Hematology/Oncology Emergencies

Dr. Gwynivere Davies
MD FRCPC (Hematology)
Apr 2019 Spring School

Disclosure Slide

Speaker: Dr. Gwyn Davies

Relationships with commercial interests:

- Grants/Research Support: Novartis, Teva
- Speakers Bureau/Honoraria: None to declare
- Consulting Fees: None to declare
- Other: None to declare

Topics/Objectives

Learn how to handle a new acute leukemic

Develop an approach to febrile neutropenia

Differentiate between causes of severe thrombocytopenia

Immune mediated pneumonitis: recognize it and management

Review TBRHSc hematology referral service

Case 1: Mr. AL

51M with right 4th finger cellulitis, pain

ER gets baseline labs, starts him on IV antibiotics and D/C

Hgb 93, WBC 8.0, platelets 1066, lytes/BUN/creat N

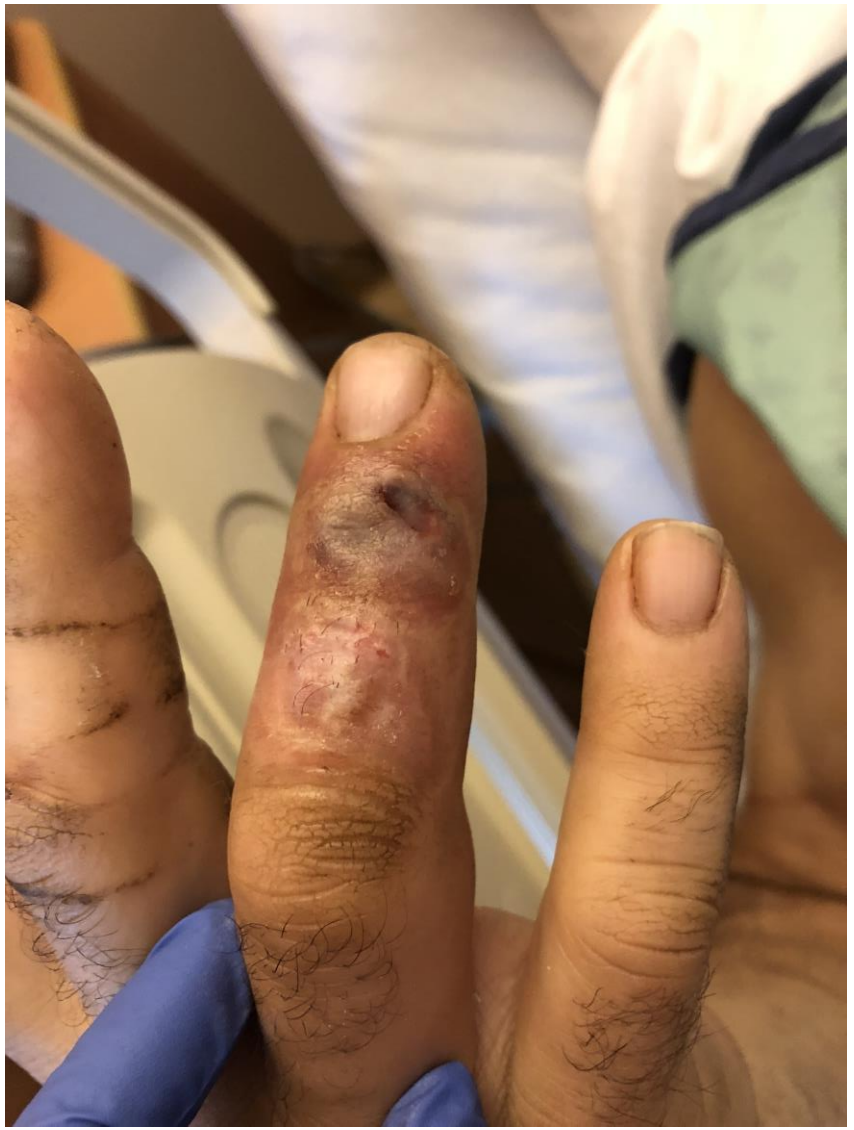
Thoughts?

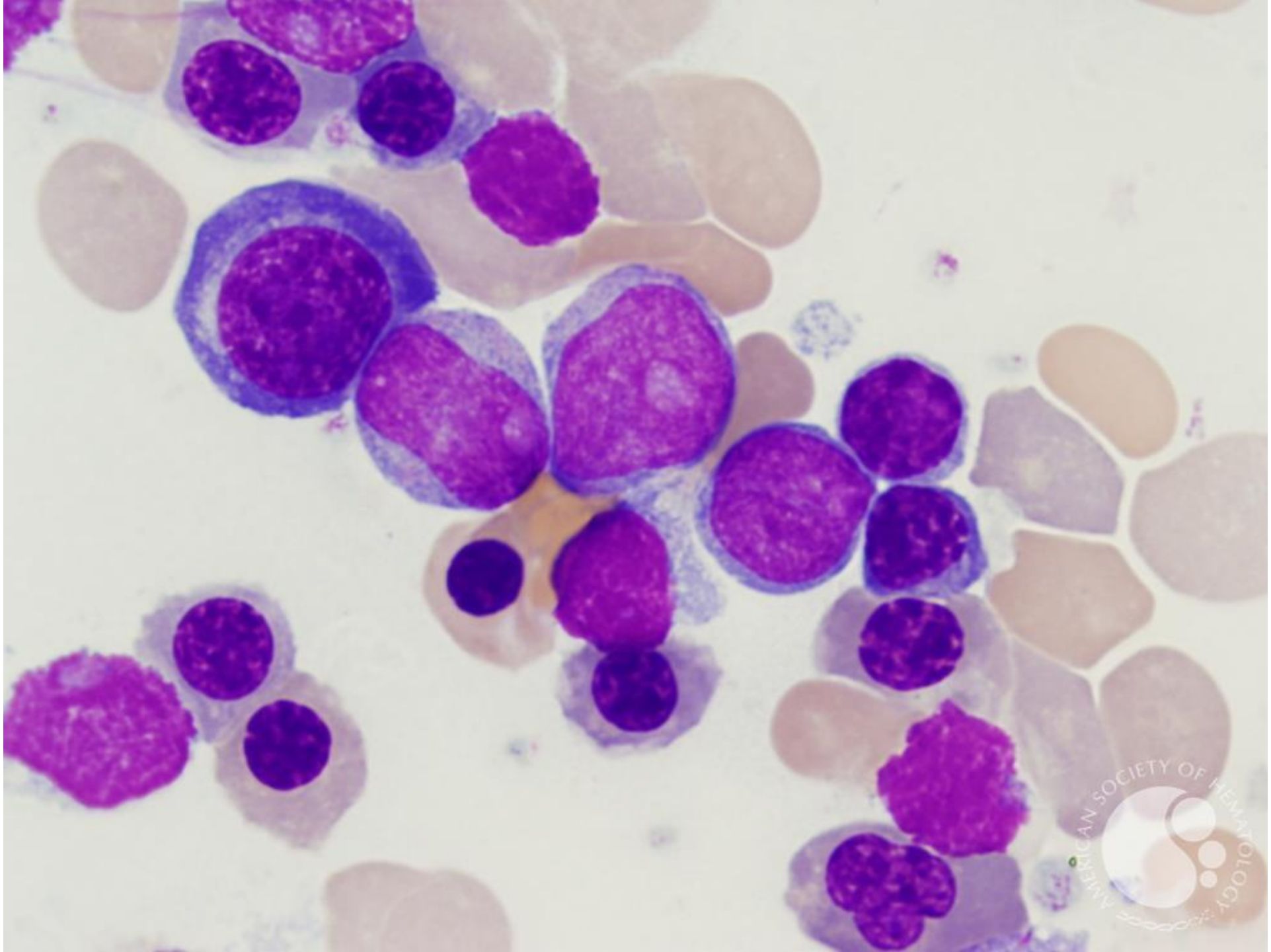
His differential comes back

Neutrophils 0.08, lymphocytes 1.60, blasts 5.52

They ask him to come back and do cultures, start him on piperacillin-tazobactam

What next?





ASH Image Bank.

Acute Leukemia

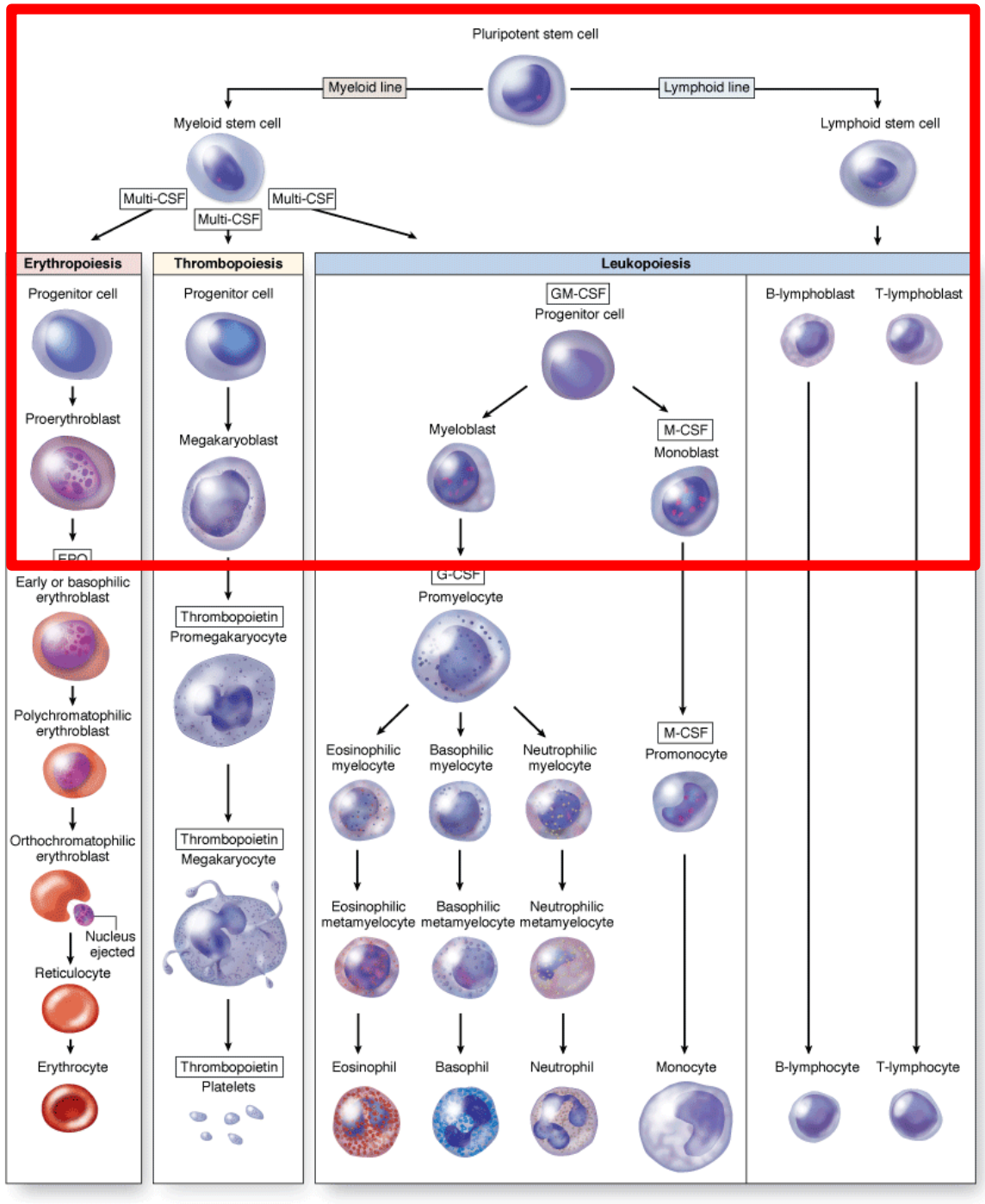
≥20% blasts in blood or bone marrow

Two main types:

- Acute myeloid leukemia (AML)
- Acute lymphoblastic leukemia (ALL)

Can be:

- de novo
- From prior disease (ie. MPN)
- From prior therapy (ie. chemotherapy, radiation)
- Genetic (ie. AML in Down's syndrome)

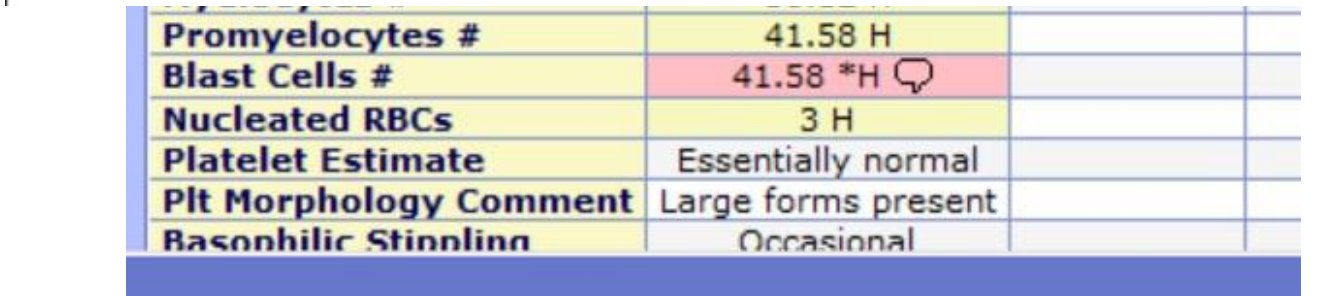


≥20% blasts?

- Manual blast count
  - CBCs are automated, so there will be issues with the Coulter counter reading the smear
  - Manual smear is read by techs, and reviewed by pathologist
- Flow cytometry
  - Detects proteins on the surface of cells
  - Like a unique fingerprint, detect if cells are clonal and type

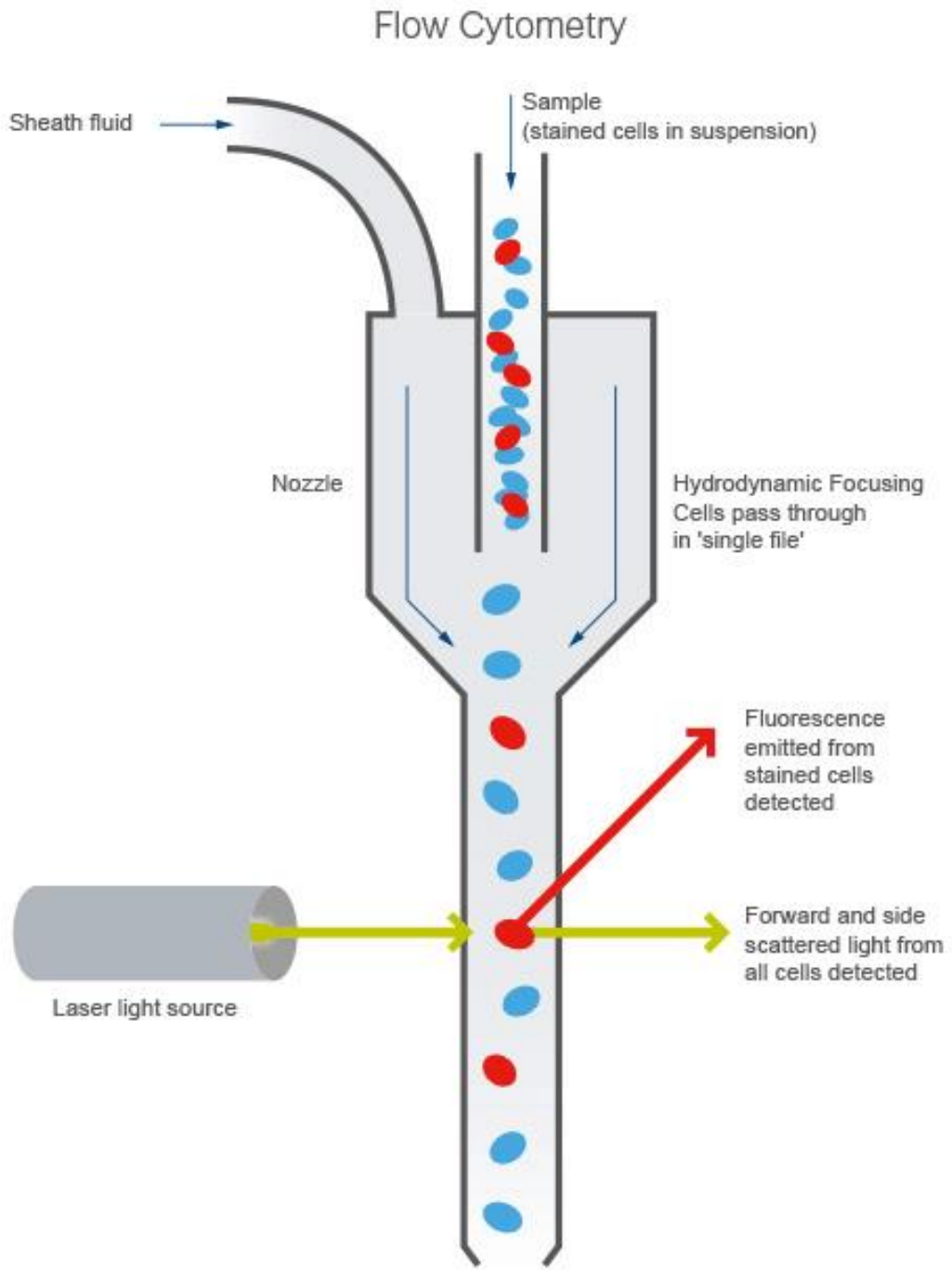
	26/11/17 12:23	26/11/17 15:45
WBC	346.5 *H	349.0 *H
RBC	2.00 L	2.16 L
Hgb	57 *L	62 L
Hct	0.18 L	0.19 L
MCV	90	88
MCH	28.7	28.8
MCHC	319 L	326

Result Comment:
INTERPRETATION-Marked leukocytosis with left shift, myelocyte bulge and basophilia most consistent with chronic myeloid leukemia (CML)-molecular confirmation required.
RED BLOOD CELLS-Normocytic anemia with 2+ anisocytosis and 2+ spherocytes
WHITE BLOOD CELLS-Marked leukocytosis with left shift, myelocyte bulge and basophilia, blasts 4%, no significant dysplasia. Auer rods not seen.
PLATELETS-Platelets normal in number and morphology.
BACKGROUND-Unremarkable.
Dr.M.Kennedy,MD,FRCP(C) November 27, 2017

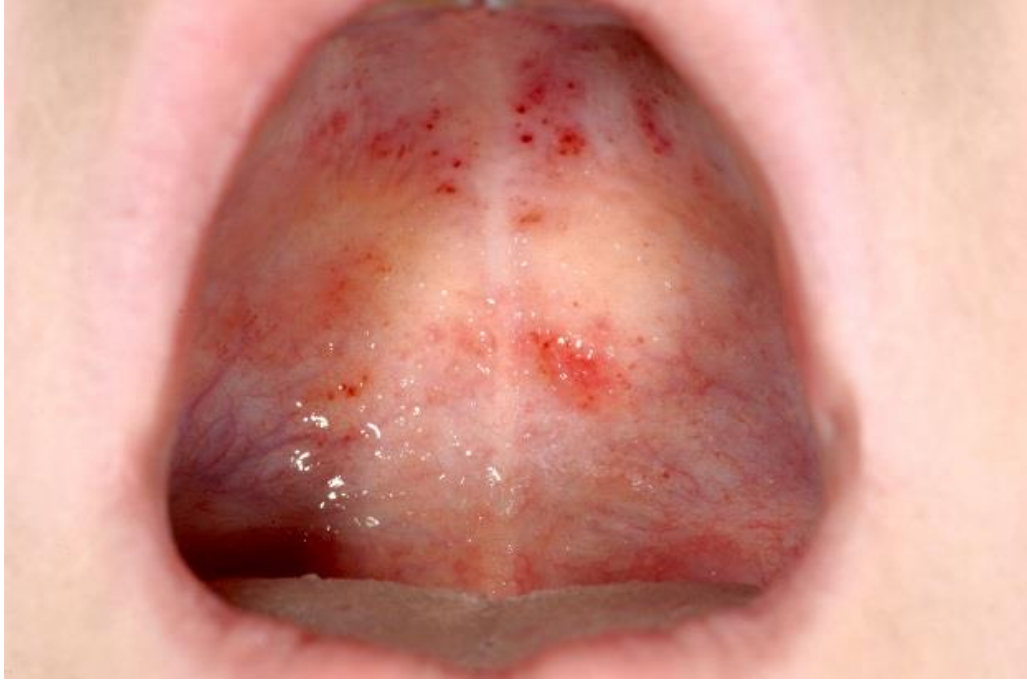


Promyelocytes #	41.58 H	
Blast Cells #	41.58 *H	
Nucleated RBCs	3 H	
Platelet Estimate	Essentially normal	
Plt Morphology Comment	Large forms present	
Basophilic Stippling	Occasional	

Flow cytometry: only for blasts and lymphocytosis



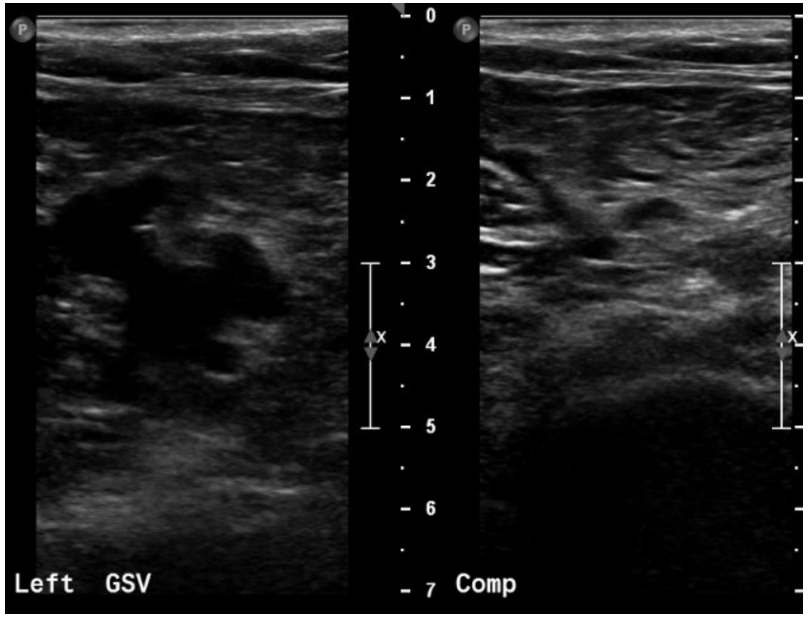
Don’t Panic!

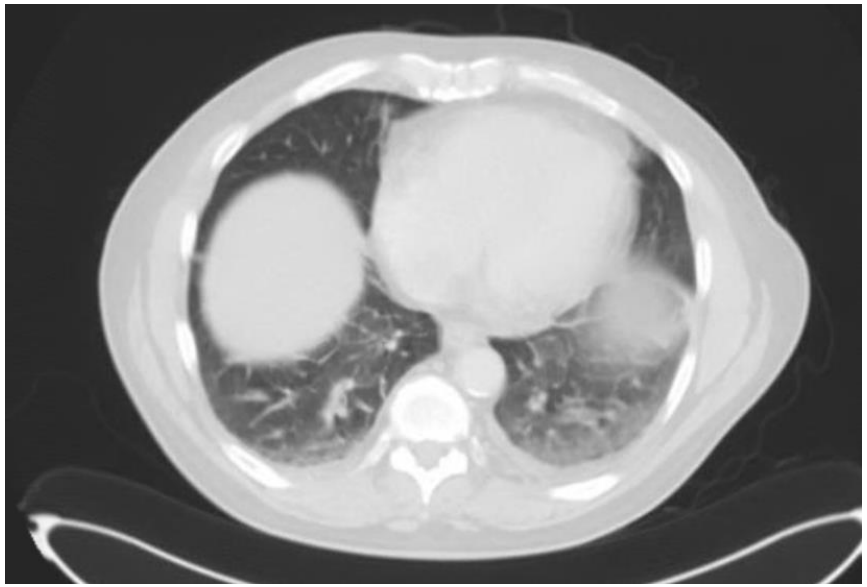


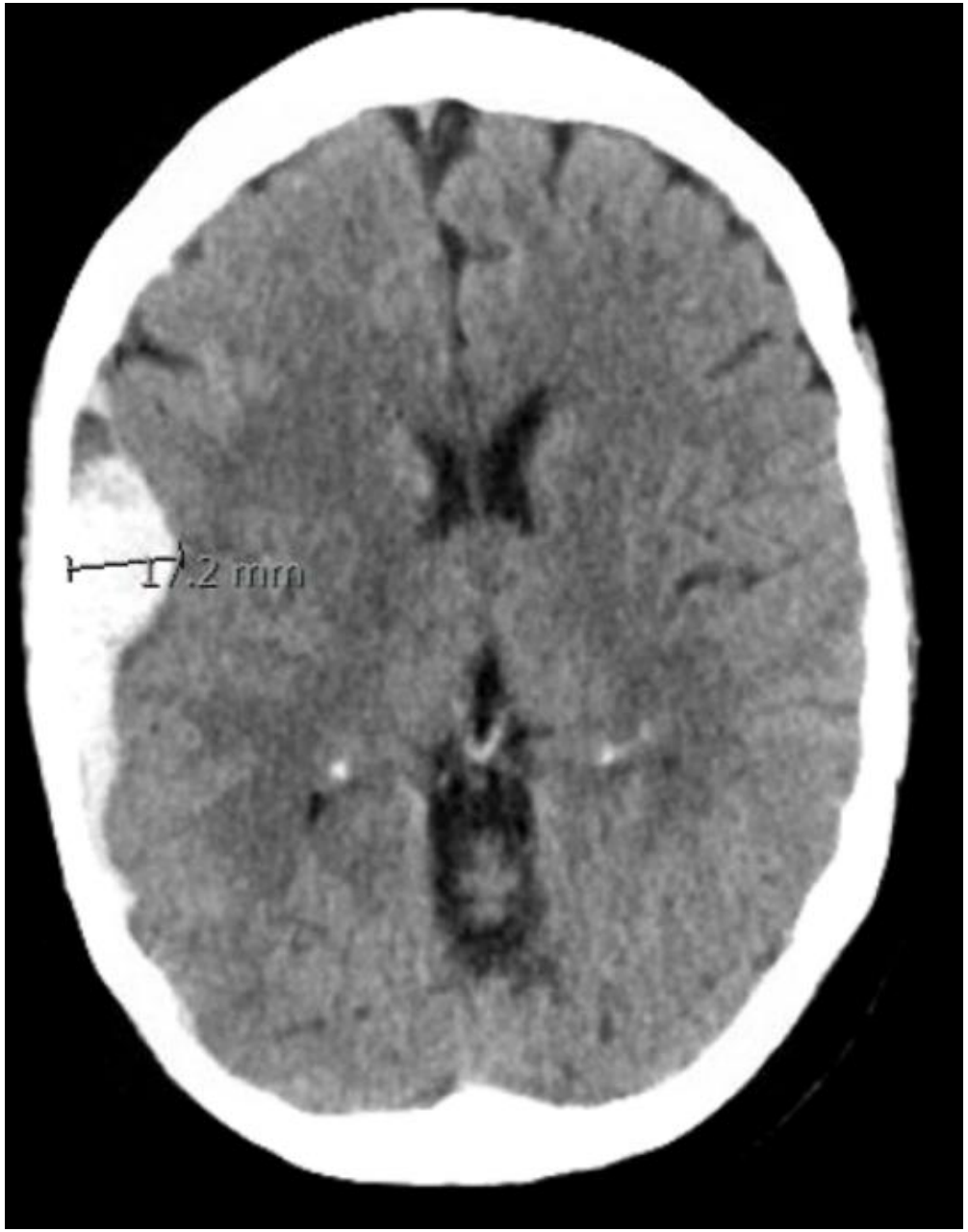
Head-to-toe survey

- Vitals: febrile, BP (infection, bleeding), O2
- Mouth: ulcers, thrush, wet purpura, gingival hyperplasia
- Lymphadenopathy: more common in ALL
- CV/Respiratory: flow murmur from anemia, respiratory infection
- Abdomen: splenomegaly
- Bleeding: CNS, ophthalmic, GI, GU, mucosal membranes, lines, etc.
- Misc: derm (leukemia cutis, cellulitis), neurologic (headache, bleed, infection), peripheries (DVT, edema), etc.

Labs: CBC, INR/PTT/fibrinogen, PB smear, lytes/BUN/creat/LDH/LETs/ext lytes/uric acid


Left GSV
Comp




7.2 mm

Acute Myeloid Leukemia (AML)

More common in adults

Certain types associated with coagulopathies

- Acute promyelocytic leukemia (APL) has the best prognosis, but 80% have some degree of DIC at diagnosis, and 30% early mortality

Lower blast counts cause more problems than in ALL

- Hyperleukocytosis at WBC 100, rather than around 400 in ALL

Initial Management

Transfusions: keep Hgb ≥70 g/L, plt ≥ 10 (≥ 20 if febrile)

- High risk for clots even with thrombocytopenia (most centres only hold DVTp with platelets <30)
- If WBC >100 and risk for hyperleukocytosis, be VERY judicious with transfusions
- Different transfusion parameters if active DIC

Assess for tumor lysis syndrome (discussed later)

Early investigation of infections, early broad spectrum antibiotics

- If mold exposures, fungal risk: consider caspofungin, voriconazole, posaconazole

Initial Management: hematologic agents

Hydroxyurea

- Slows down the bone marrow, and can prevent adverse outcomes from high WBC but does not cure acute leukemia
- Main adverse event (AE) is nausea, can worsen other cytopenias

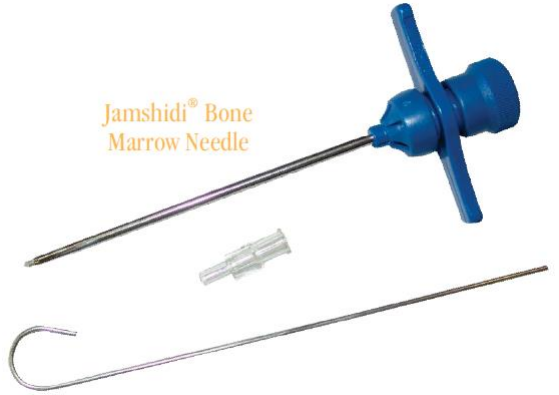
Grastofil (generic neupogen): 300 or 480 mcg sc daily

- No mortality benefit and risk of stimulating blasts in AML
- Last ditch Hail Mary if in ICU

Tranexamic acid: 1.5 g IV/po tid or 1 g IV/po qid or infusion (if VERY bad bleeding)

- If epistaxis, can squirt 500 mg on 2x2 and stick up their nose
- If you don’t have platelets, this is your next best option for bleeding

What am I going to offer?



AML:

- Young, fit: 7+3 IV chemotherapy
  - In the hospital for a month minimum while we wait for counts to recover, then do a bone marrow to assess for remission (then there is more chemotherapy or transplant)
- Elderly: azacitidine (outpatient chemotherapy sc 7 days per month), non curative
- Transfusions and supportive care

ALL:

- Young, fit: induction chemotherapy (IV, oral, ++LPs with intrathecal chemotherapy)
  - Protocol is >2 years long (and if cannot tolerate, then consider transplant)
- Transfusions and supportive care, limited non-curative chemotherapy

Back to Mr. AL

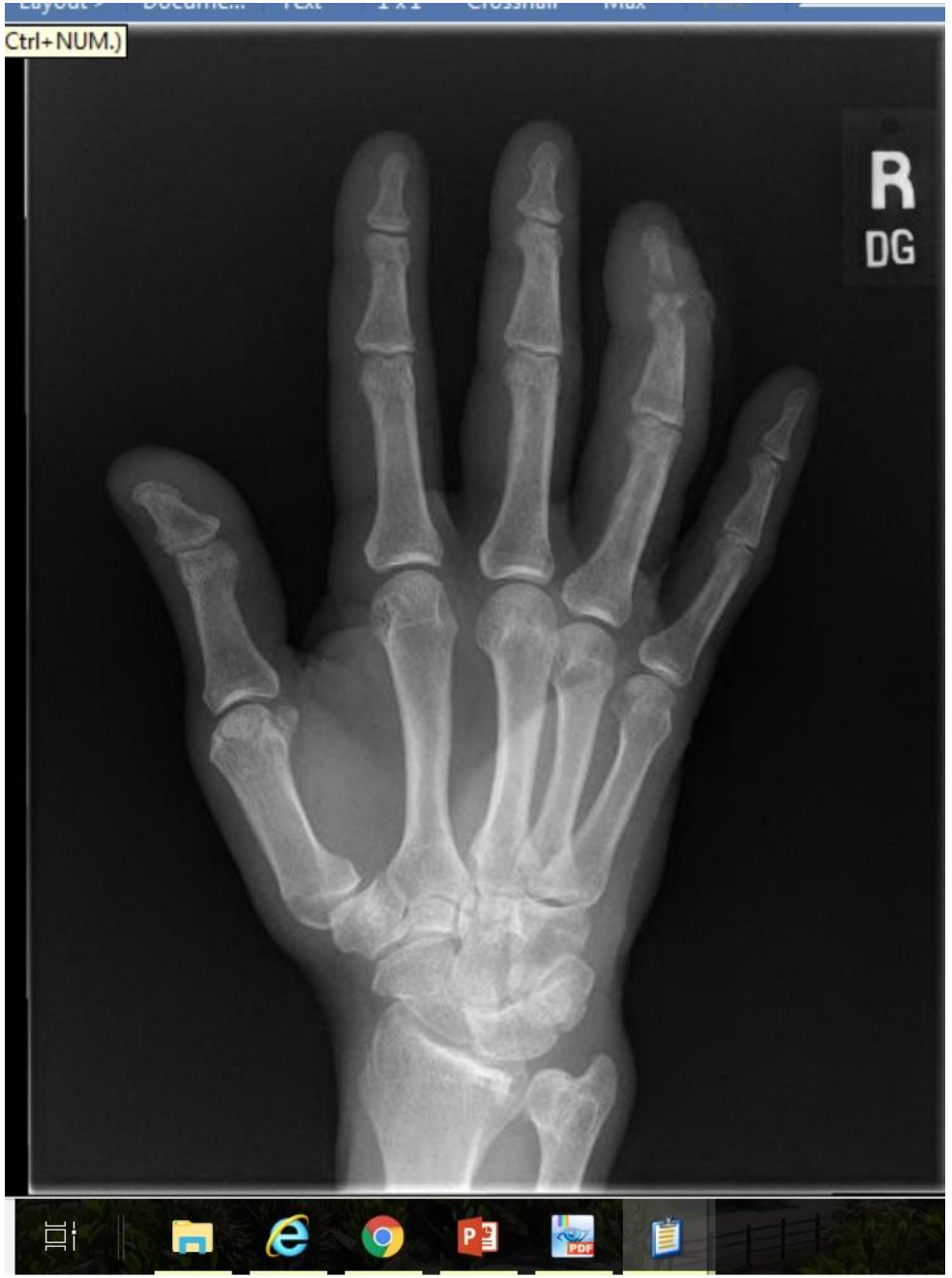
On piperacillin-tazobactam, remains febrile

CRP 204, ESR 119, blood culture/wound culture: Pseudomonas

What do you do?

Repeat Xray:

- Focal lucency and soft tissue swelling are seen at the base of the distal thorax of the 4th digit.
- Lytic cortical changes seen, ?osteomyelitis. No other focal osseous lesions or fractures



Febrile Neutropenia

What is febrile neutropenia?

Fever:

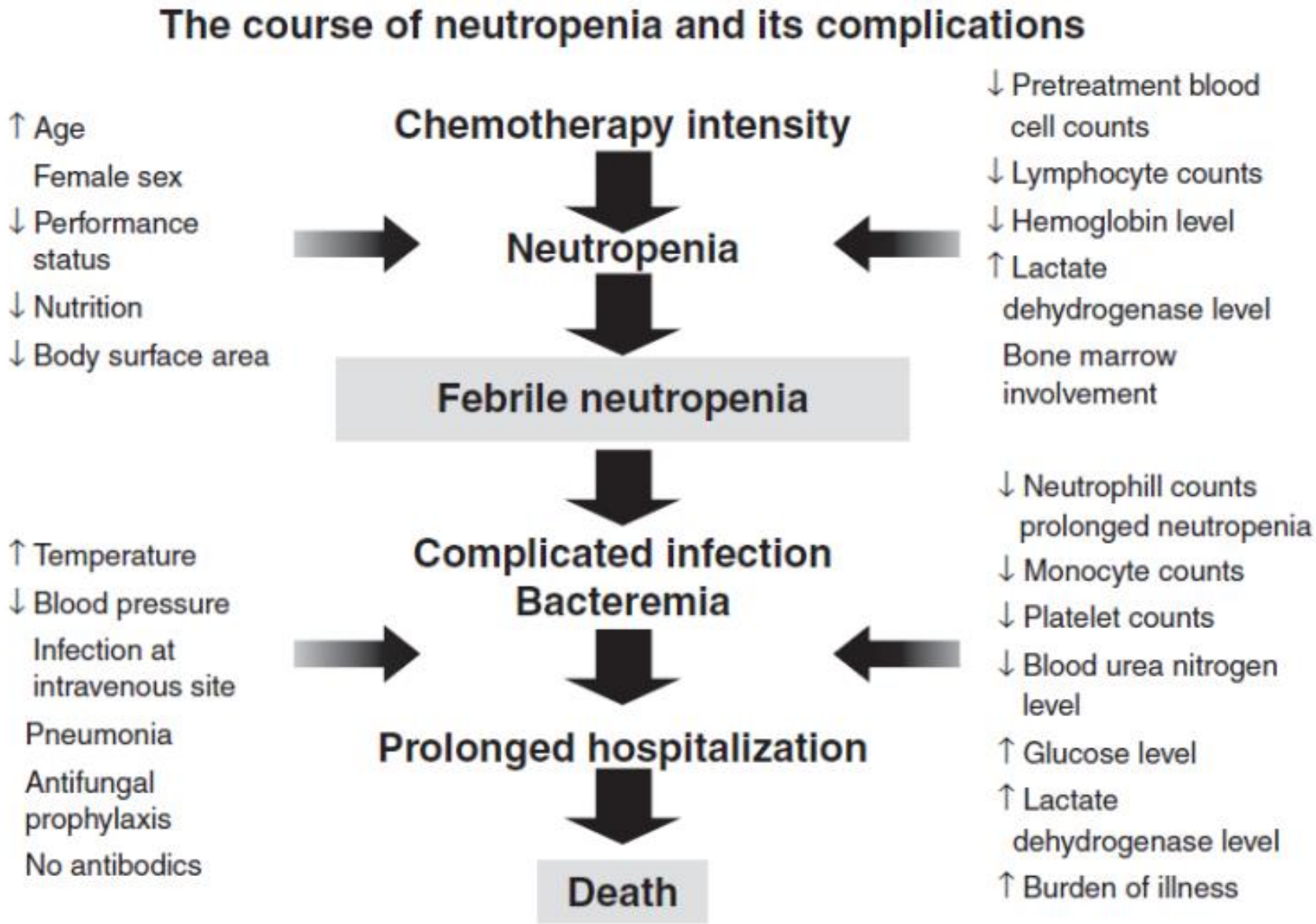
- Single oral temperature ≥38.3ºC OR
- Oral temperature ≥38.0ºC sustained over 1 (to 2) hr

Neutropenia

- Absolute neutrophil count (ANC) of <500 cells/mm^3 (=0.5 x 10^9/L) OR
- ANC expected to fall to <500 cells/mm^3 within 48 hrs
- ANC = (segmented neutrophils x 10^9/L)+(bands x 10^9/L)

Anyone can become neutropenic!

ESMO Febrile Neutropenia Guidelines, 2016. Ann Oncol.



Expert Opin Pharmacother 2011;12:851-63

Febrile Neutropenia

8 cases/1000 patients receiving chemotherapy (higher risk with heme malignancy)

20-30% require in hospital management, in hospital mortality 10%

Common:

Gram negative/positive bacteremia, pneumonia, typhilitis/enterocolitis

Mortality: 18% GN bacteremia, 5% GP bacteremia

ESMO Febrile Neutropenia Guidelines, 2016. Ann Oncol.

Febrile Neutropenia

Supportive care, early initiation of broad spectrum antibiotics

Consider previous bugs and hospital antibiograms (MDR organisms)

Drugs:

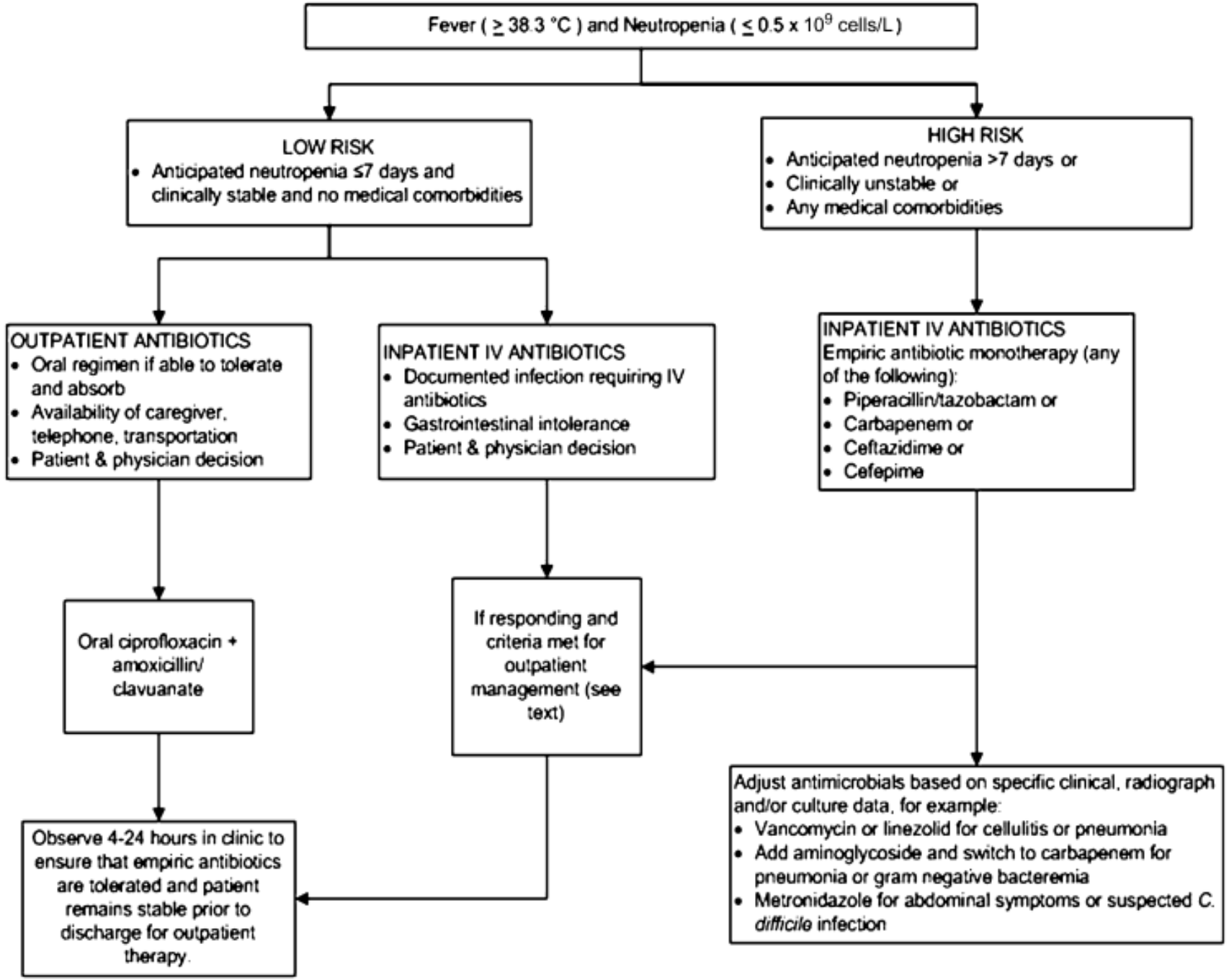
- Anti-pseudomonal monotherapy (pip-tazo on our protocol)
- Vancomycin for GP: instability, pneumonia, persistent + BC for GP, SSTI infection, MRSA
- Anti-fungals if 3-7 days without response, antivirals if mucositis or HSV infection

Measure difference in time to positivity

- If 2+ hr faster from line, it's the line!

Remove line if: tunnel infection, pocket infection, persistent bacteremia, mycobacteria and candidemia (IDSA: also if S. aureus or Pseudomonas infections)

ESMO Febrile Neutropenia Guidelines, 2016. Ann Oncol.



IDSA 2012 Guidelines.

Grastofil?

Works synergistically with bone marrow (if given with chemo)

Recommended if risk of FN >20% for all planned cycles of treatment
    50% effective at reducing FN episodes

Secondary prophylaxis: given after 1st episode of FN

Dosing: 5 ug/kg/day, usually 24-72 hr after chemo
    300 mcg and 480 mcg syringes

Expensive and no overall survival benefit

AEs: fever, bone pain, increased ALP/LDH, N/V, splenic rupture

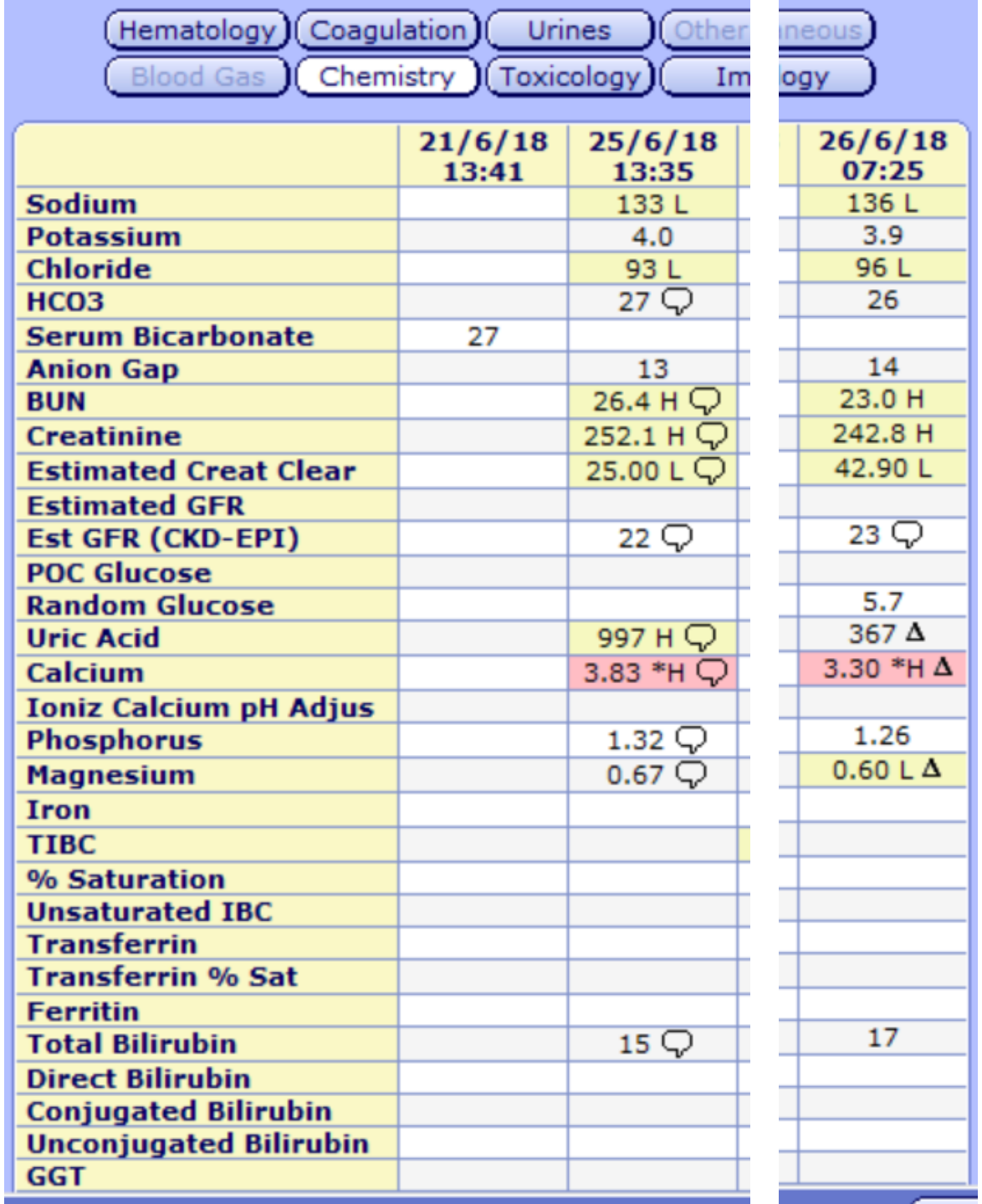
Case 2: Mr. IR

67M presents with 20 lb weight loss, drenching sweats, abdominal pain

CT shows diffuse lymphadenopathy, concern for malignancy

You get his initial labs back

What's going on?



Hematology | Coagulation | Urines | Other | neous
Blood Gas | Chemistry | Toxicology | Im | logy

	21/6/18 13:41	25/6/18 13:35	26/6/18 07:25
Sodium		133 L	136 L
Potassium		4.0	3.9
Chloride		93 L	96 L
HCO3		27	26
Serum Bicarbonate	27		
Anion Gap		13	14
BUN		26.4 H	23.0 H
Creatinine		252.1 H	242.8 H
Estimated Creat Clear		25.00 L	42.90 L
Estimated GFR			
Est GFR (CKD-EPI)		22	23
POC Glucose			
Random Glucose			5.7
Uric Acid		997 H	367 Δ
Calcium		3.83 *H	3.30 *H Δ
Ioniz Calcium pH Adjus			
Phosphorus		1.32	1.26
Magnesium		0.67	0.60 L Δ
Iron			
TIBC			
% Saturation			
Unsaturated IBC			
Transferrin			
Transferrin % Sat			
Ferritin			
Total Bilirubin		15	17
Direct Bilirubin			
Conjugated Bilirubin			
Unconjugated Bilirubin			
GGT			

Tumor Lysis Syndrome (TLS)

Mainly occurs with:

- Initiation of chemotherapy in patients with bulky disease
- Aggressive lymphomas: Burkitt or lymphoblastic lymphoma
- AML/ALL with high WBC

Can occur spontaneously as tumors outgrow their vascular supply and undergo necrosis

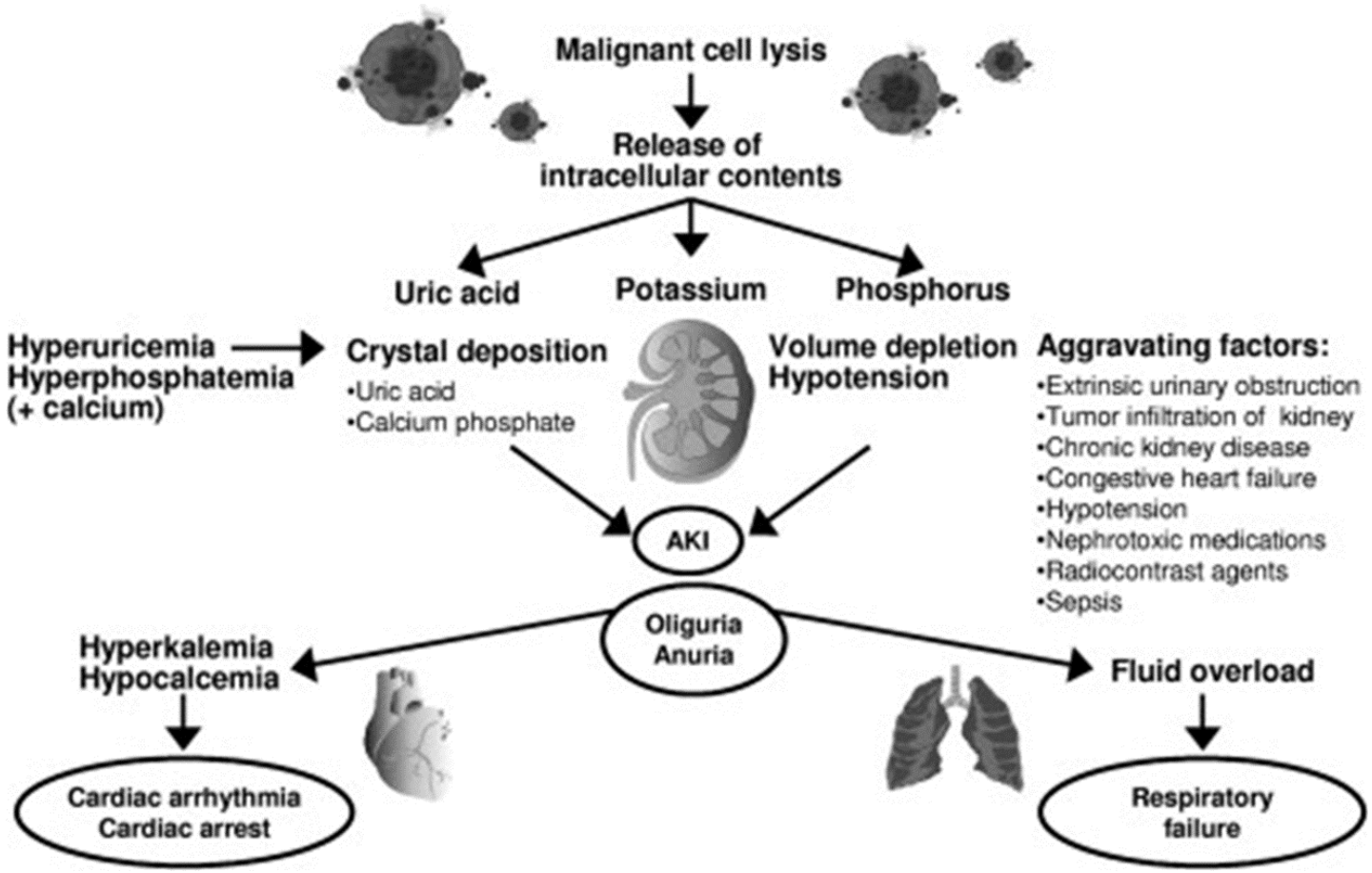
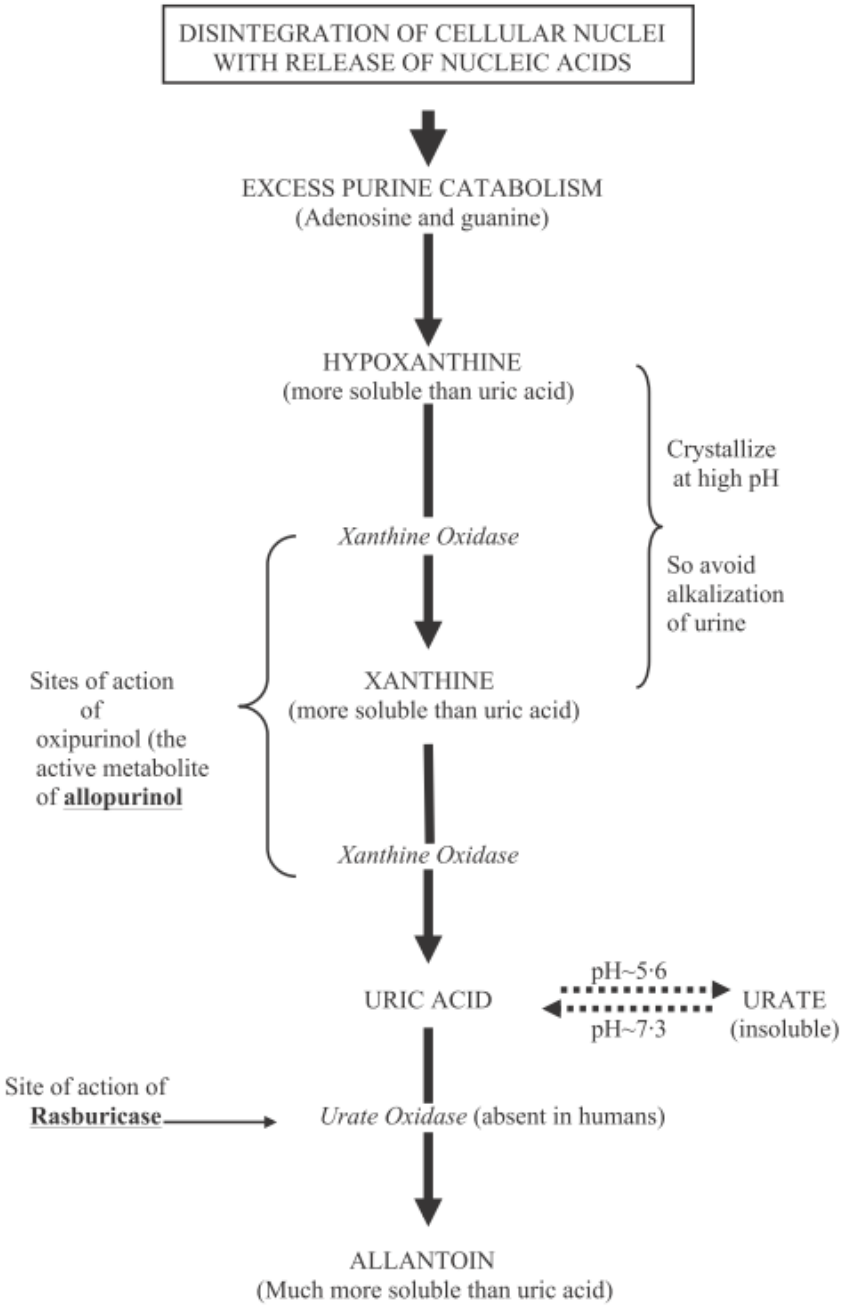


Table I. Definition of tumour lysis syndrome according to Cairo and Bishop (2004). Reproduced with permission from Cairo, M.S., & Bishop M. Tumour lysis syndrome: new therapeutic strategies and classification. *British Journal Haematology*, **127**(1):3–11 © 2004 John Wiley and Sons Inc.

Laboratory tumour lysis syndrome
The presence of two or more of the following abnormalities in a patient with cancer or undergoing treatment for cancer within 3 days prior to and up to 7 days after initiation of treatment
Uric acid ≥476 μmol/l or 25% increase from baseline
Potassium ≥6·0 mmol/l or 25% increase from baseline
Phosphate ≥2·1 mmol/l or 25% increase from baseline (Children)
≥1·45 mmol/l or 25% increase from baseline (Adults)
Calcium ≤1·75 mmol/l or 25% decrease from baseline
Clinical tumour lysis syndrome
A patient with laboratory tumour lysis syndrome and at least one of
Creatinine ≥ 1·5 × ULN (age >12 years or age-adjusted)
Cardiac arrhythmia
Sudden death
Seizure

ULN, upper limit of normal.



Management of TLS

Symptoms: depend on the degree of metabolic abnormalities

- Nausea, vomiting, diarrhea, lethargy, anorexia, lethargy, hematuria, heart failure, cardiac dysrhythmias, seizures, muscle cramps, tetany, syncope, sudden death

Predisposition:

- Pre-treatment hyperuricemia/hyperphosphatemia
- Pre-existing renal disease or nephrotoxins, oliguria, dehydration

Risk assessment, IVF, diuretics prn (will help with hyperK+), labs q6h

Prophylaxis with allopurinol, treatment with rasburicase

Dialysis indicated if: refractory fluid overload, refractory hyperuricemia, hyperkalemia or hyperphosphatemia, symptomatic hypocalcemia

Cardiac monitoring for hyperkalemia

Case 3: Ms. FA

65F with newly diagnosed metastatic breast cancer presents with extensive bruising and gingival bleeding

Oozing at the site of venipuncture

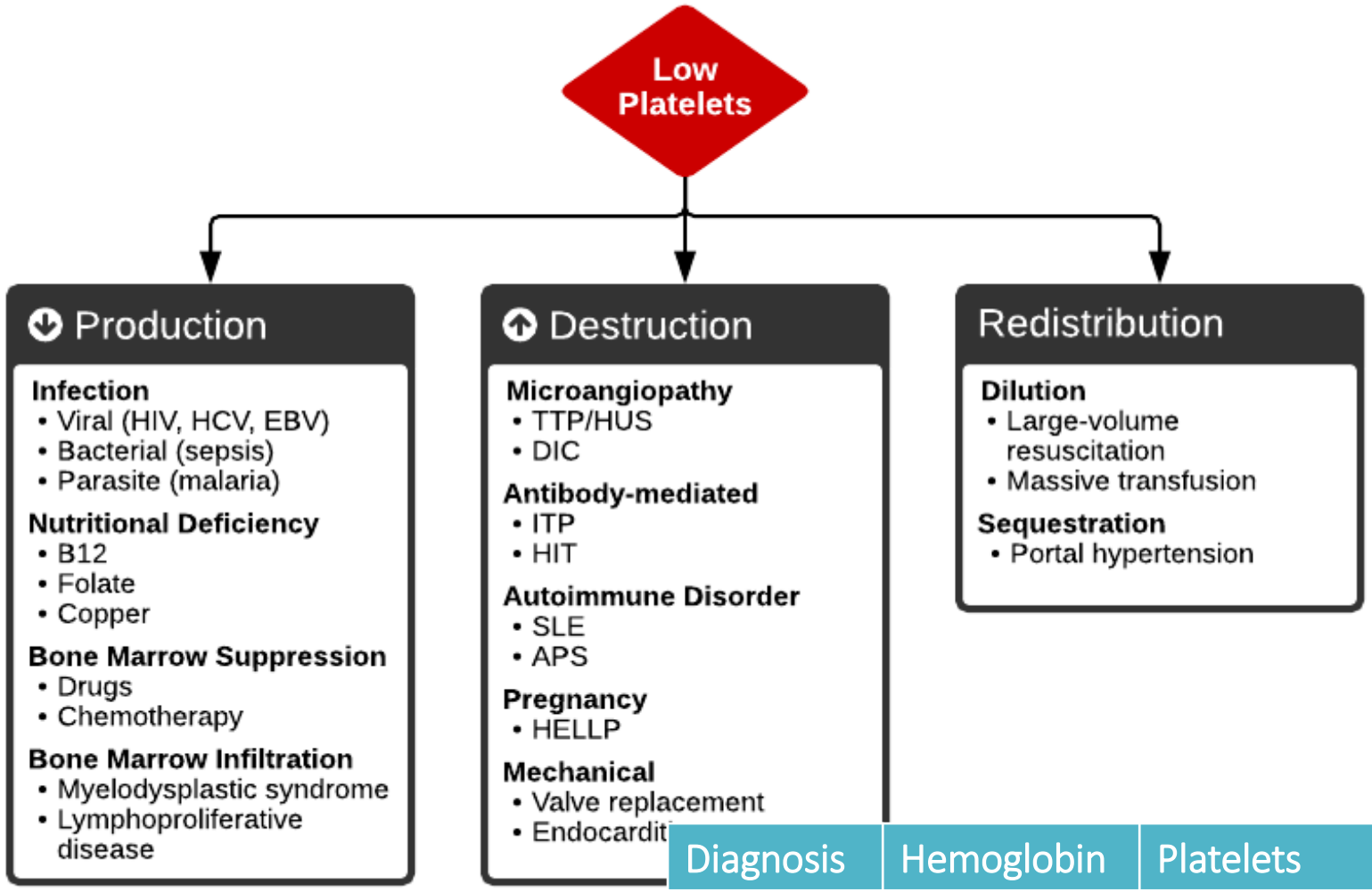
Describes blind spot in one eye

Hgb 75, WBC 10, plt 15, INR 1.6, PTT 44

What other labs would you want?

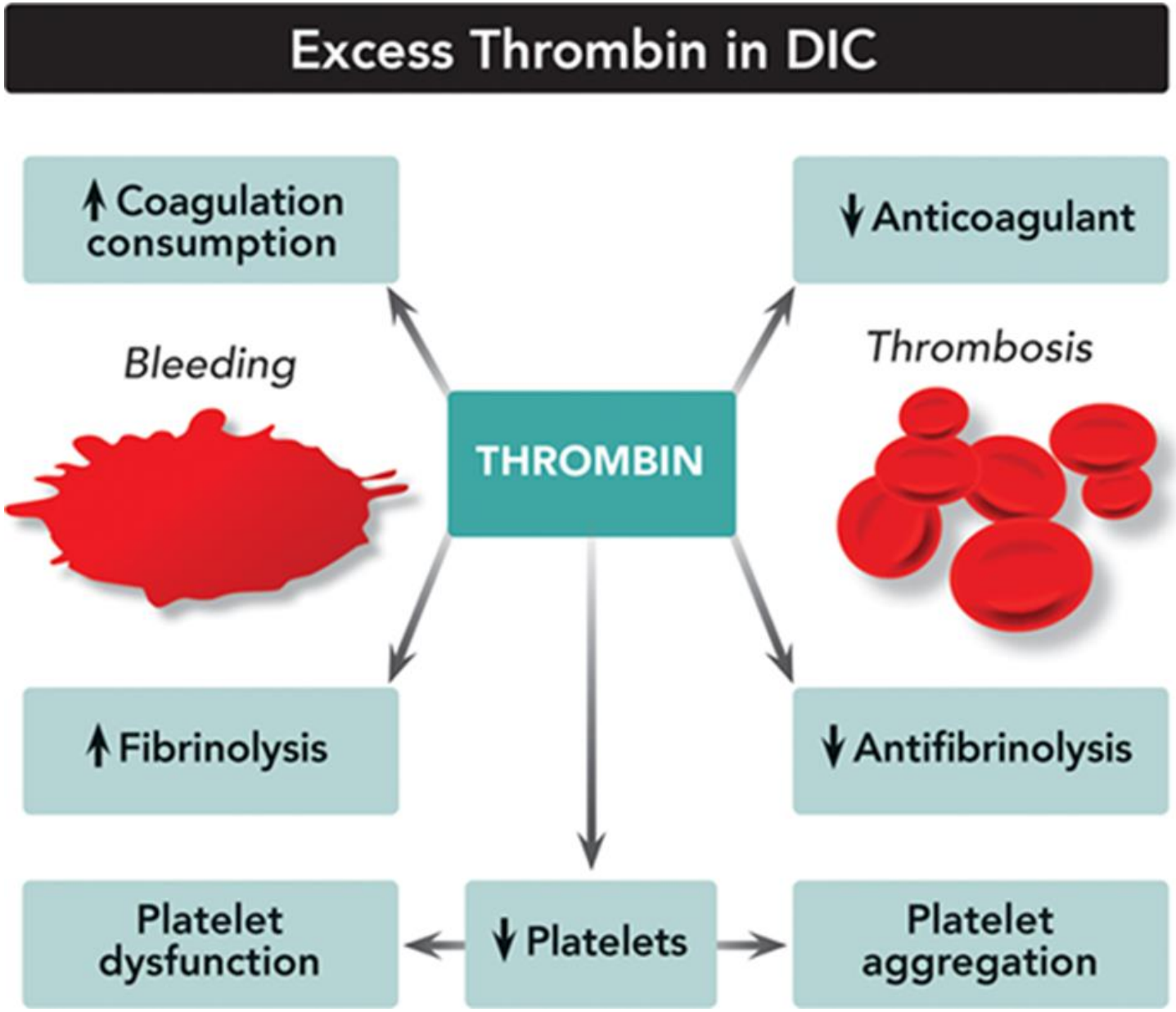
What is your management?

Would you transfuse? What would you target?



Diagnosis	Hemoglobin	Platelets	INR/PTT	Fibrinogen	Hemolysis
TTP	Low	Very low-low	Normal	Normal	Present
DIC	Low	Very low-low	High	Low	Present
ITP	Low-normal	Very low-low	Normal	Normal	Absence
HIT	Low-normal	Low	Normal	Normal	Absence

Disseminated Intravascular Coagulopathy (DIC)



Causes of DIC

Critically ill patients with underlying disorder:

- Sepsis/infection (10-20%)
- Meningococcemia
- Trauma (10-20%)
- Malignancy (10-20%)

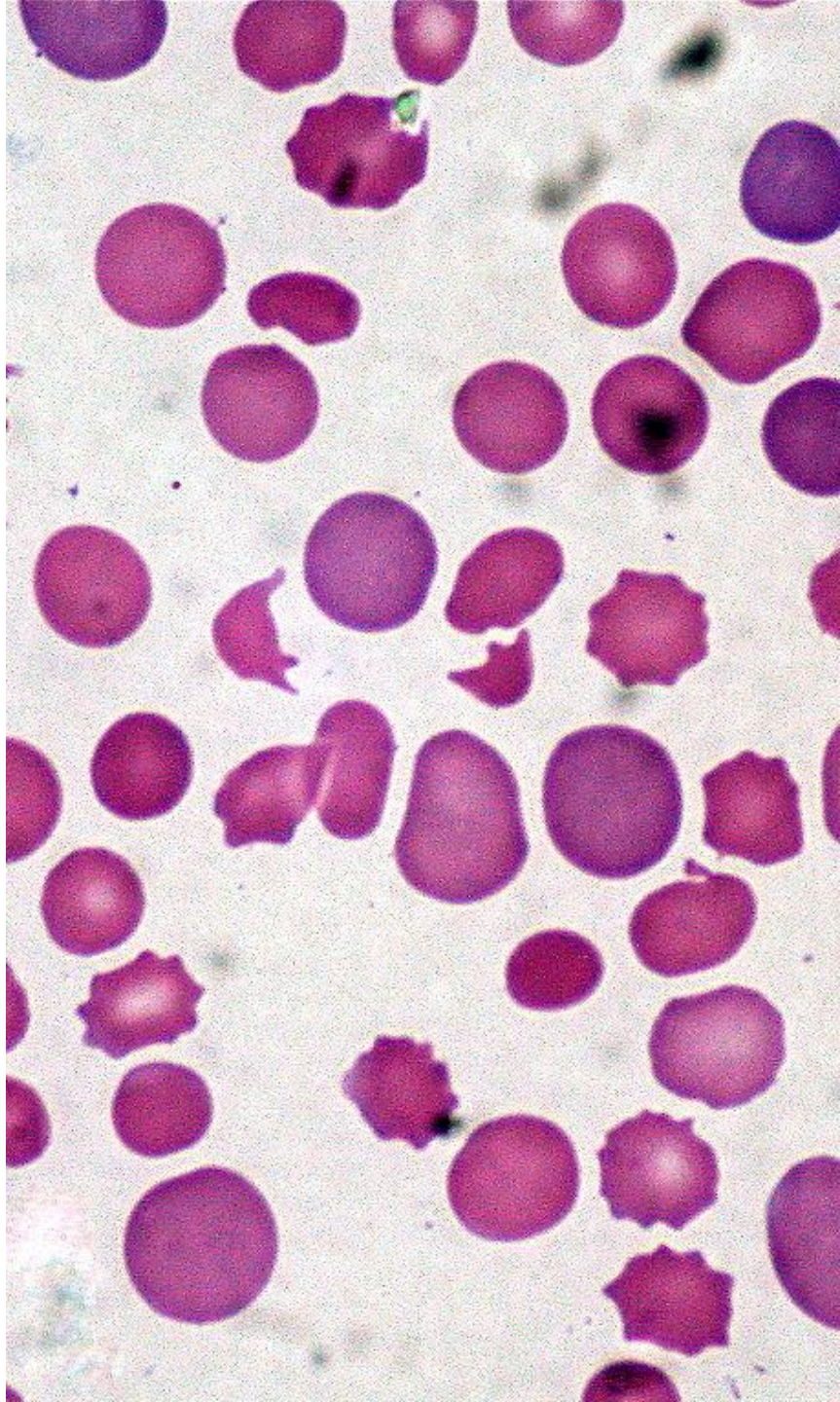
Pregnancy catastrophes: placental abruption, amniotic fluid embolism, acute fatty liver of pregnancy, retained products

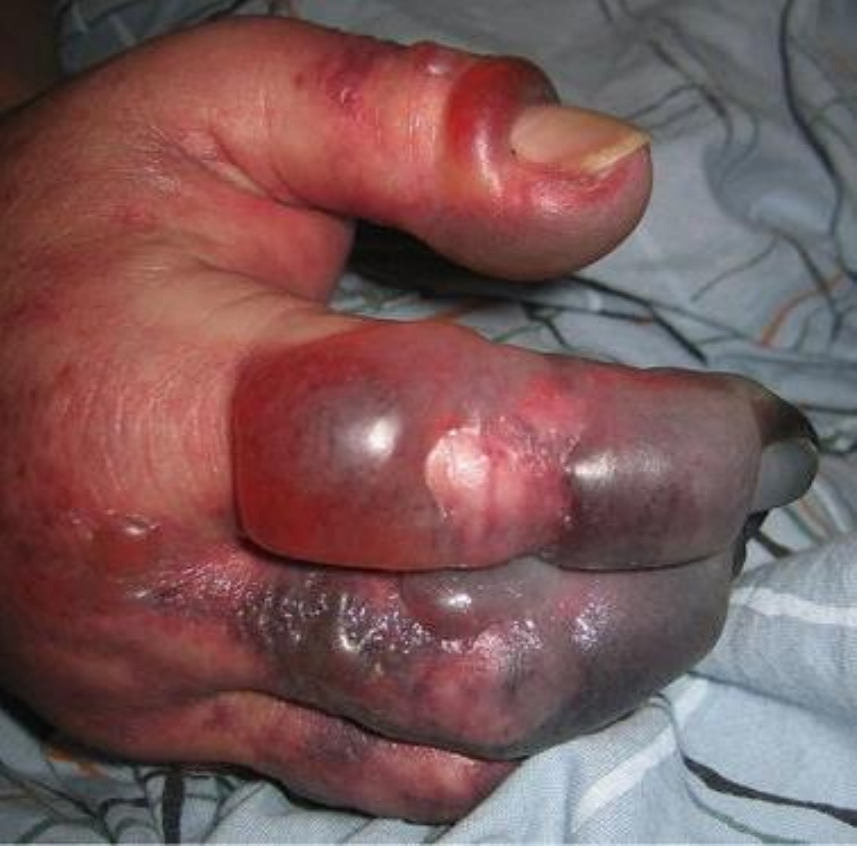
Poisoning

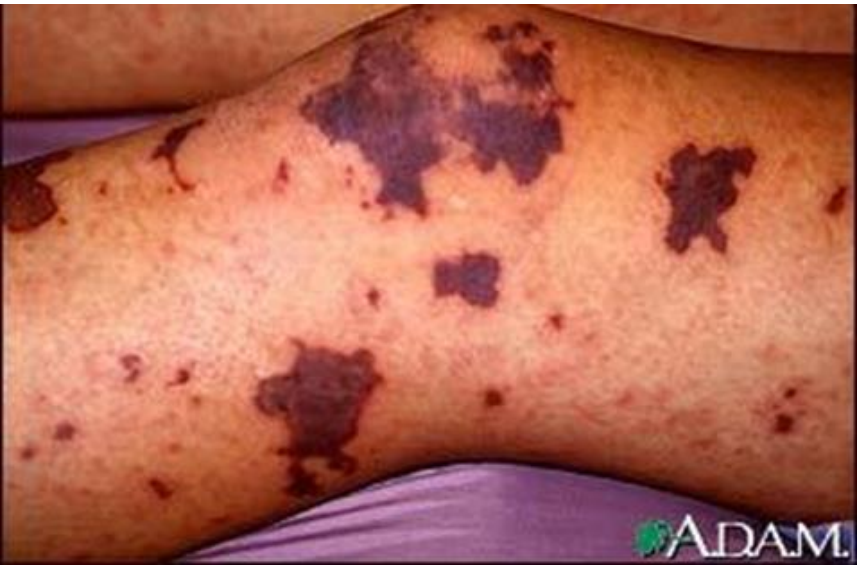
Major hemolytic transfusion reaction

Severe HIT

ASH SAP, 2016







Supportive Care

CBC, INR, PTT, fibrinogen q6h

Transfuse cryoprecipitate for fibrinogen >1.0 g/L

- 10 units cryo (1 pooled unit)
- Consumptive coagulopathy for all factors, so not ideal for fibrinogen concentrate

Transfuse: Hgb ≥70, plt ≥ 10 or ≥ 50 if bleeding

If INR ≥ 1.8, can consider FFP

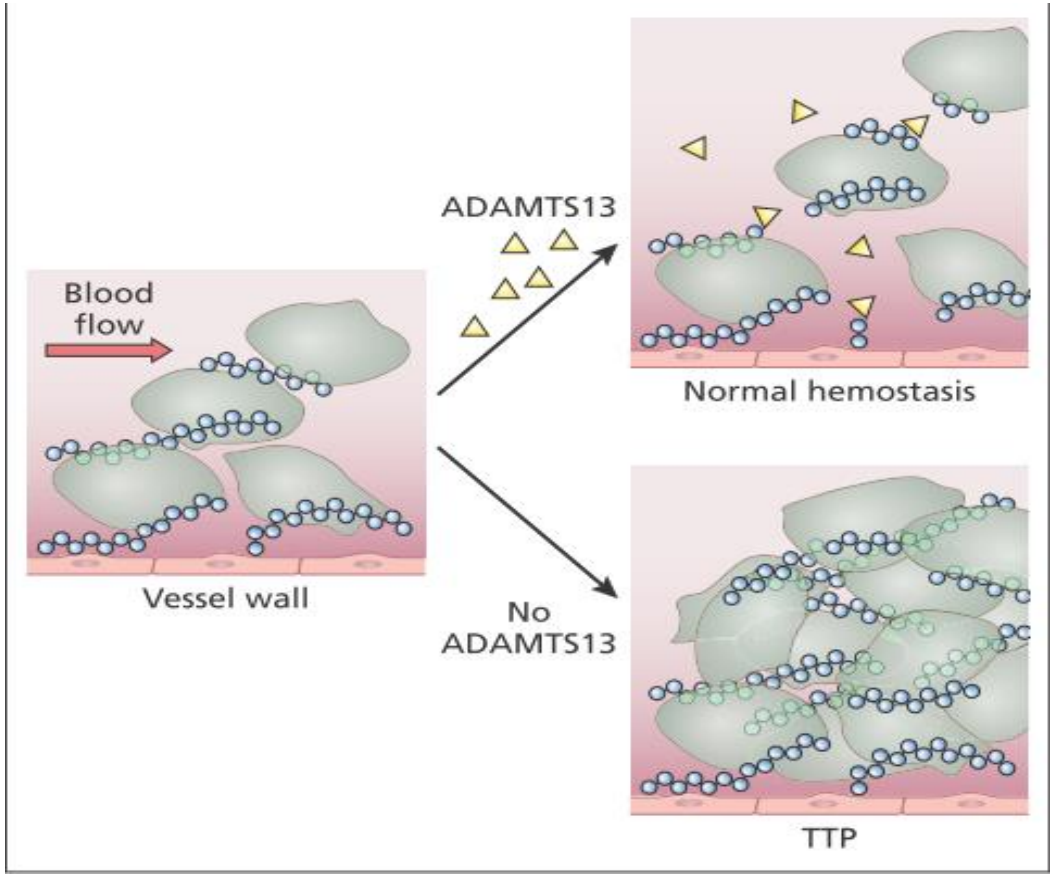
Avoid invasive procedures if possible

Assess for organ dysfunction

Thrombotic Thrombocytopenic Purpura (TTP)

Acquired auto-antibody against the ADAMTS13 protease

Accumulation of large von Willebrand factor (vWF) multimers that bind platelets



ASH SAP, 2016.

Presentation and Management of TTP

Presentation:

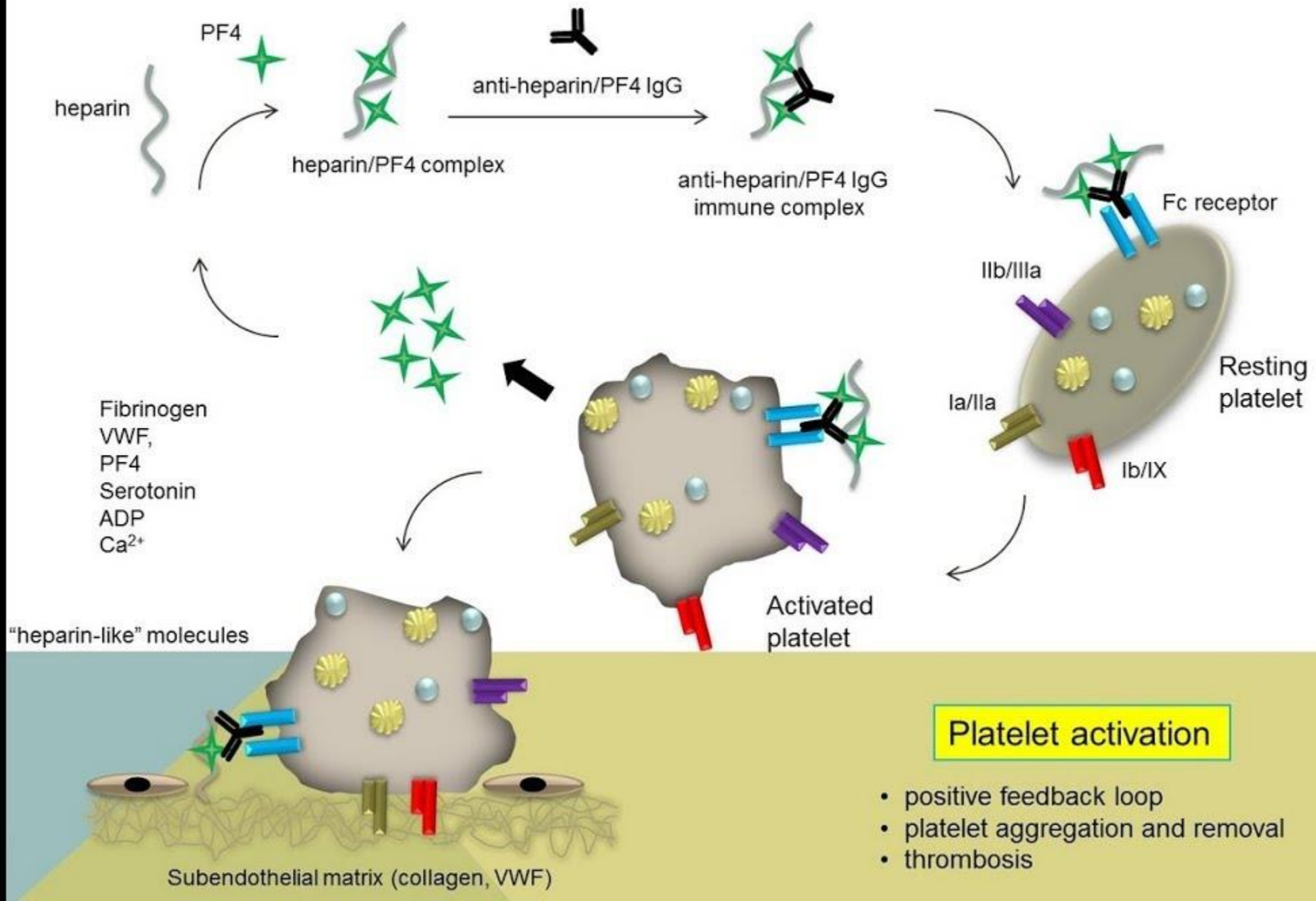
- DAT negative hemolytic anemia (schistocytes) AND thrombocytopenia
- Normal INR/PTT, high LDH and hemolytic parameters
- Acute kidney injury (more common with HUS)
- Fever
- Neurologic symptoms: stroke, confusion, coma, psychiatric

Management:

- Plasma infusion, plasma exchange (PEX/PLEX), high dose steroids
- Later therapy: Rituximab, caplacizumab

ASH SAP, 2016.

Heparin-induced thrombocytopenia (HIT)



Platelet activation

- positive feedback loop
- platelet aggregation and removal
- thrombosis

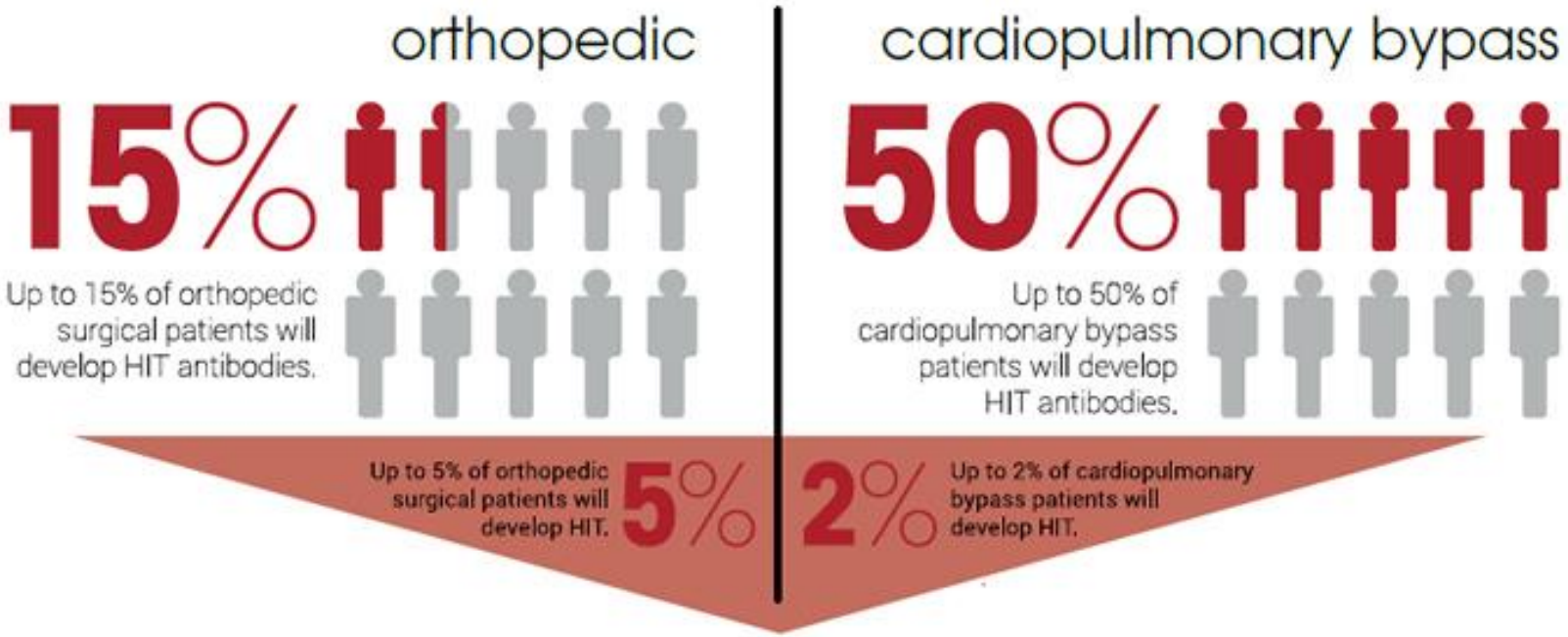
Likelihood of HIT (4T Score)

Table 10-4 4Ts scoring system for HIT

4Ts	2 points	1 point	0 point
Thrombocytopenia	Platelet count decrease of >50% and platelet nadir ≥20,000/μL	Platelet count decrease of 30%-50% or platelet nadir of 10,000-19,000/μL	Platelet count fall of <30% or platelet nadir <10,000/μL
Timing of platelet count fall	Clear onset of thrombocytopenia 5-10 days after heparin administration; or platelet decrease within 1 day, with prior heparin exposure within 30 days	Consistent with day 5-10 decrease but not clear (eg, missing platelet counts) or onset after day 10; or decrease within 1 day, with prior heparin exposure 30-100 days ago	Platelet count decrease <4 days without recent exposure
Thrombosis or other sequelae	New thrombosis (confirmed); skin necrosis (lesions at heparin injection site); acute systemic reaction after intravenous unfractionated heparin bolus	Progressive or recurrent thrombosis; nonnecrotizing skin lesions; suspected thrombosis (not proven)	None
Other causes for thrombocytopenia	None apparent	Possible	Definite

Adapted from Lo G et al. *J Thromb Haemost*. 2006;4:759-765.

High Score: 6-8 (50% probability)
Intermediate Score: 4-5 (10% probability)
Low Score: ≤3 (<1% probability) → Do not send a HIT Assay



venous or arterial thrombosis

50% If undiagnosed and untreated, up to 50% of patients with HIT will develop venous or arterial thrombosis.

Diagnosis and Management of HIT

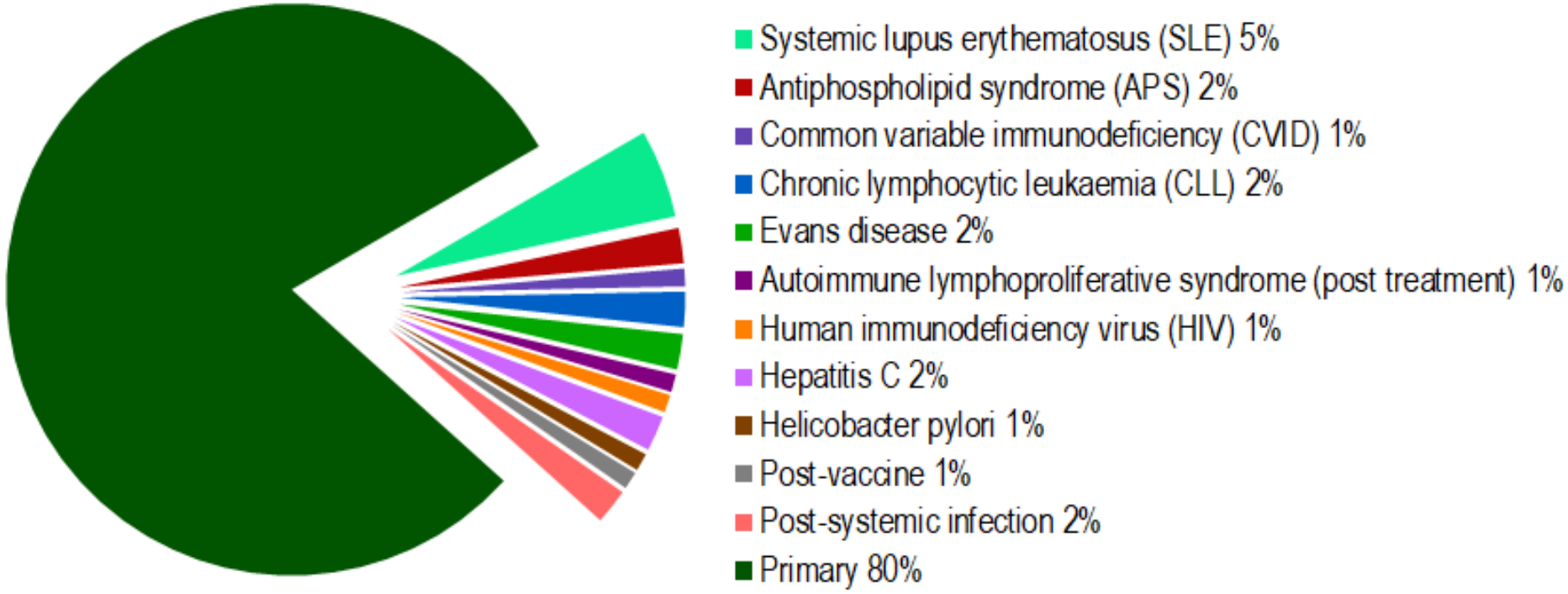
Diagnosis:

- Drop in platelets +/- thrombosis after heparin exposure
- HIT assay

Management:

- Start an alternate anticoagulant ASAP while waiting for HIT assay results
  - Argatroban, bivalirudin, fondaparinux
- Stop all forms of heparin
  - If testing positive, inform patient not to receive heparin in the future and medic alert bracelet
- Reverse warfarin immediately, do not resume until platelets >150 x2 days
- Await confirmatory testing (serotonin release assay in case of false positive)
- Monitor for thrombosis or bleeding. If clot, 3 months anticoagulation

Immune Thrombocytopenia (ITP)



ITP

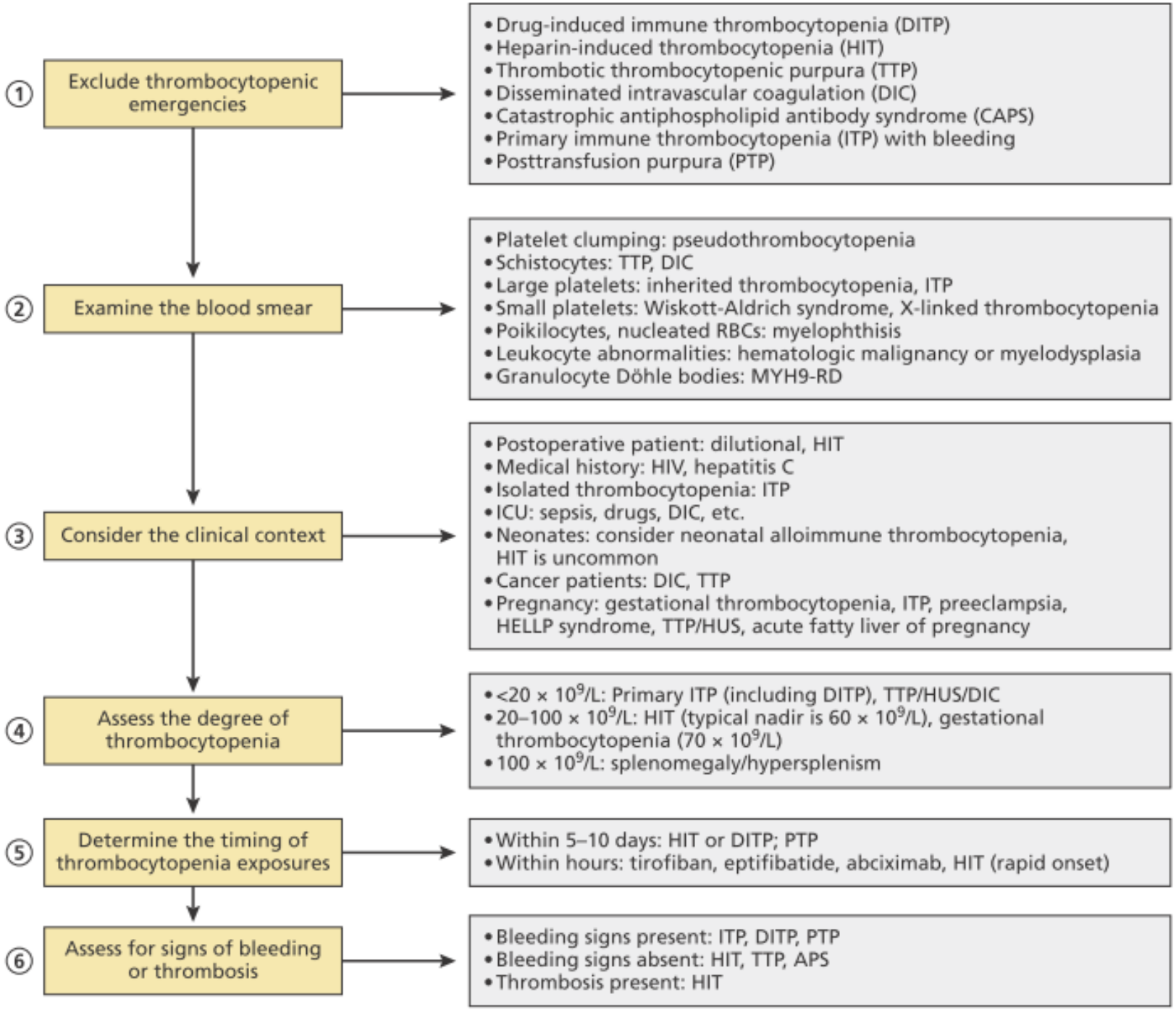
Primary ITP: platelets <100, other cell lines normal, diagnosis of exclusion

1:10,000 adults

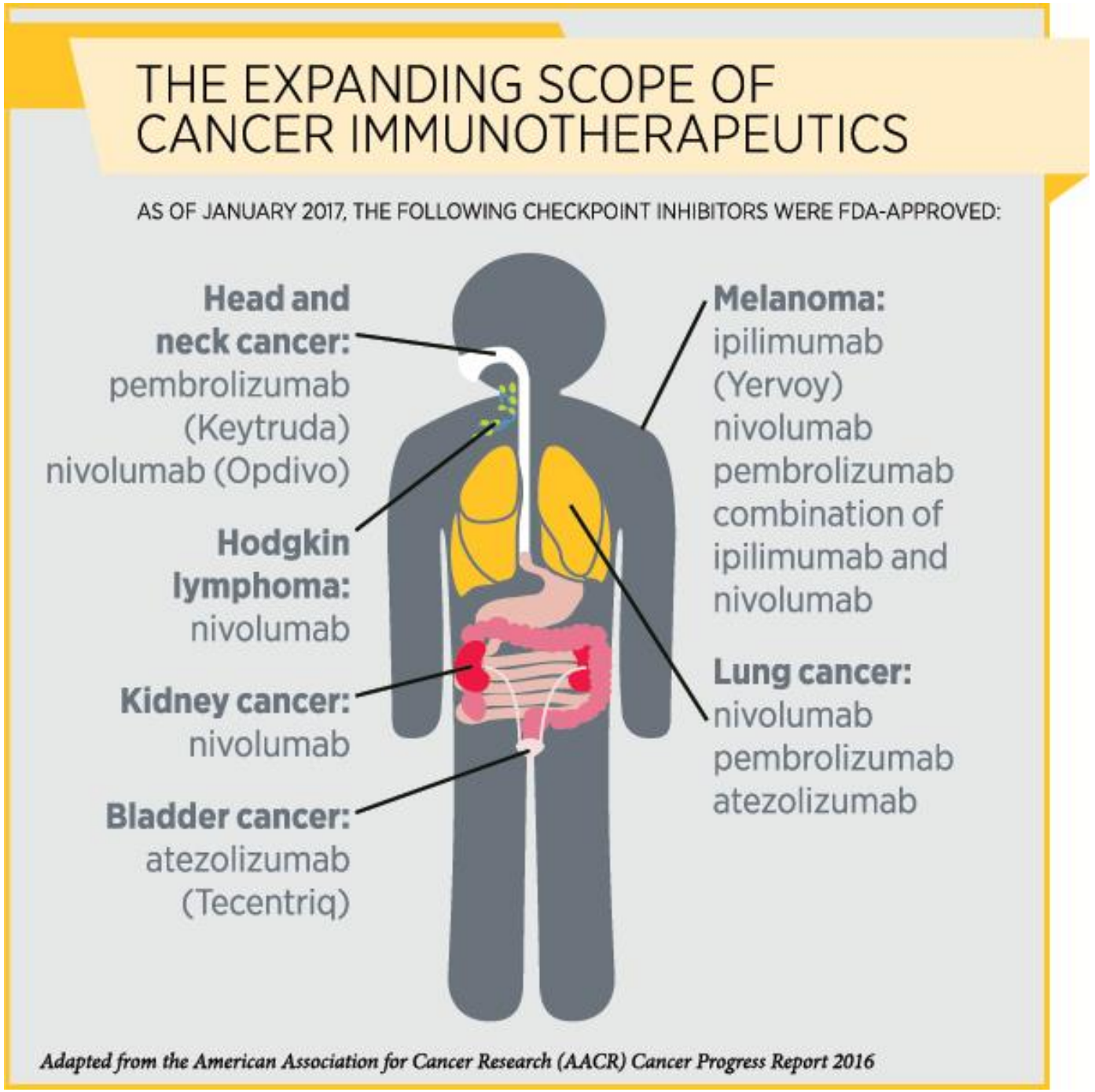
Risk: intracranial hemorrhage 1.4% adults, 0.4% children

Treatment- Indicated if platelets <30:

- Steroids: 1 mg/kg prednisone x 4wks with taper OR dex 40 mg x 4 days (works in weeks)
- IVIG: 1 g/kg IV x 1 day, lasts for 3-4 weeks (works in days)
- Splenectomy (need vaccines), rituximab, TPO receptor agonists


1
Exclude thrombocytopenic emergencies
• Drug-induced immune thrombocytopenia (DITP)
• Heparin-induced thrombocytopenia (HIT)
• Thrombotic thrombocytopenic purpura (TTP)
• Disseminated intravascular coagulation (DIC)
• Catastrophic antiphospholipid antibody syndrome (CAPS)
• Primary immune thrombocytopenia (ITP) with bleeding
• Posttransfusion purpura (PTP)
2
Examine the blood smear
• Platelet clumping: pseudothrombocytopenia
• Schistocytes: TTP, DIC
• Large platelets: inherited thrombocytopenia, ITP
• Small platelets: Wiskott-Aldrich syndrome, X-linked thrombocytopenia
• Poikilocytes, nucleated RBCs: myelophthisis
• Leukocyte abnormalities: hematologic malignancy or myelodysplasia
• Granulocyte Döhle bodies: MYH9-RD
3
Consider the clinical context
• Postoperative patient: dilutional, HIT
• Medical history: HIV, hepatitis C
• Isolated thrombocytopenia: ITP
• ICU: sepsis, drugs, DIC, etc.
• Neonates: consider neonatal alloimmune thrombocytopenia, HIT is uncommon
• Cancer patients: DIC, TTP
• Pregnancy: gestational thrombocytopenia, ITP, preeclampsia, HELLP syndrome, TTP/HUS, acute fatty liver of pregnancy
4
Assess the degree of thrombocytopenia
• <20 × 10^9/L: Primary ITP (including DITP), TTP/HUS/DIC
• 20–100 × 10^9/L: HIT (typical nadir is 60 × 10^9/L), gestational thrombocytopenia (70 × 10^9/L)
• 100 × 10^9/L: splenomegaly/hypersplenism
5
Determine the timing of thrombocytopenia exposures
• Within 5–10 days: HIT or DITP; PTP
• Within hours: tirofiban, eptifibatide, abciximab, HIT (rapid onset)
6
Assess for signs of bleeding or thrombosis
• Bleeding signs present: ITP, DITP, PTP
• Bleeding signs absent: HIT, TTP, APS
• Thrombosis present: HIT

Immune Therapies



Systemic Complications of Immunotherapy

Activating the immune system to attack the cancer so the immune system can turn on you

Can get multiorgan –itis

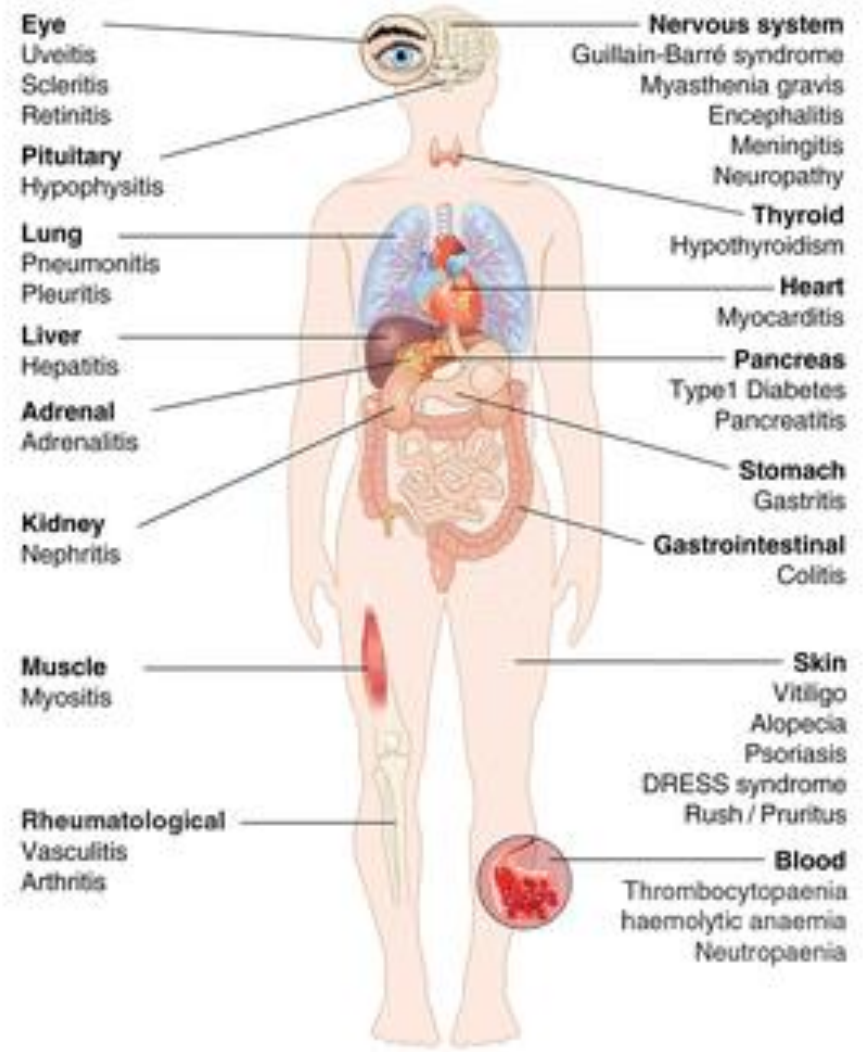
0-10% of pts, meta-analysis 2.7% pts

Higher risk with combo therapy, less resolution

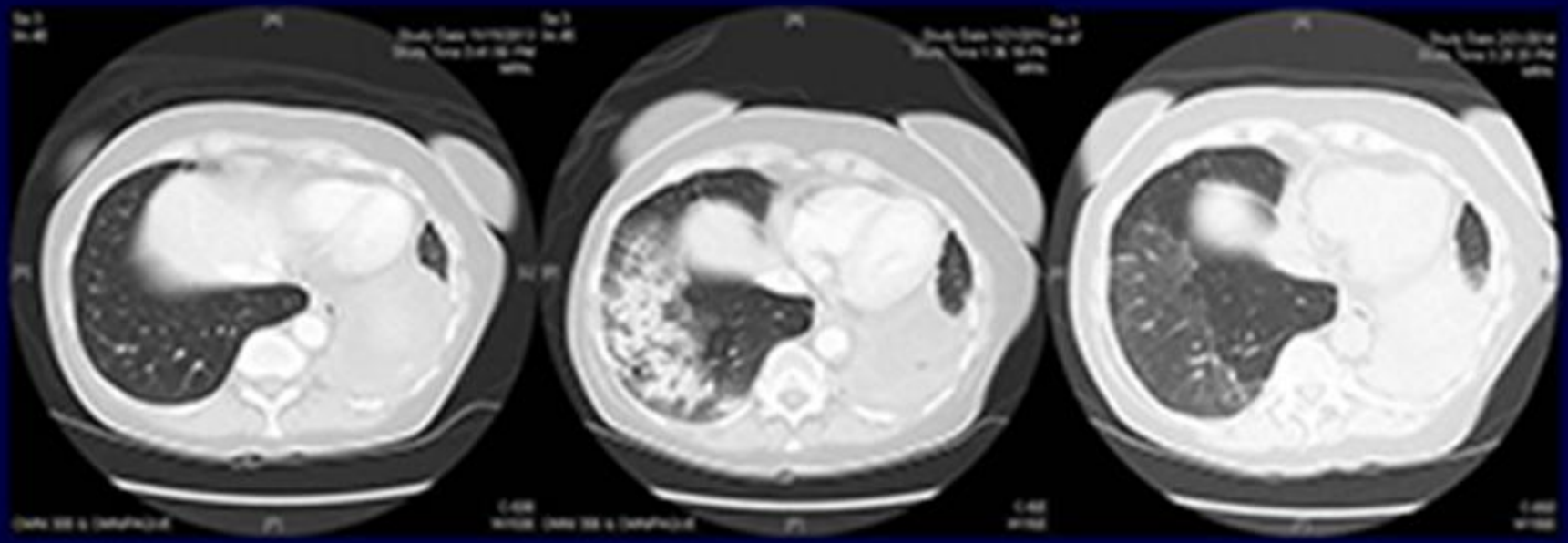
Pneumonitis: Median onset 3 months (2-24 mo)

Symptoms: dyspnea, cough, fever, CP, hypoxia

Investigations: CXR, CT, pulse oximetry



Immune-Related Pneumonitis



11/15/2013:
Prepneumonitis

1/21/14:
Pneumonitis

2/21/14:
Improved with steroids;
taper completed 3/7/14

Hold the drug, steroids, supportive care

3.1 Pneumonitis

Definition: Focal or diffuse inflammation of the lung parenchyma (typically identified on CT imaging)
No symptomatic, pathologic, or radiographic features are pathognomonic for pneumonitis

Diagnostic work-up
Should include the following: CXR, CT, pulse oximetry
For G2 or higher, may include the following infectious work-up: nasal swab, sputum culture and sensitivity, blood culture and sensitivity, urine culture and sensitivity

Grading	Management
G1: Asymptomatic, confined to one lobe of the lung or < 25% of lung parenchyma, clinical or diagnostic observations only	Hold ICPi with radiographic evidence of pneumonitis progression May offer one repeat CT in 3-4 weeks; in patients who have had baseline testing, may offer a repeat spirometry/DLCO in 3-4 weeks May resume ICPi with radiographic evidence of improvement or resolution. If no improvement, should treat as G2 Monitor patients weekly with history and physical examination and pulse oximetry; may also offer CXR
G2: Symptomatic, involves more than one lobe of the lung or 25%-50% of lung parenchyma, medical intervention indicated, limiting instrumental ADL	Hold ICPi until resolution to G1 or less Prednisone 1-2 mg/kg/d and taper by 5-10 mg/wk over 4-6 weeks Consider bronchoscopy with BAL Consider empirical antibiotics Monitor every 3 days with history and physical examination and pulse oximetry, consider CXR; no clinical improvement after 48-72 hours of prednisone, treat as G3
G3: Severe symptoms, hospitalization required, involves all lung lobes or > 50% of lung parenchyma, limiting self-care ADL, oxygen indicated G4: Life-threatening respiratory compromise, urgent intervention indicated (intubation)	Permanently discontinue ICPi Empirical antibiotics; (methyl)prednisolone IV 1-2 mg/kg/d; no improvement after 48 hours, may add infliximab 5 mg/kg or mycophenolate mofetil IV 1 g twice a day or IVIG for 5 days or cyclophosphamide; taper corticosteroids over 4-6 weeks Pulmonary and infectious disease consults if necessary Bronchoscopy with BAL ± transbronchial biopsy Patients should be hospitalized for further management

Brahmer et al, JCO 2018.

In conclusion…

Oncology patients are complex, but don’t be scared to start investigating and managing them

- If an emergency situation, supportive care is always the most important step!

Good to have a head-to-toe approach, as can decompensate quickly or have multiorgan dysfunction

Our patients themselves can be a great resource as they may have lots of experience with side effects or disease complications

We are always happy to help! ☺

Thank you for your attention

TBRHSc- Indications for Heme Consult

Pancytopenia

Thrombocytopenia

Non-nutritional anemia (ie. not Fe def anemia)

Polycythemia

Leukocytosis

Thrombocytosis

Monoclonal gammopathy

Heme conditions requiring immunosuppression/targeted therapies: ie. ITP, AIHA

ANY hematologic abnormality with malignant potential

Support adult bleeding disorders program, see referrals for ?bleeding disorder

Extra Slides

Table 2-4 Hematology consultation for leukocytosis: etiologic considerations according to leukocyte subtype affected

Neutrophilia	Monocytosis	Eosinophilia	Lymphocytosis
Eclampsia	Pregnancy	Allergic rhinitis	Mononucleosis syndrome
Thyrotoxicosis	Tuberculosis	Asthma	Epstein-Barr virus
Hypercortisolism	Syphilis	Tissue-invasive parasite	Cytomegalovirus
Crohn disease	Endocarditis	Bronchopulmonary aspergillosis	Primary HIV
Ulcerative colitis	Sarcoidosis	Coccidioidal infection	Viral illness
Inflammatory/ rheumatologic disease	Systemic lupus erythematosus	HIV	Pertussis
Sweet's syndrome	Asplenia	Immunodeficiency	*Bartonella henselae* (cat scratch disease)
Infection	Corticosteroids	Vasculitides	
Bronchiectasis	Juvenile myelomonocytic leukemia	Drug reaction	Toxoplasmosis
Occult malignancy		Adrenal insufficiency	Babesiosis
Trauma/burn		Occult malignancy	Drug reaction
Severe stress (emotional or physical)		Pulmonary syndromes	Reactive large granular lymphocytosis
Panic		Gastrointestinal syndromes	Chronic lymphocytic leukemia
Asplenia		Hypereosinophilic syndrome	Monoclonal B cell lymphocytosis
Cigarette smoking			Postsplenectomy lymphocytosis
Tuberculosis			
Chronic hepatitis			
Hereditary neutrophilia			
Medications			
Corticosteroids			
β-agonists			
Lithium			
G-CSF or GM-CSF			
Myeloproliferative neoplasm (CML, PV, ET)			

HIV = human immunodeficiency virus; CML = chronic myelogenous leukemia; PV = polycythemia vera; ET = essential thrombocythemia.

ASH SAP, 2016.

Table 2-5 Causes of acquired leukopenia

Infection associated
Postinfectious
Active infection
Sepsis
Viral (HIV, CMV, EBV, hepatitis A, B, C, influenza, parvovirus)
Bacterial (tuberculosis, tularemia, *Brucella*, typhoid)
Fungal (histoplasmosis)
Rickettsial (Rocky Mountain spotted fever, ehrlichiosis)
Parasitic (malaria, leishmaniasis)
Drug-induced
Agranulocytosis
Mild neutropenia
Autoimmune
Primary autoimmune
Secondary autoimmune (systemic lupus erythematosus, rheumatoid arthritis)
Felty syndrome
Malignancy
Acute leukemia
Myelodysplasia
Lymphoproliferative disorder
Large granular lymphocyte leukemia
Plasma cell dyscrasia
Myelophthisic process
Nutritional
Vitamin B_{12} or folate deficiency
Copper deficiency
Alcohol
Acute respiratory distress syndrome
Increased neutrophil margination (hemodialysis)
Hypersplenism
Thymoma
Immunodeficiency
Iatrogenic

CMV = cytomegalovirus; EBV = Epstein-Barr virus; HIV = human immunodeficiency virus.

Table 2-6 Causes of persistent unexplained lymphadenopathy

Localized	Generalized
Bacterial infection	Mononucleosis syndrome
Fungal infection	Epstein-Barr virus
Tuberculosis	Cytomegalovirus
Other mycobacterial infections	Primary HIV
Bartonella henselae (cat scratch disease)	Chronic HIV
Sarcoidosis	Other viral infections
Langerhans cell histiocytosis	Leptospirosis
Inflammatory pseudotumor	Tularemia
Progressive transformation of germinal cetners	Miliary tuberculosis
Malignancy (eg, NHL, HD, CLL, metastatic carcinoma)	Brucellosis
	Lyme disease
	Secondary syphilis
	Toxoplasmosis
	Histoplasmosis, coccidiomycosis, crypotcoccus
	Systemic lupus erythematosus
	Rheumatoid arthritis
	Still's disease
	Rosai-Dorfman disease
	Sarcoidosis
	Langerhans cell histiocytosis
	Phenytoin
	Drug-induced serum sickness
	Castleman disease
	Kikuchi disease
	Kawasaki disease
	Angioimmunoblastic lymphadenopathy
	Atypical lymphoproliferative process (eg, Castleman disease)
	Autoimmune lymphoproliferative syndrome (ALPS)
	Hemophagocytic lymphohistiocytosis
	Malignancy (eg, indolent NHL, HD, CLL, metastatic carcinoma)

CLL = chronic lymphocytic leukemia; HD = Hodgkin disease; HIV = human immunodeficiency virus; NHL = non-Hodgkin lymphoma.