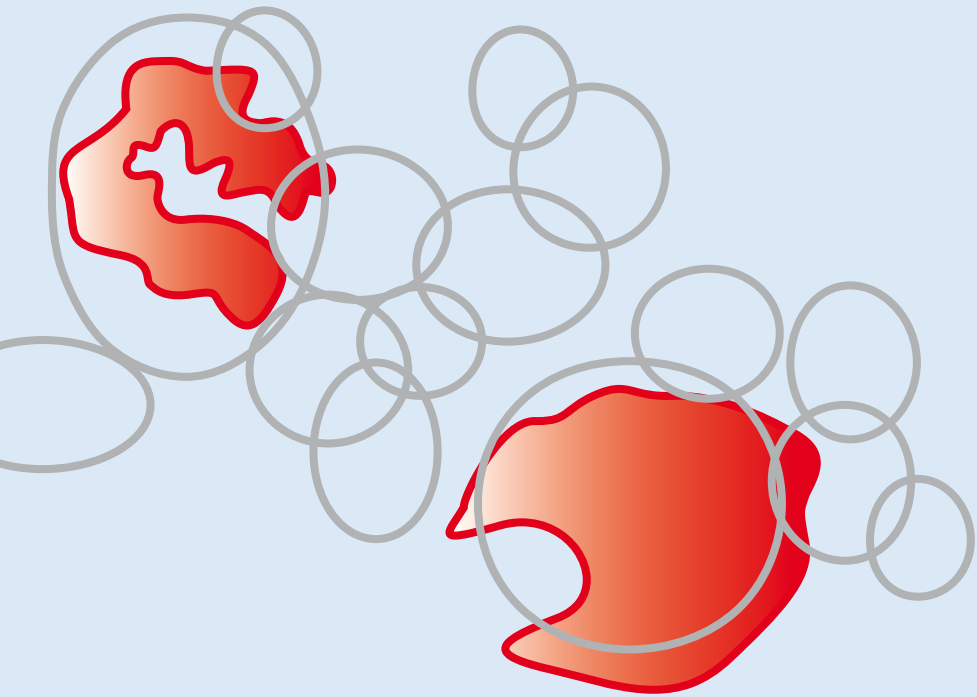


Childhood Acute Lymphoblastic Leukaemia (ALL)



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 acute lymphoblastic leukaemia?

Acute lymphoblastic leukaemia (ALL) is a form of cancer that affects the lymphocyte-producing cells in the bone marrow. Lymphocytes are white blood cells that produce antibodies and are vital parts of the body's immune system. There are two main types of lymphocytes called B and T cells. In ALL there is an accumulation in the bone marrow of immature lymphocyte precursor cells, called blast cells. Eventually the production of normal blood cells is affected by this resulting in a reduction in the numbers of red cells, normal white cells and platelets in the blood.



Who gets acute lymphoblastic leukaemia?

ALL is the only form of leukaemia that is more common in children than adults. It is the single most common form of paediatric cancer accounting for about one-third of all cases in children. About 85% of cases of childhood leukaemia are ALL. The peak incidence of ALL occurs between the ages of about two and four years. Males are affected more often than females at all ages.

What are the types of acute lymphoblastic leukaemia?

There are two ways of classifying and describing the leukaemia cells in ALL, which are used together rather than as alternatives. Both look at different cell properties; one uses markers on the cell surface and is called the immunological classification, the other looks at the appearance of the leukaemia cells down a microscope and is called the morphological classification. The only system that is of clinical importance and therefore affects how we treat the leukaemia is the immunological classification.

Immunology

The most important classification system is based on the type of lymphocyte cell type (lineage) affected, that is the B or T cell. This is known as the immunological classification which, together with the characterisation of chromosome abnormalities, is extremely useful in predicting the response to treatment. Approximately 80% of ALL in children is of early (precursor) B cell origin, about 15% is T cell, and 5% is more mature B cell derived. The mature B cell type shows some resemblance to a condition called Burkitt's lymphoma¹. Burkitt's-type ALL has many features in common with aggressive (high-grade) non-Hodgkin's lymphoma and is treated with similar drug combinations.

Morphology

The other classification system is mainly based on the morphology (appearance) of the leukaemia cells under the microscope. This is referred to as the FAB classification after the group of French, American and British haematologists who designed the system. It classifies ALL as L1, L2 or L3. L3 is the only clearly distinct type within the FAB system and usually corresponds to the mature B cell type. This system is not very important clinically because it does not help in planning treatment.

¹ There is a separate publication on Burkitt's lymphoma available from Leukaemia Research.

What causes acute lymphoblastic leukaemia?

There is no single proven cause of childhood ALL but there are a number of suggested causes, some of which are more controversial than others. A major study on the possible causes of childhood cancer, called the UK National Childhood Cancer Study, has now completed collection of data. Some results have already been published and they will continue to be published over the coming years in various medical journals.

The hypotheses around which the study was planned are summarised in the following table:

Exposure	Time Period		
	Preconceptual	In the womb	Postnatal
Ionizing radiation	*	*	*
Certain chemicals and drugs	*	*	*
Infections		*	*
Electro-magnetic fields			*

Ionizing radiation

Ionizing radiation is the term used for the kind of radiation given off by X-ray machines or by radioactive materials. It is the only clearly proven cause of childhood ALL. Children exposed to high levels of ionizing radiation before they are born or in early life have been shown to have a high risk of developing childhood leukaemia. The study has collected data to help identify whether any children in the UK are exposed to levels of radiation high enough to cause ALL; this includes testing for exposure to environmental radon gas. It has also considered the suggestion that radiation exposure of a parent before conception may increase a child's risk of developing ALL. There have been a number of studies suggesting that this is not the case and the results published so far from the national study indicate that this is not a risk factor for childhood leukaemia.

Chemicals and drugs

The study has collected information on exposure of parents and affected children to certain chemicals and drugs. These are either substances that are known to cause cancer in high concentrations, such as benzene, or substances that have been suggested as possible risk factors, such as vitamin K. There is, to date, no evidence that children in the UK are exposed to levels of benzene high enough to cause childhood leukaemia. Detailed studies on the effects of vitamin K do not support the theory that it increases the risk of childhood leukaemia, whether given by mouth or intramuscularly.

Infections

The currently most plausible proposed causes relate to the timing and pattern of exposure to infections. With improved hygiene in the general community, children are less exposed to common infections in early years. A rare consequence of a delayed first challenge to the immune system may be the development of childhood leukaemia. A related suggestion places stress on exposure to novel infections through the mixing of different populations,

for example in new towns. There is evidence that these may both be significant factors in causing childhood ALL. An important point is that the rarity of clusters of cases indicates that childhood ALL is likely to be a rare response to a common infection, rather than a common response to a rare infection. The practical importance of this is that even close contact with a child subsequently developing ALL does not imply an increased risk of leukaemia.

Electro-magnetic radiation

A somewhat controversial proposal for the cause of childhood ALL is exposure to electro-magnetic fields from power lines or electrical facilities. A recent UK study into the causes of childhood cancer looked specifically for evidence that proximity to powerlines or other electrical installations increased the risk of childhood leukaemia but found no such evidence. A number of international studies have reached the same conclusion. A recent report indicated that there might be an association between exposure to very high magnetic fields and a slight increase in risk of developing childhood leukaemia. The report stressed, however, that this association did not prove that exposure to powerlines caused leukaemia and that about 99.5% of children in the UK are never



What are the signs and symptoms of acute lymphoblastic leukaemia?

The signs and symptoms seen most often in childhood acute lymphoblastic leukaemia are:

- Anaemia (lack of haemoglobin), causing:
 - Fatigue and limited capacity for exercise
 - Breathlessness
- Low platelet counts, causing:
 - Bruising within the skin
 - Bleeding from mouth or nose and blood in the stools or vomit
- Low numbers of normal white cells, high numbers of abnormal cells and high metabolic rate, causing:
 - Persistent infections
 - Fever — this is often present even in the absence of clear indications of infection

On first being examined by a doctor about 60% of children with ALL have an enlarged liver and/or spleen. Over a half will have had frequent and persistent fevers in the past. About one-third of children with ALL will have enlarged lymph nodes (glands). In T cell ALL enlargement of the lymph nodes within the chest (mediastinum) is common. This may be seen on a chest X-ray.

About one-third of children with ALL have bone or joint pain. Night-time pain is particularly likely to be a symptom of ALL.



How is acute lymphoblastic leukaemia diagnosed?

Although the diagnosis of leukaemia may be suspected on the basis of the child's symptoms, laboratory tests are essential to confirm the diagnosis.

Full blood count

The main laboratory tests used in the diagnosis of leukaemia are a full blood count and bone marrow aspirate (a procedure where a small sample of bone marrow is taken). Most children with ALL will have a raised white cell count and almost all will have characteristic abnormal cells in the bloodstream, called blast cells. Many children also have anaemia and/or low platelet counts because the leukaemia cells both crowd-out and actively inhibit the production of normal blood cells in the bone marrow. Anaemia may be severe. Numbers of a type of white blood cell called neutrophil may be very low. As neutrophils are the most important component of the body's defence against infection, this leaves the child vulnerable to bacterial and fungal infections.

Chromosome analysis

Chromosome analysis is of importance in planning the treatment of childhood ALL. The analysis may be done on blood and/or bone marrow samples. The abnormalities being studied are only found in the leukaemia cells but not in normal body cells. Detection of the chromosome abnormalities in the leukaemia cells can be of value in guiding treatment decisions and in evaluating a child's response to treatment. An example of this is the Philadelphia chromosome seen in some leukaemia cells.

Other investigations

Children with ALL may require X-rays and other imaging procedures (CAT scan, MRI scan) to determine which organs are affected and to what extent. Lumbar puncture (sampling of the fluid around the spine and brain) is also done to see if symptoms suggest that the central nervous system is affected. About one in 20 children has a significant abnormality of the blood clotting system so tests for this are routinely included. Various other tests are performed to assess general health, for example heart, liver and kidney function. These are important to ensure that children are not particularly prone to negative side-effects from the planned treatment.

Bone Marrow Biopsy

All children with ALL will have a sample of bone marrow taken. This is done partially to confirm the diagnosis and to allow important additional tests to establish the exact type of ALL and to confirm to which risk group the child should be assigned. This involves obtaining a small amount of marrow from inside the bone with a needle, and usually a sample through the bone itself to show the structure of the bone marrow cavity. The first is known as a bone marrow aspirate, the second is a bone marrow trephine. The samples are usually obtained from the back of the hipbone. The procedure causes some discomfort but does not take very long. For adults and older children the procedure is carried out with a local anaesthetic and in most cases sedation; in young children, it is quite common for a general anaesthetic to be given.



How is acute lymphoblastic leukaemia treated?

Acute lymphoblastic leukaemia is rapidly fatal without effective treatment. The aim of treatment in children is to achieve a state called remission where almost all leukaemia cells have been killed and, by further treatment, to completely eradicate the disease and achieve a cure. A child is described as being in complete remission when it is not possible to see leukaemia cells in either the blood or the bone marrow under the microscope. This does not mean that all leukaemia cells have been killed.

Standard laboratory tests cannot detect leukaemia cells that are present below a certain number in the blood.

All treatment combinations for childhood ALL consist of four parts — these together make up a regimen. There are different regimens for different groups of children. Together these regimens make up a protocol.

The current standard therapy for children with acute lymphoblastic leukaemia consists of drugs given by either by mouth, or directly into the blood stream (intravenous), or by injection directly into the muscle (intramuscular) or into the spinal fluid (intrathecal) by a spinal tap (lumbar puncture). The drugs are given according to a protocol. Although every effort is made to adhere to the protocol, a child's specialist may modify the timing or doses of treatment in the light of that individual child's response. The treatment is mostly given as outpatient therapy but there will be periods when a child needs to stay overnight in hospital, especially when poorly.



This chemotherapy 'regimen' is made up of four parts:

The aim of the first few weeks of treatment is to return the blood and bone marrow to normal function – which is called achieving a remission. This first part of the programme is called 'remission induction'.

The following weeks of treatment are given to maintaining the remission and also to prevent the spread of leukaemia cells into the brain and spinal cord. This second part of the programme is called 'consolidation and central nervous system treatment'.

A few months after diagnosis the doctors must try to reduce the amount of leukaemia to a minimum. The standard treatment protocol involves two such courses given at roughly four and eight months from diagnosis. This phase is called 'delayed intensification therapy.' This third part of the programme uses powerful drugs which will affect a child's bone marrow and the ability of the marrow to produce blood cells. This leads to a fall in their blood count and associated problems such as infection and bleeding. The more intensive the treatment the more likely it is that a child will experience these serious side effects. The final part of the treatment programme involves continuation or 'maintenance' outpatient treatment for another 14 months or so for girls and 26 months for boys. This makes a total of two or three years for the whole programme.

With modern treatment protocols, including aggressive treatment of children with relatively resistant disease, the cure rate is high. Treatment usually commences within a few days. Although there is a degree of urgency it is sometimes considered better to wait until all the necessary information is available because this allows doctors to offer the appropriate treatment to each individual child. Virtually all children diagnosed with ALL in the UK are treated at specialist paediatric referral centres. Parents will almost certainly be asked to consider including their child in a clinical trial.² The present trial is called UKALL 2003.

² There is a separate publication on clinical trials available from Leukaemia Research.

Principles of treatment

Initial treatment aimed at achieving a remission is essentially similar for all children. Almost all children will achieve remission (the clearance of visible leukaemia cells from blood and bone marrow). For the very small number of children who fail to achieve a remission (called refractory ALL) doctors may recommend more intensive therapy. On achieving remission decisions must be made on the next stages of treatment. The child's condition will be graded as standard-, intermediate or high-risk based on the results of laboratory investigations and, very importantly, on the speed of their initial response to treatment. It is now well established that the speed of clearance is an important predictor of long-term outcome. Male sex, T cell disease, certain chromosome abnormalities and a very high white blood cell count at the time of diagnosis are each associated with a less favourable outcome if the child is given standard treatment. It has become increasingly clear that the careful choice of appropriate treatment protocols can greatly diminish the impact of these factors.

Another well established risk association is the number of chromosomes present in the leukaemic cells. Most cells normally have 46 chromosomes, in 23 pairs, but it is common to find an abnormal number of chromosomes in leukaemic cells. In cases where the number is higher than normal, children tend to respond very well to treatment and have a good chance of being cured. This is known as hyperdiploidy. In cases where the number is lower than normal, called hypodiploidy, the likelihood of cure with standard treatment is lower. A small percentage (1-2%) of children with ALL have an abnormality in their leukaemic cells known as the Philadelphia chromosome. The presence of this chromosome is associated with a higher risk of relapse on standard therapy.

High-risk disease

Provided that children with these poorer risk factors receive appropriate intensive therapy their outcomes may be as good as those for children with better risk factors. Children who do not respond promptly to initial treatment will be classed as high-risk, regardless of other features of their illness, and their treatment will be adjusted accordingly. It is important to stress that only about 10% of children are in the high-risk group. This means that 90% of all children have either standard - or intermediate-risk disease. Although an individual child's risk of relapse is low in the standard- and intermediate-risk groups, the larger number at risk means that most relapses that do happen involve children in these groups. This means that parents of such children should not be complacent. Equally, it is important to realise that, with tailored aggressive therapy, many children with high-risk disease can achieve lasting remission and cure.

In the past it was often recommended that children with high-risk disease undergo stem cell transplantation (see below) during first remission. Stem cell transplantation requires the use of high-dose chemotherapy and/or radiotherapy. These approaches carry an increased risk of severe, possibly fatal, side-effects. Due to the greater success of conventional, although aggressive, chemotherapy in this group of patients, stem cell transplantation is now less frequently recommended. The evidence shows that it is reasonable in these children to offer treatment tailored to their risk category and then consider a transplant if treatment fails or the child relapses. This appears to offer an equally good long-term outcome with fewer side-effects. Parents will be offered detailed discussion with their child's specialist in order to consider treatment strategies. One of the key benefits hoped for from the increased treatment in the high-risk MRD group in UKALL 2003 is a reduction in the number of children who need stem cell transplants.

Standard-risk disease

Parents of children with standard-risk disease will not be advised to consider a transplant since for these children the risk of the transplant procedure is greater than the risk of relapse. This group of children will normally receive extended treatment following remission induction followed by long-term oral chemotherapy. This takes their treatment duration to a total of two years for girls and three years for boys. There are currently attempts to identify an ultra low-risk group based on age, sex, blood count at the time of diagnosis and response to initial therapy. It may be safe to further reduce standard treatment in this group with no reduction in long-term survival. This would offer benefits in terms of reduced side-effects.

Supportive care

Supportive care will include intensive treatment with intravenous antibiotics or antifungal drugs if infection occurs. Children will usually require red blood cell transfusions and often require platelet transfusions. The child will usually have a tube, known as a central line, inserted into a large blood vessel to allow drugs, and possibly feeds, to be given effectively and without repeated needle-pricks. There are various types of central lines used and medical or nursing staff will inform parents of the special requirements for care of the central line. In some instances a child may find it difficult to eat or drink because of the side-effects of chemotherapy. In this case it may be necessary for nutrition to be given by tube.

Remission induction phase

This involves the use of several drugs in combination to clear all detectable leukaemia cells from the blood and bone marrow.

Treatment schedules (protocols) vary but this stage usually lasts between three weeks and two months. In children it has been found that the speed of response at this stage of treatment (time to achieve complete remission) is a strong predictor of final outcome. Children who take less than eight days to achieve complete remission have a much smaller risk of relapse if given standard therapy. Those who take longer than two weeks to achieve partial remission are called slow responders. This group is now targeted with more aggressive consolidation therapy (post-remission therapy), which has improved outcomes. They will not be eligible for randomisation in the current UKALL 2003 trial.

The remission induction phase normally employs vincristine and dexamethasone plus asparaginase. An anthracycline (daunorubicin or idarubicin) is added for higher risk or relapsed patients. These combinations can be expected to achieve remission in almost all children.

Either a drug called allopurinol or, in children with a large proportion of leukaemia blasts in their blood and marrow, a drug called urate oxidase (Rasburicase™), is given to prevent children developing kidney damage as a result of the amount of uric acid released when tumour cells are killed. Allopurinol treatment is normally started as soon as a child is diagnosed, before any specific anti-leukaemia treatment starts. In order to protect the kidneys from damage it is also important to maintain the child's fluid intake. The major short-term side effects during this period are related to bone marrow suppression. Low neutrophil and platelet counts increase the risk of infection and bleeding, respectively. Platelet transfusions can be given to reduce the risk of haemorrhage. Infection must be guarded against by good sterile precautions and prompt treatment must be given if infection occurs.

Occasionally, the destruction of cells is so rapid that a condition called tumour-lysis occurs which affects the kidneys so that the temporary use of an artificial kidney may be required.

Remission induction is followed by consolidation or central nervous system (CNS) treatment. A number of protocols also employ cyclophosphamide and cytarabine, which doctors think may improve the quality of remissions and affect outcomes in children with poor risk factors. CNS-directed therapy during this phase includes a drug called methotrexate being injected directly into the fluid around the spine. This is called an intrathecal injection. It was previously common practice to give radiotherapy directed at the head during this stage. There are significant side-effects associated with this form of radiotherapy and this is normally now omitted except for patients with CNS disease at diagnosis. High-dose intravenous methotrexate combined with intrathecal injections of the same drug are used in relapsed patients or those with Philadelphia chromosomes.

Children will spend part of this stage of treatment as inpatients because of the risks of infection and haemorrhage. The exact length of their hospital stay will vary from centre to centre and from child to child. This will be discussed with the parents at the time of treatment planning. Hair loss is almost inevitable but is temporary.



Consolidation (post-remission treatment)

Consolidation therapy is also referred to as post-remission treatment or as intensification. The disappearance of leukaemia cells from the blood and bone marrow does not mean that all the leukaemia cells in the body have been killed. In order to optimise the outcome of treatment it is necessary to give further blocks of treatment soon after completion of remission induction and CNS directed therapy. Consolidation protocols may vary greatly according to risk category and the speed at which remission is achieved. A high proportion of clinical trials in childhood ALL are directed at establishing the optimum number of blocks of treatment for children with different risk profiles. The number of treatment blocks and the exact drug combinations used vary between clinical protocols. The child's specialist will outline the details of this phase of treatment.

Maintenance or continuing treatment (see overleaf) will be given in between the blocks of consolidation therapy.

This stage of treatment typically lasts for several months mainly as an outpatient, although infections or low neutrophil counts may require admission to hospital. The drugs used are alternated to reduce the likelihood of the leukaemic cells becoming resistant to chemotherapy. Intervals of time are left between blocks of treatment. The reason for this is to allow the child's normal cells to recover and to minimise side-effects. It also allows drugs that only act at certain points during cell growth and division to have maximum impact. Current standard therapy includes one to two blocks of intensification treatment. For children with high-risk disease consolidation may be intensified by inclusion of additional blocks of treatment or by use of additional drugs in the periods of maintenance therapy between intensification blocks. During this period CNS-directed therapy consists of intrathecal injections of methotrexate.

Continuing treatment (maintenance therapy)

This phase of extended low-dose oral chemotherapy, to prevent late relapse in children who appear to be in full remission, is unique to the treatment of ALL. The exact reasons why are not known but it is clear from a number of studies that omitting this phase of treatment leads to an increased chance of relapse. This stage of treatment is as important as the other aspects of treatment. In children, continuing treatment typically extends to two years from the start of treatment for girls and to three years for boys. The extended period for boys, regardless of risk status, is based on the results of several clinical trials. It is well established that boys, if treated with the same protocols, do less well than girls. It is hoped that extended maintenance will reduce this difference. Continuing treatment can be carried out as an outpatient throughout and the child should be able to resume normal activities during this time.

Treatment during this stage involves taking daily tablets of mercaptopurine, or a similar drug, and weekly tablets of methotrexate. At monthly intervals vincristine injections are given along with five-day courses of steroid tablets. Intrathecal methotrexate is given as CNS-directed treatment every three months.

During the extended maintenance phase of treatment it is usual to monitor children every one to two weeks. It may be necessary for drug doses to be adjusted based on results of these visits to hospital and so it is important that children attend regularly. Where a child has been referred to a specialist centre for treatment it is usually possible to arrange for blood tests to be done at a local hospital if this is more convenient. This phase of treatment is usually provided on a 'shared care' basis with a partnership between the specialist centre and the child's local hospital. Although the specialist centre retains overall responsibility, much of the care during this stage of treatment is provided by the child's local hospital. This provides major benefits for the child and the family; it avoids the need for long journeys and reduces the

disruption to family life. For children who are of school age, this may also reduce the disruption to their education. The exact arrangements for each child, frequency of visits to the specialist centre etc., will vary and parents will be given a detailed care plan showing what will happen when and at which hospital. Shared care should not inhibit parents from contacting the specialist centre if, at any time, they wish to discuss their child's care with the specialists taking overall responsibility.

Central nervous system directed therapy

For all risk groups a potential site of relapse is the cerebro-spinal fluid (CSF) which surrounds the brain and spinal cord. Leukaemic cells can enter the CSF but, unfortunately, administration of drugs by mouth or by injection into a vein does not lead to sufficient accumulation of drug in the CSF to kill them. There is, therefore, a risk that leukaemia cells may survive in this site. Only about three per cent of children have detectable leukaemic cells in the CSF at the time of diagnosis but, without effective CNS-directed preventative therapy, 50% to 70% of children will develop leukaemia within the CNS. If it is not treated this may lead to symptoms affecting the nervous system including headaches and early morning vomiting (often without nausea) and the patient may eventually experience a relapse at other sites. In order to prevent these problems it is normal to give CNS-directed therapy, which commences during remission induction and continues until the end of maintenance treatment. It involves administering drugs directly into the fluid around the spine. This is done by a process called a lumbar puncture and is called intrathecal therapy. Because of the risk of giving the wrong drug into the CNS it is normal to try and avoid giving vincristine injections on the same day as an intrathecal injection. If it is necessary then vincristine should be given at a different time and/or in a different place. Some high-risk protocols may also recommend that children receive radiotherapy to the head (cranial irradiation).

The UKALL 2003 clinical trial for childhood acute lymphoblastic leukaemia

Forty years ago, almost all children diagnosed with acute leukaemia died, often within weeks. As many as 80% of all children can now be cured. One of the most important factors in achieving this progress has been the information gathered from successive clinical trials. A clinical trial is a scientific comparison of two or more treatment options to determine which offers the best outcome. All leukaemia trials are randomised which means that children entered into the trial are allocated to one of the planned treatments at random in order to compare the best currently available treatment with a new treatment(s). This ensures that the results are correct and unbiased because equal numbers of children are in each treatment group. Furthermore children are allocated treatment regardless of their physical condition at the time. For example, if all the children with a good chance of responding well were to receive the new treatment and all those with a poorer prognosis received the standard treatment the results would give a completely false picture in favour of the new treatment. It is important to emphasise that whatever the course of treatment given to a child it is effective against their disease.

It is important to understand that all families have the right to choose whether their child should or should not be included in the UKALL 2003 trial. Any child who is not included in the trial will receive the current standard treatment and will not be treated in any way less favourably than children who are included in the trial. All families will be given detailed written information and a chance to ask questions before deciding for or against entry into the trial.

Until 2009, parents of all children in the UK who are newly diagnosed with acute lymphoblastic leukaemia will be asked to consider entering their child into UKALL 2003.

There are three randomised research questions; these are:

- Can a new test called MRD (Minimal Residual Disease) be used to identify a group of children who can safely have a reduction in the total amount of treatment they receive?
- Can MRD testing identify a relatively high-risk group who will benefit from receiving more intensive treatment early on?
- Are there differences in the quality of life for children receiving each of the different treatment options in the trial?

There is also a non-randomised study that is involving all children, regardless of which group they fall in; this is to establish:

- How common is it for children to become sensitised to a drug called asparaginase and what impact does this have on their treatment?

Minimal Residual Disease

All children, at the end of their initial phase of treatment, still have some leukaemia cells in their bone marrow. It is important to know how much leukaemia is still present because this helps to predict how likely it is that the disease will return. The return of the disease is called a relapse.

The presence of small numbers of leukaemia cells that are not visible under the microscope after treatment is called minimal residual disease (MRD).

Until recently methods for detecting MRD were relatively insensitive and could only detect the presence of large numbers of cells. The new test for MRD is much more sensitive and it is expected that it will now be possible to identify children who are at very high or at very low risk of relapse and to adjust their treatment accordingly. This is the major component of UKALL 2003. In the past, when less intensive treatment was used, some children were still cured;

although the risk of a relapse and treatment failure was higher. It is hoped that by identifying the low risk group who can be cured with less intensive treatment the incidence of treatment side-effects can be reduced. Conversely by increasing the intensity of treatment for children with high-risk disease, it is hoped to reduce the risk of relapse leading to an improvement in overall survival.

The relationship between MRD and likelihood of relapse or cure

At diagnosis — there may be as many as one million million (10^{12}) leukaemia cells in the blood and marrow. This tumour level can be easily detected by examining blood or marrow under a microscope.

After initial treatment — the number of leukaemia cells can be reduced as much as one thousand-fold, however this still means as many as one thousand million (10^9) remain in the body. This level of tumour load cannot readily be seen under a microscope but can easily be detected using the sensitive MRD test.

When MRD is negative — the expectation is that cure has been achieved. It is necessary for parents to realise however that, although relapses are rare in this group, they do still occur. MRD negativity indicates that the leukaemia cells have fallen below 1 in 10,000 marrow cells but there is no test which can guarantee that every single leukaemia cell has been destroyed.

Minimal Residual Disease (MRD) studies

A sample is taken at the completion of induction therapy (see below) – which is usually 28 days after diagnosis. The very sensitive MRD test is used to determine whether or not there are still leukaemia cells present. The test used can detect as few as one leukaemia cell among 10,000 normal cells in the bone marrow. The test is repeated at intervals during treatment; it is important to stress that the MRD test is now used as a standard way of assessing response to treatment and is performed on samples from all children not just on those who are in the trial.

Eligibility for the trial

A small number of children will not be considered for inclusion in the trial.

These are:

- Children who are less than one year old at the time of their diagnosis (there is a separate trial called Interfant for this group)
- Children who have the Burkitt-like (FAB L3) type leukaemia (they will be eligible for the UKCCSG B cell NHL/ALL trial)
- Children who have Philadelphia positive ALL, a particular chromosome abnormality which increases the risk of relapse. They will start on the UKALL 2003 trial but will transfer to the European Intergroup trial as soon as they are found to be Philadelphia positive

Children who are eligible for UKALL 2003 will be placed in one of three risk groups. The risk categories described here are based on results at the time of diagnosis. This system of classifying the type of leukaemia affecting a child is well tested and is not part of the UKALL 2003 trial. All children, including those not entered in the trial, are classified in this way. The groups are:

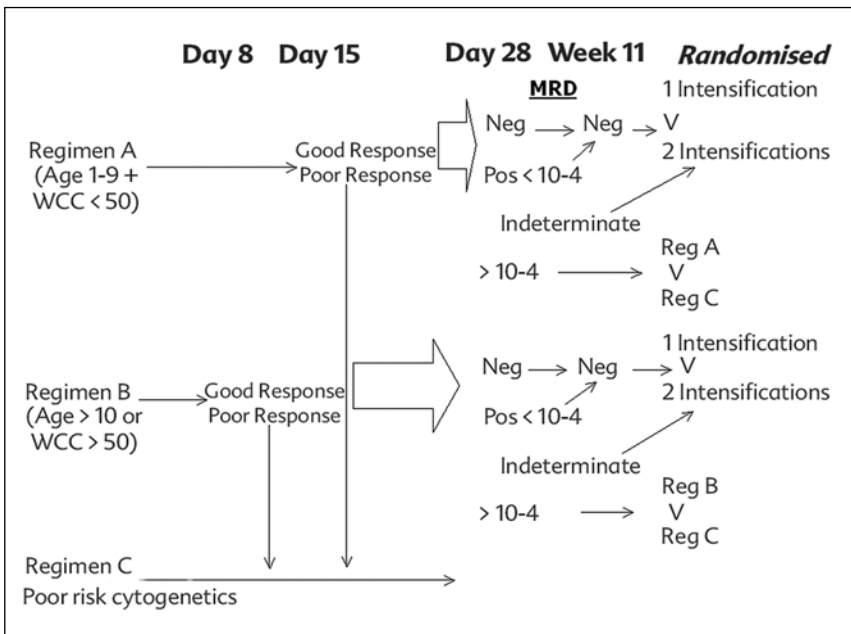
- Standard risk – 1-10 years old, white blood count less than $50 \times 10^9/l$ at diagnosis and no high-risk chromosome abnormalities
 - ✦ This group (about 60-65% of the total) will commence treatment using three drugs for the initial induction phase – regimen A

- Intermediate risk – 10 years or older, or white blood count higher than $50 \times 10^9/l$ at diagnosis (or both) BUT no high risk chromosome abnormalities
 - ✦ This group (about 20-30% of the total) will receive four drugs in the induction phase – regimen B
- High-risk – all children whose disease does not respond quickly to initial treatment or who have high-risk chromosome abnormalities
 - ✦ This group (10-12% of the total) will receive four drug induction and will receive higher intensity treatment during the later stages – regimen C

Not all children who are entered into the trial will have their treatment altered from the current standard treatment:

- All children who are classed as high-risk, either on the basis of their early response to treatment or the presence of certain high-risk chromosome abnormalities, and who start on regimen C will continue on this regimen. MRD test results do not affect the treatment of this group
- Children whose leukaemia is not in remission by day 28 of treatment will all receive higher-dose treatment, either regimen C or another regimen. The specialist will discuss this in detail
- Children whose leukaemia is classed as standard- or intermediate- risk will have their treatment reviewed on the basis of their marrow MRD results at 28 days and 11 weeks
 - ✦ If their MRD is negative at 28 days or at 11 weeks, they will continue on regimen A or B but will be randomly assigned to receive either one or two delayed intensifications
 - This part of the trial will establish whether or not a reduced amount of treatment will reduce the level of side-effects without increasing the risk of relapse

- ❖ If their MRD test is positive at 28 days they will be randomised between remaining on their existing treatment or changing to the high-intensity regimen C
 - This part of the trial will establish whether being on regimen C will reduce the risk of relapse without an unacceptable increase in side-effects of treatment
- ❖ If the results of the MRD test are indeterminate (i.e. no result or a weak positive at 28 days and 11 weeks) they will continue on their existing regimen (A or B) and will all receive two delayed intensifications
 - This is the same treatment as they would have received if they were not in the trial



Simplified flow diagram of the treatment protocol for UKALL 2003

N.B. WBC > 50 = greater than 50x10⁹/l

WBC < 50 = less than 50x10⁹/l

Treatment of relapse

Although a very high proportion (over 95%) of children with ALL will achieve a remission a significant proportion (20-25%) will relapse. This is to say their disease will return.

The proportion of children with high-risk disease who relapse is higher than the proportion of children with standard-risk disease. However, as the majority of children have standard-risk disease most relapses which do occur will occur in this group. Relapsed ALL tends to be more resistant to treatment than the original disease. One reason for this is that relapse often occurs because the leukaemia cells have become resistant to drug treatment. Drug resistance may not be specific to a particular drug – it may affect all, or virtually all, anti-leukaemia drugs. This is known as multi drug resistance (MDR). A number of drugs are being studied which may be capable of preventing or reversing resistance. Two key factors in the outlook for children with relapsed ALL are the timing of relapse and whether the relapse has affected the bone marrow at the time it is discovered. When the relapse is only apparent in the CNS, or in the testis in boys, it is termed an extra-medullary relapse or a relapse outside the bone marrow. Children who have an early relapse in the bone marrow are likely to respond less well to further treatment. This means that the worst outlook is for a bone marrow relapse within two years of initial diagnosis; whilst the best outlook is for isolated non-marrow relapses occurring late after diagnosis.

The most common site for late extra-medullary relapse is the testis. Like the CSF this is a sanctuary site where drugs do not easily penetrate and leukaemia cells may survive although destroyed elsewhere in the body. This form of relapse tends to respond well to intensive chemotherapy and radiation treatment (which must be to both testes even if leukaemia has only been detected in one). This treatment does, unfortunately, result in infertility. It will also impair production of testosterone (the male hormone) and hormone supplements may be required to stimulate puberty and during adult

life. Research is being carried out into the possibility of preserving testis cells taken at the time of diagnosis (even in pre-pubertal boys) with the aim of restoring fertility.

Although the likelihood of a relapse progressively decreases with time, particularly once continuing treatment has been completed, late relapses do occur. Children who experience late relapses can usually achieve a second remission quite easily which may be maintained for a long period of time. Repetition of the original therapy in this group does not appear to achieve long-term cures and clinical trials are considering the ideal therapy to convert second remissions into cures. Treatment options and the likelihood of cure will be influenced by a number of factors including the site of relapse. The child's specialist will discuss these in detail.

Occurrence of relapse accounts for the difference between the very high remission rate in children and the lower overall cure rate of 75-80%. The first step in treating relapsed ALL is a repeat of the remission induction programme. This may involve an increased intensity of treatment compared with the original course. There are specific clinical trials designed to determine the ideal management of relapsed childhood ALL and parents are likely to be asked to consider entering their child in such a trial. The starting point for all clinical trials is the best, currently available therapy. Parents can refuse trial entry without prejudice to their child's treatment and may withdraw at any time. The long-term success of re-treatment varies between almost 80% for the best risk group to less than 10% for the worst risk group. Clearly it is reasonable to offer children in the standard-risk group standard chemotherapy while treatment of higher risk groups is somewhat less standard. The role of transplants in the treatment of relapse is discussed below in the section on stem cell transplants.



Stem Cell Transplantation

The overwhelming majority of children with ALL will respond very well to chemotherapy and will not require a stem cell transplant. A small proportion of children with high-risk disease may be considered for a possible donor stem cell transplant while in first remission. Other than this, the place of stem cell transplantation is restricted to the treatment of those children who have experienced a relapse early in their treatment or who have suffered more than one relapse.

Stem cell transplantation (SCT) is the term now used in place of bone marrow transplantation (BMT). A bone marrow transplant is one form of SCT but for many children the source of stem cells is the circulating blood. An SCT may be either allogeneic (from a donor) or autologous (the child's own stem cells). A special type of transplant is a cord blood stem cell transplant. This uses stem cells harvested from the umbilical cord at the time of birth. It is of particular importance for children because the number of stem cells that can be obtained from this source is not sufficient for an adult. Although this is still a donor transplant with a need for tissue matching, it is thought likely that a less exact match will be acceptable. Allogeneic transplants carry a higher chance of eliminating the leukaemia but they also carry a higher risk of graft rejection and of a condition called graft versus host disease (GvHD). Conversely, autologous transplants are less inherently risky in terms of graft failure or graft versus host disease but there is a high risk of return of the original leukaemia.

The preferred donor, where available, is a sibling with a closely matched tissue type. The chance of finding a sibling that is suitable is about 1 in 4. Given the small size of most families this means that few children will have a sibling donor available. Where such a related donor is not available an unrelated donor from a volunteer panel or a cord blood bank may be considered. However, the risks of rejection and of graft versus host disease are both greater with an unrelated donor. If a child is a candidate for a transplant it is commonplace to test siblings for compatibility before a firm decision

is made. Parents should not assume that, because brothers or sisters are being tested, the decision has already been made.

Although it is not currently a routine procedure, certain centres are studying the use of parents as stem cell donors for selected high-risk children where a sibling donor is not available.

Long-term effects of treatment

Long-term survival of children with ALL has improved dramatically from around 4% in the early 1960s to around 80% in recent reports. Unfortunately, there are long-term adverse effects from certain aspects of treatment. Although efforts continue to improve survival still further, a major secondary aim of current clinical trials is to reduce the incidence and severity of the adverse effects of treatments. Use of cranial and spinal irradiation to reduce the risk of CNS relapse is associated with impairment of growth and educational achievement and with premature onset of puberty. Awareness of such long-term effects has led to a series of studies designed to ensure that children receive the absolute minimum of radiotherapy needed to minimise the risk of CNS relapse. Only a minority of children now receive cranial irradiation routinely.

In the minority of cases where whole body irradiation has been given as part of the preparation for a stem cell transplant, it is virtually inevitable that the child will be made sterile. There may also be impairment of hormone production by the testis or ovary and children may require replacement therapy to attain puberty. This is particularly likely when children have been irradiated at a young age. Boys with testicular disease may require localised radiotherapy to the testis and the younger the age at which this is done the more severe the impact on testis function. Spinal or total body irradiation may expose the thyroid gland to a high enough dose to impair its function. For this reason, children who have received radiotherapy that may affect the thyroid must have regular tests and may require thyroid supplements. The long-term effects

of chemotherapy clearly depend on the drugs used, the intensity of treatment and, in the case of some drugs, on the total amount of the drug received. It is more difficult to establish which drugs are responsible for which long-term effects in situations like childhood ALL where combinations of drugs are administered over long periods of time. There are known long-term adverse effects of certain drugs. A detailed analysis of these effects is not possible as they depend on interactions between drugs and may even vary between individuals. Detailed advice will be available from the specialists before a child begins treatment.

One common concern of parents and of older children is the effect on fertility. The majority of women who were treated in childhood for ALL using standard protocols will not have impaired fertility. Males are more likely to have impaired sperm production, and thus infertility, although this varies between patients and is hard to predict in any given case. For example, as explained above, it is almost inevitable when whole body irradiation has been given. Fortunately, the endocrine (hormone-producing) functions of the testis do not appear to be affected and most boys will undergo puberty normally and will have normal potency and sexual development. It is very important that men who were treated with chemotherapy as children are aware that fertility may return after very long periods of no sperm production. For this reason it would be unwise for a sexually active male, who has been sterile as a consequence of chemotherapy, to assume that this will always continue to be the case.



An important consideration for both males and females is whether there is a risk of adverse effects on offspring from treatment received during childhood. A number of large studies in Britain and abroad have confirmed that there is no increased risk of cancer or of an abnormality in children whose parents received treatment for cancer during childhood. The impact of radiotherapy on fertility has been discussed above.

There are certain long-term consequences seen only in children who have received stem cell transplants. Secondary cancers are a well established, although thankfully rare, consequence of drug and radiation therapy for childhood ALL. The types of cancer most often seen are brain tumours, especially in children treated with radiotherapy. Current treatment protocols, which avoid routine cranial irradiation, may well reduce the incidence of this rare complication even further. Although there are significant long-term adverse effects of treatment for childhood ALL, a recent major study concluded that most children treated for cancer achieve their life goals.



Follow-up

The main purposes of follow-up of children treated for ALL are detection of relapse and detection of treatment complications. During the first year following completion of chemotherapy children are normally checked every two to three months. Checks will then gradually become less frequent and are given annually at five years and beyond. Long-term follow-up is particularly important for those children who have received treatment that may affect reproductive maturation. For this group of children hormone therapy may be necessary at an appropriate age to ensure that they achieve puberty. Neglect of such therapy may cause severe psychosocial distress to the child and peer group rejection. It can be expected that all paediatric specialist referral centres will have a programme in place to ensure such follow-up.



Prognosis

As discussed in the treatment sections, almost all children can expect to achieve a good first remission. The major prognostic factor at this point in treatment appears to be whether there is a prompt initial response to therapy. Factors such as age, sex, type of cell affected, cytogenetics and white blood cell count at time of diagnosis may be of importance in determining whether a child should receive standard therapy or more intensive treatment. The very small numbers of children who fail to achieve a first remission will receive highly individualised care and their specialist will discuss this in detail. Overall cure rates for childhood ALL have been reported to be as high as 80%, although at present many experts consider that 75% is a more realistic figure. Of the 20-25% of children who do relapse it is important to stress that most of them will come from the group designated as standard-risk because most children fall into this group. Marked differences in prognosis in certain sub-groups (e.g. children with T-ALL) have been greatly reduced by selective use of aggressive therapy. Clinical trials currently have three main aims: to reduce the proportion of children who relapse; to improve management of relapsed disease; and to minimise the impact of side-effects of treatment on those who are successfully treated for childhood ALL.

Summary

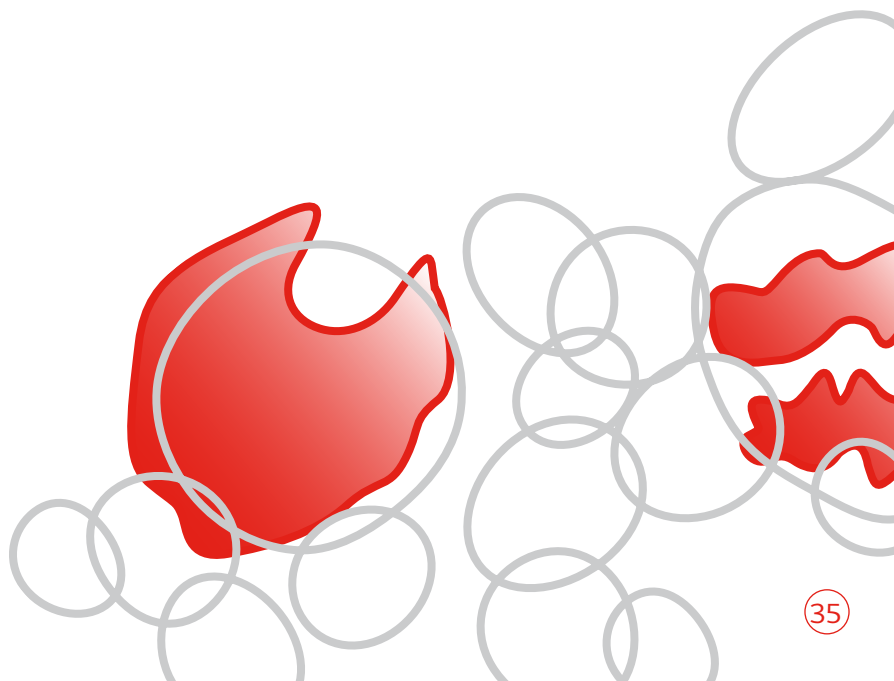
Childhood acute lymphoblastic leukaemia is a form of cancer that affects blood-producing cells in the bone marrow. Although childhood ALL is a very serious disease, which is almost uniformly fatal if not treated, it has a high chance of being curable with standard chemotherapy. Almost all children will achieve a remission but overall cure rates are between 70% and 80%. The difference between remission and cure rates is mainly accounted for by patients who experience relapse of their original disease.

Treatment is based on the use of drugs in various combinations. There are four phases to treatment of childhood ALL. The initial phase is called remission induction and uses relatively high drug doses to rapidly reduce the number of leukaemia cells in the body. This typically lasts about a month with part of that time spent as an inpatient. Consolidation and CNS therapy is intended to further reduce the number of leukaemic cells in the body. This is followed by further intensification treatment which lasts for several months. Finally, and uniquely to this form of leukaemia, there is a maintenance phase extending to two years for girls, and three years for boys, from the time of diagnosis during which patients take low doses of drugs as outpatients.

Stem cell transplantation is not used routinely in the treatment of childhood ALL. It may be appropriate for patients who are thought to be at high risk of relapse or for patients who have experienced relapse but have achieved a second remission.

The prognosis for childhood ALL varies depending in part on characteristics of the child such as age and sex and in part on the features of their disease. The most important single prognostic factor seems to be the initial response to treatment. Designations such as standard-risk or high-risk are of considerable value in conducting comparative studies and offer guidance to doctors in planning treatment. Over recent years treatment planning has been improved and refined so that several groups of children who formerly had a poor prognosis can now be expected to do well.

At the time of diagnosis, about two-thirds of all children will be in the standard-risk group, with another 20-30% in the intermediate-risk group. It must be remembered that, although the risk for any individual child in the standard-risk group is low, the large size of the group means that most deaths that do occur are of children in the initially standard-risk group. Each family should seek individual advice on their child's prognosis from that child's specialist.



Coping with childhood leukaemia

This section offers advice to try to help you as a family cope with the stresses and problems of having a child with leukaemia.

Not all of the difficulties discussed will necessarily apply to you but they may be important factors for other members of your family or other similar families.

This information has been divided into four sections. We would like to suggest that you read the first two sections within a few days of hearing the diagnosis, as they will help you through the first weeks. The remaining two are more concerned with the future and are best left a little while. They deal with practical problems and the help that is available and how to set about getting this help.

They also discuss possible long term difficulties and how to handle them.

The diagnosis and the first few days

You have recently suffered a very severe shock because you have learned that your child has leukaemia. You may have suspected this diagnosis but naturally hoped that you were wrong. Now that you know the truth you are besieged by many bewildering thoughts and feelings. It is important for you to know that this is natural and that you are not unusual in having these thoughts.

The doctor in charge of your child's treatment will by now have talked to you and tried to explain to you what leukaemia is and how it is likely to affect your child. You will probably have taken in very little of what was said and will have forgotten a great deal. Do not worry about this. The doctor understands this and will be prepared to explain everything again. If he/she does not suggest this then do not be afraid to ask for the opportunity of another talk. It is often a good idea to write down the questions which keep coming to your mind – you can then go through them with the doctor, otherwise you might forget them.

It is hard at first not to be very depressed or angry about the news but you must remember that so much can be done today for children with leukaemia and you must have hope. Children can have as good as an 80% chance of treatment being successful and these children may go on to lead completely normal lives. It is never possible for your doctor to be absolutely certain about the outlook for your child but what you are told will be a fair assessment and, even if there is some uncertainty, the doctor is being honest. No one knows at the time of diagnosis which children will survive. The doctor can only talk of risks and chances.

The doctor will explain to you what the treatment for your child is likely to entail. While it will sound very complicated and frightening to you, remember that the doctors and nurses are carrying out these treatments every

day and for them it is as much a routine as it is, for example, a policeman to direct traffic, a mechanic to find and mend a fault in a car engine or a lawyer to draw up complicated legal documents. The people treating your child are experts in their field. While this should give you confidence it may also make you feel inadequate.

Remember that you are very important to your child and by remaining calm and giving encouragement you can help him/her with the numerous tests and investigations which have to be done.

The doctors and nurses are aware of your feelings and they will want you to help nurse your child and assist in other ways. If you feel able to stay with your child while tests are being done then that should be possible, but if you find it upsetting then it is probably better for you to wait close by. If you are yourself agitated and upset you will convey this to your child and make the situation more frightening. You must not feel ashamed of these feelings; most people not used to hospitals are on edge when they first go to one and you are naturally even more anxious because of your child's serious illness. You are probably much better waiting so that you can comfort your child and play with him/her after the procedure is over.

These days most children's centres treating leukaemia give the patients an anaesthetic to do the more painful tests. In this case you will probably be allowed to stay with your child until he/she is asleep and will be able to sit at the bedside waiting for him/her to wake.

Visiting and living in hospital with your child

Children's hospitals always have free visiting for parents and this should also be the case in all children's units of district general hospitals. This means that parents can come at any time and stay until the evening. Obviously the nurses have to settle the young in their beds and cots in the early evening, but they will encourage you to see your child settled and it is best to follow your usual routine. Lots of other visitors are not welcomed because the children get tired quickly and are easily overwhelmed. They are also prone to have too many infections and it is not a good thing to have too many people around the bed. The ward sister will however usually allow brothers and sisters to visit at weekends and this is important so that the family can get together.

Most children's hospitals have facilities to allow you to live in with your child. Many of you will wish to do this but it is important to give it some thought especially if you have other children at home.

The nature of your child's illness means that repeated hospital visits and further admissions are likely in the future and the rest of the family may feel rather neglected. Parents have a great need to talk with each other about this shock which has struck the family and to discuss their feelings, reactions and worries. You both need comfort and support and it is easier to give this to each other if you have time alone together. This is very difficult if mother is living in at the hospital and father is trying to keep the rest of the family together. Some parents find that the most sensible solution is to spend as much time as possible with your child in the day and go home in the evenings. The circumstances are different from those of a short-lived acute illness where the child soon recovers and the usual family routine can be quickly restored.

The family can cope for a few days in these cases but with a disease like leukaemia the ongoing treatment, although mostly on an outpatient basis, will last about three years and it is important from the onset to work out a method for your family so that no one feels neglected or put upon.

No one will think the less of you for spending some time away from your child. We all need some time to ourselves especially at periods like this when we need to 'refuel'. The staff all realise how stressful it is to be on a busy ward for long hours with little to do yourself.



Coping with the problems of treatment

In the majority of cases the child with leukaemia responds quickly to treatment and returns to an active normal life. The period of time in hospital will vary according to the type of leukaemia and treatment programme but most children have a first stay in hospital for about three to six weeks. Your doctor will be able to give you some advice as to how long the child is likely to remain in hospital.

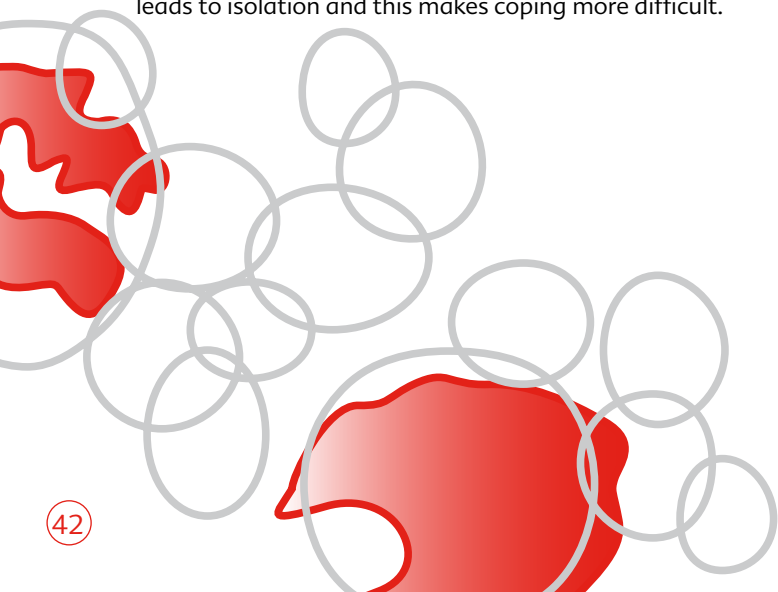
On your return home and despite the resumption of normal health and activity there will be constant reminders to you of your child's illness, for example loss of hair, variable appetite, moodiness and sometimes a more dependent attitude. The majority of these symptoms are due to the effects of the drugs which your child has to take and it is important not to pay too much attention to them.

On returning home it is essential that you try to return to the normal day-to-day life of your family and also maintain your usual routine. You will of course have to make regular visits to hospital but these will usually occur on average every two to three weeks and the doctors will not expect serious complications or deterioration to occur in a sudden way. You will be warned of the symptoms to look out for which should alert you to contact the doctor. Do not hesitate to discuss problems with the doctor who can advise you how to handle them.

Some children who have received a lot of attention while in hospital continue to be demanding while at home. This must be discouraged as it is detrimental to normal family relationships — brothers and sisters will feel neglected and then they will also play-up to gain attention. Your child with leukaemia will be happier and better able to deal with the disease if you accept it as something which you all have to try to overcome. While it cannot be ignored, it should not become the centre of all attention and conversation. Everyone in the family must remain important, with their special needs and requirements.

Your doctor will tell you when your child is fit to return to school, nursery or playgroup. This will usually be within a couple of months of diagnosis but it depends on the treatment schedule. If the child has to be readmitted for further drug treatment or for radiotherapy then return to school may be delayed. Return to normal activities should be a goal to look forward to as should family holidays.

In the early days following diagnosis a parent will probably have had time off work. This should not be prolonged unless your child's life is in immediate danger, which is very rarely the case, and if it is the doctor will have told you. Cutting yourselves off as a family from workmates, friends and other contacts leads to isolation and this makes coping more difficult.



The people who can help you

There are several groups of people whose job it is to provide help and support to families in your circumstances. In addition there may be relatives and friends who would like to help in practical ways as well as sitting talking with you about your child's illness. Within the hospital, as well as doctors treating your child, the sisters and staff nurses on the ward and in the clinic will have had a lot of experience of the way you are feeling and the kind of difficulties you may have. Most of the large children's units have nurses, social workers and health visitors specially appointed to provide assistance. It is wrong to think that these people are only there to help 'problem families', people with financial difficulties or people who cannot cope on their own. There may be a simple solution to the problem which is worrying you and even if there isn't discussing it will always help. Many Regional Centres also now have parent self-help groups. You may find it very valuable to meet other parents who have 'been through it all' themselves, so that you can share your experiences. Your local group's organiser will help to put you in touch with appropriate other parents.

Your general practitioner will be happy to listen to your personal fears and anxieties — your feelings of guilt and anger. Your neighbours and friends will be pleased to look after other children, do some shopping and maybe drive you to the hospital. Grandparents often feel lost and do not know what attitude to adopt. Family discussions can be helpful so that they too understand what is to be expected. In their young days leukaemia was almost invariably a fatal disease and they may need the reassurance of a talk with the doctor before they can believe that your more optimistic attitude is realistic.

This booklet has tried to cover many aspects. It is not intended to imply that every family will experience all the difficulties mentioned. We all have different circumstances and our response to anxiety, stress and illness is a very individual thing. It is hoped that you will be helped by those comments which seem to apply to you and if there are other problems not dealt with then mention them to the doctor or social worker. They will also be interested to hear from you about your own method of coping and how you have been helped.



Typical normal values for blood test results

	WBC x 10⁹/l	RBC x 10¹²/l	Hb g/dl	ANC x 10⁹/l	Platelets x 10⁹/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)

Chronic Lymphocytic
Leukaemia (CLL)

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