Neutropenier

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Guideline Article – Consensus based

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The 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

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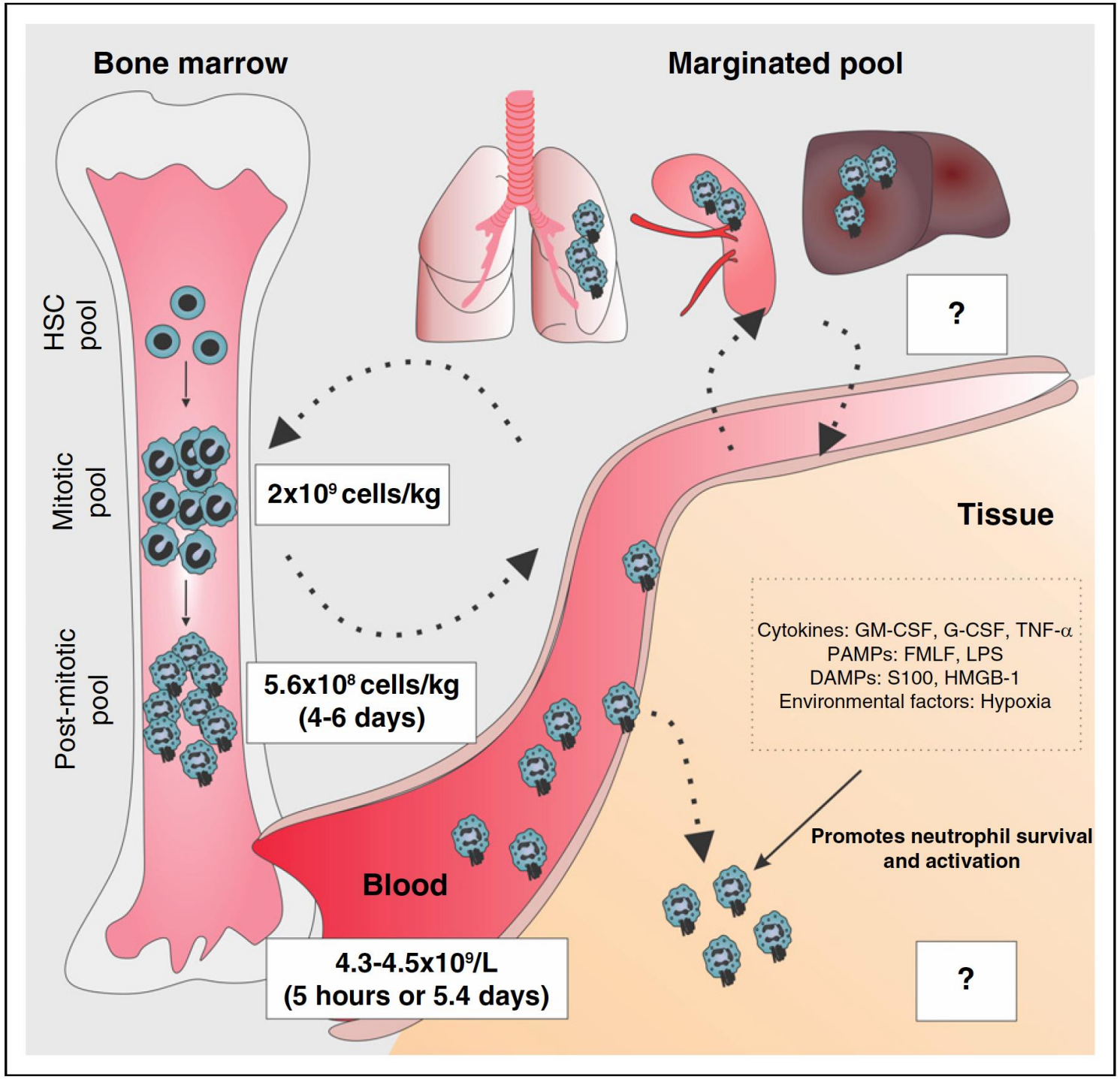

Slide: Christer Nilsson (CN)

Silvestre-Roig, *Blood*, 2016

Neutrofilens uppgifter

- Bekämpa patogener:
  - Fagocytos: syreradikaler + enzymer
  - Degranulering: antibakteriella peptider
  - Neutrophil extracellular traps (NETs)
- Modulera övriga immunförsvaret:
  - Presentera antigen för T-celler
  - B cell-hjälpar-neutrofiler
  - Påverkar NK-cellernas utveckling
  - + många andra funktioner

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Neutropeni - definition

- Neutrofila under lägre normalgränsen för patientens ålder och etniska ursprung

Table 1

ANC Cutoff Level for Definition of Neutropenia According to Age

Age	ANC[a]
From 14 d to 1 yr	$<1.0 \times 10^9$/L
Children >1 y to adulthood*	$<1.5 \times 10^9$/L
Adults[a]	$<1.8 \times 10^9$/L

[a]ANC $<1.5 \times 10^9$/L are considered normal in individuals from African and the Middle Eastern ancestry.
ANC = absolute neutrophil count.

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Table 1. Stratification of neutropenia by severity and clinical context.

Neutropenia stratification	ANC (× G/L)	Clinical context	Risk of infection
Mild	1.0–1.5	General good health Associated disease, debilitated, malnourished.	Usually none Minimal to severe[a]
Moderate	0.5–1.0	General good health Associated disease, debilitated, malnourished.	Usually minimal Moderate to severe[a]
Severe[b]	<0.5	*All clinical settings*	Moderate to severe

[a]Often because of coexistent acquired immunodeficient conditions.
[b]The term *agranulocytosis* implies a complete absence of neutrophils, but is generally used to indicate a very severe NP (i.e. ANC <0.2 × G/L).
Adapted from Wright and Palmblad [1].

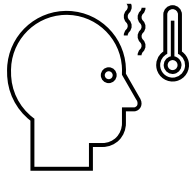
Jan Palmblad, Christer C. Nilsson, Petter Höglund & Helen A. Papadaki (2016): How we diagnose and treat neutropenia in adults, Expert Review of Hematology

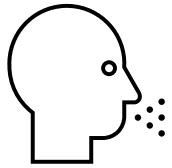
Neutropenier

- Brett spektrum av medfödda och förvärvade tillstånd
- Benigna och premaligna (predisposition för MDS/AML)
- Framsteg inom diagnostiken har avslöjat nya gener och mekanismer
- Möjlighet till skräddarsydd behandling

Infektionsrisk?

- Risken för bakteriella infektioner beror mer på individens kapacitet att rekrytera och fördela neutrofiler till vävnader än totala antalet neutrofila som kan uppmätas i blodet
- Finns dock idag inget sätt att mäta totala neutrofila (blod+vävnad)





Neutropenier - indelning

Akuta / övergående

- Läkemedel
- Sepsis
- Virus
- LON - Rituximab

Kroniska

- Severe congenital neutropenia (SCN)
- Autoimmun neutropeni (AINP)
  - Primär
  - Sekundär
- ADAN (ACKR1/DARC-associerad neutropeni)
- Idiopatisk neutropeni (INP)

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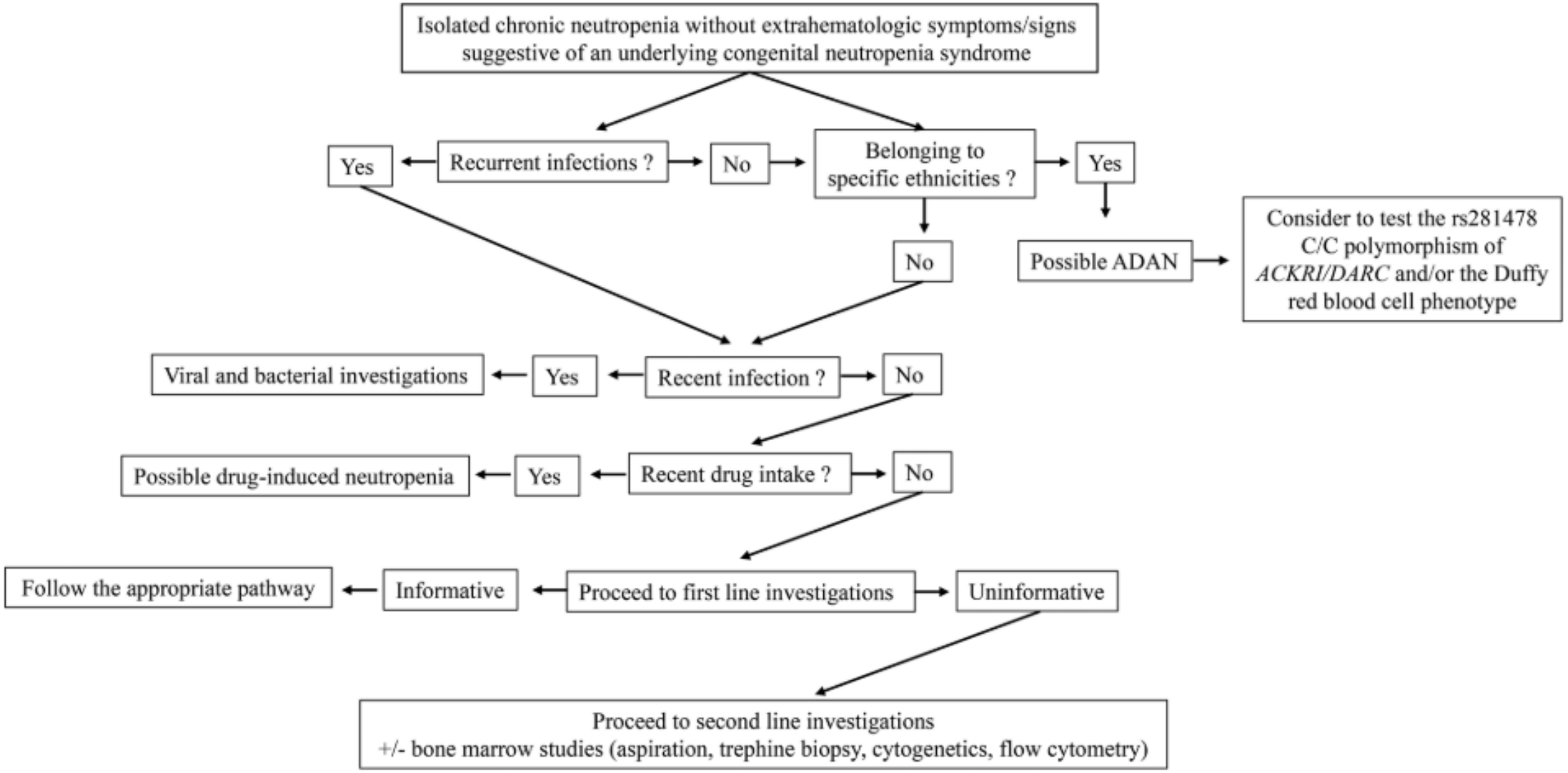

Figure 1. Flowchart for the basic evaluation of a patient with chronic neutropenia.

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Utredning - primär

- Blodstatus inkl diff, perifert blodutrstryk
- El- och leverstatus
- Immunglobulin nivåer
- CRP, kobalamin, folsyra
- Flödescytometri – lymfocyt subsets
- HepB, HepC, HIV, EBV, CMV och Parvovirus
- Neutrofilantikroppar
- Fritt T3, FT4, TSH, anti-TG och anti-TPO
- Eventuella ytterligare analyser: antifosfolipidantikroppar, flödescytometri för LGL/ TCR klonalitet, ferritin, RF, ANA, SR

Diagnostik - sekundär

- Blodstatus på familjemedlemmar
- Blodprover två ggr/vecka I 6 veckor för att utesluta cyklisk neutropeni
- Koppar; ceruloplasmin
- anti-tTG-IgA, IgG-antikroppar mot deamiderat gliadin (ffa barn) och pankreasamylas.
- Eventuellt: serum elfores, komplementnivåer, genpanel för myeloida maligniteter för att identifiera risk för MDS/AML-utveckling

Sekundär neutropeni

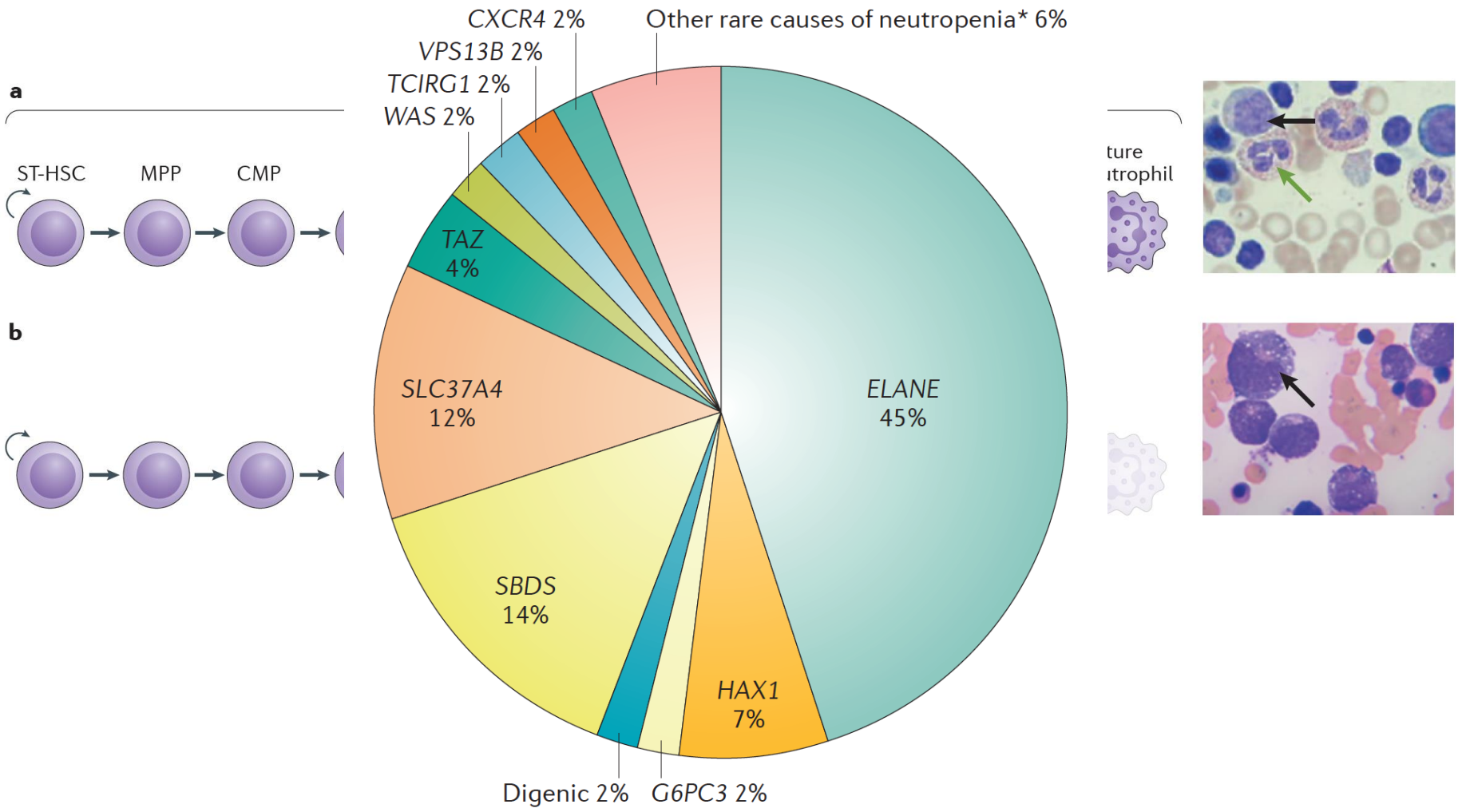
Table 3

Classification of Acquired Neutropenias

Acquired	
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].

Fioredda. Hemasphere. 2023

SCN – Severe congenital neutropenia



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Skokowa, *Nature Reviews*, 2017

Gene mutated	Disease	Other haematological abnormalities	Non-haematological abnormalities
Autosomal dominant inheritance			
ELANE	Severe congenital neutropenia	Monocytosis, eosinophilia and evolution to AML or MDS	Osteopenia
ELANE	Cyclic neutropenia	Cyclic haematopoiesis and evolution to AML or MDS	None
GFI1	Severe congenital neutropenia	Lymphopenia and increased numbers of immature myeloid cells in the peripheral blood and evolution to AML or MDS	None
GATA2	Congenital neutropenia	Severe monocytopenia, dendritic cell and natural killer cell deficiencies, aplastic anaemia and evolution to AML or MDS	Mycobacteria, fungi or human papillomavirus infections, pulmonary dysfunction including pulmonary alveolar proteinosis, warts and leg lymphoedema
TCIRG1	Severe congenital neutropenia	None	In some patients, prominent haemangiomas that became more prominent during G-CSF treatment
CXCR4	Congenital neutropenia and WHIM syndrome (warts, hypogamma-globulinaemia, infections and myelokathexis)	B cell defects and hypogammaglobulinaemia	Warts
Autosomal recessive inheritance			
HAX1	Severe congenital neutropenia	Evolution to AML or MDS	Neurological phenotype in patients with mutations affecting both isoforms of HAX1
JAGN1	Severe congenital neutropenia	Evolution to AML	Short stature and bone and teeth defects
G6PC3	Severe congenital neutropenia	Thrombocytopenia and evolution to AML or MDS	Cardiac defects, increased superficial veins visibility, urogenital malformations, endocrine abnormalities and skin hyper-elasticity
SLC37A4	Congenital neutropenia and glycogen storage disease type Ib (GSDIb)	Evolution to AML or MDS	Hypoglycaemia, fasting hyper-lactacidaemia, glycogen overload of the liver, colitis, pancreatitis and osteoporosis
SBDS	Shwachman–Diamond syndrome	Thrombocytopenia, anaemia, aplastic anaemia and evolution to AML or MDS	Exocrine pancreatic insufficiency, cardiomyopathy, metaphyseal dysplasia, mental retardation and hepatic disease
STK4	Congenital neutropenia	Monocytopenia and T cell and B cell lymphopenia	Warts and atrial septal defects
CLPB	3-Methyglutaconic aciduria type VII	Evolution to AML or MDS	Psychomotor retardation, progressive brain atrophy, cataracts, 3-methylglutaconic aciduria, facial dysmorphism, cardiomyopathy or hypertrophy and hypothyroidism
AP3B1	Hermansky–Pudlak syndrome type 2	Impaired function of T cells and natural killer cells	Oculocutaneous albinism and haemorrhagic diathesis
LAMTOR2	p14 deficiency	Accumulation of neutrophils in the bone marrow, defective cytotoxicity and lymphoid immunodeficiency	Oculocutaneous albinism and stunted growth
USB1	Clericuzio-type poikiloderma	None	Poikiloderma, generalized hyperkeratosis on the palms and soles, short stature and recurrent pulmonary infections
VPS13B	Cohen syndrome	None	Psychomotor retardation, truncal obesity, microencephaly, skeletal dysplasia, hypotonia and myopia
VPS45	Congenital neutropenia‡	Anisocytosis and poikilocytosis, hypergammaglobulinaemia, renal extramedullary haematopoiesis, bone marrow fibrosis, progressive anaemia and thrombocytopenia	Nephromegaly, splenomegaly, osteosclerosis, and neurological abnormalities such as delayed development, cortical blindness, hearing loss and thin corpus callosum
CXCR2	Congenital neutropenia	Myelokathexis due to impaired neutrophil release from the bone marrow to the peripheral blood	None
EIF2AK3	Wolcott–Rallison syndrome	None	Early infancy-onset insulin-dependent diabetes mellitus, epiphyseal dysplasia, growth retardation, hepatic and renal dysfunction, developmental delay and exocrine pancreatic deficiency

Gene mutated	Disease	Other haematological abnormalities	Non-haematological abnormalities
Autosomal recessive inheritance (cont.)			
LYST	Chédiak–Higashi syndrome	Defective natural killer cell function, lysosomal inclusion bodies in myeloblasts, promyelocytes and granulocytes, activation of macrophages and lymphoproliferative syndrome	Oculocutaneous albinism and neurodegeneration
RAB27A	Griscelli syndrome type 2	Defective cytotoxicity, hypogamma-globulinaemia, thrombocytopenia, anaemia and haemophagocytosis	Oculocutaneous albinism
AK2	Adenylate kinase 2 deficiency	Severe lymphopenia	Inner ear hearing loss
RMRP	Cartilage-hair hypoplasia	Immunodeficiency and anaemia	Hypoplastic hair, skeletal dysplasia and cartilage hypoplasia
TCN2	Transcobalamin II deficiency	Megaloblastic anaemia and pancytopenia	Methylmalonic aciduria, failure to thrive, recurrent infections, mental retardation and neurological abnormalities
Mixed autosomal inheritance patterns§			
CSF3R	Severe congenital neutropenia‖	None	None
X-linked inheritance			
WAS	Congenital neutropenia	Monocytopenia, lymphopenia, reduced numbers of natural killer cells, abrogated phagocyte activity and evolution to AML or MDS	None
TAZ	Barth syndrome	None	Cardiomyopathy, skeletal myopathy, stunted growth, cardiolipin abnormalities and 3-methylglutaconic aciduria
CD40LG	CD40 ligand deficiency, hyper-IgM syndrome type I (HIGM1)	Combined immunodeficiency; T cell, B cell and dendritic cell deficiencies; defective B cell class switching; markedly reduced levels of IgG, IgA and IgE but normal or increased levels of IgM; and reduced macrophage effector functions	Increased susceptibility to bacterial, viral and fungal infections and increased risk for developing autoimmune disorders and malignancies
Mitochondrial DNA inheritance			
Mitochondrial DNA deletion	Pearson syndrome	Refractory sideroblastic anaemia and vacuolization of bone marrow precursors and macrophages	Exocrine pancreas and renal insufficiency or fibrosis, endocrine abnormalities, neuromuscular degeneration and mitochondrial myopathy

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Skokowa, *Nature Reviews*, 2017

Hur följs patienter med SCN?

- G-SCF
- Svikt på G-CSF eller progress till AML eller MDS -> allo-SCT
- Årlig kontroll med BM-prov inkl cytogenetik och mutationsanalys (*CSF3R, RUNX1*)
- Overall survival 80% (G-SCF, antibiotika, allo-SCT). 10% dör i sepsis/svåra bakterieinfektioner

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Cyklisk neutropeni

- Mycket sällsynt tillstånd
- Regelbundna fluktuationer med neutropeni-perioder var 21:a dag
- Mutationer i ELANE-genen
- Neutrofila ofta < 0,2 x 10^9/L
- Infektioner behandlas med antibiotika
- Svåra infektioner är ovanligt

Autoimmun neutropeni

- Primär vs sekundär
- Del av annan autoimmun sjukdom: SLE, Sjögrens syndrom, PBC, systemisk skleros, Feltys syndrom etc.
- Solkänslighet, utslag, ledvärk, trötthet mm
- Autoantikroppar

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Antikroppar

- Stödjer autoimmun genes: hypergammaglobulinemi
- ANA-screening, mitokondrie-ak
- Granulocytantikroppar
  - Granulocyte immune fluorescens test (GIFT)
  - Granulocytagglutinationstest (GAT)
  - ELISA Monoclonal antibody-specific immobilization of granulocyte antigens (MAIGA)

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Idiopatisk neutropeni

- Uteslutningsdiagnos
- T-cellsklon?

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Hur följs patienter med AINP och INP?

- Sällan infektionskänsliga
- Mycket sällan behov av G-CSF
- Mycket sällan övergång i malign sjukdom

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Benmärgsprov?

- Patienter med misstänkt AIN men negativa för antikroppar
- Patienter med återkommande infektioner
- Alla patienter innan insättning av G-CSF
- Vuxna patienter med oförklarlig kronisk neutropeni

ADAN

ACKR1/DARC-associated neutropenia

And the
Atypical chemokine receptor 1, *ACKR1*, a k a *DARC*
or Duffy antigen

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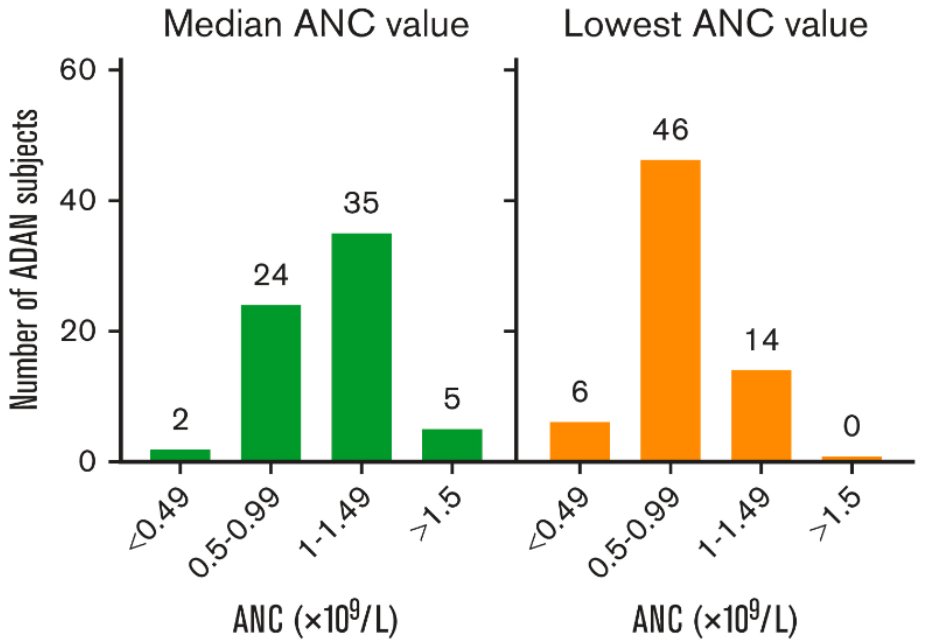
ADAN

- Orsakas av en variant i ACKR1/DARC genen
- Vanlig i Afrika och Mellanöstern
- Mild fenotyp trots varierande neutrofiltal
- Ingen ökad infektionsrisk



Palmblad, Blood Adv. 2024

ACKR1/DARC

- Varianten orsakas av en single nucleotide polymorphism (SNP)
- Leder till total avsaknad av ACKR1 i erytrocyter = Duffy noll typ
- ACKR1 tros underlätta interaktion mellan erytrocyter och HSC
- Avsaknad av ACKR1 ändrade hematopoesen i en musmodell inklusive stam- och progenitorceller
- Gav upphov till en fenotypiskt distinkta neutrofila som lätt lämnade blodbanan och migrerade till vävnaderna = neutropeni

LGL – large granular lymphocyte-leukemia

- Neutropeni-associerad sjukdom
- Diagnos ställs med flödescytometri
- Lymfoproliferativt tillstånd
- Indolent förlopp i de flesta fall
- Ökad mortalitet relaterad till infektionskomplikationer