REVIEW

The investigation and management of chronic neutropenia in children

R M James, S E Kinsey

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Unravelling the cause of a neutropenia poses a complex diagnostic challenge. The differential diagnosis ranges from life threatening disease to transient benign causes of little clinical significance. This review offers a practical guide to investigating the neutropenic child, and highlights features that merit specialist referral. Therapeutic options, the role of long term follow up, and the complications of severe chronic neutropenia are considered.

to reviews by Alter and Federman for more detailed descriptions.^{4 5}

Cyclical neutropenia

This is an autosomal dominant condition with variable expression. A family history is common. Cases also arise sporadically. The neutrophil count cycles, typically over 21 days, although this may range from 14 to 36 days.⁶ The neutrophil count may fall to a nadir of $0 \times 10^9/l$, with the period of neutropenia lasting for 3–10 days. Monocytes tend to cycle out of phase with neutrophils and cycling may also be evident in other lineages. Symptoms follow the neutrophil count, with patients at risk only during periods of severe neutropenia. Fever, mucocutaneous ulceration, cervical lymphadenopathy, and skin infections are common, but severe infections are infrequent. The bone marrow appearance varies with the cycle. It may show many, moderate, or virtually no neutrophils. Linkage studies in families with cyclical neutropenia have identified mutations in the neutrophil elastase gene.⁷ These appear to accelerate apoptosis of neutrophil precursors with the consequent interruption in differentiation producing a cyclical pattern of neutropenia.⁸ If treatment is indicated, it usually responds well to granulocyte colony stimulating factor (G-CSF).⁹ Cyclical neutropenia may improve with age, allowing G-CSF to be stopped.

Idiopathic neutropenia

This is diagnosed where there is no evidence of congenital, immune, or cyclical neutropenia, and where causes of acquired neutropenia have been excluded.¹⁰ In practice, it is often hard to distinguish between autoimmune and idiopathic neutropenia.¹¹ The underlying defect is thought to be ineffective neutrophil production, although many patients with idiopathic neutropenia still seem to possess the ability to mobilise and recruit neutrophils successfully when required. Such patients appear to have no greater risk of infection than a normal individual, and may be considered to have a benign constitutional neutropenia. Other patients do experience frequent infections requiring antibiotics, causing significant disruption to their quality of life with time off school. This group will require treatment

Neutrophils form the main defence against infection. They contain toxic cytoplasmic granules, which are released in a respiratory oxidative burst. Following microbe ingestion these are released into the phagocytic vacuole, destroying bacteria and fungi. They have a short lifespan, remaining in the blood for just 6–18 hours.

DEFINITION

Neutropenia is defined as a decrease in the circulating or absolute neutrophil count (ANC) to $<1.5 \times 10^9/l$. It may be mild ($1.0\text{--}1.5 \times 10^9/l$), moderate ($0.5\text{--}1.0 \times 10^9/l$), or severe ($<0.5 \times 10^9/l$). However, there is important variation with age and ethnicity, and these must be taken into account: up to 25% healthy black infants may have a neutrophil count $<1.0 \times 10^9/l$.¹

DIFFERENTIAL DIAGNOSIS OF CHRONIC NEUTROPENIA

There are many potential causes of neutropenia (table 1), some of which may be transient. By definition, severe chronic neutropenia (SCN) describes a heterogeneous group of congenital conditions, which cause the ANC to be $<0.5 \times 10^9/l$ on at least three occasions over 3 months.^{2 3}

Acquired or secondary neutropenia precipitated by drugs, other iatrogenic intervention, or infection is usually self-limiting. However, immune mediated disease is particularly important in childhood and is discussed further. The remaining causes of acquired or secondary neutropenia are all uncommon and require specialist management.

Congenital neutropenia

This is the most severe of the subgroups of SCN, with diagnosis usually made correspondingly early because of frequent and severe infections occurring from birth onwards. However, many of these are extremely rare and readers are referred

See end of article for authors' affiliations

Correspondence to:
Dr S E Kinsey, Consultant
Paediatric Haematologist,
Department of Paediatric
Haematology and
Oncology, Children's Day
Hospital, St James'
University Hospital, Beckett
Street, Leeds LS9 7TF, UK;
Sally.Kinsey@leedsth.nhs.uk

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Abbreviations: ANC, absolute neutrophil count; FBC, full blood count; G-CSF, granulocyte colony stimulating factor; GSD1b, glycogen storage disease 1b; HSCT, haematopoietic stem cell transplant; MDS/AML, myelodysplasia or acute myeloid leukaemia; SCN, severe chronic neutropenia; SCNIR, severe chronic neutropenia international registry

Table 1 Causes of neutropenia

Severe chronic neutropenia	Acquired or secondary neutropenia
1. Congenital Kostmann's syndrome Shwachman–Diamond syndrome Bone marrow failure syndromes Fanconi's anaemia* Dyskeratosis congenital* Bloom's syndrome* Amegakaryocytic thrombocytopenia* Inborn errors of metabolism Glycogen storage disease 1b Pearson's syndrome Methylmalonic aciduria Immunodeficiencies Hyperimmune IgM syndrome X linked agammaglobulinaemia Myelokathexis Reticular dysgenesis Cartilage-hair hypoplasia Barth's syndrome Griscelli syndrome Shimke immuno-osseous dysplasia	1. Drugs Dose dependent myeloid suppression cytotoxic drugs, anti-metabolites Aberrant drug metabolism phenothiazines, thiouracil Idiosyncratic drug responses sulphonamide, chlorpropamide, chlorthiazide Autoimmune drug hapten mechanism chlorpropamide, phenylbutazone, penicillin Other mechanisms, e.g. immune complex formation quinine, cephalosporins
2. Cyclical	2. Other iatrogenic causes Radiotherapy Radioactive treatment, e.g. radio iodide
3. Idiopathic	3. Infection Viral Rubella, measles, varicella, parvovirus*, CMV, EBV, HIV, hepatitis A, hepatitis B, influenza, RSV Bacterial Mycobacteria tuberculosis, typhoid, brucella, severe bacterial sepsis
	4. Immune mediated disease Neonatal alloimmune neutropenia Primary autoimmune neutropenia Secondary autoimmune neutropenia: Rheumatoid arthritis Systemic lupus erythematosus*
	5. Haematological disease Aplastic anaemia* Hypogammaglobulinaemias Haemophagocytic syndrome* T cell large granular lymphocytosis Myelodysplasia*
	6. Hypersplenism*
	7. Malignancy CLL* Lymphoma* Thymoma* Infiltration by secondary malignancy*
	8. Storage disease* Gaucher's disease Niemann–Pick disease
	9. Collagen vascular disorders

*These may also present with pancytopenia, or other isolated cytopenias.

with G-CSF. Spontaneous recovery has occasionally been reported.

Neonatal alloimmune neutropenia

Neonatal alloimmune neutropenia is a rare but potentially life threatening disorder of neonates.¹² Diagnosis rests on the demonstration of alloantibodies against neutrophil specific antigens shared by neonatal and paternal neutrophils in the maternal serum. These maternal immunoglobulin IgG antibodies enter the fetal circulation causing neutrophil destruction in utero and subsequently ex utero. The maternal neutrophil count will be in the normal range. The total white cell count of the affected neonate may be low, normal, or even increased due to a compensatory monocytosis. Neutropenia is usually severe. The fetus is protected from infection in utero. However, the immediate postnatal period is one of great vulnerability to both local and generalised infection. Intravenous immunoglobulin boosts the neutrophil count in the majority, possibly by competitive inhibition. G-CSF and antibiotics may also be required. Fortunately the

period of neutropenia is usually brief. Parental counselling of the implications for subsequent pregnancies is essential.

Primary autoimmune neutropenia

Primary autoimmune neutropenia (AIN), sometimes also referred to as chronic benign neutropenia of infancy/childhood, is caused by neutrophil specific antibodies and occurs predominantly in infancy.¹¹ It is 10-fold more common than SCN, occurring in 1:100 000.¹³ Despite severe neutropenia, the vast majority of cases will experience only minor infections and do not require long term treatment. Further, a large study of 240 children with AIN found that spontaneous remission occurred in 95% cases within 7–24 months of diagnosis.¹⁴ A positive anti-neutrophil auto-antibody result confirms the diagnosis, and obviates the need for bone marrow examination. The tests may need to be repeated several times before a positive result is obtained. If bone marrow examination is performed, the marrow is usually normocellular or hypocellular with a reduction in segmented neutrophils. Symptomatic treatment of infections

with antibiotics is sufficient for most, although G-CSF, corticosteroids, and intravenous immunoglobulin have all been demonstrated to raise the neutrophil count in 100%, 75%, and 50% of cases respectively.¹⁴ Consequently, G-CSF is of use when there is a temporary need to raise the neutrophil count, for example in severe infection or before surgery.

EVALUATION OF A NEUTROPENIC CHILD

History and examination

The finding of neutropenia in child should be verified by repeat testing, and, if confirmed, requires investigation. The clinical status, rather than the absolute count, is the most important factor in determining where this occurs: if the child is well, the initial work-up may be performed in the community. However, if the child is unwell, they will require hospital referral, and management by a specialist. In all situations a detailed history is the key to diagnosis. Time should be taken to elicit the exact symptoms, the age when they began, their timing, severity, and impact on quality of life. In cyclical neutropenia in particular there is often a clear family history. Useful questions to consider, and relevant signs that may be elicited on examination are considered in Table 2.

Investigation

Full blood count (FBC) forms the basis of initial investigation. If there is strong evidence of a cyclical pattern, then, ideally, thrice weekly FBCs over a 6-week period should be performed. In practice this is hard to achieve and a compromise may need to be made. If cyclical neutropenia is not thought likely, and the neutropenia cannot be accounted for by age or ethnicity, then the child should be referred to a specialist—if not already under their care. At this stage auto-antibody studies should be performed. These should be sent to the local blood transfusion centre who will direct them to an accredited granulocyte immunology centre. If these are uninformative, bone marrow examination is required, along with any specific tests suggested from the history or examination. Details of relevant tests and examples of the information that may be gained from them are highlighted in table 3.

SPECIALIST REFERRAL

In most cases the child will be under the care of a general practitioner or generalist when the neutropenia comes to light. If the child is well, initial investigations may be continued in this setting as described above. However, early

Table 2 Key points in the history and examination of a child with neutropenia

The following areas should all be covered in the history

Age

Ethnicity

Onset How old was the child when they had their first infection?
Have they had a previously normal neutrophil count?

Timing How frequently do they have infections?
Is there a cyclical pattern to this?

Site Where are the symptoms? Consider:
umbilical stump infection
oral ulceration, stomatitis
pharyngitis, tonsillitis
otitis media
skin abscesses, perirectal abscess
peritonitis
meningitis

Severity How often are antibiotics required?
Has hospital admission been necessary?
Have any episodes been life threatening?

Quality of life Is school attendance disrupted because of illness?

General health Is there evidence of failure to thrive?
Is there a history of fatty or large volume stools?

Family history Does anyone else in the family have recurrent infections?
Has anyone else ever been found to be neutropenic?
Has anyone else ever been diagnosed with a condition causing chronic neutropenia?
Do any autoimmune disorders run in the family?

Toxins Has the child received any medical treatment?
Have they had any over the counter preparations?
Have they been given any herbal or 'natural' remedies?

Always check that the child has been fully immunised

The following signs should all be sought on examination

Examination Check height and weight on a Tanner–Whitehouse chart
Is the child dysmorphic?
Are there any obvious or suspected bony abnormalities—as in Fanconi's anaemia or Shwachman–Diamond syndrome?
Are there any abnormalities of the nails or skin—suggestive of dyskeratosis congenita?
Is there current mucocutaneous infection?
Is there any evidence of a chronic chest problem, such as bronchiectasis?
Is there hepatomegaly, suggestive of a glycogen storage disorder?
Is there splenomegaly, and if so to what degree?

referral to a specialist in Paediatric Haematology is indicated when there is evidence of severe or recurrent infection, or if there are features of an underlying syndrome. The long term management may then be coordinated by the specialist, with shared care provided by the Specialist Centre, the local paediatrician, and the general practitioner.

TREATMENT

In general, the clinical severity is inversely proportional to the neutrophil count. However, there is marked individual variation, and the decision to treat is based on the clinical picture, rather than the neutrophil count. In the acute setting a child with febrile neutropenia should be treated with intravenous antibiotics, according to local sensitivities, and appropriate supportive care. However, the long term management of a child with SCN is more complex, and there are few therapeutic options.

Granulocyte colony stimulating factor (G-CSF)

The successful cloning of G-CSF in 1986,¹⁵ and its subsequent introduction in clinical practice,^{16, 17} has been the single most important advance in the treatment of SCN. By successfully increasing the mean ANC, it has dramatically reduced the mortality from infection, especially in the early years of life, and has transformed the quality of life for many patients with SCN.³ It is indicated where there is a history of recurrent severe infection in conjunction with severe neutropenia and has been demonstrated to result in fewer infective episodes, reduced antibiotic use, and reduced hospital admission.^{17, 18}

Children with severe neutropenia without a history of recurrent severe infection do not require G-CSF.

G-CSF is usually started at a dose of 5 µg/kg/day by subcutaneous injection into the abdomen, thigh, or upper arm, and is ideal for home administration. A response in the ANC may be seen within 1–2 days of starting treatment, especially in autoimmune neutropenia. Response may take longer if myeloid precursors are absent. Consequently, the ANC should be monitored very closely initially, and the dose adjusted accordingly. In practice, it is more common to see a rapid response with an overshoot of the ANC. In this case the G-CSF dose can be reduced, by reducing either the daily dose or the frequency. Many patients manage on alternate day dosing, and some achieve a satisfactory response with even less frequent administration. The final G-CSF dose should be the minimal dose required to ameliorate symptoms and prevent infections. Again it is the clinical picture, not the neutrophil count alone, which should guide this. For example, patients with cyclical neutropenia will continue to cycle, but at a higher, safer level.

If there is still no response at maximum doses of G-CSF, the patient is considered as refractory to treatment, and the G-CSF stopped. A haemopoietic stem cell transplant (HSCT) may be considered in such patients.¹⁹

Once a steady state has been reached, the FBC should be checked at least every 2–3 months. Patients on G-CSF have now been followed up for over 10 years of treatment, with no evidence of reduced sensitivity of the neutrophil precursors in the bone marrow to G-CSF over that time.²⁰ Monitoring has

Table 3 Tests indicated in the initial investigation a child with chronic neutropenia

1. Full blood count and film	Indicated in all How profound is the neutropenia? Are monocytes, eosinophils, or basophils increased as in Kostmann's syndrome? Is there a general leucopenia as in reticular dysgenesis? Do the neutrophils look toxic? Are the neutrophils hypersegmented as in myelokathexis? Are there atypical lymphocytes suggestive of a viral infection? Does the neutropenia persist on repeat testing? Is there a cyclical pattern?
2. Anti-neutrophil antibodies	Always indicated Do early if there is a history of no, or only minor, infections
3. Bone marrow examination	Indicated if no evidence of cyclical or autoimmune neutropenia Compare with peripheral neutrophil count at same time Look for the classic maturation arrest at the promyelocyte stage seen in Kostmann's syndrome Is there evidence of myelodysplasia? Are any other cell lines affected? Send for cytogenetic analysis Send for chromosome breakage studies for Fanconi's anaemia Consider specialist investigations, such as mutations in the G-CSFR, the RAS oncogene, and in neutrophil elastase
4. Serum immunoglobulins	Is the IgG elevated as in hyperimmune IgG syndrome? Is there evidence of X-linked agammaglobulinaemia?
5. Virology screen	Including evidence of hepatitis A, B, and C; HIV and EBV
6. Malabsorption screen	Indicated if there is failure to thrive, short stature, or a history of steatorrhoea
7. Sweat test	Indicated if abnormal exocrine pancreatic function has been demonstrated in order to exclude cystic fibrosis
8. Glucose-6-phosphate translocase defect	If the history is suggestive of GSD1b
9. Radiology	Indicated in suspected SDS, FA, and cartilage-hair syndrome
10. Bone densitometry	If there is a clinical history of bone pain or pathological fracture

also demonstrated an initial increase in haemoglobin to normal levels, where it has been low, and a fall in platelets towards normal, where they have been elevated at the commencement of treatment.¹⁹ Both trends appear to be sustained, and probably result from reduction in chronic inflammation and improvement in general wellbeing.

Overall, G-CSF appears to have relatively few side effects.^{17–21–22} Patients should be warned that they may experience bone pain and flu-like symptoms in the first few days and weeks, but these tend to resolve as treatment continues. Some have local reactions, including pain at the site of injection, which is reduced by rotating injection sites. Patients with an associated autoimmune disease may find that this is exacerbated, and patients with glycogen storage disease 1b (GSD1b) may develop splenomegaly. In the longer term there is concern about bone mineral density, and transformation to myelodysplasia or acute myeloid leukaemia (MDS/AML). These are discussed further below.

Haematopoietic stem cell transplant

This is the only alternative for patients with recurrent severe infections who are refractory to G-CSF.^{23–24} It is the treatment of choice for patients in whom the bone marrow shows cytogenetic evolution, or the development of either MDS/AML.²⁵ Finally, it is also indicated for the treatment of several of the specific causes of SCN such as Fanconi's anaemia,²⁶ dyskeratosis congenita,²⁷ and congenital amegakaryocytic thrombocytopenia.²⁸

Obsolete treatment options

Granulocyte macrophage colony stimulating factor is far less effective than G-CSF in increasing the number of circulating neutrophils, and also causes a higher incidence of side effects.²⁹ It is no longer available for clinical use. Prior to the advent of G-CSF, glucocorticosteroids, lithium, intravenous immunoglobulin, immunosuppressive drugs, and splenectomy have all been used in the long term management of children with SCN. However, none of these has been of significant benefit, and most carry unacceptable long term side effects.

FOLLOW UP

All patients with SCN should be reviewed at least every 3 months. A history of recent infections should be taken, and physical examination, including documentation of the height and weight, performed. An FBC should be obtained and reviewed with particular regard to any change, especially a fall in neutrophil count, haemoglobin, or platelet count; or a rise in the mean cell volume. A film should be examined to exclude the development of dysplastic features. Annual bone marrow assessment is required to look for morphological or cytogenetic change, especially in patients on G-CSF.

COMPLICATIONS IN SEVERE CHRONIC NEUTROPENIA

Specific complications, which may be related to SCN alone, or to the use of G-CSF are discussed below.^{3–20}

Thrombocytopenia

Thrombocytopenia is an uncommon occurrence, which may arise *de novo*, or as a consequence of G-CSF therapy. Although it is not related to G-CSF *dose* or to the *duration* of treatment, it may respond to reduction of the G-CSF dose or even to temporary withdrawal of the G-CSF and reintroduction at a lower dose. All patients developing thrombocytopenia require a blood film, and possibly a bone marrow examination as it may herald transformation to MDS/AML.

MDS/AML

Prior to the advent of G-CSF, leukaemic transformation was recognised as a serious long term complication in patients with the congenital, rather than the cyclical or idiopathic, form of SCN. Shwachman–Diamond syndrome appears to confer the highest risk. There is concern that G-CSF may increase the risk further, although this has not been conclusively demonstrated.

Initial review of patients enrolled in the severe chronic neutropenia international registry (SCNIR) did not find any significant association between duration or dose of G-CSF and the risk of MDS/AML.³⁰ In contrast, analysis of a smaller number of patients enrolled in the French Severe Chronic Neutropenia Study Group did find a positive association with G-CSF dose.³¹ The most recent review from the SCNIR also found a significant association between G-CSF dose and risk of MDS/AML.³² However, analysis is complicated. Looking at the SCNIR data as a whole, the authors suggested that the requirement for a higher G-CSF dose indicated a group who were likely to have a particularly severe underlying defect and it was this defect that gave rise *directly* to the increased risk of MDS/AML. This proposal is supported by the failure to demonstrate the development of MDS/AML in patients on long term G-CSF for other indications.

All patients on long-term G-CSF should have annual bone marrow examination with cytogenetic analysis. Cytogenetic change often heralds leukaemic transformation. The prognosis of SCN patients with MDS/AML treated by conventional means is poor. Accordingly, HSCT should be considered in patients with cytogenetic change on bone marrow examination or with frank MDS/AML.²⁵

Splenomegaly

Splenomegaly at diagnosis occurs in less than a quarter of patients, and is usually mild. The incidence increases slightly over time, and may be related to G-CSF use, especially in patients with GSD1b.³³ Spleen size increases over the first year of G-CSF use, plateaus, and then returns to the initial size during the third year of treatment.²⁰ Splenectomy is rarely indicated.

Hepatomegaly

Mild hepatomegaly is present in a similar number of patients. It is most common in congenital SCN, where 21% of cases may have hepatomegaly at presentation.²⁰ A slight increase in incidence may be observed during the first year of G-CSF treatment.

Growth and development

Studies suggest that children with SCN are shorter than their peers.²⁰ The difference is most marked in congenital SCN, reflecting disease severity. This disparity is seen from infancy, and increases with age so that by the age of 11 years just over 50% of children with congenital SCN have a height <10th centile of normal. The causes for growth retardation are likely to be multifactorial, including the effects of chronic infection and inflammation due to neutropenia. It might be expected that G-CSF would have a beneficial effect on height, but so far this has not been demonstrated.

Osteopenia, osteoporosis

Over the last few years, osteopenia and osteoporosis have been recognised as a clinical problem in patients with SCN.³ Bone pain, pathological fractures, and deformity due to vertebral collapse are the most common symptoms, especially in Kostmann's syndrome, a subtype of congenital neutropenia.³⁴ Skeletal abnormalities form part of the clinical features of some of the rarer syndromes causing congenital neutropenia, including Shwachman–Diamond syndrome, Fanconi's anaemia, and dyskeratosis congenita, and may contribute to

osteopenia and osteoporosis in these patients. Infection, malabsorption, periods of immobilisation, and steroid use are also implicated in reducing bone mineral density. Despite concern, there is little evidence that the use of G-CSF is contributory.³⁵

All patients with SCN should have their bone mineral density regularly evaluated. Routine radiological imaging may miss osteopenia and osteoporosis and so imaging modalities such as dexamethasone scanning and Q-CT, which appear to be more sensitive in early disease, should be considered. Patients should also receive appropriate advice on diet and exercise.

Vasculitis

This is an unusual, but recognised, feature of SCN, with an increased rate in idiopathic SCN.³ Cutaneous vasculitis is most common, with skin biopsy typically showing a leucocytoclastic vasculitis. Symptoms usually correlate with a higher ANC, and resolve when the ANC falls. G-CSF treatment does not usually need to be stopped, although dose reduction may be required.

All patients with recurrent vasculitis or with renal involvement should be investigated further, as there is an increased incidence of other autoimmune disorders and of underlying malignancies in this group. Recurrent episodes of haematuria may indicate the development of glomerulonephritis. Referral to a nephrologist, and renal biopsy are indicated. Patients with congenital SCN appear to have an increased frequency of immune complex disease, associated with Henoch-Schönlein purpura and IgA nephropathy.

Reproductive ability

G-CSF does not appear to have any adverse effects on sexual development. There is little data on its use in pregnancy, but it does not appear to increase the rate of congenital abnormalities or spontaneous abortion.^{36 37} However, spontaneous abortion is more common in pregnant women with SCN. Increasing understanding of the genetic defects in SCN may enable prenatal testing.

Mortality

G-CSF has dramatically reduced the overall mortality. Mortality from sepsis in patients with SCN maintained on long term G-CSF has been stable over the last 12 years of follow up at just under 1% per year.³²

THE SEVERE CHRONIC NEUTROPENIA INTERNATIONAL REGISTRY

The severe chronic neutropenia international registry (SCNIR) was set up in March 1994 to monitor the clinical course, treatment, and disease outcomes in patients with SCN.³ It was reorganised in January 2000, merging with the French Registry to become a research centre. It aims to maintain a longitudinal database, to promote education, and to facilitate research: for example, work on families identified through the registry led to the discovery of mutations in neutrophil elastase as a key finding in cyclical neutropenia.³⁸ It has also enabled long term monitoring of the safety of G-CSF in this population over time.^{20 30 32}

CONCLUSION

Chronic neutropenia encompasses a spectrum of conditions. It may be a benign finding with little clinical impact, or it may precipitate life threatening infections either as an isolated disorder or as part of a syndrome. Children experiencing severe or recurrent infection, and those with features of a specific syndrome should be under the care of a specialist. G-CSF is the treatment of choice for those with frequent severe infections, and has a dramatic impact on the quality of life and survival. Long term follow up of children

with chronic neutropenia, especially those treated with G-CSF, is essential.

Authors' affiliations

R M James, Epidemiology and Genetics Unit, Department of Health Sciences, University of York, UK

S E Kinsey, Department of Paediatric Haematology and Oncology, St James' University Hospital, Leeds, UK

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