Growing ideas through networks

Autoimmune Neutropenia (AIN) in adults

Helen A. Papadaki

University of Crete, Greece

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Funded by the Horizon 2020 Framework Programme of the European Union

AIN: Definitions

- Neutropenia characterized (mainly) by the presence of autoantibodies directed against neutrophils leading to their destruction
- Isolated or combined with anaemia and/or thrombocytopenia
- Acute/transient lasting less than 3 months vs chronic/persistent
- Mild (ANC 1800 – 1000/μL), moderate (1000 – 500/μL), severe (<500/μL)

  Severe neutropenia, is also called agranulocytosis. The term is usually used when ANC < 100/μL is combined with fever or signs of sepsis.

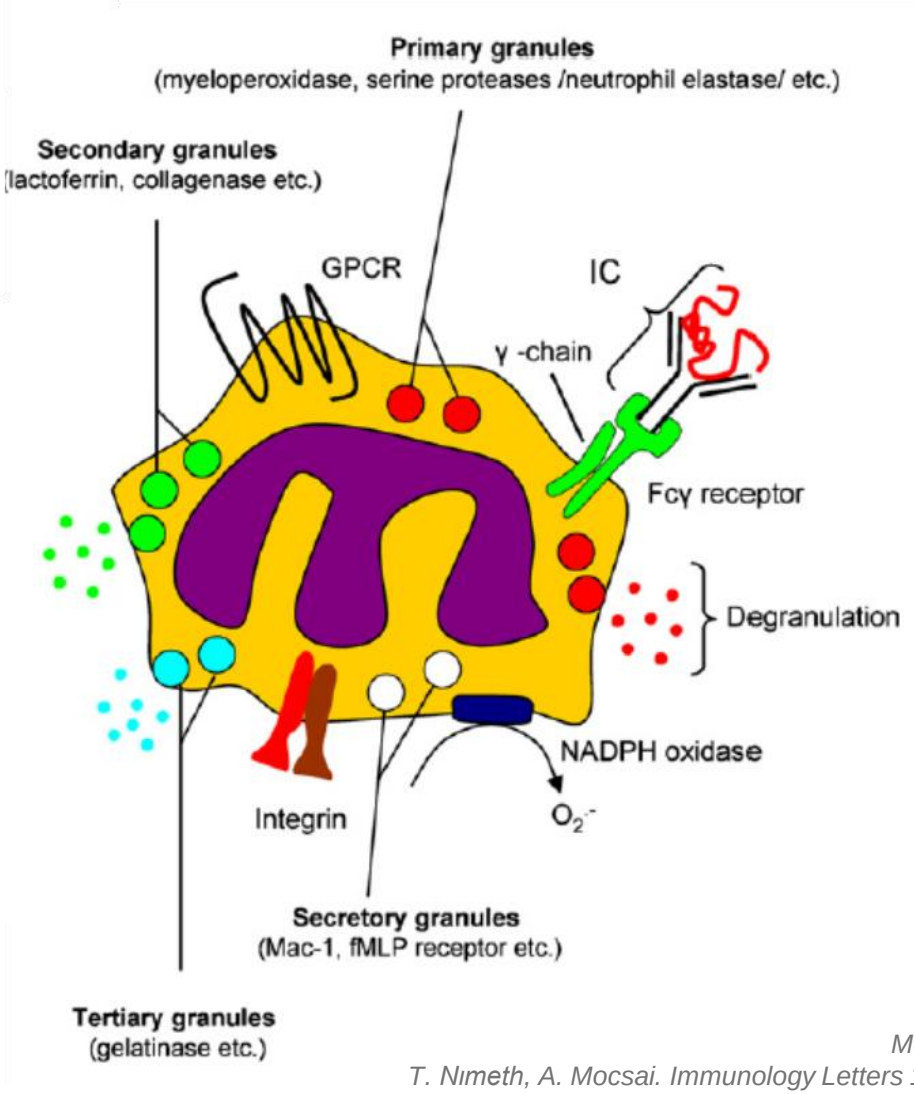
Pathophysiologic mechanisms of AIN

Presence of antibodies against neutrophil specific antigens or

Presence of immune-complexes bound on FcγRII and FcγRIIIb

- Agglutination and opsonization of neutrophils → phagocytosis mainly in the spleen or other tissues.
- Complement-mediated neutrophil destruction.
- Antibodies can affect neutrophil function (e.g defective response to chemotaxis).
- Target cells may be mature and/or progenitor cells. The earlier the targeted cell is the more severe is the neutropenia.

T-cell mediated inhibition of neutrophils and their progenitor cells via direct or indirect (IFNγ) effect.



Modified from:
T. Nımeth, A. Mocsai. Immunology Letters 143 (2012) 9

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Clinically Important Human Neutrophil Antigens (HNA)

Antigenic system	Antigen	Glycoprotein	Acronym
HNA-1	HNA-1a	FcγRIIIb/CD16	NA1
	HNA-1b	FcγRIIIb/CD16	NA2
	HNA-1c	FcγRIIIb/CD16	SH
HNA-2	HNA-2a	gp50-64	NB1
HNA-3	HNA-3a	gp70-95	5b
HNA-4	HNA-4a	CD11b	MART
HNA-5	HNA-5a	CD11a	OND

A Autrel-Moignet, T Lamy. Presse Med. 2014; 43: e105–e118

Acute AIN

Associated to infectious diseases

- **Viral**
  - HHV-6
  - Enterovirus
  - Influenza
  - EBV (up to 40%)
  - CMV
  - Parvo-B19 (rare)
  - Hepatitis C (3-20%)
  - Hepatitis B (rare)
  - HIV (5-10% in early disease)
  - HHV-8
- **Bacterial**
  - Salmonella typhi (25%)
  - Mycoplasma
  - H. Pylori

Drug-induced (idiosystatic)

- *Antithyroids (tiamazole, metimazole)*
- *Clozapine (olanzapine)*
- *Pyrithyldione*
- *Deferiprone*
- Mianserine
- Phenothiazines (alimemazine)
- Lamotrigine
- Quinine/quinidine
- Antiretroviral (HIV) therapy
- Fluconazole, ketoconazole
- *Beta-lactams, cefipime*
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- *Calcium dobesilate*
- *IVIG*
- *Rituximab*
- Infliximab, etanercep

Drugs collectively responsible for 70% of DIN cases

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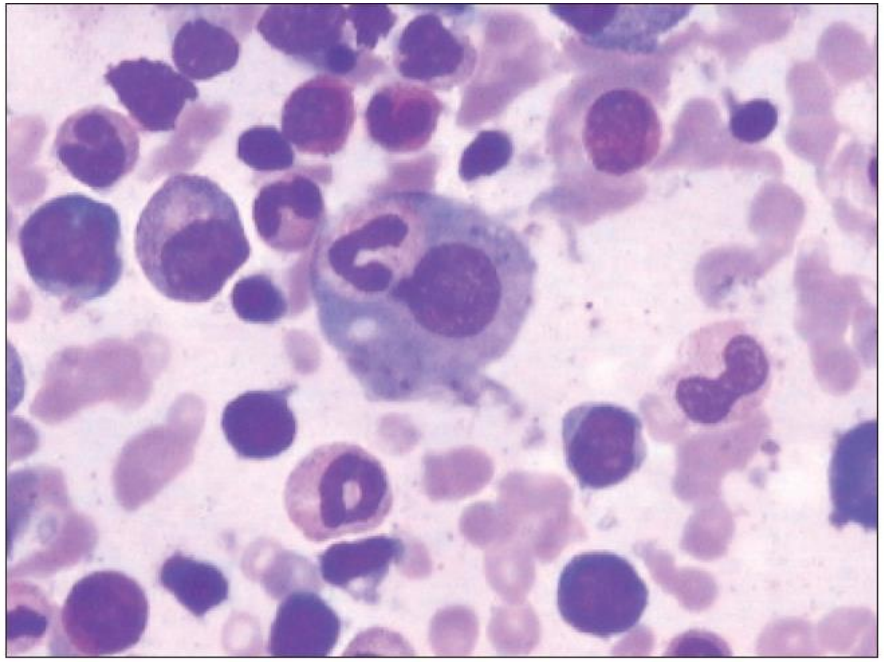
Mechanisms

- Antibodies against PB granulocytes and their BM progenitor/precursor cells
- Damage of haemopoietic cells and BM microenvironment
- Hypersplenism
- Medication
- Heamophagocytosis

Acute AIN



Published in Annals of medical and health sciences research 2014
Hemophagocytosis on Bone Marrow Aspirate Cytology: Single Center Experience in North Himalayan Region of India
H. Chandra, S. Chandra, RM Kaushik, N. Bhat, V. Shrivastava

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- Medication
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Acute AIN

DIN: Definition & Facts

- Idiosyncratic DIN is an adverse reaction to drugs due to abnormal susceptibility, peculiar to the individual.
- Patients may present with severe neutropenia with ANC < 500/μL or even < 100/μL (agranulocytosis).
- The disorder may be life-threatening (10%).
- The incidence increases with age.
- The incidence has remained remarkably stable over the last decades (3–16 cases/ per million/ per year).

Drug-induced (idiosystatic)

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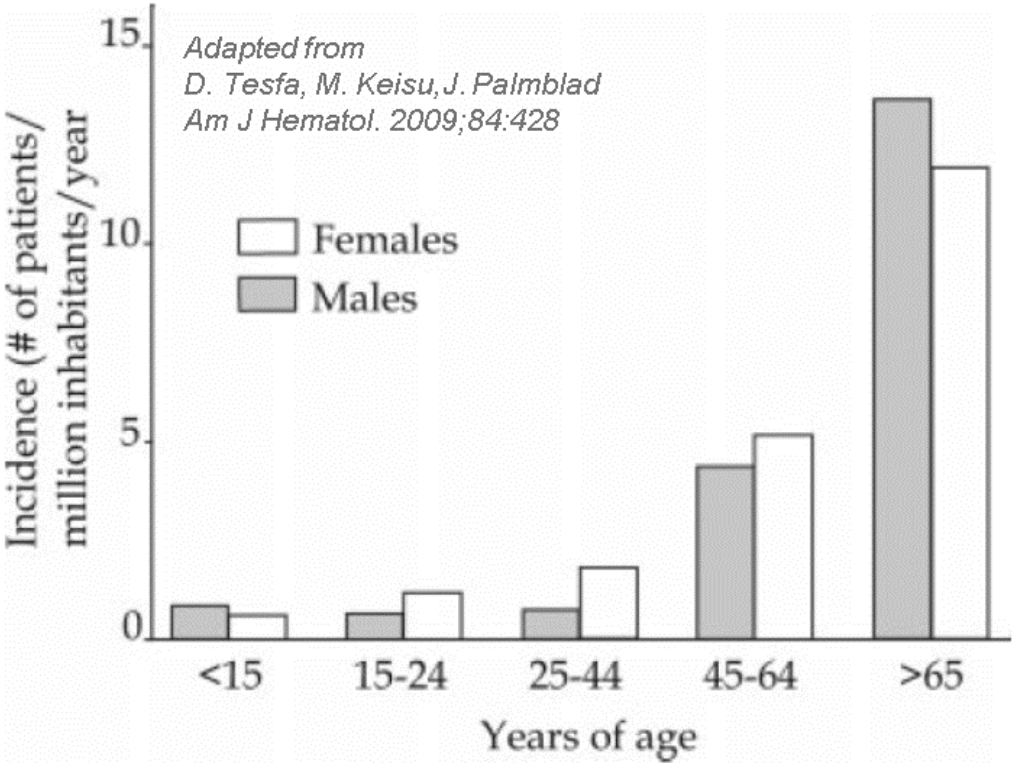
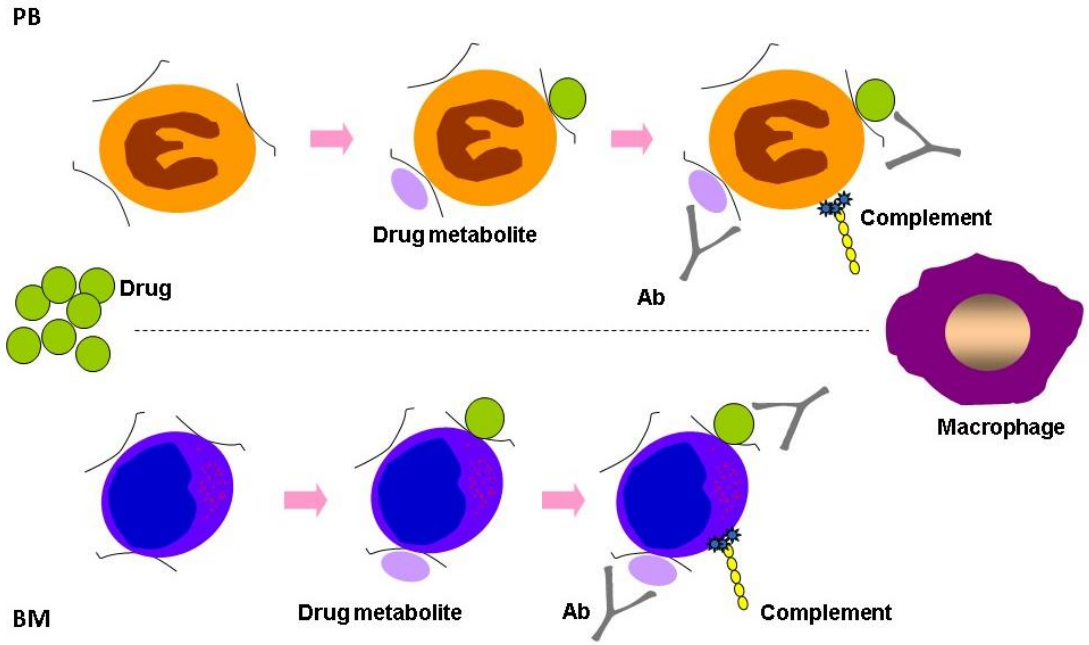


Mechanisms of idiosystatic DIN

- Immune and/or toxic mechanism
  - Via haptens or immunecomplexes
  - Via cytotoxic T-cells
  - Damage to the myeloid precursors
- Genetic polymorphisms
  - Enzymes (e.g. MPO, NADPH-oxidase)
  - HLA
- Epigenetic mechanisms, interference with miRNAs
- Drug-to-disease interactions
- Drug-to-drug interactions



Courtesy of Dr Pontikoglou C. Conference on Oral Chelation, Athens 2008

Acute AIN

Haemopoiesis Research Laboratory
University of Crete

Criteria

- Onset of neutropenia/agranulocytosis during treatment or within 7 days after exposure to the drug and complete recovery of ANC > 1500/μL within one month of discontinuing the drug
- Recurrence of neutropenia/agranulocytosis upon re-exposure to the drug (theoretically the gold method; ethically questionable)
- Exclusion criteria: history of congenital or immune neutropenia, recent infectious disease, recent chemotherapy, radiotherapy, biotherapy, presence of underlying hematological disease

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Andres E etal. J Clin Med 2019, 8, 1351; doi:10.3390/jcm8091351

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Biological therapies: mechanisms of neutropenia

Haemopoiesis Research Laboratory
University of Crete

- **Anti-TNF therapies**

  Serve as haptens and sensitize neutrophils or neutrophil precursors → immune-mediated peripheral destruction

- **Rituximab-mediated LON***

  Autoantibodies, LGL-induced, competition for growth factors between lymphopoiesis and granulopoiesis (SDF-1), genetic polymorphisms in the IgG receptor of FCγRIIIA

- **Alemtuzumab-mediated LON**

  Autoimmunity induction

- **Tocilizumab (anti-IL6R)**

  BM suppression, accelerated PB cell apoptosis, intravascular neutrophil margination.

- **Immune checkpoint inhibitors (ICI)**

  LGL-induced, autoantibodies

** Late onset neutropenia, LON: severe neutropenia occurring at least 3-4 weeks after biotherapy administration, mostly after a mean period of 3 months*

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E. Andres er al. J. Clin. Med. 2019, 8, 1351
J.M. Michot et al. Eur J Cancer 2019, 122, 72

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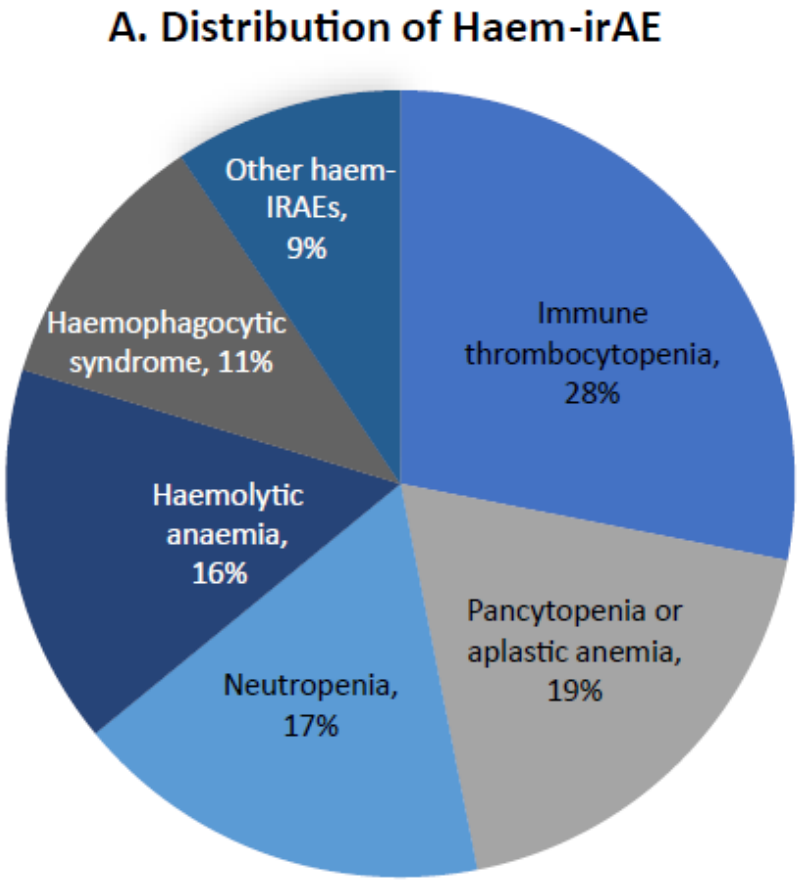
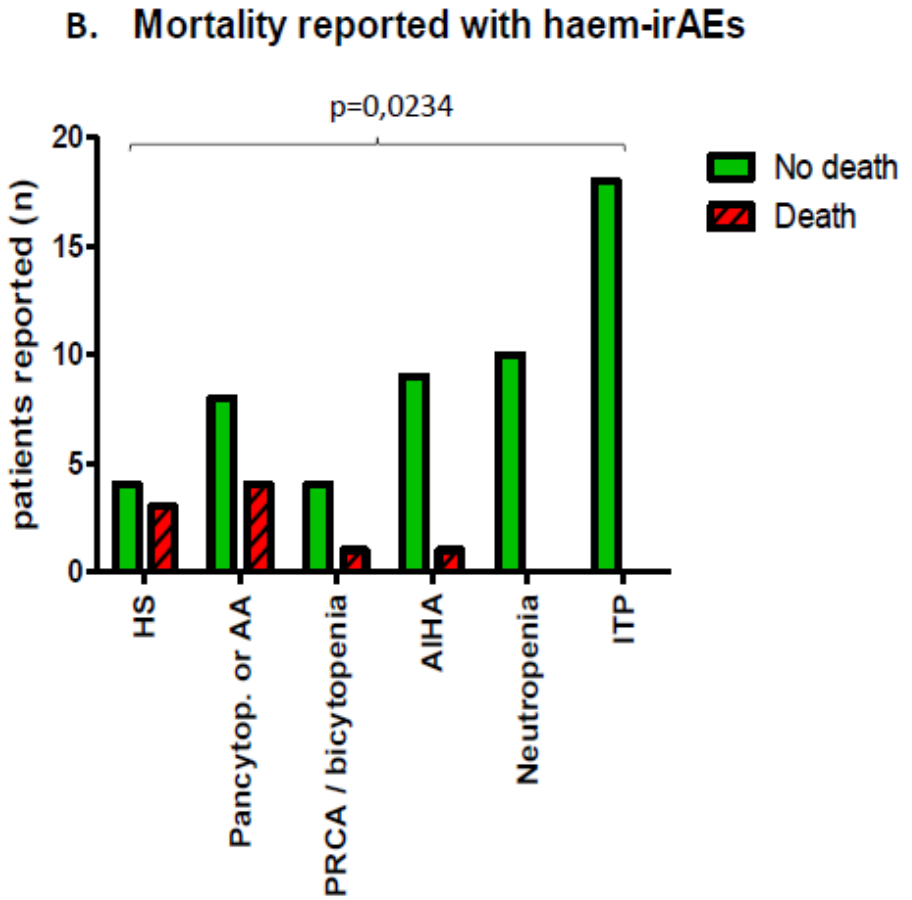
Haem-irAEs induced by ICIs





Adapted from:
J.M. Michot et al. Eur J Cancer 2019, 122, 72

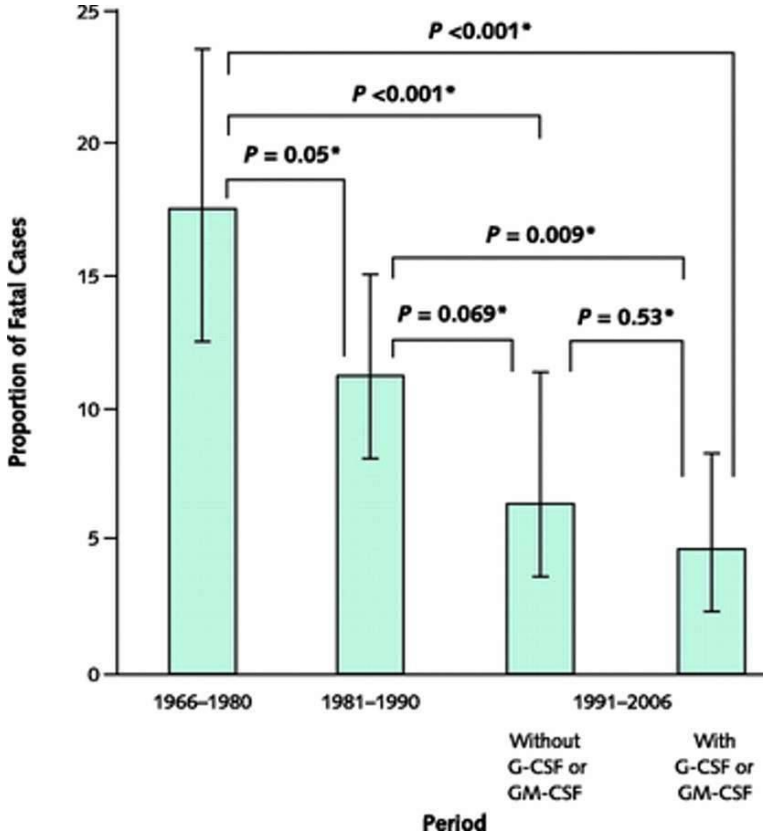
Management of drug-induced neutropenia

- Withdrawal of any potentially causative drug *
- Hospitalization: patients with any signs of infection or at high risk of complications
- Urgent antibiotherapy and symptomatic treatment of infections
- G-CSF:

  In high risk patients (age > 65 years, ANC < 100 / μL, severe infection, severe comorbidities)

  Reduces recovery time of ANC, hospitalization length, antibiotic use but not overall mortality.

- Notification of the case to pharmacological authority (Database)



Adapted from:
Andersohn F et al. Ann Intern Med 2007;146:657

* An exception to the stopping rule may be individuals with schizophrenia who respond only to clozapine.

Chronic AIN

- **Primary** ***(very rare in adults)***
- **Secondary** ***(common in adults)***
- **Autoimmune disorders**
  - Rheumatoid arthritis (Felty syndrome)
  - Systemic lupus erythematosus
  - Sjogren syndrome
  - Systemic sclerosis
  - Primary biliary cirrhosis
  - Graves's
  - Inflammatory bowel disease
- **Malignancies**
  - LGL-leukaemia
  - Hodgkin's and non-Hodgkin's lymphomas
  - Thymoma
- **Primary Immunodeficiency Syndromes**
  - Common Variable Immune Deficiency (CVID)
  - Autoimmune lymphoropliferative syndrome (ALPS)
- **Neurological disorders**
  - Multiple sclerosis
- **Post-transplant**
  - Stem cell
  - Bone marrow
  - Kidney
- **Infectious disorders**
  - Viral
  - Bacterial
- **Medications**
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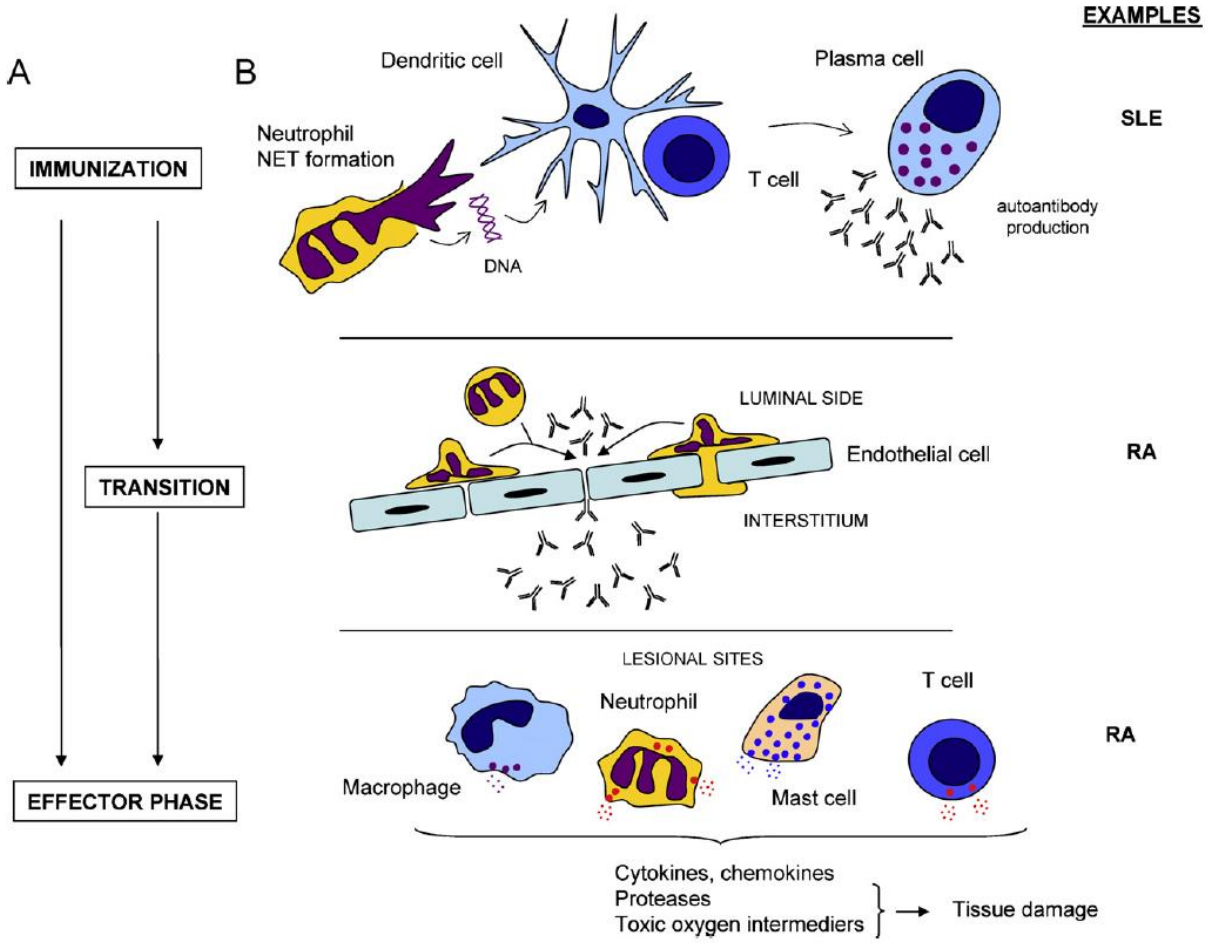
Naeutrophils may participate in different phases of autoimmune diseases



Adapted from:
T. Nımeth, A. Mocsai. Immunology Letters 143 (2012) 9– 19

AIN & Rheumatoid Arthritis

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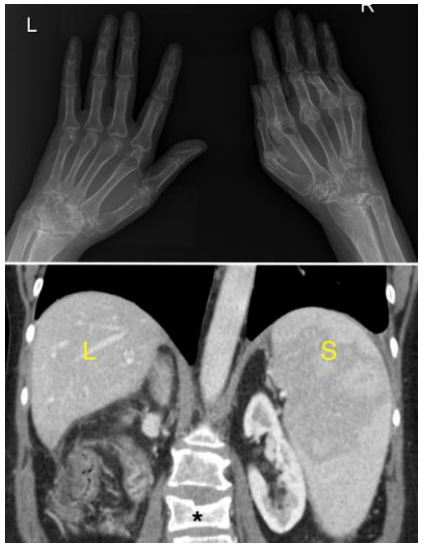
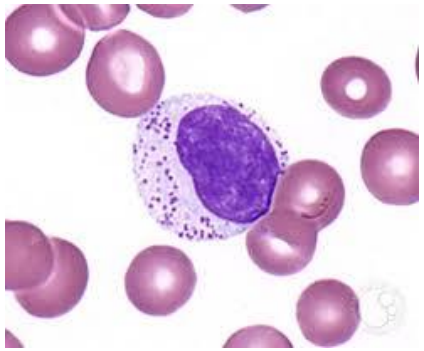
Usual in **Felty's Syndrome** (rare syndrome, 1 - 3% of RA cases; mainly women; typically characterized by positive RF and splenomegaly)

- ANC is often < 1000/μL with increased risk for infections.
- Mechanisms of neutropenia implicate peripheral and central factors.
  - Clonal T-LGL inhibiting granulopoiesis in more than 40% of cases.
  - Anti-neutrophil antibodies in 30–60% of the patients. Target: the nuclear elongation factor-1A-1 antigen (eEF1A-1).
  - Antibodies against G-CSF → maturation arrest of granulopoiesis.
  - Sequestration or destruction of neutrophils in the spleen; production of antibodies in the white pulp.
- Treatment: Methotrexate, Rituximab



Radiology. Saint Vincent's University Hospital



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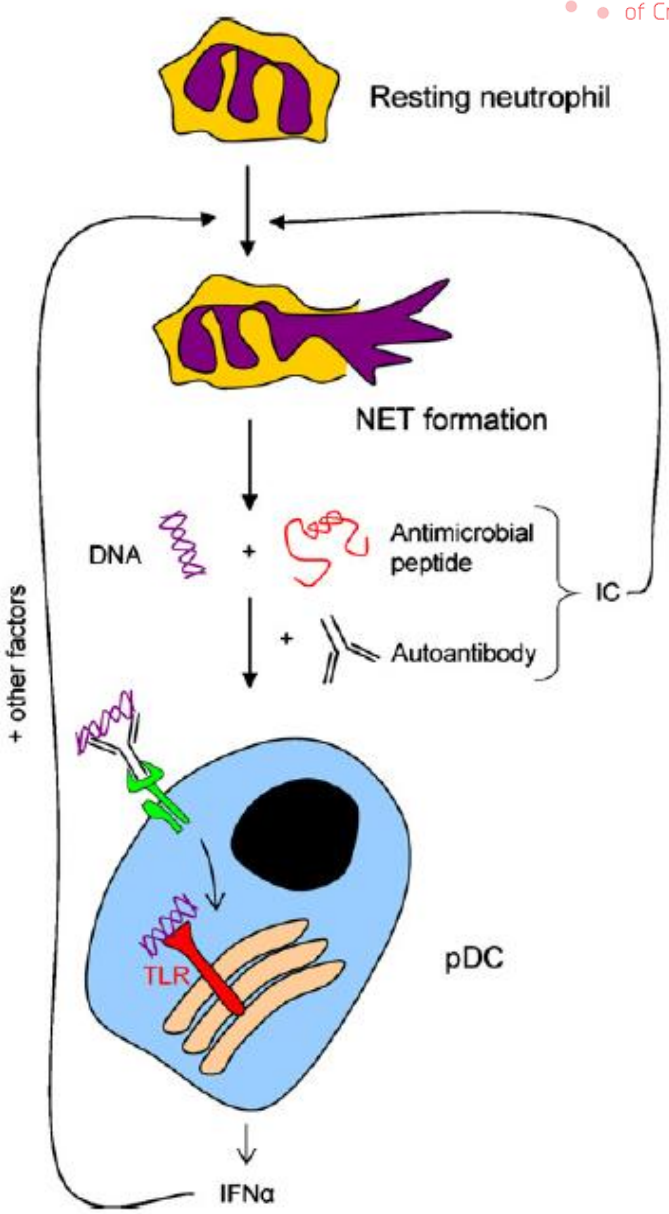
AIN & SLE

- Neutropenia may be the initial manifestation in ≈ 25% patients.
- Severe neutropenia is rare; only 5% of patients have ANC < 1000μL.

  Severe neutropenia may indicate an underlying hematologic disease (e.g. MDS/AML, AA).
- Mechanisms
  - Autoantibodies or immune-complexes.
  - Intracellular proteins expressed on neutrophil surface can trigger immune responses.
  - Fas mediated apoptosis of neutrophils or $CD34^+$ progenitor cells.
  - Iatrogenic



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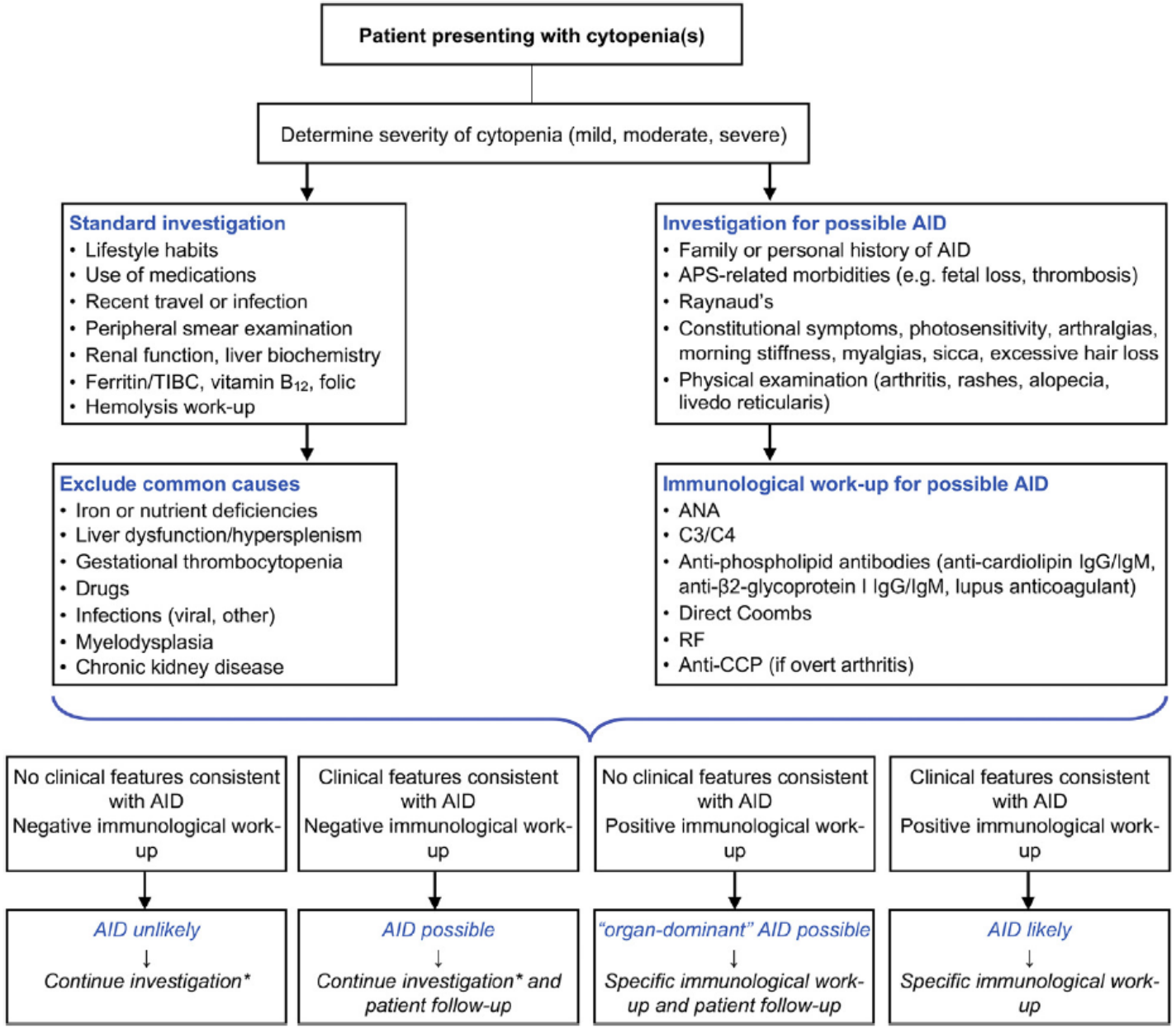
Investigation of neutropenia in patients suspected for Autoimmune Disease



Adapted from:
D. Nikolopoulos et al. Best Practice & Research Clinical Rheumatology, 2019

AIN & Thyroid Diseases

- 218 patients with unexplained neutropenia.
- The frequency of TD was **43.6 %**.
- Anti-PMN Abs were tested in 43/95 TD patients (26 HT, 5 GD, 6 TTM, 2 NTMG, 4 AN-SHP).
- Anti-PMN Abs were detected in 16/43 TD patients, i.e. **37.2%**: (13 HT, 1 GD, 2 NTMG).
- Anti-PMN Abs were positive by GIFT in all patients; in 4 anti-PMN Abs were detected by GAT as well. LIFT was negative in all cases.
- Anti-TPO titers were significantly higher in patients with positive anti-PMN Abs vs those without

Diagnostic Categories of Neutropenia in 218 Patients Enrolled in the Study

	Number of Patients, %
Thyroid disease	95 (43.6)
Hashimoto thyroiditis	51
Graves disease	9
Total thyroidectomy	6
Nontoxic multinodular goiter	18
Antibody-negative subclinical hypothyroidism	11
Chronic idiopathic neutropenia	65 (29.8)
T-large granular lymphocytosis (TLGL)	20* (9.2)
Connective tissue diseases	5† (2.3)
Systemic lupus erythematosus	3
Sjögren syndrome	1
Polymyalgia rheumatic	1
Infectious diseases	5 (2.3)
Hepatitis B	3
Hepatitis C	1
Ebstein barr	1
Drug related	11 (5.0)
B12 Deficiency	6 (2.8)
Iron deficiency	6 (2.5)
Other hematologic disorders	5 (2.3)
Myelodysplastic syndrome	2
MGUS‡	1
NHL§	1
Polyclonal B Lymphocytosis	1

EM Kyritsi et al. Medicine, Volume 94, Number 23, 2015

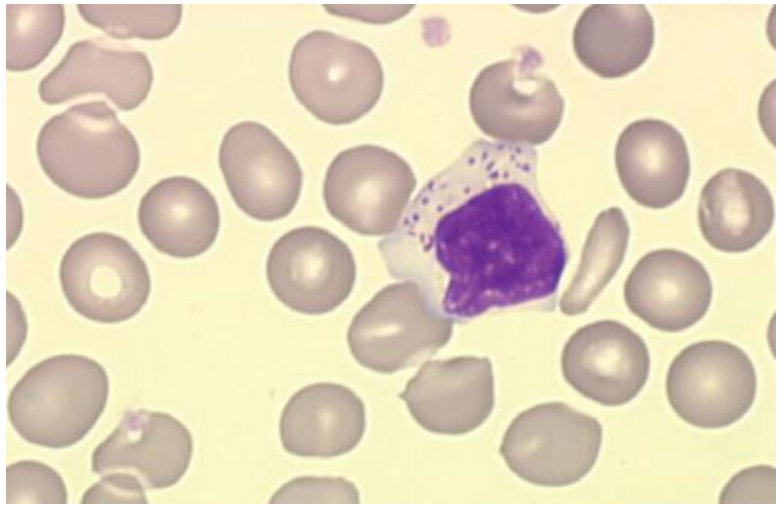
LGL-Leukaemia

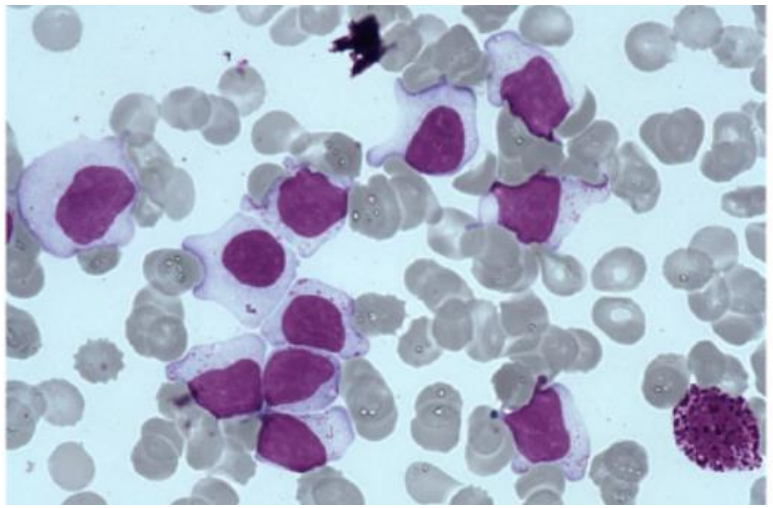
According to WHO

- CD3$^+$ T-LGL leukaemia
  (CD3$^+$/CD8$^+$/CD57$^+$/CD45RA$^+$/CD62L$^-$ ≈ terminal effector memory T-cell following antigen-driven activation)
- CD3$^-$ NK-LGL leukaemia
  (CD3$^-$/CD8$^+$/CD16$^+$/CD56$^+$)
  - Indolent
  - Aggressive

Criteria for LGL leukemia diagnosis

- LGL expansion above 500/μL
- chronic (lasting more than 6 months)
- clonality

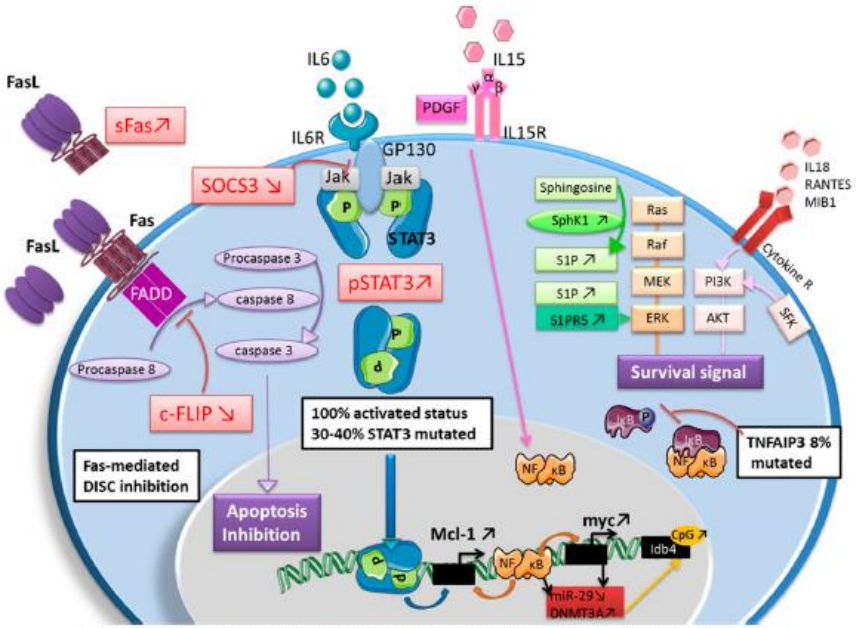




Adapted from: T. Lamy et al. Blood. 2017;129:1082

LGL-Leukaemia

- Dysregulation of several signaling pathways → constitutively active clonal cell population, which is resistant to Fas-mediated apoptosis.
- Key protein: STAT3. Nearly 40% of the patients exhibit a mutation of STAT3 in both LGL subtypes (28-75% in T-LGL, 3-48% in NK-LGL).
- Other activated signaling pathways: Ras/MEK/ERK, PI3Kinase/Akt, sphingolipids pathway with expression of shingosine-1-phophate 5 (S1PR5) receptor.
- Overexpression of PDGF, IL-6 and IL-15 contribute by promoting LGL leukaemic cell survival.

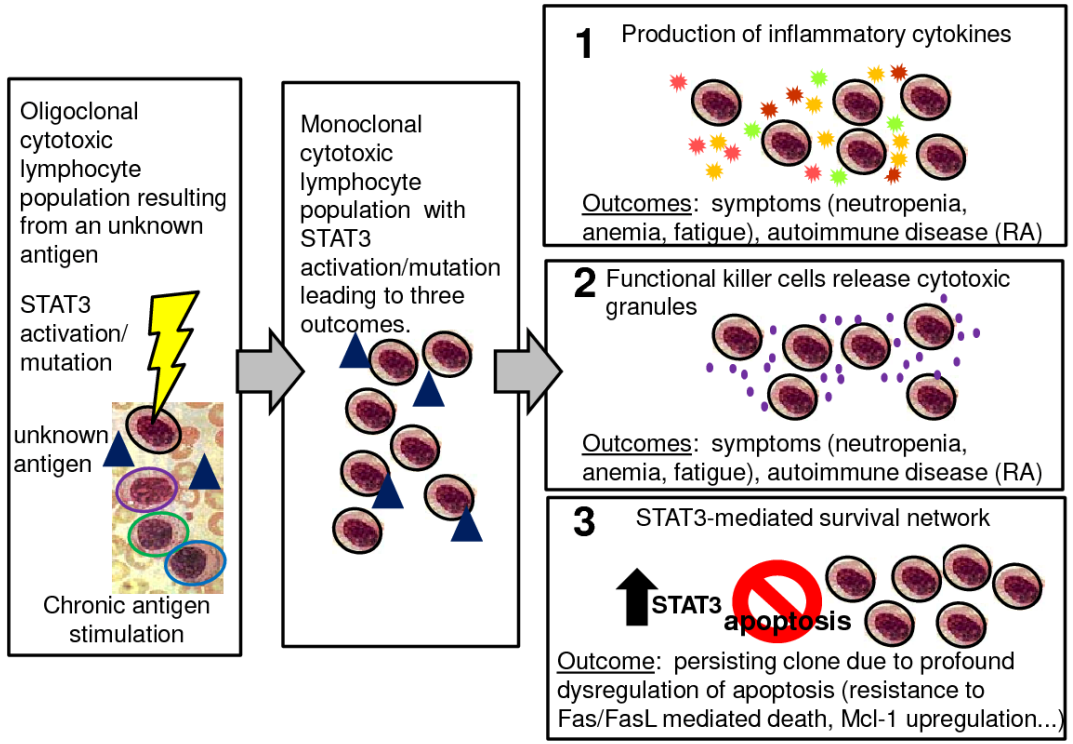


Summary of dysregulated cellular pathways in LGL leukemia. Adapted from Lamy T, et al. Blood 2017;129:1082

Mechanisms of neutropenia in LGL-leukaemia

Cellular and humoral mechanisms are implicated

- Immune complexes or anti-neutrophil Abs lead to peripheral neutrophils' opsonization and phagocytosis.
- Fas-mediated neutrophil/progenitor apoptosis
  - LGL leukemia cells are resistant to Fas-mediated apoptosis and produce increased levels of soluble Fas-ligand.
  - Mature neutrophils express CD95 (Fas) and are sensitive to Fas-induced apoptosis.
  - Immature neutrophils and neutrophil progenitor cells do not normally express Fas but only after stimulation with IFNγ and TNFα. LGL leukaemic cells produce both cytokines → induction of apoptosis.



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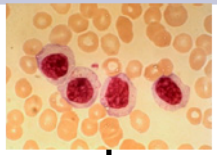
Algorithm for the diagnosis of LGL leukaemia

Adapted from: *T. Lamy et al. Blood. 2017;129:1082*

Clinical or biological context: neutropenia, recurrent infections, anemia, autoimmune conditions, RA, lymphocytosis

Careful blood smears examination: excess of large granular lymphocytes?



yes

Flow cytometry analysis using CD3/5/4/8/16/56/57, TCRγ rearrangement,
(Stat 3 mutation: recommended at this stage, Vβ repertoire and KIR phenotyping; if available,)

Polyclonal

Reactive LGL proliferation

Post-splenectomy, viral infection (CMV, HIV, EBV) BM/organ transplantation,…

Grey zone

Low LGL count around 0.5-1 x 10^9/L, and no blood clonal evidence, stat3 unmutated, pancytopenia, lymphopenia, with clinical evocative context

Bone marrow biopsy with Immunohistochemistry

Interstitial and intravascular subtle LGL
Infiltration of clusters of CD3+/CD8+ Granzyme B/TiA1+ LGL
Lymphoid nodules of B and T CD4 cells

yes

True clonal LGL expansion

T or NK LGL Leukemia
Clonal TCRγ

Additional tests (if required and not done before)
Stat3-5b/NFKB mutation,
Vβ repertoire, KIR phenotyping

BM features of LGL leukemia.

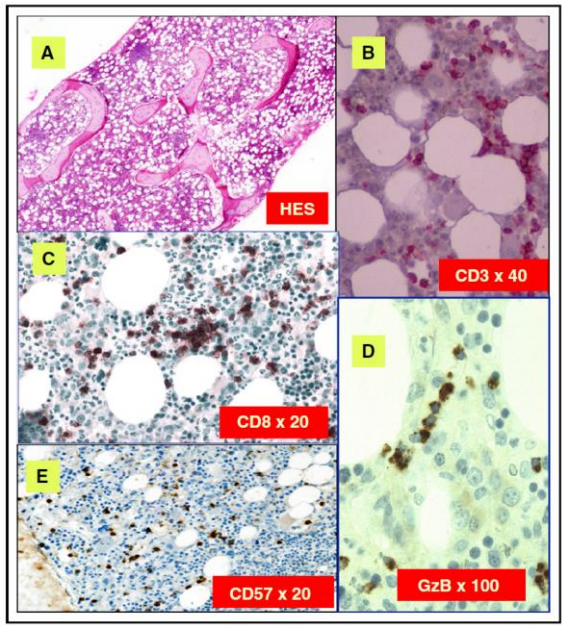
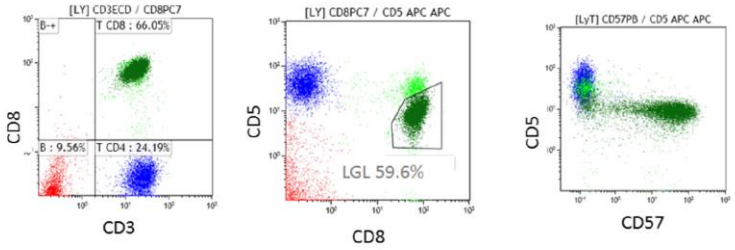
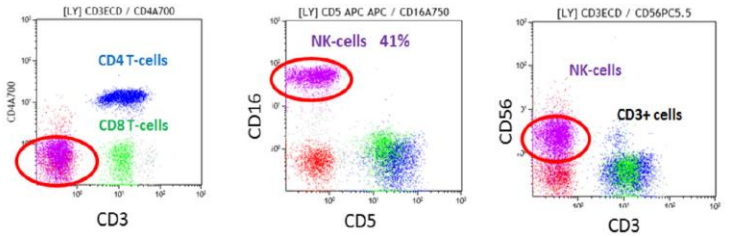


Illustration of Immunophenotyping of T-LGL and NK-LGL Leukemia

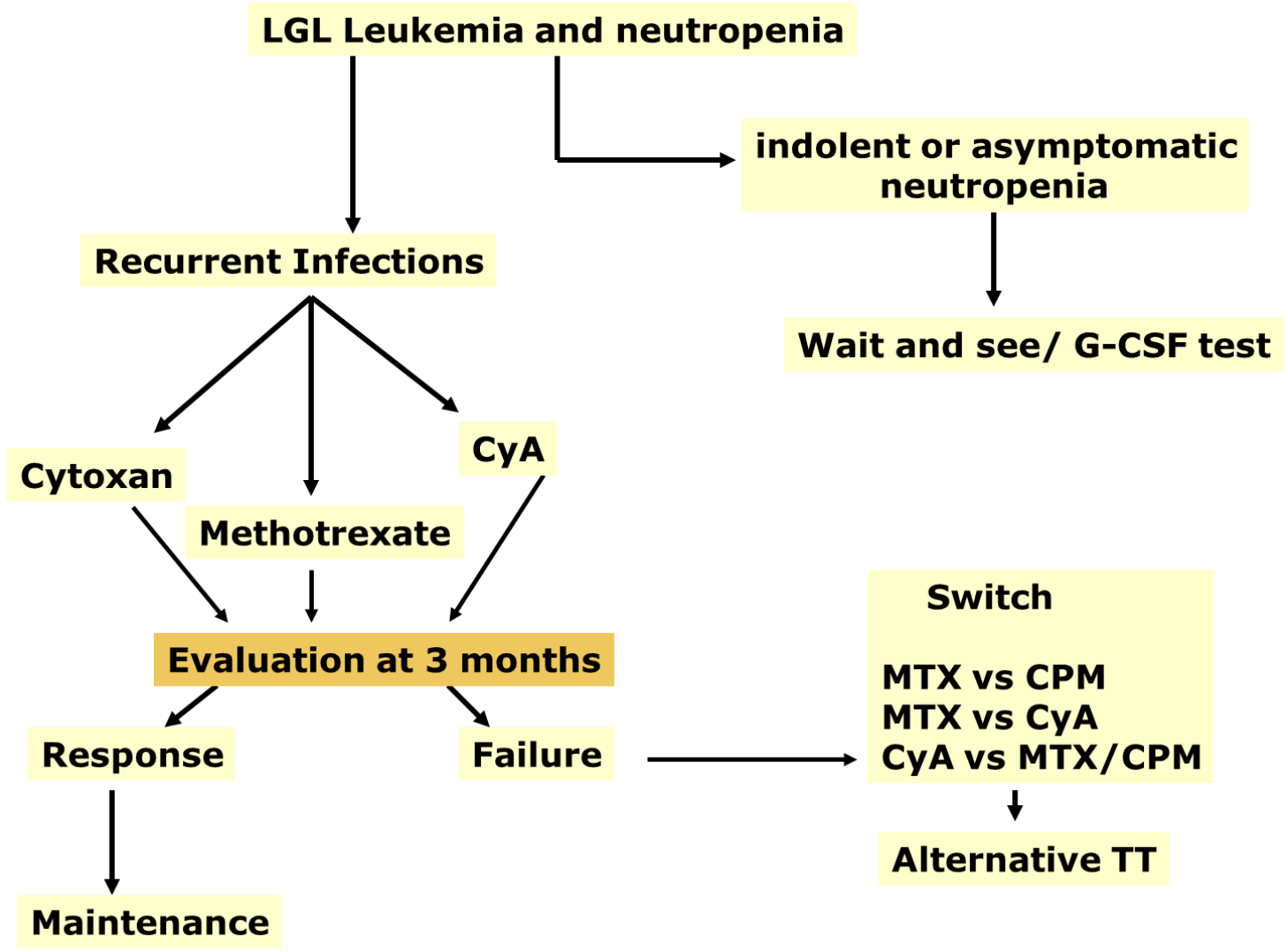
T cell subtype



Natural killer cell subtype

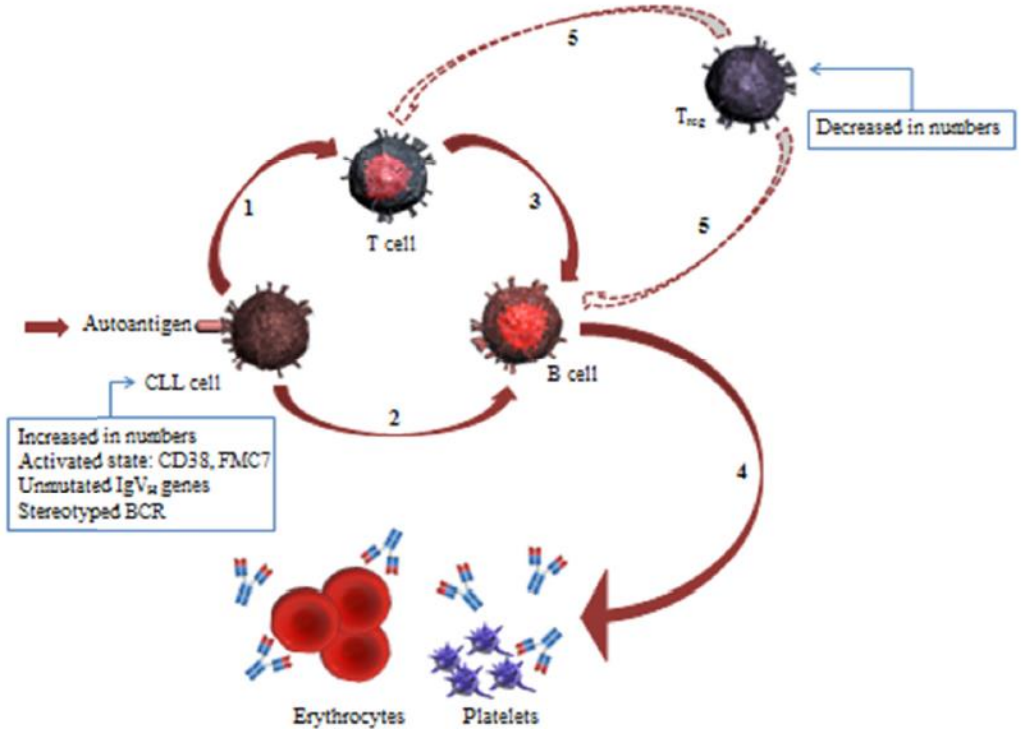


Treatment algorithm of neutropenia associated with LGL leukaemia



AIN in haematologic malignancies

- Isolated AIN may rarely occur in HD and NHL (mainly CLL and WM) (< 1% of patients).
- AIN can occur during an active phase of the disease or during a remission period. It is not always synonymous of relapsing.
- Mechanisms:
  - Loss of self tolerance and antigen presentation by malignant cells to T-cells with parallel stimulation of normal B cells through CD40L → antibody production by non-malignant cells
  - Reduction of Treg
  - Medications (purine analogues, rituximab, ICIs)



Adapted from:
Tim R. de Back et al. Expert Review of Hematology, 2018

AIN related to primary immunodeficiency syndromes

Haemopoiesis Research Laboratory
University of Crete

Common variable immune deficiency (CVID)

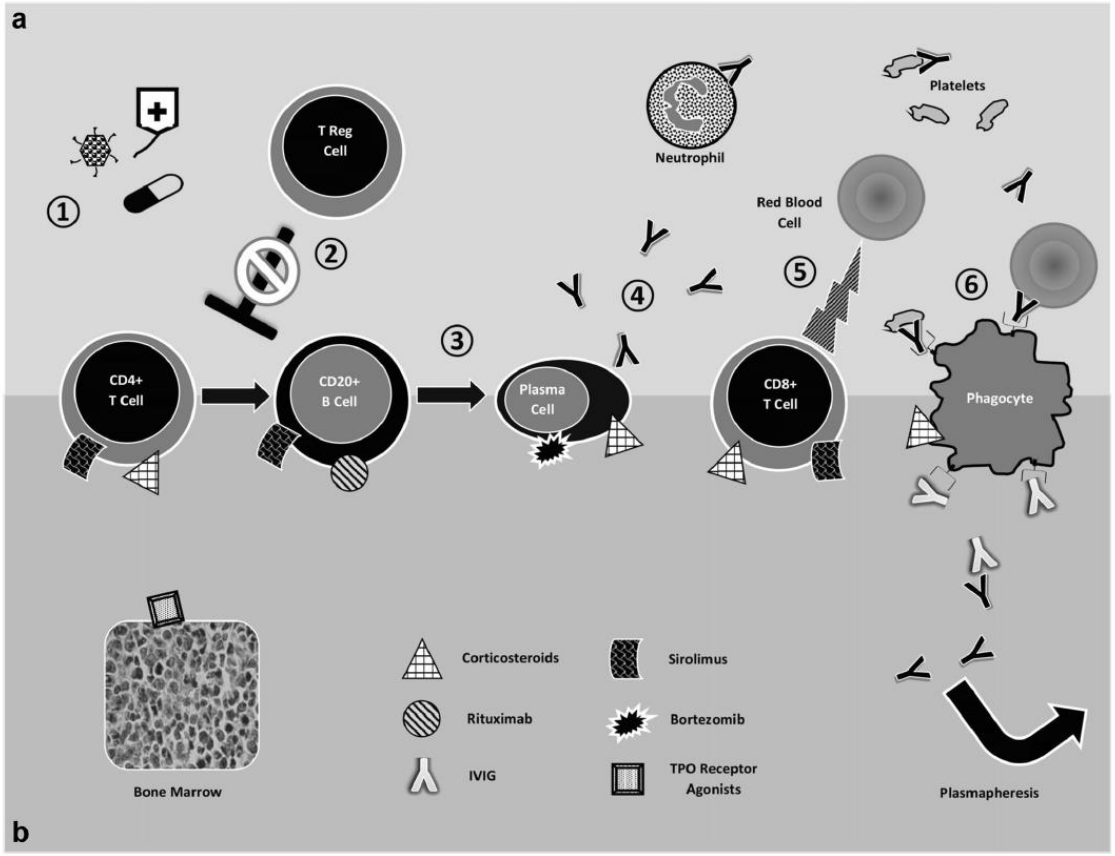
- Rare disease characterized by an Ig production defect resulting in hypogammaglobulinemia.
- The diagnosis is most often made during adulthood.
- 12% of patients present an autoimmune cytopenia (thrombocytopenia > anaemia > AIN).

The X-linked autoimmune lympho-proliferative syndrome (ALPS)

- Extremely rare, inherited, non-malignant disease characterized by the combination lymphadenopathy, splenomegaly, cytopenias, hypergammaglobulinemia.
- Increased risk of lymphoproliferative B syndrome due to an accumulation of lymphocytes secondarily to an apoptosis defect (Fas pathway genes mutation).
- Autoimmune cytopenias are very common, related to the emergence of dual negative $CD4^-/CD8^-$ T-cells and autoreactive B-lymphocytes. Antineutrophil antibodies with or without AIN has been described.

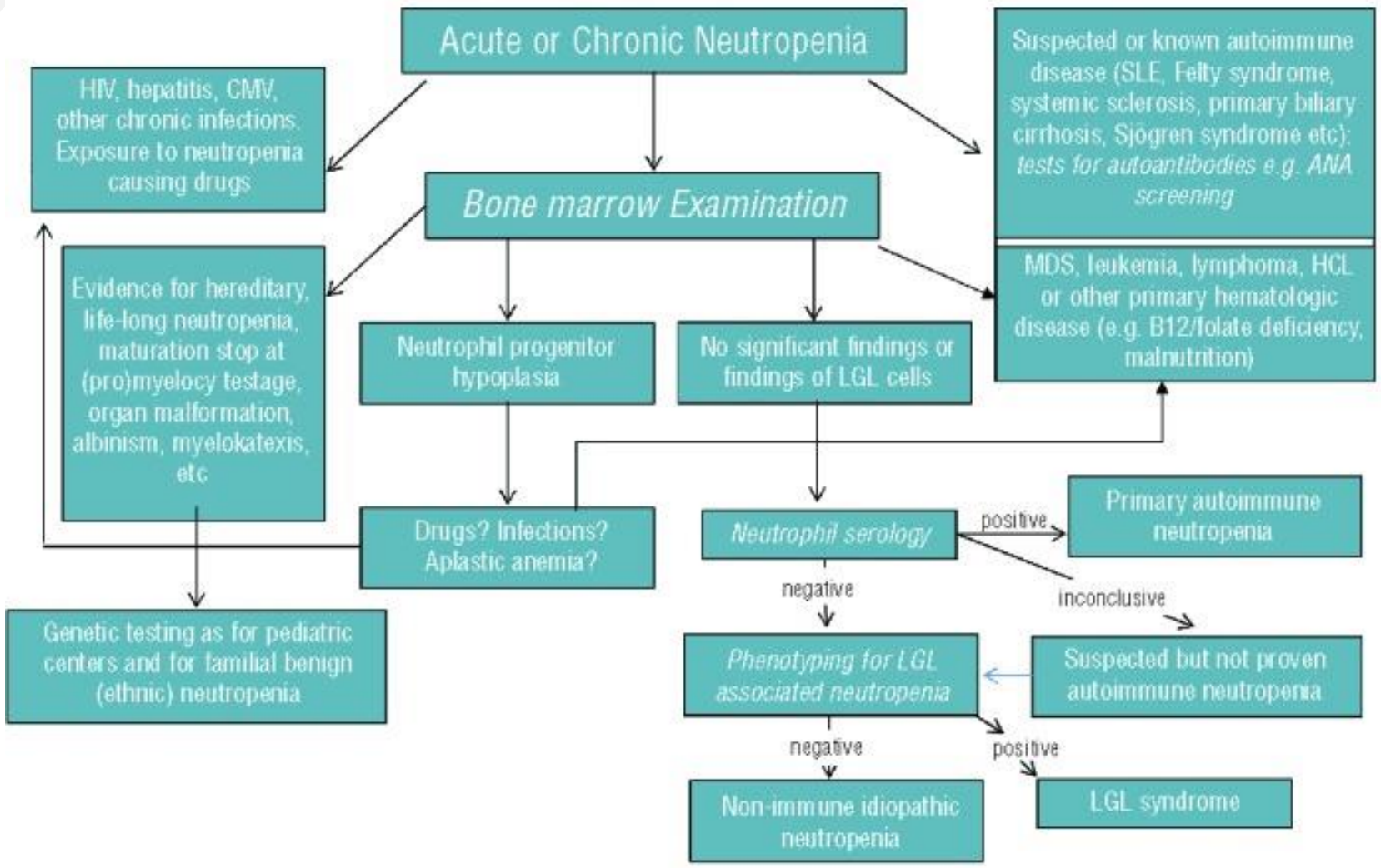
Pathophysiology of immune-mediated cytopenias (IMC) following HSCT

- Immune dysregulation due to:
  - Infectious insults (CMV, EBV, HHV-6)
  - Pre-transplant conditioning and post-transplant immunosuppression
  - GvHD and relative immunosuppressive therapy, particularly calcineurin inhibitors
- Reduced and dysfunctional T-regs with an inability to suppress auto/alloreactive T and B cells
- Higher frequency of IMC following UCB transplantation due to the relatively increased naïve T cell content in UCB



T.F. Michniacki et al. Current Oncology Reports (2019) 21: 87

How I investigate AIN



- Antineutrophil antibody measurement has high false-negative and false-positive rates
- The tests should be performed in specialized Laboratories

J Palmblad, C. Dufour, HA Papadaki. Haematologica. 2014; 99: 1130–1133.

How I investigate AIN

Haemopoiesis Research Laboratory
University of Crete

Clinical Information

- Clinical history
- Occupation
- Drug list and chronology
- History, symptoms, signs of viral infection
- History of underlying disease that might be related to AIN

Laboratory Investigation

- Blood tests
  - Blood counts and smear. Acute vs chronic AIN.
  - Viral serologies: EBV, CMV, HVB, HVC, HIV, ParvoB19, and more specific tests if clinical arguments (influenza, enterovirus etc)
  - Immunologic tests: ANA (anti-SSA, -SSB, -DNA), ANCA, RF, anti-CCP
  - Anti-neutrophil antibody testing: GAT, GIFT, MAIGA
  - Serum immunoglobulin levels
  - Immunophenotyping ± TCR rearrangement analysis
- Bone marrow (BM) studies
  - BM aspiration – smear, immunophenotype
  - BM biopsy
  - Karyotype

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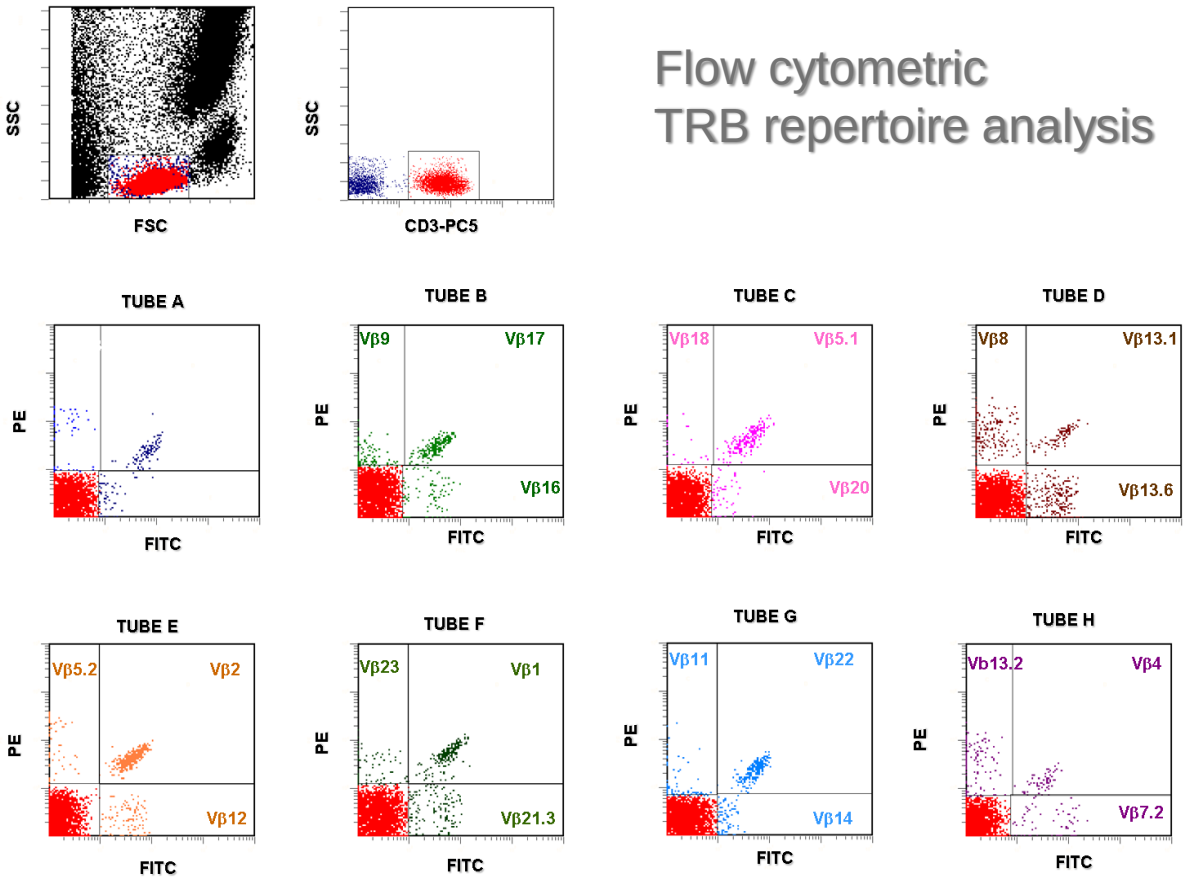
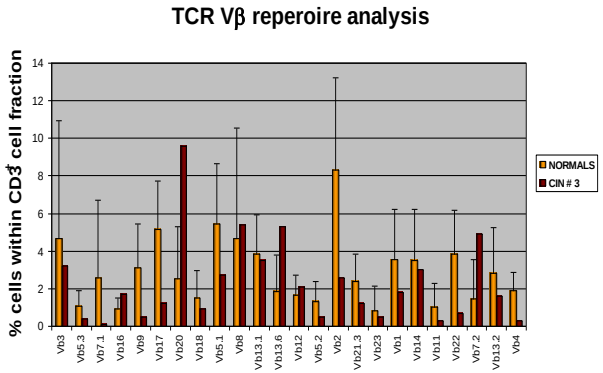
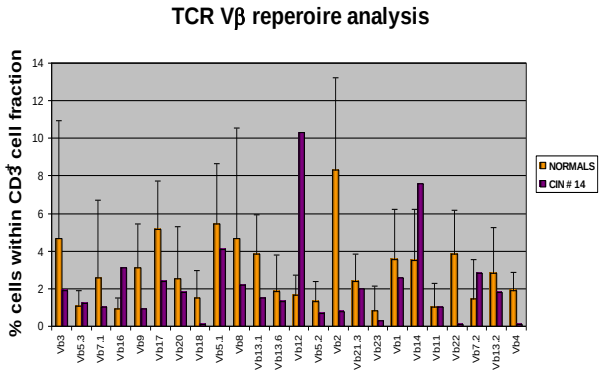
Identification of TCR clonality: flow cytometry

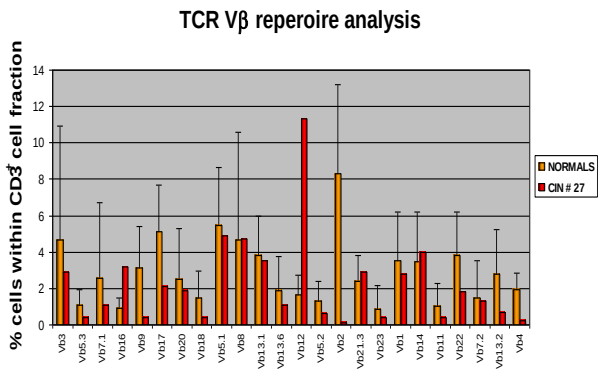
Haemopoiesis Research Laboratory
University of Crete

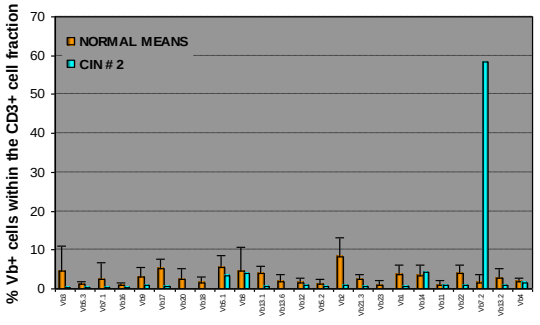


Flow cytometric TRB repertoire analysis









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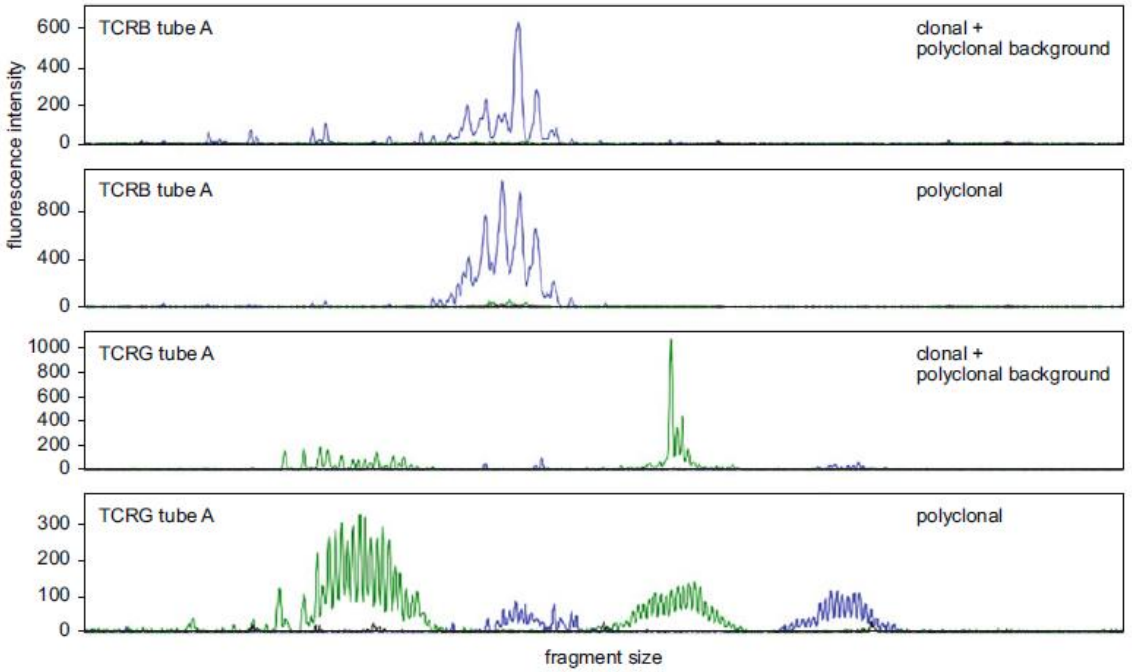
Identification of TCR clonality: molecular techniques

- Assessment of the presence of clonal lymphoproliferations via PCR based of the rearranged T-cell receptor (TR) genes.
- The method is based on the detection of TRB and TRG gene rearrangements, on the basis of the standardized multiplex PCRs as developed by the European BIOMED-2 consortium.

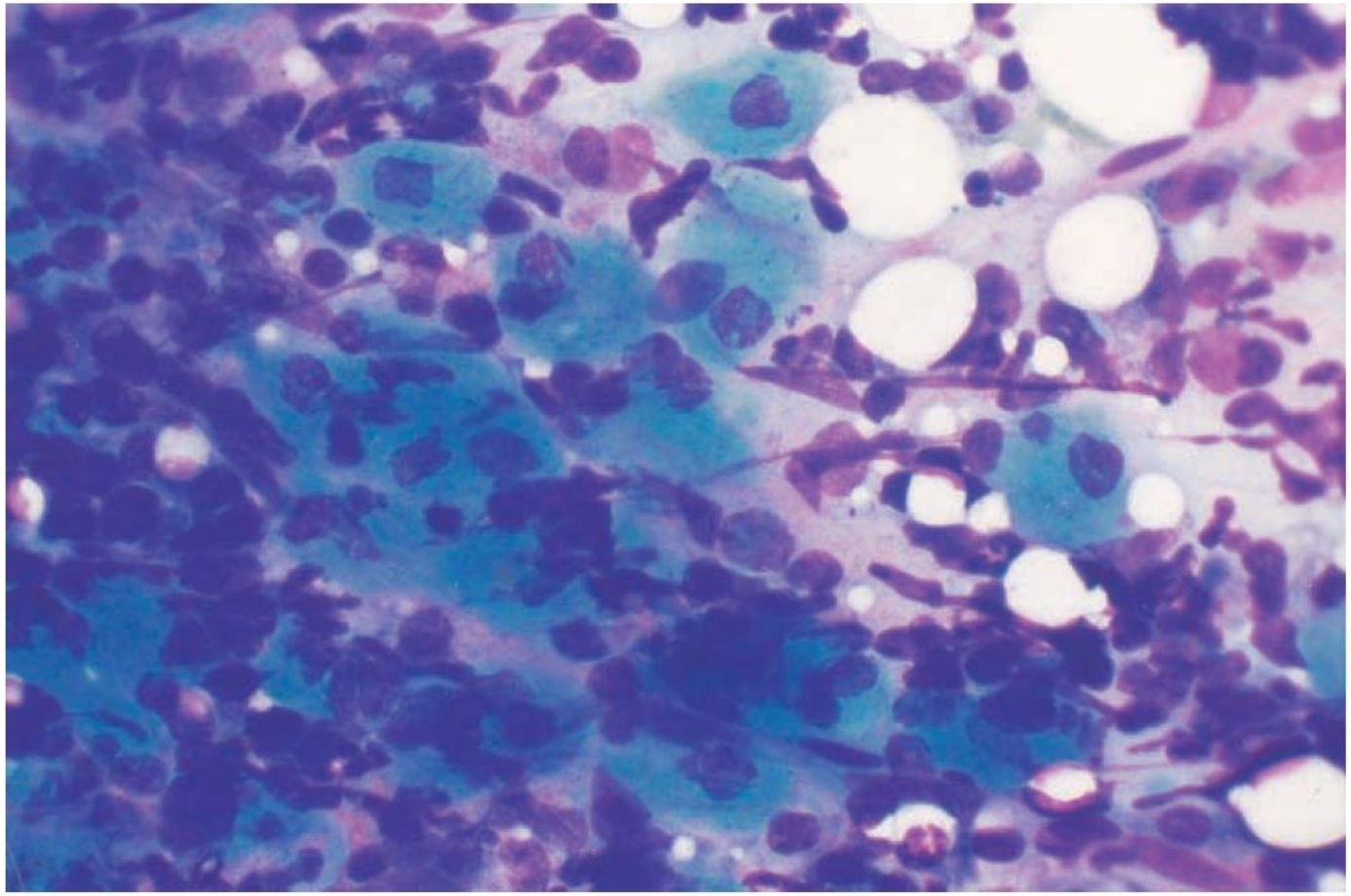
PCR GeneScan and Heteroduplex Analysis of Rearranged Immunoglobulin or T-Cell Receptor Genes for Clonality Diagnostics in Suspect Lymphoproliferations

Elke Boone, Kim C. Heezen, Patricia J. T. A. Groenen, and Anton W. Langerak and On behalf of the EuroClonality Consortium



Ralf Kuppers (ed.), Lymphoma: Methods and Protocols, Methods in Molecular Biology, vol. 1956, part of Springer Nature 2019

Severe AIN associated with BM sea-blue histiocytosis



- 37 y female with severe neutropenia.
- IgG granulocyte autoantibody with anti-Fcγ-RIIIb specificity.
- Normal plasma chitotriosidase, leucocyte and fibroblast b-glucocerebrosidase and sphingomyelinase activity.
- Hypothesis:

  the Ab-mediated increased granulocyte destruction → accumulation of membrane lipids in BM macrophages exceeding their catabolic capacity → lipid-laden sea-blue histiocyte formation.

Papadaki HA et al. Br J Haematol, 2002, 118, 931

Management of AIN: etiologic treatment

Depends on the etiology, severity and the presence of infectious complications

Acute vs chronic

Primary vs secondary

- Primary
  - Does not usually justify curative therapy since the occurrence of infection is very low
  - IVIG, corticosteroids, immunosuppressive agents, CAMPATH-1H
- Secondary
  - Treatment of the underlying disease

Management of AIN: supportive treatment

- **Broad spectrum antibiotics**
  - In acute infections
  - Prophylactic treatment is questionable
- **G-CSF**
  - In cases with acute or recurrent infections
  - Patients with adequate BM storage pools of mature neutrophils usually show immediate ANC increase
  - Start in a low range (eg, 1-2 mg/kg per day), because the rapid, vigorous responses can cause severe bone pain, which needs to be carefully balanced against the therapeutic effect.
  - Risk of flair of underlying autoimmune diseases (RA and SLE)
- **General hygiene meters**
  - Simple common-sense precautions are quite sufficient.
  - The “neutropenic diet” has questionable benefits.
  - Good dental hygiene is essential, to avoid chronic gingivitis and tooth loss.
- **Very important to adhere to recommended immunization schedules**

PE Newburger. Hematology 2016

Clinical manifestations- infections

- Infections are mainly caused by bacteria: Staphylococcus aureus and Gram-negative Bacilli are the most frequent germs.
- Gingivitis, aphtoses, stomatitis, periodontitis and cutaneous infections, like perirectal abscess and cellulitis may occur.
- This risk correlates to the ANC and increases when ANC is lower than 500/μL.
- However…..ANC itself is not sufficient to define patient risk groups and to propose a prophylactic strategy (underlying disease, monocyte counts, comorbidities etc)
- The soluble fraction of FcRIIIb (CD16b) level has been found to correlate with the risk of infections.

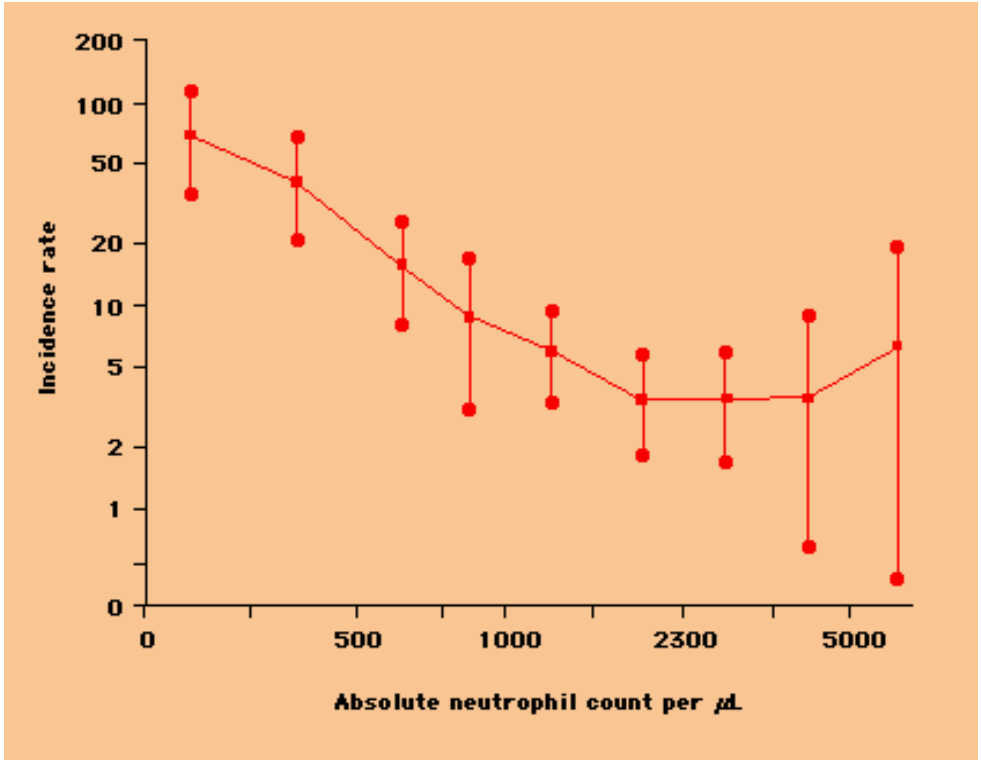


Figure from Up-to-Date