ABC of clinical haematology
Iron deficiency anaemia

Rebecca Frewin, Andrew Henson, Drew Provan

Iron deficiency is the commonest cause of anaemia worldwide and is frequently seen in general practice. The anaemia of iron deficiency is caused by defective synthesis of haemoglobin, resulting in red cells that are smaller than normal (microcytic) and contain reduced amounts of haemoglobin (hypochromic).

Diagnosing iron deficiency is usually straightforward–the major challenge is determining the cause of the anaemia

Iron metabolism

Iron has a pivotal role in many metabolic processes, and the average adult contains 3-5 g of iron, of which two thirds is in the oxygen-carrying molecule haemoglobin.

A normal Western diet provides about 15 mg of iron daily, of which 5-10% is absorbed, principally in the duodenum and upper jejunum, where the acidic conditions help the absorption of iron in the ferrous form. Absorption is helped by the presence of other reducing substances, such as hydrochloric acid and ascorbic acid. The body has the capacity to increase its iron absorption in the face of increased demand—for example, in pregnancy, lactation, growth spurts, and iron deficiency.

Once absorbed from the bowel, iron is transported across the mucosal cell to the blood, where it is carried by the protein transferrin to developing red cells in the bone marrow. Iron stores comprise ferritin, a labile and readily accessible source of iron, and haemosiderin, an insoluble form found predominantly in macrophages.

About 1 mg of iron a day is shed from the body in urine, faeces, sweat, and cells shed from the skin and gastrointestinal tract. Menstrual losses of an additional 20 mg a month and the increased requirements of pregnancy (500-1000 mg) contribute to the higher incidence of iron deficiency in women of reproductive age.

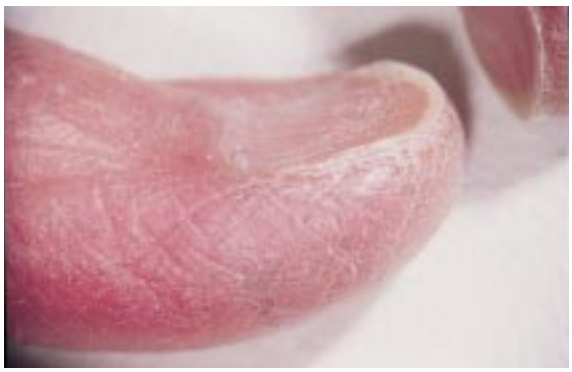
Daily dietary iron requirements per 24 hours

Male	1 mg
Adolescence	2-3 mg
Female (reproductive age)	2-3 mg
Pregnancy	3-4 mg
Infancy	1 mg
Maximum bioavailability from normal diet about	4 mg

Clinical features of iron deficiency

The symptoms accompanying iron deficiency depend on how rapidly the anaemia develops. In cases of chronic, slow blood loss, the body adapts to the increasing anaemia, and patients can often tolerate extremely low concentrations of haemoglobin—for example, <70 g/l—with remarkably few symptoms. Most patients complain of increasing lethargy and dyspnoea. More unusual symptoms are headaches, tinnitus, and taste disturbance.

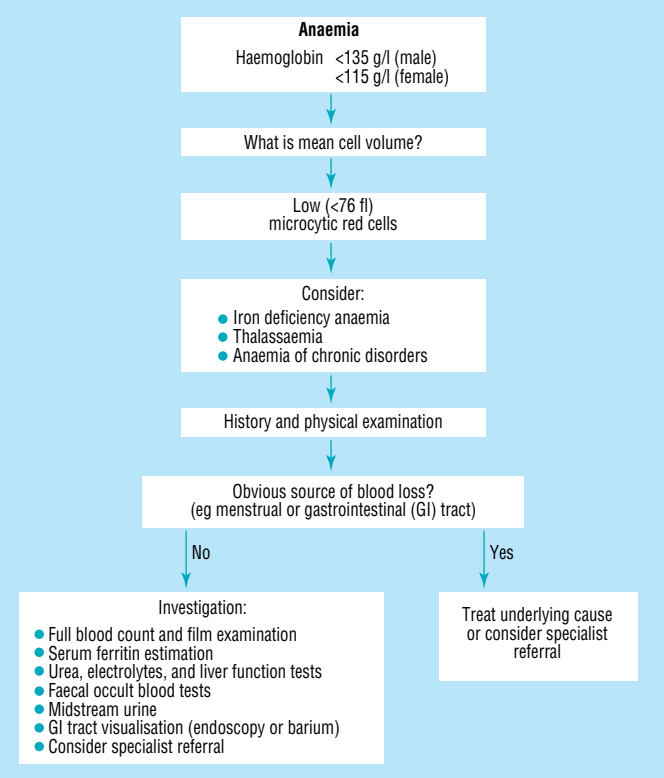
On examination, several skin, nail, and other epithelial changes may be seen in chronic iron deficiency. Atrophy of the skin occurs in about a third of patients, and nail changes such as koilonychia (spoon shaped nails) result in brittle, flattened nails. Patients may also complain of angular stomatitis, in which painful cracks appear at the angle of the mouth, sometimes accompanied by glossitis. Although uncommon, oesophageal and pharyngeal webs can be a feature of iron deficiency anaemia (consider this in middle aged women presenting with dysphagia). These changes are believed to be due to a reduction in the iron-containing enzymes in the epithelium and gastrointestinal tract.



Nail changes in iron deficiency anaemia (koilonychia).

Risk factors in development of iron deficiency

Age—Infants (especially if history of prematurity); adolescents; postmenopausal women; old age
Sex—Increased risk in women
Reproduction—Menorrhagia
Renal—Haematuria (rarer cause)
Gastrointestinal tract—Appetite or weight changes; changes in bowel habit; bleeding from rectum/melaena; gastric or bowel surgery
Drug history—Especially aspirin and non-steroidal anti-inflammatories
Social history—Diet, especially vegetarians
Physiological—Pregnancy; infancy; adolescence; breast feeding; age of weaning



Diagnosis and investigation of iron deficiency anaemia.

Increasing tachycardia and worsening cardiac failure indicate cardiac decompensation from the worsening anaemia, and in such cases prompt remedial action should be taken.

When iron deficiency is confirmed a full clinical history including leading questions on possible gastrointestinal blood loss or malabsorption (as in, for example, coeliac disease) should be obtained. Menstrual losses should be assessed, and the importance of dietary factors and regular blood donation should not be overlooked.

Diet alone is seldom the sole cause for iron deficiency anaemia in Britain except when it prevents an adequate response to a physiological challenge—as in pregnancy, for example.

Laboratory investigations

A full blood count and film should be taken. These will confirm the anaemia; recognising the indices of iron deficiency is usually straightforward (reduced haemoglobin concentration, reduced mean cell volume, reduced mean cell haemoglobin, reduced mean cell haemoglobin concentration). The blood film shows microcytic hypochromic red cells. Hypochromic anaemia occurs in other disorders, such as anaemia of chronic disorders and sideroblastic anaemias and in globin synthesis disorders, such as thalassaemia. To help to differentiate the type, further haematinic assays may be necessary. Difficulties in diagnosis arise when more than one type of anaemia is present—for example, iron deficiency and folate deficiency in malabsorption, in a population where thalassaemia is present, or in pregnancy, when the interpretation of red cell indices may be difficult.

Haematinic assays will demonstrate reduced serum ferritin concentration in straightforward iron deficiency. As an acute phase protein, however, the serum ferritin concentration may be normal or even raised in inflammatory or malignant disease.

Causes of iron deficiency anaemia

Reproductive system
- Menorrhagia

Gastrointestinal tract

Bleeding
- Oesophagitis
- Oesophageal varices
- Hiatus hernia
- Peptic ulcer
- Inflammatory bowel disease
- Haemorrhoids
- Carcinoma: stomach, colorectal
- Angiodysplasia hereditary haemorrhagic telangiectasia (rare)

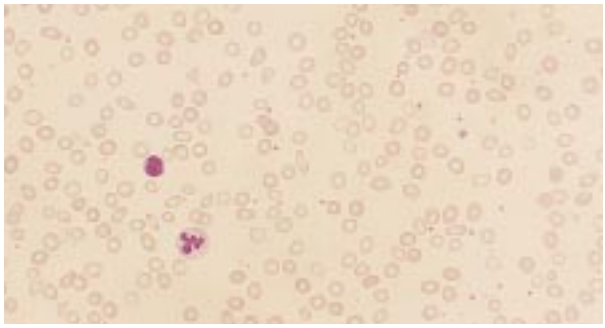
Malabsorption
- Coeliac disease
- Atrophic gastritis (also may result *from* iron deficiency)

Physiological
- Growth spurts (especially in premature infants)
- Pregnancy

Dietary
- Vegans
- Elderly

Genitourinary system
- Haematuria (?cause)

Worldwide commonest cause of iron deficiency is hookworm infection



Blood film showing changes of iron deficiency anaemia.

Differential diagnosis of hypochromic anaemia

Factor	*Iron deficiency*	*Chronic disorders*	*Thalassaemia trait (α or β)*	*Sideroblastic anaemia*
Degree of anaemia	Any	Seldom <90 g/l	Mild	Any
Mean cell volume	↓	N or ↓	↓↓	N, ↓ or ↑
Serum ferritin	↓	N or ↑	N	↑
TIBC	↑	↓	N	N
Serum iron	↓	↓	N	↑
Marrow iron	Absent	Present	Present	Present

N = normal; TIBC = total iron binding capacity

Investigations in iron deficiency anaemia
- Full clinical history and physical examination
- Full blood count and blood film examination
- Haematinic assays (serum ferritin, vitamin B_{12}, folate)
- Urea and electrolytes, liver function tests
- Faecal occult bloods
- Midstream urine (occult blood loss)
- Fibreoptic and/or barium studies of gastrointestinal tract
- Pelvic ultrasound (females, if indicated)

A prime example of this is found in rheumatoid disease, in which active disease may result in a spuriously raised serum ferritin concentration masking an underlying iron deficiency caused by gastrointestinal bleeding after non-steroidal analgesic treatment. There may also be confusion in liver disease as the liver contains stores of ferritin that are released after hepatocellular damage, leading to raised serum ferritin concentrations. In cases where ferritin estimation is likely to be misleading, it can be helpful to determine the serum iron concentration and total iron binding capacity, which are reduced and raised respectively in uncomplicated iron deficiency. In common with serum ferritin estimation, however, these measures are often difficult to interpret when inflammation is present.

Diagnostic bone marrow sampling is seldom performed in simple iron deficiency, but if the diagnosis is in doubt a marrow aspirate may be carried out to demonstrate absent bone marrow stores.

When iron deficiency has been diagnosed, the underlying cause should be investigated and treated. Often the history will indicate the likely source of bleeding—for example, menstrual blood loss or gastrointestinal bleeding. If there is no obvious cause further investigation generally depends on the age and sex of the patient. In male patients and postmenopausal women possible gastrointestinal blood loss is investigated by performing faecal occult bloods and visualisation of the gastrointestinal tract (endoscopic or barium studies). Faecal occult bloods are useful screening tests (sensitivity 50-75% in the detection of colorectal cancer), but a negative result should not preclude other investigations of the gastrointestinal tract.

Management

Effective management of iron deficiency relies on (*a*) the appropriate management of the underlying cause (for example, gastrointestinal or menstrual blood loss) and (*b*) iron replacement therapy.

Oral iron replacement therapy with gradual replenishment of iron stores and restoration of haemoglobin is the preferred treatment. Oral ferrous salts are the treatment of choice (ferric salts are less well absorbed) and should take the form of ferrous sulphate 200 mg three times daily (providing 65 mg × 3 = 195 mg elemental iron/day). Alternative preparations include ferrous gluconate and ferrous fumarate. All three compounds, however, are associated with a high incidence of side effects, including nausea, constipation, and diarrhoea. These side effects may be reduced by taking the tablets after meals, but even milder symptoms account for poor compliance with oral iron supplementation. Modified release preparations have been developed to reduce side effects but in practice prove expensive and often release the iron beyond the sites of optimal absorption.

Effective iron replacement therapy should result in a rise in haemoglobin concentration of around 1 g/l per day (about 20 g/l every three weeks), but this varies from patient to patient. Once the haemoglobin concentration is within the normal range, iron replacement should continue for three months to replenish the iron stores.

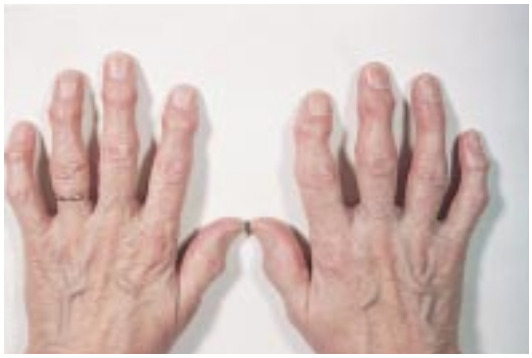
Failure to respond to oral iron therapy

The main reason for failure to respond to oral iron therapy is poor compliance. However, if the losses (for example, bleeding) exceed the amount of iron absorbed daily, the haemoglobin concentration will not rise as expected; this will also be the case in combined deficiency states.

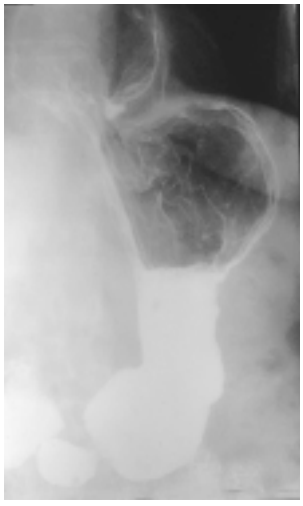
Diagnosis of iron deficiency anaemia

Reduced haemoglobin	Men < 135 g/l, women < 115 g/l
Reduced mean cell volume	< 76 fl
Reduced mean cell haemoglobin	29.5 ± 2.5 pg
Reduced mean cell haemoglobin concentration	325 ± 25 g/l
Blood film	Microcytic hypochromic red cells with pencil cells and target cells
Reduced serum ferritin*	Male < 10 µg/l, women (postmenopausal) < 10 µg/l, (premenopausal) < 5 µg/l
Reduced serum iron*	Male < 14 µmol/l, female < 11 µmol/l
Increased serum iron and total binding capacity*	> 75 µmol/l

*Check with local laboratory for reference ranges



Patient with osteoarthritis (Heberden's nodes). This patient was iron deficient secondary to gastrointestinal bleeding secondary to non-steroidal anti-inflammatory drugs.



Barium meal showing hiatus hernia leading to iron deficiency anaemia.

Oral iron replacement therapy.

Elemental iron content of various oral iron preparations

Preparation	*Amount (mg)*	*Ferrous iron (mg)*
Ferrous fumarate	200	65
Ferrous gluconate	300	35
Ferrous succinate	100	35
Ferrous sulphate	300	60
Ferrous sulphate (dried)	200	65

The presence of underlying inflammation or malignancy may also lead to a poor response to therapy. Finally, an incorrect diagnosis of iron deficiency anaemia should be considered in patients who fail to respond adequately to iron replacement therapy.

Intravenous and intramuscular iron preparations

Parenteral iron may be used when the patient cannot tolerate oral supplements—for example, when patients have severe gastrointestinal side effects or if the losses exceed the daily amount that can be absorbed orally.

Iron sorbitol injection is a complex of iron, sorbitol and citric acid. Treatment consists of a course of deep intramuscular injections. The dosage varies from patient to patient and depends on (*a*) the initial haemoglobin concentration and (*b*) body weight. Generally, 10-20 deep intramuscular injections are given over two to three weeks. Apart from being painful, the injections also lead to skin staining at the site of injection and arthralgia.

Alternative treatments

Blood transfusion is not indicated unless the patient has decompensated due to a drop in haemoglobin concentration and needs a more rapid rise in haemoglobin—for example, in cases of worsening angina or severe coexisting pulmonary disease. In cases of iron deficiency with serious ongoing acute bleeding blood transfusion may be required.

Prevention

When absorption from the diet is likely to be matched or exceeded by losses, extra sources of iron should be considered—for example, prophylactic iron supplements in pregnancy or after gastrectomy or encouragement of breast feeding or use of formula milk during the first year of life (rather than cows' milk, which is a poor source of iron).

Intravenous iron preparations

- Intravenous iron preparations are available in Britain on a named patient basis only
- These preparations are frequently associated with side effects, some of which are severe—such as anaphylaxis
- They should therefore be given only under close medical supervision and when full resuscitation facilities are available

The rise in haemoglobin concentration is no faster with parenteral iron preparations than with oral iron therapy

Drs A G Smith and A Amos provided the photographic material and Dr A Odurny provided the radiograph. The source of the detail in the table is the *British National Formulary*, No 32(Sep), 1995.

Rebecca Frewin is registrar in haematology at the Southampton University Hospitals NHS Trust.

The ABC of clinical haematology is edited by Drew Provan, consultant haematologist and honorary senior lecturer at the Southampton University Hospitals NHS Trust, and Andrew Henson, clinical research fellow, university department of primary care, Royal South Hants Hospital, Southampton.

Lesson of the week

Cyclosporin treatment for ulcerative colitis complicated by fatal *Pneumocystis carinii* pneumonia

Virginia A Quan, Brian P Saunders, Brendan H Hicks, Gordon E Sladen

Since its introduction in the 1970s cyclosporin has become the mainstay of treatment for organ rejection in transplantation. Recently, several studies have assessed its potential for treating inflammatory bowel disease. Although of limited benefit in Crohn's disease, cyclosporin seems to induce remission in about 50% of patients with exacerbations of ulcerative colitis that are unresponsive to intravenous steroids.[1-3] In transplant recipients treated with cyclosporin *Pneumocystis carinii* pneumonia is one of the early infective complications. Co-trimoxazole is effective in preventing this and is routinely prescribed during the first three to six months of immunosuppressive treatment. The doses of cyclosporin and steroids now used in acute ulcerative colitis are similar to those used in organ transplantation. Despite this, the use of co-trimoxazole as prophylaxis has not been adopted by gastroenterologists and is not included in any of the regimens described for the treatment of inflammatory bowel disease with cyclosporin.

We report a case of fatal *P carinii* pneumonia arising one month after the start of cyclosporin treatment for ulcerative colitis, and we suggest that *P carinii* prophylaxis should always be considered when high dose cyclosporin is combined with steroids.

Consider prophylaxis against *Pneumocystis carinii* pneumonia in patients treated with cyclosporin

Department of Medicine, Lewisham Hospital, London SE13 6LH
Virginia A Quan, *registrar in nephrology and general medicine*

BMJ 1997;314:363–4

continued over

Case report

A 63 year old man was admitted to hospital with a two month history of bloody diarrhoea, weight loss, and fever. Plain abdominal radiography indicated pancolitis; sigmoidoscopy showed a severely inflamed rectal mucosa. Blood and stool cultures gave negative results, and rectal biopsy confirmed a diagnosis of ulcerative colitis. He was treated with intravenous hydrocortisone, but six days later he still had regular episodes of melaena and severe colitis was still evident on sigmoidoscopy. Total colectomy was planned, but in an attempt to avoid surgery he was given intravenous

Brian P Saunders, *senior registrar in gastroenterology and general medicine*
Brendan H Hicks, *consultant in endocrinology and general medicine*
Gordon E Sladen, *consultant in gastroenterology and general medicine*
Correspondence to: Dr V A Quan, Department of Renal Medicine, Renal Unit, Guy's Hospital, London SE1 9RT.

cyclosporin, initially 4 mg/kg every 24 hours, the dose used in the controlled trial reported by Lichtiger *et al.*[1] Six days later his condition had improved considerably and he was changed from intravenous to oral cyclosporin. One week later his bowel frequency had returned to normal and he was discharged receiving cyclosporin 200 mg twice a day (equivalent to 8 mg/kg daily), prednisolone 40 mg (reduced by 5 mg weekly), mesalazine 800 mg three times a day, and hydrocortisone enemas three times a day. He was reviewed the following week as an outpatient; a sigmoidoscopy gave normal results. At this time he had a high trough cyclosporin concentration of 410 µg/l, measured in whole blood using a monoclonal immunoassay. This was above the range aimed for in transplant recipients at the same hospital (150-250 µg/l), his previous trough concentrations having been within this range. It was also just above the range suggested in the trial reported by Lichtiger *et al*, again using a monoclonal immunoassay (100-400 µg/l).[1] The dose of cyclosporin was therefore halved to 100 mg twice daily. The patient's renal and liver functions were normal at discharge, during follow up at the outpatient clinic, and on his subsequent readmission.

Six days later he was readmitted with dyspnoea, a fever of 39° C, and signs of right sided consolidation. A chest radiograph showed bilateral basal shadowing that was worse on the right. He was treated with intravenous ampicillin and erythromycin, and cyclosporin was stopped. After initially improving his condition deteriorated suddenly, and two days after admission he had a respiratory arrest and died.

At necropsy the cause of death was given as bilateral lobar pneumonia; many *P carinii* were found in the alveoli on histological examination. The patient had no reason to be immunocompromised other than his drug treatment; in particular, he had no risk factors for AIDS or malignant disease.

Discussion

P carinii causes pneumonia in immunocompromised patients. One other case of *P carinii* pneumonia in a patient receiving cyclosporin for ulcerative colitis has been reported.[4] In a review of inflammatory bowel disease treated with cyclosporin this was the only case out of 343, but many of these patients received a much lower dose than that now advised for the treatment of acute ulcerative colitis.[3] There is considerable evidence from transplant recipients, who receive similar amounts of initial immunosuppressive treatment, that prophylactic co-trimoxazole prevents *P carinii* pneumonia. Despite this none of the protocols describing the use of cyclosporin in inflammatory bowel disease suggests the use of routine prophylaxis.

Over the first half of the past decade the incidence of *P carinii* pneumonia among renal transplant recipients increased, with outbreaks described in several units.[5-7] The use of cyclosporin, introduced into most transplantation programmes by 1983, is reported as one of the factors responsible for this increase. For example, 14 out of 156 (9%) transplant recipients treated with cyclosporin and steroids developed *P carinii* pneumonia over 19 months compared with six out of 179 (3%) receiving azathioprine and steroids over four years.[7] Several studies document the effectiveness of low dose co-trimoxazole prophylaxis in such patients, with rates of *P carinii* pneumonia varying between 3.7% and 11% without prophylaxis in the first six months after transplantation, and no cases reported in patients receiving prophylactic treatment.[7-10] Most cases develop within the first four months of transplantation, with a mortality of 20-30% despite treatment.[7 9 10] As a result of these studies it is now routine for renal transplant recipients to receive co-trimoxazole 460 mg twice daily for three to six months after transplantation as prophylaxis against *P carinii* pneumonia.

The degree of immunosuppression in patients treated with high dose cyclosporin for acute exacerbations of ulcerative colitis is roughly comparable with that used initially in renal transplantation. Transplantation protocols vary between hospitals, but most use a baseline dose of steroids lower than that used in the treatment of acute inflammatory bowel disease—for example, prednisolone 0.33 mg/kg body weight daily is used in Guy's Hospital renal unit compared with 40-60 mg daily for acute ulcerative colitis.[11] The dose of cyclosporin used is also similar. Protocols for acute ulcerative colitis suggest initial doses of 4 mg/kg/day intravenously for up to 14 days or 10 mg/kg/day orally, with the aim of achieving concentrations between 100 and 400 µg/l, as measured by monoclonal immunoassay.[1-3] Renal transplant recipients at Guy's Hospital receive 4 mg/kg/day intravenously for three days before transferring to 10-14 mg/kg/day orally, with daily alterations in the dose to give trough concentrations of 150-250 µg/l.

A recent review suggested that studies of the benefits of prophylactic treatment with co-trimoxazole in patients receiving cyclosporin and prednisolone for inflammatory bowel disease should be undertaken.[3] We believe there is already considerable evidence for its benefit in transplantation and that *P carinii* prophylaxis with co-trimoxazole should be considered. Cyclosporin is also occasionally used to treat asthma and rheumatoid arthritis.[12 13] Similarly, we suggest that if high doses of cyclosporin and steroids are prescribed together *P carinii* prophylaxis should be considered.

1 Lichtiger S, Present DH, Kornbluth A, Gelernt I, Bauer J, Galler G, *et al.* Cyclosporine in severe ulcerative colitis refractory to steroid therapy. *N Engl J Med* 1994;330:1841-5.
2 Baert F, Hanauer S. CYA in severe steroid resistant UC: long term results of therapy. *Gastroenterology* 1994;106:A648.
3 Sandborn WJ. A critical review of cyclosporin therapy in inflammatory bowel disease. *Inflammatory Bowel Dis* 1995;1:48-63.
4 Smith MB, Hanauer SB. Pneumocystis carinii pneumonia during cyclosporine therapy for ulcerative colitis. *N Engl J Med* 1992;327:497-8.
5 Talseth T, Holdaas H, Albrechtsen D, Berg KJ, Fauchald P, Naalsund A, *et al.* Increasing incidence of Pneumocystis carinii pneumonia in renal transplant patients. *Transplant Proc* 1988;20:400-1.
6 Satiago-Delphin EA, Mora E, Gonzalez ZA, Morales-Otero LA, Bermudez R. Factors in an outbreak of Pneumocystis carinii in a transplant unit. *Transplant Proc* 1988;20 (suppl 1):462-5.
7 Hardy AM, Wajszczuk CP, Suffredini AF, Hakala TR, Ho M. Pneumocystis carinii pneumonia in renal transplant recipients treated with cyclosporine and steroids. *J Infect Dis* 1984;149:143-7.
8 Elinder CG, Andersson J, Bolinder G, Tyden G. Effectiveness of low dose cotrimoxazole prophylaxis against Pneumocystis carinii pneumonia after renal and/or pancreas transplantation. *Transplant Int* 1992;5:81-4.
9 Higgins RM, Bloom SL, Hopkin JM, Morris PJ. The risks and benefits of low dose cotrimoxazole prophylaxis for Pneumocystis pneumonia in renal transplantation. *Transplantation* 1989;47:558-60.
10 Branten AJW, Beckers PJA, Tiggler RGWL, Hotisma AJ. Pneumocystis carinii pneumonia in renal transplant recipients. *Nephrol Dial Transplant* 1995;10:1194-7.
11 Hanauer SB. Medical therapy of ulcerative colitis. *Lancet* 1993;342:412-7.
12 Yocum DE, Klippel JH, Wilder RW. Cyclosporine A in severe, treatment-refractory rheumatoid arthritis: a randomized study. *Ann Intern Med* 1988;109:863-9.
13 Moss RB. Alternative pharmacotherapies for steroid-dependent asthma. *Chest* 1995;107:817-25.

(Accepted 12 November 1996)