All Wales guideline on the diagnosis and management of paediatric neutropaenia

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Adapted from: The 2023 European Guidelines on Diagnosis and Management of Neutropenia in Adults and Children: A Consensus Between the European Hematology Association and the EuNet-INNOCHRON COST Action. [1]

Objectives:

1. **Provide a pragmatic approach to assessing a clinically well child with a new finding of neutropaenia.**

2. **Provide guidance on how to investigate and when to refer to a Paediatric Haematologist**

3. **Provide an overview of the potential causes of neutropaenia (congenital vs acquired) - although it is very unlikely for a diagnosis to be made on the first clinical encounter.**

This guideline does not provide guidance on how to manage a patient who has suspected/confirmed Neutropenic Sepsis.

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Definition of Neutropaenia

The definition of Neutropaenia varies according to the patient's age and ethnic origin (see Table 1)

Table 1: Definition of Neutropaenia:

- **Absolute Neutrophil Count (ANC) of less than 1.5×10^9/l (in a child aged >12 months)**
- **Absolute Neutrophil Count (ANC) of less than 1.0×10^9/l (in a child aged between 14 days and 12 months)**

Important notes:

- ANC <1.5 x 10^9/L are considered normal in individuals from African and Middle Eastern Ancestry (see Appendix 1)
- Neonates <14 days and preterm neonates have different cutoffs

Classification of Neutropaenia

There is widespread international consensus that the risk and outcome of bacterial infections resulting from neutropaenia depends on the individual's capacity to recruit and deliver neutrophils to tissues (instead of only depending on the ANC in the peripheral blood). [2] [3]

However, there is no validated method to estimate the total body neutrophil count.

Therefore, classification into mild, moderate, and severe neutropaenia is extrapolated from the individual's absolute neutrophil count in the peripheral blood. Neutropaenia is defined as acute or chronic depending on its duration - <3 months and >3 months respectively [4] (see Table 2).

Table 2: Classification of Neutropaenia

- **Severity:**
  - **Mild:** ANC between **1.0×10^9/l and 1.5×10^9/L**
  - **Moderate:** ANC between **0.5×10^9/l and 1.0×10^9/L**
  - **Severe:** ANC less than **0.5×10^9/L**
  - **Agranulocytosis:** Severe Neutropaenia with ANC <$0.2\text{x}10^9$/L. Usually associated with a high risk of severe, life-threatening infections.
- **Duration:**
  - **Acute Neutropaenia:** Duration <3 months
  - **Chronic Neutropaenia:** Duration >3 months

Congenital Neutropaenia

Congenital neutropenia (CN) comprises a group of genetic diseases characterized by impaired production, differentiation, and survival of neutrophils in the bone marrow (BM), susceptibility to infections, and increased propensity to MDS/AML transformation.

CN can be further subclassified into disorders where neutropenia is the **only abnormality** and those where neutropenia is **associated with extra haematological manifestations**, **immunodeficiency/immune dysregulation, metabolic disorders,** and **nutritional deficiencies**, or as part of more complex **BM failure syndromes**. [5-11] **See Appendix 1(B) for exhaustive list of causes.***

Acquired Neutropaenia

Acquired neutropenia can be primary or idiopathic, associated with the presence of antineutrophil antibodies or other unknown mechanisms; and secondary due to infections, autoimmune diseases, exposure to drugs, nutritional deficiencies, hypersplenism, or haematological diseases.

Likely acquired neutropenia includes mostly idiopathic or autoimmune neutropenia (AIN) of childhood, which usually seems to have a benign and uncomplicated course but does not resolve after 24–36 months (long lasting) or neutropenia, with and without antibodies, which arises after the age of 3 years (late onset). [12-20] **See Appendix 1(C) for exhaustive list of causes.***

***Please note: The information listed in the Appendix is for reference only. It has been included in this guideline to enable professionals to access it if they wish to. There is no need for referrers to know this information prior to discussing a case with Paediatric Haematology.**

Assessment of Acute Neutropaenia

Important notes

After you have completed a full history and examination, and prior to proceeding to further investigations/discussions with Specialists, please note the following:

1. **If a child aged >6 months does not have any preceding history of serious infections, this strongly hints towards autoimmune rather than congenital neutropaenia.**

2. **It is essential to check if a previous FBC has been checked. If Neutrophils were in the normal range in any previous sample, this rules out congenital neutropaenia.**

Diagram 1. Assessment of patient with Acute Neutropaenia

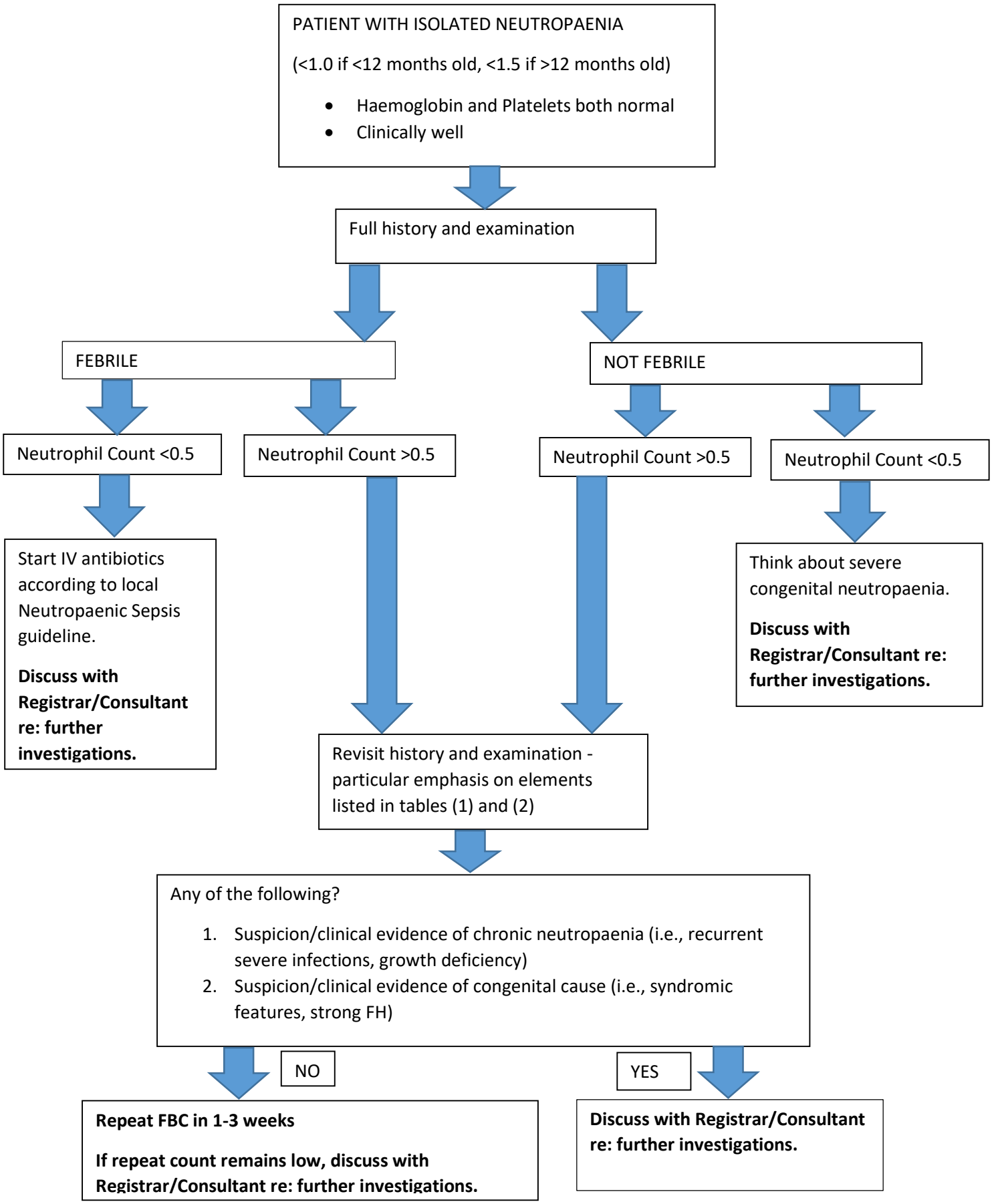
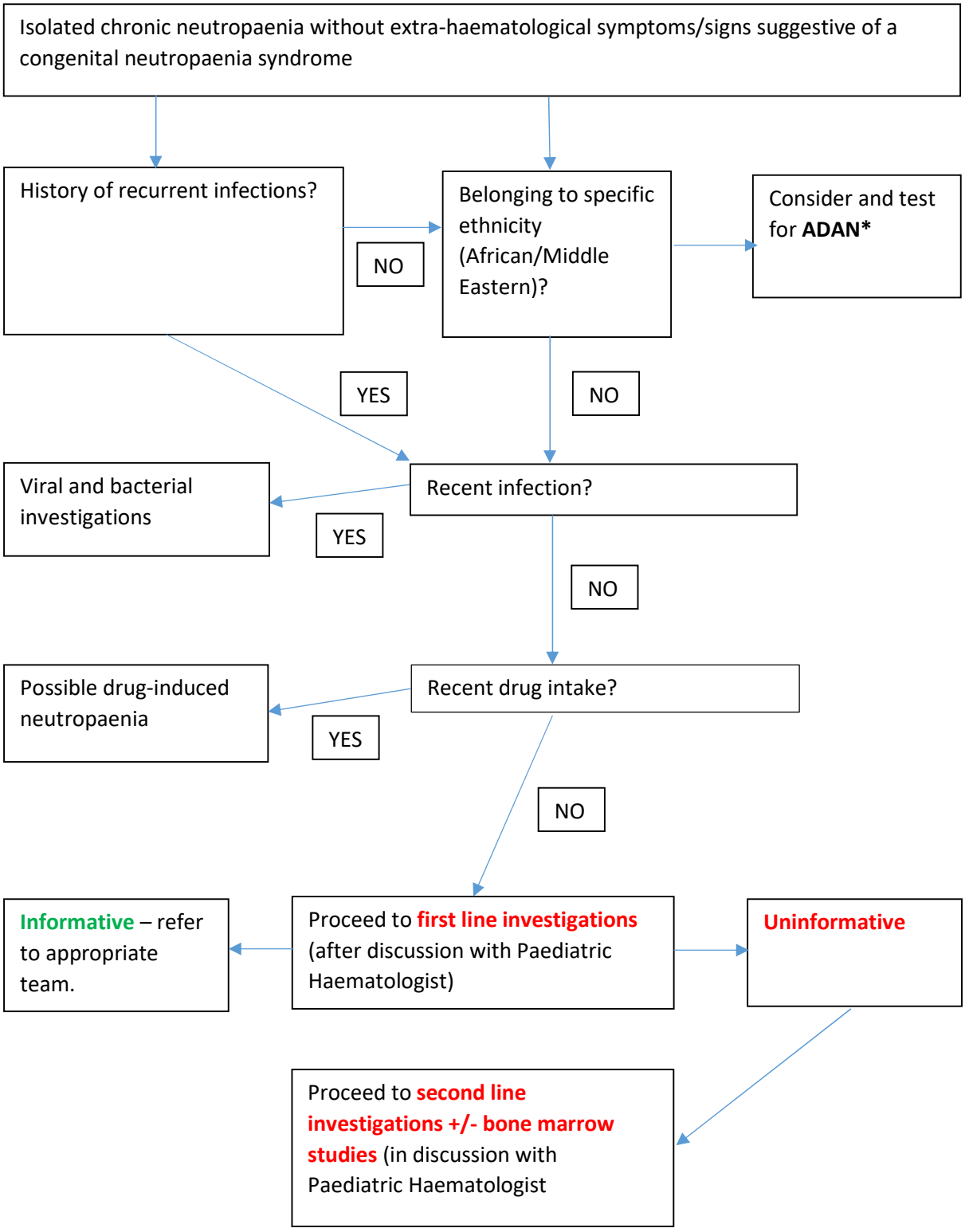


Diagram 2. Assessment of patient with chronic neutropaenia [1]

Please note: First line investigations should be requested following discussion with a Paediatric Haematologist.



***Consider testing for rs281478 C/C polymorphism of ACKRI/DARC and/or the Duffy red blood cell phenotype.**

History – how to approach

Table 1 [21]

What to ask	What it might indicate
Infection history • Severe, recurrent infections, requiring antibiotics (umbilical stump infections, skin abscesses including peri-rectal abscesses, meningitis, recurrent respiratory infections, recurrent mouth ulcers)? • Age of onset • Any "cyclical" pattern to infections?	• Neonatal infections, previous admissions, previous need for antibiotics are features of SCN: 50% children with SCN have an infection as a neonate, and 90% have had an infection by 6months. • In cyclical neutropenia the cycle may range from 14 days to 36 days: typically, 21 days
Systems review • Fatty stools, hard to flush?	• Schwachman-Diamond syndrome, Pearson syndrome (pancreatic insufficiency)
Growth and Development • Any concerns about reduced growth/delayed development?	• May be present in any causes of SCN—lack of growth problems does not rule these out.
Immunisations • Any missed doses?	• Children with frequent infections may have missed immunisation.
Drug history • Any regular/new medicines?	• Drug causes – remember over-the-counter medicines and "natural" remedies
Family history • Any FH of recurrent infections, especially mouth ulcers? • Anyone else neutropenic? • Any FH of autoimmune disorders?	• Often seen in cyclical neutropenia • Seen in familial neutropenia and in syndromic causes. • Can be associated with autoimmune neutropenia.

Examination – how to approach

Table 2 [21]

When assessing the patient, it is essential to perform a full systems examination.

In addition, it is imperative to ensure the following elements are covered:

What to do	What it might indicate
Growth • Plot height and weight **(remember: look at previous centiles if available and interpret in the context of mid-parental height)**	• >50% children with SCN have a height below the 10th centile by the age of 11 years.
Dysmorphic features – look for: • Dystrophic changes (nails) • Splinter haemorrhages (nails) • Café-au-lait spots (skin) • Vitiligo (skin) • Reticular pigmentation (skin) • Thumb/radial anomaly	 • Dyskeratosis congenita • Vasculitides • Fanconi Anaemia • Autoimmune disease • Dyskeratosis congenita • Fanconi Anaemia
Oral examination – look for: • Active gingivitis • Leukoplakia	 • Chronic cause for neutropaenia • Dyskeratosis congenita
Lymphatic system – look for: • Lymphadenopathy (cervical, axillary, inguinal) • Hepatosplenomegaly	 • If widespread, think about malignancy! • Common: malignancy, viral causes. Less common: storage disorders, haemophagocytosis.

Box 1: First-line Investigations

- FBC, Blood film
- LFTs, U&Es, CRP
- Vitamin B12, folate
- TFTs, antithyroid antibodies (Anti-TG, Anti-TPO)
- Immunoglobulins
- Lymphocyte subsets - including TCR-α/β-positive double-negative (CD4- and CD8-) CD3 PB lymphocytes.
- Virology antibody screening (Hep B, Hep C, HIV, EBV, CMV, and Parvovirus),
- Indirect antineutrophil antibodies (GIFT, GAT, and other) https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/25612/2122-0010-3e_specbagfrm1001-41_zxu1142.pdf

Box 2: Second-line investigations

- FBC in family members
- Serial FBC twice weekly over a period of 6 weeks (r/o Cyclical Neutropaenia)
- Copper, Caeruloplasmin
- IgA Anti-tTG
- IgA/IgG deamidated gliadin peptide antibodies
- Amylase
- Rheumatoid factor
- ANA, ENA, ds-DNA
- NGS panels:
  - Immune
  - Cytopenia
  - BM failure

Appendix 1

***Please note: The information listed in the Appendix is for reference only. It has been included in this guideline to enable professionals to access it if they wish to. There is no need for referrers to know this information prior to discussing a case with Paediatric Haematology**

A) *ACKR1/DARC*-associated neutropenia (ADAN)

This variation affects some individuals of African and Middle Eastern descent, **who display normal Neutrophil counts** in the range from 0.5 to 1.5 × 10^9/L. [1]

It was previously termed ethnic neutropenia and is usually inherited as an autosomal recessive trait associated with a polymorphism (rs2814778, −46T>C) in the GATA box in the promoter region of the atypical chemokine receptor-1 (*ACKR1*) gene, also known as the Duffy antigen receptor for chemokines (*DARC*). [1]

In homozygosity (C/C), the polymorphism results in the absence of Duffy antigen expression specifically on red blood cells, a phenotype known as Duffy-null. [1]

B) Congenital Neutropaenias: List of causes [1]

Congenital Neutropenias			
	Genes Involved	**Type of Inheritance**	**Main Features/Notes**
Isolated			
Severe congenital neutropenia	*ELANE*	AD	Arrest of neutrophil maturation in bone marrow
	CSF3R	AD	Arrest of neutrophil maturation in bone marrow, unresponsive to G-CSF
	CXCR2	AR	No arrest of maturation and myelokathexis
	WAS gain of function	X-linked	(WASp-XLN) Maturation delay, monocytopenia
Cyclic neutropenia	*ELANE*	AD	Intermittent/cyclic impaired differentiation

Associated with various extrahematological manifestations			
Barth Syndrome (3-methylglutaconic aciduria type II)	*TAZ*	X-linked	No maturation arrest, hypertrophic cardiomyopathy, and myopathic syndrome
Charcot-Marie-Tooth neuropathy type B	*DNM2*	AD	Distal limb muscle weakness and atrophy due to peripheral neuropathy
Cohen syndrome	*VPS13B*	AR	No maturation arrest, psychomotor retardation, microcephaly, facial features, hypotonia, joint laxity, progressive, retino-choroidal dystrophy, and myopia
G6PC3 mutation	*G6PC3*	AR	Skin hyperelasticity and prominent superficial venous network, congenital heart disease, arrhythmias, uropathy, cryptorchidism, and exocrine pancreatic dysfunction
GFI1 mutation	*GFI1*	AD	Sometimes maturation arrest, lymphopenia, increased numbers of immature myeloid cells in the peripheral blood and inner ear defect
HYOU1 deficiency	*HYOU1*	AR	Hypoglycemia and inflammatory complications
JAGN1 mutation	*JAGN1*	AR	Sometimes maturation arrest, bone and teeth abnormalities, and exocrine pancreatic dysfunction
Kostmann disease	*HAX1*	AR	Maturation arrest, mental retardation, seizures, and susceptibility to MDS/AML
P14/LAMTOR2 mutation	*LAMTOR2*	AR	Chronic neutropenia, hypogammaglobulinemia, no maturation arrest, oculocutaneous albinism, and failure to thrive
Pearson syndrome	Mitochondrial DNA deletions	Mitochondrial	Refractory sideroblastic anemia, vacuolization of bone marrow precursors, and exocrine pancreatic dysfunction
Schimke immuno-osseus dysplasia	*SMARCAL1*	AR	Spondylo-epiphyseal dysplasia, slowly progressive immune defect, and immune-complex nephritis
SEC61A1 mutation	*SEC61A1*	AD	Maturation arrest and tubulointerstitial kidney disease
SMARCD2 mutation	*SMARCD2*	AR	Dysplastic syndrome, no granules in neutrophils, chronic diarrhea, bone abnormalities, and low set ears
Specific granule deficiency	CEBPE	AR	Neutrophils with bilobed nuclei
TCIRG1 neutropenia	*TCIRG1*	AD	Variable/no maturation arrest and skin angiomatosis
VPS45 mutation	*VPS45*	AR	Myeloid hyperplasia, myelofibrosis, nephromegaly, HSM, mental retardation, epilepsy, and osteosclerosis
Wolcott-Rallison syndrome	*EIF2AK*	AR	Maturation arrest, insulin-dependent neonatal diabetes, epiphyseal dysplasia, growth retardation, hepatic and renal dysfunction, developmental delay, and exocrine pancreatic deficiency

Associated with immunodeficiency/immune dysregulation			
Adenosine deaminase 2 deficiency	*ADA2*	AR	Severe combined immunodeficiency, vasculitis, cerebrovascular disease, pure red cell aplasia, and BMF
ALPS	*FAS, FASLG, CASP10*	AD	Lymphoproliferation and autoimmune cytopenias
CD40L/hyper IgM syndrome, type I	*CD40L*	X-linked	Severe infections, autoimmune disease, and cancer predisposition
Chédiak-Higashi syndrome	*LYST*	AR	Decreased pigmentation of hair and eyes, peroxidase-positive inclusion bodies in the myeloblasts and promyelocytes of the bone marrow, peculiar malignant lymphoma
CLPB syndrome	*CLPB*	AR	Cataracts and neurologic involvement
FHLH	*PRF1*, Perforin deficiency (*FHL2*)	AR	Fever, HSM, and cytopenias
	UNC13D, UNC13D deficiency (*FHL3*)	AR	Fever, HSM, and cytopenias
GATA2 syndrome	*GATA2*	AD	Monocytopenia, deafness, and HPV infections
Griscelli syndrome, type II	*RAB27A*	AR	Hypomelanosis and neurologic impairment
Hermansky-Pudlak syndrome type2	*AP3B1*	AR	Albinism
Reticular dysgenesis	*AK2*	AR	Severe combined immunodeficiency and sensorineural deafness
STK4 mutation	*STK4*	AR	Intermittent neutropenia, monocytopenia, T- and B-lymphopenia, atrial defect, and HPV infections
WHIM syndrome	*CXCR4*	AD	No arrest of maturation, myelokathexis, and lymphopenia, cardiopathy (Tetralogy of Fallot)
Wiskott-Aldrich syndrome	*WAS* loss of function	X-linked	(WASp-XLT) Eczema, thrombocytopenia, severe infections, and bloody diarrhea
CVID	Various genes including *TNFSRF13, BAFFR, CTL4, LRBA, PI3K*	AD,AR	Infection recurrence, hypogamma globulinemia, and autoimmune cytopenias including neutropenia.
Associated with metabolic disorders and nutritional deficiency			
Gaucher disease type I	*GBA*	AR	HSM, thrombocytopenia, and osteolytic lesions
Glycogen storage disease Ib	*SLC37A4/G6PT1*	AR	Hepatomegaly, IBD, and fasting hypoglycemia
Isovaleric acidemia	*IVD*	AR	Neonatal ketoacidosis, developmenta delay, lethargy, and feeding refusal
Methylmalonic acidemia	*MMUT*	AR	Lethargy, failure to thrive, recurrent vomiting, hypotonia, hepatomegaly, and developmental delay
Propionic acidemia	*PCCB, PCCA*	AR	Lethargy, cardiomyopathy, feeding difficulties, and acute encephalopathy
Transcobalamin II deficiency	*TCN2*	AR	Developmental delay, diarrhea, vomit, lethargy, and mucosal ulceration

Associated with bone marrow failure			
Fanconi anemia	*FANC* complementation group	AR X-linked (FANCB)	Congenital malformations and cancer predisposition
Ribosomopathies			
Diamond-Blackfan Anemia	*RPS7, RPS10, RPS15, RPS17, RPS19, RPS24, RPS26, RPS27, RPS27a, RPS28, RPS29* *RPL5, RPL9, RPL11, RPL15, RPL18, RPL26, RPL27, RPL31, RPL35a*	AD	Erythroid hypoplasia, congenital malformations, growth retardation, osteosarcoma, MDS, and AML
	GATA1	X-linked	Early-onset anemia, thrombocytopenia, and bone marrow erythroid hypoplasia
	EPO	AR	Erythroid hypoplasia
	TSR2, HEATR3	X-linked AR	Erythroid hypoplasia, craniofacial defects, short stature, facial, and acromelic dysmorphic features, and intellectual disability
Cartilage-hair hypoplasia	*RMRP*	AR	Short stature (dwarfism) with other skeletal abnormalities; metaphyseal chondrodysplasia, ligamentous laxity; fine, sparse hair (hypotrichosis); and abnormal immune system function (immune deficiency), recurrent infections.
Shwachman-Diamond syndrome	*SBDS, EFL1, DNAJC21*	AR	Mild neutropenia, dysgranulopoiesis, mild dysmegakaryopoiesis, dyserythropoiesis, exocrine pancreas deficiency, metaphyseal dysplasia, cognitive impairment, cardiomyopathy, metaphyseal dysplasia, failure to thrive, and hair/skin/teeth abnormalities.
SAMD9/SAMD9L syndromes	*SAMD9/SAMD9L*	AD	Adrenal insufficiency, congenital malformations, cerebellar ataxia, severe invasive infections, and MDS predisposition
SRP54 mutation	*SRP54*	AD	Maturation arrest, severe neurodevelopmental delay, and exocrine pancreatic dysfunction
Telomere diseases	*DKC1*	X-linked	Mucocutaneous features, liver fibrosis idiopathic pulmonary fibrosis, and cancer predisposition
	hTR, TERT, TINF2, DKC1, ACD	AD	
	TERT, NHP2, NOP10, WRAP53, NOLA3,TCB1, RTEL1, CTC1, PARN	AR	
U6 small nuclear RNA biogenesis	*USB1* (Clericuzio syndrome, poikiloderma with neutropenia)	AR	Retinopathy, developmental delay, facial dysmorphisms, and poikiloderma

AD = autosomal dominant; AR = autosomal recessive; ALPS = autoimmune lymphoproliferative syndrome; MDS = myelodysplastic syndrome; AML = acute myeloid leukemia; FHLH = familial hemophagocytic lymphohistiocytosis; HPV = human papilloma virus; IBD = chronic inflammatory bowel disease; HSM = hepatosplenomegaly; BMF = bone marrow failure.

C) Acquired Neutropaenias: List of causes [1]

Primary or idiopathic: neutropenia as predominant, often isolated feature	Antibody-mediated
	Primary autoimmune
	Primary alloimmune
	Nonantibody-mediated
	Idiopathic neutropenia of infancy
	CIN/idiopathic cytopenia of undetermined significance-neutropenia (ICUS-N)
Secondary: neutropenia associated/due to	Hypersplenism (due to congestive, infiltrative, phagocytic, and reactive splenomegaly)
	Infections
	Viral (e.g., HIV, HCV, HBV, CMV, EBV, HIV, influenza, parvovirus B19, measles, and Sars-Cov-2)
	Bacterial (e.g., *Salmonella*, *Brucella*, *Rickettsia*, *Mycobacterium*, *Mycoplasma*, and *H. Pylori*)
	Parasitic (e.g., *Plasmodium spp*, visceral leismaniasis)
	Fungal (e.g., histoplasmosis)
	Autoimmune diseases
	Organ specific (e.g., thyroid diseases, inflammatory bowel disease, and primary biliary cirrhosis)
	Systemic (e.g., systemic lupus erythematosus, rheumatoid arthritis including Felty's syndrome, Sjogren syndrome, systemic sclerosis, and graft-vs-host disease)
	Nutritional deficiencies
	B12, folic acid, iron, copper, and caloric malnutrition
	Immuno-regulatory disorders
	Common variable immunodeficiency, ALPS, ALPS-like diseases, HLH, and macrophage activation syndrome
	Hematologic diseases
	Primary benign (aplastic anemia)
	Clonal (myeloid malignancies/lymphoid malignancies including LGL)
	Drug-induced
	-Chemotherapy
	-Nonchemotherapeutic drugs: analgesics and NSAIDs, antibiotics (beta-lactams, cefipime, trimethoprim-sulfametoxazole, sulfasalazine, vancomycin, rifampicin, fluconazole, ketoconazole), antidiuretics (furosemide, spironolactone), antiretroviral (HIV) therapy, antithyroids (tiamazofe, metimazole), clozapine (olanzapine), deferiprone, dipyrone (metamizole), phenothiazines (alimemazine), quinine/quinidine, IVIG, monoclonal antibodies (Rituximab), and biological therapies (Infliximab, etanercept)
	Extended list of drugs associated with neutropenia can be found in the following references: [35–38]
Likely acquired	
In children/adolescents when neutropenia, in the presence or absence of specific antibodies against neutrophils arises or persists beyond the age of 5 years, the definition of late-onset and long-lasting neutropenia may be appropriate. Recent articles identified this atypical neutropenia as an epiphenomenon of immune dysregulation with typical biochemical/immunological features and the presence of variants in genes regulating immunity.	

ALPS = autoimmune lymphoproliferative syndrome; CIN = Chronic idiopathic neutropenia; CMV = cytomegalovirus; EBV = Epstein-Barr virus; HCV = Hepatitis C virus; HLH = hemophagocytic lymphohistiocystosis; ICUS-N = idiopathic cytopenia of undetermined significance-neutropenia.

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