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Fifteen-minute consultation: Initial management of suspected acute leukaemia by non-specialists

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ABSTRACT

Leukaemia is the most common cancer of childhood. Most children with a new diagnosis of leukaemia are clinically stable at initial presentation. However, there are a number of life-threatening complications that have to be considered and monitored for. These complications include sepsis, tumour lysis syndrome, mediastinal masses, bleeding and pain. The aim of this article is to equip the general paediatrician with a framework for managing children with suspected leukaemia, prior to transfer to the primary treatment centre. The presentation, diagnosis and definitive treatment of acute leukaemia is not in the remit of this article.

INTRODUCTION

All paediatricians will at some point care for a child who presents with suspected leukaemia. A typical-sized district general hospital (DGH) can expect approximately three children to be diagnosed with leukaemia each year, with around 420 new cases diagnosed annually in England.¹

INVESTIGATIONS

While most children presenting with a new diagnosis of acute leukaemia remain clinically stable, occasionally children can become critically unwell. Early death in leukaemia is rare, although young age, particularly those under 2 years, high white cell count (more than 100×10^9 cells/L) and acute myeloid leukaemia (AML) are established risk factors.

It is important to discuss suspected cases of new leukaemia with the primary treatment centre (PTC) early while arranging investigations (table 1) and starting appropriate treatment (table 2). The overall aim of the initial management is to anticipate and, where required, manage complications prior to transfer.

It is useful to send a stained blood film and an additional EDTA sample to the PTC either before transfer or along with the child. Early availability of these samples at the PTC will greatly facilitate the diagnostic work-up, allowing blood film microscopy and flow cytometric analysis of peripheral blood. In the past, it was important to send a thiopurine methyltransferase (TPMT) level before red cell transfusion to predict the child's ability to metabolise thiopurine drugs in order to determine dosing of 6-mercaptopurine. However, TPMT enzyme levels have now been superseded by testing for the TPMT genotype, which is not affected by transfusion and will be arranged by the PTC.

Some PTCs may also request testing for glucose-6-phosphate dehydrogenase deficiency given the risk of precipitating a crisis in undiagnosed children if rasburi-case is administered.

COMPLICATIONS AND MANAGEMENT Infection

As fewer children die from their disease, infection has become one of the leading causes of death in children with leukaemia. Sepsis was responsible for over 30% of all deaths in children in the most recently completed UK childhood ALL trial, UKALL 2003, and resulted in almost as many deaths as acute lymphoblastic leukaemia itself.^{2,3}

At diagnosis, children with acute leukaemia are immunosuppressed despite not having started chemotherapy, due to a combination of bone marrow infiltration and other factors that interfere with immune cellular function. Thus, children with suspected leukaemia should be managed as per neutropaenic sepsis guidelines, irrespective of their neutrophil count. If there is any history of fever or other indicators of infection, take blood cultures and start intravenous antibiotics



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Table 1 Initial mandatory investigations

Test	Indication
Chest X-ray	To identify a mediastinal mass, consolidation due to infection or alveolar infiltrates suggestive of leucostasis.
Serial full blood counts	Assessment of white cell count and rate of change, anaemia and thrombocytopenia.
Serial urea, electrolytes, creatinine, bone profile and uric acid	Tumour lysis syndrome is characterised by hyperuricaemia hyperphosphataemia, hyperkalaemia and hypocalcaemia leading to renal injury.
Blood cultures (if indicated)	Prior to starting intravenous antibiotics, blood cultures should be taken.
Group and save	In anticipation of potential need for blood products
Clotting (prothrombin time, activated partial thromboplastin time and fibrinogen)	Disseminated intravascular coagulation is occasionally seen in association with acute leukaemia.
Blood film	Can usually be examined by the on-call haematologist at the referring hospital, with a second film made and sent with the child to the PTC.
Additional EDTA sample	Peripheral blood can be sent to the PTC for immunophenotyping, which may be sufficient to confirm or refute the diagnosis of leukaemia.
Viral serology	Pretransfusion viral serological tests (especially VZV) are required for every child with a new diagnosis of cancer. Typically a virology screen includes VZV, HSV1, HSV2, EBV, measles, hepatitis B and hepatitis C.

PTC, primary treatment centre.

according to local policies. If there is clinical evidence of sepsis, manage this as you would in any child, aggressively within ‘the golden hour’.⁴

Tumour lysis syndrome (TLS)

TLS is a metabolic disturbance resulting from the breakdown of tumour cells. Cellular lysis causes the release and degradation of intracellular contents including nucleic acids, which have the potential to overwhelm the body’s normal homeostatic mechanisms.⁵ The resulting biochemical abnormalities include hyperuricaemia, hyperkalaemia and hyperphosphataemia with secondary hypocalcaemia. Uric acid precipitates within renal tubules; phosphate crystallises with calcium within soft tissues, including the kidney. Together these can result in acute kidney injury, reducing the body’s ability to excrete electrolytes, which sets up a spiral of worsening metabolic derangement and kidney failure.

It therefore follows that children at greater risk of TLS are those with a large volume of disease. These are children with a high white cell count (more than

50×10^9 cells/L) or ‘bulky’ disease such as significant hepatosplenomegaly, lymphadenopathy or a mediastinal mass. In addition, pre-existing impaired renal function puts children at higher risk of TLS. Although TLS is most frequently seen following administration of steroids and chemotherapy agents, it can occur spontaneously.

Management of TLS is largely anticipatory to prevent its development. In acute leukaemia, some children with low count disease and without bulky disease can be managed with maintenance fluids, which can be oral or intravenous. Others at higher risk will require hyperhydration even prior to starting chemotherapy, with intravenous fluids of at least 2.5 L/m²/day.⁶ With the guidance of the PTC, the fluid rate may be increased if there is any evidence or significant risk of TLS. Potassium should not be added to fluids due to the risk of hyperkalaemia, even if potassium levels are very low. Children should be monitored for fluid overload, particularly children with severe anaemia and infants. In addition to records of fluid input and output, daily

Table 2 Management points to consider

Intervention	Indications
Oxygen	Hypoxia and/or respiratory distress that might indicate severe anaemia, infection, leucostasis within the lung vasculature or a mediastinal mass.
Antibiotics	Broad-spectrum antibiotics following local guidelines for neutropaenic sepsis should be started if there are any concerns regarding infection irrespective of neutrophil count.
Analgesia	Paracetamol±oral morphine. Non-steroidal anti-inflammatory drugs are best avoided in thrombocytopenia.
Hyperhydration Allopurinol or rasburicase	For prevention of tumour lysis syndrome following discussion with the PTC. However, transfer to the PTC should not be delayed if there is difficulty in obtaining these drugs.
Blood products	Platelets, fresh frozen plasma and/or cryoprecipitate transfusion may be required to treat bleeding. Red cell transfusion should be considered carefully particularly in the context of a high or rising white cell count because the further increase in viscosity from packed red cell transfusion can precipitate complications of hyperleucostasis.

PTC, primary treatment centre.

Box 1 The first cannula

Children undergoing cancer treatment often become needle phobic. For the first few days, and in many cases, the first month, treatment will be given through peripheral intravenous access. Therefore, it is important to aim to minimise trauma from the very first episode of cannulation. If your patient is stable enough, take your time, use a local anaesthetic cream and distraction techniques. Get all the blood bottles ready and calculate the total volume of blood required. If possible, insert a 22G or 20G cannula with the aim of using it to bleed back for regular tumour lysis blood tests. Try to avoid dorsal hand and foot veins, which may later be needed for vincristine administration. It is also preferable for the practitioner doing the cannulation to be the person most likely to be successful on the first attempt.

or twice daily weight measurements are very useful in assessing fluid balance, especially in infants. Frusemide can be used to maintain diuresis although it should be used with caution if there is risk of leucostasis.

Allopurinol should be started in children where the clinical suspicion of acute leukaemia is high.⁶ It is a xanthine oxidase inhibitor, which prevents the formation of uric acid. In children either at high risk of developing TLS or with biochemical signs of the syndrome, rasburicase may be used as an alternative to allopurinol. This recombinant urate oxidase actively degrades uric acid and is a more potent therapy against TLS. However, it should be avoided in children with glucose-6-phosphate dehydrogenase deficiency as this can precipitate a haemolytic crisis. Recommended doses for allopurinol and rasburicase may differ between leukaemia treatment protocols (eg, UKALL 2011⁶) and pharmacopoeias such as the British National Formulary (BNF). Therefore, seek advice from your PCT on current drug doses and treatment schedules for both drugs.

Initially, TLS is an asymptomatic biochemical abnormality and your PTC will guide how frequently monitoring bloods should be taken, but this may be as often as every 4 hours in high-risk cases. Note that in very high count leukaemia, cells may haemolyse in the specimen bottle en route to the laboratory, leading to false electrolyte readings. It is therefore advisable to perform paired gas machine and laboratory electrolyte measurement when the white cell count is high. It is important to discuss any abnormalities, including both elevated and low electrolytes, early and before making corrections as these may show an evolving picture. Very occasionally, children with severe TLS will require haemofiltration.

Mediastinal mass

Children with leukaemia, particularly with T cell disease, may have mediastinal lymphadenopathy, which can cause airway obstruction. Signs and symptoms of an obstructive mediastinal mass include wheezing, stridor,

orthopnoea (specifically ask about this) and signs of superior vena cava obstruction (facial swelling and prominent veins). Should a child have any symptoms or signs of a mediastinal mass, it is important to consider an early anaesthetic assessment and organise urgent transfer to the PTC. Children should be nursed sitting upright. Lying flat, even for the short duration of a CT chest, may precipitate airway obstruction.

General anaesthetic and sedation with drugs such as chloral hydrate or midazolam should be avoided if there is any suspicion of a mediastinal mass, due to the risk of precipitating airway compromise and cardiovascular instability, even in a previously asymptomatic child. This is because these drugs cause a reduction in tone in both airway and vascular structures.⁷

Hyperleucocytosis and leucostasis

Hyperleucocytosis is defined as a white cell count greater than 50×10^9 cells/L. However, this threshold is arbitrary and complications from hyperleucocytosis can be seen at lower counts, especially in AML.⁸ Hyperleucocytosis significantly increases the risk of morbidity and mortality. For instance, a recent case series reported a 30% mortality within 2 weeks of diagnosis in children with AML who had a white cell count of greater than 200×10^9 cells/L.⁹ Seeking the opinion of your local consultant haematologist on the blood film appearance may help you to identify AML early and thus identify the increased risk of complications from hyperleucocytosis.

Leucostasis is the process of increased blood viscosity, poorly deformable blasts and cytokine-induced activation of the endothelium resulting in vascular obstruction and tissue hypoxia. If this process occurs in the lungs, shortness of breath, coughing and hypoxia may ensue. A plain chest radiograph may show diffuse interstitial or alveolar infiltrates. Leucostasis can also affect cerebral vessels and cause haemorrhagic or ischaemic events leading to symptoms of confusion, dizziness, tinnitus and headaches, as well as focal neurological deficits. Other manifestations of leucostasis include priapism, limb ischaemia, renal vein thrombosis and retinal haemorrhage.⁸

Management includes oxygen, hyperhydration and urgent discussion and transfer to the PTC. Definitive treatment is that of the underlying leukaemia, and it is important this is not delayed by other interventions. However, within an intensive care setting, apheresis or an exchange transfusion may occasionally be instigated.

Coagulopathy

Serious bleeding in acute leukaemia is rare with only 3% of children showing evidence of coagulopathy at diagnosis.¹⁰ There is a greater risk of serious bleeding at presentation in some children, including those with acute myeloid leukaemia (AML) and hyperleucocytosis. There is a rare subtype of myeloid leukaemia,

Box 2 Communicating the diagnosis of leukaemia

- ▶ Not all families are aware that leukaemia is a malignant disease, and it may help to describe the condition as a 'cancer of the blood'.
- ▶ It is unlikely that a definitive diagnosis of leukaemia will be made prior to transfer. Therefore, terms such as 'suspected leukaemia' or 'likely leukaemia' may be useful and avoid committing to any specific subtype of leukaemia solely on the basis of a blood film.
- ▶ Parents may ask about prognosis, and it would be reasonable to tell them that it is highly likely that the disease will be treatable but that more specific information can only be given after the results of further tests.
- ▶ Transfer to a children's oncology ward with an uncertain diagnosis can be frightening, both for parents and children. This can be helped with sensitive preparation.

acute promyelocytic leukaemia, which requires aggressive correction of coagulopathy to prevent life-threatening bleeds at presentation. The Nordic group reported eight deaths (14%) from intracranial haemorrhage and/or disseminated intravascular coagulation, out of a total of 57 patients with AML and a WCC more than 200×10^9 cells/L.⁹ By contrast, significant coagulopathy is extremely uncommon in acute lymphoblastic leukaemia (ALL) with only two cases of intracranial haemorrhage seen in over 2500 children in the UKALL 2003 trial.¹¹

Coagulation should always be checked at diagnosis,¹² although the correlation between serious haemorrhage, coagulopathy or the use of prophylactic plasma is questionable.¹³ When considering correction of abnormal clotting results in the absence of bleeding, it is important to consider the potential risks of administering plasma components. Discuss any abnormal results with your PTC who will provide patient-specific guidance.

Blood product support

Although serious bleeding is rare, minor bleeding is much more common, affecting 38% of children with ALL at diagnosis.¹⁴ This is related to thrombocytopaenia and therefore affects predominantly the mucosa and skin. National guidelines would advise transfusing platelets if platelet counts are less than 10×10^9 platelets/L. Raising this threshold to 20×10^9 platelets/L in febrile children routinely is no longer recommended.¹⁵ In the presence of significant bleeding transfusion should be based on the clinical situation rather than the platelet count.

At presentation, many children will be anaemic, but red cell transfusions may not be required. In hyperleucocytosis, red cell transfusion should be avoided due to the risk of complications of leucostasis such as TLS or stroke. Therefore, the conventional transfusion thresholds for children undergoing chemotherapy (below

$70\text{--}80$ g/L¹⁵), do not necessarily apply at presentation, and discussion with the PCT is advised before giving red cells. When transfusion is required due to severe anaemia, in the context of hyperleucocytosis, smaller volumes are often used, such as 5 mL/kg over 4 hours, in parallel with hyperhydration.

At diagnosis, UK national guidelines¹⁶ do not recommend any special blood product requirements as all blood products are now hepatitis E negative and leucodepleted. However, your own PTC may have local guidelines regarding cytomegalovirus-screened blood products and also suggest viral serology testing before transfusion. There is no specific evidence to guide the optimum haemoglobin transfusion threshold, although current practice would suggest that a threshold between 70 g/L and 80 g/L may be reasonable.

Pain

Pain is surprisingly common at presentation in leukaemia with 43% of children having limb pain at presentation¹⁴ and this may be under-recognised. Surrogate markers of pain can be useful, such as not using limbs and being clingy or unsettled. Non-steroidal anti-inflammatory drugs are best avoided due to their effects on platelet function in a child who is already at risk of thrombocytopaenia due to their underlying disease. In this context, oral morphine sulfate may be useful. Attempts should also be made to minimise procedural pain (box 1).

COMMUNICATION

It is essential to tell the family that a diagnosis of leukaemia is suspected prior to transfer to the PTC. Families need to be prepared that they will be transferred to an oncology ward, which can be identified as such from signs, posters and patients. Similarly, children should be given age appropriate information. While a detailed discussion of how to break bad news is beyond the scope of this article, there are some specific points we would like to highlight about communicating a diagnosis of suspected leukaemia (box 2).

Clinical bottom line

- ▶ Communicate early with your primary treatment centre.
- ▶ Most children presenting with acute leukaemia are clinically stable yet have the potential to deteriorate and require intensive clinical care.
- ▶ Monitoring for complications should include infection, tumour lysis syndrome, hyperleucocytosis and coagulopathy.
- ▶ Ensure appropriate analgesia; some children will require oral morphine for adequate pain relief.
- ▶ Parents should be aware that you suspect leukaemia prior to transfer.

TRANSFER

It is important to consider and discuss with your PTC an appropriate timing for transfer, and these conversations should include senior decision makers. There are some children who require urgent transfer, such as those with a very high white cell count, mediastinal mass or clinical instability. Many children who are clinically stable and have low count disease can be safely managed in a DGH overnight, or even for several days, if there is no bed immediately available in the nearest PTC. These children need to be monitored closely with regular observations, clinical assessment and blood tests and require regular discussion with the PTC.

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