Edition ***1***

APRIL 2007 – NOVEMBER 2007

The Compendium
of
IMMUNOLOGY

CONSENSUS GUIDELINES OF THE TRENT IMMUNOLOGY & ALLERGY CONSORTIUM

EDITED BY: W A C SEWELL

IMPORTANT INFORMATION ABOUT THESE GUIDELINES

This document represents the consensus opinion of the Consultant Immunologists and Immunology Specialist Nurses of the Trent Immunology & Allergy Consortium.

Local variation to these guidelines may have been appended, and will be identified as such

These constitute guidelines for the diagnosis/management of the condition stated, for use by immunology doctors and nurses within TRIAC

Clinical judgement supersedes these guidelines whenever necessary

CENTRE: _____

CONSULTANT: _____

Operational on: _____

Withdrawn on: _____

This is copy number: _____ **of copies** _____

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Using TRIAC Guidelines in the Compendium of Immunology

INTRODUCTION

The Trent Immunology & Allergy Consortium (TRIC) produces consensus guidelines for use by Immunology Doctors and Nurses in the diagnosis and management of patients with primary immunodeficiencies. These guidelines are published every six months as the *Compendium of Immunology*. This guideline details how and when new guidelines are produced.

WHEN NEW GUIDELINES ARE PRODUCED

Guidelines are produced following discussion at regular meetings of the TRIAC medical and nursing staff. Draft Guidelines are marked 'uncontrolled' and can be freely circulated for consultation. Following acceptance by the group, Guidelines become 'operational' and should be 'controlled' by only using the material within the current edition of the *Compendium*. Expired editions of the *Compendium* archived.

ETHOS OF THE GUIDELINES

1. These documents represent the consensus opinion of the Consultant Immunologists of the Trent Immunodeficiency Consortium.

2. Local variation to these guidelines may apply, and will be clearly marked on that centre's copies as a 'local variation'.

3. These constitute guidelines for the diagnosis/management of the condition stated, for use by immunology doctors and nurses within TRIAC

4. Clinical judgement supersedes these guidelines whenever necessary.

DOCUMENT CONTROL

'Operational' documents are currently in effect for the diagnosis and management of primary immunodeficiency patients in the Consortium. One designated doctor or nurse in each centre is responsible for making sure that only the latest versions of the *Compendium* are available for clinical use. This person is the 'Document Controller'.

Using the *Compendium*:

1. Download the pdf of the *Compendium of Immunology* from the TRIAC website
2. Customise the generic Guideline for local use by:

- Adding the name of your Centre
- Adding the name and designation of the Consultant in administrative charge in each centre
- Adding any local variation to the guidelines, and marking them clearly as a 'local variation'. An example would be the storage location of particular drug, which will be held in different places in each centre.
- Printing out the required number of copies and numbering each one.

The *Compendium* has a clearly-marked expiry date; hence it is important for the designated Document Controller at each site to keep clinical areas supplied with the latest version.

Producing the next edition of the Compendium

The next edition of the *Compendium* is circulated as a Word document for each TRIAC Centre to edit prior to formal acceptance at the TRIAC meetings.

Overview of the Trent Immunology & Allergy Consortium (TRIAC)

BACKGROUND

Leicester, Nottingham, Sheffield, Hull and Path Links (covering Greater Lincolnshire) all have well established Immunology Departments offering diagnostic and therapeutic services for immunodeficiency and allergy patients, and are recognised as Home Therapy Centres for immunoglobulin replacement therapy. Long-established links exist between the departments. The formation of TRIAC represents a formalisation and extension of these links in line with the Modernisation of Pathology and Clinical Networking.

Aims of TRIAC

Accreditation as Primary Immunodeficiency Centres
Continued improvement of the current locally accessible, diagnostic and therapeutic services and sharing of expertise by:

- Standardisation and optimisation of evidence-based clinical guidelines and practice
- Promotion of audit and research on a large cohort of patients with rare conditions, and provision of local evidence-based management data.
- Broadening the training experience of the Specialist Registrars, Immunology Nurse Specialists, Clinical Scientists and Consultants by optimising experience in the management of rare conditions
- Provision of continuous telephone cross cover for medical and nursing staff
- Participation in the larger UK Primary Immunodeficiency Network (UKPIN) as accredited centres for Primary Immunodeficiency
- Development of local patient registries (compatible with the developing UK and international registries).
- Maintaining security of crucial immunoglobulin supplies, which are currently threatened by world shortages.
- Informing patients of the developments in primary immunodeficiency and allergy and including patients in the development of clinical services
- Involvement of Expert Patients in service provision

Drivers for change / advantages of TRIAC

Clinical governance agenda – improving quality of services, development of shared evidence-based guidelines, national accreditation as specialist centres of expertise, specialist commissioning, improved clinical audit etc.
Funding issues – TRIAC would be in a good position to access national funding through specialised commissioning. Additionally, shared purchasing e.g. for immunoglobulin or C1 Inhibitor would help ensure the best price. This should also help secure regular supplies of immunoglobulin in the face of the current and worsening world shortage.
Establishing an effective regional Clinical and Laboratory network.
Training and education benefits for both scientists, medical (junior and senior) and nursing staff.
Improving equity and quality of clinical care for patients

Current stage of development

Regular minuted meetings – audit, case presentations
Development of shared evidence-based guidelines
Preparations for service accreditation

Patient Literature

INTRODUCTION

Reading material on primary immunodeficiencies and updates on therapeutics should be available for patients and staff. This literature should be informative to allow patients a greater understanding of their particular illness and for dissemination to their carers/friends/relatives. Written information on therapeutic options should help patients decide on the validity and necessity for any given treatment. The literature for healthcare workers should include standard reference texts and journals for staff in the PID service, as well as "take away" literature that may be given to allied healthcare workers meeting these patients in other contexts

Patient based literature is distributed by the Immunology team on request and where appropriate.

All patients are offered a relevant selection of literature.

Patient Based Literature

It is important that available material is factually correct, unbiased and in a digestible format & language.
Where possible, material should be made available in the patients native language. When this does not exist the patient may be referred to the hospital interpreter service if needed.

Information should be available from patient support groups, public funded information resources.

Material from sources (e.g. PIA) that are known to use a medical advisory panel to screen for accuracy are preferred.

Other information sources may be made available, but patients should be encouraged to discuss the content with medical and nursing teams, and an attempt made to offer them a balanced range of written information.

The available literature should be regularly reviewed by the Immunology Team for appropriateness.

Research Literature

The local ethics committee must first approve all information for patients pertaining to clinical trials, current or proposed.

Overview of Immunoglobulin Therapy

INTRODUCTION

Immunoglobulin replacement reduces infections in patients with significant antibody deficiencies. This type of therapy has significant potential side effects and therefore the risks and benefits should be considered on an individual basis. The following provides an overview; additional information is detailed in other protocols.

INDICATIONS FOR IMMUNOGLOBULIN REPLACEMENT THERAPY

Immunoglobulin replacement should be considered for patients in whom there is both laboratory and clinical evidence of antibody deficiency. Immunoglobulin therapy is accepted as the treatment of choice in the following disorders:

X linked agammaglobulinaemia
Common Variable Immunodeficiency
Hyper IgM Syndrome
Severe Combined Immune Deficiency (as an adjunct to BMT)
X linked lymphoproliferative disease
Wiskott Aldrich Syndrome

There is also evidence that immunoglobulin replacement may benefit some patients with other primary immunodeficiencies (eg IgG subclass and specific antibody deficiency) or secondary immunodeficiencies (eg paediatric HIV infection, CLL, myeloma). Typically this group will have both laboratory and clinical evidence of antibody deficiency, and have failed an initial trial of antibiotic prophylaxis. In these patients immunoglobulin therapy will be initiated as a finite trial, using objective outcome measures to assess efficacy, with periodic review if treatment continued.

SIDE EFFECTS

Acute side effects:

Common side effects include rigors, urticaria and fever and may improve when rate of infusion is slowed or, sometimes, when product or route is changed. This type of side effect is more common when patients have active infection. Infusions may need to be delayed a few days in patients with active infection. Some reactions have been attributed to anti-IgA antibodies and presence of IgA in the immunoglobulin product.

Less common side effects include aseptic meningitis.

Transmission of infection

Viral Hepatitis: Hepatitis C has been associated with transmission in patients receiving immunoglobulin. Since the last outbreak in 1994, improved safety measures have been developed and introduced, including better testing, additional anti-viral steps. There are no reports of Hepatitis B transmission. Monitoring of LFTs, Hepatitis BsAg and Hepatitis C PCR should aid early detection of any outbreak.

HIV infection has not been transmitted by immunoglobulin to date and testing and viral inactivation procedures are known to be effective in prevention of transmission.

The prion responsible for vCJD may in theory be transmitted by blood products although is although the risk is likely to be extremely low in acellular products. There is currently no evidence to support the transmission of vCJD via immunoglobulin. However patients presenting with appropriate signs and symptoms should be investigated for spongiform encephalopathies. Consideration should also be given to obtaining permission for post-mortem examination of the brain in any patient who has received immunoglobulin.

Immunologists should also be alert to the possibility of transmission of other known or currently unknown infectious agents. Recording of batch numbers and long-term storage of serum should aid future investigation of possible outbreaks. Such records should be kept in line with pharmacovigilence legislation; computerised records are encouraged for rapid identification of contaminated batches.

DOSE AND ROUTE OF IMMUNOGLOBULIN THERAPY

The usual recommended dose is 400mg/kg/month given in divided doses – typically 3 weekly for intravenous replacement and weekly for subcutaneous replacement. However the dose and interval should be adjusted to suit individual patients based on

trough immunoglobulin levels, frequency of infections, development or progression of end organ damage eg bronchiectasis and other measures such as growth in children.

In adults, a minimum trough IgG level of 6g/l is generally considered adequate but higher levels may provide further benefit in some patients. In patients with specific antibody deficiency, trough functional antibody levels can be helpful.

Route: intravenous or subcutaneous (the intramuscular route is not recommended for immunoglobulin replacement therapy).

INITIATING IMMUNOGLOBULIN TREATMENT

The following issues should be considered and discussed with patients prior to initiating immunoglobulin therapy:

Indication for immunoglobulin therapy
Benefits of treatment should be discussed including likely time-scale. Patients should be warned if there are aspects of their illness which are unlikely to improve.
Risks of treatment should be discussed including adverse reactions and potential for transmission of infection. Steps taken to reduce these risks should also be discussed (eg avoiding infusions during acute infection, infusion rates, monitoring procedures, steps taken by manufacturers etc)
Planned duration of therapy ie life-long or a finite trial
Planned dose and route of administration
Home therapy will be discussed in suitable patients
Written consent must be obtained before initiating treatment
All patients must be given written information about immunoglobulin replacement and contact details for patient support groups such as the Primary Immunodeficiency Association.

MONITORING IMMUNOGLOBULIN THERAPY (see also other guidelines)

Blood should be taken regularly prior to immunoglobulin infusions no less than 3 monthly.

- Liver function tests
- Trough IgG level
- CRP

Additional bloods (at least annually unless specified):

- Functional antibodies in selected patients 3 monthly
- Full blood count (and haematinics as required)
- Anti-IgA antibodies (if serum IgA is below lower limit of detection and in other patients if required)
- Hepatitis BsAg and Hepatitis C PCR
- Store serum

Clinical review (at least 6 monthly) including assessment of frequency of infections, weight (and height in children) and general well being using diary charts and infusion logs where appropriate.

Appropriate samples for microbiology should be sought where possible.

Pulmonary function tests (spirometry, lung volumes and transfer factor) at least every two years and more frequently if required.

Batch numbers of immunoglobulin should be recorded

All adverse reactions should be recorded and investigated as appropriate.

Diagnosis & Management of Common Variable Immunodeficiency

INTRODUCTION

Common Variable Immunodeficiency Disorders (CVID) are a collection of poorly understood conditions, with increased risk of infections in all, and autoimmune and granulomatous diseases in some patients. The prevalence of disease is about 1 in 20,000. Specific genetic disorders continue to be identified within this group. Ninety-five per cent of cases are diagnosed after the age of 5. A recent UK audit found only 50% of the expected number indicating that this condition is still under-diagnosed.

CLINICAL FEATURES

Patients usually present with recurrent bacterial infection secondary to encapsulated organisms. Gastro-intestinal infection, bacterial conjunctivitis, boils, abscesses and herpes zoster are also common. Approximately 20% of patients have an autoimmune disorder, the commonest being thrombocytopenic purpura and thyroid disease. About a quarter of patients have granulomatous disease involving the lungs, liver, spleen and skin, and are probably a distinct subgroup.

The main complications of CVID include bronchiectasis and chronic sinusitis. There is an increased risk of B cell lymphoproliferative disease (34 fold excess) and gastric carcinoma (50 fold excess).

DIAGNOSTIC CRITERIA

Diagnostic criteria have been drawn up by the Pan-American Group for Immune Deficiencies and the European Society for Immune Deficiencies (Clin Immunol 1999, 93 p190-197).

Probable CVID
Male or female patient who has a marked decrease of IgG (at least 2 SD below the mean for age) and a marked decrease in at least one of the isotypes IgM or IgA, and fulfills all of the following criteria:

- Onset of immunodeficiency at greater than 2 years of age
- Absent isohaemagglutinins and/or a poor response to vaccines.
- Defined causes of hypogammaglobulinaemia have been excluded (see table).

Possible CVID
Male or female patient who has a marked decrease (at least 2 standard deviations below the mean for age) in one of the major isotypes (IgM, IgG and IgA) and fulfills all of the following criteria:

- Onset of immunodeficiency at greater than 2 years of age.
- Absent isohaemagglutinins and/or poor response to vaccines.
- Defined causes of hypogammaglobulinaemia have been excluded (see table).

Table of defined causes of hypogammaglobulinaemia

Drug induced
- Anti-malarial agents
- Captopril
- Carbamezepine
- Glucocorticoids
- Fenclofenac
- Gold salts
- Penicillamine
- Phenytoin
- Sulphasalazine

Genetic disorders
- Ataxia telangiectasia
- Autosomal forms of SCID
- Hyper IgM immunodeficiency
- Transcobalamin II deficiency and hypogammaglobulinaemia
- X-linked agammaglobulinaemia
- X-linked lymphoproliferative disorder (EBV associated)
- X-linked SCID

Some metabolic disorders

Chromosomal anomalies
- Chromosome 18q- syndrome
- Monosomy 22
- Trisomy 8
- Trisomy 21

Infectious diseases
- HIV
- Congenital rubella
- Congenital infection with CMV
- Congenital infection with toxoplasma gondii
- Epstein-Barr virus

Malignancy
- Chronic lymphocytic leukaemia
- Immunodeficiency with thymoma
- Non-Hodgkin lymphoma
- B cell malignancy

Systemic disorders

Immunodeficiency caused by hypercatabolism of immunoglobulin

Immunodeficiency caused by excessive loss of immunoglobulins (nephrosis, severe burns, lymphangiectasia, severe diarrhoea)

DIFFERENTIAL DIAGNOSIS

The principal differential diagnosis lies between other causes of primary antibody deficiency (especially in younger patients) and secondary causes of hypogammaglobulinaemia (especially in older individuals).

Other primary immunodeficiencies should be considered especially if there is early onset of symptoms and/or a suggestive family history.
X-linked agammaglobulinaemia
CD40 ligand deficiency
X-linked lymphoproliferative disease
Haematological malignancies especially in adults
CLL, NHL, myeloma, thymoma etc
Protein losing enteropathy / nephrotic syndrome
Drugs eg anti-convulsants, disease modifying anti-rheumatic drugs. corticosteroids

INVESTIGATIONS

Investigations should include:

- Serum immunoglobulins
- Serum and urine electrophoresis
- All individuals with an IgG > 3 g/l should have:
- Specific antibodies to tetanus, Hib and pneumococci
- IgG antibodies to previous infections and/or immunisations such as; hepatitis B, meningococcus C, measles, rubella, CMV, VZV, EBV, as appropriate.
- IgG subclasses (in selected individuals)
- If specific antibody responses are low, providing the clinical situation allows it, test immunisations (such as tetanus toxoid, pneumovax, Hib) should be given. Post immunisation blood samples should be taken after 4 weeks. **NB live vaccines must NOT be given.**
- Anti-IgA antibodies if IgA below local limit of detection, and in others if indicated
- Lymphocytes subsets including T, B and NK cell numbers
- Memory B cell subsets as indicated.

Consider specific identified defect if test available

- Liver function tests, urea & creatinine, calcium
- Urine analysis
- Full blood count and film
- Pulmonary Function test
- Microbiology and imaging (HRCT chest) as clinically indicated
- Investigation to exclude secondary causes as indicated.

GENERAL MANAGEMENT

Early diagnosis and treatment result in better outcome as measured by lifespan, quality of life and reduced morbidity.
The mainstay of treatment is immunoglobulin replacement therapy.
Patients with bronchiectasis need regular chest physiotherapy and antibiotics as appropriate.
Bacterial infections need prompt, full-dose, antibiotics for longer periods than in immunocompetent patients – GP's and patients need to be advised about this and should be given the relevant TRIAC Information Leaflets as appropriate.
Granulomatous disease usually responds to low dose steroids.
Immunisations – decisions should be made on consideration of the individual case and after referral to current guidance such as BNF and others e.g. "Immunisation of the Immunocompromised Child".
Influenza vaccine may be given but benefit unknown.

IMMUNOGLOBULIN REPLACEMENT THERAPY

Immunoglobulin can be given intravenously (usually every 2-3 weeks) or subcutaneously (often once or twice weekly). The usual starting dose of Immunoglobulin is 0.4 g/kg/month for uncomplicated disease and can be increased if clinically indicated. Loading doses may be given to bring the trough level within the normal range in the first 6 weeks if required.

Before starting treatment, the benefits and risks associated with immunoglobulin therapy should be discussed with the patient and written, informed, consent obtained. Baseline immunological investigations include Hepatitis C PCR, Hepatitis B surface Ag, long-term serum storage with specific written consent for look-back testing (for known and currently unknown infectious agents), (See also other relevant TRIAC guidelines).

HOME THERAPY

Patients can be trained to give Immunoglobulin infusions at home. Patients must be formally assessed for suitability before being accepted on the Home programme (see Assessment for Home Therapy check list).

FOLLOW-UP

Patients with CVID need follow up to:

- **Assess the efficacy of treatment**.
- **Assess overall health**
- Social / educational / psychological issues etc
- **Monitor for complications of treatment**
- Reactions
- Transmissible agents
- **Monitor for complications of disease**
- Infectious eg bronchiectasis, sinusitis, conjunctivitis etc
- Autoimmune eg cytopenias, thyroid, diabetes etc
- Granulomatous disease
- Enteropathy
- Neurological disease
- Malignancy including lymphoma

ROUTINE INVESTIGATIONS / ASSESSMENT

Blood should be taken prior to Ig infusion at least 3 monthly basis:

- Liver function tests
- Trough IgG level
- CRP

Additional bloods (at least 12 monthly):

- Full blood count (and haematinics as required)
- Anti-IgA antibodies if required. – National Blood Service, Sheffield
- Hepatitis BsAg and Hepatitis C PCR
- Save serum for look-back testing (with record of ongoing informed consent as per guideline)

Assessment of frequency of infections and general well-being

Appropriate samples for microbiology should be taken where possible.

Pulmonary function tests (e.g. spirometry, lung volumes **and** transfer factor) as required.

Imaging (eg CXR, HRCT) as indicated clinically.

All patients should be offered contact details of patient support groups such as the Primary Immunodeficiency Association (PIA) who can provide invaluable support and advice to patients and families.

ENT Services

INTRODUCTION

Patients with primary immunodeficiencies (especially antibody deficiencies) are particularly susceptible to bacterial infections in the upper respiratory tract and may present initially to ENT. Once diagnosed and on adequate immunoglobulin replacement therapy, these infections should decrease, although complete control of chronic sinus infections may not be possible with IVIG alone.

MANAGEMENT

Breakthrough infections
Consider the possibility of unusual pathogens eg fungi especially in chronic granulomatous disease, combined immunodeficiencies.
Treat with an appropriate antibiotic (eg co-amoxiclav) for 14 days, according to local infection control/antibiotic policies

Recurrent episodes of bacterial sinusitis
Consider trial of nasal corticosteroids in addition to antibiotics.
Consider referral to ENT for consideration of further investigation / management if infections continue (eg more than 4 episodes in 12 months).

Allergic rhinitis
Allergen avoidance
Treat with anti-histamines and/or nasal corticosteroids

USUAL CONTACTS

Leicester: Children: Mr A Moir, Leicester Royal Infirmary. Adults: no named consultant at present

Nottingham: Professor N Jones, Queen's Medical Centre (both adults and children)
Mr A Sama, Queen's Medical Centre (both adults and children)

Sheffield: Mr T Woolford, Royal Hallamshire Hospital (both adults and children)

Path Links: On call ENT surgeon

Hull: Prof N Stafford

Gastroenterology Services

INTRODUCTION

Patients with primary immunodeficiencies are at increased risk of gastrointestinal problems.

Antibody deficient patients are at risk of:

- gastrointestinal infection (*C. difficile*, salmonella, campylobacter, giardia)
- non-specific colitis
- nodular lymphoid hyperplasia in the gut
- atrophic gastritis of the stomach
- malignancy – lymphoma, gastric carcinoma
- bacterial overgrowth
- mouth ulcers
- subtotal villous atrophy usually unresponsive to a gluten free diet
- malabsorption resulting in osteomalacia, vitamin E deficiency (ataxia) or vitamin A deficiency (adenovirus infection of the cornea)

T cell deficient patients are at risk of:

- gastrointestinal infection as above but also atypical organisms e.g. CMV, cryptosporidiosis
- neuroendocrine tumours (CD40 ligand deficiency)

Chronic granulomatous disease patients are at risk of:

- inflammatory bowel disease
- gastric outlet obstruction

INVESTIGATION / REFERRAL TO GASTROENTEROLOGY

This should be tailored to the clinical picture and needs of the individual patient and local expertise.

In patients with diarrhoea:

Investigate for infection –
Send stool samples for microscopy and culture
Giardia is common in antibody deficiency and is often not detectable on stool samples. Therefore if this is suspected clinically a therapeutic trial of metronidazole or tinidazole should be considered. Where necessary, the diagnosis can be confirmed on jejunal biopsy.

Cryptosporidiosis should be considered in hyper-IgM syndromes and other combined immunodeficiencies, antigen/PCR testing requires analysis at the reference laboratory (arrange via microbiology department)
FBC and haematinics
CRP
LFTs and bone biochemistry
Initiate investigation for malabsorption if diarrhoea is persistent
Clotting screen (if evidence of liver disease or biopsy considered)
Biopsy – if this is required contact histopathology, microbiology/virology in advance if special tests/stains/molecular biology may be required.

CONTACTS

Leicester: Adults – Dr A Grant, Leicester Royal Infirmary. Children – Dr M Green, Leicester Royal Infirmary

Nottingham: Adults - Prof Y Mahida, Queen's Medical Centre. Children – Dr C Charlton, Queen's Medical Centre

Sheffield: Adults – Dr M Donnolly, Northern General Hospital. Children – Prof C. Taylor, Sheffield Children's Hospital

Hull: Dr H Tsai (adults), Castle Hill Hospital Dr Azaz (children) HRI

Path Links: On call gastroenterologist

Genetics Services

INTRODUCTION

Many primary immunodeficiencies have an identified genetic basis. The initial diagnosis and explanation is often given to patients and their families by Immunology. However further counselling and support from Genetics may be of significant benefit to these patients and their families especially in helping asymptomatic individuals / possible carriers to decide on whether or not to undergo testing, and if so, when. Referral to genetics services should be offered to all suitable patients and their families.

CONSENT FOR GENETIC TESTING

Consent should be obtained according to current appropriate protocols (NB this is a changing area – check for up to date details)

WHO SHOULD BE REFERRED

All patients (or parents / carers) should be informed of the genetics service and referred if they so wish (both patients and family members)
Geneticists and Obstetricians should be involved where pre-natal diagnosis is being considered.

REFERRAL LETTERS

It is important that referral letters include the following information:

- Details of the immunodeficiency – nature, prognosis, treatment
- Indicate if other family members are likely to be more / less severely affected than the index patient
- Details of the genetics – inheritance, mutation identified
- How to arrange testing (analysis is usually available via Great Ormond Street Hospital)

REFERRALS INTO IMMUNOLOGY

Links with genetics and paediatric services should be encouraged to allow referral of immunodeficient patients into the immunology services.

CONTACTS

Leicester: Dr M Barrow, Clinical Genetics Department, Leicester Royal Infirmary

Nottingham: Dr S Ritchie, Clinical Genetics Department, Nottingham City Hospital

Sheffield: Dr O Quarrell, Clinical Genetics Department, Sheffield Children's Hospital

Hull: Dr Y Crow, HRI/Leeds

Path Links: Dr Y Crow, HRI/Leeds

Hepatology Services

INTRODUCTION

Patients with primary immunodeficiencies are susceptible to iatrogenic disease (transmitted disease from therapy with blood products) and other liver diseases.

Liver disease associated with blood products:

Routine monitoring of all patients receiving blood products should be carried out in accordance with protocols for immunoglobulin replacement (recording of blood product batch numbers, regular liver function tests, regular checking of Hepatitis B surface antigen and HCV-PCR and long term storage of serum to allow retrospective testing.

Recently raised ALT/GGT (twice the upper limit of normal) on 2 occasions in the absence of haemolysis/delay in transport suggests possible viral transmission.
Hepatitis B surface antigen, HCV-PCR and any other appropriate tests should be done as soon as possible (liase with virology)
Check other patients' records to ensure no other cases have been overlooked.
If virus present – immediate referral to the hepatology service for assessment and liver biopsy. Also need to take urgent measures to prevent further transmission and identify other patients at risk.
Check batch numbers and product of affected patients, and review other possible modes of transmission.
Alert the manufacturer if an outbreak is *suspected*.
Alert hospital clinical risk manager, Senior Pharmacist, Medicines and Healthcare Regulatory Agency, as soon as possible if outbreak *confirmed*.

Other liver disease associated with immunodeficiency:

- Infection
- Liver abscesses in chronic granulomatous disease
- Cryptosporidiosis and sclerosing cholangitis are a major cause of morbidity and mortality in the hyper IgM syndrome – all such patients should receive written advice on cryptosporidiosis avoidance.
- Granulomatous liver disease – in common variable immunodeficiency
- Graft versus host disease – in patients treated with bone marrow transplant.
- Lymphoma / other malignancy
- Lymphoma is increased in most antibody and T cell immunodeficiencies
- Hepatoma, biliary tract and neuroendocrine tumours are found in hyper IgM syndrome and hepatomas in patients on long term androgenic steroids.

Investigations:

- Repeat liver function tests
- Clotting screen
- CRP
- Microbiology
- HCV-PCR, HBsAg, others as indicated
- Stool for cryptosporidiosis in hyper IgM syndrome (antigen and PCR tests may be needed)
- Liase with virologists / microbiologists as necessary
- Consider alpha-fetoprotein, blood film and lymphocyte markers if malignancy suspected
- Consider need for imaging
- Other investigations as indicated

CONTACTS

Leicester: Adults – Dr A Grant, Leicester Royal Infirmary. Children – Dr M Green, Leicester Royal Infirmary

Nottingham: Adults – Dr S Ryder, Queen's Medical Centre. Children – Dr C Charlton, Queen's Medical Centre

Sheffield: Adults – Dr D Gleeson, Royal Hallamshire Hospital. Children – Professor C Taylor, Sheffield Children's Hospital

Hull: Adults - Dr H Tsai, Castle Hill Hospital Children - Dr Azaz, HRI

Path Links: On call gastroenterologist

Lymphoproliferative Services

INTRODUCTION

There is an increased risk of malignancy in:

- Common variable immunodeficiency
- Lymphoma
- Gastric carcinoma
- CD40 ligand deficiency
- Lymphoma
- Neuroendocrine tumours
- Hepatobiliary malignancies
- Wiskott Aldrich Syndrome
- Lymphoma
- Ataxia Telangiectasia
- Lymphoma/leukaemia (especially T cell)
- X-linked Lymphoproliferative disease
- Lymphoma – usually B cell, especially extra-nodal eg ileo-caecal
- Other immune deficiency states

However in some disorders there may be non-malignant lymphoproliferation:

- Common variable immunodeficiency
- Interstitial lymphoid pneumonitis
- Non-caseating granulomata
- Gastrointestinal lymphoid hyperplasia
- XLP
- CD40 ligand deficiency

PRESENTATION

Possible modes of presentation include:

- Persistent or increasing lymphadenopathy
- Extra nodal lymphoproliferation i.e. skin, gut, lungs without an obvious cause which persist for >3weeks.
- Night sweats, weight loss

INVESTIGATION

The range of investigations required should be decided on in the light of the clinical picture in the individual patient. Where there is strong clinical suspicion of malignancy, referral should be in line with national Cancer Guidelines.

Haematology
FBC and blood film
Bone marrow examination
Additional tests are required eg kappa/lambda staining, EBV studies

Chemistry
Calcium
Lactate dehydrogenase +/- β_2 microglobulin
Renal and liver function

Immunology
Analysis of appropriate lymphocyte subsets
CRP
Serum immunoglobulins & electrophoresis +/- β_2 microglobulin
Urine electrophoresis/serum free light chain estimation
Serum and/or urine immunofixation

Imaging
CXR, ultrasound, CT , MRI, or other as appropriate

Histology
Biopsy – node / extra nodal site
Contact appropriate departments to arrange specialist tests eg immunocytochemistry, EBV studies, molecular (eg TCR, IgH gene rearrangement) studies where appropriate.

Virology
Urinary CMV early antigen where appropriate.
Appropriate samples for EBV-PCR, CMV-PCR
EBV and CMV serology where appropriate

Other
Consider possibility of XLP where appropriate – send to Great Ormond Street Hospital
TCR / Immunoglobulin gene rearrangement studies
See below for contacts for arrangement

CONTACTS

LEICESTER:

Paediatric Haematological Malignancy / Oncology: Dr M Madi, Leicester Royal Infirmary

Adult Haematological Malignancy: Prof M Dyer, Leicester Royal Infirmary

Histopathologist with interest in lymphoproliferative disease: Dr K West, Leicester Royal Infirmary

Molecular tests IgH and TCR rearrangements – Dr K West, Histopathology, Leicester Royal Infirmary

NOTTINGHAM:

Paediatric Haematological Malignancy & Oncology: Prof D Walker, Queen's Medical Centre

Adult Haematological Malignancy: Dr A Haynes, Nottingham City Hospital, Dr A McMillian, Queen's Medical Centre

Histopathologist with interest in lymphoproliferative disease: Dr D Clark, Queen's Medical Centre

Molecular tests CR - Ms N Richards/ Dr P Tighe, Queen's Medical Centre. IgH gene rearrangement studies - arrange via Mr A Deardon, Haematology, Queen's Medical Centre

SHEFFIELD:

Paediatric Haematological Malignancy & Oncology: Dr M Gerrard, Sheffield Children's Hospital

Adult Haematological Malignancy: Dr D Winfield, Dr J Rielly, Royal Hallamshire Hospital

Molecular Studies: Dr J Rielly, Royal Hallamshire Hospital

HULL:

Adults Dr M Shields
Paediatrics Leeds
Histopathology – HMDS Leeds

PATH LINKS:

Refer to local haematologist for management issues
Dr David Clark, Histopathology, Grantham for analytical issues, and HMDS

Ophthalmology Services

INTRODUCTION

Infective conjunctivitis is a feature of primary antibody deficiency. The infective organism is usually *Haemophilus influenzae* but occasionally *Staphylococcus aureus*. Patients complain of sticky eyes (especially in the early morning). Soreness and conjunctival injection are common features. The prevalence is 10 – 25% of patients with any form of primary antibody deficiency. It is usually mild but some patients develop permanent corneal damage.

Patients with malabsorption/diarrhoea may become vitamin A deficient. This predisposes to severe adenovirus infection of the cornea that is responsive to vitamin A injections.

Patients with T cell defects are at risk of opportunistic infections e.g. CMV retinitis, VZV

CONJUNCTIVITIS IN ANTIBODY DEFICIENCY

Investigation
Send swabs for bacterial culture and sensitivity
Consider sending additional swabs for viral culture
Consider checking vitamin A levels if adenovirus isolated and malabsorption suspected

Management
If symptoms present for less than 5 days treat with 7 day course of topical chloramphenicol
If symptoms present despite the above treatment, seek advice from Microbiologist.

Consider referral to Ophthalmologists for:

- Persistent symptoms despite treatment
- Frequent episodes of conjunctivitis
- Non-refractive visual impairment – new or deteriorating
- Dry eyes with sicca syndrome suspected

OTHER OPHTHALMOLOGICAL PROBLEMS

Investigate and refer as appropriate. Any clinical suspicion of CMV retinitis should result in urgent referral.

CONTACTS

Leicester: Dr J Prydal, Leicester Royal Infirmary

Nottingham: Prof H Dua, Queen's Medical Centre

Sheffield: Prof I Rennie, Royal Hallamshire Hospital

Hull: Mr J Innes, HRI

Path Links: Mr Y Manakad (Scunthorpe General Hospital), local ophthalmologist at other sites

Respiratory Services

INTRODUCTION

Chest infections and bronchiectasis are common features of a variety of primary immunodeficiencies and close liaison between clinical immunologists and chest physicians is desirable.

RESPIRATORY COMPLICATIONS OF IMMUNODEFICIENCY

Antibody deficiency
Recurrent bacterial chest infections eg Haemophilus, Pneumococcus, Moraxella, Mycoplasma spp.
Bronchiectasis
Granulomata
Pulmonary fibrosis
Lymphoid intersititial pneumonitis
Empyema/Abscess
Emphysema

T cell deficiencies
Chest infections including unusual organisms eg PCP, CMV, TB and atypical mycobacteria

Deficiencies of phagocyte function
Fungal infection e.g. Aspergillus (CGD, hyper IgE), candida (hyper IgE)
Pneumatocoeles (hyper IgE)

Others
Extranodal B cell lymphoma in lungs

MANAGEMENT

Criteria for referral to chest specialist

The following should result in consideration of referral to a chest physician:
Worsening respiratory problems / infections unresponsive to treatment
Symptoms / signs suggestive of malignancy

Prior investigations should include:
Sputum culture for bacteria and mycobacteria
Specialist testing for viruses and unusual organisms where indicated (liase with microbiologists).
CXR and other imaging as appropriate

Bronchiectasis
Patients with bronchiectasis should normally be managed in consultation with a chest physician

Monitoring of clinical disease should include:

- regular assessment in clinic
- symptom diaries in appropriate patients
- annual pulmonary function tests
- baseline CT scan, repeated as clinically indicated
- microbiology

Management should include:

- chest physiotherapy
- prompt treatment of intercurrent infection with antibiotics (after culture). Clinical opinion suggests that a minimum of 10 days of treatment is usually required, sometimes longer.
- consideration of prophylactic antibiotics
- consultation of local antibiotic policies
- consideration of resection of bronchiectatic lung in patients with localised disease.

Lymphoid interstitial pneumonitis
Rarely patients may develop diffuse lymphocytic infiltration in their lungs either within the interstitium or transbronchially.

Investigation
CXR – (typically - diffuse shadowing)
FBC – (may have eosinophilia)
Biopsy – typically reactive with polyclonal T and B cell infiltration, though one type of cell may predominate – in this case malignancy should be considered.
Exclusion of infective agents – culture, PCR and other methods to exclude both common and atypical organisms (liase with microbiologists)

Management
Without adequate therapy, patients may become extremely disabled and are at risk of malignant transformation of the (presumed) reactive lymphocytes.
Patients are usually steroid responsive in the first instance
Some patients appear to be temporarily responsive to antibiotics despite the lack of evidence of an infective aetiology.
Ciclosporin may be effective in some patients.

Intra-thoracic granulomata
Rare patients will develop intra-thoracic discrete pulmonary shadows on a chest X-ray or CT scan. Some patients go on to develop lymphoma 5-15 years later.

Investigation
If possible confirm diagnosis on biopsy
Consider other causes of granulomata, (mycobacteria and other infective organisms, including Whipple's disease - PCR at Leeds)

Management
The granulomata usually respond to relatively low dose corticosteroid therapy
Monitor for evidence of malignant transformation

CONTACTS

Leicester: Adults: Dr S Range, Glenfield Hospital. Children: Prof C O'Callaghan, Leicester Royal Infirmary

Nottingham: Adults: Dr W. Kinnear, Queen's Medical Centre. Children: Dr H. Vyas, Queen's Medical Centre

Sheffield: Adults: Dr F Edenborough, Northern General Hospital. Children: Dr R Primack or Dr M Everard or Prof M Whyte, Sheffield Children's Hospital

Hull: Adults: Dr M Greenstone, Castle Hill Hospital. Children: Dr I Beddis, HRI

Path Links: refer to local respiratory physician

Immunoglobulin Home Therapy

INTRODUCTION

The suitability of an individual for entry into the programme is assessed and agreed by the Consultant Immunologist and the Immunology Nurse Specialist.

Criteria for Entry onto the Programme

The individual being treated with immunoglobulin must:

- Demonstrate motivation and willingness to comply with the home therapy programme and all its implications and sign the appropriate consent form
- Have an infusion partner who agrees to attend the Home Therapy Centre (HTC) for training and be present throughout all infusions
- Have confirmation of support for home therapy from their General Practitioner
- Have access to a telephone at the place of infusion
- Good venous access if intravenous route used
- Have received immunoglobulin therapy at the HTC with no reactions/adverse events for a minimum of 6 infusions (IV or SC).
- Have successfully completed a competency assessment
- Agree to return to hospital based therapy if requested

The Home Therapy Training Programme

Each HTC will have its own training programme, but will include the following key areas:

- Hand washing
- Asepsis
- Preparation of equipment for infusion
- Cannulation (IVIG) or insertion of Thalaset/butterfly (SCIG)
- Blood sampling (IVIG)
- Management of infusion
- Disposal of equipment
- Documentation
- Management of adverse reactions
- Automatically injectable adrenaline/epinephrine training if used
- Documentary evidence of the individual's training and competence
- Satisfactorily complete the first home infusion with the Immunology Nurse Specialist

Post Training Requirements

The Immunology Nurse Specialist enables the individual to continue home therapy by:

- Receiving and monitoring infusion logs and other relevant documentation for any indication of difficulties/infections
- Investigating any adverse reactions/events and taking appropriate action
- Keeping the Consultant Immunologist informed of any relevant issues regarding care and treatment
- Encouraging compliance with clinic visits
- Performing an annual review of the individual and their partner's competence, to include a full infusion and an

appropriate assessment of skills and knowledge
- Liasing with the individual, their GP, Consultant Immunologist and other relevant care providers

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Hospital Administration of IVIG for Primary Immunodeficiencies

INTRODUCTION

Primary antibody deficiencies can be congenital and affect approximately 1 per 10 000 of the population. These individuals have low serum antibody levels and hence have an increased risk of infection.

INFUSIONS

Prior to commencing IVIG replacement therapy, the Immunology Nurse Specialist ensures that informed consent has been obtained and that all appropriate baseline tests have been performed as per TRIC Guideline 4: Diagnosis & Management of CVID, and UK-PIN Guidelines.

Before the first infusion, a full explanation of the procedure is given and baseline observations of pulse, blood pressure and temperature are recorded: there is no need to repeat these on subsequent infusions unless indicated.

Each infusion is prepared in accordance with the product manufacturer's instructions and administered following the UK-PIN Guidelines:

- An assessment of general health is made and medical advice sought if appropriate, prior to commencement
- Asepsis is maintained throughout
- The Immunology Nurse Specialist ensures that the IVIG is given at the prescribed dose and at an appropriate rate guided by manufacturer's data sheet and clinical response
- IVIG is given in a suitable, designated area with a telephone, adrenaline/epinephrine and resuscitation equipment readily available and in full working order
- The Immunology Nurse Specialist takes appropriate action with regard to side effects and adverse reactions and reports mild/moderate/severe reactions as per local hospital policy

MONITORING

The Immunology Nurse requests and/or takes the appropriate blood samples for monitoring purposes, as detailed in this *Compendium*.

Hospital Administration of Subcutaneous Immunoglobulin (SCIG) Therapy

INTRODUCTION

Primary antibody deficiencies can be congenital and affect approximately 1 per 10 000 of the population. These individuals have low serum antibody levels and are at increased risk of infection.

INFUSIONS

Prior to commencing subcutaneous immunoglobulin (SCIG) therapy, the Immunology Nurse Specialist ensures that informed consent has been obtained and that all appropriate baseline tests have been performed as per UK-PIN Guidelines and this *Compendium*.

Before the first infusion, a full explanation of the procedure is given and baseline observations of pulse, blood pressure and temperature are recorded: there is no need to repeat these on subsequent infusions unless indicated.

Each infusion is prepared in accordance with the product manufacturer's instructions and administered following the UK-PIN Guidelines:

- An assessment of general health is made and medical advice sought, if appropriate, prior to commencement.
- Asepsis is maintained throughout
- The Immunology Nurse Specialist ensures that the SCIG is given at the correctly prescribed dose and at an appropriate rate according to manufacturer's datasheet and clinical response
- Appropriate sites will be used e.g. lower abdomen, with a minimum distance of 2.5cm between each site
- SCIG is given in a suitable, designated area with a telephone, adrenaline/epinephrine and resuscitation equipment readily available and in full working order

- The Immunology Nurse Specialist takes appropriate action with regard to side effects and adverse reactions (see appropriate chapter in this *Compendium*) and reports mild/moderate/severe reactions as per local hospital policy

MONITORING

The Immunology Nurse Specialist requests and/or takes the appropriate blood samples for monitoring purposes, as detailed in this *Compendium*

Infection Control in Relation to IVIG Therapy

INTRODUCTION

Immunodeficient patients are particularly susceptible to both exogenous and endogenous infections. The administration of intravenous immunoglobulins can predispose the patient to an increased risk of infection unless strict hygiene measures are taken before, during and after the infusion.

Hand hygiene

Hand washing is the single most important measure in preventing cross-infection. It involves thoroughly cleaning, rinsing and drying both hands.

Indications for hand washing:

- Before commencing any direct patient contact
- Prior to setting up the infusion
- Prior to cannulation
- Prior to contact with cannula site and any part of the intravenous giving set
- Prior to changing immunoglobulin bottles
- Prior to removal of peripheral intravenous cannula
- After removing gloves
- After visiting the toilet

Suitable cleansing agents are liquid soap from a sealed unit; alcohol hand rub can be used providing the hands are not visibly dirty and/or where frequent hand washing is necessary, as long as hand surfaces are well covered with the cleaning agent.

Hand washing technique

Wet hands under running water
Apply cleansing agent and then rub as follows:

- Palm to palm
- Right palm over left dorsum and left palm over right dorsum
- Palm to palm with fingers interlaced
- Backs of fingers to opposing palms with fingers interlocked
- Rotational rubbing of right thumb clasped in the left hand and vice versa
- Rotational rubbing, backwards and forwards with fingers of right hand clasped in left palm and vice versa.

Rinse hands thoroughly using running water
Dry hands well using a minimum of two disposable paper towels.

General hand care

Ensure skin is intact, where possible
Always cover cuts and abrasions with waterproof plasters
Hand cream is recommended in order to avoid chapped and cracked skin
Avoid communal pots of hand cream preparations; hand cream should preferably be water based and dispensed within sealed units
If gloves are used wash hands after removal
Fingernails should be kept clean, short and smooth. Nail varnish or false nails must not be worn.

Disposal of clinical and other waste

The immunodeficient patient may have a concurrent infection or may be a carrier of a blood borne infective agent, such as hepatitis B or C. Careless or inappropriate disposal of waste may result in cross-infection, particularly to staff subsequently handling waste containers.

Each individual Trust is responsible for the safe handling, transportation and disposal of all clinical and non-clinical waste generated on-site, in accordance with current legislation. Therefore local policies must be adhered to.

Sharps: handling, disposal and reporting

The safe disposal of sharps and/or blood stained equipment is necessary to reduce the risk of inoculation injury to both health care workers and patients.
All health care workers have a responsibility to be aware of and adhere to the local sharps policy.

General Guidance

All sharps bins should:

Conform to UN3291
Be correctly assembled prior to use
Placed on an even surface
Be sealed when no more then two thirds full
Not be left unattended in public areas

If injury occurs:

Encourage the wound to bleed by squeezing the area
Wash thoroughly with soap and running water
Cover wound with an impermeable dressing
Report incident, as per trust policy
If injury caused by a dirty sharp, seek advice as soon as possible, as per local policy

Endnote

The above guidelines are designed to promote conformity with national and regional guidelines regarding the safe administration of intravenous immunoglobulins and are not intended to replace local trust policies or appropriate legislation.

Immunoglobulin Supply Shortage

INTRODUCTION

Patients on immunoglobulin replacement therapy require regular infusions to reduce the frequency of bacterial infections and failure to provide adequate replacement therapy results in long term morbidity. Due to the different manufacturing processes that IVIGs are subjected to, it is not appropriate to switch a patient from product to product as patients may respond adversely to change of immunoglobulin product.

There is an increasing range of other conditions treated with immunoglobulin. With restrictions in sources of blood used due to feared risks of viral transmissions, increasing and fluctuating demands on immunoglobulin, it is apparent that there may be intermittent shortages and lack of supply for those patients on essential replacement therapy. It is imperative to manage any supply crisis to ensure this group of antibody deficient patients continues to receive adequate supplies of immunoglobulin to maintain health.

When to initiate immunoglobulin restriction crisis management

It is important to plan for the management of any immunoglobulin restrictions as soon as the team is made aware there is an impending problem.

It is important to be kept informed by all manufacturers of any impending restrictions to supplies of immunoglobulin. This can be aided by maintaining good communication with representatives from the manufacturing companies and the Primary Immunodeficiency Association (PIA) and ensuring they have a clear understanding of the importance of maintaining adequate availability of product for patients on replacement therapy. Prior to commencing patients on home therapy it should be confirmed with the manufacturers that they are committed to ensuring these patients will be given priority should there be any product shortages. The manufacturers and the PIA will inform the Clinical Immunology Nurse Specialist or member of the Immunology Team. TRIC members will inform each other by email as soon as a shortage is anticipated.

How to manage supply problems

Discussions are held with pharmacy, medical and nursing teams to determine extent of problem:

- Which manufacturers are having supply problems?
- How much immunoglobulin is currently available?
- When is lack of supply likely to occur?
- Which patients will be affected – home therapy or those infusing in hospital?
- How many patients will be affected?
- How long is the shortage expected to last?
- What is the projected demand?

Patients are informed of situation and reassurance given as appropriate.

For temporary suspensions, it is acceptable to miss one infusion, providing the next infusion can be brought forward and a larger than usual infusion can be given. For example, after a six week hiatus 150% of the normal dose could be given. Alternatively, an extra dose can be given.

Where there is no supply available of the patient's usual product and they are going to miss more than one infusion they will be administered another available product, chosen by the clinician. This must be administered as if a new product at the recommended rate for a first infusion. Home therapy patients must have this treatment in the hospital for the first three infusions of the new product. Patients should then remain on the newer product rather than change back to the initial product.

For those patients on SCIG where another SCIG product is unavailable the patient is administered IVIG 2-3 weekly. The dose calculated by multiplying the weekly dose by 2 or 3 respectively. This must be administered as if a new product (even if the patient has received it previously) at the recommended rate for a first infusion. All patients must receive this in the hospital or at their shared-care centre.

Patients restarting SCIG have their first subcutaneous infusion one week following the IVIG infusion.

The bloods required for patients changing all (IVIG or SCIG) immunoglobulin products are:

HCV PCR, HBsAg, U+E, LFTs, CRP, IgG, Serum Save, FBC

These samples are taken prior to changing products and prior to recommencing the patient's usual product

Risk Assessment

Monitoring of bloods as per guideline

Home Antibiotics for Immunology Patients

INTRODUCTION

There may often be unacceptable delays in patients being able to get prescriptions for antibiotics, and it is therefore advisable in a selected patient population for them to have a supply of antibiotics to keep at home, to be commenced at the earliest signs of infection.

WHEN TO USE THIS GUIDELINE

A self-initiated course of antibiotics, kept at home, should be considered for patients with a history of recurrent sinopulmonary infection that should be started at the onset of signs of bacterial infection. Patients with bronchiectasis or those who have had recurrent sinusitis may be at increased risk of secondary bacterial infection following a viral upper respiratory tract infection – so early antibiotic therapy is desirable.

Antibiotics at home may be inappropriate in two situations;

- When there are severe symptoms, such as shortness of breath at rest, pleuritic pain.
- In patients colonized with pseudomonas (who may need IV antibiotics)

HOW TO USE THIS GUIDELINE

Patient selection

Not all patients will require antibiotics at home, only those with a documented history of recurrent infection, and when it is apparent that these persist despite treatment of the underlying cause (for example with immunoglobulin or on-going prophylactic antibiotics). Patients with known anatomical defects – either from recurrent sinusitis and polyp formation or bronchiectasis, should be considered for antibiotics at home as a matter of course.

Choosing the right antibiotic

When possible antibiotic use should be guided by anti-microbial sensitivities. Patients should always be encouraged to provide a relevant sample for analysis before commencing a course of antibiotic therapy. When samples have not been sent (for example at weekends) or sensitivities are not yet available, first line therapy should be started based on site, previous infections and antibiotic allergies.

Advising the patient how to use antibiotics at home

All patients given antibiotics for home use should be given the TRIC advice leaflet about this. This explains how antibiotics should be handled, and when to use them. It is important that patients understand that overuse or poor adherence results in resistance, but reluctant use may result in further significant damage from infection. Ensure that patients have a supply of sterile specimen containers and completed pathology forms at home.

When antibiotics are started, the patient should contact the Immunology team during working hours so that they are aware of the situation.

A failure to respond to therapy should also be reported, so that treatment may be adjusted as necessary.

RISK MANAGEMENT

Provision of antibiotics at home must be accompanied by adequate information for the safe storage and use of drugs.

LOCAL VARIATION:

Path Links antibiotics for home will be:

AMOXICILLIN 500 mg tds for 14 days unless clinical reasons suggest an alternative (eg allergy, previous resistance, etc).

Antibody Deficiency Information For GPs

This information can be provided in an information leaflet:

ANTIBODY DEFICIENCY: INFORMATION FOR GENERAL PRACTITIONERS

Types of antibody deficiency

Antibody deficiency is a common immune deficiency and can present at any age. Primary antibody deficiency is the result of a range of genetic defects, but again can present both in adults and children. Secondary antibody deficiency can occur in myeloma and lymphoma, following certain drugs (such as anticonvulsants) and when there is excessive protein loss, for example in nephrotic syndrome. There is a severity spectrum of primary antibody deficiencies and sometimes patients can progress to a more severe form of antibody deficiency.

How antibody deficiency presents

Recurrent bouts of sinusitis, otitis and chest infections are an almost inevitable consequence of antibody deficiency and if left untreated, can result in irreversible damage, such as deafness and bronchiectasis. Less frequently, patients can present with more acute problems such as meningitis or septic arthritis.

How antibody deficiency is treated

Patients with milder antibody deficiency (for example isolated IgG subclass deficiency) may be adequately managed with prophylactic antibiotics but the efficacy of prophylaxis needs to be monitored carefully. Respiratory function and infection rates will be monitored. If antibiotic prophylaxis is ineffective, patients may be offered immunoglobulin replacement therapy.

Patient monitoring involves working closely with primary care regarding the frequency of antibiotic prescribing for breakthrough infections, and hence welcome information pertaining to repeated antibiotic prescription. Wherever possible, cultures should be obtained at the start of antibiotic therapy – and we have asked patients to hand in such samples to your practice. This is essential in the management of these patients as unusual organisms and antibiotic resistance can be a problem. Antibiotics for breakthrough infections need to be prescribed at full dose for twice the normal period (e.g. amoxicillin 500 mg tds for two weeks).

Patients with more severe antibody deficiency may require immunoglobulin replacement therapy. Immunoglobulin can be given subcutaneously (weekly) or intravenously (usually three weekly). Patients can be given immunoglobulin at designated centres, or in suitable individuals, at home. Assessment and training for home therapy is only considered after a suitable period of hospital-based therapy.

Despite immunoglobulin replacement, these patients will have breakthrough infections. Hence certain patients will need to be supplied with courses of antibiotics to keep at home, to take as directed.

General Points

For empirical treatment, amoxicillin or erythromycin are adequate for most acute infections, and a 14 day high-dose course should be prescribed; this can be modified by the culture result.

Live vaccines, including measles, mumps, rubella, BCG and polio, should be avoided in these patients and use in immediate family members should be discussed with the immunology team. Patients on immunoglobulin replacement are unlikely to benefit from other vaccines. Other immunisations are not contra-indicated, but are likely to produce a suboptimal response. Other

members of the patient's household should be offered annual influenza immunisation.

The Primary Immunodeficiency Service

A range of laboratory and clinical services are offered at the immunodeficiency centre for the investigation and management of patients with primary immunodeficiencies. These include:

Diagnostic services

Telephone advice to GPs about patients with suspected immunodeficiency
Assessment of patients in clinic. For non-urgent cases, please write to the Consultants.

Clinical services

Nurse-led day care for treatment of antibody deficiency
Training patients in the management of their immunodeficiency at home
Emergency assessment of patients with established immunodeficiencies who have medical problems during office hours

Contacting the primary immunodeficiency service

[Insert local contact details here]

Glossary of primary antibody deficiency

Single gene defects: These are all very rare. Carrier status can be determined by molecular testing and antenatal diagnosis is usually possible.

X-linked agammaglobulinaemia. About 5/million births. Boys with XLA are unable to produce any immunoglobulin and present around 6 months of age with recurrent infections.
Hyper IgM syndrome. Also X linked, but affects a wider range of immune functions than immunoglobulin production alone.

Severe combined immunodeficiency. Boys and girls affected by this group of disorders have defective T cells and will present with severe infections from birth. Urgent advice should be sought on infants with failure to thrive, unexpected infections and lymphocyte counts below 2.0.

Polygenic disorders: These are much commoner and are probably caused by defects in a cluster of genes. The risk to other family members is hard to quantify, but may be about 1 in 5. Genetic testing is not possible.

IgA deficiency affects up to 1:400 people, the majority of whom are healthy. There is an increased risk of coeliac disease, allergies and other autoimmune diseases
Common variable immunodeficiency affects about 50/million. It may present in young adulthood with recurrent infections. Other manifestations include auto immunity and cancers.
IgG subclass deficiency is also relatively common and increases susceptibility to respiratory infection.

Immunoglobulin is prepared from pooled plasma in order to contain a wide range of antibodies against most common pathogens. Immunoglobulin needs to be given for life for the majority of patients with moderate to severe antibody deficiency. The major risk is of transmission of blood borne viruses. To minimise this risk, donors are screened for infection and plasma is treated in order to inactivate viruses. We monitor all patients receiving blood products.

Selective IgA Deficiency

INTRODUCTION

Complete IgA deficiency IgAD**,** (<0.07g/L) is the most common immune deficiency syndrome leading to recurrent bacterial infections. It occurs in approximately 1 in 500-700 of the Caucasian population in the UK, but there are racial differences in prevalence.

CLINICAL FEATURES

Some IgA deficient individuals are asymptomatic, however up to 80% of patients may become symptomatic over time. Patients have an increased incidence of recurrent infections, especially at mucosal sites, and organ-specific autoimmunity. All IgA deficient individuals are at increased risk of adverse reactions, to exogenous IgA in transfusions of blood products although the magnitude of this risk is unknown . IgG anti-IgA antibodies are used as an (imperfect) marker for heightened risk in some centres and by the BTS.

IgA deficiency can occasionally progress to a complete common variable immunodeficiency (CVID) picture or a combined IgA/IgG2 deficiency. This is associated with the same

MHC class III haplotypes as CVID and may represent part of the same spectrum of antibody deficiency disorders. The precise mode of inheritance is unknown. Family members of some CVID individuals may have an increased risk of IgA deficiency as well as more serious combined immunodeficiencies. The incidence of this is unknown but may be as high as 25%.

Patients usually present with recurrent bacterial sinopulmonary infections secondary to encapsulated organisms. Gastro-intestinal infection, bacterial conjunctivitis, boils, abscesses and herpes zoster are also common. Approximately 30% of patients have an autoimmune disorder, the commonest being vitiligo, idiopathic thrombocytopenic purpura and thyroid disease. Granulomatous disease involving the lungs, liver, spleen and skin can occur as in CVID. There may also be an increase in allergic disorders.

The main complications of IgAD are similar to CVID and include bronchiectasis and chronic sinusitis and organ-specific autoimmunity and malignancies. Coeliac disease is also more common in IgAD but disease specific serology for IgA antibodies will be negative.

DIAGNOSIS OF IgA DEFICIENCY

Care must be taken to distinguish low IgA (partial IgA deficiency - less than lower limit of the reference range)which may be transient and of no clinical consequence from a complete absence of IgA. Children <5 years of age often have reduced IgA levels and maximal IgA levels may occasionally be delayed until 10-14 years.

DIAGNOSTIC CRITERIA – IgA DEFICIENCY
Diagnostic criteria have been drawn up by the Pan-American Group for Immune Deficiencies and the European Society for Immune Deficiencies (*Clin Immunol* 1999, 93 p190-197).

Definitive IgA Deficiency
Male or female patient greater than 4 years of age [check] who has a serum IgA of less than 0.07 g/L but normal serum IgG and IgM, in whom other causes of hypo-gammaglobulinaemia have been excluded These patients have a normal IgG antibody response to vaccination.

Probable IgA Deficiency
As above but, serum IgA at least 2 SD below normal for age.

(See CVID chapter for table of defined causes of hypogammaglobulinaemia)

DIFFERENTIAL DIAGNOSIS

The principal differential diagnosis lies between other causes of primary antibody deficiency (esp. in younger patients) and secondary causes of hypo-gammaglobulinaemia (especially in older individuals).

INVESTIGATION

The investigations required depend upon the clinical picture.

All patients:

- Serum immunoglobulins and electrophoresis
- Confirm complete IgA deficiency using a sensitive IgA assay if below detection limit of standard assay .
- Consider IgG anti-IgA antibodies in complete deficiency
- Other investigations (including microbiology and imaging) as required to exclude other diagnoses or as indicated by clinical status (e.g. for suspected autoimmune, allergic or coeliac disease).

Patients presenting with clinical immunodeficiency:

Investigate as appropriate (see CVID guideline)

MANAGEMENT

All patients
All IgA deficient individuals should counselled regarding risks of transfusion reactions according to current NBS Guidelines. Normal immunisation protocols (including the use of live vaccines) may be followed provided there is no evidence of a wider immunodeficiency.

Treatment options for patients with isolated IgA deficiency include antibiotics to treat intercurrent infections, and prophylactic antibiotics

Follow up is required to monitor for development of a wider immunodeficiency

to monitor for complications eg bronchiectasis, autoimmune, coeliac disease, to assess efficacy and to monitor for complications of treatment.

Patient support groups such as the Primary Immunodeficiency Association (PIA) provide invaluable support and advice to patients and families.

References:

ESID Website

D Lilic, WAC Sewell: IgA Deficiency: what we should –or should not-be doing. 2001. *J Clin Pathology* **54**:337-338.

Information For Patients Keeping Antibiotics At Home

This information can be provided in an information leaflet:

INFORMATION FOR PATIENTS KEEPING ANTIBIOTICS AT HOME FOR SELF-MEDICATION OF ACUTE INFECTION

Why Keep Antibiotics at Home?

The result of recurrent infection is damage to the tissues at the site of infection. We aim to prevent this situation happening whenever possible, and to prevent worsening in those patients who already have problems such as sinus or lung damage. Antibiotics taken appropriately at the first signs of infection are one approach to achieving this goal. Keeping antibiotics available at home allows prompt treatment.

It is essential to check the type of infection you have. You must send a sample of sputum to the laboratory just before you start the antibiotics. This is because some bacteria causing infection are resistant to the antibiotics we routinely use; the only way of being certain about this is to check a sample.

When to Take Antibiotics

You will have this information sheet because we believe you are at risk of developing further infections, and trust you to treat yourself, using these instructions. If you start to develop signs (marked below) that you and your doctor have decided typically indicate infection:

Nasal stuffiness and discharge +/- pain ❑
Increasing sputum production ❑
Change in sputum colour ❑
Fever ❑
Loss of appetite ❑

You should then do the following:

If the above occurs **Mon-Fri** ring the immunology nurses to advise us that you believe you have infection and plan to commence antibiotics.
If your symptoms are severe or we know that you have a history of infections that are difficult to treat, we may advise you to come to the hospital to be seen by the team.

If the above occurs Mon-Fri 9am-5pm take a sample of sputum to either your GP, local hospital pathology department (with a request form from your GP or hospital), whichever is nearer for you.
Sputum samples should be coughed up from deep in the chest, not samples of spit (from the mouth) – ideally first thing in the morning. Samples deteriorate rapidly; it is important to get them to the laboratory as fast as possible. In some cases it may be best to actually cough up the sample at hospital or the GP clinic.

If the above occurs **at the weekend** samples will not be suitable for analysis by the next week, start taking the antibiotics as prescribed and ring the immunology nurses on Monday to let us know what is happening.

Which Antibiotics to Take

The choice of antibiotics you are given to take at home will depend on what bacteria you tend to get, the type of antibiotic that normally works against them, response to treatment and any allergies you might have. Being able to grow bacteria from the affected site and test which antibiotics work in the laboratory is one of the most useful things we can do, and will help guide future therapy.

This all adds up to saying whenever possible please provide a sample for analysis- don't forget to ask for a sterile sputum container if you run out at home.

How Long to Take Them

You must complete the whole course of antibiotics. It is tempting to stop antibiotics

when you start to feel better, however, this usually results in some bacteria being left untreated and relapse of infection. Failing to take the whole course of antibiotics may also result in the bacteria becoming resistant to the antibiotics (there are situations when you may be advised to switch therapy, which is different). Most patients will be given 10 to 14 days of treatment. Take the tablets as prescribed until you run out.

What if they are not working?

If symptoms are not improving or are getting worse after 72 hours of therapy, you should re-contact the immunology nurses for advice. If this is at the weekend contact your GP / emergency doctor.

What if You Develop Side Effects?

Minor side effects such as rash, stomach upset or thrush may be expected with many antibiotics, please ring the immunology nurses if you are concerned. Your doctor and pharmacist will make you aware of what to do should you ever suffer more severe side effects.

How to Store Antibiotics at Home

When your medication is dispensed you will be given information from pharmacy, which will also be printed on the bottle, on how to store the drugs you have been given. It is important you follow advice such as storage in a refrigerator if necessary. The most important task is that you intermittently check the expiry date. Out of date drugs may be ineffective and may have unpredictable effects. Ask for a repeat prescription if yours is out of date. Always return unused medication to the pharmacy for disposal.

Transient hypogammaglobulinaemia of infancy

BACKGROUND

Transient hypogammaglobulinaemia of infancy represents delayed maturation of normal immunoglobulin production, with an exaggeration of the normal physiological nadir at 3-6 months (1). This may be exaggerated in premature infants. In almost all children resolution of IgG levels occurs by 2y of age. IgA levels may remain low for longer, and complete resolution has been observed as late as 10 years (1,3). A small minority of infants thought to have THI will progress to common variable immune deficiency / selective IgA deficiency.

The true incidence is not known as many children are never diagnosed or do not present to an immunologist.

DIAGNOSIS OF THI

THI is a retrospective diagnosis. It may be suspected, but a firm diagnosis can only be made once immunoglobulin levels have returned to within the normal range for age.

Definitions vary, and the number of isotypes seen to be low may vary with the age at which they are measured.

An acceptable definition (adapted from 1,2) is all of:

- Concentrations of one or more Ig isotypes below 2 standard deviations for age on two or more occasions.
- Normal responses to primary vaccinations or boosters
- Clinical or laboratory evidence of normal T cell function
- Absence of protein loss or features of other immune deficiency
- Return of immunoglobulin levels to within the age related normal range

CLINICAL MANIFESTATIONS

Invasive infections are rare in THI. Children commonly present with an increased frequency of upper respiratory tract infections, in particular otitis media (1,4). Some authors have described an increased incidence of atopy and food intolerance, although this may represent ascertainment bias (3). There is an increased incidence in families with CVID and these children are more likely to be asymptomatic (5)

Initial Investigations

- Total immunoglobulin levels
- Selected vaccination responses
- responses measured dictated by local availability/preference
- e.g. Tetanus and Hib antibody levels
- FBC
- occasional patients may have a transient neutropaenia (5)
- Lymphocyte subsets

- Lymphocyte Proliferation responses are rarely necessary in children with a history suggestive of THI.

PROGNOSIS

The condition resolves in the majority of children (see above in background, Evidence level B). Levels of Igs or age at presentation do not predict which children will have persistent abnormalities. Failure of persistence of antibody responses to vaccinations or an invasive infection at presentation may predict a group who are unlikely to have a transient picture (4, Evidence level D). Children with persisting low Igs by 5 years are more likely to develop CVID (Evidence level D).

TREATMENT

(Evidence level D)
Interventions are guided by symptomatology and can be considered at 3 levels:

1. Prompt treatment of infections with antibiotics
Families and GPs should be provided with clear written instructions that prompt treatment is necessary. Longer courses may be appropriate in some individuals.

2. Prophylactic antibiotics
These are particularly useful over the winter months and should be considered in all children with frequent infections (e.g. >3 infections requiring antibiotics in one winter) or quality of life issues (missing nursery etc). At the onset of treatment it should be clarified with parents that treatment will be stopped at a future date, usually the next spring. There is no evidence from trials as to the best antibiotic to use in this setting. The following have been found useful in clinical practise:

Trimethoprim 2 mg/kg once daily
or
Azithromycin 10mg/kg once daily for 3 days every 2 weeks

Or

Augmentin – standard single dose once daily

3. Replacement immunoglobulin therapy

This is rarely required in THI (1), but should be considered if antibiotic prophylaxis is ineffective or severe failure to thrive occurs. Infants who fall into this category should have their diagnosis reassessed, must be seen by an immunologist and are more likely to progress to CVID. It should be emphasized it is a trial of therapy and a review date for stopping therapy should be agreed in advance. Efficacy of therapy should be assessed by frequency of infections and other parameters.

MONITORING

(Evidence level D, expert opinion)
The local paediatrician and GP must be closely involved.
Infants and children with THI should have Igs measured initially at least every 6 months.
If symptomatically improving, clinical and laboratory review can be reduced to annually
Levels must be monitored and the child kept under review until Igs are within the normal range for age
No routine radiological or microbiological monitoring is recommended, unless the child has had a significant number of documented LRTIs, when a CT scan may be appropriate.

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IgG Subclass and Specific Antibody Deficiency

INTRODUCTION

IgG subclass deficiency may form part of the same disease spectrum as IgA deficiency and common variable immunodeficiency (CVID) and some patients may progress towards CVID. IgG subclass deficiency may also be found as part of other immunodeficiency syndromes e.g. Wiskott-Aldrich Syndrome, ataxia telangiectasia. Many patients with apparent subclass deficiency are asymptomatic, careful clinical assessment by an Immunologist is required to establish the diagnosis. In the absence of another defined immunodeficiency, specific antibody deficiency should also be considered.

CLINICAL FEATURES

Patients may present in a similar way to CVID, with recurrent bacterial infection secondary to encapsulated organisms. Gastro-intestinal infection, bacterial conjunctivitis, boils, abscesses and herpes zoster are also common. Complications include bronchiectasis, chronic sinusitis, and autoimmune or granulomatous disease. However some patients may be asymptomatic.

DIFFERENTIAL DIAGNOSIS

The principal differential diagnosis lies between other causes of immunodeficiency, secondary causes of hypogammaglobulinaemia and delayed maturation in infants and children (IgG2 and pneumococcal antibody levels are much lower in infants than adults).

Other primary immunodeficiencies should be considered:

- X-linked agammaglobulinaemia
- CD40 ligand deficiency
- X-linked lymphoproliferative disease
- Common variable immunodeficiency
- Wiskott Aldrich Syndrome
- Ataxia telangiectasia
- Haematological malignancies especially in adults (CLL, NHL, myeloma, thymoma etc.)
- Drugs e.g. anti-convulsants, disease modifying anti-rheumatic drugs

INVESTIGATIONS

Investigations should include:

- Serum immunoglobulins
- Serum and urine electrophoresis
- Anti-IgA antibodies for those with serum IgA < 0.07g/l

All individuals with a reduced IgG but > 3 g/l should have:

- IgG subclasses
- Specific antibodies to tetanus, Hib and pneumococci
- IgG antibodies to previous infections and/or immunisations e.g. hepatitis B, meningococcus C, measles, rubella, CMV, VZV, EBV and others as appropriate.

If specific antibody responses are low, test immunisations (e.g. tetanus toxoid, Pneumovax II, Hib) should be given providing the clinical situation allows. Post immunisation blood samples should be taken after 4 weeks.

NB live vaccines must NOT be given until the diagnosis is established and cell mediated immunodeficiency excluded

- Lymphocytes subsets including T, B and NK cell numbers.
- Liver function tests, urea & creatinine, calcium (for B LPD)
- Urinalysis
- Full blood count and film
- Other investigations (including microbiology and imaging) as required by the clinical picture.

GENERAL MANAGEMENT

General points

All patients with associated IgA deficiency should be screened for anti-IgA antibodies and, where appropriate, issued with a Blood Transfusion Hazard card, as per national BTS and IgA deficiency guidelines.
Live immunisations should be considered on individual basis, taking into account clinical and laboratory evidence of immunodeficiency.
All patients should be offered contact details of patient support groups such as the Primary Immunodeficiency Association (PIA) who can provide invaluable support and advice to patients and families.

Treatment options include

- Antibiotics to treat inter-current infections
- Prophylactic antibiotics
- Immunoglobulin replacement – usually initiated as a limited trial in patients with significant problems with infection and/or evidence of progressive lung disease despite optimal therapy (see Immunoglobulin Therapy Guideline)

Patients with chest disease should receive all other appropriate therapy e.g. chest physiotherapy, inhalers etc.

Follow up is required:

- To monitor for development of a wider immunodeficiency
- To monitor for complications e.g. bronchiectasis
- To assess efficacy of, and monitor for complications of treatment
- Assess overall health
- Family, educational, psychological issues etc.

X-linked Agammaglobulinaemia

INTRODUCTION

X-linked agammaglobulinaemia is a primary antibody deficiency caused by a mutation in the *Btk* gene which results in an absence of peripheral B cells, extremely low serum immunoglobulin levels, and failure to make germinal centres in lymph nodes. Most patients with XLA develop recurrent bacterial infections, particularly otitis media, sinusitis and pneumonia, in the first two years of life. The most common pathogens involved are *S pneumoniae* and *H influenzae*. The serum IgG is usually <2 g/l and IgM and IgA are generally <0.2 g/l. Approximately 20% of patients present with a dramatic, overwhelming infection, often with neutropenia. Another 10-15% have higher concentrations of serum immunoglobulin than expected or are not recognised to have immunodeficiency until after the age of 5 years.

DIAGNOSTIC CRITERIA

ESID criteria for the diagnosis of XLA are:

Definitive XLA

Male patient with <2% CD19+ B cells and at least one of the following:

- Mutation in *Btk*
- Absent *Btk* mRNA on northern blot analysis of neutrophils or monocytes
- Absent *Btk* protein in monocytes or platelets
- Maternal cousins, uncles or nephews with <2% CD19+ B cells

Probable XLA

Male patient with <2% CD19+ B cells in whom all of the following are positive:

- Onset of recurrent infections in the first 5 years of life
- Serum IgG, IgM, and IgA more than 2SD below normal for age
- Absent isohaemagglutinins and /or poor response to vaccines
- Other causes of hypogammaglobulinaemia have been excluded

Possible XLA

Male patient with <2% CD19+ B cells in whom other causes of hypo-gammaglobulinaemia have been excluded and at least one of the following is positive:

- Onset of recurrent bacterial infections in the first 5 years of life
- Serum IgG, IgM, and IgA more than 2SD below normal for age
- Absent isohaemagglutinins

Differential diagnosis

ESID Guidelines for differential diagnoses to be considered are:

- Drug-induced hypogammaglobulinaemia
    - Antimalarial agents, captopril, carbamazepine, glucocorticoids, fenclofenac, gold salts, penicillamine, phenytoin, sulfasalazine
- Infectious diseases
    - HIV, congenital rubella, congenital infection with CMV, congenital infection with toxoplasma gondii, Epstein-Barr virus

- Malignancy
    - Chronic lymphocytic leukaemia, immunodeficiency with thymoma, non Hodgkin's lymphoma, B cell malignancy
- Systemic disorders
- Immunodeficiency caused by hypercatabolism of immunoglobulin, immunodeficiency caused by excessive loss of immunoglobulins (nephrosis, severe burns, lymphangectasia (beware low IgG with normal IgA and IgM, severe diarrhoea)
- Genetic disorders
    - Ataxia-telangectasia, autosomal forms of SCID, hyper-IgM immunodeficiency, transcobalamin II deficiency with hypogammaglobulinaemia, X-linked hypogammaglobulinaemia, X-linked lymphoproliferative disorder, some metabolic disorders e.g. hypogammaglobulinaemia with growth hormone deficiency
- Chromosomal abnormalities
    - Chromosome 18q syndrome, monosomy 22, trisomy 8, trisomy 21

Although not in the ESID Guidelines for diagnosis of primary immunodeficiency, careful consideration needs to be given to other causes of immunodeficiency including:

- Hypogammaglobulinaemia without B cells (μ-chain deficiency, λ-5 deficiency, Ig-α deficiency, BLNK deficiency)
- Hyper-IgM-like syndromes: AID deficiency (HIGM type 2) and HIGM types 3 (CD40) and 4 (CSR deficiency) and NEMO mutations and other variants.

These are individually extremely rare and require diagnostic testing on an individual basis – see senior clinical staff for guidance

XLA should be considered in any male with:

- Recurrent* sinopulmonary infections, particularly if onset is under two years of age.
- Neutropenia and recurrent* infections
- Dermatomyositis/fasciitis
- Meningoencephalitis due to enteroviruses
- Absent B cells or other laboratory features found incidentally

*Recurrent upper respiratory tract infections are normal in healthy children. There is no widely-accepted definition of what constitutes normality for the maximum number of infections/year, but as a guide more than 8 episodes of otitis/year in young children is generally accepted as abnormal. A clinical decision should be made based on the frequency, type, location and severity of the infections, and the impact they are having on the child and their family before commencing investigations for immunodeficiency.

Because they do not produce B cells, XLA patients have absent tonsils and lymph nodes.

LABORATORY & CLINICAL INVESTIGATIONS

- Examine the child for absence of tonsils
- Measure serum immunoglobulins IgG, IgA, IgM
- Measure lymphocyte phenotypes
- Measure full blood count in particular lymphocyte count, neutrophil count, platelet count (and size)
- Other investigations as per CVID Guideline.

If the diagnosis of XLA is suspected from these results, definitive diagnosis will require genetic testing for mutations in the *Btk* gene which is only available at GOS (discuss with Dr Cale or Dr Gilmour 020 7813 8466). Families with a suspected diagnosis of XLA will require appropriate counselling prior to these tests and the genetic assays need to be arranged in advance and a normal control is needed.

TREATMENT

Live oral polio vaccine must not be given to patients or their close contacts.

MMR advice from GOS.

Household contacts should be immunised with MMR.

On confirming the diagnosis, it is important to discuss the implications for both the patient and the family. If there is the possibility of undiagnosed male patients or pre-menopausal female carriers, consider involving a genetic counsellor for these discussions.

The mainstay of treatment is adequate immunoglobulin replacement therapy. There is very good evidence for the use of immunoglobulin in XLA. In general trough levels are run somewhat higher even if well, to reduce risk of enteroviral infections (>= 8g/L).

FOLLOW-UP

Three-monthly monitoring is advised especially in childhood.

Monitoring of immunoglobulin replacement is performed as per CVID guideline.

X-Linked Lymphoproliferative Disease (XLP)

INTRODUCTION

This is a rare X-linked genetic disorder that is characterised by an abnormal immune response to Epstein Barr virus (EBV). Other viruses may be involved,. Defects in the expression of SAP (SLAM-Associated Protein) have been found in the majority of patients although not all have identifiable genetic lesions. SAP appears to be involved in signalling and communication between activated B and T cells. Some patients have a mutation in XIAP (X-linked inhibitor of apoptosis) (XLPS2).

CLINICAL FEATURES

Males with this condition are usually asymptomatic until they develop EBV (or other viral) infection which usually presents in 3 main ways:

- Fulminant fatal infectious mononucleosis (60%)
- Non-Hodgkin's or Hodgkin's lymphoma (30%)
- Hypogammaglobulinaemia with abnormal NK function (30%)

Less common manifestations of X linked lymphoproliferative (XLP) disease include aplastic anaemia, EBV associated haemophagocytic syndrome or vasculitis. Some individuals manifest an XLP phenotype with SAP mutation without serological or genomic evidence of EBV infection (other viral infections may act as triggers). The vast majority of patients (85%) will die in childhood; survival rate is very poor for males with fulminant hepatitis (<5%) and higher for those with isolated dysgammaglobulinaemia (50%).

DIFFERENTIAL DIAGNOSIS

Other diagnoses to consider include:

- Langerhans cell histiocytosis
- Haemophagocytic syndromes (both primary and secondary to haematological malignancy or infection eg EBV, Herpes simplex or Varicella zoster virus, CMV)

DIAGNOSTIC CRITERIA

Diagnostic criteria have been drawn up by the Pan-American Group for Immune Deficiencies and the European Society for Immune Deficiencies (*Clin Immunol* 1999, **93**: 190-197).

Definite XLP
Male patient with lymphoma/Hodgkin's Disease, fatal EBV infection, immunodeficiency, aplastic anaemia or a lymphohistiocytic disorder and who has a mutation in SH2D1A/SAP/DSHP.

Probable XLP
Male patient experiencing death, lymphoma/Hodgkin's disease, immunodeficiency, aplastic anaemia, or a lymphohistiocytic disorder following acute EBV infection and having maternal cousins, uncles or nephews with a history of similar diagnoses following acute EBV infection.

Possible XLP
Male patient experiencing death, lymphoma/Hodgkin's disease, immunodeficiency, aplastic anaemia, or a lymphohistiocytic disorder following acute EBV infection.

LABORATORY INVESTIGATIONS

The diagnosis may be difficult, particularly if there is no family history. SAP studies are carried out at Great Ormond Street, phone to arrange Dr Cathy Cale [0207 4059200]. A courier will also need to be arranged – usual requirement 5-10 ml blood in EDTA plus a normal control.

- Serum immunoglobulins and electrophoresis
- Urine electrophoresis
- Lymphocyte subsets
- EBV serology (VCA & EBNA) and EBV PCR
- IgG to EBV VCA may be weak or become negative despite infection
- IgG to EBNA usually remains negative despite infection
- Other viral serology as indicated by clinical picture
- FBC and blood film
- LFTs
- Additional investigations as needed
- Bone marrow examination (look for haemophagocytosis, lymphoma)
- Biopsies (look for evidence of EBV infection in addition to usual studies.

TREATMENT

Acute Fulminant EBV Infection

This manifestation of XLP has a very high mortality with liver necrosis one of the main problems. The majority of damage is mediated by an over-exuberant cytotoxic T cell response rather than being directly due to EBV itself. Since this is very rare and optimal treatment protocols have not been established, advice should be sought from those with expertise in this area (GOS or Royal Free).

Replacement IVIG and aciclovir are usually recommended but may not be effective. Therapy with immunosuppressive agents is usually recommended but there is no standard protocol. Agents which have been used include steroids, etoposide, cyclophosphamide and ciclosporin**. There is a national protocol for management of this (HLH94). A search for a suitable bone marrow donor should be started early, since this is the only real hope for a long-term cure.**

Hypogammaglobulinaemia

IVIG should be given and optimal replacement ensured. Bone marrow transplantation should be considered in those with a family history of classical XLP. The place of BMT in other patients has not been fully established at present.

Lymphoma

Bone marrow transplantation is recommended for patients with lymphoma.

ASYMPTOMATIC FAMILY MEMBERS

Genetic counselling and testing should be offered to other family members. If the family prefer they can be referred to the local Clinical Genetics Service . Ensure that the referral letter contains detailed information about the nature of XLP and how to arrange the tests.

Bone marrow transplantation should be considered in affected family members prior to the development of EBV or disease complications. Immunoglobulin therapy should also be considered in an attempt to provide neutralising antibodies against EBV.

Patients and their families should be offered information on the PIA patient support group.

FOLLOW UP

Patients need regular (minimum 3 monthly) follow up to:

- Monitor for development of new infections
- Monitor for development of malignancy
- If there is any suspicion of lymphoproliferative disease patients should be referred promptly to Haematology
- Monitor for other complications such as vasculitis
- Monitor immune function (hypogammaglobulinaemia may develop over time)
- Monitor complications of treatment
- Those receiving immunoglobulin therapy should have monitoring bloods as per protocol.
- Those who have had bone marrow transplantation need multi-disciplinary follow up for the long-term complications of this procedure (growth retardation, chest disease, cataracts, late onset malignancy etc.).
- Patients and their families may also benefit from the support and advice of the PIA patient support group.

Saving Serum Samples

INTRODUCTION

Patients with primary immunodeficiency may be exposed to a range of blood products e.g.

IVIG, SCIG, C1Inhibitor concentrate and Fresh Frozen Plasma. There is a theoretical risk of the transmission of blood borne infection, in particular Hepatitis C, from any pooled human blood product.

All steps possible are taken to protect patients from this risk. Patients are only given blood products when there is a clear clinical need, the blood products used come from nationally and internationally accredited suppliers who follow rigorous quality control procedures to minimise the risk of infection transmission.

Nonetheless it is part of our duty of care to ensure that should such an infection occur it would be possible to determine as far as possible if this were from a blood product or another source. Should a blood product be causative it is then possible to identify the product and batch, if serum has been saved in accordance with the protocol. The policy to save patient serum to allow tracing of transmitted infection runs in association with an annual screening program for hepatitis C monitoring.

SAVING SERUM

CONSIDER TAKING CONSENT FOR ANNUAL SERUM STORAGE FOR THESE PURPOSES (LOOKBACK SURVEILLANCE FOR RELEVANT PATHOGENS) WHEN IMMUNOGLOBULIN THERAPY IS STARTED.

Saved patient serum may be used for other diagnostic purposes with consent e.g. patients with unexplained immunodeficiency at present may have new tests conducted on saved samples as greater understanding of the conditions arise. In the future, it may be possible to performance retrospective surveillance for prions on serum. **All of these things require informed consent from the patient.**

Patient serum should be saved:

- Immediately prior to the first infusion of a blood product and annually thereafter.
- If a patient switch blood products serum should be saved before the first infusion of the new product and annually thereafter.

Samples should be stored locally, preferably at minus 70/80 ^{o}C. Multiple aliquots are helpful.

Food Safety for Immunodeficient Patients

This information can be provided in an information leaflet:

ADVICE ON FOOD SAFETY FOR IMMUNODEFICIENT PATIENTS

Food safety guidelines are especially important to follow when your immune system is weakened. Germs and toxins (which are poisons made by the germs) can be passed to you by food that has been incorrectly stored, handled and cooked.

Food poisoning symptoms include fever, tummy cramps and headaches as well as nausea, vomiting and diarrhoea. You should seek medical attention if you suspect you have food poisoning.

The following recommendations may seem daunting, but bearing them in mind might save you a stay in hospital!

SHOPPING

Buy food as fresh as possible.
Check any 'best before dates'.
Keep the food cool if you are not going straight home. Carry a cool box and use it for perishable items rather than putting food directly into a hot car.
If you intend freezing any item such as meat or fish do so as soon as possible. Don't store it for a couple of days before freezing it.

STORAGE

- Your fridge should be between 2^{o}C and 4^{o}C, freezer at or below minus 18^{o}C
- Raw meats and fish - avoid drips contaminating food that is ready to eat.

Cook meat or fish within 2 days or freeze on day of purchase.
Keep your fridge, hands & kitchen clean.

PREPARATION

Make sure you **WASH YOUR HANDS** before preparing food and after touching meat/fish
If any part of a piece of food has gone mouldy (except blue cheese) throw out the entire piece - toxins can travel into the 'good' parts and poison them as well.
Marinade food in the fridge and not at room temperature.

Chopping boards- Keep a separate board for raw meat and fish
Wash fruit and salad vegetables before eating*.
Keep pets away from food and work surfaces.

*Some of you may be advised to take specific measures to avoid cryptosporidial infection, in which case you need to ensure that all water is appropriately treated.

COOKING

Shellfish and steamed fish MUST be cooked for at least 7 minutes.
Make sure everything is well cooked in the middle. If you like roasts consider a meat thermometer - centre should reach 70^{o}C - 85^{o}C.
Cook eggs thoroughly - make sure both the white and the yolk are hard.
Cook boiled or fried rice according to the instructions and eat it immediately -do not re-heat.
Barbecued food is a common source of food poisoning.

LEFT OVERS

Allow food to cool, wrap well and store in the fridge. Plastic boxes with well fitting lids are ideal for storage, or use foil or cling film.
Eat left-overs within 2 days. Reheat the food thoroughly, to >70^{o}C in the middle.
Remember microwaved food is hotter at the edges - stir!
Do not reheat cooked food more than once.

FOODS to AVOID

Beware shellfish especially in restaurants who only cook shellfish for 2-3 minutes
Avoid Sushi dishes with raw fish.
Avoid RAW i.e. unpasteurised milk e.g. soft ripened cheeses e.g. uncooked Brie and Camembert, some goats' milk.
Meat pastes and pâtés and cold rice are best avoided
Avoid raw or lightly cooked eggs in home-made mayonnaise, Caesar salad dressing or Hollandaise sauce, tiramisu, 'luxury' ice creams and mousses. Most mayonnaise purchased in jars will be made from pasteurised eggs and is OK

EATING OUT

Avoid grubby places!
Ask for your meat, fish or poultry to be well cooked or medium-well done.
When your food arrives check that is well cooked and hot.
Make sure that all foods which are supposed to be cold are properly chilled.
Be careful with food from salad bars. Check it is cool and fresh.

Enjoy your meal!

Antibody Deficiency And Pregnancy

ANTIBODY DEFICIENCY AND PREGNANCY

The major primary antibody deficiency affecting women is common variable immunodeficiency (CVID). Although there may be a possible increased risk of pelvic inflammatory disease, CVID is not known to impair fertility.

This guideline should be used in the care of antibody deficient women who are, or who plan on becoming pregnant.

PLANNED PREGNANCY

It is generally easier to manage the immunodeficiency aspects of pregnancy prior to becoming pregnant, so women of childbearing age should be asked to inform their immunologist if they are planning on having children so that appropriate measures can be taken in a relaxed pre-meditated fashion.

Establish liaison with the obstetric team (both Obstetrician and Midwife) responsible for the care of the pregnancy.

They may not be familiar with CVID and may need advice and reassurance. Occasionally surgical and obstetric teams react to CVID patients as if they have complete neutropenia - this is upsetting for the mother and leads to 'over-management' of the pregnancy. Education of the entire team is important - midwives must be quite clear that CVID is not HIV/AIDS and is not infectious.

Because of the possible increased risk of pelvic infection, examination and testing for chlamydia may be appropriate prior to attempted conception or at obstetric booking in.

Special considerations for patients on prophylactic antibiotics:

Various classes of antibiotics are not licensed for use in pregnancy.
The risk/benefit ratios for prophylaxis of infection differs from treatment of acute infection, so it is probably better to restrict prophylactic antibiotics to those known to be as safe as possible in pregnancy.
Information on these drugs changes with time, and it is safest to discuss all drugs for use in pregnancy with pharmacy in case new restrictions are in force.

Examples of antibiotics commonly used in this situation include:

Some antibiotics which can be used: If in doubt consult with microbiologist/drug information/Pregnancy section of BNF

PENICILLINS/AMOXYCILLIN are not known to be harmful in pregnancy
CEPHALOSPORINS are not known to be harmful in pregnancy, except for Cefpirome
ERYTHROMYCIN is not known to be harmful in pregnancy

Uncertain
AZITHROMYCIN is not known to be harmful in pregnancy, but the manufacturer advises that alternatives should be sought

Antibiotics which MUST be avoided include:

CIPROFLOXACIN - 4-quinolones have produced arthropathy in pregnant animals; the effect in humans has not been established - so probably should be avoided
TETRACYCLINE has caused skeletal defects in animal studies avoid
TRIMETHOPRIM- folate antagonist - teratogenic

Antibiotic therapy for acute infections:

Antibiotic therapy should not be denied to pregnant women with CVID.
Antibiotic therapy should be based on information from microbiological identification and sensitivity testing if possible (as per CVID guideline), and appropriate advice from Microbiology and Pharmacy should be obtained where necessary.

Pregnancy and Immunoglobulin replacement therapy:

Actions pre-delivery

- Pregnancy is not a contra-indication to IVIG therapy.
- The total dose usually needs to be increased on a g/kg basis as the patient's weight increases through gestation.
- Trough IgG may be done more frequently during the second and third trimester if the levels start to fall or weight increases rapidly, or there is a multiple pregnancy.
- Top up infusions are usually unnecessary prior to delivery.
- Patients should contact the Immunology team if they experience infections.

After delivery:

- IVIG dose will need to be reduced based on the patient's weight.
- Prophylactic antibiotic therapy may be restarted if curtailed during pregnancy
- Advice from Pharmacy for the latest information about antibiotics in breast-feeding should be sought - some antibiotics get into breast milk and are contraindicated.

For the commonest antibiotics used in this situation, restrictions on breast-feeding are:

No specific contraindication in breast feeding

AMOXYCILLIN
CEPHALOSPORINS (most OK, check in BNF)
ERYTHROMYCIN
TRIMETHOPRIM - short course only
AZITHROMYCIN - manufacturer advises only use if no alternative

Avoid in Breast Feeding
TETRACYCLINE

ADVICE

The mother may have concerns that her child will develop or even have primary immunodeficiency [PID]. She should be counselled prior to conception if possible.

There is no contraindication or special precautions necessary for Caesarian Sections.

Influenza Management Proposals 2005

INTRODUCTION

This guideline outlines the TRIC consensus strategies for preventing and treating influenza infection in patients with primary immunodeficiencies (PID). The measures taken depend on the level of infection in the community, and the patients' underlying disease.

BACKGROUND INFORMATION ABOUT INFLUENZA

Influenza types A, B and C can infect humans. There are many subtypes of influenza A, and immunity to one type does not necessarily lead to protection against the others. Minor changes (called antigenic drift) in the virus occur from year to year, so influenza vaccine has to be made to suit the most prevalent strains occurring each year. Influenza virus from other non-human species can 'interbreed' with the influenza virus that affects humans, and produce totally new strains of influenza, this is called antigenic shift. These new strains are especially dangerous because a vaccine will not be available until the 'new' virus emerges, and no one will have natural immunity to the new strain.

SYMPTOMS OF INFLUENZA

Many different respiratory viruses all cause similar symptoms, so in the absence of proof of infection with influenza virus, the term 'influenza-like illness' (ILI) is used. Influenza usually incubates in 2-3 days (sometimes 1-7 days). Typical symptoms for uncomplicated influenza are cough, malaise, fever, chills, headache, nasal congestion, sore throat and aching muscles. However, presentation can range from asymptomatic infection, through respiratory illness (particularly bronchitis and pneumonia), to multi-system complications affecting the heart, lungs, brain, liver, kidneys and muscles. Influenza associated death usually results from viral or bacterial pneumonia.

INFLUENZA VACCINE

Every year a new influenza vaccine is produced, providing approximately 70% protection against the commonest strains of influenza expected that year. The TRIC consensus strategy is that **patients with primary immunodeficiencies should be offered influenza immunisation every year**, as should their household members, to provide 'herd immunity' and prevent spread of infection. Immunodeficient patients may not respond reliably to immunisation, but universal immunisation is unlikely to do harm.

INFLUENZA DRUGS

Anti-viral drugs offer some additional protection against influenza, over and above that provided by immunisation, and can be used to treat influenza infection if started soon enough. They are likely to be effective against new strains of influenza, not present in the annual vaccine. However, the vaccine provides important protection against common strains so anti-viral drugs are not an acceptable alternative prevention on their own.

Oseltamivir (Tamiflu) is licensed for the treatment of influenza A and B in people of one year of age or older, within 48 hours of the onset of symptoms. The dose of oseltamivir should be adjusted for people with severe renal impairment. Viral resistance to oseltamivir has not been widely encountered. Oseltamivir is recommended for the post-exposure prophylaxis of influenza in at-risk people aged 13 years or older who are not effectively protected by vaccination.

Dosage depends on whether oseltamivir is being used to **treat** or **prevent** influenza infection.

Prevention dose in adults: 75 mg (one capsule) once daily for seven days, **or** for up to six weeks in an epidemic.

Treatment dose in adults: 75 mg (one capsule) twice daily for five days. Treatment has to start within 48 hours of onset of symptoms, otherwise it is ineffective.

Treatment dose in children: depends on the weight of the child, and is given twice daily for five days, providing initiated within 48 hours of onset of symptoms. Paediatric suspension (60 mg/5 ml is available). If child <15 kg use 30 mg bd. For children 16-23 kg use 45 mg bd. For children 24-40 kg use 60 mg bd. For children >40 kg use adult dose.

Oseltamivir is not licensed for the *treatment* of children <1 year old, and is not licensed for *prevention* in children <13 years old.

ALL TRIC CENTRES SHOULD UNDERTAKE THE FOLLOWING:

- Arrange for all PID patients, their household contacts, and clinical staff to have the annual influenza immunisation.
- Arrange for each PID patient to have a one week prophylaxis or treatment course of oseltamivir to hold at home (i.e. 14 x 75 mg capsules so could take 7d of 75mg od, or 5 d of 75 mg bd for prophylaxis or treatment in an adult)
- Arrange for each PID patient to have a course of self-initiated antibiotics for bacterial infections.
- Educate each patient about symptoms of influenza, and steps to take if exposed or infected (see separate TRIC leaflet). Emphasise that it is important that they should contact their GP / immunology team within 36 hours of exposure or symptoms.
- Check the Health Protection Agency (HPA) website on a regular basis to determine the level of influenza activity www.hpa.org.uk
- Notify other TRIC centres of a change of influenza activity status.
- Notify patients of a change of influenza activity status.

LEVELS OF INFLUENZA INFECTION IN THE COMMUNITY

Four levels of influenza infection are described, based on the current numbers of reports of influenza-like infections reported from general practitioners to the Health Protection Agency. Appropriate treatment and prevention measures depend on the current level of infection, and the type of underlying medical problem that the patient has.

STEPS TO TAKE ACCORDING TO INFLUENZA INFECTION LEVEL

Exposure to ILI is defined as being in *close contact* with someone who *lives in the same home* environment as a person who has been suffering from symptoms of an influenza-like illness.

1 – Normal Baseline

This is the normal level of influenza infection expected in the community, 0-30 infections per 100 000 population per week. No special measures are needed for PID patients, apart from annual immunisation. Reassure patients. Ensure patients have antibiotics at home for self-management of bacterial respiratory infections.

2 – Normal Seasonal Activity

Normal levels of influenza for the winter season, 30-200 infections per 100 000 population per week. The HPA will declare that increased levels of influenza are circulating. PID patients should receive a one week treatment course of oseltamivir on standby. If exposed to influenza-like illness start *prophylactic* dose within 48 hours (if ≥13 years old) for seven days. If symptomatic start *treatment* dose within 48 hours if ≥1 year old.

3 – Epidemic

Over 200 infections per 100 000 population per week. If exposed to an influenza-like illness: non-cellular immunodeficiency, and patients with good cardio-respiratory reserve – prophylaxis and treatment as for Level 2. For cellular immune defects, or patients with poor cardio-respiratory reserve – initiate oseltamivir prophylaxis (if 13 years or older) for up to six weeks. Treat symptoms of influenza-like illness with oseltamivir in any group, providing initiated within 48 hours of onset, and over 1 year old.

4 – Pandemic

Significant numbers of infections. HPA will notify all medical staff of pandemic influenza status. Prevention and treatment continue as for an epidemic. HPA may advise additional measures to be taken at the time.

X-linked hyper IgM syndrome (XHIM or HIGM 1)

INTRODUCTION

X-linked hyper IgM syndrome (XHIM or HIGM 1) is caused by mutations in the gene for CD154 present on the X chromosome. CD154 is a costimulatory molecule and the defect results in an inability of T cells to provide signals to B cells via the CD40/CD40-L pathway and vice versa. This results in failure of B cells to switch from making IgM to other immunoglobulin isotypes, and also causes defective T cell function leading to autoimmunity as well as cellular immunodeficiency. Affected individuals produce IgM, sometimes in increased amounts,

but have low IgA or IgG. IgM alone does not provide sufficient antibody mediated immunity, leading to increased incidence of sinopulmonary infections..

XHIM can present in a number of ways:
Recurrent bacterial and opportunistic infections, starting in the first year of life
Antibody deficiency in late infancy
In childhood with cryptosporidial diarrhoea, biliary disease or liver cancer
At any age with neutropenia
In adulthood, presenting with recurrent infections due to antibody deficiency, similar to individuals with common variable immune deficiency

WHO SHOULD USE THESE GUIDELINES

These guidelines should be used by all healthcare staff involved in the diagnosis and management of patients with suspected or confirmed hyper IgM syndrome

WHEN TO USE THESE GUIDELINES

XHIM should be considered in any male with:

- Recurrent bacterial infections
- Pneumocystis carinii infections
- Sclerosing cholangitis
- Cryptosporidium associated diarrhoea
- Hypogammaglobulinaemia, with normal or elevated IgM

All patients with suspected XHIM should be managed using these guidelines until the diagnosis is either confirmed or excluded.

DIAGNOSIS AND INVESTIGATIONS

The European Society for Immunodeficiencies (ESID) and the Pan American Group for Immunodeficiency (PAGID) have published the following diagnostic criteria – see ESID website at www.esid.org

Definitive

Male patient with serum IgG concentration at least 2 SD below normal and one of the following:

- Mutation in the CD40L gene
- Uncles, nephews or maternal cousins with confirmed diagnosis of XHIM

Probable

Male patient with serum IgG concentration at least 2 SD below normal for age and all of the following:

- Normal number of T cells and normal T cell proliferation to mitogens
- Normal or elevated numbers of B cells but no antigen specific IgG antibody
- One or more of the following infections or complications
- recurrent bacterial infections in the first 5 years of life
- pneumocystis carinii infection in the first year of life
- neutropenia
- cryptosporidium related diarrhoea
- sclerosing cholangitis
- parvovirus induced aplastic anaemia
- Absent CD40 ligand cell surface staining on activated CD4+ T cells as assessed by flow cytometry

Possible

Male patient with serum IgG concentration at least 2 SD below normal for age, normal numbers of B and T cells and one or more of the following:

- Serum IgM concentration at least 2 SD above normal for age
- Pneumocystis carinii infection in the first year of life
- Parvovirus induced aplastic anaemia
- Cryptosporidium related diarrhoea
- Sclerosing cholangitis

INVESTIGATIONS

- FBC
- Serum immunoglobulins
- Specific antibodies: TT, anti-pneuomococcal Ab+/- Hib, childhood vaccines if appropriate ie polio, pertussis, IgG anti-EBV IgM anti rubella
- Immunisation responses where appropriate
- Lymphocyte subsets: minimum panel CD3/4/8/19/56 plus CD154 on activated T cells
- CXR
- Liver function tests
- Liver ultrasound +/- biopsy/ERCP
- Other tests as necessary to exclude other immunodeficiency,

CD154 genotyping is currently only available in the UK at Great Ormond Street – contact Dr Cale or Dr Gilmour on 020 7813 8466. CD154 mutation identification may take up to 6 months.

Confirmation of XHIM has implications for other family members and referral for genetic counselling may be appropriate, see appropriate guidelines (See chapter on Genetic Counselling and Testing)

Genetic tests are required for women requesting carrier status and should be carried out when the mutation has been identified. Non-random inactivation of T cells does not occur in carriers of XHIM and therefore cannot be used to determine carrier status.

Laboratory features

- Serum concentration of IgG is usually <2g/l
- Serum IgM is not always elevated despite the name of the syndrome
- Normal number of T cells and normal T cell proliferation to mitogens
- Normal or elevated numbers of B lymphocytes in the peripheral blood
- No detectable antigen specific IgG antibody (functional antibody responses to vaccination or infection)
- Lack of expression of CD154 (CD40L) on the surface of activated lymphocytes

Some patients may express CD154 but at low levels, therefore the absence of CD154 is not a prerequisite for genetic testing; normal neonates may express low levels of CD40L and equivocal results should be repeated after 6 months, rather than with genetic testing

Alternative causes of raised IgM and primary antibody deficiency

These should be considered in boys with negative confirmatory testing and in girls with a hyper IgM phenotype. Other HIGM types have now been described:
HIGM 2, HIGM 3 (CD40 deficiency), HIGM 4 (B cell class-switch recombination defect)

Autosomal recessive hyper IgM type 2 is caused by activation induced cytidine deaminase (AID) deficiency. These patients often have prominent lymphoid hyperplasia
Common variable immunodeficiency (CVID): some adults with CVID have a defect in immunoglobulin class switching and there may be a monoclonal or oligoclonal increase in IgM which may be transient, in response to infection.
PBC can occur with CVID

MANAGEMENT

XHIM is a complex disorder: patients will require input from several specialities but **must** be under the care of the immunology team in your local TRIAC centre.

- The antibody deficiency component of XHIM is treated with immunoglobulin replacement infusions, aiming for a trough level of 8-10g/l, but guided by incidence of infections.
- Newly diagnosed asymptomatic neonates may have normal levels of immunoglobulins for age; in any case they should be given immunoglobulin infusions (recommendation grade D – see appendix A)
- Immunoglobulin replacement therapy should be given and monitored as per the appropriate guidelines (Overview of Immunoglobulin Therapy). There have been no clinical trials of immunoglobulin replacement therapy in XHIM, but there is no reason to suggest that the delivery, efficacy, risks of treatment should differ from other primary antibody deficiencies
- Intercurrent infections should be investigated and treated promptly with adequate courses of antibiotics: exclude opportunistic infections
- Co-trimoxazole (Septrin) should be given as prophylaxis against *Pneumocystis carinii* pneumonia (PCP)
- Refer for consideration of bone marrow transplant (BMT) and identify potential bone marrow donors. Even when immunoglobulin is given, mortality approaches 50%[1], but observational evidence suggests that BMT may be curative[1].
- Refer to a hepatologist if liver complications suspected eg abnormal LFTs: see chapter on Hepatology Services for Immunodeficient Patients
- Live vaccines **must not** be given to these patients
- Oral polio vaccine should not be given to household contacts; inactivated vaccine should be offered as an alternative (D)
- The patient/parent(s)/guardian must be informed of the risks associated with cryptosporidium and the measures to take to avoid infection: provide a copy of the

Primary Immunodeficiency Association's Information Sheet no.2 "Cryptosporidiosis" or the TRIAC leaflet on avoiding Cryptosporidia

- The Bouchier Report 1988 provides advice on limiting exposure – see Appendix B for a summary
- Possible drugs for cryptosporidium prophylaxis include azithromycin, nitazoxamide or paromomycin but evidence of efficacy is lacking
- The consequences of cryptosporidium infection are severe and therefore surveillance for cryptosporidium and liver and biliary tree disease should be carried out, although there is no good evidence of exactly how this should be done. There is evidence that molecular screening appears to be more sensitive than stool microsocopy[2] (B) Swansea is the cryptosporidium reference centre and can perform immunofluorescence studies on stool. PCR may be available on a research basis from HPA Collingdale (Dr Jim McCloughlin)
- Monitor for cryptosporidium infection: stool samples should be taken 3 times per year and whenever there is diarrhoea – molecular screening is recommended if available; screen for microsporidium when there is no evidence of cryptosporidium. Ensure that the local microbiology protocol does not prevent the use of microscopy ion formed stool (which may still be crypto positive)
- Monitor for liver and biliary tree damage: LFTs every 6 weeks and yearly liver ultrasound; gastroenterology advice should be sought even in asymptomatic cases
- For established cryptosporidium infection, involvement of a gastroenterologist and microbiologist is recommended. Paromomycin has been recommended, but the evidence for this is, at best, level C. A recent RCT in HIV infection showed no difference from placebo[3].
- Full blood counts should be taken every time there is an infection to check for neutropenia related to XHIM and aplastic anaemia from parvovirus infection.

RISK MANAGEMENT/AUDIT

The risks of untreated XHIM are overwhelming infection and liver disease. Even with immunoglobulin replacement therapy there is a substantial risk of mortality, therefore these patients require early referral for appropriate specialist input, including gastroenterologists and to supraregional centres for possible BMT. Close monitoring for complications is important and requires audit.

References

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Morgan U M, Pallant L, Dwyer B W et al: Comparison of PCR and microscopy for detection of cryptosporidium parvum in human faecal specimens: clinical trial. *Journal of Clinical Microbiology* 1998 **36**(4): 995-8

Hewitt R G, Yiannoutsos C T, Carey J T, Geiseler P J et al: Paromomycin: no more effective than placebo for treatment of cryptosporidiosis in patients with advanced HIV infection. *Clinical Infectious Diseases* 2000 **31**(4) 1084-92

Prevention, Diagnosis and Treatment of Cryptosporidosis

INTRODUCTION

Cryptosporidium is a single celled parasite that can only grow in a living host. The parasite develops in the gut lining where it goes through various stages of a complex life cycle. When the oocysts are swallowed, sporozites are released which attach themselves to the gut lining. Patients with hyper IgM syndromes, SCID, and some patients with other hypogammaglobulinaemic conditions are at high risk of this infection.

Symptoms include: loss of appetite, nausea, abdominal pain, and can be followed by profuse, watery diarrhoea, and vomiting (especially in children). Incubation varies (2-7 days). There may be a mild fever and weight loss.
In immunocompetent individuals symptoms may last for one to three weeks but some can last longer although not usually more than a month. In people with immunodeficiency, the infection can persist and occasionally have serious consequences such as sclerosing cholangitis.

WHEN TO USE THIS GUIDELINE

1. In immunodeficient patients with current or previously documented infection.
2. Patients with a particular susceptibility to cryptosporidia:
-XHIM
-SCID and related disorders

HOW TO USE THIS GUIDELINE

Prevention
This infection may be acquired from consumption of water, from animals, the environment, and also via person to person spread. It may be transmitted by unpasteurised milk, and the consumption of offal and occasionally undercooked meat.

Drinking Water
Simply boiling the water in the kettle is sufficient to kill cryptosporidia. **Only** boiled, cool water should be used for drinking, in the preparation of food, making ice cubes etc. Tap water is satisfactory for general purposes such as hand washing, dishes, and clothes and for showering and bathing. Do not assume all commercially bottled water is free from pathogens, so should also be boiled. Water filters cannot be relied upon.

Other measures

- The risk of passing the oocysts can greatly be reduced by good personal and domestic hygiene.
- Washing of hands followed by complete drying of the hands. (especially if preparing uncooked foods).
- Surfaces should be washed down with a soapy disinfectant solution followed by thorough drying of the surface.
- People with compromised immunity may be advised to limit their contact with livestock and domestic pets.
- Exercise scrupulous hand hygiene measures with children in nappies or with diarrhoeal diseases.
- Children visiting farms should be warned not to eat sweets or suck their fingers, they should wash their hands before eating again
- Do not swallow water in swimming pools, as this can be contaminated with Cryptosporidium.
- Beware oocysts are not reliably killed by household bleach.
- Beware that hands may be contaminated by footwear.

Diagnosis

Diagnosis is by isolation of *Cryptosporidium* (organism or genome) from the gut or stool samples; direct microscopy, immunofluorescence and PCR techniques can all be used. Be aware that some microbiology departments do not routinely test formed stools for *Cryptosporidium*.

Treatment

See hyper-IgM guidelines for the sequence of antimicrobial agents to use.

Adequate hydration is essential. Failure to do so may lead to dehydration and require hospital admission.

RISK MANAGEMENT

Strategies for primary prevention, screening and early treatment can be subject to audit.

Diagnosis & Management of Severe Combined Immunodeficiency (SCID)

INTRODUCTION

Severe combined Immunodeficiency (SCID) patients usually develop failure to thrive and persistent diarrhoea, respiratory tract symptoms and/or thrush in the first 2-7 months of life. Pneumocystis jiroveci pneumonia, significant bacterial infections and disseminated BCG infection are common presenting illnesses.

Occasional patients do not have failure to thrive and are not recognised to have immunodeficiency until later. SCID is usually fatal within the first two years of life unless the patient is treated with extremely restrictive isolation, haemopoietic stem cell transplant or therapy that replaces the abnormal gene or gene product.

WHEN TO USE THIS PROTOCOL

The full SCID protocol *must* be followed in any child suspected to have SCID because of:

- A persistently low unexplained lymphocyte count <3000/μl (<3.0 $x10^9$/L) in any child < 2 years

- Less than 20% $CD3^+$ T cells in any child < 2 years (unless DiGeorge / variant syndrome or other recognised cause eg HIV infection)
- Maternal lymphocytes detected in the circulation
- Recurrent diarrhoea, failure to thrive and opportunistic infections
- Strong clinical suspicion of SCID

HOW TO USE THIS PROTOCOL

In any child with suspected SCID, contact your local Immunology service first for advice. Cases may require input/referral to Paediatric Immunology at GOS/Newcastle.

Great Ormond Street Hospital (0)20 7405 9200
Newcastle General Hospital 0191 2336161

Immediate steps to take:

- Move child immediately to protective microbiological isolation
- Blood products must be CMV-negative and irradiated (not applicable to IVIG)
- No live vaccines (including BCG and MMR)
- No contact with people who have recently received BCG
- No contact with people with active infections
- Consider prophylactic co-trimoxazole
- Arrange urgent lymphocyte phenotyping (phone laboratory to arrange; EDTA sample)
- Send appropriate samples for microbiology (including opportunistic infections)

SCID is a paediatric emergency – if suspected, seek urgent advice from Immunology

DIAGNOSTIC CRITERIA

The ESID Guidelines for diagnosis of SCID are:

Definitive SCID

Male or female patient less than 2 years of age with either:

a) engraftment of transplacentally-acquired maternal T cells; or
b) less than 20% CD3+ T cells, an absolute lymphocyte count of less than 3000/ul (<3.0 x109/L) and at least one of the following:

- Mutation in the cytokine common gamma chain γ_c
- Mutation in Jak3
- Mutation in RAG1 or RAG2
- Mutation in IL-7Rα
- ADA activity of less than 2% of control or mutations in both alleles of ADA

Probable SCID
Male or female patient less than 2 years of age with <20% CD3+ T cells, absolute lymphocyte count of less than 3000/ul (<3.0 x109/L) and proliferative responses to mitogens of <10% of control; or the presence of maternal lymphocytes in the circulation.

There is an urgent requirement in children suspected of having SCID to:

- Recognise the diagnosis quickly
- Avoid live vaccines
- Use irradiated and CMV negative blood products
- Consider prophylaxis against *Pneumocystis jiroveci* pneumonia
- Refer to Supraregional SCID Units in London (Great Ormond Street Hospital) or Newcastle (Newcastle General Hospital)

LABORATORY FEATURES

- Lymphopenia (<3.0 x 10^9/l)
- T cell lymphopenia (CD3 positive T cells <20%)
- Low lymphocyte proliferation (PHA response <10% control)
- Maternal lymphocytes in circulation where maternal engraftment has occurred
- Hypogammaglobulinaemia may or may not be present
- Eosinophilia may be present

INVESTIGATIONS

Do not delay referral if there is a high clinical suspicion in order to complete investigations:

- Urgent FBC with differential WCC
- Lymphocyte Immunophenotyping
- Appropriate samples for microbiology including opportunistic infections (serology usually unhelpful because of immunodeficiency)
- Consider HIV testing (mother and child)
- Radiology as appropriate

Diagnosis and Management of Hereditary Angioedema (HAE)

INTRODUCTION

Hereditary angioedema (HAE) is characterised by recurrent cutaneous and mucous membrane swellings in any part of the body. The prevalence is 1 in 50,000 across all ethnic groups. HAE is due to a deficiency of C1 inhibitor and is inherited in an autosomal dominant fashion. Although most patients have a positive family history, approximately 25% of cases are due to new mutations. Over 100 different C1 inhibitor gene mutations have been described.

HAE type I (up to 85% of patients)
Deficiency of C1-inhibitor protein in the plasma as only one gene functions. Plasma levels are 5-30% of normal

HAE type II
The quantity of circulating C1-inhibitor is normal (or even raised) but it is non-functional

HAE type III
Is a dominantly inherited form of angioedema, with predominant female inheritance, characterised by a normally functional C1inh Protein and C4 levels. This guidance is not applicable to this condition.

CLINICAL FEATURES

Patients experience recurrent attacks of peripheral or laryngeal angioedema or abdominal pain (due to bowel/mesenteric oedema). Attacks are not associated with itch or urticaria although there is occasionally a prodromal rash. Involvement of tongue, pharynx and larynx contributes to the mortality. Phenotype is variable in frequency, severity and site of attacks. 40% of patients have their first attack by the age of 5 years, 50-75% by the age of 12 years. Attacks can be precipitated by minor trauma such as dental work. Other triggers include drugs (ACE inhibitors and oestrogens), infections and emotional stress.

DIFFERENTIAL DIAGNOSIS

Acquired C1 inhibitor deficiency
C1 inhibitor deficiency may be acquired either due to the development of autoantibodies to C1 inhibitor or consumption of C1 inhibitor (e.g. in active lupus or in lymphoproliferative disease). The clinical and laboratory features of acquired C1 inhibitor deficiency are similar to HAE but patients are usually older and may not have overt evidence of an underlying disease at the time of presentation.

Angioedema secondary to other causes
E.g. type 1 hypersensitivity, drugs, physical causes and idiopathic angioedema (some of which have autoantibodies to IgE receptors).

DIAGOSTIC CRITERIA / LABORATORY FEATURES

- C4 levels are always low during attacks, and usually between attacks – if untreated
- Normal C4 level during an attack essentially excludes C1 inhibitor deficiency.
- C1 inhibitor levels are low in the majority of Type I and acquired cases.
- In the minori ty of cases with normal/raised quantitative C1 inhibitor levels, C1 inhibitor function is reduced (Type II)
- Patients with acquired C1 inhibitor deficiency typically have low C1q levels (normal in HAE) and may have other features such as paraproteins and autoantibodies

INVESTIGATION

- C3 and C4 levels (if necessary, during an attack)
- Quantitative C1 inhibitor levels
- Functional C1 inhibitor levels if necessary (PRU, Sheffield or Immunology, Leicester)
- Baseline FBC (a raised WCC should raise suspicion of other/co-existing pathology)
- U&E
- LFT
- Consider lipids depending on other cardiovascular risk factors.
- Baseline Hepatitis-BsAg, Hepatitis-C antibodies and store serum for look-back testing for infectious agents with written informed consent.
- Additional investigations as required to exclude other causes of angioedema
- Other investigations as required by the clinical picture.

Patients should be counselled on the risk:benefit ratio of C1inh therapy and

prospective consent obtained for future therapy.

MANAGEMENT OF ACUTE ATTACKS

- Treatment of **acute attacks** depends on severity and site of involvement.
- Peripheral swellings usually do not require treatment
- Life-threatening airway involvement requires prompt infusion of appropriate weight-related dose of C1-inhibitor concentrate (usually 1000-1500 plasma units in adults; adjust dose in children).
- Where C1 inhibitor concentrate is not available and symptoms are life-threatening, 1 to 2 units of fresh frozen plasma (FFP) may be given instead although there are rare anecdotal reports of worsening of angioedema with FFP
- Tracheostomy should be considered if un-responsive to treatment
- Severe abdominal attacks may also be treated with C1 inhibitor concentrate / FFP to terminate a severely painful attack. Significant improvement should be expected within an hour in most cases. If this does not occur the diagnosis should be reconsidered.
- Non life-threatening attacks may be aborted (less rapidly) by prompt treatment with tranexamic acid orally.
- Adrenaline, anti-histamines and steroids are of doubtful benefit

PREVENTION OF ATTACKS

The need for prophylactic treatment should be assessed on an individual basis and depends upon the frequency and severity of attacks (which may change over the years), age, family planning and patient preference.

Useful **long-term prophylaxis** can be achieved with antifibrinolytic agents (tranexamic acid) and/or androgens (usually danazol).
Anabolic steroids should be avoided in pregnancy (due to teratenogicity) and, where possible, in children.

Short term prophylaxis for surgical procedures (eg traumatic dental work, intubation, bronchoscopy, upper GI endoscopy, any potentially traumatic ENT examination of upper airways) should take into account the nature of the procedure, the severity of HAE and response to previous procedures.
Patients considered to be at high risk of laryngeal obstruction should normally receive 1000- 1500 Plasma Units (slow iv) of C1-inhibitor shortly before (0-24 hours) the planned procedure with a further dose available in the event of developing angioedema. They should also be observed overnight in hospital.
Patients considered to be at lower risk may have procedures performed as day cases with either pre-medication with C1 inhibitor concentrate as above or maximal dose danazol or tranexamic acid started 1 week prior to, and continuing for 24 hours after the procedure.
Prophylaxis is not normally required for minor surgical procedures such as removal of a mole or toenail under local anaesthesia.

Pregnancy is usually (but not always) associated with a reduction in attacks. Danazol is known to be teratogenic and should be stopped at least 3 months prior to conception and avoided throughout pregnancy.
Tranexamic acid is not known to be teratogenic in pregnancy although is best avoided. Should treatment with tranexamic acid be considered, women should be counselled regarding the uncertainties and potential risks. C1-inhibitor concentrate can be used, as in the non-pregnant women. The obstetrician should be made aware of the condition and the need to have ready access to C1 inhibitor concentrate at time of delivery.
C1 inhibitor concentrate is not required for normal vaginal delivery but is required for general anaesthesia & operative delivery.

Hepatitis B immunisation should be considered.

GENERAL ISSUES

Patient education is critical.
All patients should be provided with a "to whom it may concern" letter outlining management of acute attacks TR28
Patients should be advised to obtain Medic Alert bracelet or equivalent.
A detailed family history should be obtained and testing offered for other potentially affected individuals.
Genetic counselling can be arranged with local genetic services if required.
All patients should be offered contact details of patient support groups such as the Primary Immunodeficiency Association (PIA) who can provide invaluable support and advice to patients and families.

FOLLOW UP

Patients with HAE need regular follow-up to:

- Assess disease activity and need for treatment
- Monitor for complications of treatment especially hepatitis/cholestasis/hepatoma in patients on danazol.
- Assess overall health
- Continued education and monitoring of compliance/knowledge of treatment options and risks

All patients on treatment require:

- C4 and C1 inhibitor levels if required
- Hepatitis BsAg and Hepatitis C antibodies annually if received C1Inh concentrate.
- Annual storage of serum for look-back screening –starting pre-treatment

Patients on anabolic steroids

- 3-6 monthly LFTs
- Annual lipids
- Liver ultrasound and alpha-fetoprotein if LFTs abnormal (ALT>2x normal).
- USS liver 2 yearly (annual if>10 years Rx)

Patients on anti-fibrinolytic agents

- 6 monthly LFTs and FBC
- Routine eye examination is not recommended by ophthalmologists. However patients should be warned to report visual symptoms especially halos around lights and, in these circumstances an ophthalmology opinion should be obtained.
- Prothrombotic screen where required

Letter for Patients with Hereditary Angioedema (HAE, C1 Inhibitor Deficiency)

This information can be provided in an information leaflet:

To Whom it May Concern

Re: [Name of Patient and demographic details]

Diagnosis: Hereditary Angioedema (HAE / C1 inhibitor deficiency)

This patient suffers from Hereditary Angioedema resulting in recurrent episodes of swelling affecting the airway, gut or limbs. Surgery and dental work may trigger attacks.

When is treatment required?

Laryngeal/pharyngeal oedema is life threatening and should be treated immediately with purified C1 inhibitor. Adrenaline, anti-histamines & steroids are unlikely to help.

Gastrointestinal angioedema may cause severe abdominal pain. Symptoms usually begin to improve within 30-90 minutes of receiving purified C1 inhibitor. If symptoms persist, other diagnoses should be considered.

Prophylactic C1 inhibitor is required to cover procedures that involve potential trauma to the upper respiratory tract e.g. surgery, intubation, gastroscopy, bronchoscopy, dental work. Ideally purified C1 inhibitor should be given with the premed but can be given in theatre.

How to obtain and give C1 inhibitor concentrate (Trade name BERINERT P)

C1 inhibitor is available at **[Insert name of hospital]** but is **NOT** available at all other hospitals

C1 inhibitor should be obtained from the **Emergency Department.** Out of hours contact the on-call pharmacist.

The dose of C1 inhibitor is 1000-1500 units (2-3 vials) for adults, infused intravenously over 10 minutes.

Symptoms should improve within 30-90 minutes of treatment. If they do not, consider other potential causes of the problem.

If C1 inhibitor is unavailable **and** symptoms are immediately life threatening, 1-2 units of fresh frozen plasma should be given.

In the event of difficulties, please contact the Immunology medical staff at the number above or through the hospital switchboard.

Availability of C1 inhibitor concentrate at local hospitals

BASSETLAW

Bassetlaw General Hospital - obtain from Pharmacy
Bleep on call pharmacist via switchboard

KETTERING
Kettering General Hospital - obtain from Pharmacy
Bleep on call pharmacist via switchboard

LEICESTER
Leicester Royal Infirmary – obtain from Pharmacy
Bleep on call pharmacist via switchboard

NOTTINGHAM
Queens Medical Centre / University Hospital Nottingham – obtain from Blood Transfusion Telephone ext 43660 (office hours) / bleep on call MLSO for Blood Transfusion (out of hours)

SCUNTHORPE
Scunthorpe General Hospital – obtain from Accident & Emergency

SHEFFIELD
Northern General Hospital and Royal Hallamshire – obtain from Pharmacy
Bleep on call pharmacist via switchboard

Diagnosis and Management of CGD

INTRODUCTION

Chronic granulomatous disease (CGD) is caused by a genetic defect (either X-linked or autosomal recessive) in one of the components of the NADPH oxidase complex required for the generation of reactive oxygen species used to kill phagocytosed pathogens. CGD is characterised by recurrent infections at epithelial surfaces eg skin, lungs and gut. Common infecting organisms include catalase-positive bacteria and fungal infection especially *Aspergillus species* but also *Candida albicans*, *Cedosporium apiospernum* and *Chyrosporium zonatum*. The prevalence of CGD is approximately 1 in 200,000. Most patients develop symptoms before the age of two years but diagnosis may be delayed into early adult life. Boys with X-linked CGD have more severe clinical phenotype and present earlier than patients with autosomal recessive CGD.

DIAGNOSTIC CRITERIA / LABORATORY FEATURES

Diagnostic criteria have been drawn up by the Pan-American Group for Immune Deficiencies and the European Society for Immune Deficiencies (Clin Immunol 1999, 93 p190-197).

Definitive CGD
Male or female patient with abnormal NBT or respiratory burst in activated neutrophils (less than 5% of control) who has one of the following:

- Mutation in gp91, p22, p47 or p67 phox.
- Absent mRNA for one of the above genes by Northern blot analysis.
- Maternal cousins, uncles, or nephews (or other close relatives) with an abnormal NBT or respiratory burst.

Probable CGD
Male or female patient with abnormal NBT or respiratory burst in activated neutrophils (less than 5% of control) who has one of the following:

- Deep-seated infection (liver, peri-rectal or lung abscess; adenitis; or osteomyelitis) due to *Staphlococcus*, *Serratia marcescens*, *Candida*, or *Aspergillus* or organisms listed above
- Diffuse granulomata in respiratory, gastrointestinal, or urogenital tracts.
- Failure to thrive and hepatosplenomegaly or lymphadenopathy.

CLINICAL FEATURES

- Infections
- Lymphadenitis
- Skin and subcutaneous abscesses
- Pneumonia
- Liver abscesses
- Osteomyelitis
- Failure to thrive
- Hepatosplenomegaly
- Granulomatous inflammation
- Colitis (diarrhoea)
- Gastric outlet obstruction
- Urinary tract obstruction
- Pericardial effusion
- Chorioretinitis
- Other features
- Iron deficiency anaemia - often resistant to therapy

- B12 deficiency secondary to malabsorption
- Mouth ulcers

Pathogens
Catalase positive bacteria – *S Aureus*
Gram negative enterobacteria – *Salmonella*, *Klebsiella*, *Aerobacter* S*erratia*, *Pseudomonas (Burkholderia) cepacia*
Fungi – *Aspergillus, Candida, Scedosporium, Apiospernum, Chyrosporium Zonatum*

CGD should be considered in all adults or children who present with:

- Recurrent abscesses - especially if deep-seated
- Osteomyelitis
- Orofacial or other granulomata
- Liver abscess
- Infections with unusual catalase-positive organisms eg aspergillus, nocardia, serratia

DIFFERENTIAL DIAGNOSIS

- Leukocyte adhesion deficiency
- Sarcoidosis
- Hyper IgE syndrome
- CVID
- Glucose-6-phosphatase dehydrogenase deficiency
- Crohn's disease
- Neutropenia

INVESTIGATION

Investigations should include:

- Respiratory burst - may be measured in PMA stimulated neutrophils by either the Nitroblue Tetrazolium Test (read by an experienced observer to minimise the risk of reporting a falsely normal result) or by flow cytometry using DHR reduction; carrier detection may be best done by DHR flow cytometry – beware false negative results in severely infected patients and abnormal but not absent curves in AR cases.
- FBC
- Liver function tests, urea & creatinine
- C reactive protein
- Serum immunoglobulins
- Baseline Aspergillus precipitins or EIA
- Other investigations (including microbiology and imaging) as required by the clinical picture to identify complications or exclude other diagnoses.

Initial screens by western blotting for gp91phox available through GOSH.

The genetic lesion may be identified by sending samples to Dr Dirk Roos, CLB, Plesmanlaan 125, 1066 CX Amsterdam, The Netherlands, direct telephone 20-512-3377, fax 20-512-3332.

GENERAL MANAGEMENT

- Early diagnosis
- Prompt investigation and treatment of infections
- Anti-microbial prophylaxis
- Avoid live **bacterial vaccines (including BCG and oral typhoid)** but may have live viral vaccines eg polio and MMR**.**
- Bone marrow transplantation/gene therapy may have a role in some patients – discuss with Supraregional NSCAG centres (GOSH and NGH)

TREATMENT

Acute infections

- Patients need to be aware of the importance of prompt investigation and treatment of infections.
- Clinicians must maintain a high degree of suspicion of infection
- Lesions should be considered infective until proven otherwise
- The possibility of fungal infection should be considered
- Presumptive treatment should be initiated before culture results are available
- Where possible all appropriate samples should be obtained for culture
- Antibiotics with good penetrance into neutrophils should be used to treat acute infections after discussion with your local microbiologists. Useful drugs include: flucloxacillin, ciprofloxacin, azithromycin, teicoplanin, co-trimoxazole, fosfomycin, rifampicin, liposomal amphotericin for fungal infection (usual dose 5mg/kg/day). Consider

additional therapy if needed such as intravenous itraconazole 5mg/kg to reach appropriate serum levels, or flucytosine 150mg/kg/day. Prolonged courses of antibiotics are often necessary.
- Interferon gamma may be useful in persistent infections 50mg/m^2 surface area given subcutaneously 3 times weekly
- Infusion of leukophoresed normal ABO- & rhesus -matched granulocytes may be useful in severe unresponsive infections

Granulomatous complications
- May respond to topical or systemic steroids but may relapse on stopping
- Additional agents eg ciclosporine, sulphasalazine, thalidomide and G-CSF have been used

Long term management
- Patient education
- All lacerations and abrasions should be cleaned promptly with antiseptic
- Attention to maintenance of general skin and dental hygiene.
- Avoidance of fungal infections (minimise contact with compost, hay, straw, house plants, humidifiers, use of cannabis, building sites/construction work, damp buildings, rotten vegetation)
- Avoid smoking
- Anti-microbial prophylaxis (recommended in the majority of cases
- Co-trimoxazole 960mg daily in adults (adjust dose in children)
- Itraconazole – starting dose 5mg/kg daily (adjust in children if LFTS abnormal- trough levels may be checked – measure after 10 days)
- Interferon gamma may provide additional protection - 50mg/m^2 surface area given subcutaneously 3 times weekly (not used routinely)
- Consider antibiotic prophylaxis for dental and surgical procedures.
- Avoid live **bacterial** vaccinations e.g. BCG and Typhoid (live viral and non-live vaccines may be given)
- Bone marrow transplantation has been undertaken successfully in CGD and should be considered for newly diagnosed infants with X-linked CGD and a matched sibling donor. The place of matched unrelated BMT and BMT in older patients is not clear but individual cases may be discussed with the supra-regional centres (GOSH and Newcastle GH).
- Gene therapy – initial trials are underway (contact Dr Adrian Thrasher, GOS).

FOLLOW UP

Patients with CGD need regular follow up to:

- Assess overall health (and growth and development in children)
- Monitor efficacy and complications of treatment
- Social / educational / psychological issues etc
- Monitor for complications of disease
- Infections
- Granulomatous disease
- Pulmonary disease

ROUTINE INVESTIGATIONS / ASSESSMENT

Blood should usually be taken 3 monthly for:

- FBC
- U&Es
- LFTs
- CRP
- Regular Aspergillus precipitins / EIA - may be useful as baseline when investigating acute infections unresponsive to initial treatments
- Itraconazole levels -if required
- Consider imaging eg CXR, CT and PFTs, as required clinically
- Other investigations as indicated by the clinical picture

GENETIC COUNSELLING

Genetic counselling and testing should be offered to other family members as appropriate. If the family prefer, they can be referred to the local Clinical Genetics Service. Ensure that the referral letter contains detailed information about the nature of CGD and how to arrange the tests.

Prenatal diagnosis can be offered in CGD – either:

- Chorionic villous sampling (CVS) - where the genetic lesion has been identified
- Neutrophil respiratory burst on fetal blood taken during the second trimester.

OTHER

Patients and their families should be offered information on the PIA patient support group and the CGD Trust.

A CGD specialist nurse based at GOSH is available for the support of all UK patients.

Patients With Recurrent Boils

INTRODUCTION

Individuals with recurrent skin abscesses are frequently referred to immunologists for investigation of suspected immunodeficiency. The commonest pathogen responsible is *Staphylococcus aureus*. Immunodeficiency is an unusual cause of recurrent staphylococcal infection. There is a broad differential diagnosis, and a staged approach to testing is recommended to avoid unnecessary and expensive tests being performed prior to the exclusion of common disorders.

The differential diagnosis includes:

- Chronic staphylococcal carriage. [swabs]
- Diabetes mellitus. [blood glucose]
- Alcohol abuse. [history]
- HIV infection. [HIV test, counselling]
- Specific granule deficiency. [FBC film]
- Dermatitis artefacta.
- Cushing's syndrome. [Cortisol/ACTH]
- Chronic granulomatous disease [NBT]
- Hyper-IgE syndrome. [IgE levels]
- Other hypogammaglobulinaemic states. [Igs]
- Type Ib glycogen storage disease.
- Glucose-6-phosphate dehydrogenase deficiency. [G6PD levels]
- Chediak Higashi syndrome. [FBC film]

WHEN TO USE THESE GUIDELINES

Minor staphylococcal skin abscesses are common in the healthy population. There are no evidence-based guidelines for when recurrent boils require investigation, but it would be reasonable to consider investigating patients with:

- More than one episode/year of boils requiring antibiotics to clear
- More than one episode/year of boils requiring surgical drainage
- Boils caused by unusual organisms e.g. *Pseudomonas.*

HOW TO USE THESE GUIDELINES

Investigations are best performed in two stages.

Stage 1 investigations

Exclude the commonest causes of recurrent boils:

Exclude diabetes by random blood glucose and urinalysis – follow up any abnormality with fasting glucose testing and if required a formal glucose tolerance test and HbA1c assessment
Full blood count and differential, particularly neutrophil count
Serum IgE
Serum IgG, IgA and IgM
Swab skin around the boil, groin, nose and anogenital region and send for culture and sensitivity
NBT test

Stage 2 investigations

These will need to be discussed with senior clinical staff, but may include:

- Wright's stain of blood film for specific granule deficiency
- Interval FBCs for cyclical neutropenia (2-3 times weekly for four weeks)
- HIV test (Counselling will be required)

Other investigations may include assessment of neutrophil chemotaxis, testing for G6PD deficiency, etc.

Management of boils thought to be due to staphylococcal colonisation

Treatment consists of hygiene measures and skin disinfection
Naseptin [0.1% Chlorhexidine], or Bactroban Nasal cream [Mupiricin 2%]. Consider separate tubes for each nostril.
Hibiscub [Chlorhexidine gluconate 4% baths [dilute 1 in 10 and rub all over with a clean face cloth avoiding broken skin and eyes] or Ster-Zac bath concentrate
[Triclosan 2%] [1 Sachet per bath], once daily for seven days.
Hibiscrub [Chlorhexidine gluconate 4%, used as a hair rinse during bathing for seven days
Change towels and face cloths daily, do not share, wash towels in hot 60 degree wash.

- Conscientious use of this protocol is needed to enable maximum effectiveness
- Other family members should be screened for carriage and should also be treated at the same time.
- Other measures: don't share towels, consider changing bedding and clothing daily.

Note: none of these measures are evidence-based, so these are listed as a consensus viewpoint; local practice may vary.

RISK MANAGEMENT

Failure to diagnose an underlying cause of recurrent boils with subsequent metabolic derangement or overwhelming infection remains the major risk factor. Patients with severe/recurrent abscesses are generally keen to have a rapid diagnosis made and treatment instituted, therefore risk reduction involves informing referring GPs and hospital practitioners of the diagnostic services that the Immunology Clinic can provide for these patients.

Patient Information on Recurrent Boils

This information can be provided in an information leaflet:

INFORMATION FOR PATIENTS WITH RECURRENT BOILS

Introduction

Human skin is home to millions of bacteria. The most common type of bacteria living on the skin is called staphylococcus. This is completely natural and helps the skin keep out infection. However, sometimes skin can become colonised with more aggressive strains of staphylococcus. These may cause problems, such as outbreaks of pustules or boils.

The cleansing procedure reduces the numbers of bacteria on the skin and allows more benign bacteria to take the place of the problem bacteria.

People living in the same household are very likely to be colonised with similar strains of bacteria. For this reason, everyone in the household should be treated, even if they have no problems.

Who should undergo skin cleansing?

People with recurrent boils or pustules
All people in the same household

Instructions:

Treatment consists of hygiene measures and skin disinfection using some of the following (as directed by your Immunologist):

In the nose: use the prescribed nasal ointment, twice daily. Rub a small amount into each nostril. Use up the whole tube over a two week period. Treat right and left nostrils with separate tubes – don't confuse them! Example ointments include: Bactroban, Naseptin.
On the skin: rub the skin cleanser over the whole skin using a face cloth – do this once daily for one week. Dilute the cleanser according to manufacturer's instructions. Examples include: Triclosan, Ster-Zac.
For the hair: use the hair rinse daily for seven days. Examples include: Hibiscrub.

Change towels and face cloths daily, do not share. Wash towels in hot 60 degree wash. If possible, change clothing and the bedclothes daily.
- Conscientious use of this treatment is needed to enable maximum effectiveness
- Other family members should be screened for carriage and should also be treated at the same time.
- Sharing of towels and face cloths will allow staphylococcus to spread and reduce the likelihood of successful eradication.

Each patient should have their own supply of cream.

Warning: some of the preparations can stain bathroom furniture and some plastic surfaces. Clean the bath after treatment so that the next user doesn't get infected.

Autoimmune Lymphoproliferative Syndrome

INTRODUCTION

The Autoimmune Lymphoproliferative Syndrome (ALPS) is a rare disease of defective cellular apoptosis. Failure of lymphocytes to undergo apoptosis results in disturbed homeostasis, with a lymphocytosis and enlargement of secondary lymphoid tissue, autoimmunity and hypergammaglobulinaemia. An increased number of CD4/CD8 double

negative, TCR αβ-positive T cells (Double negative (DN) T cells) in the peripheral blood is a characteristic finding. Mutations in the Fas-mediated apoptosis pathway are responsible for the majority of cases of ALPS. Inheritance may be autosomal dominant (with highly variable penetrance), or rarely recessive.

CLINICAL FEATURES

Lymphadenopathy, splenomegaly
Autoimmunity:

- Autoimmune haemolytic anaemia
- Thrombocytopaenia
- Neutropaenia
- Skin (urticaria, vasculitis)
- Other organ-specific diseases (e.g. glomerulonephritis, Guillian-Barré syndrome)
- Failure to thrive
- Malignancy: lymphoma, carcinoma, adenoma

Diagnostic criteria

Lymphoproliferation – hepatosplenomegaly, lymphadenopathy
Lymphocytosis, with increased B cells and DN T cells (>15%).
Evidence of autoimmune disease

Proposed classification:

ALPS 0-Autosomal recessive Fas mutation
ALPS Ia - Autosomal dominant Fas mutation
ALPS Ib - Autosomal dominant Fas Ligand mutation (only 1 case in SLE patient)
ALPS IIa - Defective Fas-mediated apoptosis without Fas mutation e.g. caspase 10
ALPS II b
ALPS III - ALPS with normal Fas-mediated apoptosis

LABORATORY FEATURES

- >1 % CD4-/CD8- TCRαβ+ T cells. These cells are typically CD45RA+, HLA-DR+ and CD57+
- Lymphocytosis
- Hypergammaglobulinaemia
- Coomb's positivity or other autoantibodies.
- Failure of Fas-induced apoptosis *in vitro* (in ALPS types 0, Ia and II)

INVESTIGATION

- FBC
- Immunoglobulins
- Autoimmune screen, Coomb's test and any antibodies suggested by clinical picture.
- Lymphocyte subsets, specifically requesting numbers of DN T cells if available by special arrangement.
- Fas-induced apoptosis*
- Fas gene sequencing*
- Family studies are indicated in view of the possible increased risk of malignancy and to aid genetic counselling.

*One UK laboratory can currently offer these tests by special arrangement GOS, Adrain Thrasher, a.thrasher@gos.nhs.uk.). The Necker Hospital in Paris (Dr F Rieux-Laucat) can provide them if required (rieux@necker.fr)

TREATMENT

- No treatment may be required for the lymphoproliferation.
- If splenomegaly is troublesome cytotoxic drugs have been used e.g. mercaptopurine, or anti-thymocyte globulin.
- Autoimmune cytopaenias may require steroids, other immunosupression or splenectomy
- Other autoimmune diseases should be treated as necessary
- Bone marrow transplantation may be an option.
- Genetic counselling should be offered.

Patient details should be submitted to the ALPS database maintained at when available.

FOLLOW UP

Many of the lymphoproliferative and autoimmune syndromes moderate with age. Patients need regular (minimum 6 monthly) follow up to:

- Monitor lymphadenopathy and splenomegaly clinically.
- Monitor population of DN T cells.
- Monitor for development of other complications including autoimmunity and malignancy

Minimum investigations

- FBC at each visit

- Annual serum immunoglobulins
- Annual lymphocyte subset analysis including DN T cells
- Annual autoimmune screen

References

Françoise Le Deist, Jean-François Emile, Fredéric Rieux-Laucat, Malika Benkerrou, Irene Roberts, Nicole Brousse, Alain Fischer Clinical, immunological, and pathological consequences of Fas-deficient conditions. *Lancet* 1996; **348**: 719-23

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Diagnosis and Management of Hyper-IgE Syndrome

INTRODUCTION

The Hyper-IgE Syndrome is a rare multi-system disorder characterised by immunodeficiency, elevated serum IgE, and associated abnormalities of face, skeleton and dentition. The underlying cause for this disorder is unknown, although family studies suggest an autosomal dominant pattern of inheritance with variable penetrance.

CLINICAL FEATURES

- Atypical eczematous rashes – typically from very early life, often involving face and extensor surfaces rather than flexural.
- Recurrent infections
- Skin abscesses (often "cold")
- Pneumonia (often with pneumatocele formation)
- Candidiasis – mucosa and nails
- Other sites affected – ears, sinuses, eyes, oral mucosa
- Organisms: often staph aureus, but also candida, aspergillus, haemophilus, pneumococcus, gram negative organisms, & other fungi.
- Abnormalities of face, skeleton and dentition
- Abnormal facies: facial asymmetry, prominent forehead, deep-set eyes, broad nasal bridge, rough skin with prominent pores
- High arched palate (even cleft palate)
- Failure (or delay) in shedding primary teeth
- Fractures on minimal trauma – often in association with decreased bone density
- Scoliosis
- Joint hyper-extensibility
- Other reported features/complications include lupus, vasculitis, lymphoma

DIAGNOSTIC CRITERIA

WHO description *Clin Exp Immunol* 1999:118 suppl1,1-28 & Puck et al *NEJM* 1999:340,692-702

- Elevated serum IgE
- Eczematous rashes
- Unusual, severe, recurrent infections eg skin abscesses, candidiasis and pneumatocele-forming pneumonias, in the absence of any other known underlying defect in the immune system.

LABORATORY FEATURES

Raised serum IgE: typically >2000 kU/ml, often >20,000 kU/ml (check)
However levels can fluctuate and even become normal in a few adult patients
In contrast to atopic eczema, patients may have no specific IgE to common allergens
Eosinophilia is often present
Neutrophil function defects have been reported – impaired chemotaxis, phagocytosis and killing.
Specific antibody deficiencies are found in some patients.

INVESTIGATION

- FBC including eosinophil count
- Serum IgE, plus allergen specific IgE if there are clinical features of allergy

- Serum immunoglobulins
- Specific antibodies to tetanus, Hib and pneumococci with a view to test immunisation if appropriate
- IgG antibodies to previous infections and/or immunisations e.g. consider hepatitis B, meningococcus C, measles, rubella, CMV, VZV, EBV and others as appropriate.
- Lymphocyte subsets
- CXR – look specifically for pneumatoceles, abscesses, reticulonodular shadows, scoliosis etc.
- Consider need for dental assessment
- Other tests as suggested by the clinical picture and to exclude other immunodeficiencies

TREATMENT

Intercurrent infections should be investigated and treated promptly.
Anti-microbial prophylaxis – usually with flucloxacillin and itraconazole (starting dose 5mg/kg daily, adjust in children and also on the basis of trough levels if available– measure after 10 days- discuss with microbiology).
Immunoglobulin replacement therapy should be considered for those with antibody deficiency failing to respond to prophylactic antibiotics.
Other therapeutic options although not of proven efficacy include cimetidine and gamma-interferon.
Bone marrow transplantation is not currently recommended
Other specialist input may be required (e.g. Cardiothoracic, Orthopaedic)

FOLLOW UP

Patients need regular (minimum 6 monthly) follow up to:

- Prevent and treat further infection
- Monitor immune function e.g. for development of antibody deficiency
- Monitor for development of bronchiectasis
- Monitor for development of other complications e.g. osteoporosis
- Monitor for complications of long term antibiotic therapy
- Monitor immunoglobulin replacement therapy (if applicable)

Suggested investigations

- CRP and ESR at each visit
- Annual serum immunoglobulins, functional antibodies
- Annual serum IgE
- Annual FBC
- Annual urea, creatinine & liver function tests
- Annual aspergillus precipitins
- Baseline CXR, lung function tests with follow up testing as required. Consider chest CT if indicated.
- Consider the need for regular DEXA scanning (or equivalent) to monitor for the development of osteoporosis.

NB patients on replacement immunoglobulin therapy require additional monitoring as per the local IVIG/SCIG guidelines.

All patients should be offered contact details of patient support groups such as the Primary Immunodeficiency Association (PIA) who can provide invaluable support and advice to patients and families.

Type I Cytokine Deficiencies

INTRODUCTION

Defects in interferon-γ (IFN-γ) and IL-12 production and their receptors have been described. IFN-γ is secreted by activated T cells and stimulates the activity of other cells, particularly macrophages. Macrophages have a wide range of immune functions, but are indispensable in the killing of intracellular organisms, including mycobacteria and salmonella. These actions are augmented by IFN-γ. In addition, macrophages secrete the cytokine IL-12, which boosts the activity of Th1 T cells, resulting in the secretion of more IFN-γ. This is referred to as a cytokine loop. Defects of IL-18 and signalling mechanisms (STAT etc.) are also part of this family of conditions.

A number of mutations affecting the IFN-γ receptor have been described. The most severe forms are autosomal recessive. Milder defects are autosomal dominant. Macrophages respond poorly, or not at all, to IFN-γ,IL-12 and related cytokines and have impaired killing of intracellular organisms.

Newly described patients with auto-antibodies to IFN-γ & TNF-α may have a similar syndrome.

DIAGNOSTIC CRITERIA

Patients with unusual mycobacterial infection should be tested for IFN-γ defects. This includes:

- Patients with tuberculosis, if extra-pulmonary and non-responsive to treatment, despite a sensitive organism and good adherence.
- Patients with extra-pulmonary atypical mycobacterioses, for example infection with M BCG, *M chelonei* and *M avium* complex.

A diagnosis of Type 1 cytokine pathway defects is also more likely if there is a family history of unusual mycobacterial or salmonella infection.
Patients usually have normal or slightly reduced T cell numbers and no other indicators of cellular immunodeficiency (herpes zoster, PCP etc).

Before embarking on investigating Type 1 cytokine pathway defects, the following should be excluded:

- SCID (low T cell numbers)
- Obtain informed consent and test for HIV infection
- Other causes of secondary immunodeficiency, for example corticosteroids or cytotoxics.

LABORATORY INVESTIGATION

- HIV testing (if not already performed)
- Exclude other relevant immunodeficiencies according to clinical history, and depending on local laboratory repertoire

Samples or patients may be referred to Dr Kumararatne, Addenbrooke's Hospital. Discuss all investigations with Addenbrooke's (Dr Kumararatne or Dr Rainer Doffinger) before arranging testing

A normal control must be sent.

Cambridge also provides anti IFN-γ or TNF-α antibody assay.

All patients with genetic disorders must give informed consent before testing. This process should involve patients families whenever possible.

TREATMENT

There are no clinical trails on the safety and efficacy of IFN-γ in these patients, but some of the conditions respond to IFN-γ treatment. A trial IFN-γ I may be considered where appropriate in some patients prior to definitive diagnosis.

IFN-γ is given as 500μg subcutaneously three times a week. Higher doses are need in some mutations.

Patients should be advised they may have pyrexial reactions (which respond to paracetamol) and monitoring of liver function and full blood count should be done initially every fortnight. Efficacy can be measured through improvement of specific clinical features, weight gain and culture of infected sites. ESR and CRP do not appear to consistently improve in parallel with clinical improvement.

FOLLOW-UP

Close follow-up is required depending on clinical response to therapy:

- Monitoring of FBC, LFTs etc. appropriate to anti-tuberculous therapy.
- Repeat cultures and sensitivities as required. Sputum should be periodically obtained and screened for MTB.

Patients may have ‘open’ TB, appropriate infection control measures should be in place. Joint management with local TB service (Respiratory or Infectious disease services) is recommended.

Patients should have stool tested for Salmonella carriage, particularly if they develop diarrhoea.

IFN-γ treatment is expensive. It should not be continued long term unless a cellular or genetic diagnosis has been confirmed.

Diagnosis & Management of Chronic Mucocutaneous Candidiasis

INTRODUCTION

Chronic mucocutaneous candidiasis (CMC) occurs as a part of a spectrum with CMC in isolation, CMC with autoimmune phenomenon & CMC with other infections. Autosomal dominant, recessive and sporadic forms have been described. The underlying defect is unknown. Patients with autoimmune polyendocrinopathy Type 1 (APECED) have a defect in a protein (AIRE) on chromosome 21 that regulates gene transcription.

CLINICAL FEATURES

Patients may present with persistent candida affecting the nails, mouth and more rarely the oesophagus.
There may be a family history.
The endocrine manifestations of this disease include autoimmune adrenal insufficiency, thyroid disease and parathyroid disease. The latter may present with hypocalcaemia and/or tetany.
Defects in cell mediated immunity are associated with nail, mucosal candidiasis, cerebral toxoplasmosis, tuberculosis, HSV, VZV, CMV and EBV infection.
Defects in humoral immunity increase the risk of bacterial infections of the chest, sinuses and ears.

LABORATORY INVESTIGATIONS

There is no specific diagnostic test in patients with CMC.

- Candida IgG precipitins are found in all patients.
- Low specific antibodies, with poor or absent test immunisation responses to carbohydrate antigens, are found in some patients.
- Lymphocyte subsets
- Lymphocyte proliferation assays may be helpful– Mitogens and candida.
- Adrenal, thyroid, parathyroid, islet cell, gonadal, gastric parietal cell and smooth muscle antibodies should be checked.
- All patients require endocrine function tests (electrolytes, calcium, TSH, blood glucose).

TREATMENT

Azole antifungal agents (fluconazole or itraconazole) are used to treat superficial candidiasis. The disease usually relapses when anti-fungal agents are withdrawn. Resistance is a problem with long term anti-fungal therapy. Systemic azole therapy or amphotericin B is required for refractory disease.

Aggressive nail infection may require removal of the infected nail.

Patients with antibody deficiency should be managed as per appropriate guidelines.

FOLLOW UP

Patients with CMC need follow up to ensure adequate therapy of superficial candidiasis, need to detect the onset of either immunodeficiency or autoimmune endocrine disease.

Monitor for endocrine dysfunction as clinically indicated.

Advice For Patients With Primary Immunodeficiency Travelling Abroad

This information can be provided in an information leaflet:

Advice for patients with Primary Immunodeficiency travelling abroad

North America, Western Europe, Japan, Australasia
No special precautions need to be taken, except Sushi!
Japanese encephalitis

Other countries, particularly Africa, Middle and Far East and South America

Diarrhoea
Diarrhoea is the most frequent problem for travellers, and may be more severe and prolonged in patients with immunodeficiency. Patients should carry ciprofloxacin tablets with them, and in particularly unhygienic conditions it is wise to take ciprofloxacin continuously at 250 mg twice daily. For those living in cleaner environments and staying in Westernised hotels, ciprofloxacin can be taken immediately the diarrhoea starts and continued for at least 7 days.

If the diarrhoea does not improve within 24 hours of taking ciprofloxacin, then local medical advice should be taken. Metronidazole (Flagyl) is then the best drug to take at a dose of 400 mg every 8 hours for 5 days. For those travelling to unhygienic out-of-the-way places, it is sensible to carry a supply of metronidazole with you.

Food – eat cooked food and avoid salads, sea food, skinned fruit, ice-cubes and ice cream. Drink bottled or boiled water (see food hygeine and cryptosporidial leaflets)

Water
Use boiled or reputable bottled water only. Do not rely on water filtration kits or purification tablets (see cryptosporidia leaflet).

Chest infections
There is no evidence that patients with immunodeficiency are more prone to chest infections when travelling abroad, than at home in the UK. However, we advise taking a supply of co-amoxiclav (Augmentin) with you as a first line treatment for bronchitis, which should be taken for at least 7 days. For those on continuous ciprofloxacin, they should also take Augmentin for a relapse of their bronchitis. (See general advice on antibiotic use overleaf).

Protection against malaria
Please make sure that you take anti-malarials (as advised by your travel agent or local doctor) if you are travelling into infected areas.

Immunoglobulin therapy & top-up infusions
It is important to plan when travelling abroad, so that your routine i.v. immunoglobulin infusion can be brought forward to a few days before you leave the country. If you are abroad for more than 3 weeks we will need to give appropriate advice. Beyond that, you will need to arrange an infusion abroad, which again will need some special planning. Please discuss this with us before-hand.
Subcutaneous infusions require special arrangements for absences over a week. Please discuss with us

Vaccinations
No vaccinations are required if you have a severe immune defect because you will not make any response. Those with more mild immune defects may benefit from vaccination; seek advice from us. Antibodies in your regular immunoglobulin infusions will cover you against most infectious agents, except perhaps for yellow fever (this LIVE vaccine is absolutely contraindicated in antibody deficient patients). If you plan to travel into the yellow fever belt, then please discuss these precautions with one of our doctors well before you leave.

Di George Syndrome

INTRODUCTION

Microdeletions on the long arm of chromosome 22 are associated with a wide range of clinical manifestations, and in particular with a number of complex syndromes, including:

- Di George syndrome
- Velocardiofacial syndrome
- CHARGE syndrome[1]
- Opitz syndrome
- Noonan's syndrome
- Craniocardiocerebellar syndrome

The range of abnormalities most frequently seen in children with 22q11 microdeletions is encompassed by the acronym 'CATCH 22':

- Cardiac
- Abnormal facies
- Thymic hypoplasia
- Cleft palate
- Hypocalcemia

However a variety of other abnormalities can be associated, including renal, skeletal, neurological, and psychological[1]. Possible autoimmune manifestations such as arthritis and vitiligo are anecdotally reported.

Patterns of immunological abnormality

Although three patterns of immunological abnormality are recognised[1], it must be are stressed that the majority of children have the mildest phenotype, with minimal immunological abnormalities:

Severe T cell immunodeficiency (complete Di George)

[1] Colobmata, Heart abnormalities, Atresia choanae, Retardation of growth and development, Genital anomalies and Ear anomalies including deafness.

Very low or absent T cells (below the 5th percentile for age), with variable immunoglobulin production (rare, <5% of all cases)

Milder T cell abnormalities (Partial Di George)

Low T cell numbers, usually normal T cell proliferative responses, with variable minor Immunoglobulin abnormalities

Minimal (Partial Di George)

Normal T cell numbers and function, minor Immunoglobulin abnormalities, particularly low IgM levels in older children.

Although it is well recognised that T cell numbers in infants with Di George syndrome may increase in the first few years of life, little is known about the longer term natural history of the immunological abnormality in 22q11 microdeletion syndrome, and further studies are necessary. Preliminary work suggests that T cell numbers and/or diversity may decline with time[5,6].

CLINICAL MANIFESTATIONS

These depend on the severity of the immune defect, and the interaction of other manifestations of the syndrome with the immunological abnormalities. In most children with 22q11 microdeletions the immunodeficiency is relatively less important than other features of the disorder e.g. facial dysmorphism and congenital heart disease themselves predisposing to increased severity of respiratory tract infection.

Infants with severe T cell immunodeficiency will be susceptible to viral and opportunistic infections – see guidelines for SCID

Most children with milder abnormalities have an increased frequency of upper respiratory tract infections

SCOPE OF THE GUIDELINE

Di George syndrome has a huge range of manifestations, and may present to a variety of different specialties. This guideline will focus only on the immunological aspects of the syndrome. The importance of a holistic approach should not be overlooked when assessing and managing the patients and their families. Ideally, a general paediatrician/physician should co-ordinate all aspects of care.

DIAGNOSIS

Clinical

The diagnosis should be suspected in any child with a combination of any of: congenital heart defect, hypocalcaemia (in the neonatal period), cleft lip/palate/ velopharyngeal insufficiency, recurrent infections and facial dysmorphism. Developmental delay may also occur. Many children with a mild phenotype present to cleft lip and palate services.

Genetics

Fluorescent In situ hybridisation should be undertaken to look for deletions in 22q. If no deletion is found, 10p deletions should also be excluded. These tests are available in regional cytogenetics laboratories.

In children with deletions, parents should be referred to the genetics department and tested for an appropriate deletion.

Immunology

All patients, regardless of their symptoms, should have a baseline immunological assessment.
This should include:

- Total immunoglobulin levels
- Specific antibody responses (vaccinations)
- T cell numbers (lymphocyte subsets including CD3, CD4, CD8)
- T cell proliferation may be appropriate in selected cases

MANAGEMENT

Management of the immune defect in 22q11 microdeletion syndrome is dependent on the degree of immunodeficiency, in the context of any other clinical problems.

Severe T cell immunodeficiency
These patients should be managed as children with SCID (see separate guideline). In brief:

Supportive

- Reverse isolation
- All blood products irradiated and CMV negative
- PCP prophylaxis: Co-trimoxazole (30mg/kg of the complex once daily).
- No live vaccines
- Immunoglobulin replacement therapy

Definitive

Patients should be referred to a centre experienced in paediatric immune deficiency transplantation (currently Newcastle and GOS are funded in the UK for this service)

Bone marrow transplant – if matched sibling donor available
or
Thymic transplant[3] – if no HLA matched sibling. This must be undertaken in conjunction with one of the centres mentioned above.

Mild T cell deficiency or other minor Immunoglobulin abnormalities

Treatment is supportive and depends on clinical problems. For mild defects with only recurrent minor infections broad spectrum antibiotic prophylaxis may be needed – e.g. azithromycin 10mg/kg for 3 days every 2 weeks, or a once daily dose of Augmentin. Cotrimoxazole prophylaxis may be indicated if CD4+ T cells are < 400/mm^3. Immunoglobulin replacement may occasionally be necessary if a significant antibody defect is demonstrated and prophylactic antibiotics do not ameliorate symptoms.

Vaccination

All children should receive routine non-live vaccines.
If CD4+ T cells >400, and adequate specific antibody response demonstrated to tetanus and Hib, MMR can be given.
Avoid BCG

See RCPCH guidelines on vaccination in immunocompromised children

MONITORING

Clinical

This depends on degree of immunodeficiency. Those with any significant T cell defect should be seen regularly by an immunologist – every 3-6 months. Those with milder defects can be reviewed annually by immunology teams. Long term follow up into adult life is recommended for those with significant immunological defects. Those with mild immunological defects who are clinically well should be made aware of the need to return to clinic if infections become a problem.

Referral to appropriate sub-specialists may be required, although most children are already under regular review by palatal surgeons, dentists and often ENT. Multidisciplinary coordination of follow-up should be attempted.

Biochemistry
Require monitoring of serum calcium.

Immunology
Annual (or biannual) T cell numbers and total immunoglobulins
Responses should be measured after routine vaccinations

Advice to parents/patients

Practical

All household members avoid smoking
Seek advice early for intercurrent infection
May keep supply of antibiotics for breakthrough infection

Information leaflets/patient support groups

Max Appeal: support group and information leaflet. www.maxappeal.org

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Complement deficiency

INTRODUCTION

This guideline specifically excludes defects in C1 esterase inhibitor function or levels (Hereditary angioedema), which is covered in a separate guideline.

Deficiency of complement components is most commonly secondary to consumption in inflammatory disease processes. Genetically determined primary deficiencies of all the complement cascade factors can occur, but are rare.

The factors can be classified into:

- **Early Classical Pathway:** C1q,r and s, C2, C4
- **Alternate pathway:** factors B, D, H, I, properdin
- **C3**
- **Late lytic:** C5, C6, C7, C8, C9
- **Mannose binding lectin:** MASP 1 and MASP2

Deficiencies of these components result in susceptibility to infections either specifically to Neisseria species in some cases or to bacterial infections generally. There is also a marked susceptibility to autoimmune disease in early complement component defects. This may be due to impaired clearance of immune complexes.

The genetic basis and clinical features of the complement deficiencies are summarised in **Appendix 1**

WHO TO INVESTIGATE FOR COMPLEMENT DEFECTS

Infections:

- Recurrent meningococcal disease (40% incidence of complement deficiency) (B)
- Single episode of meningococcal disease caused by an unusual sero-group organism eg W135,X, Y (20-50% incidence of complement deficiency) (B)
- Family history of meningococcal disease (10% incidence of complement deficiency) (B)
- Recurrent pneumococcal, streptococcal or Haemophilus infections (C)
- Recurrent minor infections in preschool children with normal Igs (MBL pathway) (C)

Autoimmune disease:

- Severe, familial, early onset or atypical systemic lupus erythematosus (C)
- ANA negative SLE (C)

HOW TO INVESTIGATE COMPLEMENT DEFECTS

- Verify normal levels of C3 and C4
- If normal, check haemolytic ability of the patient's classical and alternative pathways (CH50/100 and AP50/100)

CH100 measures classical (C1,2,4 and C3) pathway activity and terminal (C5-9) complement component activity. AP50 Measures alternative pathway and terminal complement component activity.

	CH100	AP50
Classical Pathway defect	Abnormal	Normal
Alternative pathway defect	Normal	Abnormal
Terminal pathway defect	Abnormal	Abnormal

- Individual complement components can then be measured (see appendix 1)[2]
- In children with recurrent minor infections or where MBL deficiency is suspected, MBL levels should be measured. Investigation for the common polymorphisms that predispose to low levels of MBL can be undertaken on a research basis.

NB It should be remembered that many of the complement factors are labile so that serum , EDTA samples need to be separated and frozen at -70^0 C within 2 hours of collection.

MANAGEMENT

These conditions are all rare (except MBL deficiency).

Autoimmune disease

Management is as for non-complement deficient disease, although the disease may be

[2] In active autoimmune disease it may be difficult to distinguish between consumption and primary deficiency. Consideration should be given to genetic testing (if available).

more severe and require more aggressive treatment.

Infections

Supportive

- Antibiotic prophylaxis to be considered as per local microbiological advice. Penicillin V if susceptibility restricted to neisserial disease. Azithromycin, Co - Amoxiclav, Cefixime or Co-trimaxozole if broader susceptibility (D)
- Provide treatment dose of appropriate antibiotic at home
- Vaccinate appropriately against encapsulated bacterial pathogens : Hib, meningococcal C conjugate and polyvalent meningococcal polysaccharide vaccine (A, C, Y, W135), and Pneumococcal conjugated Vaccine followed by Pneumococcal polysaccharide Vaccine (c).

NB: Vaccine responses may be sub-optimal and the duration of memory may be shorter than in normal individuals. Responses should be checked and re-vaccination given as necessary.

Replacement

Fresh frozen plasma infusion can be given to replace factors in the context of severe infection but there is no good evidence that these help, and some evidence that it may not. If found to be of benefit in an individual patient and long term or repeated plasma infusions is to be used, use of a detergent-treated plasma product should be considered. There is no definitive treatment.

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Sullivan KE, Winkelstein J. Primary Immunodeficiency Diseases. Eds Ochs H, Smith CIE , Puck J. Oxford University Press, 1999.

Appendix 1 **Clinical features and genetic basis of Complement deficiencies**

Component	**Gene name**	**Chromosomal location**	**Inheritance**	**Ethnic predisposition**	**Incidence (if reported)**	**Clinical Manifestations**
C1q	CIQA, C1QB, C1QG	1p36.3- p34.1	AR	None	30 patients reported	1. SLE 2. Recurrent infections
C1r/C1s	C1R/C1S	12p13	AR	None	12 patients reported	1. SLE 2. Recurrent infections
C4	C4A, C4B	6p21.3	AR	None	Complete deficiency rare (20 cases reported) Heterozygous null alleles common (12-14 % Caucasians heterozygous for C4A*QO, 15-16% for C4B*QO). Homozygous null alleles 1%	1. SLE 2. Recurrent infections
C2	C2	6p21.3	AR	Caucasian	1: 10 000 2% blood donors in Brazil	1. SLE 2. Recurrent infections
C3	C3	19q13	AR	None	20 patients reported	1. Severe pyogenic infections especially *S. pneumoniae, S pyogenes, H influenzae, N meningitides* 2.Glomerulonephritis
C5	C5	9q34.1	AR	None	30 patients reported 0.0014 % in Japan	Neiserrial infection
C6	C6	5p13	AR	African	80 patients reported 0.0027 % in Japan. 1:1600 American africans	1. Neiserrial infection 2. SLE (complete and subtotal deficiencies described)
C7	C7	5p13	AR	None	70 patients reported 0.0041 % in Japan	1. Neiserrial infection 2. Autoimmune disorders
C8A/B	C8A/C8B	1p32	AR	None	70 patients reported 0.0027% in Japan	Neiserrial infection
C8G	C8G	9	AR			
C9	Cp	5p13	AR	Asian	0.009% in Japan	?Neiserrial infection
Factor B	BF	6p21.3	AR	Unknown		Neiserrial infection

Factor D			Not known	Unknown		Recurrent infections
Factor H	HF1	1q32	AR	None		1. Renal disease (HUS) 2. Neisserial infections
Factor I	IF	4q25	AR	None		1. Neisserial infections 2. Streptococcal infections
Properdin	PFC	Xp11.4-q11.23	X-linked recessive	Caucasian		Neisserial and other bacterial infections
C4bp	C4BPA, C4BPB	1q32	Not known	Unknown		Angioedema and Behcets syndrome
C1 inhibitor	C1NH	11q11-q13.1	AD	None		1. Angioedema 2. SLE
DAF (CD55)	DAF	1q32	AR	Unknown		Inab phenotype (absence of blood group antigens of the Cromer complex)
CD59	CD59	11p13	AR	Unknown		Haemolysis (single patient) Acquired CD59 abnormalities are associated with paroxysmal nocturnal haemoglobinuria.
MBL	MBL	10q11.2-q21	AD and AR	None	Common 3.2 % of children with recurrent infections	Recurrent infections

Appendix 2 – Laboratories offering complement tests

Note: tests for HAE are excluded. Note: functional assays of classical and alternative pathways should be undertaken first to direct specific factor/genotypic assays.

The following table is provided as a guide for centres that have not already identified a centre for assays, and is not intended as a recommendation that all assays are sent to these labs.

Laboratories should be contacted directly to ascertain sample requirements, in addition other assays may have been developed at that centre.

Test	PRU Sheffield	Immunology, Addenbrookes, Cambridge	Immunology, Barts/Royal London	Immunology, Royal Victoria Infirmary, Newcastle	Immunology, Cardiff	Immunology, Great Ormond Street
C1q level	•	•	•	•	•	
C2 level	•	•	•	•	•	
C5 level	•	•		•	•	
C6 level	•	•		•	•	
C7 level	•	•		•	•	
C8 level	•	•		•	•	
C9 level	•	•		•	•	
Factor H level		•		•	•	
Factor B levels				•	•	
Factor B levels					•	
MBL genotyping		•				•
MBL levels	•				•	•
Classical pathway genotyping			•		In development	
Alternative pathway genotyping			•		In development	