Oncology Patient with Fever

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What is a Clinical Pathway?

An evidence-based guideline that decreases unnecessary variation and helps promote safe, effective, and consistent patient care.
Objectives of Pathway

• Decrease time to antibiotics
• Decrease morbidity/mortality from infection
• Improve rate of correct antibiotic coverage for neutropenic oncology patients with different risk factors
• Decrease unnecessary long-term antibiotic use and associated toxicities
• Increase rate of proper anti-fungal coverage
• Decrease unnecessary admissions for low risk patients
Why is Pathway Necessary?

• Febrile events occur in 1/3 \textsuperscript{rd} of neutropenic patients with cancer

• Infection is a major cause of morbidity/mortality

• Fever is often the first sign of potential infection

• Standardized protocols for fever & neutropenia have been shown to improve outcomes
**Organisms Identified**

- **Shift towards a dominance of gram-positive organisms due to prophylactic antimicrobials and CVLs**
  - Most common organisms
    - Coagulase-negative staph
    - Strep viridans
    - Staph aureus (including MRSA)

- **Aerobic gram negative bacilli account for 1/3 to 1/2 of bacteremias**
  - Most common organisms
    - E. coli
    - Klebsiella
    - Pseudomonas
    - Acinetobacter
    - Enterobacter

*Need for broad gram-positive and gram-negative coverage, including Pseudomonas*
Time to Initial Antibiotics

- Early intervention of antibiotics in septic patients has been shown to improve outcomes\(^1\)
- Early antibiotic administration is associated with higher survival rates in febrile neutropenic patients\(^2\)
- Implementing a standard protocol for children with febrile neutropenic patients has been shown to decrease the time to antibiotic administration\(^3\)
Initial Antibiotic Choices

• Zosyn
  o Good anaerobic, gram positive & gram negative coverage including pseudomonas
  o No MRSA coverage
• Ceftazidime
  o Only has gram negative coverage (including pseudomonas)
  o Poor gram positive or anaerobic coverage
• Vancomycin
  o Gram positive coverage including MRSA
  o No gram negative coverage
Vancomycin

- Early vancomycin treatment may reduce mortality in high risk patients
- However, judicious use of vancomycin is warranted as there has been a link between its overuse and the development of drug resistance in Enterococcus species and S. aureus.
- Recommend discontinuing use, after 2-3 days of therapy, if susceptible species are not grown on culture\(^4\)
Acute Kidney Injury

- Vancomycin known to cause nephrotoxicity
- Recent evidence shows that Zosyn may augment Vancomycin nephrotoxicity
- When starting Vancomycin:
  - Zosyn should be discontinued and ceftazidime started (for gram negative coverage)
- Ceftazidime not associated with nephrotoxicity
- When discontinuing Vancomycin:
  - Ceftazidime should be switched to Zosyn
  - Ceftazidime has virtually no gram positive coverage, therefore it cannot be used as monotherapy
This is the Oncology Patient with Fever Clinical Pathway.

We will be reviewing each component in the following slides.
**Inclusion Criteria:**

1. Oncology patients who are receiving chemotherapy/radiation AND
2. Fever (38 or higher) sustained for an hour OR >38.5 at anytime OR ill appearing

**Exclusion Criteria:**

1. Completed chemotherapy >1 month AND no longer have a central line
2. Bone marrow transplants
Initial Management:
ED Triage: Triage ESI Level 2

**ED RN:**
- Obtain vitals ASAP upon presentation
- Obtain vascular access and labs per Nursing Treatment Protocol
  - Access port/central line if present. Place IV if unable to access or no CVL
  - Blood cultures from all lumens of CVL; peripheral blood ox only if IV placed.
  - CBC with auto diff
- If febrile and not already given in last 4 hours:
  - Give acetaminophen 15 mg/kg PO

*Do NOT give any medications per rectum.
Do NOT give NSAIDs (contraindicated in oncology patients).*

**ED Provider:**
- **STAT:** Order antibiotics and labs (CBC w diff, blood cultures if not done by RN) – see dosing below
- Obtain H&P
- Type of cancer; stage of treatment; recent chemo (type, date); hx of prior infections; mucositis; CVL erythema/discharge/pain; prior complications; signs of neutropenic enterocolitis
- Consider further work up as indicated (CRP, chemistries, LFTs, UA/Ucx, CXR, type & screen)

**Signs of sepsis:** Notify attending/fellow immediately and proceed to Septic Shock Pathway.

*** If signs of septic shock, notify attending immediately and start Septic Shock Pathway ***
**GIVE ANTIBIOTICS within 1 hour of presentation!**
Do NOT wait until labs have returned!
Review any labs completed in past 24 hours.

- **Standard Risk:**
  - ANC ≥ 500 (on CBC done in last 24h) AND well appearing; OR no CBC available:
    - Ceftriaxone 75 mg/kg IV (max 2 g) x 1 dose
    - If allergy: Levofloxacin 6 mo-4 yr: 10 mg/kg, 5-9 yrs old: 7 mg/kg, ≥ 10 yrs old: 10 mg/kg (max 750 mg) x 1 dose
  - ANC <500 (on CBC done in last 24h) OR ill appearing:
    - Piperacillin/Tazobactam 100 mg/kg (max 4.5 g) x 1 dose
    - If allergy: Clindamycin 10 mg/kg q6hr IV (max 600 g/dose) AND Ciprofloxacin 10 mg/kg q8hr IV (max 400 mg/dose)

- **High Risk?**
  - Ill-appearing
  - Skin soft tissue infection
  - Mucositis
  - Concern for neutropenic enterocolitis
  - Pneumonia
  - Hx of staph viridans or known ESBL colonization
  - If ANC < 500:
    - ALL, not in maintenance - AML
    - Relapsed ALL/Lymphoma
    - Down syndrome

**How to calculate Absolute Neutrophil Count (ANC):**

\[
ANC = WBC \times (\%\text{Neutrophils} + \%\text{Bands})
\]

- **ANC> 500 and well appearing** give Ceftriaxone (or Levofloxacin if allergy)
- **ANC<500 or ill appearing** give Piperacillin/Tazobactam (if allergy, Clindamycin AND Ciprofloxacin).

***ANTIBIOTICS SHOULD BE GIVEN WITHIN 1 HOUR OF PRESENTATION***
Do not wait for labs to return

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High Risk Patients:

- Are at greater risk for progression to septic shock or other adverse outcome
- Require broader spectrum antibiotic coverage
- These patients are either
  - Initially designated as high risk at admission (see High Risk box)
  - Or have failed low risk therapy after 72 hours

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  - If allergy: **Clindamycin** 10 mg/kg q6hr IV (max 600 g/dose) AND **Ciprofloxacin** 10 mg/kg q8hr IV (max 400 mg/dose)

**High Risk**
- Ceftazidime 50 mg/kg IV x1 dose AND
- **Vancomycin** 15 mg/kg IV (max initial dose 1 g/dose) x1 dose

**ANC**
- On CBC done in last 24h
- Well appearing: ANC ≥ 500
- Ill-appearing: ANC < 500
- ALL, not in maintenance
- AML
- Relapsed ALL/Lymphoma
- Down syndrome

**CLINICAL PATHWAY: Oncology Patient with Fever**

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  - Review any labs completed in past 24 hours.

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  - ANC ≥ 500 (on CBC done in last 24h) AND well appearing; OR no CBC available:
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    - If allergy: Clindamycin 10 mg/kg q6hr IV (max 600 g/dose) AND Ciprofloxacin 10 mg/kg q8hr IV (max 400 mg/dose)

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  - Ceftazidime 50 mg/kg IV x1 dose AND
  - Vancomycin 15 mg/kg IV (max initial dose 1 g/dose) x1 dose

- **ANC**
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  - Well appearing: ANC ≥ 500
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  - Vancomycin 15 mg/kg IV (max initial dose 1 g/dose) x1 dose

- **ANC**
  - On CBC done in last 24h
  - Well appearing: ANC ≥ 500
  - Ill-appearing: ANC < 500
  - ALL, not in maintenance
  - AML
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Admission decision is made based on patient’s ANC, clinical appearance, and risk factors

- ANC >500 and well appearing
  - Patient will be able to be discharged home as long as they have good follow up.
- ANC <500 or ill appearing
  - Patient will likely be admitted to Heme/Onc

Discharge home if following criteria met:
- Family able to return q24hr if still febrile
- Discussion with Heme/Onc attending re: disposition
- Follow-up with Heme/Onc
- If Ceftriaxone allergy: Provide Rx for 24 coverage of levofloxacin:
  - 6 mo-5yr: 12 mg/kg q12hr
  - 5-10yr: 8 mg/kg q12hr;
  - >10yr: 10 mg/kg q24hr
  - max 750 mg/day for all ages

ED to call Heme/Onc to discuss admission and High Risk vs Standard Risk status
Patients with Current ANC <500 or who are ill appearing will be admitted.

Treatment will be based on Risk status:

- **High Risk**
  - Ill-appearing
  - Skin soft tissue infection
  - Mucositis
  - Concern for neutropenic enterocolitis
  - Pneumonia
  - Hx of strep viridans or known ESBL colonization

- **If ANC < 500:**
  - ALL, not in maintenance
  - AML
  - Relapsed ALL/Lymphoma
  - Down syndrome

**Antibiotics:**

**Start antibiotics ASAP** (if not already given in the ED)

- Piperacillin/Tazobactam 100 mg/kg q6hr IV (max 4.5 g/dose)
  - If allergy: Clindamycin 10 mg/kg q6hr IV (max 600 g/dose) AND Ciprofloxacin 10 mg/kg q8hr IV (max 400 mg/dose)

**Labs:**

- CBC q24hr
- Blood culture q24hr from all CVL lumens if patient remains febrile

**Febrile >72 hours?**

- Yes
- **Antibiotics:**
  - Vancomycin 15 mg/kg (max initial dose 1 g/dose) subsequent dosing per pharmacy AND Ceftazidime 50 mg/kg q8hr (max 2 g/dose)
  - If allergy: Vancomycin AND Ciprofloxacin 10 mg/kg q8hr IV (max 400 mg/dose) AND Concern for neutropenic enterocolitis: ADD Metronidazole 10 mg/kg IV q8hr (max 500 mg/dose)

- **Yes**
  - **Antibiotics:**
    - Vancomycin AND Ciprofloxacin 10 mg/kg q8hr IV (max 400 mg/dose)
    - Concern for neutropenic enterocolitis: ADD Metronidazole 10 mg/kg IV q8hr (max 500 mg/dose)

  **Labs:**
  - CBC w diff q24hr
  - Blood culture q24hr from all CVL lumens if patient remains febrile

- **No**
  - **Antibiotics:**
    - Vancomycin AND Ciprofloxacin 10 mg/kg q8hr IV (max 400 mg/dose)
    - Concern for neutropenic enterocolitis: ADD Metronidazole 10 mg/kg IV q8hr (max 500 mg/dose)

  **Labs:**
  - CBC w diff q24hr
  - Blood culture q24hr from all CVL lumens if patient remains febrile

**ED to call Heme/Onc to discuss admission and High Risk vs Standard Risk status**

**Standard Risk**

- Ill-appearing
- Skin soft tissue infection
- Mucositis
- Concern for neutropenic enterocolitis
- Pneumonia
- Hx of strep viridans or known ESBL colonization

**Antibiotics:**

**Start antibiotics ASAP** if not given in the ED.

- Vancomycin IV 15 mg/kg (max initial dose 1 g/dose) subsequent dosing per pharmacy AND Ceftazidime 50 mg/kg q8hr (max 2 g/dose)

- If allergy: Vancomycin AND Ciprofloxacin 10 mg/kg q8hr IV (max 400 mg/dose) AND Concern for neutropenic enterocolitis: ADD Metronidazole 10 mg/kg IV q8hr (max 500 mg/dose)

  **Labs:**
  - CBC w diff q24hr
  - Blood culture q24hr from all CVL lumens if patient remains febrile

- **Yes**
  - **Antibiotics:**
    - Vancomycin AND Ciprofloxacin 10 mg/kg q8hr IV (max 400 mg/dose) AND Concern for neutropenic enterocolitis: ADD Metronidazole 10 mg/kg IV q8hr (max 500 mg/dose)

  **Labs:**
  - CBC w diff q24hr
  - Blood culture q24hr from all CVL lumens if patient remains febrile
Standard Risk patients will get Piperacillin/Tazobactam as first line therapy.

High Risk patients will get Vancomycin AND Ceftazidime as first line.

### Antibiotics:

- **Standard Risk**
  - **If not already given in the ED**
  - **Piperacillin/Tazobactam** 100 mg/kg q6hr IV (max 4.5 g/dose)
    - **If allergy: Clindamycin** 10 mg/kg q8hr IV (max 600 mg/dose) AND **Ciprofloxacin** 10 mg/kg q8hr IV (max 400 mg/dose)

- **Labs:**
  - CBC q24hr
  - Blood culture q24hr from all CVL lumens if patient remains febrile

- **High Risk**
  - **Current ANC <500 or Ill-appearing**
    - **ED to call Heme/Onc to discuss admission and High Risk vs Standard Risk status**
  - **Antibiotics:**
    - **Vancomycin** IV 15 mg/kg q6hr; ≥12 yr old q8hr (max initial dose 1g/dose) **AND**
    - **Ceftazidime** 50 mg/kg q8hr (max 2g/dose)
    - **If allergy: Vancomycin AND Ciprofloxacin** 10 mg/kg q8hr IV (max 400 mg/dose)
    - **Concern for neutropenic enterocolitis:** ADD **Metronidazole** 10 mg/kg q8hr IV (max 500 mg/dose)

- **Labs:**
  - CBC w diff q24hr
  - Blood culture q24hr from all CVL lumens if patient remains febrile

*If a Standard Risk patient remains febrile at 72 hours, proceed to the High Risk pathway*
Considerations:

- If negative blood culture x 48hrs and well appearing:
  - Discontinue Vancomycin
  - Change Ceftazidime to Piperacillin/Tazobactam

- If positive blood culture or history of multidrug resistant organisms
  - Consider Infectious Disease (ID) consult

High Risk

Antibiotics:
Start antibiotics ASAP if not given in the ED.
(if initially low risk, change antibiotics to below)
- Vancomycin IV 15 mg/kg (max initial dose 1 g/dose) subsequent dosing per pharmacy AND
- Ceftazidime 50 mg/kg q8hr (max 2 g/dose)
- If allergy: Vancomycin AND Ciprofloxacin 10 mg/kg q8hr IV (max 400 mg/dose)
- Concern for neutropenic enterocolitis: ADD Metronidazole 10 mg/kg IV q8hr (max 500 mg/dose)

Labs:
- CBC w diff q24hr
- Blood culture q24hr from all CVL lumens if patient remains febrile
Discharge Criteria:

- Well appearing
- Tolerating PO
- Afebrile for 24 hours
- Negative blood cultures
- APC >200 and rising ANC for 2 days
- Follow up in place

How to calculate Absolute Phagocyte Count (APC):

$$APC = WBC \times \left( \frac{%\text{Segmented Neutrophils} + %\text{Bands} + %\text{Monocytes}}{100} \right)$$

How to calculate Absolute Neutrophil Count (ANC):

$$ANC = WBC \times (%\text{Neutrophils} + %\text{Bands})$$
Quality Metrics

• Percentage of patients with pathway order set usage
• Average time from arrival (or start of fever) to initial antibiotic order
• Average time from antibiotic order to antibiotic administration
• Average time from arrival (or start of fever) to antibiotic administration
• Percentage of patients who received the correct initial antibiotic regimen as indicated per pathway
• Percentage of patients that are appropriately changed from Ceftazidime to Piperacillin/Tazobactam once Vancomycin is discontinued
Pathway Contacts

- Andrea Orsey, MD
  - Hematology/Oncology
- Natalie Bezler, MD
  - Hematology/Oncology
References

About Connecticut Children’s Medical Center Pathways Program

Clinical pathways guide the management of patients to optimize consistent use of evidence-based practice. Clinical pathways have been shown to improve guideline adherence and quality outcomes, while decreasing length of stay and cost. Here at Connecticut Children’s, our Clinical Pathways Program aims to deliver evidence-based, high value care to the greatest number of children in a diversity of patient settings. These pathways serve as a guide for providers and do not replace clinical judgement.