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Chapter 13

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad Chapter 13

Pharmacology

• Prior to initiating a TNF-alpha inhibitor, all patients should be screened for: tuberculosis,
 hepatitis B, and
 hepatitis C. • All forms of anti-TNF therapy are given by injection. Etanercept is given as subcutaneous injection twice per week. Infliximab is given as an infusion (intravenous).
 requires intravenous infusion in a hospital setting.
 It is given 2-4 weekly initially and then on a 6-8 weekly basis and as per protocol. Infliximab monotherapy induces the production of anti-infliximab antibodies, which may reduce its effectiveness. Adding methotrexate to infliximab therapy may prevent this response. Adalimumab is given as (subcutaneous injection) on alternate weeks (every second week). • Unlike methotrexate,
 there is little problem with nausea.
 Nor is there the same concern for effects on blood cells and the liver which means less blood tests are required. • TNF-α inhibitors should normally be used in combination with methotrexate.
 If methotrexate is intolerant, adalimumab and etanercept may be given as monotherapy.

Monoclonal antibodies

Overview • manufactured by a technique called somatic cell hybridization.
• This involves the fusion of myeloma cells with spleen cells from a mouse that has been immunized with the desired antigen. The resulting fused cells are termed a hybridoma and act as a 'factory' for producing monoclonal antibodies.
• The main limitation to this is that mouse antibodies are immunogenic leading to the formation of human anti-mouse antibodies (HAMAs). This problem is overcome by combining the variable region from the mouse body with the constant region from an human antibody.

Rituximab - monoclonal antibody against CD20 Cetuximab - monoclonal antibody against the epidermal growth factor receptor

Some monoclonal antibodies in clinical use include: monoclonal antibodies Action Indication Digibind Digoxin-binding antibody
for treatment of overdoses Abciximab Glycoprotein IIb,IIIa receptor
for unstable angina. Pexelizumab Anti-C5 (complement) - antiinflammatory

Rituximab Anti-CD20 non-Hodgkin's lymphoma Infliximab anti-TNF rheumatoid arthritis and

Crohn's Cetuximab anti-epidermal growth factor receptor and head and neck cancer Trastuzumab anti-HER2, anti EGF receptor metastatic breast cancer Alemtuzumab anti-CD52 chronic lymphocytic leukemia Abciximab anti-glycoprotein IIb/IIIa receptor ischemic events in patients OKT3 anti-CD3 prevent organ rejection Tocilizumab directed against IL-6 receptor
treatment of moderate-to-

DMARDs and/or anti-TNF Nivolumab PD-1 (programmed cell death) inhibitor (PD-1 receptors are found on the surface of T cells.) melanoma and lymphoma.

Monoclonal Antibodies in Rheumatoid Arthritis Monoclonal Antibodies Directed Against TNF-α Antibodies Against B Cells

Antibodies That Interfere With IL-6 Function Antibodies That Interfere With IL-1 Function Infliximab Adalimumab
Golimumab Certolizumab
Rituximab

Tocilizumab

(increases clearance). reduces myocardial infarction and death following coronary artery bypass graft (CABG) and angioplasty. metastatic colorectal cancer undergoing PCI, prevention of severe RA in patients with an inadequate response to carcinoma of the lung
Nivolumab in combination with ipilimumab used in metastatic Anakinra

Pharmacology

Monoclonal antibodies are also used for: • medical imaging when combined with a radioisotope • identification of cell surface markers in biopsied tissue • diagnosis of viral infections Side effects • Nivolumab (PD-1 inhibitor) and ipilimumab (CTLA-4 inhibitor) are checkpoint inhibitors which are used in the treatment of metastatic melanoma. Effects on the endocrine system are being increasingly reported with prolonged therapy (hypophysitis and hypothyroidism) and therefore it is important to assess patients carefully who present with symptoms of hypothyroidism whilst on these drugs.

Abatacept • What is the mechanism of action of abatacept? Chimeric protein that inhibits T-lymphocyte activation CTLA4 homologue Abatacept is a cytotoxic lymphocyte antigen 4 (CTLA 4) homologue –
• Indication licensed for RA treatment.

Proton pump inhibitors • The proton pump is only contained in the tubo-vesicles of the parietal cell secrete acid. • Proton-pump inhibitors (e.g omeprazole) binds to gastric K+/H+-ATPase proton pump irreversibly • However, as the half-life of the pump is 24-36 hours, the duration of the effect of protonpump inhibitors is limited by the degradation of these pumps.

Sildenafil

Action • Sildenafil is a phosphodiesterase type V inhibitor (PDE-5 inhibitors) used in the treatment of impotence. • It increases intracavernosal cGMP levels, thereby competitively inhibiting the PDE-5 enzyme, and allowing nitric oxide-induced vasodilation. it blocks cGMP phosphodiesterase, which is normally responsible for the breakdown of cGMP. Sildenafil therefore leads to increased levels of cGMP, which has vasodilatory effects to relax smooth muscle. Contraindications • patients taking nitrates and related drugs such as nicorandil • hypotension • recent stroke or myocardial infarction (NICE recommend waiting 6 months) • non-arteritic anterior ischaemic optic neuropathy Side-effects • visual disturbances e.g. blue discolouration, non-arteritic anterior ischaemic neuropathy Sildenafil is a PDE-5 inhibitor, but at high doses it also inhibits PDE-6, which leads to blue discoloration of vision.This can often be managed by reducing the dose of Sildenafil. • nasal congestion
• flushing • gastrointestinal side-effects • headache

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Anaesthetic drugs
halothane hepatitis (medical-masterclass.com 2017 mrcp part 2) • There are many causes of post-operative jaundice, but the fact that the surgery was uncomplicated, the time course, the presence of joint / muscle pains and an eosinophilia, all suggest halothane hepatitis as the most likely diagnosis. This is thought to result as a hypersensitivity reaction. Treatment is supportive. Effects on the liver • Halothane
 Halothane undergoes ~25% metabolism by oxidative phosphorylation via hepatic cytochrome P450 systems.
 The major metabolite is trifluoroacetic acid (TFA), which is protein-bound and this TFA–protein complex can induce a T-cell-mediated immune response resulting in hepatitis ranging from mild transaminitis to fulminant hepatic necrosis and possibly death.
 the risk of fatal hepatic necrosis one in 10 000 anaesthetics.
 Adult females are more commonly affected.
 Repeated exposure increases the risk of hepatitis. Halothane and hepatitis Halothane can cause a mild liver dysfunction in approximately 30% of patients, due to the binding of reactive halothane metabolites to hepatocytes Halothane oxidation by cytochrome P450 enzymes leads

to the synthesis of trifluoroacetyl chloride, which covalently binds to hepatic molecules and causes an immune reaction Fulminant hepatitis results from the reactive metabolite, trifluoroacetyl chloride Further exposure to halothane anaesthesia may lead to a fulminant hepatitis, where the mortality is approximately 90%. Halothane induced hepatitis typically occurs five to seven days after exposure • Less commonly hepatitis has been described after exposure to enflurane > isoflurane > desflurane.
• Sevoflurane is not metabolized to antigenic TFA–protein complexes.

Inhaled anaesthetic-like agent
• If patient was markedly comatose on arrival but quickly regains consciousness. This suggests a short acting (probably) inhaled anaesthetic-like agent e.g Inhaled solvent glue. • The inhaled solvents, due to their lipophilicity, are rapidly absorbed through the lungs and then quickly distributed to the brain and other organs. The effects therefore appear within minutes of inhalation.
• Typical substances that are inhaled include toluene, aromatic hydrocarbons and butane.

Pseudocholinesterase deficiency
Overview • Pseudocholinesterase is a glycoprotein enzyme, produced by the liver.
• It specifically hydrolyzes exogenous choline esters. • most common in European; rare in Asians.
• Pseudocholinesterase deficiency results in delayed metabolism of the following:

1. Succinylcholine. depolarizing neuromuscular blocking agent (the most clinically important drug) • Suxamethonium is a depolarising neuromuscular blocking agent,

metabolised by plasma pseudocholinesterases.
• Approximately 1 in 2500 individuals have deficiency of this enzyme, resulting in prolonged neuromuscular blockade if they are given suxamethonium. 2. mivacurium. 3. procaine. 4. cocaine.
• After an intravenous dose of succinylcholine in individuals with normal plasma levels of normally functioning pseudocholinesterase enzyme: hydrolysis and inactivation of 90-95% of i.v succinylcholine occurs before it reaches the neuromuscular junction.
 The remaining 5-10% of the dose acts as an acetylcholine receptor agonist at the neuromuscular junction, causing prolonged depolarization of the postsynaptic junction of the motor-end plate.
 This depolarization initially triggers fasciculation of skeletal muscle.
 As a result of prolonged depolarization, endogenous acetylcholine released from the presynaptic membrane of the motor neuron does not produce any additional change in membrane potential after binding to its receptor on the myocyte.
 Flaccid paralysis of skeletal muscles develops within 1 minute. • In normal subjects, skeletal muscle function returns to normal approximately 5 minutes after a single bolus injection of succinylcholine as it passively diffuses away from the neuromuscular junction.
• Pseudocholinesterase deficiency can result in higher levels of intact succinylcholine molecules reaching receptors in the neuromuscular junction, causing the duration of paralytic effect to

continue for as long as 8 hours. • This condition is recognized clinically when paralysis of the respiratory and other skeletal muscles fails to spontaneously resolve after succinylcholine is administered as an adjunctive paralytic agent during anesthesia procedures. Diagnosis: • by plasma assays of pseudocholinesterase enzyme activity.

Management
• prolonged ventilation until the action of the drug wears off.
• Relatives of affected patients should be screened. Prognosis • exposed to succinylcholine excellent when close monitoring and respiratory support measures.
• exposed to cocaine, sudden cardiac death can occur.

Succinyl choline
• Depolarizing Skeletal muscle relaxants
• Also called suxamethonium • Analogue of acetyl choline, acts on nicotinic Nm receptors • Only depolarizing skeletal muscle relaxant • Fastest onset of action, Shortest duration of action • can stimulate autonomic ganglia • Side effect and contraindications (CI) Cause hyperkalemia in patients with nerve and muscular disorders so CI in: nerve disorders (Paraplegia, hemiplegia, GBS) and
 muscular disorders(muscular dystrophy, Myasthenia, crush injury, burns, rhabdomyolysis) Increases all pressures so CI in:

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 glaucoma,
 head injury, increase BP,
 nausea and vomiting due to intragastric pressure. Trigger malignant hyperthermia when used with halothane

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Local spinal anesthetics Hypotension and bradycardia following spinal anesthesia suggest neurogenic shock. • Local spinal anesthetics, can interrupt the transmission of nerve impulses in spinal sympathetic pathways, causing a loss of sympathetic vascular tone that ultimately results in neurogenic shock.
• Neurogenic shock is a type of distributive shock characterized by: generalized vasodilation (causing diaphoresis and flushed skin).
 This vasodilation leads to decreased preload and subsequently reduced cardiac output, which results in hypotension and bradycardia.
 Consequently, cerebral perfusion is impaired, leading to a loss of consciousness.

Fentanyl • Large, rapidly given doses of specific opioids such as fentanyl, sufentanil, remifentanil, and alfentanil are associated with systemic skeletal muscle rigidity.
 Of most concern to the anesthesiologist is chest wall rigidity (which impairs mask and bag ventilation) and rigidity of the jaw muscles which can prevent the insertion of an advanced airway.

Ketamine • Ketamine is commonly used as a recreational drug.
adverse effects include: • stimulation, euphoria, depersonalisation, floating feeling
• synaesthesia (a sensory stimulus in one modality is perceived as a sensation in another), eg: being able to 'smell sounds'
• delirium,
• vivid dreams
• hallucinations.

Topoisomerase inhibitors

Overview
• Topoisomerase I and II are enzymes that control the changes in DNA structure during the normal cell cycle. • Topoisomerase inhibition leads to apoptosis and cell death. • Used in: chemotherapy treatments.
 as antibacterial agents :Quinolones (including nalidixic acid and ciprofloxacin)

Topoisomerase I inhibitors • Agent:
 Irinotecan: used mainly for Colorectal cancer Topotecan: used mainly for Ovarian cancer and Small-cell lung cancer

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• Mechanism of action: Inhibition of topoisomerase I → ↓ DNA unwinding → ↓ DNA replication and DNA degradation (because of ssDNA breaks) • Side effects : Myelosuppression and GI symptoms (e.g., diarrhea) Topoisomerase II inhibitors • Agent: Etoposide • Indications: used for Solid tumors, Testicular cancer, Small-cell lung cancer, Leukemias, Lymphomas • Mechanism of action: Inhibition of topoisomerase II → ↑ DNA degradation (dsDNA breaks) and ↓ DNA replication (cell cycle arrest in S and G2 phase) • Side effects: Myelosuppression, Alopecia By what mechanism does topoisomerase catalyse DNA replication? Helix torsion release Topoisomerase releases torsion in the DNA helix during replication. It accomplishes this by cutting the DNA helix at specific points to allow it to unravel and then ligates the ends together again. This allows large proteins such as DNA polymerase to replicate DNA along the sequence.

Notes & Notes For MRCP part 1 & 11 By Dr. Yousif Abdallah Hamad Basic sciences Biochemistry & metabolism Updated

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Anion gap (AG) • The anion gap allows for the differentiation of 2 groups of metabolic acidosis.

1. Metabolic acidosis with a high AG is associated with the addition of endogenously or exogenously generated acids.
2. Metabolic acidosis with a normal AG is associated with the loss of HCO3 or the failure to excrete H+ from the body. • The anion gap is calculated by: (sodium + potassium) - (bicarbonate + chloride) • A normal anion gap is 8-14 mmol/L • It is useful to consider in patients with a metabolic acidosis: Causes of a normal anion gap or hyperchloraemic metabolic acidosis gastrointestinal bicarbonate loss: diarrhoea, ureterosigmoidostomy, fistula renal tubular acidosis drugs: e.g. acetazolamide ammonium chloride injection Addison's disease Causes of a raised anion gap metabolic acidosis lactate: shock, hypoxia ketones: diabetic ketoacidosis, alcohol urate: renal failure acid poisoning: salicylates, methanol mnemonic of high anion gap acidosis: • DR. MAPLES: D-DKA; R-renal; M-methanol; A-alcoholic ketoacidosis; P-paraldehyde, phenformin; L-lactic (ie, CO, HCN); E-ethylene glycol; S-salicylates Remember the mnemonic MUDPILES →high anion gap acidosis M Methanol U Uremia D Diabetic ketoacidosis P Paraldehyde I Infection L Lactic acidosis E Ethylene glycol S Salicylates Metabolic acidosis associated with bladder reconstruction (e.g: for carcinoma of the bladder). • Hyperchloraemic metabolic acidosis is a documented complication of neobladder formation. However, it usually improves with time and is mild. • Severe and persistent metabolic acidosis may manifest when patients undergo further surgery for other reasons, as is the case in this patient. • Neobladder formation following radical cystectomy or cystoprostatectomy is becoming increasingly more common, and medical staff treating patients with neobladders should recognise and treat metabolic acidosis with intravenous fluids and bicarbonate.

Metabolic alkalosis Pathophysiology • Metabolic alkalosis may be caused by a loss of hydrogen ions (H+) or a gain of bicarbonate (HCO3). • It is due mainly to problems of the kidney or gastrointestinal tract • The initial disturbance of metabolic alkalosis is an increased HCO3

- concentration, followed by a compensatory response of increased Pco2. • All renal tubular defects result in metabolic alkalosis, except for Fanconi syndrome. ABG picture • pH : Elevated • PCO2: Expected compensatory response: ↑ • HCO3: Elevated Compensation mechanism • Hypoventilation is an immediate compensatory response to metabolic alkalosis. • ↑ Arterial and CSF pH (with ↑ HCO3-) → ↓ stimulation of the medullary chemoreceptors → ↓ respiratory rate and/or tidal volume (hypoventilation) → ↑ CO2 retention → ↑ PCO2 Causes • Vomiting / aspiration (e.g. peptic ulcer leading to pyloric stenos, nasogastric suction) • Diuretics • Liquorice, carbenoxolone • Hypokalaemia • Bulimia nervosa Mechanism of metabolic alkalosis • The main mechanisms of metabolic alkalosis in the setting of vomiting are increased H+ excretion in the distal tubule and increased bicarbonate reabsorption in the proximal tubule. ECF depletion (vomiting, diuretics) → Na+ and Cl- loss → activation of reninangiotensin II-aldosterone (RAA) system → ↑aldosterone →reabsorption of Na+ in exchange for H+ in the distal convoluted tubule • In hypokalaemia, K+ shift from cells to ECF, alkalosis is caused by shift of H+ into cells to maintain neutrality A patient with liver cirrhosis develops metabolic alkalosis. What is the most likely pathological mechanism? →Reduced urea synthesis A patient in the intensive care unit following liver transplant surgery has a metabolic alkalosis. What is the most likely cause? Diuretic-induced volume depletion Cirrhosis →hypoalbuminaemia

→ low colloid osmotic pressure →Relative volume depletion →↑aldosterone, (which is not adequately metabolised by an impaired liver). Furosemide use in the post-operative period further exacerbates alkalosis driven by hyperaldosteronism . Notes & Notes for MRCP
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• Primary hyperaldosteronism Liddle syndrome Con syndrome • Cushing's syndrome • Bartter's syndrome • Gitelman syndrome • Congenital adrenal hyperplasia

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Basicsciences Biochemistry&metabolsm Aetiology of metabolic alkalosis Mechanism Causes Chloride-responsive metabolic alkalosis (urine chloride < 25 mEq/L) Gastrointestinal losses: due to vomiting, nasogastric suction, or diarrhea Renal losses: due to loop or thiazide diuretics Cystic fibrosis Chloride-resistant metabolic alkalosis (urine chloride > 40 mEq/L) Severe magnesium deficiency Extreme hypercalcemia, hypokalemia High alkali load (e.g., due to antacid use, alkalization therapy) Loop or thiazide diuretics Other (less common causes) Associated with low or normal blood pressure Bartter syndrome Gitelman syndrome Associated with high blood pressure Hyperaldosteronism Cushing syndrome Liddle syndrome Licorice ingestion Ingestions or drugs (Laxative abuse, ampicillin, penicillin) Recovery from starvation Hypoalbuminemia Prognosis • when the pH is greater than 7.65 → mortality rate is 80% Treatment • Chloride-responsive metabolic alkalosis Start isotonic saline to increase urinary bicarbonate excretion and correct extracellular volume loss • Chloride-resistant metabolic alkalosis Consider bicarbonate excess as a potential cause and administer acetazolamide. Acetazolamide is a diuretic used to alkalinize the urine or treat metabolic alkalosis as it inhibits carbonic anhydrase.

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Respiratory acidosis Causes Mechanism Causes Acute respiratory acidosis Acute lung disease (e.g., pneumonia , pulmonary edema) Acute exacerbation of chronic obstructive airway disease (e.g., COPD, asthma) CNS depression due to: Head trauma Postictal state Drug toxicity (e.g., from opiates, barbiturates, benzodiazepines) Central sleep apnea Chronic respiratory acidosis Airway obstruction (e.g., COPD, asthma) Respiratory muscle weakness, e.g., due to: Myasthenia gravis ALS Guillain-Barré syndrome Poliomyelitis Multiple sclerosis Severe hypokalemia Features Signs and symptoms of respiratory acidosis Central nervous system Respiratory system Cardiovascular system Cerebral vasodilation Breathlessness Flushing, bounding pulse Increased intracranial pressure Cyanosis Cor pulmonale Headache, confusion, agitation Pulmonary hypertension Systemic hypotension Hallucinations, transient psychosis Arrhythmias Myoclonic jerks, flapping tremor, extensor plantars, depressed reflexes Initially good cardiac output, then decreases Papilloedema, constricted pupils Seizures, coma

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Mechanism • Alveolar hypoventilation → CO2 retention ABG picture • pH : low • PCO2: elevated • HCO3: Expected compensatory response: ↑ Treatment • Consider noninvasive or invasive mechanical ventilation.

Respiratory alkalosis Mechanism • ↑ Respiratory rate and/or tidal volume → alveolar hyperventilation → CO2 washout Causes • Anxiety leading to hyperventilation (Hyperventilation will result in carbon dioxide being 'blown off', causing an alkalosis.) →high PH , low PCO2 , normal PO2. not associated with hypoxia. • pulmonary embolism • Acute severe asthma associated with hypoxia and normal or rising CO2 • Drugs (salicylates, progesterone) salicylate overdose leads to a mixed respiratory alkalosis and metabolic acidosis. Early stimulation of the respiratory centre leads to a respiratory alkalosis whilst later the direct acid effects of salicylates (combined with acute renal failure) may lead to an acidosis. • CNS disorders: stroke, subarachnoid haemorrhage, encephalitis • High altitude • Pregnancy • Pain • Excessive mechanical ventilation. • Hepatic failure ABG picture • pH : elevated • PCO2: low • HCO3: Expected compensatory response: ↓ Differential diagnosis of respiratory alkalosis with type 1 respiratory failure (low pO2 and low pCO2.): • Chronic venous thromboembolism (most likely). • Pulmonary fibrosis (but basal crackles may be expected).

Calcium metabolism see endocrinology Hypercalcaemia see endocrinology Hypocalcaemia see endocrinology Vitamin D see endocrinology

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Hyperkalaemia Definition • Serum potassium level > 5 mEq/L Regulation • Plasma potassium levels are regulated by a number of factors including: Aldosterone acid-base balance insulin levels. • Metabolic acidosis is associated with hyperkalaemia as hydrogen and potassium ions compete with each other for exchange with sodium ions across cell membranes and in the distal tubule. Causes • Potassium excess: due to altered K+ metabolism or intake Reduced excretion: acute and chronic kidney disease Endocrine causes: hypocortisolism, hypoaldosteronism Drugs: potassium-sparing diuretics, ACE inhibitors, angiotensin receptor blockers, NSAIDs, and trimethoprim-sulfamethoxazole Type IV renal tubular acidosis Increased intake High potassium diet, e.g., bananas, oranges, kiwi fruit, avocado, spinach, tomatoes K+ containing IV fluids • Extracellular shift Acidosis → ↑ extracellular H+ → inhibition of the Na+/H+ antiporter → ↓ intracellular Na+ → ↓ sodium gradient inhibits the Na+/K+-ATPase → ↑ extracellular K+ concentration Hyperkalemia → ↑ extracellular K+ concentration → ↑ potassium gradient stimulates the Na+/K+-ATPase → ↑ extracellular Na+ → ↑ sodium gradient stimulates the Na+/H+ antiporter → ↑ extracellular H+ → acidosis Exceptions: In renal tubular acidosis and acetazolamide toxicity, findings include hypokalemia and metabolic acidosis. Hyperosmolality Insulin deficiency (manifests with hyperglycemia) Drugs Beta blockers Succinylcholine: (esp. when given with preexisting burns and/or muscle trauma) , Digoxin: inhibits the Na+/K+-ATPase → ↑ extracellular K+ concentration • Extracellular release Pathological cell lysis

Rhabdomyolysis Tumor lysis syndrome Hemolysis High blood cell turnover: e.g., thrombocytosis, erythrocytosis, leukocytosis Pseudohyperkalaemia: resulting from iatrogenic red blood cell lysis Blood drawn from the side of IV infusion or a central line without previous flushing Prolonged use of a tourniquet

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 Fist clenching during blood withdrawal Delayed sample analysis Features • May be asymptomatic • Nausea, vomiting, diarrhea • Cardiac: Arrhythmias (e.g., atrioventricular block, ventricular fibrillation) • Neuromuscular: Muscle weakness, paralysis, paresthesia, ↓ Deep tendon reflexes Weakness and fatigue are the most common complaints • ECG changes Early changes (typically seen at a serum potassium level of 5.5-6.5 mEq/L) tall, peaked T waves shortened QT interval ST-segment depression. At a serum potassium level of 6.5-8.0 mEq/L, in addition to peaked T waves: Decreased or disappearing P wave Prolonged PR interval Widening of the QRS Amplified R wave Treatments Immediate treatment principles include:

1. Providing calcium salts to reduce the risk of arrhythmia (‘protect the heart’);
2. Administering intravenous glucose and insulin (‘shift potassium into cells’);
3. Reducing intake and increasing output of potassium (‘remove potassium from the body’). When K+ shifts out of the cell, it's a BAD LOSS! – Beta blockers, Acidosis, Digoxin, Lysis, hyperOsmolality, high Sugar, Succinylcholine

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• Precipitating factors should be addressed (e.g. acute renal failure) and aggravating drugs stopped (e.g. ACE inhibitors). • Mild chronic hyperkalaemia (eg: 5.6 mmol/l) is well tolerated and not a cause for concern. If serum potassium rise to >6.0 mmol/l, standard practice would be to stop the ACEi and - if K >6.0 mmol/l were to persist - to advise a low potassium diet. • Stabilisation of the cardiac membrane intravenous 10 ml 10% calcium gluconate (or calcium chloride) The effects of intravenous calcium occur within 1 to 3 minutes but last for only 30 to 60 minutes. • Short-term shift in potassium from extracellular to intracellular fluid compartment Combined insulin/dextrose infusion: The most effective agent . In hyperglycaemic patients (serum glucose >15 mmol/L) insulin may be given without additional intravenous glucose. The dose: 10 units of soluble insulin Nebulised salbutamol Less effective than iv insulin and glucose (not recommended as monotherapy) Patients prescribed beta blockers may be ‘resistant’ to the hypokalaemic effects of salbutamol. • Removal of potassium from the body Calcium resonium (orally or enema) Loop diuretics Dialysis May 2020 exam: H/O muscle weakness and lethargy. K+ = 6.3 mmol/l. What is the most appropriate initial treatment to lower the serum potassium level? Insulin/dextrose infusion

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Pseudohyperkalaemia Causes • Haemolysis during venepuncture • Delay in the processing of the blood specimen • Abnormally high numbers of platelets, leukocytes, or erythrocytes (such as

myeloproliferative disorders or essential thrombocytosis) • Familial causes Management • Re-check a fresh sample at the hospital • Measuring an arterial blood gas will give a quick and accurate measure of true serum potassium.

Hypokalaemia and acid-base balance Definition • Serum potassium (K+) level < 3.5 mEq/L

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Causes Hypokalaemia with alkalosis • Vomiting • Diuretics • Cushing's syndrome • Conn's syndrome (primary hyperaldosteronism) Hypokalaemia with acidosis • Diarrhoea • Renal tubular acidosis • Acetazolamide • Partially treated diabetic ketoacidosis Drug induced hypokalaemia • Intracellular shifts of potassium with normal total body potassium, for example: theophylline β-agonists caffeine insulin Other causes • Loss of potassium stores, for example: chronic diuretic use • Magnesium deficiency may also cause hypokalaemia. In such cases, normalizing the potassium level may be difficult until the magnesium deficiency has been corrected In hyperthermia, as body temperature increases, what is the earliest biochemical abnormality? Hypokalaemia As body temperature increases, such as occurs in hyperthermia due to heatstroke, the earliest abnormality is hypokalaemia. This is thought to be due to increased K+ uptake by muscles as catecholamines stimulate the NA-K-ATPase transporter. As the body temperature rises further, hyperkalaemia can develop with rhabdomyolysis and lactic acidosis. The acid-base picture is of metabolic acidosis with compensatory respiratory alkalosis. Features • Cardiovascular : cardiac arrhythmias • Neuromuscular: o Muscle cramps and spasms o Muscle weakness K+ acts like H+: Hypokalemia leads to alkalosis and vice versa Hypomagnesemia can lead to refractory hypokalemia

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o Decreased deep tendon reflexes • Gastrointestinal: Constipation ECG findings in hypokalemia • Mild to moderate hypokalemia T-wave flattening or inversion ST depression Prolonged PR interval • Moderate to severe hypokalemia QT prolongation Presence of U waves Treatment • If K >2.5 with no symptoms or ECG changes →oral potassium • If K <2.5 with symptoms or ECG changes →IV potassium • In life-threatening cases →1L IV 0.9% NaCL with 40 mmol/l KCl infused over four hours Cardiac monitoring. Potassium should be given in NaCl. Concentration should not exceed 40 mmol/l No more than 10-20 mmol/hour should be given. Daily maintenance requirements (NICE guidelines): • Water →1500-2500 ml/ day (25-30 ml/kg/day) • Potassium, Sodium and Chloride →1 mmol/kg/day Sodium →70 mmol potassium →(40-80 mmol/day) In the absence of kidney disease or hyperkalaemia (around 1 mmol/kg per day) Estimation of total body potassium loss: • a drop in 1 mmol/L K+ of serum potassium in approximately equivalent to a 200 mmol K+ total body loss. In patients with hypokalemia, avoid solutions containing dextrose, which can increase insulin secretion and worsen hypokalemia.

Chapter 14

Hypernatraemia Hypernatraemia associated with hypovolaemia occurs due to a free water deficit. Common causes include reduced water intake (e.g. elderly), GI losses (e.g. vomiting and diarrhoea), skin losses (e.g. burns), and renal losses (e.g. osmotic diuresis) Hypernatraemia associated with hypervolaemia can occur due to hypertonic saline, hypertonic sodium bicarbonate, excess salt in diet, or hyperaldosteronism Causes • Insufficient water • free water loss: renal (diabetes insipidus, diuretics, osmotic diuresis as with hyperglycaemia), GI (diarrhoea, vomiting), skin (sweating, burns) • Salt overload e.g. acute salt poisoning (hypertonic saline, hypertonic sodium bicarbonate), hyperaldosteronism Treatment • Treatment is aimed at the underlying cause. • Hypernatraemia should be corrected with great caution. • Although brain tissue can lose sodium and potassium rapidly, lowering of other osmolytes (and importantly water) occurs at a slower rate, predisposing to cerebral oedema, resulting in seizures, coma and death. • acute hypernatraemia can be corrected quickly but if chronic (>24hours) then it should be corrected at <0.5mmol/L/hr. • Fluid resuscitation should involve oral water, 0.45% saline or 5% dextrose IV.

Hyponatraemia (serum sodium less than 135 mEq/L) Mechanisms of causes

1. Water excess
2. Sodium depletion.
3. Pseudohyponatraemia: hyperlipidaemia (increase in serum volume) hyperproteinemia (e.g: myeloma) taking blood from a drip arm. Cause of hyponatraemia Urinary sodium > 20 mmol/l Urinary sodium < 20 mmol/l Sodium depletion, renal Patient often euvolaemic loss (patient often hypovolaemic) • diuretics • Addison's • diuretic stage of renal failure • SIADH (urine osmolality > 500 mmol/kg) • hypothyroidism Notes & Notes for MRCP
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Sodium depletion, Water excess (patient often hypervolaemic and extra-renal loss (hypovolaemic) oedematous) • secondary hyperaldosteronism: heart failure, cirrhosis • reduced GFR: renal failure • IV dextrose, psychogenic polydipsia • diarrhoea, vomiting, sweating • burns, adenoma of rectum

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Features • Fatigue • Muscle weakness • Gait disturbance • Falls • Disorientation • Cerebral oedema • Seizures Investigations • Urinary sodium and osmolarity levels aid making a diagnosis. urinary sodium Reduced urinary sodium excretion [less than 30 mmol/l] may indicate total body sodium depletion even if plasma sodium levels are normal. may be misleading in the presence of renal impairment or diuretic therapy.

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Management • It is important with hyponatraemia to ascertain volume status as this will determine management. • The management of each is as follows: Hypovolaemic hyponatraemia Diagnosis may supported by an elevated urea suggesting dehydration. rehydration with sodium chloride 0.9% or a balanced crystalloid (Hartmann's) avoid rapid correction of sodium in order to reduce the risk of osmotic complications such as central pontine myelinolysis The rate of correction of hyponatremia should not exceed eight mEq/L per day. Euvolaemic hyponatraemia check urine and serum osmolality. Does the patient meet the criteria for SIADH? treat the underlying cause where possible in SIADH fluid restriction (500-750mls/day) monitor fluid balance and perform daily weights consider demeclocycline or tolvaptan (under specialist supervision). Both inhibit the action of antidiuretic hormone. Hypervolaemic hyponatraemia fluid and salt restriction consider diuretics treat the underlying cause (e.g. cardiac failure) Hyponatraemia: correction Acute hyponatraemia • predisposing factors to acute hyponatraemia: Over consumption of fluids, prolonged race duration and inadequate training • Pathophysiology When hyponatraemia develops over a short duration the ability of the brain to adapt is exceeded and cerebral oedema can result which may lead to confusion, seizures and coma. As a result patients may die from brain herniation. • Treatment The correct treatment to give is hypertonic saline. Decompressive craniotomy would help alleviate raised intracranial pressure due to cerebral oedema however is not an appropriate first line treatment. A small, quick increase in the serum sodium is required in order to decrease intracranial pressure. Hypertonic saline (3%) boluses are the most appropriate treatment to improve neurological status in such patients.

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Hyponatremia in patients with advanced cirrhosis • Mechanism systemic vasodilation,(The most important factor) which leads to activation of endogenous vasoconstrictors including antidiuretic hormone (ADH); ADH promotes the water retention that is responsible for the fall in serum sodium. • Tolvaptan (Vasopressin receptor antagonists) should not be used in patients with cirrhosis, because of its known potential for hepatotoxicity. Central pontine demyelinolysis Central pontine myelinolysis (CPM): • Due to rapid correction of hyponatraemia • the classical presentation is spastic quadriparesis, pseudobulbar palsy, and emotional lability (pseudobulbar affect) (locked in syndrome.) • Definition: damage to the myelin sheath of the white matter in the CNS caused by a sudden rise in serum osmolality (rapid correction of chronic hyponatremia) • Affects the central region of the pons • Pathophysiology: rapid sodium correction →Sudden rises in plasma osmolarity →fluid shift from the cerebral intracellular space to the extravascular space (loss of water from the intracellular compartment) →cerebral shrinking and demyelination →end result is central pontine myelinolysis (CPM). • Features Symptoms first develop several days after the correction of hyponatremia. Central pontine myelinolysis Altered level of consciousness, including coma Locked-in syndrome Impaired cranial nerve function: dysarthria, dysphagia, and diplopia Worsening quadriparesis • Diagnosis: MRI brain • Treatment: supportive care • Prevention: Avoid hypernatremia Many authorities recommend that increases in serum sodium of <12 mmol/24 hours are likely to be safe for the majority of patients. Certain patients with hypokalaemia, liver disease, poor nutritional state or burns are at higher risk of demyelination and should have a rate of sodium correction of <8 mmol/24 hours. "Saline depletion, for example due to excessive diuretic exposure, is best managed with a balanced electrolyte solution such as Hartmann's." Osmolar gap • Osmolar gap is the difference between the calculated osmolarity and the measured osmolality. •

The normal value is 10-15 but may be increased in the presence of unmeasured 'abnormal' osmotically active ions in the plasma. • An elevated osmolar gap provides indirect evidence for the presence of an abnormal solute that may be present in significant amounts. • Ethanol, ethylene glycol (anti-freeze), acetone and methanol are solutes that will cause elevation of the osmolar gap in this way. • Calculated osmolarity = 2 (Na + K) + Glucose + Urea (all in mmol/L). • Normal serum osmolarity is 285-295 mOsm/L. • Osmolality is measured in the laboratory using an osmometer.

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Hypomagnesaemia Definition • Low magnesium below 0.7 mmol/L . Overview • Normal plasma magnesium (0.7-0.9 mmol) • The thick ascending limb (TAL) of the loop of Henle is the major site of reabsorption (60-70%) (unlike most ions, those reabsorbed in the proximal convoluted tubule) • In the TAL, magnesium is passively reabsorbed. In the distal convoluted tubule, magnesium is reabsorbed via an active, transcellular TRPM6 channel . Uses for magnesium include: • polymorphic ventricular tachycardia (torsade de pointes), • acute asthma • prevention/treatment of seizures in pre-eclampsia. • Magnesium salts can be given as laxatives Causes of low magnesium • Inadequate intake: Malnutrition, and Alcohol dependence. Hypomagnesemia is the most common electrolyte abnormality observed in alcoholic patients Total parenteral nutrition • Malabsorption: Inflammatory bowel disease Long term PPI therapy Gluten enteropathy Intestinal bypass, and Radiation enteritis. • Renal tubular disease: Hyperaldosteronism Hyperparathyroidism Obstructive uropathy Potassium depletion, and Drugs (including diuretics, amphotericin, cisplatin, ciclosporin, amikacin, gentamicin, laxatives, and tacrolimus). • Intracellular shift: Post myocardial infarction Post parathyroidectomy Recovery from diabetic ketoacidosis (K+ and PO4- also enter cells) Refeeding syndrome (PO4- also enters cells), Acute pancreatitis. • Drugs: cisplatin diuretics cyclosporine cardiac glycosides Colorectal cancer treatment with cetuximab/panitumumab (EGF receptor inhibitors) ↓ TRPM6 hypomagnesemia. Omeprazole hypomagnesaemia hypoparathyroidism hypocalcaemia.

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• Diarrhoea • Metabolic acidosis Chronic metabolic acidosis ↓renal TRPM6 expression in the DCT ↓Mg reabsorption ↓serum Mg. • Hypercalcaemia Hypercalcemia activation of calcium-sensing receptor (CaSR) ↓Mg reabsorption • Hypokalaemia, hypocalcaemia • Genetic diseases Features • General lack of appetite. Lethargy fatigue • neuromuscular hyper-excitability muscle weakness including fasciculations changes in personality paraesthesia tetany seizures • cardiac • arrhythmias • ECG features similar to those of hypokalaemia • The ECG change most typically associated with hypomagnesaemia is QT prolongation. • exacerbates digoxin toxicity • decreased PTH secretion → hypocalcaemia • Hypokalemia (in 40-60%) Associations with hypomagnesemia • Hypoparathyroidism ↓Mg ↓magnesium-dependent adenyl cyclase generation of cyclic adenosine monophosphate (cAMP) ↓PTH hypoparathyroidism • DM (↓Mg ↓insulin sensitivity and secretion) • Cardiac: CAD, Hypertension (Mg plays a role in BP

regulation), cardiac arrhythmia (prolongation of the QT interval , Torsade de pointes) Investigation • blood magnesium levels can guide but do not accurately reflect total body magnesium status. Attempts to find a marker of cellular magnesium status include measuring erythrocyte or monocyte Mg but these are not generally available. • Urine Mg excretion is a useful guide. When there is inadequate intake or malabsorption, the kidneys would normally conserve Mg, giving urine Mg concentrations <7 mmol/24 hours. The reference range is around 2-7 mmol/24 hours. Treatment • <0.4 mmol/l intravenous replacement is commonly given. An example regime would be 40 mmol of magnesium sulphate over 24 hours •

> 0.4 mmol/l oral magnesium salts (10-20 mmol orally per day) diarrhoea can occur with oral magnesium salts

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Hypermagnesaemia Overview • Hypermagnesaemia is much less common than hypomagnesaemia and is often iatrogenic in cause. Causes of hypermagnesaemia • Iatrogenic: Treatment with magnesium sulphate to prevent/treat seizures in patients with eclampsia or pre-eclampsia Treatment with Mg containing antacids Use of citrate-glucuronic acid solutions to dissolve renal calculi either through bladder irrigation or via a nephrostomy tube Over-zealous IV treatment of hypomagnesaemia Chronic use of Mg-containing enemas. • Other causes: Acute or chronic renal failure release of Mg from tissues, Mg in dialysate, Mg in phosphate binding drugs Familial hypocalciuric hypercalcaemia. Lithium can cause hypermagnesaemia Features • Mild hypermagnesemia often asymptomatic • Nausea, Lethargy • Reduced deep tendon reflexes • Blurry vision • Cardiac: Vasodilatation, Hypotension, Bradycardia • ECG changes: ↑ PR interval, ↑ QRS duration, ↑ QT interval • Blurry vision • Hypocalcemia • Severe hypermagnesemia Muscle paralysis (flaccid quadriplegia) Bradycardia, Cardiac arrest Respiratory failure Treatment • If mild/moderate and iatrogenic, often it is enough to identify and stop the cause. • In an emergency, dialysis or administration of IV calcium glucuronate (10 ml of 10%) will reduce the effects of hypermagnesaemia.

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