

# Immunodeficiency

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The British Society of Immunology is the largest immunology society in Europe. Our mission is to promote excellence in immunological research, scholarship and clinical practice in order to improve human and animal health. We represent the interests of more than 3,000 immunologists working in academia, clinical medicine, and industry. We have strong international links and collaborate with our European, American and Asian partner societies in order to achieve our aims.

## Key points:

- Immunodeficiency disorders result in partial or full impairment of the immune system, leaving the patient unable to effectively resolve infections or disease.
- Immunodeficiency disorders can either be primary or secondary in nature. There are over 300 forms of primary immunodeficiency and, although rare, the condition can be life threatening.
- Secondary immunodeficiencies are the result of disease or other environmental factors weakening the immune system.
- Although affecting fewer patients than other classes of immune illness, immunodeficiency patients may require expensive definitive therapy (e.g. bone marrow transplant), or may remain life-long patients with complex care needs, and the cost-burden on the NHS is significant.
- Immunological research provides hope of improved curative therapies through the development of new technologies. Continued and increased investment is critical to ensure these potential advances are realised.

In healthy individuals the immune response comprises two phases. The first line of defence is the innate system, made up of specialised cells that provide a rapid response that is not tailored to the specific microbe that has infiltrated the body. Sometimes this can clear the infection alone but usually the innate response will contain the infection long enough for the adaptive immune system to activate. The adaptive response is the second line of defence and takes several days to assemble. The response is specific to the microbe and leaves a lasting immune memory, which makes the response to future

reinfection more efficient ([see here](#) for more information). In a person with an immunodeficiency disorder, one or more components of either the adaptive or innate immune response is impaired, resulting in the body being unable to effectively resolve infections or disease. This leaves immunodeficient individuals at high risk of recurrent infection, and vulnerable to conditions that would not usually be of concern to otherwise healthy individuals.

There are two types of immunodeficiency disorder:

- *Primary immunodeficiency (PID)* – inherited immune disorders resulting from genetic mutations, usually present at birth and diagnosed in childhood.
- *Secondary immunodeficiency (SID)* – acquired immunodeficiency as a result of disease or environmental factors, such as HIV, malnutrition, or medical treatment (e.g. chemotherapy).

## Primary immunodeficiency (PID)

PID disorders are inherited conditions often caused by single-gene mutations, which are usually diagnosed during infancy or childhood. They are relatively rare in the general population but are extremely diverse – over 300 individual mutations have been identified so far.<sup>i</sup> Up to 70% of PIDs occur in males because many of the genes that mutate are linked to the X-chromosome (males have only one X chromosome compared with two in females, so a faulty gene on the female X chromosome is more likely to be masked by a working gene on the other X chromosome).<sup>ii</sup> PIDs are categorised based on the part of the immune system that is disrupted.

## Examples of primary immunodeficiency disorders

- *B cell immunodeficiencies (adaptive)* – B cells are one of two key cell types of the adaptive immune system. Their main role is to produce antibodies, which are proteins that attach to microbes, making it easier for other immune cells to detect and kill them. Mutations in the genes that control B cells can result in the loss of antibody production. These patients are at risk of severe recurrent bacterial infections.
- *T cell immunodeficiencies (adaptive)* – T cells are the second of two key cell types of the adaptive immune system. One role of the T cell is to activate the B cell and pass on details of the microbe's identity, so that the B cell can produce the correct antibodies. Some

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T cells are also directly involved in microbe killing. T cells also provide signals that activate other cells of the immune system. Mutations in the genes that control T cells can result in fewer T cells or ones that do not function properly. This can lead to their killing ability being disrupted, and can often cause problems with B cell function too. Therefore, T cell immunodeficiencies can often lead to combined immunodeficiencies (CIDs), where both T and B cell function is defective. Some forms of CIDs are more severe than others.

- **Severe combined immune deficiencies (SCID) (adaptive)** – SCID disorders are very rare but extremely serious. In SCID patients there is often a complete lack of T cells and variable numbers of B cells, resulting in little-to-no immune function, so even a minor infection can be deadly. SCID patients are usually diagnosed in the first year of life with symptoms such as recurrent infections and failure to thrive.
- **Phagocyte disorders (innate)** – phagocytes include many white blood cells of the innate immune system, and these cells patrol the body eating any pathogens they come across. Mutations typically affect the ability of certain phagocytes to eat and destroy pathogens effectively. These patients have largely functional immune systems but certain bacterial and fungal infections can cause very serious harm or death.
- **Complement defects (innate)** – complement defects are some of the rarest of all the PIDs, and account for less than 1% of diagnosed cases. Complement is the name given to specific proteins in the blood that help immune cells clear infection. Some deficiencies in the complement system can result in the development of autoimmune conditions such as systemic lupus erythematosus and rheumatoid arthritis (please see our autoimmune briefing for more information). Patients who lack certain complement proteins are highly susceptible to meningitis.

## Treatments and outcomes

The prognosis of patients with PIDs is extremely variable and depends on the condition. Most SCID patients will die before the age of 1 without prompt treatment, although 95% of those that receive a bone marrow transplant (BMT) before 3 months of age will survive.<sup>iii</sup> Forty-three states in the USA now screen for SCID disorders at birth, but this is not yet routinely available in the UK.<sup>iv,v</sup> A famous SCID

disorder patient was David Vetter, known as “the boy in the bubble”, who from birth was isolated into a sterile environment while his family searched for a suitable bone marrow match. He died at the age of 12 from Burkitt’s lymphoma probably triggered by the Epstein-Barr virus, which lay dormant and undetected in the transplanted bone marrow he received. BMT is the preferred long-term treatment option for CIDs/SCIDs and some phagocyte disorders, although some SCIDs are now routinely treated with gene therapy. Supportive therapy for all PID conditions involves routine preventative use of antibiotics and antifungals. B cell disorders can also be managed with immunoglobulin (antibody) replacement therapy, where immunoglobulin G is purified from the blood plasma of healthy donors and infused into the patient.<sup>vi</sup>

Key vaccines are recommended for patients with innate deficiencies, but live vaccines (such as MMR) must be avoided for CID/SCID patients. It is therefore crucial that there is enough vaccine coverage in their local communities to generate “herd immunity”, where vaccine rates are at 95% or above ensuring resistance to disease transmission exists across the whole community, even for the few patients who cannot be vaccinated (please see our vaccine briefing for more information).

## Secondary immunodeficiency (SID)

SIDs are more common than PIDs and are the result of a primary illness, such as HIV, or other external factor such as malnutrition or some drug regimens. Most SIDs can be resolved by treating the primary condition.

### Examples of secondary immunodeficiency disorders

**Malnutrition** – Protein-calorie malnutrition is the biggest global cause of SIDs which can affect up to 50% of the population in some communities in the developing world.<sup>vii</sup> T cell numbers and function decrease in proportion to levels of protein deficiency, which leaves the patient particularly susceptible to diarrhoea and respiratory tract infections. This form of immunodeficiency will usually resolve if the malnutrition is treated.

**Drug regimens** – There are several types of medication that can result in secondary immunodeficiencies, but these drugs also perform critical roles in certain areas of healthcare. Immunosuppression is a common side-effect of most chemotherapies used in cancer treatment. The immune system usually recovers once the chemotherapy treatment has finished. Another common use for

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immunosuppressive drugs is the prevention of transplant rejection, where medication is required to suppress the transplant recipient's immune system and prevent it from targeting the transplanted tissue. These drugs can have significant side-effects and often suppress more areas of the immune system than are required, leading to susceptibility to opportunistic infections. Use of a new generation of medicines called biologics are becoming more widespread in treating transplant rejection. These drugs are derived from biological sources like cells, rather than chemical structures. Monoclonal antibodies are one such class of biologics and these drugs are made by farming antibodies from B cells that will act against a specific part of the disease process. These agents are more specific in their action than traditional drugs and have fewer side effects on non-target immune cells.

**Chronic infections** – There are a number of chronic infections which can lead to SID disorders, the most common of which is acquired immune deficiency syndrome (AIDS), resulting from HIV infection. The virus attacks CD4+ T cells, a type of white blood cell that plays a critical role in preventing infection, and gradually depletes their numbers. Once the T cell count is less than 200 cells per ml of blood, symptoms of AIDS begin to manifest and the patient is at high risk of recurrent infections that will eventually lead to death. Anti-viral therapies, such as the HAART regimen (Highly Active Antiretroviral Therapy), allow the T cell population a chance to recover and resume normal function. These drugs have had a huge impact on increasing the life expectancy for HIV/AIDS patients and improving their quality of life. Prior to the introduction of HAART, patients with HIV diagnosed at age 20 had an average of 10 years before developing AIDS. Nowadays on average, patients diagnosed at age 20 can expect to live well into their 60s.<sup>viii</sup> However, these drugs must be taken every day for life as they are not curative, and are only available to patients and healthcare systems that can afford them.

## Treatments and outcomes

For many SID disorders treatment of the primary condition will lead to resolution of the immunodeficiency. 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. With advances in medical science the prognosis for these patients is now much improved. There is evidence to suggest that more patients with HIV now die from toxicity associated with the anti-retroviral therapy

than the disease itself, and that managing this is the next big challenge.<sup>x</sup> Comorbidities, such as secondary infections, are a major cause for concern and account for a high proportion of deaths in SID patients. As with PIDs, high community vaccine rates and herd immunity are vital to prevent transmission of common diseases to immunocompromised individuals, who cannot be vaccinated.

## How many people are affected by immunodeficiency?

No figures exist for the total number of people affected by all individual PID and SID disorders but some estimates are as follows:

- Around 6 million people live with a PID worldwide but between 70-90% are undiagnosed.<sup>x</sup>
- Around 5,000 individuals in the UK are thought to have a PID disorder.<sup>xi</sup>
- According to the NHS there were 39,000 PID-related hospital admissions in England in 2014-2015.<sup>xii</sup>
- Up to 50% of the poorest communities in the developing world are affected by malnutrition-related SID disorders.<sup>vii</sup>
- There were around 100,000 patients with HIV in the UK in 2015, of which 96% are on treatment.<sup>xiii</sup>
- Around 600 UK deaths were attributed to HIV/AIDS in 2015.<sup>xiii</sup>
- According to the NHS there were 15,000 HIV-related hospital admissions in England in 2014-2015.<sup>xii</sup>

Although the numbers of people affected by these illnesses are relatively small, the specialist nature of their care and the risk of severe complications adds up to a significant cost-burden for their treatment. For example, delayed diagnosis of SCID in infants can result in treatment costs of well over \$1million (USD) per patient. Diagnosis before 3.5 months of age could reduce costs to \$50,000 (USD) per child, as recurrent infections are prevented.<sup>xiv</sup> Estimates of transplant patient numbers are not available but over 4 million prescriptions for immunosuppressant drugs were dispensed in England during 2015 at a cost of £220 million.<sup>xv</sup>

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## The importance of supporting immunodeficiency research

Primary immunodeficiencies are rare but can be extremely serious, and a PID diagnosis is life-changing for both the young child affected and their families. Current therapies provide some management of the condition but patients may remain susceptible to severe, recurrent infections. Novel therapies such as gene therapy represent an opportunity to fix the faulty gene responsible and allow these children the chance to have a normal life. Gene therapy is currently offered for a small number of immunodeficiency conditions, but with further research it is hoped that the therapy can be offered to more patients in the coming years. The technique involves replacing a mutated copy of the gene with a healthy copy in stem cells isolated from the patient, which are then transfused back into the body – a process known as autologous stem cell transplantation. Results from a recent trial of this technique in a SCID disorder show 100% survival rates at 7 years post-treatment,<sup>xvi</sup> compared with 85% survival in patients receiving a stem cell transplant from a healthy sibling. However, a major limitation of this technique is that the vector carrying the healthy copy of the gene is inserted randomly, sometimes close to genes that have the potential to cause cancer. Therefore, in some cases the process of inserting the healthy gene can increase the activity of cancer-linked genes, leading to tumour formation.

Use of gene therapy in conjunction with a new genome-editing technology, CRISPR/Cas9, would allow the specific insertion of the healthy gene into sites in the genome that are known to be located far away from cancer-linked genes, reducing the risk of tumour formation. The first UK license for CRISPR/Cas9 use in editing genes in human embryos was granted in 2016,<sup>xvii</sup> and CRISPR-edited cells to treat lung cancer were administered in the world's first human trials for the technique by a Chinese group in late 2016.<sup>xviii</sup> This technology is still in the early stages of development and continued research is vital in order to translate the technology into the clinic for PID gene therapy as soon as possible.

Secondary immunodeficiencies are more common and some of the primary causes of them are global health issues. While immunological research will not solve SID issues related to malnutrition, further research into HIV/AIDS prevention and treatment is essential to reducing the impact of this devastating disorder, particularly in the developing world. Anti-retroviral therapy has been very

successful in reducing mortality from HIV/AIDS but relies on the patient taking an oral dose every day. There are myriad reasons why access to reliable supplies of anti-retroviral therapy may not be possible in the developing world, and HIV patients in the developed world are not immune from forgetting to take their daily dose. Non-compliance in teenagers and young adults is particularly high, with around 40-50% of adolescents and young adults not adhering to the therapy regimen in Europe and the USA.<sup>xix</sup> Research into long-acting anti-retroviral therapy represents an exciting opportunity to tackle these issues and reduce the global burden of HIV related secondary immunodeficiency.

<sup>i</sup>Mukherjee S, *et al.* 2013 *Gene* **525** 174–181

<sup>ii</sup>Patient 2015 Immunodeficiency (Primary and Secondary)

<sup>iii</sup>Encyclopaedia of Children's Health 2017 Severe combined immunodeficiency

<sup>iv</sup>Immune Deficiency Foundation 2017 IDF SCID Newborn Screening Campaign

<sup>v</sup>PID UK 2015 SCID UK Newborn Screening Programme

<sup>vi</sup>Immune Deficiency Foundation 2013 Immunoglobulin Therapy & Other Medical Therapies for Antibody Deficiencies.

<sup>vii</sup>Chinen, J *et al.* 2009 *The Journal of Allergy and Clinical Immunology* **125** S195-S203

<sup>viii</sup>Aidsmap 2014 Life expectancy now considerably exceeds the average in some people with HIV in the US

<sup>ix</sup>Reisler RB *et al.* 2003 *Journal of Acquired Immune Deficiency Syndrome* **34** 379-386.

<sup>x</sup>McCusker C, *et al.* 2011 *Allergy, Asthma & Clinical Immunology* **7** S11

<sup>xi</sup>NHS England 2013 2013/2014 *Standard contract for specialised immunology (all ages)*

<sup>xii</sup>NHS England 2015 *Hospital Episode Statistics, Admitted Patient Care – England, 2014-2015*.

<sup>xiii</sup>Avert 2017 HIV and AIDS in the UK

<sup>xiv</sup>Immune Deficiency Foundation: Questions about Severe Combined Immunodeficiency Disease

<sup>xv</sup>HSCIC 2015 *Prescription Cost Analysis England 2015*

<sup>xvi</sup>Cicalese MP, *et al.* 2016 *Blood* **128** 45-54

<sup>xvii</sup>Callaway 2016 *Nature* **530** 18

<sup>xviii</sup>Cyranoski 2016 *Nature* **539** 479

<sup>xix</sup>Kim SH, *et al.* 2014 *AIDS* **28** 1945-1956