IPOPI
INTERNATIONAL
PATIENT ORGANISATION
FOR PRIMARY IMMUNODEFICIENCIES

PRIMARY **IMMUNODEFICIENCIES**

RHEUMATOLOGICAL, AUTOIMMUNE & AUTOINFLAMMATORY CROSSOVERS

ABBREVIATIONS

APECED	Autoimmune polyendocrinopathy candidiasis extodermal dystrophy
CAPS	Cryopyrin-associated periodic syndrome
CGD	Chronic granulomatous disease
CINCA	Chronic infantile neurological cutaneous and articular syndrome
CRMO	Chronic recurrent multifocal osteomyelitis syndrome
CVID	Common variable immunodeficiency
FCAS	Familial cold autoinflammatory syndrome
FMF	Familial Mediterranean fever
HIDS	Hyperimmunoglobulinaemia D and periodic fever syndrome
IBD	Inflammatory bowel disease
IL	Interleukin
IPEX	Immune dysregulation, polyendocrinopathy and enteropathy X-linked
MWS	Muckle-Wells syndrome
NOMID	Neonatal onset multi-system inflammatory disease (NOMID)
NSAID	Non-steroidal anti-inflammatory drug
PAPA	Pyogenic arthritis, pyoderma gangrenosum and acne syndrome
PID	Primary immunodeficiency
WAS	Wiskott-Aldrich syndrome
XLA	X-linked (or Bruton's) agammaglobulinemia
TNF	Tumour necrosis factor
TRAPS	Tumour necrosis factor receptor-associated periodic fever syndrome

PIDs, rheumatological issues and autoimmunity (1st edition).

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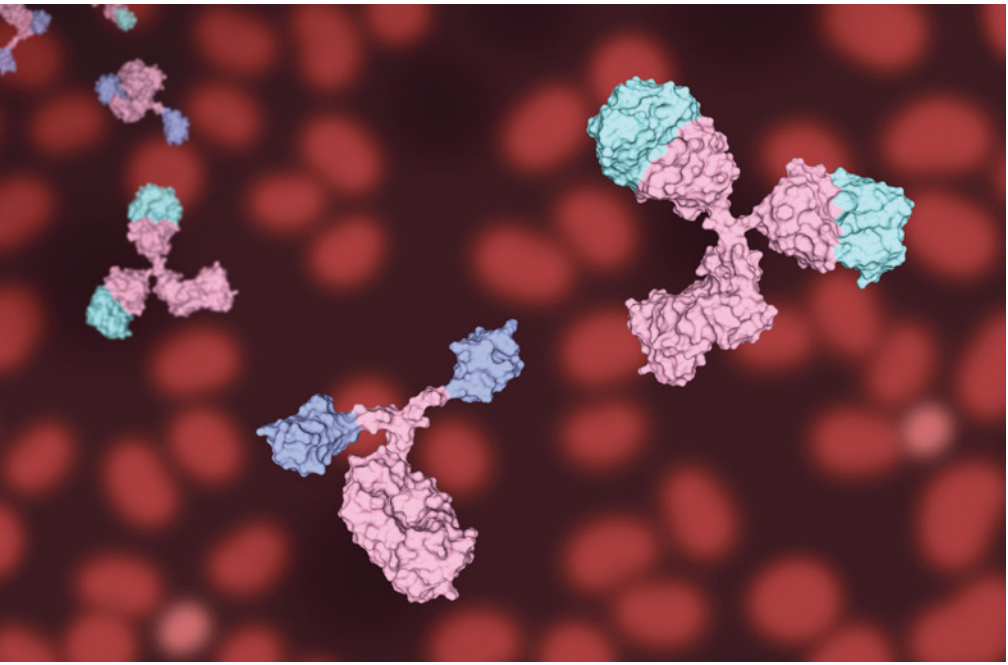
INTRODUCTION

This booklet explains the crossovers between PIDs and rheumatological, autoimmune and autoinflammatory diseases and how these diseases are managed in patients with PIDs.

Primary immunodeficiencies (PIDs) are a group of rare diseases that occur when some components (mainly cells and/or proteins) of the immune system do not work properly. People with PIDs are more susceptible to infection, less able to fight infections and require life-long management.

PIDs are frequently complicated by rheumatological, autoimmune and autoinflammatory diseases, which are often managed by clinicians specialising in rheumatology. Dysfunction of the immune system is responsible for many rheumatological, autoimmune and autoinflammatory diseases. However, different components of the immune system are 'overactive' and responsible for the symptoms – often the adaptive immune system is overactive in autoimmune disorders and the innate immune system is overactive in autoinflammatory disorders, although there is overlap in these disorders. In the following sections, we explain the relationship between PIDs and rheumatological, autoimmune and autoinflammatory diseases and how these diseases are managed in patients with PIDs.



SHARED GENETIC PREDISPOSITION FOR PIDS AND RHEUMATOLOGY/AUTOIMMUNE/ AUTOINFLAMMATORY DISEASES

An estimated 1 in 4 patients with a PID will experience one or more autoimmune or anti-inflammatory complications during their lifetime.[1] This may be due to a shared genetic component. PIDs are caused by mutations in genes that encode components of the immune system and mutations in these same genes may also cause rheumatological, autoimmune and autoinflammatory diseases. In addition to a shared genetic basis, the immunodeficiency associated with PIDs can predispose individuals to autoimmune or autoinflammatory disease by disrupting one of the many mechanisms involved in maintaining the balance of the immune system (also known as “immune homeostasis”). Indeed, some people with a rheumatological, autoimmune and autoinflammatory disease may also have an underlying PID. For these people, blood tests may reveal a persistent hypogammaglobulinaemia, a characteristics feature of PIDs.

PIDs AND RHEUMATOLOGICAL AND AUTOIMMUNE DISEASES

Autoimmune diseases arise when the adaptive immune system mistakenly identifies the body’s own compoments (such as tissues, cells or proteins) as foreign and attacks the things that it would normally ignore. The adaptive immune system usually responds only to invading pathogens that it recognises (such as viruses or bacteria) to protect us from infectious diseases. When the adaptive immune system mistakenly recognises our own body components as foreign, rheumatological and autoimmune diseases can develop such as rheumatoid arthritis or lupus. Rheumatological and autoimmune diseases can affect multiple areas of the body (**Table 1**).

[1] Fischer A, et al. Autoimmune and inflammatory manifestations occur frequently in patients with primary immunodeficiencies. J Allergy Clin Immunol 2017;140:1388-93.

TABLE 1

ORGANS AFFECTED BY AUTOIMMUNE DISEASES	
Organs and tissues (non exhaustive list)	**Symptoms** (non exhaustive list)
Joints	Pain and swelling (arthritis)
Skin	Rashes, swelling and eczema
Liver	Enlargement of the liver (hepatomegaly), inflammation of the liver (hepatitis)
Spleen	Enlargement of the spleen (splenomegaly)
Intestine	Inflammatory bowel disease, lymphoid hyperplasia
Blood cells and plasma proteins	Anaemia, thrombocytopenia, neutropenia, blood clotting disorders

There are more than 80 different types of autoimmune disorders and people can have more than one disorder at any one time. In people with PIDs, autoimmune complications are seen in 25% of patients.1 For example, autoimmune complications affect more than a quarter of people with common variable immunodeficiency (CVID). Some of the most common autoimmune disorders experienced by people with PIDs are shown in **Table 2**.

TABLE 2

COMMON AUTOIMMUNE DISORDERS EXPERIENCED BY PEOPLE WITH PIDS

PID (non exhaustive list)	**Possible autoimmune disorders** (non exhaustive list)
Common variable immunodeficiency (CVID)	Thrombocytopenia, Evans syndrome, autoimmune haemolytic anaemia, IBD, neutropenia, rheumatoid arthritis, pernicious anaemia, systemic lupus erythematosus, psoriasis
X-linked chronic granulomatous disease (CGD)	Inflammatory bowel disease
X-linked (or Bruton's) agammaglobulinaemia (XLA)	Juvenile rheumatoid arthritis, rheumatoid arthritis/dermatomyositis
Wiskott-Aldrich syndrome (WAS)	Thrombocyopenia, haemolytic anaemia, dermatitis, IBD, vasculitis
Hyper IgM syndrome (hyper IgM)	Autoimmne neutropenia, autoimmune haemolytic anaemia, IBD, rheumatoid arthritis, uveitis
Immune dysregulation, polyendocrinopathy and enteropathy X-linked (IPEX)	Cytopenias (thrombocytopenia, anaemia, neutropenia), dermatitis, IBD, type 1 diabetes
Autoimmune polyendocrinopathy candidiasis extodermal dystrophy (APECED)	Several autoimmune endocrinopathies (adrenal insufficiency, dysthyroidism)

Symptoms of autoimmune disorders can include fatigue, muscle aches, a low fever and a general feeling of being unwell. Such symptoms may indicate a sub-clinical infection but may also be consistent with autoimmune disease.

PIDS AND AUTOINFLAMMATORY DISEASES

Autoinflammatory diseases are a group of rare, hereditary inflammatory disorders that occur in the absence of any infection. The innate immune system is often responsible for autoinflammatory disease. The innate immune system is a first line of defense against invading pathogens and causes a range of non-specific inflammatory responses. However, these non-specific inflammatory responses can cause organ damage if they continue uncontrolled. People with autoinflammatory diseases typically have intense and recurring attacks of inflammation, which cause symptoms such as fever, rash, joint swelling, abdominal pain, diarrhoea, fatigue and weight loss (**Table 3**).

TABLE 3

COMMON AUTOINFLAMMATORY DISORDERS AND ASSOCIATED SYMPTOMS

Disease	Symptoms
Familial Mediterranean fever (FMF)	• Short duration of fever (24–48 hours) • Abdominal and chest pain • Erysipelas (super infection of the skin)
Tumour necrosis factor (TNF) receptor-associated periodic fever syndrome (TRAPS)	• Recurring fevers • Muscle, abdominal and chest pain • Rash • Nausea, vomiting, diarrhoea • Sore eyes
Hyperimmunoglobulinaemia D and periodic fever syndrome (HIDS)	• Recurring fevers • Abdominal pain • Vomiting, diarrhoea • Joint pain • Skin lesions • Headache

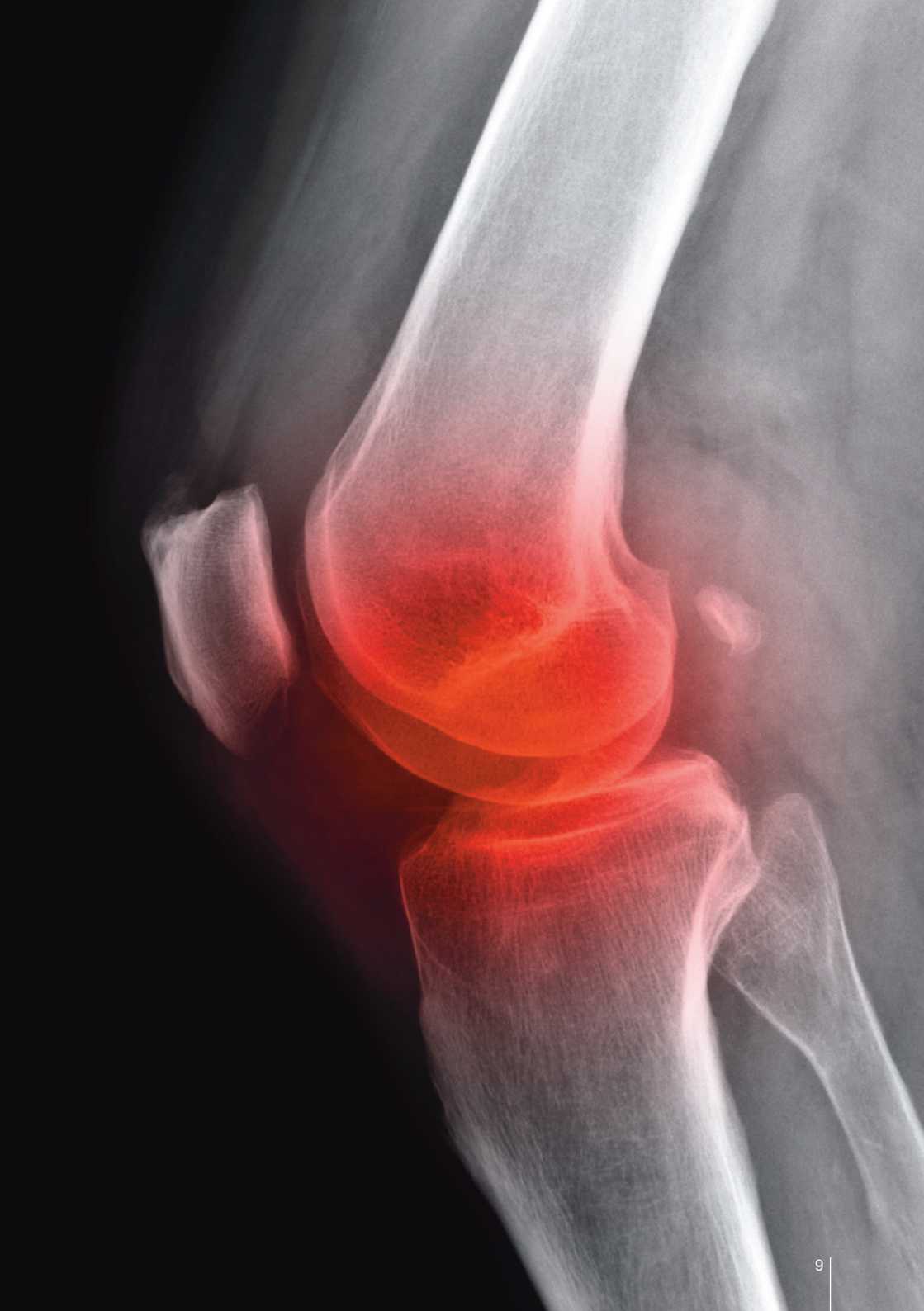


TABLE 3

COMMON AUTOINFLAMMATORY DISORDERS AND ASSOCIATED SYMPTOMS

Cryopyrin-associated periodic syndrome (CAPS) • Familial cold autoinflammatory syndrome (FCAS) • Muckle-Wells syndrome (MWS) • Neonatal onset multi-system inflammatory disease (NOMID)/ chronic infantile neurological cutaneous and articular syndrome (CINCA)	• Headache • Rash • Joint and muscle pain • Fever after cold exposure (seen in FCAS) • Kidney impairment (seen in MWS) • Hearing problems (seen in MWS) • Conjunctivitis (seen in MWS) • Organ damage (seen in NOMID)
Blau's syndrome	• Rheumatoid arthritis • Inflammation of the eye • Skin rash and granuloma
Crohn's disease	• Diarrhoea • Abdominal pain • Fatigue • Weight loss • Blood and mucus in stools
Pyogenic arthritis, pyoderma gangrenosum and acne syndrome (PAPA)	• Pus-producing arthritis • Skin ulcers • Cystic acne
Chronic recurrent multifocal osteomyelitis syndrome (CRMO)	• Recurring fevers • Bone pain and lesions
Majeed syndrome	• Recurring fevers • Bone pain • Skin inflammation

TREATMENT OF RHEUMATOLOGICAL, AUTOIMMUNE AND AUTOINFLAMMATORY DISEASES

For many people with PIDs and rheumatological and autoimmune disorders, they may be treated with a compendium of immunomodulatory drugs, including corticosteroids and high doses of immunoglobulin. As long-term use of corticosteroids is associated with serious side-effects, other immunosuppressive agents may also be used such as azathioprine, leflunomide, methotrexate, mycophenolate, tacrolimus, cyclophosphamide or cyclosporine.

For patients with autoinflammatory conditions, anti-inflammatory agents (such as non-steroidal anti-inflammatory drugs [NSAIDs], colchicine or immunomodulators) may be used. Biological therapies may also be needed if immunosuppressive or anti-inflammatory therapy is not effective. These therapies include tumour necrosis factor (TNF) inhibitors, such as etanercept, infliximab and adalimumab, interleukin (IL)-1 and IL-6 targeted therapies such as anakinra, canakinumab, riloacept or tocilizumab.

These medicines should always be used under the guidance of your doctor, who will regularly monitor you to check if there is any change in your disease and if you develop any side-effects.

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 worldwide, please visit **IPOPI.org**.

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