Abciximab

Abciximab (c7E3 Fab, ReoPro – Eli Lilly) is a novel antiplatelet agent. It is a chimeric monoclonal humanized murine IgG antibody to the platelet receptor, glycoprotein (GP) IIb/IIIc. GP IIb/IIIc is the receptor which, following platelet activation, binds fibrinogen and other adhesive molecules, so that platelet aggregation can proceed. Abciximab thus blocks this receptor and causes a temporary thrombasthenia-type platelet function defect.

Abciximab has a short half-life, with an initial phase of 10 min and a subsequent phase of 30 min. However, being platelet-bound it stays in the circulation for several days, though clinically adequate platelet function returns within 48 h.

It is used primarily in percutaneous transluminal coronary angioplasty (PTCA) as an adjunct to heparin and aspirin, where it has been shown to enhance significantly coronary patency rates. It has also been studied in a variety of other acute thrombotic situations where antiplatelet therapy could be of value.

It is given in a standard dose of 0.25 mg/kg by iv bolus followed by 0.125 μg/kg/h by continuous IV infusion for 12 h. It is very expensive. Its chief adverse effects are bleeding and sometimes thrombocytopenia.

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Abortion (see Pregnancy)

Acanthosis nigricans (see Pigmentation disorders)

Acetazolamide (see Carbonic anhydrase inhibitors)

Acetylsalicylic acid (see Aspirin)

Achlorhydria

Achlorhydria refers to the lack of secretion of gastric acid. The diagnosis of achlorhydria may be less than rigorous if it is based on the pH of spot samples of gastric contents rather than on formal testing of basal or stimulated gastric secretion.

The absence of gastric acid even after stimulation (i.e. absolute achlorhydria) has a number of associations, including

- gastric carcinoma;
- gastric polyps;
- pernicious anaemia;
- iron deficiency;
- hypogammaglobulinaemia;
- increased susceptibility to gastrointestinal infection.

Achlorhydria is, of course, also seen after:

- extensive gastric surgery or irradiation (permanently);
- potent ATPase inhibitors (temporarily).

Gastric acid is a prerequisite for peptic ulceration, and the demonstration of increased acid secretion may sometimes be helpful in the assessment of refractory or recurrent peptic ulceration (see Zollinger–Ellison syndrome).

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Acidosis, renal tubular (see Renal tubular acidosis)

Acquired immunodeficiency syndrome

Acquired immunodeficiency syndrome (AIDS) has become a well recognized entity throughout all of clinical medicine and beyond.

In Intensive Care, as in many other specialties, the most common presenting features of AIDS are **opportunistic infections**. Patients presenting with these, even if their HIV status is unknown and provided they have no other known immunodeficiency, are generally not difficult to recognize as likely to have AIDS.

These infections are often unusually chronic, recurrent or invasive. In many such patients presenting with fever and a presumptive diagnosis of infection, a specific microbiological cause is never identified. Although the patient may be a risk to others, particularly if tuberculosis is not promptly recognized, the patient is clearly also at risk of acquiring other, nosocomial infections while in hospital and especially while in Intensive Care.

Respiratory infections are the most common infections suffered by AIDS patients admitted for Intensive Care, but the clinical presentation is dependent on the patient's immune status, most simply assessed by the CD4 count.

- If the CD4 count is normal or nearly so, the infection is most likely to be bacterial or perhaps tuberculosis.
- If the CD4 count is < 200/μL, the infection is most likely to be caused by, in order,
  - *P. carinii*;
  - bacteria (especially pneumococci, but also legionella, listeria, nocardia, salmonella);
  - mycobacteria (either TB or MAC);
  - fungi (candida, aspergillus);
  - protozoa (toxoplasma);
  - viruses (CMV, HSV, VZV, E–B).

Bacillary angiomatosis and bacillary peliosis hepatis are serious infective complications of cat-scratch disease (q.v.), seen in immunocompromised patients such as those with AIDS.

The second most common group of presenting features comprises **neoplastic conditions**, especially Kaposi's sarcoma, but also non-Hodgkin's lymphoma and primary cerebral lymphoma.

Less common presenting features may be seen as the **direct effects** of HIV infection. A very broad collection of such features may be seen, including

- an acute infectious mononucleosis-like illness which commonly persists for several months;
- thrombocytopenia;
- wasting;
- neurological disease:
  - subacute encephalitis;
  - encephalopathy;
  - myelopathy;
  - peripheral neuropathy;
  - aseptic meningitis;
- abnormalities of:
  - myocardium;
  - kidneys;
  - gut;
  - thyroid;
  - joints.

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Acromegaly (see also Pituitary)

Acromegaly is a rare condition, produced in adults by excessive growth hormone which is usually derived from a pituitary adenoma. Its incidence is about 4 cases per million per year and its prevalence is about 50 cases per million of the population.

The pituitary adenoma usually arises from somatic mutation of the gene coding for part of a regulatory G protein, thus causing the production of growth hormone to become continuous instead of varying greatly during the day as it normally does in response to many stimuli, including exercise, stress, hypoglycaemia and adrenergic influences. Excessive growth hormone in children may produce **gigantism** as an occasional phenomenon.

Growth hormone (GH) is a 191 amino acid peptide, which is secreted by the anterior pituitary and which acts by stimulating the hepatic production of **somatomedin C** (or insulin-like growth factor 1, IGF-1), one of the body's many growth factors which circulate and bind to target cell receptors. IGF, which as an ultimate anabolic agent has been called the 'wonder drug of the late 20th century', is now described as a system and is the subject of an extensive literature.

The pituitary secretion of growth hormone is regulated by two neuropeptides secreted by the hypothalamus into the pituitary portal circulation, namely growth hormone releasing hormone (GHRH) which is stimulatory and somatostatin which is inhibitory. Acromegaly may thus also occur from excessive pituitary stimulation by GHRH either from the hypothalamus or ectopically from tumours, particularly benign foregut tumours such as bronchial carcinoid or pancreatic adenoma.

The clinical features of acromegaly include both local (mechanical or parasellar) and distal (hormonal) changes, as for all pituitary tumours.

- **Local** (mechanical or parasellar) features include headache and visual impairment (both of fields and of acuity).
- **Distal** (hormonal) features include acral and soft tissue overgrowth (affecting especially the face, hands and feet), increased bodily hair, sweating and odour, sleep apnoea, husky voice, diabetes and skin tags (fibroma molluscum).

Most patients have sleep apnoea (q.v.), and both the obstructive and central forms of this condition may occur. Since the hormonal changes of acromegaly which lead to clinical recognition tend to develop slowly, the adenoma is generally a macro-adenoma (i.e. >10 mm) and parasellar features are usual when the diagnosis is made.

Investigations show an elevated plasma growth hormone level which is not suppressed after a glucose load (i.e. > 3 μg/L, despite glucose 75 g 1–2 h previously in a standard oral glucose tolerance test). The plasma somatomedin C level which reflects average growth hormone activity is increased. The sella itself is best imaged by CT or perhaps MRI. If pituitary hyperplasia rather than a discrete adenoma is present, the source of GHRH should be sought either in the hypothalamus or an ectopic site.

*Treatment of a pituitary adenoma is usually by trans-sphenoidal **resection**.*

- *Postoperative **radiotherapy** is required if the GH and IGF-1 remain elevated, as is often the case.*

- *If GH levels still remain elevated, symptoms may be improved by medical treatment, using agents such as **bromocriptine** (a dopamine agonist, given in a dose of 2.5–10 mg orally twice daily) or **octreotide** (a synthetic analogue of somatostatin, given in a dose of 250 μg sc twice or thrice daily). Bromocriptine is particularly useful in patients with prolactin-secreting tumours.*

Pituitary apoplexy is an emergency complication which can complicate any pituitary tumour. It presents with headache, coma and abnormal eye signs.

*It requires urgent treatment with **corticosteroids** and **surgery**.*

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ACTH (see Adrenocorticotropic hormone)

Actinomycosis

Actinomycosis is due to infection with a Gram-positive bacterium, *Actinomyces israelii*, previously thought to be a fungus because of its filamentous hyphae-like appearance. It is an obligate anaerobe, related to nocardia and often part of the normal oral flora.

Infection arises when there is injury to the mucosal barrier, especially in association with necrotic tissue or a foreign body. Most infections are facio-cervical, but occasionally the infection may involve the lungs or become disseminated. It is also an uncommon cause of pelvic inflammatory disease in women.

It is a chronic deep granulomatous infection with sinus formation. Inspection of exuded material may show the characteristic 'sulfur granules', tiny pale particles which on microscopy are masses of filaments.

Laboratory identification can sometimes be difficult, as the organisms on smear may fragment to give coccobacilli appearing like diphtheroids and on culture are slow growing under anaerobic conditions.

*Treatment is with **penicillin** 7.2–14.4 g (12–24 million U) iv daily in divided doses for 2–4 weeks, then orally in reduced dose for 3–6 months. In penicillin-sensitive patients, tetracycline may be used.*

- *Surgical clearance may be required, and hyperbaric oxygen should be considered in severe infections.*

The prognosis is generally good.

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Acute brain syndrome (see Delirium)

Acute fatty liver of pregnancy

Acute fatty liver of pregnancy is a rare and potentially fatal condition of the third trimester. It presents with nausea, vomiting, abdominal pain and jaundice.

Liver function tests are abnormal, and there is usually a coagulopathy. Hypoglycaemia can be severe and sustained. The liver biopsy shows diffuse panlobular fatty change (i.e. steatosis).

*Treatment is with emergency **delivery** and Intensive Care support.*

Acute lung irritation

Acute lung irritation can be produced by a large number of chemical pollutants in the form of noxious gases and fumes (see Occupational lung diseases). Irritation generally occurs in the upper respiratory tract (and often elsewhere), as well as in the lung.

Clinical features of acute lung irritation thus include;

- sneezing, rhinorrhoea, lacrimation;
- stridor;
- cough;
- wheeze;
- dyspnoea.

Systemic effects may also be seen on occasion, including

- fever;
- chills;
- leukocytosis.

Bronchiolitis, pulmonary oedema and subsequent bronchopneumonia are possible consequences of acute lung irritation.

Toxic gases and fumes include:

- ammonia;
- chlorine;
- sulfur dioxide;
- oxides of nitrogen;
- ozone;
- isocyanates, which may also cause occupational asthma (q.v.);
- osmium tetroxide,
- metal fumes
  - especially oxides of copper, magnesium and zinc;
  - also oxides of antimony, beryllium, cadmium, cobalt, iron, manganese, nickel, selenium, tin, tungsten and vanadium;
- mercury;
- platinum salts;
- polymer fumes (Teflon degradation products).

Systemic abnormalities are also produced following the inhalation of:

- carbon monoxide (q.v.);
- cyanide (q.v.).

Asphyxia may be caused by excess:

- carbon dioxide;
- nitrogen;
- methane.

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Acute pulmonary oedema

Pulmonary oedema is defined as an increased amount of extravascular fluid (water and solute) in the lung, where it may be interstitial or alveolar or both.

Pulmonary oedema is one of the commonest respiratory disorders and may follow a wide variety of local and systemic insults. Although pulmonary oedema due to left heart failure is the classical clinical picture, pulmonary oedema also occurs in a number of other common settings. In these, the left atrial pressure may be normal or even low.

These non-cardiac settings include:

- serious medical or surgical illness in the form of the acute (adult) respiratory distress syndrome (ARDS);
- an important component in:
  - viral pneumonia;
  - aspiration pneumonitis;
  - respiratory burns;
  - uraemia;
  - endotoxaemia (systemic inflammatory response syndrome);
  - drowning;
  - head injury;

– severe upper airway obstruction;
– altitude-related illness.

Pulmonary oedema may therefore present in diverse settings with different pathogenetic mechanisms and thus with different therapeutic implications.

The causes of pulmonary oedema are:

1. **Increased capillary hydrostatic pressure**

- cardiogenic (left heart failure);
- blood volume overload;
- pulmonary veno-occlusive disease.

2. **Increased capillary permeability**

- acute (adult) respiratory distress syndrome (ARDS);
- viral and other pneumonia;
- inhaled toxic substances (including oxygen);
- circulating toxic agents (including sepsis);
- disseminated intravascular coagulation;
- uraemia, radiation, burns, near-downing.

3. **Decreased plasma oncotic pressure**

- hypoalbuminaemia.

4. **Decreased tissue hydrostatic pressure**

- rapid lung re-expansion, after
  - drainage of a pneumothorax or large pleural effusion;
  - pneumonectomy;
- laryngospasm (and other causes of acute upper airway obstruction, when associated with strong inspiratory effort).

5. **Decreased lymphatic drainage**

- lymphangitis carcinomatosa;
- lymphangiomyomatosis;
- lung transplantation.

6. **Uncertain mechanisms**

- high altitude;
- neurogenic (raised intracranial pressure);
- drug overdose (especially IV heroin);
- pulmonary embolism.

In practice

- the first two groups of causes are by far the most commonly encountered;
- the third group is probably not a cause in its own right, but lowers the threshold for pulmonary oedema from other causes;
- groups four, five and six are less common.

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Acute respiratory distress syndrome (see Acute pulmonary oedema)

Acyclovir

Acyclovir is the most important of the available antiviral drugs. It has replaced vidarabine (ara-A), the first available antiviral agent for systemic use in serious infections. It is a synthetic purine nucleoside analogue, structurally related to guanosine. Its unique mechanism of action inhibits DNA synthesis and thus viral replication. It therefore does not affect the latent virus. There is a low incidence of development of resistance, but unwarranted use is unwise.

The antiviral effects of acyclovir are particularly relevant for herpesviruses, as follows. It is

- especially effective against **herpes simplex virus** (HSV) types 1 and 2;
- less effective but still very useful for **varicella-zoster virus** (VZV);
- of intermediate efficacy against **Epstein–Barr virus** (EBV);
- ineffective against **cytomegalovirus** (CMV) (the related agent, **ganciclovir**, is however effective against CMV–q.v.).

> The greatest value of acyclovir is in **HSV encephalitis**, in which trial results have shown a survival rate of about 80% and complete neurological recovery in about 50%. It is also of value in oral-labial, genital, rectal and neonatal HSV infections.

In **VZV infections**, it is helpful in:

- the elderly, especially those with widespread lesions or trigeminal involvement;
- herpes zoster encephalitis;
- varicella pneumonia;
- immunocompromised patients (in whom interferon alpha and/or VZV immune globulin are also useful).

Acyclovir

- is not indicated in **infectious mononucleosis**, except perhaps in severe cases,
- is not indicated in **cytomegalovirus infections**, except for prophylaxis after bone marrow transplantation in seropositive patients, in whom it is effective when given in high-dose, i.e. 500 mg/m^2 tds iv for the 1st month),
- is not effective in the **chronic fatigue syndrome**.

Acyclovir is not protein-bound but is distributed evenly throughout the total body water, except in the CSF in which the level is 25–50% of that in plasma. The urinary concentration is about 10 times the plasma concentration. It has a half-life of about 3 h, which rises six-fold in severe renal failure, since it is primarily excreted in the urine. It is 60% removed by dialysis. It is probably not mutagenic nor carcinogenic. Although fetal risk has not been shown, it crosses the placenta and should be used in pregnancy only if there is a strong maternal indication. It is excreted into breast milk.

It is available as a powder for iv administration, as capsules for oral use and as an ointment for mucocutaneous lesions or keratitis. Intravenously, it is given as 5–10 mg/kg 8 hourly for 5–10 days. Typically, 500 mg are reconstituted in 20 mL, diluted to 100 mL and administered over 1 h, giving a mean steady-state peak plasma concentration of 20 μg/mL.

Although the solution is widely compatible, it undergoes irreversible crystallization if refrigerated. Intravenous acyclovir is normally well tolerated, but it is potentially phlebitic because of its alkaline nature unless given diluted and slowly, and it can sometimes give rise to nausea or a rash. Rarely, reversible

encephalopathy or renal dysfunction may occur from very high concentrations.

Ganciclovir is structurally similar to acyclovir and is given in the same dosage. Its chief difference is that it is active against cytomegalovirus (q.v.). It is therefore used, often with immune globulin, in CMV retinitis or pneumonia, for example after bone marrow transplantation. Unlike acyclovir, it can produce bone marrow depression. It is teratogenic and mutagenic in animals. The usual dose is 5 mg/kg iv 12 hourly.

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Addison's disease (see Adrenal insufficiency)

Adenosine

Adenosine is an **autacoid**, one of a broad range of substances normally present in the body and functioning in humoral regulation at a local level (and thus separate from hormones, neurotransmitters and cytokines). Autacoids have short half-lives, since they act near to their site of synthesis and are not blood-borne. In addition to adenosine, other examples of autacoids include bradykinin, eicosanoids, histamine, PAF and serotonin.

Adenosine is an endogenous purine nucleoside of molecular weight 267 d, and it has receptors (A1 or A2) on most cell membranes. It is released when ATP is used and may thus help maintain the balance between oxygen availability and utilization. It is involved in many local regulatory processes and in particular is a vasodilator and an inhibitor of neuronal discharge.

Its cardiac effects were first recognized in 1929 and are extensive. They especially involve decreased conduction and ventricular automaticity, coronary vasodilatation and the blunting of the effects of catecholamines. On balance, it is thus 'cardioprotective'. Both A1 and A2 receptors are present in the heart, A1 in the cardiomyocytes and A2 in the endothelial cells and vascular smooth muscle cells.

Clinically, its particular use is in the diagnosis and treatment of tachyarrhythmias.

- It is of most value in the treatment of supraventricular tachycardia, especially that associated with the WPW syndrome, with an average time to termination of arrhythmia of 30 s.
- It has no effect in atrial fibrillation or atrial flutter.
- It is not of value in ventricular tachycardia unless catecholamine-induced.

Its effects are antagonized by theophylline and potentiated by dipyridamole, but it may be administered without altered efficacy in the presence of other cardiac drugs or in liver or renal disease. It is of potential clinical use in electrophysiological studies, in cardiac stress testing and in the assessment of coronary blood flow reserve. It has no useful effect on coronary ischaemia. Since its half-life is only 10 s, it is given as a rapid iv bolus of 3–6 mg. A further bolus of 12 mg may be given 1–3 min later if necessary.

It can produce unpleasant and marked though transient side-effects, including flushing, sweating, tingling, headache, light-headedness, nausea and apprehension. Bronchospasm may

be precipitated in asthmatics. It can also produce cardiac pain, which is angina-like but not in fact ischaemic.

Adrenal insufficiency

Acute adrenal insufficiency is an uncommon condition and is usually due to haemorrhage (especially from heparin), hypotension or shock (as in the Waterhouse–Friderichsen syndrome, q.v.).

It thus occurs mostly in seriously ill patients, in whom it should remembered as an uncommon cause of hyperdynamic shock.

The clinical features include nausea, weakness and abdominal pain, as well as circulatory failure. Typically, there is hyponatraemia with hyperkalaemia, and the plasma urea may be elevated.

Relevant investigations include failure of the plasma cortisol level to increase after the injection of synthetic ACTH (see below) and direct imaging with CT.

Treatment is with physiological doses of ***hydrocortisone*** *iv.*

Chronic adrenal insufficiency (Addison's disease) is due to:

- autoimmune disease (sometimes polyglandular);
- a space-occupying lesion, typically a metastasis or granuloma (e.g. TB);
- pituitary deficiency, due either to
  - global hypopituitarism (when hypothyroidism is also typically present), or
  - previous administration of corticosteroids in pharmacological doses (when diabetes is commonly associated);
- HIV infection, with associated CMV adrenal infection,
- drugs, such as ketoconazole, rifampicin.

Clinical features comprise:

- weakness;
- weight loss;
- pigmentation especially in body creases;
- hypotension;
- hypovolaemia (except that blood volume remains normal in pituitary deficiency, since aldosterone secretion is primarily controlled by the renin–angiotensin system).

Investigations show mild hyperkalaemia and proneness to hyponatraemia from water overload. In patients who are sufficiently hypovolaemic to have pre-renal renal failure, there is more marked hyperkalaemia with hypoglycaemia, raised plasma urea and raised haematocrit. Specific testing shows a low plasma cortisol, which fails to rise after **synthetic ACTH** 250 μg iv (normal >150 nmol/L and a rise at 30 min by at least 300 nmol/L to a peak of >550 nmol/L). This short synthetic ACTH stimulation test is simple and safe.

If adrenal insufficiency is clinically overt and corticosteroids have been commenced, confirmatory testing is very difficult, unless dexamethasone can be temporarily substituted and then ceased pending a long (i.e. 3 day) synthetic ACTH stimulation test.

The plasma ACTH level is >20 pmol/L in primary adrenal failure, but in hypopituitarism it is low (as are the other pituitary hormones – q.v.). A rise in plasma cortisol still occurs in hypopituitarism following ACTH, though this may be subnormal due to chronic ACTH deficiency.

Treatment of adrenal insufficiency is urgent if there is circulatory failure (i.e. adrenal crisis), with ***hydrocortisone*** *100 mg iv then 10–15 mg/h, together with fluids, electrolytes and glucose. Chronic treatment requires maintenance therapy with cortisone (approximately 35 mg daily given about 2/3 in the morning and 1/3 in the evening), together with fludrocortisone 100 μg daily.*

Patients with adrenal insufficiency exposed to stress require increased doses of corticosteroids. Typically, double the usual dose is used for minor stress and hydrocortisone 100 mg/8 h iv for severe stress, though recently it has become recognized that these doses are excessive. In fact, doses of 25–150mg of hydrocortisone per day for a maximum of 3 days are adequate.

Hypothalamic–pituitary–adrenal function is suppressed by previously administered corticosteroids in pharmacological doses.

- This may not recover for a year or more after such steroids are ceased.
- There is no simple and accurate prediction of hormonal reserve function, based on the previous dose or duration of steroid treatment.
- Prophylactic hydrocortisone (as above) is also routinely recommended in such patients exposed to stress. This cover is continued for two days, and then if the clinical situation is satisfactory it is tapered over the next few days.

If time permits, the cortisol response to ACTH may be assessed prior to anticipated stress, such as elective major surgery, but a normal value after ACTH does not necessarily imply a normal response to other stress. A more relevant adrenal assessment may be provided by the cortisol response to insulin-induced hypoglycaemia, but this test is probably unsafe.

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Adrenocorticotropic hormone (see also Adrenal insufficiency, Cushing's syndrome and Ectopic hormone production)

Adrenocorticotropic hormone (corticotropin, ACTH) is the main controlling factor for the adrenal production of cortisol and androgens. It is produced in the anterior pituitary by cleavage of a large and complex polypeptide (241 amino acids), called **propiomelanocortin** (POMC), which also includes melanocyte-stimulating hormone (MSH), beta-endorphin, met-enkephalin, beta-lipotropin, and a number of other peptides of presently unknown function.

The secretion of ACTH is controlled primarily by the hypothalamus-derived **corticotropin releasing hormone** (CRH) and secondarily by catecholamines and vasopressin. ACTH release is also stimulated by stress and by hypoglycaemia. CRH production and ACTH release is inhibited by both natural and synthetic corticosteroids, which suppress mRNA for POMC synthesis. ACTH is released in pulses, especially in the mornings, thus explaining the diurnal rhythm of cortisol secretion. The normal level of ACTH is 1.3–16.7 pmol/L.

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