HEMATOLOGICAL ISSUES IN ACUTE CARE - PART B
Dheeraj Reddy, MD

Objectives - Part B

- Approach to Platelet and coagulation disorders
  - Thrombocytopenia/Thrombocytosis
  - Supratherapeutic INR
- Approach to WBC disorders
  - Leukopenia/Neutropenia
  - Hypergammaglobulinemia
  - Leukemias
- Approach to Lab abnormalities
  - Elevated ESR (erythrocyte sedimentation rate)
  - Abnormalities in partial thromboplastin and prothrombin coagulation times

Hematopoiesis

- Production of all types of blood cells including formation, development, and differentiation of all types of blood cells.
- \(10^{11} - 10^{12}\) new blood cells are produced daily in our body to maintain steady state levels in the peripheral circulation
- All types of new blood cells are derived from “pluripotent stem cells”
Sites of Hematopoiesis in pre- and postnatal periods

MUCH SIMPLER!
Platelet anatomy

- Shape: round and flat discs, with diameter of 1–2 µm and volume of 7–9 fL.
- Plasma membrane
  - Receptor glycoproteins eg GPIIb / IIIa (αIIbβ3)
  - Surface-connected canalicular system
- Cytoskeleton
- Organelles
  - Mitochondria, lysosomes, and peroxisomes
  - Alpha granules (~ 80 per platelet)
  - Dense granules (3 – 8 per platelet)
Platelet Turnover and Aging

- Average platelet lifespan: 7 – 10 days
- Removed from circulation by monocyte-macrophage system
- Approximately 25 – 35% of circulating platelets located in the spleen
- 15 – 25% of the daily turnover of all platelets utilized for maintenance of vascular integrity
- Thrombopoietin (TPO) is the primary regulator of megakaryocyte development and platelet number.
Platelet count

- Normal platelet count: 150-400 x 10⁹/L
- 2.5% will have platelet count < 150 x 10⁹/L
- Count can vary slightly
  - Menstrual cycle phase
  - Decrease during near-term pregnancy (gestational thrombocytopenia)
  - Increase in response to inflammatory cytokines (secondary, or reactive, thrombocytosis).

Major mechanisms of thrombocytopenia

- Increased Destruction
  - Immune-mediated: ITP, infection, drugs
  - Non-immune mediated: DIC
- Decreased Production (marrow related)
- Sequestration; hypersplenism
- Dilutional
- Pseudothrombocytopenia (platelet clumping)

Pseudothrombocytopenia

- In vitro clumping of platelets, resulting in artificially low platelet
- Most often due to EDTA-dependent antibodies against platelets (most IgG)
- Diagnosis
  - Suspect when thrombocytopenia is reported in non-bleeding patient
  - Platelet clumps on blood film from EDTA specimen
  - Accurate platelet counts may be obtained by:
    - Examination of EDTA blood at 37°C
    - Manual platelet count performed
    - on blood collected by finger stick into citrate anticoagulant
Clinical presentation

- Epistaxis (U/L vs B/L, duration, trauma related?)
- Post surgical bleeding
- Site of the bruises
- Joint swelling/pain
- Menorrhagia
- Anemia
- Petechiae

Major considerations in gathering a patient history

- Medical Hx: Cirrhosis!! Renal disease, Malabsorption
- Surgical Hx: Easy bleeding/bruising
- Medications: Anti-epileptics, Antibiotics (more acute exposure typically)
- Social Hx: Risk factors for B12 or folate deficiency, Alcohol use, Risk factors for Hepatitis/ HIV
- Family Hx: Type and severity of bleeding, Age of onset, Relation to patient → inheritance pattern
- Review Prior Labs if available: Other cell lines (MDS, Lymphoproliferative disorder), Liver function (occult cirrhosis)
Platelet problem or clotting factor problem?

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>Bleeding Disorder</th>
<th>Clotting Factor Deficiency</th>
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</thead>
<tbody>
<tr>
<td>Site of bleeding</td>
<td>Nasi, mucous membranes (gastro, ear, genitourinary tract)</td>
<td>Deeper soft tissues (joint, muscle)</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Edema</td>
<td>Small, superficial</td>
<td>Large, palpable</td>
</tr>
<tr>
<td>Hemorrhage, muscle/septum</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>Bleeding after tooth extraction</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Bleeding after surgery</td>
<td>Intraocular, mild</td>
<td>Delayed, severe</td>
</tr>
</tbody>
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Laboratory evaluation

Prolonged Activated Partial Thromboplastin Time (aPTT) (>26-35 s) - I, II, V, VII, IX, X, XI, XII, prekallikrein and HMWK

- No clinical bleeding → ↓ factors XII, HMWK, prekallikrein
- Variable, but usually mild, bleeding → ↓ factor XI, mild ↓ FVIII and FIX
- VWD
- Frequent, severe bleeding → severe deficiencies of FVIII and FIX
- Heparin

Prolonged Prothrombin Time (PT) (>10-14 s) - I, II, V, VII, X

- Factor VII deficiency
- Vitamin K deficiency → Warfarin anticoagulation

Prolonged aPTT and PT

- Factor X, V, K, or fibrinogen deficiency
- Vitamin K deficiency → Late Direct thrombin inhibitors
- DIC
- Liver disease

Additional tests

- Mixing study
- Individual factor assays
- FXIII deficiency
- APLA (Immunoglobulins directed against anionic PL or PL-plasma protein complexes)
- APS: Can be associated with various conditions

**NOT TO BE ROUTINELY ORDERED $$$**

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Case # 5

39 year-old man who presents to the Emergency Room with complaints of fevers, RUE swelling and erythema.

Past Medical History; HTN
Medications; Lisinopril (non compliant)
Social History; IV drug use and daily alcohol use (heavy liquor use)
Vitals: Temp; 39.1°C, BP; 89/60, RR: 18, HR: 126 o/e; Exam consistent with RUE cellulitis.

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**CBC**

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<tr>
<td></td>
<td>10.2</td>
<td>13.6</td>
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<td></td>
<td>122</td>
<td>30</td>
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</table>

- Diff; neutrophils > 80%
- schistocytes

**BMP**

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<tr>
<td></td>
<td>141</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>4.5</td>
<td>20</td>
</tr>
</tbody>
</table>

AG 21, Lactate; 29 mg/dL (8-16 mg/dL)

- Prothrombin time; 31.8 seconds (normal: 11.5 to 15.5 seconds)
- Activated partial thromboplastin time (aPTT) 53 seconds (normal: 25.2 to 36 seconds)
- INR; 2.12 (normal: 1 to 1.25)
- Serum fibrinogen was <0.32 g/L (normal: 1.3 to 3.5 g/L)
- Plasma concentration of d-dimers was >4 μg/mL (normal: ≤0.40 μg/mL)
Disseminated Intravascular Coagulation (DIC)

- A heterogeneous group of clinicopathologic syndromes
- Characterized by dysregulated generation of thrombin (pathologic thrombin formation)
- Leading to intravascular fibrin formation, and
- Secondary fibrinolysis (plasmin generation),
- Often resulting in hemorrhage, thrombosis, and/or multi-organ system failure

Some Causes of DIC

- Infections
  - Bacteremia
  - Rickettsial infections
- Metabolic disorders
  - Hypotension
  - Hypoxia
  - Hyper/hypothermia
- Obstetrical complications
  - Placental abruption
  - Placenta previa
  - Pregnancy-induced HTN
  - Amniotic fluid embolism
  - Retained dead fetus
- Tumors
  - Adenocarcinoma
  - Tumor Lysis Syndrome
  - AML M3(APL), M4 or M5
- Trauma
  - Crush injuries
  - Head injuries
- Toxins
  - Viper venom bites
- Drugs
  - L-asparaginase
  - Prothrombin complex concentrates
  - Heparin (via HIT)

Pathogenesis of Disseminated Intravascular Coagulation in Sepsis.

Peripheral blood smear: schistocytes, low platelets

Tests for DIC
- D-dimer *
- FDP
- Platelet count
- Fibrinogen
- PT/INR
- aPTT
* more specific for DIC

Treatment of DIC:
Special Situations
- Prohemorrhagic patients
  - Placental abruption: obstetrical intervention, treat defibrination (cryoprecipitate)
  - Prostate CA with hyperfibrinolysis: Replace fibrinogen (cryoprecipitate), antifibrinolytic therapy (tranexamic acid, ε-aminocaproic acid)
- Acute Promyelocytic Leukemia:
  - All-trans-retinoic acid (ATRA)
Treatment of DIC:

Special Situations

- Prothrombotic patients
  - Adenocarcinoma (Trousseau's syndrome):
    - Heparin, avoid warfarin
  - Septicemia with acral gangrene (purpura fulminans):
    - Vitamin K, heparin, FFP
  - Heparin-induced thrombocytopenia:
    - Unusual DIC picture with increased thrombin generation without low fibrinogen, ↑PT, ↑aPTT, THUS use agent that reduces thrombin generation (lepirudin, argatroban, danaproid)

Laboratory Findings in Various Platelet and Coagulation Disorders in the ICU

<table>
<thead>
<tr>
<th>Condition</th>
<th>Prothrombin Time</th>
<th>Activated Partial Thromboplastin Time</th>
<th>Fibrinogen</th>
<th>Platelet Count in apheresis</th>
<th>Bleeding Time</th>
<th>Platelet Count on Arrival</th>
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<tbody>
<tr>
<td>Venous thromboembolism</td>
<td>Prolonged</td>
<td>Prolonged</td>
<td>Normal</td>
<td>Prolonged</td>
<td>Normal</td>
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<td>Arterio-venous injuries</td>
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<td>Early stage</td>
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<tr>
<td>Late stage</td>
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<td>Unaffected</td>
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<tr>
<td>Disseminated intravascular coagulation</td>
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<tr>
<td>Thrombotic thrombocytopenia</td>
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<tr>
<td>Hypofibrinemia</td>
<td>Unaffected</td>
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<td>Unaffected</td>
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AAAB guidelines on prophylactic platelet transfusion (2015)

- Prophylactic platelet transfusion, with therapy-induced hypoproliferative thrombocytopenia. <10 × 10^9 cells/L to reduce the risk for spontaneous bleeding. Give single apheresis unit or equivalent. Greater doses are not more effective, and lower doses equal to one half of a standard apheresis unit are equally effective.
- Patients having elective central venous catheter placement with a platelet count less than 20 × 10^9 cells/L.
- Patients having elective diagnostic lumbar puncture with a platelet count less than 20 × 10^9 cells/L.
- Patients having major elective nonneuraxial surgery with a platelet count less than 50 × 10^9 cells/L.
- No role routine for patients who are nonthrombocytopenic and have cardiac surgery with cardiopulmonary bypass.
Case # 6

47 year old man presents to ER for LLE swelling. He had a 3 day hospitalization, 4 weeks ago for a non-ST elevation myocardial infarction for which he underwent cardiac catheterization and was given low molecular-weight heparin.

Current medications: aspirin, clopidogrel, pravastatin, and lisinopril.

o/e: Left thigh is swollen and tender.

CBC, BMP, LFTs are unremarkable except for a platelet count of 102,000/µL (150,000-350,000/µL previously)

Duplex ultrasonography ➔ + Deep venous thrombosis

Unfractionated heparin is administered. Twelve hours later, the patient's platelet count is 27,000/µL.

Heparin-induced thrombocytopenia

- Complication of heparin therapy.
- 2 types of HIT.
  - Type 1 HIT: NON IMMUNE MEDIATED within the first 2 days after exposure to heparin, and the platelet count normalizes with continued heparin therapy. Results from the direct interaction of heparin with the platelet membrane, resulting in enhanced platelet aggregation
  - Type 2 HIT: IMMUNE MEDIATED disorder that typically occurs 4-10 days after exposure to heparin and has life-and limb-threatening thrombotic complications
Risk factors;
- include unfractionated rather than LMW heparin (but HIT can occur in any patient following any heparin exposure)
- higher heparin doses
- female sex
- possibly age
- Thrombosis → skin necrosis, limb gangrene, and organ infarction

Clinical features
- Patients present typically 5–14 days after starting heparin treatment, with a fall in platelet count of more than 30% from baseline → NOTE count may still be in the reference range.
- Can be asymptomatic, or develop venous/arterial thrombosis and skin lesions, including overt skin necrosis.
- May complain of pain/itch at injection or shivering following heparin injections.
- 4 T score

4-T score

<table>
<thead>
<tr>
<th>Category</th>
<th>2 points</th>
<th>1 point</th>
<th>0 point</th>
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<tbody>
<tr>
<td>Thrombocytopenia</td>
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<tr>
<td>Timing of platelet count fall</td>
<td>&lt;50% fall in platelet count, or nadir of 20–100 × 10⁹/L</td>
<td>30–50% fall in platelet count, or nadir of 50–150 × 10⁹/L</td>
<td>30% fall in platelet count or nadir &lt;30 × 10⁹/L</td>
</tr>
<tr>
<td>4 days or more after recent heparin exposure</td>
<td>(Day 5–14, or &gt;3 days)</td>
<td>(Day 15–28)</td>
<td>(Day 1)</td>
</tr>
<tr>
<td>Thrombosis or other sequelae</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Thrombosis or skin necrosis</td>
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<td></td>
</tr>
<tr>
<td>Other causes for thrombocytopenia</td>
<td></td>
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</table>

Possible

Diagnostic score

Pre-test probability of the diagnosis is assessed using the 4Ts scoring system.
Diagnostic Algorithm

Management

- Heparin MUST be discontinued as soon as HIT is diagnosed and an alternative anticoagulant which does not cross-react with the antibody is substituted.
- Argatroban/ Bivalirudin (direct thrombin inhibitor) /OR fondaparinux (factor Xa inhibitor) are commonly used.
- Warfarin bridge
- In asymptomatic patients with HIT who do not receive an alternative anticoagulant, around 50% will sustain a thrombosis in the subsequent 30 days.
- Patients with established thrombosis have a poor prognosis.
- Duration of Rx: 2-3 months if no Thrombosis. 3-6 months if + thrombosis

Case # 7

- 79 yo male with Hx of Afib, DM, CKD (CHADS=3) presented with a 12 hour history or back pain. He has been on warfarin for 5 years.
- o/e VS all stable.
- Labs: Hb: 8.8g/dL (Labs 2 weeks prior reveal Hb 11.9g/dL), Cr Cl 35ml/min. INR: 7.5
- CT of the abdomen; 12cm x 16cm retroperitoneal hematoma
General Principles of Management of Anticoagulant Associated Bleeding

**HASHTI**
1. Hold further doses of anticoagulant
2. Consider Antidote
3. Supportive treatment: volume resuscitation, inotropes as needed
4. Local or surgical Hemostatic measures: topical agents (aminocaproic acid, tranexamic acid)
5. Transfusion (red cells, platelets, FFP as indicated)
6. Investigate for bleeding source

American Society of Hematology - 2011 pocket guide

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**EMERGENT TREATMENT OF BLEEDING**

- Only antidote for the newer oral anti-coagulants, Dabigatran; idarucizumab
- Oral activated charcoal retards absorption of recently ingested drug within a couple hours of presentation
- Hemodialysis removes Dabigatran (as only 35% is protein-bound), but not Apixaban/Rivaroxaban
- Recombinant Factor VIIa- reverse life-threatening bleeds (but can cause disseminated intravascular coagulation and systemic thrombosis)
- Prothrombin Complex Concentrates- 3/4factor prothrombin complex concentrates (PCCs)- these contain Vitamin K dependent factors in high doses and have only been demonstrated in small trials.
Back to the patient

- The patient received 10mg IV Vitamin K, 4 units of FFP and Prothrombin Complex Concentrates.
- H/H dropped to 7.3/22. He also received 2 units of packed red blood cells.
- INR returned to 1.1.
- Extensive conversation was held with patient regarding benefits vs risks of anticoagulation. His PCP was also involved, and mutually agreed that it's safer for patient to be off anti-coagulation.

Thrombocytosis

- Presence of high levels of platelets.
- Can be primary (not common) or secondary (Reactive; much more common).
- Primary: Essential Thrombocytosis ➔ myeloproliferative disorder. Diagnosis of Exclusion:
  - Platelet count > 450 × 10^3/µL for at least 2 months.
  - Acquired V617F JAK2 mutation present.
  - bleeding/thrombosis, headache, nausea, vomiting, abdominal pain, visual disturbances, dizziness, fainting, and numbness.

Secondary Thrombocytosis

- Inflammation:
  - Acute and chronic infection
  - Connective tissue disease
  - Malignancy
  - Kawasaki syndrome
- Iron deficiency
- Marrow recovery
- Sickle cell disease
- Post-splenectomy
Neutropenia

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased Production</td>
<td>Drug-induced:&lt;br&gt;• Chemotherapy&lt;br&gt;• Nonsteroidal agents, antibiotics (chloramphenicol, penicillins, sulfonamides), phenothiazines, anticonvulsants (carbamazepine), antipsychotics (clozapine), anti-inflammatory agents, antithyroid drugs&lt;br&gt;Hereditary diseases: aplastic anemia, cyclic neutropenia, juvenile genetic disorders, Turner syndrome, myelofibrosis&lt;br&gt;Nutritional deficiency: vitamin B12, folic acid (especially alcoholics)</td>
</tr>
<tr>
<td>Peripheral Destruction</td>
<td>Antineutrophil antibodies and/or splenic or lung trapping&lt;br&gt;Autoimmune disorders: Felty's syndrome, rheumatoid arthritis, lupus erythematosus, drugs</td>
</tr>
<tr>
<td>Peripheral Pooling</td>
<td>Overwhelming bacterial infection (acute endotoxemia) and/or splenic or lung trapping&lt;br&gt;Cardiopulmonary bypass</td>
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Case #8

- 66 year old female recently diagnosed with AML underwent induction chemotherapy 7 days prior. She presents to the ER with complaints of fevers, malaise, sore throat, and easy bruising.
- Temp 39.2°C, HR 88, BP 122/80, RR 12 O2 sat 94% on RA
- Physical examination: oral mucosa, indwelling vascular catheter site (port), heart, lungs, abdomen, and perianal region are all normal.
- A chest radiograph is normal, and blood cultures are obtained.

Labs:

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<tr>
<th></th>
<th>0.8</th>
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<tbody>
<tr>
<td>Neutrophils</td>
<td></td>
<td></td>
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<tr>
<td>Lymphocytes</td>
<td>138</td>
<td>105</td>
<td>12</td>
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<tr>
<td>Monocytes</td>
<td>4.8</td>
<td>27</td>
<td>0.9</td>
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- 17% Total protein 5.1, albumin 2.5, AST 42, ALT 54, Alkaline phosphatase 80, total bilirubin 1.0

Neutropenic Fever

- Neutropenia: Absolute neutrophil count (ANC) of less than 500/µL or less than 1000/µL with an anticipated decline to less than 500/µL in the next 48-hour period.
- Neutropenic fever is a single oral temperature of 38.3°C (101°F) or a temperature of greater than 38.0°C (100.4°F) sustained for more than 1 hour in a patient with neutropenia.
- ANC = WBC x (% polymorphonuclear cell count + % bands)

- Fever during neutropenia is a common side effect after myelosuppressive chemotherapy/radiotherapy; the incidence correlates directly with length and severity of the neutropenia.
- Up to 15% of patients with febrile neutropenia develop severe sepsis or septic shock.
**Approach to patient**

- Does the patient have any localizing symptoms?
  - May indicate the location of the infection.
- Does the patient have any existing central lines or ports?
  - Indwelling devices such as central lines and ports pose a potential nidus of infection and should be screened for in all patients in whom infection is considered.
- Does the patient complain of any oral symptoms?
  - Mucositis is often a complication of systemic chemotherapies associated with the development of bacteremias from coagulase-negative staphylococci and viridans group streptococci.
- Did the patient receive antibiotic prophylaxis?
  - Antibiotic prophylaxis (often with a fluoroquinolone) is usually recommended for patients with an ANC less than or equal to 100 cells/mm³ expected to last greater than 7 days. If patient had been receiving such an agent but still developed febrile neutropenia, suspicion for resistant organism should be raised.
- What is the anticipated duration of neutropenia?
  - Patients with prolonged anticipated neutropenia (i.e., greater than 7 days) are considered higher risk for complications related to febrile neutropenia.

**Approach to patient**

- Fever, general symptoms, weakness, reduced performance, diarrhea, dysuria, PAIN.
- Local signs of inflammation: catheter infection, skin infections, mucositis, gingivitis, abscesses, sinusitis, signs of pulmonary infection, meningitis, headache, amnesia
- Physical examination:
  - Intravenous access sites/catheter ports
  - Skin and oral mucous membranes
  - Perianal region
  - Pulmonary auscultation and percussion
  - Abdominal tenderness
  - Pain/pressure over paranasal air sinuses,
  - Lymphadenopathy
  - Meningeal signs

**Diagnostic/Treatment Approach**

Emergency: With fever during neutropenia, rapid initiation of treatment is essential:

1. Microbiological analysis; blood cultures, fecal cultures, throat swabs, sputum cultures.
2. Immediate initiation of empirical antibiotic treatment: broad-spectrum antibiotic with effectiveness
3. Optimization of tissue oxygenation; nasal cannula/mask. If applicable, advanced support (non-invasive: CPAP; invasive: intubation)
4. Volume substitution +/- Pressors
5. Initiate intensive medical care at an early stage
Empiric antibiotics (based on 2010 IDSA guidelines)

- All high-risk patients with febrile neutropenia should be placed on antipseudomonal beta-lactam; Cefepime/Carbapenem (meropenem or imipenem-claizactin) or piperacillin/tazobactam.

Role for additional agents?

- Vancomycin (and other agents directed at aerobic gram positive cocci) are not part of the standard initial empiric regimen for febrile neutropenia unless certain clinical situations:
  - Evidence of severe sepsis
  - Hemodynamic instability
  - Suspected catheter-related infection, skin or soft-tissue infection
  - Pneumonia
  - Severe mucositis

Role for antifungals?

- Persistent fever after 4-7 days of appropriate antibiotics and/or in whom an invasive fungal infection is suspected or proven.

Further Measures

- Further diagnosis (imaging, ultrasound, bronchoalveolar lavage (BAL), abscess aspiration/biopsy, etc.)
- If persistence of neutropenia is expected, administer G-CSF to support bone marrow reconstitution.
- Basic hospital hygiene; conduct of invasive procedures under aseptic conditions
- Patient hygiene, especially skin care, dental care, mucositis prophylaxis; avoid foods with high germ counts
- If neutropenia persists for more than 7 days: regular monitoring, even if afebrile — Consequent treatment of fever in neutropenia
- Administration of hematopoietic growth factors. Filgrastim and Peg-Filgrastim

Back to the case:

- 2 sets of blood cultures obtained
- Started empirically on IV cefepime, and admitted to the hospital.
- Evaluation including chest x-ray and urinalysis is negative for source of infection.
- On hospital day 3, patient defervesces and both sets of blood cultures return positive and grow a pan-sensitive Eschericia coli.
- Transitioned to oral ciprofloxacin. After one day of follow up after completion of antibiotics and endorses no further fevers.
Case # 9

- A 22 year old female with past medical history significant for Down's Syndrome is admitted to the hospital with blurry vision. Her care giver reports a 3 week history of high grade fevers and night sweats as well as weight loss of 15 pounds.
- During the evaluation, the patient has a tonic clonic seizure that lasted 1 minute. The patient has no known history of seizure disorder.
- VS; Temp 39.7 C, BP 118/80, RR 18 needing supplemental O2 (3L/min) satting 92%. HR 108
- Retinal hemorrhages are seen on ophthalmologic exam.

CBC

- 10.6
- 105.6
- 88
- 30

- Myeloblast predominance

BMP

- 137
- 100
- 36

- 4.5
- 24
- 1.31

- A peripheral blood smear is sent
- PT/INR, APTT all normal.

Hyperleukocytosis: Elevated WBC

- Seen in leukemias
  - ALL>=200,000 WBC
  - AML>=100,000 WBC
- Risks
  - Stroke
  - TLS
- Management
  - Hydration, hydration, hydration=first line
  - Leukopheresis if the WBC doesn’t come down to below the above levels with hydration

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Peripheral blood smear

Diagnosis?
AML

AML

- Group of clonal diseases with transformation of an early myeloid precursor.
- Different types of AML correspond to the differentiation stages of myeloid progenitor cells.
  - Cytogenetic: frequent chromosomal translocations
  - Molecular genetic: oncogene activation
  - Epigenetic: hypermethylation
- Complex classification system

Risk Factors

- Bone marrow damage: ionizing radiation, alkylating substances, topoisomerase inhibitors, benzol, cigarette smoke
- Predisposing hematological diseases:
  - myelodysplastic syndromes, myeloproliferative syndromes, aplastic anemia, multiple myeloma, paroxysmal nocturnal hemoglobinuria → development of “secondary” AML
- Genetic factors: increased risk with Trisomy 21
Acute myeloid leukemias (AML)
Classification - FAB
- M0: minimally differentiated
- M1: myeloblastic leukemia without maturation
- M2: myeloblastic leukemia with maturation
- M3: hypergranular promyelocytic leukemia
- M4: myelomonocytic leukemia
- M4Eo: variant, increase in marrow eosinophils
- M5: monocytic leukemia
- M6: erythroleukemia
- M7: megakaryoblastic leukemia

Common symptoms of Leukemia
- Systemic:
  - Weight loss
  - Fever
  - Frequent infections
- Lungs:
  - Easy shortness of breath
- Muscular:
  - Weakness
- Bones or joints:
  - Pain or tenderness
- Psychological:
  - Fatigue
  - Loss of appetite
- Lymph nodes:
  - Swelling
- Spleen and/or liver:
  - Enlargement
- Skin:
  - Night sweats
  - Easy bleeding and bruising
  - Purplish patches or spots

- CNS involvement with headache, nausea / vomiting, visual impairment, central nervous disturbances, polydipsia (rare)
- DIC; AML M3 (acute promyelocytic leukemia, APL), hyperfibrinolysis
- In particular with AML M4 / M5: skin infiltrates, gingival hyperplasia, CNS involvement
- Leukostasis (frequent with leukocytes > 100,000/μl):
  - Pulmonary symptoms (dyspnea, pulmonary leukemic infiltrates), cerebral stasis (ischemia, hemorrhage), arterial embolism
**Medical History, Clinical Signs;** History with risk factors, family history (immediate search for possible matched related blood stem cell donors)

**Examination:** skin, mucous membranes (gingival hyperplasia), lung (infections), lymph node, abdomen (hepatosplenomegaly), neurological findings

**Laboratory Tests**
- CBC with differential blood count, Peripheral blood smear
- BMP, LFTs
- LDH (elevated with increased cell turnover)
- Coagulation parameters (DIC, hyperfibrinolyis)
- Microbiological diagnostics if febrile, virus serum titers
  - Bone marrow aspirate
  - HLA typing of patient and all siblings (search for HLA-identical family donor for possible matched related allogeneic blood stem cell transplantation)
- Leukocytosis with detection of the same blast population as in the bone marrow.
- Anemia and thrombocytopenia as signs of suppression of normal hematopoiesis

**Back to the patient…..**
- Immediate measures, will be to aggressively hydrate, and monitor her hematologic parameters
- Monitor respiratory status.
- Role of Leukapharesis in controversial, but was successfully administered.
- Rapid cytoreduction can be achieved with induction chemotherapy → WBC count decreased to 35K within 24 hours.
She now carries the diagnosis of acute myeloid leukemia. She began chemotherapy with cytarabine and daunorubicin 36 hours ago. She notes feeling fatigued, having palpitations.

Physical Exam
- HR - irregular 80-100
- Right upper extremity →
  (Hint; same arm as BP cuff)

Her EKG:

Labs

- CBC (pre-treatment WBC; 105.6K)
  - 7.1
  - 23.6 | 82

- BMP
  - 141 | 105 | 36
  - 7.5 | 12 | 3.31

- Anion Gap 24
- Calcium 5.3 mg/dL (9.0-10.5 mg/dL)
- Phosphorus 9.7 mg/dL (3.0-4.5 mg/dL)
- Uric Acid 12 mg/dL (2.5-8 mg/dL)
- Lactic acid 24 mg/dL (6-16 mg/dL)
Tumor lysis syndrome

- Syndrome arising due to rapid destruction / decomposition of large amounts of tumor tissue with release of intracellular components, including K+, phosphate, and uric acid in rapidly proliferating malignancies
- Occurs in up to 10% of cases after effective treatment of acute leukemia, risk can be reduced to 1% with adequate pre-treatment

**HEMATOLOGIC/ONCOLOGIC EMERGENCY!!**

**Tumor Characteristics:**
- High cell turnover rate, rapid growth rate, high tumor bulk
- Poorly differentiated lymphomas (Burkitt's lymphoma), Non-Hodgkin Lymphomas (NHL), acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), and chronic myelogenous leukemia (CML)

**Patient Characteristics:**
- Elevated baseline serum creatinine, renal insufficiency
- Dehydration

**Chemotherapy Characteristics:**
- Chemo-sensitive tumors, such as lymphomas, carry a higher risk for the development of tumor lysis syndrome.
Back to the patient……..

1. ICU, tele, BMP, CBC, TLS labs Q 4-6 hrs.
2. Adequate hydration: NaCl 0.9%, minimum 2,000–3,000 ml/day
3. Hyperkalemia (> 5 mg/dl): Kayexelate p.o. or enema every 6 hrs. Glucose plus insulin (1 U per 2 g of glucose). ATTENTION: rebound effect when discontinued, as K⁺ is not fully eliminated but bound intracellularly. Pt had hemodialysis.
4. Hypocalcemia (< 8 mg/dl): Calcium gluconate 10% i.v. 10–40 mg, repeat every 12 h if necessary
5. Hyperuricemia: Rasburicase (recombinant urate oxidase) Allopurinol orally after treating this emergency.

Case# 10

- 74 year old woman is brought to the emergency room after falling off a step stool and injuring her right hip. Her past medical history is significant for several bouts of pneumonia during the past year.
- ROS; 3-day history of progressive worsening of fatigue, forgetfulness, constipation, excessive thirst, and increased urination.
- Past medical HX; Hypertension, Type 2 diabetes mellitus
On physical examination, she appears somnolent but is easily arousable.

Temp is 37.1 °C (98.8 °F), BP 110/70 mm Hg, HR 120/min, and respiration rate is 17/min.

Oral mucosa is dry, and the conjunctivae are pale. The lungs are clear.

No lymphadenopathy

X-ray, right hip reveal multiple lytic bone lesions.

**CBC**

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<td>WBC</td>
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<td></td>
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<tr>
<td></td>
<td></td>
<td>2.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>150</td>
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<td></td>
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**BMP**

<table>
<thead>
<tr>
<th>Ca</th>
<th>P</th>
<th>ALP</th>
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<tbody>
<tr>
<td>133</td>
<td>105</td>
<td>36</td>
</tr>
<tr>
<td>10</td>
<td>27</td>
<td>2.95</td>
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</tbody>
</table>

- AG, 1
- Laboratory studies:
  - Calcium 13.6 mg/dL
  - Total protein 9.6 g/dL.
  - Albumin 2.2 g/dL.
  - Urinalysis: Negative for protein
  - Erythrocyte sedimentation rate (ESR) is elevated @ 105mm/hour.
Elevated Erythrocyte Sedimentation Rate

- Measures the rate at which red blood cells sediment in a period of one hour.
- Non-specific measure of inflammation
- Indicator of the balance between + charged pro-sedimentation factors (mainly fibrinogen) vs – anti-sedimentation factors (mainly erythrocytes).

**Erythrocyte Sedimentation Rate**

- Simple, inexpensive BUT non-specific test that is used to help detect inflammation associated with conditions such as infections, cancers, and autoimmune diseases.
- ESR > 100 mm/hr →
  - Multiple myeloma
  - Temporal arteritis
  - Polymyalgia rheumatic
  - Flares
    - Systemic lupus erythematosus
    - Rheumatoid arthritis
    - Inflammatory bowel disease

\[ \text{ESR (mm/hr)} \leq \frac{\text{Age (in. years)} + 10 \text{ (if female)}}{2} \]

- Peripheral blood smear; Normochromic, normocytic erythrocytes with rouleaux formation
- Bone marrow; Plasma Cells
Multiple Myeloma

- Neoplastic clonal proliferation of terminally differentiated B-lymphocytes (plasma cells); characterized by monoclonal immunoglobulins ("paraprotein"), osteolysis, renal dysfunction, and immunodeficiency.
- The plasma cells proliferate in the bone marrow and often result in extensive skeletal destruction with osteolytic lesions, osteopenia, and/or pathologic fractures.

When to suspect Multiple Myeloma

- Bone pain with lytic lesions discovered on routine skeletal films.
- An increased total serum protein concentration and/or the presence of a monoclonal protein in the urine or serum.
- Systemic signs or symptoms suggestive of malignancy, such as unexplained anemia.
- Hypercalcemia, which is either symptomatic or discovered incidentally.
- Acute renal failure with a bland urinalysis or rarely the nephrotic syndrome due to concurrent primary amyloidosis.

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>%</th>
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<tbody>
<tr>
<td>Osteolysis, bone pain, spontaneous fracture</td>
<td>70%</td>
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<tr>
<td>Anemia, pallor, fatigue, reduced performance status</td>
<td>40–60%</td>
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<tr>
<td>Renal failure, oliguria, anuria</td>
<td>20–50%</td>
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<tr>
<td>Thrombocytopenia, hemorrhages (petechial type)</td>
<td>15%</td>
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<tr>
<td>Granulocytopenia, antibody deficiency, susceptibility to infection</td>
<td>15%</td>
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<tr>
<td>Cardiac failure (amyloidosis)</td>
<td>10%</td>
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<tr>
<td>Impaired vision, seizures, peripheral neuropathy</td>
<td>5–10%</td>
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<tr>
<td>Hyperviscosity syndrome, perfusion abnormalities</td>
<td>5%</td>
</tr>
<tr>
<td>Weight loss, fever, night sweats</td>
<td>&lt; 5%</td>
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International Myeloma Working Group Criteria for the Diagnosis of Multiple Myeloma

1. Monoclonal plasma cells in the bone marrow >10% and/or presence of a biopsy-proven plasmacytoma.
2. Monoclonal protein present in the serum and/or urine.
3. Myeloma-related organ dysfunction (1 or more):
   - Calcium elevation in the blood (serum calcium >10.5 mg/L [2.63 mmol/L] or upper limit of normal)
   - Renal insufficiency (serum creatinine >2 mg/dL [186.6 µmol/L])
   - Anemia (hemoglobin <10 g/dL [100 g/L] or 2 g < normal)
   - Lytic bone lesions or osteoporosis

Laboratory Tests

- CBC with differential
- BMP, Ca²⁺, serum creatinine, urea, uric acid, bilirubin,
- albumin, LDH, CRP, ESR ↑, β2-microglobulin ↑
- Total serum protein ↑, serum protein electrophoresis, immunofixation, detection of monoclonal paraprotein ("M-gradient")
- Urinary protein, urinary protein electrophoresis (M-gradient), detection of urinary light chains ("Bence-Jones proteinuria") in 60% of cases
- Detection of serum light chains (recently available assay), serum analysis more sensitive than urinary analysis
- Quantitative immunoglobulin level determination
  - immunoelectrophoresis

Serum Electrophoresis

- NORMAL
- MULTIPLE MYELOMA

Serum electrophoresis demonstrates an M-protein spike
M-protein usually presents as a single narrow peak, like a church spire, in the gamma, beta, or alpha-2 region of the densitometer tracing
Imaging

- X-ray (lateral skull, lateral spine, humerus, pelvis, femur): osteolysis or diffuse osteoporosis of the axial skeleton, multiple osteolytic skull lesions (punched-out skull)
- Suspected risk of fracture due to osteolysis (spinal column): CT / MRI / PET
- Spinal Cord compression; from an extramedullary plasmacytoma or a bone fragment due to fracture of a vertebral body → Suspected in patients presenting with severe back pain along with weakness/paresthesia of the lower extremities, or bladder or bowel dysfunction or incontinence; EMERGENCY!!

**Avoid iodine-containing contrast media due to potential nephrotoxicity**

Back to the Patient - Immediate support

- High fluid intake to treat renal impairment and hypercalcemia
- Analgesia for bone pain.
- Bisphosphonates → Rx hypercalcemia and to delay other skeletal related events
- Allopurinol → prevent urate nephropathy.
- Lenalidomide–dexamethasone, bortezomib induction therapy was initiated.

References

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- 2012 Clinical Practice Guide on Red Blood Cell Transfusion
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