CONSENSUS DOCUMENT FOR THE DIAGNOSIS AND MANAGEMENT OF PATIENTS WITH PRIMARY ANTIBODY DEFICIENCIES

The Royal College of Pathologists

The Royal College of Physicians

The Primary Immunodeficiency Association

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CONTENTS

BACKGROUND

Primary antibody deficiency syndromes include congenital and acquired antibody deficiencies but not those secondary to other diseases (such as myeloma, CLL or protein-losing enteropathies). Formerly, hypogammaglobulinaemia was the term used for those patients with low serum immunoglobulin levels; these patients are more accurately described as having primary antibody deficiency.

	per 10^5 population
Rheumatoid arthritis	1000
Insulin dependent diabetes	200
Multiple sclerosis	60
Systemic lupus erythematosus	50
Primary antibody deficiency	4
Scleroderma	3

Figure 1
Prevalence of primary antibody deficiency
Comparison with other diseases
[data from the Oxford Textbook of Medicine 1990]

The term "primary antibody deficiency" has been expanded to include several types of deficiencies *(see below)* of which common variable immune deficiency (CVID) is the most widespread. In the UK we expect around 2,500 patients[1] *[Figure 1]* but at present the UK Register for Primary Immune Deficiencies[2] records less than 1,500 CVID patients. Furthermore a survey in the North West Region[3] showed that an average diagnostic delay in CVID was 2.5 years in children and 5.5 years in adults, illustrating the poor awareness of this condition. It is likely that only one in four hospital consultants and one in fifteen general practitioners will see a CVID patient.

A common reason for the lack of awareness of these diseases in adults is the widespread but erroneous belief that all primary immune deficiencies present in childhood. Ninety five percent of patients with common variable immune deficiency present after the age of 6 years[4] *[Figure 2]*. Diagnostic delay results in unnecessary morbidity from untreated disease and makes patients with complications from longstanding primary antibody immunodeficiency difficult to manage. Confusion with HIV disease has caused considerable distress in many patients.

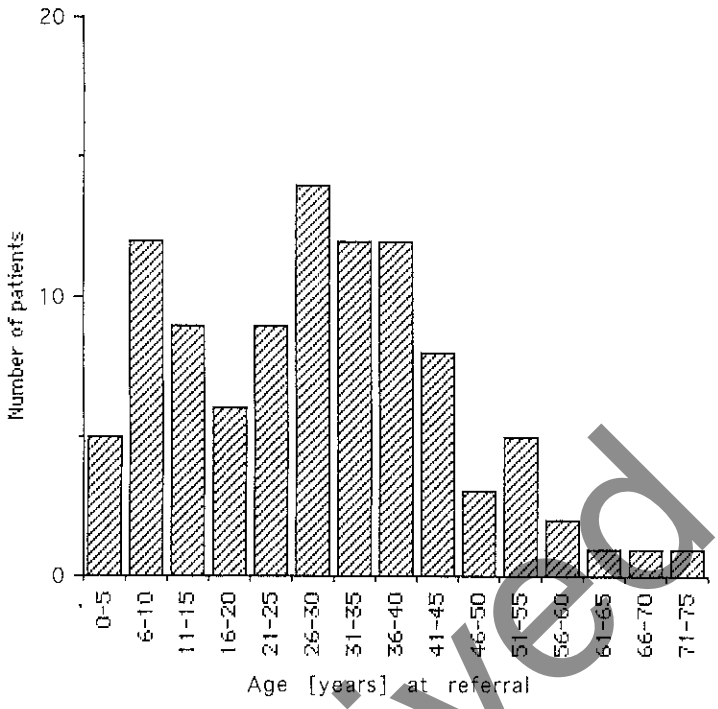

Figure 2
Ages (at referral) of patients with common variable immune deficiency
[data from reference 4]

The scarcity of clinical immunology services in the past has resulted in many patients being managed in centres where only a few patients with antibody deficiencies are seen. As a result of the lack of experience, the management of some patients has been inadequate to say the least. With the recent expansion of immunology services, the availability of services has become more widespread and there is quicker provision of medical advice resulting in opportunities for better patient care.

As the result of an initiative from the Primary Immunodeficiency Association (PiA), a small group of physicians, paediatricians and specialists in related disciplines met with representatives from the Royal College of General Practitioners, Royal College of Nursing and a consultant in Public Health Medicine (for purchasers) to develop guidelines for the diagnosis and management of patients with primary antibody deficiencies *[see list of Panel members, p.ii].*

A shortened version of this document has been published in the British Medical Journal *(BMJ February 1994;308:581-585).*

DEFINITIONS OF SUBGROUPS OF PRIMARY ANTIBODY DEFICIENCIES

There is a spectrum of primary antibody defects; the clinical significance of some subgroups has been recognised only recently *[Table 1]*.

Common variable immune deficiency (CVID)
X-linked antibody deficiency
IgG subclass deficiencies
Specific antibody deficiency
Selective IgA deficiency

Table 1

- **Common variable immune deficiency (CVID)** encompasses those patients with primary antibody deficiencies who have low levels of serum IgG and IgA, including IgG sub-classes, with or without a low serum IgM[5] *[Figure 3]*.

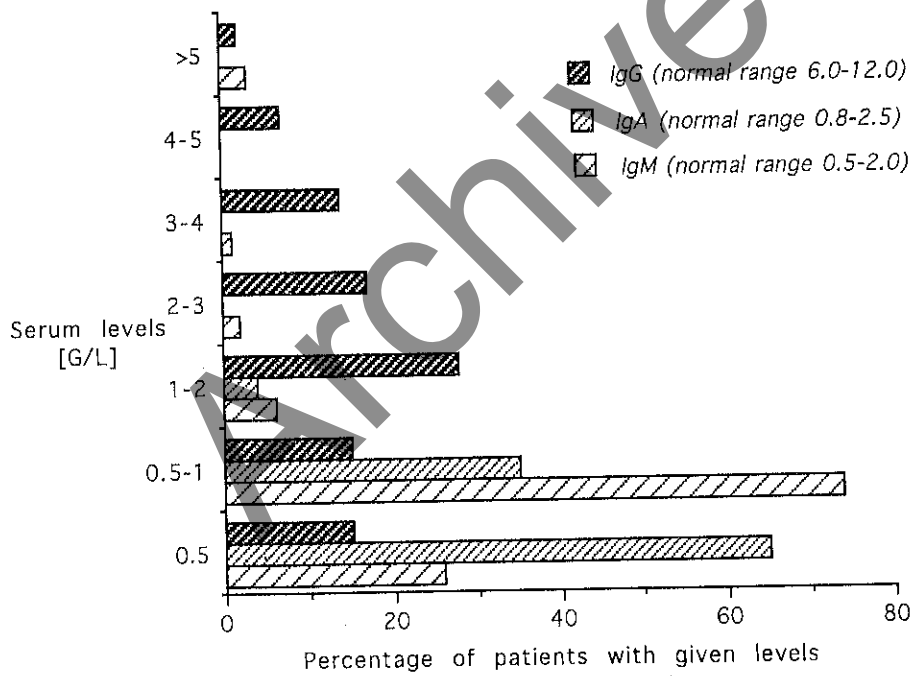

Figure 3
Serum levels of immunoglobulins at presentation for patients with common variable immune deficiency
[data from reference 4]

- **X-linked antibody deficiency** occurs in boys before the age of 2 years, some of whom have a definite family history[5].

- **IgG sub-class deficiencies** in patients with recurrent infections may be an indication for immunoglobulin replacement therapy[6], provided there is associated antibody failure following test immunisations.

- **Specific antibody deficiency** refers to those patients with a classical history of humoral immune deficiency who fail to respond to test immunisations, despite normal serum levels of total IgG, IgA, IgM and IgG sub-classes[7].

In addition there are those individuals who lack only IgA; this is known as **selective IgA deficiency** and is common (1:700 population). Many people with complete absence of IgA remain asymptomatic, particularly those in whom this deficiency is detected by chance. However, patients with IgA deficiency and recurrent infections may also have an underlying IgG sub-class or specific antibody deficiency[8].

IN WHOM TO SUSPECT ANTIBODY DEFICIENCY

Clinical history is the most important aspect of suspecting a diagnosis of primary antibody deficiencies. ***NB Not all patients present with recurrent infections, even those with adult onset disease*** *[Figure 4].*

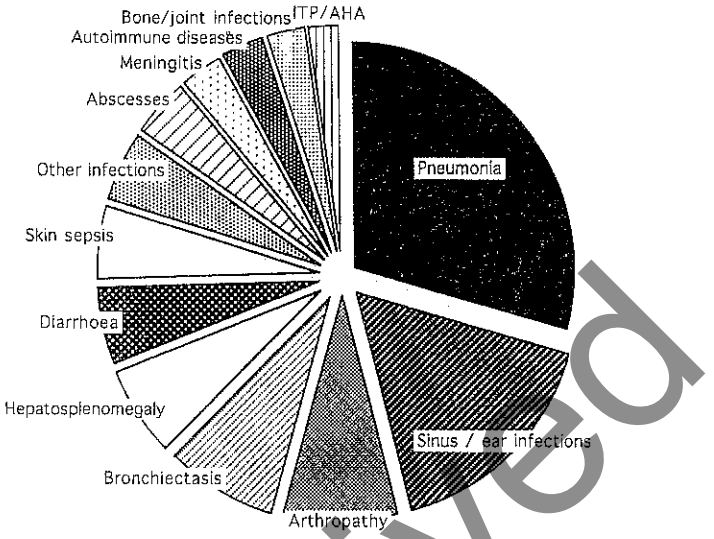

Figure 4
Presenting features in patients with common variable immune deficiency
[data from reference 19]

The following clinical clues should raise suspicions of immune deficiency so that referral to a specialist immunologist for appropriate tests may be made:

- Unexplained failure to thrive in childhood.
- An excess of infections; these may be manifest by:
  - recurrent infections at different sites, or even within a single system, requiring frequent use of antibiotics
  - particularly severe, unusual or persistent infections, even if the serum immunoglobulin levels are normal
  - children in whom there are documented, recurrent bacterial, upper respiratory tract infections

- surgical intervention for chronic infection such as lobectomy for bronchiectasis, tonsillectomy, adenoidectomy, recurrent insertion of grommets or recurrent incision of boils
- the instigation of second line tests for chronic infection such as sweat tests or ciliary beat measurements
- infections in patients with pre-existing-autoimmune disease *[Figure 5]*.

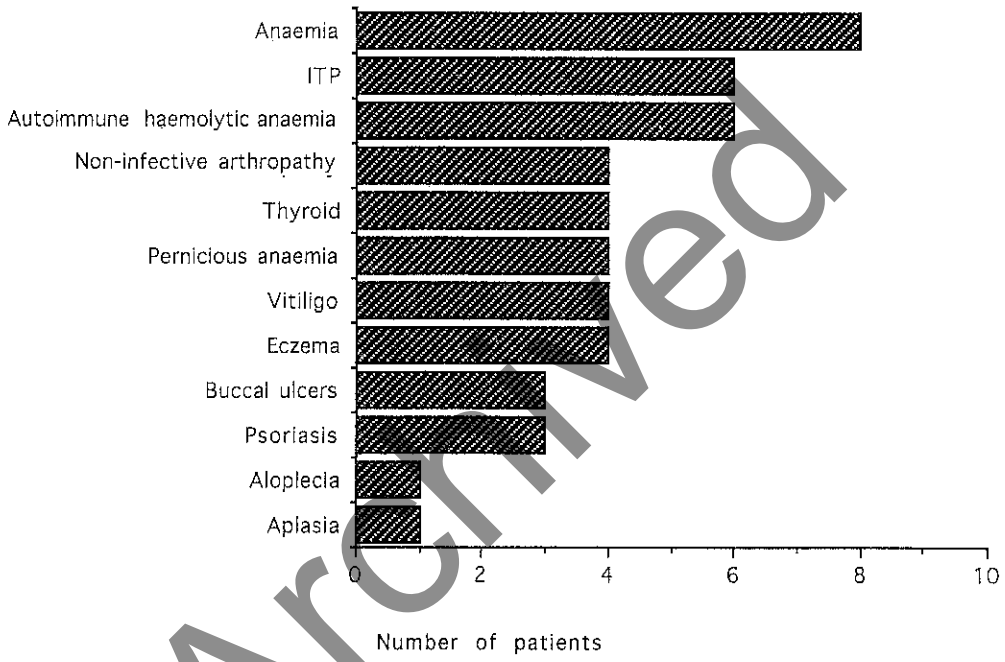

Figure 5
Autoimmune diseases in patients with common variable immune deficiency
[data from reference 19]

- Abnormal lymphoid tissue, such as nodular lymphoid hyperplasia in the gut or the congenital absence of tonsils.
- Unexplained signs such as hepatosplenomegaly or arthropathy.

MAKING A DIAGNOSIS OF ANTIBODY DEFICIENCY

All patients in whom there is a definite or suspected antibody defect should be referred to a specialist immunologist. The specialist will assess antibody responses to protein and carbohydrcte antigens in conjunction with measurements of IgG subclasses and quantitation of those lymphocyte subpopulations involved in antibody production *ie* CD4, CD8, CD19, CD23 positive lymphocytes. Since antibody deficiencies are relatively uncommon, there is a need for considerable clinical experience in interpreting the tests as well as in assessment of the clinical history. Interpretation of poor or suboptimal immunisation responses requires in-depth training and expertise. All patients should be seen by the specialist immunologist.

Serum immunoglobulin levels are interpreted in relation to the normal range for age. Levels of serum immunoglobulins in the low part of the normal range and the presence of a history of recurrent infections, are indications for further investigation. Confirmatory tests, such as the absence of specific antibodies to both immunisations and infections to which the patient is known to have been exposed, are required. Patients should receive test immunisations with a range of immunogens to cover responses to protein and carbohydrate antigens. The assays should be isotype specific and of sufficient sensitivity to define an abnormal immune response clearly. Measurements of IgG subclasses should also be related to the normal range for age.

In the presence of markedly abnormal serum immunoglobulin levels, confirmatory tests are not always necessary.

Patients must have a full immunological assessment prior to immunoglobulin treatment. This is best done by referral to their nearest immunologist *[Table 2]*. It is important not only to measure immune responses to test immunisations but also to assess the extent of concurrent T cell deficiency. Most patients will require treatment; appropriate therapy and monitoring can then be instituted.

Specialist Immunology Centres
for patients with primary antibody deficiencies
(*Home Therapy Centre)

Aberdeen	Aberdeen Royal Infirmary
Belfast	* Royal Victoria Hospital
Birmingham	* Birmingham Heartlands Hospital
	Dudley Road Hospital
Bristol	* Southmead Hospital
Cambridge	Addenbrooke's Hospital
Cardiff	Cardiff Royal Infirmary
Dublin	St James's Hospital
Edinburgh	Edinburgh Royal Infirmary
Glasgow	Glasgow Royal Infirmary
Leeds	St James's Hospital
Leicester	Leicester Royal Infirmary
London	* Great Ormond Street Hospital
	* St George's Hospital
	St Mary's Hospital, Paddington
	* Royal Free Hospital
Manchester	Manchester Royal Infirmary
Newcastle	* Newcastle General Hospital
Nottingham	* Queen's Medical Centre
Oxford	* Oxford Radcliffe Hospital
Salford	* Salford Royal Hospital
Sheffield	Sheffield Children's Hospital

Table 2

Most consultant immunologists prefer to start therapy in their own centre where specialist immunology nurses can assist with the management of the patients. A high proportion of patients can join a recognised self-infusion immunoglobulin programme *(Home therapy[9] see page 24)*. Those who are unsuitable may be referred back to their local hospital for maintenance immunoglobulin replacement therapy which will be supervised by the specialist immunology nurse; the treatment of these patients is assessed regularly at the specialist centre. Some patients also need continued advice from their organ based specialist.

It is important that immunologists continue to review patients regularly on an out-patient basis, to assess progress and to watch for possible complications. Shared care between the immunologist and the district physician or paediatrician and general practitioner will always be necessary and is essential if the patient lives a long way from the immunology centre. Patient or parent-held records are recommended to ensure good communication. These are not a substitute for physician records. Patients with a classical immunodeficiency history, in whom investigations are normal at the time of initial study, require specialist follow-up. There have been reports of patients who have developed antibody deficiency following the gradual cessation of antibody production. Some patients, who continue to have symptoms, need replacement therapy several years after apparently normal initial investigation.

The choice of immunoglobulin therapy, both product and route of administration, is complex. Immunologists are familiar with the wide range of products and their availability, and so can tailor replacement therapy to the individual patient needs.

AIMS OF MANAGEMENT

The aims of management, which are largely the same in adults and children, are to enable a normal working capability and life expectancy and, in children, to ensure optimal growth and development:

- To prevent further acute infections
- To halt the progress of complications if present, and to reverse prior damage where possible
- To recognise early and to manage further complications, particularly those not amenable to replacement immunoglobulin therapy
- To avoid complications of replacement immunoglobulin therapy
- To evolve approaches to management, based on individual needs, for the life-long replacement of immunoglobulin by facilitating self-administration of replacement therapy where possible
- To encourage greater participation of the patients in the management of their disease and to ensure good liaison with patients and all their medical advisers.

REPLACEMENT IMMUNOGLOBULIN THERAPY

Immunoglobulin replacement therapy is essential; failure to provide adequate replacement therapy results in long-term morbidity.

Immunoglobulin replacement therapy is available in three forms depending on the route of administration: intramuscular, subcutaneous or intravenous. Preparations for therapy are the same whichever route is chosen.

Preparation for immunoglobulin therapy

- Accurate diagnosis of the subgroup of primary antibody deficiency responsible for symptoms. If the patient has sinus, chest or gastrointestinal symptoms, specialist advice regarding investigation and management may be needed.

- Select the route of administration and the appropriate immunoglobulin preparation for the individual patient.

- Discuss fully the risk of transmissible viruses and possible adverse reactions to immunoglobulin therapy with the patient; give the patient an opportunity to discuss immunoglobulin replacement therapy with a patient who has experienced replacement by the same route.

- Establish baseline liver transaminases and serum creatinine levels and exclude the presence of anti-IgA antibodies if indicated.

- Exclude overt active infection on the day of infusion, as immunoglobulin infusions during an acute infection may result in serious adverse reactions: *ie* check temperature and take an immediate history from the patient.

Choice of route

(a) Intravenous immunoglobulin [IVIg]

This is the method of choice in most patients with antibody deficiencies. WHO have produced criteria for the production of suitable IVIg preparations[10]. Each is the product of a different manufacturing process. IVIg products should not be used interchangeably. Indiscriminate use of more than one product in a given patient will prevent identification of the source of Hepatitis C or other transmissible agent if such an infection occurs. The incidence of infusion-associated adverse reactions varies with product and patient.

(b) ***Intramuscular immunoglobulin***

Intramuscular immunoglobulin (IMIg) has been given for over 40 years but is now largely superseded by intravenous immunoglobulin which provides higher more efficacious doses *[Table 3]*. Standard preparations of IMIg contain largely IgG but also significant amounts of IgA. They are available as 16% solutions. Intramuscular immunoglobulin from different manufacturers are strikingly uniform. Proven transmission of infectious agents, including hepatitis viruses, by IMIg is not reported in the literature. The risk of an immediate adverse reaction is considerable; up to 20% of patients have a reaction at some time, and these reactions may be severe (anaphylactoid). In the unusual situation of intramuscular immunoglobulin being the preferred route for a given patient, small doses of 10 - 15 G of intravenous immunoglobulin provide a satisfactory way of loading a new patient with IgG, prior to intramuscular maintenance. IMIg must **NOT** be given intravenously.

(c) ***Rapid subcutaneous immunoglobulin***

Some IMIg and IVIg preparations are suitable for administration subcutaneously. Rapid subcutaneous immunoglobulin infusions are still at an experimental stage in the UK, though there is experience in adults in Sweden[11].

26 Adult hypogammaglobulinaemic patients
diagnosed at least 12 years previously - all receiving intramuscular (IM) therapy

	FEV % predicted value		VC % predicted value	
	>75%	<75%	>75%	<75%
Conventional IM replacement therapy *ie* >25 mg/Kg/week	12	2	11	3
Poor replacement therapy *ie* <25 mg/Kg/week	4	8	3	9

Figures given are numbers of patients *[Data from ref 20]*

Table 3

Shows lung function test [FEV^1 and VC] results in patients receiving intramuscular replacement therapy for over 12 years. Data shows that this type of replacement therapy is not satisfactory, even at conventional IM doses

Efficacy in prevention of bacterial infections

Infections in patients with primary hypogammaglobulinaemia and chronic chest disease
Blind, crossover study, one year

	Months when serum IgG < 500 mg/dl	Months when serum IgG > 500 mg/dl
n	72	72
Major Infections		
Acute bronchitis or peneumonia	11	3
Sinusitis	4	0
Arthritis	1	0
Minor Infections		
URTI	23	10
OM	4	1
Urethritis	1	0
Skin infections	3	1
Patients free of major infections n= 12	12	9

[Data from Roifman et al 1987]

Table 4

The efficacy of immunoglobulin was originally shown by the Medical Research Council trial (1955 - 1970) and more recently intravenous immunoglobulin was shown to be as good as intramuscular. Later trials demonstrated increased efficacy of higher doses of IVIg[12] *[Table 4]*.

Dose and interval of infusion

The dose of IVIg required by a given patient is initially determined by the severity and frequency of infections *[Figure 6]* as well as the starting level of serum IgG concentration. Most patients receive approximately 400 mg/kg/month, usually in 2 doses, two weeks apart, since the half-life of IVIg is 3 weeks. Very few patients require doses of 1G/kg/month in divided weekly doses[12]. Initially IVIg infusions may be given in higher doses to provide protection against infection rapidly. Adjustment of both dose and infusion interval is empirical and should be based on the patient's clinical state and the preinfusion serum IgG level.

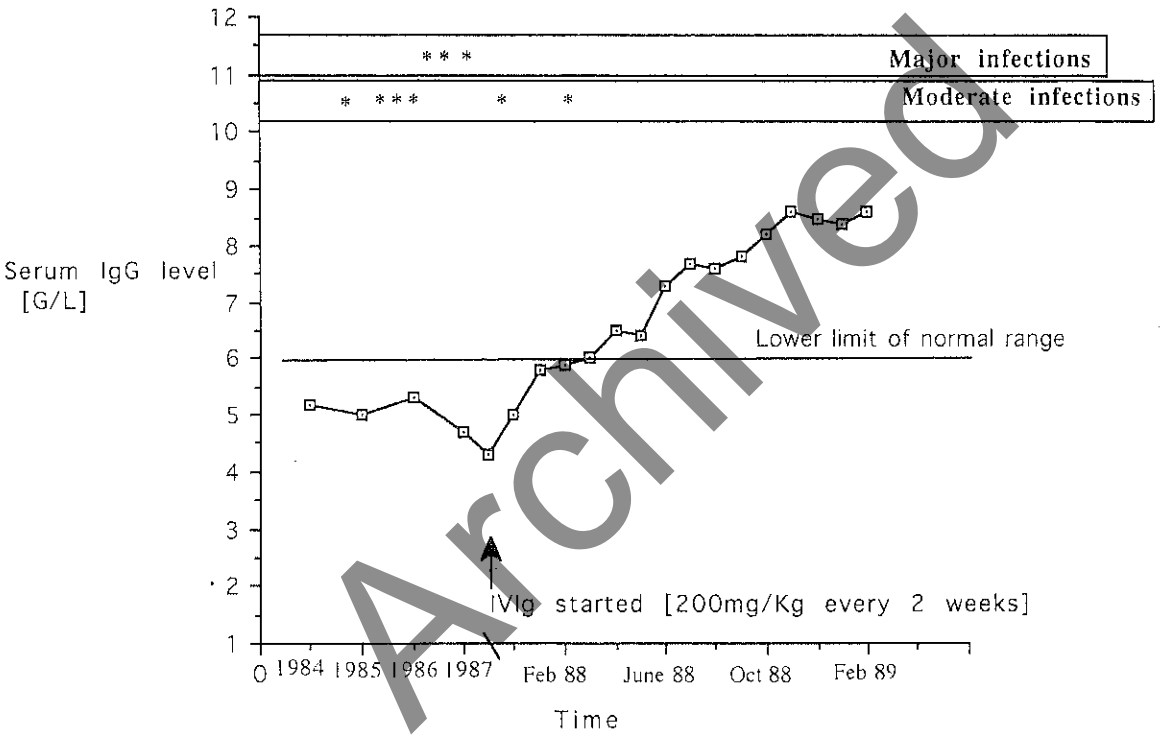

Figure 6
Efficicacy of IVIg treatment in prevention of infections in relation to serum IgG levels in a patient with common variable immune deficiency

Administration

The product insert must be followed to avoid adverse reactions, which are mostly related to infusion rates. The first few infusions should be given very slowly with antihistamine and hydrocortisone available. Adrenaline (*eg* Min-i-Jet or Epi-pen) should always be available, even at home, in case of anaphylaxis. Intensive antibiotic therapy may be given for two weeks prior to the first infusion to reduce the bacterial load if chronically infected. Many products are stored at 4°C but all should be at room temperature before administration. The use of butterfly needles, rather than cannulae, is encouraged to preserve venous access for repeated infusions.

Adverse reactions

Adverse reactions may be mild, moderate or severe[14] *[Table 5]*. Mild reactions include headache, flushing, chills, low back pain, muscle pains, nausea and fatigue. Children who are too young to describe symptoms may show distress. Such reactions do not necessarily require the infusion to be stopped, but the rate should be slowed until the symptoms have subsided.

Infusion-related reactions to intravenous immunoglogulin

Mild	Moderate	Severe
Headache	Chest tightness	Anaphylaxis
Flushing	Mild wheezing	
Low backache		
Muscle pain		
Nausea		
Chills		
Abdominal pain		

Table 5

Moderate reactions, such as chest tightness, mild wheezing or vomiting require the infusions to be discontinued. Antihistamines, aspirin, indomethacin or hydrocortisone may be used as prophylaxis or treatment for such adverse reactions. Adrenaline (*eg* Min-i-Jet) may be needed if an anaphylactoid reaction (hypotension and bronchospasm) occurs, though this is extremely uncommon with the present generation of IVIg products.

Some patients get delayed symptoms, particularly headaches or abdominal pain, within 24 hours following an infusion. These are usually mild, do not persist and respond to aspirin or paracetamol.

Rare patients with IgG subclass deficiency and complete absence of IgA may develop anti-IgA antibodies after infusion of blood, plasma or immunoglobulin containing IgA[15]. Three patients with very high and rising titres of anti IgA antibodies have been reported in whom life-threatening, anaphylactic reactions occurred after only a few millilitres of immunoglobulin containing IgA were infused[16]. IgA free material should be used for patients with very high or rising titres of anti IgA antibodies and titres should be monitored regularly.

Transmission of viruses

To date no immunoglobulin preparation has been found to transmit retroviral infection, probably due to the destruction of this group of viruses by cold ethanol during manufacture[17]. However, several preparations have been associated with outbreaks of non-A non-B hepatitis *[Table 6]*; such transmission was related to

Outbreaks of Hepatitis C [non-A non-B]
with ethanol fractionated material

UK England	1984 pilot preparation
US Seattle	1985 pilot preparation
Sweden	1988
UK Scotland	1989
Europe and US	1994

Table 6

particular batches of IVIg[18]. Since fractionation does not completely activate/eliminate this group of viruses, the transmission of non-A, non-B - including hepatitis C - viruses is probably due to the size of the inoculum. To prevent contaminated donations being used, all manufacturers are now required to test all blood donations for hepatitis C antibodies as well as HIV antibodies and HBs antigen. IVIg products are now available in which a validated step is included in the manufacturing process specifically to reduce the risk of virus transmission. Batch numbers of preparations infused into individual patients must be recorded, to enable a contaminated batch to be traced if viral transmission occurs. Testing immunoglobulin preparations for hepatitis C-RNA remains controversial at present, until reliable assays are widely available.

COMPLICATIONS OF PRIMARY ANTIBODY DEFICIENCIES

Acute infections

Despite adequate immunoglobulin therapy, breakthrough infections may occur. All patients with acute bacterial infections should receive appropriate antibiotics quickly. These should be given at the maximum dose and for longer than in immunocompetent patients and entered on the patient-held record. Both the patient and the GP should be made aware of this. Prophylactic antibiotics should only be given after consultation with the organ-based specialist. Unusual organisms may be the cause of infection. For example, acute respiratory infection or acute urethritis or cystitis may be due to mycoplasmas, which are difficult organisms to culture. In cases of genito-urinary infection, the patient and his/her partner should both be treated with appropriate antibiotics.

A feature of X-linked antibody deficiency is the rare complication of meningoencephalitis due to an enterovirus. This may present acutely but is often persistent; it is fatal in 50% of those affected. Specialist treatment, preferably in a centre with experience of this problem, is required.

Chronic disease

Chronic disease may be associated with the natural history of the condition, delayed diagnosis or inadequate therapy[4,19].

(a) Chest

All patients with persistent purulent sputum should be assessed and managed jointly with a chest physician, to prevent progressive lung damage and to monitor functional impairment[20]. A search for other causes of bronchiectasis is important to exclude their co-existence with an antibody deficiency. Despite full replacement immunoglobulin therapy, patients with chronic chest infection always require meticulous attention to additional chest treatment *eg* postural physiotherapy, antibiotics, broncho-dilators and local anti-inflammatory agents, if insidious progression of lung damage is to be arrested. Rarely non-resolving infections may be fungal; biopsy or lavage may be needed to detect these pathogens.

Discrete, often transient, shadows on chest x-rays may represent polyclonal lymphoid aggregates or granulomata. These are often asymptomatic. Their extent is best judged by a high resolution chest CT scan. Since these lesions may be present without progression for years or even decades, the patient may not require treatment specifically for these; immunosuppression is not indicated though symptomatic lesions may respond to oral corticosteroids. If lymphoma is suspected for other reasons, biopsy is necessary, particularly as CVID patients are known to have an increased risk of lymphoma[4,19]*[see Figure 7]*.

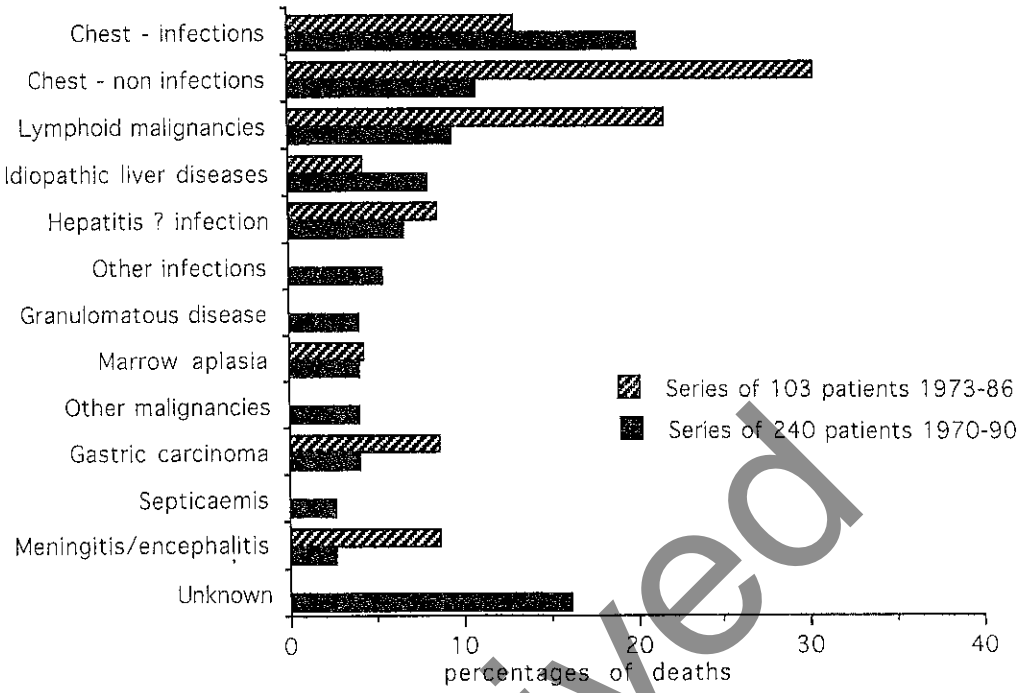

Figure 7
Causes of death in patients with common variable immune deficiency
[Data from references 4 and 19]

Patients with antibody deficiencies and their families should not smoke and all encouragement to stop should be given to those that do smoke.

(b) Sinusitis

The initial hospital presentation of adults with primary antibody deficiency is frequently with recurrent sinusitis. Such adults should have a full ENT assessment including nasendoscopy and CT scan to assess ethmoiditis and the osteomeatal complex and hence the adequacy of sinus drainage. Local therapy to the nose in the form of betamethasone nose drops (rather than a spray), used in the head down and forward position together with regular nasal douching, may help to decrease the frequency of infections. The drops must be stopped immediately if they appear to be causing irritation or hyposmia.

Early diagnosis is desirable and immunoglobulin treatment is essential, though recent reports suggest that after a late diagnosis, immunoglobulin replacement therapy does not eradicate ENT infections, possibly because of

the structural damage caused to the mucociliary system. Prolonged use of antibiotics up to 3 months has been demonstrated to improve not only symptomatology but also ciliary function in patients with chronic rhinosinusitis.

(c) ***Gastrointestinal***

Recurrent or persistent diarrhoea and/or malabsorption may be due to infection, super-infection, food-sensitive enteropathy, an autoimmune enteropathy, colitis, sclerosing cholangitis or coexistent disease *eg* Crohn's, ulcerative colitis or coeliac disease. Several, careful attempts should be made to detect a pathogen in the stool. Referral to a gastro-enterologist for further investigation and management may be required. Endoscopy may be needed to obtain appropriate biopsies which should always be stained for specific pathogens (*eg* giardia, cryptosporidia).

(d) ***Liver***

Patients with gastrointestinal complications of primary antibody deficiencies are more susceptible to naturally acquired hepatitis. Abnormal liver function tests may indicate infection with other pathogens, the presence of non-infective granulomata (as in other organs) or associated autoimmune diseases (chronic active hepatitis, primary biliary cirrhosis and sclerosing cholangitis). Persistently abnormal liver function tests require full investigation in collaboration with a liver specialist.

(e) ***Arthropathy***

Septic arthropathy may present insidiously. Chronic arthropathy/arthralgia is often sterile, transient and usually related to infection elsewhere, suggesting an immune complex aetiology. In a few patients it may be persistent especially if diagnosis and treatment have been delayed. In the absence of an obvious site of infection, patients with chronic arthropathy need thorough investigation for covert infection (bronchiectasis, abscess, *etc*) and a rheumatological opinion to consider differential diagnoses.

(f) ***Cytopenias***

Autoimmune haemolytic anaemia (AIHA) and, more commonly, immune thrombocytopenic purpura (ITP) may be acute presenting features or represent chronic complications. Treatment is the same as that in immunocompetent individuals and should be undertaken in conjunction with a clinical haematologist. Institution of replacement therapy in adequate doses (particularly in children) may resolve the cytopenia if this is infection-related; this should be tried initially. These patients are better without high dose steroids if avoidable. A course of high dose IVIg (1 G/Kg over at least 2 days) is also worth trying in ITP, though there is only anecdotal data to support this.

(g) ***Anaemia***

Some patients are prone to iron deficiency anaemia or anaemia of chronic illness. Attempts must be made to resolve which type of anaemia is present in a given patient. Iron deficiency anaemia is more frequent in those patients with diarrhoea or atrophic gastritis and may reflect inadequate absorption from a standard diet. Oral iron supplements usually overcome this and should be tried for a few months. Persistent iron deficiency needs investigation by a haematologist.

Aplastic anaemia is a rare complication and requires haematological collaboration. Some patients have responded to high dose IVIg (2G/Kg). Such immunoglobulin should be crossmatched with the patient's red cells before infusion, since some products contain relatively high titres of isohaemagglutinins (anti A or anti Rhesus D).

(h) ***Neurological***

Acute enteroviral meningoencephalitis has been discussed above. There are rare patients with chronic, persistent low grade encephalopathy, not sensitive to IVIg. Chronic cerebral granulomata may cause gradually increasing intracranial pressure. CT and NMR scanning should define the extent of the lesion. A neurological opinion is required.

(i) ***Spleen***

Thirty per cent of patients have unexplained splenomegaly. This may be idiopathic, associated with granulomata or, rarely, due to a lymphoma complicating primary antibody deficiency *(see below)*.

The only indications for splenectomy, which should be avoided if at all possible in view of the additional infection risk, are persistent and life threatening ITP or AIHA or clinical hypersplenism.

(j) ***Cancer***

The long term risk of malignant disease is about 10%. This may be gastric carcinoma or lymphoma. Lymphoma must be distinguished from aggregates of polyclonal lymphoid cells and granulomata.

MONITORING

Regular follow-up by an immunologist is essential *(see page 8)*; in patients with specific complications, shared care with an appropriate organ based specialist is necessary.

Monitoring immunoglobulin therapy

The dose and interval of IVIg replacement therapy is titrated primarily against the clinical state of the patient. This is complex and requires experience of these unusual conditions. All patients should be warned that the benefit of IVIg therapy may not be clinically apparent for several months. Serum IgG levels are measured prior to each infusion to ensure that reasonable levels are reached within a few months. Once the steady state is reached, serum IgG levels should continue to be checked regularly to ensure that IgG is not lost via the kidney, gastrointestinal tract or into inflamed tissues, even if the patient remains well. This is especially important for children, who need dose adjustment with growth. The level at which the IgG is maintained in order for the patient to stay free of infection varies between patients; a general aim is to keep the IgG concentration within the normal range for the patient's age, although a few patients may be better with higher IgG levels.

Liver function tests must be measured regularly (every 3 months) to exclude subclinical, passively transmitted hepatitis. It is important to seek help from a liver specialist if liver function tests are persistently abnormal, since a liver biopsy might be indicated in view of benefits now being shown with interferon-alpha treatment in virus-induced liver problems[21].

Monitoring infections

The use of symptom diaries by the patient can be an effective way to monitor infections *[Figure 8]*. The diaries can be "personalised" to include details of volumes of sputum production, number of bowel actions, antibiotics *etc* as appropriate; they can be kept with the patient-held records. Regular serum CRP measurements can also be helpful.

DAILY PATIENT DIARY - B

NAME

PLEASE COMPLETE ONE FORM FOR EACH MONTH.
RECORD WITH A " + " IF ANY OF THESE APPLY TO YOUR CHILD/YOU

MONTH/YEAR

DATE	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
COUGH																															
WHEEZE																															
DIARRHOEA																															
SPUTUM (WRITE Y FOR YELLOW AND G FOR GREEN) EARLY MORNING																															
SPUTUM (WRITE Y FOR YELLOW AND G FOR GREEN) LATE AFTERNOON																															
JOINT PAIN																															
SORE THROAT																															
SINUS ACHE																															
NASAL DISCHARGE																															
DAILY TEMPERATURE																															
VISITED GP																															
ON ANTIBIOTICS																															
UNFIT FOR SCHOOL OR WORK																															
ADMITTED TO HOSPITAL																															
OTHER (SPECIFY)																															

COMPLETED BY: DATE

INVESTIGATOR DATE

Figure 8
Daily diary
as used by patients with primary immune deficiencies
for monitoring infections

Monitoring disease progression

The commonest cause of death in the past has been chronic pulmonary failure *[Figure 7]*, Chest disease should be monitored in conjunction with a chest physician using pulmonary function tests and, if necessary (if the clinical need merits the radiation dose) appropriate techniques to image both structural damage and inflammatory activity within the bronchial tree, to avoid subclinical deterioration due to insufficient antibody replacement. It is important to note that even with optimal antibody replacement therapy, chest damage may insidiously progress unless full ancillary chest treatment is instituted.

Regular endoscopic examination (every 6 - 12 months) of the nose and sinuses should be undertaken in those with chronic sinus disease. Routine plain sinus x-rays are not helpful, but can aid the diagnosis of acute maxillary sinusitis when a fluid level is present. Repeat CT scans are not advisable routinely, but can be repeated if surgery is contemplated or complications such as abscesses are suspected.

SPECIAL NEEDS OF PATIENTS

Community liaison

Unless a practitioner has a patient with an identified immune deficiency, their awareness of different types of conditions may be sketchy or heavily biased by the literature on HIV disease. When a patient is diagnosed with an antibody deficiency, it is important for everyone involved, the patient, general practitioner, district nurse, as well as the referring consultant, to be sent the appropriate literature on primary antibody deficiencies *[Figure 9]*. Information on the following is included:

- Primary antibody deficiencies are not contagious conditions
- The risk of breakthrough infections even with immunoglobulin treatment, and the need for rapid and sustained antibiotic therapy to compensate for lack of immunity
- Adverse reactions to immunoglobulin therapy
- Very low risk of transmission of viruses by immunoglobulin
- Need for specialist immunology follow-up and availability of local immunoglobulin services
- Contribution of physiotherapists to those with chronic chest disease
- The differences between primary antibody deficiencies and other immune compromised patients (due to immunosuppressive drugs, HIV or post splenectomy)

The patient held records are available from the specified Immunology Centres; they include details of diagnosis, dose and route of immunoglobulin therapy and possible side-effects.

Support for patients - PiA

The patient support organisation - the PiA - provides literature to members and non-members *[see figure 9]*. This covers a range of information, from practical help in understanding and accepting the condition, to overviews of similar states and contact names for support.

PiA address: Primary Immunodefiency Association
Alliance House
12 Caxton Street
London SW1H 0QS Tel: 0171 976 7640
Fax: 0171 976 7641

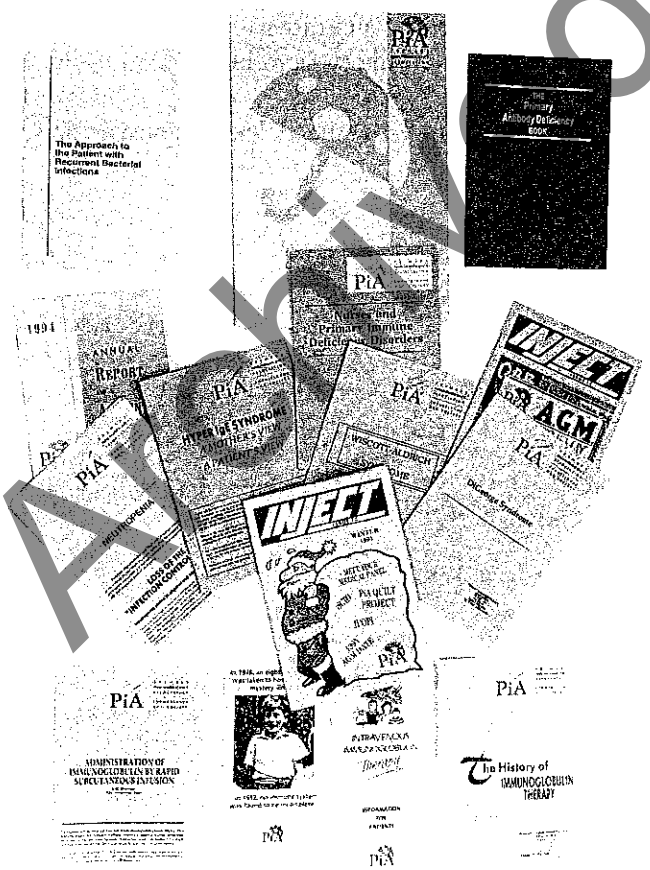

Figure 9
Literature available from the Primary Immune Deficiency Association

Guidelines for self infusion of immunoglobulin (home therapy)

The low incidence of adverse reactions with current IVIg preparations and the ability to take measures to prevent such reactions has enabled self-infusion at home to be undertaken safely[22]. Such "Home Therapy" programmes are available in specified centres *[see Figure 10]*. Guidelines for Home Immunoglobulin Therapy have been approved by the professional medical bodies and by the Department of Health and recently up-dated. Patients in the UK must be formally trained in a recognised centre, the numbers of which are increasing. It is hoped that home therapy programmes will be available in Wales and Scotland before too long. A register of all trained patients is held in Oxford.

Self infusion at home provides vastly greater convenience for the patient, who avoids travel to and from the hospital as well as time off work. Patients also have a greater involvement in their therapy and disease, giving increased self esteem and confidence. It also enables infusion intervals to be reduced to weekly if necessary.

Home therapy has been shown to be a much less expensive option than hospital based infusions[9].

AWARENESS OF CONDITION

An important component of management is increasing both the patient's and the community's awareness of the disease. Self administration serves as a stimulus but all patients must be informed of the risks and benefits of replacement immunoglobulin. Patients should be made aware of the PiA, and given an invitation to join.

Centres for home therapy for immunoglobulin replacement

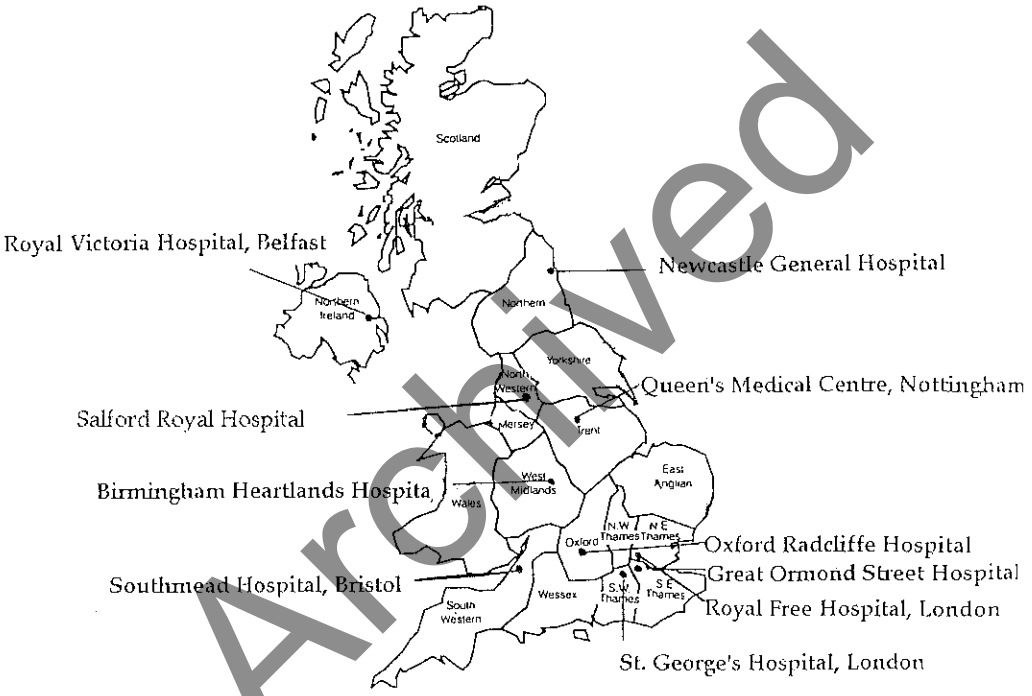

Figure 10

FUTURE

Audit

Currently a nationwide audit *(Organiser: Dr G Spickett, Liverpool)* has been funded to determine the incidence and extent of diagnostic delay, the extent of inadequate replacement therapy, and the possibly medical consequences. However, audit is only useful for those patients already registered on the UK PiD register. The under-diagnosis and lack of awareness of the register will make such audit incomplete. We hope that these guidelines will improve the situation and that a review of the register in 2 years will show an increase in cases diagnosed and notified.

Replacement by subcutaneous route

Rapid subcutaneous immunoglobulin infusions have been used in both adults and children. A European collaborative group is investigating the use of such infusions in children. A multi-centre study in adults is also underway in Europe to compare the efficacy of such infusions with IVIg in adults.

Research on immunopathogenesis

The European Society for Immunodeficiencies is a collaborative group of scientists and clinicians; it provides a forum for shared research and dissemination of ideas and information. Several UK members are active participants at the regular two yearly meetings.

The PiA collects monies to fund research and awards financial grants each year after peer review of the current applications. The PiA is a founder member of the International Patient Organisation for Primary Immunodeficiencies (IPOPI).

* * * * *

This document has been approved by the following professional bodies:

Royal College of Pathologists
Royal College of Physicians
Royal College of Surgeons
Royal College of Nursing
Royal College of General Practitioners
Association of Clinical Pathologists
British Society for Immunology
British Society of Laryngology
British Thoracic Society

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