Ashford and St. Peter's Hospitals
NHS Foundation Trust

Management of Isolated Neutropenia in Paediatrics

Author: Dr Claire Mitchell

Supervisor:

Contact details: claire.mitchell15@nhs.net

Guideline History		
Date	**Comments**	**Approved By**
18/09/2024	First created	Paediatric Guidelines Committee

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1.

Isolated neutropenia

Guidance

The following guidelines are for the appropriate investigation and referral of children and neonates with isolated neutropenia. If Hb or platelets are also low do not follow this guideline.

Definition:

Neutropenia is defined as:

- Infants (<12 months) = neutrophil count < 1.0 $x10^9$/L
  *Babies with LBW are more likely to be neutropenic.
- Children (12 months and older) = neutrophil count < 1.5 $x10^9$/L

Causes:

In neonates the most common causes are sepsis, perinatal asphyxia, IUGR, congenital infections, haemolytic disease of the newborn/Rh D disease, and neonatal allo-immune neutropenia (NAIN).

Also consider severe congenital neutropenia (SCN), inherited bone marrow failure, and inborn errors of metabolism.

In children > 1month old the most common causes are transient myelosuppression secondary to infection, infant autoimmune neutropenia (AIN), chronic idiopathic neutropenia (CIN).

Also consider cyclical neutropenia, benign ethnic neutropenia, hypersplenism, primary immunodeficiency, severe congenital neutropenia (SCN).

Important questions to ask in the history:

1. Ethnic origin

Afro-Caribbean, Yemenite Jews, Ethopians and certain Arabic communities naturally have a lower neutrophil count. When first noted, re-check FBC and film after 7-10 days to ensure not evolving into leukaemia then only investigate if neutrophil count is < 1.0 $x10^9$/L or if other related concerns.

2. History of recent infection – transient immunosuppression or **severe infection requiring hospitalisation** – severe congenital neutropenia or immunodeficiency

3. History of illness that can lead to hypersplenism (e.g. sickle cell disease (<5 yr olds), hereditary spherocytosis). Neutrophils pool in the over-sized spleen, along with other types of cells such as red cells and platelets

4. Is there a cyclical pattern (about 21 days)

Cyclic neutropenia usually appears in 1st year of life – occurs every 21 days – repeated episodes of fever, malaise, oral ulcers and skin infections. Caused by apoptosis of the myeloid precursors. Severe infection is rare but needs urgent treatment. Known genetic mutation on ELANE/ELA2 gene (IBMFS panel). Treatment – daily GCSF

5. What medications are they taking? – certain drugs are known to induce myelosuppression. Commonly seen with Carbimazole, anti-epileptics, anti-psychotics, Eltrombopag, Hydroxycarbamide. If mild will respond well to reduction/cessation of drug, otherwise may need GCSF.

Management of isolated neutropenia in children >1 month

Neutropenia identified
Infant <12m = neutrophil count < 1.0 x10^9/L
Child > 12m = neutrophil count < 1.5 x10^9/L

If unwell
- look for signs of sepsis
- treat for infection
- consider possibility of leukaemia
- discuss with Haematology if neutrophils do not recover as expected post-illness

If well
- Check for hepatomegaly, splenomegaly, and lymphadenopathy – if present then it is not isolated neutropenia and leukaemia/other causes need to be excluded

If no concerns:
- Arrange to repeat FBC + film in 7 – 10 days' time and safety net for features of leukaemia
* arrange repeat bloods on Ash ward/ED
- Repeat bloods even if neutropenia is likely to be secondary to ethnicity
- Check viral serology for HIV/CMV/EBV/parvovirus

Transient vs Chronic
The majority of isolated neutropenia is secondary to transient myelo-suppression following common infections, commonly parvovirus, EBV and CMV. The neutropenia should resolve within 3 months.
- Repeat FBC 6 weeks and 12 weeks after initial diagnosis of neutropenia
- Ask about recurrent/unusual infections
- Check for growth failure (related to primary immunodeficiency)
- Consider syndromic associations *see below

If neutropenia persists > 4 months:
- Refer to SPH Paediatric Haematology Clinic and arrange second line investigations:
  - FBC, film, reticulocytes
  - ESR/CRP
  - Autoimmune profile
  - Iron studies, ferritin, Vit B12/folate
  - TFTs
  - Viral PCR and serology for HIV/CMV/EBV/parvovirus (if not already done)
  - Immunoglobulins
  - Lymphocyte subsets
  - Lactate (venous sample) – Pearson's syndrome
  - Granulocyte immunology (online form available on NHSBT website – send for autoimmune neutropenia

Possible causes:

Acute post-infectious - This is often transient (<3 months)

Infant autoimmune neutropenia (AIN)
Caused by antibodies against neutrophils but often this cannot be detected. Instead send infant autoimmune screen for granulocyte immunology (send to IBGRL, Bristol).

This is often primary PAIN (onset 4m -28m) – this has an excellent prognosis – frequent infections but good response to prophylactic antibiotics. Spontaneous recovery typically 6-24m. The most severe benefit from GCSF treatment.

It can be secondary SAIN (average age 10yrs old). This is caused by systemic autoimmune disease, infection, neoplasia, bone marrow or organ transplantation, drug administration or immunodeficiency.
It is not easy to differentiate from congenital neutropenia – but it is not the same.

Neonatal alloimmune neutropenia (NAIN)
Antibodies against foetal neutrophils cross the placenta and thus the neonate has very low levels of neutrophils. Common (1:500) but often found incidentally and remain asymptomatic. The antibodies wear off over the first 2 months.
Send parental and child blood samples to NHSBT

Benign ethnic neutropenia (see above for details)

Cyclical neutropenia (see above for details)

Hypersplenism (see above for details)

Vit B12/folate deficiency and copper deficiency with low ceruloplasmin
Has been known to interfere with bone marrow output and thus neutropenia.

Primary immunodeficiency
Neutropenia can be associated with other immune disorders – check immunoglobulins and lymphocyte subsets

Severe congenital neutropenia
Usually present in first year of life with severe, recurrent, systemic infections. Associated thin skin and urogenital abnormalities. Often there is a history of parent consanguinity, family history of neutropenia, and life-threatening infection. More common in Turkish population.
This is rare! A molecular diagnostic test is indicated (ELANE G6PC3 – IBMFS panel)

Conditions associated with neutropenia to consider:
Trisomy 21 syndrome
Shwachman-Diamond syndrome
Kostmann syndrome
Hermansky-Pudlak syndrome
Barth syndrome
SCID (severe combined immunodeficiency), CVID (common variable immunodeficiency),
Di-George syndrome (22q deletion)
X-linked agammaglobulinaemia (Bruton's disease)

Guidance for parents

Children with neutropenia 1.0 – 1.5 x10^9/L do not have a significantly increased risk during infection but should be reviewed if febrile or unwell.

Children with neutropenia <1.0 x10^9/L may be at higher risk of infection. There are some conditions where the neutrophil count is low in the peripheral blood but there isn't a deficiency within the bone marrow – these children are able to mount a normal immune response.
- Prior to a confirmed diagnosis all will need to be treated similarly.
- All should be assessed urgently if they appear unwell or have fever.
- Depending on previous severe infections, and severity of current infections a decision will be made between high dose oral antibiotics or intravenous antibiotics.

Children with severe neutropenia (<0.5 x10^9/L) should be treated using the febrile neutropenia pathway (See Paediatric Microguide). This includes IV Tazocin and Gentamicin within one hour of presentation with fever or illness. After a period of observation, they may well be able to be discharged on 5 days of PO high dose Co-Amoxiclav.

Immunisations
For children with neutropenia <1.0 x10^9/L live immunisations should be avoided. All inactivated/attenuated vaccines can be given. Beware that immunisations given when immunocompromised may not be as effective at protecting. If a child must avoid the live vaccines it is important to ensure those living in close contact with the child are fully immunised to protect them.

Live Vaccines	
Influenza nasal spray	Inactivated form – IM injection
MMR	
Rotavirus	
Varicella	
BCG	
Shingles	
Oral typhoid	
Yellow fever	

References:

University Hospitals Bristol and Weston Clinical Guideline: Neutropenia in Childhood – Investigation and Referral Guideline. Author: Maria Pelidis, Consultant Paediatric Haematologist. Ratified Nov 2022. Next review Nov 2025.

NHS Blood and Transplant (NHSBT) Hospitals and Science Histocompatability and Immunogenetics (H&I) test request forms

UpToDate article Overview of Neutropenia in children and adolescents. Author T. Coates et al. Published Sept 2022, reviewed August 2024.
https://www.uptodate.com/contents/overview-of-neutropenia-in-children-and-adolescents

The Green Book: Immunisations against Infectious Diseases, Chapter 6. Contraindications and Special Considerations.
Contraindications and special considerations: the green book, chapter 6 - GOV.UK (www.gov.uk)

2. Guideline Governance

a. Scope

This guideline is relevant to all staff caring for all children from 0-18 years old across the emergency department, inpatient ward and outpatient department.

b. Purpose

i. This guidelines aims to facilitate a common approach to the management of children. At times deviation from the guideline may be necessary, this should be documented and is the responsibility of the attending consultant.

ii. This guideline is subject to regular review to ensure ongoing evidence based practice.

c. Duties and Responsibilities

All healthcare professionals responsible for the care of all children 0-18years should be aware of practice according to this guideline.

d. Approval and Ratification

This guideline will be approved and ratified by the Paediatric Guidelines Group.

e. Dissemination and Implementation

i. This guideline will be uploaded to the trust intranet 'Paediatric Guidelines' page and thus available for common use.
ii. This guideline will be shared as part of ongoing education within the Paediatric Department for both medical and nursing staff.
iii. All members of staff are invited to attend and give comments on the guideline as part of the ratification process.

f. Review and Revision Arrangements

a. This policy will be reviewed on a 3 yearly basis by the appropriate persons.
b. If new information comes to light prior to the review date, an earlier review will be prompted.
c. Amendments to the document shall be clearly marked on the document control sheet and the updated version uploaded to the intranet. Minor amendments will be ratified through the Paediatric Guidelines Group. A minor amendment would consist of no major change in process, and includes but is not limited to, amendments to documents within the appendices.

g. Equality Impact Assessment

Background • Who was involved in the Equality Impact Assessment
Author and the supervising consultants.
Methodology • A brief account of how the likely effects of the policy was assessed (to include race and ethnic origin, disability, gender, culture, religion or belief, sexual orientation, age) • The data sources and any other information used • The consultation that was carried out (who, why and how?)
All groups of staff and patients were taken into consideration and there is no bias towards or against any particular group.
Key Findings • Describe the results of the assessment • Identify if there is adverse or a potentially adverse impacts for any equalities groups
There is no evidence of discrimination.
Conclusion • Provide a summary of the overall conclusions
There is no evidence of discrimination.
Recommendations • State recommended changes to the proposed policy as a result of the impact assessment • Where it has not been possible to amend the policy, provide the detail of any actions that have been identified • Describe the plans for reviewing the assessment
This guideline is appropriate for use.

h. Document Checklist

To be completed (electronically) and attached to any document which guides practice when submitted to the appropriate committee for approval or ratification.

Title of the document: Management of Isolated Neutropenia in Paediatrics

Policy (document) Author: Dr Claire Mitchell

Executive Director: N/A

		Yes/No/ Unsure/NA	Comments
1.	**Title**		
	Is the title clear and unambiguous?	**Y**	
	Is it clear whether the document is a guideline, policy, protocol or standard?	**Y**	
2.	**Scope/Purpose**		
	Is the target population clear and unambiguous?	**Y**	
	Is the purpose of the document clear?	**Y**	
	Are the intended outcomes described?	**Y**	
	Are the statements clear and unambiguous?	**Y**	
3.	**Development Process**		
	Is there evidence of engagement with stakeholders and users?	**N/A**	
	Who was engaged in a review of the document (list committees/ individuals)?		**Dr Rubina Malik – Consultant Haematologist SGH.**
	Has the policy template been followed (i.e. is the format correct)?	**Y**	
4.	**Evidence Base**		
	Is the type of evidence to support the document identified explicitly?	**Y**	

		Yes/No/ Unsure/NA	Comments
	Are local/organisational supporting documents referenced?	**N/A**	
5.	**Approval**		
	Does the document identify which committee/group will approve/ratify it?	**Y**	
	If appropriate, have the joint human resources/staff side committee (or equivalent) approved the document?	**N/A**	
6.	**Dissemination and Implementation**		
	Is there an outline/plan to identify how this will be done?	**Y**	
	Does the plan include the necessary training/support to ensure compliance?	**Y**	
7.	**Process for Monitoring Compliance**		
	Are there measurable standards or KPIs to support monitoring compliance of the document?	**N**	
8.	**Review Date**		
	Is the review date identified and is this acceptable?	**Y**	
9.	**Overall Responsibility for the Document**		
	Is it clear who will be responsible for coordinating the dissemination, implementation and review of the documentation?	**Y**	
10.	**Equality Impact Assessment (EIA)**		
	Has a suitable EIA been completed?	Y	

Committee Approval (Paediatric Guidelines Group)			
If the committee is happy to approve this document, please complete the section below, date it and return it to the Policy (document) Owner			
Name of Chair	**Alexandra Jones**	**Date**	**20/9/24**
Ratification by Management Executive (if appropriate)			
If the Management Executive is happy to ratify this document, please complete the date of ratification below and advise the Policy (document) Owner			
Date: n/a			