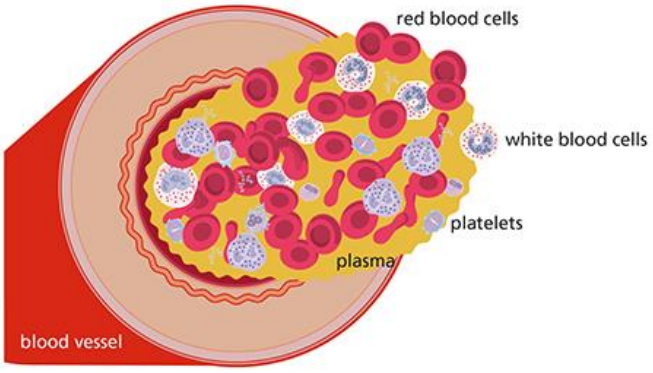
Great Ormond Street Hospital for Children
NHS Foundation Trust

Aplastic anaemia: information for families

Aplastic anaemia is a serious condition affecting the blood, where the bone marrow and stem cells do not produce enough blood cells. It is also called bone marrow failure and can happen suddenly (acute) or develop over a period of time (chronic). This leaflet explains about aplastic anaemia, how it is treated and what to expect when your child comes to Great Ormond Street Hospital (GOSH) for treatment.

Bone marrow is a substance found in the spongy centre of bones and is where blood cells are formed. The bone marrow forms 'stem cells' which develop into any of the three types of blood cell – red blood cells, white blood cells and platelets. Normally, the bone marrow controls the number of blood cells formed and released into the blood stream, so the body remains healthy. Too many or too few of any of the blood cells can cause problems. The number of blood cells is often referred to as a blood count and is often separated into the different types of blood cells.



Red blood cells – about three million red blood cells are produced by the bone marrow every second. They carry a protein called 'haemoglobin' which carries oxygen to all parts of the body providing energy. The normal level of haemoglobin in a child's blood varies with age but is around 10 to 12 grams per decilitre (g/dl). Another name for red blood cells is erythrocytes.

White blood cells – these are larger than red blood cells and have different functions. The two main white blood cells are neutrophils – which fight bacterial infections – and lymphocytes – which help fight viruses like chicken pox and measles and other non-bacterial infections. The normal level of all white blood cells in a child's blood is about six to 16 x 10^9/l. The normal level of neutrophils is between 1.5 and 8.5 x 10^9/l and lymphocytes between two and 9.5 x 10^9/l.

Platelets – these are much smaller than red blood cells and help the blood clot by sticking together. The normal level of platelets is between 150 and 400 x 10^9/l.

What are the symptoms of aplastic anaemia?

In aplastic anaemia, all types of blood cells are reduced. This is called pancytopenia – pan means all, cyto means cells and penia means few. A bone marrow sample, which would normally contain large numbers of immature blood cells, will contain very few such cells in a patient with aplastic anaemia. A below normal number of red

cells is called anaemia, reduced numbers of platelets is called thrombocytopenia and a reduced numbers of neutrophils is called neutropenia.

The most common symptom of aplastic anaemia is bruising. Your child may bruise easily often without having a fall or knock. This is caused by low numbers of platelets in your child's blood stream, which reduces the blood's ability to clot. Your child's gums may bleed after tooth brushing, and they may have nosebleeds.

Sometimes, the low number of platelets shows as petechiae, which are red pinprick spots under the skin. The medical term for a low platelet count is thrombocytopenia and is categorised as a platelet count of less than 150 x 10^9/l.

Another symptom is anaemia, which is caused by a low red blood cell count. This means that oxygen is not getting to the muscles as normal, which can make your child lack energy and become tired more quickly. They may also seem pale and lethargic, and become out of breath after exercise.

Neutropenia is another symptom of aplastic anaemia, and is the medical term for a low neutrophil count. This means your child may seem to catch more infections than normal or they last longer than in other children. The risk of infection depends on the neutrophil count. Neutropenia is diagnosed when the neutrophil count falls below 0.5 x 10^9/l.

What causes aplastic anaemia?

Aplastic anaemia can be inherited. It can also develop for unknown reasons – we call this idiopathic aplastic anaemia.

In idiopathic aplastic anaemia the immune system sees the body's bone marrow cells as the 'enemy' and starts to attack them. Generally we do not know what triggers this immune reaction but about one in ten patients with aplastic anaemia have had a recent viral infection, often hepatitis.

However, there is no evidence that any specific virus is more likely than others to cause aplastic anaemia. In these cases, aplastic anaemia probably happens because the patient's stem cells have some surface proteins which are similar to those on the virus. The immune system becomes 'confused' and produces antibodies which are targeted at the virus but also damage blood-forming stem cells.

Inherited causes of aplastic anaemia are less common; the commonest inherited cause is called Fanconi anaemia.

How common is aplastic anaemia and whom does it affect?

Aplastic anaemia is a rare disease, with about thirty to forty children diagnosed with it each year. It does not seem to affect one race more than another and also affects males and females equally. It can affect anyone at any age but seems to occur most often in children and people over 60 years old

How is it diagnosed?

You will probably have already seen your child's family doctor (GP) or local paediatrician for blood tests to explain his or her symptoms. The results of these tests – particularly the full blood count – may show the bone marrow is not producing enough healthy blood cells. While this test is useful, it cannot prove your child has aplastic anaemia. Sometimes, the symptoms and test results of aplastic anaemia can be confused with leukaemia.

At this stage, your child will usually be referred to a paediatric haematologist – a doctor specialising in blood disorders affecting children. The only method of diagnosing aplastic anaemia with certainty, is by examining a sample of bone marrow under a microscope. For more information about this, please read our leaflet *Your child is having a bone marrow test* available from the team or on our website. If your child has aplastic

anaemia, the results will show fewer normal cells than usual, whereas in leukaemia there will also be abnormal cancer cells too. Your child's haematologist may also suggest other tests to rule out other causes of bone marrow failure, and genetic studies to rule out the rarer, inherited form of aplastic anaemia.

Once your child has been diagnosed with aplastic anaemia, the severity of their condition will be classified as follows:

Very severe

- Neutrophils less than 0.2 x 10^9/l
- Platelets less than 20 x 10^9/l
- Bone marrow activity less than 30 per cent

Severe

- Neutrophils less than 0.5 x 10^9/l
- Platelets less than 20 x 10^9/l
- Bone marrow activity less than 30 per cent

Non-severe

- All cases which do not follow the above classification

What treatments are available?

The aim of treatment for aplastic anaemia is twofold – supportive management to correct your child's initial symptoms and treatment of the bone marrow failure.

Supportive management

When your child is diagnosed with aplastic anaemia, the first treatment is to correct their blood count. This may involve blood transfusions of platelets and red blood cells. All blood is screened to reduce the risk of reactions. If your child develops a temperature or becomes unwell especially if they are neutropenic, this will need to be treated immediately with antibiotics. As your child will need repeated blood tests and infusions, we suggest they have a 'central venous access device' inserted. This can be a central venous catheter, implantable port or a PICC. This stays in place all the time, and removes the need for repeated injections, although your child may still need to have some blood tests taken in the usual way. While this treatment should improve your child's symptoms, it will not treat the underlying condition.

Treatment options

Until recently, children and adults with idiopathic aplastic anaemia have been treated in a similar manner. Children are, however, very different to adults. They are more likely to have an inherited form of aplastic anaemia. They also do better than adults with stronger treatment options such as bone marrow transplantation. Expectations for children and teenagers can often be different to that of adults. The majority will be going to school, participating in sports, and will hopefully have a very long life expectancy. For many teenagers, their appearance and future fertility are major concerns.

Deciding which treatment option for a child with aplastic anaemia is best needs to take into account these expectations. Therefore the ideal situation is to have a form of treatment which would lead to normal blood counts, but not have too many side effects and be achieved with one definitive procedure without the need to be on long-term medicines.

The best treatment for idiopathic aplastic anaemia remains a bone marrow transplant from a brother or sister who is a tissue match. A quarter of children will be able to have a matched sibling bone marrow transplant. For those children who do not have a matched sibling, we have in the past given them immunosuppressive treatment with a medicine called ATG and ciclosporin. This is a relatively safe treatment, but only works in six out of ten children at best. However, even when it works, it is not perfect; many children relapse after successful ATG treatment, or develop further bone marrow problems later. Even when blood

counts do respond following ATG, they often tend to be low.

In the four out of ten children in whom ATG has had no benefit, we have then historically recommended a bone marrow transplant from a closely matched unrelated volunteer donor. We call this type of transplant a matched unrelated donor (MUD) transplant. Results from this type of transplant have now become so good that they are similar to the results seen with transplants from matched siblings. Currently nine out of ten children, who have not responded to ATG, are cured with matched unrelated donor transplants. Due to the excellent results now seen with matched unrelated donor transplants in childhood idiopathic aplastic anaemia, many paediatric haematologists in the UK are offering unrelated donor transplants upfront, rather than waiting to see if children respond to ATG.

Children with idiopathic aplastic anaemia will now have different pathways of treatment to that of adults. We will continue to promote bone marrow transplants from matched sister or brother as the best treatment option. However, unlike in adults where ATG is then considered to be the next treatment option, many centres in UK may consider a transplant from a matched unrelated donor as the next option.

Not all children will have a matched unrelated donor and so for them treatment with ATG will continue to be the best option. Parents will need to discuss with their clinician which option would be best for their child. More information about each follows:

Bone marrow transplantation

This replaces your child's defective bone marrow with a healthy one. As with blood transfusions and organ transplantation, the donated bone marrow has to be a good match for your child's body, to reduce the risk of it being rejected. When your child is diagnosed, we will take blood samples from your other children and yourselves, to see whether you or your children are a good match.

During the bone marrow transplant your child will need to have chemotherapy to damp down their immune system. This will prevent your child's body rejecting the donated bone marrow. The bone marrow itself is given like a blood transfusion. It takes a few weeks for the bone marrow to engraft or take root, and during that time your child will need to stay in hospital, as they will be at risk of infection.

Immunosuppressive therapy

The aim of this treatment is to reduce the number of lymphocytes circulating in the bloodstream using medicines called antithymocyte globulin (ATG) and ciclosporin, which stimulate the bone marrow to restart blood cell production. The ATG is given intravenously through the central venous access device over a period of five days. There is a chance your child could have an allergic reaction to ATG which originates from horse serum (part of the blood), but this usually occurs during the first few days of treatment.

Over the next few weeks, a problem called serum sickness can occur, which can cause high temperatures, rashes and swollen, painful joints. This is uncomfortable but can be treated successfully with steroids. The ciclosporin is given by mouth – for more information about this, please see our leaflet. The main side effect of ciclosporin is extra hair growth on the body, which may be quite obvious on the face. This will stop when the ciclosporin is stopped.

It can take a while for the blood counts to recover using this treatment, sometimes taking many months. During this time, your child will continue to be at risk from infection and bleeding, and so may still need transfusions of platelets and red blood cells. Other drugs are often given alongside ATG and ciclosporin. The main drug used is prednisolone, a steroid which helps deal with any side effects from ALG. These drugs can cause your child's appetite to increase, which may show as weight gain on the face. The steroids are

usually given in short burst of treatment, to minimise the side effects.

What is the outlook for children with aplastic anaemia?

Your child will need to have regular check-ups for a few years after treatment has finished, as some children can relapse and develop aplastic anaemia again. These check-ups will usually involve blood tests to check their full blood count. However, they will also be checked for any long-term side effects of both aplastic anaemia and the treatments used.

Are any new treatments in development?

Eltrombopag is a medicine which was originally developed for patients with severe deficiency of platelets due to reduced production or destruction of platelets. Unexpectedly, it was found that in some patients with aplastic anaemia, eltrombopag could increase production of red cells and white cells as well as platelets. A clinical trial using eltrombopag with ATG and ciclosporin is planned in children but is not currently open.

Talk to your clinical team about research and the development of new treatments. You can also visit our Research and Innovation website at www.gosh.nhs.uk/research-and-innovation.

Further information and support

The Aplastic Anaemia Trust can offer support and information to anyone affected by aplastic anaemia. Call their helpline on 0300 102 3202 or visit their website at www.theaat.org.uk.

Marrowkidz is a section of the Aplastic Anaemia Trust website at www.theaat.org.uk/marrowkidz that offers an interactive and dynamic area aimed at our young patients, their siblings, families and friends. One of the key objectives of Marrowkidz is the provision for everyone affected by aplastic anaemia and other rare bone marrow failures with the information, emotional and practical support they need – when they need it, how they need it and where they need it the most. This includes children, adult patients and their loved ones.