**Fifteen-minute consultation: A guide to managing a child with a new finding of neutropenia**

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**ABSTRACT**

Objective To describe a structured approach for managing a child with a new finding of neutropenia.

Method Literature review and consensus practice of clinicians in our regional centre.

Conclusion Neutropenia may arise in a variety of situations from a well child with a physiological neutropenia to a sick infant with life-threatening infection. In most cases a thoughtful history and directed examination will help to identify the severity in order to determine an appropriate care pathway.

**WHAT DO YOU NEED TO LOOK FOR ON EXAMINATION?**

As well as ascertaining the immediate clinical severity, ensure the following are included in your examination:

**Growth**

Plot the height and weight. Short stature increases the likelihood of this being congenital: over 50% children with congenital severe chronic neutropenia (SCN) have a height below the 10th centile by the age of 11 years.

**Dysmorphic features**

Look carefully. Many of the congenital syndromes are associated with a range of anatomical abnormalities. Examine the nails for dystrophic changes (dyskeratosis congenita) or splinter haemorrhages (vasculitides). Examine the skin for café au lait spots (Fanconi anaemia), reticular pigmentation (dyskeratosis congenita) or vitiligo (autoimmune disease). If there is any suggestion of a thumb or radial anomaly then request a hand X-ray (Fanconi anaemia). Skeletal abnormalities, such as metaphysial dysostosis, are also common in Shwachman-Diamond syndrome and cartilage-hair hypoplasia.

**Oral examination**

Look for evidence or recurrent mucocutaneous infection. Active gingivitis suggests a more chronic cause for neutropenia. Leukoplakia is a classic hallmark of dyskeratosis congenita.

**Lymphadenopathy**

Examine for palpable cervical, axillary and inguinal lymphadenopathy, which...
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**Box 1 What is neutropenia?**

Neutropenia is defined as a neutrophil cell count of less than $1.5 \times 10^9/l$. It may be:
- Mild, from $1.0 \times 10^9/l$ to $1.5 \times 10^9/l$
- Moderate, between $0.5 \times 10^9/l$ and $1.0 \times 10^9/l$
- Severe, less than $0.5 \times 10^9/l$

The term severe chronic neutropenia is used when the neutrophil count is less than $0.5 \times 10^9/l$ on three occasions over a 3-month period.

There are small but important ethnic variations in the normal range for neutrophil counts. It is not uncommon for people with black African/Caribbean ancestry to have a normal count in the $1.0–1.5 \times 10^9/l$ range and as an isolated finding requires no investigation.

suggest chronicity. If widespread these may be associated with malignancy.

**Hepatosplenomegaly**

Hepatosplenomegaly is associated with malignancy, storage disorders, haemophagocytosis, secondary autoimmune neutropenia and viral causes of neutropenia. In contrast, splenomegaly and hepatosplenomegaly are found in less than a quarter of children with SCN at diagnosis.

**WHAT EXAMINATIONS ARE REQUIRED?**

**Full blood count and film**

An increase in monocytes, basophils or eosinophils is often seen in severe congenital neutropenia. Atypical lymphocytes suggest a viral infection, and a monospot test is helpful to look for evidence of Epstein-Barr virus. If there is also anaemia and/or thrombocytopenia then you are most likely to be looking at bone marrow failure or bone marrow infiltration. The film may show toxic neutrophils suggesting severe bacterial sepsis. In acute leukaemia, blasts are usually present on the film, unless the total white cell count is low. In either case, leukaemia may be confirmed by immunophenotyping of the peripheral blood, and subsequently by bone marrow examination. The history is important so look for old results, which will help differentiate congenital from acquired neutropenia, and which may suggest a cyclical pattern. Cyclical neutropenia typically cycles over a 21-day cycle, with a range from 14 days to 36 days, and a diagnosis is supported by weekly full blood counts over a 6-week period, but such aggressive investigation is rarely appropriate in children. In a well child, without any other features of underlying illness, a reasonable compromise may be to undertake a repeat full blood count after 1 week and 4 weeks, and only investigate further should there be evidence of continuing neutropenia or cyclical pattern.

**Microbiological tests**

If the child is unwell, then comprehensive microbiological screening is required, including blood cultures, a urine sample and swabs from any obvious focus of infection. If the child is well, and there is a clear focus then samples may be limited to this area. In a neonate or infant, or in a child with chronic neutropenia, infection with hepatitis A, B and C, HIV, Epstein-Barr Virus and cytomegalovirus should be excluded.

**Reticulocyte count, iron, folate and basic biochemistry**

The assessment of liver, renal, nutritional and marrow function is important to assess for neutropenia secondary to other conditions, such as liver failure syndromes and an insight into the functioning of other cell lines.

**Malabsorption testing**

This is required if the child has short stature, failure to thrive or steatorrhoea. If abnormal exocrine pancreatic function is confirmed then a sweat test is necessary to

**Table 1 Congenital causes of neutropenia**

<table>
<thead>
<tr>
<th>Congenital cause</th>
<th>Possible hints</th>
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<tbody>
<tr>
<td>1. Kostmann’s syndrome</td>
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<tr>
<td>2. Shwachman-Diamond syndrome</td>
<td>Skeletal abnormalities, hard to flush stools</td>
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<tr>
<td>3. Bone marrow failure, including Fanconi anaemia *, dyskeratosis congenita *, Bloom’s syndrome *, amegakaryocytic thrombocytopenia *</td>
<td>Café au lait spots, thumb or nail abnormalities— Fanconi Dystrophic nails, Leukoplakia dyskeratosis</td>
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<tr>
<td>4. Inborn errors of metabolism (including glycogen storage disease 1b, Pearson’s syndrome, methylmalonic aciduria)</td>
<td>Hepatosplenomegaly</td>
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<td>5. Immunodeficiency (including hyperimmune I gM syndrome, X linked agammaglobulinaemia, hypogammaglobulinaemia)</td>
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<td>6. Myelokathexis</td>
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<td>7. Reticular dysgenesis</td>
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<tr>
<td>8. Cartilage-hair hypoplasia</td>
<td>Skeletal abnormalities</td>
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<tr>
<td>9. Barth’s syndrome</td>
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<td>10. Griscelli syndrome</td>
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<td>11. Schinke immuno-osseous dysplasia</td>
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*These may also present with pancytopenia, or with other isolated cytopenias.
exclude cystic fibrosis. If this is negative, then confirmatory tests for Shwachman-Diamond syndrome or Pearson syndrome are indicated.

Further testing may also be required. These will often be undertaken by, or in discussion with, a specialist paediatric haematologist.

**Antineutrophil antibodies**

These are indicated if repeat tests confirm SCN. In the UK, they are sent away for testing through the National Blood and Transplant Service. If positive these support a diagnosis of autoimmune neutropenia, which is 10-fold more common than congenital causes of SCN.

**Serum immunoglobulins**

An elevated IgG is seen in hyperimmune IgG syndrome. Reduced immunoglobulins may indicate X linked agammaglobulinaemia or hypogammaglobulinaemia.
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Chromosome breakage studies
These should be sent to the cytogenetics laboratory if Fanconi anaemia is suspected.

Imaging
An X-ray of the hand and/or arm is needed if an abnormality is suspected. If the history and examination have suggested a cause associated with congenital renal abnormalities then a renal ultrasound is required (Fanconi anaemia, Diamond-Blackfan anaemia).

Bone marrow examination
If the history and examination point to severe congenital neutropenia, or to a serious underlying case, a bone marrow examination is indicated. It should also be considered in persistent neutropenia with no evidence of cyclical or autoimmune neutropenia. An aspirate and trephine should be taken, and samples sent for morphology, flow cytometry and cytogenetics.

WHEN DO YOU NEED TO REFER TO A SPECIALIST?
Febrile neutropenia can be life-threatening and requires prompt treatment with intravenous antibiotics, given according to local protocols and in line with the recent National Institute for Health and Care Excellence guidelines. Commencing antibiotics in clinically well children with moderate or mild neutropenia is unnecessary, but unwell children and those with severe neutropenia (≤0.5 × 10^9/l) deserve empirical therapy pending further review. Consultant review and discussion with a specialist paediatric haematologist is indicated urgently if:

► The child is clinically unwell.
► Neonatal alloimmune neutropenia is suspected—this is rare, but may be life-threatening.

Referral to a specialist is also required if:

► There are findings indicating a chronic neutropenia.
► There are features indicating it is part of a wider problem.

FINAL MESSAGE
If you are in any doubt about the clinical severity of neutropenia then pick up the phone and call your local paediatric haematologist to discuss your concerns.

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