PRIMARY IMMUNODEFICIENCIES:

An Introduction for Managers

Executive Summary

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Introduction

The primary immunodeficiencies are a group of rare diseases that remain poorly recognised and treated by non-specialist healthcare professionals. While severe combined immunodeficiencies and related disorders have received funding through national specialist commissioning arrangements, services for other primary immunodeficiencies have developed largely due to individual effort, often expanding in a relatively unstructured and inadequately resourced way. The central message of this publication – that adults and children suffering from these disorders should receive specialist care from health professionals appropriately trained in their management – is clearly set out and is fully endorsed by UK Primary Immunodeficiency Network (UKPIN).

This document is consistent with, broadens and explains the information provided in the National Specialised Definitions Set (Specialised Immunology, number 16). ***Dr. Phil Wood*** - *Chair, UKPIN*

What are primary immunodeficiencies?

The immune system is the body's defence against infection. Any defect in this defence system will predispose affected individuals to recurrent, severe infection leading to disability or death.

In the primary immunodeficiencies (PIDs), the problem arises from defects within the immune system itself, sometimes because of inherited gene mutations. Patients with PIDs will develop serious infections throughout life unless adequately diagnosed and treated.

PRIMARY IMMUNODEFICIENCIES	SECONDARY IMMUNODEFICIENCIES
SCID	HIV
XLA	Cancer
CVID	Chemotherapy
Antibody deficiency	-

Rhys Evans (centre) was born with X-SCID and no resistance to infection. X-SCID is one of the most severe primary immunodifficiencies.

"Commissioning arrangements need to ensure PID patients receive specialist care and that they have access to appropriate treatment delivered via home therapy or hospital clinic."

There are over 80 conditions[(i)] that have been identified as PIDs. These often present in the form of 'ordinary' infections, which are treated by physicians who often miss the underlying cause. This allows the illnesses to recur and leaves the patient vulnerable to vital organ damage, physical disability, and even death[(ii)]. Research has estimated that average diagnostic delays range from 2 to 5 years for the commonest forms of PID, the Primary Antibody Deficiencies[(iii) (iv)]. The life expectancy of patients is significantly reduced, largely because of respiratory failure and malignancies.

Included in this group are individuals with Hereditary Angioedema (HAE), or C1 inhibitor deficiency, a condition in which potentially life-threatening attacks of tissue swelling (angioedema) can occur in an unpredictable manner. These patients are often managed by immunologists within PID centres.

Epidemiological data suggest there are about 2500-3000 people with PID in the UK. Mean cost per patient year is estimated at £15,000 with a mean prevalence of 8 per 100,000. Hospital based inpatient activity related to PID patients can be identified in Trust systems by ICD10 codes, although these give a limited picture that does not reflect infusions or outpatient appointments, or specific areas of activity such as lifelong, home-based treatment regimens. ICD coding is thought to be particularly inaccurate for rare conditions.

Diagnosis and management

Concise guidelines[v] on the recognition, clinical diagnosis and referral of patients with primary antibody deficiencies (PADs) were published in December 2009, by the Royal College of Physicians (RCP) and the UK Primary Immunodeficiency Network (UKPIN).

The guidelines offer recommendations on the identification of those patients who should be referred to clinical immunology services. The guidelines note that diagnostic delay is associated with considerable morbidity, particularly recurrent pneumonias with secondary structural lung damage, such as bronchiectasis, associated pulmonary hypertension and, ultimately, pulmonary heart disease.

Treatment

The principal aim of treatment is to minimise the risk of infection. For the majority of patients with significant primary immunodeficiency, life-long immunoglobulin replacement is the core of optimal management. There is good evidence that immunoglobulin reduces the risk of subsequent infection and consequent morbidity. Adequate doses of immunoglobulin can be delivered intravenously (usually every three weeks) or subcutaneously (usually at least weekly).

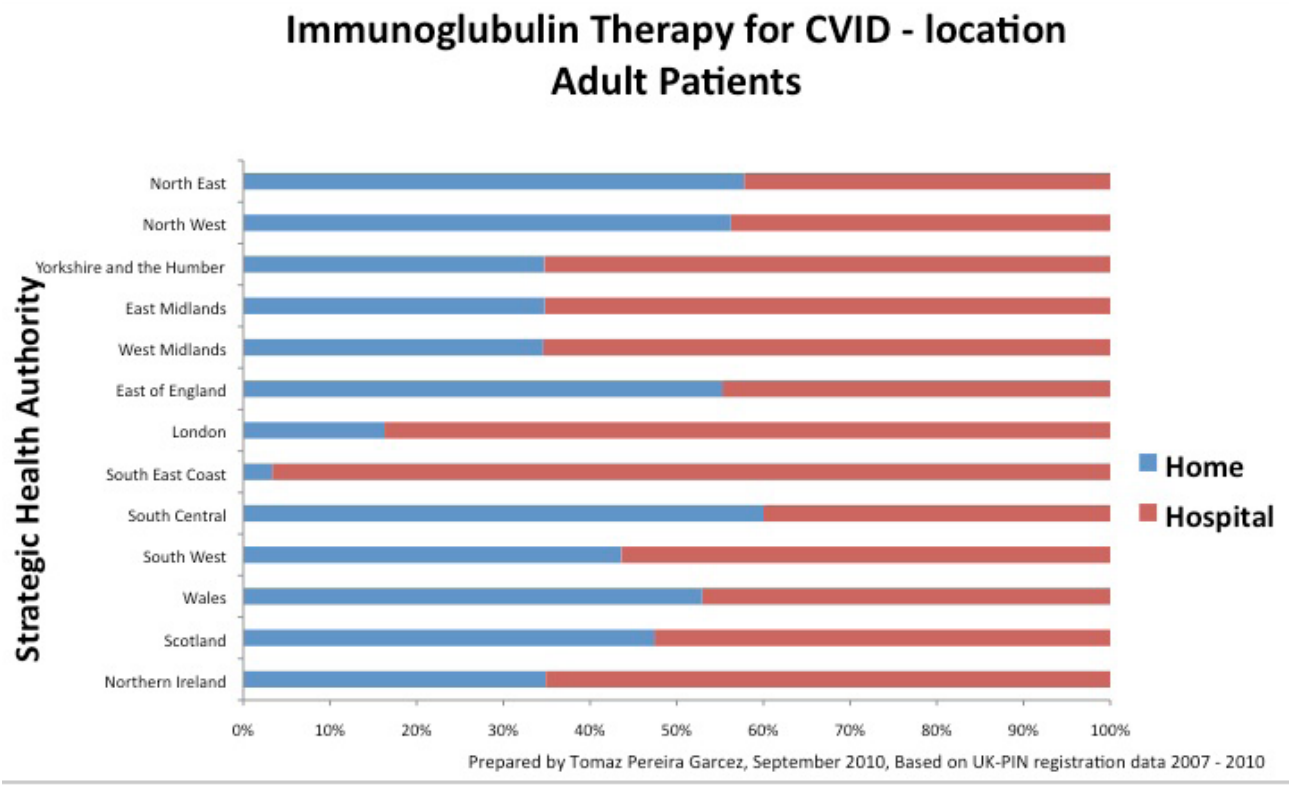
Immunoglobulin infusions are well tolerated in the majority of cases. Once stabilised in hospital, many patients can be trained to self-infuse by either route at home. At the current time, 60% and 40% of patients receive intravenous and subcutaneous immunoglobulin, respectively.

The proportion of patients receiving subcutaneous immunoglobulin is likely to grow over the next few years. For children with PAD, parents are trained to infuse immunoglobulin at home in many cases. Access to home therapy is subject to "post code prescribing", with patients in some areas finding it very difficult to access funding for subcutaneous home therapy. UK PIN national data reveals differences in patient access to or uptake of home therapy ***(See table right)***.

The recommendations are summarised below.

Note: *The cause of the most common primary immunodeficiencies is PAD and these recommendations should therefore also be considered for the diagnosis of PIDs.*

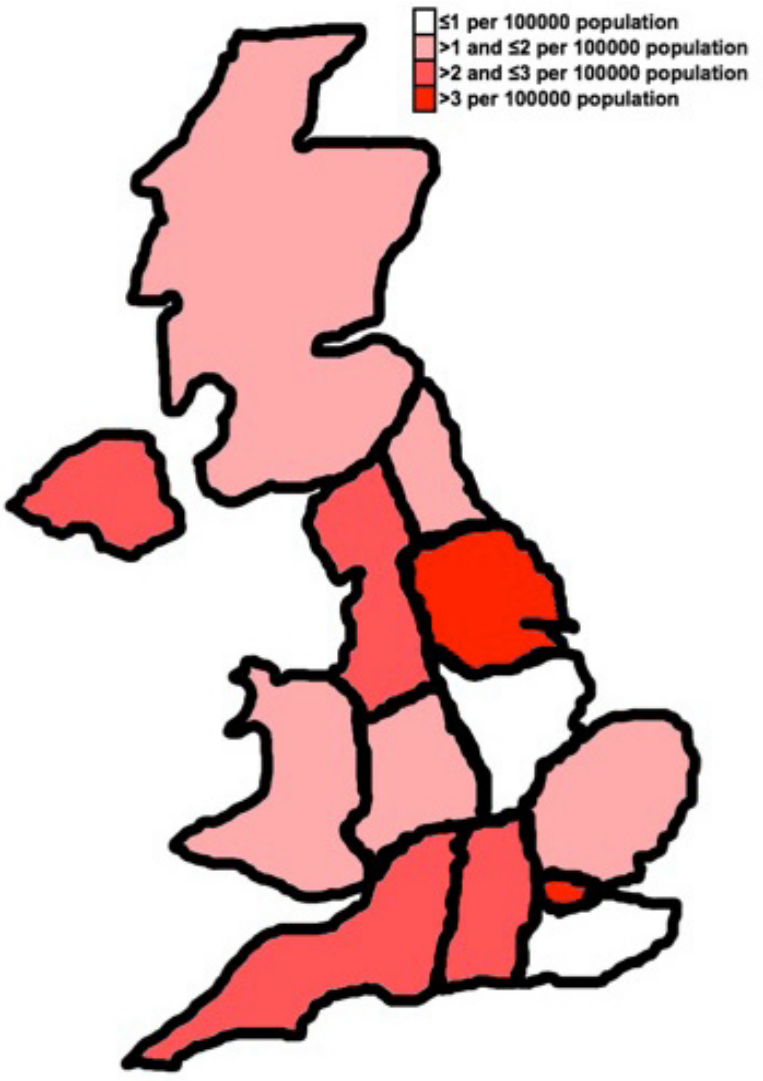
RCP/UK PIN CONCISE GUIDELINES SUMMARY OF RECOMMENDATIONS	GRADE	LEVEL OF EVIDENCE
1. Primary Antibody Deficiency should be considered in all patients with severe, persistent, unusual or recurrent infections.	B	2++
2. Serum immunoglobulins should be measured in any patient with severe, persistent, unusual or recurrent infections.	B	2++
3. Reduced levels of any of the three major immunoglobulin isotypes (IgG, IgA and IgM) in the serum should prompt referral to a clinical immunologist.	D	4
4. Normal levels of immunoglobulin do not exclude a diagnosis of Primary Antibody Deficiency and referral to a Clinical Immunologist for further investigations should be considered in any individual with severe, persistent, unusual or recurrent infections.	C	2
5. Individuals with suspected or proven Primary Antibody Deficiency should be referred to a Clinical Immunologist.	D	4
6. All patients with a proven Primary Antibody Deficiency should receive immunoglobulin replacement therapy as it increases life expectancy and leads to a reduction in the rate of bacterial infection - higher doses may provide additional benefit.	A	1+
7. All patients with a Primary Antibody Deficiency should be monitored regularly for the occurrence of acute infection, even when receiving immunoglobulin replacement therapy.	B	2++
8. All patients with a Primary Antibody Deficiency should be monitored regularly for the development of disease complications.	B	2++
9. The management of all patients with any form of Primary Antibody Deficiency should be led by a Clinical Immunologist with appropriate training and experience.	D	4
10. Patients should be offered a choice of route (intravenous or subcutaneous) and location (hospital or home) for immunoglobulin replacement therapy if appropriate.	B	2++



Patients with HAE require access to plasma-based infusion therapy with C1 inhibitor concentrate, usually given intravenously within a hospital setting although in some centres through a controlled home-therapy programme. Newer non-plasma based drugs such as icatibant are given subcutaneously within a hospital setting. Additional therapies for this condition are becoming available for use.

Clinical governance of immunoglobulin use

In 2007, the Department of Health introduced guidance on the governance of immunoglobulin supplies. The guidance is based on nationally agreed indications for immunoglobulin treatment and steps to ensure demand management. These steps consist of setting up local panels to review prescriptions for immunoglobulin, national data collection on immunoglobulin use and measures to manage shortages. These guidelines are being updated regularly and are likely to provide the framework for immunoglobulin use in the medium term.



Different diagnostic rates of PID in the UK

A study on the cost-effectiveness of immunoglobulin in PID calculated the incremental cost-effectiveness ratio to be £30,000 per QALY.

This figure is very sensitive to changes in the cost of immunoglobulin, cost of home versus hospital therapy and results of efficacy studies. Accurate data collection is a priority. UKPIN has collected national data that highlights differences in diagnostic rates across the UK for the commonest form of antibody deficiency, Common Variable Immunodeficiency (CVID), see map on previous page.

Data collection for PID activity

- Patients being referred to assess whether they have a PID should attend a specific clinic with a dedicated code. The diagnostic activity (pathology and radiology) should be included in this item. Only 10% of these patients will ultimately be diagnosed with a PID and will not need to return.

- Outpatient as well as inpatient activity for diagnosed patients should be measured using hospital systems to detect patients with the ICD codes. This activity should include the cost of immunoglobulin.

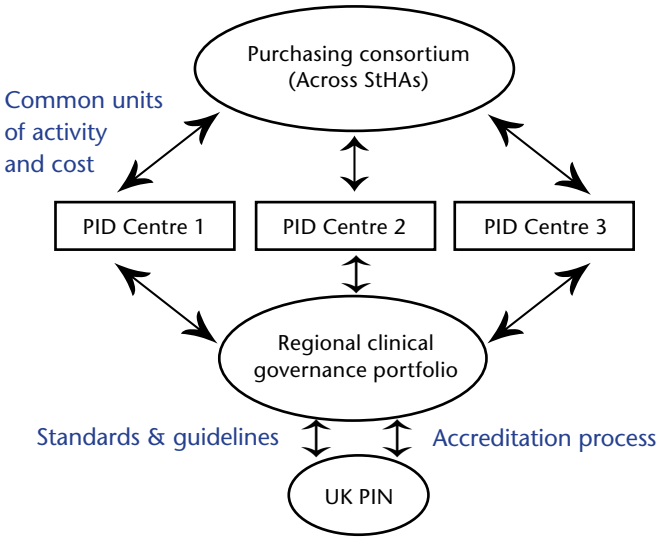
- There should be a mechanism to collect data on activity related to patients infusing at home. This should include the costs of immunoglobulin, disposables, delivery and nurse time for training and lifelong monitoring.

- There should be a mechanism to collect individualised data on patients receiving high dose immunoglobulin (for autoimmune disease and PID). Payment by results may not be sensitive for some PID activities and explicitly excludes other activities from tariffs.

Clinical governance of centres

UKPIN has developed consensus standards to ensure quality of service by the UK's 32 Immunology teams. They have been designed to define staffing and facilities and ensure internal audit of clinical management against protocols developed from national guidelines. Voluntary accreditation assessment of PID centres is conducted by trained peer assessors, who inspect centres against these standards.

A Proposed Model for Regional PID Consortia



In London, four adult centres and one paediatric PID centre participate as providers in the PID Consortium. Identical activity data are collected from each of the centres, which are refunded by regional funding. Each centre acts autonomously, although practitioners participate in frequent, structured clinical governance meetings.

The proposed national model is that similar regional consortia are developed. These facilitate clinical governance and cross cover, particularly for single handed consultants. These provider centres should use common measures of activity in order for services to be purchased by local groups such as regional consortia.

The recommended process will not create 'new money' for PID services. Rather, it will ensure that the costs of governable services are transparent to PCTs under current commissioning structures. It is hoped that under new commissioning arrangements as outlined in the White Paper "Liberating the NHS", the NHS Commissioning Board will take a major role in ensuring national provision of PID services.

During this process, centres with very low levels of activity, those unable to participate in the voluntary accreditation scheme, or those unable to make appropriate links with other local units, are likely to withdraw or become satellites of larger centres.

Conclusion

Commissioning arrangements need to be in place to ensure that individuals suffering from PIDs receive specialist care from health professionals appropriately trained in their management and also that they have access to appropriate treatment delivered to meet their needs via home therapy or hospital clinic.

References

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