Neutropenia and the ICU Patient

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Neutropenia and the ICU Patient

Neutropenia: Reduction in circulating neutrophils in systemic circulation.
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WBC have 2 Main Categories

• Granulocytes
• Agranulocytes
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Granulocyte:
- Make up approximately 70% of all WBCs.
- Neutrophils, eosinophils, & basophils.
- Produced in bone marrow from blood stem cells.

Agranulocytes:
- Make up remaining 30% of all WBCs.
- Monocytes, macrophages & lymphocytes.
- Also produced in bone marrow from blood stem cells.
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Blood stem cell

Myeloid stem cell

- Myeloblast
  - Red blood cells
  - Platelets

- Granulocytes
  - Eosinophil
  - Neutrophil

Lymphoid stem cell

- Lymphoblast
  - B lymphocyte
  - T lymphocyte
  - Natural killer cell

White blood cells
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• Hematopoiesis: Is the process of blood cells being formed in the bone marrow.
• Bone Marrow has enormous production capacity, steady state per hour.
• Numbers are kept at steady state but can be greatly amplified on demand.
• Granulopoiesis maturation is facilitated by G-CSF. Granulocyte Colony Stimulating Factor. GCSF also facilitates the release of mature neutrophils from bone marrow into circulation.
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Granulocyte Colony Stimulating Factor GCSF:

• Myeloid growth factors.
• Facilitate not only the maturation of neutrophils but also their release from the bone marrow into the systemic circulation.
• Drug form revolutionized Bone Marrow Transplant programs.
• Filgratim (Neupogen) or Pegfilgastim (Neulasta)....fertility drugs for bone marrow.
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Neutrophils

- First responders against bacteria, fungus & viruses. They are drawn there by a process of chemotaxis.
- Constitutes 55% of total WBC count.
- Takes 10-14 days for maturity.
- In circulation half life is 4-8hrs.
- Once in tissue live for several days.
- There are about 100xs more neutrophils in bone marrow than in circulation.
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- Chemotaxis:
- Process by which neutrophils are drawn to pathogen.
- Microorganism sends out signals.
- Neutrophils released by marrow to travel to pathogen (GCSF).
- Neutrophils age & die at site of infection over next 72hrs (apoptosis).
- Dead neutrophils give symptoms of infection....pus & sputum.
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• Chemotaxis:
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Neutrophil.....How does it mature?

- Bands
- Mature neutrophil
- “Shift to the left “
- Bands are capable of full phagocytic (“killer”) activity and are included in neutrophil count.
- Full maturation takes 10-14 days.
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Neutropenia and the ICU Patient

Why Does it Happen?

• **Acquired:** Infection, Collagen Vascular Diseases such as Lupus, Drug Induced, Chronic Idiopathic, Post Chemotherapy, Acute/Chronic Leukemia, Pre/post Bone Marrow Transplant (BMT).

• **Congenital:** Rare
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Acquired:
Disease Induced or Treatment Induced.

Disease Induced: Acute & Chronic Leukemias, Aplastic Anemia.

Treatment Induced: Chemotherapy & Total Body Irradiation.

Why these 2? We know these patient have little or no Bone Marrow Reserve.
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• With no neutrophils in the marrow on reserve.....there is no way to fight an invading pathogen.....bacteria, fungus, virus.....
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Disease Induced

Acute Leukemias:
1. Acute Myloegenous Leukemia (AML) adults.
2. Acute lymphocytic Leukemia (ALL) children.

Progress rapidly, immature cells (blasts) in bone marrow crowd out all other BM cells & prevent development of normal cells.

Signs & symptoms: Bone pain, fatigue, bleeding/brusing.

Treatment Induced

Cancer Treatment:
1. High Dose Chemotherapy.
2. Total Body irradiation.

Chemotherapy for solid tumour cancer or leukemias. Chemotherapy kills bone marrow cells. Limiting factor for some treatments but is the goal for leukemia treatment.

Total Body Irradiation (TBI) is part of conditioning regime for Bone Marrow Transplant.
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Red Blood Cells
- Lymphocyte
- Monocyte
- Eosinophil
- Basophil
- Neuropil

White Blood Cells
- Platelets

Marrow

Common symptoms of Leukemia
- Systemic: Weight loss, Fever, Frequent infections
- Psychological: Fatigue, Loss of appetite
- Lungs: Easy shortness of breath
- Muscular: Weakness
- Bones or Joints: Pain or tenderness
- Skin: Night sweats, Easy bleeding and bruising, Purplish patches or spots
- Lymph nodes: Swelling
- Spleen and/or liver: Enlargement
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- Total Body Irradiation is part of the “Conditioning” Regime for BMT.
- This plus high dose chemo.
- Goal is to wipe out their existing marrow & kill any remaining cancer cells any that may have seeded in their nervous system.
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• So.....chemotherapy for leukemic patients & conditioning regime (Chemo plus TBI) for BMT patients makes these patients neutropenic at extreme high risk for infection.
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Scope for Ottawa:

- Approx 30,000 patients in clinic for leukemia or lymphoma.
- Approx 120 BMTs performed per year.
- 24-40% BMT patients require ICU support.
- Neutropenia is the single most important predisposing factor to infection in the person with cancer.
- Infection is the most common cause of death in the cancer patient.
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Recognizing Neutropenia

- Low WBC count on blood work.
- Need differential.
- Absolute Neutrophil Count (ANC).
- ANC takes into account the mature neutrophils & bands.

\[ \text{ANC} = \text{Total WBC Count} \times (\% \text{neutrophils} + \% \text{bands}). \]

Neutrophil Count N 2.0-7.5

Remember this only accounts for circulating neutrophils....only 3% of body’s neutrophils.
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Relation of ANC to Risk of Infection:

- **Mild**: ANC between 1-1.5 $\times 10^9$/L.
- **Moderate**: ANC between 0.5-1.0 $\times 10^9$/L.
- **Severe**: < 0.5 $\times 10^9$/L
- **Profound**: < 0.1 $\times 10^9$/L & needs to be confirmed by manual count.
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What puts them at risk for Infection?

• Degree of neutropenia (ANC). Neutrophil count < .5.
• Duration of neutropenia.
• Indwelling catheters.
• Loss of other defence mechanisms (endothelium/mucosa) primarily from treatments.
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Indwelling catheters provide an entrance for endogenous bacteria to enter the blood stream.

Chemotherapy Induced Mucositis. Obvious in mouth/throat & runs the entire alimentary tract.
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The Gut & the Risk for Infection....

Approximately 400 species of microbes in our gut.

Neutrophils are constantly doing surveillance of the gut to keep things “in check”.

Once the gut mucosa breaks down.....the microbes move in.....neutropenic enterocolitis.
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- Mucositis
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- Chemotherapy induced pneumonitis.
- Damage from radiation (TBI or site specific).
- Lack of pulmonary macrophages.
Febrile Neutropenia

Febrile neutropenia still represents the most common and lethal complication of chemotherapy administration. Prior to empiric antibiotic therapy infection accounted for approximately 75% of mortality related to chemotherapy.
Recognizing Febrile Neutropenia……

• A temperature of 38°C or higher.

Is that all.........
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What else.......recognizing febrile neutropenia.

- ANC & relative risk
- Mucositis
- Corticosteroids
- Hypothermia
- LOC
- Hypotension
- Tachycardia
- Clinical deterioration (severe sepsis or septic shock)

RACE CALLING CRITERIA

CONSIDER calling RACE if there is:

<table>
<thead>
<tr>
<th>Acute change in</th>
<th>Physiology</th>
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<tbody>
<tr>
<td>Airway</td>
<td>Threatened</td>
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<tr>
<td></td>
<td>Respiratory rate ≥30 or ≤30</td>
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<tr>
<td></td>
<td>Distressed breathing</td>
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<tr>
<td></td>
<td>Saturations &lt;90% or 50% O2 or 5 liters/min</td>
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<tr>
<td>Breathing</td>
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<td></td>
<td>Systolic blood pressure ≤90mmHg or ≥200mmHg or decrease greater than 40mmHg</td>
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<td></td>
<td>Heart rate ≤60 or ≥130</td>
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<tr>
<td>Circulation</td>
<td>Decreased level of consciousness (GCS decrease ≥2 points)</td>
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<td>Urine output ≤100ml over 4hrs (except dialysis patients)</td>
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<tr>
<td>Neurology</td>
<td>Worsen concern about the patient</td>
</tr>
<tr>
<td>Other</td>
<td>Need medical assistance</td>
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To call – dial 7-5555 or 1-5555 and ask for code RACE to room ####

From 0730 to 1930 the team will include a dedicated MD, RN and RT. After hours the ICU resident will respond to calls.

JUST CALL!!
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The Patient with Febrile Neutropenia is a Medical Emergency
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47 year old female with a diagnosis of Acute Myeloid Leukemia. She is post induction chemotherapy. AM vitals:

- Oral Temp 38.1°C
- HR 110 bpm,
- BP 88/55.
- Feels “unwell” & PICC site is sore.
- ANC .5 (moderate ....she’s on the bubble for severe risk)
- Stomatitis present.
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- Transfer to ICU.
- 2 signs of SIRS
- Already has one system failure.
- Septic Shock can come on fast.....really fast.
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• Endogenous Source of Infection
Endogenous flora are an important component of the innate immune system protecting you from invasion by more pathogenic microorganisms.......however breakdown the normal defence barriers and infection can result. (Bowel)
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Assessment:
- Neuro
- Vitals
- Lung sounds (crackles) & WOB
- GI: Abdomen for tenderness & pain “pear shaped abdomen”, diarrhea, rectum (no rectal exam)
- Mucositis (stem-stern)
- Skin lesions
- Lines & sites...to remove or not remove...that is the question...
- Foley catheter
- Bleeding & risk for bleeding.

ALERT: There will be no or few obvious signs & symptoms of infection.
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Tests:

- Culture ASAP blood, lines, sites, lesions urine stool.
- Bronchoscopy
- Blood cultures only positive 20% of the time.
- Bld Work Elytes, Cr Bili, WBC, Diff, HgB
- Diagnostic Imaging again risk & benefit.
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Interventions & Management

• Sepsis management (fluid resuscitation, pressors, ventilation, VAP prevention, CRRT, source control).

• Most are in organ failure from septic mediators or from chemotherapy. Respiratory, Cardiovascular, Renal.

• Antibiotics within the first hour. Every hour you delay.........Think Golden Hour.
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Bugs & Drugs & ICU:
• Broad spectrum to cover gram negatives & gram positive.
• Gram negatives are “nasty” especially if they turn up in blood cultures (Ecoli, Klebsiella, HFlu.)
• Gram positive (Strep, S.aureus S epi.)

Piperacillin/Tazobactam and Vancomycin for febrile neutropenia on sepsis bundle for ICU.
Pip/Tazo covers gut & lungs
Vanco covers lines.
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- Haematology Program has standard orders & antibiotic recipes for their patients.
- BMT program now gives Ceftriaxone (3rd generation Cephalosporin) preemptive for ANC < .5. For CAP.
- Offending organism usually bacterial or fungal....but can be viral.
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Monitoring & Meticulous Care.

- ICU supportive care.
- Response to antibiotics. If no response within 48hrs add antifungal.
- How do you know if they are responding to antibiotics?
- Private room/Visitors (Flu season)
- Mouth & skin care
- Bowel management (risks & benefits)
- Enteral feeding (bleeding & hang times).
- Risk for bleeding (overt/covert).
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- Blood products & triggers to administer (HgB >90).
- No IM injections
- Pain Control (mucositis, dressings).
- Monitor blood work for neutrophils CBC & Diff platelets & HgB.....marrow recovery.
- As neutrophil count increases so will the signs & symptoms of infection.
- Will continue GCSF until there is improvement in neutrophil count.
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Family:

- Communicating with ICU team and Oncology/Hematology Team.
- May find “conflicting” perspectives.
- ICU mortality and Hope.
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- Want marrow recovery.
- Want response to antibiotics.
- Want a response to sepsis management.
- Want to avoid catastrophic event.
- Want to give the family “good” news.
Questions
References

Thanks

- Dr G Jones ICU TOH
- Linda Hamelin APN, BMT Program TOH
- Christel Johanson Pharmacist ICU TOH
- Joe Murphy Dietitian ICU TOH