Acid-Base balance in the ICU

The Stewart Approach

Intensive Care Training Program
Radboud University Medical Centre Nijmegen
Relation $[\text{H}^+]$ and pH
Changes in the metabolic component

- **HCO₃⁻**
  - Related to PCO₂ and no information on severity and presence of “other acids”

- **Base Excess**
  - Changes in-vivo under influence of PCO₂ and [hemoglobin] - body does not regulate BE

BE = \{[HCO₃⁻] - 24.4 + (2.3 \times [Hb] + 7.7) \times (pH - 7.4)\} \times (1 - 0.023 \times [Hb])
BE changes in-vivo with PCO₂

<table>
<thead>
<tr>
<th></th>
<th>Initial</th>
<th>After 2 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.16</td>
<td>7.30</td>
</tr>
<tr>
<td>PaCO₂ (mm Hg)</td>
<td>172</td>
<td>124</td>
</tr>
<tr>
<td>[HCO₃⁻] (mmol/L)</td>
<td>59</td>
<td>59</td>
</tr>
<tr>
<td>BE (mEq/L)</td>
<td>19.1</td>
<td>23.5</td>
</tr>
<tr>
<td>SBE (mEq/L)</td>
<td>29.1</td>
<td>30.7</td>
</tr>
</tbody>
</table>

Exacerbation COPD

SBE = extracellular BE - Hb 50 g/l
Stewart-Figge theory

• Body water is inexhaustible source of H\(^+\) ions

• Three independent components influence the dissociation of water
  ▶ PCO\(_2\)
  ▶ Total concentration of weak acids (A\(_{TOT}\))
  ▶ Strong Ion Difference
Relation $\text{PCO}_2$ and $\text{pH}$

![Graph showing the relationship between $\text{PCO}_2$ (mm Hg) and pH for different SBE values: SBE = +15 mEq/L, SBE = 0 mEq/L, SBE = -15 mEq/L.]

- SBE = +15 mEq/L
- SBE = 0 mEq/L
- SBE = -15 mEq/L
Relation $A_{TOT}$ and pH
Strong Ion Difference

Electrical neutrality

Apparent SID

Effective SID

Strong Ion Gap = SID_a - SID_e

Normal SID_a
40 - 42 mEq/l
Effective SID

- $\text{HCO}_3^- \rightarrow \text{HCO}_3^-$
- $[\text{Alb}^-] \rightarrow [\text{Alb}] \times (0.123 \times \text{pH} - 0.631)$
- $[\text{P}^-] \rightarrow [\text{P}] \times (0.309 \times \text{pH} - 0.469)$
Relation SID and pH

PCO$_2$ 40 mmHg
$A_{TOT} = 20$ meq/l
Unmeasured anions in the ICU

Metabolic acidosis
N = 50

Number of patients

Strong Ion Gap

Moviat M. Crit Care 2003;7:R41-R45
Relation Anion Gap - Strong Ion Gap

\[ y = 0.5417x - 1.9509 \]

\[ R^2 = 0.7223 \]
Relation corrected Anion Gap - Strong Ion Gap

Corrected anion gap = anion gap + 0.25 (40 - actual albumin)

\[ y = 0.8494x + 2.1877 \]

\[ R^2 = 0.9344 \]
Metabolic acidosis in the ICU

Metabolic acidosis  
$N = 50$

Strong Ion Gap

Chloride

Lactate

Moviat M. Crit Care 2003;7:R41-R45
# Pathophysiology

<table>
<thead>
<tr>
<th>Respiratory</th>
<th>Acidosis</th>
<th>Alkalosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>PaCO</td>
<td>PaCO</td>
<td></td>
</tr>
</tbody>
</table>

## Metabolic

1. Changes in SID
   - a) $H$
   - b) Change in strong anions
     - chloride $↑$ or $↓$
     - unmeasured anions $↑$
   - SID

2. Changes in weak acids
   - a) Albumin $\left[ Alb \right] \uparrow$
   - b) Anorganic phosphate $\left[ P \right] \uparrow$
   - $\left[ Alb \right] \downarrow$
   - $\left[ P \right] \downarrow$
# Acidosis and mortality

<table>
<thead>
<tr>
<th></th>
<th>All cases SBE &lt; -2</th>
<th>Lactic acidosis</th>
<th>SIG acidosis</th>
<th>Hyperchloremia</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>546</td>
<td>237</td>
<td>205</td>
<td>104</td>
</tr>
<tr>
<td>Acidosis (%)</td>
<td>100</td>
<td>43</td>
<td>38</td>
<td>19</td>
</tr>
<tr>
<td>ICU LOS (d)</td>
<td>18,02</td>
<td>19,38</td>
<td>21,41</td>
<td>14,42</td>
</tr>
<tr>
<td>LOS (d)</td>
<td>31,2</td>
<td>33,2</td>
<td>33,6</td>
<td>29,3</td>
</tr>
<tr>
<td>Mortality (%)</td>
<td>46</td>
<td>57</td>
<td>40</td>
<td>30</td>
</tr>
</tbody>
</table>

Gunnerson KJ. Crit Care 2006;10:413
Nature of unmeasured anions

Plasma [microEq/l] vs. Disease State

- DKA
- Lactic
- Unknown
- NAG
- Control

Nature of unmeasured anions:
- Citrate
- Isocitrate
- Alfa-ketoglutarate
- Succinate
- Malate
- D-lactate

BE < -8 mEq/l

References:
Forni LG.Crit Care 2005;9:R591-R595
Determinants of SIG

• Comparison of low versus high SIG group
  ▸ Ion exchange column chromatography (amino acids)
  ▸ Reverse phase HPLC (uric acid)
  ▸ Gas chromatography / mass spectrometry (organic acids)
## Analysis of SIG

<table>
<thead>
<tr>
<th></th>
<th>SIG</th>
<th>SIG</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIG (mEq/l)</td>
<td>0.9 (0.04-1.59)</td>
<td>7.3 (5.62-9.61)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ARF, n (%)</td>
<td>0 (0)</td>
<td>9 (75)</td>
<td>0.006</td>
</tr>
<tr>
<td>Mortality</td>
<td>0 (0)</td>
<td>4 (33)</td>
<td>0.068</td>
</tr>
<tr>
<td>Sepsis, n (%)</td>
<td>0 (0)</td>
<td>6 (50)</td>
<td>0.0177</td>
</tr>
<tr>
<td>SIDa (mEq/l)</td>
<td>27.1 (25.1-29.1)</td>
<td>33.1 (30.6-35.6)</td>
<td>0.002</td>
</tr>
<tr>
<td>Phosphate (mmol/l)</td>
<td>1.04 (0.99-1.17)</td>
<td>1.79 (1.43-2.26)</td>
<td>0.009</td>
</tr>
<tr>
<td>Creatinine (μmol/l)</td>
<td>84 (73-93)</td>
<td>217 (109-307)</td>
<td>0.006</td>
</tr>
</tbody>
</table>
## Plasma amino acids

<table>
<thead>
<tr>
<th></th>
<th>SIG</th>
<th>SIG</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspartic acid</td>
<td>4 (3-4)</td>
<td>9 (5-12)</td>
<td>0.001</td>
</tr>
<tr>
<td>Isoleucine</td>
<td>33 (27-40)</td>
<td>45 (38-61)</td>
<td>0.023</td>
</tr>
<tr>
<td>Ornithine</td>
<td>24 (18-44)</td>
<td>59 (44-82)</td>
<td>0.003</td>
</tr>
<tr>
<td>Tryptophan</td>
<td>22 (17-26)</td>
<td>13 (10-15)</td>
<td>0.002</td>
</tr>
<tr>
<td>Total anionic AA</td>
<td>39 (27-53)</td>
<td>35 (31-72)</td>
<td>0.643</td>
</tr>
</tbody>
</table>

*Moviat M. Crit Care Med 2008;36:752-758*
## Organic acids

<table>
<thead>
<tr>
<th></th>
<th>SIG</th>
<th>SIG</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Succinic acid</td>
<td>6 (4-8)</td>
<td>8 (6-9)</td>
<td>0.024</td>
</tr>
<tr>
<td>Pyroglutamic acid</td>
<td>22 (18-25)</td>
<td>41 (31-54)</td>
<td>0.002</td>
</tr>
<tr>
<td>p-Hydroxyphenyl</td>
<td>3 (2-5)</td>
<td>6 (3-11)</td>
<td>0.032</td>
</tr>
<tr>
<td>lactic acid</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total organic acids</td>
<td>227 (203-252)</td>
<td>294 (259-356)</td>
<td>0.023</td>
</tr>
<tr>
<td>Uric acid</td>
<td>281 (218-326)</td>
<td>383 (296-507)</td>
<td>0.021</td>
</tr>
</tbody>
</table>
### Total contribution to SIG

<table>
<thead>
<tr>
<th>Component</th>
<th>Absolute delta SIG contribution</th>
<th>Relative delta SIG contribution (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total anionic amino acids</td>
<td>5</td>
<td>0.07</td>
</tr>
<tr>
<td>Uric acid</td>
<td>169</td>
<td>2.2</td>
</tr>
<tr>
<td>Total organic acids</td>
<td>430</td>
<td>5.6</td>
</tr>
<tr>
<td>Total quantified anions</td>
<td>604</td>
<td>7.9</td>
</tr>
</tbody>
</table>

**Delta SIG** = Difference between the mean SIG's in the high and low SIG groups (7.7 mEq/l)

*Moviat M. Crit Care Med 2008;36:752-758*
Pyroglutamic acid or 5-Oxoproline

- High anion gap (SIG) metabolic acidosis
- Basic underlying mechanism is glutathione deficiency
- Usually during prolonged acetaminophen treatment - mostly women
- Clinically often diminished consciousness
**γ-Glutamyl cycle**

- **Cell membrane**
  - Aminoacid (AA)
  - γ-glutamyl transpeptidase
  - Glutathione
  - Cysteine - Glycine
  - Glutamate - AA

- **Glutathione**
  - γ-glutamyl - AA
  - γ-glutamyl transpeptidase
  - Glutathione synthase
  - Dipeptidase
  - γ-glutamyl cyclotransferase

- **Cysteine - Glycine**
  - γ-glutamyl cysteine synthase
  - Cysteine
  - L-glutamate
  - 5-oxoprolinase

- **Glutamate - AA**
  - 5-oxoprolinase
  - Renal failure

- **Negative feedback**
  - Acetaminophen
  - Alcohol
  - Diet
  - Malnutrition
  - Liver disease

- ** γ-glutamyl cycle = gluthatione stores are reduced and negative feedback falls away**
Treatment

• Withdraw the underlying causes
• Bicarbonate infusion with severe acidosis
• Acetylcysteine infusion
• CVVH
Acute Renal Failure

Acute Renal Failure  APACHE II matched controls without ARF  ICU controls

pH 7.30  PCO2 37.9  BE - 7.5

pH 7.38  PCO2 40.5  BE - 1.5

pH 7.43  PCO2 42.3  BE 2.9

Rocktaeschel J. Crit Care 2003;7:R60
Renal function and chloride excretion

\[ y = 0.0019x + 0.4198 \]

\[ R^2 = 0.329 \]

\[ p < 0.001 \]

Moviat M. 2009 (submitted)
Metabolic alkalosis
Metabolic alkalosis

Serum Potassium (mmol/L)

Serum Sodium (mmol/L)

Serum Chloride (mmol/L)

pH urine

Urinary SID

Time (hrs)

P = NS

P = NS

P < 0.0001

P < 0.005

P < 0.02

Moviat M. Crit Care 2006;10:R14
Fluid infusion

- PaCO$_2$
- A$_{TOT}$
- Strong Ion Difference

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<thead>
<tr>
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<th>Alkalosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>PaCO</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>A</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>SID</td>
<td>↓</td>
<td>↑</td>
</tr>
</tbody>
</table>

PaCO$_2$ and A$_{TOT}$ can cause acidosis or alkalosis, affecting SID and A$_{TOT}$ accordingly.
Substitution fluid

Optimal SID substitution fluid is 24 mEq/l

Do we make a more accurate diagnosis?  

N = 935

120 patients undetected

All detected by SID $↑$

108 detected by $\text{AG}_{\text{cor}}$ $↑$

Metabolic acidosis

Dubin A. Crit Care Med 2007;35:1264-1270
Analysis
Metabolic Acidosis

Immediate treatment?

Mixed Acid-Base disturbance?

Determine metabolic cause

Causal treatment

NaHCO₃ if pH < 7.0

Expected PaCO₂ 40 +SBE ± 4

1 Decrease in SID
Chloride ↑?
Lactate ↑?
Free H₂O ↑?

2 Unmeasured anions
Measure corrected anion gap
If cAG - 12 - lactate > 2  +

3 Weak acids
Albumin?
Phosphate?
Conclusions

• Stewart-Figge methodology gives a thorough insight into the nature of acid-base disturbances in the ICU

• There is no evidence that this expanded knowledge translates in a better diagnosis or outcome for our patients

• The nature of the substances responsible for the SIG remains largely unknown
Is there a difference?

\[ \text{pH} = \text{p}K_1 + \log \frac{\text{HCO}_3^-}{\alpha \text{PCO}_2} = \frac{[\text{SID}^+] - K\alpha [\text{A}_{\text{TOT}}] / K\alpha + 10^{-\text{pH}}}{\alpha \text{PCO}_2} \]

**No**

HH is a limited form of the more general Stewart-Figge equation

Case history (1)

- 21-year-old-female with recent leukemia
- Fever, dyspnea and hypotension
- Severely ill, T 41°C, HR 135, BP 80/40, RR 37
- Fine crackles over left lower lobe
Case history (2)

- pH 7.07 - PaCO₂ 6.6 kPa (50 mmHg), PaO₂ 9 kPa (68 mmHg), HCO₃⁻ 14 mmol/l, SBE -14 mEq/l

- Na 135, Cl 113, K 3.9, Alb 8, Lactate 3.3, P 1.1
According to traditional thinking

- Combined metabolic and respiratory acidosis
  - $\text{HCO}_3^-$ and SBE ↓
  - Expected $\text{PaCO}_2 = [\text{HCO}_3^-] + 8 \pm 4$ (mmHg) = 18 - 26

- Hypercapnia due to increased production, excessive dead space ventilation and exhaustion
BE depends on PaCO$_2$ and [A$_{TOT}$] - so what

Our patient
PaCO$_2$ 6.6 - pH 7.31
Low albumin (25%)
What causes the metabolic acidosis?

Loss of $[\text{HCO}_3^-]$ with chloride retention or presence of new acid (strong anion)?

- Anion gap = $[\text{Na} + \text{K}] - [\text{Cl} + \text{HCO}_3^-] = 11.9$ (normal 8 - 12)

At least correct for low albumin

$$\text{AG(cor)} = \text{AG(calc)} + \frac{1}{4} (40 - \text{albumin})$$

$$= 11.9 + \frac{1}{4} (40 - 8)$$

$$= 19.9$$

A new acid must be present
Is this the only reason for metabolic acidosis?

• Calculate the $\Delta$ gap - in an isolated anion gap acidosis the increase in the anion gap should match the decrease in $\text{HCO}_3^-$

★ Increase in anion gap is 7.9 and decrease in $\text{HCO}_3^-$ is 10 → $\Delta$ gap = 2.1 indicating a slight additional loss in $\text{HCO}_3^-$

Combined metabolic (both new acid and $\text{HCO}_3^-$ loss) and respiratory acidosis
Which acid explains the anion gap acidosis?

- Lactate - but only for a small part (lactate increase 1.3 mmol/l with anion gap increase of 7.9 mmol/l)
- Ketones? (No clues)
- Toxins (No clues)
- 5-oxoproline - pyroglutamic acid (No clues)
- Frequently unknown
In conclusion

• Stewart approach is unnecessarily complex and for most people the underlying physicochemical principles are difficult to understand

• Stewart approach does not result in a better diagnosis

• Stewart approach does not result in a different therapy

Until we know more - don’t bother