Pathology Course
CHEMICAL PATHOLOGY
Tom Marjot

Kindly sponsored by:
Coming up...

• Acid base
• Calcium, phosphate, bones
• Kidney stones
• Water and electrolytes
• Pituitary
• Lipids
ACID-BASE DISTURBANCE

• Body normally controls pH within a tight range; normal pH is required for functioning of many enzyme systems.

• Profound acidosis (pH<7) → no cellular function and death

• Series of questions need to ask yourself in order to unpick blood gas results. Be systematic
Questions to ask......

• What do I think clinically? – “vomiting child,” “gastroenteritis,” “Diabetic”

• Acidotic, alkalotic or normal range?

• Is the acid-base disturbance due to a metabolic or respiratory cause?

• REMEMBER
  1) CO2 is acidic and HCO3 is alkaline
  2) HCO3 equals ‘metabolic’ and CO2 equals ‘respiratory’
  3) Base excess abnormal equals ‘metabolic’
• Is there any compensation; whichever chemical is causing the imbalance is it counteracted by the opposite chemical?

• Eg high bicarbonate → increase in pCO2

REMEMBER
1) Body can never overcompensate; ie initial acidosis the body can not make it an alkalosis
2) pH will stay on the acidic side of normal (<7.4)
• “4 week baby admitted to hospital with projectile vomiting……” *Pyloric stenosis*

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<table>
<thead>
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<tbody>
<tr>
<td><em>pH</em></td>
<td>7.5</td>
<td>(7.35-7.45)</td>
</tr>
<tr>
<td><em>pCO2</em></td>
<td>6.5 kPa</td>
<td>(4.7-6)</td>
</tr>
<tr>
<td><em>HCO3</em></td>
<td>37 mmol/L</td>
<td>(22-28)</td>
</tr>
</tbody>
</table>

1) Alkalotic
2) Metabolic
3) *pCO2* is increased; there is respiratory compensation. Not sufficient (yet) to bring *pH* into normal range
“4 week baby admitted to hospital with projectile vomiting......” *Pyloric stenosis*

What else would you expect to see on ABG and on U&Es?

- **Base excess** (NR -2 to +2)   
  - High ? - Low ? - Normal ?   
  **HIGH >2**

  “amount of strong acid that must be added to each litre of fully oxygenated blood to return the pH to 7.40”

- **Chloride**   
  - High ? - Low ? - Normal ?   
  **LOW**

  loss of HCl (gastric acid)

- **Potassium**   
  - High ? - Low ? - Normal ?   
  **LOW**

- gastric contents and hypovolaemia → increased aldosterone
- Hypokalaemia $\rightarrow$ alkalosis
- Hyperkalaemia $\rightarrow$ acidosis
If you see Acidosis in presence of hypokalaemia

• Think renal tubular acidosis

• Failure of acid secretion → leads to an inability to acidify the urine to a pH of less than pH5.3.

• Inherited or secondary to autoimmune disease – RA, SLE, Sjrogrens

• Acidosis, hypokalaemia, stones
Vomiting....

Try and make links within path and with the specialities

Haem:
• 52 year old man with Hodgkins disease just started ABVD chemotherapy, shallow respirations

O&G
• “26 year old female, 10 weeks pregnant, severe intractable vomiting”

Psyche
• “13 year old girl, pitting of the teeth and Russell's sign”
pH 7.3, HCO3 ↑, pCO2 ↓, Base excess <2

Metabolic acidosis

May be due to

1) Increased H+; DKA or lactic acidosis or toxins

2) Decreased H+ excretion: Renal tubular acidosis

3) Loss of bicarbonate: ++diarrhoea, pancreatoduodenal fistula
The graph illustrates the relationship between arterial pH and arterial [H+] (nmol L⁻¹) and arterial Pco₂ (kPa). The highlighted area suggests a potential cause for metabolic acidosis. The graph also distinguishes between respiratory alkalosis and respiratory acidosis, as well as acute and chronic respiratory alkaloses.

- **Metabolic acidosis** is indicated in the red shaded area.
- **Respiratory alkalosis** and **respiratory acidosis** are shown in blue and green, respectively.
- **Acute respiratory acidosis** and **chronic respiratory alkalosis** are also highlighted.

The graph helps in understanding how changes in arterial pH and [H+] are associated with specific types of acid-base imbalances.
ANION GAP
(Na\(^+\) + K\(^+\)) – (Cl\(^-\) + HCO\(_3\)\(^-\))

Normal range 10-18

High anion gap metabolic acidosis:

- Ketones (DKA)
- Uraemia (renal failure)
- Lactic acid (metformin, ischaemia, sepsis)
- Toxins (methanol)

The H\(^+\) released by all of these is **buffered by** HCO\(_3\) → increased anion gap
ANION GAP

$$\text{(Na}^+ + \text{K}^+) - (\text{Cl}^- + \text{HCO}_3^-)$$

Normal range 10-18

Normal anion gap metabolic acidosis:

- GIT HCO$_3^-$ loss: Diarrhoea/fistula
- Renal HCO$_3^-$ loss: proximal renal tubular acidosis
- Failure of H+ secretion: distal RTA
- Addison's disease

Drop in HCO$_3^-$ is compensated for almost completely by an increase in Cl$^-$ and hence is also known as **hyperchloraemic acidosis**
Respiratory acidosis
CALCIUM, PHOSPHATE, BONES
Only 7 diagnoses to choose from

1. Malignancy
2. Hyperparathyroidism
3. Osteomalacia
4. Pagets
5. Osteoporosis
6. Familial hypocalcuric hypercalcaemia
7. Others
Calcium 2.2 - 2.6 mmol/L

- Controlled by two hormones, PTH and activated vitamin D
- **PTH** has a more powerful effect
  - Reabsorption of Ca\(^{2+}\) from BONE
  - Reabsorption of Ca\(^{2+}\) from KIDNEYS
  - Excretion of Phosphate from kidney
  - Increases renal 1-alpha hydroxylation of vitamin D
- **1,25(OH)\(_2\)D** only causes reabsorption of Ca\(^{2+}\) from GIT
- (NB **calcitonin** – reduces Calcium, marker for medullary Thyroid Ca)
"If in the presence of hypercalcaemia PTH is not reduced to zero then diagnosis is PRIMARY HYPERPARATHYROIDISM"

- A benign hypersecreting adenoma
Hypercalcaemia in malignancy

• Often in very advanced disease
• Due to
  – boney metastasis
  – PHrP “parathyroid hormone related peptide”
→ Humoral hypercalcaemia

Squamous cell lung carcinoma
Vitamin D deficiency → low/normal calcium, slightly raised PTH but never enough to cause hypercalcaemia
OSTEOPOROSIS: All biochemistry is normal. Diagnosis via DEXA scanning.

PAGETS DISEASE: Defined by +++ increase in ALP, NB risk of osteosarcoma.
ALKALINE PHOSPHATASE

A rise in alkaline phosphatase can be caused by each one of the following except:

A. Pregnancy  
B. Pagets disease  
C. Healing fractures  
D. Hypoparathyroidism  
E. Osteomalacia

NB: Myeloma has normal ALP

<table>
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<tr>
<th>Raised ALP and normal calcium</th>
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OSTEOSARCOMA

- Highly malignant
- 60% at knee
- Peak in adolescence
- Look for ‘codmans triangle’

EWINGS SARCOMA

- Highly malignant
- Long bones & pelvis
- Peak in adolescence
- “small round cells”
- Onion skinning of periosteum
- Stains for CD99 (MIC2)
- t(11,22)
↓Ca and ↓↔PTH
HypOparathyroidism

- Much rarer than hyperparathyroidism
- Congenital or acquired

**Congenital**: absence of Parathyroid glands (DiGeorges syndrome)

**Acquired**:
- post thyroid surgery (temporary or permanent)
- Autoimmune
- Magnesium deficiency (alcoholics)

Receptor resistance to parathyroid hormone \(\rightarrow\) pseudo-hypoparathyroidism
CALCIUM, PHOSPHATE, BONES

Only 6 diagnoses to choose from

1. Malignancy ✓
2. Hyperparathyroidism ✓
3. Osteomalacia ✓
4. Pagets ✓
5. Osteoporosis
6. Familial hypocalcic hypercalcaemia

7. Others
Osteoporosis:

- **S**teroids
- **H**yperthyroidism
- **A**lcohol and smoking
- **T**hin (BMI<22)
- **T**estosterone ↓ (prostate cancer treatment)
- **E**arly menopause
- **R**enal failure
- **E**rosive Rheumatoid arthritis
- **D**iet - malabsorption
Familial Hypocaluric Hypercalcaemia

Consider this diagnosis in ...

- **Asymptomatic** hypercalcaemia
- **Young** patient
- **Known** family history
- **Low** urinary calcium <200mg/day

- Due to loss of function mutations in calcium sensing receptor in kidney → increased reabsorption
- Completely benign
Others

- A 30-year old man has recently developed a cough, and shortness of breath on exertion. Chest X-ray shows bilateral hilar lymphadenopathy. Routine blood tests show a calcium of $2.8 \text{ mmol/l}$

**SARCOIDOSIS**

Granulomatous conditions, epitheloid cells (macrophages) can ectopically 1-alpha hydroxylate vitamin D.

**PATH GRANULOMAS:**
PBC, Sarcoid, TB, Leprosy, Histoplasmosis, Cryptococcus, Crohns
Renal stones

A. Calcium oxalate
B. Ammonium magnesium phosphate
C. Cysteine
D. Xanthine
E. Urate

A 26 year old woman develops severe right flank pain radiating to the groin. She has recently been treated for a urinary tract infection. Urinary MC&S confirmed the presence of ureaplasma urylticum
Renal stones

A. Calcium phosphate
B. Ammonium magnesium phosphate
C. Cysteine
D. Xanthine
E. Urate

A 26 year old woman develops severe right flank pain radiating to the groin. She is also noted to be breathing very heavily, ABG shows a pH of 7.31, She is known to suffer from Sjogren's disease. Xray of kidneys ureter and bladder show a small opacification just lateral to the psoas shadow.
Renal stones

A. Calcium phosphate
B. Ammonium magnesium phosphate
C. Cysteine
D. Xanthine
E. Urate

A 26 year old woman develops severe right flank pain radiating to the groin. She has just undergone aggressive combination chemotherapy for treatment of a Burkitt lymphoma.

Chronic – Gout
Acute – tumour lysis syndrome
WATER AND ELECTROLYTES
A 25 year old man complains of thirst & polyuria. Investigations: Na 151mmol/l, K 4.0mmol/l, Urea 7.1mmol/l, Creatinine 115umol/l, urine specific gravity 1.005 (normal 1.001–1.035), Glucose 4.3mmol/l (3.0-6.1), Calcium 2.4mmol/l (2.2-2.6), Phosphate 0.9mmol/l (0.8-1.6).

A 25 year old man complains of thirst & polyuria. Investigations: Na 129mmol/l, K 3.7mmol/l, Urea 4.2mmol/l, Creatinine 90umol/l, urine specific gravity 1.002, Glucose 4.6mmol/l, Calcium 2.38mmol/l, Phosphate 1.0mmol/l.

A 40 year old woman complains of thirst & polyuria. Investigations: Na 145mmol/l, K 4.0mmol/l, Urea 6.2mmol/l, Creatinine 100umol/l, Urine specific gravity 1.030, Glucose 4.5mmol/l, Calcium 2.91mmol/l, Phosphate 0.4mmol/l.
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- A  SIADH
- B  Diabetes insipidus
- C  Diabetes mellitus
- D  Psychogenic polydipsia
- E  Primary hyperparathyroidism
- F  Sarcoidosis
- G  Amyloidosis
- H  Addison’s disease
- I  Vitamin D deficiency
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DIABETES INSIPIDUS
Cannot produce a concentrated urine due to:
• a deficiency of antidiuretic hormone (ADH) or
• renal resistance to ADH
• High concentrated plasma (high osmolality)
• **Hypernatraemia** in presence of very dilute urine (+polyuria and polydipsia)

PSYCHOGENIC POLYDIPSIA
• Excessive water drinking in absence of physiologic stimuli
• Well tolerated
• **Hyponatraemia** in presence of dilute urine (+polyuria and polydipsia)
**Diagnosis: 8hr fluid deprivation test**

**Normal**: Urine concentration ↑
>600mOsmol/kg

**Primary polydipsia**: Urine concentrates >400-600mOsmol/kg

**Cranial DI**: urine concentrates only after giving desmopressin

**Nephrogenic DI**: zero concentration urine after desmopressin
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• 1,25(OH)$_2$D only causes reabsorption of Ca$^{2+}$ from GIT
Water, sodium and potassium

• Water never actively transported anywhere in the body
• Moves depending on change in solute content of a fluid compartment
• Solute content of EXTRACELLULAR FLUID = osmolality

NB osmolarity and osmolality are basically the same
Tiny difference in the technology used to measure solute concentrations

\[ 2(Na^+ + K^+) + \text{Urea} + \text{Glucose} \]

NR: 275-295 mosmol/l
$2(Na^+ + K^+) + \text{Urea} + \text{Glucose}$

NR: 275-295 mosmol/l

Even slight loss of water (in water deprivation) $\rightarrow$ will increase osmolality and result in movement of H2O from ICF to ECF

$\rightarrow$ Stimulate thirst centres in hypothalamus $\rightarrow$

VASOPRESSIN RELEASE
Osmolar gap

Measured Osmolality – Calculated Osmolality

Should be roughly equal (<10)

Significant discrepancy provides indirect evidence that extra osmotically active species are present in plasma.

Ethanol, methanol & ethylene glycol
Hyperosmolar non-ketotic coma

- $2(Na^++K^+) + \text{Urea} + \text{Glucose}$

In a patient with hyperosmolar non ketotic coma. TRUE OR FALSE

1. Heparin in a useful treatment
   - T
2. The prognosis is worse than in DKA
   - T
3. The patients diabetes can subsequently be controlled by diet alone
   - T
4. The degree on unconciousness is most closely associated with plasma osmolality
   - T
5. Very large amounts of insulin are required
   - F
Hyponatraemia

• Sodium concentration relies on both sodium and water in the plasma
• Low concentration does not necessarily imply sodium depletion

Diagnosis relies on asking **2x questions**

1 – what is the **osmolality**
2 – what is the **fluid status** of the patient (clinically)
1/ “What is the osmolality?”

Hyponatraemia

Measure osmolality

Increased or normal

Hyperglycaemia
Mannitol
Hypertonic IV infusion
Lipaemia
Hyperproteinaemia
Isotonic IV infusion

Decreased

True hyponatraemia
1/ “What is the volume status?”

True Hyponatraemia

Assess ECF volume

Increased

SODIUM and H2O excess
  CCF
  Hepatic F
  Nephrotic syndrome
  Hypotonic saline

Normal

Water excess
  Excessive intake + impaired excretion
  SIADH

Decreased

Sodium depletion
  Renal
  GIT
  Cutaneous
Scenario

- 89 year old woman bought to A and E having suffered **two brief fits** at home. She is currently drowsy but has no headache. Husband states she has never been to hospital but that her GP has just started her on an **antihypertensive**. She has reduced skin turgor and no focal neurology.

- Thiazide diuretics => ↓Na
Which of the following is not caused by thiazide diuretics?

A. Hyponatraemia
B. Hypokalaemia
C. Hypocalcaemia
D. Gout
E. Insulin resistance
F. Hyperlipidaemia
THIAZIDES. 4 hyper 2 hypos

- **HYPO**
  - Hyponataemia
  - Hypokalaemia

- **HYPER**
  - Hypercalcaemia
    - (↓calcium excretion, therefore Rx recurrent stones)
  - Hyperuricaemia → gout
  - Hyperlipidaemia
  - Hyperglycaemia
SIADH

- True Hyponatremia
- Euvolaemic
- No Renal, Adrenal, cardiac disease
- Not on Drugs (eg Diuretics)
- U. Na > 20 + ↑ U. Osmo
You get phoned about this patient's potassium

5.7mmol/l

Which one of the following would not explain this result?

A. Delay ion transport to the laboratory
B. Losartan therapy
C. Addisons disease
D. Acute renal failure
E. Conns syndrome
Aldosterone

Increases —> ↓K⁺
Conns syndrome

Decreases —> ↑K⁺
Addisons
ACEI and ARBs
Potassium-sparing dieuretics
• Caution should always be exercised when combining diuretics. However, which one of the following combinations is always contraindicated?

A. Metolozone + bumetanide  
B. Bendroflumethiazide + furosemide  
C. Amiloride + spironolactone  
D. Bendroflumethiazide + triamterene  
E. Spironolactone + furosemide
NB that cortisol at high levels has mineralocorticoid effects

- Mineralocorticoid = aldosterone

- 67 year old Long term smoker with 1 month history of haemoptysis admitted to hospital for investigation. On examination you notice significant abdominal striae, a proximal myopathy and he is quite confused. ECG shows inverted T waves and large PR interval.

1. Hypokalaemia
2. ? Cushingoid symptoms
3. Lung cancer

Small cell lung cancer can produce **ectopic ACTH**
ACTH \( \rightarrow \) ++ Cortisol \( \rightarrow \) **Cushings** syndrome
High cortisol has aldosterone-like effects \( \rightarrow \) **Hypokalaemia**
Aldosterone continued...

1. Complete pituitary failure (no ACTH)
2. Congenital adrenal hyperplasia (no cortisol or aldosterone)

• Emergency treatment is always HYDROCORTISONE. – Glucocorticoid (cortisol) effects and Mineralcorticoid (aldosterone) effects.
Pituitary failure

• Use combined pituitary function test (CPFT) – triple bolus test

• Administer

1. **Gonadotrophin releasing hormone**
2. **Insulin**
3. **Thyrotrophin releasing hormone**

4. Measure **LH** and **FSH**
5. Measure **cortisol** and **growth hormone**
6. Measure **prolactin** and **TSH**
LIPOPROTEIN METABOLISM

Age-adjusted incidence of Coronary Heart Disease relative to Serum Cholesterol (Law et al, 1994)

Increases in triglyceride and CHD risk associated with apoA-V promoter genotypes (Sarwar et al, 2010)

Comparative effects of lipid-regulating drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>LDL-C</th>
<th>HDL-C</th>
<th>TG</th>
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</thead>
<tbody>
<tr>
<td>Atorvastatin 40 mg</td>
<td>-51</td>
<td>+5</td>
<td>-32</td>
</tr>
<tr>
<td>Nicotinic acid 4 g</td>
<td>-9</td>
<td>+43</td>
<td>-34</td>
</tr>
<tr>
<td>Gemfibrozil 1.2 g</td>
<td>-18</td>
<td>+12</td>
<td>-40</td>
</tr>
<tr>
<td>Ezetimibe 10 mg</td>
<td>-18.5</td>
<td>+3.5</td>
<td>-5</td>
</tr>
<tr>
<td>Colestyramine 24 g</td>
<td>-23</td>
<td>+8</td>
<td>+11</td>
</tr>
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</table>
1. Basics of lipid transport and metabolism
2. Understand Chylomicrons, LDL, HDL, TG, ApoE, B100 etc
3. LDL receptor
4. Causes of primary hyperlipidaemia
5. Causes of secondary hyperlipidaemia
Lipoprotein metabolism

It is divided into two pathways,

1. Exogenous – dietary fats
2. Endogenous – originating from liver
Dietary fat enters the intestine, where it is processed into chylomicrons and released into the bloodstream. Chylomicrons are broken down by lipoprotein lipase (LPL) in adipose tissue and muscle, releasing free fatty acids (FFA). The remnants of chylomicrons and VLDL are transported to the extrahepatic cells, where they are further metabolized.

Endogenous lipids are processed in the liver, with lipoprotein lipase (LPL) and hepatic lipase (HL) playing key roles. LDL is metabolized in muscle and adipose tissue, and HDL is involved in lipid transport.

Additional enzymes like LCAT (lecinthin: cholesterol acylhydrolase) are also involved in lipid metabolism, facilitating the conversion of IDL to LDL.
CHYLOMICRON

VLDL

LDL

TRIGLYCERIDE

70%

B100

50%

CHOLESTEROL

85%
• Most systemic **triglyceride** carried in **VLDL**
• Most systemic **cholesterol** carried in **LDL**
• Both are atherogenic

• When a cell needs cholesterol, LDL-receptors are mobilised to cell surface where they bind **apoprotein B100**. LDL is then internalised and metabolised. LDL receptors are recycled.
Primary hyperlipidaemia

• Fredrickson classification (1 – 5)
• Describes six characteristic patterns of changes in the individual lipid moieties.
• Does not consider HDL
WHAT IS THE MOST LIKELY DIAGNOSIS

A. FAMILIAL HYPERTRIGLYCERIDAEMIA
B. COMBINED HYPERCHOLESTEROLAEMIA
C. DYSBETALIPOPROTEINAEMIA
D. CHRONIC RENAL FAILURE
E. NEPHROTIC SYNDROME
## Hyperlipidaemia

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<td></td>
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<td>↓LPL</td>
<td>XANTHOMA</td>
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<td>3</td>
<td>Dysbeta-lipoproteinaemia</td>
<td>IDL</td>
<td>APOE2</td>
<td>PALMAR XANTHOMA</td>
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<td>4</td>
<td>Hypertriglyceridaemia</td>
<td>VLDL</td>
<td>?</td>
<td>CAN ➔ PANCREATITIS</td>
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ApoE

• ApoE is essential for the normal catabolism of triglyceride-rich lipoprotein (chylomicrons, VLDL, IDL)
• 3 isoforms ApoE 2, 3 and 4
• ApoE2 isoform leads to reduced clearance of systemic lipid particles.
SECONDARY HYPERLIPIDAEMIA

Hormonal factors
Pregnancy
Exogenous sex-hormones
Hypothyroidism

Metabolic disorders
Diabetes – *juvenile onset, maturity onset*
Gout
Obesity
Progressive partial lipodystrophy
Storage disorders

Renal dysfunction
Nephrotic syndrome
Chronic renal failure, on dialysis or post-transplant

Obstructive liver disease

Toxins
Alcohol
Dioxin and chlorinated hydrocarbons

Iatrogenic
Antihypertensives
Immunosuppressants
Other drugs

Miscellaneous causes

“breast tenderness and hyperpigmentation of linea alba”

“polyuria and polydipsia and weight loss”

“Hypoalbuminuria, proteinuria and oedema”

“Raised MCV, deranged LFTs and intention tremor”

“recently started on rate control medication for atrial fibrillation”
• Which one of the following is not part of the diagnostic criteria for the metabolic syndrome?

1. High triglycerides
2. Low HDL
3. High LDL
4. Central obesity
5. Hypertension

HDL responsible for reverse cholesterol transport. From circulation to liver