INTERSTITIAL LUNG DISEASE
1 Introduction

Synonyms: interstitial lung disease, diffuse parenchymal lung disease.

1.1 Description

- Interstitial lung disorders (ILD) encompass a diverse range of diseases affecting the gas exchanging regions of the lung, which may progress to diffuse lung fibrosis.[1][2]
- Some of these present acutely, whereas others have a sub-acute or chronic course.
- The overall prevalence in the United Kingdom is 1 in 3,000 – 4,000, and ILDs account for 3,000 deaths per year.[3]
- Aetiology and individual prevalence are described under the separate conditions below. Sarcoidosis is also a cause of interstitial lung fibrosis (see Tuberculosis and Sarcoidosis Protocol).

1.2 Diagnosis

- Common features of ILD are a history of progressive dyspnoea and a dry cough, associated with a chest radiograph (CXR) that shows widespread pulmonary shadows.
- The presence of finger clubbing is a variable sign in ILD. It occurs in 70% of patients with cryptogenic fibrosing alveolitis and the interstitial alveolitis associated with rheumatoid arthritis; however, it is almost never seen in the fibrosing alveolitis associated with systemic sclerosis and extrinsic allergic alveolitis.[4]
- On auscultation, dry, fine end-inspiratory, basal ‘velcro’ crackles are commonly heard.

1.3 Investigations

1.3.1 Lung Function Tests

- Spirometry: a restrictive defect reduced total lung capacity and forced vital capacity (FVC), with normal FEV$_1$/FVC ratio of greater than 70% (FEV$_1$ = forced expiratory volume in 1 second).
- Blood gases: hypoxaemia and hypocapnia. Impaired gas diffusion (reduced transfer factor$^{1a}$).
- Serial measurements over a period of time are often needed to assess slightly low values and recognise excessive longitudinal decline.

$^{1a}$ Transfer factor is normally measured by the carbon monoxide absorption rate per unit volume of ventilated lung - DLco – the gas transfer coefficient.
1.3.2 Radiography

- **CXR**: lung size; distribution; size and nature of nodular and reticular abnormalities; the presence of pleural disease; hilar lymphadenopathy and confluent shadows allow the experienced eye to differentiate the types of interstitial lung disorders. This has largely been superseded by computed tomography scans for diagnosis, but CXR and physiology are the mainstays of follow up.

- **High-resolution computed tomography (HRCT)** allows detailed evaluation of the lung parenchyma by using 1 - 2mm thick slices with a reconstruction algorithm that maximises spatial resolution. This allows earlier diagnosis and narrows the diagnosis based on HRCT pattern.

1.3.3 Biopsy

- Small samples of lung parenchyma can be obtained by transbronchial biopsy with a flexible bronchoscope; however, because of the small sample size it should not be used to assess the degree of fibrosis.[5]

- Larger samples can be obtained under GA by either thoracotomy or video-assisted thoracoscopy. Surgical lung biopsy is recommended in patients without contraindications to surgery.

- The histology is often diagnostic in the early stages, but in advanced disease may show non-specific lung fibrosis with no clue to aetiology.

1.3.4 Bronchoalveolar Lavage (BAL)

- Performed during bronchoscopy; yields fluid for cytology and biochemical analysis.

1.4 Differential Diagnosis

- Other causes of diffuse lung infiltrates such as pulmonary oedema, bronchiectasis, and alveolar cell carcinoma are usually distinguishable with the above investigations, which also help to differentiate the following conditions.
2 Idiopathic Pulmonary Fibrosis

Synonym: - Cryptogenic Fibrosing Alveolitis (CFA).

2.1 Definition
Historically, Idiopathic Pulmonary Fibrosis (IPF) was a family of idiopathic pneumonias, sharing the clinical features of dyspnoea, radiological diffuse pulmonary infiltrates and various findings of inflammation, fibrosis or both on biopsy. (Appendix A: Table 1)
A consensus statement, published in 2000,[5] now limits IPF to patients with a specific histological finding on biopsy, that of ‘usual interstitial pneumonia’ (UIP). However, as few patients in the UK undergo open lung biopsy,[6] the group will retain its heterogeneity, making prognosis more difficult.

2.1.1 Aetiology of IPF

- The cause of IPF is unknown, but it is probably an inflammatory and immune response to lung damage in genetically predisposed individuals.[4] Reports have described familial cases of IPF with an autosomal dominant pattern of inheritance.[7] Some cases may be associated with previous exposure to dusts (e.g. metal or wood), and about 30% have auto-antibodies such as rheumatoid or anti-nuclear factor. Cigarette smoking may be an independent risk factor, 75% of cases of IPF are current or former smokers.[8] Latent viral infections have also been implicated, but to date no candidate virus has been shown to cause IPF.[8]

2.1.2 Prevalence of IPF

- The precise prevalence of IPF is unknown but is estimated at between 3 - 6 cases per 100,000 in the general population[5] and it is slightly more common in males than females.[8]
- The incidence of IPF increases with age. Patients become symptomatic in the fifth and sixth decade and approximately 2/3 of patients are over the age of 60 at the time of diagnosis.[5] In the age group 35 - 44 years the prevalence is 2.7/100,000.[5]

2.2 Diagnosis

- Insidious onset of non-productive cough and progressive dyspnoea.
- Dyspnoea most prominent and disabling symptom.
- Clubbing in 70%.
- Dry, end-inspiratory, ‘velcro’ basal crackles in 80%. With disease progression these become pan-inspiratory and extend to the upper zones.
- Cyanosis, cor pulmonale, an accentuated pulmonary second sound, right ventricular heave and peripheral oedema may be observed in the late phases of the disease.
2.3 Investigation

2.3.1 Pulmonary Function Testing in IPF

- Reduced total lung capacity (TLC), functional residual capacity (FRC) and residual volume (RV).
- Smokers and patients with superimposed COPD may have normal volumes early in the disease.
- Patients are tachypnoeic, taking rapid shallow breaths.
- FEV₁ and FVC are reduced. But FEV₁/FVC ratio is normal or raised (> 70%).
- The gas transfer factor DL\textsubscript{CO} is reduced because of a reduction in capillary volumes as well as ventilation and perfusion abnormalities.
- Formal cardiopulmonary exercise testing is more sensitive in the detection of abnormalities of oxygen transfer. Exercise gas exchange is a sensitive parameter to monitor the clinical course, but is not often performed in UK practice.

2.3.2 CXR in IPF

- Most have abnormal CXR at time of presentation and basal reticular shadowing may be present for years before the development of symptoms. A normal CXR does not exclude the histological finding of usual interstitial pneumonia (UIP) on biopsy.
- Peripheral reticular opacities at lung bases, with reduced lung volumes are common findings. Patients with co-existing emphysema may have preserved or increased lung volumes.

2.3.3 High Resolution Computed Tomography in IPF

- Pattern in IPF of patchy, predominantly peripheral, sub-pleural, bibasal reticular abnormalities.\textsuperscript{[5]} A normal HRCT scan cannot exclude infiltrative disease. One third of cases will be missed if HRCT scans alone are used for diagnosis.\textsuperscript{[5]}
- Patients with predominant reticular opacity or honeycombing usually progress despite treatment.
- The extent of lung fibrosis on HRCT is an important predictor of survival.\textsuperscript{[5]}

2.3.4 Bronchoalveolar Lavage in IPF

- Despite its value as a research tool, the diagnostic use of BAL in IPF is limited.\textsuperscript{[5]}

2.3.5 Lung Biopsy

- UIP is the histological pattern that identifies patients with IPF.\textsuperscript{[5]} However, a review of 200 patients in the UK showed that transbronchial or open lung biopsies were performed in only 33% and 7.5% of patients respectively: the diagnosis of IPF was made on clinical grounds in most cases.\textsuperscript{[6]}
2.4 Treatment

- Conventional treatment options include corticosteroids, immunosuppressives (e.g. azathioprine), cytotoxic agents (e.g. cyclophosphamide) and antifibrotic agents (colchicines or d-penicillamine) either alone or in combination.
- Given that there is no clinical evidence that treatment improves survival or quality of life, (and that treatment is associated with risk of complications) therapy may not be indicated for all patients. [5]

2.4.1 Corticosteroids

- Used ubiquitously, but no randomised controlled trial data: 10-30% objective improvement; 40% report subjective improvement. [3]
- High doses used 40-100mg for 2-4 months and then dose reduced.
- If improvement occurs, it happens in the first 3 months of treatment, and responsive patients are maintained on corticosteroid therapy.
- Relapses or deterioration whilst on steroids warrant escalation of dose or addition of an immunosuppressive agent.

2.4.2 Cytotoxic Treatment (Azathioprine/Cyclophosphamide)

- Used for steroid non-responders or those with side effects on steroids. [3][5]
- Favourable responses in a few small treatment trials.

2.4.3 Lung Transplantation

- Patients <55 years old, without complicating medical illnesses should be referred early to regional transplantation centres. [8] Patients up to 65 years old may be considered for transplantation.

2.5 Prognosis

- IPF kills about 1500 people p.a. in the UK[3] and the mortality is increasing. The highest rates of mortality in the UK occur in the industrialised central areas of England and Wales. The mean length of survival from the time of diagnosis varies between 3.2 and 5 years. [5]
- The cause of death is respiratory failure in 40%. In the majority death is triggered by a complicating illness, mainly coronary artery disease and infections. Bronchogenic carcinoma occurs in 10-15% of patients.
- Spontaneous remissions do not occur.
- Some patients follow an indolent course over many years, and these are thought to represent other disorders misdiagnosed as IPF. [7]
- Indicators of longer survival include: younger age at onset (< 50), female sex, beneficial response or stable disease 3 - 6 months after initial corticosteroid treatment. [5]
- Following lung transplantation a 5-year survival rate of 50 - 60% is quoted. [5]
3 Connective Tissue Diseases

3.1 Description
In about 35% of cases the typical features of IPF occur as part of a connective tissue disease, which often has various other lung complications.\[9\]

3.2 Rheumatoid Disease
- Interstitial lung disease is clinically detected in less than 5% of patients with rheumatoid arthritis, although studies have shown a much higher prevalence of interstitial changes using HRCT scans.\[10\][11]
- The natural history of interstitial lung disease in rheumatoid arthritis has not been well studied, and there are no data on prognostic factors. The radiological changes on HRCT scanning were more peripherally distributed in RA compared to IPF.\[12\] Rheumatoid factor may prove to be protective against progressive fibrosis. Drugs such as methotrexate, gold or penicillamine may cause lung fibrosis.

3.3 Systemic Sclerosis (Scleroderma)
- Progressive systemic sclerosis and the CREST variant: (Calcinosis; Raynaud’s phenomenon; oesophageal dysfunction/dysmotility; Sclerodactyly; and Telangiectasia) have interstitial lung involvement that is indistinguishable from idiopathic fibrosing alveolitis.\[13\]

3.4 Systemic Lupus Erythematosus
- **Acute lupus pneumonitis** occurs in only 0.9% of cases and generally develops during a generalised flare of SLE with multi-system involvement. This presents clinically as severe dyspnoea of recent onset, tachypnoea, fever, basal crackles and hypoxaemia. CXR shows diffuse basal alveolar infiltrates and pleural effusions. The mortality is high (50%) and survivors have evidence of a restrictive ventilatory defect with hypoxaemia.\[9\][14]
- **Chronic diffuse interstitial lung disease.** Symptomatic interstitial lung disease has a prevalence of 3%. All patients present with dyspnoea and half have pleuritic pain. Restrictive defects are present on pulmonary function testing and diffusion capacity is reduced.\[9\][14]
- **Shrinking lungs syndrome (SLS)** is characterised by unexplained dyspnoea, small lung volume with restrictive physiology and an elevated diaphragm that is thought to be due to a myopathy. Corticosteroids are the mainstay of treatment with most patients returning to their previous pulmonary function.\[15\]
3.5 Polymyositis and Dermatomyositis

- Interstitial lung disease is detected in 5 - 40% of patients and may present clinically as three types[16]:
  1. Acute/sub-acute: with severe rapidly progressive dyspnoea and hypoxaemia.
  2. Chronic: with slowly progressive dyspnoea.
  3. Asymptomatic.
- The onset of respiratory symptoms may precede, coincide or follow the onset of the myositis. Corticosteroids are the mainstay of treatment. Immunosuppressant and cytotoxic agents are used second-line. The decision to treat is usually based on clinical, (rather than radiological), activity.
4 Extrinsic Allergic Alveolitis

Synonym: - hypersensitivity pneumonitis.

4.1 Description
Extrinsic allergic alveolitis (EAA) is an immunologically induced inflammatory lung
disease resulting from repeated inhalations of any one of a variety of causative
agents, including organic dusts and active chemicals. This response involves
antibody reactions, immune complex formation, complement activation and cellular
responses, causing inflammation of the lung parenchyma, alveolar walls and
terminal airways.[17]

4.1.1 Aetiology
- **Farmer’s and mushroom/malt/sewage-worker’s lung** – inhalation of spores from
  various fungi which grow in warm damp hay/straw/grain; vegetable/mushroom
  compost; whisky maltings and sewage. Occupational exposure to cheese
  mould, mouldy corks and sugar cane mould are also implicated in EAA.
- **Bird-fancier’s lung** – inhalation of avian antigens by keepers of racing pigeons
  and pet birds.
- **Humidifier lung/ventilation pneumonitis** – inhalation of bacteria/fungi/moebae/
  nematode debris from water in air conditioners/humidifiers.
- **Pituitary snuff-taker’s lung** – inhalation of cattle or pig pituitary extracts.
- **Plastic/laboratory workers and paint/vineyard-sprayers** – inhalation of solvents,
  isocyanates, fungicides and other chemicals.[17] Isocyanates cause occupational
  asthma in the majority of cases, with hypersensitivity pneumonitis accounting for
  1-4.7%.[18]

4.1.2 Prevalence
- Estimated to contribute less than 1% to occupational lung disease.[19]
  Approximately 50% of cases affect farm workers, and 15% affect workers in
  material, metal or electrical processing trades.[17] Smokers are less likely to
develop all types of EAA.
- In the UK bird-fancier’s lung is the most prevalent at present, since 12% of the
  population keep birds and of these 0.5 to 7.5% will develop bird-fancier’s lung.
- In areas of high rainfall, where ‘traditional’ farming methods are used, the
  prevalence of farmer’s lung may reach 10%. However, where modern farming
  methods are used, the prevalence is 2 - 3% or less and the farming population
  represents only 1 - 2% of the total population.
- In developed countries humidifier lung is being recognised with increasing
  frequency, both at work and at home.
4.2 Diagnosis

- There is no diagnostic test that is pathognomonic for EAA. The clinical presentation can be acute, sub-acute or chronic, as summarised in Table 2 (Appendix A).
- EAA should be distinguished from the effects of toxins (e.g. paraquat) and dusts (e.g. asbestos).

4.3 Treatment

The acute exacerbation of EAA may be treated with corticosteroids, which produces a rapid clinical improvement. There is some debate as to whether this rapid improvement increases the likelihood of further exposure, by decreasing antigen avoidance.\textsuperscript{[20]}

The mainstay is complete avoidance of exposure to the provoking antigen. Those unable or unwilling to change their causative occupation can use industrial respirators, which filter out 98% of respirable dust from the ambient air.\textsuperscript{[17]}

Continuing exposure should be accompanied by surveillance (with regular CXRs and lung function tests). When there is progressive disease exposure should cease.

4.4 Prognosis

\textit{If exposure to the antigen ceases:} The risk of continuing symptoms on cessation of the exposure increases with the duration of exposure. Following acute EAA, continuing inflammation and membrane leakiness was found for 2 - 15 years, even when patients were asymptomatic.

\textit{Continuation of antigen exposure:} The risk of continued exposure is progressive fibrosis; however this only occurs in a minority of affected subjects.\textsuperscript{[17]} A follow-up study of farmers with acute farmer’s lung showed that, whilst the majority continued to live on farms, only 39% developed radiological changes of fibrosis and only 30% developed an impairment of gas transfer.\textsuperscript{[21]}
5 Main Disabling Effects

- The chronic interstitial lung disorders cause a restrictive pattern of ventilatory impairment, which leads to an overall reduction in lung volume and impaired gas diffusion across the alveolar-capillary membrane. As lung function deteriorates, progressive dyspnoea will restrict exertional activities.
- Corticosteroids are the mainstay of treatment in IPF and other forms of diffuse lung disease. These are used at high doses and for long periods of time, increasing the risk of side-effects, which may be disabling (Table 3).
- Problems may occur with reduced atmospheric pressure. Commercial air travel usually involves depressurisation to a cabin altitude of 6,000ft (1,830m). The reduced partial pressure of oxygen has little effect on healthy travellers, but with pulmonary disease may cause symptoms or subtle signs of hypoxia.

5.1 Assessing The Claimant

- Clinical respiratory examination findings do not correlate well with functional ability and the assessment is best made from the:
  1. The History of Activities of Daily Living (Typical Day), taking variation into account.
  2. Informal Observation of the claimant’s activities at examination.
- In the IB-PCA, the functional areas first affected are ‘walking up/down stairs’, and ‘walking’. Other physical functional areas may be affected by the musculo-skeletal side effects of high-dose steroid therapy, namely proximal myopathy and osteoporotic fracture. Vision may be affected by the development of cataracts and glaucoma. Mental health may also be affected by high-dose steroid therapy and psychological side effects are more common with increasing age.[5] Euphoria may cause patients to underestimate their level of disability.
- Exemption from the IB-PCA should be considered if the limitation of effort tolerance is severe and progressive, causing significant limitation of normal daily activities that require more than minimal exertion (e.g. climbing stairs/washing/dressing). Clinical examination in these cases may show clinical signs of cor pulmonale.

5.2 Occupational and Legislative Issues

- Assessment of fitness for work in the presence of chronic lung disease depends essentially on whether the various elements of pulmonary function are adequate and whether there is any restriction, through breathlessness, of capacity to undertake the level of physical exertion required by the job in its particular environment. Rarely, cough alone may be sufficiently distressing to the worker (or fellow workers) to limit effective work capacity.
- With mild degrees of impairment (e.g. FEV₁ > 60% predicted) the results of lung function tests correlate poorly with symptoms and the results of exercise tests. However, most subjects with FEV₁ in the range 40 - 60% of predicted have
symptoms on strenuous exertion, and with FEV$_1$ < 40% of predicted heavy manual work becomes very difficult to sustain.[22]

- The degree of impairment of lung function is only one of a number of factors that determine work capacity, psychological factors such as motivation and mood are also important.
- Most occupational respiratory hazards are controlled by the Control of Substances Hazardous to Health (COSHH) Regulations 1994 and/or the management of Health and Safety at Work Regulations 1992.
- These regulations place a duty on employers to assess whether the use of any substance constitutes a risk to the health of employees. Where a risk of ill health exists and medical tests can identify pathological change at an early stage (when remedial action can be taken), such tests must be provided.
- The risk must also be controlled by appropriate means, such as elimination of the harmful agent, enclosure of the process, exhaust ventilation or the provision of respiratory protection. Workers exposed to respiratory sensitisers giving a risk of EAA should be subject to periodic assessment by questionnaire and measurements of ventilatory function. EAA is a prescribed disease (B6) under the Social Security Contributions and Benefits Act (1982), so affected workers in the relevant occupations are eligible to claim Industrial Injuries Scheme Benefit which, if awarded, is usually payable for life.
- Most occupational causes of EAA are associated with the handling of mouldy vegetable produce; drying vegetable material before storage could prevent most cases.

5.3 Rehabilitation

- Pulmonary rehabilitation programmes use a supportive environment in which to restore muscle strength and endurance, maximise functional level and improve quality of life.
- Objective measures are necessary to assess functional improvement, such as the 6-minute walking test or the shuttle walk test. It has been claimed that a 6-minute walking distance of 150 feet represents the minimum distance necessary to maintain independent living in an apartment setting.
- There is little published data on exercise reconditioning and ILD. One study showed an improvement in 6-minute walking distance from 213 to 506 feet after the training programme, despite no substantial improvement in pulmonary function tests. Although the improvement appeared substantial, the investigators did not assess the impact on quality of life scores.[23]
- Patients with end-stage interstitial lung disease may not be referred to rehabilitative programmes as they may be considered beyond rehabilitation. Referral early in the course of the disease may improve functional capacity.[23]
Appendix A - Tables

Table 1: Historical Classification

<table>
<thead>
<tr>
<th>IDIOPATHIC INTERSTITIAL PNEUMONIAS</th>
<th>Clinical Terminology</th>
<th>Pathological Findings</th>
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<tbody>
<tr>
<td>Idiopathic Pulmonary Fibrosis</td>
<td></td>
<td>Usual interstitial pneumonia</td>
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<tr>
<td>Desquamative interstitial pneumonia or</td>
<td>Desquamative interstitial pneumonia or</td>
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<tr>
<td>Respiratory bronchiolitis interstitial lung disease</td>
<td>Respiratory bronchiolitis interstitial lung disease</td>
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<tr>
<td>Acute interstitial Pneumonia</td>
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<td>Diffuse Alveolar Damage</td>
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<td>Non specific interstitial pneumonia</td>
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<td>Non specific interstitial pneumonia</td>
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<tr>
<td>Cryptogenic organising pneumonia</td>
<td>Organising pneumonia, peribronchiolar inflammation</td>
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<tr>
<td>Bronchiolitis obliterans organising pneumonia</td>
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Table 2: Presentation of Extrinsic Allergic Alveolitis

<table>
<thead>
<tr>
<th>FEATURES</th>
<th>Acute</th>
<th>Sub-acute</th>
<th>Chronic</th>
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<tbody>
<tr>
<td>Fever Chills</td>
<td>+</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Dyspnoea</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Cough</td>
<td>Non-productive</td>
<td>Productive</td>
<td>Pr productive</td>
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<tr>
<td>Malaise</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Weight loss</td>
<td>-</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Crackles</td>
<td>Bibasal</td>
<td>Diffuse</td>
<td>Dif fuse</td>
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<tr>
<td>CXR</td>
<td>Nodular infiltrates</td>
<td>Nodular infiltrates</td>
<td>Fib ros is</td>
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<tr>
<td>Pulmonary Function</td>
<td>Restrictive</td>
<td>Mixed</td>
<td>Mi xe</td>
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<td>Tests</td>
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<tr>
<td>DLCO</td>
<td>Decreased</td>
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Adapted from Grammer 1999[24]
### Table 3: Potential Side Effects of High Dose Steroids

<table>
<thead>
<tr>
<th>SIDE EFFECT</th>
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<tbody>
<tr>
<td><strong>Musculo-skeletal</strong></td>
<td>Osteoporosis</td>
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<td></td>
<td>Vertebral compression fracture</td>
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<td></td>
<td>Aseptic necrosis of femoral or humeral head</td>
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<td>Myopathy</td>
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<td><strong>Psychological</strong></td>
<td>Depression</td>
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<td></td>
<td>Euphoria</td>
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<td>Psychosis</td>
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<td><strong>Cardiovascular</strong></td>
<td>Hypertension</td>
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<td><strong>Endocrine and Metabolic</strong></td>
<td>Truncal obesity</td>
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<td></td>
<td>Hyperglycaemia/diabetes</td>
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<td></td>
<td>Metabolic alkalosis</td>
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<td>Secondary adrenal insufficiency</td>
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<td><strong>Ophthalmic</strong></td>
<td>Posterior capsular cataracts</td>
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<td></td>
<td>Raised intra-ocular pressure</td>
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</tbody>
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6 References


