SECONDARY IMMUNODEFICIENCIES **(SIDs)**

ABBREVIATIONS

CLL	Chronic lymphocytic leukaemia
G-CSF	Granulocyte–colony stimulating factor
GVHD	Graft-versus-host disease
HIV	Human immunodeficiency virus
HSCT	Haematopoietic stem cell transplantation
Ig	Immunoglobulin
IPOPI	International Patient Organisation for Primary Immunodeficiencies
MM	Multiple myeloma
PID	Primary immunodeficiency
SAD	Secondary antibody deficiency
SLE	Systemic lupus erythematosus
SID	Secondary immunodeficiency

Secondary immunodeficiencies (1st edition)

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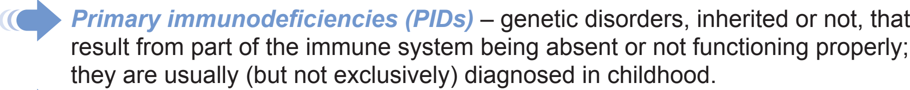
SUMMARY

Secondary immunodeficiencies (SIDs) are acquired immunodeficiencies that occur as a result of diseases or external factors, such as infections, medications, malnutrition or other underlying conditions. The signs and symptoms of SIDs are usually the same as those for primary immunodeficiencies (PIDs), namely frequent, prolonged, severe or unusual infections often with a difficult recovery, together with inflammatory or autoimmune complications. As for PIDs, the severity of SIDs and the specific immune components involved can vary greatly. There are many potential causes of SIDs, including blood or bone marrow disorders, some cancers and medications, malnutrition and nutritional deficiencies. The medicines that principally cause problems are those that target the immune system, which include immunosuppressant drugs, biologics and chemotherapy. These medicines may be used to treat autoimmune or inflammatory conditions and diseases (such as rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease or psoriasis) and some cancers (haematological or solid tumour therapies). The management of an individual with a SID should focus on improving the primary condition (e.g., by adjusting medications or improving nutrition) and, when possible, the removal of any offending environmental factors. If the underlying cause (such as medication or malnutrition) can be removed, then in many individuals the immune system returns to normal; however, for others, the treatment of the SID may be long-term or even life-long. General supportive measures to consider for individuals with a SID include measures to reduce exposure to infections as well as the administration of antibacterial, antiviral and/or anti-fungal prophylaxis, and long-term immunoglobulin replacement therapy. As with PIDs, vaccination strategies (for the individuals and for their entourage) are of crucial importance as high community vaccine rates and herd immunity are vital to prevent transmission of common diseases to immunocompromised individuals who cannot be vaccinated.

WHAT IS SECONDARY IMMUNODEFICIENCY?

There are two major types of immunodeficiencies:



- ***Primary immunodeficiencies (PIDs)*** – genetic disorders, inherited or not, that result from part of the immune system being absent or not functioning properly; they are usually (but not exclusively) diagnosed in childhood.
- ***Secondary immunodeficiencies (SIDs)*** – acquired immunodeficiencies that occur as a result of diseases or external factors, such as medications, infections, malnutrition, or other underlying conditions.

The signs and symptoms of SIDs are usually the same as for PIDs. For SIDs, if the underlying cause (such as malnutrition or medication) can be removed, then in many individuals the immune system returns to normal. For others, this is not

the case and the SID-related treatment may be long-term or even life-long. SIDs usually occur more frequently in adult patients and have higher prevalence than PIDs. In addition, SIDs can be the result of a wide range of conditions and causes, with the severity of the condition and the specific immune components affected varying greatly.

CAUSES OF SECONDARY IMMUNODEFICIENCY

There are many potential causes of SIDs with the most common examples being blood or bone marrow disorders and medications. Some cancers can be responsible for SIDs *per se*, too. The medicines that predominantly cause problems are those that target the immune system, including immunosuppressant drugs, biologics and chemotherapy. These medicines may be used to treat autoimmune or inflammatory conditions and diseases (such as rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease or psoriasis), and cancers (haematological or solid tumour therapies that include allogeneic haematopoietic stem cell transplantation [HSCT]).[1]

There are other medicines that are recognised as causing specific complications with the immune system, but these effects are not directly related to the way the drug works (for example, antibody deficiency caused by some anti-epileptic drugs). Some rare, inherited conditions or diseases, such as transcobalamin deficiency or gut lymphangiectasia, are not PIDs but cause failure of antibody production or loss of antibodies from the gut. These causes can be treated and/or immunoglobulin replacement therapy given when required.

Although Human Immunodeficiency Virus (HIV) infection is a cause of SID, this is usually treated as a separate disease in its own right. That said, it is often something that doctors wish to exclude before considering other causes for PID or SID.

Malnutrition and nutritional deficiencies, particularly protein-energy malnutrition, can also impair immune cell function. In addition, environmental exposure to certain toxins or conditions can also weaken the immune response. SIDs owing to the environment are a hazard for certain occupations, such as astronauts, high-altitude air pilots, or miners.[1] In addition, exposure to immunotoxicants in the environment is known to have an adverse effect on the immune system.[2,3]

SYMPTOMS AND DIAGNOSIS

The signs and symptoms of SIDs are usually the same as for PIDs, namely frequent, prolonged, severe or unusual infections often with a difficult recovery, together with inflammatory or autoimmune complications. Testing for SIDs usually requires blood samples (amongst other tests) to assess the immunodeficiency. This blood test may include blood cell counts and lymphocyte phenotyping to measure neutrophils, monocytes, T cells, B cells, and natural killer (NK) cells. Measurement of levels of serum immunoglobulins (Igs) G, A, M and E and antibody responses to previous immunisations (e.g., tetanus, pneumococcus) or infections (e.g., cytomegalovirus, Epstein–Barr virus) are helpful to evaluate humoral immunity. Total protein and total albumin serum levels help to identify hypoproteinaemia, which raises the suspicion of either malnutrition or protein-losing diseases.

Early detection of SIDs is crucial for timely intervention, management and future prevention. Hence, the findings from taking a clinical history, in particular patterns of infections, and physical examination abnormalities are essential to guide the assessment of the immune system.

TREATMENT

The management of a patient with a SID should be focused on the improvement of the primary condition (e.g., adjusting medications, improving nutrition) and, when possible, the removal of any offending environmental factor. This is of limited use in chronic conditions such as organ transplantation or HIV, where the emphasis is on managing the condition to minimise immunodeficiency.

General/supportive measures to consider for the patient with a SID include measures to reduce exposure to infections as well as administration of antibiotic prophylaxis and long-term Ig replacement therapy (Table 1). As with PIDs, vaccination strategies (for the patients and for the entourage) are crucial, as high community vaccine rates and herd immunity are vital to prevent transmission of common diseases to immunocompromised individuals who cannot be vaccinated.

TABLE 1. Management of individuals with immunodeficiencies (PID or SID)

1	Reduce risk of contact with potentially infectious persons and with environmental pathogens (e.g., avoid crowded or communal places).
2	Periodic clinical follow-up for prompt diagnosis of systemic and invasive infections.
3	Consider antibiotic (with or without antiviral and/or antifungal) prophylaxis to reduce the risk of infections.
4	Consider IgG replacement therapy for patients with significantly low serum IgG levels or significantly altered antibody response to immunisation (e.g., tetanus, pneumococcus).
5	Immunisations for infections by encapsulated bacteria, for example, *Streptococcus pneumoniae* and *Haemophilus influenzae* type b, are indicated in persons with altered specific antibacterial immunity, or when a high risk of invasive infection has been observed, for example, for patients receiving cochlear implants.
6	Complete scheduled immunisations, except for live vaccines for persons with severe immunodeficiency as they might induce vaccine-associated disease in these individuals, are recommended whenever possible. Vaccination of the entourage of the patient is of crucial importance in the reduction of microbial circulation and exposure.

Footnote: IgG, immunoglobulin G.

Treatments that are used for the different types of SIDs are summarised below:

- ***Antibody deficiency:*** Some SIDs may result in secondary antibody deficiency (SAD) mimicking the signs and symptoms of any of the primary antibody deficiencies. The level of treatment depends on the clinical and biological severity. A test vaccination may be recommended which, if successful, will stimulate the production of appropriate amounts of specific antibodies; in this case, an additional therapy might not be needed.
- ***Neutropenia:*** A low neutrophil count can be caused by immunosuppression or other medical treatments and is an indication to consider a change of therapy. If this is not possible or the treatment has already been stopped, individuals may require prophylactic treatment with both antibiotic and anti-fungal therapies. Sometimes an injectable treatment (granulocyte–colony stimulating factor [G-CSF]) to stimulate the bone marrow to make and release more neutrophils can be used.
- ***T-cell deficiency:*** Defects in T-cell function and/or number caused by a medication or external factor may be very clinically significant and subsequent health problems may improve if the causative factor is removed. Individuals with poor T-cell function or number may often suffer from viral and bacterial infections, including organisms such as *Mycobacterium avium* complex.

- For individuals who have poor T-cell function as a consequence of being a HSCT recipient (e.g., for cancer treatment), it may be possible to 'top up' their immunity with an additional treatment of donor lymphocytes ("donor lymphocyte infusion"). For some individuals, the treatment for graft-vs-host disease (GVHD) may result in this immune deficiency and, in such cases, a donor lymphocyte infusion is usually not possible.

WHY ARE SIDs OF INTEREST IN THE PID FIELD?

Several groups of individuals with SIDs face very similar medical challenges to those with PIDs, are cared for by the same immunology specialists, but they currently lack specific representation and support from established patient associations, sometimes lacking equitable access to diagnosis, treatment, and care. Persons with a SID have shared challenges in the diagnosis and treatment that individuals with a PID face. Furthermore, many persons with myeloma or chronic lymphocytic leukaemia (CLL) do not consider these SIDs as a disease but as a side effect of treatment.

Increasing awareness of PIDs that underlie SIDs is also crucial because there may be undiagnosed patients in this situation.

EXAMPLES OF SID TYPES THAT SHARE CHALLENGES IN THE DIAGNOSIS AND TREATMENT WITH PID PATIENTS	
SID patients with antibody deficiencies who depend on Ig replacement therapy and targeted therapies.	SID patients with chronic and/ or severe/refractory (transient) immunodeficiency and high risk of infection.

SIDs WITH SHARED CHALLENGES IN THE DIAGNOSIS AND TREATMENT AS PIDs

B-CELL LYMPHOPROLIFERATIVE DISORDERS AND OTHER HAEMATOLOGICAL DISEASES

B-cell lymphoproliferative disorders and other haematological diseases, such as CLL, lymphomas (B-cell lymphomas, such as diffuse large B-cell lymphoma [DLBCL], and marginal zone lymphoma) and multiple myelomas (MM), are a group of haematological diseases characterised by the excessive, uncontrolled and abnormal proliferation (in the bone marrow, lymph nodes, spleen, or peripheral blood) of B cells — a major type of white blood cell that plays a vital role in the normal immune system. Common symptoms include swollen lymph nodes, fatigue, night sweats, weight loss and enlarged spleen or liver.

These disorders are not a single disease but rather a spectrum of conditions with varying clinical, pathological, and imaging characteristics. B-cell lymphoproliferative disorders can be classified as reactive (benign) or malignant, based on the origin of the cells and clinical behaviour.

Lymphomas are cancers that originate in the lymphatic system, and B-cell lymphomas are the most common type of lymphoma. B-cell lymphomas can affect organs outside the lymphatic system, such as the skin, gastrointestinal tract, or lungs, and diagnosis often involves blood tests, bone marrow biopsy, lymph node biopsy, and imaging using PET/CT scans.

Treatment options vary depending on the specific disorder, stage and patient's overall health and may include chemotherapy, radiation therapy, targeted therapy, or stem cell transplantation. These diseases are of interest because they commonly cause severe antibody deficiency and recurrent infections that necessitate the use of therapies similar to those in patients with PID, including Ig replacement therapy.

HAEMATOPOIETIC STEM CELL TRANSPLANTATION

HSCT, also known as blood and bone marrow transplantation, is a medical procedure that replaces unhealthy blood-forming stem cells with healthy ones. HSCT offers a potential cure for patients with a wide range of blood-related disorders and cancers, such as leukaemia, lymphoma, myeloma, severe aplastic anaemia, sickle cell anaemia and thalassemia, and immune system disorders that include some PIDs. Also, HSCT can be used to cure diseases that do not fall in the previous category (e.g., some inherited metabolic diseases, also called 'inborn errors of metabolism').

HSCT is a potentially curative treatment for some PIDs by replacing a patient's defective stem cells with healthy ones from a donor, hence directly addressing the genetic defects causing the PID. However, HSCT carries risks; it can cause or worsen SID by damaging the patient's original immune system, commonly causing severe antibody deficiency and recurrent infections that necessitate the use of therapies similar to those in patients with a PID, including Ig replacement therapy and prophylactic antibiotics (and other antimicrobials).

SECONDARY ANTIBODY DEFICIENCY INDUCED BY DIRECT B-CELL INHIBITING DRUGS

Secondary antibody deficiency (SAD) can be induced by direct B-cell inhibiting drugs or therapies, often used in treating autoimmune and haematological/ oncological conditions such as systemic lupus erythematosus (SLE), nephrotic syndrome and some malignancies. These drugs, while targeting B cells, can impair the body's ability to produce antibodies, leading to an increased risk of infections. For example, medications such rituximab, epratuzumab, CD19-targeted CAR-T cells, alemtuzumab and belimumab can cause antibody deficiency.

Patients with SAD have a higher susceptibility to infections caused by encapsulated bacteria due to the weakened immune response. Common causes of SAD include:

- ***B-cell targeted therapies:*** used in conditions such as rheumatoid arthritis, SLE and some cancers (amongst others).

- ***Immunosuppressants:*** corticosteroids, cyclophosphamide and mycophenolate mofetil (amongst others).
- ***Haematological malignancies:*** disorders such as CLL and MM (amongst others) can cause SAD, even before treatment.

Diagnosis and management of SAD

Diagnosis and management of SAD require a comprehensive immunological workup that includes assessing infection history, measuring specific antibody responses and IgG subclasses (amongst others). Regular monitoring of antibody levels, especially after B-cell-depleting treatments, is crucial. Strategies such as prophylactic antibiotics and/or immunoglobulin replacement therapy may be necessary to prevent infection, while assessment of vaccine responses, particularly to polysaccharide vaccines, can help in the evaluation of immune function.

Throughout, it is important to distinguish between disease and treatment – it can be challenging to determine if SAD is due to the underlying disease or the treatment itself. Furthermore, management of SAD requires a personalised approach, considering the patient's specific situation and risk factors.

These B-cell-inhibiting drugs can commonly cause severe antibody deficiency and recurrent infections that necessitate the use of therapies similar to those in patients with PID, including Ig replacement therapy.

ADDITIONAL IMPORTANT CONSIDERATIONS

It is important to always keep in mind that patients with a SID may have an underlying PID. Moreover, there can be ***considerable crossover between the various PIDs and SIDs*** in terms of diagnosis, treatment and management – the complexity of PIDs and SIDs requires the involvement of a multidisciplinary team. Hence, the need for awareness to explore further in case of a SID and/or lack of recovery after certain treatments – this highlights the importance of clinical history, family history, and other tests, including genetic, if there are grounds for it. Additionally, immunological screening is important before the implementation of treatments that can cause SIDs.

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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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