SPAD

Specific antibody deficiency (SPAD)

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IMMUNO DEFICIENCY UK

Supporting families affected by primary and secondary immunodeficiency

About this booklet

This booklet provides information on specific antibody deficiency. It has been produced by the Immunodeficiency UK Medical Advisory Panel and Patient Representative Panel to help answer the questions that patients and their families may have about this condition but should not replace advice from a clinical immunologist.

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Summary

Antibodies help to protect the body from infections. Specific antibody deficiency (SPAD) is considered as a diagnosis in individuals with a history of recurrent upper and lower respiratory infections but normal total levels of immunoglobulins and no major findings in other components of the immune system.

SPAD is a mild type of primary immunodeficiency, where those affected do not produce sufficient antibodies to protect the body from certain bacteria. It can affect both sexes and all ages. Symptoms of SPAD include an increased occurrence of upper and lower respiratory infections. Treatments include prompt treatment of infections with antibiotics, use of antibiotics to prevent infection and very rarely the use of immunoglobulin replacement therapy. With appropriate treatment, most people with SPAD live normal, healthy lives, and the outlook is generally good.

What is specific antibody deficiency (SPAD)?

Antibodies, also known as immunoglobulins, play a vital role in the immune system and keeping us healthy. They protect us from infections and against subsequent reinfection. At certain ages, however, this protection does not always work so well, and SPAD can be thought of as a more extreme form of this normal impairment to protection against certain organisms that can cause infections or diseases.

In people with SPAD, the ability to make good quality antibodies to certain bacteria never develops properly. The diagnosis of SPAD was originally restricted to the body's failure to make a response to a specific type of encapsulated bacteria called pneumococcus (*streptococcus pneumoniae*). Encapsulated bacteria are bacteria coated with sugars called polysaccharides. Now, many immunologists make the diagnosis when the total levels of antibody production in a patient are normal but there is an absent or poor response to any encapsulated bacteria (see Table 1). Although there are a range of microbes that cause infection, doctors will not test for responses to all of them. The basis of a diagnosis of SPAD will be made on the response to a vaccine.

Table 1. Types of encapsulated bacteria and possible infections caused

Name	Possible infections
Streptococcus pneumoniae	Pneumonia, bronchitis, rhinitis, acute sinusitis, otitis media, conjunctivitis, meningitis. RARELY sepsis, osteomyelitis, septic arthritis, endocarditis, peritonitis, pericarditis, cellulitis, brain abscess
Klebsiella pneumonia	Bronchopneumonia, bronchitis, lung abscess
Group B Streptococci	Sepsis, usually in newborns and occasionally in the elderly
Escherichia Coli (E.coli)	Gastroenteritis, urinary tract infections, neonatal meningitis, mastitis, pneumonia, sepsis
Neisseria meningitides	Meningitis
Haemophilus influenzae	Pneumonia, meningitis, epiglottitis, sepsis, otitis media, conjunctivitis, sinusitis

SPAD affects males and females, all age groups and can vary in its severity. It is not possible to diagnose SPAD early in life because children are not expected to respond to encapsulated bacteria for their first few years (see page 5). SPAD can sometimes be referred to as selective antibody deficiency, partial antibody deficiency and impaired polysaccharide responsiveness.

Encapsulated bacteria, conjugate vaccines and immune responses

Encapsulated bacteria, such as *streptococcus pneumoniae* or pneumococcus, can cause pneumonia and meningitis, with babies and older people at particular risk. Young children with developing immune systems are unable to make responses against pneumococcus and similar bacteria reliably for the first few years of life because the sugary coating of the bacteria makes it difficult for the immune system to respond. Babies are therefore at risk of invasive disease from these types of bacteria because they cannot eradicate the bacteria quickly. For this reason, protection is included in the childhood vaccination schedule through the vaccine Prevanar™ that does not rely on a polysaccharide response. (Other vaccines, such as Apexxnar™ or Vaxneuvance™, are used in some parts of the world.)

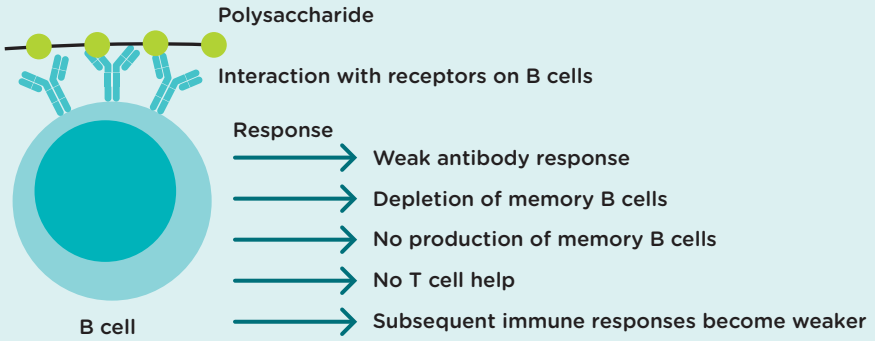
Our immune system is designed to make antibodies to proteins and not sugars. Accordingly, to help children with developing immune systems make protective antibodies to encapsulated bacteria, vaccines have been developed that integrate a way of tricking the immune system to respond. This is done by linking the sugars from the coating of the bacteria to a carrier protein (e.g. parts of diphtheria or tetanus protein). This allows antibodies in children previously vaccinated against diphtheria or tetanus to respond and helps amplify the immune response (see Figure 1). Vaccines that have this protein-sugar (polysaccharide) structure are called conjugated vaccines.

In later life, when the immune system wanes, infections caused by pneumococcus can become a problem again and so older people are vaccinated with the whole inactivated bacteria (Pneumovax™) to help give them protection against developing pneumonia. There are plans to change the adult vaccine to Prevanar because the protection offered is often more robust.

Pneumovax™ is also used throughout life as a booster vaccination for people at risk from more severe invasive infection; for example, people with immune deficiency or asthma.

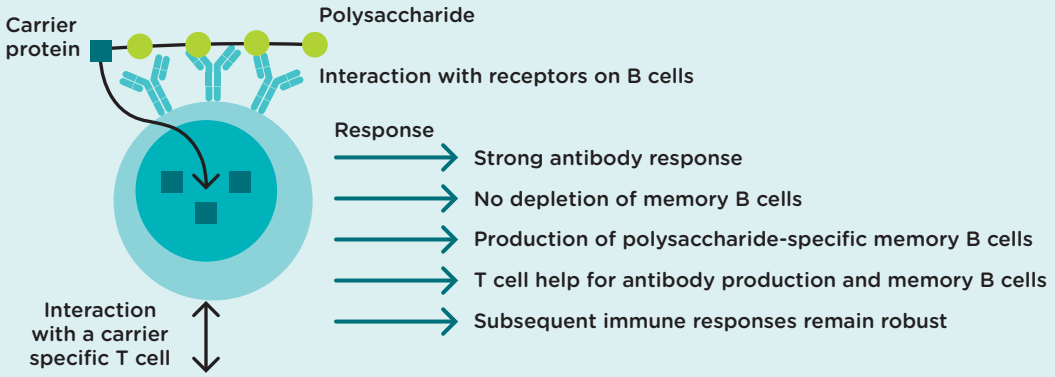
Figure 1. The immune response to polysaccharide and protein-polysaccharide conjugate vaccines

Immune response to polysaccharide vaccines



Polysaccharides from the encapsulated bacteria that cause disease in early childhood stimulate B cells and drive the production of antibodies (immunoglobulins). This process results in the lack of production of new memory B cells and a depletion of the B cell memory cell pool, such that subsequent immune responses are decreased.

Immune response to protein-polysaccharide conjugate vaccines



The carrier protein from protein-polysaccharide conjugate vaccines is processed by a polysaccharide-specific B cell and presented to a carrier specific T cell. This results in T cell help for the production of antibody-producing B cells and memory B cells.

Adapted from Pollard, A., Perrett, K. & Beverley, P. 'Maintaining protection against invasive bacteria with protein–polysaccharide conjugate vaccines'. *Nature Reviews Immunology* 9, 213–220 (2009). https://doi.org/10.1038/nri2494

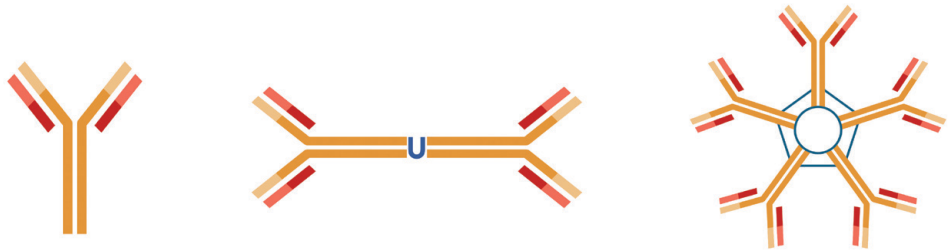
How did I get SPAD?

There are three major classes of immunoglobulins. Each class has a slightly different function in preventing microorganisms from successfully invading body tissues and causing serious infections.

- **Immunoglobulin G (IgG)** is the most abundant immunoglobulin, found in blood and tissue fluids. IgG functions mainly against bacteria and some viruses.
- **Immunoglobulin A (IgA)** is found in nasal fluids, bile, tears, sweat and saliva. It protects the tissues of the respiratory, reproductive, urinary and digestive systems.
- **Immunoglobulin M (IgM)** is a rapid response antibody and is the first type of protective antibody produced in response to infection.

A type of immune cell, known as a B cell, is responsible for the production of antibodies. In the immune system there is normally constant communication between B cells and other immune cells. The purpose of this communication is to ensure that B cells make antibodies against the correct targets. B cells should make antibodies against infections to help your immune system fight them off. Why some people develop SPAD is the subject of ongoing research, and the causes are not fully understood. One theory is that a problem with the communication between B cells and other cells leads to SPAD.

Structure of the three major classes of immunoglobulins



What are the symptoms of SPAD?

Antibodies help the immune system to fight off infections, especially bacterial infections that tend to arise in the upper airways (nose, sinuses, throat and ears).

Patients with SPAD may be susceptible to increased numbers of chest and sinus infections (e.g. pneumonia) and ear infections (e.g. otitis media).

Symptoms may vary from one person to another, and some people may be asymptomatic (showing no symptoms) because other parts of their immune system are working well.

The other components of the immune system work normally in SPAD, and so even though there is a problem with the production of antibodies, the other ways in which the immune system fights infections still work.

How is SPAD diagnosed?

In investigations of SPAD:

- There must be a history of relevant infection. SPAD cannot be diagnosed when antibody responses are poor but there is no infection history.
- Levels of immunoglobulins (the three main classes: IgG, IgA and IgM) should be normal.
- Checks are made for the presence of specific immunoglobulins that can fight infection, e.g. using antibody levels against prior vaccination to specific bacteria as a guide. If the specific immunoglobulins are low, then the response of the immune system to vaccination is assessed.
- A count of the numbers of the different types of immune cells in the blood should be normal in SPAD.

What treatments can be used for SPAD?

Infections should be treated promptly with antibiotics. Often, high-dose antibiotics continued for at least 10 days are used. If infections are frequent, then someone may be started on prophylactic antibiotics, which is a low dose of antibiotics taken regularly, even when the individual is well and infection free. The aim of prophylactic antibiotics is to prevent an infection from starting. The antibiotic chosen varies from person to person, according to individual circumstances. For example, allergies to antibiotics, the species of bacteria and the site(s) of infection will all influence the choice of antibiotic prescribed. Many patients may take antibiotics during the winter months only, when coughs and colds increase the likelihood of bacteria causing a secondary infection.

For more information, please see our booklet ‘Use of antibiotics in the treatment of immunodeficiency’.

Very rarely, antibiotics on their own are not enough, and immunoglobulin replacement therapy (IG therapy) may be required for a period of time. This replaces the low levels of immunoglobulins to specific organisms (see our information on immunoglobulin therapy). As vaccines have been introduced to children and better vaccines for adults exist, the occurrence of SPAD appears to be declining.

Inheritance of SPAD

There is no clear-cut pattern of inheritance for SPAD.

Associated health complications

If an individual has had lots of infections, then they may have sinus or airways damage (bronchiectasis). In this case, more specific treatments (e.g. sinus surgery) may be needed and additional interventions or monitoring for bronchiectasis.

A small number of patients with SPAD will have selective IgA deficiency (sIgAD). It is not clear if the two conditions are linked, because sIgAD is common (1:500 northern Europeans) and is usually asymptomatic. In individuals with sIgAD and SPAD, the frequency of infection may be higher.

Immunisation

Patients with SPAD can safely receive live vaccines, assuming there are no other reasons for not having a vaccine. Responses to other vaccines should be normal and so patients should take up the offer of additional protection, as advised.

Glossary of terms

Abscess a collection of pus that has built up within a tissue of the body.

Allergy hypersensitivity to a particular substance.

Antibiotics a substance, such as penicillin, produced by or derived from certain microorganisms that can destroy or inhibit the growth of other microorganisms, especially bacteria. Antibiotics are widely used in the prevention and treatment of infectious diseases.

Antibody a type of protein (immunoglobulin) that is produced by certain types of white blood cells (plasma cells – a type of B cell). The role of antibodies is to fight bacteria, viruses, toxins, and other substances foreign to the body.

Asthma a long-term condition affecting children and adults. The air passages in the lungs become narrow due to inflammation and tightening of the muscles around the small airways. This causes symptoms such as cough, wheeze, shortness of breath and chest tightness.

Autoantibodies antibodies that attack the body's own tissues.

Bacteria single-celled, or simple, organisms that are invisible to the naked eye. Most are harmless but some bacteria can cause infections in humans. **Encapsulated bacteria** are bacteria that are coated in a layer made up of complex sugars known as polysaccharides. This layer is called a capsule.

B cell a type of white blood cell (lymphocyte) that produces antibodies.

Bronchiectasis a widening of the tubes (bronchi) that lead to the air sacs of the lung; this can happen because of repeated bouts of infections.

Conjunctivitis inflammation or infection of the eye.

Gastroenteritis inflammation of the lining membrane of the stomach and the intestines; characterised by nausea, vomiting, diarrhoea and abdominal pain.

Immune deficiency when the immune system's ability to fight infectious disease is compromised or entirely absent.

Immunoglobulins proteins (globulins) in the body that act as antibodies. They work to fight off infections. They are produced by specialist white blood cells (plasma cells/B cells) and are present in blood serum and other body fluids. There are several different types (IgA, IgE, IgG and IgM), and these have different functions.

Immunoglobulin replacement therapy a plasma-based treatment. The immunoglobulin contains antibodies that help fight infection. This treatment can be given through a vein or through the skin.

Meningitis an infection of the protective membranes that surround the brain and spinal cord (meninges). Meningitis can be very serious if not treated quickly.

Osteomyelitis an unusual bacterial infection of bone and bone marrow.

Otitis media inflammation or infection of the ear.

Peritonitis inflammation of the inner lining of the abdominal cavity.

Pneumonia swelling (inflammation) of the tissue in one or both lungs. It is usually caused by a bacterial infection or a virus. **Bronchopneumonia** is a subtype of pneumonia. It is the acute inflammation of the bronchi, accompanied by inflamed patches in the nearby lobules of the lungs.

Respiratory tract the passages through which air enters and leaves the body, including the nose and nasal passages, the pharynx, larynx, trachea, lungs, bronchi and alveoli.

Sepsis a life-threatening reaction to an infection. It happens when the immune system overreacts to an infection and starts to damage the body's own tissues and organs. Sepsis is sometimes called septicaemia or blood poisoning.

Sinuses air-filled spaces within the bones of the face and around the nose. Infection of the sinuses is called sinusitis.

T cells (or T lymphocytes) specialised lymphocytes that develop in the thymus, an organ in the chest. They are responsible, in part, for carrying out the immune response.

Vaccine a substance that is put into the body of a person or animal to protect them from a disease by causing them to produce antibodies.

Virus a submicroscopic infectious agent that replicates only inside the living cells of an organism.

Notes

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About Immunodeficiency UK

Immunodeficiency UK is a national organisation supporting individuals and families affected by primary and secondary immunodeficiency.

We are the UK national member of IPOPI, an association of national patient organisations dedicated to improving awareness, access to early diagnosis and optimal treatments for PID patients worldwide.

Our website has useful information on a range of conditions and topics, and explains the work we do to ensure the voice of patients with primary and secondary immunodeficiency is heard. If we can be of any help, please email us or call on the number above, where you can leave a message.

Support us by becoming a member of Immunodeficiency UK. It's free and easy to do via our website. Members get monthly bulletins.

Immunodeficiency UK is reliant on voluntary donations. To make a donation, please go to **www.immunodeficiencyuk.org/donate**

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