When a fever is not just a fever…. Neutropenic fever in the cancer population

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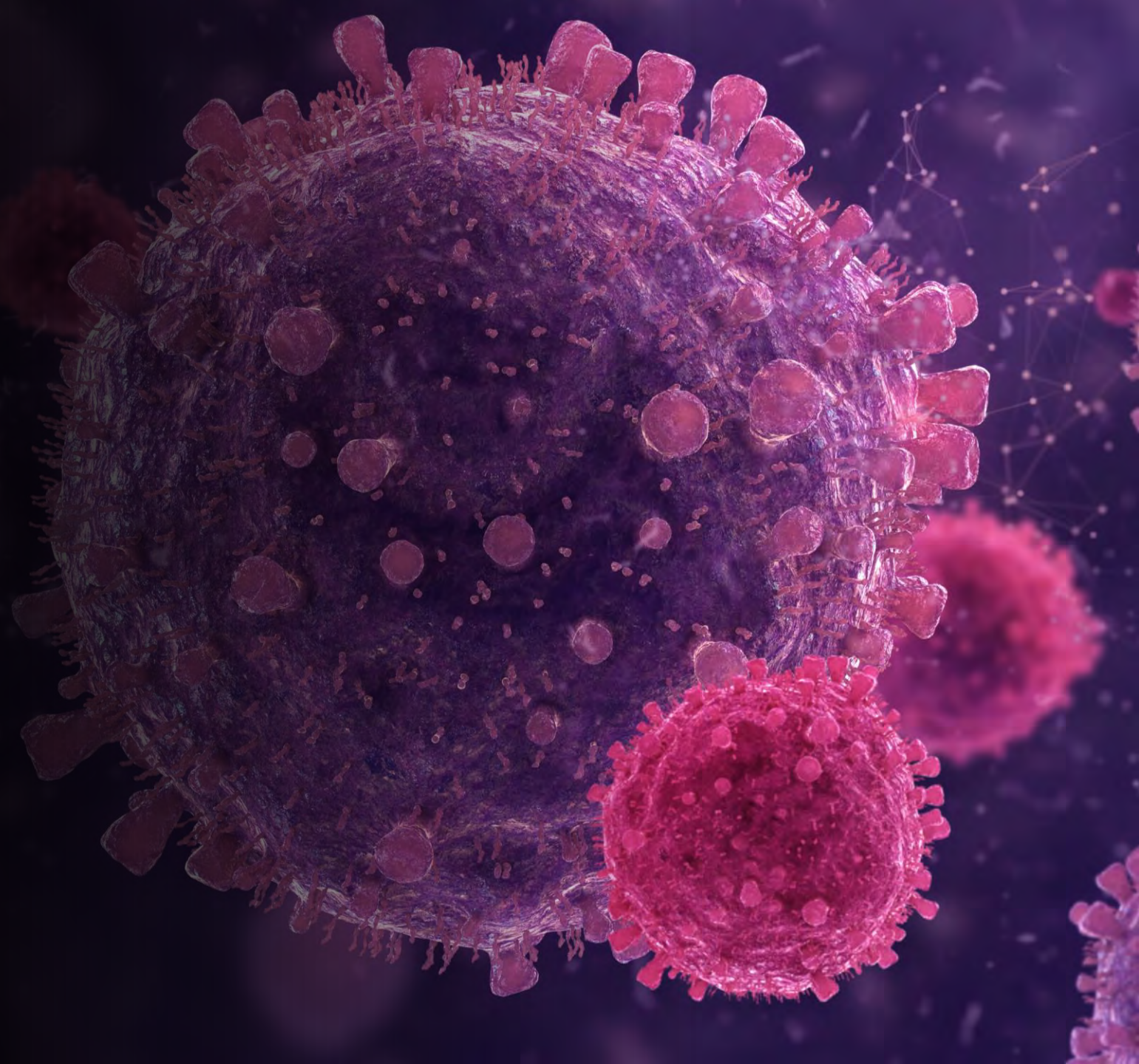
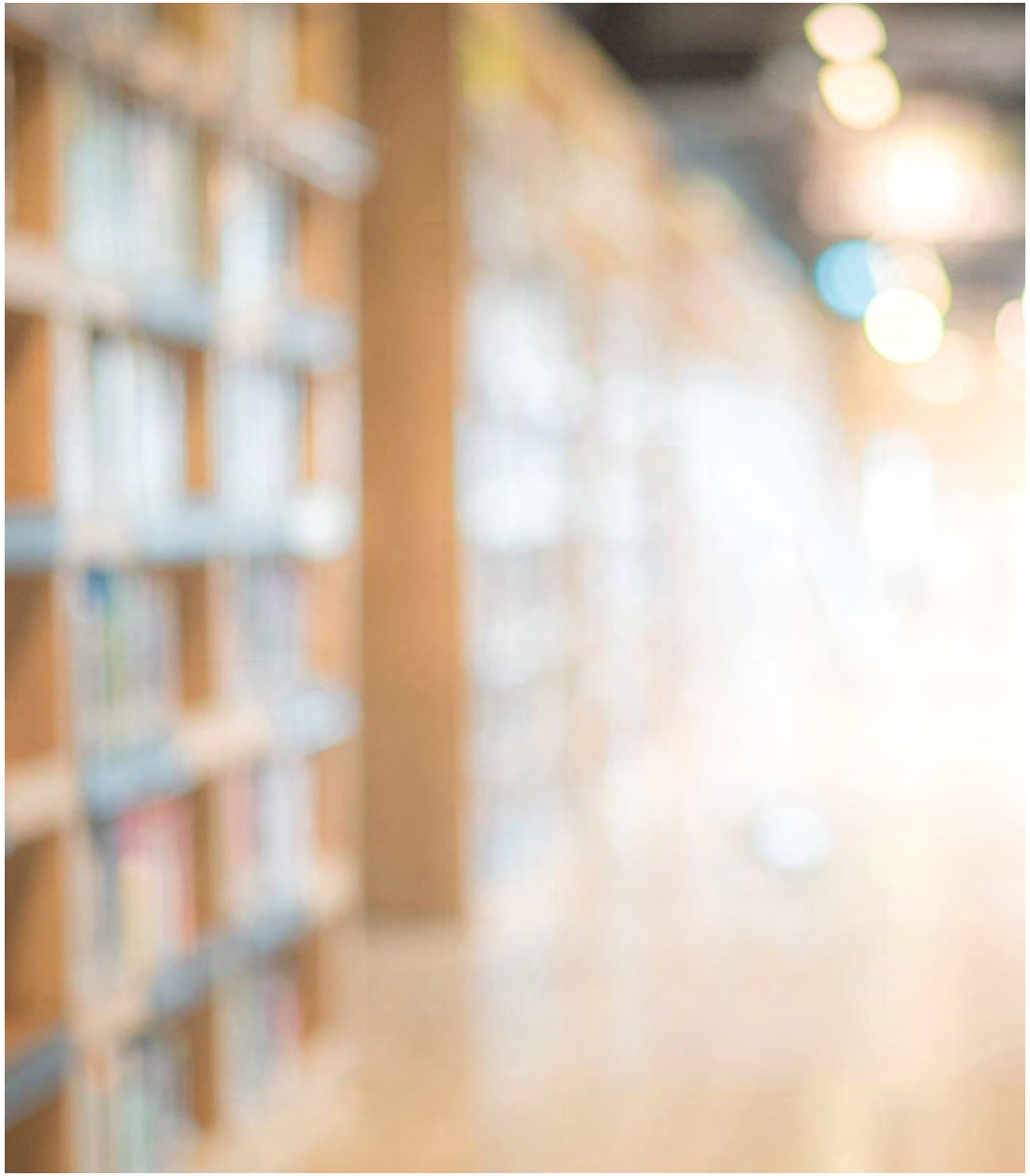


Learning Objectives

Identify 3 characteristics that place patients at high-risk for neutropenic fever

List three actions to prioritize infectious work-up and treatment

Differentiate between neutropenic fever in patients with solid tumors and hematological malignancy



Brief Review of Neutropenia

Neutropenia

Defined as a significant reduction in the absolute number of circulating neutrophils in the blood

Typically defined as an ANC less than 1,500

Depth of neutropenia is defined by levels

1. Mild: ANC is less than 1,500/mm3
2. Moderate: ANC equals 500 - 1000/mm3
3. Severe: ANC is less than 500/mm3
4. Chronic: Neutropenia lasting longer than 3 months

The degree and duration of neutropenia directly correlates with risk of infection and infection related deaths

The lower the ANC the higher the risk!

Calculating the ANC

- ANC = WBC x [(%polys) + (%bands)] x1000

- If WBC = 2.2k, 12% polys, 2% bands:
- Example
  - ANC = 2.2 x [0.12 + 0.02] x 1000 = 308

Risk Factors for Neutropenia

Treatment related	Comorbidities	Cancer Related
• Previous chemotherapy • Dose intensity of chemotherapy • Concurrent or prior irradiation of bone marrow • Pre-existing neutropenia • Multimodal treatment (chemo + radiation)	• COPD • Cardiovascular disease • Liver Disease • Renal Insufficiency • Diabetes • Age > 65 • Female sex • Poor Performance Status / Poor nutritional status / Decreased body surface area	• Bone marrow involvement of the tumor • Advanced Cancer • Type of Malignancy – Leukemia, Lymphoma, MDS, Lung

Other Causes of Neutropenia:

- Congenital
- Medications
  - Antibiotics
  - Antimalarials
  - Anti-inflammatory Drugs
  - Psychotropic Drugs
  - Antithyroid Drugs
  - Cardiovascular drugs
  - Antiseizure Medications
- Nutritional Deficiency

Neutropenic Fever Definition:

- A single oral temperature > than or = to 101

OR

- A temperature > than or = to 100.4 Fahrenheit for at least one hour

AND

- An ANC (absolute neutrophil count) less than 500 cells

- Remember…
  - *Signs and symptoms of infection commonly minimized or absent due to blunted inflammatory responses*
  - *Fever MAY be the only sign of infection*

NCCN Definition

The NCCN Guidelines define neutropenia as either

1. An ANC less than 500 neutrophils/mcl

OR

2. An ANC less than 1000 neutrophils/mcl and a predicted decline to 500 neutrophils/mcl or less over then next 48 hours

CLINICAL PRESENTATION → **INITIAL EVALUATION OF FEVER AND NEUTROPENIA** → **MICROBIOLOGIC EVALUATION** → **Initial Risk Assessment (FEV-2)**

Fever:
- Single temperature equivalent to ≥38.3°C orally

or
- Equivalent to ≥38.0°C orally over 1-hour period

Neutropenia:
- ≤500 neutrophils/mcL

or
- ≤1000 neutrophils/mcL and a predicted decline to ≤500/mcL over the next 48 hours

- Complete H&P including supplemental history:
  - Major comorbid illness
  - Type and time since last chemotherapy
  - History of prior significant infections Recent antibiotic therapy/prophylaxis
  - Medications
  - Use of devices
- Epidemiologically relevant exposures
- Laboratory/radiology assessment:
  - CBC with differential, comprehensive metabolic panel
  - Consider chest x-ray and urinalysis

- Blood culture x at least 2 sets (one set = 2 bottles)
  - One peripheral + one catheter (preferred but not required)[a]
- Urine culture (only if patient has symptoms or abnormal urinalysis; exercise caution in interpreting results if urinary catheter is present)
- Site-specific diagnostics:
  - Diarrhea (*Clostridioides difficile* [*C. difficile*] assay, enteric pathogen screen)
  - Skin (aspirate/biopsy of skin lesions or drainage)
- Viral diagnostics:
  - PCR- and/or direct fluorescence antibody (DFA)-based tests for vesicular/ulcerated lesions on skin or mucosa
  - Throat or nasopharynx for respiratory virus symptoms, especially during outbreaks

[a] Preferred for distinguishing catheter-related infections from secondary sources.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Etiology of Neutropenic Fevers

- Infectious etiology is only identified in 40-50% of patients with neutropenic fever
  - 10-30% of patients having bacteremia

- Bacterial
- Viral or Parasitic
- Fungal – Typically seen in chronic neutropenia
- Fever of unknown origin (FUO)

- *Translocation of bacteria --- mucosal barrier injury*

- *Approximately 50% of patients with febrile neutropenia will develop infection severe enough to lead to Sepsis*

  - ***Sepsis is the LEADING cause of death in patients undergoing treatment causing neutropenia***

Neutropenic Fever is a Medical Emergency

- Neutropenic fever occurs when a neutropenic patient encounters an infectious pathogen
- Due to a weakened immune system, patient's no longer have the ability to fight off infections

The overall mortality rate of febrile neutropenia is 5-20%

Rising to 50% in patients with shock

- ***ACT FAST!***
  - ***Save a life!***

High and Low Risk Patients with Fever and Neutropenia

High Risk:

- Anticipated prolonged (> 7 days) duration of neutropenia
- Profound neutropenia: ANC < / = to 100
- Significant medical comorbidities
- Hemodynamic Instability
- Inpatient status at the time of the fever
- Any alteration in physical barriers – Skin, mucosal lining of GI tract, catheters and implanted devices (Ports, stents, etc.)

Low Risk:

- Anticipated brief (< 7 days) neutropenic period
- No or few comorbidities and no history of fungal infections
- <60 years in age, asymptomatic or mild to moderate symptoms and STABLE vital signs
- Outpatient status at the time of the fever

Most Common Bacterial Culprits

- Gram Negative Rods
  - Most common cause of blood stream infections
    - 47-75%
    - Most common organism Enterobacteriaceae and Pseudomonas aeruginosa
    - Gram negative bacteria – specifically P. aeruginosa (accounts for 10% of infections) associated with higher mortality rates
      - Concern over global rise in Gram-negative resistance
- Gram Positive Rods
  - Account for 24-49% of blood stream infections
    - Mainly coagulase-negative Staphylococcus, Staphylococcus aureus and Enterococcus

Initial Patient Evaluation

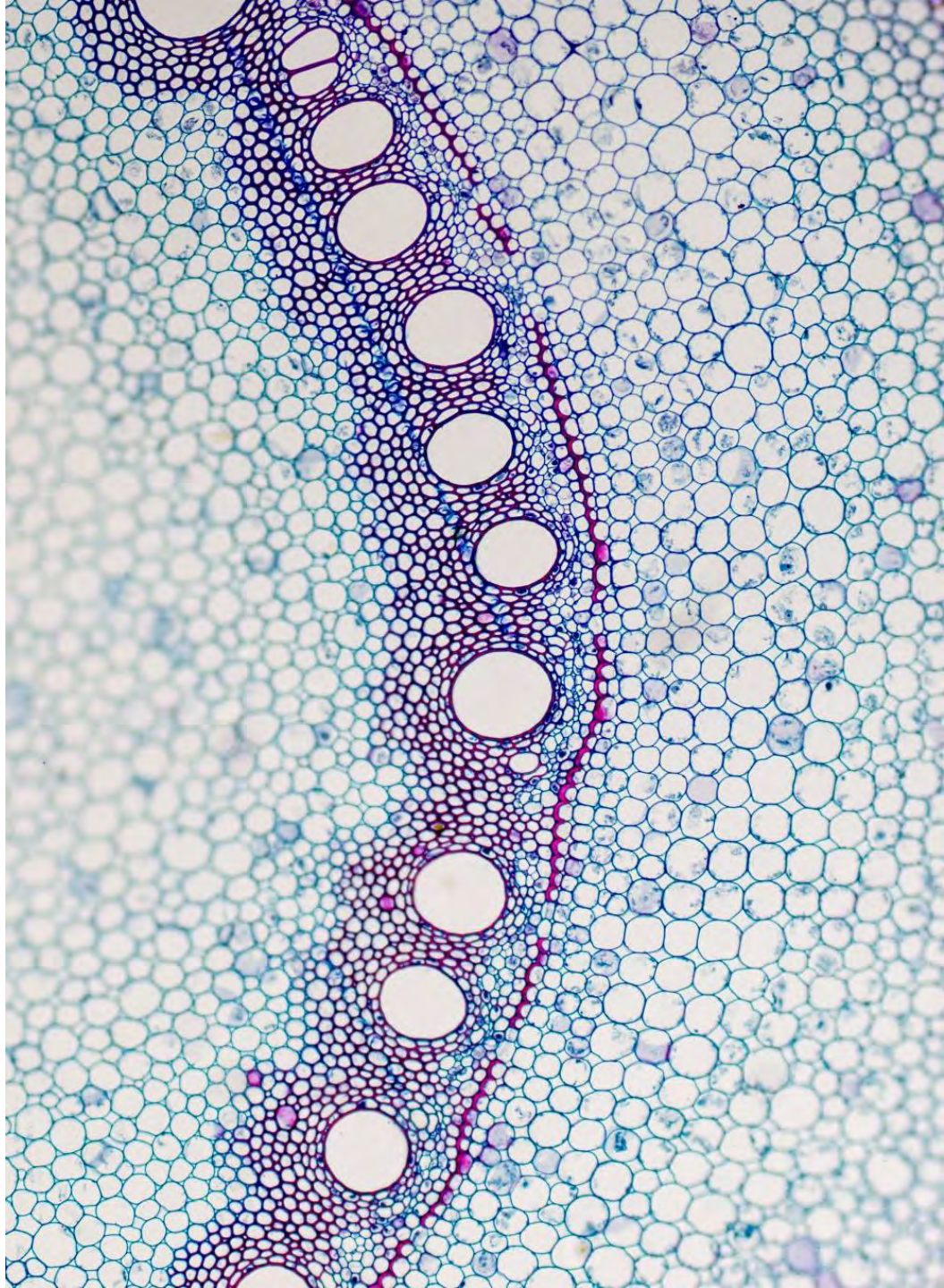
Patient Assessment

- Complete Patient Assessment
  - Comprehensive review of systems
  - Type and time since last chemotherapy
  - Major comorbid illness
  - History of prior significant infections including recent antibiotic therapy and prophylactic use
  - Potential sick contacts
  - Recent travel
  - Social history

- Physical Examination – detailed and site specific
  - CHECK EVERYWHERE!

Site –Specific Evaluation

- Mouth and Esophageal infections
  - Thrush, vesicular lesions, HSV, mucositis, dental infections
- Sinus or Nasal Infections
  - Rhinovirus, Adenovirus, Metapneumoviruses
- Lung Infections
  - COVID, RSV, Influenza, CAP, Hospital Acquired Pneumonia
  - Pulmonary infiltrates – CHF, Pulmonary edema, Hemorrhage, infarction, drug-induced pneumonitis, radiation injury, ARDS
- Abdominal, Rectal, Urinary, and Liver Infections
  - Cholangitis, Clostridium difficile colitis, Enterocolitis, Typhlitis, abscess, cystitis, urinary tract infection, pyelonephritis
- Skin and Soft Tissue
  - Any trauma, cellulitis, vesicular lesions, DIC, necrotizing fasciitis
- Vascular Access Device Infections
- Central Nervous System Infections
  - Meningitis



The First Hour

-Establish IV access
-CBC w/diff
-CMP
-Serum Lactate
-Procalcitonin Level**
-2 sets of blood cultures
    Port and peripheral
-Respiratory Viral Panel
    COVID/Flu/RSV
-Stool Studies for C-diff and Enteric Pathogens
-Urinalysis w/micro
-Sputum culture
-Wound Culture
-HSV Culture
-Chest X-ray

Diagnostic imaging
-CT scans – lungs, abdomen/pelvis, head
    We are very liberal in ordering CT scans!

Treatment

Delays in antibiotic therapy are associated with an overall decrease in survival… for each hour of delay, there is a 7.6% increase in mortality

Neutropenic Fever Antibiotic Order Set Power Plan

Component	Status	Dose ...	Details
Criteria for Neutropenic Fever: ANC of less than 500 cells/mm3 AND fever as defined by single ORAL temperature of 38.3 degrees C (101 degrees F) or ORAL temperature of 38.0 degrees C (100.4 degrees F) sustained over a 1 hour period			
Management for Neutropenic Fever: To be initiated for patients that meet the above criteria: Start antibiotics STAT after obtaining cultures EVEN IF LABS ARE PENDING.			
No known Beta-Lactam Allergy			
cefepime (Maxipime for Neutropenic Fever)			DOSE: 2,000 mg, inj, IVPB, Q8HR, Indication: Febrile neutropenia Priority: STAT, (Start) T;N
Non-anaphylactic allergic reaction (distant history of rash & no respiratory compromise)			
Non- anaphylactic penicillin allergy			
cefepime (Maxipime for Neutropenic Fever)			DOSE: 2,000 mg, inj, IVPB, Q8HR, Indication: Febrile neutropenia Priority: STAT, (Start) T;N
Non - anaphylactic cephalosporin allergy			
piperacillin-tazobactam			DOSE: 3.375 gm, inj, IVPB, ONCE, Indication: Febrile neutropenia Priority: STAT, Infuse Over: 30 min
piperacillin-tazobactam (Zosyn for Neutropenic Fever)			DOSE: 3.375 gm, inj, IVPB, Q8HR, Indication: Febrile neutropenia Priority: Routine, (Start) T;N+240, Infuse ... Start four hours after initial dose
Anaphylactic Beta Lactam allergy (angioedema, shortness of breath, hypotension, hives in recent past). For ceftazidime allergic patients discuss ID pharmacist or consider ID consult.			
aztreonam			DOSE: 2 gm, inj, IVPB, Q8HR, Priority: STAT, (Start) T;N
AND			
tobramycin			DOSE: 7 mg/kg, inj, IVPB, ONCE, Indication: Febrile neutropenia Priority: STAT, (Start) T;N Pharmacy to round to nearest 20mg. Pharmacy to dose future doses.
Tobramycin - Pharmacy to Manage			T;N, Routine, DAILY, Pharmacy to round to nearest 20mg. Pharmacy to dose future doses.
vancomycin			DOSE: 15 mg/kg, inj, IVPB, Q12HR, Indication: Febrile neutropenia Priority: STAT, (Start) T;N Pharmacy to round to nearest 250mg with max dose of 2000mg. Pharmacy to dose future doses.
Vancomycin - Pharmacy to Manage			T;N, Routine, DAILY, Pharmacy to round to nearest 250mg with max dose of 2000mg. Pharmacy to dose future doses.
Evaluate if expanded Gram positive coverage is indicated: ADD Vancomycin* ONLY if any of the following conditions are met. *Hypotension or septic shock without an identified pathogen *Positive blood cultures for Gram positive bacteria, before final identification and susceptibility testing available *Clinically suspected serious catheter-related infection (chills with infusion through catheter & cellulitis around the catheter) *Skin or soft - tissue infection at any site			

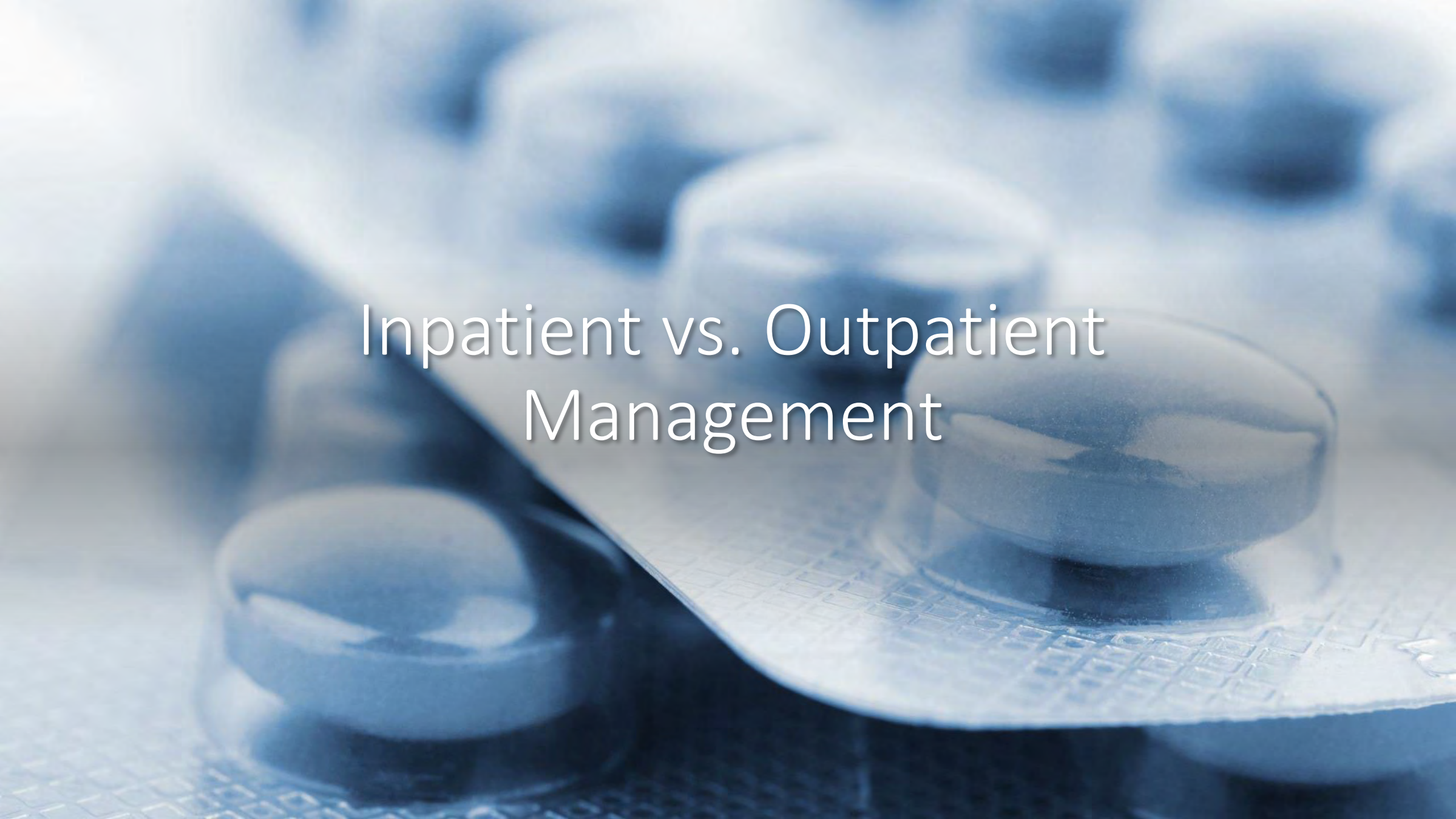
Sepsis

Septic Shock in Neutropenic Fever

- Estimated that up to 50% of patients with febrile neutropenia will develop an infection that can lead to Sepsis
  - Sepsis is the LEADING cause of death in patients with neutropenic fever
- ***Identify Early***
- Hypotension
- Tachycardia
- Lactic Acidosis
  - Greater than 2mmol/L indicative of increased oxygen consumption or decreased oxygen delivery to tissue = poor tissue perfusion
  - Oxygen
- Treatment
  - 30cc/kg of IV Crystalloid Fluid (Normal Saline)
  - If BP is NOT responsive to fluid resuscitation start vasopressors to keep the MAP >65
    - First line is Norepinephrine
      - May be administered peripherally until central-line access is obtained
        - WHY?

Sepsis Order Set/Power Plans

	Patient Care	
☑	Vital Signs	Routine, T;N, BP, Q1H while on fluid resuscitation, then Q4H
☐	Hemodynamic Monitoring	Routine, T;N, CVP, QSHIFT
☐	Hemodynamic Monitoring	Routine, T;N, Goals: CVP 8-12 mmHg ...
☐	Hemodynamic Monitoring	Routine, T;N, Goals: MAP 65 mmHg or greater
☐	Hemodynamic Monitoring	Routine, T;N, Urine output greater than 0.5 mL/kg/hr
	MAP Optimization with Fluids (SBP less than 90 mmHg or SBP is 40 mmHg less than normal or MAP less than 65 mmHg)	
☐	Sodium Chloride 0.9% (Sodium Chloride 0.9% *bolus*)	DOSE: 30 mL/kg, inj, IV, ONCE, Priority: NOW, Rate: 999 mL/hr ...
☐	Sodium Chloride 0.9%	1,000 mL, inj, IV, Priority: Routine, (Start) T;N, mL/hr
	Antibiotic Therapy	
	Infuse IV Antibiotics within the first hour of recognition of sepsis	
☐	Consult Inpatient MD/Program	Routine, T;N, Infectious Disease
☑	Pharmacy Consult *Other Monitoring - See Comment*	Priority: Routine, (Start) T;N Pharmacy to dose and follow levels of all medications
	Recommended for Sepsis/Septic Shock of Unclear Etiology - Non-neutropenic Patient	
	Vasopressors	
	DOPamine dosage:	
	Low dose: 1-5 mcg/kg/min = increased renal blood flow and urine output	
	Medium dose: 5-15 mcg/kg/min = increased renal blood flow, heart rate, cardiac contractility, and cardiac output	
	High dose: Greater than 15 mcg/kg/min = alpha-adrenergic effects begin to predominate, vasoconstriction, increased blood pressure	
☐	DOPamine 400mg in D5W 250mL Critical Care	mcg/kg/min Titration Range: 5-10 mcg/kg/min Titration Frequency: Every 5 min or more Maintain MAP Gre... (conc = 1,600 mcg/mL) Titrate to goal MAP. Usual starting dose 2 to 10 mcg/kg/min. May increase or decre...
☐	DOBUTamine 500mg in D5W 250mL Critical Care	mcg/kg/min Titration Range: 0.5-2.5 mcg/kg/min Titration Frequency: Every 2 min or more Maintain MAP G... (conc = 2,000 mcg/mL) Titrate to goal MAP. Usual starting dose 0.5 to 2.5 mcg/kg/min. May increase or dec...
☐	EPINEPHrine 4mg in NS 250mL Critical Care	mcg/kg/min Titration Range: 0.05-0.1 mcg/kg/min Titration Frequency: Every 2 min or more Maintain MAP ... (conc = 16 mcg/mL) Titrate to goal MAP. Usual starting dose 0.05-0.25 mcg/kg/min. May increase or decrea...
	**NONSTANDARD norepinephrine infusions -- please allow for preparation time **	
☐	norepinephrine 16mg in NS 250mL Critical Care	mcg/kg/min Titration Range: 0.01-0.25 mcg/kg/min Titration Frequency: Every 2 min or more Maintain MAP... (STANDARD Conc = 64 mcg/mL) Titrate to goal MAP. Usual starting dose 0.01 to 0.5 mcg/kg/min. May incre...
☐	phenylephrine 50mg in NS 250mL Critical Care	mcg/kg/min Titration Range: 0.1-2 mcg/kg/min Titration Frequency: Every 2 min or more Maintain MAP Gre... (STANDARD Conc = 200 mcg/mL) Titrate to goal MAP. Usual starting dose 0.5 to 2.5 mcg/kg/min. May incre...
☐	vasopressin 20 units in NS 100mL	100 mL, inj, IV, Priority: Routine, (Start) T;N, Rate: 9 mL/hr



Inpatient vs. Outpatient Management

Risk Stratification

- The Multinational Association of Supportive Care in Cancer (MASCC) risk index is the most widely used risk assessment tool
- MASCC is derived from weighted scores for seven variables that determine whether a patient has a low or high risk of a poor outcome, including death
- 7 Variables
  - Symptom burden of febrile neutropenia
  - Presence of hypotension
  - History of chronic obstructive lung disease
  - Solid tumor or hematologic malignancy with previous fungal history
  - Dehydration
  - Outpatient status
  - Age >60

MASCC Score

Burden of illness (symptom severity) As determined by attending physician at presentation	**None or mild**	**+5**
	Moderate	+3
	Severe	0
Hypotension sBP <90 mmHg	**No +5**	Yes 0
Active COPD Active chronic bronchitis, emphysema, decreased FEV, or need for oxygen therapy, corticosteroids, and/or bronchodilators	**No +4**	Yes 0
Type of cancer	**Solid tumor**	**+4**
	Hematologic, no prior fungal infection	+4
	Hematologic, prior fungal infection	0
Dehydration requiring IV fluids	**No +3**	Yes 0
Status at onset of fever	**Outpatient +3**	
	Inpatient 0	
Age (years)	**<60 +2**	≥60 0

MD+CALC

Outpatient Management

- Per NCCN Guidelines
  - Outpatient should <u>ONLY</u> be considered
    - Following an observation period of 2-12 hours
    - Patients at low risk must have
      - 24/7 care
      - Have a telephone
      - Telephone follow-up should be performed within 12-24 hours
      - Be within 1-hour travel time of a hospital/medical center
      - Must be able to be assessed daily x 72 hours following initiation of antibiotics
    - Antibiotic Recommendations
      - Ciprofloxacin plus Amoxicillin/Clavulanate
        - OR
      - Ciprofloxacin plus Clindamycin in penicillin-allergic patients

Burden to the Healthcare System

Neutropenic Fever Facts

Febrile neutropenia is considered a medical emergency with an overall mortality rate of 5-20%

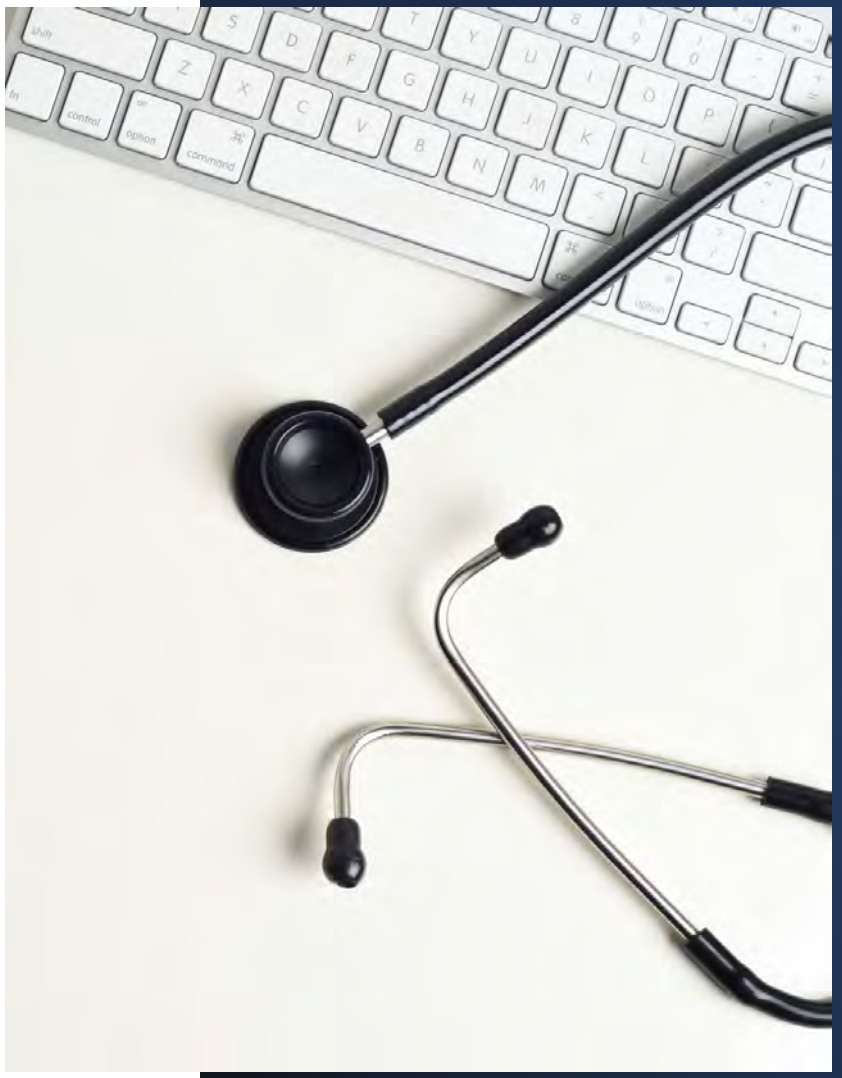
Mortality rate can increase to 50% in patients with febrile neutropenia that develop Septic Shock

In the US drug-incidence neutropenia is 2.4-15.4 cases/million each year

Incidence of febrile neutropenia is 7.8/1000 patients with cancer

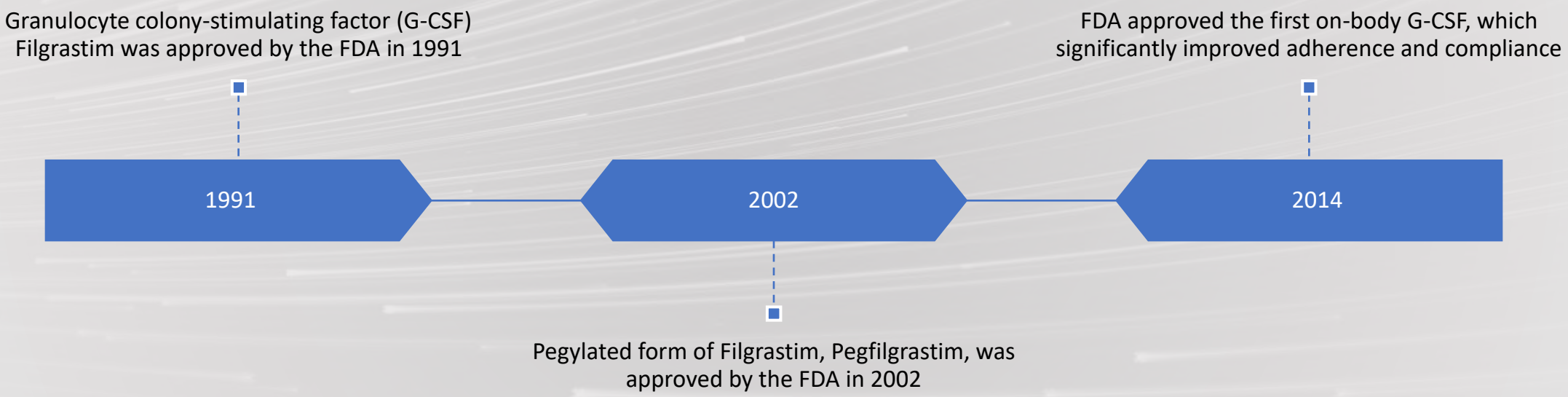
Febrile Neutropenia can result in hospitalization and antibiotic treatment, reducing the intensity or delaying critical treatment (Chemotherapy), which may potentially shorten overall survival as well as diminishing quality of life

- Average LOS of patients admitted to the hospital for febrile neutropenia is 5.7 – 9.6 days
- Mortality rate among hospitalized patients
    - 2.6 – 7% for solid tumors
    - 7.4% for hematological malignancy
- 2012 Data
    - Total costs of hospitalization for neutropenia among adult patients with cancer
        - $2.3 Billion
        - Mean hospitalization cost $20-40,000
- **Imagine the cost now…..**



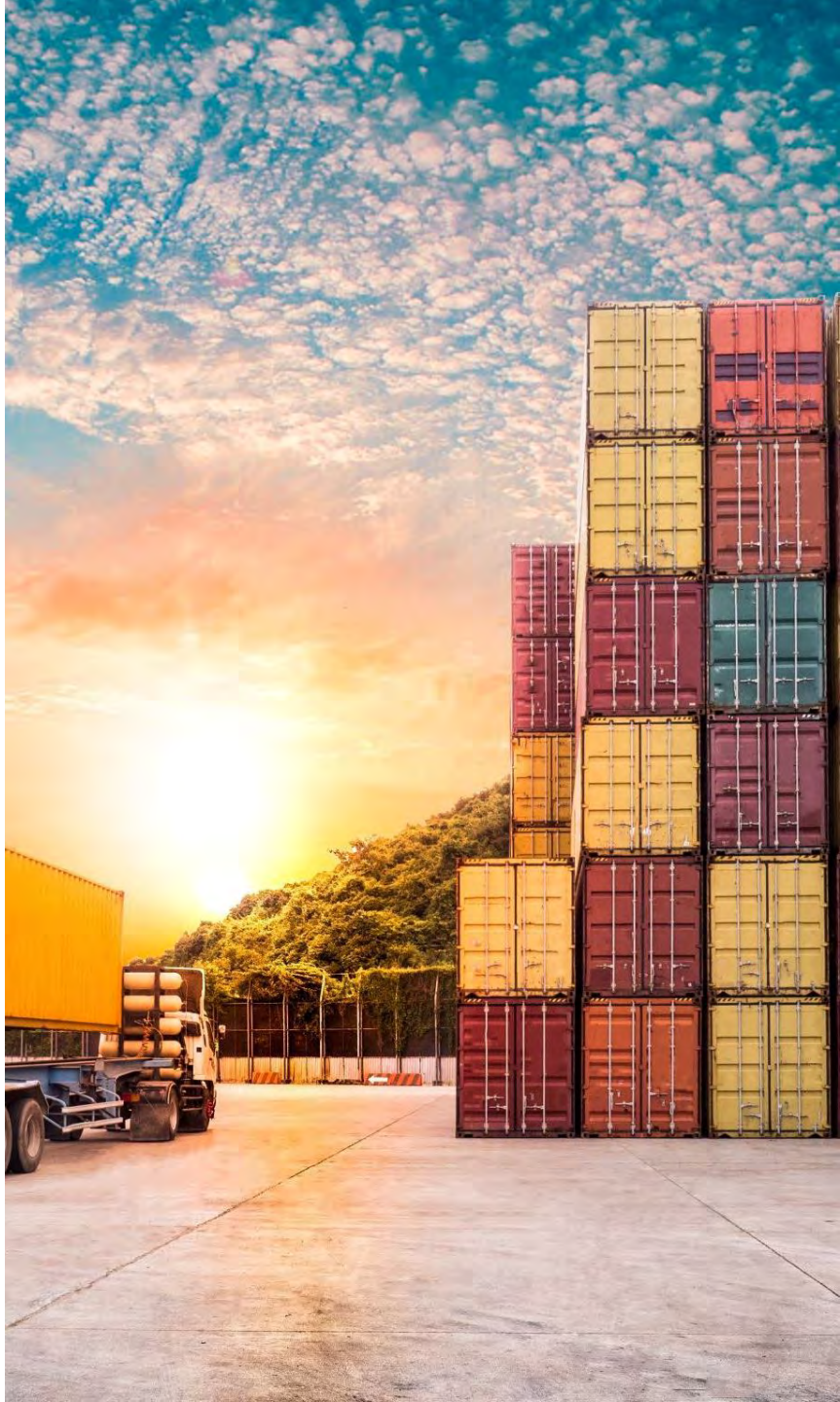
Emerging Trends

Future Trends:



Barriers

- COST
- Logistics of administration
- Access Disparities



The Future….

- As of November 2022
  - Currently 3 FDA-approved filgrastim biosimilars and 6 pegfilgrastim biosimilars
  - Saving an estimated $54 billion dollars over 10 years
    - Saving an average of $3000 per patient per year
  - These innovations have increased the use of G-CSF in both commercially insured and Medicare populations
  - G-CSF use in high-risk febrile neutropenic populations increased from 75-83% in commercially insured individuals and from 75-86% in Medicare populations

Case Studies

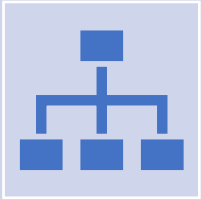
Which of the following Neutropenic patients are at high risk for serious complications?

- 26-year-old woman with AML, Fever of 102.0, with mucositis
- 70-year-old man with colon cancer, fever of 101.0 with MASCC score of 22
- 60-year-old man with CLL, fever of 101.0 on Alemtuzumab
- A & C
- All of the above

BR is a 62-year-old man with HTN and CMML and newly diagnosed PTCL, currently on CHOP, completed C2 8-days ago, presented to urgent care with a 3-day history of increased weakness and fatigue, intermittent chills, without documented fever. He presents today with a documented fever at home of 103.7, taking 1gm of Tylenol prior to arrival. He reports nausea with 1 episode of vomiting prior to arrival. He denies any other associated symptoms.

What diagnostic evaluation should be considered for this patient?

Based on the available information, what is the most likely diagnosis and why?

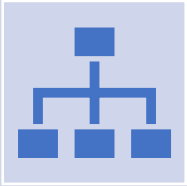


What is the proposed management?

GN is a 65-year-old man with ALL, s/p multiple lines of therapy, currently on Blincyto + Ponatinib and IT MTX/Ara-c, started on C4D22 3 days ago. He presents to urgent care from clinic with redness and pain to right arm PICC line, with purulent drainage around the catheter, fever of 102.9, and leukocytosis.

What diagnostic evaluation should be considered for this patient?

Based on the available information, what is the most likely diagnosis and why?

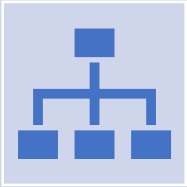


What is the proposed management?

PT is a 36-year-old man with newly diagnosed AML in the setting of a several month history of pancytopenia, currently on Decitabine/Venetoclax, starting C1 14 days ago. He presented to urgent care today reporting a 2-week history of sore throat and new oral mucositis.

What diagnostic evaluation should be considered for this patient?

Based on the available information, what is the most likely diagnosis and why?



What is the proposed management?

Questions?


Thank you all so much!!!!