.* calculated change serum Na^+



- **Change serum Na^+ with 1L infusate**

$$\frac{{}_{infusate}Na^+ - {}_{serum}Na^+}{\text{total body water} + 1}$$

CJASN

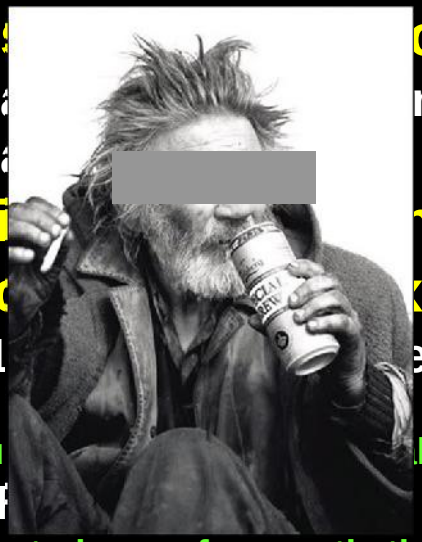
Mohmand HK *et al*. 2007.
Hypertonic saline for hyponatraemia: risk of inadvertent overcorrection.
Clinical Journal American Society of Nephrology 2: 1110-1117.

Manchester Academic Health Science Centre
MANCHESTER 1824
The University of Manchester
NHS

Treatment recommendations

what if hyponatraemia is corrected too rapidly?

- **Recommendation: …on to re-lower Na^+** (1D)
  - if serum Na^+ increa… …n first 24 hours
  - if serum Na^+ increa… … any 24 hours thereafter
- **We recommend di… …ngoing treatment** (1D)
- **We recommend co… …xpert**
  - discuss infusion 1… …e-free water (1D)
    - over 1 hour
    - strict monitoring u… …lance
  - discuss *i.v.* DDAVP…
    - should not be repeated more frequently than 8 hourly

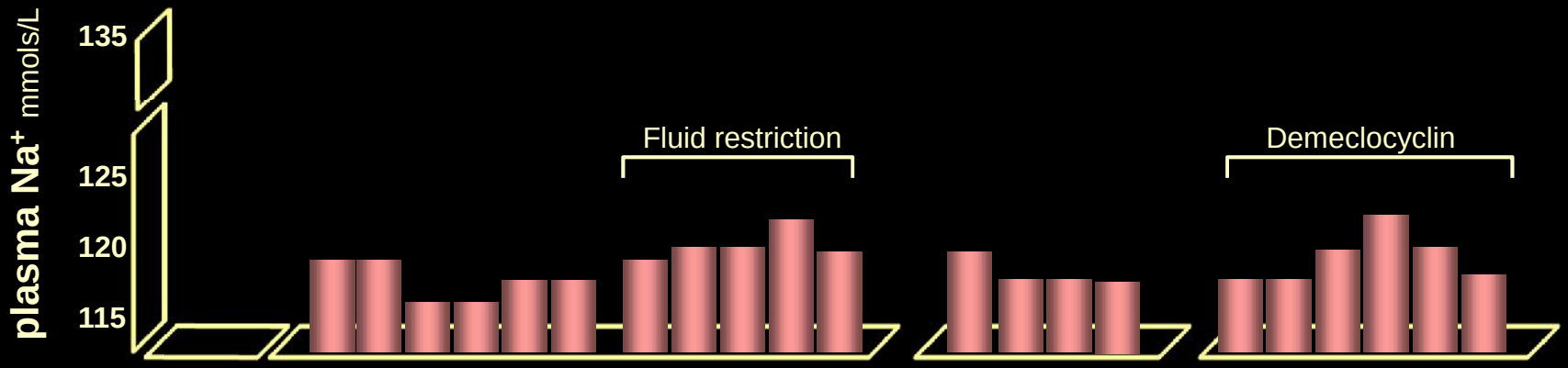


ERBP ESICM The Intensive Connection European Society of Endocrinology the European hormone society

Manchester Academic Health Science Centre
MANCHESTER 1824 The University of Manchester NHS

Important….but not urgent

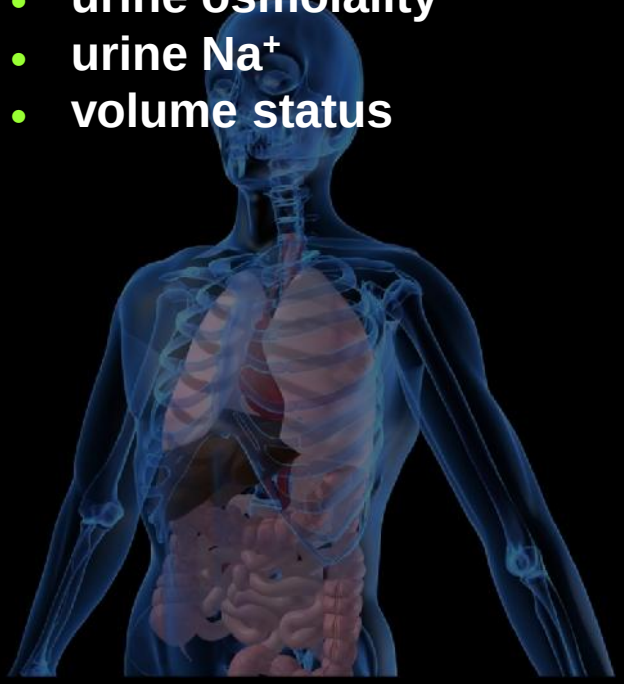
Frank’s story

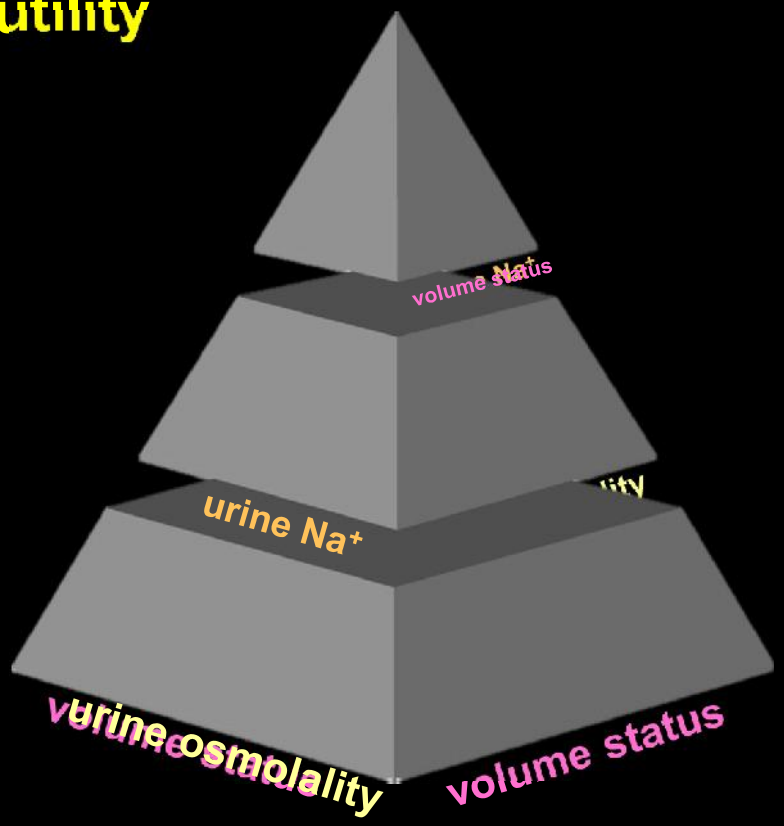


Diagnostic recommendations

the evidence base

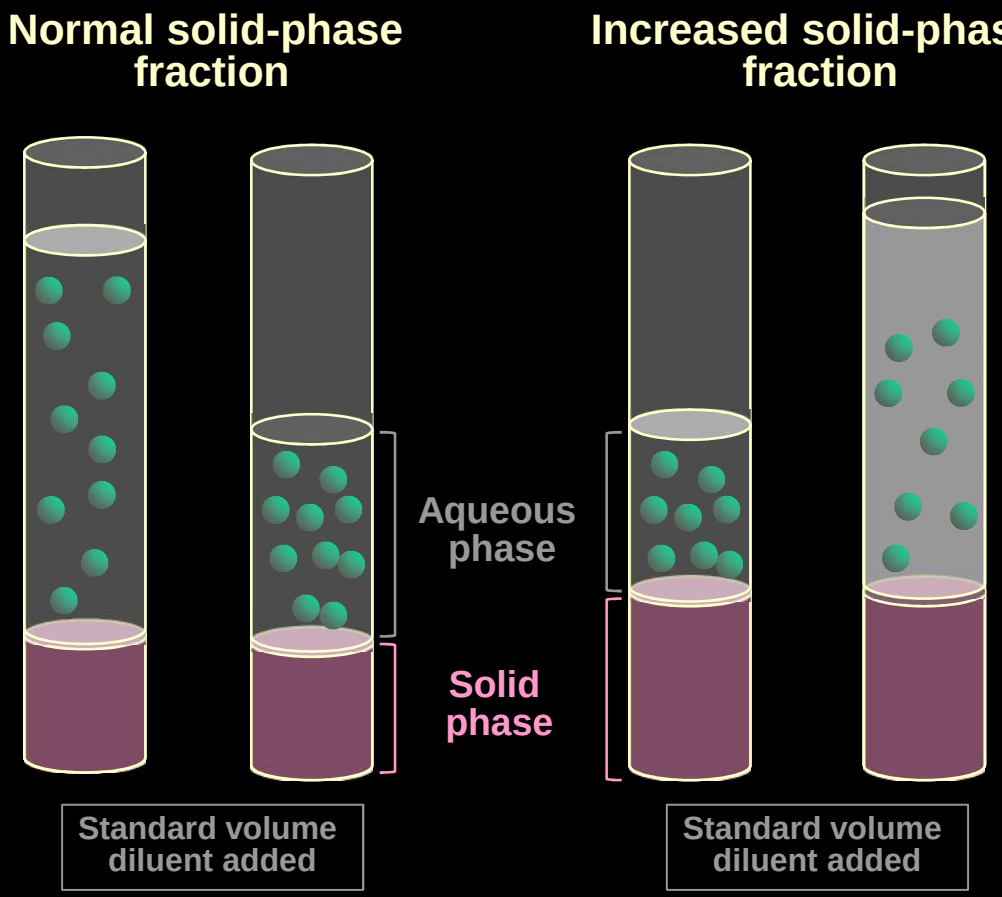
- **Weighting proportionate to utility**
  - urine osmolality
  - urine Na^+
  - volume status





Effect of solid-phase components

low Na^+ artifacts in dilution-based methods

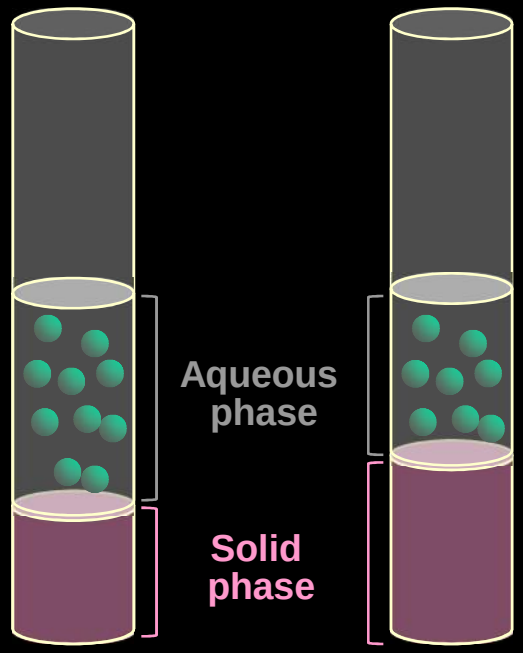


Manchester Academic Health Science Centre
The University of Manchester

Hyponatremia

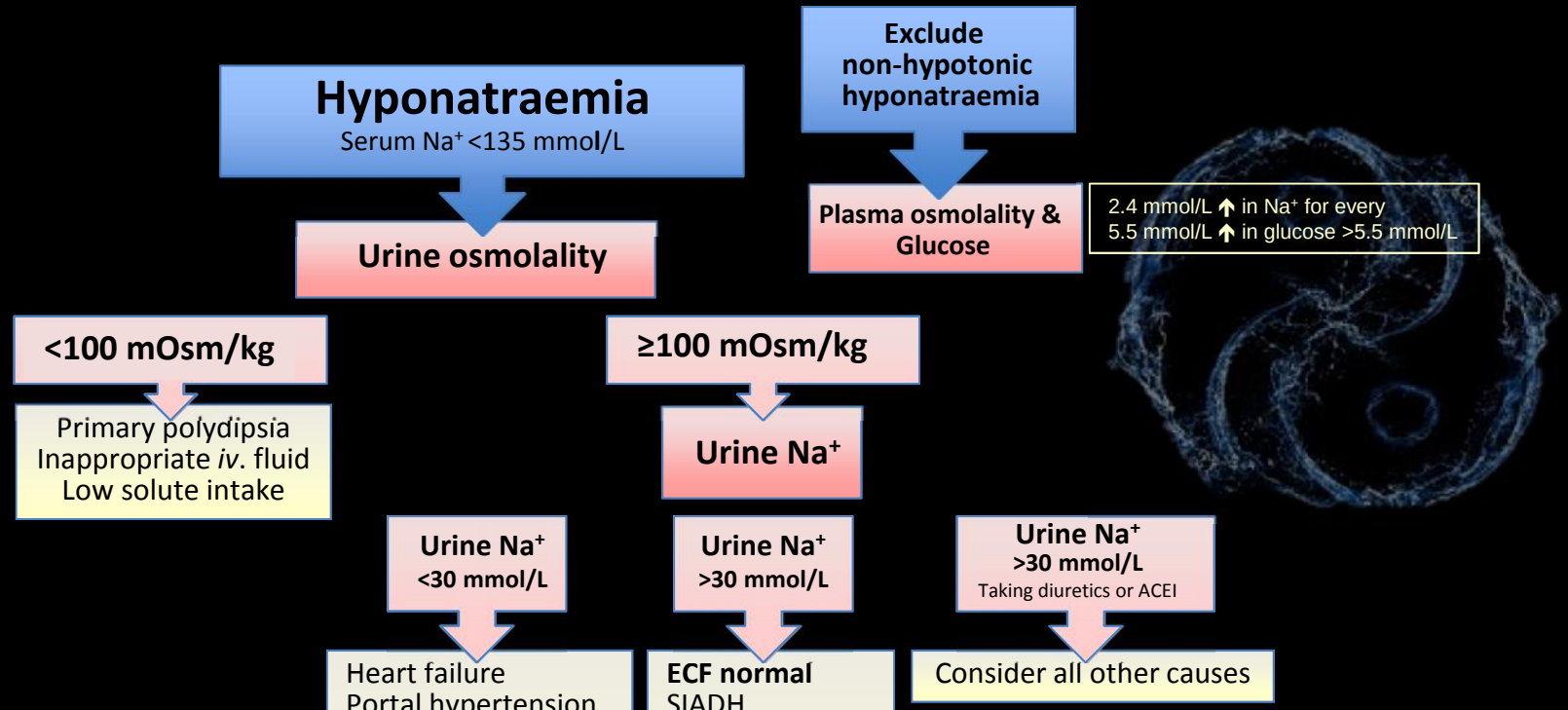
Na^+ measurement by direct potentiometry

- **No dilution step**
  - **independent of solid phase fraction**



Diagnostic recommendations

working out the cause



ERBP

ESICM
The Intensive Conversation

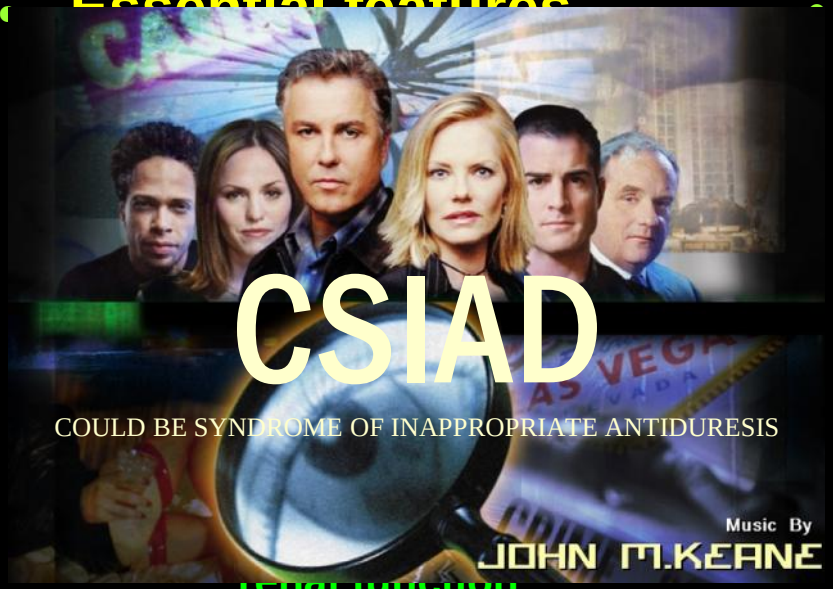
European Society of Endocrinology
the European hormone society

Manchester Academic Health Science Centre
MANCHESTER 1824
The University of Manchester
NHS

Diagnosis of SIADH

AVP fingerprint when there should be none

- Essential features
- Suppo
  - seru
    - <
  - failu
  - corre
  - fract
  - fract
  - fract
  - seru
    - <



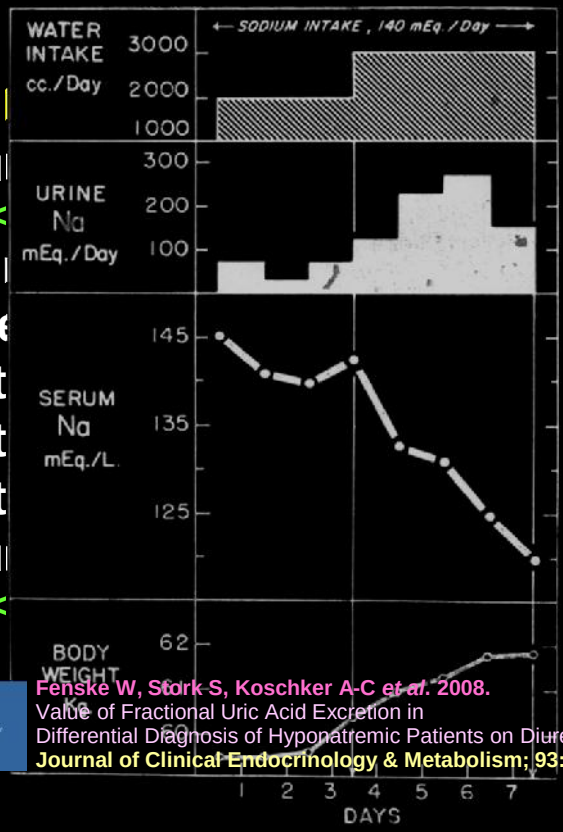
renal function

ine

%

%

%



JCEM

Fenske W, Stork S, Koschker A-C *et al.* 2008.
Value of Fractional Uric Acid Excretion in Differential Diagnosis of Hyponatremic Patients on Diuretics.
Journal of Clinical Endocrinology & Metabolism; 93: 2991-2997.

The American Journal of Medicine

Schwartz WB, Bennett W, Curelop S, Bartter FC. 1957
A syndrome of renal sodium loss and hyponatremia probably resulting from inappropriate secretion of antidiuretic hormone.
The American Journal of Medicine 23: 529

Treatment recommendations

hyponatraemia without symptoms I

- **General management**
  - **stop non-essential fluids & contributing factors** (Not graded)
  - **we recommend cause-specific treatment** (1D)
  - **in mild hyponatraemia, we suggest against treatment with sole aim of increasing serum Na^+ concentration** (2C)
  - **in moderate or profound hyponatraemia**
    - **avoid increase in Na^+ >10mmol/L during first 24 hours** (1D)
    - **avoid increase Na^+ >8mmol/L per 24 hours thereafter** (1D)
    - **check Na^+ 6 hourly until stable on stable treatment** (1D)
  - **in case of unresolved hyponatraemia**
    - **reconsider diagnostic algorithm** (Not graded)
    - **ask for expert advice** (Not graded)

ERBP ESICM The Intensive Connection European Society of Endocrinology the European hormone society

Treatment recommendations

SIADH without symptoms

- **Patients with SIA**
  - in moderate or pr**mia, we suggest fluid restriction as firs**t
  - in moderate or pr**mia, we suggest the following be cons**ne treatments (2D)
    - **increasing solute**
    - **combination of lo**al sodium chloride
  - in moderate or pr**mia, we recommend against lithium or demecl**
  - AVP receptor ant
    - **we do not recomn**onatraemia (1C)
    - **we recommend ag**ponatraemia (1C)

ERBP

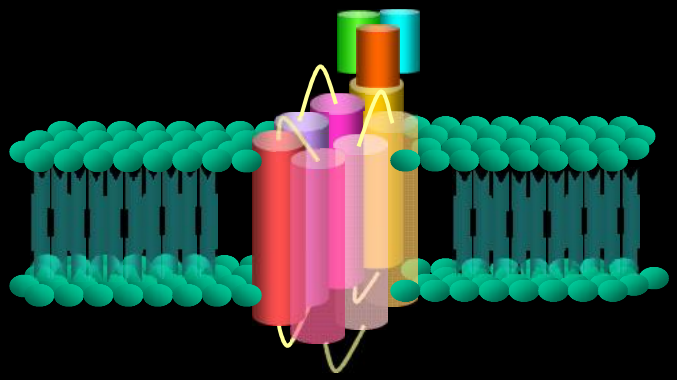
ESICM
The Intensive Care Society

European Society of Endocrinology
the European hormone society

Manchester Academic Health Science Centre
MANCHESTER 1824
The University of Manchester
NHS

AVP receptor antagonists

aquaretics…the designer drug for SIADH



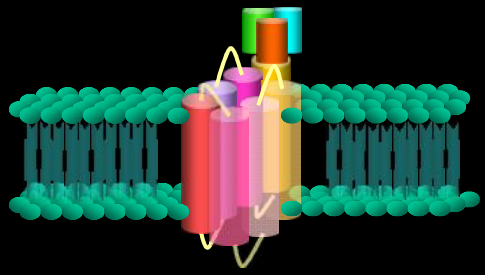
- **Meta analysis**
  - PICOM methodology
    - patients
    - intervention
    - comparator
    - outcome
    - methodology
  - evidence
    - 18 trials
    - 6405 patients
  - patient groups
    - Na^+ 125-134 mmol/L
  - Intervention
    - vaptan *vs*. placebo

AVP receptor antagonists

balancing attraction & efficacy

- **Mortality**
  - RR 1.06 (95% CI 0.77-1.44)
- **Quality of life**
  - no validated data sets
- **Increase in Na^+**
  - 3-7 day mean 4.2 mmol/L
  - 7 month mean 3.49 mmol/L
- **Adverse effects**
  - rapid rise in Na^+ RR 1.61
    - osmotic demyelination syndrome
  - 3 cases serious liver injury
  - ALT elevation in 4.4%

- **Methodology**
  - blinding
  - unbalanced fluid restriction
  - incomplete outcomes
  - industry sponsorship



Torres *et al*. 2012.
Tolvaptan in patients with autosomal dominant polycystic kidney disease.
New England Journal of Medicine 367: 2407-2418

ERBP

ESICM
The Intensive Connection

European Society of Endocrinology
the European hormone society

Manchester Academic Health Science Centre
MANCHESTER 1824
The University of Manchester
NHS

Using evidence in medicine
variance in clinical practice

- **Proof of principle studies ✔✔**
- **Evidence & experience of efficacy ✓**
- **Evidence of clinical utility ✗**

Hyponatraemia & mortality

the link….

THE AMERICAN JOURNAL of MEDICINE

Waiker SS, Mount DB, Curhan GC 2009.
Mortality after hospitalisation with mild, moderate & severe hyponatraemia
The American Journal of Medicine 122: 857-865

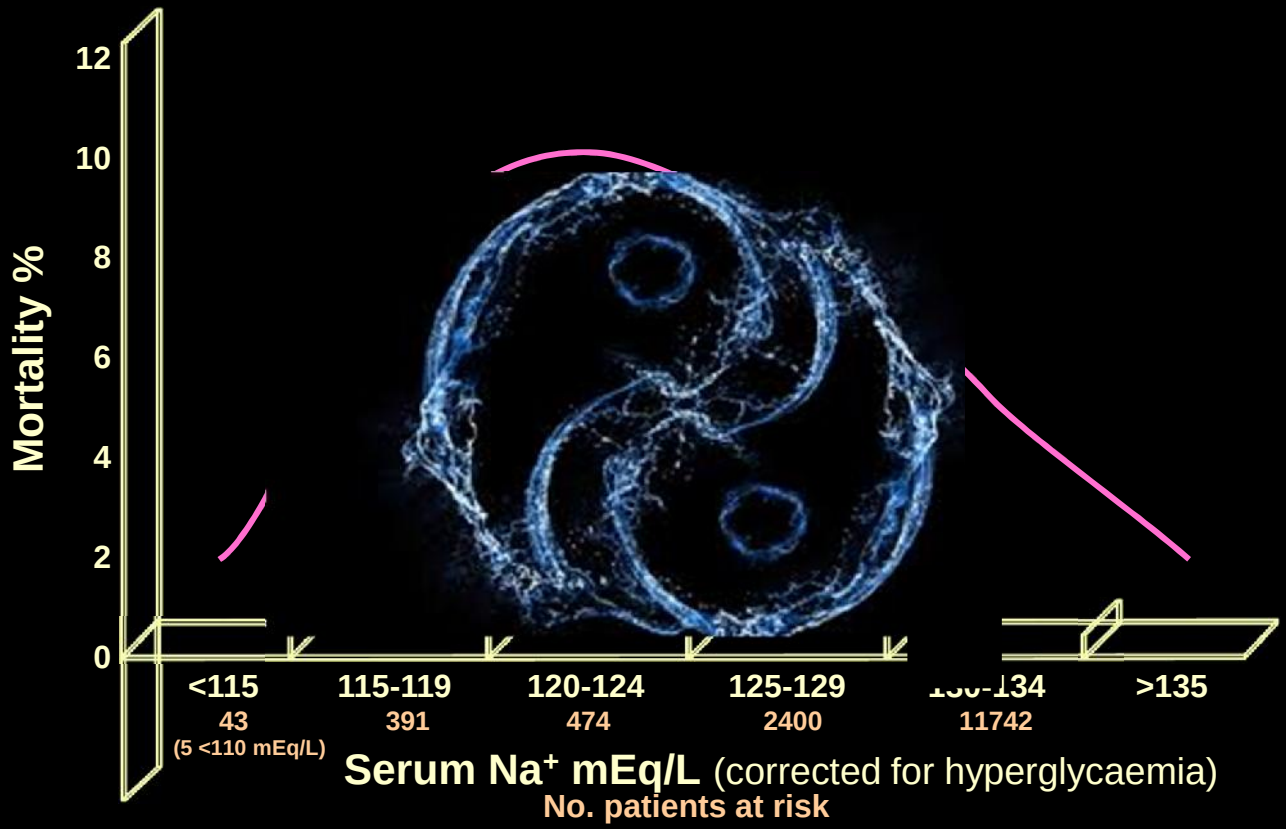
Mortality

Hyponatraemia

Manchester Academic Health Science Centre
The University of Manchester

Association *vs*. causation

death with low Na^+ *vs*. death from low Na^+



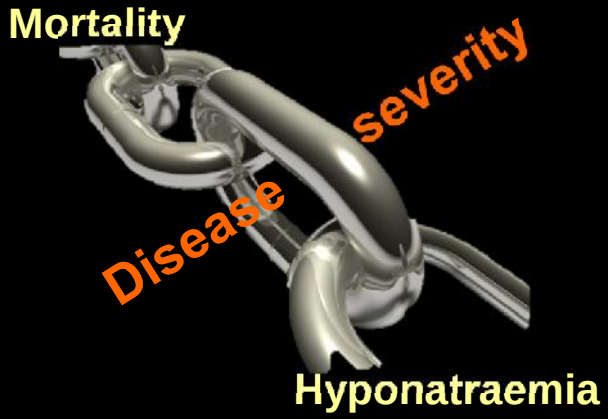
Chawla A, Sterns RH, Nigewaker SU, Cappucchio AD 2011.
Mortality and serum sodium: do patients die with or from hyponatremia?
Clinical Journal American Society Nephrology 6: 960-965.

Manchester Academic Health Science Centre
The University of Manchester

Hyponatraemia & mortality

so….what is the link?

- **Independent *vs.* dependent variables?**
  - **both linked with disease severity**



Hyponatraemia

directions for future work

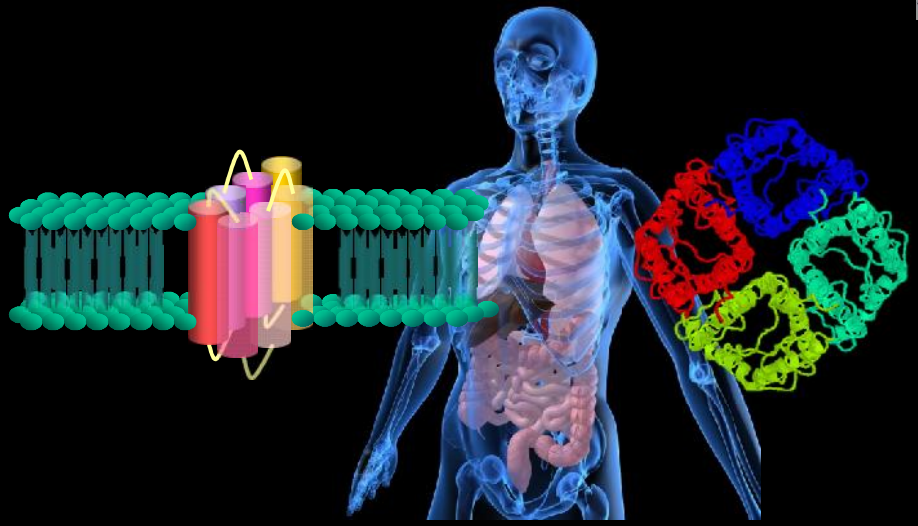
- **Risk stratification**
  - patients
  - presentations
- **Optimum strategies for rise in Na^+**
  - speed
  - methods
- **Managing over-correction**
  - risk stratification
  - optimising methods

Manchester Academic Health Science Centre
The University of Manchester

Hyponatraemia

for Homer Simpson……

- **Everybody's problem……**
  - the clinical context
  - guidance
  - approaches to management
  - moving forward…..



- **Thanks**

ERBP

ESICM
The Intensive Connection

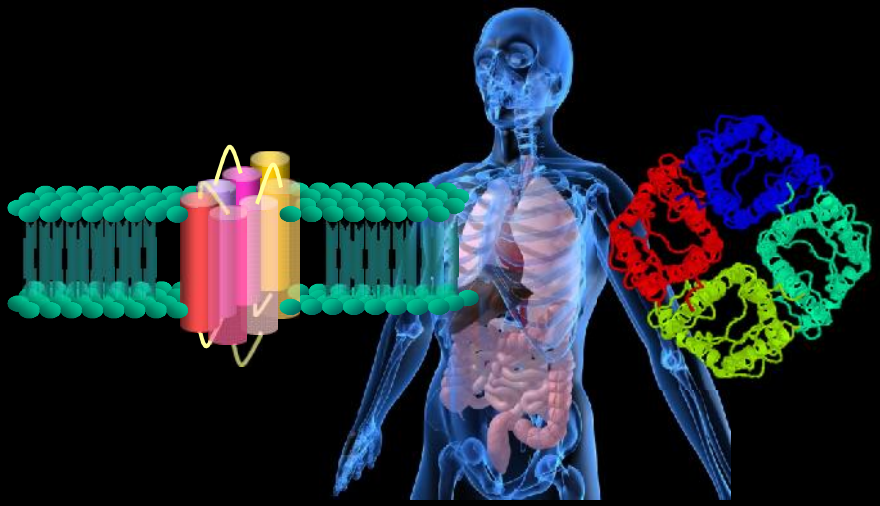
European Society of Endocrinology
the European hormone society

Manchester Academic Health Science Centre
MANCHESTER 1824
The University of Manchester
NHS

ABCD Meeting, Manchester, April 2016

Hyponatraemia

.....for Homer Simpson



Steve Ball

Central Manchester University Hospitals NHS Trust &
Manchester Academic Health Science Centre, UK

Manchester Academic Health Science Centre

The University of Manchester

Manchester Academic Health Science Centre

The University of Manchester