Hyponatraemia guidelines
an inside view

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Hyponatraemia
assessment, management & guidance

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

- **Multivariable-adjusted odds ratio**
  - Overall: 1.47
  - MI: 1.30
  - CCF: 1.44
  - Sepsis: 1.06
  - Pneumonia: 1.00
  - CKD: 1.55
  - Liver disease: 0.91
  - GI bleed: 1.08
  - Volume depletion: 1.21
  - Metastatic cancer: 2.05
  - CVS surgery: 1.34
  - CVS medical: 2.26
  - MS surgery: 2.31
  - NS surgery: 1.45
  - NS medical: 1.38
  - RS medical: 1.07

**References**

Evidence in medicine
what determines clinical practice?

Opinion
What we think

Experience
What we have done

Evidence
What we really know

Best 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

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
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 ≤5 participants
  - all studies noting adverse outcome

• **Extraction, critical appraisal & bias analysis**
  - AMSTAR & Cochrane Risk of Bias Tool
  - Newcastle Ottowa scale & QUADRAS

• **Evidence profiles**
  - GRADE toolbox
## Guidance methodology

### Hierarchy of outcomes

<table>
<thead>
<tr>
<th>Hierarchy</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Critically important</td>
<td>Patient survival</td>
</tr>
<tr>
<td></td>
<td>Coma</td>
</tr>
<tr>
<td></td>
<td>Brain damage/oedema</td>
</tr>
<tr>
<td></td>
<td>Osmotic demyelination</td>
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<tr>
<td></td>
<td>Respiratory arrest</td>
</tr>
<tr>
<td></td>
<td>Quality of life</td>
</tr>
<tr>
<td></td>
<td>Cognitive function</td>
</tr>
<tr>
<td>Highly important</td>
<td>Bone fractures</td>
</tr>
<tr>
<td></td>
<td>Falls</td>
</tr>
<tr>
<td></td>
<td>Length of hospital stay</td>
</tr>
<tr>
<td>Moderately important</td>
<td>Serum Na(^+) concentration</td>
</tr>
</tbody>
</table>
Guidance methodology
grade system for recommendations

Strength of recommendation
1 Strong
2 Weak

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

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

## Grading quality of evidence

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

*Guyatt GH *et al.* 2008.*

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# Guidance methodology

implications of recommendations for stakeholders

<table>
<thead>
<tr>
<th>Grade</th>
<th>Implications</th>
<th>Policy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Strong</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>‘we recommend’</td>
<td>Patients: Most people in situation would want recommended course of action, only small proportion would not</td>
<td>Clinicians: Most people should receive recommended course of action</td>
</tr>
<tr>
<td></td>
<td>Policy: Recommendation can be adopted as policy in most situations</td>
<td></td>
</tr>
<tr>
<td><strong>Weak</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>‘we suggest’</td>
<td>Patients: Most people in situation would want recommended course of action, but many would not</td>
<td>Clinicians: Recognize different choices will be appropriate for different patients. Help each to arrive at decision consistent with values &amp; preferences</td>
</tr>
<tr>
<td></td>
<td>Policy: Policy making will require substantial debate &amp; involvement of many stakeholders</td>
<td></td>
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Diagnosis of hyponatraemia

classification of hyponatraemia
Hyponatremia classification based on biochemical severity

• **Mild hyponatraemia**
  - serum Na⁺ concentration 130 -135 mmol/l
  - measured by ion-specific electrode

• **Moderate hyponatraemia**
  - serum Na⁺ concentration 125 -129 mmol/l
  - measured by ion-specific electrode

• **Profound hyponatraemia**
  - serum Na⁺ 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

<table>
<thead>
<tr>
<th>Severity</th>
<th>Symptom</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate</td>
<td>Nausea without vomiting confusion Headache</td>
</tr>
<tr>
<td>Severe</td>
<td>Vomiting Cardiorespiratory arrest Abnormal &amp; deep somnolence Seizures Coma (Glasgow coma scale ≤8)</td>
</tr>
</tbody>
</table>
Hyponatraemia guidance
diagnostic recommendations
Diagnostic recommendations
the evidence base

- Weighting proportionate to utility
  - urine osmolality
  - urine Na⁺
  - volume status
Diagnostic recommendations
the evidence base

• Weighting proportionate to utility
  • urine osmolality
  • urine Na⁺
  • volume status
Diagnostic recommendations

diagnostic pathway

1. Urine osmolality (1D)
   - <100 mOsm/kg
     - Relative excess water intake (1D)
     - Primary polydipsia
     - Inappropriate iv. fluid
     - Low solute intake
     - Beer potomania
   - ≥100 mOsm/kg
     - Urine Na⁺ (1D)
     - <30 mmol/L
       - Low effective arterial volume (2D)
     - ≥30 mmol/L
   - Patient on diuretics? (2D)
     - ACEI, AIIRA

2. Yes
   - Consider diuretics
   - Consider all other processes

3. No
   - If ECF contracted consider
     - Vomiting
     - Primary adrenal failure
     - Renal salt wasting
     - Cerebral salt wasting
   - If ECF normal consider
     - SIADH
     - Secondary adrenal failure (Hypothyroidism)
     - Consider occult diuretics

4. If ECF expanded consider
   - Heart failure
   - Liver cirrhosis
   - Nephrotic syndrome

5. If ECF contracted consider
   - GI loss
   - Third space loss
   - Previous diuretic use
Hyponatraemia guidance
treatment recommendations
What best to do?

Susan’s story

Plasma Na⁺ mmols/L

135
130
120
110
100

Fluid restrict
N-saline

+36  +38  +44
Hours
Treatment recommendations
management pathway

Acute or severe symptoms?

No
Cause-directed treatment

Yes
Consider immediate treatment with 3% NaCl
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+
iv infusion 150 mL 3% hypertonic saline or equivalent (2D)
20 mins

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)
Treatment recommendations
hyponatraemia with severe symptoms II

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

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

Indications for stopping infusion (1D)
Symptom improvement
Na+ increases 10 mmol/L in total
Na+ reaches 130 mmol/L (whichever is first)

Explore other causes of symptoms (1D)

Na+ monitoring (2D)
Every 4 hours during 3% hypertonic saline use
Treatment recommendations
chronic hyponatraemia without symptoms
Persistent hyponatraemia
Frank’s story

Fluid restriction

Demeclocyclin
Treatment recommendations
chronic hyponatraemia without symptoms

- **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)
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 of 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

- Meta analysis
- PICOM approach
  - patients
  - intervention
  - comparator
  - outcome
  - methodology

- The evidence
  - 18 trials
    - 6405 patients
- Patient groups
  - Na⁺ 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$^+$
    - 3-7 days mean 4.2 mmol/L
    - 7 months mean 3.49 mmol/L
  - adverse effects
    - rapid rise in Na$^+$ RR 1.61
    - ODS
    - 3 cases serious liver injury
    - ALT elevation 4.4%

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

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Treatment recommendations
over-correction of hyponatraemia
Over-correction of Na⁺

John’s story

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

<table>
<thead>
<tr>
<th>Days</th>
<th>plasma Na⁺ mmols/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>107</td>
</tr>
<tr>
<td>2</td>
<td>114</td>
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<tr>
<td>3</td>
<td>130</td>
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<td>6</td>
<td>145</td>
</tr>
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<td>7</td>
<td>146</td>
</tr>
<tr>
<td>8</td>
<td>155</td>
</tr>
</tbody>
</table>
Safe correction
limiting Na⁺ 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⁺ (1D)**
  - if serum Na⁺ increases >10 mmol/L in first 24 hours
  - if serum Na⁺ 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 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
Hyponatraemia guidelines
an inside view

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