A step-by-step approach to paediatric neutropenia

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Abstract

Neutropenia is a common laboratory finding in children. The aetiology varies from benign transient post-viral suppression to overwhelming systemic disease. For medical providers, identification of the aetiology of neutropenia can be difficult, but clarification of the cause is important for determining management and prognosis. Neutropenia in children may be discovered during evaluation of a fever or illness, or may be found incidentally when a full blood count is undertaken for other reasons. It may be an isolated finding or may be associated with suppression of other cell lines. It is important to distinguish between transient or benign causes and severe congenital neutropenia or neutropenia associated with serious haematological or systemic disease. Appropriate advice and treatment must be given while further assessment and investigation take place. In this review, we will discuss how and where patients may present, initial management and investigation and when and with what urgency to refer to specialty care.

Keywords aetiology; investigation; neutropenia; paediatrics

What is the role of the neutrophil?

Most haematopoiesis takes place in the bone marrow and involves exposure of pluripotent stem cells to multiple growth factors in sequence. White blood cells are generally classified into myeloid (granular) and lymphoid and monocytic (agranular) cells. Stem cells that differentiate into myeloid cells mature sequentially from myeloblasts to polymorphonuclear cells (PMNs), which further differentiate to neutrophils, basophils, or eosinophils. Neutrophils make up the majority of circulating white blood cells and play a critical role in innate immunity. PMNs collectively respond to infection, allergic reactions and inflammation. As the neutrophil is the prime responder to infection, patients with neutropenia are at increased risk of bacterial and fungal infections.

Once a neutrophil leaves the bone marrow, it enters the circulation from where it can be rapidly recruited to sites of inflammation or injury. Neutrophils first roll along and then adhere to vascular endothelial surfaces. They then move through endothelial junctions (diapedesis) and migrate to extravascular sites of inflammation, tissue injury or infection. Once recruited, they bind to pathogens, release their toxic granules, and phagocytose foreign materials, including bacteria.

Neutrophils have a short half-life once in the circulation, remaining there only 7–12 hours before undergoing apoptosis. The circulatory half-life shortens further during infective episodes but is increased in the tissues to enhance microbial killing. The combination of a short circulatory half-life and rapid migration of activated neutrophils can result in neutropenia during an infective episode. This is particularly so where the storage pool is reduced and there is an inadequate boost to neutrophil production, such as occurs with a hypoplastic bone marrow, e.g. Fanconi Anaemia, post chemotherapy. Similarly, neonates can become neutropenic because the storage pool is limited and production is already near maximal. However, the neutropenia may be the primary problem that then increases the risk of infection. Although initial treatment will be the same, if the neutrophil count does not recover once the infection is adequately treated, this should prompt further investigation to determine the underlying cause.

What is a normal neutrophil count?

Neutropenia is defined as a reduction in the number of neutrophils in the peripheral blood when compared to age, sex and race matched healthy populations. Appropriate reference ranges are important to avoid misdiagnosing a child with neutropenia. Relative to white Caucasians, people of African, Afro-Caribbean, and Arabic decent have lower neutrophil counts; up to 25% of people of African descent have neutrophil counts of less than 1.0×10^9/litre. This 'ethnic neutropenia' tends to be benign, in that these individuals do not show increased rates of infection and further investigations are not generally necessary. However, if accompanied by recurrent infection or other significant symptoms and signs, further consideration of cause is warranted. Similarly, for infants the lower limit of normal is 1.0×10^9/litre, and children prior to onset of puberty tend to have neutrophil counts lower than adults. Neutropenia secondary to artefact is uncommon and may be due to white cell aggregation or agglutination, a clot in the specimen, an improperly stored sample, or one that is more than 72 hours old. Morphological review of a blood film is essential in the evaluation of neutropenia to pick up both artefact and pathology. A repeat full blood count, especially if the neutropenia is unexpected, is important to confirm the low count before undertaking further investigation. In all cases, clinical circumstances should guide interpretation of the results. Laboratory reference ranges should be stratified for age and where appropriate ethnicity.

The severity and persistence of neutropenia can help predict the risk and severity of bacterial infection. Aetiology of the neutropenia is also important, as the risk is higher in those conditions where production is reduced rather than consumption or destruction increased. Neutropenia is mild and the risk of infection low if the absolute number is below the lower limit of normal but more than 1.0×10^9/litre. Risk is increased for moderate neutropenia with counts between $0.5–1.0 \times 10^9$/litre. For those in the severe and very severe range, 0.2 less than 0.5×10^9/litre and less than 0.2×10^9/litre respectively, the risk of life-threatening infection is significantly increased, particularly if the neutropenia persists more than a few days.

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What are the important features in the history and physical examination?

Individuals may present before neutropenia has been identified. They may be acutely unwell, mildly unwell or asymptomatic. A child can present at any age, but congenital neutropenia is more likely in a young infant than an older child. Patients may present to their general practitioner or to hospital, and the scenarios are likely to be different depending on where the patient presents. If the child is known to have neutropenia, then presentation is most likely to be precipitated by a fever. Neutropenia may be chronic or acute and symptoms and signs will differ. For those with chronic severe neutropenia, symptoms and signs such as recurrent oral disease, poor dental health and perineal problems are seen. There may be a history of recurrent or unusual infections, including fungal infection such as oral thrush. Acute neutropenia, if severe, usually presents with a febrile illness, with or without an obvious focus of infection. Figure 1 shows an algorithm for management and investigation of neutropenia.

Presentation to a general practitioner

A child with undiagnosed neutropenia may present to their general practitioner (GP) not acutely unwell, the neutropenia only becoming apparent once a full blood count has been processed. Symptoms may include coryza, cough or fever, recurrent infection and mouth ulcers, but many children with mild neutropenia are asymptomatic. A repeat count should taken, which may be at the GP surgery or at the local hospital. Important points to note in the history:

- have any previous blood counts shown a normal neutrophil count?
- is there a history of recent viral or recurrent or unusual bacterial infection?
- how long have any symptoms been present?
- has there been any drug exposure, accidental or prescribed?
- is there a family history of recurrent infection or unexplained infant death?
- are any constitutional or systemic symptoms such as fatigue, joint pain or a limp present?

Important points to note in the examination:

- is there mucositis, buccal ulceration, gingivitis or poor dental health?
- is there evidence of infection: skin, upper respiratory tract, pneumonia?
- are perineal or perirectal lesions or fissures present?
- is there evidence of short stature or microcephaly?
- are there any skeletal, skin or nail abnormalities?
- is there any bruising or bleeding?
- is lymphadenopathy or hepatosplenomegaly present?

These points are summarised in Table 1.

If the child is unwell, whether or not there are signs of constitutional or systemic disease, immediate referral to the hospital is mandatory. The presence of neutropenia and a limp or bone pain is a typical presentation of acute leukaemia.

If neutropenia secondary to drug exposure is suspected, the drug should be discontinued immediately and the child referred promptly to a specialist for close monitoring and assessment. Excluding cytotoxic chemotherapy, such medication reactions tend to be idiosyncratic and are rare. They are either immune-mediated or due to direct myeloid toxicity leading to agranulocytosis, the latter being associated with significant infectious

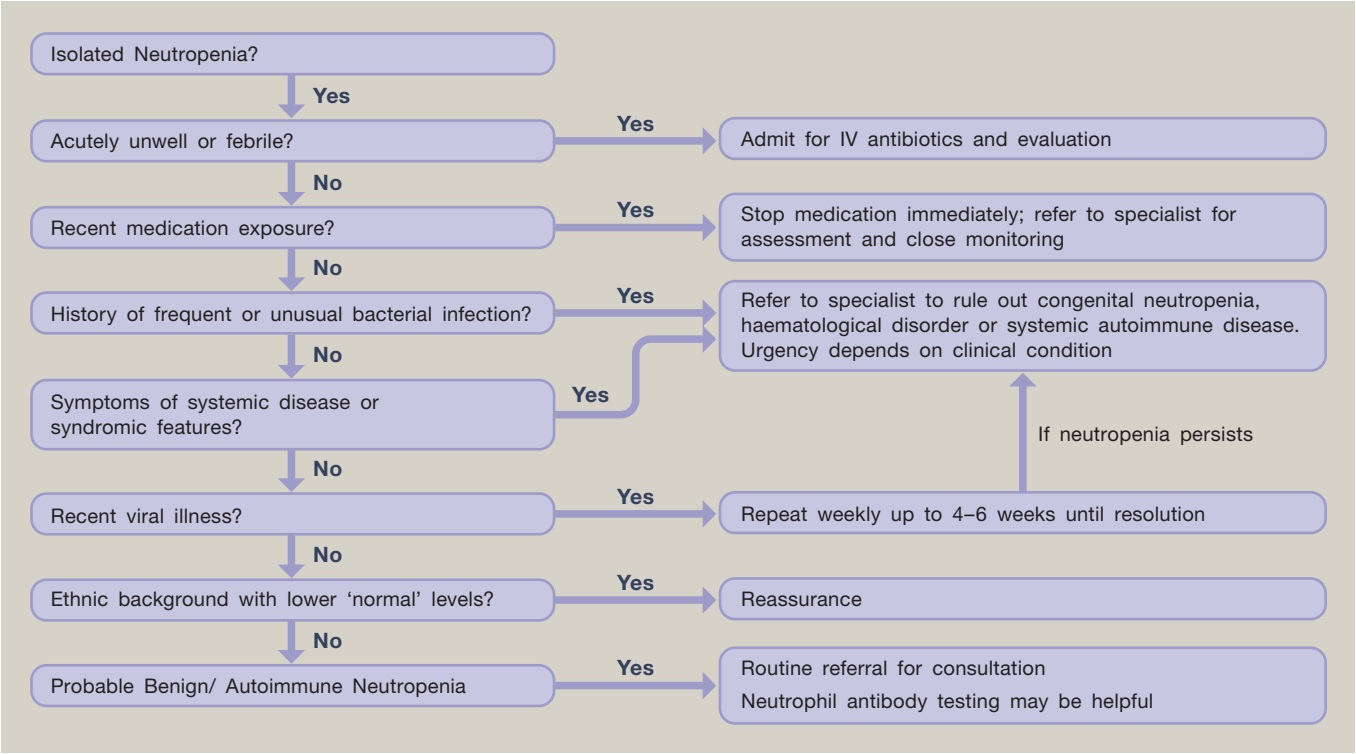

Figure 1 Algorithm: initial investigation and management of neutropenia.

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