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CLINICAL REVIEW

# Acute leukaemia in children: diagnosis and management

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Acute leukaemia is the commonest malignancy of childhood. In the United Kingdom, one in 2 000 children develop the disorder, with around 450 new cases being diagnosed annually.[1] However, most general practitioners will see a case of childhood leukaemia only once or twice in their careers[2] and, since management generally takes place in tertiary referral centres, non-specialist paediatricians will encounter relatively few patients.

Compared with the 1970s, the outcome today for children with acute leukaemia has improved dramatically. Numerous high quality randomised controlled trials have shown that over 85% of children can now be cured.[3 4] Goals for the future should focus on keeping treatment and side effects to a minimum for patients at low risk of recurrent disease, and improving the outcome for the small proportion of children at high risk of relapse.[5]

In this review, we summarise current knowledge about the presentation, diagnosis, and optimum management of children with acute leukaemia. We also suggest strategies for early diagnosis of the disease in primary care, which should minimise avoidable complications and allow for early supportive care.

## What causes acute leukaemia?

Acute leukaemia arises from genetic mutations in blood progenitor cells. These mutations generate both an uncontrollable capacity for self-renewal and the developmental arrest of the progenitor cells at a particular point in their differentiation.[6] The body is therefore overwhelmed by immature cells or blasts that infiltrate the bone marrow, reticulo-endothelial system, and other extra-medullary sites. Eighty per cent of children with acute leukaemia have acute lymphoblastic leukaemia; most of the remainder have acute myeloid leukaemia.[7] Chronic leukaemia in children is extremely rare.[8]

Usually, newly diagnosed children have been previously well, with no identifiable environmental risk factors for leukaemia such as exposure to ionising radiation. In our experience, many parents therefore crave an explanation for their child's illness, asking whether it is their fault or "something in the family," particularly if an adult family member has died of leukaemia. However, the predominant leukaemia of early childhood, acute lymphoblastic leukaemia, is not inherited and is distinct from the leukaemias more commonly seen in adults (acute myeloid leukaemia, chronic myeloid leukaemia, and chronic lymphocytic leukaemia).[9] Fewer than 5% of all cases are associated with inherited predisposing genetic syndromes such as Down's syndrome, in which there is a 20-fold increase in the risk of developing leukaemia.[10]

Acute lymphoblastic leukaemia probably arises from the interaction of environmental risk factors with a pre-existing genetic susceptibility. It is now known that a pre-natal mutation leads to the production of a pre-leukaemic clone which expands postnatally. A second mutation is required for overt disease to develop, most commonly between the ages of 2 and 5 years. What causes this second mutation is contentious. One hypothesis, that of "population mixing," suggests that when genetically susceptible children move into new, rapidly expanding towns, their immune response to unfamiliar local infections is abnormal, causing leukaemia to develop.[11] Alternatively, the "delayed infection hypothesis" suggests that susceptible children from excessively hygienic environments are protected from normal childhood infections, causing an aberrant immune response to later infections which triggers leukaemia.[12]

### SOURCES AND SELECTION CRITERIA

We searched Medline for articles between January 1998 and December 2008 relating to the diagnosis and management of childhood acute leukaemia. Key terms used included "acute", "leukaemia", "paediatric", "diagnosis", "presentation", "management", "treatment", and "therapy". We also searched the Cochrane Library for all entries under "childhood cancer". From these searches, we identified randomised controlled trials, meta-analyses, and reviews. In addition, we drew from our personal archives of references from recognised authorities in this field.

## How does acute leukaemia present in children?

Presentations of acute leukaemia relate to three main pathological processes: bone marrow failure due to extensive infiltration by blast cells, infiltration of other tissues by blasts, and systemic effects of cytokines released by tumour cells.

Leukaemia may be strongly suspected when a child presents with classical signs of anaemia, thrombocytopenia, and pronounced hepatosplenomegaly or lymphadenopathy. However, as one high quality systematic review recently highlighted, the presenting symptoms are often vague and non-specific, mimicking those of common, self-limiting childhood illnesses.[13] In our experience, parents frequently decide to consult their GP simply because their child, in some intangible way, "is just not right," perhaps with pallor, lethargy, or malaise.

At present, there is no definitive evidence base enabling doctors, particularly GPs, to discriminate with confidence between those children for whom wait and see is appropriate practice, those for whom phlebotomy is advisable, and those who should be referred urgently to the emergency department. We failed to find any studies conducted in primary care that evaluated the positive and negative predictive value of signs and symptoms for the diagnosis of acute leukaemia, although such research is currently ongoing. Table 1, based on a wide number of case reports, review articles and our own departmental experience, outlines the range of potential presentations.[13-15] We encourage inclusion of acute leukaemia in the differential diagnosis for all children presenting with such signs and symptoms, particularly when the parent insists there is something amiss with their child.

**Table 1 | Presentations of acute leukaemia in children**

| Underlying pathophysiology | Symptoms and signs |
|---|---|
| Systemic effects of cytokines | Malaise<br>Fatigue<br>Nausea<br>Fever |
| Bone marrow infiltration | |
| Anaemia | Pallor<br>Lethargy<br>Shortness of breath<br>Dizziness<br>Palpitations<br>Reduced exercise tolerance |
| Neutropenia | Fever<br>Infection in general<br>Recurrent infection<br>Unusual infections, eg oral candida |
| Thrombocytopenia | Bruising<br>Petechiae<br>Epistaxis |
| Reticuloendothelial infiltration | Hepatosplenomegaly<br>Lymphadenopathy<br>Expiratory wheeze secondary to mediastinal mass (due to lymphadenopathy, or thymic infiltration or expansion). |
| Other organ infiltration | |
| CNS | Headaches<br>Vomiting<br>Cranial nerve palsies<br>Convulsions |
| Testes | Testicular enlargement |
| Leucostasis | Headache<br>Stroke<br>Shortness of breath<br>Heart failure |

Leucostasis=increased plasma viscosity secondary to extremely high white cell counts, typically $>100\times10^9$/l

### Critical points in the management of children with acute leukaemia

- Early referral to specialist tertiary referral centre to provide knowledge and support to families, and to manage major complications during the first few weeks of therapy
- Urgent admission blood tests (full blood count, electrolytes, liver function tests, a coagulation screen) and chest x-ray to exclude life threatening complications such as a mediastinal mass which may compromise the airway
- Rapid institution of early supportive care: securing airway; intravenous fluids; blood products; broad spectrum antibiotics; correction of electrolyte abnormalities and hyperuricaemia or hyperphosphataemia; renal dialysis or haemofiltration
- Once patient is stable, bone marrow aspirate for precise diagnosis, categorisation of leukaemic subtype and risk stratification
- Definitive treatment and longer term plan for subsequent phases of treatment (for acute lymphoblastic leukaemia, 2-3 years of remission-induction, consolidation and maintenance therapy; for acute myeloid leukaemia, a maximum of 6 months chemotherapy)
- Allogenic bone marrow transplant is reserved for patients at especially high risk of relapse
- Management of short term adverse effects of treatment (particularly infection, but also thrombosis and avascular necrosis of bone).
- Psychosocial aspects of caring for child and family
- Management of long term adverse effects of treatment (endocrine, cardiac, respiratory, growth, fertility, neurological, and psychological)

Occasionally, acute leukaemia presents with a life threatening complication requiring immediate hospital management.[16] Our experience suggests that delay in such instances may be fatal, although there is no clear evidence on this issue. We recommend that if GPs are concerned about any of these complications (table 2), they should not wait for phlebotomy and subsequent results, but rather refer immediately to the emergency department or call the on-duty haematology registrar.

## How is acute leukaemia diagnosed?

When leukaemia is first suspected, the most important initial investigations are a full blood count and blood film. These quick and inexpensive tests are highly sensitive, permitting accurate diagnosis of leukaemia in most patients. Furthermore, if both are within normal ranges, acute leukaemia can be ruled out with a fair degree of confidence.

Typically, the full blood count will demonstrate pancytopenia secondary to bone marrow infiltration by blasts. Although the patient is likely to be neutropenic, millions of circulating blasts tend dramatically to elevate the overall white cell count, with blasts clearly evident on the film.

**Table 2 | Life threatening early complications of acute leukaemia**

| Mechanism | Complication |
|---|---|
| Neutropenia | Infection: overwhelming, usually Gram-negative sepsis, with or without disseminated intravascular coagulation |
| Thrombocytopenia | Bleeding: stroke, pulmonary haemorrhage, gastrointestinal haemorrhage |
| Electrolyte imbalance | Hyperkalaemia and hyperphosphataemia secondary to blast cell lysis<br>Acute renal failure secondary to hyperuricaemic nephropathy |
| Reticuloendothelial infiltration | Acute airway obstruction secondary to mediastinal thymic mass |
| Leucostasis | Stroke, acute pulmonary oedema, heart failure |

Leucostasis=increased plasma viscosity secondary to extremely high white cell counts, typically >$100\times10^9$/l

Sometimes, however, the white cell count may be only slightly raised and, if blasts remain sequestered within the bone marrow, it can even be lower than normal. Nor are clearly identifiable blasts always present. In these cases, the only clue that there is a serious underlying problem may be a few atypical cells in the blood film or the presence of leukoerythroblastic features. In our experience, any abnormal count or film, in conjunction with a suspicious clinical picture, should prompt urgent referral to a specialist centre for further investigation or, as a minimum, telephone discussion with an on-duty haematologist.

## How is a child with acute leukaemia managed?

After urgent investigations and supportive care (box), the tertiary referral centre will aspirate bone marrow, usually under general anaesthetic in children, to obtain a definitive diagnosis of acute leukaemia. The aspirate provides morphological, immunological, and genetic information which, alongside clinical factors such as the child's age, sex, presenting white cell count, and initial response to chemotherapy, enables patients to be categorised according to their risk of subsequent relapse.

Simple light microscopy will usually allow classification of the diagnosis as acute lymphoblastic leukaemia or acute myeloid leukaemia. Immunophenotyping using flow cytometry identifies patterns of cell surface antigens associated with particular subtypes of acute lymphoblastic leukaemia or acute myeloid leukaemia. For example, the majority of children with acute lymphoblastic leukaemia have the precursor B cell type, which is positive for the CD10 and CD19 cell surface markers. Around 15% of children with acute lymphoblastic leukaemia will have the T cell (CD3 positive) phenotype.[3] These children tend to be male and older, with more frequent central nervous system involvement and bulkier disease, including mediastinal masses. Cytogenetic analysis identifies specific genetic abnormalities, such as the TEL/AML1 or BCR-ABL gene fusions, which correlate with a good or poor prognosis, respectively.[17]

Patients are categorised into low, standard, or high risk groups, with treatment determined, as far as possible, by risk status. For example, in both acute lymphoblastic leukaemia and acute myeloid leukaemia, very intensive treatment such as allogeneic bone marrow transplant is reserved for very highrisk cases (<10% of cases), protecting standard risk patients from unnecessary toxic side effects.[18] Bespoke therapy has been further refined over the last 10 years by PCR- based techniques for the assessment of "minimal residual disease." These techniques are over a hundred times more sensitive than morphological methods at identifying residual leukaemia (they can pick out one cell in 100 000), enabling clinicians to predict future, as yet subclinical, relapse and plan treatment accordingly.[19]

### Acute lymphoblastic leukaemia

In the UK, girls with acute lymphoblastic leukaemia currently receive two years of treatment and boys three years, because boys have an increased risk of relapse which, to some extent, can be offset by a longer period of treatment. Since the 1960s, a strategy of "total therapy" has applied: systemic therapy targets the primary disease site (the bone marrow), while intrathecal therapy is directed at leukaemic cells within the central nervous system which would otherwise evade chemotherapy.

**Table 3 | Phases of treatment for acute lymphoblastic leukaemia**

| Treatment phase | Goal | How goal is realised | Duration |
|---|---|---|---|
| Remission-induction | Rapid eradication of at least 99% of the initial leukaemic cell burden, leading to prompt restoration of normal haematopoiesis. | In most standard risk cases, IV administration of a 3 drug induction combination, typically dexamethasone, vincristine, and asparaginase; in high and very high risk cases, daunorubicin is added.<br>Early assessment of marrow response: <25% leukaemic blasts in marrow is good; >25% (slow early response) requires intensification of therapy. Clinical remission (<5% leukaemic cells remaining) occurs in 96-99% of children by day 29. Early marrow response may be supplanted by day 29 assessment of minimal residual disease | 4-6 weeks |
| Consolidation and therapy directed at central nervous system | Eradication of residual, drug-resistant leukaemic cells, reducing the risk of relapse. Reduction in risk of CNS relapse. | Stratified by risk of relapse. Slow early responders receive augmented therapy<br>Weekly intrathecal methotrexate for 3 doses in this phase, and then subsequently every 3 months throughout continuing therapy | 4-12 weeks |
| Intensification | Reduction in relapse risk. | Reinduction and reconsolidation mimicking the early phases of induction and consolidation | 8-12 weeks |
| Continuation therapy | | Daily oral methotrexate and weekly oral methotrexate with monthly vincristine and dexamethasone pulses. Doses titrated to neutrophil and platelet counts, indicating degree of marrow toxicity. 2-3 years of therapy, most of which is continuation | 2-3 years |
| Allogeneic bone marrow transplant | Elimination of residual leukaemic cells in highrisk subtypes refractory to chemotherapy. | Myeloablation, often using total body irradiation and cyclophosphamide, followed by peripheral intravenous administration of allogeneic haemopoietic stem cells. Substantial morbidity and mortality owing to overwhelming infection and graft versus host disease in particular | |

### A patient and their family's perspective

AH, aged 13, was diagnosed with acute lymphocytic leukaemia three years ago. After a bone marrow transplant, she remains in remission.

**AH**

I first felt ill when my neck became really swollen and the joints in my legs seemed really heavy. I thought it was growing pains but it wasn't, it was cancer, and so we went to the clinic. I didn't really know what was happening but my Mum was really crying so I guessed it was something bad.

I remember the doctors saying I would lose my hair and I was a bit freaked out. I didn't really know how that would happen: would I just wake up and find my hair lying on the pillow? But it came out gradually—it kept falling into my food so my Mum cut it short and then, a couple of days later, she shaved it.

I feel like I've gained a whole bunch of things. Before, I didn't know about leukaemia, I didn't even know it existed, but now I'm braver. If I have to have an injection now I get a bit teary but sometimes I don't cry. Leukaemia's not the worst thing possible—there are worse things—but it's taught me to be grateful because people who don't have it are so lucky.

**AH's father**

The first thing I noticed was that she was pale and she'd get tired very easily. One morning she woke up so swollen in her neck you couldn't recognise her. We went to the doctor right away and he said it could be leukaemia. We were in a state of shock. You don't want to believe it, you don't want to think this is happening to your kid. It's just a whirlwind of emotions: how serious is it? Is she going to be okay? I didn't have a clue about leukaemia. I just knew it was cancer and when someone mentions that you obviously think the worst.

She was very scared. The pain was what scared her the most. The chemo started straight away and we were amazed at the results we got instantly. The swelling went down, the pain in her bones went away, and you could see her face again.

Now, dealing with the anxiety of "what if it comes back" is really scary, especially whenever she gets pale. You can't help thinking about it. We just kind of deal with it on a day by day basis. There is always that fear.

Typically, treatment comprises four phases of chemotherapy (table 3). Most children have central venous catheters, such as Hickman lines, inserted after the first month of treatment. Much of the continuation phase of treatment is carried out locally, and children are able to pursue a relatively healthy social and academic life. Hair grows back once the intensive phase of treatment is over.

High quality randomised control trial data spanning the last four decades demonstrate a steady increase in the proportion of patients being cured and have also facilitated significant reductions in therapy, leading to fewer long term treatment related complications by demonstrating that similar outcomes can be achieved with less therapy.[3 20] For example, most patients no longer receive any cranial radiotherapy whereas in the 1980s and 1990s all patients received it.

### Acute myeloid leukaemia

All children with acute myeloid leukaemia in the UK are treated with four courses of chemotherapy at roughly monthly intervals. There is no maintenance therapy afterwards, so most will have completed therapy within 6 months of diagnosis.

In the early 1980s, the outcome for acute myeloid leukaemia was poor with relapse-free survival rates at 5 years of just 18%. However, the most recent trial by the UK Medical Research Council showed a 5-year overall survival of 66%, with an event-free survival of 56%.[21] Today, patients with low risk cytogenetic abnormalities are identified at diagnosis, and have better prospects of long-term cure than patients with other abnormalities. Patients with adverse cytogenetic features or a poor response to therapy do badly even with the use of allogeneic bone marrow transplant, and fewer than 20% are cured.

## What are the key complications of treatment for acute leukaemia?

The longer term side effects of the commonly used chemotherapeutic agents range from peripheral neuropathy (vincristine) and cardiotoxicity (doxorubicin) to decreased fertility (cyclophosphamide) and hepatotoxicity (cytarabine).[13] However, most children will have few, if any, long term complications of therapy, especially now that the use of cranial radiotherapy has been minimised.

By far the most important acute complication is neutropenic sepsis which, as with meningococcal sepsis, can rapidly trigger overwhelming multi-organ failure. A delay of even an hour or two in prescribing appropriate broad spectrum antibiotics (guided by local protocols) may impair the child's chances of survival.[22] Before leaving the tertiary care centre, parents are educated in the risks of subsequent fever in their child and the urgent need to visit the emergency department if, for example, they take one temperature reading over 38.5°C or two over 38.0°C. Typically, tertiary referral centres also supply parents with written guidelines about when to contact primary and secondary

### Tips for non-specialists

- Include acute leukaemia in the differential for any child presenting with bone pain, atypical wheeze, bruising, or petechiae.
- Consider having a lower threshold for doing a full blood count in any child with unexplained malaise, fatigue, or pallor.
- Not all children with acute leukaemia present with the obvious signs of anaemia, bleeding, and infection.
- Absence of a very high white cell count, hepatosplenomegaly, and lymphadenopathy does not rule out acute leukaemia.

## SUMMARY POINTS

Presentation of acute leukaemia can be non-specific, and not always have the classic signs and symptoms of anaemia, bruising, bleeding, hepatosplenomegaly, and lymphadenopathy.

Diagnosis can be difficult, and delays can contribute to additional, sometimes life threatening problems during the period of initial treatment.

Relatively simple, inexpensive tests—a full blood count and examination of the blood film—will diagnose acute leukaemia in most cases.

Overall survival has risen from less than 5% in the 1960s to over 85% today.

physicians, and secondary physicians with written protocols for how to manage complications.

Parents frequently worry about travel abroad and routine immunisations. A comprehensive review of trial evidence and expert opinion advises that no routine immunisations should be given while the child is on therapy or for 6 months afterwards. The review outlines recommended schedules for subsequent immunisation. Unless it is particularly frequent or extensive, foreign travel is considered safe.[23]

### Where should research be directed next?

- The aetiology of acute leukaemia, particularly gene-environment interactions
- Refined selection, on the basis of cytogenetic and molecular data, of patients at either very low or very high risk of relapse
- Novel immunotherapeutic agents that target specific molecular defects such as gene fusions.

In the future, standard combination chemotherapy protocols might be tailored to an individual's unique genetic profile; this approach, together with novel molecular agents directed at leukaemia specific mutations, would continue with the current goals of minimising treatment toxicity for patients at low risk of relapse while improving the outlook for patients at high risk.

### Additional educational resources

Children's Cancer and Leukaemia Group (www.cclg.org.uk)—National professional body responsible for the organisation of treatment and management of children in the UK. Coordinates national and international clinical trials, and provides information for clinicians, patients, and families.

Institute for Cancer Research (www.icr.ac.uk)—Conducts independent research into the causes, prevention, diagnosis, and methods of treatment of all cancer, including paediatric leukaemias.

Leukaemia Research Fund (www.lrf.org.uk)—Only charity in the UK dedicated exclusively to researching haematological malignancies, including paediatric.

Foundation for Children with Leukaemia (www.leukaemia.org)—Campaigning charity that funds research into causes and treatments, and supports families through welfare programmes.

Cancer and Leukaemia in Childhood Sargent (www.clicsargent.org.uk)—Offers practical support and information to families by providing specialist nurses, play specialists, family support, patient information, grants and telephone helpline.

Cancerbackup (www.cancerbackup.org.uk)—Recently merged with Macmillan Cancer Support. Offers cancer information, practical advice and support to cancer patients and their families through online publications, telephone helpline, specialist nurses, etc.

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