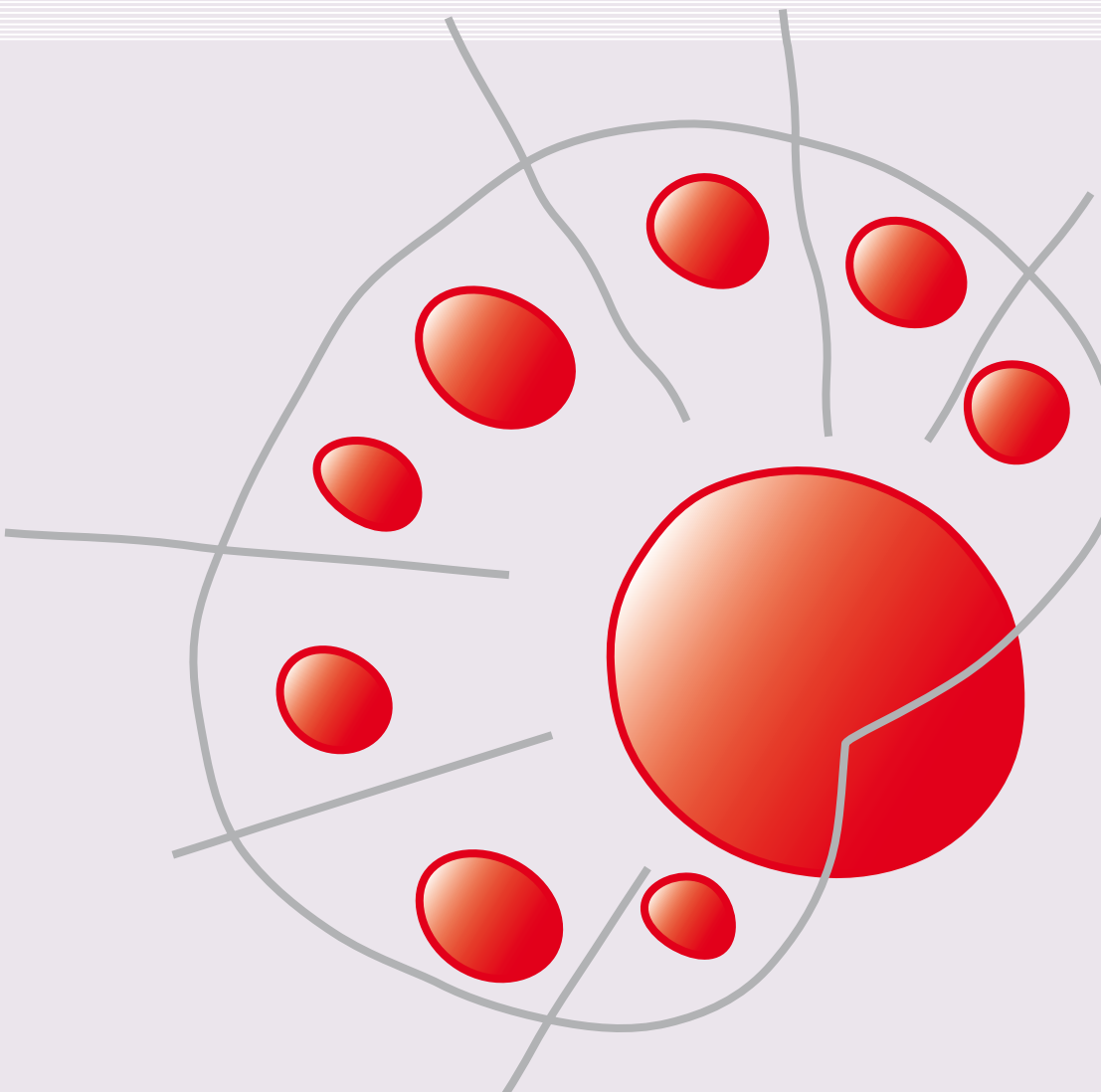


Non-Hodgkin's Lymphoma (NHL)



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 diseases 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.

Leukaemia Research

43 Great Ormond Street, London, WC1N 3JJ

020 7405 0101 www.lrf.org.uk

email: info@lrf.org.uk

Registered charity 216032 (England & Wales) SC037529 (Scotland)

Series compiled by Ken Campbell, revised 2006. A list of advisors can be found at www.lrf.org.uk/advisors

The design of this booklet has been produced with kind assistance from Euro RSCG Life.

© All rights reserved. No part of this publication may be reproduced or transmitted without permission in writing from Leukaemia Research.

What is non-Hodgkin's lymphoma?

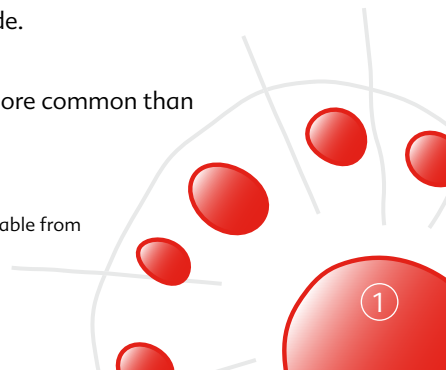
Lymphoma is a cancer of the lymphatic system – the network of lymph glands and channels which occurs throughout the body. This collects lymph which is the fluid that bathes all the body cells. The lymphatic system is also a very important part of the immune system which keeps the body free of infection. This is mainly achieved by the cells within the lymph nodes and other lymphatic tissues. These are called lymphocytes and, like other blood cells, originate within the bone marrow. Lymphocytes can be classified as T or B cells according to markers on the surface of the cells. The T and B lymphocytes have distinct functions within the immune system. B cells produce antibodies while T cells have a variety of roles including regulation of the immune system and direct killing of bacteria or parasites.

Tumours of the lymphatic tissues are known as lymphomas. There are 35 different types of lymphoma recognised in the most recent classification system. These are grouped into two main types called Hodgkin's lymphoma (five sub-types), and non-Hodgkin's lymphoma (thirty sub-types). Hodgkin's lymphoma (HL) is distinguished from all other types of lymphoma by the presence of a distinctive abnormal lymphocyte called a Reed-Sternberg cell.¹

All types of lymphoma except Hodgkin's lymphoma are collectively known as non-Hodgkin's lymphoma (NHL). Although detailed classification of NHL is very complex, for treatment planning purposes most clinicians group all cases as either indolent (slow-progressing) or aggressive. Indolent may be called low-grade and aggressive may be called high-grade.

Non-Hodgkin's lymphoma is about seven times more common than Hodgkin's lymphoma.

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

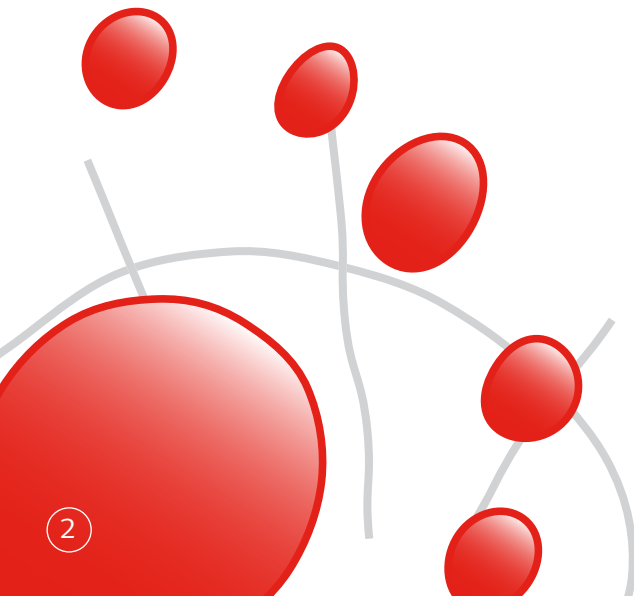


Who gets non-Hodgkin's lymphoma?

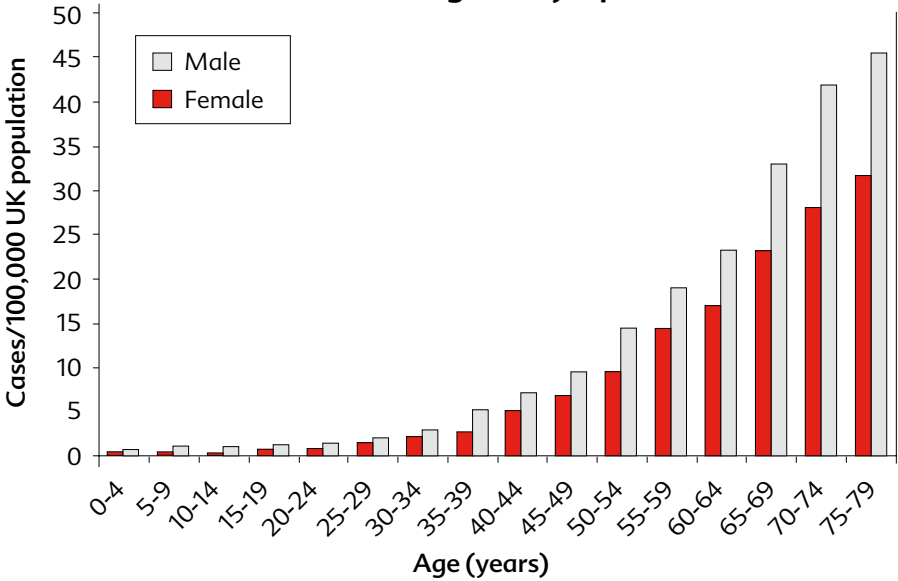
The frequency of non-Hodgkin's lymphoma and the age profile of patients differ widely between geographical communities. The contrast is particularly striking between the developed world and the developing world. A distinct pattern is seen in populations of mainly European descent as found in Europe itself, the United States and Australia; this is sometimes referred to as the 'European type' of non-Hodgkin's lymphoma.

In all countries the incidence of European type non-Hodgkin's lymphoma has been rising over the last 40 to 50 years. The reasons for this are not clearly established. The rate of increase in the UK is about 4% per year. If this level of increase is sustained it will mean that by 2025 non-Hodgkin's lymphoma incidence will be comparable with that of breast, colon, lung and skin-cancer.

The incidence of non-Hodgkin's lymphoma is about seven times greater than that of Hodgkin's lymphoma with about 8,450 new cases each year in the UK.



Incidence of non-Hodgkin's lymphoma in the UK



With the exception of some rare types of aggressive NHL which are more common in younger adults, both aggressive and indolent NHL are more common in older patients with an average age at diagnosis of around 65. Non-Hodgkin's lymphoma is uncommon in children, although it is still the third most common cancer of childhood. Given the increase in incidence mentioned above and the increasing proportion of older people within the UK population, the number of cases of non-Hodgkin's lymphoma diagnosed each year is likely to increase dramatically.

What are the types of non-Hodgkin's lymphoma?

For many years, the study of non-Hodgkin's lymphoma was bedeviled by the existence of a number of different classification systems which were not easily comparable. This made it very difficult to evaluate the results of clinical trials. An international panel of experts has developed the Revised European American Lymphoma (REAL) classification. With minor modifications this has been adopted by the World Health Organization and is now known as the REAL/WHO classification. It is now the most widely used system for classification of non-Hodgkin's lymphoma.

The REAL/WHO system recognises some 30 different subtypes of non-Hodgkin's lymphoma. For some purposes, such as clinical trials and epidemiology, the exact subtype must be defined. In day-to-day clinical practice, a much simpler division of lymphomas according to their clinical features is more commonly used.

In clinical practice non-Hodgkin's lymphomas are grouped either as aggressive lymphoma or as indolent lymphoma (also known as low-grade lymphoma). Patients will be advised by their specialist whether their form of lymphoma is considered indolent or aggressive.

	Indolent	Aggressive
Percentage of cases	30-40%	60-70%
Curable	Rarely with standard treatment	Potentially with standard treatment
Progression	Slow, may not require treatment initially	Rapidly fatal if untreated
Morphology	Usually follicular	Usually diffuse

Classification of non-Hodgkin's lymphoma is based on three main features of the disease. The appearance under the microscope of the lymphoma (morphology), the surface markers carried by the cells (immunology), and the chromosome changes present in the lymphoma cells (cytogenetics).

Morphology

The different types of NHL are distinguished by the appearance of sections from the lymphoma viewed under the microscope. The important features are the appearance of the cells and their arrangement within the node. In normal lymph nodes, many of the lymphocytes are arranged in roughly circular structures, called follicles. In follicular lymphomas these structures are present although they may not appear normal. When the organised structure of the follicles has been replaced the lymphoma is termed diffuse. Generally, follicular lymphoma tends to be relatively indolent whereas diffuse lymphomas are usually more aggressive.

Immunology

Immunological classification allows non-Hodgkin's lymphoma to be classed as either B cell or T cell in origin. The great majority (over 90%) of non-Hodgkin's lymphoma is B cell in origin as is most Hodgkin's lymphoma and most lymphoid leukaemia. The markers present on the surface of the lymphoma cells may also be useful in determining the REAL/WHO category.

Cytogenetics

All cancers arise from alterations in the structure and behaviour of genes controlling cell division, maturation and death. These changes may be very small or relatively large-scale, such as part of one chromosome swapping with another (a translocation). The presence and type of these defects are of great value in classifying non-Hodgkin's lymphoma.

Some changes are virtually always associated with certain types of non-Hodgkin's lymphoma – for example an exchange between chromosomes 14 and 18, $t(14;18)$, is found in almost all cases of follicular lymphoma (FL). It is not, by itself, a basis for diagnosis of follicular lymphoma because it is sometimes seen in other types but its absence would cast doubt on the accuracy of the diagnosis of FL. Another example is $t(8;14)$ which is very strongly associated with a type of NHL called Burkitt's lymphoma.²

² There is a separate publication on Burkitt's lymphoma available from Leukaemia Research.

How is non-Hodgkin's lymphoma staged?

In most forms of cancer, some form of staging is used to assist in treatment planning and in assessing likely prognosis. Staging relates chiefly to the spread of the cancer from its original site. It is very important in all forms of lymphoma including non-Hodgkin's lymphoma.

The Ann Arbor staging

As with many other cancers, NHL is categorized by the extent of spread of the disease. The Ann Arbor System is the most widely used system for classifying lymphoma. Full details of this system are given in Appendix A.



What causes non-Hodgkin's lymphoma?

The cause of non-Hodgkin's lymphoma cannot be identified in the majority of cases. Certain factors are known to increase the risk of developing NHL. None of the currently known risk factors could possibly explain more than a small percentage of the increase in non-Hodgkin's lymphoma which has been reported in all developed countries for which data is available.

Infection

One clearly defined risk category includes certain viral infections. It should be stressed that, although the viruses are transmissible, there is absolutely no risk of catching lymphoma even through intimate contact. The viruses that have been implicated are the Epstein-Barr virus (EBV), the HIV (AIDS) virus, and human T cell leukaemia/lymphoma virus (HTLV-1).

Epstein-Barr virus is an extremely common virus. Almost all adults in the Western world have antibodies in their blood which show that they have been infected at some time with EBV. In most people who are exposed it causes either no clinical illness at all or a flu-like illness called glandular fever or infectious mononucleosis. EBV is discussed in the section on immunosuppression.

Non-Hodgkin's lymphoma is one of the diseases considered to define the transition from being infected with HIV to having AIDS. The increased risk of non-Hodgkin's lymphoma in people with HIV infection is probably a consequence of immunosuppression which is discussed below. As is well known, HIV can be transferred by contact with infected body fluids. Appropriate precautions must be taken when in contact with fluids that may be contaminated with HIV. An important feature of HIV/NHL is that it tends to present as unusual types of lymphoma and/or in unusual locations.

An example is lymphoma arising in the brain which is rare except in patients who have HIV/AIDS.

HTLV-1 is a virus first discovered in Japan and subsequently found to be present in Caribbean populations. It is rare in the UK and there is no evidence that the incidence is increasing. There is a very long interval between infection with HTLV-1 and development of lymphoma.

Bacterial infection with an organism called *Helicobacter pylori* is strongly associated with a specific form of lymphoma called MALT lymphoma affecting the stomach (gastric MALTOMA). Gastric MALTOMA is a rare form of lymphoma and accounts for only about ten percent of cases. Antibiotic therapy to eradicate the *Helicobacter pylori* infection may cure the lymphoma if this is done early in the course of the disease. If the disease is established it is treated as for other low grade lymphomas.

Immunosuppression

For many years it was assumed that all, or most, cancers arose because of failure of the immune system to destroy cancers at an early-stage. The widespread use of therapeutic immunosuppression for organ transplantation has modified this belief because there is no generalised increase in cancer in patients who are immunosuppressed. The exception to this principle are lymphomas which are seen more commonly in this group. Immunosuppressed patients develop non-Hodgkin's lymphoma at a much higher rate than the general population. This is probably because B cells multiply rapidly in response to certain stimuli and control of this process relies on the normal function of T lymphocytes. When this normal function is disrupted B cell proliferation may progress to malignant transformation resulting in a lymphoma. Many of the cases of non-Hodgkin's lymphoma seen in immunosuppressed patients are related to EBV infection.

Although still uncommon, non-Hodgkin's lymphoma is seen significantly more often in patients who are receiving drugs to prevent rejection of a transplanted organ e.g. kidney, heart. The transplant specialist will advise patients who are awaiting transplants about such risks.

Radiation

It has been proposed that non-ionizing radiation (such as from mobile phones) may increase the risk of developing lymphoma. Evidence for this is very weak and most experts consider it unlikely that this type of radiation causes lymphoma.

Ionizing radiation (for example from radioactive materials or from X-rays) is a known potential cause of non-Hodgkin's lymphoma. The most common source of exposure to X-rays leading to non-Hodgkin's lymphoma in the UK is the use of radiation for the treatment of other forms of cancer. It is very unlikely that any members of the public are otherwise exposed to radiation levels high enough to cause NHL.

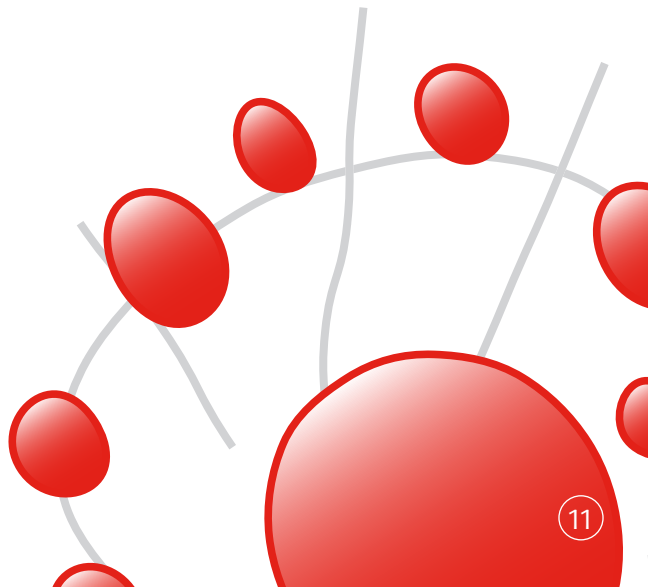
Occupational exposures

There is no clear evidence of any chemical agent causing non-Hodgkin's lymphoma. Agricultural workers are more likely to develop NHL than the general population, and although it has been suggested that this might result from exposure to agricultural chemicals, there is no excess of NHL in workers who manufacture these chemicals.

An excess of non-Hodgkin's lymphoma has also been reported in those who work in the petrochemical industry, although the evidence for this is less clear than for agricultural occupations.

Other factors

Other factors that have been mentioned as possible causes of non-Hodgkin's lymphoma include exposure to sunlight and genetic factors. It is important to stress that, although there is some evidence for the occurrence of familial non-Hodgkin's lymphoma at least 95% of cases are diagnosed in patients with no family history of NHL or related conditions.



What are the signs and symptoms of non-Hodgkin's lymphoma?

A significant number of patients with NHL have no obvious symptoms or signs at the time of diagnosis. Their disease is discovered as a result of investigations carried out for other reasons e.g. a routine chest X-ray. Patients with aggressive non-Hodgkin's lymphoma are more likely to present with fast-growing lymph nodes early in their illness. Other patients with indolent lymphoma present when the lymphoma is affecting superficial nodes and are found to be in a late stage. Because the nodes in indolent lymphoma enlarge so slowly patients may wait months or even years before seeking medical advice.

The most common symptom that does occur in patients with non-Hodgkin's lymphoma is presence of one or more enlarged, usually painless, lymph nodes (glands) in the neck, collar bone region, axilla (armpit) or groin. It is important to stress that most patients who have enlarged lymph nodes are found to have simple, easily treated infections. This is especially true for children in whom non-Hodgkin's lymphoma is very uncommon. Infected lymph nodes are usually painful and tender to the touch. Usually when an infection clears up the enlarged nodes will return to normal within a few weeks or months.

Lymph nodes that are enlarged because of lymphoma are almost always painless. Unfortunately, it is not possible to use this feature to reliably distinguish between enlarged nodes in response to infection and lymphoma. If affected nodes are large or they are persistent or recurrent and there are any other suspicious symptoms, the doctor may arrange for an immediate biopsy to obtain a definitive diagnosis. If the node(s) is smaller and there is other evidence of infection, it may be preferable to wait and see whether the nodes disappear spontaneously. Aspiration of the node by a fine needle to examine the cells under a microscope may help in deciding whether to 'watch

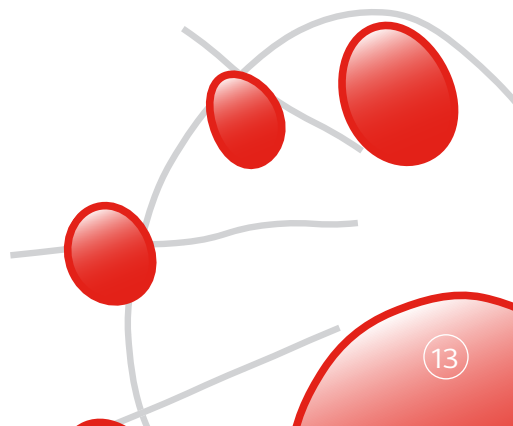
and wait' or to proceed to a full biopsy. Although this is a reasonable course of action it is not unknown for lymphoma nodes to shrink and regrow. For this reason, any patient who experiences such a pattern should be referred to a surgeon for excision biopsy (removal of a complete node).

At later stages of the disease more generalised (constitutional) symptoms develop. The presence or absence of such symptoms is of considerable importance in staging non-Hodgkin's lymphoma. The symptoms included for the purpose of staging are:

- Recurrent fevers (greater than 38°C)
- Night sweats (drenching)
- Weight loss (greater than 10% in less than six months)
- Fatigue (severe and persistent).

Anaemia (low haemoglobin) is fairly common in non-Hodgkin's lymphoma. Low white cell and platelet counts may also occur even when there is no evidence of lymphoma cells in the bone marrow.

Non-Hodgkin's lymphoma may be associated with symptoms of local complications such as obstruction of bile ducts, major blood vessels, kidneys, windpipe or gastrointestinal tract. A diagnosis may be made as the result of an investigation of symptoms of obstruction or pressure on other tissues.



How is non-Hodgkin's lymphoma diagnosed?

When a doctor examines a patient with NHL there are no specific signs like the rashes seen in some infections. The physical features, size and distribution of affected lymph nodes may be strongly suggestive of lymphoma. Non-Hodgkin's lymphoma is not a clinical diagnosis; it requires the results of laboratory tests on a biopsy sample to confirm the diagnosis.

The following guidelines have been issued by the Department of Health to indicate when GPs should urgently refer patients as possibly having lymphoma:

- Lymphadenopathy (enlarged lymph glands) persisting for six weeks
- Hepatosplenomegaly (enlarged liver or spleen)
- Constellation of three or more of the following symptoms
 - fatigue
 - night sweats
 - weight loss
 - itching
 - breathlessness
 - bruising
 - recurrent infections
 - bone pain.

The accepted procedure for investigation of a suspect lymph node is to take a biopsy of one or more of the affected nodes. If the node is easily accessible then this can be done under local anaesthetic. An excision biopsy means that the whole affected lymph node is removed for examination in the laboratory.

Sometimes for children, or if the tumour is deeper, a general anaesthetic is given. An alternative method of sampling tissue is called fine needle aspiration (FNA). This method involves taking a small sample with a needle and syringe and may be acceptable for the initial screening in patients who are thought to have benign lymph nodes or are not fit for a general anaesthetic required for a full biopsy. It may also be used for monitoring response to treatment. The risk of a false negative result (failure to detect the presence of tumour cells) is considered too great for it to be routinely used for diagnosis.

The larger sample obtained by surgical biopsy also provides much more tissue for specialist tests such as cytogenetics (chromosome studies) and immunocytochemistry (classifying the affected cells). It is particularly important to demonstrate the presence or absence of Reed-Sternberg cells as this is central to differentiating between Hodgkin's lymphoma and non-Hodgkin's lymphoma.

Any patient who is thought to have lymphoma will have X-rays and either a CT or MRI scan. X-rays and CT/MRI scans are known as imaging methods. These methods are particularly important for staging. A chest X-ray will probably be done before the results of the biopsy are available, whereas CT/MRI scans will only usually be done if the results of the biopsy are positive.

Once a diagnosis of non-Hodgkin's lymphoma has been made it is necessary to find out if the bone marrow has been affected. In order to do this a bone marrow sample is taken. This again is usually done under local anaesthetic, although children and particularly anxious patients may receive a general anaesthetic. The bone marrow biopsy is obtained from the pelvis. Bone marrow involvement usually occurs late in the disease. Because indolent lymphoma is usually diagnosed at a late-stage, some 70% of patients with this type of NHL will have bone marrow involvement at the time of diagnosis.

Various other tests are performed to assess general health, for example heart, liver and kidney function. These are important to ensure that patients are not particularly prone to negative side-effects from planned treatment.

How is non-Hodgkin's lymphoma treated?

Principles of treatment

The mainstay of treatment for non-Hodgkin's lymphoma is the use of drugs in various combinations (chemotherapy). In some cases chemotherapy may be combined with the use of radiation (radiotherapy). Radiotherapy alone may be used for the small number of patients who have early-stage indolent lymphoma at diagnosis. For many patients with indolent lymphoma, no treatment is needed initially.

An exception to the general principle of using combinations of drugs is treatment of advanced stage indolent lymphoma. Drugs that may be used as single agents for this condition include chlorambucil and fludarabine. The drugs may be used alone or in combination with radiotherapy. When radiotherapy is used alongside drug treatment it is usually delivered locally (involved-field radiotherapy) to deal with local bulky masses of lymphoma.

The most common drug combination (the protocol) used for aggressive NHL or for later stage indolent non-Hodgkin's lymphoma is known as CHOP. This uses the drugs cyclophosphamide, hydroxydaunorubicin (adriamycin), Oncovin (vincristine) and prednisolone. CHOP has been in use now for about 20 years. Although many other combinations of drugs have been tried CHOP continues to be the 'gold standard' for treatment of non-Hodgkin's lymphoma against which all other treatment options are measured. Recent studies suggest an improvement in outcome by combining CHOP with an antibody called rituximab (Mabthera™ or Rituxan™).

There are several innovative approaches to the treatment of non-Hodgkin's lymphoma, some of which are already in clinical trials and others of which

are still in the development stages. Monoclonal antibodies are very specific molecules, produced in the laboratory and targeted at a specific marker on the surface of the lymphoma cell. In some cases, the antibody may be linked to a drug or to a radioactive isotope that can then be delivered directly to the lymphoma cells. This offers a very specific way to attack the lymphoma cells with minimal or no impact on surrounding tissues. Monoclonal antibodies may be used alone in non-Hodgkin's lymphoma or in combination with standard chemotherapy drugs. A specific example of a monoclonal antibody is rituximab (Mabthera or Rituxan), which is directed against a specific molecule called CD-20, which is present on the surface of normal and malignant B lymphocytes. CD-20 is present in very large amounts on about 95% of follicular lymphoma cells. Rituximab is licensed for use as a single agent in the treatment of relapsed low-grade follicular lymphoma, where it has achieved response rates greater than 50%, durable remissions and minimal side-effects. It has also been shown to be active in a large number of other low-grade lymphomas. A number of current clinical studies are being carried out to determine the exact role of rituximab in treatment of non-Hodgkin's lymphoma. Among the questions being studied are whether monoclonal antibodies produce better results when used in combination with conventional chemotherapy.

Stem cell transplants tend to be reserved for patients whose disease does not respond to standard therapy or in whom the disease returns after an initial response. Studies are being carried out to establish the value of early transplants for high-grade NHL. Transplants from a matched donor are not widely used in the treatment of non-Hodgkin's lymphoma. Autologous transplants, in which a patient's stem cells are collected before they receive intensive therapy, are used more extensively in non-Hodgkin's lymphoma.

Treatment planning

The most important factors in planning treatment for non-Hodgkin's lymphoma are differentiation between low-grade (indolent) and high-grade

(aggressive) NHL and staging. Clinical features of the disease may provide indications of the grade and stage of the illness but these can only be confirmed by laboratory investigations. It is normal to wait until all laboratory results are available before commencing treatment. Any slight delay is offset by the advantage of planning the ideal treatment strategy.

Certain REAL sub-types of non-Hodgkin's lymphoma are treated differently from the others. The most important of these are lymphoblastic lymphoma, Burkitt's lymphoma and mantle cell lymphoma. Treatment of these special types is discussed separately at the end of the treatment section below.

Indolent (low-grade) non-Hodgkin's lymphoma

This group represents about 30% to 40% of all non-Hodgkin's lymphoma with the majority of cases being follicular lymphoma as defined by the REAL classification.

∴ Early (stages 1 and 2)

Very few patients will be in this category. Most patients with low-grade NHL have advanced (stage 3 or 4) disease at the time they are diagnosed. For this small group localised radiotherapy is potentially curative.

∴ Advanced (stages 3 and 4)

Most cases of indolent non-Hodgkin's lymphoma will be advanced at the time of diagnosis. If patients in this group do not have any symptoms at the time of diagnosis the evidence from clinical trials has shown there is no survival advantage from early treatment. When treatment is necessary the disease is usually responsive to both chemotherapy and radiotherapy but remissions are rarely long lasting. The most widely used treatment in the first instance for symptomatic non-Hodgkin's lymphoma is oral chlorambucil. This will achieve remission in as many as 75% of patients. The median overall survival is about 10 years. Some centres use a combination of cyclophosphamide, Oncovin

(vincristine) and prednisolone (VP or COP), but the overall results are similar to those with chlorambucil.

If the disease relapses it may do so as a further episode of indolent NHL or it may undergo transformation into an aggressive NHL. The treatment options for these two situations are discussed in the section on treatment of relapse.

MALT lymphoma

This form of the disease affects accumulations of lymphoid tissue within certain organs, particularly the stomach, salivary gland, lung and thyroid gland. MALT NHL of the stomach is associated with infection with a bacterium called *Helicobacter pylori* and may be cured by the use of antibiotics to eradicate the infection. Gastric MALT NHL not cleared by *Helicobacter pylori* eradication, or in organs other than the stomach, is treated in the same way as any other indolent non-Hodgkin's lymphoma.

Aggressive (intermediate/high-grade) non-Hodgkin's lymphoma

The majority of cases of aggressive NHL belong to the REAL category diffuse large B cell lymphoma (DLBCL). If it is responsive to chemotherapy and/or radiotherapy, it is potentially curable. The treatment of patients whose disease is resistant to standard therapy, or who experience a relapse, will depend on whether their condition responds to more intensive therapy. If it does they may be curable with high dose therapy followed by stem cell transplantation, if it does not they may be advised to consider novel therapies in a clinical trial, if one is available. It is not yet clear whether best survival is obtained by transplanting all eligible patients in first remission or by more conservative therapy with transplants reserved for relapsed patients.

✦ Early (stages 1 and 2)

Diagnosis in early-stage disease is much more common in aggressive NHL than for patients with indolent NHL. The rapid growth of affected lymph

nodes in aggressive NHL means patients are likely to attend their GP earlier and to be referred to a specialist promptly.

Early-stage aggressive NHL is typically treated with several courses of multi-drug chemotherapy (usually CHOP), followed by radiotherapy directed at the affected node(s). It has a good chance of achieving a cure with overall survival rates of over 80% reported in several studies. There is some evidence to suggest that combined modality treatment (radiotherapy plus chemotherapy) may improve survival but this is not yet resolved.

A potential benefit of combined radiotherapy and chemotherapy is that the intensity of each form of treatment can safely be reduced and this leads to reduced toxicity (side-effects) of treatment. Patients who do not respond to this approach or who relapse are treated with combination therapy. This is discussed in detail below as treatment of relapse.

⌘: **Advanced (stages 3 and 4)**

Patients with advanced aggressive NHL receive similar drugs to those used for early-stage disease but over a longer duration. Around 45% of patients will achieve a complete remission with CHOP. A proportion of these patients will achieve long-term disease-free survival and can thus be considered cured. As mentioned previously, results may be improved by combining the CHOP regime with rituximab. Patients who either fail to respond to treatment or who relapse are treated in a similar fashion. This is discussed below under treatment of relapse.

Treatment of relapse

⌘: **Indolent non-Hodgkin's lymphoma**

There are several treatment options for patients with relapsed indolent non-Hodgkin's lymphoma and clinical trials are seeking to find the ideal combination(s) of treatment for individual groups of patients. Some treatment options are based on single drugs while others use combinations of agents.

There are several different combinations which have been proposed for treatment of chemosensitive relapse. One of the most common of these is called CVP, which stands for cyclophosphamide, vincristine and prednisolone. A relatively new approach is the use of monoclonal antibody against a marker on the cell surface; the antibody is called rituximab. This drug is currently licensed in the UK for treatment of relapsed low-grade follicular lymphoma.

Relapse as aggressive non-Hodgkin's lymphoma

Development of aggressive NHL in a patient who has indolent NHL is sometimes referred to as transformation. Transformation of indolent NHL to aggressive NHL has a poor prognosis and is an indication for intensive therapy with chemotherapy such as CHOP possibly followed by an autologous stem cell transplant. In elderly patients or those whose medical condition precludes aggressive treatment, palliative care may be offered with relatively low dose chemotherapy directed at symptom control.

∴ Aggressive non-Hodgkin's lymphoma

A significant proportion of patients with aggressive NHL will either not respond to treatment or will relapse. For this reason, there has been considerable effort devoted to developing so-called 'salvage' therapies for this group. Typically, these involve the use of more powerful drug combinations in an attempt to achieve a remission. If the patient responds well to such high dose chemotherapy then high dose therapy followed by an autologous stem cell transplant may be curative. In patients who have a poor response, or no response, to intensive chemotherapy the focus is likely to be on palliative care. Such patients may be asked to consider taking part in a clinical trial to evaluate a novel therapeutic approach.

Lymphoblastic lymphoma

Lymphoblastic lymphoma is rare, making up about 2% of adult non-Hodgkin's lymphoma. This form of NHL occurs mainly in young adults with males being

more prone than females to this disease. The condition is very aggressive and is often treated with the same protocols as those used for adult acute lymphoblastic leukaemia (ALL).³ Nervous system involvement often occurs in this form of NHL and therefore CNS directed therapy is likely to be given. Most patients respond well initially but the long-term prognosis is poor with a high relapse rate. The prognosis for those who fail to respond to initial therapy is particularly bad. Many patients in this group will be offered high dose therapy with stem cell transplantation at some stage.

Burkitt's lymphoma

Burkitt's lymphoma is also rare, making up 2% to 5% of cases of NHL. It is an extremely aggressive tumour with a rapid rate of growth. It is usually very responsive to initial chemotherapy but relapses are common. Application of intensified therapy similar to that given for mature B cell ALL in this group has produced very promising results. It is important that patients should receive CNS directed therapy because of the high risk of nervous system involvement.

Mantle cell lymphoma

Mantle cell lymphoma makes up between 2% to 8% of NHL. It is more common in older patients (from middle age onwards). There is a male excess at all ages. This subtype of non-Hodgkin's lymphoma tends to have a poor prognosis with a median survival of two and a half to four years. Current clinical trials are studying the possible value of novel chemotherapy agents, monoclonal antibodies or high dose chemotherapy with stem cell transplantation.

³ A separate publication on adult acute lymphoblastic leukaemia is available from Leukaemia Research.

Stem cell transplantation⁴

A bone marrow transplant is one form of stem cell transplantation (SCT) but for many patients the source of stem cells is the circulating blood. A SCT may be either allogeneic (from a donor) or autologous (the patient's own stem cells). A stem cell transplant involves the use of very high dose chemotherapy (and possibly whole-body radiotherapy) to destroy the patient's bone marrow. The latter is termed myeloablation and immune suppression. The destroyed marrow and immune system must then be restored with the patient's own stem cells or, less frequently in non-Hodgkin's lymphoma, stem cells from a donor. The major hazard of this procedure is infection during the period when blood cell production is essentially absent. Improved supportive care, especially nursing, during this period has reduced the infection risk and significantly decreased transplant related mortality from 20% to 10% over the last 15 years.

Transplants from a matched donor are not widely used for patients with non-Hodgkin's lymphoma. Autologous transplants are less inherently risky than donor transplants and the risk of relapse is less severe compared with leukaemia because the bone marrow is usually not heavily contaminated with NHL cells. Relapse is much more likely to occur where laboratory tests show that there are large numbers of lymphoma cells contaminating the stem cell harvest.

The European Blood and Marrow Transplant Handbook recommendations for use of stem cell transplants in non-Hodgkin's lymphoma emphasise that, while autologous transplant has a place for selected patients, allogeneic transplantation is not widely used except in the context of clinical trials. The main indications for transplant are either patients who have relapsed from indolent or aggressive NHL and whose disease responds to salvage therapy or patients with subtypes of NHL known to respond poorly to standard therapy. The latter group includes patients with lymphoblastic lymphoma, mantle cell lymphoma and aggressive NHL which is resistant to initial chemotherapy.

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

Long-term effects of treatment

Many of the treatments employed for NHL are likely to impact on fertility and, in women, possibly on ovarian function. Male patients who are awaiting treatment should discuss possible options to protect fertility. If they are post-pubertal then they should be able to arrange for storage of sperm; this must be arranged before chemotherapy or radiotherapy is commenced.

Female patients have fewer options, at present, for protection or preservation of fertility. It may be possible to participate in a study of storage of ovarian tissue, although this is not yet a routine procedure comparable to sperm banking. Irradiation of the ovaries may cause ovarian failure leading to early menopause and a need for long-term hormone replacement therapy. Female patients should discuss the possible options in detail at the earliest stages of treatment planning.

The long-term effects of treatment depend on the exact treatments used. They will differ according to what, if any, radiotherapy was administered and whether any chemotherapy protocols were applied. Two particular issues related to radiotherapy are thyroid and breast cancer screening.

Breast cancer screening is particularly important for women who have received radiotherapy involving the breasts. It may be advisable for males to consider routine screening if there is evidence of a genetic predisposition towards breast cancer in the family.

Long-term survival of patients with non-Hodgkin's lymphoma has improved dramatically although the overall outlook is not as good as that for the less common form of lymphoma, Hodgkin's lymphoma. Most patients with indolent NHL are quite old and the standard treatment they are offered is relatively mild. This means that long-term consequences are primarily an issue for patients treated for aggressive non-Hodgkin's lymphoma, especially when they are treated at a younger age with a long potential life span.

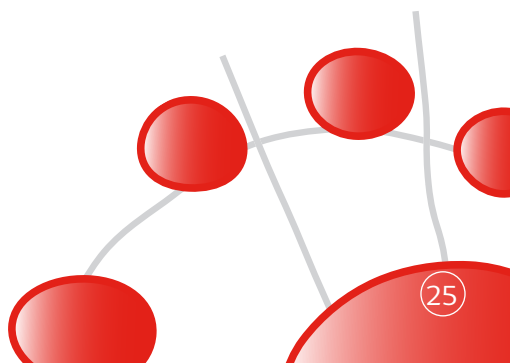
When patients have received localised radiotherapy, the long-term effects will depend primarily on which organs have been exposed to radiation.

For example, radiotherapy to the neck may cause thyroid dysfunction and if it gives rise to scar tissue it may lead to difficulty with swallowing.

In a similar way the side-effects associated with chemotherapy will depend in part on which drugs have been used and also on what dosages have been given and over how many courses. CHOP chemotherapy, for example, includes prednisolone which may lead to an increased risk of developing diabetes.

It is beyond the scope of this booklet to give a detailed account of the possible side-effects which may follow treatment for non-Hodgkin's lymphoma.

Patients should ensure that they discuss these matters in detail with the medical and nursing staff both during their treatment and again before they complete their therapy.



Follow-up

The main reasons for follow-up of patients treated for non-Hodgkin's lymphoma are detection of relapse and detection of treatment complications. High proportions of relapses are first detected as a result of patients self-referring when they feel that something is 'not right'. Similarly, patients with indolent NHL which transforms to aggressive NHL will frequently detect signs of progression of their illness between scheduled follow-up visits. Patients should not hesitate to contact their specialist either directly or through their GP if they believe that there has been a change in the behaviour of their illness.



Prognosis

International Prognostic Index

The International Prognostic Index (IPI) was developed as a refinement of non-Hodgkin's lymphoma staging. It is primarily intended for assessment of patients with aggressive NHL. There is much less variation in the prognosis for indolent lymphomas. The median survival of patients with indolent lymphoma is around ten years.

The single most valuable use of the IPI is in making treatment recommendations. If it is clear that a patient has a very good chance of responding well to standard therapy then there is no reason to undergo the risks of aggressive therapy. If, on the other hand, a patient clearly has a high-risk of failing standard therapy then aggressive therapy can be offered early with a better chance of success. An additional benefit is in the design of clinical trials. The IPI can provide trial organisers with a valuable way of ensuring a fair comparison between different treatments. It would obviously not be valid to compare two treatments based on a trial in which all high-risk patients were in one arm of the trial; and all low-risk patients in the other arm. Details of the IPI are given as Appendix B.

Summary

Non-Hodgkin's lymphoma is a term which encompasses a varied group of cancers all of which arise within the lymphoid tissues. They can be divided based on their biological features (morphology, immunology, and cytogenetics) and on their clinical behaviour (indolent, aggressive). Within each of these classifications, the conditions can be staged according to the extent of spread from the initial focus of the condition.

The main groupings can be summarised as:

Type/Stage	Frequency	Prognosis
Indolent, early-stage	Rare	Potentially curable with radiotherapy
Indolent, late-stage	Common	Rarely curable with standard treatment
Aggressive, early-stage	Common	Potentially curable with chemotherapy and radiotherapy combined
Aggressive, late-stage	Common	Potentially curable with chemotherapy

The standard treatments used for non-Hodgkin's lymphoma are localised radiotherapy for early-stage disease and chemotherapy with CHOP. Autologous stem cell transplants are used for selected groups of patients. Transplants from matched donors are rarely used for NHL. Developments in treatment include the use of several newer drugs as single agents for early-stage disease and various methods of immunotherapy.

The prognosis for non-Hodgkin's lymphoma depends on the type and stage of disease at the time of diagnosis.

Appendix A

The Ann Arbor staging

As with many other cancers, NHL is categorised on the extent of spread of the cancer. The Ann Arbor system is the most widely used system for classifying lymphoma.

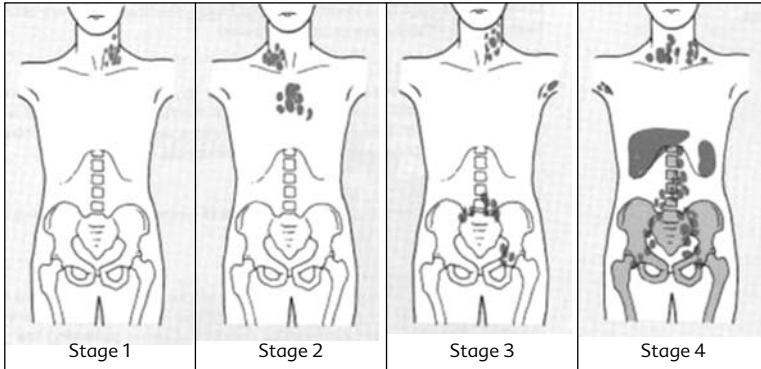
The Ann Arbor Staging groups are as follows:

Stage Features

- 1 🌀 NHL is limited to one lymph node group (e.g. neck, underarm, groin, etc.) above or below the diaphragm⁵, or the tumour is in an organ or site other than the lymph nodes (extranodal) but has not spread to other organs or lymph nodes.
- 2 🌀 NHL is limited to two lymph node groups on the same side of the diaphragm or is limited to one extranodal organ and has spread to one or more lymph node groups on the same side of the diaphragm.
- 3 🌀 NHL is in two lymph node groups, with/without partial involvement of an extranodal organ or site above and below the diaphragm.
- 4 🌀 NHL is extensive (diffuse) in one organ or site, with/without disease in distant lymph nodes.

After an NHL patient has been assessed for disease stage additional terms may be used to fully define a particular case of NHL.

⁵ The diaphragm is the sheet of muscle that separates the chest from the abdomen.



(Reprinted from *Atlas of Clinical Haematology 3/e*, Hoffbrand, Pettit, p137, 2000, by permission of the publisher Mosby).

✚ **Additional terms** (which may apply to any stage of NHL):

- A – absence of symptoms
- B – presence of symptoms
 - ✚ fever (greater than 38⁰C)
 - ✚ drenching night sweats
 - ✚ unexplained weight loss of 10% or more within the last six months
- E – involvement of a single extranodal (other than the lymph nodes) site that directly adjoins or is next to the known nodal group
- X – presence of ‘bulky’ disease, that is, any affected node whose greatest dimension is more than 10 centimeters in size, and/or a widening of the mediastinum (middle chest) by more than one-third of the width of the chest.

The stage of the disease as defined by this system is one of the factors included in a system called the International Prognostic Index (IPI). The index is described in Appendix B. The IPI is used in planning treatment and is particularly important for patients who may enter clinical trials. The IPI gives a more complete indication of an individual patient’s likely prognosis and is therefore of value in ensuring that groups of patients included in comparative studies are genuinely comparable.

It is usual to apply both a clinical stage and a pathological stage.

- CS — clinical stage as obtained by doctor's examinations and tests.
- PS — pathological stage as obtained by exploratory laparotomy⁶ (surgery performed through an abdominal incision) with splenectomy (surgical removal of the spleen).

∴ **Additional terms** (used in pathological staging of NHL):

- **N+ or N-** Lymph node positive or negative by biopsy,
- **H+ or H-** Liver positive or negative by biopsy,
- **S+ or S-** Spleen positive or negative following splenectomy,
- **L+ or L-** Lung positive or negative by biopsy,
- **M+ or M-** Bone marrow positive or negative by biopsy or smear,
- **P+ or P-** Pleura or pleural fluid positive or negative by biopsy or by cytological examination,
- **O+ or O-** Bone positive or negative by biopsy,
- **D+ or D-** Skin positive or negative by biopsy.

An example would be — CS IIA, PS III S+N+H-M- Clinical stage IIA, three lymph node regions involved Pathological stage III with spleen positive, abdominal lymph node positive, liver biopsy negative, bone marrow biopsy negative.

⁶ Although staging laparotomy is not carried out routinely in NHL patients it remains as part of the official Ann Arbour definitions.

Appendix B

International Prognostic Index

The IPI predicts the probability of disease-free and overall survival based on the following factors, each of which scores one point on the IPI index:

- Age greater than 60 years
- Stage of disease (Stage III or greater)
- Poor performance status (general health)
- More than one extranodal site(s) (sites other than the lymph nodes)
- Presence of an elevated level of lactate dehydrogenase (LDH)

International prognostic index scoring versus survival:

IPI score	5-year overall survival
0-1	73%
2	51%
3	43%
4 or 5	26%

Age adjusted IPI scoring versus survival:

IPI score	5-year overall survival
0	83%
1	69%
2	46%
3	32%

Age is such a strong independent factor affecting prognosis that a modified version of the IPI may be used for patients younger than 60 years old. This uses only stage, LDH level and number of extranodal sites.

It is important to remember that statistical indices like these are based on how a group of people may do. The data is valuable in guiding treatment choices and in giving patients some indications of the likely progression of their condition. Patients should guard against becoming dispirited (or unduly complacent) based solely on their scoring on the index.

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:

--	--	--	--	--	--

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.

The following patient information booklets are available free of charge from Leukaemia Research. You can download them from our website or request copies by phone or post (see form inside):

Leukaemia and Related Diseases

Acute Promyelocytic Leukaemia (APL)

Adult Acute Lymphoblastic Leukaemia (ALL)

Adult Acute Myeloid Leukaemia (AML)

Aplastic Anaemia (AA)

Bone Marrow and Stem Cell Transplantation (BMT)

Chemotherapy – what do I need to know?

Childhood Acute Lymphoblastic Leukaemia (ALL)

Childhood Acute Myeloid Leukaemia (AML)

Chronic Lymphocytic Leukaemia (CLL)

Chronic Myeloid Leukaemia (CML)

Clinical Trials

Complementary and alternative medicine (CAM)

Donating stem cells – what's involved?

Donor Lymphocyte Infusion (DLI) – what's involved?

Hodgkin's Lymphoma (HL)

Jack's Diary: an illustrated children's book to help young patients understand and deal with blood cancers, treatment and life changes

Multiple Myeloma (MM)

Non-Hodgkin's Lymphoma (NHL)

Supportive care

The Myelodysplastic Syndromes (MDS)

The Myeloproliferative Disorders (MPD)

The Seven Steps – Blood & Bone Marrow Transplantation

Treatment Decisions

Young Adults with a blood cancer – what do I need to know?

Leaflets on a range of associated blood disorders are also available

Leukaemia Research, 43 Great Ormond Street, London, WC1N 3JJ

T: 020 7405 0101 • F: 020 7405 3139 • E: info@lrf.org.uk