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Hypophosphataemia Definition • serum phosphate level of less than 2.5 mg/dL (0.8 mmol/L). Causes Causes Consequences • alcohol excess • acute liver failure • diabetic ketoacidosis • refeeding syndrome • primary hyperparathyroidism • osteomalacia • Hyperventilation Mechanisms • The three major mechanisms of hypophosphataemia are:

1. Redistribution of extracellular phosphate into cells hyperventilation respiratory alkalosis activating phosphofructokinase moves phosphate into cells stimulates intracellular glycolysis. Glycolysis leads to phosphate consumption as phosphorylated glucose precursors are produced. Any cause of hyperventilation (eg, sepsis, anxiety, pain, heatstroke, alcohol withdrawal, diabetic ketoacidosis [DKA], hepatic encephalopathy, salicylate toxicity, neuroleptic malignant syndrome [NMS]) can precipitate hypophosphatemia.
2. Decreased intestinal absorption, chronic diarrhea, malabsorption syndromes, severe vomiting, nasogastric (NG) tube suctioning.
3. Depletion due to increased urinary loss. the most common cause of hypophosphatemia primary and secondary hyperparathyroidism. Osmotic diuresis, such as seen in hyperosmolar hyperglycemic syndrome (HHS) Fanconi syndrome (proximal tubule dysfunction) X linked hypophosphataemic rickets Oncogenic hypophosphataemic osteomalacia MRCPUK- part-1-Sep 2017: what is the mechanism of Hypophosphataemia during treatment of DKA? Shift from extracellular to intracellular space Notes & Notes for MRCP
   By Dr. Yousif Abdallah Hamad

• red blood cell haemolysis • white blood cell and platelet dysfunction • muscle weakness and rhabdomyolysis • central nervous system dysfunction

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MRCPUK-part-1-Sep 2017: what is the mechanism of Hypophosphataemia in alcoholic patients after hospital admission ? Shift from extracellular to intracellular space The alcoholic patient often has chronic phosphate depletion, and, after admission to the hospital, is prone to severe hypophosphatemia resulting from redistribution of extracellular phosphate into the cells. Two

factors may contribute to this shift:

1. I.V therapy with dextrose-containing solutions or refeeding ↑Glucose ↑ insulin release ↑ phosphate uptake by the cells
2. alcohol withdrawal hyperventilation acute respiratory alkalosis intracellular alkalosis stimulates intracellular phosphofructokinase ↑ glycolysis movement of phosphate into cells

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Hyperphosphataemia Overview • The healthy adult usually ingests about 8400 mg per week of phosphate through their diet • Absorption occurs mainly in the jejunum • Renal reabsorption: the majority (70%) of filtered phosphate is reabsorbed by type 2a sodium phosphate cotransporters located on the apical membrane of the renal proximal tubule. • The normal adult range for phosphorus is 2.5-4.5 mg/dL (0.81-1.45 mmol/L). • Renal excretion : About 5400 mg of phosphate is excreted per week through the kidneys. Causes • Usually iatrogenic • ↓calcium + ↑phosphate levels seen in (decreased phosphate excretion) renal failure hypoparathyroidism, and pseudohypoparathyroidism • ↑calcium + ↑phosphate seen in vitamin D intoxication (↓PTH + ↑vitamin D) milk-alkali syndrome (↓PTH + ↓vitamin D) • Disorder that shifts intracellular phosphate to extracellular space Tumor lysis Rhabdomyolysis • Increased phosphate intake (e.g., phosphate-containing enemas) Laxative (Phospho-soda) abuse Foods that are characteristically rich in phosphate include: dairy products, (Cheddar cheese), fibre rich foods, chocolate, and processed meats. Features • Often asymptomatic • High PO43- levels cause the formation of an insoluble compound with calcium, which can lead to: Hypocalcemia → hypocalcemic symptoms (muscle cramps, tetany, and perioral numbness or tingling). Nephrolithiasis Calcifications in the skin

Management • Treat the underlying cause. • Discontinue phosphate intake (dietary or medication). • Give phosphate binders (e.g., aluminium hydroxide, calcium carbonate). • Consider dialysis (especially in severe cases of hyperphosphatemia in patients with renal failure).

Collagen Types Types of collagen Tissue distribution Related conditions Type I Bone (produced by osteoblasts), skin, tendons, collagen ligaments, fascia, dentin, cornea, internal organs, scar (90% of tissue (late stages of wound healing) body collagen) Type II Cartilage (including hyaline), vitreous humor of the eye, collagen intervertebral discs (nucleus pulposus) Type III Reticular fibers in skin, blood vessels, granulation tissue, collagen uterus, scar tissue (early stages of wound healing), fetal (reticulin) tissue in early embryos and throughout embryogenesis Type IV Basement membranes, lens Alport syndrome: collagen Type V Bone, skin, fetal tissue, placenta Ehlers-Danlos syndrome collagen

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Vitamin B3 (Niacin) deficiency Causes • Malnutrition • Heavy drinking (more common in alcoholics) • Conditions associated with tryptophan deficiency Hartnup disease: decreased renal and intestinal tryptophan absorption Carcinoid syndrome (if metabolically active): increased tryptophan metabolism • Vitamin B6 deficiency (e.g., due to treatment with isoniazid): decreased niacin synthesis from tryptophan. Notes & Notes for MRCP
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Osteogenesis imperfecta type I: decreased production Achondrogenesis (type II) Ehlers-Danlos syndrome (vascular type): decreased production decreased production Goodpasture syndrome: autoantibodies target type IV collagen (classic type)

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• Chronic consumption of grains that have not been processed by nixtamalization (common cause in developing countries) Features • Atrophic glossitis the tongue is pink or red appears glossy and smooth due to the atrophy of papillae. can be painful. • Pellagra (caused by severe deficiency) Characteristic dermatitis Circular broad collar rash on the neck (Casal necklace); affects dermatomes C3 and C4 Hyperpigmented skin lesions in sun-exposed areas (especially on the limbs) Diarrhea and vomiting Neurologic symptoms (e.g, dementia, hallucinations, anxiety, insomnia, encephalopathy)

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itamin C (ascorbic acid) (scurvy) • Vitamin C is a water soluble vitamin. • Dehydroascorbic acid, the oxidative product of ascorbic acid metabolism, passively penetrates cellular membranes and is the preferred form for erythrocytes and leukocytes. Functions • Antioxidant (Ascorbic acid provides electrons needed to reduce molecular oxygen. These anti-oxidant capabilities also stabilize vitamin E and folic acid.) • It is a cofactor for reduction of folate to dihydro-and-tetrahydrofolate. Therefore macrocytic anaemia in scurvy may occur due to two reasons: oxidative hemolysis and folate metabolism defects. • collagen synthesis: acts as a cofactor for enzymes that are required for the hydroxylation proline and lysine in the synthesis of collagen Vitamin C deficiency (scurvy) leads to defective synthesis of collagen resulting in capillary fragility (bleeding tendency) and poor wound healing • facilitates iron absorption • cofactor for norepinephrine synthesis • cofactor for reduction of folate to dihydro-and-tetrahydrofolate. Causes • occurs in people with poor dietary intake, who eat little or no fruit and vegetables, commonly alcoholics and elderly people existing on a ‘tea and toast’ diet. • Pregnancy, lactation and thyrotoxicosis increase ascorbic acid requirements and may precipitated scurvy. Features vitamin C deficiency • gingivitis, loose teeth • poor wound healing Pellagra The classical features are the 3 D's - Dermatitis, Diarrhoea and Dementia. Caused by nicotinic acid (niacin) deficiency.

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• bleeding from gums, haematuria, epistaxis • general malaise • anaemia macrocytic anaemia in scurvy may occur due to two reasons: oxidative hemolysis and folate metabolism defects. normochromic, normocytic anaemia reflects bleeding into tissues Continued deficiency leads to: • Anaemia • Myalgia • Bone pain • Bruising • Petechial and perifollicular haemorrhages • Corkscrew hairs • Mood changes • Fragility • scleral icterus (late, probably secondary to haemolysis), and • pale conjunctiva. • Fractures, dislocations and tenderness of bones are common in children. • Bleeding into muscles and joints may be seen Late stages can lead to: • Generalised oedema • Severe jaundice • Haemolysis • Haemorrhage • Neuropathy • Convulsions, and • Death. The classical skin manifestations of scurvy are: • perifollicular hyperkeratotic papules • perifollicular

haemorrhages • purpura, and • ecchymoses. Treatment • vitamin C supplementation, • recovery is usually complete within three months.

Vitamin B12 deficiency Overview • Vitamin B12 is mainly used in the body for red blood cell development and also maintenance of the nervous system. • It is absorbed after binding to intrinsic factor (secreted from parietal cells in the stomach) and is actively absorbed in the terminal ileum. • A small amount of vitamin B12 is passively absorbed without being bound to intrinsic factor. Approximately 1 percent of a large oral dose of vitamin B12 is absorbed by this second mechanism. This pathway is important in relation to oral replacement. • Once absorbed, vitamin B12 binds to transcobalamin II and is transported throughout the body. • Exhaustion of vitamin B12 stores usually occurs after 12 to 15 years of absolute vitamin B12 deficiency. Causes • Malabsorption ↓ Intrinsic factor (IF) Atrophic gastritis due to Autoimmune atrophic gastritis: most common cause of vitamin B12 deficiency

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 H. pylori infection Gastrectomy Reduced uptake of IF-vitamin B12 complex in terminal ileum due to: Alcohol use disorder Crohn disease, celiac disease Pancreatic insufficiency Surgical resection of the ileum Diphyllobothrium latum (tapeworm) infection Bacterial overgrowth Enteritis Achlorhydria • Malnutrition Strict vegan diets: occurs only after years of a strict diet that excludes all animal products (unlike folate deficiency, which occurs within a few months of insufficient intake) • Increased demand: e.g., during pregnancy, breastfeeding, fish tapeworm (Diphyllobothrium latum) infection • Metformin (Chronic metformin use results in vitamin B12 deficiency in 30% of patients) Features • Macrocytic anaemia • Sore tongue and mouth • Neurological symptoms: Peripheral neuropathy Subacute combined degeneration of spinal cord The neurological symptoms can occur without anemia • Autonomic dysfunction: impotence and incontinence • Psychiatric disorders symptoms: including impaired memory, irritability, depression, dementia and, rarely, psychosis • Cardiovascular effect: Similar to folic acid deficiency, vitamin B12 deficiency produces hyperhomocysteinemia, which is an independent risk factor for atherosclerotic disease. Serum high concentrations of homocysteine and low levels of folic acid and vitamin B12 are significantly correlated with the categories of coronary artery diseases Investigations • Serum cobalamin levels are the initial test A normal serum cobalamin level does not exclude cobalamin deficiency. • Diagnosis of vitamin B12 deficiency is typically based on measurement of serum vitamin B12 levels; however, about 50 percent of patients with subclinical disease have normal B12 levels. • A more sensitive method of screening for vitamin B12 deficiency is measurement of serum methylmalonic acid and homocysteine levels, which are increased early in vitamin B12deficiency. elevated methylmalonic acid level is more specific for vitamin B12 deficiency than an elevated homocysteine level. Vitamin B12 or folic acid deficiency can cause the homocysteine level to rise, so folic acid levels also should be checked in patients with isolated hyperhomocysteinemia. two enzymatic reactions are known to be dependent on vitamin B12.

1.

methylmalonic acid is converted to succinyl-CoA using vitamin B12 as a cofactor. Vitamin B12 deficiency, therefore, can lead to increased levels of serum methylmalonic acid. 2. homocysteine is converted to methionine by using vitamin B12 and folic acid as cofactors. In this reaction, a deficiency of vitamin B12 or folic acid may lead to increased homocysteine levels. Management • if no neurological involvement 1 mg of IM hydroxocobalamin 3 times each week for 2 weeks, then once every 3 months oral vitamin B12 has been shown to have an efficacy equal to that of injections in the treatment of pernicious anemia and other B12 deficiency states. Although the daily requirement of vitamin B12 is approximately 2 mcg, the initial oral replacement dosage consists of a single daily dose of 1,000 to 2,000 mcg. This high dose is required because of the variable absorption of oral vitamin B12 in doses of 500 mcg or less. • if a patient is also deficient in folic acid then it is important to treat the B12 deficiency first to avoid precipitating subacute combined degeneration of the cord Large amounts of folic acid can mask the damaging effects of vitamin B12 deficiency by correcting the megaloblastic anemia caused by vitamin B12 deficiency without correcting the neurological damage that also occurs Sep 2017 part 1: Which structure in the body are able to synthesize vitamin B12? gut bacteria It is synthesized by gut bacteria in humans, but humans cannot absorb the B12 made in their guts, as it is made in the colon which is too far from the small intestine, where absorption of B12 occurs. Therefore diet is the only source of vit B12.

Vitamin B1 (Thiamine) deficiency Overview • the biologically active form of this vitamin is thiamine pyrophosphate (TPP) • the most important biochemical reactions requiring the availability of thiamine includes glycolysis and tricarboxylic acid (TCA) cycle. • There are three enzymes that require the presence of thiamine pyrophosphate as a cofactor:

1. a-ketoglutarate dehydrogenase
2. branched chain amino acid dehydrogenase
3. pyruvate dehydrogenase Causes • Heavy alcohol drinking • Malnutrition, starvation • Malabsorption • Malignancy

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Basicsciences Biochemistry&metabolsm Pathophysiology • Thiamine deficiency → impaired glucose breakdown → ATP depletion → tissue damage that primarily affects highly aerobic tissues (e.g., brain, heart) • High-dose glucose infusions lead to increased ATP depletion, which can trigger Wernicke encephalopathy. In malnourished individuals and chronic alcohol users/heavy drinkers, thiamine should be administered before glucose infusions. Features • Beriberi: inadequate thiamine uptake due to malnutrition, heavy drinking, or increased demand (e.g., hyperthyroidism, pregnancy) Dry beriberi Symmetrical peripheral neuropathy (sensory and motor) Progressive muscle wasting Paralysis Confusion Wet beriberi Oedema High-output cardiac failure (dilated cardiomyopathy) • Wernicke encephalopathy The triad of: Encephalopathy, Ataxia and Oculomotor dysfunction (usually nystagmus) • Korsakoff's psychosis

characterised by both anterograde and retrograde amnesia with confabulation What happens if you do not give the thiamine first before starting an intravenous glucose infusion? • ATP failing to be adequately generated • The inability of pyruvate to enter the TCA cycle → accumulate of pyruvate → pyruvate converted to lactate in order to be able to maintain glycolysis →↑acidosis. • Inability of the pentose phosphate pathway to protect the cell from reactive oxygen species that damage cellular structures, results in either cell death or activation of apoptosis. Vitamin function as a co-factors: Biotin for carboxylase reactions. Thiamine for dehydrogenase reactions B9 (folate) for transferases. Vit C for hydroxylases.

Vitamin E deficiency Active form: tocopherol Function • Lipid-soluble antioxidant in the glutathione peroxidase pathway removes the free radical intermediates protects cell membranes from oxidation by reacting with lipid radicals produced in the lipid peroxidation chain reaction. Therapeutic uses → Nonalcoholic steatohepatitis

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Features • Neurologic dysfunction Demyelination of the posterior column and spinocerebellar tract → ↓ proprioception and vibration sensation; ataxia Neurologic symptoms are similar to vitamin B12 deficiency, except that vitamin E deficiency does not lead to hypersegmented neutrophils, megaloblastic anemia, and increased methylmalonic acid levels. • Hemolytic anemia; increased fragility of erythrocytes and membrane breakdown • Acanthocytosis • Muscle weakness Hypervitaminosis E
• interfere with vitamin K metabolism →vitamin K deficiency →increased tendency to bleed.

Vitamin K Deficiency Sources of vitamin K • Leafy green vegetables (vitamin K1) • Synthesized in small amounts by intestinal bacteria Functions • Cofactor for γ-carboxylation of glutamate residues on vitamin-K-dependent proteins involved in: Coagulation: maturation of factors II (prothrombin), VII, IX, and X, protein C, protein S Bone formation: osteocalcin (bone Gla protein), matrix Gla protein Causes • Liver failure • Fat malabsorption • Prolonged broad-spectrum antibiotic therapy • Vitamin K antagonists (e.g., warfarin) Features • Hemorrhage (e.g., petechiae, ecchymoses) • Vitamin K deficiency bleeding (VKDB) ↑ PT and aPTT, normal bleeding time Postnatal prophylaxis: vitamin K injection at birth

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Vitamin A deficiency Over view of vitamin A • Active forms: Retinal and Retinoic acid • Sources Plant sources; yellow and leafy vegetables Animal sources: in storage form; liver Causes • Disorders associated with fat malabsorption: inflammatory bowel disease (e.g., Crohn disease), celiac disease, cystic fibrosis, pancreatic insufficiency

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Features • Ocular manifestations Night blindness (nyctalopia) Xerophthalmia Keratomalacia Bitot spots: gray, triangular, dry patches on the bulbar conjunctiva, covered by a layer with a foamy appearance Typical sign of vitamin A deficiency Caused by squamous cell metaplasia and keratinization of the conjunctiva • Keratinizing squamous metaplasia of the bladder (pearl-like plaques on cystoscopy) • Xerosis cutis (dry skin) • Immunosuppression 0BVitamin A toxicity Causes: increased intake via supplements or drugs Acute toxicity: Nausea, vomiting, Vertigo, Blurred vision Chronic toxicity: Alopecia, Dry skin, scaling Arthralgias Hepatosplenomegaly, hepatic toxicity Pseudotumor cerebri Which substances in vitamin A is most likely to be maximally involved in correcting the visual disturbance? Retinaldehyde Retinaldehyde is derived from the oxidation of retinol What would you give the patient who taking long term steroids to help his wound heal faster? Vitamin A Vitamin A is believed to counteract the effect of steroids on slowing wound healing by stimulating TGF-beta and IGF-I, as well as collagen production. However, high levels (which can accumulate because vitamin A is fat soluble) can also be toxic and inhibit collagen synthesis, such as in the skin.

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Vitamin deficiency The table below summarises vitamin deficiency states Vitamin Chemical name Deficiency state A Retinoids Night-blindness (nyctalopia). dry skin. B1 Thiamine Beriberi • polyneuropathy, Wernicke-Korsakoff syndrome • heart failure (dilated cardiomyopath) B2 (riboflavin) Angular stomatitis, cheilosis, corneal vascularization B3 Niacin Pellagra • dermatitis • diarrhoea • dementia B6 Pyridoxine Anaemia, irritability, seizures B7 Biotin Dermatitis, seborrhoea B9 Folic acid Megaloblastic anaemia, deficiency during pregnancy - neural tube defects B12 Cyanocobalamin Megaloblastic anaemia, peripheral neuropathy C Ascorbic acid Scurvy • gingivitis • bleeding • poor wound healing D Ergocalciferol, cholecalciferol Rickets, osteomalacia E Tocopherol, tocotrienol ↑ fragility of RBCs. Mild haemolytic anaemia in newborn infants, ataxia, peripheral neuropathy K Naphthoquinone Haemorrhagic disease of the newborn, bleeding diathesis Selenium Selenium Keshan disease (cardiomyopathy).

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Zinc deficiency Features • perioral dermatitis: red, crusted lesions • (rough and dry skin) • acrodermatitis • alopecia • short stature (dwarfism) • hypogonadism • hepatosplenomegaly • geophagia (ingesting clay/soil) • cognitive impairment Treatment • Zn supplementation has been shown to improve neuropsychological function in Chinese children. • Zn deficiency is associated with adverse pregnancy outcomes.

Pyruvate kinase • Pyruvate kinase is the rate-limiting step in glycolysis and gluconeogenesis • It catalyses the transfer of a phosphate group from phosphoenolpyruvate to ADP, yielding a molecule of pyruvate and a molecule of ATP • Deficient pyruvate kinase activity may result in the

development of hereditary haemolytic anaemias Which biochemical processes is likely to contribute most to energy creation in long distance running? Fatty acid oxidation

Third edition Notes & Notes For MRCP part 1 & 11 By Dr. Yousif Abdallah Hamad Basic sciences Immunology Updated

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Basic sciences Immunology

Human leukocyte antigen (HLA) Overview • The human leukocyte antigen (HLA) is a gene complex that encodes the major histocompatibility complex (MHC) proteins. • MHC proteins play a vital role in initiating immune responses as they present antigen fragments to T cells and bind T-cell receptors. • Found on chromosome 6 • 2 classes: Class I → HLA A , B, C expressed on all cells, except erythrocytes and trophoblasts interact with CD8+ class II → HLA DP, DQ, DR expressed on B cells, dendritic cells, and monocytes most important in transplant → (DR) MRCP-part-1-2018: Which HLA subtypes is usually implicated with respect to matching for avoiding hyperacute rejection? HLA-C Anti-HLA-C IgG antibodies are usually implicated in hyperacute rejection; specifically, HLA-CW5 subtype antibodies have been implicated most in hyperacute rejection of renal transplant. MHC I-associated loci (HLA-A/-B/-C) only have 1 letter after the hyphen, while MHC IIassociated loci (HLA- DR/- DP/- DQ) have 2 letters.

HLA associations • The most important HLA associations are listed below: Associated diseases HLA type Hemochromatosis HLA-A3 Behcet's disease HLA B51 is a split of B5 HLA-B5 21-hydroxylase deficiency HLA-B47 Psoriasis HLA-CW6 Diabetes mellitus type 1(but more with HLA-DR4) HLA-DR3 + DR4 combined steroid-responsive nephrotic syndrome HLA-DR7 HLA-DR2 HLA-DR4 HLA-B27 HLA-DR3

Cluster of Differentiation (CD Markers) Function and usage of CDs: • The CD system is commonly used as cell markers in immuno-phenotyping, allowing cells to be defined based on what molecules are present on their surface. • often acting as receptors or ligands (the molecule that activates a receptor) • cell signaling: Errors in cellular information processing are responsible for diseases such as cancer, autoimmunity, and DM • Cell adhesion: essential for the pathogenesis of infectious organisms, eg: HIV has an adhesion molecule termed gp120 that binds to its ligand CD4, which is expressed on lymphocyte. Notes & Notes for MRCP
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 Narcolepsy Goodpasture's hay fever, systemic lupus erythematosus, multiple sclerosis. Felty's syndrome (90%) →most common Rheumatoid arthritis (70%) Diabetes mellitus type 1 (> DR3) Drug-induced SLE IgA nephropathy HOCM Ankylosing spondylitis Post-gonococcal arthritis Reiter's syndrome (reactive arthritis) Acute anterior uveitis Autoimmune hepatitis Primary biliary cirrhosis
 Coeliac disease (95% associated with HLA-DQ2) Diabetes mellitus type 1 Primary Sjögren syndrome Dermatitis herpetiformis

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The table below lists the major clusters of differentiation (CD) molecules Cluster of differentiation Function CD1 MHC molecule that presents lipid molecules CD2 Found on thymocytes, T cells, and some natural killer cells that acts as a ligand for CD58 and CD59 and is involved in signal transduction and cell adhesion CD3 The signalling component of the T cell receptor (TCR) complex CD4 Found on helper T cells. Co-receptor for MHC class II Used by HIV to enter T cells CD5 Found in the majority of mantle cell lymphomas CD8 Found on cytotoxic T cells. Co-receptor for MHC class I Found on a subset of myeloid dendritic cells CD14 Cell surface marker for macrophages CD15 Expressed on Reed-Sternberg cells (along with CD30) CD 21 Epstein-Barr virus uses the CD21 receptor to invade B cells. CD28 Interacts with B7 on antigen presenting cell as costimulation signal CD95 Acts as the FAS receptor, involved in apoptosis Clusters of differentiation • CD4 Found on helper T cells. Co-receptor for MHC class II Used by HIV to enter T cells GP120 →fuses to CD4 →allow GP41 to penetrate the cell membrane • CD 8 Found on cytotoxic T cells. Co-receptor for MHC class I Found on a subset of myeloid dendritic cells • CD14 →Cell surface marker for macrophages • CD18 →the absence of it causes Leukocyte adhesion deficiency GP41 play a role in the initial step for HIV entry into cells Gp120 fuses to the CD4 receptor, this then allows GP41 to penetrate the cell membrane

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Complement pathways • Activation may occur via three pathways:

1. Classical pathway: Activated by IgM or IgG complexes binding to the pathogen C1q, C1r, and C1s activation → C1 complex → split of C4 into C4a and C4b and C2 into C2a and C2b → formation of C3 convertase (C4b2b) from C4b and C2b C2 is involved in activation via the classical pathway
2. Alternative pathway: Activated directly by pathogen surface molecules rather than by antigenantibody complexes C3 is split into C3a and C3b → binding of factor B → formation of C3 convertase (C3bBb). Generates early innate response that does not require antibody for activation.
3. Lectin pathway: Activated by mannose or other sugars on pathogen surface Mannose-binding lectin (MBL) binds to mannose → formation of the C1-like complex, which cleaves C4 into C4a and C4b → C4b binding C2 and splitting of C2 into C2a and C2b → formation of C3 convertase (C4b2b). • All complement pathways have one final common pathway at C3. IgG and IgM activate the classic pathway

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Basic sciences Immunology

Hypersensitivity The Gell and Coombs classification divides hypersensitivity traditionally divides reactions into 4 types: Type Mechanism Examples Type I - Anaphylactic Antigen reacts with IgE bound to mast cells (IgE-mediated) Type II - Cell bound IgG or IgM binds to antigen on cell surface (antibodymediated) Type III - Immune complex Free antigen and antibody (IgG, IgA) combine (Immune complex deposition) Type IV - Delayed hypersensitivity T-cell mediated (cell-mediated)
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• Anaphylaxis • Atopy (e.g. asthma, eczema and hayfever) Diagnosed by plasma tryptase (protease released from mast cell). • Autoimmune haemolytic anaemia • ITP • Goodpasture's syndrome • Pernicious anaemia • Acute haemolytic transfusion reactions • Rheumatic fever • Pemphigus vulgaris / bullous pemphigoid • Serum sickness • Systemic lupus erythematosus • Post-streptococcal glomerulonephritis • Extrinsic allergic alveolitis (especially acute phase) • Tuberculosis / tuberculin skin reaction • Graft versus host disease • Allergic contact dermatitis • Scabies • Extrinsic allergic alveolitis (especially chronic phase) • Multiple sclerosis • Guillain-Barre syndrome

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In recent times a further category has been added: Type Mechanism Examples Type V Antibodies that recognise and bind to the cell surface receptors. This either stimulating them or blocking ligand binding • Graves' disease • Myasthenia gravis What is the hallmark signs of mast cell degranulation? • Classical wheal and flare

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Anaphylaxis Definition • a severe type 1 hypersensitivity reaction that can cause life-threatening and multisystem effects due to IgE-mediated mast cell activation Pathophysiology • Immunoglobulin E is the most common immunoglobulin involved in the pathogenesis of anaphylaxis. • Anaphylaxis (type I hypersensitivity reaction) or anaphylactoid reactions → degranulation of mast cells → massive histamine release → systemic vasodilation → increased capillary leakage → anaphylactic shock • Mediators involved in the development of anaphylaxis include: Tryptase, histamine, leukotrienes, prostaglandins, IL4, IL13 , Heparin and platelet aggregating factor, which are generated by mast cell degranulation. • Triggers for anaphylactic reactions: heat, cold, sexual activity, exercise Causes

1. Anaphylaxis (IgE mediated): Food (e.g. Nuts) - the most common cause in children Drugs The most common IgE-mediated triggers are drugs, typically penicillin or other beta-lactam antibiotics. Neuromuscular blocking agents (eg vecuronium) are responsible for 6070% of allergic reactions related to anaesthesia. Latex Venom (e.g. Wasp sting)
2. Anaphylactoid (non-IgE mediated). The reactions that produce the same clinical picture as anaphylaxis but are not IgE mediated.’ plasma proteins or compounds, which act directly on the mast cell membrane, such as Vancomycin

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 Quinolone antibiotics Aspirin or other non-steroidal anti-inflammatory drugs Opiates Colloid plasma expanders Radiographic contrast media Anaphylaxis following a blood transfusion can be due to immunoglobulin A deficiency. Anaphylaxis VS Anaphylactoid Is it anaphylactic OR anaphylactoid reaction? (IgE-mediated anaphylactic Is sensitization required? Yes No Can reaction occur in first exposure? How much exposure is needed very little (dose independent) usually more than for to elicit reaction? Is reaction predicted by skin allergy test? Which feature is the most important predictor of anaphylaxis in asthmatic patient with peanut allergy? Poorly controlled asthma Poorly controlled asthma is an important risk factor for fatal anaphylaxis in this situation. Patients such as this should have their asthma well controlled and have ready access to, and knowledge of how to use, self-injectable adrenaline. Features (Usually takes 15-30 minutes from the time of exposure to the antigen) • Skin or mucous membranes: Flushing, erythema, pruritus, Swelling of the eyelids, angioedema • Respiratory: hoarseness, Chest tightness, Dyspnea (due to bronchospasm or laryngeal edema), tachypnea, Stridor, wheezing, Hypoxia, cyanosis • Gastrointestinal: Nausea, vomiting (especially in food allergies), Abdominal pain, diarrhea • Cardiovascular: Hypotension, Tachycardia Investigations • Serum mast-cell tryptase: if elevated, supports the diagnosis of anaphylaxis has a half-life of 2 h, peaking at 1 h after anaphylaxis onset and return to baseline by 6 hours. Both sensitivity and specificity to confirm diagnosis is 95% Normal tryptase results do not exclude anaphylaxis • Complement C4 levels: can be low in hereditary angioedema • Total serum IgE level is non-specific and unhelpful. Notes & Notes for MRCP
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Anaphylactic Anaphylactoid (Non IgE-mediated reactions) anaphylactic reactions) No Yes anaphylaxis Yes No

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Management • Airway assessment and management: Rapid sequence intubation (RSI) for airway compromise • Adrenaline the most important drug in anaphylaxis and should be given as soon as possible. The dose for adult and child > 12 years : 500 micrograms (0.5ml 1 in 1,000) The best site for IM injection is the anterolateral aspect of the middle third of the thigh. Adrenaline can be repeated every 5 minutes if necessary. • Hydrocortisone 200 mg • Chlorphenamine 10 mg • IV fluids Evidence from a large randomised controlled trial (RCT) suggests there is no difference between normal saline and Hartmann’s solution [also known as Ringer’s lactate] for resuscitation of critically ill patients. • Observation: It is recommended to observe patients after resolution of an anaphylactic episode for 24 hours for possible second-phase reactivation. Late-phase reaction In IgE mediated reactions such as asthma or anaphylaxis what therapy inhibits the important late-phase reaction? steroids • The late phase reaction is due to attraction of T cell, release of leukotrienes and prostaglandins often characterised by asthma • prevented by the administration of steroids (Hydrocortisone). • Approximately 30% of deaths related to anaphylaxis occur as a consequence of this late-phase reaction

Exercised induced anaphylaxis Definition • a rare disorder in which anaphylaxis occurs after physical activity. Features • usually occur around 10 minutes after exercise and follow a sequence of pruritus, widespread urticaria and then subsequently respiratory distress and vascular collapse. Epinephrine injections for anaphylaxis should always be given intramuscularly in a concentration of 1:1,000 (as opposed to the 1:10,000 solution used in cardiac arrest). Injecting the 1:1,000 solution into a vein can lead to cardiac arrhythmia/arrest. Antihistamines and steroids should be administered in anaphylaxis only after the initial resuscitation measures (IM epinephrine, fluids and/or vasopressors) have been given. A lack of response to epinephrine, antihistamines, and steroids should raise suspicion of differential diagnoses such as bradykinin-mediated angioedema, which requires its own specific treatment

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Pathophysiology • may be related to endorphin release during exercise → excessive histamine release from mast cells in susceptible individuals. Associations • Co-factors such as foods, alcohol, temperature, drugs (eg, aspirin and other nonsteroidal anti-inflammatory drugs), humidity, seasonal changes, and hormonal changes are important in the precipitation of attacks. • most associated with wheat ingestion. • The foods most commonly implicated in food-dependent exercise-induced anaphylaxis are wheat, shellfish, tomatoes, peanuts, and corn. • The patients can usually eat the causative food without problems so long as they do not exercise afterwards. Treatment • managed in the same manner as anaphylaxis. • usually resolves on stopping exercise • Reducing physical activity to a lower level may diminish the frequency of attacks. • Patients should be instructed on the proper use of emergency injectable epinephrine and have one available at all times. • Patients should wear a medical alert bracelet with instructions on the use of epinephrine.

Anaphylactic reactions associated with anaesthesia Risk factors • Neuromuscular blocking drugs and latex appear to cause anaphylaxis more commonly in female patients • Individuals with a history of atopy, asthma or allergy to some foods appear to be at increased risk of latex allergy but not anaphylaxis to neuromuscular blocking drugs or antibiotics • Patients with asthma or taking b-blocking drugs may suffer a more severe reaction. Causes • Neuromuscular blocking agents (NMBAs) Most common cause 60% of cases of anaesthesia-related anaphylaxis are due to neuromuscular blocking agents. 80% of NMBA reactions occur without prior exposure Quaternary ammonium ions (QAI) are proposed to be the allergenic epitopes in NMBAs. Common environmental chemicals such as toothpastes, washing detergents, shampoos, and cough medicines share these allergenic epitopes with the NMBAs, predisposed individual to become sensitised to QAIs and thus be at risk of developing anaphylaxis to NMBAs during anaesthesia. succinylcholine is the NMBA most likely to be associated with allergic anaphylaxis (carries the highest risk) • Latex Latex hypersensitivity is the second most common cause of anaesthesia related anaphylaxis in many studies (up to 20% of cases). But now decreased due to decline in the use of latex gloves. • Antibiotics Approximately 15% of anaesthesia-related anaphylactic episodes are due to antibiotics. Skin testing is only approximately 60% predictive of clinical

hypersensitivity. Penicillins and

 cephalosporins which share the b-lactam ring are responsible for approximately 70% of antibiotic-induced anaphylaxis. There is a higher rate of antibiotic allergy in smokers • Anaesthetic induction agents Anaphylaxis to propofol is very uncommon Anaphylaxis to thiopental has become extremely uncommon, probably reflecting the decline in its use. • Antiseptics and disinfectants Reactions to chlorhexidine have come into greater prominence in recent years. Anaphylaxis has occurred when chlorhexidine was used as an antiseptic for urological and gynaecological procedures as well as insertion of central venous and epidural catheters. Allowing chlorhexidine to dry before beginning a procedure may reduce the risk of reaction. Anaphylaxis to other antiseptics is rare. Diagnosis • Timings Type I reactions typically occur within seconds to minutes after i.v. exposure. An insidious or delayed onset may occur (e.g. with latex, antibiotics, and colloids and a tourniquet may delay onset until after surgery). • History of atopy and asthma has a clear link with latex allergy.

Allergy tests Skin prick test • Most commonly used test as an easy to perform and inexpensive. • the first line for detection of allergen-specific IgE • Drops of diluted allergen are placed on the skin after which the skin is pierced using a needle. • A large number of allergens can be tested in one session. • Normally includes a histamine (positive) and sterile water (negative) control. • A wheal will typically develop if a patient has an allergy. • Can be interpreted after 15 minutes • Useful for food allergies and also pollen. It is a reliable way of excluding IgE-mediated food allergies, although the positive predictive value is around 50% or less (the sensitivity of a negative skin prick test to foods is high) • It can induce anaphylaxis, and must therefore be done in an environment where resuscitation facilities are available. Radioallergosorbent test (RAST) • Determines the amount of IgE that reacts specifically with suspected or known allergens, for example IgE to egg protein. • Results are given in grades from 0 (negative) to 6 (strongly positive) • Useful for food allergies, inhaled allergens (e.g. Pollen) and wasp/bee venom • Blood tests may be used when skin prick tests are not suitable, for example if there is extensive eczema or if the patient is taking antihistamines Skin patch testing • Useful for contact dermatitis. • Around 30-40 allergens are placed on the back. • Irritants may also be tested for. • The patches are removed 48 hours later with the results being read by a dermatologist after a further 48 hours

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If a history of anaphylaxis is given it would not be appropriate to perform a skin prick test, thus Radioallergosorbent test (RAST) is the most appropriate first-line test to investigate the cause of the reaction Reasons for a false negative RAST test • Immediately following anaphylaxis / allergic reaction (transient drop in IgE) • Waning of allergen-specific IgE with time following a reaction. • Unstable allergens in the RAST substrates (especially food allergens) Only IgE-mediated allergic reactions can be tested by skin prick testing The wheal size resulting from the skin prick test is an

excellent predictor of a positive food challenge to peanuts

Latex allergy Definition • A type I or type IV hypersensitivity to latex-based products (e.g., exam gloves, condoms) Epidemiology • 8–12% of health care workers are affected • NHS trusts in the UK have moved away from the routine use of latex gloves precisely because of the risk of allergy. As a result, latex allergy in hospital is now very rare in the UK. • Latex allergy is more common in children with myelomeningocele spina bifida. Pathophysiology • Sensitivity to latex may cause several problems: type I hypersensitivity (anaphylaxis) it is very unlikely that a latex allergy would explain an anaphylaxis during anaesthetic induction (latex allergies typically used to commence when a surgeon began handling internal organs). type IV hypersensitivity (allergic contact dermatitis) Type 4 hypersensitivity is usually due to accelerators or chemicals used in the manufacturing process, whereas type 1 hypersensitivity is due to the latex proteins themselves irritant contact dermatitis Latex-fruit syndrome • It is recognised that many people who are allergic to latex are also allergic to fruits, particularly banana, pineapple, avocado, chestnut, kiwi fruit, mango, passion fruit and strawberry. However, bananas are the most commonly associated with latex/rubber allergy MRCPUK part-1-May 2016 exam: A nurse who is known to have an allergy to latex develops a widespread urticarial rash and facial oedema shortly after eating lunch. Which food is she most likely to have consumed? Banana Latex allergy can be associated with certain foods such as bananas, avocado, kiwi and melon.

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad

Serum Sickness Definition • Serum sickness is a classic example of a type III hypersensitivity reaction, which usually develops as a complication of antitoxin or antivenom administration. Aetiology • Antivenom or antitoxin containing animal proteins • Medications most frequently antibiotics (e.g., penicillin, amoxicillin, cefaclor, trimethoprimsulfamethoxazole) • Infections: Hepatitis B virus Pathophysiology • exposure to an antigen (e.g., antivenom, drug) → formation of antibodies → deposition of antibody-antigen complexes in tissue → activation of the complement cascade → tissue damage and systemic inflammation Features • Symptoms appear 1–2 weeks following initial exposure (because antibodies take several days to form), and usually resolve within a few weeks after discontinuation of the offending agent. • Fever • Rash (urticarial or purpuric) • Arthralgias • Lymphadenopathy Subtypes and variants: serum sickness-like reaction • much more common than actual serum sickness • Aetiology: similar to that of serum sickness • Infections (e.g., hepatitis B, rabies) • Medications that can act as haptens (e.g., allopurinol, cephalosporins, penicillin). Diagnostics: Urinalysis may show mild proteinuria. Treatment: Stop the offending agent.