



PRIMARY IMMUNODEFICIENCIES

PRIMARY IMMUNODEFICIENCIES AND ALLERGIES



KEY ABBREVIATIONS

IgE	Immunoglobulin E
CID	Combined Immunodeficiency
IL5	Interleukin 5
IPOPI	International Patient Organisation for Primary Immunodeficiencies
PID	Primary immunodeficiency

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INTRODUCTION

This booklet explains why some primary immunodeficiencies are linked with allergies, and how these allergies can best be prevented and treated.

Primary immunodeficiencies (PIDs) are rare diseases that occur when components of the immune system are either not present or are not functioning normally. The immune system protects the body from infections. By interfering with this system, PIDs leave people open to infections. Over 300 different PIDs are now recognised and these have a variety of effects (see the IPOPI leaflet '*How are primary immunodeficiencies classified?*').

Certain PIDs cause imbalances in the immune system that can make patients susceptible to allergies, which are exaggerated reactions to specific triggers (or 'allergens') such as pollen, dust, foods or drugs. For example, some PIDs cause patients to have high levels of a protein called immunoglobulin E (IgE), or immune system cells called eosinophils, both of which are involved in allergic responses. This susceptibility to allergies is sometimes called 'atopy'. People who are atopic commonly have multiple allergic diseases, such as eczema, rhinitis (hay fever), asthma and food allergies. Atopy often first appears in infancy or early childhood.

Allergies are sometimes a warning sign that leads to a diagnosis of a certain PID. Doctors need to consider the possibility of a PID in patients (especially infants or young children) with atopy that is severe or which does not respond to usual treatment, or when the patient also shows a susceptibility to infections.

People with PIDs may also experience allergies related to their treatment. Very rarely, allergic reactions may occur to immunoglobulin replacement therapy, the main treatment for most people with PIDs. PID patients may also develop allergies to other drugs used in their treatment, such as antibiotics.

It is important to report allergic reactions to the doctor so that the trigger factor can be identified and the reaction treated. Any allergy that develops in a patient already diagnosed with a PID should be reported to their PID doctor, which will usually be an immunologist (a doctor who specialises in the immune system and allergy). If this is not possible, or if the allergy is only mild, a general practitioner may be consulted initially.

The following sections explain the main allergies that can occur in people with PIDs, and how these can be prevented and treated.

ECZEMA

WHAT IS ECZEMA?

Also known as atopic dermatitis, eczema is a condition that causes the skin to become itchy, red, dry, scaly and inflamed. It can affect small patches of skin, or it can be more widespread across the body. People with eczema often also have respiratory allergies, such as allergic rhinitis, asthma or food allergies.

Some PIDs can result in eczema-like skin conditions. In particular, PIDs that cause high levels of IgE in the body commonly cause eczema-like symptoms. These PIDs include autosomal dominant STAT3 (Loss of function) deficiency (so called “hyper IgE syndrome”), Combined ID (such as Wiskott-Aldrich syndrome, DOCK8 (dedicator of cytokinesis 8) deficiency, phosphoacetylglucosamine mutase-3 (PGM3) deficiency), and several immunodysregulation syndromes such as polyendocrinopathy enteropathy X-linked (IPEX)

Scratching itchy skin in eczema can cause the skin to become broken and this can lead to infections of the skin and even the bloodstream. This is a particular problem for people with PIDs, who are more susceptible to infections than other people. Contrarily, skin infections can also cause exacerbations (or ‘flare-ups’) of eczema.

PREVENTION AND TREATMENT

Where possible, any allergic factors (or ‘allergens’) that trigger eczema should be identified so that these can be avoided. These can include certain fabrics (such as wool), animal dander (skin flakes, like human dandruff), grass pollen, ingredients (such as fragrances) in soaps, detergents or other skincare products, and foods. Possible trigger factors can be investigated using tests on the skin (known as skin prick tests and patch tests) or by blood tests.

Treatments that can be useful for eczema include:

- Regular bathing (using a non-irritating soap) is recommended, together with the use of moisturiser (or ‘emollient’) creams or ointments to soothe and hydrate dry skin, especially after bathing
- Creams or ointments containing corticosteroids can help to reduce itchiness and inflammation. Mild corticosteroid products (e.g. hydrocortisone) can usually be bought without a prescription (for example from pharmacies), while stronger ones are available on prescription. Corticosteroid products should be used carefully according to the instructions provided by the doctor or patient information leaflet.
- Wet wraps (also called occlusive dressings) can be used to hydrate the skin and avoid scratching. These are usually left on overnight and may help patients sleep better.

- Oral antihistamine medicines may reduce itching in eczema by blocking the action of histamine, a chemical in the body that is involved in allergic reactions. However, antihistamines may not be as effective in eczema as in other allergic reactions, such as allergic rhinitis (below).
- Medicines called calcineurin inhibitors (tacrolimus and pimecrolimus) are sometimes used topically (as creams or ointments) to treat eczema that does not respond to the treatments above. These work by blocking chemicals that cause inflammation.
- In some cases, certain oral medicines that affect the immune system are used to treat severe eczema that does not respond to topical treatment. These medicines include oral corticosteroids, ciclosporin, methotrexate and azathioprine.
- Phototherapy, using ultraviolet light, may sometimes be used to treat chronic eczema.
- Antimicrobial washes may help to prevent skin infections that may result from eczema. Infections that do occur require treatment with antibiotics (see the IPOPI leaflet, '*Primary immunodeficiencies and infections*').

ALLERGIC RHINITIS

WHAT IS ALLERGIC RHINITIS?

Also known as hay fever, allergic rhinitis causes sneezing, itching, runny or stuffy (congested) nose. The timing and severity of symptoms depends on the allergic trigger – this can be a seasonal allergen (e.g. pollen) or household dust, fungi (e.g. moulds) or pets.

In most cases, allergic rhinitis is caused by the overproduction of IgE in response to the trigger allergen, although other mechanisms can also be involved.

PREVENTION AND TREATMENT

Where possible, the allergen that triggers rhinitis should be identified and then avoided through measures such as:

- **Pollen:** reducing outdoor exposure at peak pollen times, showering after being outside and avoid grassy areas.
- **House dust:** good household hygiene, removal of carpets, using allergy-proof (or 'hypoallergenic') bedding, using air-conditioning filters.
- **Pets:** limiting contact (especially in the bedroom, or exclusion from the house), regular washing, and washing pet bedding and soft furnishings.

Irrigating the nose with saline (a salt solution) can help to reduce the symptoms of allergic rhinitis.

Medications commonly used for allergic rhinitis include

- Antihistamines, given orally or as an intranasal spray
- Intranasal corticosteroids
- Intranasal cromones (e.g. cromoglycate and nedocromil)
- Intranasal ipratropium
- Intranasal or oral decongestants (e.g. phenylephrine and pseudoephedrine), which can help to relieve nasal congestion
- Oral leucotriene receptor antagonists (e.g. montelukast, pranlukast and zafirlukast) – these medicines block the action of leucotrienes, which are chemicals that promote inflammation in the body.

Immunotherapy can be a treatment option for patients whose rhinitis is not controlled by usual avoidance measures or medicines. Immunotherapy, which involves gradually giving increasing doses of the trigger allergen (by injection or as drops or tablets) to make the immune system less sensitive to it, is not commonly used in PID treatment and should be carefully discussed with the patient's PID doctor.

- Congestion in the sinuses can lead to infection, which may need to be treated using antibiotics.

ASTHMA

WHAT IS ASTHMA?

Asthma is a lung disease that causes breathing difficulties such as wheezing, shortness of breath, chest tightness and coughing. Allergic asthma, the most common form of the disease, is linked with eczema, allergic rhinitis and food or drug allergies.

Asthma is a feature of a certain number of PIDs with or without increased plasma IgE levels. It is important that asthma is distinguished from other forms of breathlessness and lung disease that some PIDs can cause. Other forms of lung disease in PIDs include damage from lower respiratory tract infections (especially when these are chronic or recurrent), granulomatous interstitial lung disease (which affects the 'interstitium', a network of tissue around the air sacs in the lungs) and lung cancers. More information is available in the IPOPI leaflet '*PIDs and respiratory disorders*'.



PREVENTION AND TREATMENT

People with allergic asthma should avoid known trigger factors, which can include cold air, exercise and chest infections. Since smoke can exacerbate asthma, patients should stop smoking and avoid areas where people smoke.

A 'stepwise' approach to asthma treatment is recommended, whereby medicines are added and adjusted according to the patient's symptoms and response. The main treatments can be grouped as follows:

- **Controller medications:** these are used daily as 'maintenance' therapy to control symptoms and reduce the risk of flare-ups (exacerbations). Inhaled corticosteroids (such as beclomethasone or budesonide) are generally recommended for first-line use. Other options, depending on the circumstances, include long-acting beta2 agonists (e.g. salmeterol or formoterol fumarate), leukotriene antagonists and theophylline. Short courses of oral corticosteroids may be needed to treat severe asthma or exacerbations.
- **'Reliever' medications** (inhaled short-acting beta2 agonists, e.g. salbutamol and terbutaline) are used for as-needed relief of symptoms, including exacerbations, and to prevent exercise-induced exacerbations.
- Patients with severe allergic asthma associated with high IgE levels may benefit from omalizumab, an antibody that inhibits the action of IgE.
- Patients with severe asthma associated with high levels of immune cells called eosinophils may benefit from mepolizumab or reslizumab. These medicines are antibodies that counteract a chemical called interleukin (IL) 5, which promotes the action of eosinophils.
- Immunotherapy may be used in patients with asthma and allergic rhinitis, or who have exacerbations despite inhaled corticosteroids (see the 'Allergic rhinitis' section).

FOOD, DRUG AND OTHER ALLERGIES

WHAT ARE FOOD AND DRUG ALLERGIES?

Food allergies can cause various reactions, including eczema, asthma, swelling of the face, eyes and mouth (angioedema), nausea, vomiting and diarrhoea, and a severe type of reaction called anaphylaxis (see box below).

Allergic reactions to food can occur rapidly within hours of the trigger food being eaten, or be delayed. Any foods can cause allergy, but the most common causes include milk, eggs, wheat, fish, shellfish and nuts. Food allergies are different from food intolerances (e.g. to lactose or gluten), which do not involve allergic immune reactions.

Food allergies are most often mediated by IgE. As such, they are most common in people with certain PIDs that can cause high IgE levels, including DOCK8 deficiency, IPEX and Comel-Netherton syndrome.

Food allergies are diagnosed using 'sensitisation tests' to confirm whether the patient has a specific allergy to the suspected trigger food. These can involve a skin prick test or blood test to measure IgE levels. Sometimes a 'challenge' test – where the trigger food is given again under medical supervision – is needed to confirm the diagnosis.

Patients can also have allergic reactions to medicines, such as antibiotics and non-steroidal anti-inflammatory drugs (e.g. aspirin and ibuprofen – used to treat pain and inflammation). In rare instances PID patients can have severe reactions to immunoglobulin replacement therapy. Patients should record any drug allergies that occur and remind healthcare staff when any new treatment is chosen, so that a medicine unlikely to cause the same reaction can be selected.

Allergies may also occur to insect bites or stings and have stronger effects than on other people.

PREVENTION AND TREATMENT

It is recommended that mothers follow a normal diet during pregnancy and breastfeeding, and when introducing solid foods to infants, rather than deliberately avoiding potentially allergenic foods. Exclusive breastfeeding is recommended for at least first 4–6 months of life. If breastfeeding is insufficient or not possible, infants at high-risk of food allergies are recommended to use a hypoallergenic formula for the first 4 months.

Once a food allergy has been identified, measures to avoid the trigger allergen, by carefully reading food labels and checking the ingredients in food eaten outside of the home, should be taken. Patient education programs are broadly available in food allergy clinics. These can help patients and care-givers interpret food labelling, find alternative ingredients and recipes, and provide supplements where necessary. Schools also have an important role to play in helping children to avoid and cope with food allergies.

In some cases, the trigger food can be reintroduced at a later point under careful supervision in a hospital setting.

Patients, family members and school staff should also understand what to do if the food allergy, or an allergy to medicine or insect sting, occurs in the future. This is particularly important for patients at risk of anaphylaxis (see box).

Other measures that can be taken to help manage food, drug or insect allergies include:

- Treatment of local symptoms (e.g. eczema) as per the sections above.
- Immunotherapy may be an option in some patients with food allergies.

ANAPHYLAXIS – URGENT MEDICAL TREATMENT IS NECESSARY

Anaphylaxis is a severe, potentially life-threatening allergic reaction that develops quickly. Food, medicines and insect stings are among the most common causes. The symptoms include swelling of the tongue and throat, breathing problems, fast heartbeat, confusion, dizziness and even unconsciousness, as well as other allergic symptoms described in this booklet.

Anyone who has an anaphylactic reaction needs urgent medical treatment. People at risk of anaphylaxis should carry an adrenaline pen injector (or auto-injector) to help to stop an anaphylactic reaction. They, along with family members, caregivers and school staff, should know how to use it promptly if anaphylaxis occurs. People with an anaphylactic reaction need to go to hospital, where they may be treated with oxygen, fluids, antihistamines and steroid medicines.



FURTHER INFORMATION AND SUPPORT

This booklet has been produced by the International Patient Organisation for Primary Immunodeficiencies (IPOPI). Other booklets are available in this series. For further information and details of PID patient organisations in 63 countries worldwide, please visit www.ipopi.org.



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