


# 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.

**Scenario** A 6-year-old boy presented earlier in the day to the acute assessment unit with lethargy and a sore throat. At handover time his blood results are phoned through and show that he is neutropenic.

## WHAT QUESTIONS DO YOU NEED TO ANSWER NOW?

A child with neutropenia (see [box 1](#)) may be asymptomatic or may be at risk of life-threatening sepsis. It may be a transient phenomenon, or may be a symptom of a serious underlying illness. The immediate focus is not on determining the underlying diagnosis, although this may be possible, but rather:

- ▶ To identify the clinical impact.
- ▶ To determine the appropriate place of care.
- ▶ To decide the pace at which investigation and referral occur.

The differential diagnosis of congenital neutropenia is given in [table 1](#) and of acquired in [box 2](#). Many of the congenital causes are extremely rare. In general, congenital neutropenia is more likely to be severe, while acquired or secondary neutropenia is usually—but not always—self-limiting.

## WHAT DO YOU NEED TO COVER IN THE HISTORY?

Once you have asked what has triggered the current presentation, you need to

take a detailed history. This should give you many of the clues needed to begin to narrow down the differential. Important areas to cover are given in [table 2](#).

## 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 metaphyseal dysostosis, are also common in Shwachman-Diamond syndrome and cartilage-hair hypoplasia.

### Oral examination

Look for evidence of 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  $1.0\text{--}1.5 \times 10^9/l$  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

| Congenital cause  | Possible hints   |
|---|--|
| 1. Kostmann's syndrome  |  |
| 2. Shwachman-Diamond syndrome   | Skeletal abnormalities, hard to flush stools   |
| 3. Bone marrow failure, including Fanconi anaemia*, dyskeratosis congenita*, Bloom's syndrome*, amegakaryocytic thrombocytopenia* | Café au lait spots, thumb or nail abnormalities— Fanconi<br>Dystrophic nails, Leukoplakia dyskeratosis |
| 4. Inborn errors of metabolism (including glycogen storage disease 1b, Pearson's syndrome, methylmalonic aciduria)                | Hepatosplenomegaly   |
| 5. Immunodeficiency (including hyperimmune IgM syndrome, X linked agammaglobulinaemia, hypogammaglobulinaemia)                    |  |
| 6. Myelokathexis  |  |
| 7. Reticular dysgenesis   |  |
| 8. Cartilage-hair hypoplasia  | Skeletal abnormalities   |
| 9. Barth's syndrome   |  |
| 10. Griscelli syndrome  |  |
| 11. Schimke immuno-osseous dysplasia  |  |

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

## Box 2 Acquired causes of neutropenia

## Physiological

1. **Ethnic variation**
2. **Cyclical neutropenia**

## Idiopathic

## Infection

1. **Viral (especially rubella, measles, varicella, parvovirus\*, cytomegalovirus, Epstein-Barr virus, HIV, hepatitis A, hepatitis B, influenza, respiratory syncytial virus)**
2. Bacterial (notably **severe bacterial sepsis**, mycobacterium tuberculosis, typhoid, brucella)

## Autoimmune

1. **Primary autoimmune neutropenia**
2. Secondary autoimmune neutropenia (including rheumatoid arthritis, systemic lupus erythematosus\*)

## Alloimmune

## Neonatal alloimmune neutropenia

## Iatrogenic

1. **Cytotoxic drugs**
2. Abnormal metabolism, for example, phenothiazines, thiouracil
3. Idiosyncratic drug reaction, for example, sulphonamide, chlorpropamide, chlorthiazide
4. Autoimmune drug hapten mechanism, for example, chlorpropamide, phenylbutazone, penicillin
5. Immune complex formation, for example, cephalosporins, quinine
6. Radiotherapy
7. Radioactive therapy, for example, radio-labelled iodine

## Malignancy

1. **Acute lymphoblastic leukaemia\***
2. Lymphoma\*
3. Thymoma\*
4. Metastatic bone marrow infiltration\*

## Haematological

1. **Aplastic anaemia\***
2. Haemophagocytosis\*
3. Myelodysplasia\*
4. T cell large granular lymphocytosis

## Storage disease

1. Gaucher's disease
2. Niemann-Pick disease

\*These may also present with pancytopenia, or with other isolated cytopenias. The most common causes are in bold.

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,

Table 2 Questions to cover in the history

## Questions to cover in the history What answers may indicate

## Age

## Ethnicity

## Infection history

- |  |  |
|--|--|
| Have they been admitted to hospital before?      | Neonatal infections, previous admissions, previous need for antibiotics are features of SCN:     |
| Have they required antibiotics before?           | 50% children with SCN have an infection as a neonate, and 90% have had an infection by 6 months. |
| Have infections been severe or life-threatening? |  |
| How old were they when infections began?         |  |
| Specific questions:                              |  |
| ▶ Umbilical stump infection                      |  |
| ▶ Recurrent mouth ulcers,                        |  |
| ▶ Recurrent respiratory infections,              |  |
| ▶ Skin abscesses including perirectal abscesses  |  |
| ▶ Meningitis.                                    |  |

If they have frequent infective symptoms, do these occur in any kind of cyclical pattern?

In cyclical neutropenia the cycle may range from 14 days to 36 days; typically 21 days.

## Growth and development

Have there been concerns about their growth? May be present in any causes of SCN—lack of growth problems do not rule these out.

Do they have fatty stools that are hard to flush?

Seen in Shwachman Diamond syndrome, Pearson syndrome.

Are they fully immunised?

Children with frequent infections may have missed immunisation.

## Drug history

Are they on any medicines?

Always consider drug causes.

Have they had any over-the-counter medicines or herbal or 'natural' remedies?

## Family history

Does anyone in the family have recurrent infections, especially mouth ulcers?

Often seen in cyclical neutropenia.

Has anyone else been found to be neutropenic?

Seen in familial neutropenia and in syndromic causes.

Are there any autoimmune disorders in the family?

Not very specific, but seen more with autoimmune neutropenia.

## Social history

How many days of school/nursery are missed through infection?

This gives an idea of the burden of illness, and may be helpful to gauge indication for granulocyte colony stimulating factor treatment.

SCN, severe chronic 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.

**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 ( $<0.5 \times 10^9/l$ ) 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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