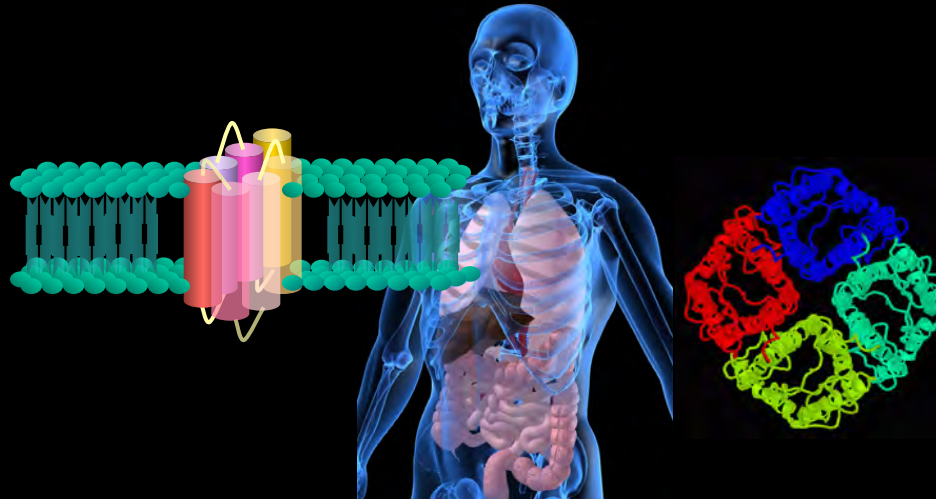


Caledonian Society Endocrinology & Diabetes, Dunkeld 2014

# Hyponatraemia guidelines

## an inside view



**Dr Steve Ball**

*Endocrine Unit,  
Newcastle Hospitals NHS Trust &  
The Medical School*



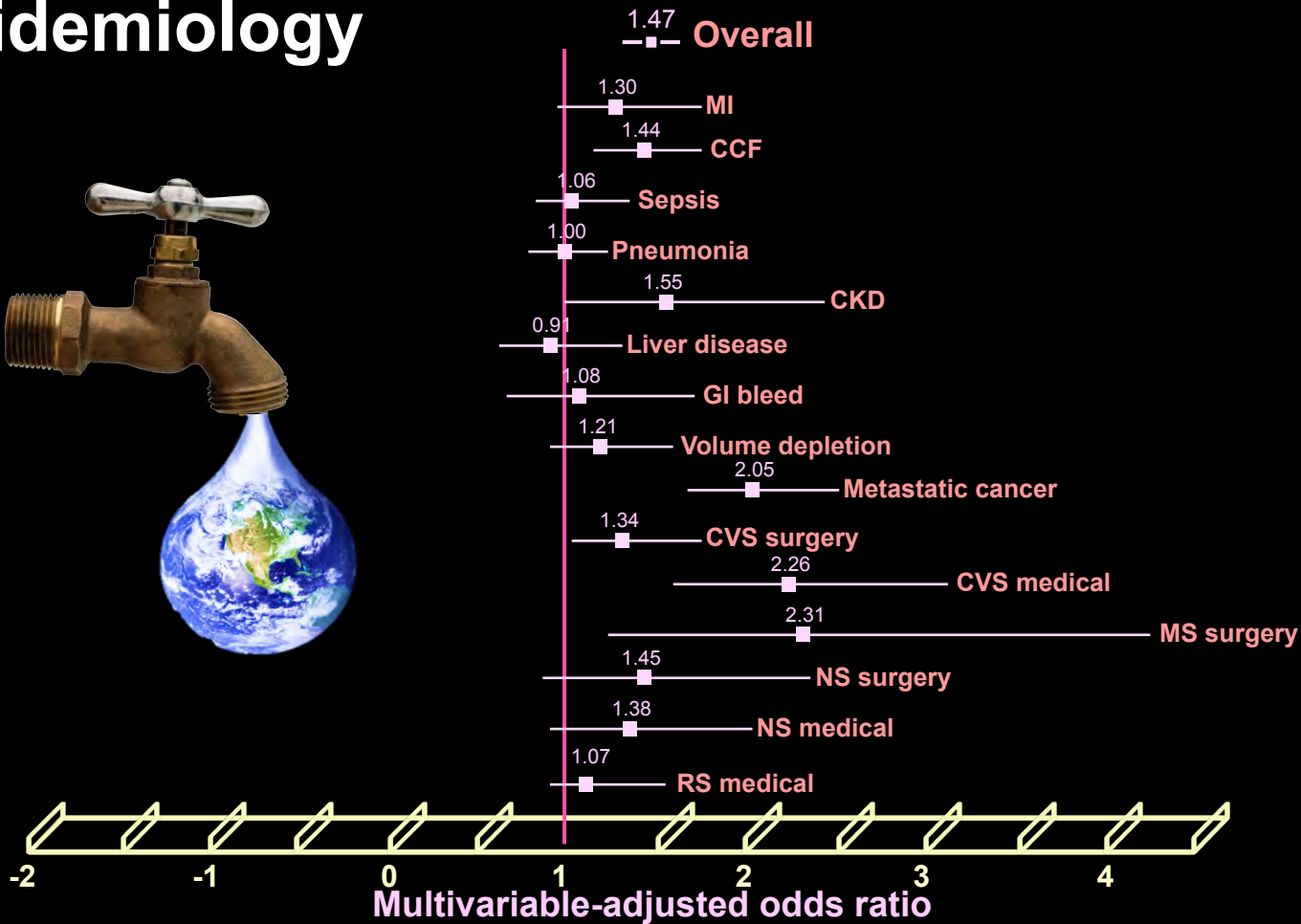
# Hyponatraemia

## assessment, management & guidance

- **Context**
- **Guideline development**
- **Recommendations on diagnosis**
- **Recommendations on treatment**
- **Challenges & future work**



# Hyponatraemia & mortality epidemiology

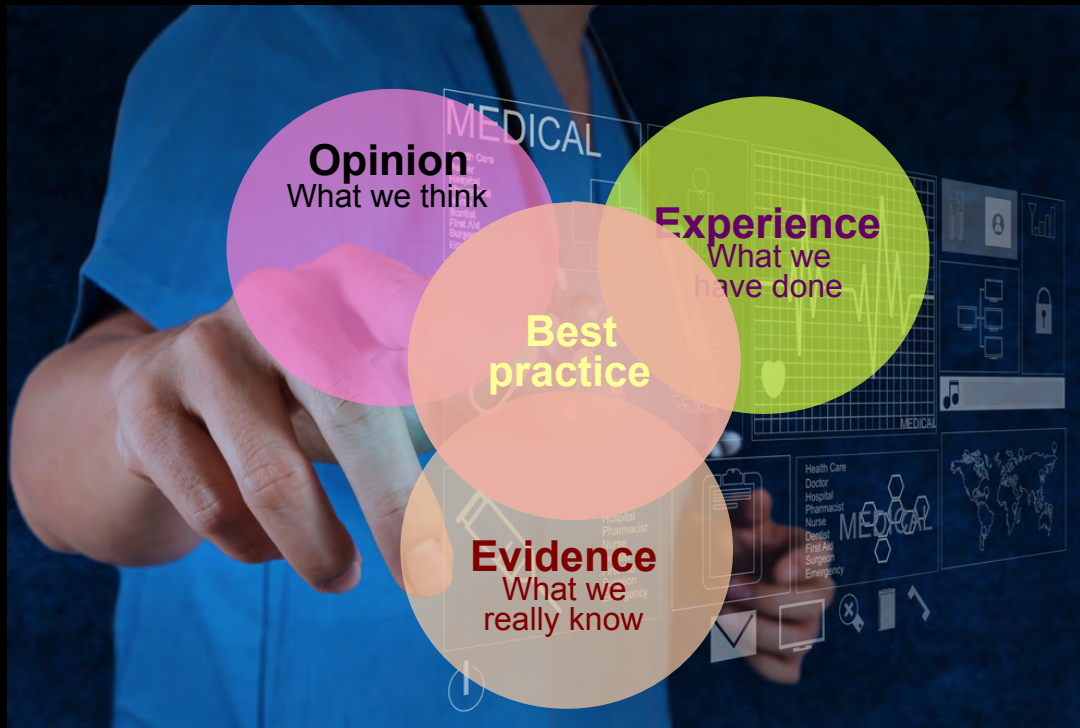


THE AMERICAN  
JOURNAL of  
MEDICINE.

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

# Evidence in medicine

## what determines clinical practice?



# The trouble with guidance

## why we struggle

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



# European guideline group multidisciplinary, evidence-based



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## Clinical practice guideline on diagnosis and treatment of hyponatraemia

Goce Spasovski, Raymond Vanholder, Bruno Alolio, 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



# Guidance methodology

## searching the evidence base

- **Sources**
  - Cochrane data base systematic reviews (to 2012)
  - DARE (to 2012)
  - CENTRAL (to 2012)
  - Medline (1946-2012)
    - 1997 onwards only for ODS
- **Selection**
  - excluded case series  $\leq 5$  participants
  - all studies noting adverse outcome
- **Extraction, critical appraisal & bias analysis**
  - AMSTAR & Cochrane Risk of Bias Tool
  - Newcastle Ottawa scale & QUADRAS
- **Evidence profiles**
  - GRADE toolbox



# Guidance methodology

## hierarchy of outcomes

Hierarchy	Outcomes
<b>Critically important</b>	Patient survival Coma Brain damage/oedema Osmotic demyelination Respiratory arrest Quality of life Cognitive function
<b>Highly important</b>	Bone fractures Falls Length of hospital stay
<b>Moderately important</b>	Serum Na <sup>+</sup> concentration





# Guidance methodology

## grade system for recommendations



Guyatt GH et al. 2008.

GRADE: an emerging consensus on rating quality of evidence & strength of recommendations

British Medical Journal 336: 924-926.



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# Guidance methodology

## grading quality of evidence

Grade	Quality level	Definition
A	High	We are confident that true effect lies close to that of the estimate of the effect
B	Moderate	True effects are likely to be close to the estimates, but there is a possibility that they are substantially different
C	Low	The true effects might be substantially different from the estimates of the effects
D	Very low	The estimates are very uncertain & often will be far from the truth



Guyatt GH et al. 2008.

GRADE: an emerging consensus on rating quality of evidence & strength of recommendations

British Medical Journal 336: 924-926.



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# Guidance methodology

## implications of recommendations for stakeholders

Grade	Implications		
	Patients	Clinicians	Policy
<b>Strong</b> <i>'we recommend'</i>	Most people in situation would want recommended course of action, only small proportion would not	Most people should receive recommended course of action	Recommendation can be adopted as policy in most situations
<b>Weak</b> <i>'we suggest'</i>	Most people in situation would want recommended course of action, but many would not	Recognize different choices will be appropriate for different patients. Help each to arrive at decision consistent with values & preferences	Policy making will require substantial debate & involvement of many stakeholders



Guyatt GH et al. 2008.

GRADE: an emerging consensus on rating quality of evidence & strength of recommendations

British Medical Journal 336: 924-926.

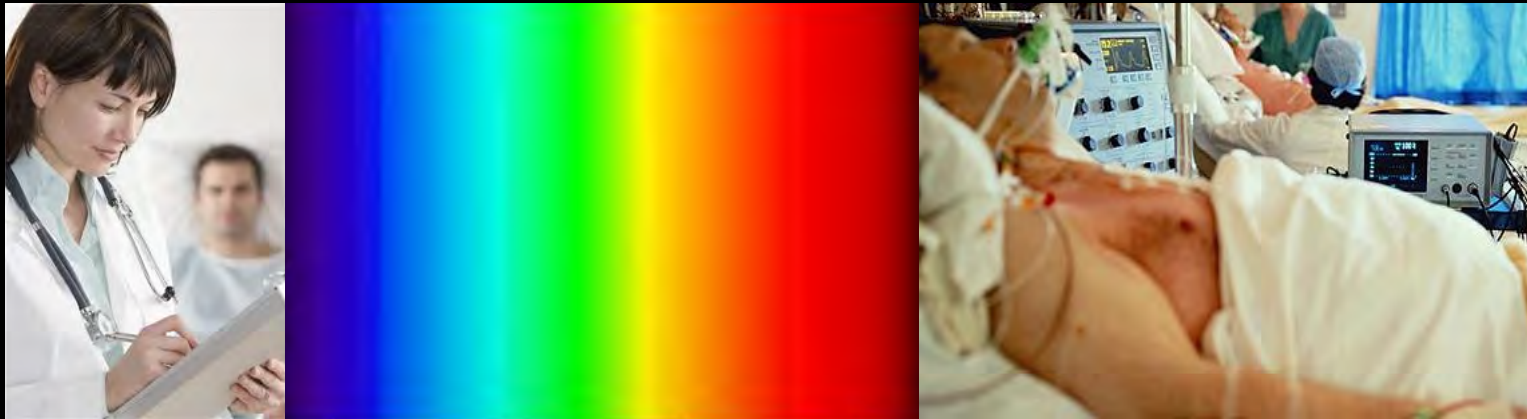


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# Diagnosis of hyponatraemia

## classification of hyponatraemia



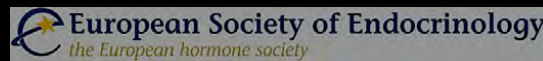
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# Hyponatremia

classification based on biochemical severity

- **Mild hyponatraemia**
  - serum Na<sup>+</sup> concentration 130 -135 mmol/l
  - measured by ion-specific electrode
- **Moderate hyponatraemia**
  - serum Na<sup>+</sup> concentration 125 -129 mmol/l
  - measured by ion-specific electrode
- **Profound hyponatraemia**
  - serum Na<sup>+</sup> concentration <125 mmol/l
  - measured by ion-specific electrode



# Hyponatraemia

## classification based on symptoms

- **Moderately symptomatic**
  - any degree hyponatraemia
  - moderately severe symptoms
- **Severely symptomatic**
  - any degree hyponatraemia
  - severe symptoms

Severity	Symptom
Moderate	Nausea without vomiting confusion Headache
Severe	Vomiting Cardiorespiratory arrest Abnormal & deep somnolence Seizures Coma (Glasgow coma scale $\leq 8$ )



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# Hyponatraemia guidance

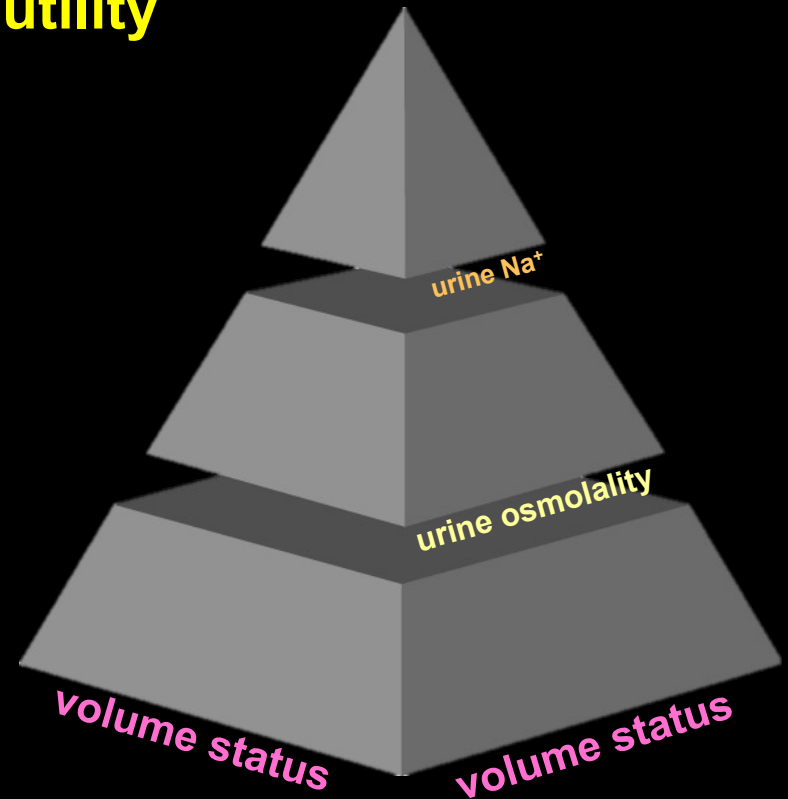
## diagnostic recommendations



# Diagnostic recommendations

## the evidence base

- **Weighting proportionate to utility**
  - urine osmolality
  - urine  $\text{Na}^+$
  - volume status

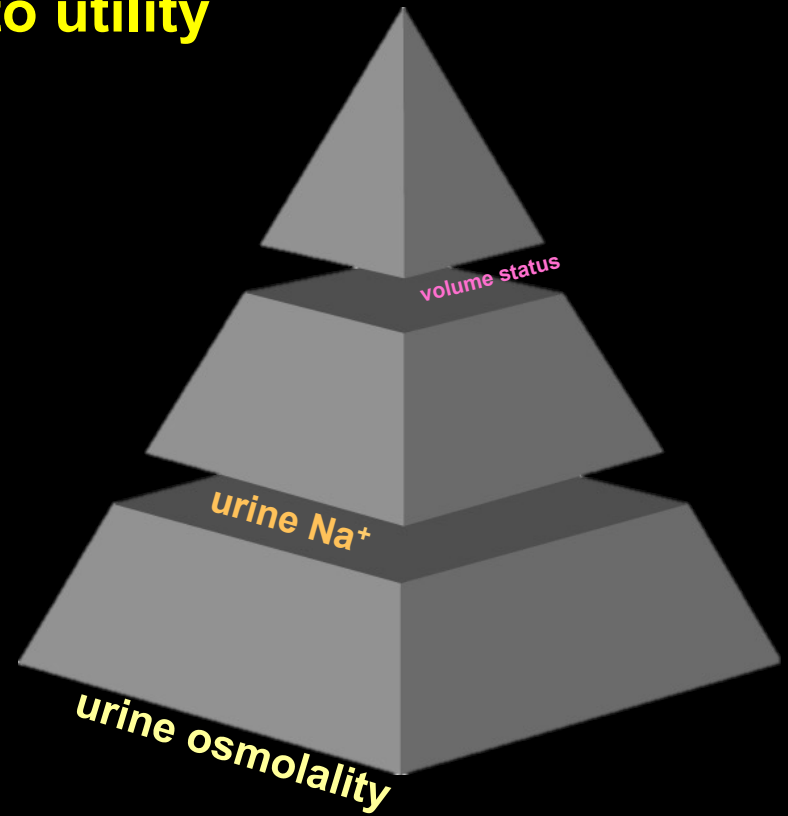




# Diagnostic recommendations

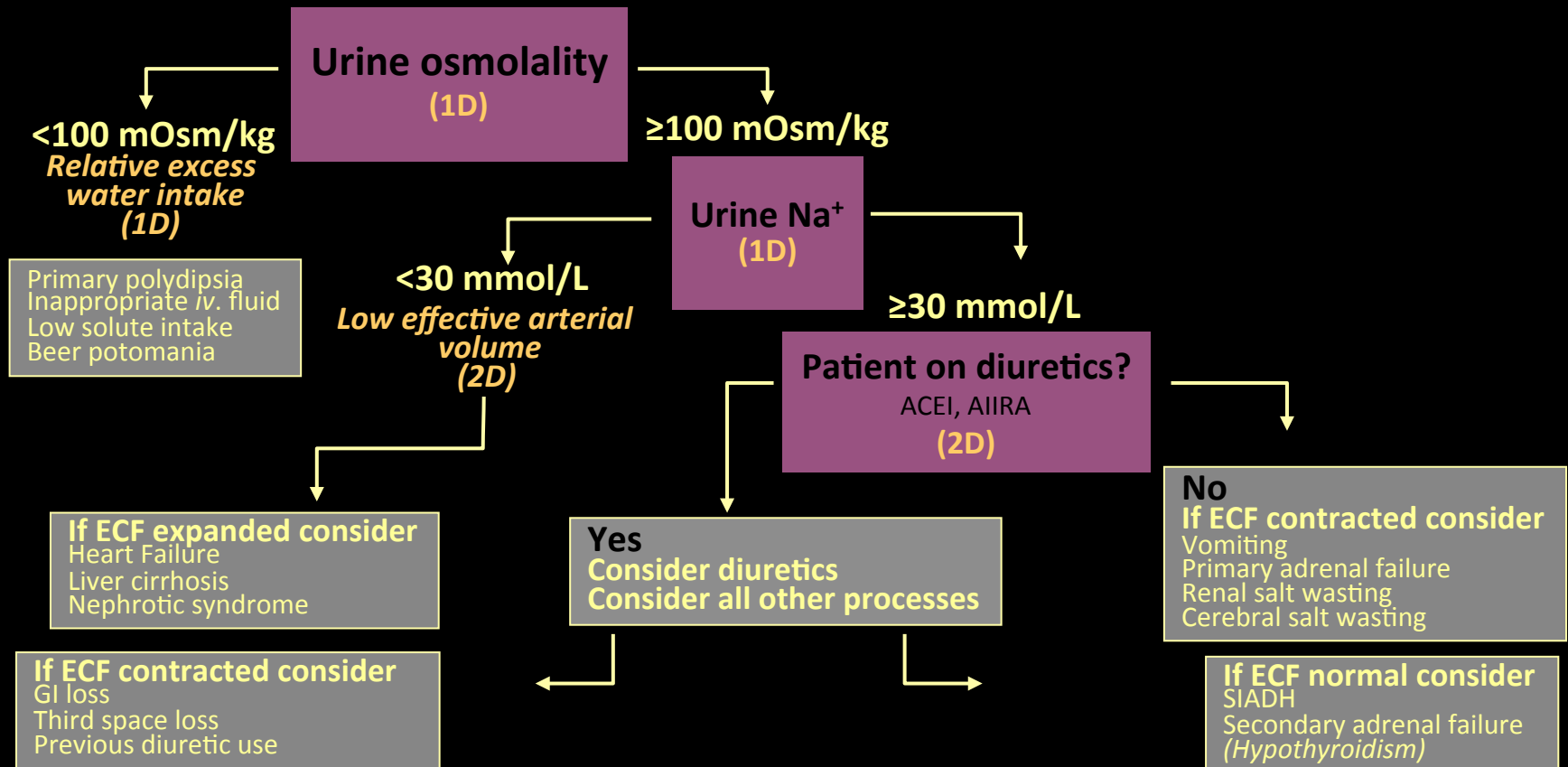
## the evidence base

- **Weighting proportionate to utility**
  - urine osmolality
  - urine Na<sup>+</sup>
  - volume status



# Diagnostic recommendations

## diagnostic pathway

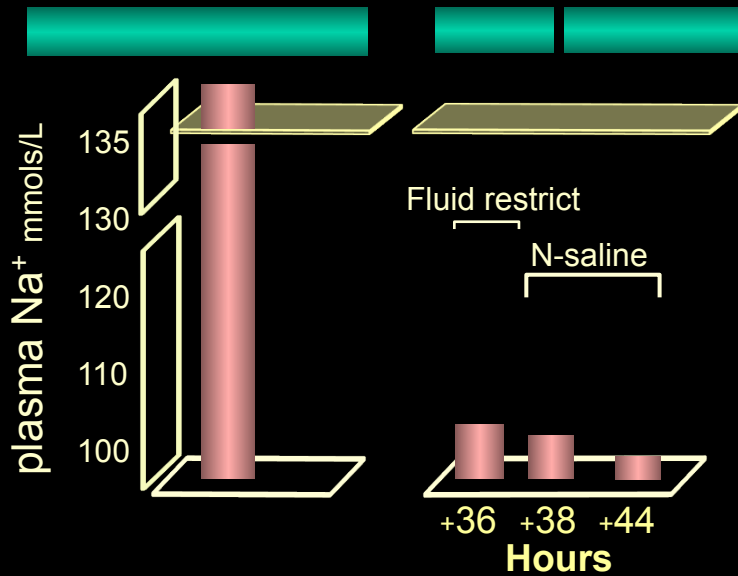
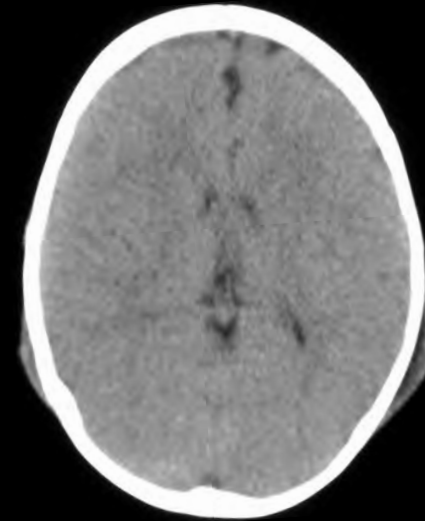


# Hyponatraemia guidance treatment recommendations

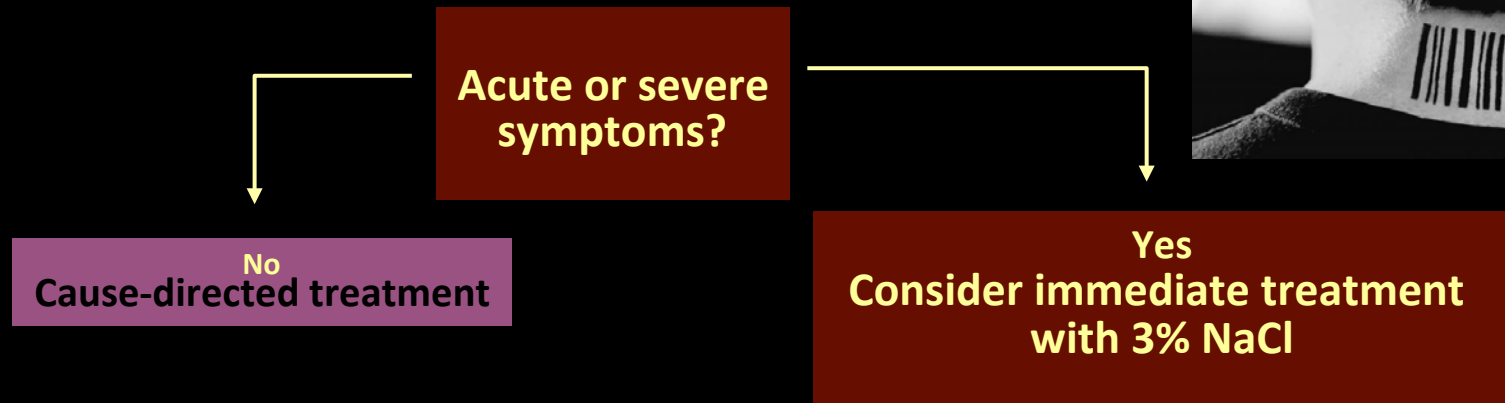


# What best to do?

## Susan's story



# Treatment recommendations management pathway



# Treatment recommendations

## hyponatraemia with severe symptoms

### Within first hour

**iv infusion 150 mL 3% hypertonic saline or equivalent (1D)**  
20 mins

Close monitoring environment (Not graded)

### Check Na<sup>+</sup>

**iv infusion 150 mL 3% hypertonic saline or equivalent (2D)**  
20 mins

**Repeat twice or until 5mmol/L increase in Na<sup>+</sup> (2D)**

### Follow up management after 5 mmol/L rise Na<sup>+</sup>

Stop infusion hypertonic saline (1D)

Keep iv line open minimum volume 0.9% saline (1D)

Start diagnosis-specific treatment (1D)

Limit increase Na<sup>+</sup> to 10 mmol/L first 24 hours (1D)

Limit increase Na<sup>+</sup> to additional 8 mmol/L every 24 hours thereafter until Na<sup>+</sup> 130 mmol/L (1D)

Check Na<sup>+</sup> 6 hours, 12 hours & daily until stable under stable treatment (1D)



# Treatment recommendations

## hyponatraemia with severe symptoms II

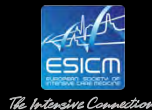
If no improvement after 5 mmol/L rise Na<sup>+</sup> in first hour

**iv infusion 150 mL 3% hypertonic saline or equivalent (1D)**  
Aim additional 1 mmol/L/hour increase in Na<sup>+</sup>  
Close monitoring environment not graded

**Indications for stopping infusion ID**  
Symptom improvement  
Na<sup>+</sup> increases 10 mmol/L in total  
Na<sup>+</sup> reaches 130 mmol/L (whichever is first)

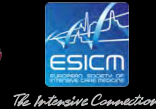
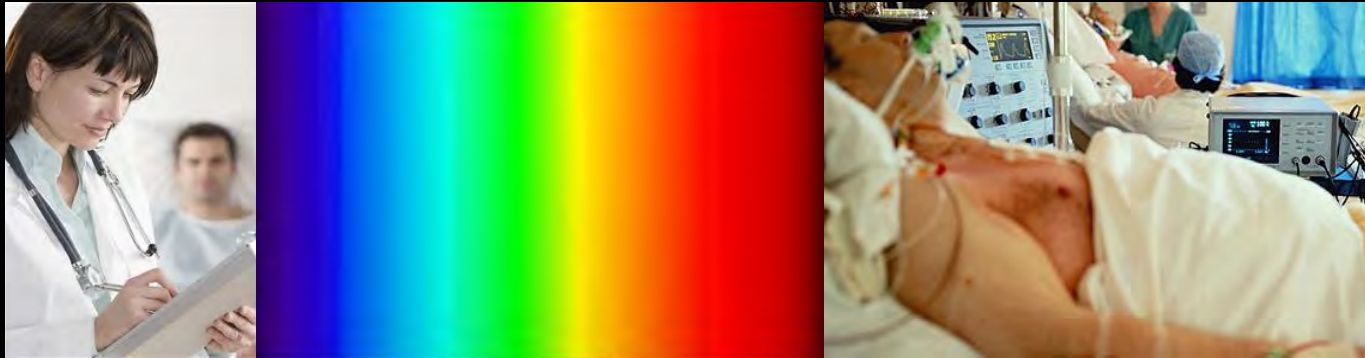
**Explore other causes of symptoms (1D)**

**Na<sup>+</sup> monitoring 2D**  
Every 4 hours during 3% hypertonic saline use



# Treatment recommendations

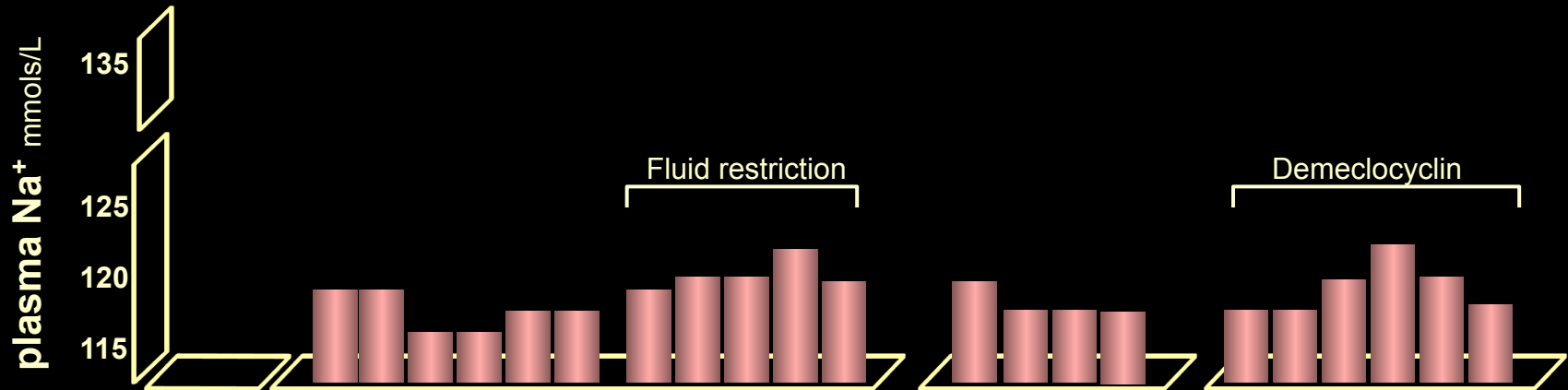
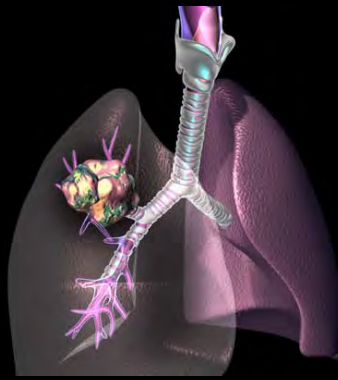
## chronic hyponatraemia without symptoms





# Persistent hyponatraemia

## Frank's story



# Treatment recommendations

## chronic hyponatraemia without symptoms I

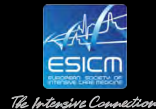
- **General management**
  - stop non-essential fluids & contributing factors (Not graded)
  - we recommend cause-specific treatment (1D)
  - in mild hyponatraemia, we suggest against treatment with sole aim of increasing serum Na<sup>+</sup> concentration (2C)
  - in moderate or profound hyponatraemia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



# Treatment recommendations

## chronic hyponatraemia without symptoms II

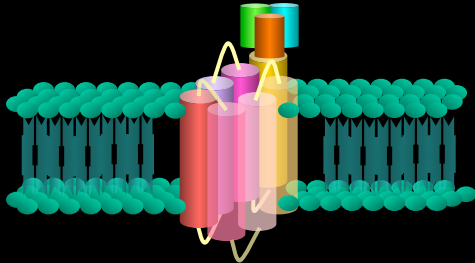
- **Patients with SIAD**
  - in moderate or profound hyponatraemia, we suggest fluid restriction as first line treatment (2D)
  - in moderate or profound hyponatraemia, we suggest the following be considered as second-line treatments (2D)
    - increasing solute intake with urea 0.25-0.50 g/kg
    - combination of low dose loop diuretic & oral sodium chloride
  - in moderate or profound hyponatraemia, we recommend against lithium or demeclocyclin (1D)
  - VR antagonists
    - we do not recommend use in moderate hyponatraemia (1C)
    - we recommend against use in profound hyponatraemia (1C)



# AVP receptor antagonists

## balancing attraction & efficacy I

- **Meta analysis**
- **PICOM approach**
  - patients
  - intervention
  - comparator
  - outcome
  - methodology
- **The evidence**
  - 18 trials
    - 6405 patients
  - **Patient groups**
    - Na<sup>+</sup> 125-134 mmol/L
  - **Intervention**
    - vaptan vs. placebo
  - **Comparator**



# AVP receptor antagonists

## balancing attraction & efficacy II

### • Outcome

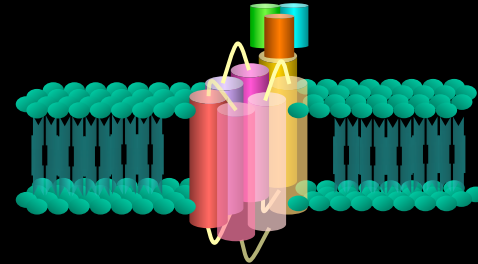
- mortality
  - RR 1.06 (95% CI 1.07-1.44)
- QoL
  - no validated data sets
- increase Na<sup>+</sup>
  - 3-7 days mean 4.2 mmol/L
  - 7 months mean 3.49 mmol/L
- adverse effects
  - rapid rise in Na<sup>+</sup> RR 1.61
  - ODS
  - 3 cases serious liver injury
  - ALT elevation 4.4%



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

### • Methodology

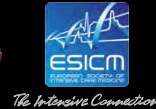
- blinding
- unbalanced fluid restriction
- incomplete outcomes
- industry sponsorship



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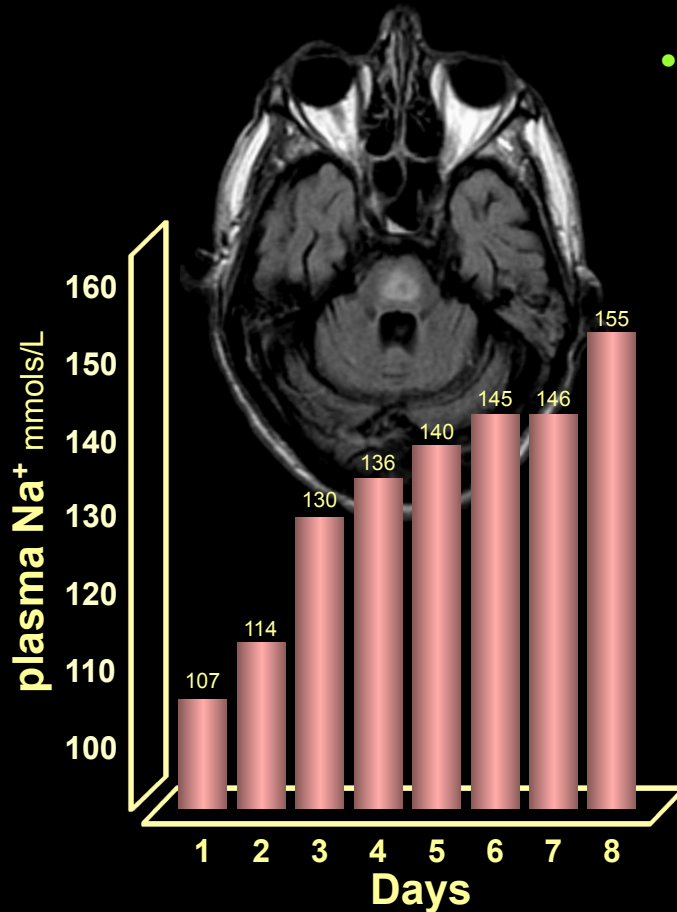


# Treatment recommendations over-correction of hyponatraemia



# Over-correction of Na<sup>+</sup>

## John's story

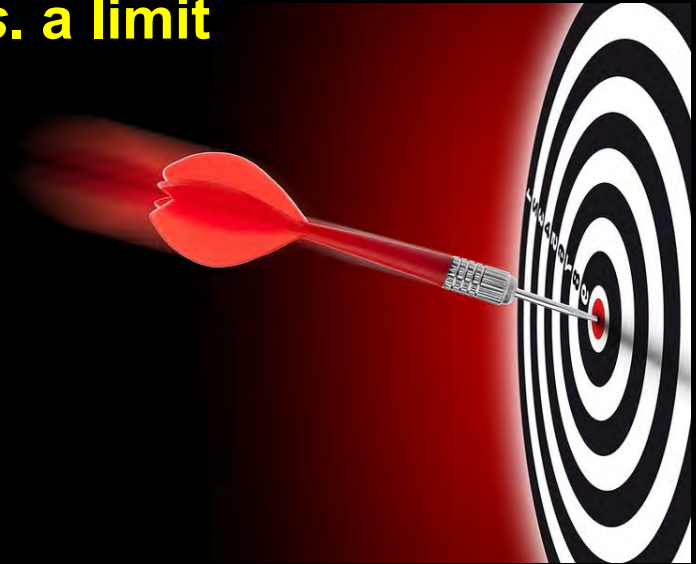


- **Osmotic demyelination syndrome**
  - neurology
    - quadriplegia
    - ophthalmoplegia
    - pseudo-bulbar palsy
    - coma
  - pathology
    - de-myelination
    - necrosis

# Safe correction

## limiting Na<sup>+</sup> rise & over-correction

- **The difference between aim vs. a limit**
  - limit 10 mmol/L first 24 hours
  - aim 6 mmol/L
- **Over-correction**
  - active management





# Treatment recommendations

what if hyponatraemia is corrected too rapidly?

- **Recommendations for intervention to re-lower Na<sup>+</sup> (1D)**
  - if serum Na<sup>+</sup> increases >10 mmol/L in first 24 hours
  - if serum Na<sup>+</sup> increases >8 mmol/L in any 24 hours thereafter
- **We recommend discontinuing on-going treatment (1D)**
- **We recommend consulting an expert**
  - discuss infusion 10 ml/kg electrolyte-free water (1D)
    - over 1 hour
    - strict monitoring urine output and fluid balance
  - discuss *i.v.* DDAVP 2 mcg (1D)
    - should not be repeated more frequently than 8 hourly



# Hyponatraemia

## suggestions for future research

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



# Evidence in medicine

## variance in clinical practice



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

# Variance in practice managing change

- **Dissemination**
- **Engagement**
- **Implementation**
  - barriers
  - managing conflicts



# Hyponatraemia

## guidance on assessment & management

- **Context**
- **Guideline development**
- **Recommendations on diagnosis**
- **Recommendations on treatment**
- **Challenges & future work**



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**Nephrology Dialysis &  
Transplantation**



**Eur J Endocrinol**



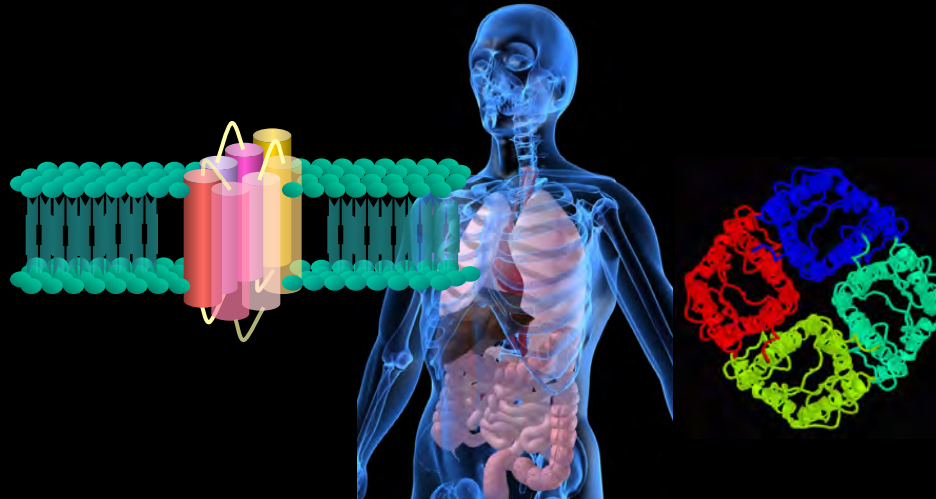
**Intensive Care  
Medicine**



Caledonian Society Endocrinology & Diabetes, Dunkeld 2014

# Hyponatraemia guidelines

## an inside view



**Dr Steve Ball**

*Endocrine Unit,  
Newcastle Hospitals NHS Trust &  
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