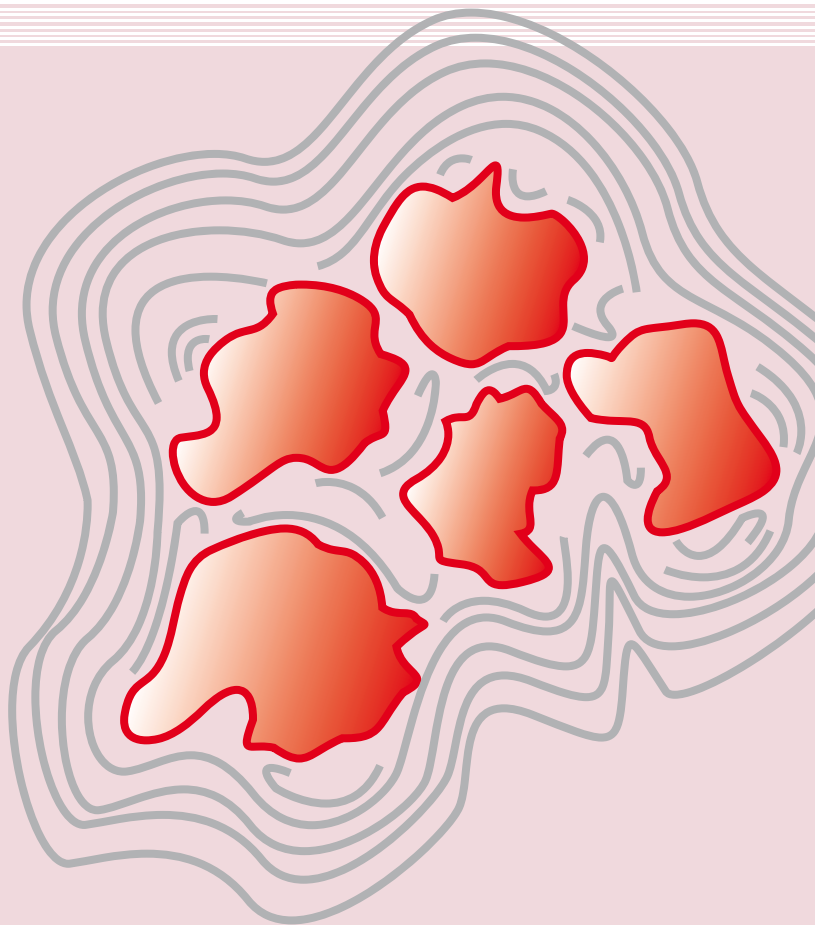


Aplastic Anaemia (AA)



The diagnosis of a blood cancer can be a devastating event for patients, families and friends. It is therefore vital for everyone to have access to reputable and understandable information to help cope with the illness. Whenever possible our booklets are written in line with national guidelines for the treatment of patients with a blood cancer. The information in our booklets is more detailed than in many others but is written in a clear style with all scientific terms explained for the general reader.

We recognise that the amount and level of information needed is a personal decision and can change over time. Particularly at the time of diagnosis, patients may prefer less detailed information. A number of alternative sources of information are available which complement our publications.

The booklets in this series are intended to provide general information about the topics they describe. In many cases the treatment of individual patients will differ from that described in the booklets.

At all times patients should rely on the advice of their specialist who is the only person with full information about their diagnosis and medical history.

For further advice contact the clinical information team on 020 7269 9060.

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What is aplastic anaemia?

Aplastic anaemia is a rare acquired disorder in which there is a failure of the bone marrow to produce sufficient blood cells for the circulation. Acquired means that the condition is neither present at birth nor inherited but has developed during the patient's life. Blood cells come from special cells in the bone marrow, called stem cells. Less than 1 in 5,000 of the marrow cells is a stem cell. The stem cells give rise to a progressively maturing series of different cell types which eventually lead to all the functional blood cells found in the circulation. In aplastic anaemia blood production by stem cells fails resulting in a lack of red cells (anaemia), white cells (leading to an increased risk of infection) and platelets (which are needed to prevent bleeding and bruising). Aplastic anaemia is not a form of cancer. There is a lack of cells within the blood and the blood forming stem cells within the marrow are replaced by fat cells. Any remaining cells look more or less normal in contrast to leukaemia and other blood cancers.

The failure of the stem cells to produce mature blood cells can vary from partial to almost complete thus producing a disease of varying severity in different people. The degree of marrow failure may change with time in a given patient. Symptoms are slow to emerge because the loss of stem cell function is gradual. Often patients only realise that they have been less than fully fit for some time after their symptoms have been investigated with a blood test.

The diagnosis is suggested by the blood count and by examination of the blood film but it can only be confirmed by a bone marrow examination. There are two parts to a bone marrow examination, the 'aspirate' and the 'trephine'. The aspirate is obtained by sucking a small amount of cells from the marrow through a hollow needle, spreading it on a glass slide and then stained and examined in the laboratory. This reveals the appearance of individual cells and

helps to exclude other diagnoses such as leukaemia. The trephine gives an overall picture of the marrow and is important in determining the severity of the marrow failure. In normal bone marrow about half of the space is taken up by fat cells with the remainder being blood producing (haemopoietic) cells. In aplastic anaemia almost the entire space is taken up by fat cells. Occasionally there may be patchy loss of haemopoietic cells within the bone marrow. It may be necessary to repeat the examination at a different site to be quite sure of the diagnosis.

Though aplastic anaemia can occur at any age, it appears to be more common in two age groups, those aged between 10 and 20 years and in people aged 40 years or over. The condition appears to be slightly more common in men. People of all ethnic groups may be affected. There is a higher frequency in tropical countries and the Far East. This is probably related to some factor in the environment rather than any particular race. People who move from these regions to Europe or the USA seem to acquire the same chance of developing aplastic anaemia as the local population.

The lack of blood cells produces a potentially very serious or fatal disease unless properly managed. Until about 1980 the majority of patients with severe disease did not survive more than a year but fortunately new methods of support and treatment have completely changed this gloomy outlook. Successful treatment requires a long time. Patience and care are required by all involved including the family, friends and the medical team.

What are the types of aplastic anaemia?

The term aplastic anaemia is usually understood to refer to the acquired disorder. The deficiency of the cells in the blood and the appearances of the bone marrow, however, are not seen just in acquired aplastic anaemia but may develop in a number of other conditions. These other conditions have to be ruled out when reaching the final diagnosis of acquired aplastic anaemia. Some of these are congenital disorders (i.e. present at birth). Others which develop during life have some similarity to acquired aplastic anaemia.

Treatment with high doses of chemotherapy or radiation will produce an aplastic appearance in the bone marrow as well as loss of cells in the blood. The timing and duration of the bone marrow depression are predictable from the type of treatment given and the dose received. Rarely aplastic anaemia may follow accidental exposure to large doses of radiation such as the Chernobyl nuclear power station accident in the Ukraine. Such cases are excluded from the definition of aplastic anaemia. Failure of blood production for these reasons is often termed **'inevitable aplastic anaemia'**. In this situation the fall in blood cells occurs rapidly over one or two days and recovery takes place in the majority of patients if they are supported through the period of marrow depression with blood transfusions. In rare cases damage to the bone marrow may be more severe and a stem cell transplant may be needed to restore blood cell production.

Inherited aplastic anaemias. There are a number of rare inherited diseases which develop into bone marrow failure with a fatty marrow and loss of circulating blood cells. The most common is called Fanconi anaemia.¹ There is wide variation in the presentation of this type of aplastic anaemia but it is

¹ There is a separate publication on Fanconi anaemia available from Leukaemia Research.

usually fairly easy to differentiate from acquired aplastic anaemia. Fanconi anaemia affects brothers and sisters within a family whereas the parents have a normal blood system. Typically the children are rather short and have abnormalities of the forearms or hands and a gradual but progressive failure of the bone marrow. The aplastic phase usually develops in childhood but may not present until adolescence or even early adult life.

Fanconi anaemia can be diagnosed and clearly distinguished from acquired disease by a special test on the blood.

Malignant conditions. Acute leukaemias usually present with an increase in white blood cells, although red blood cell and platelet numbers may be reduced. Typically, regardless of the blood count, the bone marrow will be packed with very large numbers of very immature white cells called blasts. In rare cases, particularly but not exclusively in children, acute leukaemia may present with blood and marrow appearances indistinguishable from aplastic anaemia. In these instances the aplastic anaemia seems to recover spontaneously after about three to six weeks and the blood count returns to normal. The acute leukaemia then reveals itself some six weeks to six months later (or even longer).

This presentation of acute leukaemia usually suggests a good response to treatment so any delay in arriving at a diagnosis does not affect the outcome. A change in diagnosis from aplastic anaemia to acute leukaemia may cause distress and confusion to families unless they have been forewarned of the possibility. In fact the outlook for both diseases in childhood is broadly similar even though the treatment is entirely different.

The most difficult disorder to distinguish from aplastic anaemia is called hypoplastic myelodysplastic syndrome (hypoplastic MDS). MDS is a collection of disorders which affect mainly older patients in which failure of bone marrow function is associated with the appearance of slightly

abnormal looking (dysplastic) cells in the blood and bone marrow.² In most cases the marrow is overactive and this, together with the dysplastic cells makes the diagnosis straightforward. Sometimes the MDS marrow has few cells and increased fat (hypoplastic marrow) and abnormal cells are hard to find. It is fortunate that the distinction is not critical since both aplastic anaemia and hypoplastic MDS respond to similar treatment. Indeed there is close similarity between the two conditions and they are sometimes called ‘overlap syndromes’.

² There is a separate publication on the myelodysplastic syndromes available from Leukaemia Research.

What causes acquired aplastic anaemia?

The apparent cause of the disease does not influence the response to treatment. All patients have the same chance of responding to treatment when the severity of the bone marrow failure is taken into account. It is thought that in most cases of acquired aplastic anaemia the damage to bone marrow stem cells is caused by an auto-immune reaction. This happens when the body's immune cells become confused and start to attack body tissues. In about three quarters of all cases this auto-immune reaction has no clear underlying cause. This is called idiopathic acquired aplastic anaemia (idiopathic means 'of unknown cause'). In the remaining cases there seems to be an identifiable factor triggering the auto-immune response.

The basis for suspecting that certain drugs, chemicals or virus can cause aplastic anaemia is the occurrence of the disease following exposure. There are no specific tests that can be used to identify with certainty the cause of the aplastic anaemia in any particular case. Despite all the difficulties in deciding whether a given factor may have caused the aplastic anaemia, it is very important to obtain a careful account of all drug or chemical exposure from each patient or their family. It is known that the delay between exposure and the development of a fall in blood count is typically about eight weeks. Drugs which have been taken for the first time less than eight weeks before symptoms develop are less likely to have triggered the disease, unless the drug had been taken intermittently or regularly before. If a drug was stopped more than a year before the symptoms develop it becomes less probable that the drug caused the illness.

Drugs which are most strongly suspected of causing aplastic anaemia include several which are used to treat arthritis, (particularly anti-inflammatory which

are used for the treatment of rheumatoid arthritis), drugs used to control overactive thyroid, some drugs used in psychiatry and a few antibiotics. The risk of developing aplastic anaemia as a side effect of drug treatment is very small; for the antibiotic chloramphenicol, one of the more widely studied triggers for the disease, about one person in 25,000 taking the drug may develop aplastic anaemia.³ For most drugs, monitoring the blood count is not of use in preventing the disease because of the delay between taking the drug and the risk of developing aplastic anaemia. Once the disease has been triggered, withdrawal of the drug will not reverse the process. One exception is gold salts used to treat rheumatoid arthritis where monitoring is essential as it may allow the drugs to be withdrawn before there has been irreversible damage.

It is more difficult to assess a possible link between a workplace chemical exposure and the development of aplastic anaemia. Many factors have to be weighed and it may be impossible to make a definite judgement. The list of chemicals which have been suspected of causing aplastic anaemia is very long but the evidence against any individual compound is often rather weak. There is a need to monitor the patient carefully if they return to their previous place of work following treatment. Non-workplace exposures to chemicals are even more difficult to assess; examples of chemicals to be suspected are wood preservatives, adhesives and other organic compounds.

Some patients, perhaps one in ten, have had a virus infection shortly before developing aplastic anaemia. The most common indication of this is a patient with abnormalities of the liver which suggest hepatitis. The patient may first notice jaundice or a general fatigue and loss of appetite. The bone marrow failure follows a few weeks later. Although several viruses have been identified as causing hepatitis no particular one has been found to cause aplastic anaemia as well.

³ Chloramphenicol eye-drops are widely used, often for children, but very little drug is absorbed into the body and careful studies have shown no risk of aplastic anaemia from chloramphenicol eye-drops.

What are the signs and symptoms of aplastic anaemia?

The signs and symptoms derive entirely from the deficiency of the blood cells. These are not specific to aplastic anaemia but occur in any condition where there is a significant deficiency of all blood cells. This differs from blood cancers (leukaemia and related conditions) where there may also be symptoms caused by the large numbers of abnormal cells and these are the main diseases from which aplastic anaemia has to be separated. This can only be achieved by blood and marrow tests.

Deficiency of red blood cells produces anaemia and the patient may notice:

- Fatigue and tiredness
- Shortness of breath on moderate exercise, for example going up stairs
- Paleness
- Pulsating noise in the ears and/or headache

Deficiency of white blood cells, in particular neutrophils, causes an increased risk of infection. Common infections include:

- Recurrent or persistent sore throat
- Skin infections
- Chest infection

Deficiency of platelets causes a tendency to bleed. Common sites include:

- Gum bleeding, particularly after brushing the teeth
- Nose bleeds
- Heavy or prolonged periods
- Blood blisters in the mouth
- Skin, shown by easy bruising even in the absence of a knock, or a rash composed of small red spots most prominent on the legs (called a 'petechial' rash)

These signs and symptoms are not specific to aplastic anaemia but occur in any condition where there is a significant deficiency of all blood cells. They are also typical of acute leukaemias and these are the main diseases from which aplastic anaemia has to be separated. This can only be achieved by blood and marrow tests.



How is aplastic anaemia diagnosed?

Aplastic anaemia cannot be diagnosed on clinical findings alone. The results of laboratory tests are necessary to exclude other causes of low numbers of cells in the blood and to confirm the diagnosis. The main problem in diagnosing aplastic anaemia is the exclusion of other diseases with similar signs and symptoms.

The main tests used in diagnosis of aplastic anaemia are a full blood count and a bone marrow biopsy. The bone marrow sample(s) indicate whether the marrow contains normal amounts of active blood forming tissue. This is called the cellularity of the marrow. This must be interpreted according to the age of the patient because the proportion of the marrow which is actively producing blood cells decreases with increasing age. Terms used to describe the amount of active marrow include 'hypocellular' which means low numbers of cells and 'hypoplastic' which means reduced blood forming tissue. The opposite terms 'hypercellular' and 'hyperplastic' indicate increased activity. Most patients with aplastic anaemia will have reduced numbers of white cells, red cells and platelets in their blood. It is a part of the definition of aplastic anaemia that marrow is hypoplastic.

Most other conditions in which low blood counts are seen involve either a malignancy of the blood forming cells (leukaemia, myeloma etc.) or an increase in blood cell production but with many immature blood cells being destroyed before they leave the marrow (e.g. myelodysplastic syndromes). The marrow in these conditions is typically hyperplastic. A hypoplastic (empty) marrow is not always an indication of aplastic anaemia but a hyperplastic (overactive) marrow rules out this diagnosis.

Aplastic anaemia is diagnosed when there is a fall below normal of all cell types in the blood. The most important elements of the full blood count in aplastic anaemia are the numbers of red cells and their haemoglobin content (Hb), numbers of reticulocytes, and numbers of platelets and neutrophils. The normal number and function of these cells are described in Appendix A.

Normal blood values

Red blood cells	4.5-6.5 × 10 ¹² /l (male) 4.0-5.5 × 10 ¹² /l (female)
Reticulocytes	50-150 × 10 ⁹ /l (0.5-2.5% of total RBC)
Absolute neutrophils	1.5-8 × 10 ⁹ /l
Platelets	150-400 × 10 ⁹ /l

How is the severity of aplastic anaemia determined?

It is important to have a measure of the amount of damage to the bone marrow because this influences the treatment strategy. There is a simple but effective classification based mainly on the findings in the blood count. The disease can be divided into three groups, non-severe aplastic anaemia (NSAA), severe aplastic anaemia (SAA) and very severe aplastic anaemia (VSAA). The names were devised when there was less effective treatment than there is now and the differences are not as alarming as the names might suggest. Nevertheless the classification is still a guide as to which type of treatment is most likely to produce the best result for a particular patient.

Non-severe aplastic anaemia (NSAA)

The blood counts are low with a hypoplastic marrow but the condition is not severe enough to meet the criteria for severe aplastic anaemia. These patients may require red blood cell transfusions but not usually platelet transfusions. They are not particularly at risk from spontaneous infection.

Severe aplastic anaemia (SAA)

This is present when the marrow is hypoplastic for the age of the patient and any two of the following features are present:

- A low platelet count (less than $20 \times 10^9/l$)
- A reticulocyte count less than $25 \times 10^9/l$ (corrected reticulocyte count of less than 1%)
- An absolute neutrophil count less than $0.5 \times 10^9/l$.

Very severe aplastic anaemia (VSAA)

The definition is the same as for severe aplastic anaemia but with a very low absolute neutrophil count, less than $0.2 \times 10^9/l$.



How is aplastic anaemia treated?

Principles of treatment

Treatment of aplastic anaemia can be divided into supportive therapy, which is directed at treating consequences of low red cell, white cell and platelet counts, and definitive therapy which is aimed at restoring the function of the marrow so that the patient becomes independent of blood transfusion, is no longer at risk from bleeding or abnormal infections, and can lead a normal life. Definitive treatment takes weeks to months to achieve its greatest effect. Supportive therapy is essential during this time when patients will be at risk from anaemia, bleeding/bruising problems and infections.

Supportive therapy

Supportive therapy will be needed for patients with anything other than very mild aplastic anaemia.

∴ Red blood cell transfusions

Virtually all patients with aplastic anaemia who need treatment will require transfusions of red blood cells. They may also need transfusions of platelets. Since patients may require many transfusions they should always receive blood products from which as many as possible of the white cells have been removed. This is done because white cells are likely to provoke the patient's immune system to produce antibodies. These antibodies can cause problems in future transfusions and may cause complications if a stem cell transplant is performed. Removal of white blood cells from all blood transfusion products is called 'leucodepletion'. This is now routinely applied to all transfusion units collected in the UK before delivery to hospitals.

If a patient is being considered for a stem cell transplant it is particularly important that they do not receive transfusions of blood or blood products from any family member. This is because such transfusions may seriously compromise the likelihood of success of a later transplant from a related donor.

Red cell transfusions may (rarely) produce problems in patients with aplastic anaemia. Some patients produce antibodies to so-called 'minor' blood groups. This sometimes means that they need carefully selected blood which may need to be specially ordered from the National Blood Service. Without these precautions the presence of antibodies would mean the transfused blood would not last very long.

Rarely a red cell transfusion may cause fever and even rigors (shaking). These can be controlled with injections of hydrocortisone and Piriton™. Piriton™ is a strong antihistamine which often makes people sleepy.

One unit of transfused red blood cells typically raises the haemoglobin level by about 1.0g/dl. It is usual to need three to four units each month. Repeated red cell transfusions given over many years may lead to accumulation of iron in the body. This can produce problems with the heart and hormone producing (endocrine) glands unless precautions are taken. Few patients with aplastic anaemia need transfusion programmes which are prolonged enough to cause such problems.

Platelets are shorter-lived cells; a single unit transfused should raise the platelet count significantly for about two to three days. Response to platelet transfusions is much more variable from one patient to another. Sometimes patients develop antibodies to platelets and special donors have to be found by the transfusion service.

All patients who are being treated with only supportive therapy need to be monitored regularly to detect any worsening of their condition. In milder cases this involves visits to the out-patients or day care unit to check the full blood count and general health and to determine the time of any transfusions needed. In more severe cases, where patients are very vulnerable to infection, they may need to spend some time in the hospital in a special protected environment. If patients with a low neutrophil count develop a fever they must be treated promptly with antibiotics without waiting for proof of infection. If symptoms persist despite first line antibiotics then additional drugs, which counteract fungal infections, are given. Any patient with aplastic anaemia who thinks they are developing an infection should consult with their doctor so that any necessary treatment can be commenced as soon as possible.

Definitive therapy

Except for a minority of patients with mild aplastic anaemia, all patients will require some form of definitive therapy. The long-term outcome is very poor for patients with severe or very severe aplastic anaemia who receive only supportive treatment.

The underlying disease process in acquired aplastic anaemia is destruction of blood-forming stem cells by the immune system. Definitive therapy is aimed at either blocking this process by suppressing the immune system or, alternatively, at curing the disease by replacing the diseased marrow and abnormal immune system using a stem cell transplant from a donor. Once a decision has been made that definitive treatment is necessary, this should be initiated as soon as possible. This is because patients remain at risk of life-threatening infection and/or bleeding until their blood counts can be restored to normal. In the case of stem cell transplants the fewer blood transfusions a patient has received prior to the transplant the lower the risk of graft rejection. This is another reason why if a transplant is planned it should be done as soon as possible.

Stem cell transplant⁴

The only truly curative treatment for a patient with severe or very severe aplastic anaemia is a stem cell transplant using normal stem cells from a donor. These replace the damaged marrow with healthy marrow. More importantly, they also replace the cells in the patient's immune system which are responsible for destruction of the bone marrow stem cells in the first place. Stem cell transplantation is most successful in children and young adults who have a brother or sister (a sibling) as a suitable donor. This is known as an allogeneic sibling transplant. Patients who are aged below 40 years and who have SAA or VSAA and are eligible for a transplant are usually offered this treatment as the first option. The risk of transplantation increases with age and for older patients a transplant is usually suggested only for patients with VSAA or whose disease has not responded to a first course of immunosuppressive treatment. Transplants from volunteer matched donors may be successful, particularly in children, but the risk is much higher than with sibling transplants.

Although a sibling-donor transplant is the preferred treatment for SAA or VSAA only a minority of patients are of the appropriate age group and have a donor available. For this reason transplantation is not widely used as a treatment for adults. Any patient who is being considered for a transplant will have detailed discussions of the risks and benefits with their specialist.

∴ Immunosuppression

For patients who are not eligible for a transplant, treatment is aimed at suppressing the immune activity which causes the damage or prevents the recovery of the marrow stem cells. This is called immunosuppressive treatment and offers a good chance of long-term survival and a normal or near normal lifestyle. The usual therapy used to suppress the immune system in aplastic anaemia is the use of antilymphocyte or antithymocyte globulins (ALG or ATG) and cyclosporin.

⁴ There is a separate publication on stem cell transplantation available from Leukaemia Research.

ALG (or ATG) is a preparation of antibodies which can remove certain cells of the immune system. They are typically obtained from the serum of either rabbits or horses which have been immunised with human lymphocytes. The differences between ALG and ATG are determined by the type of human lymphocytes which are used to immunise the donor animal in order to produce the antibodies. Because they are biological products produced by different techniques they are not standardised and dose schedules vary from one type to another.

All preparations of ALG and ATG contain proteins from species other than man and so they can provoke an immune reaction. There is a delayed reaction which comes on seven to fourteen days after the treatment. This is called serum sickness and is the result of the patient producing antibodies against the foreign protein. The patient may experience fever, joint pains and skin rash which can be managed with steroids and analgesics.

There may also be an acute reaction which produces high fever and sometimes rigors on the first two days of administration. This affects nearly all patients and is related to the destruction of the lymphocytes. There may also be a skin rash.

Giving ALG or ATG to patients with aplastic anaemia briefly increases the risk of infection through suppression of the immune system. This treatment should always be given in a hospital where strict isolation from infection is available. The normal course of treatment is given over five days through a drip line (called a central line) which is fed into a large vein to avoid problems with local inflammation. The patient usually stays in hospital for about three weeks to allow the immune system to recover and to ensure there is no further risk of serum sickness.

There is no clear evidence to prove that either ALG or ATG is better for treatment of severe aplastic anaemia. ATG or ALG is most commonly used in combination with ciclosporin, another immunosuppressive drug.

Ciclosporin is usually started after completion of the ALG treatment and is continued for at least six months. Side effects of ciclosporin are fortunately not very troublesome for most patients though care has to be taken in adjusting the dose for each patient so that maximum effect is achieved without causing kidney or liver damage

∴ Other treatments

A number of other approaches have been used in the treatment of severe aplastic anaemia. Anabolic (androgenic) steroids were the first specific therapy for aplastic anaemia before immunosuppressive treatment became available. This treatment is not effective in severe or very severe aplastic anaemia but may have a place in less severe cases that fail to respond to immunosuppression. The side effects are often unpleasant, particularly for female patients, and so this treatment should not be offered without a considerable amount of explanation and discussion. Anabolic steroids are useful for patients with Fanconi anaemia, the inherited type of aplastic anaemia.

Growth factors are naturally occurring substances which are essential for the normal control of blood production. Granulocyte colony stimulating factor (G-CSF) is the natural protein which stimulates neutrophil production and function. Therapy with additional G-CSF may increase neutrophil numbers to a level which reduces the risk of spontaneous infections. An exception to this is in patients with very severe aplastic anaemia in whom G-CSF is not effective.

There are two G-CSF preparations available, Filgrastim™ and Lenograstim™. The best way to use this additional treatment is still under investigation. Most growth factors such as erythropoietin (which increases red cell production) and thrombopoietin (which controls platelet production), are produced at high level in patients with aplastic anaemia and additional therapy is not helpful.

Treatment planning

The treatment plan for each patient will be determined by the severity of the disease, their age, the availability of a suitable potential stem cell donor and their general health at the time of diagnosis. A very important part of the early discussion of treatment options includes the recognition that recovery may take a long time, that different treatments are not mutually exclusive, and that it may be necessary to change between different treatments.

There is always a delay in confirming the diagnosis of aplastic anaemia, in part so that other causes of the symptoms and low blood count can be excluded. During this time patients often require transfusions of red cells and platelets. Such small numbers of transfusions do not compromise the outcome of later treatment and are important in keeping the patient as well as possible. During this time patients may need antibiotics to control infection.

Once the initial investigations and discussions have been completed the treatment options will be discussed and explained and a treatment plan will be agreed upon. For most patients the decision will centre on whether immunosuppressive therapy or a stem cell transplant should be the first option. For children and younger adults with SAA who have a brother or sister as a potential donor, a stem cell transplant will usually be the first choice. For others immunosuppression may be preferred as initial treatment, with transplantation as a later option if immunosuppression is unsuccessful.

∴ Immunosuppression

For most patients immunosuppression will be the treatment of choice for the disease. The treatment and the response fall into a number of stages.

To receive treatment with ALG (ATG) the patient needs to be in hospital and preferably in an isolation room. The main side effects and problems with ALG (ATG) have already been described. These are fever and rigors on the first two days of receiving the treatment and the delayed serum sickness. The patient

usually spends two to three weeks in hospital. In many schedules the patient continues to take ciclosporin after leaving hospital.

Initially nothing will seem to have happened and the patient will still require transfusions. The first signs of recovery usually do not appear before six to eight weeks and may be delayed much longer. A rise in the neutrophil count or a lessening of the need for platelet transfusions is often the first sign of recovery. A full reassessment of marrow activity is usually made at about three to four months post treatment. When patients show signs of recovery cyclosporin is continued and the blood counts carefully checked. As the recovery becomes more clearly established the intervals between tests get longer so that only a test every three to four weeks may be needed. It is important to realise that this treatment is aimed at achieving freedom from transfusion and protection from excessive infections rather than cure. This is called remission and occurs in about two out of every three patients so treated. The blood count may remain mildly abnormal for many years and even in patients who achieve a truly normal blood count it is possible to show residual damage in the bone marrow stem cells.

If the first course of treatment fails there are a number of options. For most patients a second course of treatment can be given using the same or different type of ALG (ATG). Indeed, several courses of immunosuppression can be given for repeated failure or for relapse. For patients with a family donor this may be the time to consider a stem cell transplant.

It is important to realise that recovery from aplastic anaemia can occur at any time, even after several years of transfusion dependence. It is therefore necessary to continue to keep the patient in the best possible health with transfusions and antibiotics even though this may prove a great burden to the patient. None the less patients and families should never give up the hope and expectation that remission may come.

∴ Long term follow up after immunosuppression

The marrow shows some residual damage even after complete return to normal blood counts. For just over half the patients who have a good response the counts remain constant for many years and they may eventually be considered cured. For other patients some change or deterioration in the blood count may occur sometime in the ten years following completion of treatment and this often leads to a return to the need for blood transfusions.

True relapse, that is a return of the original condition of aplastic anaemia, affects perhaps one in ten patients. Relapse is especially likely to occur in pregnancy or following a heavy immune challenge such as multiple immunisations at the same time. Only very rarely can relapse be attributed to re-exposure to the original cause of the disease.

In twenty to thirty percent of cases a new, abnormal type of blood cell will emerge. This is perhaps a result of abnormal cells escaping the damage which caused the aplastic anaemia in the first place. These cells lack certain proteins on their surface and the condition is called after its most dramatic manifestations, paroxysmal nocturnal haemoglobinuria⁵ (PNH). The most dangerous type of relapse is the change from aplastic to preleukaemic blood production (myelodysplastic syndrome) or even to acute leukaemia (acute myeloid leukaemia). Such changes are rare but if they do occur then the risks associated with unrelated donor transplant may become much more acceptable.

The possibility of relapse means that patients need to be followed up for many years after treatment. As time goes by the frequency of checks can be reduced so that eventually only annual blood counts are needed or even just occasional contact with the specialist unit.

⁵ Paroxysmal nocturnal haemoglobinuria (PNH) is a rare condition affecting mainly the red blood cells but also other blood cells. In PNH the red blood cells are destroyed more rapidly than normal. Occasionally this causes the urine to turn very dark (haemoglobinuria). PNH is so called because the colour may occur intermittently (paroxysmal) when the urine is generally darkest first thing in the morning (nocturnal haemoglobinuria).

Such contacts can provide reassurance and a chance to discuss special issues, for example the risks and management of pregnancy or of foreign travel.

Stem cell transplantation

Stem cell transplantation for aplastic anaemia from a matched brother or sister has a very good outcome in the majority of younger patients (under 30 to 40 years). Overall, about seven out of ten patients so treated will have a successful transplant without long-term side effects and many may be considered cured.

For children and young adults, particularly if the disease is severe, transplantation from a suitably matched volunteer donor may be appropriate. Although the success rates for such transplants are not quite as good as from a brother or sister, they still offer a good chance for a cure. The risks and benefits of unrelated transplants will be discussed in detail before a patient or parent is asked to make a decision. The results of unrelated transplants are beginning to improve but such procedures should only be carried out in specialist units when all treatment options have been thoroughly discussed.

The main risks are those of the transplant and include graft failure, the reaction of the graft against the patient (graft versus host disease, GvHD) and development of severe infections. The most disabling long-term complication is chronic GvHD which may result in an extensive, scarring skin rash and liver disease and/or diarrhoea. The risk of these complications increases with age. This is why this treatment is not recommended as first line for all patients with a suitable donor.

Unlike a transplant to treat leukaemia or a related blood cancer, the pre-transplant conditioning needed to prevent graft rejection is relatively mild for patients with aplastic anaemia. Radiation treatment is not required and patients who have a successful transplant are fertile and have a normal

chance of becoming a parent. The conditioning does not even abolish the possibility of later recovery of the patient's own marrow.

The schedule for transplantation starts with admission to a specialist transplant unit. The patient is given an isolation room. This is a room with a clean filtered air supply, from which as many potentially dangerous organisms as possible have been removed. A diet of specially prepared food is started which again aims to remove potentially harmful organisms. Discussion with the dietician on particular needs, likes and dislikes is helpful at this time, as is an explanation to friends and relatives of what is and is not permitted in the way of supplementary food. Rules concerning visitors may vary from unit to unit but in general visitors are restricted to close family or friends who are instructed in the protocols of hand washing and so on needed to preserve the clean environment. In most cases a detailed discussion of what is going to happen will take place before admission.

During the transplant process many blood transfusions, antibiotics and other fluids will need to be given directly into the circulation by a vein. To achieve this with minimum discomfort and inconvenience to the patient a central line is put in place which will remain there for the whole of the transplant procedure. Occasionally these lines may become infected and have to be changed but in general they have proved to be of enormous benefit in coping with the requirements of treatment.

Conditioning is the word used to describe the drugs given to prepare the patient to receive the graft. The combinations of drugs that are used vary from one centre to another so explanations of side effects and duration of conditioning will be different. A common schedule includes specific immunosuppressive drugs like ALG followed by cyclophosphamide, a drug used in chemotherapy. The immediate side effects are usually not very troublesome though some patients need treatment to stop them being sick. Conditioning also further increases the risk of infection, hence the need

for isolation. A major side effect of conditioning is subsequent loss of hair. Fortunately it will grow again in about six months.

The stem cells, which may be collected from the donor either from the marrow or from the blood after mobilisation, are given through the central line. Reactions are rare and usually consist of mild fever as the stem cells are given.

The patient is given ciclosporin to reduce the risk of graft rejection and GvHD. This may commence either a few days before the transplant or at the time the stem cells are given to the patient. The dose is adjusted for individual patients. Patients transplanted for aplastic anaemia need to continue on this drug for up to a year post transplant. Despite taking this drug the patient can usually return to a normal life style after about six months.

It takes about three weeks to a month for the new graft to become established and the patient remains in isolation during this time. Quite commonly in this period the patient develops fevers which need treatment with antibiotics.

Some degree of GvHD is also not unusual, perhaps with a skin rash or mild diarrhoea. This may resolve without treatment or require a course of cortisone. More severe GvHD needs more aggressive management.

Once the graft is established the patient normally leaves hospital but still needs to take care to avoid infections as far as possible and careful explanations of what is allowable are given before discharge. Some infections, particularly certain virus infections, may be reactivated in the first few months after discharge and so careful checking of the patient and the blood counts is required. Although the patient with a successful graft feels well after about six months and may go back to work or school, complete recovery of the immune system takes about two years. Re-vaccination is needed once the ciclosporin is stopped.

Summary

Acquired aplastic anaemia is a rare, potentially life threatening disorder. In most cases the cause is unknown; in a few cases drug or chemical exposure is suspected. The mainstays of management are support with blood transfusions and protection from infection. A few patients may receive only this but most patients will require definitive treatment with immunosuppression or a stem cell transplant. The condition is chronic but recovery may occur even after several failed attempts at achieving remission. The disease used to have a fearsome reputation but now, thanks to the greatly improved means of support and treatment, seventy to eighty percent of patients should recover.

Useful contacts

The Aplastic Anaemia Trust

Tel: 0870 487 0099

Fax: 020 7840 7841

Website: www.theaat.org.uk



Appendix A

Red Blood Cells (RBC): The normal red blood cell count is $4\text{-}5.5 \times 10^{12}/\text{l}$ in women and $4.5\text{-}6.5 \times 10^{12}/\text{l}$ in men. For assessing the degree of anaemia, the usual measurement is the haemoglobin (Hb), which is normally 11.5-15.5 g/dl for women and 13.5-17.5 g/dl for men. The degree of anaemia is not used to assess severity because the value is often altered by blood transfusion. The reticulocyte count estimates the numbers of newly produced red cells present in the blood. The count is often given as a percentage of all red blood cells. With modern cell counting machines in the laboratory the actual number of reticulocytes can be measured, which is more useful than an estimate of the percentage of reticulocytes. The normal range is $50\text{-}150 \times 10^9/\text{l}$ (0.5-2.5% of the normal RBC count). A low reticulocyte count is an indication of the marrow's failure to produce red cells and is used in the assessment of severity.

The **absolute neutrophil count** (ANC) indicates whether white blood cells are being produced normally. Neutrophils have a short survival once they leave the marrow and so they give a useful estimate of current marrow activity. The neutrophil count is often reported as a percentage of the total white count. The absolute neutrophil count is the percentage count multiplied by the total number of white cells. This gives a more accurate indication of numbers of white cells than the percentage count. The normal range is about 1.5 to $8.0 \times 10^9/\text{l}$, (a slightly lower value may be seen in healthy people of Afro-Caribbean descent).

The **platelet count** is an automated count of the number of platelets in the blood. The normal range is between 150 and $400 \times 10^9/\text{l}$.

Notes



Typical normal values for blood test results

	WBC x 10 ⁹ /l	RBC x 10 ¹² /l	Hb g/dl	ANC x 10 ⁹ /l	Platelets x 10 ⁹ /l
Adult male	3.7 to 9.5	4.3 to 5.7	13.3 to 16.7	1.7 to 6.1	143 to 332
Adult female	3.9 to 11.1	3.9 to 5.0	11.8 to 14.8	1.7 to 6.1	143 to 332
West Indian	2.8 to 9.8			1.0 to 6.5	122 to 374
African	2.8 to 7.8			0.9 to 4.2	115 to 342
Child 2-5 yrs	5 to 13	4.2 to 5.0	11 to 14	1.5 to 8.5	143 to 332
Child 6-9 yrs	4 to 10	4.3 to 5.1	11 to 14	1.5 to 6.0	143 to 332
Child 9-12 yrs	4 to 10	4.3 to 5.1	11.5 to 15.5	1.5 to 6.0	143 to 332

Normal ranges vary slightly between laboratories so you may wish to ask your doctor to enter your normal values below:

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WBC	White blood cell count
RBC	Red blood cell count
Hb	Haemoglobin concentration
ANC	Absolute neutrophil count

Separate ranges are quoted for West Indian and African populations as these groups have different normal ranges for white cell counts, absolute neutrophil counts and platelet counts.

This information is adapted, with permission, from *A Beginner's Guide to Blood Cells*, Dr Barbara Bain. Pub. Blackwell, Oxford, 1996.



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**Childhood Acute
Myeloid Leukaemia (AML)**

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