IPOPI
INTERNATIONAL
PATIENT ORGANISATION
FOR PRIMARY IMMUNODEFICIENCIES

PRIMARY **IMMUNODEFICIENCIES**

A GUIDE FOR **GASTROENTEROLOGISTS**



ABBREVIATIONS

CVID	Common variable immunodeficiency
GI	Gastrointestinal
IPOPI	International Patient Organisation for Primary Immunodeficiencies
PID	Primary immunodeficiency
SCID	Severe combined immunodeficiency
IG	Immunoglobulin

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INTRODUCTION

This booklet explains the complex presentation of patients with primary immunodeficiencies (PIDs) who may be referred to gastroenterology services due to non-specific gastrointestinal (GI) symptoms. Clinical indicators that may raise a suspicion for PID are reviewed as is the need for members of a multidisciplinary team to care for such patients.

Primary immunodeficiencies (PIDs) are rare diseases that occur when components of the immune system are either not present or are not functioning normally, rendering the patient susceptible to potentially life-threatening infections.

The presentation of PID is often complex with clinical indicators suggestive of multiple potential diagnoses. Such patients may be referred to a gastroenterologist with specific and non-specific gastrointestinal symptoms, including recurrent gastrointestinal infections and inflammatory colitis. Gastroenterologists, therefore, have an opportunity to identify patients with PIDs, ensuring they receive a timely diagnosis and intervention to minimise the chronic effects of PIDs and to initiate prophylactic therapies.

The following sections review the complex clinical presentations of patients with PIDs and the clinical indicators that may raise a suspicion for PIDs. Management strategies, including building a multidisciplinary team, are also explored.



PIDs: NOT JUST A PAEDIATRIC DIAGNOSIS

To date, over 400 different PIDs have been identified genetically, biochemically and phenotypically, ranging from the very rare (e.g. severe combined immunodeficiency [SCID]) to the relatively common (e.g. selective immunoglobulin A deficiency). Around one third of PIDs are thought to have a gastrointestinal (GI) component that may represent the presenting symptomatology.[1]

The most severe forms of PIDs are diagnosed during childhood. However, others are frequently identified during adulthood because of their late onset and because they have been misdiagnosed or undiagnosed. PIDs can have widely differing presentations, from relatively mild to life-threatening. Some PIDs develop over time and worsen as late manifestations or complications arise. Many patients with PIDs go undiagnosed for several years, during which time they are often treated several times with antimicrobial agents.

People with PIDs are more susceptible to infections, allergies, autoimmunity, malignancies and complications resulting from infections and inflammation. The relatively non-specific nature of the presentation of PIDs can mean that they are referred for internal medicine evaluation with an array of chronic symptoms.

GASTROINTESTINAL INDICATORS FOR PIDs

PID can often mimic GI diseases and a suspicion of a PID should be raised especially in infants or children presenting with atypical GI disease and failure to respond to conventional therapies.[2]

Typical GI symptoms in patients with PIDs include prolonged or recurring diarrhoea, mouth ulcers, inflamed gums, bloating, blood in stool, abdominal pain, inflammatory bowel-like disease, liver disease and rectal ulcers. Failure to thrive infants and weight loss in teenagers and young adults may indicate an inadequately treated PID and may be indicative of a GI component.

[1] Hartono S, et al. Gastrointestinal disorders associated with primary immunodeficiency diseases. Clin Rev Allergy Immunol 2018; Epub ahead of print

[2] Nazi N, Ladomenou F. Gastrointestinal manifestations of primary immune deficiencies in children. Int Rev Immunol 2018; 37:111-8



The table below highlights the main GI symptoms that could alert a gastroenterologist to a potential PID presentation.[3]

GASTROINTESTINAL MANIFESTATIONS OF PIDS [4]

GI manifestation	Potential PID
Colitis and hepatitis (CMV), candidiasis, chronic diarrhoea, GvHD. Symptoms can be present from birth	Severe combined immunodeficiency (SCID)
Diarrhoea, hepatosplenomegaly, eosinophilic enteropathy	Omenn syndrome
Hepatitis (autoimmune, toxic), diarrhoea, colitis and hepatitis (CMV), candidiasis,	Adenosine deaminase deficiency
Protracted diarrhoea (*Cryptosporidium*), progressive liver disease, sclerosing cholangitis, colitis and hepatitis (CMV), candidiasis,	MHC-II deficiency (Bare lymphocyte syndrome)
Oral ulcers, diarrhoea (*Cryptosporidium*), progressive liver disease, sclerosing cholangitis, malabsorption	Hyper IgM syndrome
Diarrhoea (*Giardia lamblia*), coeliac sprue, nodular lymphoid hyperplasia	Selective IgA deficiency
Acute and chronic diarrhoea, malabsorption	X-linked agammaglobulinaemia
Diarrhoea (*Giardia lamblia*), nodular lymphoid hyperplasia, villous blunting, IBD-like colitis, pernicious anaemia, progressive liver disease	Common variable immunodeficiency (CVID)
Colitis, bloody diarrhoea, eosinophilic enteropathy, lymphoma, malabsorption	Wiskott-Aldrich syndrome
Periodontitis, liver abscesses, eosinophilic enteropathy	Hyper-IgE syndrome

[3] Al-Muhen SZ. Gastrointestinal and hepatic manifestations of primary immune deficiency diseases. Saudi J Gastroenterol 2010;16:66-74

[4] Al-Muhsen SZ. Gastrointestinal and hepatic manifestations of primary immune deficiency diseases. Saudi J Gastroenterol 2010;16:66-74.

GASTROINTESTINAL MANIFESTATIONS OF PIDS [4]

GI manifestation	Potential PID
Oesophageal candidiasis	Chronic mucocutaneous candidiasis
Hepatic veno-occlusive disease, hepatosplenomegaly	Hepatic veno-occlusive disease with immunodeficiency
Severe enteropathy, severe chronic diarrhoea, malabsorption and failure to thrive	Immunodeficiency, polyendocrinopathy, Enteropathy, X-linked (IPEX)
Granulomatous colitis	Hemansky-Pudlak syndrome
Post-EBV fulminant hepatic failure, hepatosplenomegaly, lymphoma	X-linked lymphoproliferative syndrome (XLP)
Oral ulcers, oesophageal dysmotility, gastric outlet obstruction, small bowel obstruction, colitis, perianal fistula and abscesses, hepatitis, liver abscesses	Chronic granulomatous disease (CGD)
Omphalitis, periodontitis, perianal ulcers	Leukocyte adhesion defect
Pancreatic enzyme insufficiency, diarrhoea, malabsorption	Shwachmann-Diamond syndrome
Salmonella gastroenteritis, mycobacterial liver and spleen abscesses	IFN-y and IL-12 circuit defect (MSMD)
Peritonitis, abdominal pain	Periodic fever syndrome
Crohn's disease	Blau syndrome
Intestinal wall oedema, severe abdominal pain	Hereditary angioedema

ADA, adenosine deaminase deficiency; CMV, cytomegalovirus; EBV, Epstein Barr virus; GvHD, graft versus host disease; MHC, major histocompatibility syndrome; IBD, inflammatory bowel disease; MSMD, Mendelian susceptibility to mycobacterial disease.

ACHIEVING A DIAGNOSIS OF PID

Initial investigations, which may have been performed in the primary care setting, should involve complete blood count including leucocytes and differentiation, IgA, IgM, IgG and IgE. A CT scan should be requested in cases of recurrent pulmonary infections to assess lung damage. Evidence of autoimmunity symptoms should be looked for.

GI-specific evaluations should include physical examination to check for oral or anal ulcers, fluid or tenderness in the abdomen, enlarged or tender liver and spleen. Blood tests should be ordered to check for signs of intestinal bleeding or inflammation. Stool tests or video capsule investigation should be undertaken to identify inflammation and infections; liver or bowel biopsies; gastroscopy/ colonoscopy to evaluate the mucosa. It may be necessary to involve additional specialities to achieve a diagnosis, usually an immunologist but possibly also a specialist in infectious diseases or a haematologist. A key step is to rule out haematological malignancy as an alternative diagnosis.



CARING FOR THE PATIENT WITH A PID

Common management strategies for patients with GI symptoms associated with a PID are summarised in the table below.

INFECTION/ CONDITION	TYPICAL TREATMENTS
Bacterial infections	As for non-PID patients but may require longer antibiotic courses and careful monitoring for complications
Giardia lamblia infection	Metronidazole (may require several courses in patients with different forms of PIDs) Steroid therapy; prolonged therapy not recommended Other immune modulators might be considered, including 6-MP or AZA in addition to anti-infective drug and to transient increase in doses of Ig replacement therapy
Inflammatory colitis	Corticosteroids, 5-aminosalicylic acid, 6-MP and AZA, or biologic agents (such as anti-TNF)
Asymptomatic IgG-deficient patients with GI symptoms	As per non-PID patients but monitor for progression to CVID
Chronic enteroviral diarrhoea	High-dose peripheral and intraventricular Ig have been used in patients with profound panhypogammaglobulinemia or agammablobulinemia (Such as Bruton's disease)

6-MP, 6-mercaptopurine; AZA, azathioprine; CVID, common variable immunodeficiency; TNF, tumour necrosis factor

Patients with PID should be offered dietary advice and support including dietary adjustment (e.g. exclusion of gluten) and dietary considerations during prophylactic antibiotics. Treatments to support the gut microbiome may also be appropriate. Patients with PID are more susceptible to foodborne disease that are individuals without a PID and should be offered advice on low microbial diets (high-risk foods and how to substitute them).[5]

[5] Lund BM, O'Brien SJ. The occurrence and prevention of foodborne disease in vulnerable people. Foodborne Pathog Dis 2011;8:961-73

BUILDING A MULTIDISCIPLINARY TEAM FOR PATIENTS WITH PIDS, OTHER COMORBIDITIES AND COMMON DISEASES

Patients with PIDs may present with metabolic conditions (including hypercholesterolaemia and diabetes mellitus) that may require the involvement of additional specialist physicians. An additional complication is the risk associated with intravenous immunoglobulin treatment, namely fluid load, which can increase a patient's risk of congestive heart disease – in this case a cardiologist should be consulted – and haemolytic anaemia, which requires input from both cardiology and haematology specialists.

Patients with PIDs are more vulnerable to the development of malignancies, especially GI cancers (in particular, gastric cancer in patients with CVID) and lymphoma. Oncology specialists may need to be included as part of a multidisciplinary team. Referral to other disciplines or to centres specialising in the management of patients with PIDs may be appropriate where available.



PIDs: A GUIDE FOR GASTROENTEROLOGISTS

- Around one third of PIDs are thought to have a GI component that may represent the presenting symptomatology and associated pathology.
- Patients with complex, non-specific conditions may be referred for specialist evaluation by gastroenterologists for whom a variety of clinical indicators can raise the suspicion for PIDs.
- Typical GI symptoms in patients with PIDs include prolonged or recurring diarrhoea, mouth ulcers, inflamed gums, bloating, blood in stool, abdominal pain, inflammatory bowel-like disease, liver disease and rectal ulcers.
- Failure to thrive infants and weight loss in teenagers and young adults may indicate an inadequately treated PID and may be indicative of a GI component.
- Autoimmune and/or inflammatory GI manifestations can occur throughout a patient's life.
- Patients with PIDs may require care from a range of specialties depending on their individual symptoms and the organ systems affected.



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 67 countries worldwide, please visit **www.ipopi.org**.

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PID UK
Supporting families affected by primary immunodeficiencies

IPOPI National Member Organisation for the UK

PID UK's website at **www.piduk.org** provides useful information on a range of conditions and topics, and explains the work we do to ensure the voice of PID patients is heard.

If we can be of any help, please contact us at **hello@piduk.org** or on **0800 987 8986** where you can leave a message.

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