Thrombozytopenie: Wann Gefährlich? Wann nicht?

15. Frühlingszyklus
16. März 2022

Sacha Zeerleder

Abteilung Hämatologie

27-jährige Lehrerin mit Petechien

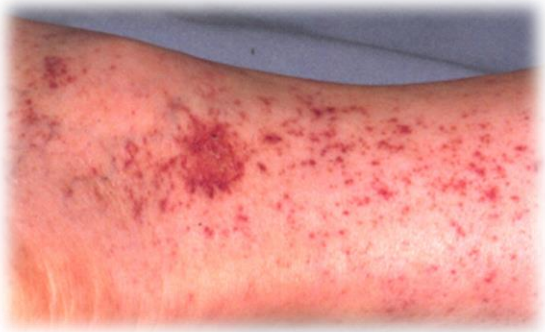
27-jährige Lehrerin mit Petechien

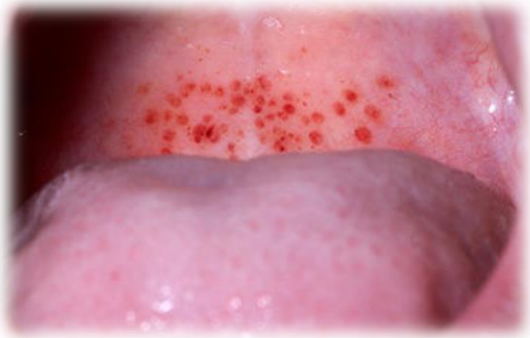
Anamnese
- ✓ Seit einigen Wochen Müdigkeit
- ✓ Seit 2 Tagen “rote Punkte” an den Unterschenkel/Fussrücken

Persönliche Anamnese
- ✓ 2 Schwangerschaften, komplikationslos
- ✓ Appendektomie (mit 18 Jahren)

Status
- ✓ Petechien Unterschenkel und enoral

Medikamente
- ✓ Pille



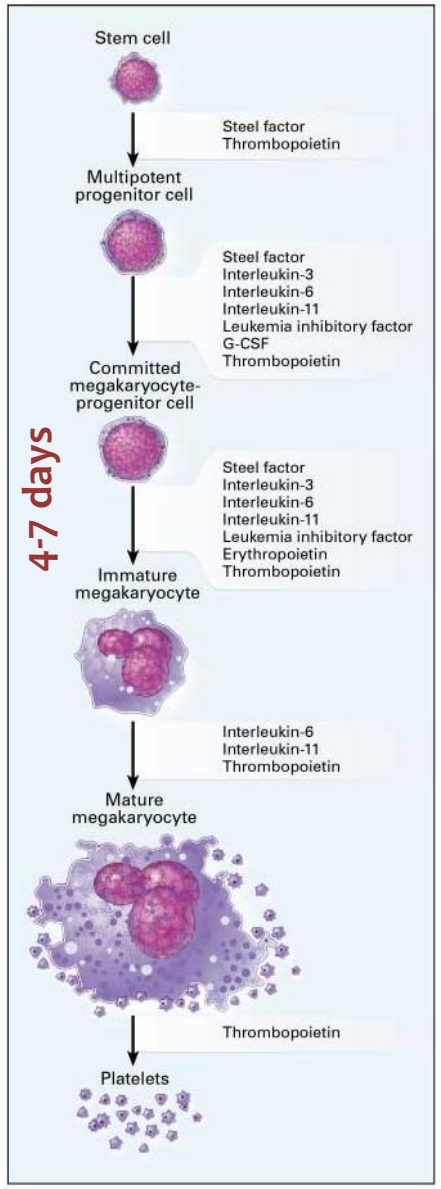


Hb	11.9 g/L
Lc	5.2 x10^9/L (norm. Diff)
Plts	<10 x10^9/L

Ihre Diagnose?
Welche Diagnostik veranlassen Sie?
Starten Sie eine Behandlung?

Platelets and beyond

Megakaryopoiesis - platelets

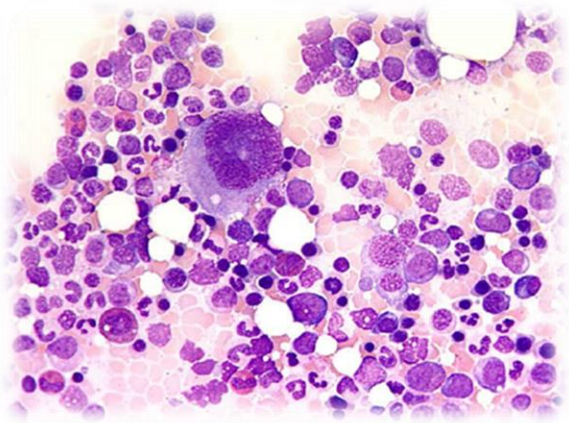


Kaushansky K. N Eng J Med 1998

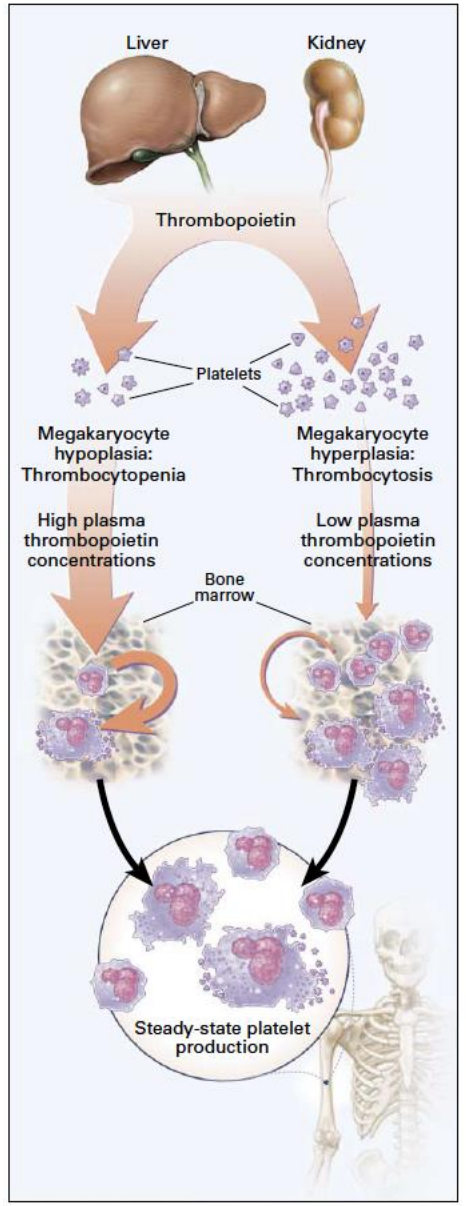
production

→ **Platelet pool** →

- Circulatory lifespan: **10 days**
- Production
  - ✓ $1x10^{11}$ platelets per day
  - ✓ $1x10^{8}$ megakaryocytes per day

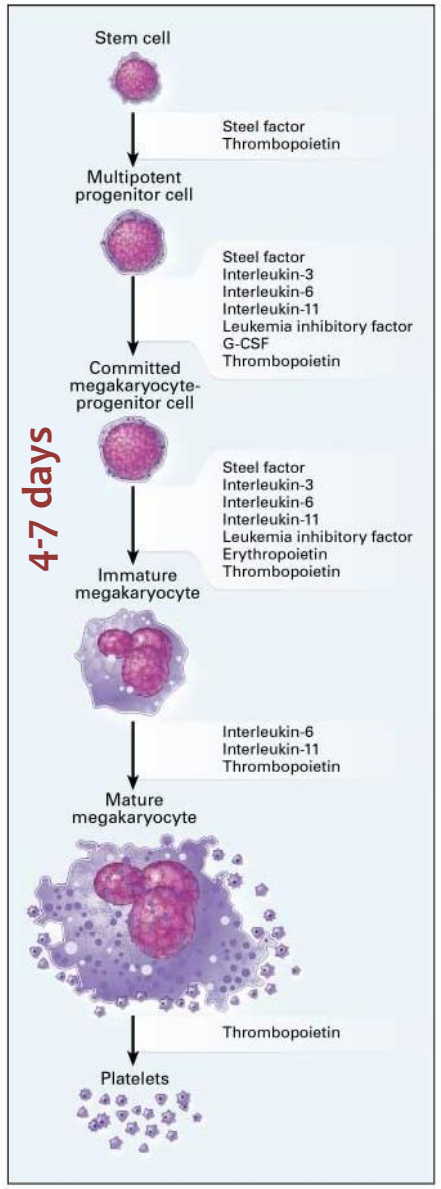


courtesy PD. Dr. A. Rovo



https://www.freenet.de/lifestyle/gesundheit/pictureshow/alles-ueber-die-milz_5557444_4747384_5557442_0.html; Kaushansky K, Williams 9th Edition 2016, Chapter 111

Megakaryopoiesis - platelets

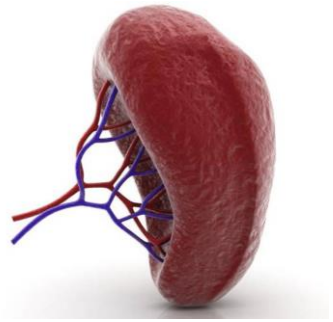


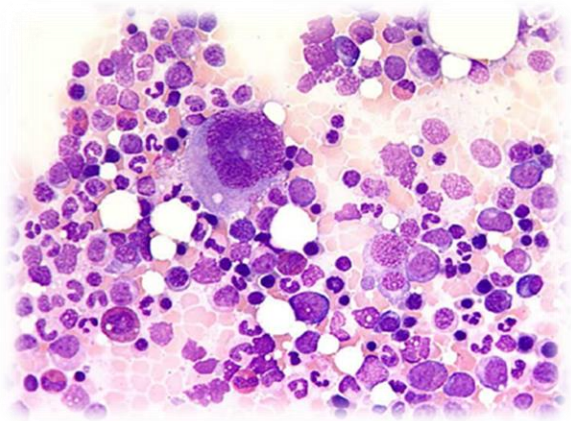
Kaushansky K. N Eng J Med 1998

production

Platelet pool

consumption





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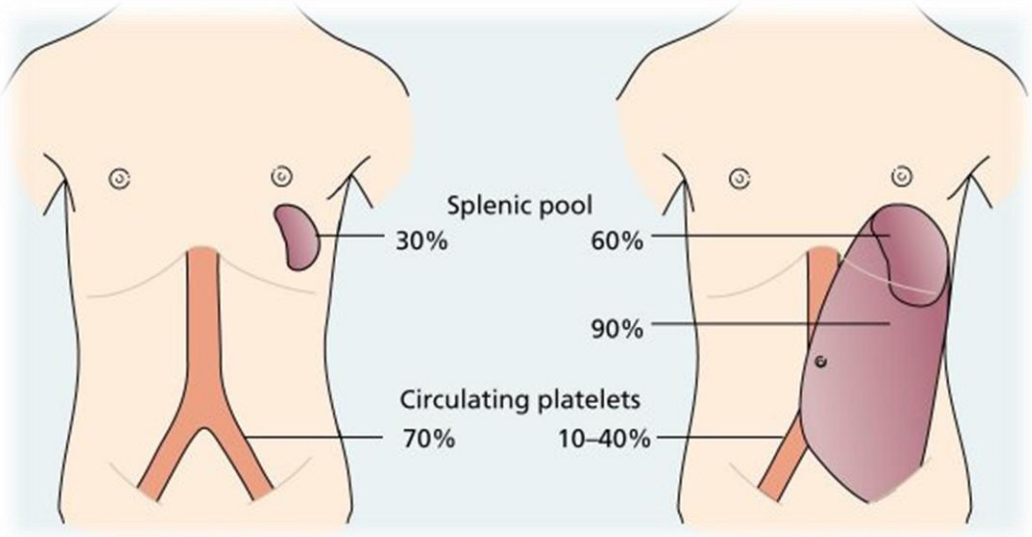


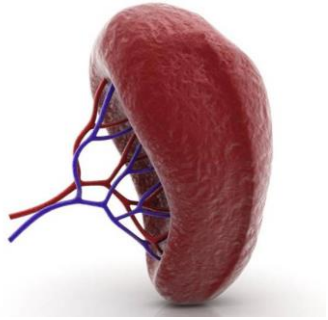
https://www.freenet.de/lifestyle/gesundheit/pictureshow/alles-ueber-die-milz_5557444_4747384_5557442_0.html; Kaushansky K, Williams 9th Edition 2016, Chapter 111; www.wiley.com/go/essentialhaematology

Thrombocytopenia – differential diagnosis

production

Decreased production
- ✓ Radiation
- ✓ Chemotherapy
- ✓ Displacement (AML, lymphoma)
- ✓ Myelopthysis
- ✓ Infection
- ✓ Liver disease

Platelet pool



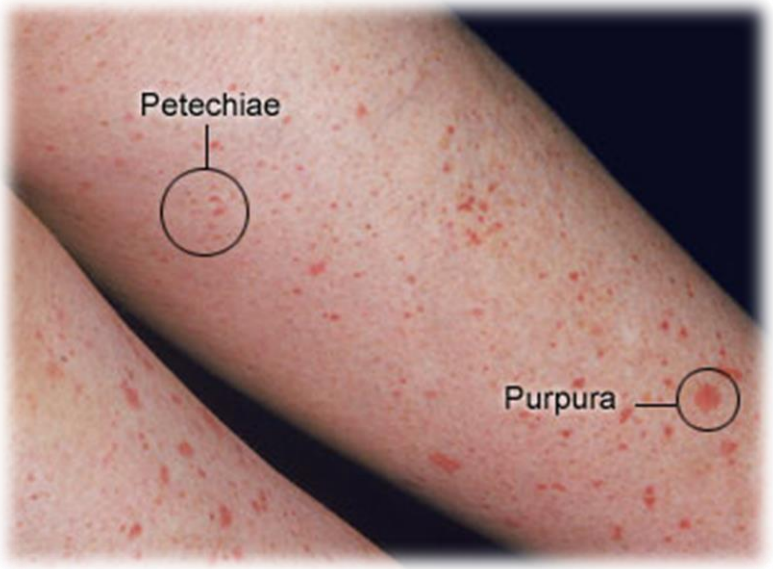
Sequestration
- ✓ Hypersplenism
- ✓ Aneurism
- ✓ haemangioma

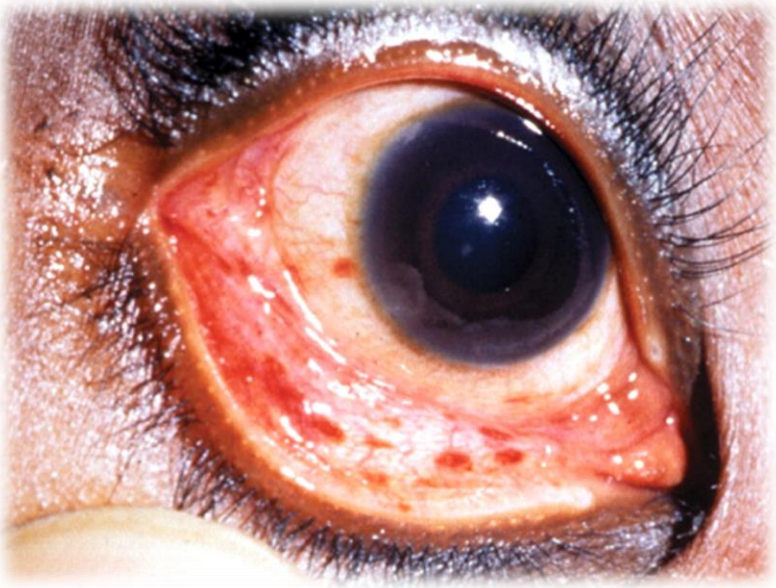
consumption

Immunological destruction
- ✓ Heparin-induced thrombocytopenia (HIT)
- ✓ immune thrombocytopenia (ITP)
- ✓ Allo-antibodies to platelet antigens
- ✓ Posttransfusion purpura (PTP)
- ✓ drugs

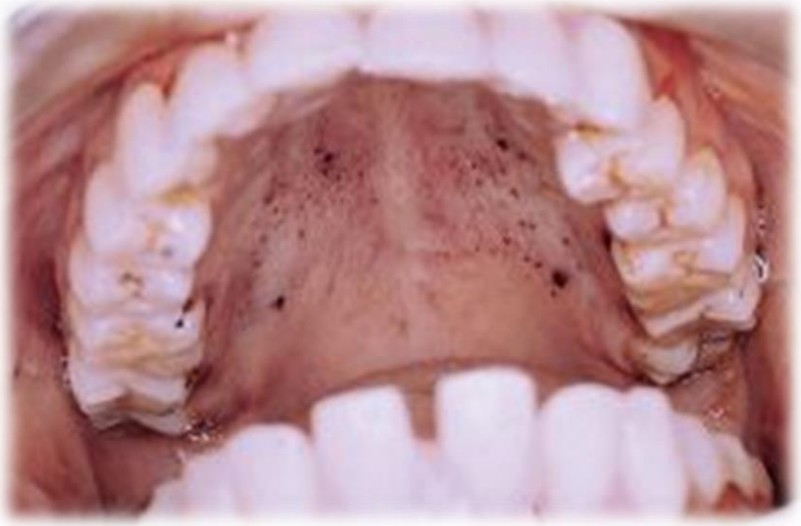
Consumption
- ✓ Major bleeding
- ✓ Extenisve thrombosis (PE)
- ✓ Disseminated intravascular coagulation (DIC)
- ✓ Infection (e.g. severe sepsis, malaria, Dengue)
- ✓ Thrombotic microangiopathy (TTP-HUS, HELLP)
- ✓ Extracorporal- /intravascular device

Thrombocytopenia – clinical signs





	Platelets/vessel wall diseases	Coagulation diseases
Mucosal bleeding	Common	Rare
Petechiae	Common	Rare
Deep haematomas	Rare	Characteristic
Bleeding from skin cuts	Persistent	Minimal
Sex of patient	Equal	>80% male



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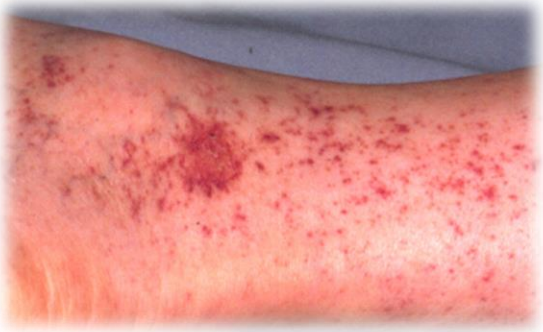
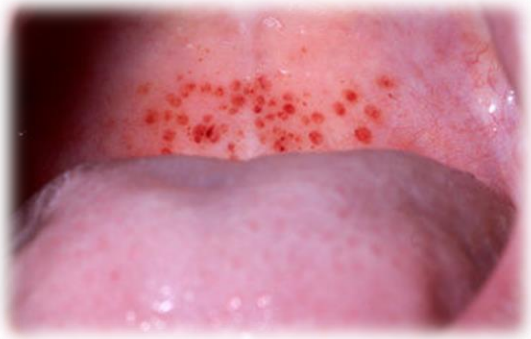




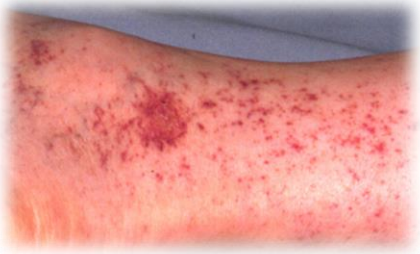
Hb	11.9 g/L
Lc	5.2 x10^9/L (norm. Diff)
Plts	<10 x10^9/L

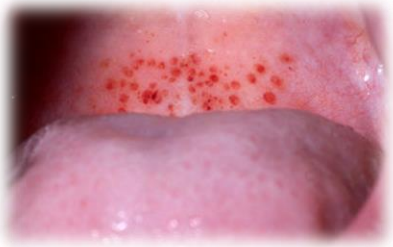
ImmunThrombozytoPenie
ITP

Immunthrombozytopenie

Diagnose ITP

Hb	11.9 g/L
Lc	5.2 x10^9/L (norm. Diff)
Plts	<10 x10^9/L





Immunthrombozytopenie (ITP)

Ausschluss einer sekundären Ursache

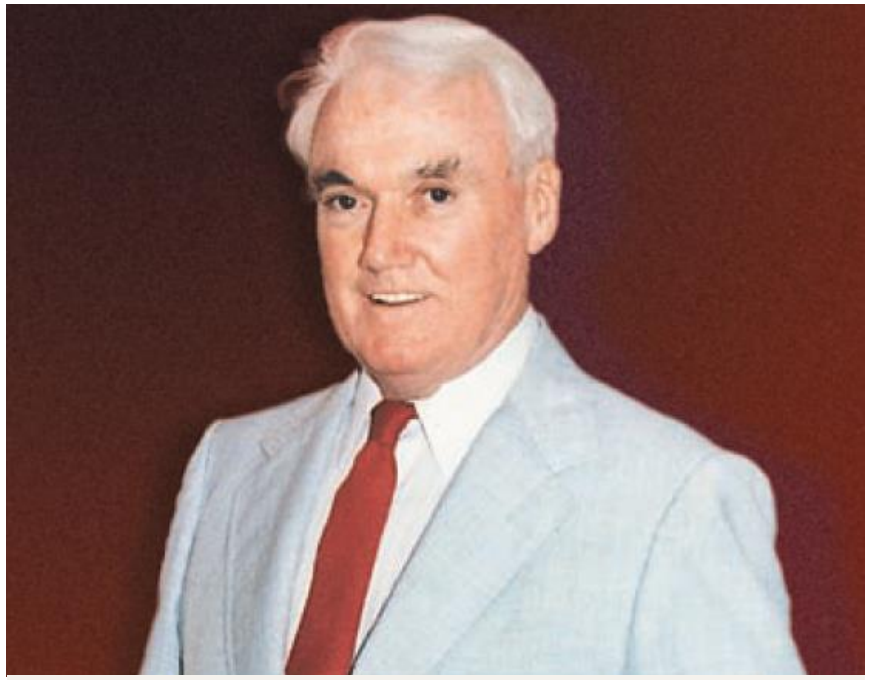
- ✓ Infektiös: HIV, HBV, HCV
- ✓ Autoimmunität (CAVE SLE)
- ✓ Malignom, e.g. Lymphom (could be a herald of lymphoma)
- ✓ Splenomegalie

Weitere Diagnostik:

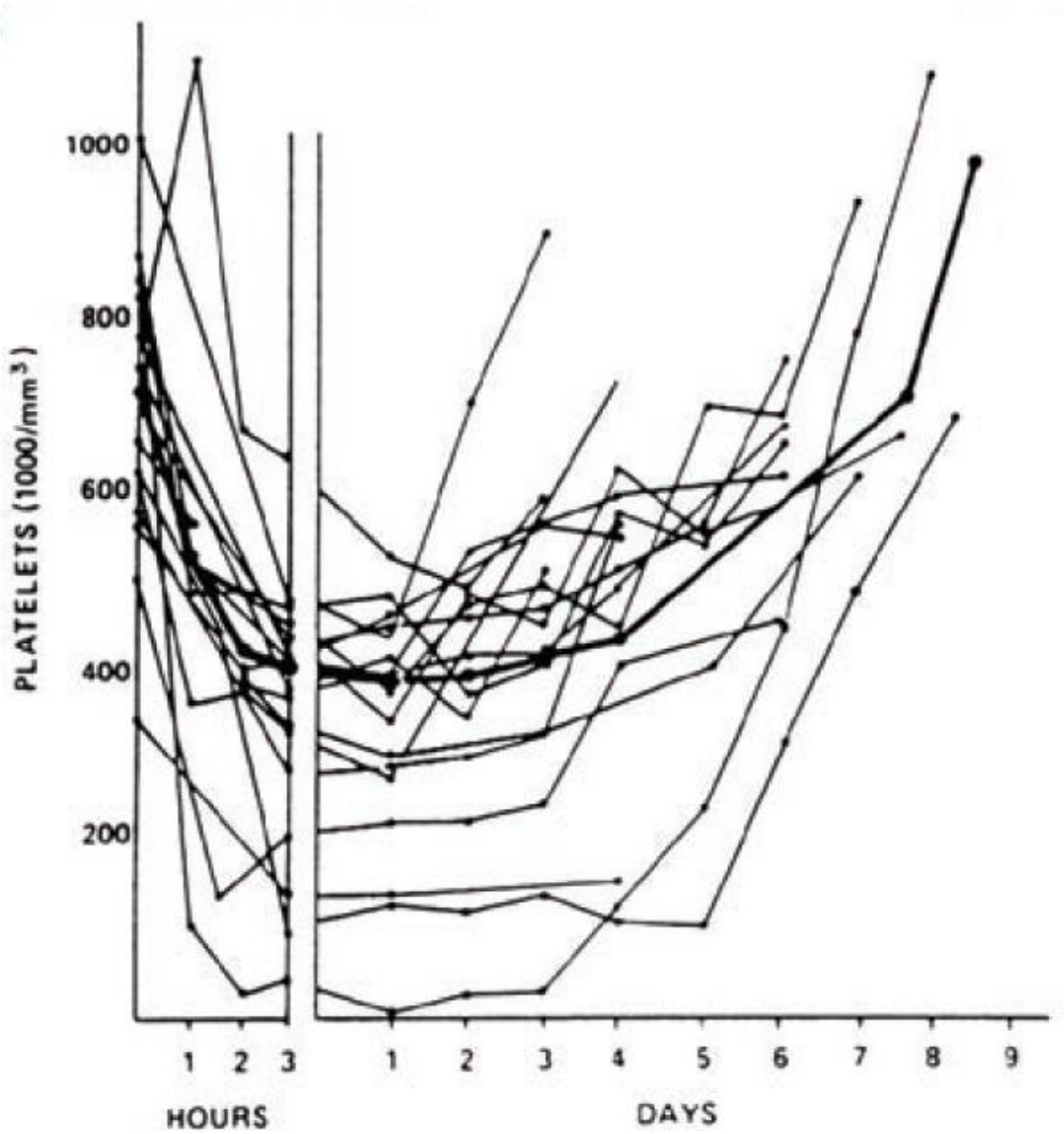
- KMP: nicht nötig für Diagnose, auf Indikation
- Anti-Plättchen Antikörper: “nice to know” aber nicht unbedingt nötig

Neunert et al. Blood Adv 2019

Pioneers in ITP



William J. Harrington (1924–1992)



A plasma-derived factor induces thrombocytopenia

antiplatelet antibodies directed against "dominant" epitopes (GP Iib/IIIa or GPIb/IX (less frequently))

Harrington WJ, *et al. J Lab Clin Med*. 1951;38:1-10.

27-jährige Lehrerin mit neu-diagnostizierter ITP –und nun?

Würden Sie die Patientin behandeln??

- ✓ YEP: Tc<30 G/L

Wie würden Sie die Patientin behandeln?

- ✓ Steroide: PDN 1mg/kg bw (0.5-2.0 mg/kg) oder Dexa 40mg/Tag über 4 Tage
- ✓ PDN und Dexa ws vergleichbar betreffend Effizienz induzieren einer Remission
- ✓ Dexa scheint schneller einen Effekt zu haben (schon nach 7 Tagen)

Würden Sie die Patientin ambulant behandeln?

- ✓ Patient anschauen! Komorbiditäten (Hypertonie, Alter), soziale Situation, etc?
- ✓ ASH Guidelines empfehlen: Tc<20 G/L und asymptomatisch/kleine mukokutane Blutungen: Hospitalisation

Verweisen Sie die Patientin auf die Hämatologie?

- ✓ Ja, wenn möglich (oder minimal Kontakt mit Hämatologie)
- ✓ Notfallzuweisung bei Blutung, resp. hämatologische Konsultation innerhalb 24 Std

Neunert et al. Blood Adv 2019

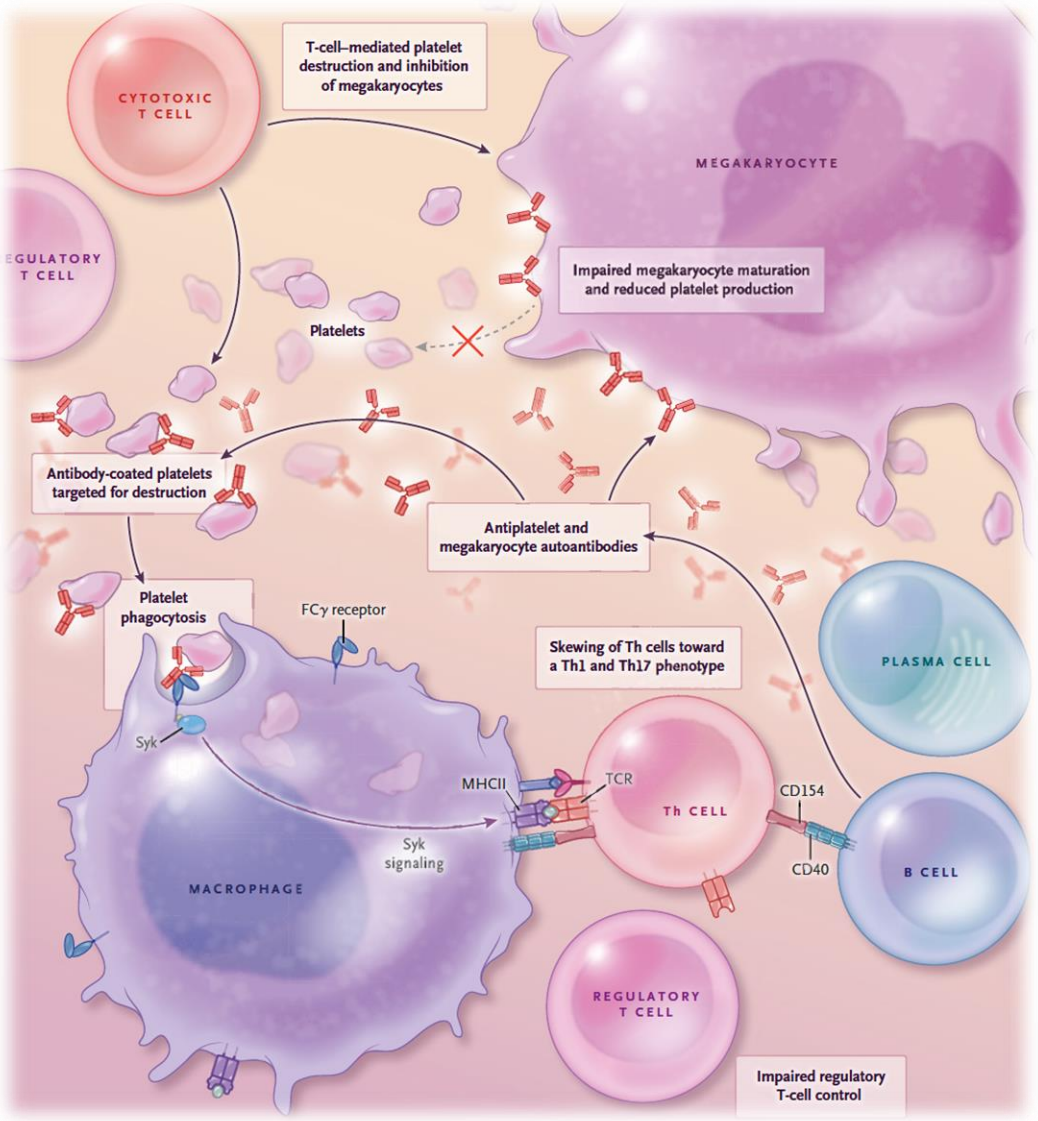
Immune thrombocytopenia- therapeutic approaches

IVIG

Cyclokapron

platelet concentrate

splenectomy



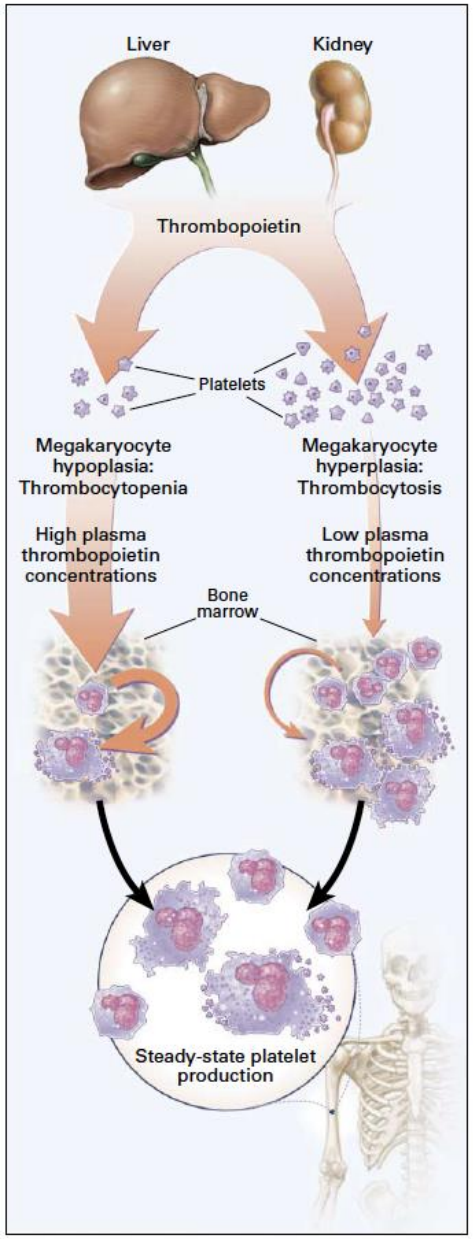
Copper & Ghanima, N Eng J Med 2019

TPO-RA
Romiplostin
revolade

Relatively inadequate proliferation of megakaryocytes and platelet production

anti-CD20

Prednison
dexamethason



27-jährige Lehrerin mit Petechien und Epistaxis

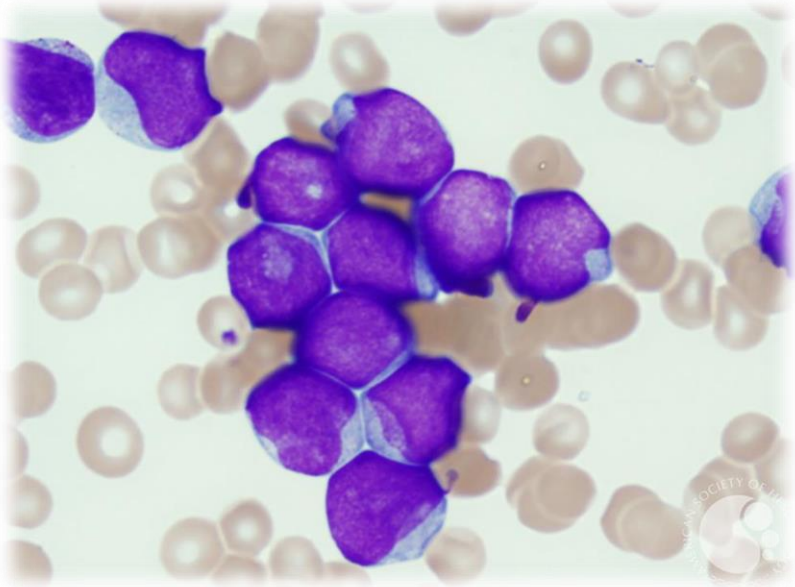
27-jährige Lehrerin mit Petechien und Epistaxis

Anamnese
- ✓ Seit ein paar Wochen müde, auch Dypnoe
- ✓ Seit 2 Tagen Fieber
- ✓ Vor 1 Woche Episode mit scherer Epistaxis
- ✓ Seit gestern rote Punkte auf den Unterschenkeln/Fussrücken

Persönliche Anamnese
- ✓ 2 Schwangerschaften, komplikationslos
- ✓ Appendektomie (mit 18 Jahren)

Status
- ✓ Petechien Unterschenkel/Fussrücken, enoral
- ✓ Fieber (39.2 °C)

Hb	**4.8 g/L**
Lc	**0.7 x10^9/L**
Tc	**<10 x10^9/L**



Was ist Ihre Diagnose/DD?

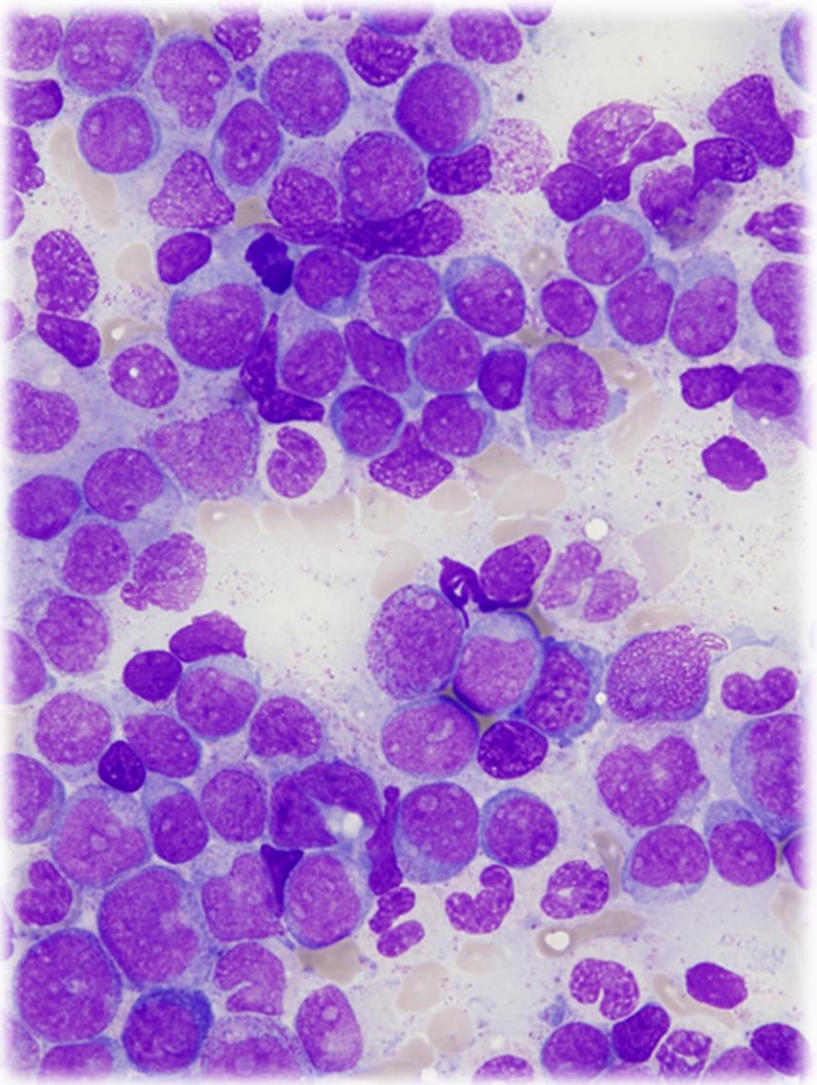
https://imagebank.hematology.org/image/60026/acute-myeloid-leukemia-with-mutated-npm1?type=upload

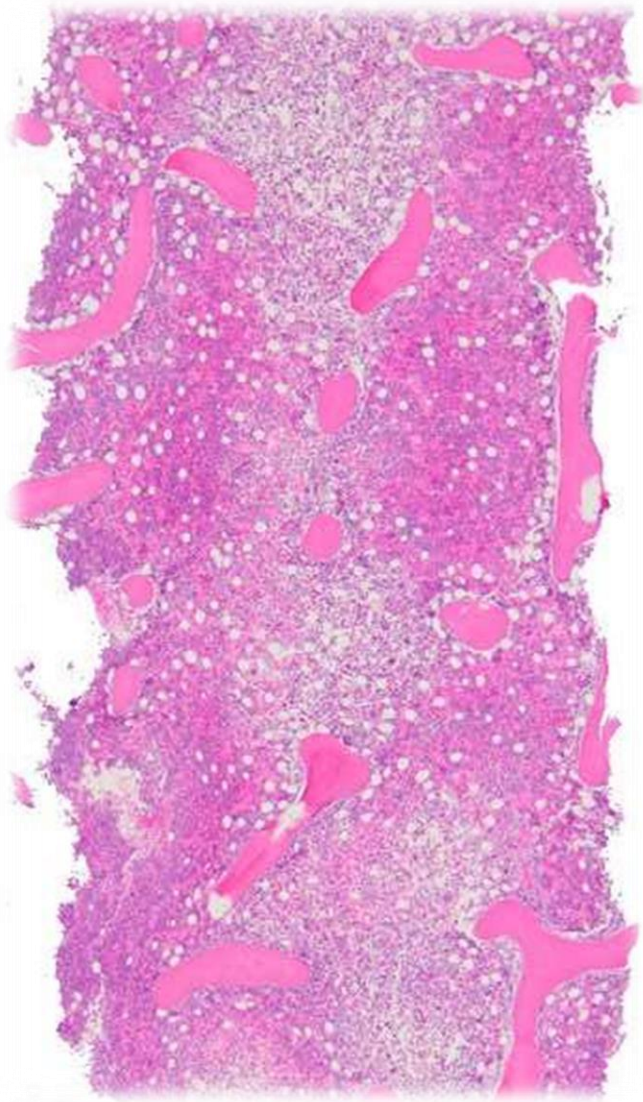
27-jährige Lehrerin mit Petechien und Epistaxis

production

Decreased production

- ✓ Radiation
- ✓ Chemotherapy
- ✓ Displacement (AML, lymphoma)
- ✓ Myelopthysis
- ✓ Infection
- ✓ Liver disease

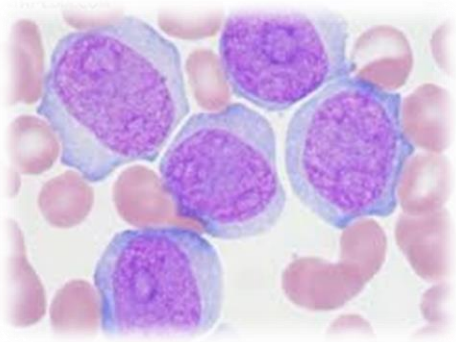




http://atlasgeneticsoncology.org/Anomalies/t0611q15q23ID1522.html
https://www.pathpedia.com/education/eatlas/histopathology/bone_marrow/acute_myeloid_leukemia_with_maturation_(aml-m2).aspx

Thrombozytopenie durch Verdrängung der Megakaryopoiese durch AML-Blasten

27-jährige Lehrerin mit Petechien und Epistaxis

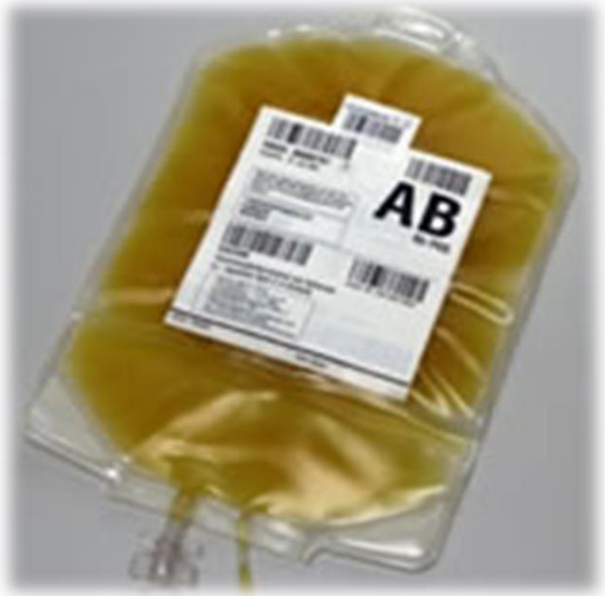


Akute myeloische Leukämie (AML)
Neutropenes Fieber
Hämorrhagische Diathese

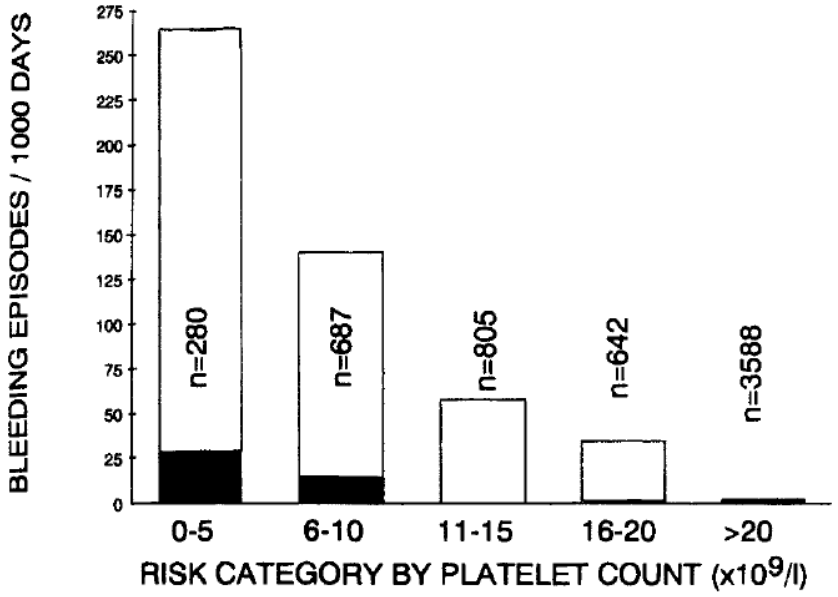
Hb	4.8 g/L
Lc	0.7 x10^9/L
Tc	<10 x10^9/L

Und jetzt? Was machen Sie?

- ✓ Blutkulturen
- ✓ Antibiotika i.v.
- ✓ Thrombozyten Transfusion
- ✓ Kontakt Hämatologie

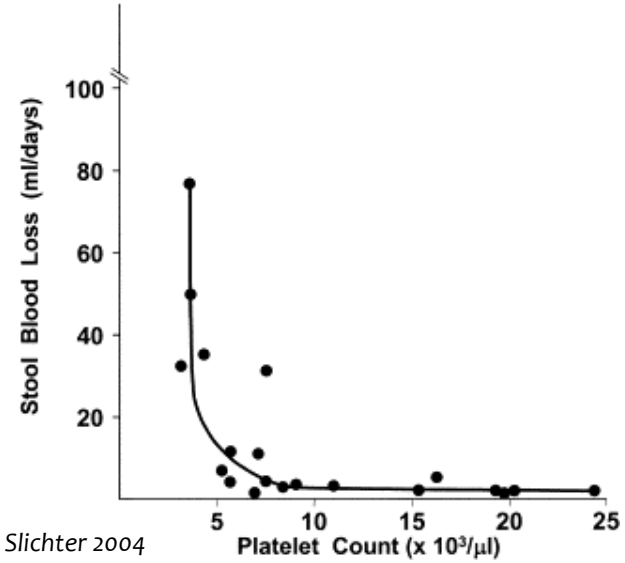


Platelet transfusion in patients with hematological malignancies

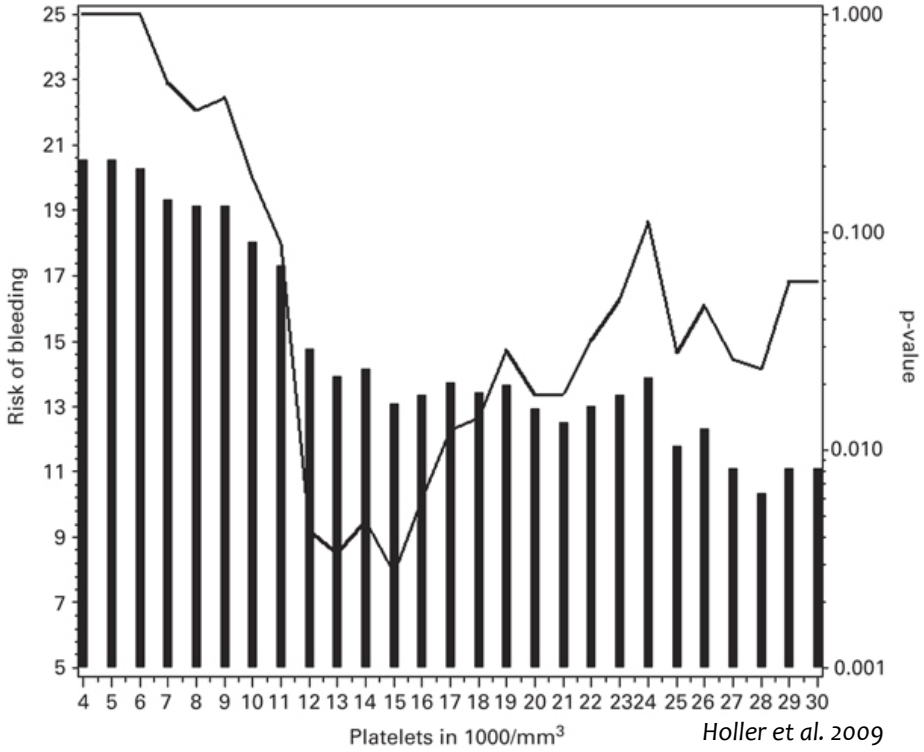


Relation of bleeding risk to blood platelet counts: computed per 1000 days at risk.

Gmur et al. 1991



Slichter 2004



Holler et al. 2009

Prophylactic platelet transfusion for haemorrhage after chemotherapy and stem cell transplantation (Review)

THE COCHRANE COLLABORATION®

<u>10 vs 20x10⁹/L:</u>

No statistically significant differences with regard to mortality and bleeding events

27-jägrige “Celebrity” mit tiefen Plättchen

27-jährige “Celebrity” mit erniedrigten Plättchen

Patientin wurde auf Grund eines “zufällig” entdeckten Plättchenwert von 65 G/L mit einer ITP diagnostiziert. Der Hämatologe hat Ihr geraten Ihren Lifestyle anzupassen und z.B. kein Fitness mehr zu machen, und auch auf Flugreisen zu verzichten. Die Patientin kommt nun für eine Zweitmeinung.

Anamnese

- ✓ Fühlt sich gut, so richtig im “Saft“
- ✓ „genießerischer“ Lebensstil
- ✓ Manchmal THC, selten MDMA
- ✓ Gelegentlich Gefühl der Erschöpfung
- ✓ Gelegentlich Hämatome

Persönliche Anamnese

- ✓ bland

Status

- ✓ bland

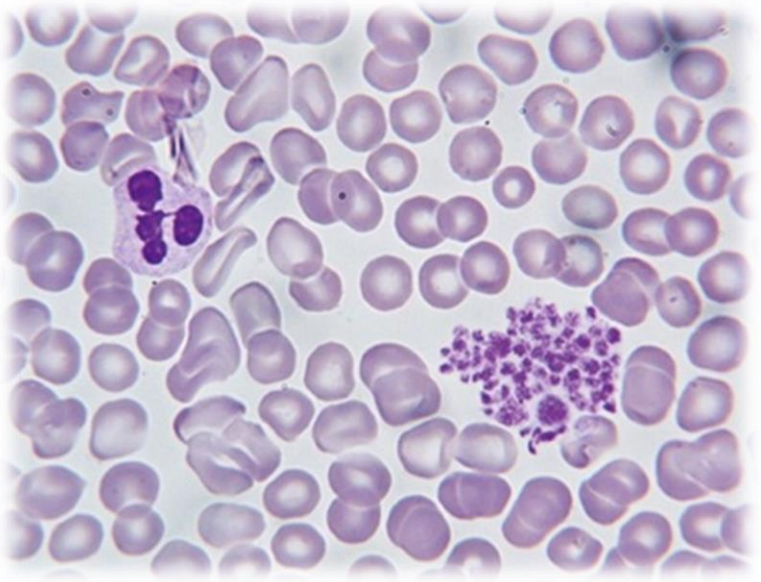
	EdTA
Hb	11.9 g/L
Lc	5.2 x10^9/L (norm. Diff)
Plts	80 x 10^9/L

https://imagebank.hematology.org/image/1825/pseudothrombocytopenia--4; https://imagebank.hematology.org/image/12960/pseudothrombocytopenia?

27-jährige “Celebrity” mit erniedrigten Plättchen

Bestätigen Sie die Diagnose
Machen Sie noch zusätzliche Diagnostik?
Welche Behandlung wählen Sie?

	EdTA
Hb	11.9 g/L
Lc	5.2 x10^9/L (norm. Diff)
Plts	80 x 10^9/L



Pseudothrombozytopenie
✓EdTA ex-vivo aggregation

https://imagebank.hematology.org/image/1825/pseudothrombocytopenia--4; https://imagebank.hematology.org/image/12960/pseudothrombocytopenia?

Pseudothrombozytopenie!

27-jährige Lehrerin mit Schwangerschaftswunsch

27-jährige Lehrerin mit Schwangerschaftswunsch

Anamnese
- ✓ Manchmal ein wenig müde
- ✓ Schwangerschaftswunsch

Persönliche Anamnese
- ✓ Appendektomie (mit 18 Jahren)

Status
- ✓ bland

\Medikamente
- ✓ Bis vor kurzem die Pille

Hb	8.5 g/L
Lc	5.2 x10^9/L (norm. Diff)
Plts	70x10^9/L

Ihre Diagnose?
Welche Diagnostik veranlassen Sie?
Starten Sie eine Behandlung?

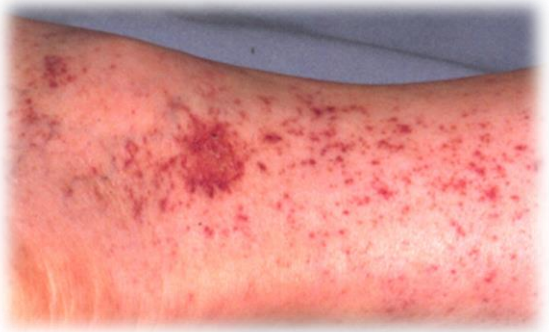
Verdacht auf milde ITP
Zuweisung Hämatologie

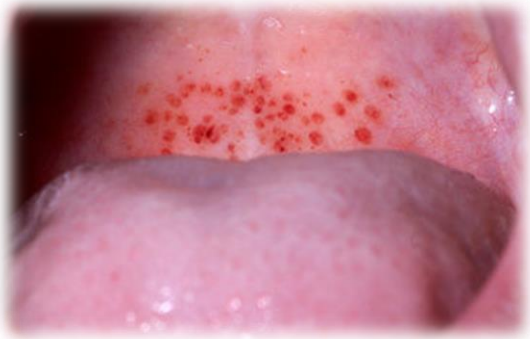
Leichte Thrombozytopenie
Immunthrombozytopenie

27-jährige Lehrerin mit Petechien und Dysarthrie

27-jährige Lehrerin mit Petechien und Dysarthrie

Anamnese
- ✓ Seit Wochen erschöpft
- ✓ Seit 2 Tagen Petechien Unterschenkel/Fussrücken
- ✓ Letzte Woche 3 Episoden mit verwaschener Sprache
- ✓ Transiente Schwäche linker Arm





Persönliche Anamnese
- ✓ 2 komplikationslose Schwangerschaften
- ✓ Appendektomie im Alter von 18 Jahren

Hb	**4.8 g/L**
Lc	**5.2 x10^9/L (norm. Diff)**
Plts	**<10 x10^9/L**

Status
- ✓ Petechien Unterschenkel/Fuss und Mund
- ✓ "Zungenschlag"
- ✓ Ikterus

- ➢ **Thrombozytopenie**
- ➢ **Blutung? TEE?**
- ➢ **Hämolyse?**

Ihre Diagnose?
Zusätzliche Diagnostik?
Behandlung?

27-jährige Lehrerin mit Petechien und Dysarthrie

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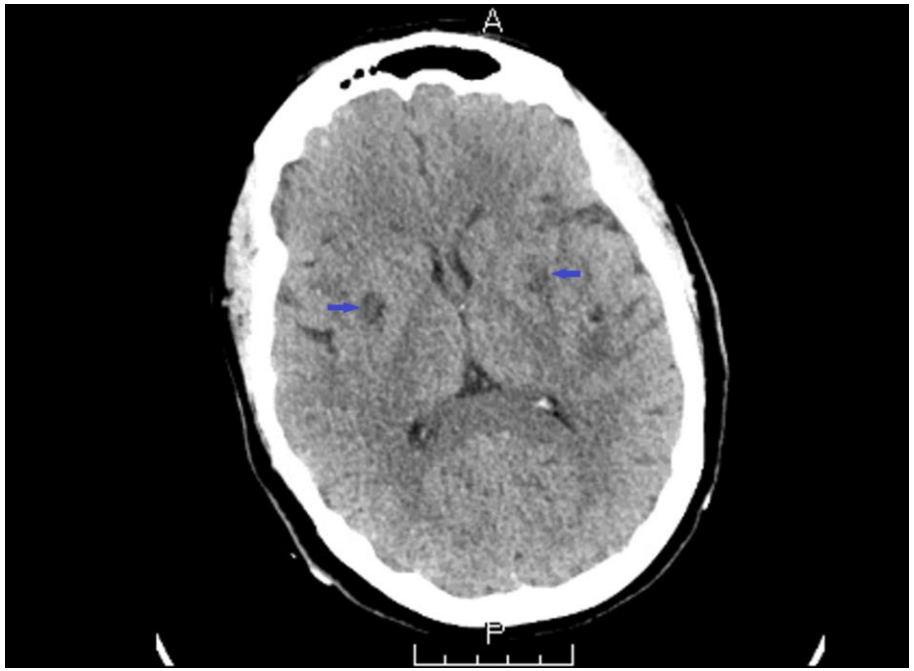
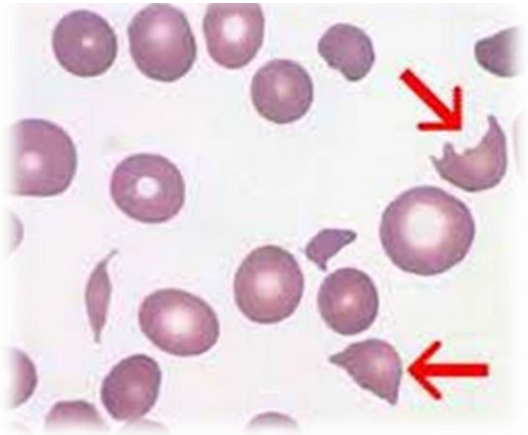


https://www.cureus.com/articles/11509-a-case-report-on-refractory-moschcowitz-syndrome



Coombs-neg. hämolytische Anämie + Thrombozyten + Fragmentozyten

Thrombotische Mikroangiopathiey TTP-HUS

Thrombotic microangiopathy – an emergency?

Hb	4.8 G/L
Lc	5.2 x10^9/L (norm. Diff)
Plts	<10 x10^9/L
Reti	3.5%
Creat	85 umol/L
LDH	690 U/L
Bilirubine total	88 umol/L
haptoglobine	<0.02 g/L
DAT	negative

Coombs-negative hemolytic anemia + thrombocytopenia + schistiocytosis

TMA

Without treatment >90% mortality!!!

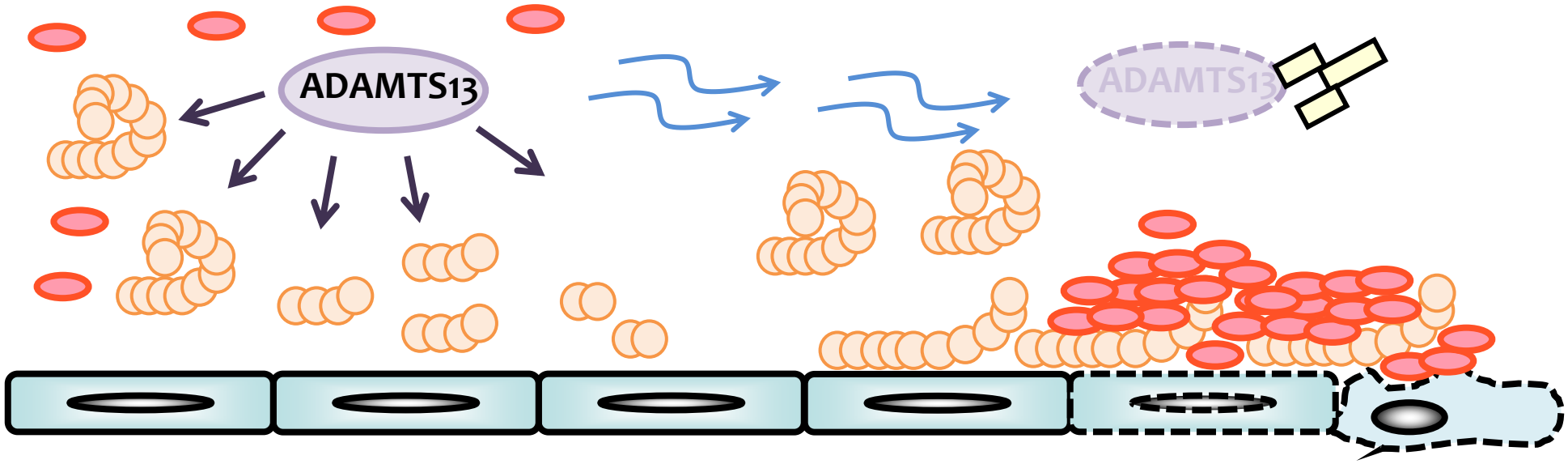
Draw samples for diagnostics (e.g. ADAMTS13)

Start plasmapheresis ASAP

Kremer Hovinga et al. Nat Rev Dis Primers 2017

Thrombotic microangiopathy TTP/HUS

ADAMTS13: **A D**isintegrin-like **A**nd **M**etalloprotease with **T**hrombo**S**pondin type 1 repeats



ADAMTS13 act: <5%
- ***Congenital***
- ***autoantibodies***

2nd hit
- **Infection**
- ***Pregnancy***
- **……**

TTP

Adapted from Kremer Hovinga et al. Nat Rev Dis Primers 2017

Thrombotic microangiopathy TTP/HUS

TTP

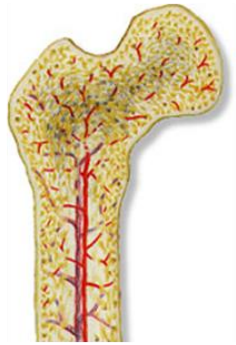
aHUS

- ✓ **Classical TTP:** ADAMTS13 activity <5% (acquired vs congenital)
- ✓ Pregnancy associated TTP
- ✓ **Drug-associated:** - ADP-antagonists (ticlopindine, clopidogrel)
  - immunosuppressives (cyclosporine, tacrolimus)
  - varia (TMP, simvastatin, peg IFN-γ)
- ✓ HIV infection
- ✓ Allogeneic HSCT (TMA)
- ✓ (catastrophic) APS
- ✓ Malignancy-associated TMA
- ✓ **Diarrhea-associated HUS** (EHEC or Shiga-toxin producing shigella spp)
- ✓ **aHUS:** - acquired (pneumococci)
  - congenital (functional mutations in complement (regulatory proteins)

Thrombotische Mikroangiopathie

Take home message

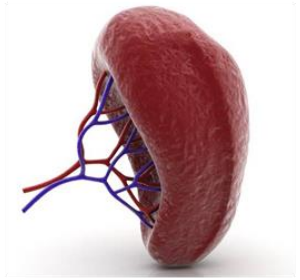
Take home message



production

Decreased production
- ✓ Radiation
- ✓ Chemotherapy
- ✓ Displacement (AML, lymphoma)
- ✓ Myelopthysis
- ✓ Infection
- ✓ Liver disease

Platelet pool



Sequestration
- ✓ Hypersplenism
- ✓ Aneurism
- ✓ haemangioma

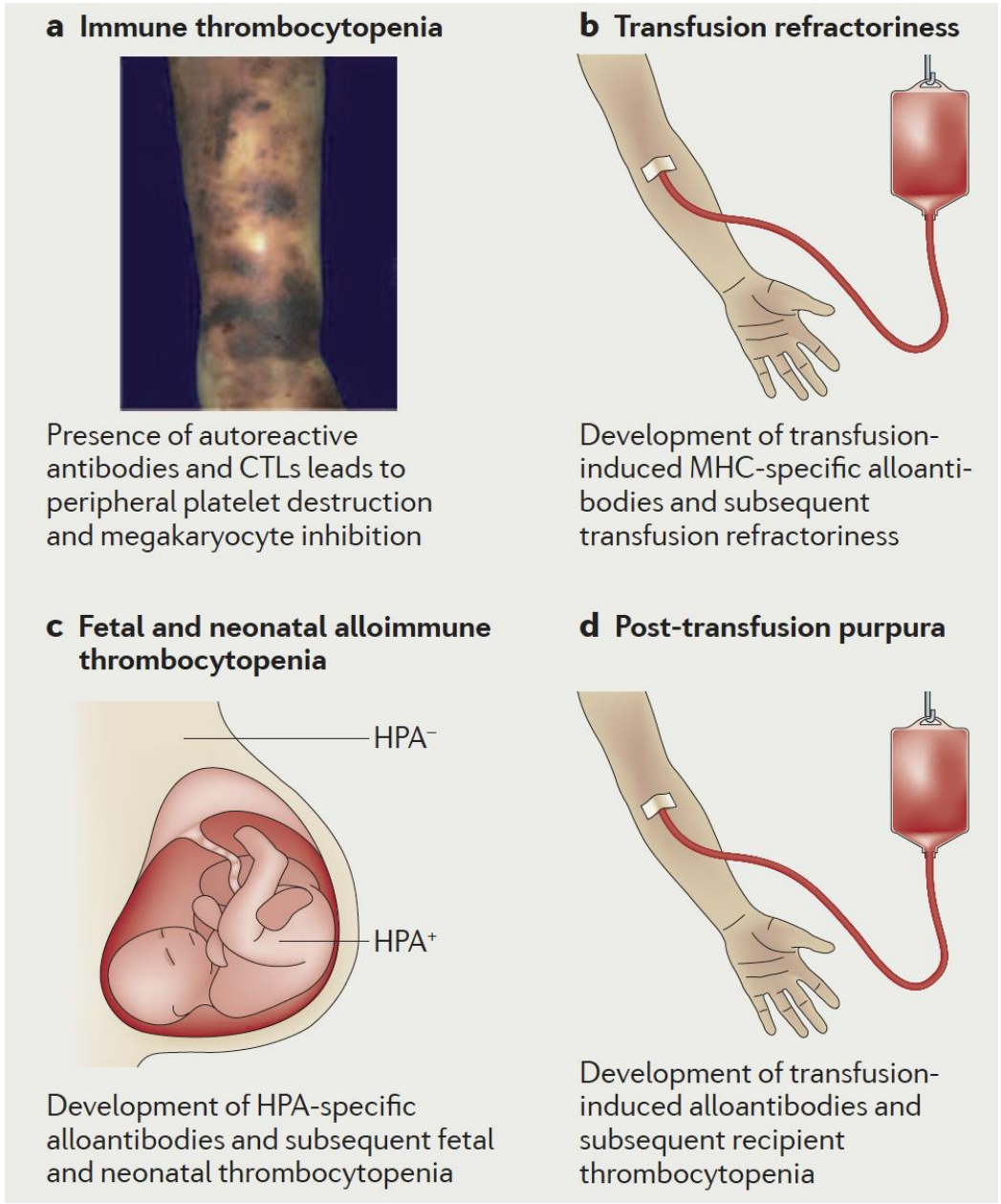
consumption

Immunological destruction
- ✓ Heparin-induced thrombocytopenia (HIT)
- ✓ immune thrombocytopenia (ITP)
- ✓ Allo-antibodies to platelet antigens
- ✓ Posttransfusion purpura (PTP)
- ✓ drugs

Consumption
- ✓ Major bleeding
- ✓ Extenisve thrombosis (PE)
- ✓ Disseminated intravascular coagulation (DIC)
- ✓ Infection (e.g. severe sepsis, malaria, Dengue)
- ✓ Thrombotic microangiopathy (TTP-HUS, HELLP)
- ✓ Extracorporal-/intravascular device

Thrombocytopenia requires further diagnostics
Severe thrombocytopenia is an emergency

Immune thrombocytopenia (ITP)



Semple et al. Nat Rev Immunol. 2011

consumption

Immunological destruction

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ITP diagnosis and management – ASH guidelines 2019

CLINICAL GUIDELINES

blood advances

American Society of Hematology 2019 guidelines for immune thrombocytopenia

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Background: Despite an increase in the number of therapies available to treat patients with immune thrombocytopenia (ITP), there are minimal data from randomized trials to assist physicians with the management of patients.

Objective: These evidence-based guidelines of the American Society of Hematology (ASH) are intended to support patients, clinicians, and other health care professionals in their decisions about the management of ITP.

Methods: In 2015, ASH formed a multidisciplinary guideline panel that included 8 adult clinical experts, 5 pediatric clinical experts, 2 methodologists with expertise in ITP, and 2 patient representatives. The panel was balanced to minimize potential bias from conflicts of interest. The panel reviewed the ASH 2011 guideline recommendations and prioritized questions. The panel used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, including evidence-to-decision frameworks, to appraise evidence (up to May 2017) and formulate recommendations.

Results: The panel agreed on 21 recommendations covering management of ITP in adults and children with newly diagnosed, persistent, and chronic disease refractory to first-line therapy who have non–life-threatening bleeding. Management approaches included: observation, corticosteroids, IV immunoglobulin, anti-D immunoglobulin, rituximab, splenectomy, and thrombopoietin receptor agonists.

Conclusions: There was a lack of evidence to support strong recommendations for various management approaches. In general, strategies that avoided medication side effects were favored. A large focus was placed on shared decision-making, especially with regard to second-line therapy. Future research should apply standard corticosteroid-dosing regimens, report patient-reported outcomes, and include cost-analysis evaluations.

Summary of recommendations

Background

These guidelines are based on updated and original systematic reviews of evidence conducted under the direction of the University of Oklahoma Health Sciences Center (OUHSC). The guideline panel followed best practice for guideline development recommended by the Institute of Medicine and the Guidelines International Network (GIN).[1-4] The panel used the Grading of Recommendations

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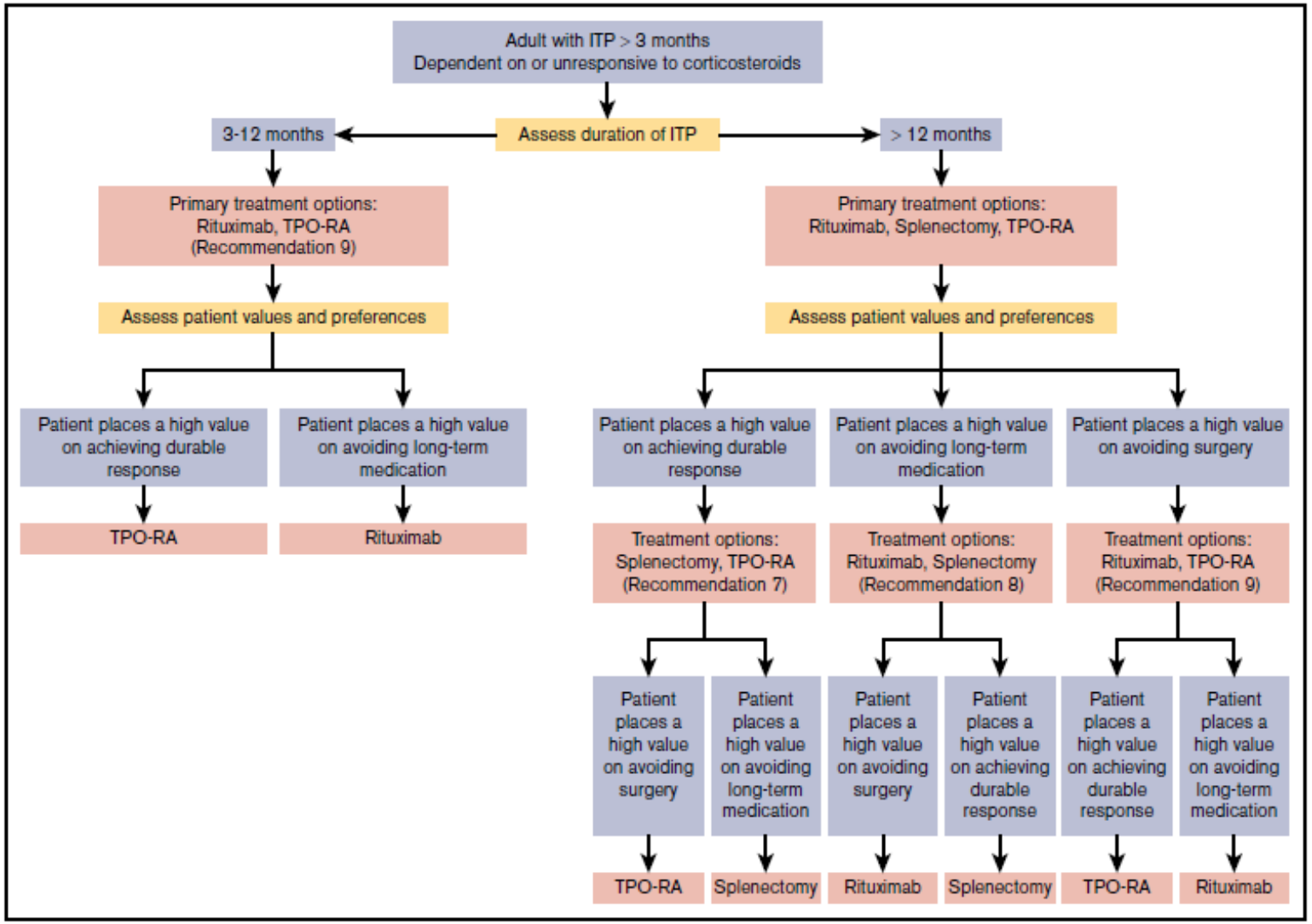
The full-text version of this article contains a data supplement.



Neunert et al. Blood Adv 2019