The Weekly Probe

17th February 2017 **Volume 14 Issue 6**

THIS WEEK

LAST WEEK'S CASE

A 59yo lady presents with cough , lethargy and fevers. Background of SLE – on prednisone 5mg/d. On exam T 37.8C – conjunctival pallor – rest of exam NAD (incl PR)

Bloods showed :

FBC - Hb 54 ↓↓ (MCV 100 ↑– MCH 35 ↑)- WCC 7.7 Pl 115

B12, folate N – iron studies showed increased ferritin only

VBG – pH 7.36 CO2 23 BE -13 Bicarb 13 - lactate 1.4 (N) – ketone 0.5 (normal <0.6)

UEC – 126 / 5.2 / 96 / 12 / 7.3 / 76 - Alb 31↓ Protein 91↑ Bili 29 ↑

There are problems cross matching the sample due to antibodies.
What are the potential causes for the anaemia and the metabolic acidosis, the 2 "meatiest" parts of the results?
What other test could we consider to clarify these issues and the diagnosis ?

ANAEMIA

The most prominent issue with the patient was anaemia, a common issue for ED patients. One article from 2015 looked at an approach to evaluation in the anaemic patient- as the name suggests "Anaemia: An approach to evaluation 2014" by Kuriakose which is available online.

Microcytic (MCV < 80 fL) Normocytic (MCV 80-100fL) Macrocytic (MCV > 100fL)

In this case the MCV was 100 – borderline of normo and macrocytic. What could be causing this?

MICROCYTIC – most common ED scenario

1. Iron Deficiency Anaemia (IDA) – serum ferritin is the key test +/- Total iron binding capacity (TIBC) /transferrin saturation/ serum iron).

   The complicating issue with using ferritin alone is that it is an "acute phase reactant " which will rise with inflammatory problems (as in this case) and you need to use the other components of the iron studies.

   When distinguishing IDA from anaemia of chronic disease (ACD) , the ferritin is classically low in IDA but the TIBC will be high in IDA and often low or normal in ACD.

   A rise in the platelet count may also be suggestive of iron deficiency.

Another parameter mentioned that I had never looked at is the RDW or Red cell distribution width which:

- if increased this favours the diagnosis of IDA
- if the RCW is normal, a increase in the red cell count may be suggestive of thalassaemia trait

2. Thalassaemia – abnormal globin synthesis with microcytosis. First test is haemoglobin electrophoreseis (HbEPG) yet this does not always detect the presence of thalassaemia

   a. Alpha thal – spectrum of 1-4 genetic defects – 1 defect =carrier – 2 = mild anaemia – 3 = severe anaemia (Haemoglobin H) – 4 fatal. HbEPG may be normal if 1-2 defects
   b. Beta thal – trait or symptomatic Dx

3. Other:

   a. Anaemia of Chronic Dx (ACD) - see below

   b. Sideroblastic anaemias – uncommon – increased RDW – acquired (malignant Dx of the bone marrow, alcohol, lead) or hereditary

Table 1: Differentiating between IDA, ACD, and combined IDA/ACD using iron studies

	IDA	ACD	Combined anemia (IDA/ACD)
Iron	Decreased	Decreased	Decreased
Transferrin	Increased	Decreased-normal	Decreased
Transferrin saturation	Decreased	Decreased	Decreased
Ferritin	Decreased	Normal-increased	Decreased-normal
Soluble transferring receptor	Increased	Normal	Normal-increased

IDA: Iron deficiency anemia, ACD: Anemia of chronic disease

NORMOCYTIC ANAEMIAS

1. Anaemia of Chronic Disease- need appropriate clinical context with otherwise unremarkable blood film. Probably related to cytokine mediated inhibition of RBC production or interference with erythopoeitin production / function

   Usually normocytic yet can be microcytic

2. Bone marrow disorders - via marrow infiltration or marrow aplasia – seen with other components of pancytopenia – normochromic / cytic yet can be macrocytic

3. Combined iron deficiency with vitamin B12 / folate deficiency

4. Haemolytic anaemias – which are associated with evidence of :

   - cellular destruction (raised LDH),
   - increased Hb catabolism (raised bilirubin),
   - decreased haptoglobin (which binds free Hb + is then removed by RE cells),
   - increased RBC production (raised retic count),
   - urinary haemosiderin (evidence of intravascular haemolysis).

   Categorised as either:
   - Extravascular (in spleen or liver)
     i. red cell intrinsic – spherocytosis, elliptocytosis, sickle cell
     ii. immune mediated – Autoimmune with Coombs +ve
       1. warm (idiopathic, SLE, other autoimmune Dx, CLL, lymphomas , drugs)
       2. cold (idiopathic, infections (mycoplasma, EBV), SLE, lymphoma

- Intravascular – lysis within blood vessels – microangiopathic anaemias – assoc with DIC, TTP / HUS , malignant Ht'n- blood film contains RBC fragments

- Other causes of haemolysis (most IV) include:

iii. Sickle cell Dx
iv. hypersplenism
v. infections - malaria, clostridia
vi. extensive burns
vii. tox – oxidising drugs such as dapsone, chemical poisoning – lead
viii. hypophosphataemia

Table 2: Differentiating between intravascular and extravascular hemolysis

	Intravascular	Extravascular
Reticulocyte count	Increased	Increased
Lactate dehydrogenase	Increased	Increased
Indirect bilirubin	Increased	Increased/normal
Haptoglobin	Decreased	Decreased
Urinary hemosiderin	Present	Absent

In this case:

- reticulocyte count significantly elevated – evidence of bone marrow production ++
- bilirubin elevation – evidence of red cell turnover (mild increase)
- LDH elevation – reflective of tissue destruction
- Haptoglobin – very low – the haptoglobin transports the free Hb back to the liver where the Hb-haptoglobin complex is removed
- Coomb's test – Direct antiglobulin - strongly +ve
- UA - +ve for blood ++ yet < 10 RBC on urine microscopy- indicative of free Hb / haemosiderin in the urine

MACROCYTIC ANAEMIA

1. **Folate deficiency** – recent dietary changes can effect serum levels so check RBC folate levels

2. **Vit B12 deficiency**– may be falsely low in the elderly, pregnant patients or in those with low WBC counts

3. **Misc:**

- alcohol
- Drugs- hydroxyurea, chemo agents, AZT
- Liver Dx , hypothyroidism, haemolysis with increase in reticulocytes
- Primary bone marrow dx – myelodysplasia, aplastic anaemias, myeloma

Progress: The patient was found to have a coombs +ve haemolytic anaemia of unknown aetiology (with reticulocytosis) which responded to steroids and supportive Mn including transfusion

Refs – Kuriakose P Anaemia: An approach to evaluation, 2014 *CHRISMED J Health and Research* Apr-Jun 2015; 2(2): 9599 / Hoffbrand AV , Pettit JA, Essential Haematology Blackwell Scientific publications

Metabolic Acidosis

The essential first step is to assess the available history, examination, investigations and use these to make a clinical decision as to the possible and most likely acid-base diagnosis. Always place the results in clinical context. **Be very wary of over-interpretation** - Always check for other evidence to

support the diagnosis as an unexpected value without any other evidence should always be treated with great caution. **Treat the patient not the results alone**.

The Six Steps of Systematic Acid-Base Evaluation

1. pH: Assess the net deviation of pH from normal- note that the pH may be normal of compensation is complete
2. Pattern: Check the pattern of bicarbonate & pCO2 results
3. Clues: Check for additional clues in other investigations
4. Compensation: Assess the appropriateness of the compensatory response
5. Formulation: Bring the information together and make the acid base diagnosis
6. Confimation: Consider if any additional tests to check or support the diagnosis are necessary or available & revise the diagnosis if necessary

Some Clues to Interpretation of Acid-Base Disorders

"Clue"	*Significance*
High anion gap	*Always* strongly suggests a metabolic acidosis.
Hyperglycaemia	If ketones also present – suggestive of diabetic ketoacidosis
Hypokalaemia and/or hypochloraemia	Suggests metabolic alkalosis
Hyperchloraemia	Common with normal anion gap acidosis
Elevated creatinine and urea	Suggests uraemic acidosis or hypovolaemia (prerenal renal failure)
Elevated creatinine	Consider ketoacidosis: ketones may interfere in the laboratory method used for creatinine measurement & give a falsely elevated result; typically urea will be normal.
Elevated glucose	Consider ketoacidosis or hyperosmolar non-ketotic syndrome

Calculating the anion gap enables the patient to be categorised as either normal anion gap & high anion gap acidosis.

Anion gap = Na + K - (Cl + HCO3).
Normal = 15 +/- 2,. The anion gap is normally due to sulphates, phosphate, protein, especially albumin, organic acids eg. lactic acid.

In this case the AG was 126 + 5.2 – (96+12) = 23.2 – thus elevated AG.

Increased anion gap acidosis can be due to:

- increased anion production (DKA, lactic acidosis, starvation, alcoholic ketoacidosis, inborn errors) or
- ingestion of toxins (salicylate OD, paraldehyde, methanol, ethylene glycol, cyanide, isoniazid, toluene), or
- acute/chronic renal failure.

There are some mnemonics to help you remember the causes of the acidosis.
DULSI (like the old women's name) is the easiest – Diabetes, Uraemia, Lactic acidosis, Salicylates , Intoxicants
Increased Anion Gap acidosis: **MUDSLEEP**. Methanol, Uraemia, DKA, Salicylate, Lactate, Ethanol, Ethylene glycol, Paraldehyde + cyanide,.
Some people use the pneumonic **MUDSLIDE** to help them remember. - inborn errors of metabolism, + iron, isoniazid.

Lactic Acidosis can be divided into Type A or Type B.

- Type A: due to poor perfusion with tissue hypoxia eg. severe hypoxia, severe anaemia, haemorrhage, CCF, CO/CN poisoning, generalised seizures.
- Type B is where tissue hypoxia is not apparent such as in diabetes mellitus, Renal & liver failure, malignancy such as lymphoma, leukaemia or sarcoma, & drug ingestion such as ethanol, methanol & biguanides, salicylates, isoniazid, fructose, sorbitol; & congenital enz deficiencies (G6Pase defic).

Editor: Peter Wyllie

Also consider the *Osmolar Gap*.
Normal serum osmolality 280-300.
Calculated serum osmolality = (2xNa) + Glucose + Urea.
Osmolar Gap = Measured - Calculated. An osmolar gap > 10 is significant & indicates the presence of osmotically active substances eg. ethanol, methanol, ethylene glycol, isopropyl alcohol, mannitol.

In this case, the lactate was normal, the ketones 0.3 (normal), Urea + Cr normal -? Related to error of metabolism secondary to severe anaemia.
It also prompted the question as to whether this was a mixed acid-base problem?

Normal Anion Gap acidosis can be due to:

- GIT loss of HCO3 (diarrhoea, ureterosigmoidostomy, anion-exchange resin, small bowel drainage, Ca Cl2, Mg Cl2., or
- Renal loss of HCO3 (carbonic anhydrase inhibitors, renal tubular acidosis, hyperparathyroidism, hypoaldosteronism), or other (dilutional acidosis, hyperalimentation acidosis, sulphur ingestion, HCl ingestion).

You can use the mnemonic **USED CARP**. Ureteroenterostomy / obstructive uropathy, Small bowel fistula, Extra Cl, Diarrhoea, Carbonic anhydrase inhibitors, Addisons, Renal tubular acidosis, Pancreatic fistula.

Low anion gap acidosis: can be due to Lithium toxicity (increased unmeasured cation), multiple myeloma (increased positive charge of abnormal proteins), hypercalcaemia, hyperMg, bromide intoxication.

Also note you can get 2 pathologies occurring simultaneously – respiratory and metabolic eg aspirin overdose causing metabolic acidosis and respiratory alkalosis.

Is there a combined mixed metabolic acid–base disturbance?
To do this we can use the **Delta ratio**. The delta ratio is the comparison between the increase (delta) in the anion gap above the upper reference value (e.g., **12** mmol per liter) and the change (delta) in the concentration of bicarbonate ions from the lower reference value of bicarbonate ions (e.g., **24** mmol per liter).

In this case the **AG is 23.2 which is 11.2 above** the upper reference range
The **delta bicarb is 24 – 12 = 12**

The **Delta ratio = (Increase in Anion Gap / Decrease in bicarbonate)**

In this case it is **11.2 / 12 = 0.9**

Note that if you go via Firstnet to CIAP - "Tools" – "MD calc"- look for the anion gap calculator and this will include the delta ratio

Delta Ratio	Assessment Guideline
< 0.4	Hyperchloraemic normal anion gap acidosis eg patients treated with excessive normal saline
0.4 - 0.8	Consider combined high AG & normal AG acidosis (note that the ratio is often <1 in acidosis associated with renal failure)
1 to 2	Usual for uncomplicated high-AG acidosis Lactic acidosis: average value 1.6 DKA more likely to have a ratio closer to 1 due to urine ketone loss (esp if patient not dehydrated)
> 2	Suggests a pre-existing elevated HCO_3 level so consider: • a concurrent metabolic alkalosis, or • a pre-existing compensated respiratory acidosis

This case - 0.9 ? mixed disorder

Read on if you want more details re acid-base read on – if your head is spinning, stop now.

Another way of looking at this problem is to use the **Stewart Approach -**When looking at cid base problems we often focus on the H+ and HCO3 as the heart of a pH problem.

Editor: Peter Wyllie

However there is a thought that these are dependent variables in that they change as a result of other factors, other ions which influence their levels and subsequently the pH.

Stewart's described 3 independent variables which are amenable to change in-vivo:

- partial pressure of carbon dioxide (PCO_2),
- Strong Ion Difference [SID].
- total weak non-volatile acids [A_{TOT}],

1) PCO_2:- controlled by lung

Changes in acid-base status are either respiratory or metabolic:
The effects of changes on PCO_2 are well understood and produce the expected alterations in $[H^+]$:
$CO_2 + H_2O <—> H_2CO_3 <—> HCO_3^- + H^+$

Metabolic disturbances, cannot be viewed as a consequence of bicarbonate concentration because bicarbonate is merely a dependent variable ie it changes because of something else. The two possible sources of metabolic (ie non-repiratory) acidosis and alkalosis are either [SID] or [A_{TOT}].

2) SID:- largely controlled by kidney

The Strong Ion Difference is the difference between the sums of concentrations of the strong cations and strong ions and is based on the idea of electroneutrality ie all the +ve ions = all the –ve ions :
$[SID] = [Na^+] + [K^+] + [Ca^{2+}] + [MG^{2+}] - [CL^-] - [Other\ Strong\ Anions]$.

With normal protein levels, the [SID] is about 40mEq/L. Any departure from this normal value is roughly equivalent to the standard base excess, i.e., if the measured [SID] were 45 mEq/L, the BE would be about 5 mEq/L, and a measured [SID] of 32 mEq/L would approximate to a BE = -8 mEq/L.

However as there are smaller contributions from most of the cations and anions we can simplify this to use only **Na and Cl**- using **38** as a cutoff. Note that this is a similar concept to the AG yet the bicarb is not included.

In this case the Na – Cl was 126-96 = 30 c/w a low SID

1. If difference shrinks (i.e. relatively more Cl) more acidotic
   Principle of electrical neutrality requires more H+ to offset the additional Cl
2. If difference increases (i.e. relatively more Na) more alkalotic
   Principle of electrical neutrality requires more bicarb to offset the additional Na

Low SID if <38
- Strong ion acidosis = hyperchloremic acidosis = non-gap acidosis
- Causes include:
  - Fluid administration
    - Any fluid that has SID of <24 can cause acidosis (e.g. NS, ½ NS, D5W)
  - Renal Tubular Acidosis
    - Calculate Urine Anion Gap: (Urine Na + K – Cl); if negative, not RTA
      - Type I: Urine pH <5.55
      - Type II: Urine pH >5.55
      - Type IV: Hyperkalemic; from aldosterone deficiency, diabetes
  - Diarrhea

High SID if >38
- This is suggestive of metabolic alkalosis
- Causes include:
  - Nasogastric suction
  - Diuretics
  - Hyperaldosteronism
  - Volume depletion

[A_{TOT}]- controlled by liver:

[A_{TOT}] is the total plasma concentration of the weak non-volatile acids, inorganic phosphate, serum proteins, and albumin- the proteins especially albumin (acting as a weak acid) making the greatest contribution to acid-base balance:
In this case the total protein is high – making the pH more acidotic
Hypoproteinemia, therefore, causes a base excess and vice versa.
Phosphate levels are normally make a minimal contribution except in the setting of renal failure where high phosphate levels contribute to the acidemia.

NSAIDS and the kidney- changes in sodium excretion and HT'n /can cause interstitial nephritis / nephrotic syn / acute tubular necrosis- explaining the low alb, hypoK and elevated Cr .

Editor: Peter Wyllie

In this case the bloods were pre-fluids and there was no diarrhoea – thus possible RTA (yet no urinary electrolytes were done).

Nevertheless the main principle was supportive management – transfusion, steroids for her autoimmune haemolytic anaemia, fluid management, antibiotics for potential sepsis and bicarbonate.

As in this example some of the tools help, some don't. Use the numbers of guide your diagnosis and management and they should be taken in the context of the history and exam. Treat the patient not the numbers

Refs – uptodate - http://www.anaesthesiamcq.com/AcidBaseBook / http://www.acid-base.com/strongion.php

JOKE / QUOTE OF THE WEEK

"You slept with her, didn't you?"

An Englishman, Scotsman, Irishman, Australian, Welshman, a Latvian, a Turk, a Yank, a Egyptian, a Mexican, a Jap, a Russian, a Greek, a Belgian, a Serb, a Bulgarian , an Italian and a Norwegian went to a night club.

The bouncer said:

"Sorry, I can't let you in without a Thai"

Please forward any funny and litigious quotes you may hear on the floor (happy to publish names if you want)

THE WEEK AHEAD

Tuesdays - 14:30 – 15:30 Intern & JMO teaching -Thomas & Rachel Moore
Wednesday- 0800-0900 Critical Care Journal Club. ICU Conf Room / 14:30 – 15:30 Intern & JMO teaching -Thomas & Rachel Moore
Thursday 0730-0800 Trauma Audit. Education Centre / 0800-0830 MET Review Education centre / 1300-1400 Medical Grand Rounds. Auditorium.

Editor: Peter Wyllie