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Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad

Prescribing N-acetyl cysteine (NAC) • Action: it is a precursor of glutathione and hence can increase hepatic glutathione production • Root and administration: Acetylcysteine is the treatment of choice and is given intravenously (in the US and some other places it is still occasionally given orally). Although the oral route is simpler, it frequently causes nausea and vomiting and is unpleasant. Additionally, the standard oral regimen is 72 hours in duration compared with 21 hours intravenously, Acetylcysteine should be administered by intravenous infusion preferably using Glucose 5% as the infusion fluid. Sodium Chloride 0.9% solution may be used if Glucose 5% is not suitable.
• Indications: N-Acetylcysteine is recommended in all cases where the paracetamol overdose exceeds 150 mg/kg body weight All patients with a plasma paracetamol level ≥ 100 mg/L at 4 hours or ≥ 15 mg/L at 15 hours after ingestion should receive acetylcysteine regardless of risk factors for hepatotoxicity. The paracetamol level is not used to guide treatment in the setting of a staggered overdose, and N-acetylcysteine should be given without delay to reduce the risk of liver failure. In the case of staggered overdose or unclear timing of overdose, acetylcysteine should be given.

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• When to be started: N-acetylcysteine is most effective when administered within 8 h of ingestion
 If acetylcysteine is started within 8 hours of the ingestion, hepatotoxicity is extremely unlikely.
 The urgency of treatment is underlined by the fact that the incidence of hepatotoxicity is worse if treatment is delayed. Trials of N-acetylcysteine suggest that the incidence of hepatotoxicity is 1% in those treated within eight hours as opposed to 46% in those treated after 16 hours. • Infusion rate: The new guidelines have increased the recommended duration of the first infusion to 60 minutes from 15 minutes previously. The MHRA now recommends extending the time of the initial infusion from 15 minutes to 60 minutes in order to reduce the incidence of adverse reactions.
• Doses:
 The full course of treatment with acetylcysteine comprises of 3 consecutive intravenous

infusions.
 The patient should receive a total dose of 300 mg/kg body weight over a 21-hour period.

1. First infusion Add the appropriate volume of acetylcysteine injection to 200 mL of infusion fluid and infuse over 1 hour.
2. Second infusion Add the appropriate volume of acetylcysteine injection to 500 mL of infusion fluid and infuse over the next 4 hours.
3. Third infusion Add the appropriate volume of acetylcysteine injection to 1 litre of infusion fluid and infuse over the next 16 hours. • Reactions to NAC
   Features: (eg: patient became flushed and hypotensive) Mechanism: Reactions to NAC are well recognized and are not related to hypersensitivity.
   The majority of dose-related adverse reactions occur within the first hour of the initial infusion of acetylcysteine.
   Any 'hypersensitivity-like' reactions are more likely to be anaphylactoid in nature (i.e. not immunologically mediated) and therefore may not occur on repeated exposure. Management:
   NAC can almost always be safely restarted, and total dose safely administered after symptomatic treatment.
   Even if a patient has a history of a previous reaction to intravenous acetylcysteine, the benefits outweigh the risks and patient should receive treatment.
   IV chlorpheniramine and restart NAC infusion once symptoms resolved What is the most appropriate next step after iv antihistamine? Re-start the N-acetylcysteine infusion at half rate Oral methionine may be an alternative but is definitely second line.
   Patients often have an associated history of alcohol intake and episodes

of vomiting, which can affect the pharmacokinetics of oral medications. Paracetamol overdose during pregnancy • resulting toxic metabolites can cross the placenta and lead to hepatocellular necrosis of maternal and fetal liver cells. • NAC can bind the toxic metabolites in the mother and fetal circulation as it crosses the placenta.
• NAC appears to be safe during pregnancy and therefore should be administered.

King's College Hospital criteria for liver transplantation in paracetamol-induced acute liver failure List for transplantation if: • Arterial pH <7.3 or arterial lactate >3.0 mmol/L after adequate fluid resuscitation; OR • If all three of the following occur in a 24-hour period: Creatinine >300 µmol/L. PT >100 seconds (INR >6.5). Grade III/IV encephalopathy. Strongly consider transplantation if: • Arterial lactate >3.5 mmol/L after early fluid resuscitation.

The criteria for transfer to a specialist liver unit are: (poor prognostic factors) • Encephalopathy • INR: >2.0 at < 48 hours, or > 3.5 at < 72 hours synthetic function (as determined by INR or PT) is the best indicator. • Serum creatinine: >200 µmol/L • Blood pH: <7.3 • Systolic BP: <80 mmHg. Monitoring and endpoints for treatment Hepatotoxicity • In patients being treated with acetylcysteine for liver toxicity the acetylcysteine should be continued until the INR is 1.3 or less OR INR is falling towards normal on two consecutive blood tests, and less than 3.0. • Blood tests

(urea and electrolytes, creatinine, INR, and ALT) should be re-checked every 8 to 16 hours to assess the progress of the hepatic injury. There is no clinical benefit in continuing treatment with acetylcysteine for a rise in ALT if the INR has normalised. Time-sensitive treatment issues • 8-hour window the need for acetylcysteine treatment should be based on a serum paracetamol concentration determined within this 8-hour window.
 acetylcysteine within 8 hours of an acute ingestion prevent hepatic injury in nearly all patients
 Empiric acetylcysteine therapy should be initiated for patients who:
 present later than 8 hours after ingestion; when serum paracetamol concentrations cannot be determined within 8hours;

Pharmacology or if the exact timing of the ingestion is uncertain. adverse effects • oral acetylcysteine nausea and vomiting.
• intravenous acetylcysteine anaphylactoid reaction (e.g., nausea, flushing, vomiting, rash, urticaria, pruritus, angio-oedema, dyspnoea, wheezing, bronchospasm, tachycardia, and hypotension),
• Previous anaphylactoid reaction to acetylcysteine is not a contraindication to receiving acetylcysteine. Patients with a previous anaphylactoid reaction should be given an H1 and an H2 antagonist.
 Patients with previous bronchospasm reaction to acetylcysteine can be given nebulised salbutamol. Patients considered at risk of anaphylactoid reactions (e.g., those with atopy, bronchospasm, asthma, or a previous reaction) should be administered prophylactic medication such as antihistamines to reduce adverse reactions. • Methionine is used as an oral antidote for paracetamol poisoning in those who cannot tolerate N-acetylcysteine

Paracetamol and smoking • Enzyme induction with cigarette smoking does affect paracetamol metabolism. Its importance however, is in toxicity.
• Smokers would be classified as in a high risk for paracetamol overdose and are assessed using a different time - paracetamol level curve. Complications • Untreated paracetamol poisoning may cause varying degrees of liver injury over the 2 to 4 days following ingestion, including fulminant hepatic failure. Hepatotoxicity is extremely rare in patients treated with acetylcysteine within 8 hours of an acute paracetamol overdose. • Lactic acidosis is recognised complication
• Hypoglycaemia is seen when paracetamol toxicity leads to significant impairment of hepatic synthetic function Severe hypoglycaemia affects 40% of patients with fulminant liver failure, which exacerbates encephalopathy.
• Paracetamol nephrotoxicity
 can develop later than liver toxicity The mechanism of kidney injury is similar to that of the liver, there is little evidence that N-acetyl cysteine confers any renal protection. usually the renal function returns to baseline after a few weeks.
 Haemodialysis may be required to support the patient during the acute episode.

Prognosis • The prognosis is poor in those with Blood PH less than 7.0 Prolonged prothrombin time (more than 100s) and Serum creatinine more than 300 uM. Mortality is greater if the patient is more than 40 years of age.

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paracetamol overdose treatment nomogram

Adult Dosage Table (Royal College of Emergency Medicine Guidance. http://www.rcem.ac.uk)

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Paraquat poisoning Properties of Paraquat • Paraquat is a very toxic compound • As little as 2 g is potentially fatal (10 ml of a concentrated 20% solution) Presentation • Initial signs of toxicity are due to its corrosive effects on the gastrointestinal tract and oropharynx Pathology • Paraquat is rapidly absorbed and is sequestered in the lungs, where it reacts with oxygen to form hydrogen peroxide and superoxide anions • Hydrogen peroxide and superoxide anions are responsible for cell death, which leads to an acute alveolitis Prognosis • Death tends to occur within hours to days in patients who have ingested more than 6 g of Paraquat • Death tends to occur within days in those who have ingested 3-6 g of Paraquat • Illness following ingestion of 1.5-3 g Paraquat follows a much more protracted course and delayed pulmonary • fibrosis can lead to death up to 6 weeks after ingestion Management • supportive care • activated charcoal to reduce absorption • oxygen supplementation can increase pulmonary toxicity, by increasing the rate of hydrogen peroxide and superoxide anion production

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Organophosphate insecticide poisoning Organophosphate is an anticholinesterase, thus prolonging the effects of acetylcholine. One of the effects of organophosphate poisoning is inhibition of acetylcholinesterase Organophosphates are rapidly absorbed through the gastrointestinal and respiratory tracts and the skin Mechanism
• The principal action of organophosphates is inhibition of acetylcholinesterases • This results in the accumulation of acetylcholine at muscarinic receptors, nicotinic receptors and in the central nervous system Features can be predicted by the accumulation of acetylcholine (mnemonic = SLUD)
Hypersalivation and miosis are the specific clues to acetycholine overactivity. • Salivation • Lacrimation • Urination • Defecation/diarrhoea • cardiovascular: hypotension, bradycardia • also: small pupils, muscle fasciculation Presentation The presentation relates to the sites of accumulation of acetylcholine • Accumulation at muscarinic receptors leads to: miosis hypersalivation sweating diarrhoea excessive bronchial secretions • Accumulation at nicotinic receptors leads to: muscle fasciculations tremor • Accumulation in the central

nervous system leads to: anxiety loss of memory headache coma • Organophosphate-induced neuropathy starts to develop 2 weeks after exposure Initial presentation of neuropathy is a flaccid paralysis Later, hypertonia, hyperreflexia and a spastic paralysis occur Management • atropine • the role of pralidoxime(an activator of cholinesterase) is still unclear - meta-analyses to date have failed to show any clear benefit

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Carbon Monoxide (CO) Poisoning Risk factors • A hypoxemic poisoning syndrome seen in patients who have been exposed to automobile exhaust, smoke inhalation, barbecues, or old appliances in poorly ventilated locations. Pathophysiology • CO binds with high affinity to haemoglobin, forming carboxyhaemoglobin. CO also binds myoglobin and mitochondrial cytochrome oxidase. Features • Presents with hypoxemia, cherry-red skin (rare), confusion, and headaches. Coma or seizures occur in severe cases. • Chronic low-level exposure may cause flu-like symptoms with generalized myalgias, nausea, and headaches. Ask about symptoms in others living in the same house. • Suspect smoke inhalation in the presence of singed nose hairs, facial burns, hoarseness, wheezing, or carbonaceous sputum. • CO poisoning causes tissue hypoxia, anaerobic metabolism and lactic acidosis. Diagnosis • Check an ABG and serum carboxyhemoglobin level (normal is < 5% in nonsmokers and < 10% in smokers). • Check an ECG in the elderly and in patients with a history of cardiac disease. Treatment • 100% O2 • after which transfer to a centre with hyperbaric oxygen should be considered. • Patients with airway burns or smoke inhalation may require early intubation, since upper airway edema can rapidly lead to complete obstruction.

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Antiemetic

Antiemetics • Aprepitant is a neurokinin receptor blocker used in the prevention of chemotherapy induced nausea. • Hyoscine antiemetics functions as a cholinergic muscarinic antagonist It acts as a competitive antagonist at muscarinic acetylcholine receptors; it is thus classified as an anticholinergic or as an antimuscarinic drug. • Metoclopramide is a dopamine receptor antagonist that can induce parkinsonism. It can also worsen control in patients with idiopathic Parkinson's disease to its antagonistic effect on dopamine receptors. • Domperidone is also a dopamine antagonist but acts peripherally. Best drug for nausea and vomiting associated with Parkinson treatment. Drugs such as apomorphine and bromocriptine cause vomiting through peripheral stimulation of the chemoreceptor trigger zone. Worsening of Parkinson’s disease may result from the use of dopamine antagonists; however, domperidone is much less likely to cross the blood–brain barrier and is therefore the preferred agent in this case.
• Haloperidol: the main site of action for haloperidol with regards anti-emetic effects --> Chemoreceptor trigger zone Haloperidol is an anti-dopaminergic agent licensed for and used

mainly as an anti-psychotic agent It does result in more extrapyramidal side-effects than phenothiazine-type agents, but is associated with less hypotension • Phenothiazines (e.g. promethazine) and domperidone are also used as anti-emetic agents and act at the chemoreceptor trigger zone • Cyclizine is an anticholinergic antihistamine acting through the vomiting centre.

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Group Drug Antagonize d receptor Mechanism Specific features Side effects Dopamin e receptor antagoni sts/ proki netic agents Prochlor perazine D2 • Antiemetic effect at the area postrema Domperi done • Antiemetic effect at the area postrema • Prokinetic effect Metoclo pramide • Antiemetic effect in the CNS and at the area postrema • Prokinetic effect : ↑ gastric contractions, duodenal and jejunal motility, resting tone of the lower esophageal sphincter and decreased pylorus sphincter activity allow food to pass quickly Serotoni n receptor antagoni sts Ondans etron (Zofran®) 5-HT3 • Central- acting antiemetic effect • Peripheral inhibition of the intestinal tract's vagal nerve signals Anticholi nergic Agents Scopola mine M2 • Antiemetic effect at the area postrema • Peripheral inhibition of the intestinal tract's vagal nerve signals Antihista mines Meclizin e, dimen hydrinat e, diphen hydramin e, doxyla mine, pr omethazi ne H1 • Antiemetic effect in the CNS Notes & Notes for MRCP
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• Depression • Fatigue • Diarrhea • Hyperprolactinemia • Overdose leads to reversible extrapyramidal syndrome (e.g., dystonia, park insonism, tardive dyskinesia, and akathisia) and neuroleptic malignant syndrome • Antidote: biperide n(anticholinergic agent) • Do not combine metoclopr amide with antipsyc hotics because of the increased risk of dyskinesia! • Domperidone may cause cardiac arrhythmias. • Antipsychotic agent • Used in severe hyperemesis gravidarum • Prokinetic effect: to treat diabetic and post-surgery gastroparesis (delayed gastric emptying) • Used in severe hyperemes is gravidarum • Chemotherapy and radiationinducedvomiting and pos toperative nausea and vomiting (PONV) ∗Headaches ∗Constipation or diarrhea ∗QT interval prolongation(torsades de pointes) ∗Increase in liver enzymes ∗Serotonin syndrome • Especially effective against motion sickness or vesti bularinducednausea and vomiting • Anticholinergic side effects: dry mouth, mydriasis, t achycardia, urinary retention • Antidote: physostig mine(cholinesteras e inhibitor) • Strong sedative • Used in hyperemesis gravidarum (also see “Drugs of choice in pregnancy” (antiemetics) • drowsiness and confusion • Anticholinergic side effects: dry mouth, dilated pupils, blurred vision, reduced bowel sounds, and urinary retention) →antidote: physo stigmine

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5-HT3 antagonists • 5-HT3 antagonists are antiemetics used mainly in the management of chemotherapy related nausea.
• They mainly act in the chemoreceptor trigger zone area of the medulla oblongata. Examples • Ondansetron Ondansetron is a selective 5-HT3 (5-hydroxytryptamine 3A receptor) antagonist both centrally and peripherally and as such is a potent antiemetic. Ondansetron is the first line

drug for chemotherapy related nausea and vomiting. Its effects are on both peripheral and central nerves.
 One part is to reduce the activity of the vagus nerve, which is a nerve that activates the vomiting center in the medulla oblongata,
 the other is a blockage of serotonin receptors in the chemoreceptor trigger zone. Common side effects of ondansetron are headache, drowsiness, and dizziness. • granisetron Adverse effects • constipation is common

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Metoclopramide Action • D2 receptor antagonist Indications • mainly used in the management of nausea.
• gastro-oesophageal reflux disease • prokinetic action is useful in gastroparesis secondary to diabetic neuropathy • often combined with analgesics for the treatment of migraine (migraine attacks result in gastroparesis, slowing the absorption of analgesics) Adverse effects • extrapyramidal effects: oculogyric crisis. This is particularly a problem in children and young adults , especially girls , usually subsides within 24 hours following cessation of treatment and can be treated with procyclidine 5-10 mg i.m. (antimuscarinic). • hyperprolactinaemia • tardive dyskinesia Acute dystonic-dyskinetic reactions
• Risk factors mostly occur in children and young adults
 about 70% of cases are female.
 It occurs more commonly when excess of the recommended dose of metoclopramide is administered. • Time frame
 The effects usually occur within 72 hours but have been reported to occur within 30 minutes of starting treatment.
• Features oculogyric crisis opisthotonus torticollis trismus,
 tetanus-like reactions.

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 A blue discolouration of the tongue has also been described. • Treatment generally self-limiting,
 the reaction can be reversed by an anticholinergic such as benzatropine or procyclidine or an antihistamine such as diphenhydramine.

MRCPUK-part-2-march-218: A 21-year female presented with acute spasm of her neck after metoclopramide injection. What is the most appropriate intervention? Procyclidine

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Other drugs

Antihistamines • Antihistamines (H1 inhibitors) are of value in the treatment of allergic rhinitis and urticaria.
• Sedation and headaches are the most common adverse effects of antihistamines • First

generation antihistamines (chlorpheriramine and diphenhydramine) are more sedating than the newer agents.

Sedating antihistamines • Cyproheptadine • Chlorpheniramine As well as being sedating these antihistamines have some antimuscarinic properties (e.g. urinary retention, dry mouth). Non-sedating antihistamines • loratidine • cetirizine • Desloratadine is a long-acting H-1-receptor antagonist has poor penetration into the central nervous system does not interact with antibiotics or other co-administered medications • Of the non-sedating antihistamines there is some evidence that cetirizine may cause more drowsiness than other drugs in the class. • Of the newer antihistamines, cetirizine and levocetirizine are more sedating than loratadine and desloratadine, and possibly more sedating than fexofenadine.

Other notes • Terfenadine (a pro-drug) has been associated with cardiac arrhythmias (torsades de pointes) especially in individuals with prolonged QT intervals. Fexofenadine is the active metabolite of terfenadine and does not appear to have the same arrhythmogenic effects as terfenadine. second-generation antihistamine has fewer sedative and anticholinergic side effects. in patients with allergy + history of narrow-angle glaucoma Fexofenadine first-generation antihistamines (eg: Chlorpheniramine) have anticholinergic side effects that can cause mydriasis and trigger an acute attack in patients with a history of narrow-angle glaucoma, • Cetirizine, desloratadine and fexofenadine are prescribed for allergic rhinitis (hay fever) and

all three are equally effective • cetirizine and fexofenadine interact with erythromycin and other macrolides • Chlorphenamine maleate and terfenadine cause drowsiness and also interact with erythromycin

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Human and animal bite • Co-amoxiclav is recommended as first-line treatment for all cat or human bites and other complicated animal bites. • In patients who are pencillin allergic, doxycycline plus metronidazole is a typical first choice regimen. • Only 15 - 20% of dog bites become infected, and providing the wound is appropriately cleaned and not considered at risk (for example, crush or deep wounds) then antibiotic prophylaxis may not be required.

Botox Paralysis of frontalis eyebrows are drooping (eyebrow ptosis). • Botox (onabotulinumtoxinA) is an injectable neuro-toxin used for the treatment of chronic migraines, limb spasticity, axillary hyperhidrosis, cervical dystonia, strabismus, and blepharospasm.
• Botox is a neurotoxin derived from the bacteria, Clostridium botulinum. It blocks neuromuscular transmission inhibition of acetylcholine release at the presynaptic membrane. The end result is that the muscle contraction is inhibited. • The action of Botox is not permanent because collateral axonal sprouting establishes new neuromuscular junctions, restoring muscle function.
• Frontalis is a quadrilateral muscle found on the forehead that elevates the eyebrows; hence paralysis of this muscle can lead to eyebrow ptosis.

D-Penicillamine
• used to reduce the body copper in Wilson's disease & as a chelating agent in lead poisoning • D-Penicillamine is associated with pancytopenia and tubulointerstitial nephritis

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Isotretinoin

• Isotretinoin is an oral retinoid used in the treatment of severe acne. • Two-thirds of patients have a long term remission or cure following a course of oral isotretinoin Adverse effects • Teratogenicity: ♀s MUST be using two forms of contraception (e.g. COCP and condoms). Women must have a negative pregnancy test before treatment and be on effective contraception for at least a month before the course begins, during the course and for a month after it finishes

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 Congenital deafness , CNS and heart defects may occur in children exposed to isotretinoin in utero • Dry skin, eyes and lips: the most common side-effect of isotretinoin • Low mood, depression • Raised triglycerides • Hair thinning • Nose bleeds (caused by dryness of the nasal mucosa) • Benign intracranial hypertension: isotretinoin treatment should not be combined with tetracyclines for this reason

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Cinnarizine
• Cinnarizine is thought to be particularly useful for the treatment of motion sickness as it has a dual action: it acts as a depressant of the vestibular system it dampens down smooth muscle contraction in the gut

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Ergotamine • Ergotamine is an old drug and a member of the family of ergot alkaloids.
• It is licensed as a treatment and prophylaxis for migraines but has been largely superseded by newer agents despite its efficacy, cost and relatively benign side effect profile.
• A derivative of the drug, ergometrine, is used in obstetrics to reduce the incidence of post partum haemorrhage. • Ergotamine, like all ergot alkaloids, is a potent vasoconstrictor which is partly how it exerts its clinical effects, however in overdosage it can cause significant peripheral vasoconstriction causing critical ischaemia and gangrene. Coronary vasoconstriction may occur, with or without flow limiting lesions causing cardiac ischaemia which may be manifest as chest pain, arrhythmia or even sudden death.
• Contraindications to the use of ergotamine are flow limiting coronary lesions or peripheral vascular disease. • Additionally, ergotamine has a complex series of effects on central nervous neurotransmitter systems including serotonergic, dopaminergic and noradrenergic systems which can cause excitement, confusion, paranoia, visual and auditory hallucinations and delusions in overdose. • It is also a metabolic precursor to the highly hallucinogenic chemical lysergic acid diethylamide (LSD) which inactivates 5-HT2A receptors in the brain.
• At normal doses, side effects of ergotamine are relatively minor and unlikely to cause significant

clinical signs in the absence of underlying pathology. However, metabolism of ergot alkaloids is predominantly by the hepatic enzyme CYP3A4 which is almost totally inhibited by macrolide antibiotics. Co-administration of ergotamine and clarithromycin may be expected to produce a rapid picture of ergotism with confusion, psychosis, muscle cramps, seizures, peripheral and coronary vasospasm, severe headache and gastrointestinal symptoms of bowel ischaemia, cramps, diarrhoea and GI haemorrhage. Myocardial infarction, renal infarction, stroke and critical limb ischaemia may occur if not treated. • Interestingly, ergot alkaloid derivatives are naturally produced by the fungus Claviceps purpurea which may infect crops.
• Historically, significant outbreaks of ergotism have been seen due to ingestion of crops contaminated with ergot and there is some historical evidence that claims of witchcraft are ascribable to the psychosis of ergot poisoning.

Finasteride

• Finasteride is an inhibitor of 5 alpha-reductase. • 5-α-Reductase converts testosterone to dihydrotestosterone (DHT) • DHT is much more active than testosterone and binds more avidly to cytoplasmic receptors • DHT stimulates prostate growth and may be responsible for benign prostatic hyperplasia in the elderly

Indications • benign prostatic hyperplasia • male-pattern baldness Adverse effects • impotence • decrease libido • ejaculation disorders • gynaecomastia and breast tenderness Finasteride causes decreased levels of serum prostate specific antigen

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Acetazolamide Action • carbonic anhydrase inhibitor, hence causing the accumulation of carbonic acid • Inhibits proximal tubule bicarbonate reabsorption in a similar fashion to type-2 renal tubular acidosis (RTA) associated with metabolic acidosis • By excreting bicarbonate, the blood becomes acidic, causing compensatory hyperventilation with deep respiration (Kussmaul respiration), increasing levels of oxygen and decreasing levels of carbon dioxide in the blood. Hence used in treatment of high altitude sickness. Indications • intracranial hypertension
 post-haemorrhagic hydrocephalus (often with furosemide) primary idiopathic pseudotumour cerebri (benign intracranial hypertension) • reducing intraocular pressure • prevent acute mountain sickness • preventative agent for contrast nephropathy Side effects • metabolic acidosis, due to bicarbonate loss in the proximal and distal tubules through inhibition of reabsorption hyperchloraemic, normal anion gap metabolic acidosis. • Hypokalaemia • Acute interstitial nephritis (AIN)
• Agranulocytosis and thrombocytopenia • hyponatremia, • hyperglycemia, hypoglycemia, glycosuria,
• crystalluria (and hematuria), and polyuria.
• peripheral paresthesiae

Pharmacology carbonic anhydrase works to control the equilibrium between carbon dioxide and carbonic acid in order to maintain proper blood pH. Through which mechanism does carbonic anhydrase exert its influence on reaction kinetics? Lowers the activation energy
 Enzymes like carbonic anhydrase lower the energy of activation that is needed to initiate a reaction.
 Inhibition of carbonic anhydrase prevents the conversion of carbon dioxide (CO_2) and water (H_2O) to carbonic acid (H_2O_3) thus affecting the blood pH.

Bicarbonate therapy • Can increase extracellular pH only if the carbon dioxide (CO_2) produced can be removed by adequate ventilation. • Indeed, if hypercapnia occurs then as CO_2 crosses cell membranes easily, intracellular pH may decrease even further with further deterioration of cellular function. • Bicarbonate has a negative inotropic effect, • reducing cerebral blood flow; • It shifts the oxygen dissociation curve to the left, inhibiting oxygen release to tissues. • Exacerbates intracellular acidosis in cardiorespiratory arrest

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Bisphosphonates

Bisphosphonates are analogues of pyrophosphate, a molecule which decreases demineralisation in bone. They inhibit osteoclasts by reducing recruitment and promoting apoptosis.

The mechanism of action of bisphosphonates involves the inhibition of farnesyl diphosphate synthase within osteoclasts. In doing this they interfere with geranylgeranylation (attachment of the lipid to regulatory proteins), which causes osteoclast inactivation. This leads to reduced bone turnover, increased bone mass and improved mineralisation.

Clinical uses • prevention and treatment of osteoporosis Bisphosphonates licensed for the prevention and treatment of osteoporosis include alendronate, risedronate and ibandronate. • hypercalcaemia • Paget's disease • pain from bone metastases The bisphosphonates zoledronate and pamidronate are used for the treatment of metastatic bone disease and short term management of hypercalcaemia. Adverse effects

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• oesophageal reactions: oesophagitis, oesophageal ulcers (especially alendronate) • osteonecrosis of the jaw: This is a consequence of potent anti-resorptive action of the nitrogen containing bisphosphonates. Most cases have been associated with zoledronic acid and pamidronate given intravenously for metastatic bone disease. The reported incidence in patients with malignancy treated with these drugs is between 1.34.0%. Dental disease is a recognised predisposing factor. The lesions usually heal with minimal surgical debridement, chlorhexidine mouthwashes, antibiotics and analgesia. • Bisphosphonate infusions can lead to hypocalcaemia although it is more common when using larger doses in malignancy induced hypercalcaemia as oppose to the smaller dose used in osteoporosis. • increased risk of atypical stress fractures of the proximal femoral shaft in patients taking alendronate The BNF suggests the following counselling for patients taking oral bisphosphonates • 'Tablets should be swallowed whole with plenty of water

while sitting or standing; to be given on an empty stomach at least 30 minutes before breakfast (or another oral medication); patient should stand or sit upright for at least 30 minutes after taking tablet'

Botulinum toxin As well as the well publicised cosmetic uses of Botulinum toxin ('Botox') there are also a number of licensed indications: • blepharospasm • hemifacial spasm • focal spasticity including cerebral palsy patients, hand and wrist disability associated with stroke • spasmodic torticollis • severe hyperhidrosis of the axillae • achalasia

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Immunoglobulins: Therapeutics The Department of Health issued guidelines on the use of intravenous immunoglobulins in May 2008 Uses • Primary and secondary immunodeficiency • Idiopathic thrombocytopenic purpura (ITP) • Myasthenia gravis • Guillain-Barre syndrome • Kawasaki disease • Toxic epidermal necrolysis (TEN) • Pneumonitis induced by CMV following transplantation • Low serum IgG levels following hematopoietic stem cell transplant for malignancy • Dermatomyositis • Chronic inflammatory demyelinating polyradiculopathy Basics • Formed from large pool of donors (e.g. 5,000) • IgG molecules with a subclass distribution similar to that of normal blood • Half-life of 3 weeks

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Malignant hyperthermia (MH) Overview • condition often seen following administration of anaesthetic agents • characterised by increased temperature and muscle rigidity during anaesthesia, which results from abnormal skeletal muscle contraction and increased metabolism. • caused by excessive release of Ca2+ from the sarcoplasmic reticulum of skeletal muscle • associated with defects in a gene on chromosome 19 encoding the ryanodine receptor, which controls Ca2+ release from the sarcoplasmic reticulum • neuroleptic malignant syndrome may have a similar aetiology Causative agents • halothane (volatile anaesthetic agents) • suxamethonium • other drugs: antipsychotics (neuroleptic malignant syndrome) Investigations • Serum creatine kinase(CK) elevation and myoglobinuria are suggestive but not diagnostic of MH.(both known to increase after giving suxamethonium to normal patients) • Contracture tests with halothane and caffeine are the investigations of choice. • Muscle biopsies may appear histologically normal. Management • dantrolene - prevents Ca2+ release from the sarcoplasmic reticulum Intravenous dantrolene (up to 10 mg/kg) is the only available specific treatment Care must be taken when administering as the solution has a pH of 9-10. Prognosis • The prognosis of malignant hyperpyrexia is good when the appropriate treatment is instigated early, mortality being less than 5% (prior to dantrolene the mortality was 80%).

Intravenous fluid therapy

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Intravenous fluid therapy in adults in hospital (NICE guidelines 2013) • Indicators for urgent fluid resuscitation: systolic blood pressure is less than 100 mmHg heart rate is more than 90 beats per minute capillary refill time is more than 2 seconds or peripheries are cold to touch respiratory rate is more than 20 breaths per minute National Early Warning Score (NEWS) is 5 or more passive leg raising suggests fluid responsiveness • Resuscitation • If patients need IV fluid resuscitation, use crystalloids that contain sodium in the range 130– 154 mmol/l, with a bolus of 500 ml over less than 15 minutes. • Consider human albumin solution 4–5% for fluid resuscitation only in patients with severe sepsis. • Routine maintenance • If patients need IV fluids for routine maintenance alone, restrict the initial prescription to: • 25–30 ml/kg/day of water and • approximately 1 mmol/kg/day of potassium, sodium and chloride and • approximately 50–100 g/day of glucose to limit starvation ketosis. (This quantity will not address patients' nutritional needs) (patients rarely need more than a total of 3 litres of fluid per day)
• Consider prescribing less fluid (for example, 20–25 ml/kg/day fluid) for patients who: • are older or frail • have renal impairment or cardiac failure • are malnourished and at risk of refeeding syndrome
• When prescribing for routine maintenance alone, consider using 25–30 ml/kg/day sodium chloride 0.18% in 4% glucose with 27 mmol/l potassium on day 1. • Prescribing more than 2.5 litres per day increases the risk of hyponatraemia. These are initial prescriptions and further prescriptions should be guided by monitoring. • Consider delivering IV fluids for routine maintenance during daytime hours to promote sleep and wellbeing.

British Consensus Guidelines on Intravenous Fluid Therapy (2011) Recommendation
• Because of the risk of inducing hyperchloraemic acidosis in routine practice, when crystalloid resuscitation or replacement is indicated, balanced salt solutions e.g. Ringer’s lactate/acetate or Hartmann’s solution should replace 0.9% saline, except in cases of hypochloraemia e.g. from vomiting or gastric drainage. • Hypochloraemia is an indication for the use of 0.9% saline, with sufficient additions of potassium and care not to produce sodium overload.
• Losses from diarrhoea/ileostomy/small bowel fistula/ileus/obstruction should be replaced volume for volume with Hartmann’s or Ringer-Lactate/acetate type solutions.
• “Saline depletion,” for example due to excessive diuretic exposure, is best managed with a balanced electrolyte solution such as Hartmann's. Daily requirement
• The typical daily requirement is: 1.5 ml/kg/hr fluid - for a 80kg man around 2-3 litres/day 70-150mmol sodium 40-70mmol potassium • This is why the typical regime prescribed for patients is:

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 1 litre 5% dextrose with 20mmol potassium over 8 hours 1 litre 0.9% normal saline with 20mmol potassium over 8 hours

The table below shows the electrolyte concentrations (in millimoles/litre) of plasma and the most commonly used fluids: Na+ Cl- K+ HCO3- Ca2+ Plasma 135-145 98-105 3.5-5 22-28 2.3-2.6 0.9% normal saline

-

5% dextrose

-

Hartmann's solution

Normal saline has a pH of 5 and may produce a mild metabolic acidosis with significant infusions.

Which fluid would be the most appropriate to replace the fluid being lost in a patient with a paralytic ileus draining 2 litres of fluid a day through a nasogastric tube? 0.9% sodium chloride with potassium according to electrolytes it is essential to supply sufficient chloride ions to replace the chloride being lost in the gastric fluid (gastric juice is essentially dilute hydrochloric acid).

Lactulose
• Lactulose MOA Osmotic laxative • Causes hypomagnesaemia associated with diarrhoea • Is not absorbed • Does not affect the absorption of spironolactone and • May be used in diabetics. • It reduces proliferation of ammonia producing bacteria It is used in patients with cirrhosis/hepatic encephalopathy to limit the proliferation of ammonia-forming gut organisms and increase the clearance of protein load in the gut. • lactulose broken down by colonic bacteria production of lactic acid and other organic acids contents of the gut become more acidic (↓ PH) ↓↓ absorption of ammonia ↑↑ ammonia in the gut ↑↑ water drawn into the lower bowel

laxative abuse
Features • most commonly seen in young female patients complaining of chronic diarrhoea.
 The diarrhoea is frequently high volume
• underweight girl with calluses on her knuckles may point towards induced vomiting and a diagnosis of bulimia, which would fit with possible laxative abuse.
• Hypokalaemia
 Due to increased GI potassium loss
 symptoms of fatigue which are consistent with hypokalaemia.
 GI loss leads to renal conservation of potassium, a urinary concentration of potassium of less than 1 mmol/l being highly suggestive of laxative abuse.

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Bismuth
• subsalicylate is a colloidal substance frequently included in over-the-counter treatments for

gastrointestinal discomfort. • It has anti-secretory, anti-inflammatory, and antibacterial properties.
• It may be included in multidrug regimens against H. pylori.
• Its most unique side-effect is the appearance of black stool or a black tongue, both secondary to the drug's interaction with sulfur.

Non-steroidal anti-inflammatory drugs (NSAID)

Non-steroidal anti-inflammatory drugs (Nice 2015) • If an NSAID is needed, use ibuprofen (1200 mg a day or less) or naproxen (1000 mg a day or less). • Naproxen (1000 mg a day or less) and low-dose ibuprofen (1200 mg a day or less) are considered to have the most favourable thrombotic cardiovascular safety profiles of all NSAIDs. • Co-prescribe gastroprotective treatment (a proton pump inhibitor) with NSAIDs
• In October 2012, a European Medicines Agency (EMA) review on the cardiovascular safety of NSAIDs confirmed that diclofenac is associated with cardiovascular risks that are higher than ibuprofen and naproxen, and similar to the COX-2 inhibitors. • etoricoxib should not be prescribed to people whose blood pressure is persistently above 140/90 mmHg • the arterial thrombotic risk with diclofenac is similar to that of COX-2 inhibitors. • diclofenac is now contraindicated in patients with established:
 ischaemic heart disease peripheral arterial disease cerebrovascular disease congestive heart failure (New York Heart Association [NYHA] classification II–IV)

Indometacin is an inhibitor of both prostaglandin synthase and lipoxygenase enzymes

Side effects • Current evidence suggests that naproxen, a nonselective NSAID, is associated with the lowest risk of cardiovascular events. Therefore, naproxen is the NSAID of choice in patients with high cardiovascular risk.
• Optic neuritis is described as being rarely associated with diclofenac therapy.

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• A range of other CNS side effects has also been noted on the summary of product characteristics, these include headache, dizziness, vertigo and in rare circumstances drowsiness. • gastrointestinal bleeding occurs due to depletion of mucosal prostaglandin E (PGE) levels • Endoscopic evidence of peptic ulceration is found in 20% of NSAID users even in the absence of symptoms • The relative risk of causing Gl bleeds differs with different preparations: ibuprofen has a low risk piroxicam and azapropazone have the highest risk • While all NSAIDs may contribute to anaemia, usually via gastrointestinal bleeding, mefenamic acid is particularly associated with immune haemolytic anaemia. • NSAIDs reduce glomerular perfusion by inhibiting production of prostaglandins which dilate the afferent arteriole of the glomerulus. The reduction in blood supply to the kidney results in impairment of kidney function. • NSAIDs can also cause an interstitial nephritis but this is often accompanied by a nephrotic syndrome-like picture. Non-steroidal anti-inflammatory drugs are contraindicated in chronic liver disease for a variety of reasons: • their gastrointestinal side effects increase the risk of bleeding, particularly in those with varices. • Additionally, due to systemic

vasodilatation renal circulation is very dependent upon prostaglandin production to maintain glomerular filtration. Inhibition of this mechanism by non-steroidals, in addition to their other nephrotoxic effects, means that their use in patients with chronic liver disease, especially where there is pre-existing renal impairment, can precipitate renal failure. Overdose with (NSAIDs) Presentation and aetiology GIT upset (epigastric tenderness, nausea, vomiting and diarrhea) These effects are mainly due to the inhibition of cyclo-oxygenase convulsions (10-20%) more common in mefenamic acid over dose Large overdoses can present with: acidosis renal impairment gastrointestinal haemorrhage CNS effects (drowsiness, coma, cerebellar signs) Management Activated charcoal in patients presenting within the first hour Supportive care Oral H2-histamine blockers and proton-pump inhibitors may reduce the symptoms of gastrointestinal toxicity

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Celecoxib (COX)-2 inhibitor) Celecoxib is an NSAID that is safe to use in patients with gastritis or gastric ulcers as it does not affect COX1 action at the stomach.

Cox-2 inhibitors have a much lower risk of gastrointestinal bleed and high risk of cardiovascular events, they should not be prescribed to those with cardiovascular disease, or in those with high risk of cardiovascular disease.

Action • Celecoxib is a selective cyclo-oxygenase(COX)-2 inhibitor
 differing from the other non-steroidal anti-inflammatory drugs (NSAIDs) such as naproxen which affects both COX-1 and COX-2. COX-1 is involved in platelet aggregation and inhibition of this by the NSAIDs produces its beneficial cardiovascular effects.
 platelet aggregation is not affected by COX-2. Celecoxib has a lower level of anti-platelet activity than naproxen
Advantages • Naproxen and celecoxib have been shown to be as effective at reducing inflammation.
• One of the benefits of celecoxib is its reduced incidence of upper gastrointestinal side effects.
Side effects • As with the non-specific NSAIDS, hepatotoxicity may occur with the COX-2 specific inhibitors resulting in cholestatic, hepatocellular or mixed liver injury. Rates seem to be comparable between the traditional NSAIDs and the COX-2 selective inhibitors. • The cardiovascular effects of the COX-2 inhibitors remains under study, and care should be taken before prescribing them to patients with a past medical history of significant cardiovascular disease. • Rofecoxib (Vioxx) has been withdrawn due to its increased cardiovascular events compared with naproxen.
• What is the mechanism of celecoxib-induced deterioration in renal function? inhibition of afferent arteriole vasodilatation

Interaction • Co-administration of diuretics and COX-2 inhibitors should be avoided if possible, as COX-2 inhibitors may reduce the antihypertensive and diuretic effects of diuretics. This may be due to impaired prostaglandin synthesis, which results in salt and water retention. In addition, COX-2 inhibitors have nephrotoxic effects which can be exacerbated by diuretics.

Aminosalicylate drugs • 5-aminosalicyclic acid (5-ASA) is released in the colon and is not absorbed. It acts locally as an antiinflammatory. The mechanism of action is not fully understood but 5-ASA may inhibit prostaglandin synthesis • The safety of the 5-aminosalicylic acid (5-ASA) drugs in pregnancy is best supported by the data on Salazopyrin which have been available for the longest.

Sulphasalazine • a combination of sulphapyridine (a sulphonamide) and 5-ASA • many side-effects are due to the sulphapyridine moiety: rashes, oligospermia, headache, Heinz body anaemia, megaloblastic anaemia • other side-effects are common to 5-ASA drugs (see mesalazine) Mesalazine • a delayed release form of 5-ASA • sulphapyridine side-effects seen in patients taking sulphasalazine

are avoided • side-effects: GI upset, headache, agranulocytosis, pancreatitis, interstitial nephritis

pancreatitis is 7 times more common in patients taking mesalazine than sulfasalazine Olsalazine • two molecules of 5-ASA linked by a diazo bond, which is broken by colonic bacteria

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Anti-TNF therapy (NICE January 2016)

Drugs
• adalimumab, Golimumab, infliximab, certolizumab, tocilizumab • etanercept,
Action • tumour necrosis factor alpha (TNF-α) inhibitors
Indications • Refractory Crohn's disease,
• rheumatoid arthritis: for adults who have both the following characteristics: Active rheumatoid arthritis as measured by disease activity score (DAS28) greater than 5.1 confirmed on at least two occasions, 1 month apart. Have undergone trials of two disease-modifying anti-rheumatic drugs (DMARDs), including methotrexate (unless contraindicated).
 A trial of a DMARD is defined as being normally of 6 months, with 2 months at standard dose, unless significant toxicity has limited the dose or duration of treatment. Use of the TNF-α inhibitors for rheumatoid arthritis in adults not previously treated with methotrexate or other DMARDs is not recommended. Follow up Continue treatment only if there is a moderate response measured using European League Against Rheumatism (EULAR) criteria at 6 months after starting therapy. monitored 6-monthly
 withdraw treatment if a moderate EULAR response is not maintained.

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• Plaque psoriasis
 Adalimumab is recommended for adults with plaque psoriasis only if: condition is severe and not improved with other treatments such as ciclosporin, methotrexate and PUVA (psoralen and long-wave ultraviolet radiation), or they have had side effects with these in the past or there is a medical reason why they should not be given these treatments. Follow up Adalimumab treatment should be continued beyond 16 weeks only if the psoriasis has clearly improved within this time. • ankylosing spondylitis NICE states that adalimumab, etanercept and golimumab may be used for ankylosing spondylitis (AS) only if: treatment with two or more NSAIDs for four weeks at the highest possible dose has not controlled the symptoms confirms that condition has not improved by 2 methods:

1. level of pain is assessed twice (using a simple scale to fill in) 12 weeks apart and confirms that condition has not improved
2. Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) is tested twice, 12 weeks apart, and confirms that condition has not improved
   BASDAI is a set of measures to evaluate condition, by asking a number of questions about symptoms Side effects • Reactions
   Injection site reactions Cutaneous reactions, including psoriasis Infusion reactions
   Infusion reactions with infliximab are classified as one of two types: Acute reactions : occur within 24 hours.
   Delayed reactions: develop between 1 and 14 days
   • Neutropenia • Infections risk of reactivation of tuberculosis or new infection including miliary TB and some unusual extra-pulmonary TB
   If patient had previous active TB, the optimal TB screening test in this situation Interferon gamma release assay • Demyelinating disease exacerbation of neurologic disorders associated with demyelination, such as multiple sclerosis. • Heart failure Given the evidence to date, patients with symptomatic HF should be treated with strategies other than TNF-alpha inhibitors. In a patient who develops HF while on a TNF-alpha inhibitor, a drug-induced cause should be suspected. • Malignancy • Induction of autoimmunity

Usage