LEUKOCYTES, RED BLOOD CELLS AND PLATELETS DISORDERS

ANEMIAS, LEUKOPENIAS, LEUKOCYTOSIS, LEUKEMIAS, THROMBOCYTOPENIAS, THROMBOCYTOPATHY, THRMBOCYTEMIAS

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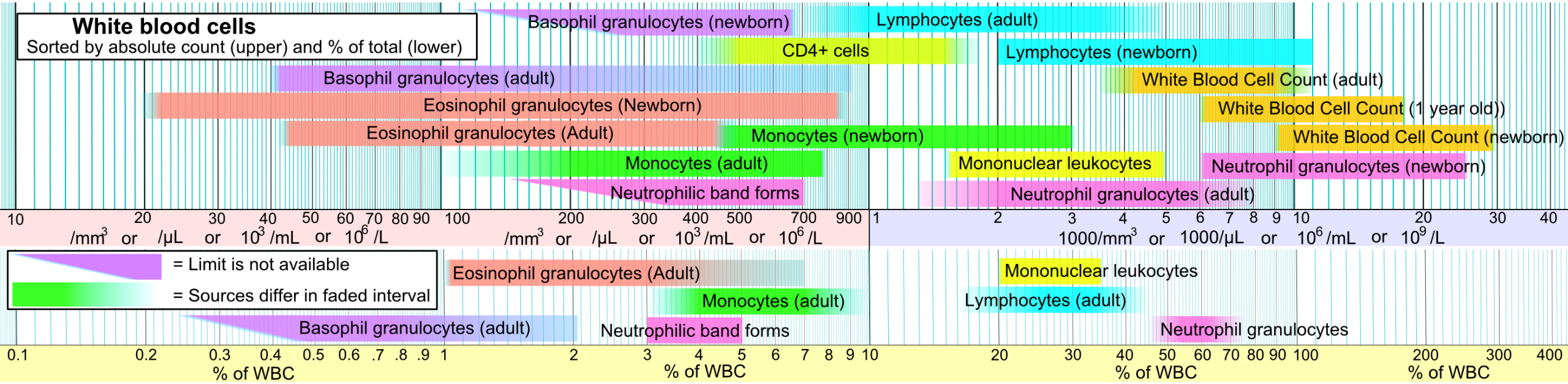
WHITE BLOOD CELLS – LEUKOPENIA, LEUKOCYTOSIS, LEUKEMIA

PHYSIOLOGICAL DATA OF WHITE BLOOD CELLS



https://upload.wikimedia.org/wikipedia/commons/b/b5/Reference_ranges_for_blood_tests_-_white_blood_cells.png

LEUKOPENIA, NEUTROPENIA, LYMPHOPENIA

- Leukopenia - <4000 cells/μl
- Neutropenia - <1500 cells/μl
- Lympho(cyto)penia – adults <1000 cells/μl (symptomatic <300 cells/μl) vs. children <3000 cells/μl

- Causes
  1. Decreased production
  2. Increased destruction or cells utilisation

When you haven't been paying attention to the lecture and the professor asks you what labs you would like to order

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LEUKOPENIA

- Drop in one or more white blood cells subpopulations in peripheral blood
- It is a SYMPTOM!!!

- „Leukopenia“ and „neutropenia“ might be used interchangeably -> neutrophiles comprise 50-75 % of all leukocytes in adults

- Agranulocytosis – clinical manifestations of severe neutropenia
  - Fatigue, fever, severe to fatal course of (even mild) diseases
  - Oral cavity – mucosa ulcers –gingiva and pharynx

LEUKOPENIA CAUSES

Decreased production

- Aplastic anemia
- Genetics
- Autoimmune disorders
- Medication induced
- Onkohematologic diseases
  - Leukemias and lymphomas

Increased utilisation and/or destruction

- HIV infection
- Onkohematologic diseases
  - Leukemias and lymphomas

NEUTROPENIA AND AGRANULOCYTOSIS

- Neutrophils
  - 50–75 % of all leukocytes
  - Non-specific defense, „first-contact troops“
  - Exposure to viruses, bacteria, physical and chemical factors, malignancies
  - Functions – DEGRANULATION, phagocytosis, chemotaxy and inflammatory reponse regulation
- Neutropenia degrees
  - Mild– 1000 – 1500 cells/µl
  - Moderate – 500 – 1000 cells/µl
  - Severe - <500 cells/µl (AGRANULOCYOSIS, some sources state <100 cells/µl)
  - Critical - <100 cells/µl -> extreme morbity and mortality risk

AGRANULOCYTOSIS

- Congenital (rare)
  - AD, ar, X-rec. – genes ELANE, HAX1, WAS (X-rec.), G6PC3, etc.
  - Autoimmune neutropenia
- Decreased production
  - Chemotherapy – destruction/"crippling" of hemopoetic stem cell – e.g. adriamycin, doxorubicin, cyclophosphamide, cisplatina, paclitaxel, carboplatina, etc.
  - Onkohematological diseases – myelodysplastic sy., leukemias, lymphomas, etc.
  - Nutrients defficiency – vit. B9, B12
- Increased destruction
  - Autoimmune diseases – e.g. systemic lupus erythematosus, Crohn disease, rheumatoid arthritis
  - Drug-induced – idiosyncratic drug reactions

ELANE – elastase, neutrophile expressed, HAX1 – proteín X1 asociovaný s hematopoeticky bunkovo-špecifickým substrátom Lyn 1, G6PC3 – katalytická podjednotka glukóza-6-fosfatázy

The risk categories of chemotherapy regimen to induce febrile neutropenia (FN)

Cancer type	FN risk category (%)/Chemotherapy regimen		
	< 10	10–20	> 20
Breast cancer	AC	FEC/docetaxel	AC- docetaxel
	Epirubicin/cyclophosphamide ± lonidamide	FEC-120	Docetaxel-AC
		FEC-100	
	Doxorubicin/cyclophosphamide–paclitaxel	Cyclophosphamide/mitoxantrone	Doxorubicin/docetaxel
	CMF	Paclitaxel (every 21 days)	Doxorubicin/paclitaxel
	Doxorubicin/cyclophosphamide	DDG doxorubicin/Cyclophosphamide-paclitaxel	TAC
			TCH
	FAC 50	Doxorubicin/vinorelbine	
		AC	
Small cell lung cancer	CAV - PE	Etoposide/carboplatin	ACE
		CAV	Topotecan
		Etoposide/carboplatin	ICE
		Paclitaxel/carboplatin	VICE
		Tirapazamine/cisplatin/etoposide/irradiation	DDG CAV -PE
		CODE	

https://pmc.ncbi.nlm.nih.gov/articles/PMC7721096/table/tb003/

The risk categories of chemotherapy regimen to induce febrile neutropenia (FN)

Cancer type	FN risk category (%)/Chemotherapy regimen		
	< 10	10–20	> 20
Non-small cell lung cancer	Gemcitabine/cisplatin	Paclitaxel/cisplatin	Docetaxel/carboplatin
		Vinorelbine/cisplatin	
		Paclitaxel/carboplatin	
		Cisplatin/docetaxel	
		Etoposide/cisplatin	
		Docetaxel	
Non-Hodgkin lymphoma		ACOD	DHAP
		(R)-CHOP	ESHAP
		Fludarabine/mitoxantrone	R-ESHAP
		Dose adjusted EPOCH	
		Mega dose-CHOP	VAPEC-B
		(R)-GEM-P	ACVBP
		(R)-GEMOX (elderly patients)	(R)-Hyper-CVAD
		GDP	ICE/R-ICE
		CHP	Stanford V
			MOPPEB-VCAD
			FC
			FCR
Hodgkin's disease			BEACOPP
			ABVD
			CEC
			IGEV
Ovarian cancer	Gemcitabine/cisplatin	Paclitaxel/carboplatin	Docetaxel
			Topotecan

https://pmc.ncbi.nlm.nih.gov/articles/PMC7721096/table/tb003/

The risk categories of chemotherapy regimen to induce febrile neutropenia (FN)

Cancer type	FN risk category (%)/Chemotherapy regimen		
	< 10	10–20	> 20
Urothelial cancer		Paclitaxel/carboplatin	MVAC
			DDGc MVAC
			BOP--VIP-B46
Germ cell tumours		Cisplatin/etoposide	VeIP
		BEP - EP	
Colorectal cancer	Irinotecan	FOLFOX	
	IFL	FOLFIRI	
Gastric cancer		Docetaxel-irinotecan	DCF
		FOLFOX	TC
		LVFU-cisplatin	TCF
		LVFU-irinotecan	ECF
			ECX
			EOF
			EOX
Esophagal cancer		Irinotecan/cisplatin	
Other malignancies	Doxorubicin/cisplatin (endometrial cancer)	Gemcitabine/irinotecan (pancreatic cancer)	TIC (head and neck cancers)
		FOLFIRINOX (pancreatic cancer)	
	TAP (endometrial cancer)	Stanford V (Hodgkin's lymphoma)	MAID (sarcoma)
	TPF (laryngeal cancer)	Paclitaxel/cisplatin (cervical cancer)	
		Gemcitabine/docetaxel (occult primary- adenocarcinoma)	

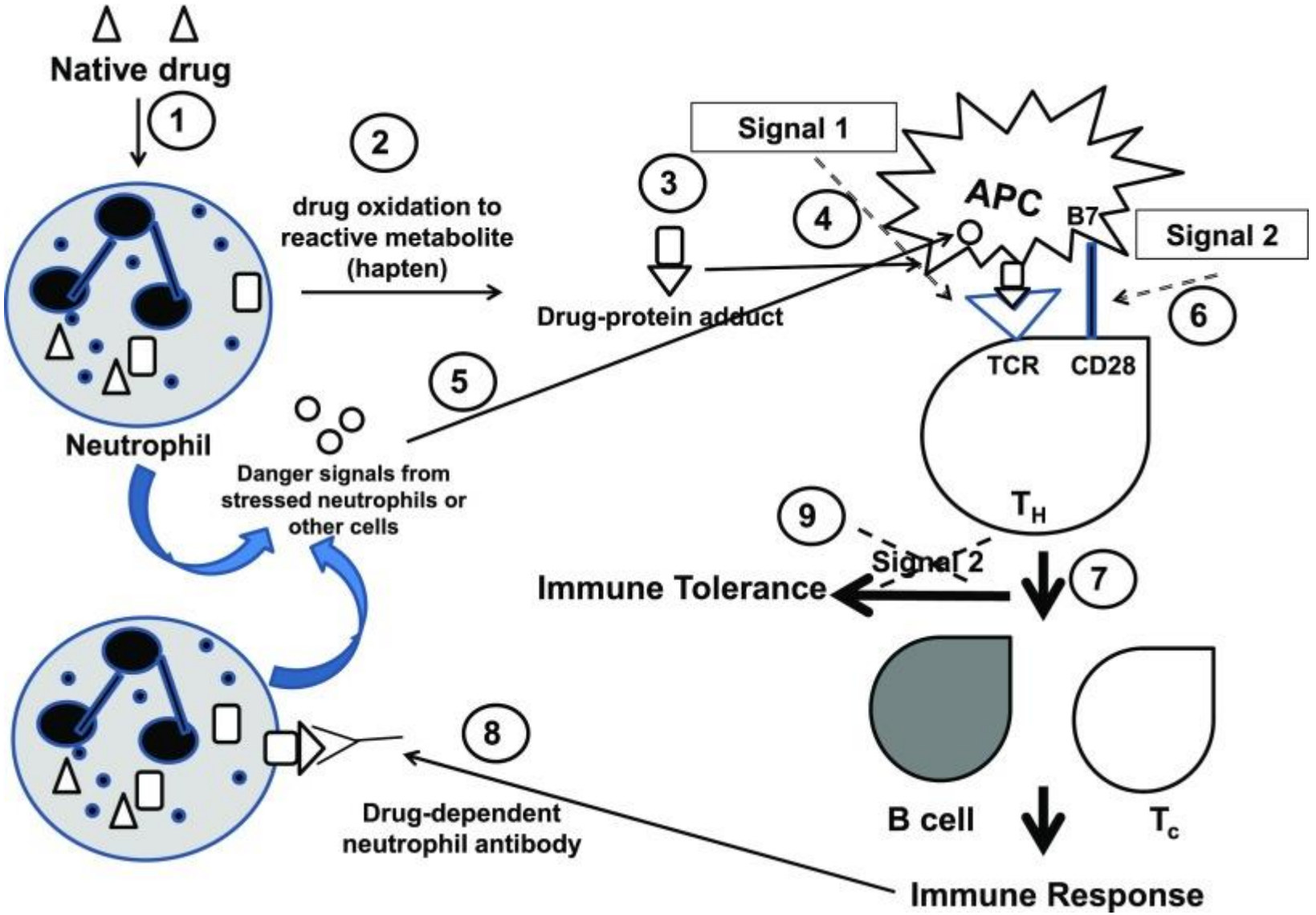
DD, dose-dense; DDG, dose-dense with G-CSF; AC, Cyclophosphamide+Adriamycin; FEC, Epirubicin+Cyclophosphamide+Fluorouracil; CMF, Methotrexate+Cyclophosphamide+Fluorouracil; TAC, Docetaxel+Epirubicin+Cyclophosphamide; TCH, Docetaxel+carboplatin+trastuzumab; ACE, Etoposide+Epirubicin+Cyclophosphamide; CAV, Vincristine+Etoposide+Epirubicin; PE, Etoposide+Cisplatin; ICE, Ifosfamide+Epirubicin+Cyclophosphamide; VICE, Ifosfamide+carboplatin+etoposide+vincristine; CODE, Vincristine+Etoposide+Cisplatin+Epirubicin; CHOP, cyclophosphamide++vincristine+doxorubicin+ponisone; GDP, gemcitabine+dexamethasone+cisplatin/carboplatin; CHP, cyclophosphamide+doxorubicin,+prednisone; DHAP, cisplatin+cytarabine+dexamethasone; ESAP, cytarabine+etoposide+ 6-mercaptopurine+cisplatin; ABVD, doxorubicin+bleomycin+vinblastine+dacarbazine; BEACOPP, etoposide+doxorubicin+cyclophosphamide+vincristine+bleomycin+prednisone+procarbazine; EPOCH, etoposide+vincristine+cyclophosphamide+doxorubicin+prednisone; StanfordV, doxorubicin+vincristine+nitrogenmustard+vinblastine+bleomycin+etoposide+prednisone; MAID, mesner+doxorubicin+ifosfamide+dacarbazine; IGEV, Isophosphoramide+gemcitabine+vinorelbine+prednisone; FOLFOX, oxaliplatin+fluorouracil+calciumleucovorin; FOLFIRI, Irinotecan+fluorouracil+calciumleucovorin; DCF, Docetaxel+cisplatin+fluorouracil; TCF, Taxol+cisplatin+fluorouracil; ECF, Epirubicin+cisplatin+fluorouracil; EOF, Epirubicin+oxaliplatin+ fluorouracil; EOX, Epirubicin+oxaliplatin+capecitabine; ECX, Cisplatin+capecitabine+epirubicin; BEP, Bleomycin+etoposide+cisplatin; TPF, Taxol+cisplatin+fluorouracil; FOLFIRINOX, Irinotecan+oxaliplatin+fluorouracil + calcium leucovorin.

https://pmc.ncbi.nlm.nih.gov/articles/PMC7721096/table/tb003/

DRUG INDUCED (IDIOSYNCRATIC) NEUTROPENIAS

1. Hapten hypothesis
   - A condition to create a covalent bond with neutrophils surface glycoproteins
   - Drugs undergoing biotransformation -> more reactive metabolites, longer elimination half-time
   - „Allo-antigen“ established -> DDABs targetting neutrophils produced
   - „Myeloperoxidase“ hypothesis -> biotransformation process may be also in neutrophils (partial – cells affected down to promyelocyte)
2. „Danger“ hypothesis – „two signals“ hypothesis
   - A hapten – signal 1, „danger“ signal 2 – HSPs, hyaluronans fragments
     - Signal 2 as the decisive -> absence leading to immunotolerance vs. presence to neutrophiles destruction
   - „Stressed“ neutrophiles -> „danger“ signals produced
   - Drugs congujates -> inflammasome activation -> IL-1β and IL-18 produced

DDABs – drug-dependent antibodies, HSPs – heat shock proteins



https://pmc.ncbi.nlm.nih.gov/articles/PMC6142577/figure/F1/

DRUG INDUCED (IDIOSYNCRATIC) NEUTROPENIAS

- HLA antigens association -> immune system „participation“
  - Graves disease -> HLA-B*38:02 ev. HLA-DRB1*08:03.
- CAVE! – decreased neutrophils count at onset of therapy - <1500 bb/µl

NEUTROPENIA AND AGRANULOCYTOSIS SIGNS

- Repeated and prolonged infections
- Fever (severe, often >38 °C)
- Fatigue
- Pharyngitis
- Lymphadenopaties (often painful)
- Oral cavity and perianal ulcerations
- Pain, swelling and rush at infection site
- Diarrhea
- Burning sensation during urination, painful urination, urgencies; vaginal discharge, pruritus, pain

GENERAL RULES OF NEUTROPENIA/AGRANULOCYTOSIS MANAGEMENT

General rules

- Discontinuation of medication causing neutropenia/agranulocytosis (consider benefit-to-risk ratio or dosage alteration)
- Corticosteroids to contain autoimmunity to be considered
- G-CSF administration
  - Some clinical trials showed benefit (neutropenia duration decreased from cca. 9 days to 4-5 days)
  - Controversial, careful consideration

Infection prevention

- Strict hygiene rules
  - Not sharing dinnerware, hands cleaning, own towels, etc.
- Getting vaccinations available
- Gardening with gloves only
- Meat to be separated from vegetables, to be processed as the last part of meal
- To avoid animal feces (cats, dogs, bunnies, etc.) and diapers change (if necessary, gloves and a surgical mask to be used)
- Prophylactic medication administered (respiration, urogenital, probiotics!)
- Administration to hospital in case of severe agranulocytosis (strict aseptic and antiseptic protocol)

LYMPHOPENIA

- Decrease in one or more lymphocytes subpopulations under physiological levels for that certain age group
  - Adults <1000 cells/μl
  - Children below 2 years of age <3000 cells/μl
    - Adults have a neutrophils prevailing with 25 % lymphocytes only vs. 67-38 % lymphocytes in children depending on their age
- Classification
  - T-lympho(cyto)penia – CD4+ „officers and generals“ and CD8+ „melee fighters, special commandos“
  - B-lympho(cyto)penia – antibodies production, „long-range artillery“
  - NK-lympho(cyto)penia – „police“ – destruction of infected, invaded and altered cells

LYMPHOPENIA CAUSES

Acute lymphopenia

- Acute viral infection (influenza H1N1, SARS-CoV-2, hepatitis)
- Starvation
- Physical/psychical stress
- Corticoseroids administration
- Chemotherapy/radiotherapy
- Ionising radiation exposure (nuclear power plant disaster, „dirty“ bomb)

Chronic lymphopenia

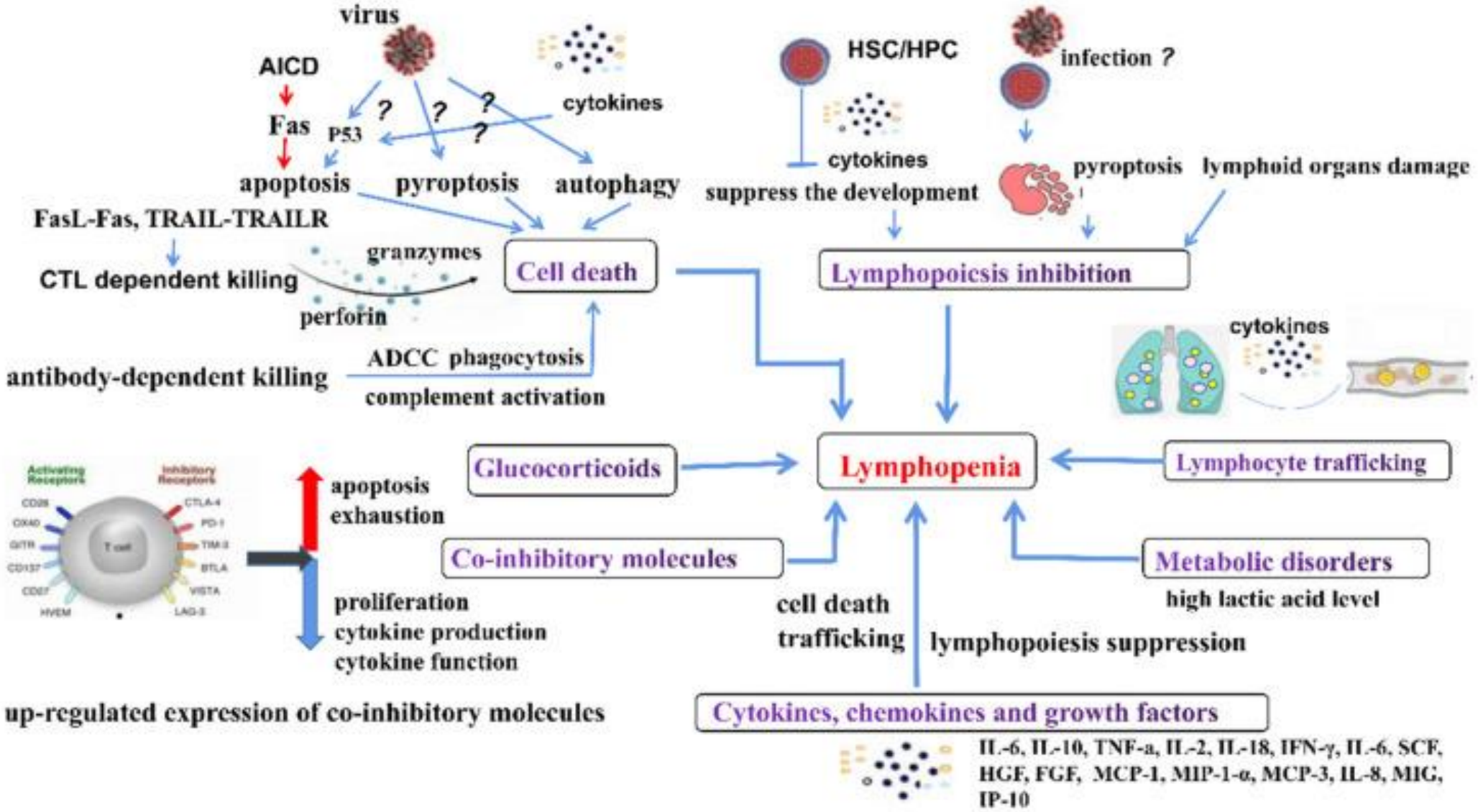
- Genetics
  - Monosomy 22q11.2 (DiGeorgeov sy), Wiscott-Aldrich sy, SCID, ataxia teleangiectatica, WHIMs
- Malnutrition
- Autoimmune diseases – e.g. lupus erythematosus, rheumatoid arthritis, myasthenia gravis
- Chronic infections e.g. HIV, miliary TBC
- Leukemias and lymphomas
- Long-term corticosteroids use, Cushing syndrome
- Sarcoidosis

SCID – severe combined immunodeficiency, WHIMs – wharts, hypogammaglobulinemia, infections and myelokathexis – mature neutrophiles and T-, B- and NK-lymphocytes retention in bone marrow; gain-of-function (?AD) CXCR4 receptor mutation (with ligand SDF-1; stroma-derived factor), for cell release into peripheral blood an inactivation of this receptor is necessary)

LYMPHOPENIA PATHOMECHANISMS (SELECTED EXAMPLES)

1. Transient lymphopenia during viral infections
   - Cytokines selection affected, lymphopoesis blocked, cell death induction
   - Possible cell death types of lymphocytes for this scenario
     - Apoptosis – direct infection e.g. MERS-CoV, HIV, measles
     - Pyroptosis – e.g. HIV, SARS-CoV-2 ->↑↑↑IL-1β
     - Autophagy – detection of gp41 in non-infected CD4+ lymphocytes in HIV+ patient
     - ADCC – viral antigens targetting antibodies attack also infected cells (surface antigen match)
     - Viral-specific CD8+ cytotoxic Ly -> FasL/FasR and TRAIL/TRAILR interaction
     - Dendritic cells – FasL/FasR – influenza virus H5N1 upregulated FasL on dendritic cells -> viral-specific CD8+ Ly destruction
     - Activation-induced cell death -> SARS-CoV-2, RSV, CDV -> FasL expression indirectly proportional to CD4+ count -> surrounding T-Ly destruction

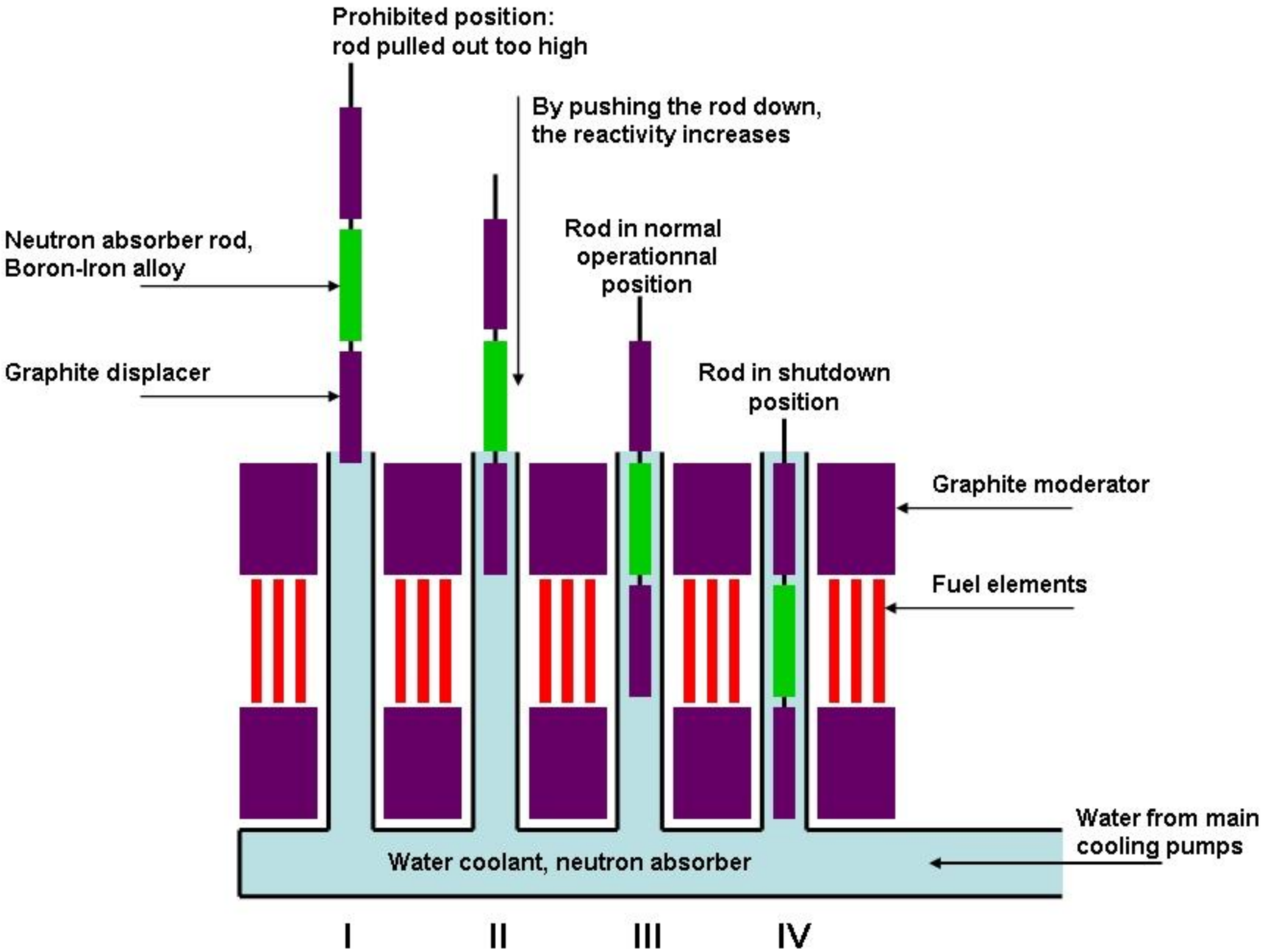
TRAIL(R) – TNF-related apoptosis inducing ligand (receptor), CDV – „canine distemper virus“


virus
AICD
Fas
P53
?
?
?
?
cytokines
apoptosis
pyroptosis
autophagy
FasL-Fas, TRAIL-TRAILR
CTL dependent killing
granzymes
perforin
Cell death
antibody-dependent killing
ADCC phagocytosis
complement activation
HSC/HPC
cytokines
suppress the development
infection ?
pyroptosis
lymphoid organs damage
Lymphopoicsis inhibition
cytokines
Glucocorticoids
Lymphopenia
Lymphocyte trafficking
Activating Receptors
Inhibitory Receptors
CD28
OX40
GITR
CD137
CD27
HVEM
CTLA-4
PD-1
TIM-3
BTLA
VISTA
LAG-3
T cell
apoptosis
exhaustion
proliferation
cytokine production
cytokine function
Co-inhibitory molecules
Metabolic disorders
high lactic acid level
cell death
trafficking
lymphopoiesis suppression
up-regulated expression of co-inhibitory molecules
Cytokines, chemokines and growth factors
IL-6, IL-10, TNF-a, IL-2, IL-18, IFN-γ, IL-6, SCF, HGF, FGF, MCP-1, MIP-1-α, MCP-3, IL-8, MIG, IP-10

CYTOKINES EFFECT ON SUPPRESION OF LYMPHOCYTES COUNT

- IL-6
  - Chronic infections, hemopoesis inhibition – STAT-3 cascade activated
- IL-10
  - T-Lymphocytes proliferation suppresion, T-lymphocytes „exhaustion“ induction, CD9+ regulatory B-lymphocytes activated
- TNF-α, interferons
  - Apoptosis induction (TNF-α, IFN-γ), lymphocytes recirculation reduction (IFN-α)
- Hemopoesis limitation with granulocytes preferred, thymus involution
- Lymphocytes redistrubuted to infected places and lymphatic nodes
- Co-inhibitory molecules upregulated – e.g. CTLA-4. PD-1 („lymphocytes exhaustion“ markers)
- CAVE! – corticosteroids in patient with initial lymphopenia may induce temporary improvement but will backfire ultimately („Chornobyl control rods“)

CTLA-4 – cytotoxic T-lymphocyte associated protein 4, PD-1 – „programmed death“ protein 1



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LYMPHOCYTES EXHAUSTION SCHEME, CYTOKINE STORM INDUCTION AND EXTENSIVE NEUTROPHILES ACTIVATION IN CORTICOSTEROIDS ADMINISTRATION DURING LYMPHOPENIA

MDSC – myeloid-derived suppresor cells

Sufficient lymphocytes count at onset

CD4+ Lymphocytes

CD4+ Lymphocytes

CD8+ Lymphocytes

CD8+ Lymphocytes

CD4+ memory cells

CD8+ memory cells

B-cell memory cells

Neutrophils

MDSC

Lymphocytes defficiency

Corticosteroids

Neutrophils

REGULATED REPONSE

Lymphocytopenia at onset

CD4+ Lymphocytes

CD4+ Lymphocytes

CD8+ Lymphocytes

CD8+ Lymphocytes

CD4+ memory cells

CD8+ memory cells

B-cell memory cells

Neutrophils

MDSC

Lymphocytes defficiency

Corticosteroids

MDSC

Neutrophils

Neutrophils

SIRS/CYTOKINE STORM

LYMPHOCYTES SENESCENCE AND EXHAUSTION

Senescence

- Too many lymphocytes cell divisions
- CD57 upregulated -> apoptosis-prone
- Decreased IL-2 production

- HIV+ patients contain high counts of senescent T-Ly, HIV infection effect questionable

Exhaustion

- Prolonged antigen exposure
- PD-1 upregulated
  - Also on APC, e.g. macrophages and dendritic cells
- T-lymfocytov donwregulation
- TCR (T-cell receptor) intracellular signalisation downregulation
- Immunologic memory and tollerance interference
- HIV -> ↑PD-1 in both CD4+ and CD8+ cells
- Circulating and effector memory subpopulation decrease (Ki-67+)

SYMPTOMS OF LYMPHOPENIA AND ITS MANAGEMENT

Signs and symptoms

- General – repeated bacterial, viral, parasitic, fungal infections, SIRS-prone
- HIV/malignancy -> enlarged lymphatic nodes, spleen
- Respiratory infection -> cough, catarrh, fever
- Immunity disorders -> lymphatic nodes and tonsills shrinking
- RA/SLE -> joints pain, rash

Management

- Treating the triggering cause
- Gammaglobulines when low antobodies levels detected
- Bonw marroe transplantation (hereditary conditions, oncohematologic diseases)
- HIV –> effective antiretroviral therapy
- CAVE! -> lymphopenia may aid to autoimmune disease establishment (tolerace-breaking condition)

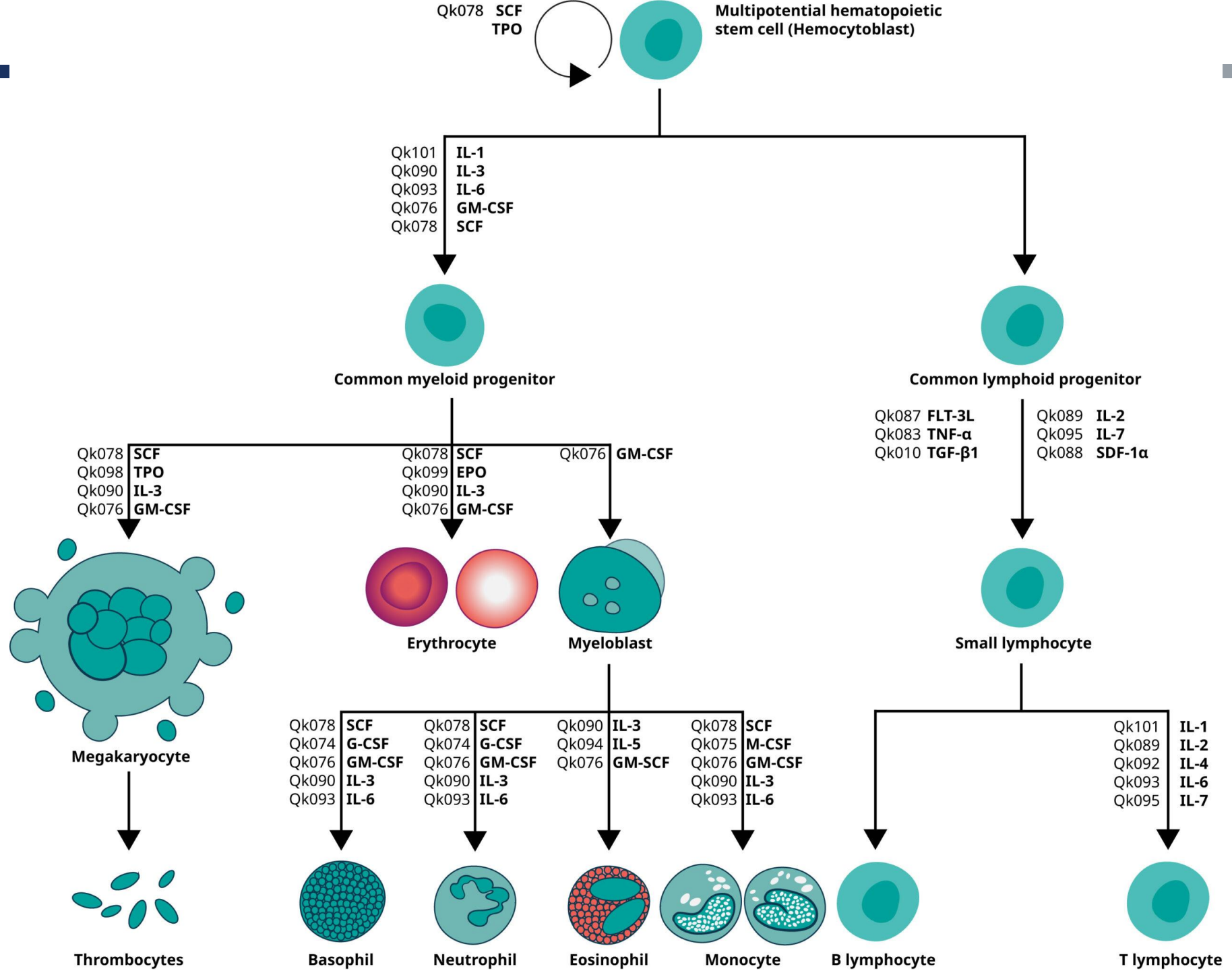
LEUKOCYTOSIS

- Elevation of leukocytes in peripheral blood >10 000 cells/μl
  - Equally or selective (neutrophilia, eosinophilia, basophilia, lymphocytosis, monocytosis)
- Causes
  - Neutrophilia – bacterial infections, pyogenic infections, sterile inflammation, MI, burns
  - Eosinophilia – allergy, parasitic infections, malignancies (Hodgkin, non-Nodgkin lymphomas), systemic autoimmune disease (SLE), vascullitis
  - Basophilia – CML (rare)
  - Monocytosis – chronic infections (TBC, bacterial endocarditis, rickettsiosis, malaria), systemic autoimmunity (SLE), IBD (ulcerous collitis), chronic myelomonocytic leukemia (immature)
  - Lymphocytosis – chronic infections (TBC, brucellosis), viral infections (hepatitis, CMV, EBV), pertusis, ALL and CLL (leukemias)
  - Immature forms – leukemias and lymphomas*

*as for teaching purposes leukemias and lymphomas are stated separately

LEUKOCYTOSIS DEVELOPMENT MECHANISMS

1. Increased bone-marrow synthesis and „storage pools“ release
   - Metamyelocyt lost mitotic ability -> „band“ transformation -> 3–5 % of circulating neutrophils
2. Decreased leukocytes adhesions to blood vessel walls
   - 50 % neutrophils circulate and 50 % adhering during physiological conditions
3. Decreased leukocytes extravasation
4. Increased bone-marrow precursors count
   - More efficient reaction to G-CSF, GM-CSF, cytokines effect, e.g. TNF-α, IL-2, IL-7, TGF-β1;, IL-1, IL-3, IL-4, IL-5, IL-6



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LEUKEMOID REACTION

- Elevation of peripheral leukocytes >50 000 bb/µl
- Temporary condition mostly
- Causes
  - Severe infections – *C. difficile,* miliary TBC, Shigellosis (*S. dysenteriae*)
  - „Hyperinflammation“ - ↑↑IL-6
  - Terapeutic (iatrogenic) – e.g. corticosteroids therapy, minocyclin, G-CSF, GM-CSF
  - Rare – mesenteric inflammatory pseudotumor (benign neoplasia), alkoholic steatohepatitis, hemorrhage (massive, retroperitoneal)
  - Correlation/unclear causality – ATRA-therapy, asplenia, diabetic ketoacidosis, hepatic necrosis, trsomy of ch. 21 (cca. 10 % incidence), paraneoplastic syndrome (extremely rare)

ATRA – all-*trans*-retinoic acid

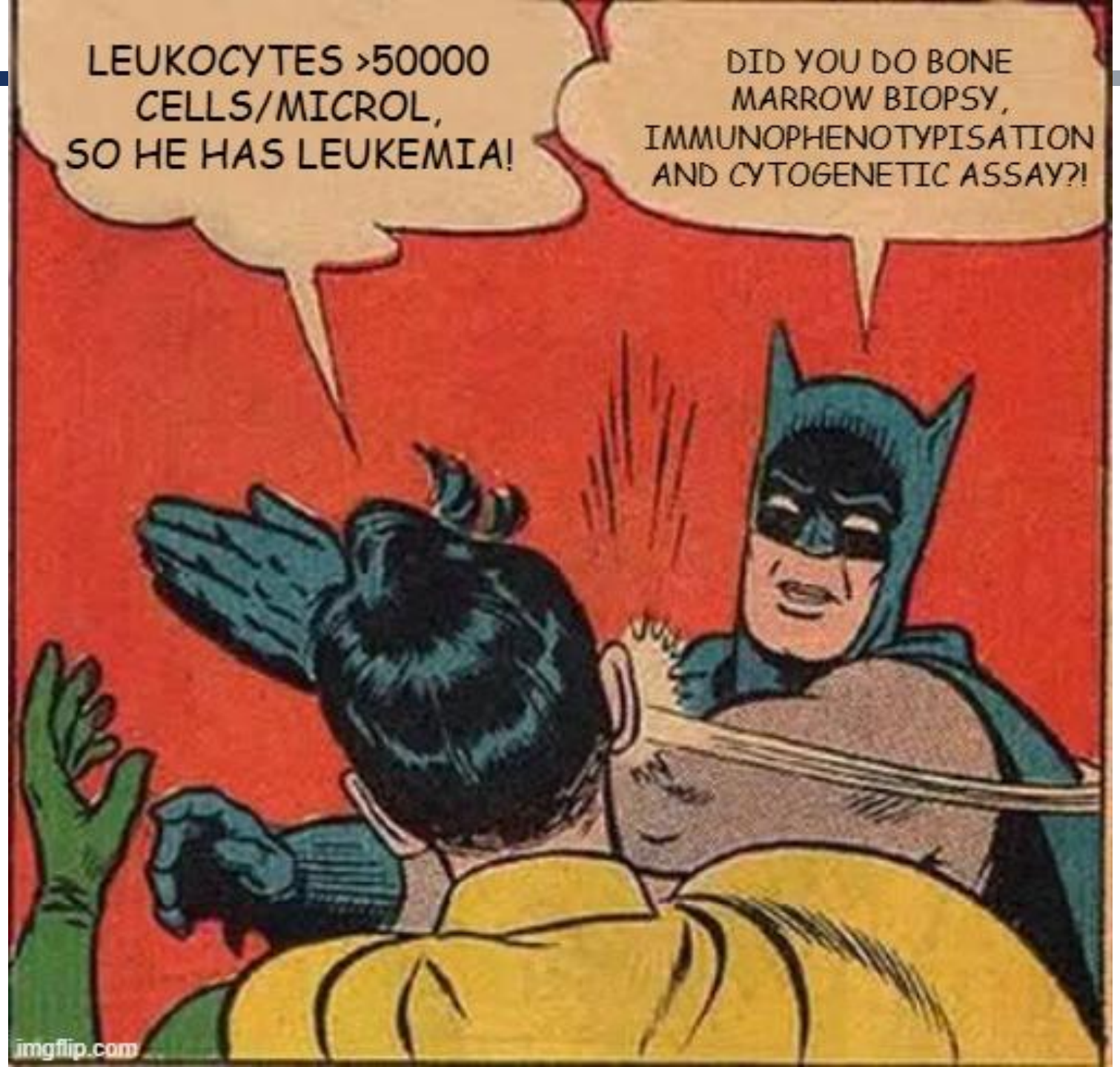
LEUKEMOID REACTION

- Characteristics
  - Peripheral blood - POLYCLONAL neutrophils (also less mature forms – metamyelocytes, „bands“)
    - Chronic myeloid leukemia - monoclonal neutrophils (immunophenotypisation assessed)
    - Lymphoid leukemoid reaction also possible
  - ↑S-ALP (leukemias - ↑ - CNL but ↓ - CML)
  - Vit. B12 in physiological range (leukemias and G-CSF administration - elevated – liver supplies mobilised)
  - Bone-marrow biopsy - hypercellular, yet physiological
    - Leukemias and oncohematologic disorders – monoclonal pathologic occupation mostly

- CAVE! – leukemoid reation means no oncohematological disease usually but observation is necessary (possible leukemia onset)!

DIF. DG. AMONG LEUKEMOID REACTION AND CNL WITH CML RESPECTIVELY

Condition / Parameter	Leukemoid reaction (LR)	Chronic myeloid leukemia (CML)	Chronic neutrophilic leukemia (CNL)
Perihperal blood	Neutrophils, „left"-shift („bands")	Immature precursors and cells, Basophils, eosinophils	Extreme neutrophilia, No immature cells!
S-Leu-ALP	↑	↓	↑
S-vit. B12	Varying or ↑	↑	↑
Bone marrow biopsy	Myeloid hyperplasia, physiol. Maturation and morphology	Basophilia, eosinophilia, monocytosis, ↑blasts, reticullin fibrosis	Similar morphology to LR, packed bone marrow, ↑reticullin
Cytogenetic assay	No genetic abnormalities	Bcr-abl	Various genetic abnormalities (cca 37 % of all cases)
Immunopheno-typisation	CD13+, CD15+, CD34-, HLA-DR-	CD13+, CD15+, CD34-, HLA-DR+	CD13+, CD15+, CD34-, HLA-DR+
Serum G-CSF	↑	↓	↓
Cell clonality	Polyclonal	Monoclonal	Monoclonal



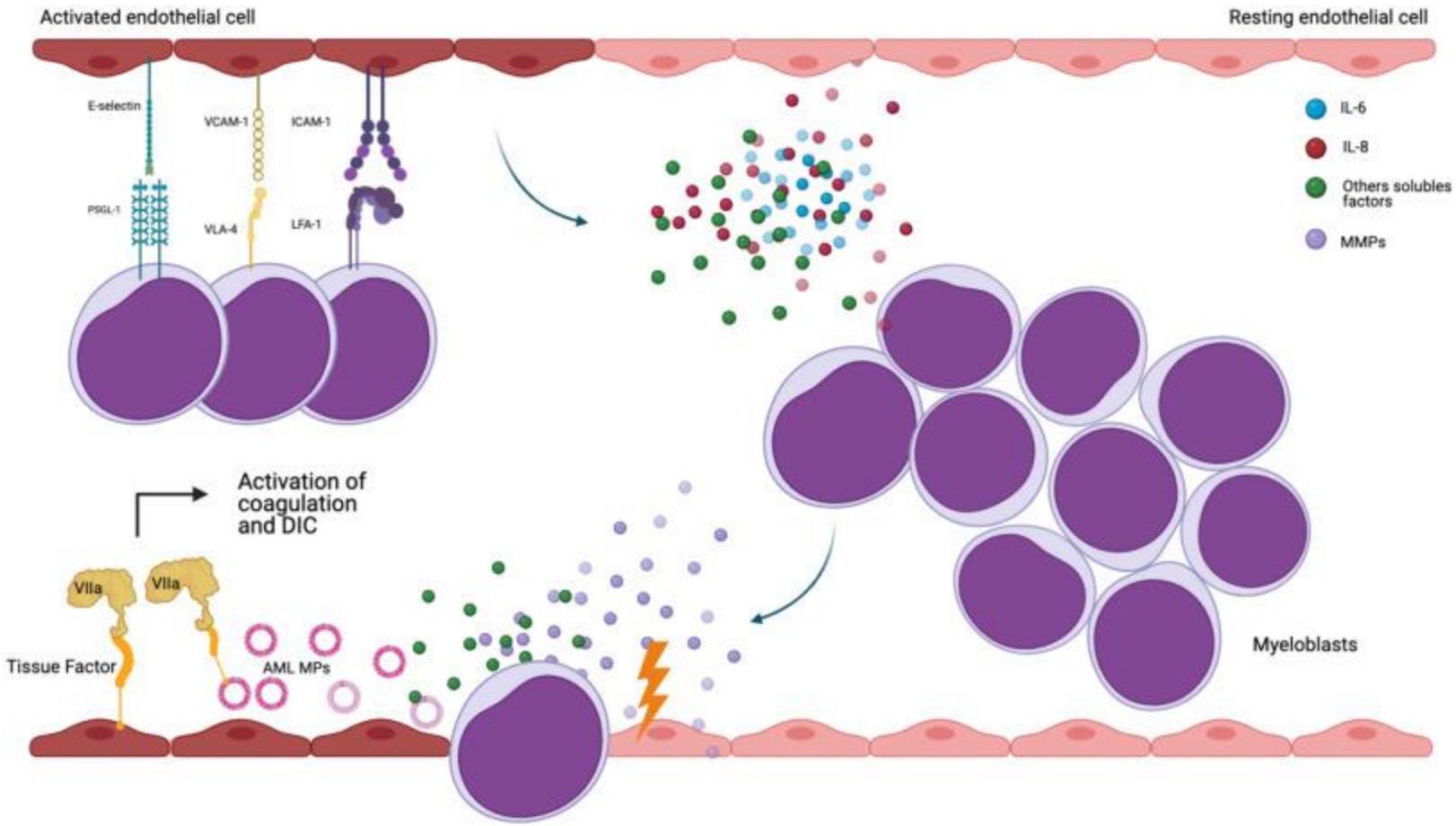
Source: author‘s work ☺

LEUKOSTASIS (ALIAS SYMPTOMATIC HYPERLEUKOCYTOSIS)

- Leukocytes and immature precursors rise in peripheral blood >100 000 cells/μl (hyperleukocytosis definition)
  - Acute myeloid leukemia (AML) may manifest these symptoms even with lower counts (from 30 000 cells/μl) -> larger leukemic cells (volume)
- Always states leukemia or oncohematological disease presence (leukemisation)!
  - Present during diagnostics
    - AML (10–20 %), ALL (20–30 %)
    - CML (rare, symptoms may not manifest even at 200 000 – 300 000 cells/μl), (CLL (?, rare) -> frequent hyperleukocytosis
- Severe to life-threatening condition – immediate admińistration to hospital and intervention necessary
  - Poor prognosis – mortality 20–40 % when untreated (pulmonar complications, transitory ischemic attack, stroke (mainly ischemic), CVS collapse)

HYPOTHESES, MECHANISM AND MANIFESTATION OF LEUKOSTASIS

- Hypotheses
  1. Elevation of rigid blasts count -> microcircullation obstruction
  2. „Hypoxic theory“ – tissue hypoxia -> ↑mitotic blasts activity -> ↑cytokínov production -> endothelial damage and subsequent hemorragies -> ↑blasts migration to capillaries
- Mechanism – capillaries obstruction and tissue hypoxia emergence
- Manifestation
  - Pulmonary – dyspnoe, cough, hypoxia (arteficial ventillation often necessary); Chest X-ray – diffuse alveolar or interstitial infiltrates, stetoscopic - rumbles
  - CNS – confusion, blurred vision, vertigo, ataxia, tinnitus, headache, disorder of consciousness (somnolence to coma); seizures, focal neurologic functions defficiency (e.g. arm)
  - Ophtalmology – retinal edema and hemorrhages, blood vessels dilation
  - Tissue – pain in various body parts, (?)fever
  - Rare – priapism (erection without stimulation or lasting for hours after cessation of stimuli)



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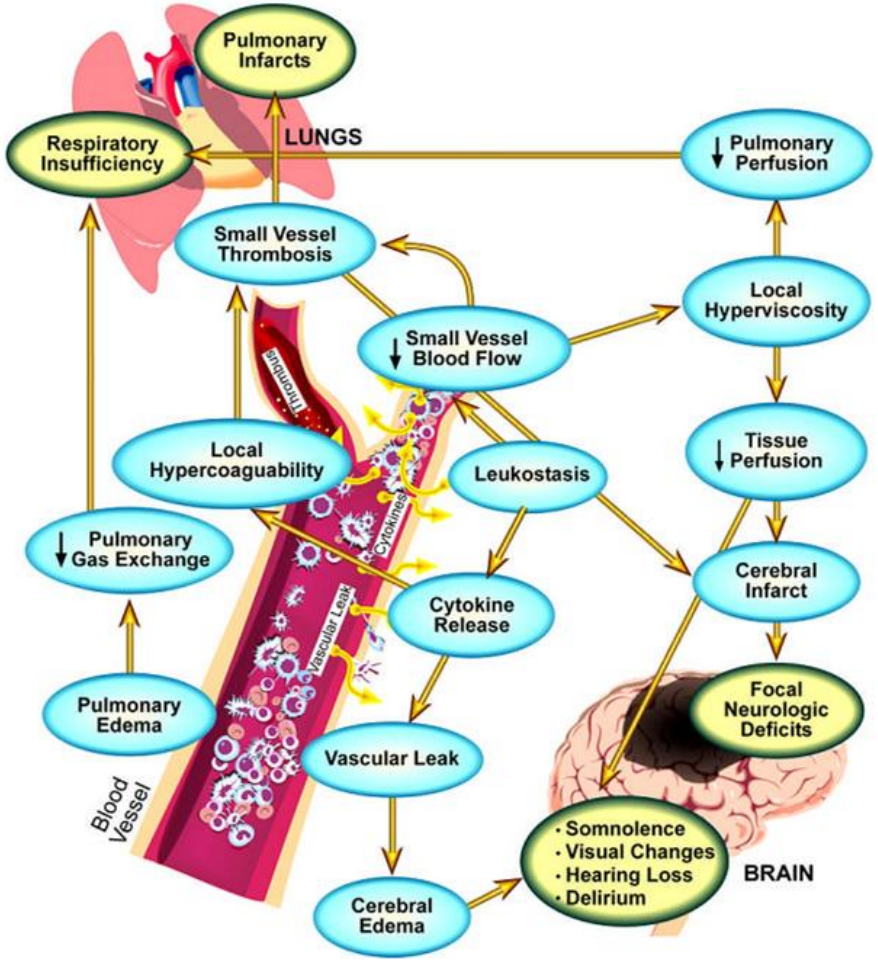
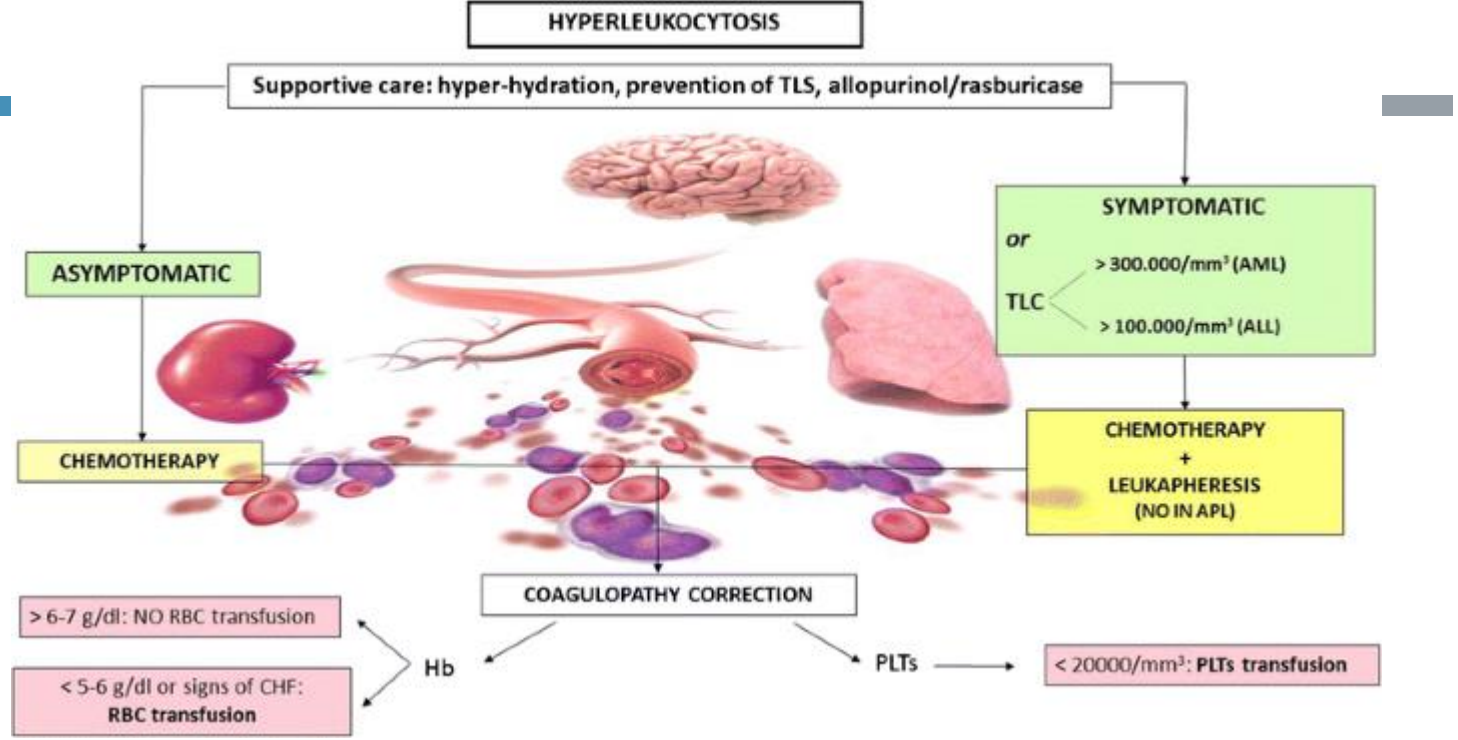
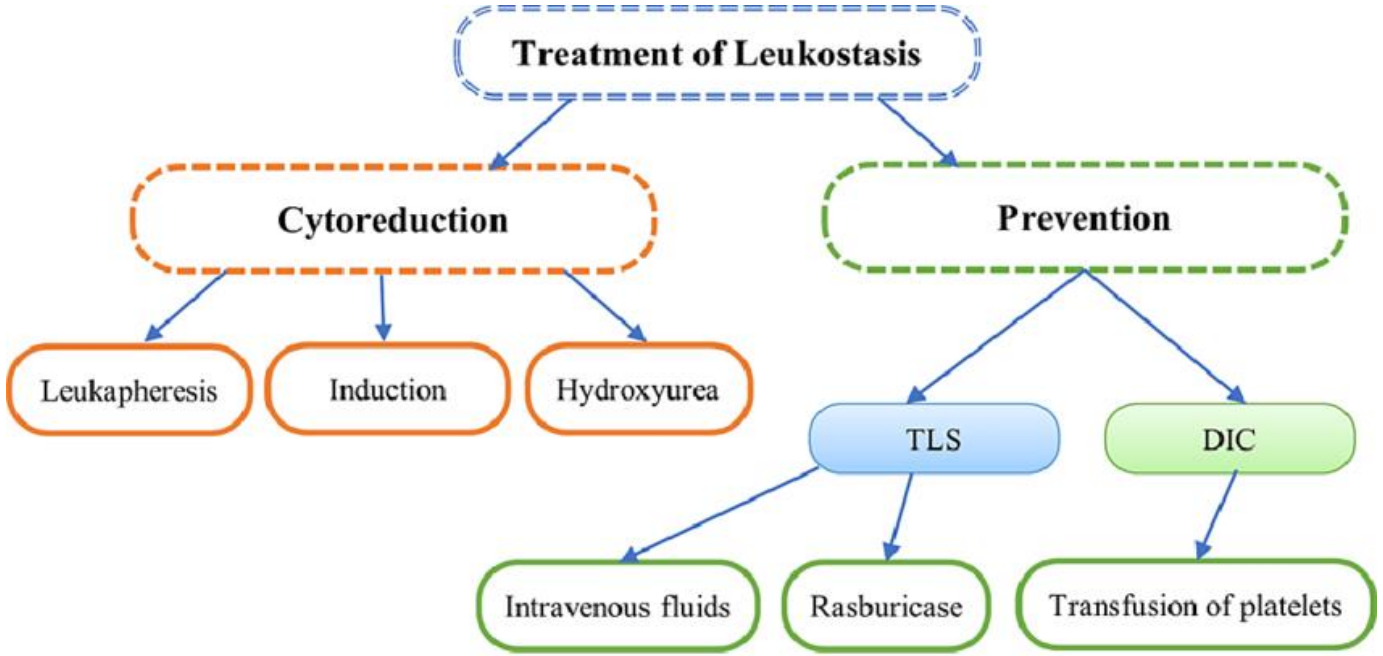


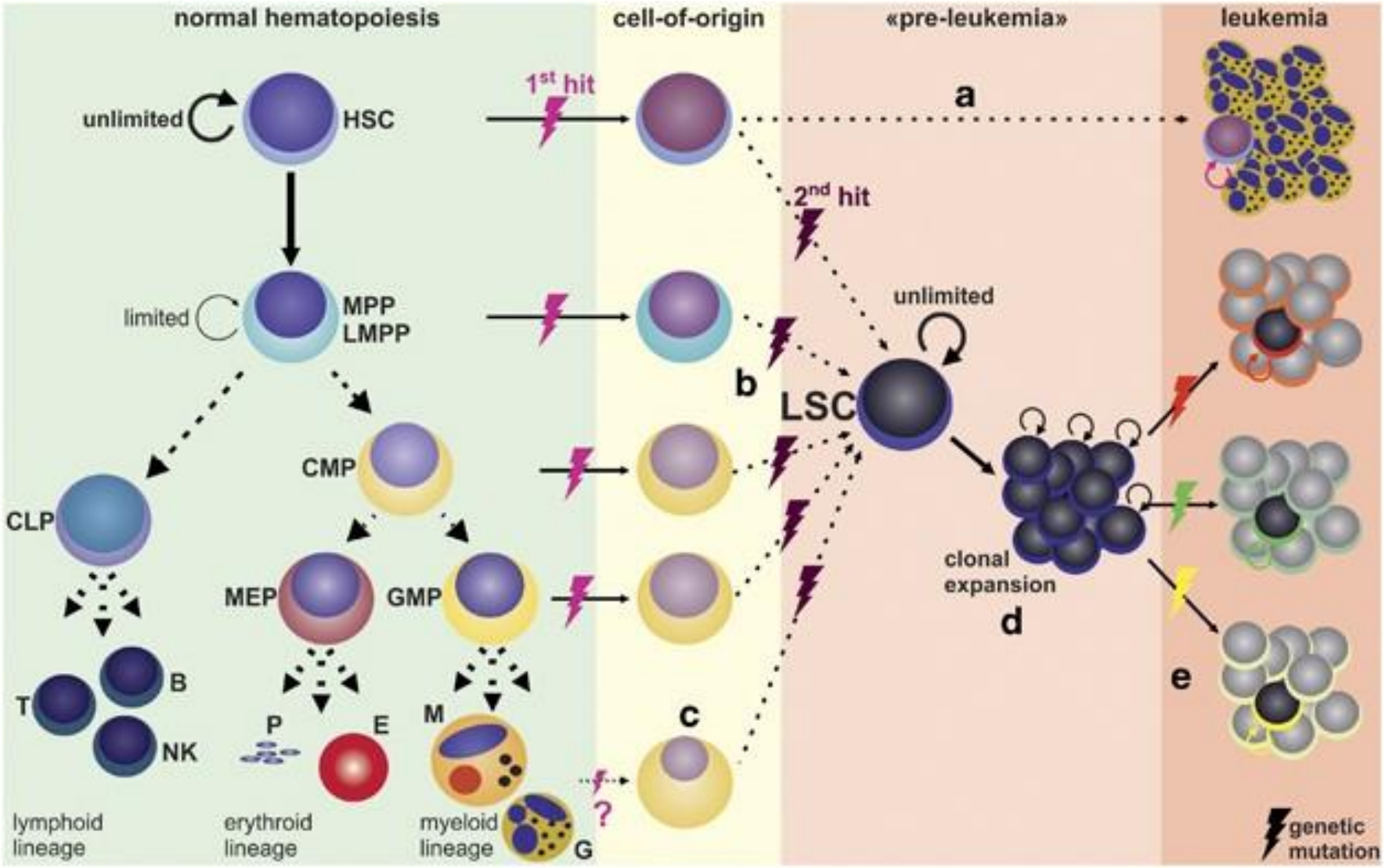




https://www.researchgate.net/publication/379195520/figure/fig4/AS:11431281230993721@1711199151555/Treatment-of-leukostasis-the-arrows-indicate-based-on.png
https://telemedicina.med.muni.cz/pediatric-oncology/res/photogallery/1-hyperleukocytosis-02.jpg
https://media.springernature.com/lw685/springer-static/image/art%3A10.1007%2Fs11864-015-0387-8/MediaObjects/11864_2015_387_Fig1_HTML.gif

LEUKEMIAS AND LYMPHOMAS – GENERAL CHARACTERISTICS

- Oncohematologic diseases
- „Founder cell“ – monoclonal
- Bone marrow occupation and destruction -> hemopoesis decreased
- Non-specific symptoms usually
  - Fatigue, tiredness, repeated subfevers and fevers (ev. „night chills“ or periodic fever), unexplained weight loss or cachexia
  - Frequent infections
  - Anemia – normocytic normochromic (anemic hypoxia)
  - Thrombocytes functions affected – petechias, purpuras, ecchymoses, bleeding manifestations
  - Lymfadenopathy (one or more groups)
- BONE MARROW BIOPSY IS DECISIVE FOR DIAGNOSIS CONFIRMATION!



https://media.springernature.com/full/springer-static/image/art%3A10.1038%2Fcdd.2014.89/MediaObjects/41418_2015_Article_BFcdd201489_Fig1_HTML.jpg

Pathophysiology Behind the Leukemias

https://calgaryguide.ucalgary.ca/wp-content/uploads/2020/01/Pathophysiology-Behind-the-Leukemias.jpg

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** MD at time of publication*

Point Mutation (in DNA)

Chromosomal Abnormality (duplication, loss, recombination error)

Combinations of these genetic defects causes reduced tumor suppressor gene expression and/or increased oncogene expression

In White Blood Cells and their precursors:
- Lack of cell growth inhibition and / or apoptosis.
- Over stimulation of cell division/growth

Neoplastic blood cell incapable of regulated cell division

Neoplastic cells uncontrollably divide in a monoclonal way: one neoplastic cell originates all successive cells

Genes regulating differentiation/maturation <u>disrupted</u>, affected neoplastic cells are incapable of further differentiation/maturation

Specific mutations cause slower disease progression

CML: Chronic Myeloid Leukemia

Degeneration during CML's "blast crisis"

Specific mutations cause rapid division and buildup of existing neoplastic cells → Acute/rapid disease progression.

<u>ALL</u>: Acute Lymphoblastic Leukemia
<u>AML</u>: Acute Myeloid Leukemia

Genes regulating maturation remain <u>intact</u> (affected neoplastic cell is capable of further differentiation/maturation)

Some neoplastic cells <u>take time to mature</u> further → **less rapid disease progression** (more indolent disease); cells don't die

<u>CLL</u>: Chronic Lymphoid Leukemia

	Initiating Mutational Event
ALL	Any combination of mutations, chromosomal alterations, or other genetic abnormalities that creates a neoplastic cell (incapable of regulating cell growth/division).
AML	
CLL	
CML	Translocation between Chr 9 and Chr 22 → Philadelphia chromosome (abnormal Chr 22) → BCR-ABL1 oncogene (along with other genetic abnormalities)

Note:
Although it is tempting to group the leukemias together for study purposes, it is best to learn the 4 main types of leukemias independently of one another, as they have a uniquely different pathophysiology and clinical presentation

LEUKEMIAS AND ONCOHEMATOLOGICAL DISEASES CLASSIFICATION

Leukemias

1. Acute myeloid leukemia
2. Chronic myeloid/myelocytic leukemia
3. Acute lymphocytic/lymphoblastic leukemia
4. Chronic lymphocytic leukemia

Lymphomas and other

- Hodkgin lymphoma
- Non-Hodgkin lymphoma

- Myelodysplastic syndrome
- Polycytemia vera rubra
- Essential thrombocytemia
- Myelofibrosis
- Mastocytosis

ACUTE MYELOID LEUKEMIA

- Onkohematological disease from immature myeloid precursors in bone marrow and peripheral blood
  - Include states with overt production of red blood cells, platelets and their precursors - megykaryocytes
- Epidemiology and statistics
  - Cca. 22 000 pacients dg. per rok 2025 estimated in USA (cca 11 000 deaths)
    - 217 new cases in Slovakia in 2023 (incidence 2,6/100000 inhabitants/year)
  - Men affectedy slightly more
  - Age of onset usually >45 years
  - 33 % of leukemias (although 1 % of malignancies)

AML PATHOMECHANISM

- Multistep process
  - „Preleukemický HSPC“ creation (NPM1, TET2, SMC1A) -> driver and key mutations acquired -> leukemic hemopoesis

- Genetic preconditioning
  - Low genetic burden compared to other leukemias however with high penetrance!
    1. Somatic mutations (acquired during life)
    - Signal and kinase cascades (FLT3, „RASopatie“), epigenetic modifiers (DNMT3A, TET2, IDH1, -2, MLL/KMT2A), transcription factors (CEBPA, RUNX1), RNA-splicing factors (SRSF2), tumor-suppressor genes (-TP53) and nucleophosmin (NPM1)
    2. Gametic/“germline
    - M. Down (GATA1 gene), RUNX1, DDX41

FLT3 – Fms-like tyrosin kinase 3, DNMT3A – DNA-methyltransferase 3α, TET2 – Tet methylcytosinedioxygenase 2, IDH1, 2 – isocitrate dehydrogenase 1, 2; MLL/KMTA2 – mixed lineage leukemia/histone-lysine N-methyltransferase 2A, CEBPA – CCAAT/enhancer-binding protein alpha, RUNX1 – Runt-related transcription factor 1, SRSF2 – serine/arginine-rich splicing factor 2
Note – examples are stated here, complete gene list is more extended, suggested further reading - https://link.springer.com/content/pdf/10.1007/s11864-022-01021-8.pdf

AML PATHOMECHANISM

- Epigenetic mechanisms
  - Methylation dysregulation - DNA – DNMT3A^{R882H} hypomethylated with „dominant phenotype “, TET2 „loss-of-function“, MLL fused gene hypomethylation (CpG sequences)
  - Non-coding RNA alterations
    - Micro-RNA – miR-145 and miR-146 deletion, miR-9 and miR-155 upregulated -> selective advantage for clones, adaptation and inflammatory response adjusted in favour of blasts
    - Long non-coding RNA (LncRNA) – conformation affect, may be as „oncogenes/TSG“ - HOTAIR (*cis*-HOTAIRM1), RUNXOR (RUNX1 promotor to enhancer interactions and translocations, chromosomal „looping“)
- Microenvironment alteration
  - Dicer1 deletion, VEGF-A secretion, interleukines secretion, CXCL12 reduced, GAS6 upregulated, WNT-ligands upregulated

GAS6 – growth arrest signal 6, Dicer1 – dsRNA endoribonuclease

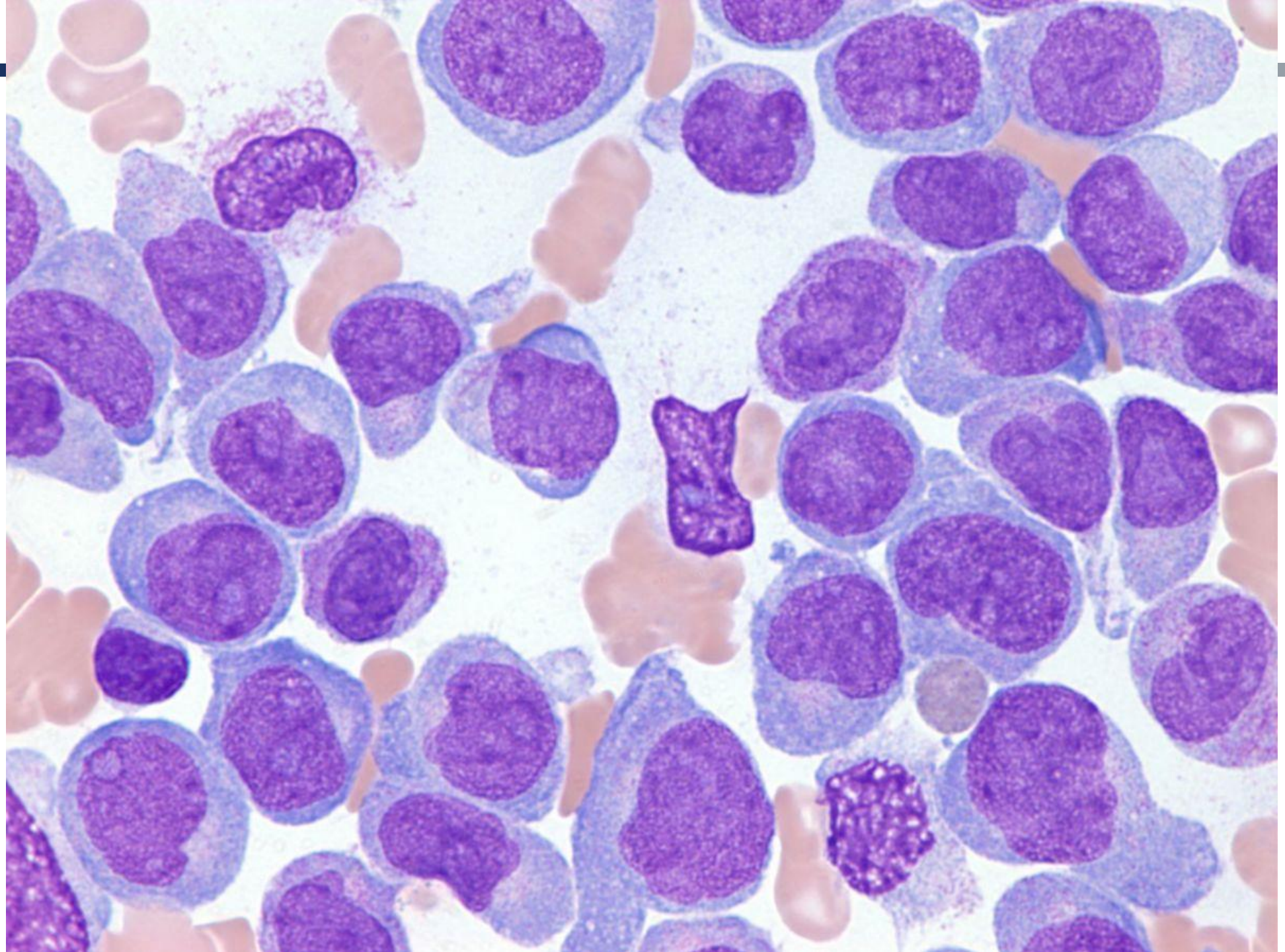
AML THERAPY EVASION

- Blasts acquiring resistance to chemotherapy -> selection pressure -> chemoresistant AML established

1. Fatty acids-rich microenvironment -> leukemic stem cells (LSC) homing to gonadal adipose tissue
   - Scavenger receptor CD36 and FABP4 expression -> oxidative metabolism
2. Endosteal region migration of chemoresistnent LSCs
   - E-selektínu and CXCL12/SDF-1 expressed, adhesion molecules CD44, expression, VLA4-VCAM1 axis upregulation, CXCL12R and CXCL4R upregulation

- Prognosis
  - Complete remission - 50–80 % paatients (relaps within 3 year usually, 60 % in favourable prognosis types, 85 % in poor prognosis types)
  - 5-year survival – cca 29,5 % (adults) vs. 66 % (children and teenagers <19 years of age)

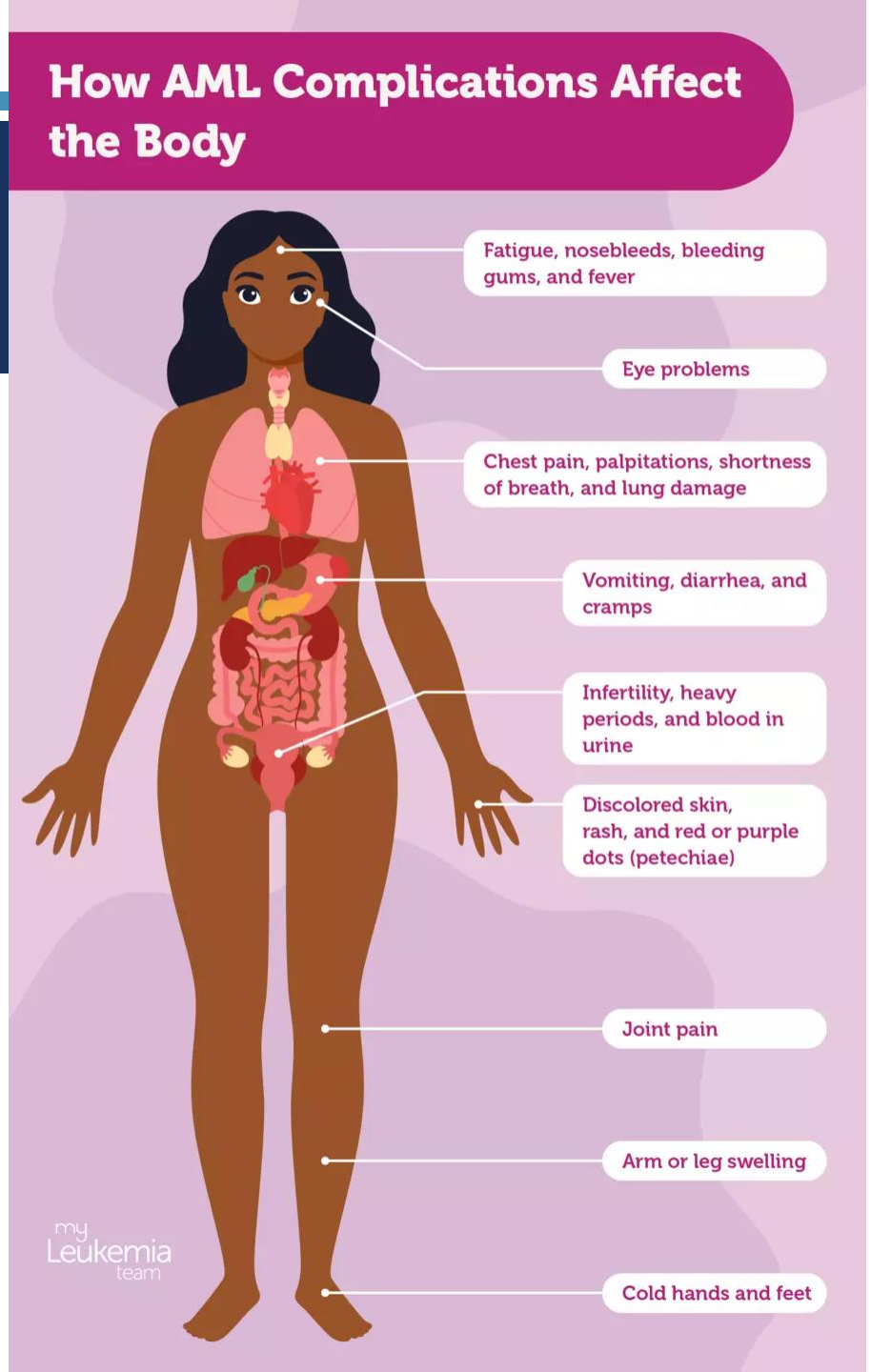
CXCL12/SDF-1 – CXC-motif chemokine 12/stromal cell derived factor-1, VLA4 - integrin



https://stjude.scene7.com/is/image/stjude/aml-leukemia-bm-m4?fit=crop,1&wid=1200

AML SYMPTOMS AND MANIFESTATIONS

- Hemopoesis disorders
  - Normocytic normochromic anemia
  - Leukocytosis with functional leukopenia
    - Prone to bacterial, fungal infections of skin and mocosa
  - Trombocytopenia -> bleeding manifestations
  - DIC risk – blasts presence
- Leukemic invasion
  - Hepatomegaly, splenomegaly, lymphadenopathy
- Leukostasis symptoms



https://cdn.myhealthteams.com/graphic/65086ee7fe9c0e0a2fc68441/woriginal/MyLeukemiaTeam_ComplicationsFromAcuteMyeloidLeukemia_Graphic-8aa00c4332a348bf15e8bec3c81763cc.webp?1695051492

ACUTE LYMPHOCYTIC/LYMPHOBLASTIC LEUKEMIA

- Onkohematological disease typical with elevation of immature lymphocytes form in bone marrow and peripheral blood
- Epidemiology and statistics
  - Peak – 2–5 years of age (USA – 2025 estimate – incidence 6100 cases, mortality 1400 cases)
    - 2015 – 7.7/100000 children vs. 1/100000 adults per year (CZE)
  - Men affected slightly more
  - Prognosis
    - Children – favourable (60 % of all ALL)
    - Adults – poor (80 % deaths to ALL despite 40% of ALL cases)

FACTORS LEADING TO ALL DEVELOPMENT

- Genetics
  - Children – hyperploidy (51 – 65 chromosomes in blasts - 25 % children vs 11 % adults), t(12,21)/TEL-AML1 (ETV6-RUNX1 – 20–25 % children vs <3 % adults)
    - These mutations are with favourable prognosis
  - Adults – Ph+ (Philadelphia chromosome, t(9,22 – BCR-ABL – 25 % adults vs 5 % children), hypoploidy (<46 Ch in cells – 5 % adults vs. 5 % children)
    - These mutations are associated with poor prognosis
- Environmental factors
  - Children – unknown, genetics (Down sy, Klinefelter sy, Fanconi anemia, neurofibromatosis, ataxia teleangiectatica, Bloom syndrome, Li-Fraumeni sy – one allele p53 loss inherited)
  - Adults – chemical (benzene), biological (HTLV-1, EBV), radiation, malignancy treatment in early age (chemotherapy)

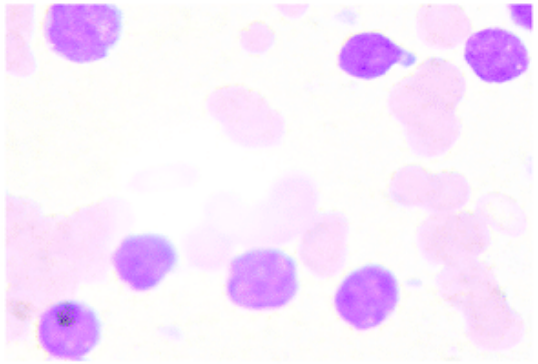
ETV6 – Ets-leukemia virus 6

ALL MECHANISM AND ITS PROGRESS

1. Genetic abnormalities accumulation in B- and T-cells precursors
2. „Founder cell“ transformation -> leukemic stem cells (LSCs) -> bone marrow invasion and destruction
3. Physiological hemopoesis suppression -> leukocytosis (even normal count or leukopenia) with functional pancytopenia
4. Peripheral blood invasion
5. Lymphatic nodes migration and spleen occupation -> lymphadenopathy and splenomegaly
6. High turnover of tumour cells -> ↑LDH

CAVE! – possible blast migration to CNS -> intracranial bleeding, seizures, neuropathies, leukoencephalopathy, thrombosis, meningitis (even lethal!), long-term cognitive functions defficiency -> intrathecal chemotherapy as a prophylaxis and treatment

FAB classification of lymphoblastic leukaemia



L1 Lymphoblastic leukaemia with homogeneous structure

Frequency:

Between 25% and 30% of cases in adults, and 85% of cases in children.

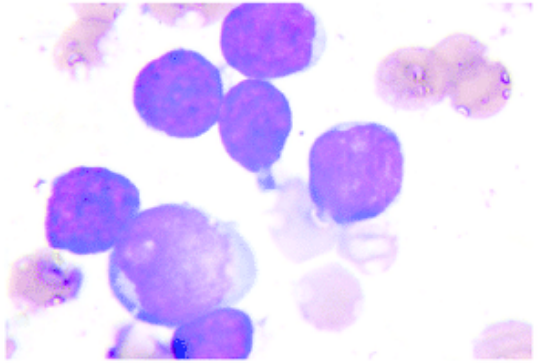
Morphology:

Blasts are homogeneous, nucleus is regular, chromatin is homogeneous, small or no nucleoli, scanty cytoplasm, and mild to moderate basophilia.

Immunophenotype

B:	T:
• CD19	•CD3
•CD22	•CD7
•CD79a	•CD5
•CD10	•CD2
•CD20	•CD4

•Cytoplasmic or superficial immunoglobulin



L2 Lymphoblastic leukaemia with varied structure

Frequency:

Accounts for 70% of cases in adults, and 14% in children.

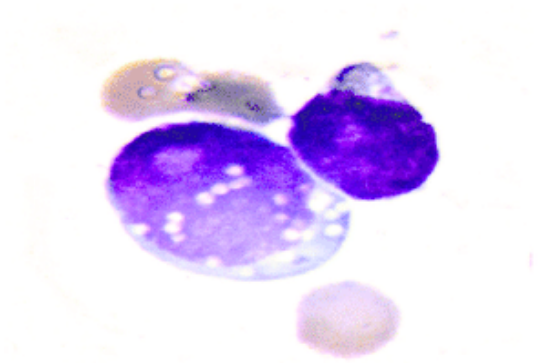
Morphology:

Nucleus is irregular, heterogeneous chromatin structure, large nucleoli.

Immunophenotype

B:	T:
•CD19	•CD3
•CD22	•CD7
•CD79a	•CD5
•CD10	•CD2
•CD20	•CD4

•Cytoplasmic or superficial immunoglobulin



L3 Burkitt's leukaemia

Frequency:

Rare subtype, accounting for less than 1% to 2% of cases.

Morphology:

Large blasts, prominent nucleoli, stippled homogeneous chromatin structure, abundant cytoplasm, abundant cytoplasmic vacuolation (bubble type) covering the nucleus.

Immunophenotype

B:	T:
•CD19	•CD3
•CD22	•CD7
•CD79a	•CD5
•CD10	•CD2
•CD20	•CD4

•Cytoplasmic or superficial immunoglobulin

ALL according to cells origin	ALL percentage
B-cell precursors	80–85 %
T-cell precursors	10–15 %
NK-cells precursors	0–1 %

2015

https://www.researchgate.net/profile/Adrian-Santoyo-Sanchez/publication/284069311/figure/fig1/AS:401297940193303@1473363459583/French-American-British-FAB-classification-of-acute-lymphoblastic-leukaemia-FAB.png

4th edition	5th edition
B-lymphoblastic leukemia/lymphoma, NOS	Unchanged
B-lymphoblastic leukemia/lymphoma with hyperdiploidy	B-lymphoblastic leukemia/lymphoma with high hyperdiploidy
B-lymphoblastic leukemia/lymphoma with hypodiploidy	Unchanged
B-lymphoblastic leukemia/lymphoma with *iAMP21*	Unchanged
B-lymphoblastic leukemia/lymphoma with t(9;22)(q34;q11.2); *BCR-ABL1*	B-lymphoblastic leukaemia/lymphoma with *BCR::ABL1* fusion
B-lymphoblastic leukemia/lymphoma, *BCR-ABL1*-like	B-lymphoblastic leukemia/lymphoma with *BCR::ABL1*-like features
B-lymphoblastic leukemia/lymphoma with t(v;11q23.3); *KMT2A*-rearranged	B-lymphoblastic leukemia/lymphoma with *KMT2A* rearrangement
B-lymphoblastic leukemia/lymphoma with t(12;21)(p13.2;q22.1); *ETV6-RUNX1*	B-lymphoblastic leukemia/lymphoma with *ETV6::RUNX1* fusion
B-lymphoblastic leukemia/lymphoma with t(1;19)(q23;p13.3); *TCF3-PBX1*	B-lymphoblastic leukemia/lymphoma with *TCF3::PBX1* fusion
B-lymphoblastic leukemia/lymphoma with t(5;14)(q31.1;q32.1); *IGH/IL3*	B-lymphoblastic leukemia/lymphoma with *IGH::IL3* fusion
B-lymphoblastic leukemia/lymphoma with other defined genetic abnormalities	B-lymphoblastic leukemia/lymphoma with other defined genetic abnormalities

5th edition
B-lymphoblastic leukemia/lymphoma with *ETV6::RUNX1*-like features
B-lymphoblastic leukemia/lymphoma with *TCF3::HLF* fusion

B-cells classification changes according to WHO (left, 4th ed – 2017, 5.thed. -2022 respectively)
New diagnoses for 5th ed. (right and top)

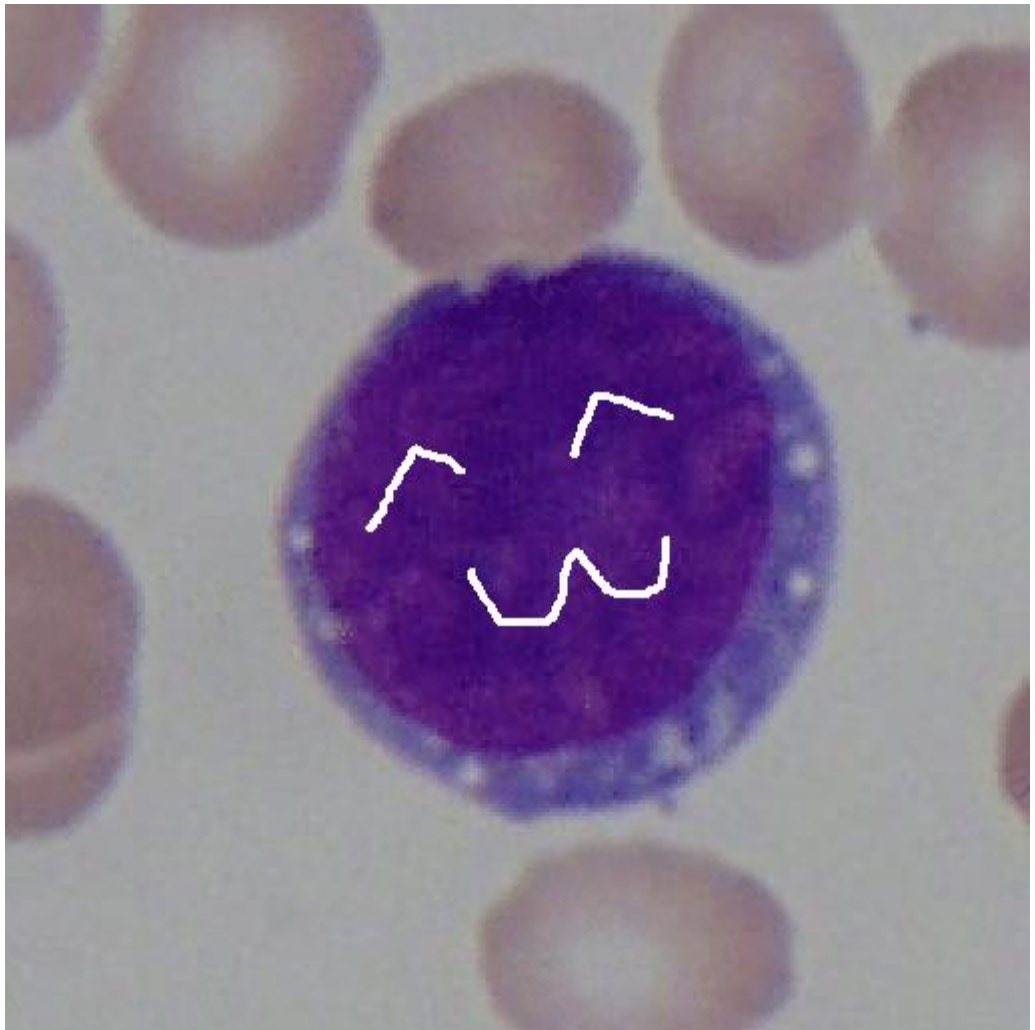
https://lymphoblastic-hub.com/medical-information/the-5th-edition-of-the-world-health-organization-classification-of-haematolymphoid-tumors-key-updates-to-all-classification

T-CELL ALL CLASSIFICATION - WHO (4TH ED. – 2017, 5TH ED. – 2022)

4th edition	5th edition
T-lymphoblastic leukemia/lymphoma	T-lymphoblastic leukemia/lymphoma, NOS
Early T-cell precursor lymphoblastic leukemia	Early T-precursor lymphoblastic leukemia/ lymphoma
NK-lymphoblastic leukemia/lymphoma	Entity deleted

https://lymphoblastic-hub.com/media/images/aa/d0/who-all-figure3.png
https://img.freepik.com/premium-vector/cartoon-cute-anime-girl-crying-illustration-creative_638892-439.jpg

THOSE TYPOS... – „A CUTE LYMFOCYTIC LEUKEMIA“



ALL MANIFESTATIONS

- Hemopoesis affected
  - >20 % blasts in peripheral blood and bone marrow
  - Functional pancytopenia -> anemia; prone to infections; bleeding manifestations (skin, GIT)
  - DIC imminent! – blasts in peripheral circulation
  - Bone pain – bone marrow invasion
- Lymphadenopathy (multiple groups together)
- Hepato- and splenomegaly
- „Night chills“, subfevers, fevers

ALL TREATMENT IN CHILDREN AND ADULTS (JUST FYI) – AMERICAN CANCER SOCIETY

Children

1. Induction
   - L-asparaginase, vincristine, dexamethasone (if high-risk (HR) + anthracyclines – e.g. daunorubicine)
   - If Ph-Ch+ - imatinib
2. Consolidation
   - According to ALL type – e.g. methothrexate, 6-merkaptopurine, vincristine, L-asparaginase (if HR – doxorubicine, etoposide, cyclophosphamide, cytarabine)
   - Sometimes a „second wave“ treatment necessary – delayed consolidation
3. Maintenance
   - 6-merkaptopurine (daily), methothrexate (weekly) p.o.; vincristine + corticosteroids i.v. (á 4–8 weeks)
4. Radiotherapy (bone marrow ablation)
5. Bone marrow transplantation

Adults

1. Induction
   - Vincristine + dexamethasone/prednisone – doxorubicine/daunorubicine
   - If Ph-Ch+ - imatinib, dasatinib
2. Consolidation (intensification)
   - Imatinib
   - Immunotherapy - blinatumomab
3. Maintenance (2 years)
   - 6-merkaptopurine, methothrexate (Ph-Ch+)
4. Radiotherapy (bone marrow ablation)
5. Bone marrow transplantation (possible even druing phase 2)

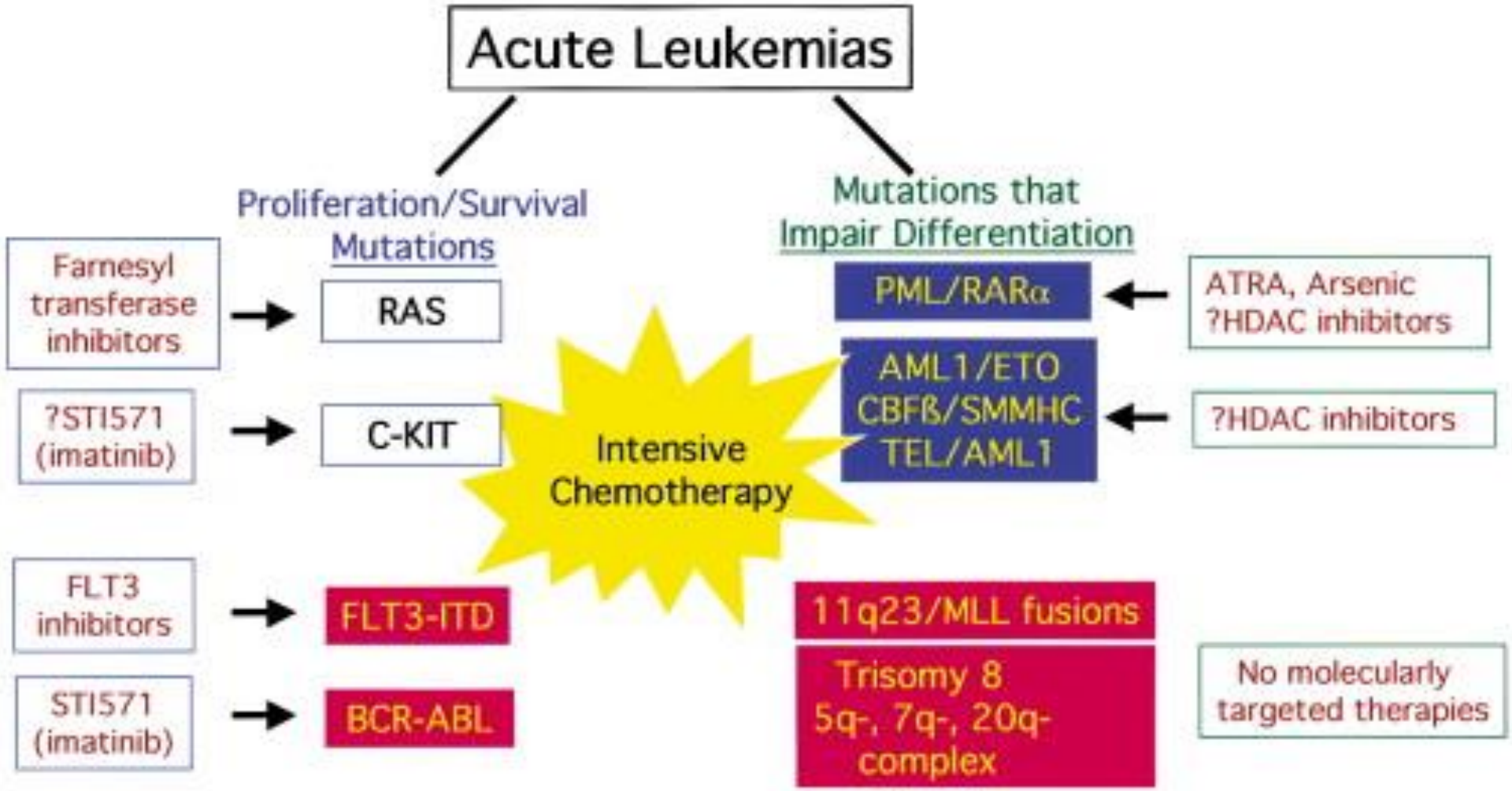
PROGNOSIS OF ALL AND TREATMENT OF RESISTANT FORMS

Children

- Prognosis
  - Remission – 90–98 %
  - Relapse – cca 10 %
- Recurrent and resistant ALL treatment
  - CAR-T-cell treatment (chimeric antigen receptor)
  - Drug and antibody conjugate – inotuzumab ozogamicín

Adults

- Prognosis
  - Remission – 80–90 %
  - Relapse – 40–45 %
- Recurrent and resistant ALL treatment
  - CAR-T – B-cell-ALL
  - Ph-Ch+ - imatinib
  - KMT2A+ - revumenib
  - Nelarabine – T-cell ALL



HDAC – histone deacetylase

https://www.cell.com/cms/10.1016/S1535-6108(02)00081-8/asset/e39034e4-7311-44be-b4e5-cf41a700ee3c/main.assets/gr1.jpg

CHRONIC MYELOID LEUKEMIA

- Oncohematological disease typical with increase in myeloid precursors of higher maturity degree compared to AML
- Epidemiology
  - USA 2025 estimate – incidence 9 500 cases, mortality cca 1 300 cases
  - 50 % patients aged 65+, rarely in children or <40 years of age
- Fusion gene BCR-ABL1 establishment typical
  - T(9;22)(q34;q31)
  - Chromosome 22 contain several points of possible breaks and translocations – variations e13a2 and e14a2 (210 kDa)
    - Variations 190 kDa (e1a2 – B-cell-ALL), resp. 230 kDa (chronic leukemias)
  - This gene solely allows leukemic transformation

CML PATHOMECHANISM

1. BCR-ABL1 fusion gene -> protein
   - Tyrosin kinase activity
   - Cascades JAK/STAT, PI3K/AKT, RAF, MYC and RAS/MEK stimulated -> proliferation, cell survival and resistance to apoptosis cell advantage
   - BCR-ABL negative CML -> SETBP1, ASXL1, NRAS/KRAS, SRSF2, CSF3R, U2AF1 gene mutations, etc.
2. Leukemic stem cells development -> chronic phase

SETBP1 – Set binding protein 1, ASXL1 – additional sex chromatine human homologue 1, NRAS – neuroblastoma RAS viral homologue, KRAS – Kirsten rat sarcoma virus, SRSF2 – serin/arginin-rich splicing factor 2
U2AF1 – U2 small nuclear RNA auxilliary factor 1

CML COURSE

1. Chronic phase (3–5 years, 85 % patients during dg.)
   - <10 % bone marrow blasts, possible anomalies in peripheral blood (↑Tr, ↑Leu - ↑Neu, ↑Ba, ↑Eo, „left“ shift)
   - „Myelocyte bulge“ – myelocytes prevail over mature metamyelocytes
   - Asymptomatic patient or non-specific symptoms – weight loss, fever/“night chills“, weakness, splenomegaly
2. *Accelerated phase (7–12 months without treatment)*
   - *Additional mutations acquired – p53-; CDKN2A-; GATA2-; RUNX1; IKZF1; ASXL1; WT1*
   - *Additive cytytogenetic abnormalilites (ACA) mark worse prognosis and increasing severity (5–10 % in chronic phase vs. 80 % v blastic phase)*
   - *Anemia development, symptoms from chronic phase more intense of starting to manifest*

CDKN2A –cycline-dependentkinase inhibitor 2A; GATA2 – GATA-binding protein 2; RUNX1 –Runt-related transcription factor 1; IKZF1 – Ikarus family zinc finger 1; ASXL1 – Additional sex chromatine human homologue 1; WT-1 – Wilms tumor 1

CML COURSE

3. Blastic phase (blastic crisis; 3–6 months; survival median 1.8 years)
   - Bone-marrow and peripheral blasts >20 %
   - High cells turnover -> ↑K^+, ↑LDH, ↑uric acid
   - Organs infiltration -> lymphadenopathy, splenomegaly, bone pain
   - Sternal bone „softening“ -> hemopoesis bone marrow expansion to phylogenetic older locations
   - AML/ALL transformation

Chronic Myeloid Leukemia (CML): *Pathogenesis and Clinical Presentation*

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Translocation of a Chr 9 segment onto Chr 22, creating a Philadelphia chromosome (Chr 22) containing the BCR-ABL1 fusion gene

Mutations from ionizing radiation

Other genetic abnormalities

These genetic abnormalities accumulate in the earliest cell of the blood cell differentiation sequence: the pluripotent hematopoietic stem cell

Hematopoietic stem cell division in the bone marrow becomes unregulated → Multifactorial causes, most with unclear mechanisms → Weight loss, malaise, fever/ chills, night sweats

https://calgaryguide.ucalgary.ca/wp-content/uploads/2015/05/CML.jpg

1. Chronic Stage (85% of clinical presentation): Hematopoietic stem cell division/differentiation in the bone marrow results in ↑ production of multiple blood cell lines (detectable on CBC, but patients are usually asymptomatic at this stage)

- Neoplastic division of platelet precursor cells → Thrombocytosis
- Neoplastic division of WBC precursor cells, especially neutrophil precursors → **Leukocytosis:**
  · Neutrophilia, basophilia, & eosinophilia
  · "Left shift": ↑ neutrophil & band production
  · Disorderly WBC differential: i.e. "myelocyte bulge"
  → Trapping of WBC's in the spleen enlarges the spleen → **Splenomegaly:**
  · Left upper quadrant pain
  · Early satiety (large spleen compresses the stomach)
  · Associated hepatomegaly (if spleen is overfilled & WBCs spill over into liver)

Acquired ↑ genetic abnormalities

2. Accelerated Stage
More and more immature precursor cells ("blasts") divide and accumulate in bone marrow (where 10-19% of blood cells are "blasts".) Blasts start to spill over into the peripheral blood

Dividing "blasts" limit the space and resources available for RBC synthesis → Anemia → *↓ oxygenation of blood means blood is less red & body tries to compensate* → Pallor, Dyspnea, Tachycardia

Acquired ↑ genetic abnormalities

3. Blast crisis (transformation into AML/ALL)
Neoplastic blast cells have filled up the bone marrow (where >20% of blood cells are blasts). More blasts spill out into the peripheral blood.

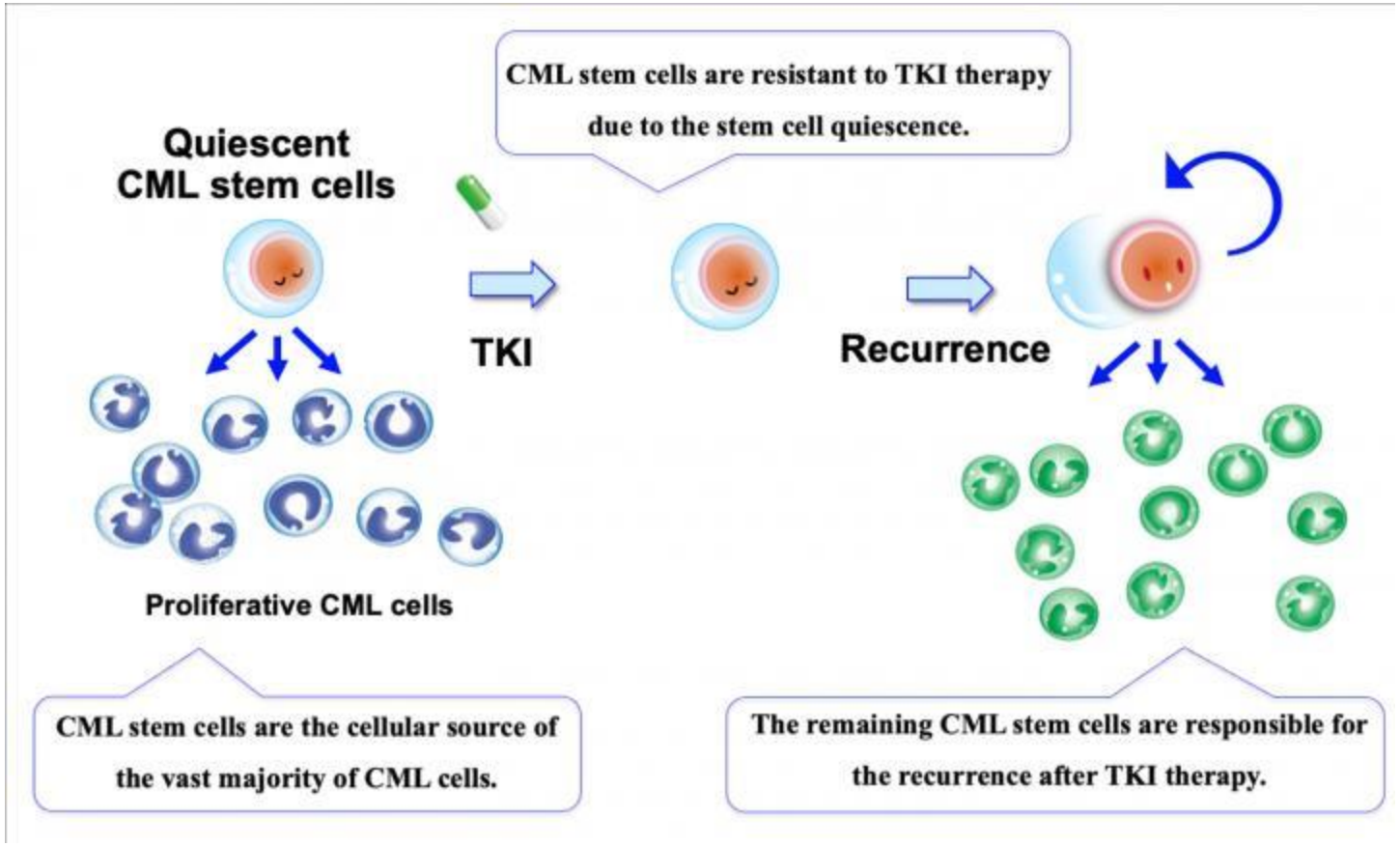
- High turnover of these cancerous cells → excess cell lysis → Release of intracellular contents (uric acid, K+, LDH) into plasma
  - · Hyperkalemia
    · High (LDH) → Gout
  - Hyperuricemia → Acute Kidney Injury
- Expanding marrow pushing on bone → Bone pain
- Bone marrow expands into sternum → Sternal tenderness

Legend: Pathophysiology | Mechanism | Sign/Symptom/Lab Finding | Complications

Re-Published **June 15, 2019** on www.thecalgaryguide.com

CML TREATMENT AND PROGNOSIS

- Treatment
  - GOLDEN STANDARD – Tyrosine kinases inhibitors - Imatinib mesylate, dasatinib, nilotinib, etc.
  - Chemotherapy, immunotherapy
  - High-dose ChT + bone marrow transplantation
  - Donor lymphocytes transfusion -> bone marrow transplantation success increased– „graft vs. host“ – donor lymphocytes attack acceptor blasts
  - Surgery - splenectomy
- Prognosis
  - 5-year survival – 90 % (85 % survive for 10 years)
  - Remission – 40–60 %, relapse 60 % (most in 6 months after treament termination, imatinib – responding well)



https://genengnews.com/wp-content/uploads/2020/09/Sep18_2020_KazuhitoNaka_CMLstemcells.jpg

CHRONIC LYMFOCYTIC LEUKEMIA

- Oncohematologic disease typical with leukocytes increase in bone-marrow and periphjeral blood (also organs infiltration often) – monoclonal B-cells
  - Partial preservation of signalisation, B-cell receptor (BCR) including
  - Packing of monoclonal B-cells -> oppression of healthy cells, defective defensive functions, CD5+, CD23+
- Classification
  - Slowly progressing CLL (indolent)
  - Fast progressing CLL (aggresive)
- Epidemiology and statistics
  - USA 2025 estimate – incidence 24 000, mortality 4 500 cases
  - Average age during diagnosis - 70 years of age, rarely <40 years of age

CLL PATHOMECHANISM

1. Monoclonal-B-lymphocytosis – „pre-leukemic condition“
   - Definition – „low-grade“ (<500 MBLy-Ly/μl) vs „high-grade“ (500 – 5000 MBLy/μl)
   - Genetics - „first hit“
     - Classic factors (SNP, partial monosomies) – locus 13q21.33-22.2, m-del q11, m-delq13, m-del p17; 47, XX/XY,+12;
     - NOTCH1, BIRC3, SF3B1, MYD88, ATM a TP53 factors mutations
     - V(D)J components mutations – e.g. IVGH4-59/61 („low-grade“) vs. IGHV1-69, IGH2-5, IGHV3-23, etc. („high-grade“) -> genomic transformation failure (antobodies production necessity) -> „second hit“
   - Environmental factors influence (benzene; EBV; chemotherapy in medical history)
   - Packed MBLy in bone marrow and their release into periphery
   - Asymptomatic, average CLL/SLL transfromation time is 6.4 years

„m-“ marking partial monosomy, SLL – small-cell lymphoma

CLL PATHOMECHANISM

2. CLL transition
   - CLL may start even without MBLy
   - Genetic and epigenetic abnormalities accumulation -> bone-marrow microenvironment change
   - Enviromental factors – as in MBLy + insecticides, Agent Orange, radiation
   - Survival cascades regulation -> „Goldilocks and three bears“ -> BCR, NF-κB
   - Bone-marrow occupation, „immunosuppression“ established -> malignant B-Ly with leukocytosis
   - Asymptomatic for a long time -> MBLy in peripheral blood, „smudge/basket“ cells, hypogammaglobulinemia

CLL MANIFESTATIONS

- Long-term asymptomatic
- Decresed functional leukocytes + hypogammaglobulinemia – frequent infections
- Inflammatory cytokines production -> fever, „night chills“, weight loss, appetite loss
- Splenomegaly, lymphadenopathy
- ↓Ery -> normocytic normochromic anemia
- ↓Tr – bleeding manifestations

CLL TREATMENT AND PROGNOSIS

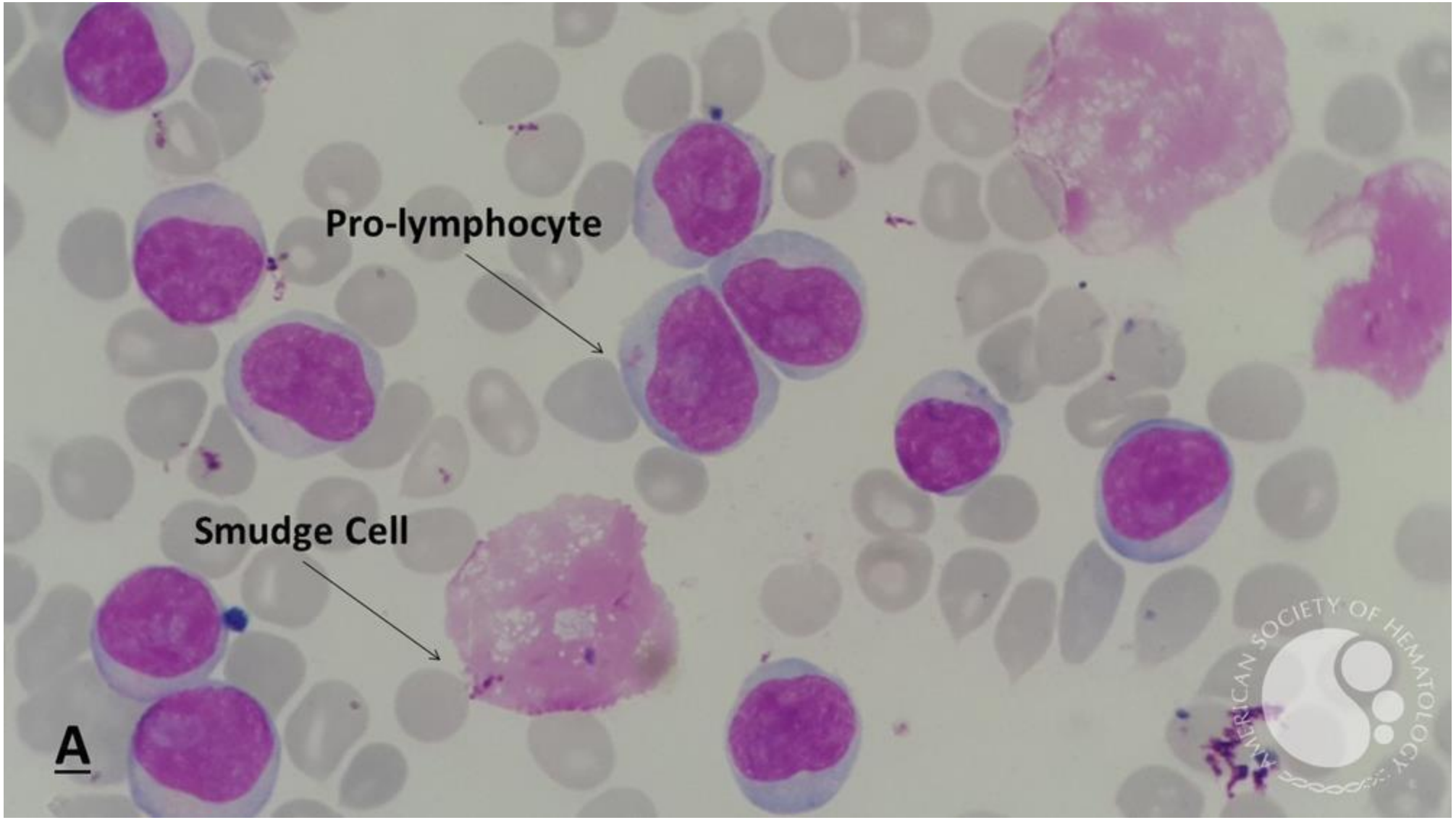
Treatment

1. Bruton kinase inhibitors – e.g. ibrutinib, zanubrutinib
2. Bcl-2 inhibitors – venetoclax + obinutuzumab (anti-CD20)
3. Bruton kinase inhibitors + Bcl-2 inhibitors

Prognosis and risks

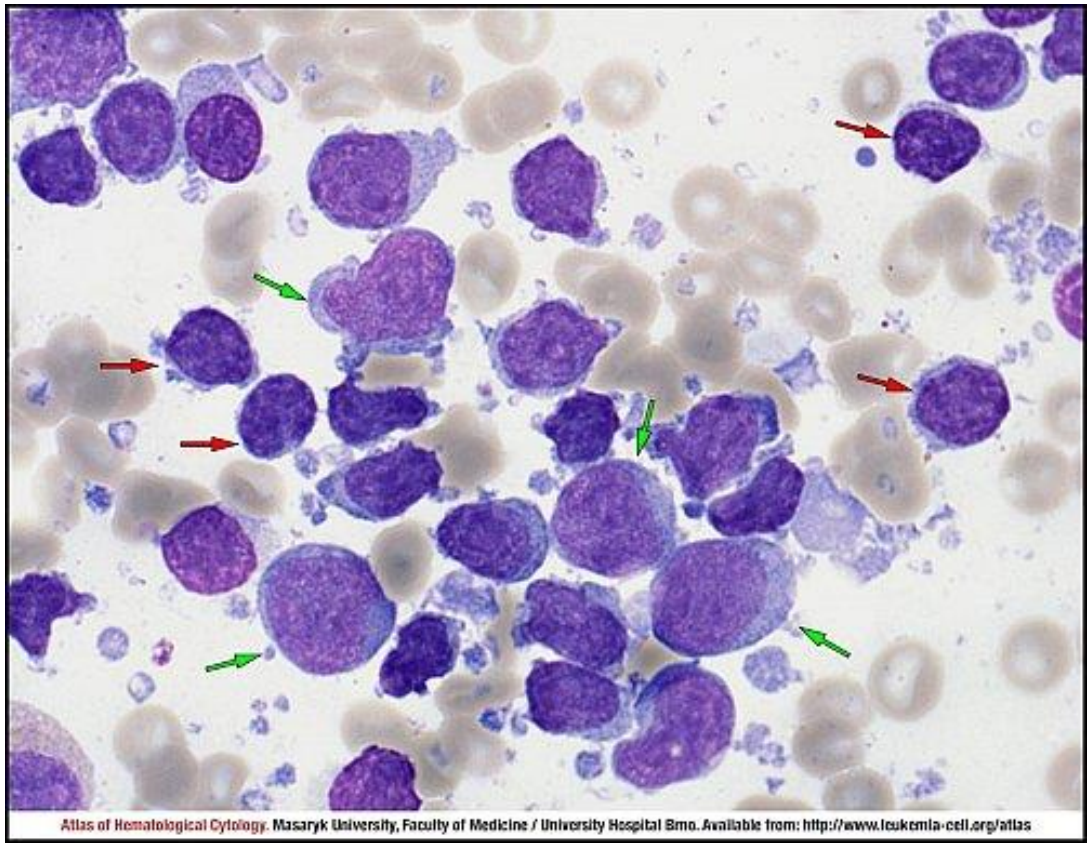
- Prognosis
  - 5-year survival – 87 % patients
  - Remission - ? % (complete, partial), relapse – 20+ % (relapse within 6 mesiacov, but may even after 7 yrs)
- Risks
  - Autoimmune disease trigger – hemolytic anemia (5–10 %), thrombocytopenia
  - Richter transformation -> diffuse large-B-cell lymphoma, Hodgkin lymphoma (rare)
  - Aggresive leukemic transformation – lymphoblastic lymphoma, „hairy cell“ leukemia, T-cell lymphoma , AML, etc.

Bcl-2 – B-cell lymphoma 2



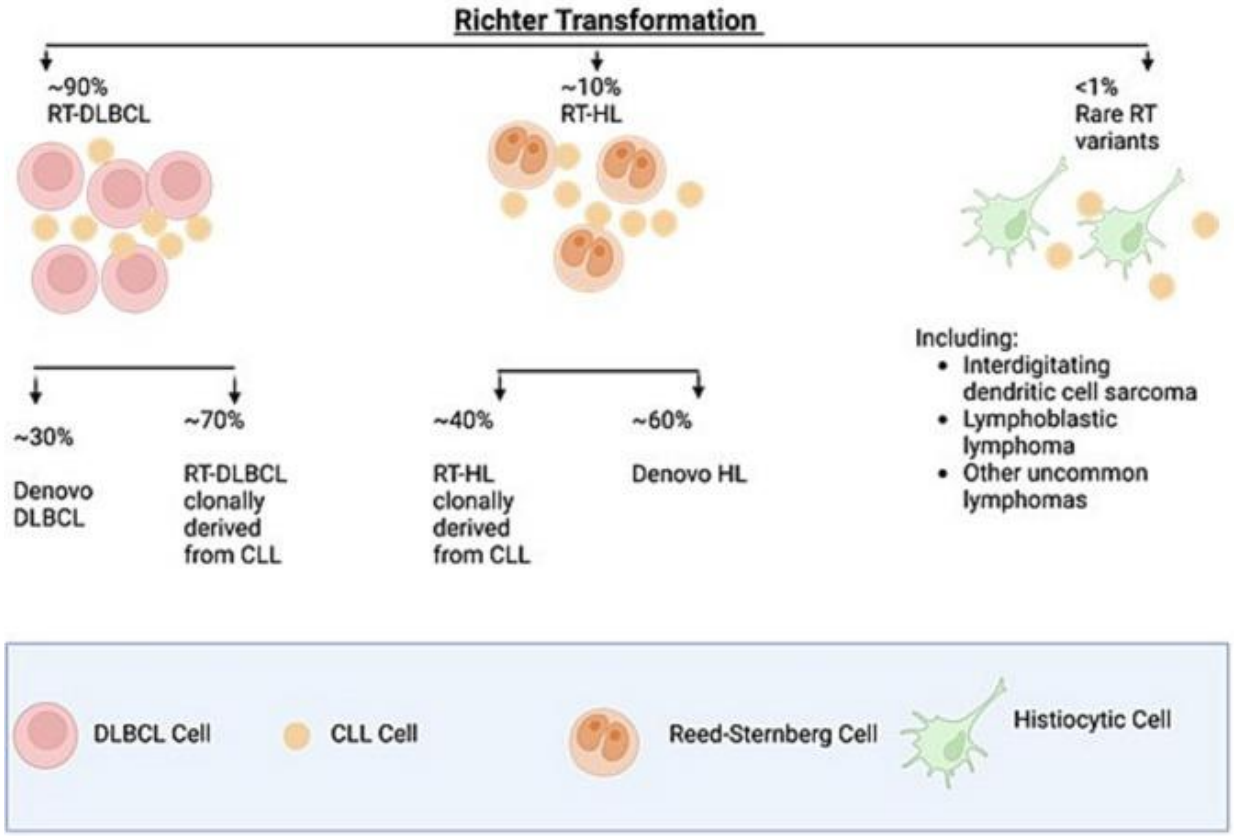
https://imagebank.hematology.org/getimagebyid/62207?size=3

RICHTER TRANSFORMATION (RT) – B-CELL-CLL TO DIFFUSE LARGE B-CELL LYMPHOMA



Red arrows - monoclonal B-cells, green - blasts

https://www.leukemia-cell.org/atlas/res/photogallery/th-richter1.jpg



RT may include also Hodgkin lymphoma a other, mainly mutation in monoclonal B-Ly (Bcl-2 susp.)

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LYMPHOMAS

- Oncohematological diseases from peripheral lymphocytes of various maturation degrees (B-, T-, NK-cells)
- Heterogenic disease groups (progression and malignancy degree varying)
- Possible start both in bone marrow and peripheries
  - Leukemic transformation possible -> ALL mostly
- Classification
  - Hodgkin lymphomas
  - Non-Hodgkin lymphomas

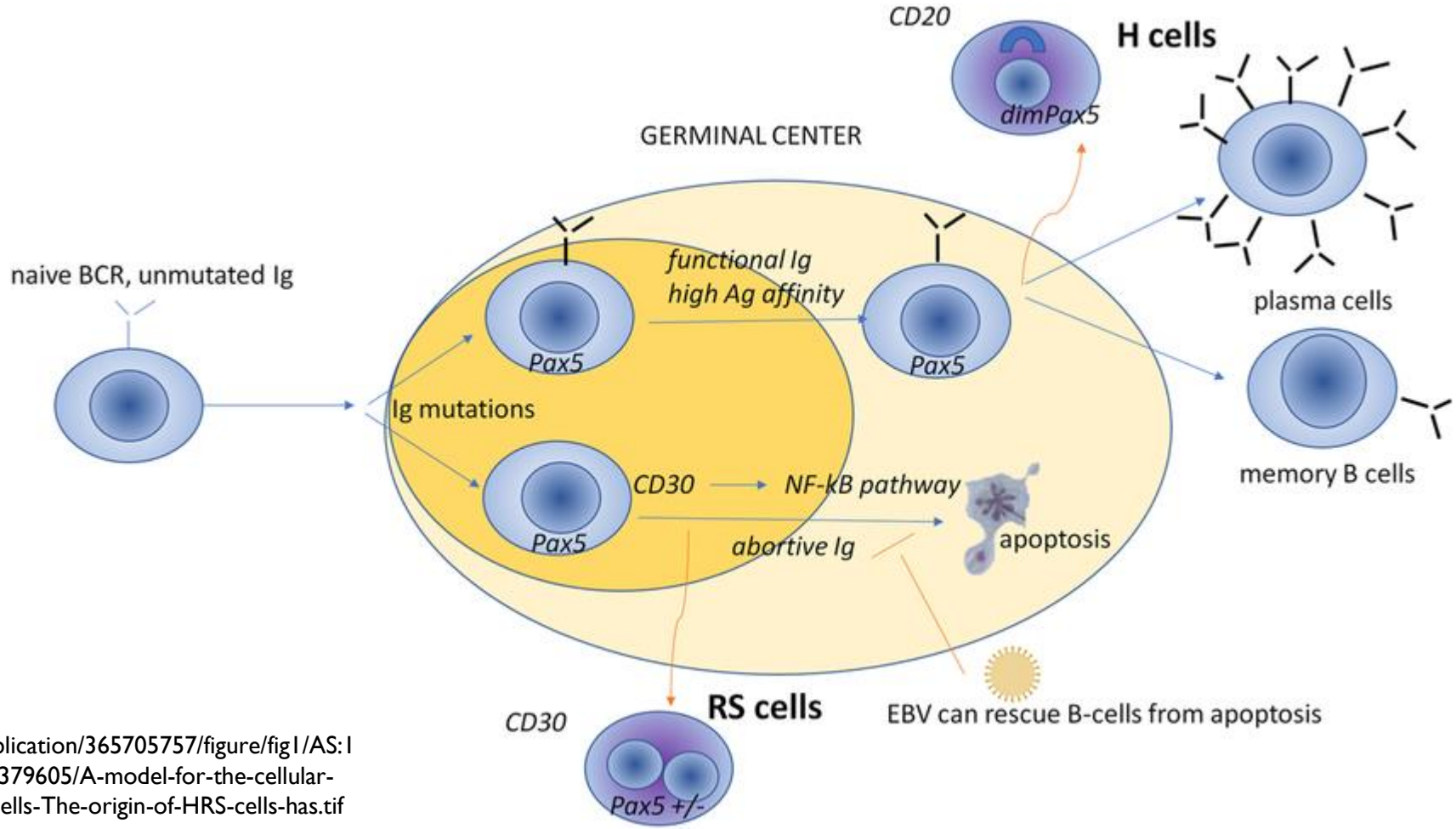
LYMPHOMAS

- Epidemiology and statistics (cca 5 % of all malignancies)
  - Hodgkin lymphoma
    - USA 2025 estimate – incidende 8 700 cases, mortality 1 150 cases
    - Peak (age groups) – 15–19 years of age and 55+ years of age
  - Non-Hodgkin lymphomas
    - USA 2025 estimate – incidence 80 400 cases, mortality 19 400 cases
    - Peak (age groups) – risk increasing with age, 50 % case in 65+years of age

LYMPHOMAS PATHOMECHANISM

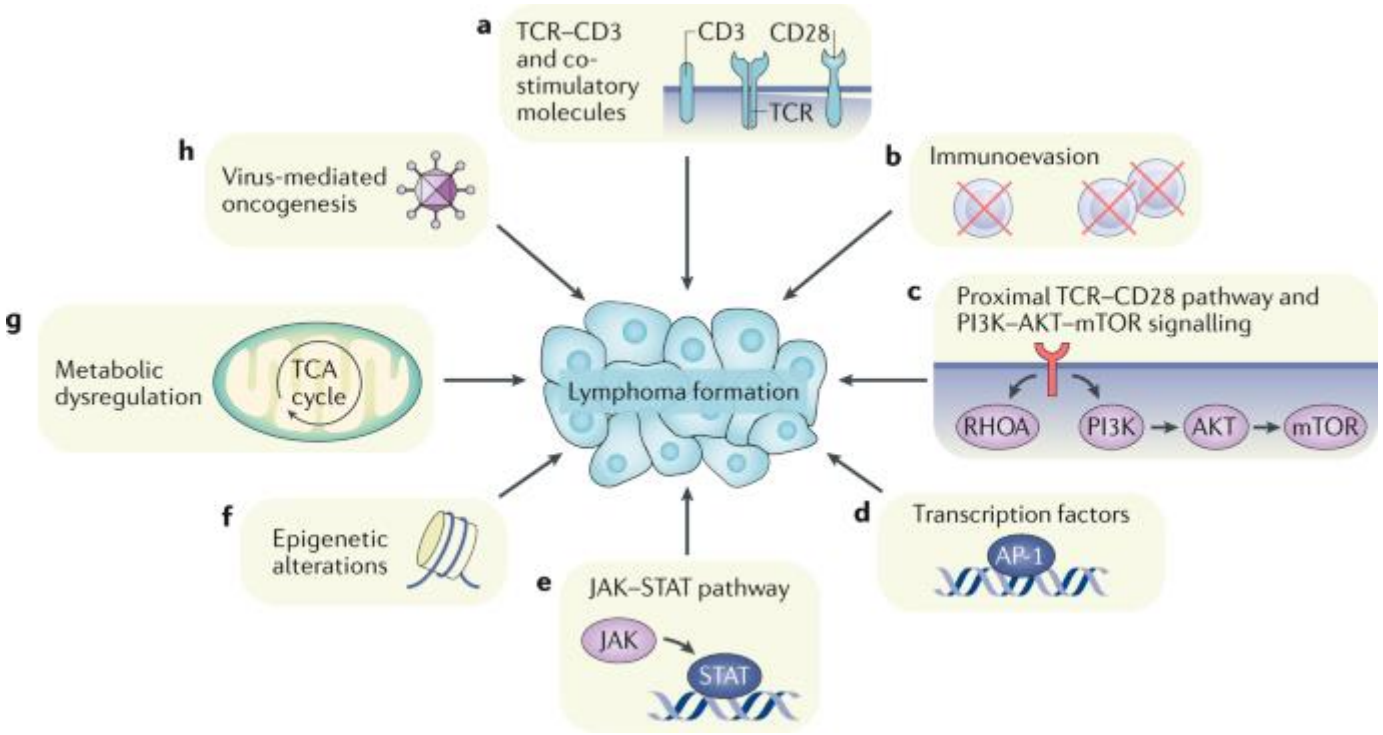
- Hodgkin lymphoma
  - B-cell to plasmocyte transformation failure -> Ig genes mutations and apoptosis escape
  - Genetic factors unknown – even monozygotic twins do not have increased risk
  - EBV viral effect -> apoptosis escape („cell dame fortune“)
- Non-Hodgkin lymphomas
  - Genetics – various anomalies
    - B – t(14;18)/Bcl2, t(11,14)/Cycline D1, t(8;14)/c-MYC, Bcl6
    - T – RASopathies, mutations in PIK3R1, PIK3CA, PTEN, monosomies (45, X0; m-del-3p, Y-deletion, aneuploidies +3, +7, +21, +X, +Y), TCRδ genes translocation (14q32) and TCRα translocation (14q11)
  - Environmental influence – oncogenic viruses (HTLV-1, EBV, HIV), chemical (benzene, chemotherapy), physical (radiation), etc.
  - „Two“ to „three“ hypothesis theory – according to lymphoma type
  - Frequent „bystander“ cells role -> lymphocytes activated without Ag stimulation (intercellular communication)

HODGKIN LYMPHOMA



https://www.researchgate.net/publication/365705757/figure/fig1/AS:11431281258505454@1720099379605/A-model-for-the-cellular-germinal-center-origin-of-HRS-cells-The-origin-of-HRS-cells-has.tif

NON-HODGKIN LYMPHOMAS



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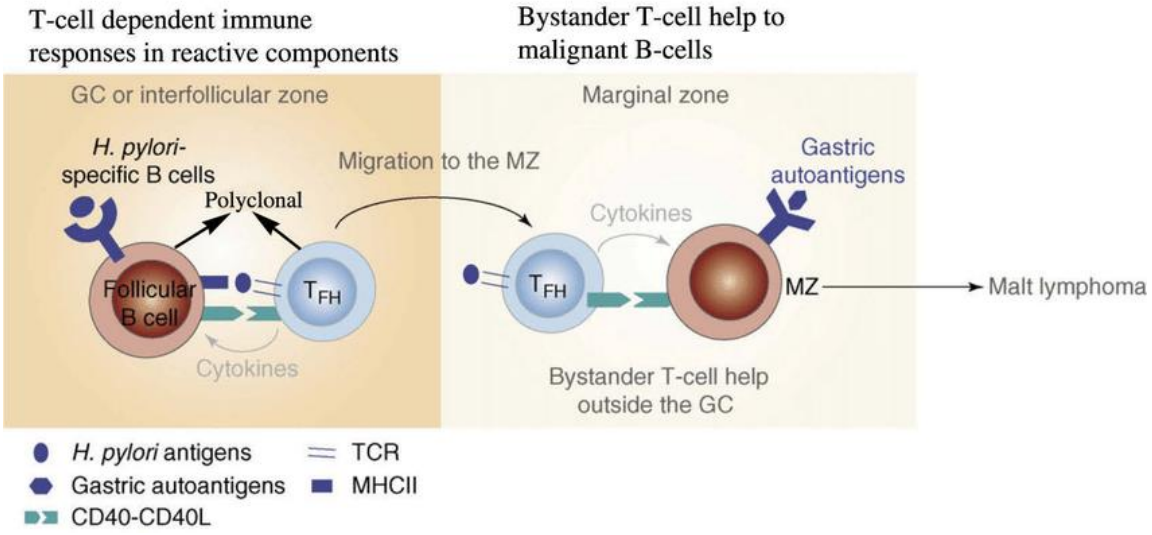
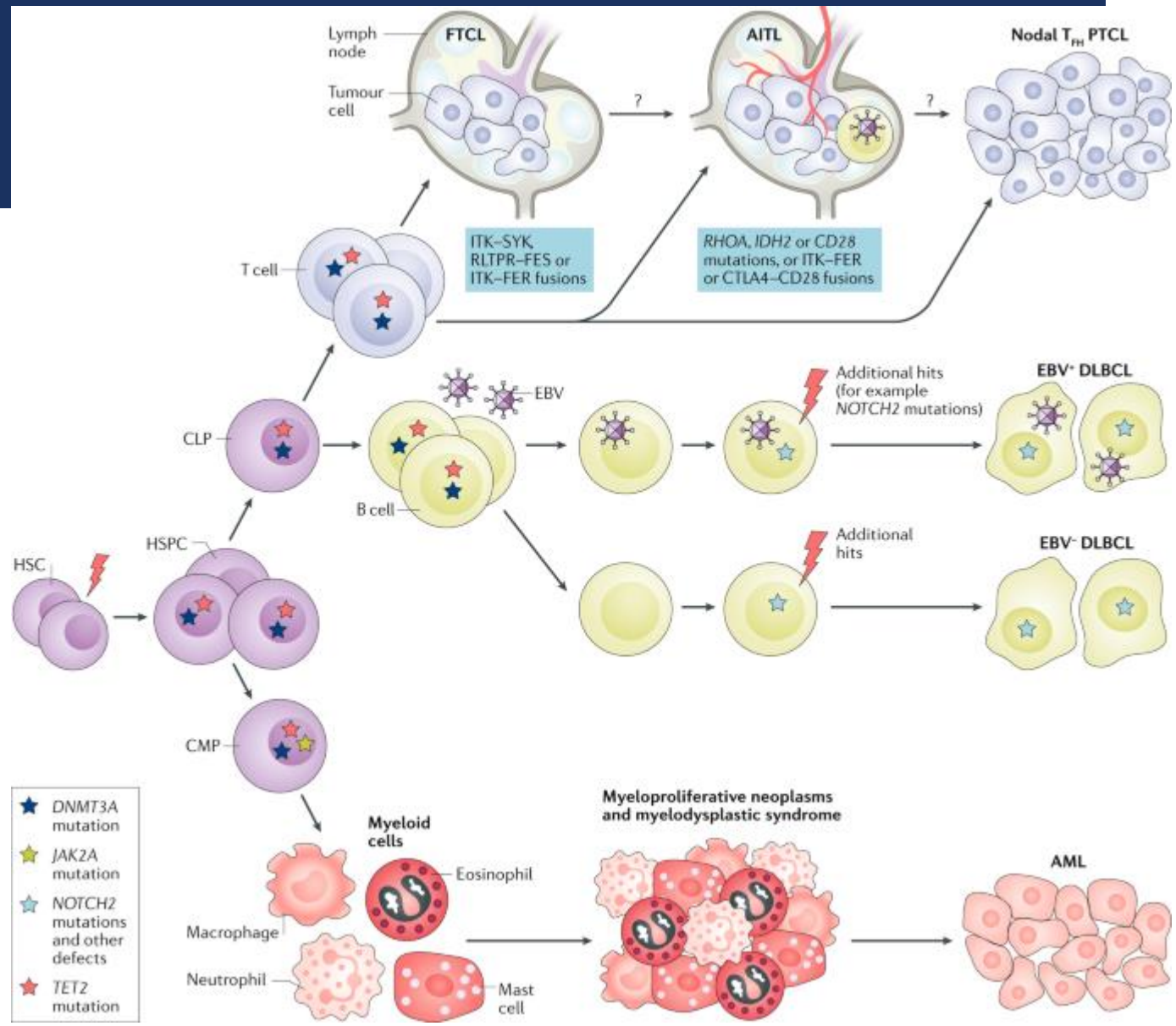
NON-HODGKIN LYMPHOMAS





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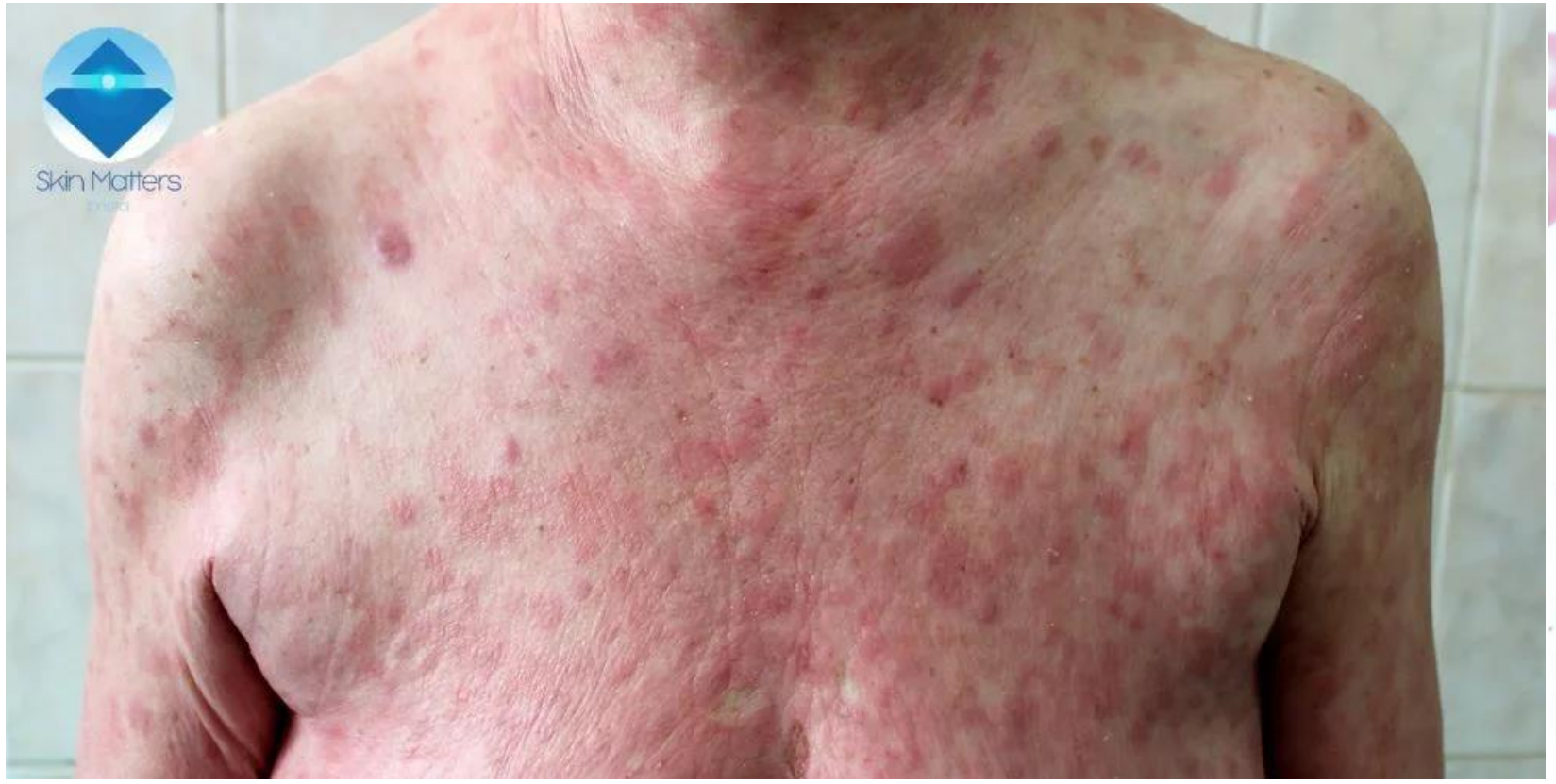
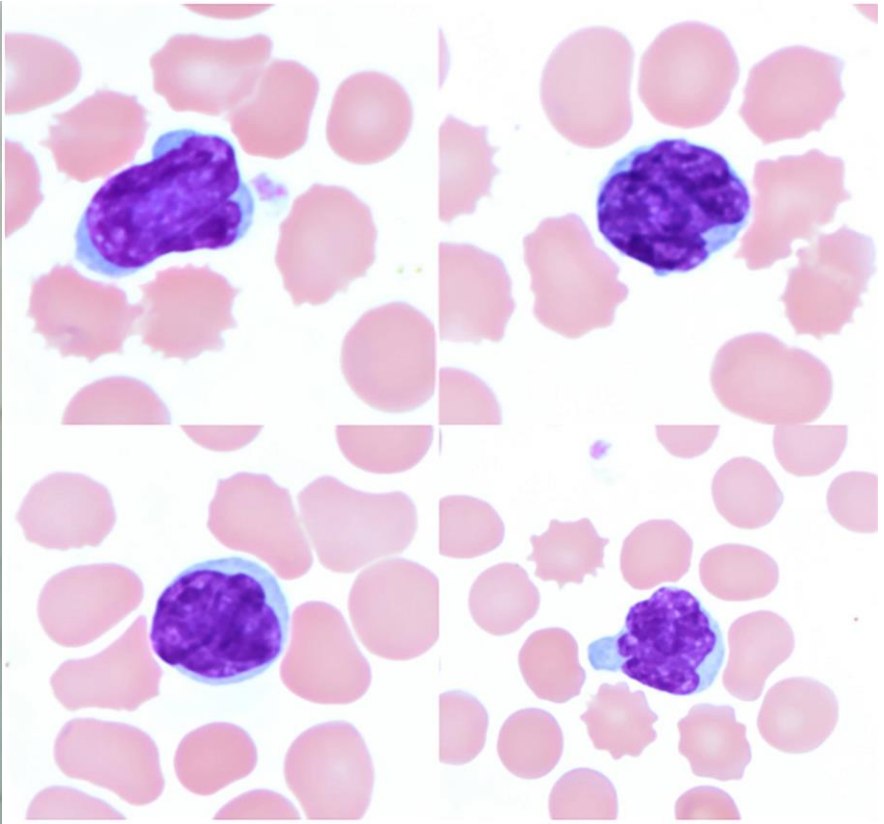
https://www.researchgate.net/publication/303388820/figure/fig2/AS:651522887143450@1532346569265/The-role-of-T-and-B-cell-interaction-in-the-development-of-MALT-lymphoma-FH-Follicular.png

T-LYMPHOMA – MYCOSIS FUNGOIDES



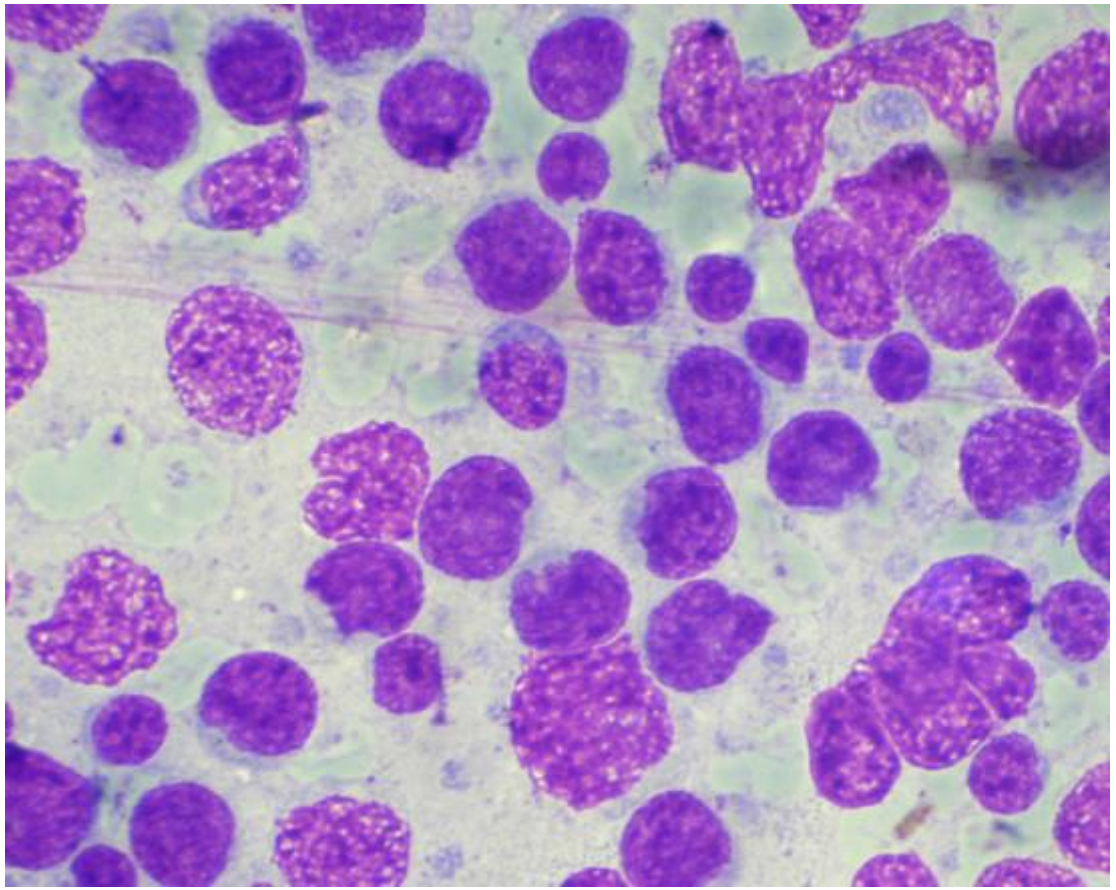
https://www.skinmattersbristol.com/wp-content/uploads/2025/01/Understanding-Mycosis-Fungoides-How-UVB-Light-Can-Slow-Disease-Progression.jpg.webp



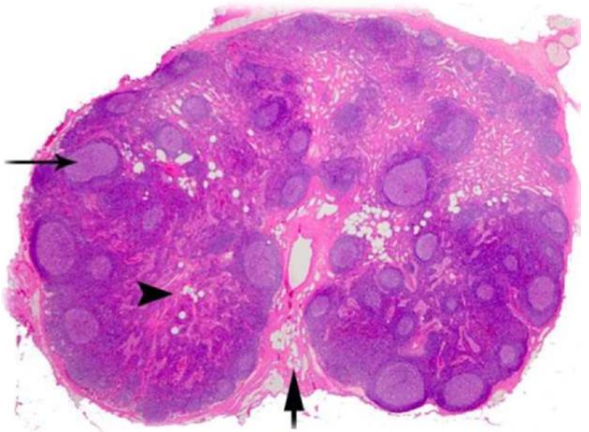
https://www.pathologyoutlines.com/imgau/lymphomanonBsezaryMirandamicro1.jpg

Sézary cells in circulation („hemispheric“ nuclei)

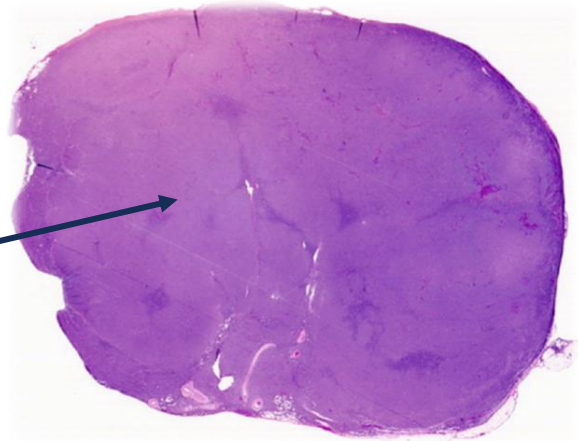
DIFFUSE LARGE B-CELL LYMPHOMA



Physiological lymphatic node (arrows marking germinal centers)



Lymphome affected lymphatic node
Germinal centers destroyed, dif. blasts spreading, rarely invades bone marrow (compared to Richter transformation)



https://wiki.clinicalflow.com/sites/default/files/DLBCLimage.jpg
https://media.springernature.com/full/springer-static/image/art%3A10.1038%2Fs41408-020-00389-w/MediaObjects/41408_2020_389_Fig1_HTML.png

LYMPHOMA MANIFESTATION

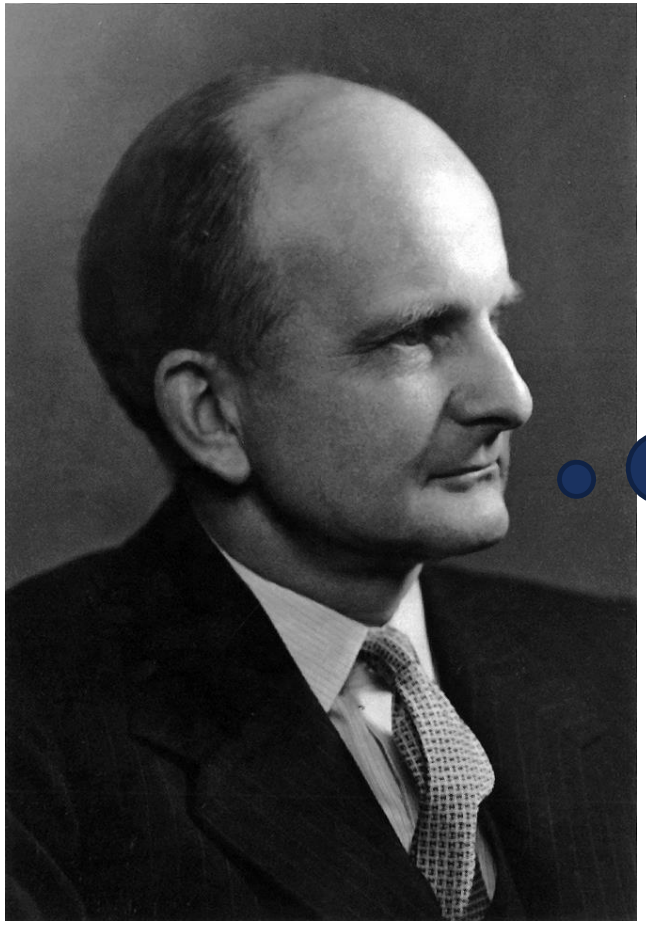
Hodgkin lymphoma

- Lymphadenopathy
  - Sole lymphatic nodes group, upper body, painless
- Systemic signs
  - Pruritus, night sweats, weight loss, mild fever, fatigue
  - Hepato- and/or splenomegaly
  - Pulmonar, cardiovascular, bone marrow invasion
- Pel-Ebstein fever?

Non-Hodgkin lymphoma

- Lymphadenopatia
  - Multiple groups – skin, neck, armpit
- Systemic signs
  - Fever and chills
  - Fatigue, abdominal „mass“ perception
  - Chest pain, chest pressure

DOES PEL-EBSTEIN FEVER EXIST? (A PHENOMENON THAT SOMEBODY NAME)



"Every student and every doctor knows that cases of Hodgkin's disease may show a fever that is high for one week and low for the next week and so on. Does this phenomenon really exist at all?..."

Richard Asher (GBR, endocrinologist and hematologist, 1912-1969)

https://en.wikipedia.org/wiki/Richard_Asher#/media/File:Richard_Asher_for_Wikipedia.jpg

LYMPHOMAS PROGNOSIS

Hodgkin lymphomas

- Prognosis
  - 87 % survive 5 years
  - 25 % cases turn out to be refractory

Non-Hodgkin lymphomas

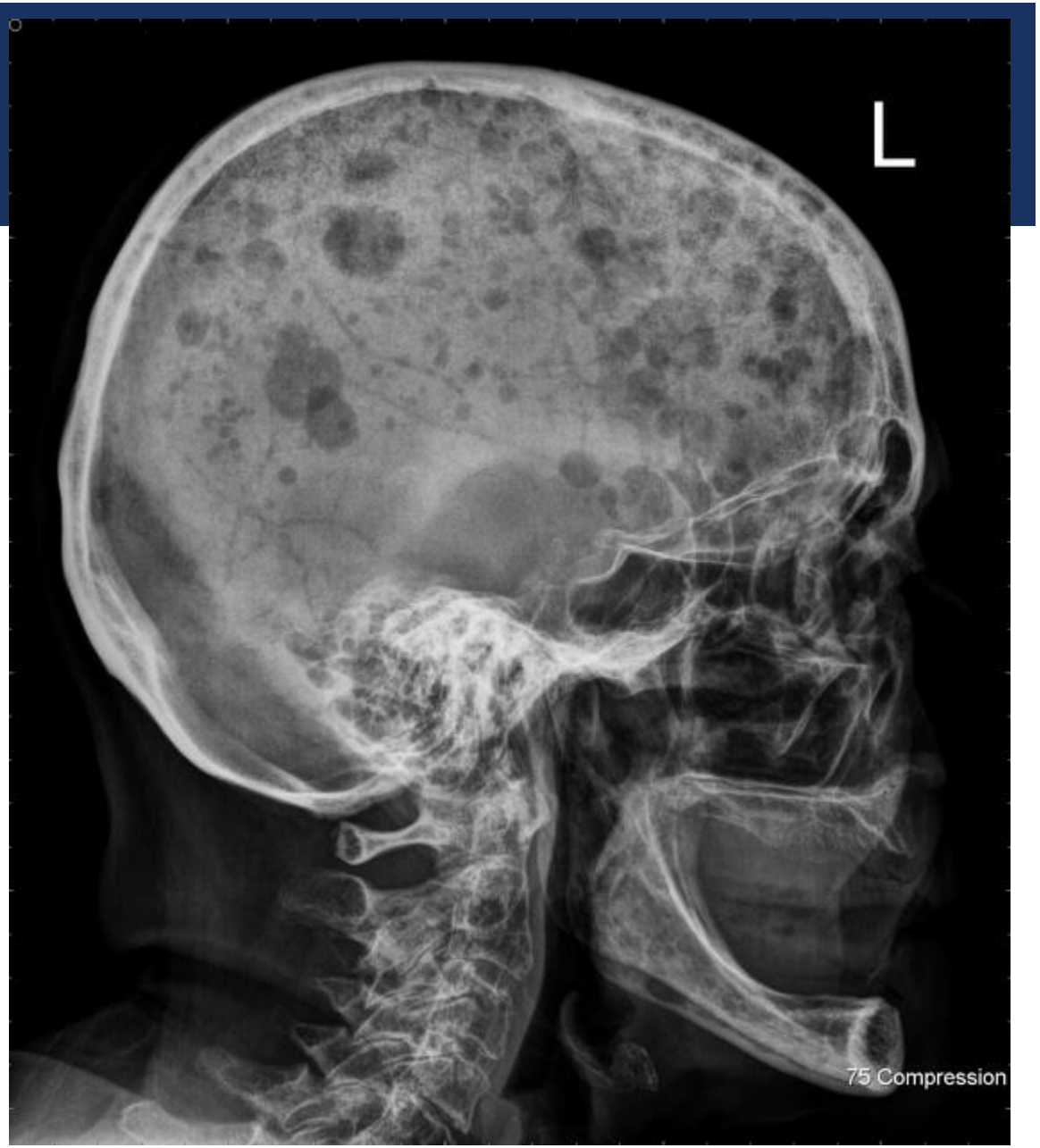
- Prognosis
  - High relapse percentage
  - 4–40 % (worst prognosis for diffuse large B-cell lymphoma)

MYELOMAS

- Oncohematological disease derived from plasmoblasts (plasmocytes precursors) or activated B-memory cells
- Multiple myeloma (MM)
  - Genetic abnormalities – heavy chain gene (14q32) and oncogene (e.g. 11q13, 4p16.3, 6p21, 16q23 a 20q11) translocation
  - Translocation of Ch14 -> plasmoblasts group emerge -> monoclonal gamapathy of uncertain significance (MGUS) -> „smouldering“ MM -> MM -> plasmoblastic leukemia
  - IL-6 -> decisive factor
  - Manifestations – CRAB (hyperCalcemia, Renal insufficiency , Anemia, Bone lesions -> patolhogic fractures)
  - Bence-Jonesova protein filtrated to urine

MYELOMAS

- Other important myelomas and monoclonal gamapathies
  - Waldenström macroglobulinemia
  - Primary amyloidosis
  - Heavy-chain disease
- Statistics
  - Risk 3–5 % >50 years of age
  - Remissions and relapses according to types
    - MM relapsing in almost all patients after them being „cured“



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OTHER IMPORTANT ONCOHEMATOLOGIC DISORDERS AND CONDITIONS – MYELOID PRECURSOR

- Pre-leukemic states or leukemia development risk factors

- Myelodysplastic sy.
- Polycytemia vera rubra
- Essential (primary) thrombocytemia
- Myelofibrosis
- Mastocytosis

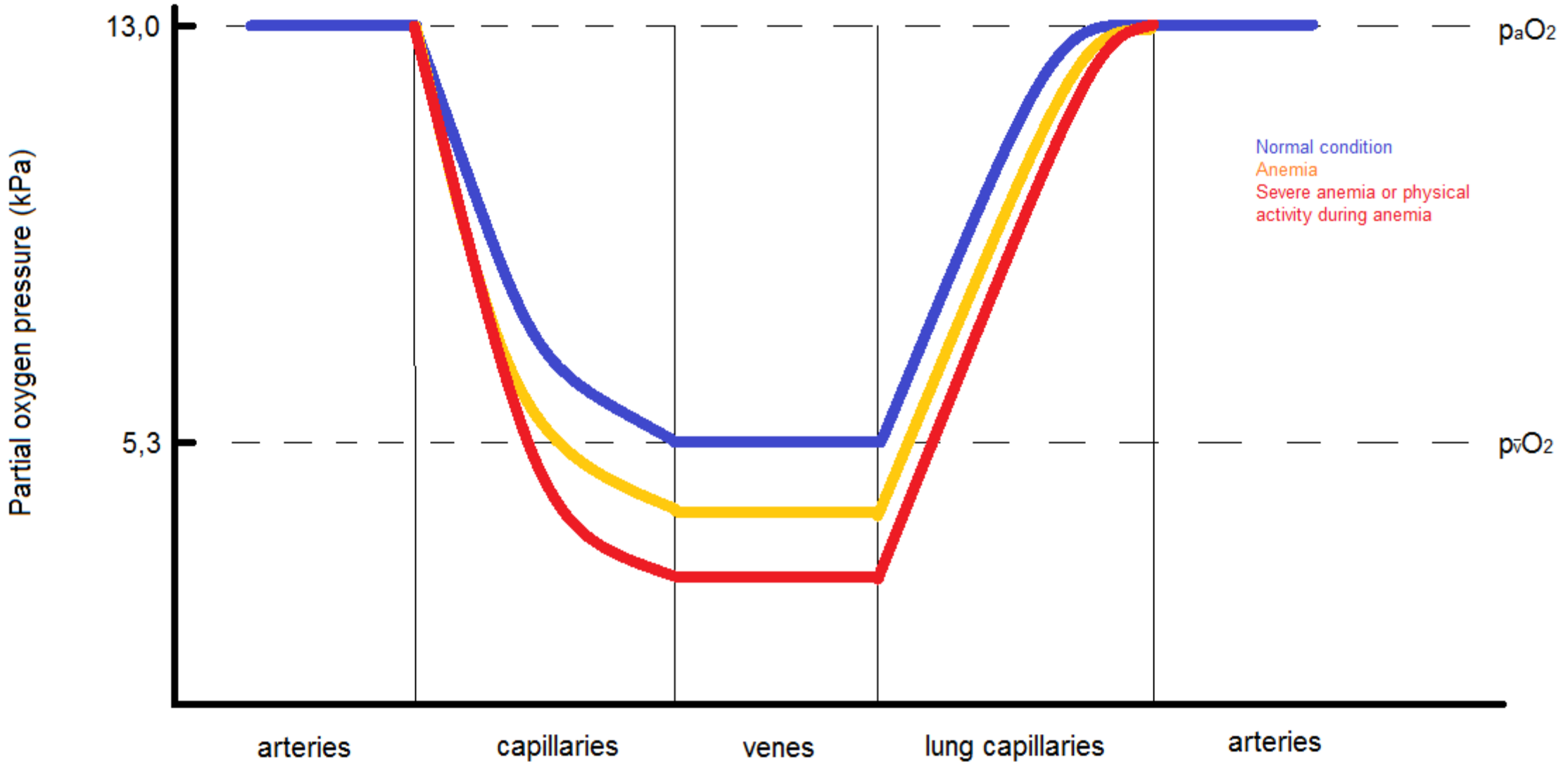
RED BLOOD CELLS – ANEMIAS AND POLYCYTEMIAS

ANEMIAS

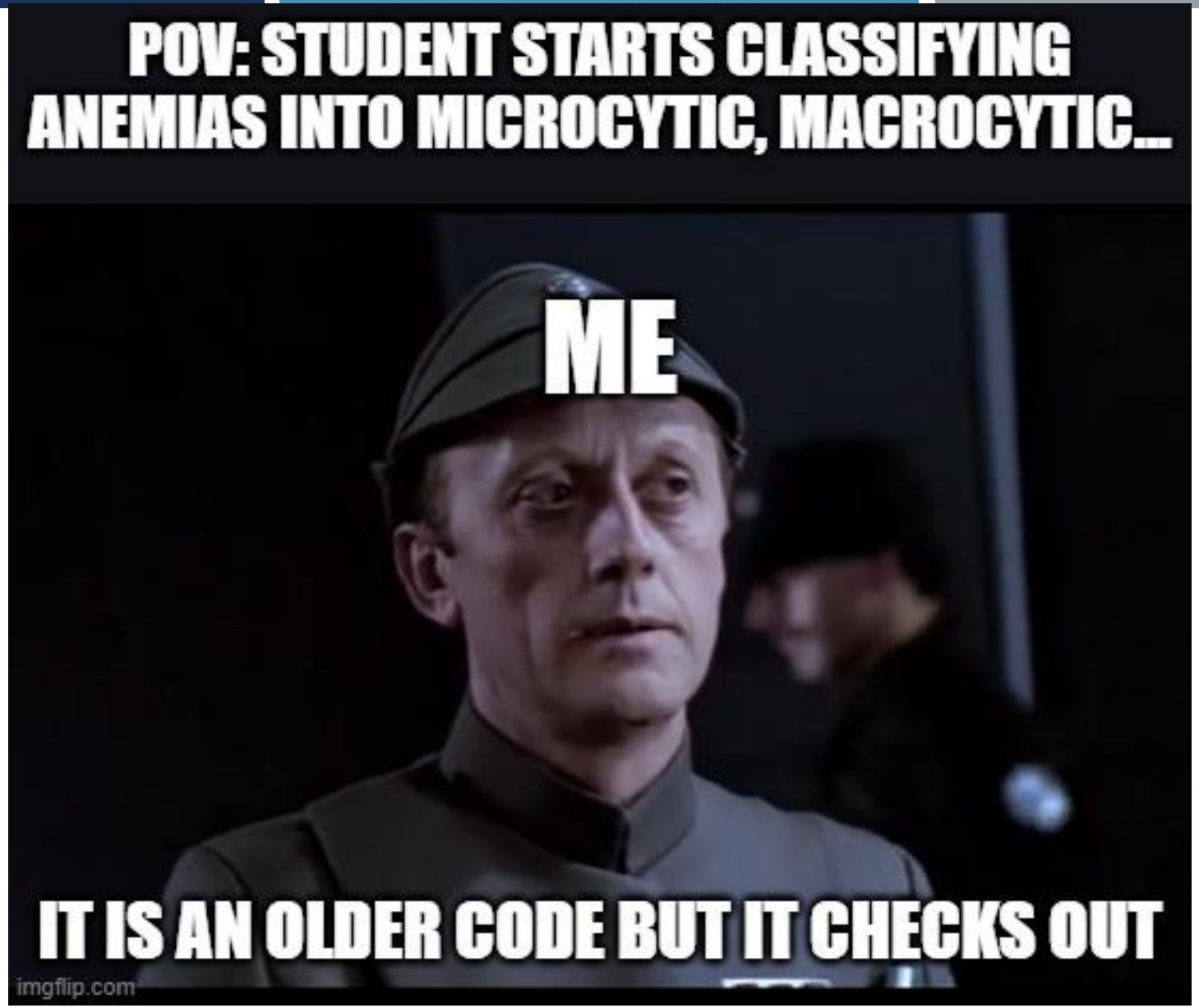
- Hemoglobin concentration in peripheral blood drop (♂ <130 g/l; ♀ <115/120 g/l) -> decreased ability of blood to maintain adequate oxygen pressure in microcirculation
  - Red blood cells or hematocrit decrease may or may not be present
- SYMPTOM! -> pathologic cause, blood volume increase, etc.
- Classification according to severity
  - Mild - 90 - 130 (resp. 120) g/l
  - Moderate – 60 – 90 g/l
  - Severe - <60 g/l

ANEMIC SYNDROME

- A consequence of hemoglobin concentration drop and increased oxygen extraction in peripheral tissues
- Symproms
  - General – pale mucosa and skin, fatigue, decreased physuical and mental performance, dypnoe and tachycardia (more intense during physical activity)
  - Specific – according to cetrain anemia type (e.g. sideropenic – koilonychia, tongue burning sensation, atrophic gastritis, anemic stomatitis, xerostomia, aphthous ulcerations, oral candidosis, lingual varicosities, angular cheilitis, pica syndrome)
- Medical history! (chronicbetter tolerated, but stay alerted!)
  - Pregnant woman – sideropenic anemia in chronic form (Hb 72 g/l during delivery), though asymptomatic
  - Bleeding during delivery -> Hb drop <50 g/l -> sudden severe anemic syndrome manifestation -> transfusion



Anemia and hemoglobin changes in various part of circulation (Nečas, 2009)



Zdroj: Author‘s work ☺

ANEMIA CLASSIFICATION

Morphologic

Cell size	Hb content	Examples
Microcytic	Hypochromic	Sideropenic anemia
	Normochromic	HIV, endocarditis
	Hyperchromic	Severe hered. spherocytosis
Normocytic	Hypochromic	-
	Normochromic	Chronic diseases, renal failure, liver failure
	Hyperchromic	-
Macrocytic	Hypochromic	Vit. B9, B12 defficiency
	Normochromic	Pernicous anemia
	Hyperchromic	(?)Vit. B9, B12 defficiency

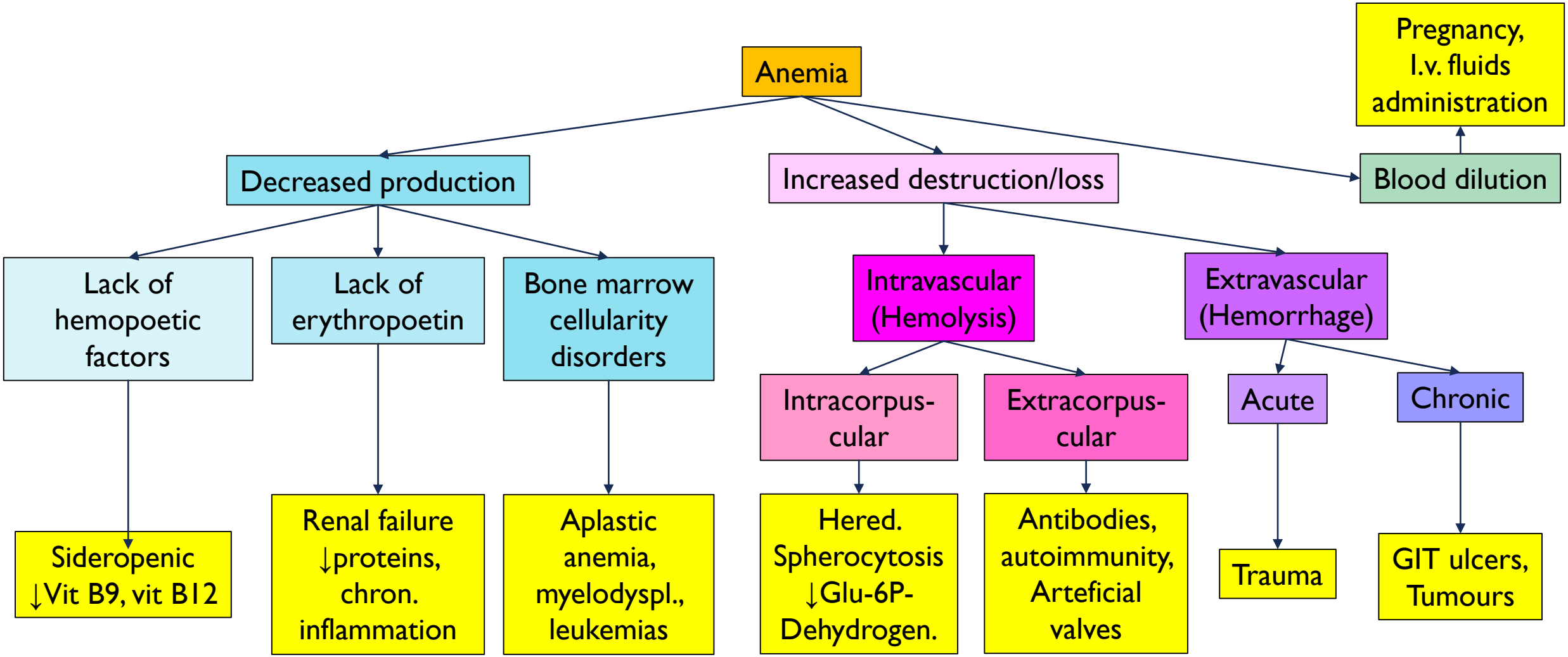
Patophysiologic

Type	Examples
Decreased production	Sideropenic, sideroblastic, vit. B9, B12 defficiency, renal failure
Increased destruction/loss	Hemorrhages, hemolysis, dilution anemia, hemoglobinopathies, iatrogenic, etc.

Time frame

Acute	Chronic

PATHOPHYSIOLOGIC ANEMIA SUBTYPES



SIDEROPENIC (IRON DEFFICIENCY) ANEMIA

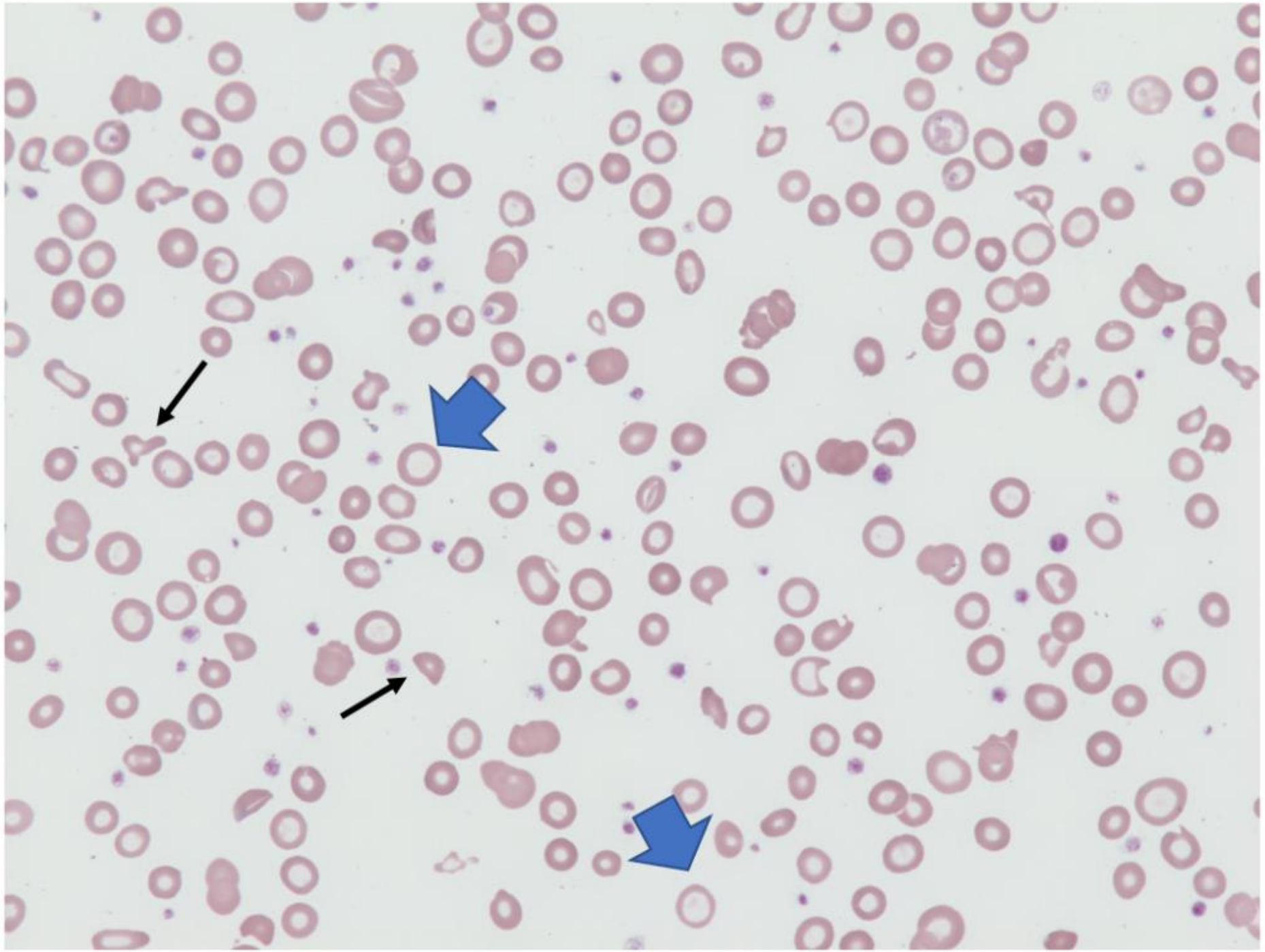
- Cause
  - Lack of iron available for bone marrow (dietary, losses – menzes, etc., increased demands and other)
- Pathomechanism
  - ↓s-Fe^{2+} -> ↓IRP-1 in kidney -> ↓EPO -> inefective hemopoesis
    - ↓hepcidin (from liver) -> ↑ferroportin – attemt to enhance Fe^{2+} intestinal resorption and its release from macrophages
    - (?)↓hephaestin -> ↓transport Fe^{3+} via transferrin
  - ↓s-Fe^{2+} -> ↓aconitase in Ery -> ↑protein kinase C - ↑erythroid-inhibition factor (PU.1) -> ↓Ery precursors development
- Result
  - ↓Ery, ↓MCH, ↓MCV, ↓Ret-Ery, ↑s-TFR, ↓Hb, ↓Ht

IRP-1 – iron regulatory protein 1, Ret-Ery – retikulocyty, s-TFR – solubile transferrin receptor

IRON DEFFICIENCY ANEMIA PHASES

1. Pre-latent sideropenia
   - Decreased iron supplies
   - ↓Ferritin, other parameters in normal range
2. Latent iron defficiency
   - Iron-defficient hemopoesis without anemia
   - Iron supplies diminished (macrophages, bone marrow – cells containing ferritin, etc.)
   - ↓ferritin, ↓s-Fe, ↑s-TFR, other ok
3. Iron defficiency anemia
   - ↓ferritin, ↓s-Fe, ↓MCV, ↓MCH, ↓Hb, ↓Ht; ↑sTFR, ↑RDW
   - Transferrin saturation <16 %
   - ↓hepcidin – possible early sign!

RDW – red blood cells distribution width

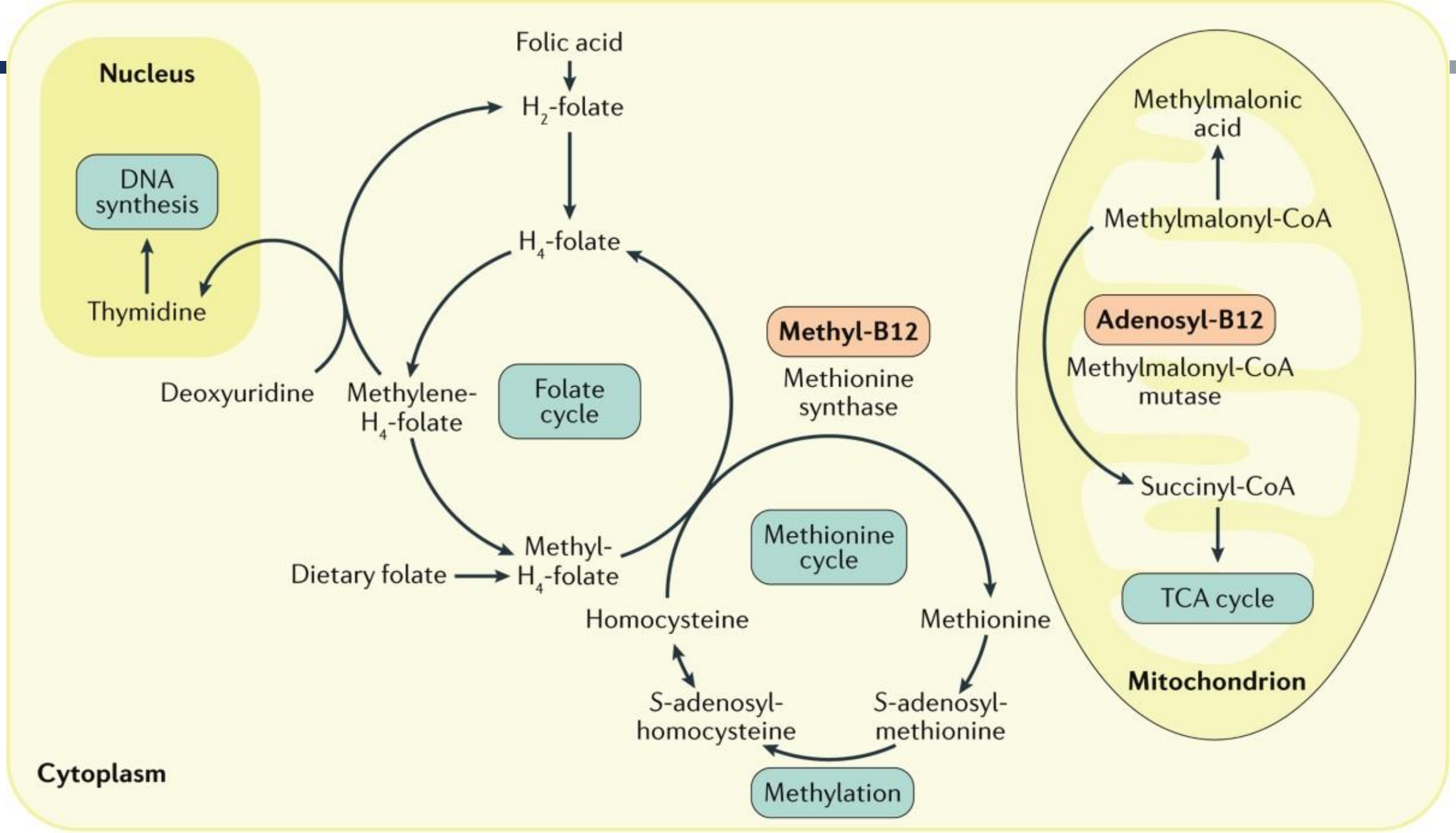


https://www.thebloodproject.com/wp-content/uploads/2021/08/Iron-deficiency-anemia-1-1024x779.png

MEGALOBLASTIC ANEMIA

- Cause – vitamins B9, B12 defficiency; (hereditary) orotic aciduria, Fanconi anemia
  - ↓Vit. B9 (folate; $-CH_3$ group donor) -> ↓uracyl to thymine conversion -> ↓synthesis and repair of DNA
  - ↓Vit. B12 -> ↓methionin synthetase -> ↑5-methyl-folate -> ↓folate
    - ↓methylmalonyl-CoA-mutase -> ↓succinyl-CoA but ↑methylmalonyl-CoA, ↑propionyl-CoA, ↑abnorm.-FA -> ↓(dys)myelinisation
  - Orotic aciduria (ar)* -> ↓UMPS -> ↓pyrimidine synthesis
  - Fanconi anemia (ar)* -> claster defects in DNA-repair (homologus recombination) responsible genes
- Pathomechanism
  - Dysproportion between nucleus and cytosol maturation -> S-phase prolonged with less frequent mitoses
- Pernicious (malignant) anemia – autoimmune disease – antibodies against intrinsic factor

UMPS – uridine-monophosphate synthase; contains OPRT – orotate-phosphoribosyltransferase and ODC- orotate-5-phosphatedecarboxylase
*Orotic acidura and Fanconi anemia are non-responsive to vit. B9 and B12 administration



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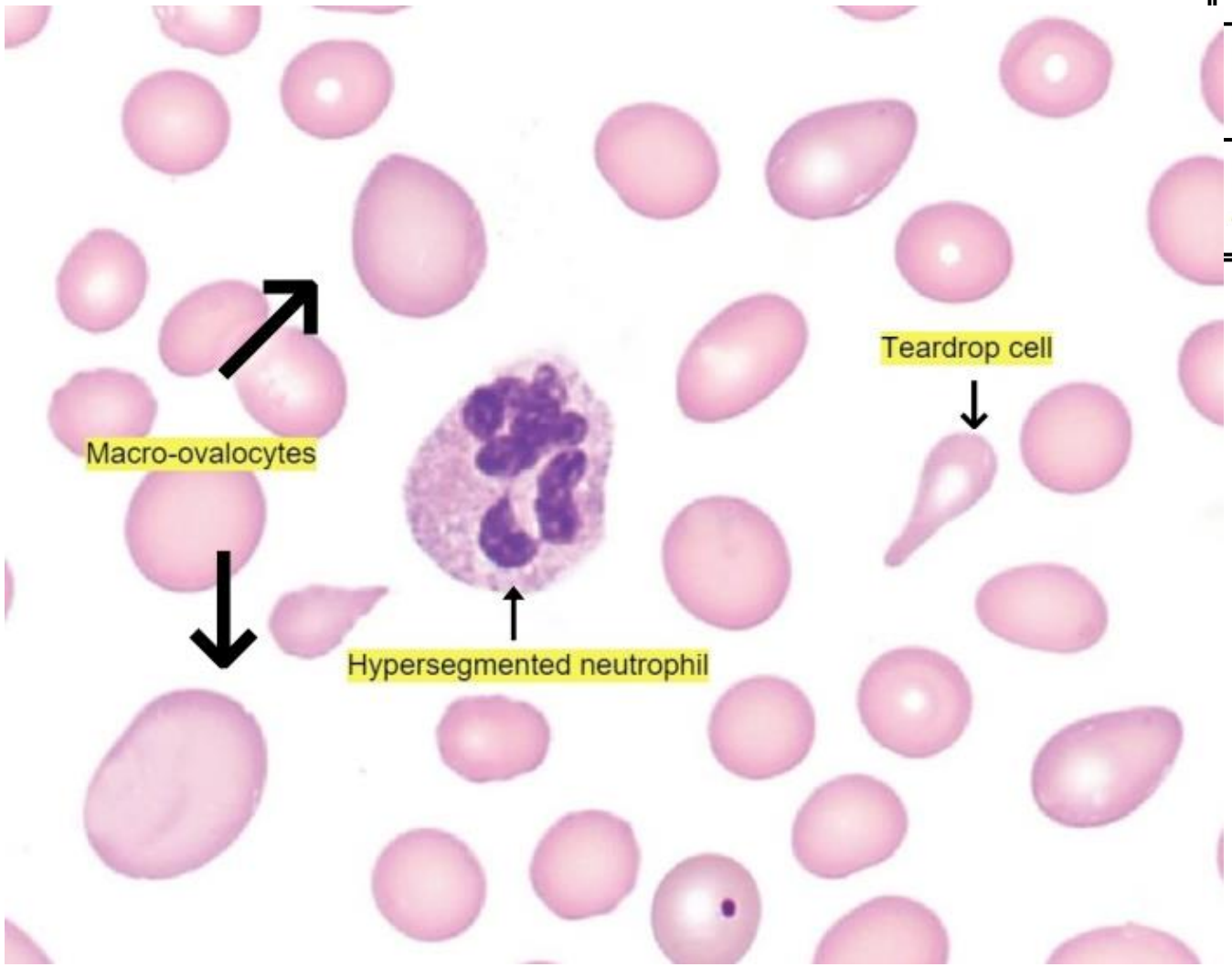


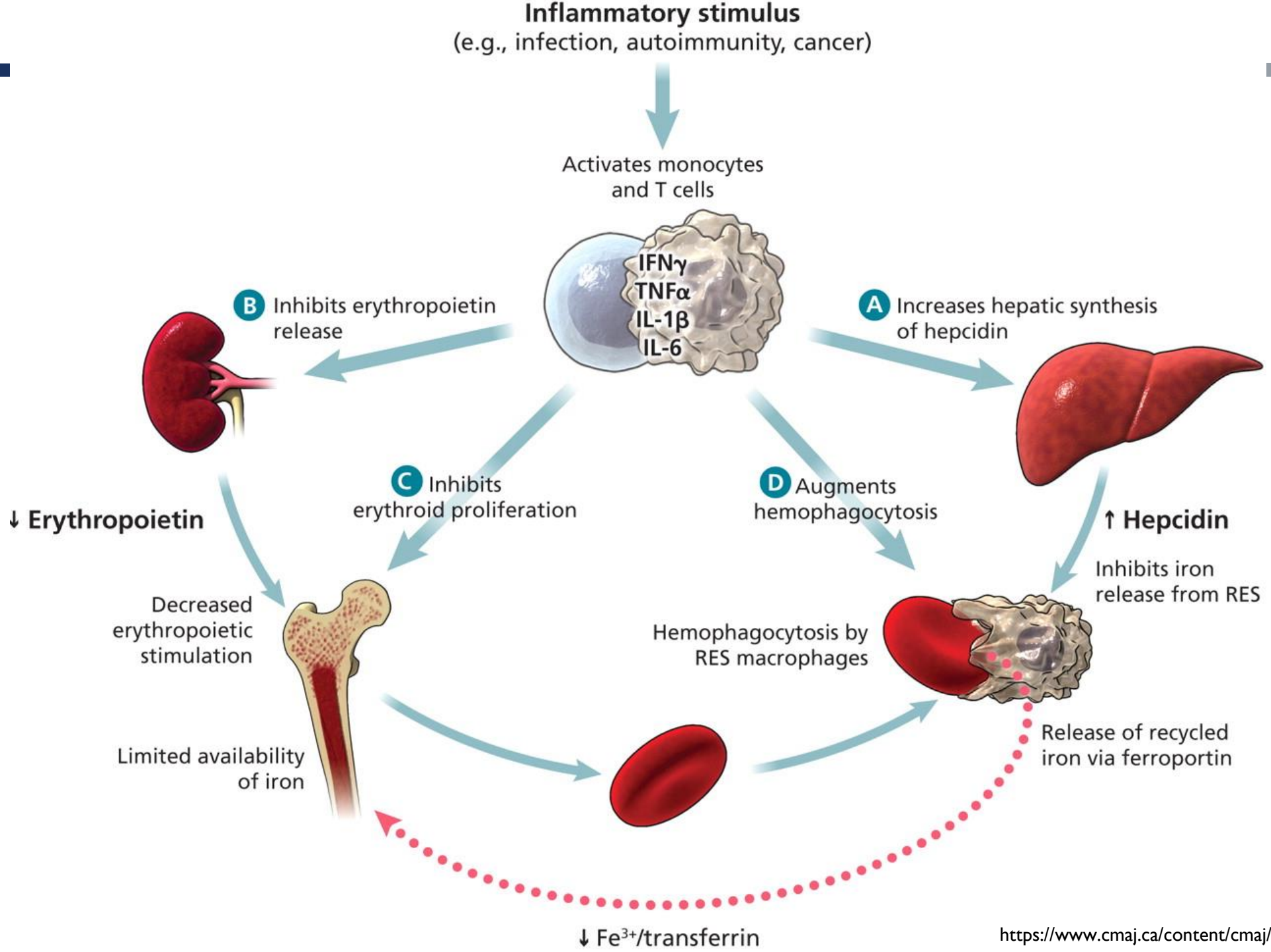
	B_{12} Deficiency	Folate Deficiency
Methymalonic acid <0.4 umol/L	Elevated	Normal
Homocysteine 4-12 umol/L	Elevated	Elevated

Elevated CVS risk

https://img.grepmed.com/uploads/13497/b12-hematology-deficiency-diagnosis-folate-original.jpeg
https://laboratorytests.org/wp-content/uploads/2019/07/Megaloblastic-anemia.png

CHRONIC DISEASES (CHRONIC INFLAMMATORY RESPONSE) ANEMIA

- Cause – chronic disease or persistant inflammatory reaction with overproduction of IL-6
- Pathomechansm
  - ↑IL-6 -> ↑hepcidine -> ↓ferroportin externalisation -> Fe sequestrated in macrophages
  - Inflammatory cytokines -> ↓bone marrow reaction to EPO -> ineffective hemopoesis
- Manifestation
  - Normocytic (ev. microcytic) normochromic anemia
  - Ferritin – normal or increased (acute phase reactant; iron-defficiency leads to decrease)
  - TIBC – normal or decreased (iron in cells; iron-defficiency leads to increase)
- Poor prognosis (treating of triggerin cause required) – EPO + i.v. iron-derivates controversial
  - Hepcidine antagonists for future?/It is a problem at all?

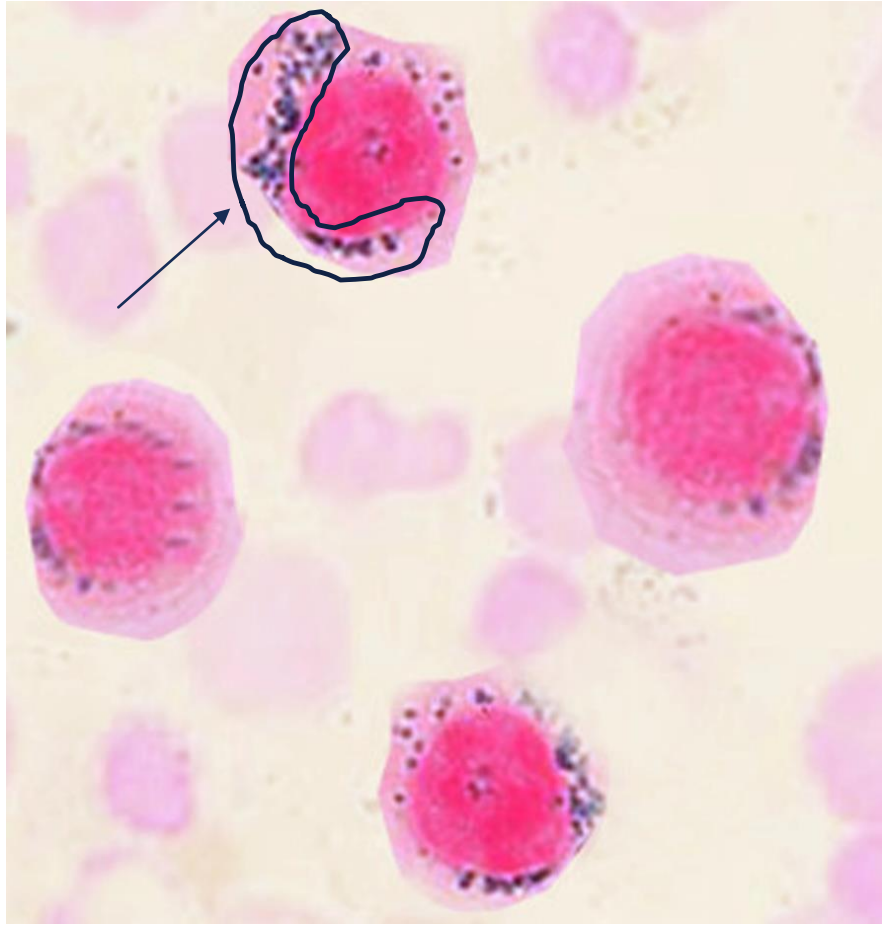


https://www.cmaj.ca/content/cmaj/179/4/333/F1.large.jpg

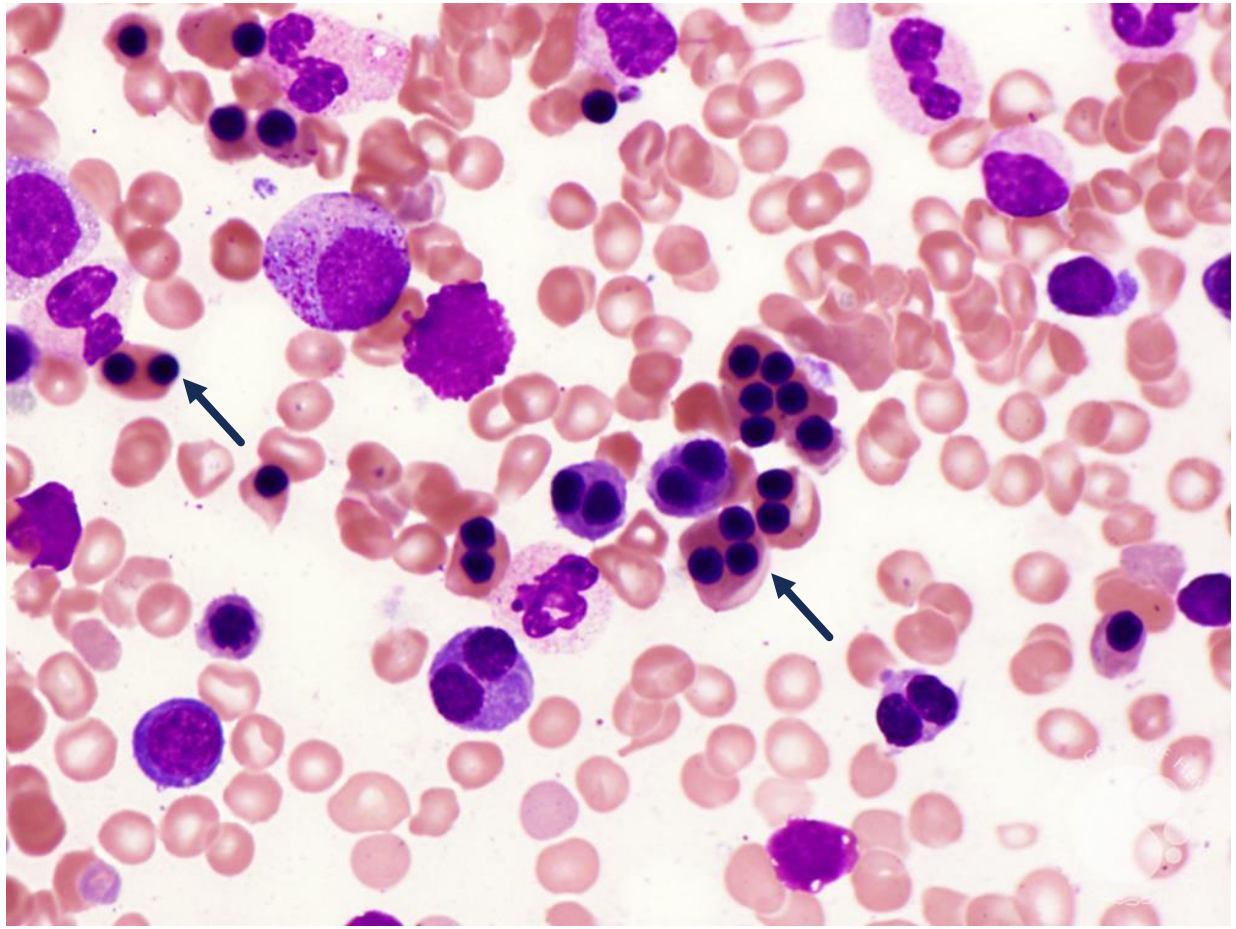
OTHER IMPORTANT DECREASED PRODUCTION ANEMIAS

Type	Mechanism	Possible causes
Aplastic anemia	Myeloid precursor disorder or decreased bone marrow cellularity	Idiopatic, cytostatic treatment, parvovirus B19, benzene
Isolated red blood cells aplasia	Isolated Ery precursor disorder	Congenital – Diamond-Blackfan sy Acquired – idiopatic, thymoma, lymphoma, HIV, EBV, SLE, rheumat. arthritis, Anti-EPO antobodies
↓EPO anemia	Increased Ery precursor apoptosis	Bilateral nephrectomy, renal failure, hemodialysis, chronic inflammation and malignancies
Sideroblastic anemia	Inability to incorporate iron to heme, mitochondria accumulation -> ring arouf nucleus formation	Congenital – X-linked (ALAS2 gene), ar, Acquired – clonal sideropenic anemia; alcoholism, vit. B6 defficiency, lead poisoning, chloramphenicole, isoniazid, etc.
Congenital dyserythropoetic anemia	Multiple Ery precursor disorders, incomplete mitoses, chromatine bridges, bi- and multinuclear precursors	Type Ia – CDAN1 (15q15), Type Ib – C15ORF41 (15q14), Type II - SEC23B (20p11.2), Type III – KIF23 (15q21), Type IV – KLF (19p13.13-13.12)

ALAS2 – delta-amino-levulonate synthase 2



Sideroblastic anemia- ring has to encircle at least one third of nucleus and contain at least 5 granules



Congenital dyserythropoetic anemia type II – bi- and multinucleated precursors present (arrow)

https://d1irpg7po1rqdm.cloudfront.net/page/J72Sd9e2zQbHIyvkjRG1miblZNOHdGHSS0AxIXbE.webp
https://imagebank.hematology.org/getimagebyid/60891?size=3

HEMOLYTIC ANEMIAS - INTRACORPUSCULAR

- Hemoglobin concentration in peripheral blood due to hemolysis directly derived from red blood cells
- Causes
  - Cytoskeleton and red blood cells membranes disorders – hereditary spherocytosis, eliptocytosis, paroxysmal nocturnal hemoglobinuria, etc.
  - Glycid metabolism disorders
    - Pentose cycle enzymes – glucose-6-phosphatedehydrogenase (G6PD), glutathione reductase
    - Embden-Mayerhof cycle enzymes – hexokinase, 2,3-phosphoglycerate mutase, pyruvate kinase
  - Hemoglobinopathy and hemoglobinisation disorders – thalassemias, some hemoglobinopathies, sickle cell anemia

INTRACORPUSCULAR HEMOLYTIC ANEMIA PATHOMACHANISM ACCORDING TO THE CAUSES

1. Red blood cells and cytoskeleton disorders
   - Defficiency or loss of structural proteins - e.g. hereditary spherocytosis – ankyrin, spectrin, protein 3, protein 4.1 -> cytoplasmatic membrane detachment from cytoskeleton -> spherical cell shape
   - Capillaries trespassing disorders -> microcirculation obstruction
   - Red blood cells partial loss in spleen -> e.g. biconcave red blood cells
   - Bone marrow not affected -> ↑reticulocytes
   - Decreased osmotic stability -> ↓decreased resistance in hypotonic solution

   - Paroxysmal nocturnal hemoglobinuria -> PIG-A gene disorder -> night hemolysis prevalent (loss of protection against complement)

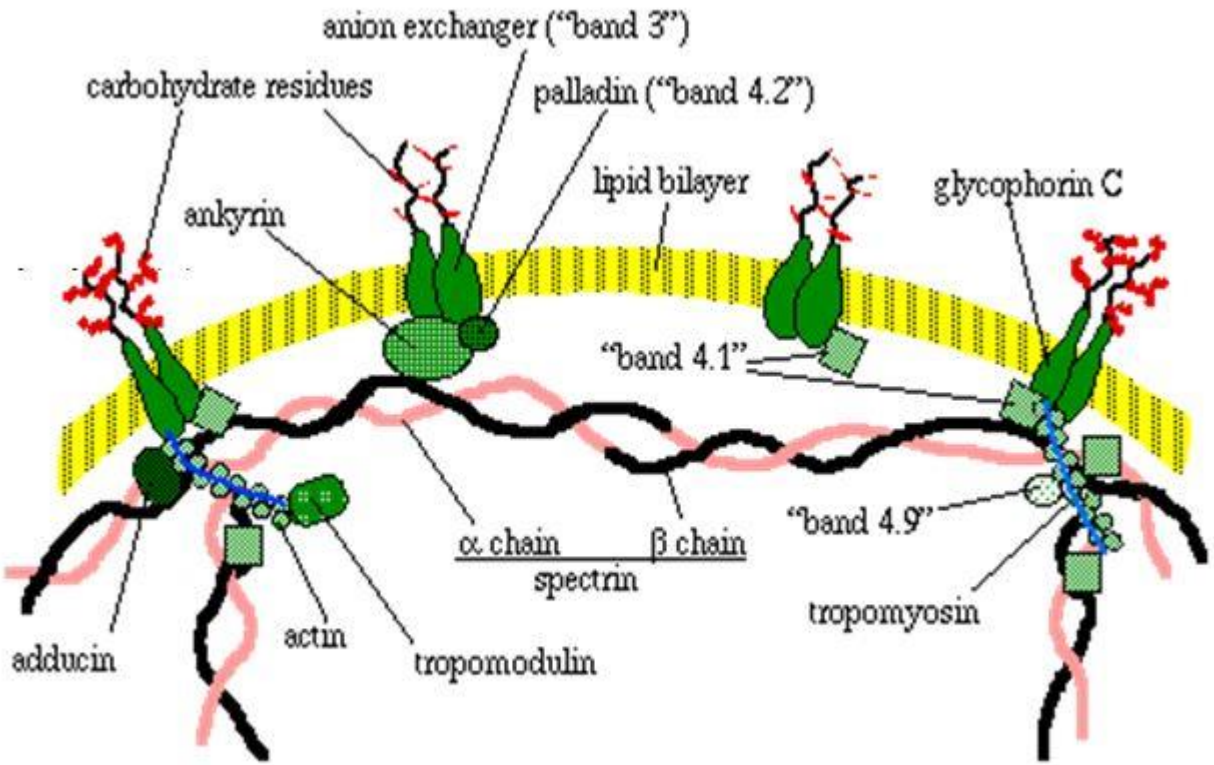
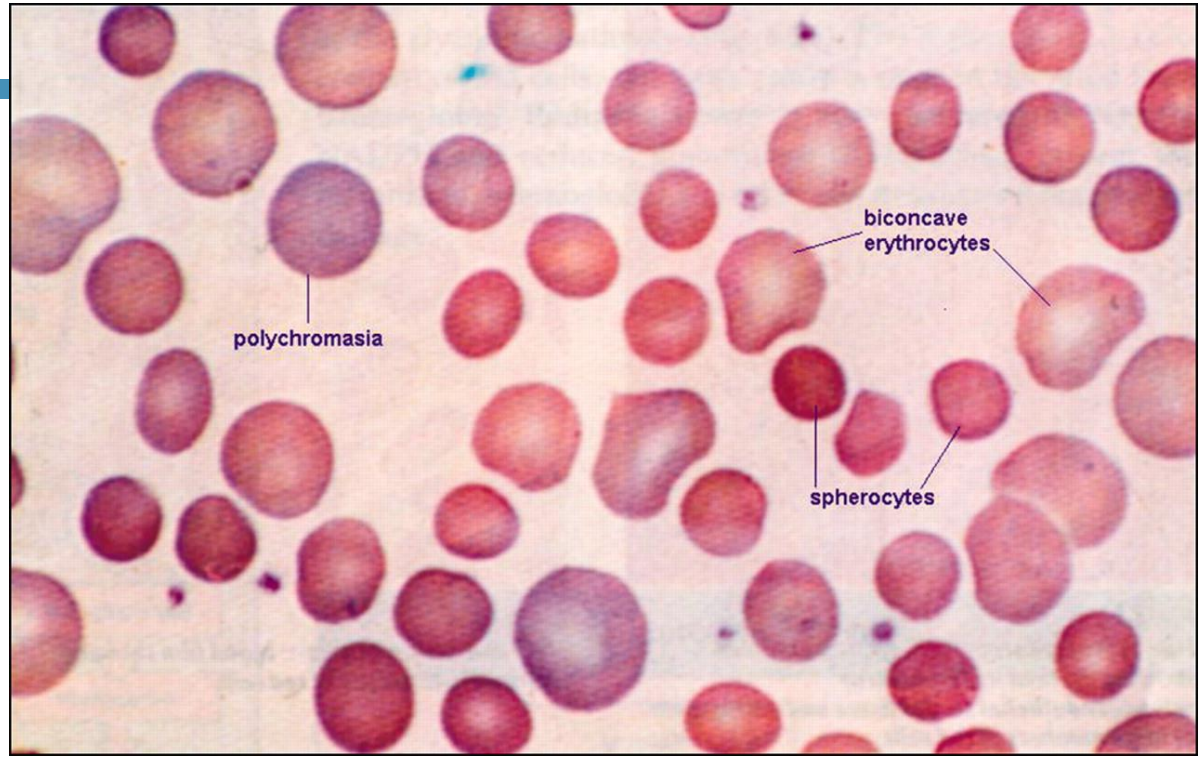
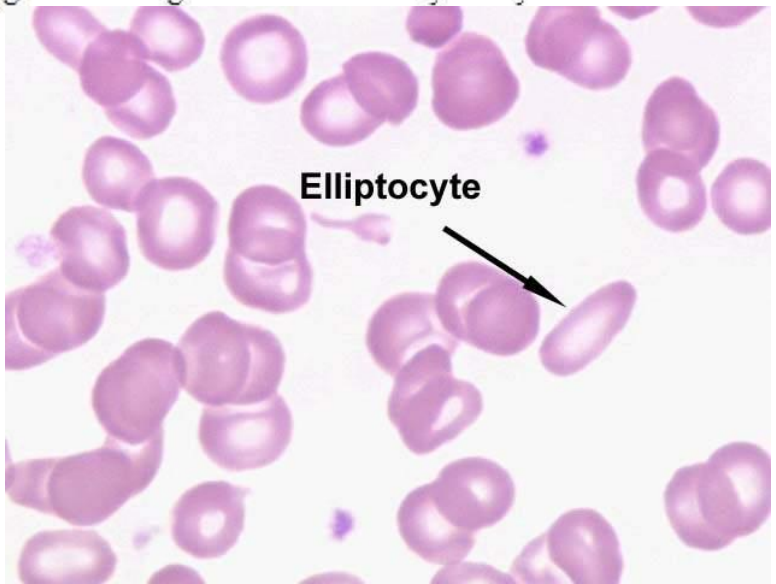


Figure: 4.1 Organization of the Erythrocyte Membrane





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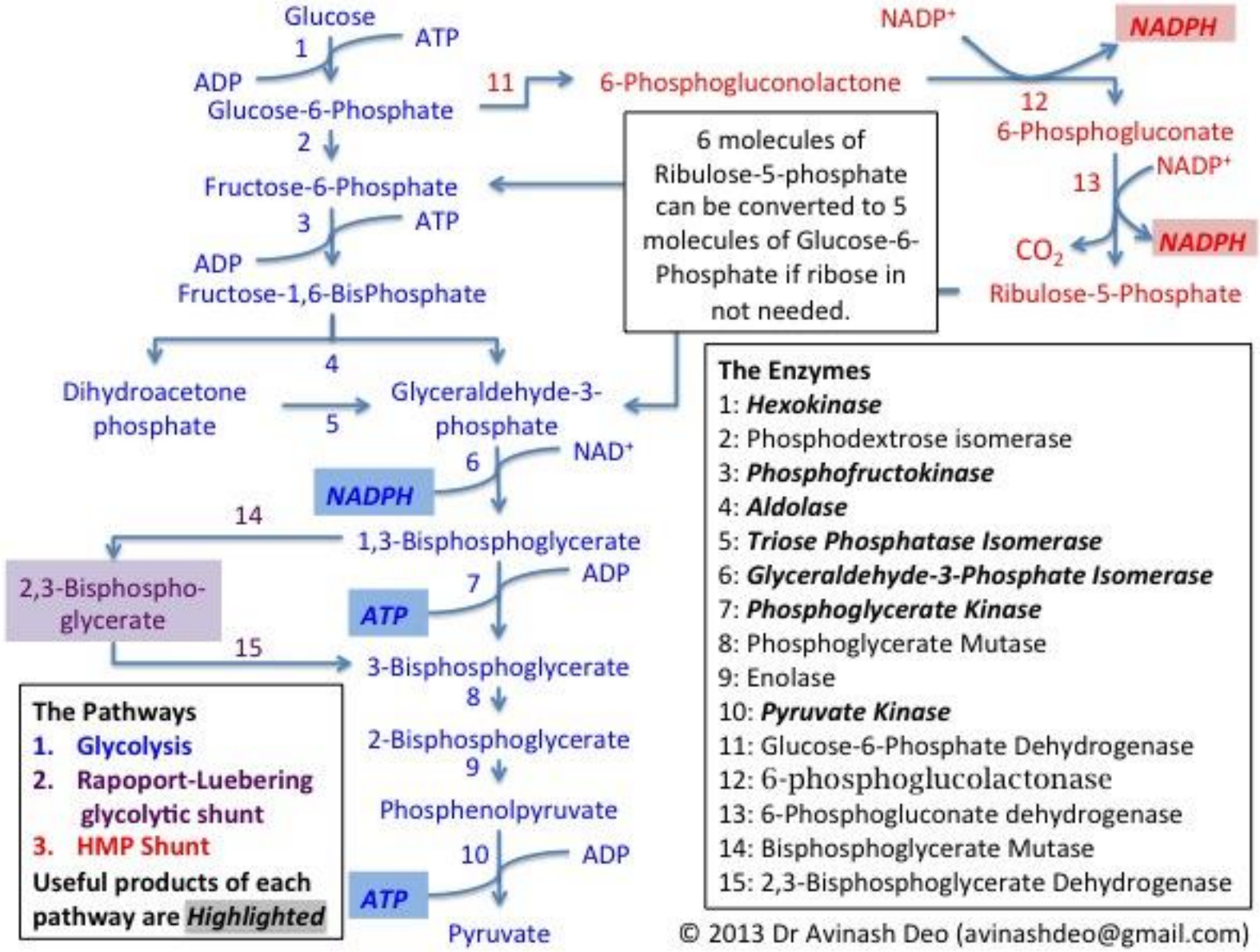
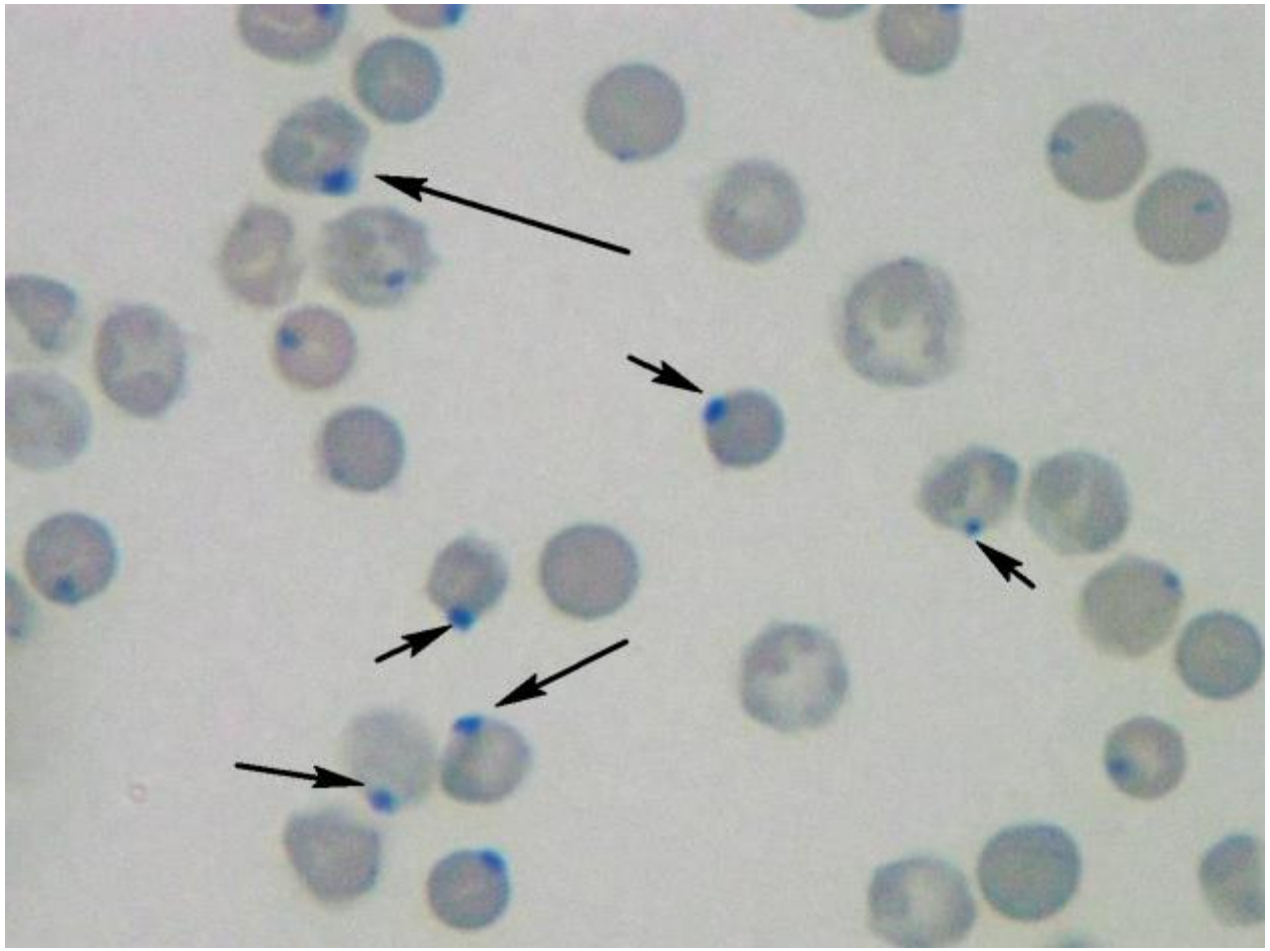
https://encrypted-tbn0.gstatic.com/images?q=tbn:ANd9GcRLPTJzLc1QvF6-1f8jJ2escXIpIgVPUOyuYLvLCaWQtasrxIB34FtuIGnU60N5xXbL9ko&usqp=CAU
https://www.stepwards.com/wp-content/uploads/2016/01/slide014ellipt2.jpg

INTRACORPUSCULAR HEMOLYTIC ANEMIA PATHOMACHANISM ACCORDING TO THE CAUSES

2. Red blood cells metabolism disorders
   - Red blood cells unable to restore lost and damaged enzymes (nuclear extrusion during orthochrome normoblast stage)
     - ATP produced by anaerobic glycolysis; reduced glutathione production, methemoglobine reductase, 2,3-bisphosphoglycerate
   - Glucose-6-phosphate dehydrogenase defficiency
     - X-recessive -> ↓enzyme levels -> ↓antioxidant defense -> hemolysis (G-6PD drop <50 % physiological capacity)
     - Geographic location -> Sardinia, central Afrika, south China
     - Drugs contraindication – antimalarics, sulphonamides, nitrofurantoin
     - Favism -> legumes eating leading to hemolysis (Vicia fava - beans)
     - Heinz bodies -> denaturated hemoglobin due to oxidative stress
   - Pyruvate kinase – AR – rigid red blood cells, no spherocytosis



https://allaboutblood.files.wordpress.com/2013/08/glucosemetaboloisrbc.jpg



https://www.stepwards.com/wp-content/uploads/2015/12/Heinz-Bodies.jpg

EXTRACORPUSCULAR HEMOLYTIC ANEMIAS

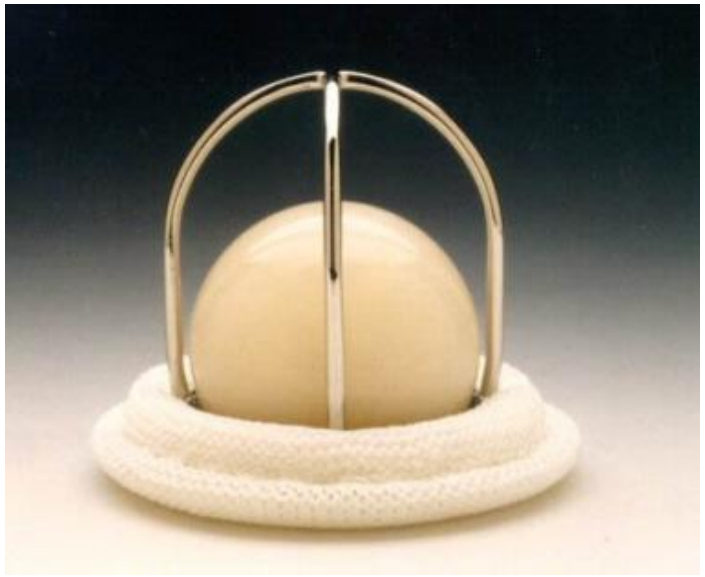
- Hemoglobin concentration drop in peripheral blood due to red blood cells from causes not linked to red blood cells
- Causes
  - Mechanical – arteficial valves, hemodialysis
  - Toxines and parasites – bacterial, malaria; burns, liver cirhhosis, copper metabolism disorders
  - Antibodies and complement mediated damage
  - Antibodies targetting red blood cells antigens

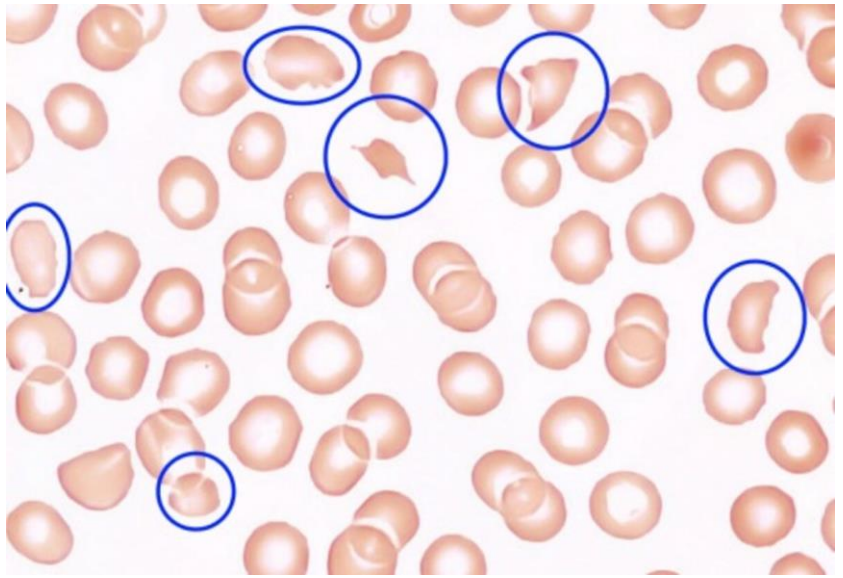
EXTRACORPUSCULAR HEMOLYTIC ANEMIAS PATHOMECHANISM ACCORDING TO CAUSES

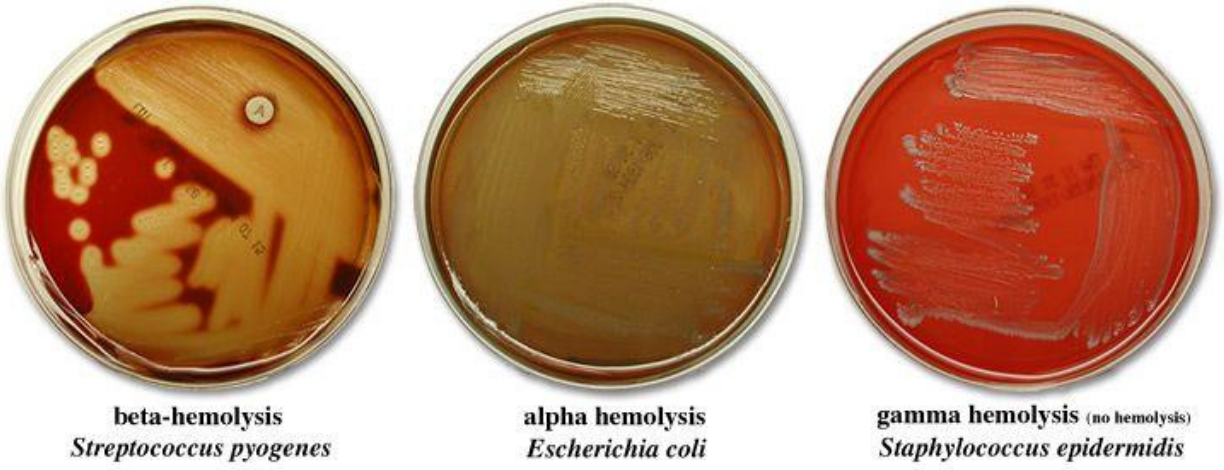
1. Mechanical damage
   - Microcirculation transition in case of fibrin deposits or thrombi
   - Thrombotic thrombocytopenic purpura -> mechanic damage of red blood cells during attempt to squize past thrombi
   - Hemolytic-uremic syndrome
     - Older hypothesis of „narrow vessels“
     - Recent hypothesis – Shiga (Shiga-like) toxine bound to red blood cells membrane -> complement activation
   - DIC
   - Arteficial valves, etc.
- Mutual sign – schistocytes and fragmentocytes

EXTRACORPUSCULAR HEMOLYTIC ANEMIAS PATHOMECHANISM ACCORDING TO CAUSES

2. Bakcterial – α-hemolysis (viriding bacteria), β-hemolysis (complete), γ-hemolysis (none)
   - Clostridium welchii, Staphylococcus spp., Streptococcus pneumonia, E. coli, Haemophilus influenzae
3. Parasites – malaria
   - Plasmodium falciparum, vivax, ovale, malariae -> merosoites attacking red blood cells and multiply inside -> periodic „rupture“ Ery -> periodic fevers -> microcirculation damage and red blood cells adhering to capillaries
4. Copper – hemodialysis, m. Wilson
5. Burns
6. Liver cirrhosis -> ↑circulating LDL -> rigid red blood cells membrane







http://img.medscapestatic.com/pi/meds/ckb/71/40471tn.jpg
https://upload.wikimedia.org/wikipedia/commons/thumb/2/25/Blood_smear_with_typical_schistocytes_in_TTP_marked_in_blue_1.tif/lossy-page1-1200px-Blood_smear_with_typical_schistocytes_in_TTP_marked_in_blue_1.tif.jpg
http://i.stack.imgur.com/pGhk0.jpg

EXTRACORPUSCULAR HEMOLYTIC ANEMIAS PATHOMECHANISM ACCORDING TO CAUSES

7. Antobody-mediated damage –> antobodies-coated red blood cells retained in spleen due to FcR ->microspherocytes
   - Warm type antobodies -> hapten forming drugs – 1-2 weeks after therapy IgG, IgA produced -> hemolysis and hemoglobinuria (e.g. alpha-metyldopa)
   - Cold type agglutinins –> viral infections (CMV, EBV, influenza), bacteria (M. pneumoniae) -> IgM mostly – acral manifestation (temperature <30 °C, optimal at 0–4 °C) -> Red blood cells amaged by complement
   - Cold type hemolysins – paroxysmal cold hemoglobinuria -> in children after viral infections -> antobodies binding in acral parts-> full effect reached in central parts of circulation
8. Donor red blood cells isoagglutinins
   - AB0 – congenital -> incompatible transfusion -> acute hemolysis
   - Rh-system -> sensibilisation necessary -> hemolytic disease of newborn (repeated pregnancies mother Rh-, fetus Rh+)
     - The first pregnancy – Fetal red blood cells into maternal circulation (delivery or abortion mostly) ->IgM produced (unable to trespass placental barrier), memory cells produced
     - The second or later pregnancy –IgG production -> placental trespassing -> fetal red blood cells destroyed
9. Delayed hemolytic reaction, medical history of hemolysis

HEMOGLOBIN RECYCLING – WHY POSES INTRAVASCULAR HEMOLYSIS SUCH A PROBLEM?

1. Extravascular hemolysis
   - Macrophages engaged -> liver, spleen, bone marrow-> iron and globin reutilised
   - Heme -> bilirubin (concrements development risk)
2. Intravascular hemolysis
   - Hemoglobin bound to haptoglobin (1 g/l)
   - Extra hemoglobin->αβ-dimers -> hemoglobinuria
   - Partial reabsorption by tubular cells -> transformed to hemosiderin -> after 3-4 days -> hemosiderinuria
     - Tubular cells damage -> ↓haptoglobin
   - Peripheral blood -> ↑Ery-lactate dehydrogenase

ACUTE VS. CHRONIC HEMORRHAGE

1. Acute hemorrhage
   - 500+ ml blood loss -> hypovolemic shock imminent -> 10 % red blood cells lost
   - 1000 ml blood loss -> 500 mg iron depleted
   - Short-term perspective -> dilution anemia (physiological solution, etc.) -> iron defficiency anemia risk
2. Chronic hemorrhages -> cumulative iron loss

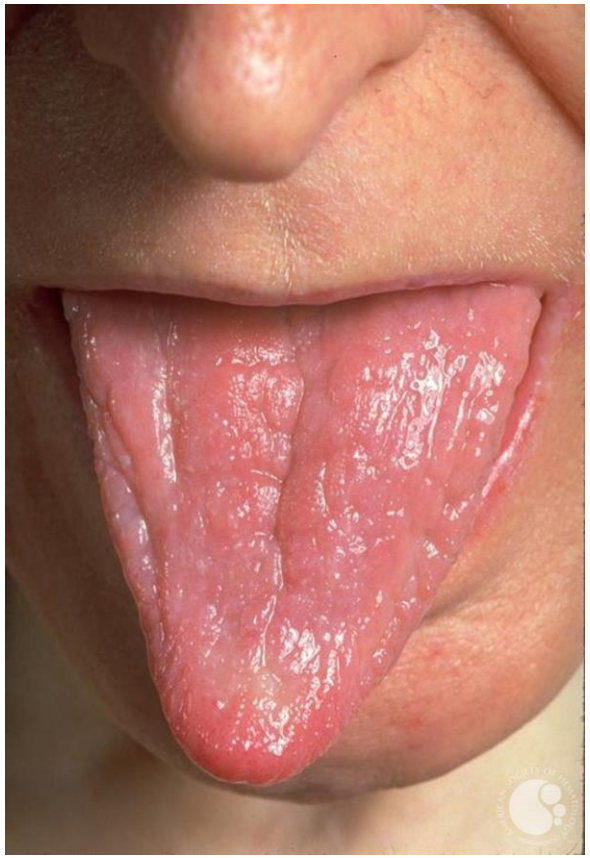
- Hemolysis leads to decrease red blood cells destruction in spleen, hemorrhages trigger this mechanism at a slower rate -> red blood cells increase in bone marrow immediately increases spleen destruction rate

SPECIFICS AND RISKS IN PREGNANCY ANEMIA

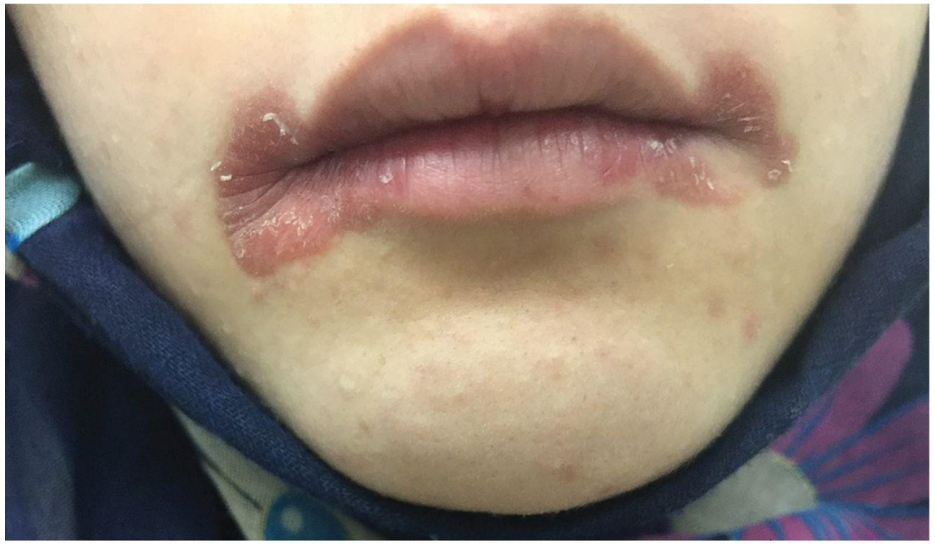
- Pregnancy increases demands on maternal organism
- Fetal iron transport prioritised
- Vit. B9, B12 – fetal transport priority -> intesnive cells mitoses in progress
- Blood volume in maternal organism increases in 500–1000 ml -> placentary circulation supplementation

- Pregnant woman may suffer to sideropenic, megaloblastic, dilution anemia or their combination!
  - „You‘re pregnant thus tired“ -> HELL NO!
- Parameters assessment!
  - Pacient – Hb 108 g/l, Ery 3,33.10^{12}/l, MCV 98 fl, MCH 32,1 pg -> iron prescription (not great, not terrible?)

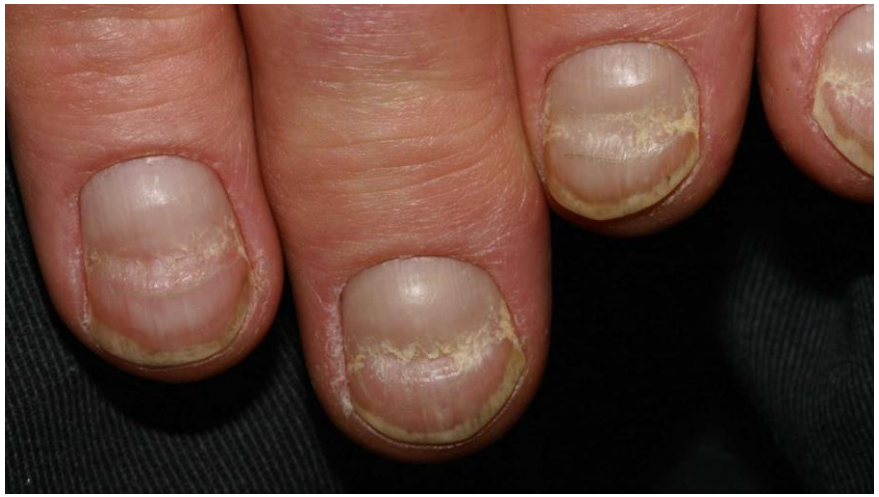
IRON DEFFICIENCY ANEMIA IN ORAL CAVITY



Atrophic glossitis
https://imagebank.hematology.org/getimagebyid/60222?size=3



Angular cheilitis
https://www.ccjm.org/content/ccjom/85/8/581/F1.large.jpg



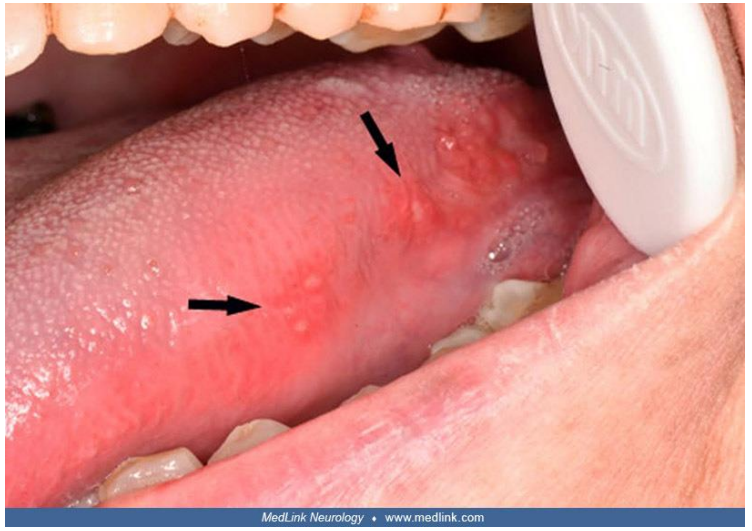
Koilonychia („spoon-shaped“ nails)
https://i.insider.com/56a3a18edd0895ad088b45cb

B12 DEFFICIENCY ANEMIA IN ORAL CAVITY MANIFESTATION

Frequent ulcerations and inflammed, red and smooth tongue (glossitis)

Cheilitis

Lateral tongue ulcerations



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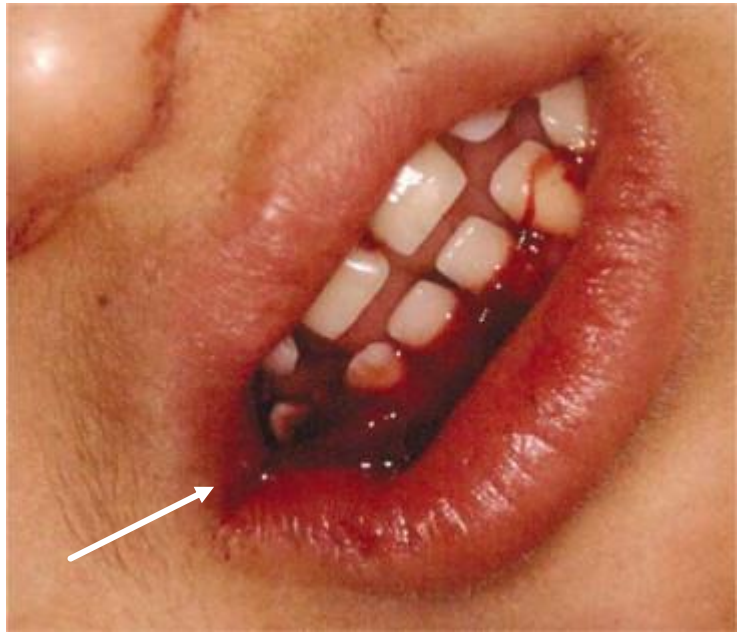
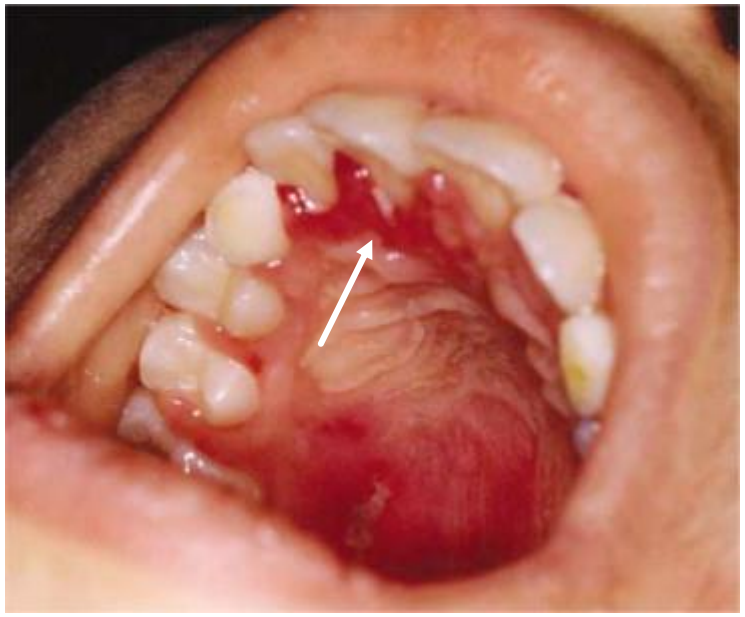
https://assets.medlink.com/content/article-media/dlvb4.jpg

APLASTIC ANEMIAS AND HEMORRHAGIC ANEMIA IN ORAL CAVITY





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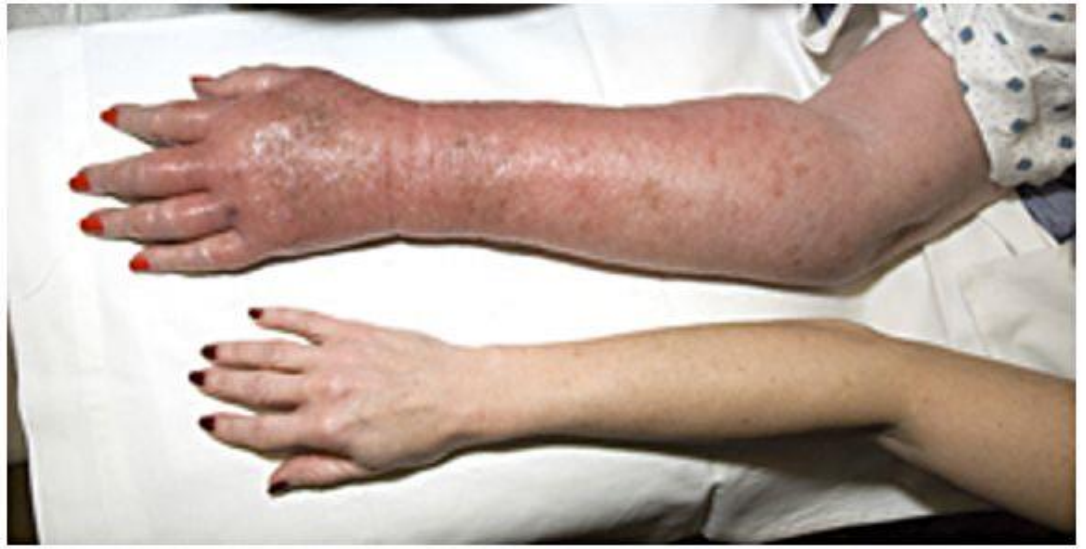
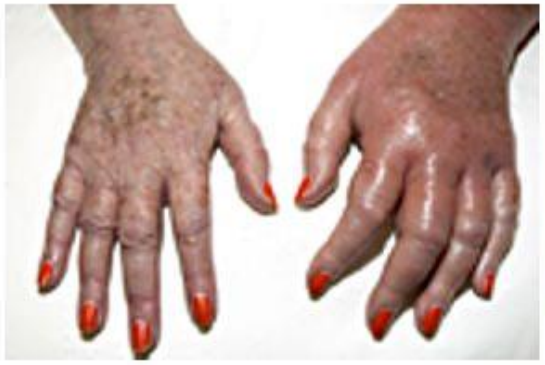
https://ars.els-cdn.com/content/image/1-s2.0-S0002177146071 45-gr1.jpg

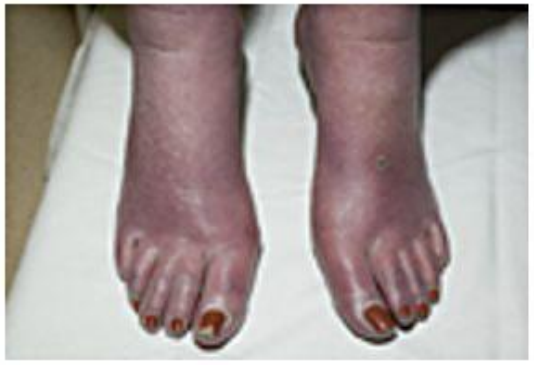
POLYCYTEMIAS

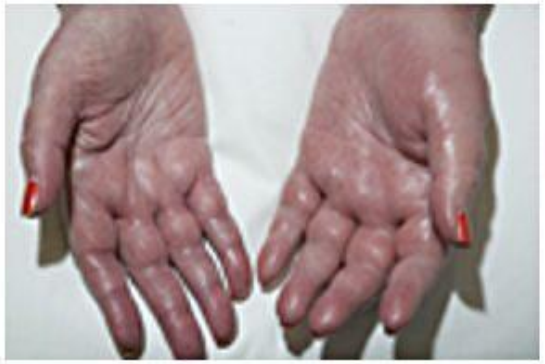
- Primary (polycythemia vera, m. Vasquez)
  - Somatic mutation in JAK2 (V671F) -> extensive myeloid precursor proliferation-> ↑Ery, Tr, Leu (panmyelosis) -> cells maturation not affected
  - ↓EPO -> extensive red blood cells feedback
  - Manifestation -> asymptomatic, ev. pruritus, gout, ulcers, swollen and red limbs, frequent cyanosis (viscous blood and elevated hemoglobin)
- Secondary
  - Hypoxia, heart failure, dopping – exogenous testosterone, „blood dopping“, EPO
  - Paraneoplastic syndrome – EPO or EPO-like substances producing tumours (e.g. renal cell carcinoma)

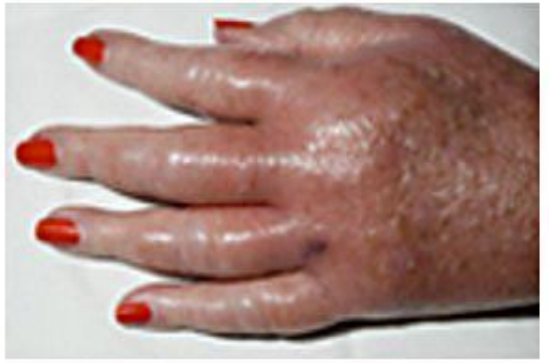
JAK2 – Janus kinase 2











https://upload.wikimedia.org/wikipedia/commons/a/a4/Erythromelalgia.jpg

PLATELETS

THROMBOCYTOPENIAS, THROMBOCYTOPATHIES; TROMBOCYTOSIS

THROMBOCYTOPENIAS (COUNT)

- Perihperal blood platelets drop <50 000 cells/μl (factical <150 000 cells/μl)
- Causes
  1. Decreased production
     - Dehydratation, vit. B9 and B12 defficiency
     - Leukemias, myelodysplastic syndrome, aplastic anemia
     - Liver failure -> ↓thrombopoetin
     - Sepsis, systemic viral/bacterial infection, leptospirosis
     - Congenital – napr. Bernard-Soulierov syndrome, Fanconi anemia, Glanzmann thrombastenia, May-Hegglin anomaly

THROMBOCYTOPENIAS (COUNT)

- Causes (continued)
  2. Increased destruction
     - Immune (idiopathic) thrombocytopenic purpura, thrombotic thrombocytopenic purpura, antiphospholipid syndrome, Dengue fever, Gaucher disease, Zika virus, DIC
  3. Drug induced
     - Valproate, methothrexate, carboplatina, interferon, isotretinoins, proton pump inhibitors
  4. Other
     - Laboratory error, snake poison, Lyme disease, thrombocytapheresis, Niemann-Pick disease

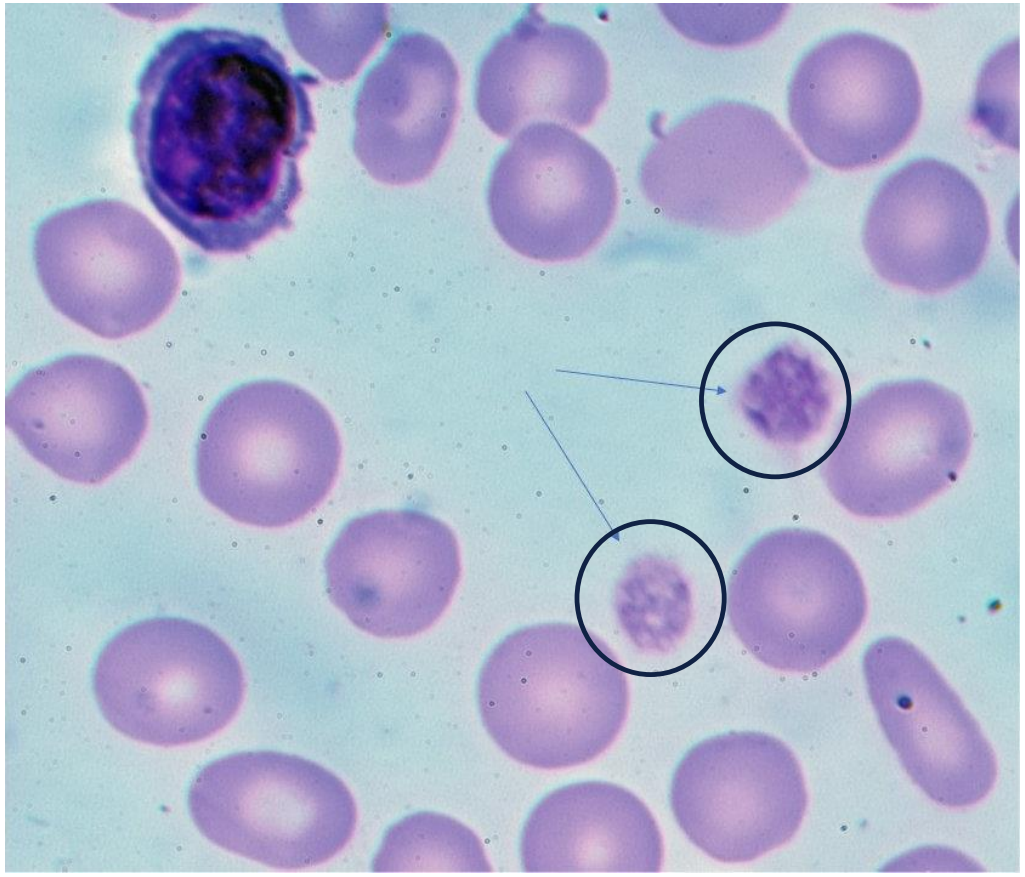
IDIOPATHIC THROMBOCYTOPENIC PURPURA

- Autoimmune disease typical with decreased platelet counts and hemostasis disorders in absence of other causes
- Forms
  - Acute – children mosty, after viral infections
  - Chronic – adults mostly, unclear mechanism
- Pathomechanism
  - ? -> IgG against glycoprotein IIb-IIIa or Ib-IX -> Tr opsonisation -> Tr retained by macrophages (spleen) and Liver (Kupffer cells)
  - Antibodies damaging megakaryocytes, decreased thrombopoetin production (possible T-cells hyperactivity)

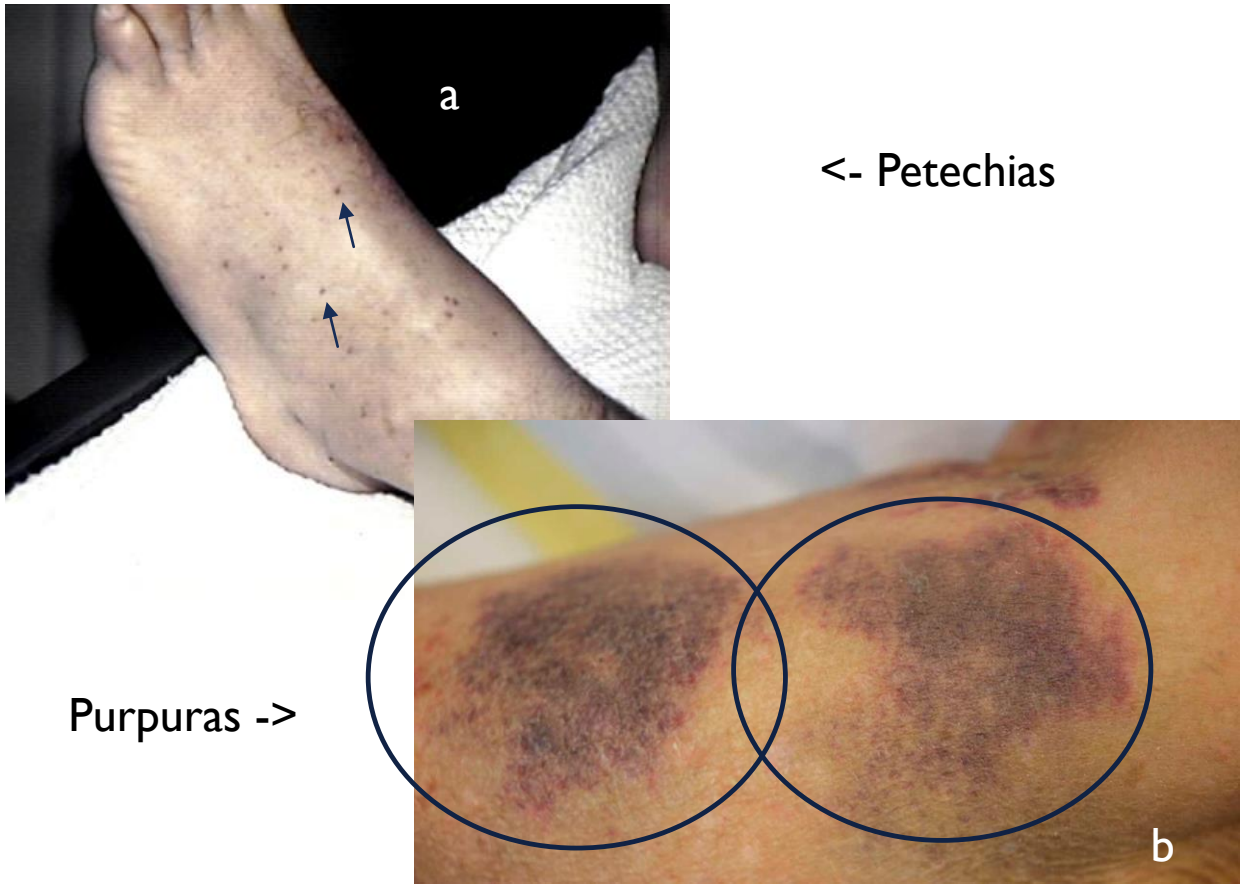
IDIOPATHIC THROMBOCYTOPENIC PURPURA

- Manifestations
  - Tr <50 000 cells/μl – petechias and purpuras
  - Tr <20 000 cells/μl – epistaxis, mouth bleeding, menorrhage
  - Tr <10 000 cells/μl – spontaneous hematoma emerging (oral cavity, mucosa), prolonged bleeding time in bruises and small wounds
  - Tr <5 000 cells/μl – spontaneous subarachnoidal/intracerebral bleeding, aboral GIT blood loss, internal bleeding
- Prognosis
  - Good, only small patients percentage experience a fatal bleeding episode

IDIOPATHIC THROMBOCYTOPENIC PURPURA



Macrothrombocytes (Giemsa method)
https://upload.wikimedia.org/wikipedia/commons/9/9a/Giant_platelets_in_ITP.jpg



<- Petechias

Purpuras ->

https://upload.wikimedia.org/wikipedia/commons/1/13/Petechiaesmall.jpg
https://media.post.rvohealth.io/wp-content/uploads/sites/3/2022/12/purpura-skin-slide1.jpg

THROMBOCYTOPATHIES (FUNCTION DISORDER)

- Platelets functions disorder, platelets count may or may not be decreased
- Causes
  1. Congenital
     - Adhesion disorders – Bernard-Soulier syndrome
     - Activation disorders – Hermansky-Pudlak syndrome, grey platelets syndrome
     - Aggregation disorders – Glanzmann thrombastenia, Wiskott-Aldrich syndrome
     - Coagulation activity disorders – Scott syndrome
  2. Acquired
     - Paroxysmal nocturnal hemoglobinuria, asthma, aspirin, tumours, malaria...

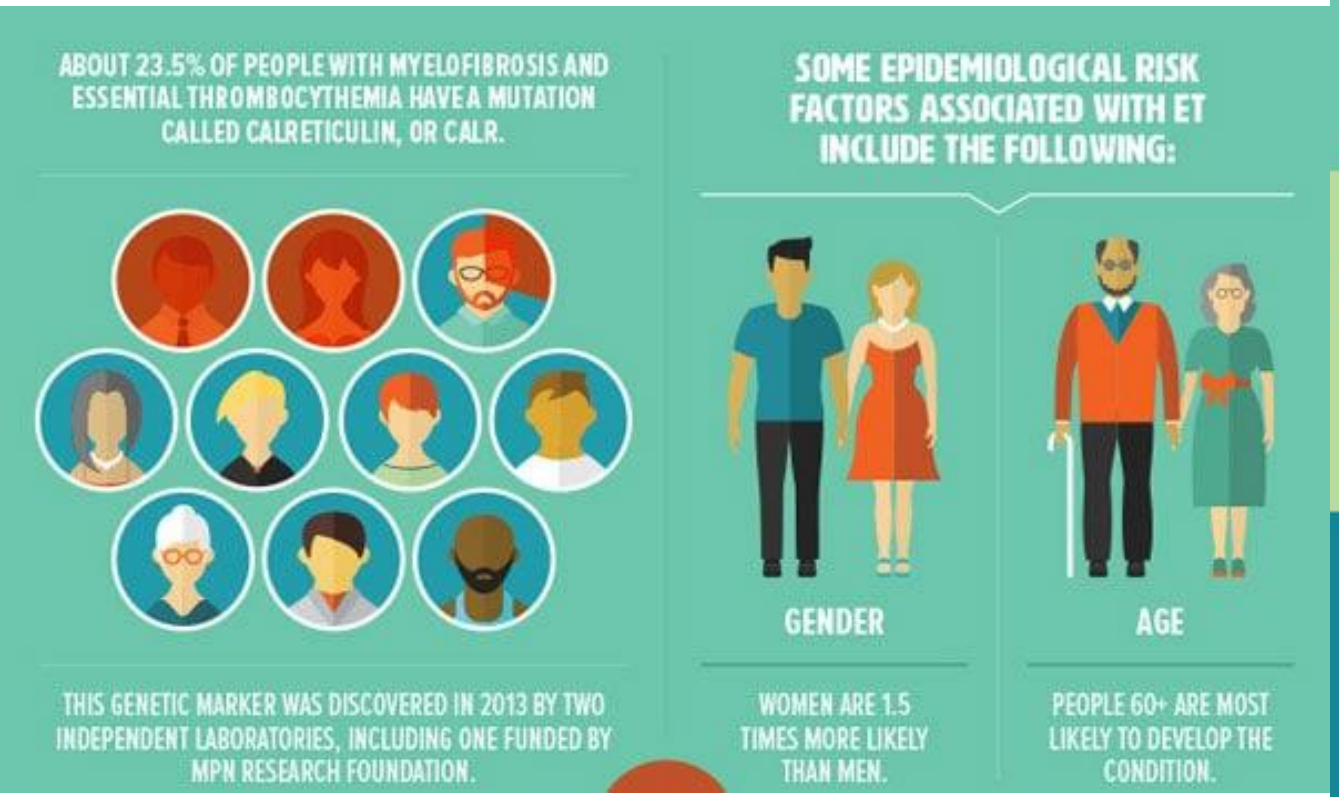
ASPIRIN-INDUCED THROMBOCYTOPATHY

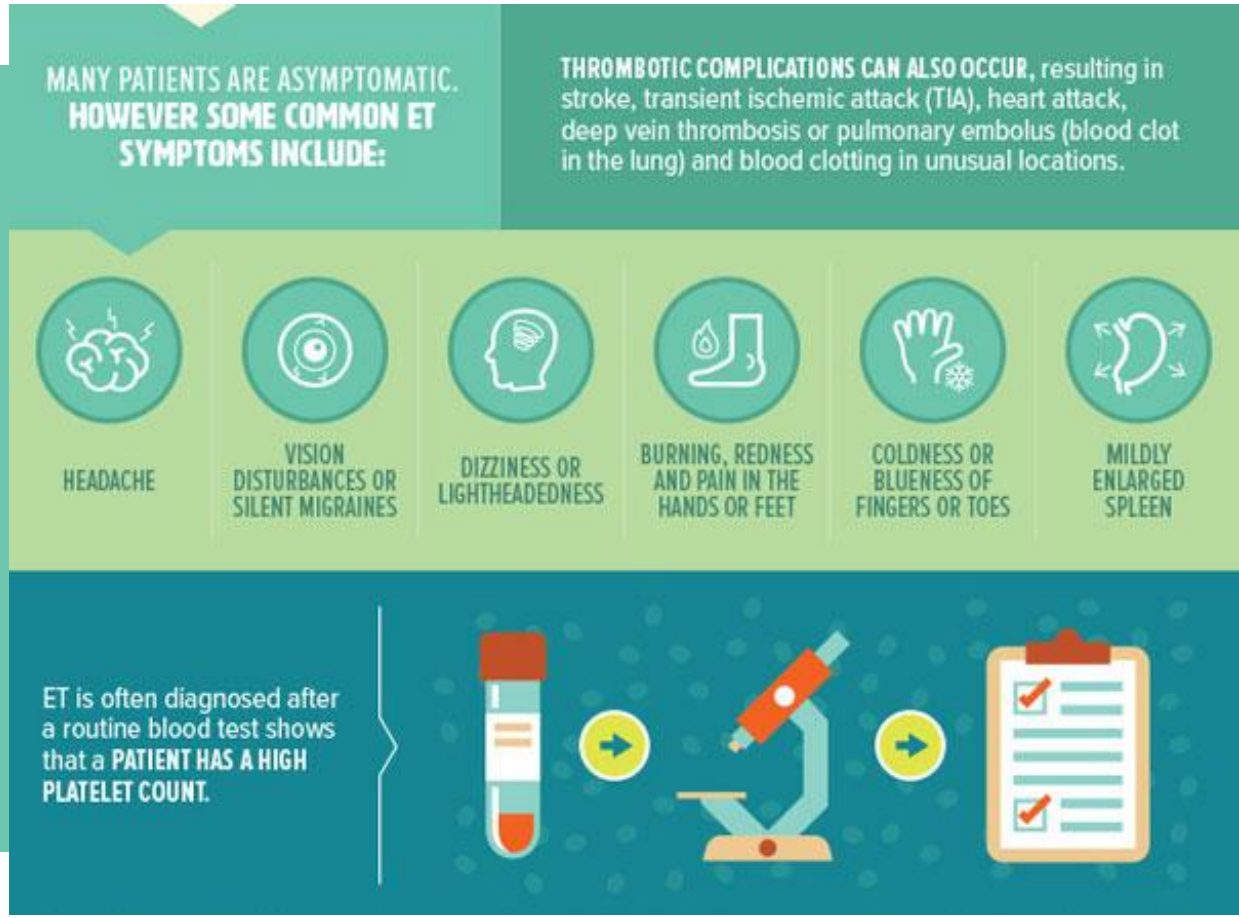
- Aspirin (acetylsalicylic acid) -> cyklooxygenase blocked
  - Platelets prostaglandins synthesis decreased
- ADP production inhibited, also platelets reaction to granuli release after collagen exposure
- Aspirin does not decrease platelets count!

- Aspirín may induce auto-antibodies production – auto-anti-gp-IIb/IIIa, auto-anti-gp-Ia/Iia -> increased platelets destruction -> thrombocytopenia

THROMBOCYTOSIS (THROMBOCYTEMIA)

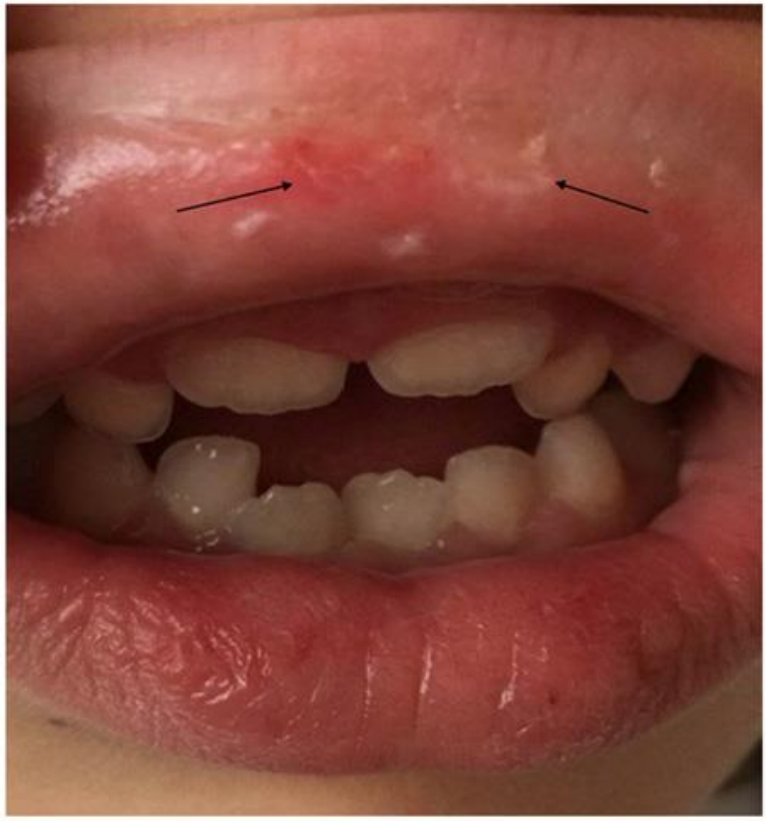
- Platelets count elevated in peripheral blood >750 000 cells/μl (reference range >420 000 cells/μl) with or without platelets function affected
- Causes
  - Myeloproliferation states – primary (essential), CML, polycythemia vera, primary myelofibrosis
  - Reactive – 88–97 % of adult trhombocytemias (almost 100 % in children)
    - Acute infection, chronic infection, tissue damage, malignancies; SARS, post-surgical states, drugs, iron deffciency, „rebound“ phenomenon after bone marrow suppression, physical activity
    - Asymptomatic mostly
  - False positive – platelets-like elements presence – cryoglobulin crystals, leukemic cells debris, bacteria, red blood cells microvesicles
- Erythromelalgia – burning sensation in red coloured limb -> aspirin and/or cold relieve the sensation
- Thrombophilia does not automatically mean thrombocytemia!

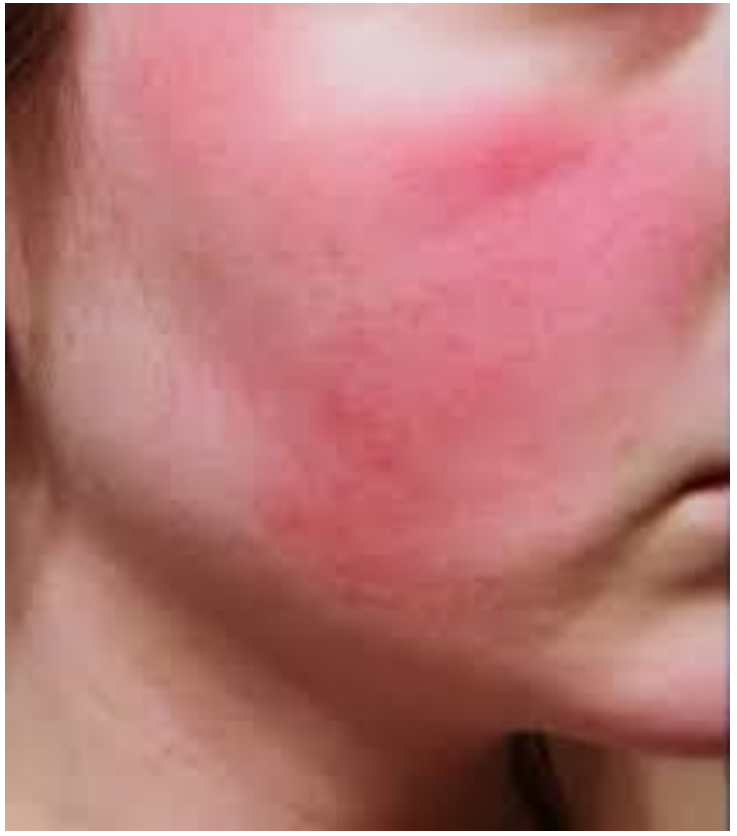


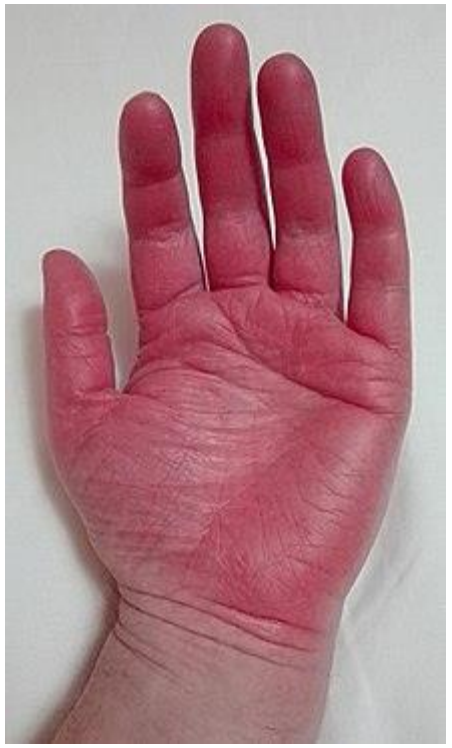


https://hohmanrehab.com/wp-content/uploads/2020/10/Essential-Trombocythemia-Statistics.jpg
https://images.ctfassets.net/tytuahdkbx9m/patientpower_ArticlePage_asset_45741d58b054f6f62f31e6e9bc5278349/47e05bd75d570184832ed8706fcfc243/patientpower_ArticlePage_asset_45741d58b054f6f62f31e6e9bc5278349

PLATELETS COUTN AND FUNCTION DISORDERS IN ORAL CAVITY MANIFESTATION – ERYTHROMELALGIA (HAND AS A COMPARISON)







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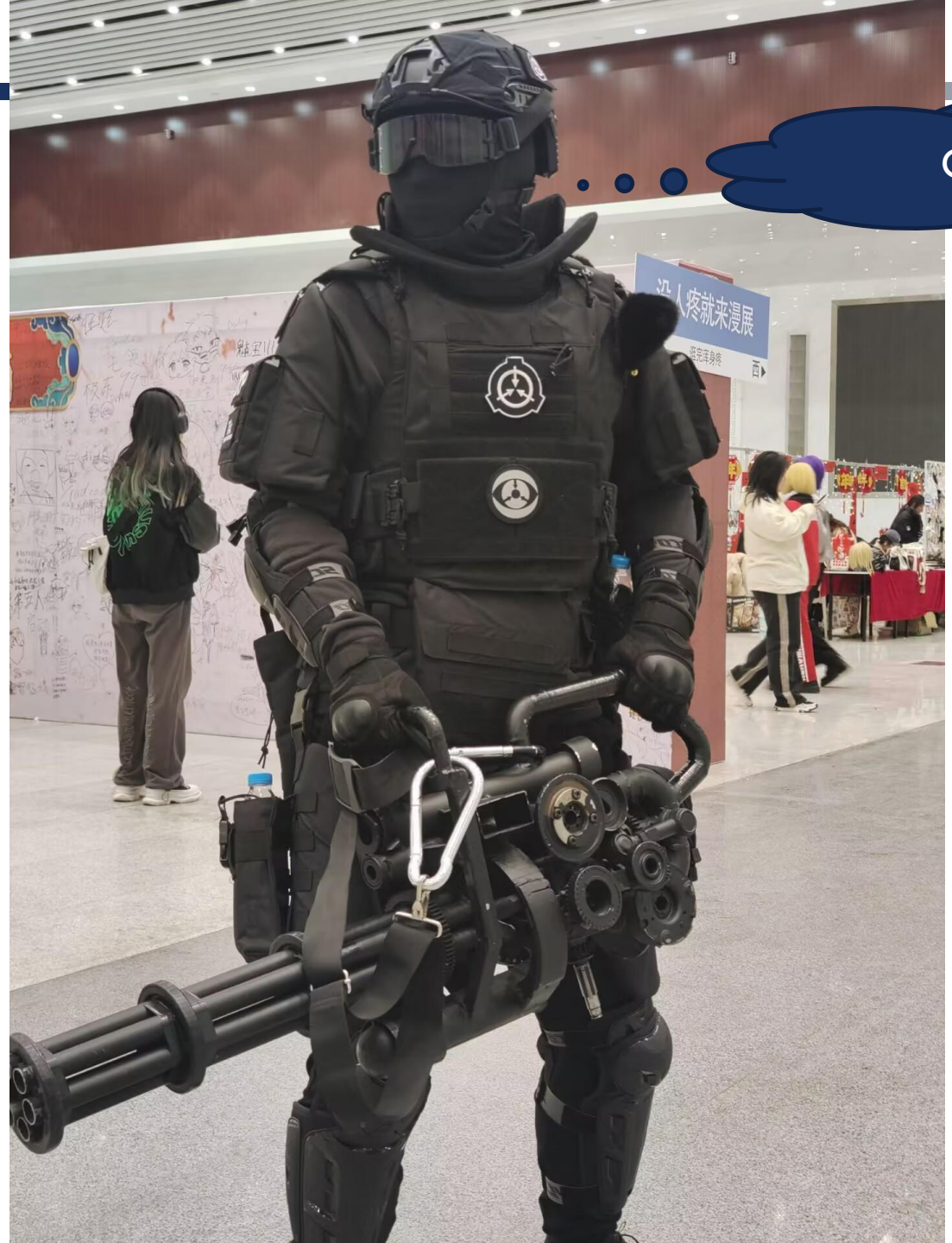

Questions?

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