Clinical Pathways

Oncology Patient with Fever

Andrea Orsey MD
Natalie Bezler, MD

Connecticut Children's

BEST CHILDREN'S HOSPITALS U.S.News RANKED IN 4 SPECIALTIES 2020-21

MAGNET RECOGNIZED AMERICAN NURSES CREDENTIALING CENTER

BEST CHILDREN'S HOSPITAL WOMEN'S CHOICE AWARD 2020

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 1/3rd 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
  - Good anaerobic, gram positive & gram negative coverage including pseudomonas
  - No MRSA coverage
- Ceftazidime
  - Only has gram negative coverage (including pseudomonas)
  - Poor gram positive or anaerobic coverage
- Vancomycin
  - Gram positive coverage including MRSA
  - 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[5]
- When starting Vancomycin:
  - Zosyn should be discontinued and ceftazidime started (for gram negative coverage)[6]
- Ceftazidime not associated with nephrotoxicity
- When discontinuing Vancomycin:
  - Ceftazidime should be switched to Zosyn
  - Ceftazidime has virtually no gram positive coverage, therefore it can not be used as monotherapy

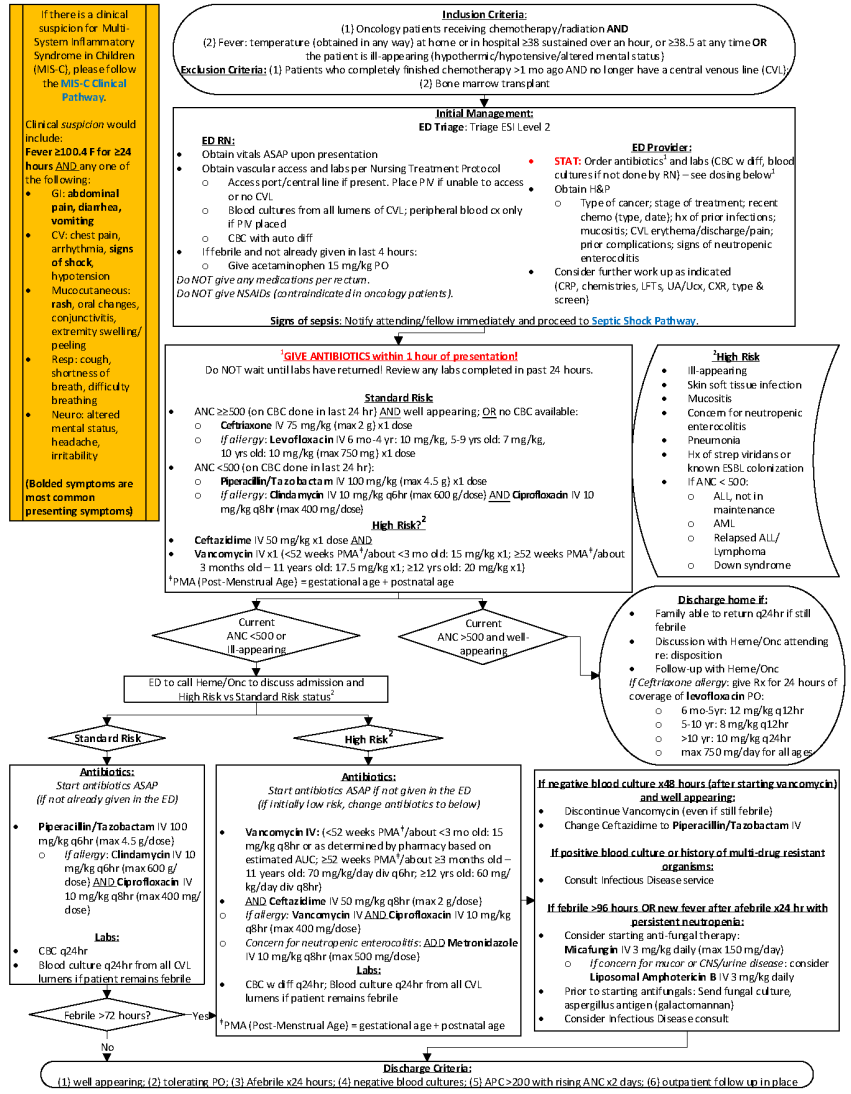
This is the Oncology Patient with Fever Clinical Pathway.

We will be reviewing each component in the following slides.

CLINICAL PATHWAY:

Oncology Patient with Fever

THIS PATHWAY SERVES AS A GUIDE AND DOES NOT REPLACE CLINICAL JUDGMENT.



CONTACTS: NATALIE BEZLER, MD | ANDREA ORSEY, MD

LAST UPDATED: 03.15.21

CLINICAL PATHWAY:

Oncology Patient with Fever

THIS PATHWAY SERVES AS A GUIDE AND DOES NOT REPLACE CLINICAL JUDGMENT.

Inclusion Criteria:

(1) Oncology patients receiving chemotherapy/radiation **AND**
(2) Fever: temperature (obtained in any way) at home or in hospital ≥38 sustained over an hour, or ≥38.5 at any time **OR** the patient is ill-appearing (hypothermic/hypotensive/altered mental status)

Exclusion Criteria:

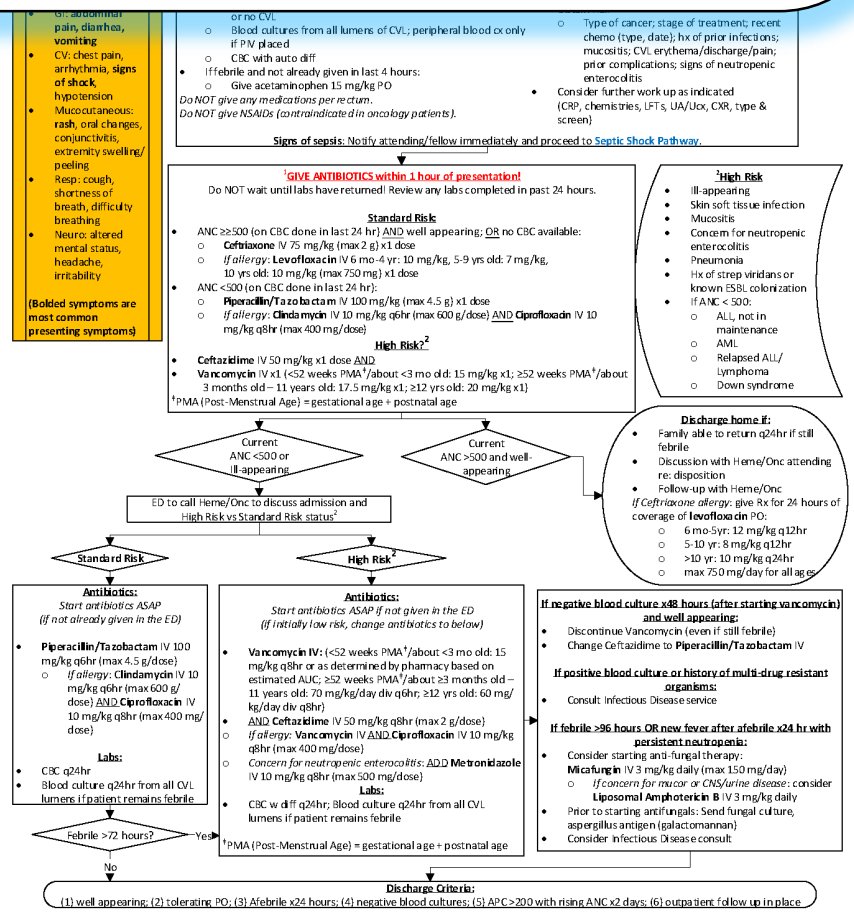
(1) Patients who completely finished chemotherapy >1 mo ago AND no longer have a central line; (2) Bone marrow transplant

Inclusion criteria:

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

Exclusion criteria:

- Completed chemotherapy > 1 month AND no longer have central lines
- Bone marrow transplants



CONTACTS: NATALIE BEZLER, MD | ANDREA ORSEY, MD

LAST UPDATED: 03.15.21

CLINICAL PATHWAY:

Oncology Patient with Fever

THIS PATHWAY SERVES AS A GUIDE AND DOES NOT REPLACE CLINICAL JUDGMENT

Immediate evaluation is necessary to ensure management is initiated quickly.
Care is outlined for nurses and providers.

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 PIV if unable to access or no CVL
  - Blood cultures from all lumens of CVL; peripheral blood cx only if PIV placed.
  - CBC with auto diff
- If febrile and not already given in last 4 hours:
  - Give acetaminophen 15 mg/kg PO

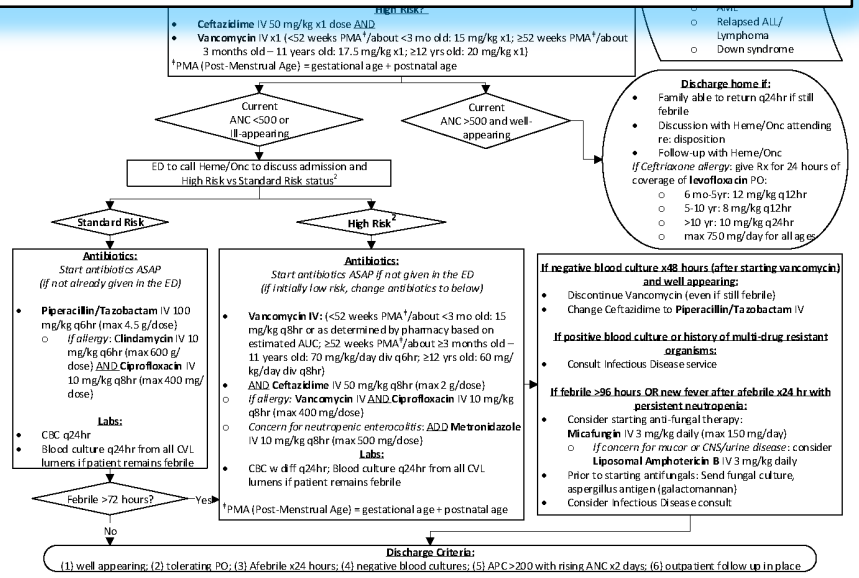
Do NOT give any medications per rectum.
Do NOT give NSAIDs (contraindicated in oncology patients).

ED Provider:

- **STAT:** Order antibiotics[1] and labs (CBC w diff, blood cultures if not done by RN) – see dosing below[1]
- 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 are present, notify attending immediately and start the Septic Shock Pathway *****



CONTACTS: NATALIE BEZLER, MD | ANDREA ORSEY, MD

LAST UPDATED: 03.15.21

ANTIBIOTICS SHOULD BE GIVEN WITHIN 1 HOUR OF PRESENTATION

Do not wait for labs to return!

Antibiotics are chosen based on ANC and risk factors of the patient.

ANC

How to calculate Absolute Neutrophil Count (ANC):

ANC = WBC * (%Neutrophils + %Bands)

If no "High risk factors" are present:

- Those with ANC ≥500 and are well appearing (or if ANC is unknown) will be started on ceftriaxone for coverage.

- If there is significant neutropenia or the patient is ill-appearing, coverage needs to be broadened to zosyn, which has:
  - Good anaerobic, gram positive & gram negative coverage including pseudomonas
  - No MRSA coverage

CLINICAL PATHWAY:
Oncology Patient with Fever

THIS PATHWAY SERVES AS A GUIDE AND DOES NOT REPLACE CLINICAL

[1]**GIVE ANTIBIOTICS within 1 hour of presentation!**

Do NOT wait until labs have returned! Review any labs completed in past 24 hours.

Standard Risk:

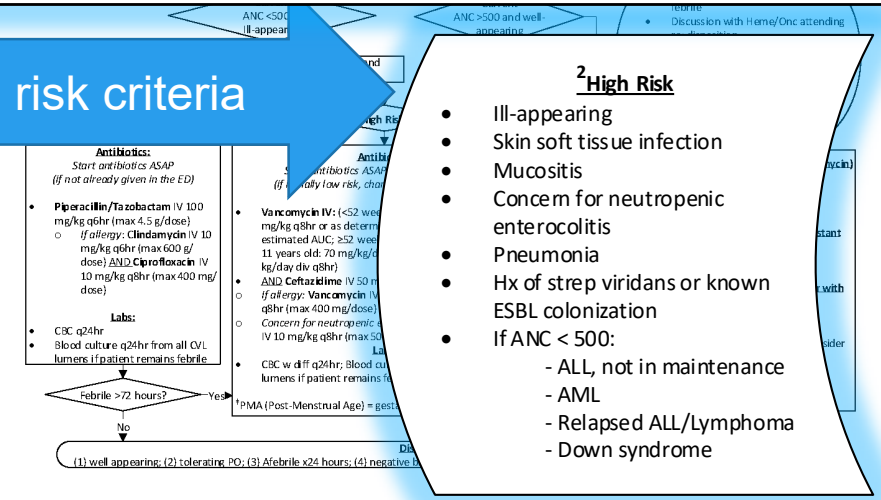
- ANC ≥ 500 (on CBC done in last 24 hr) AND well appearing; OR no CBC available:
  - **Ceftriaxone** IV 75 mg/kg (max 2 g) x1 dose
  - *If allergy*: **Levofloxacin** IV 6 mo-4 yr: 10 mg/kg, 5-9 yrs old: 7 mg/kg, ≥ 10 yrs old: 10 mg/kg (max 750 mg) x1 dose
- ANC <500 (on CBC done in last 24 hr):
  - **Piperacillin/Tazobactam** IV 100 mg/kg (max 4.5 g) x1 dose
  - *If allergy*: **Clindamycin** IV 10 mg/kg q6hr (max 600 g/dose) AND **Ciprofloxacin** IV 10 mg/kg q8hr (max 400 mg/dose)

High Risk?[2]

- **Ceftazidime** IV 50 mg/kg x1 dose AND
- **Vancomycin** IV x1 (<52 weeks PMA[‡]/about <3 mo old: 15 mg/kg x1; ≥52 weeks PMA[‡]/about ≥3 months old – 11 years old: 17.5 mg/kg x1; ≥12 yrs old: 20 mg/kg x1)

[‡]PMA (Post-Menstrual Age) = gestational age + postnatal age

High risk criteria



[2]**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

CONTACTS: NATALIE BEZLER, MD | ANDREA ORSEY, MD

LAST UPDATED: 03.15.21

Connecticut Children's

High Risk Patients:

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

- Require broader spectrum antibiotic coverage, including MRSA coverage.
- Because the combination of zosyn and vancomycin is associated with AKI, antibiotics should be changed to ceftazidime and vancomycin.

Ceftazidime
- Only has gram negative coverage (including pseudomonas)
- Poor gram positive or anaerobic coverage

Vancomycin
- Gram positive coverage including MRSA
- No gram negative coverage

CLINICAL PATHWAY:
Oncology Patient with Fever

THIS PATHWAY SERVES AS A GUIDE AND DOES NOT REPLACE CLINICAL

[1]**GIVE ANTIBIOTICS within 1 hour of presentation!**

Do NOT wait until labs have returned! Review any labs completed in past 24 hours.

Standard Risk:

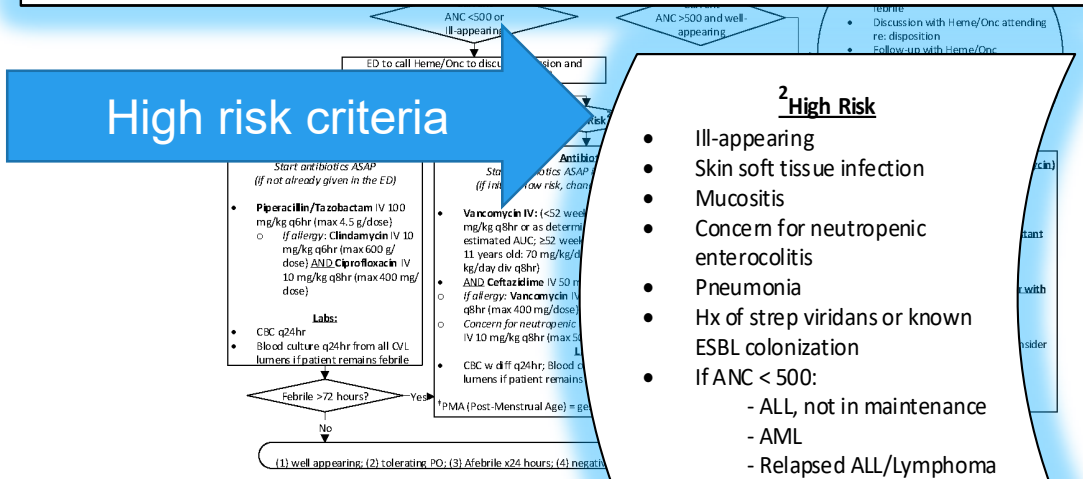
- ANC ≥ 500 (on CBC done in last 24 hr) AND well appearing; OR no CBC available:
  - **Ceftriaxone** IV 75 mg/kg (max 2 g) x1 dose
  - *If allergy*: **Levofloxacin** IV 6 mo-4 yr: 10 mg/kg, 5-9 yrs old: 7 mg/kg, ≥ 10 yrs old: 10 mg/kg (max 750 mg) x1 dose
- ANC <500 (on CBC done in last 24 hr):
  - **Piperacillin/Tazobactam** IV 100 mg/kg (max 4.5 g) x1 dose
  - *If allergy*: **Clindamycin** IV 10 mg/kg q6hr (max 600 g/dose) AND **Ciprofloxacin** IV 10 mg/kg q8hr (max 400 mg/dose)

High Risk?[2]

- **Ceftazidime** IV 50 mg/kg x1 dose AND
- **Vancomycin** IV x1 (<52 weeks PMA‡/about <3 mo old: 15 mg/kg x1; ≥52 weeks PMA‡/about ≥3 months old – 11 years old: 17.5 mg/kg x1; ≥12 yrs old: 20 mg/kg x1)

‡PMA (Post-Menstrual Age) = gestational age + postnatal age

High risk criteria

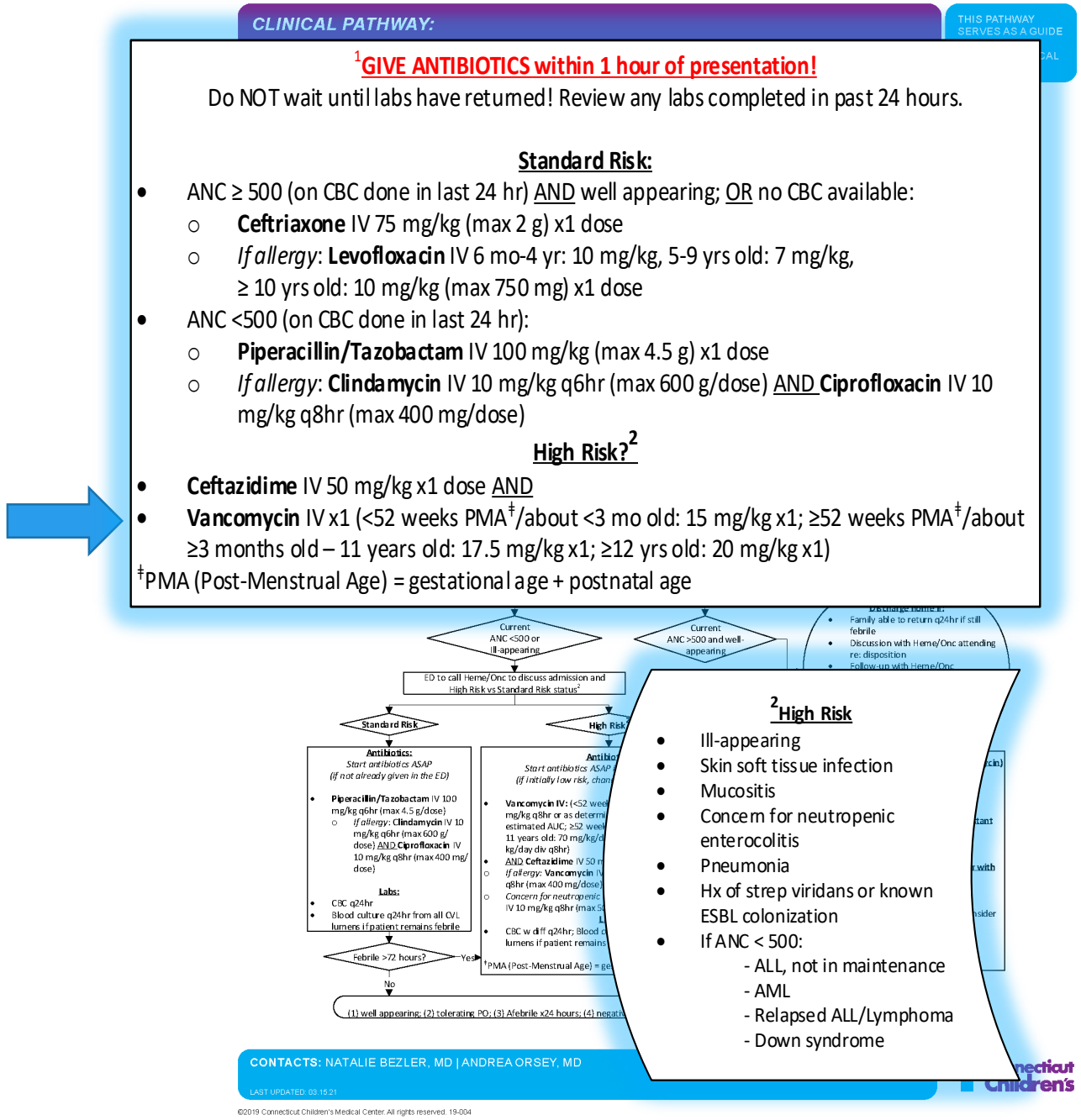


CONTACTS: NATALIE BEZLER, MD | ANDREA ORSEY, MD

LAST UPDATED: 03.15.21

The pharmacy's vancomycin protocol was updated in Feb 2021.

- All patients who have vancomycin IV ordered will be followed by the clinical pharmacist to help determine appropriate dosing parameters.
- Providers will order initial doses per pathway/order set and provide indication within the order.
- IV vancomycin dosing and recommended labs will be managed by pharmacy in conjunction with primary teams.



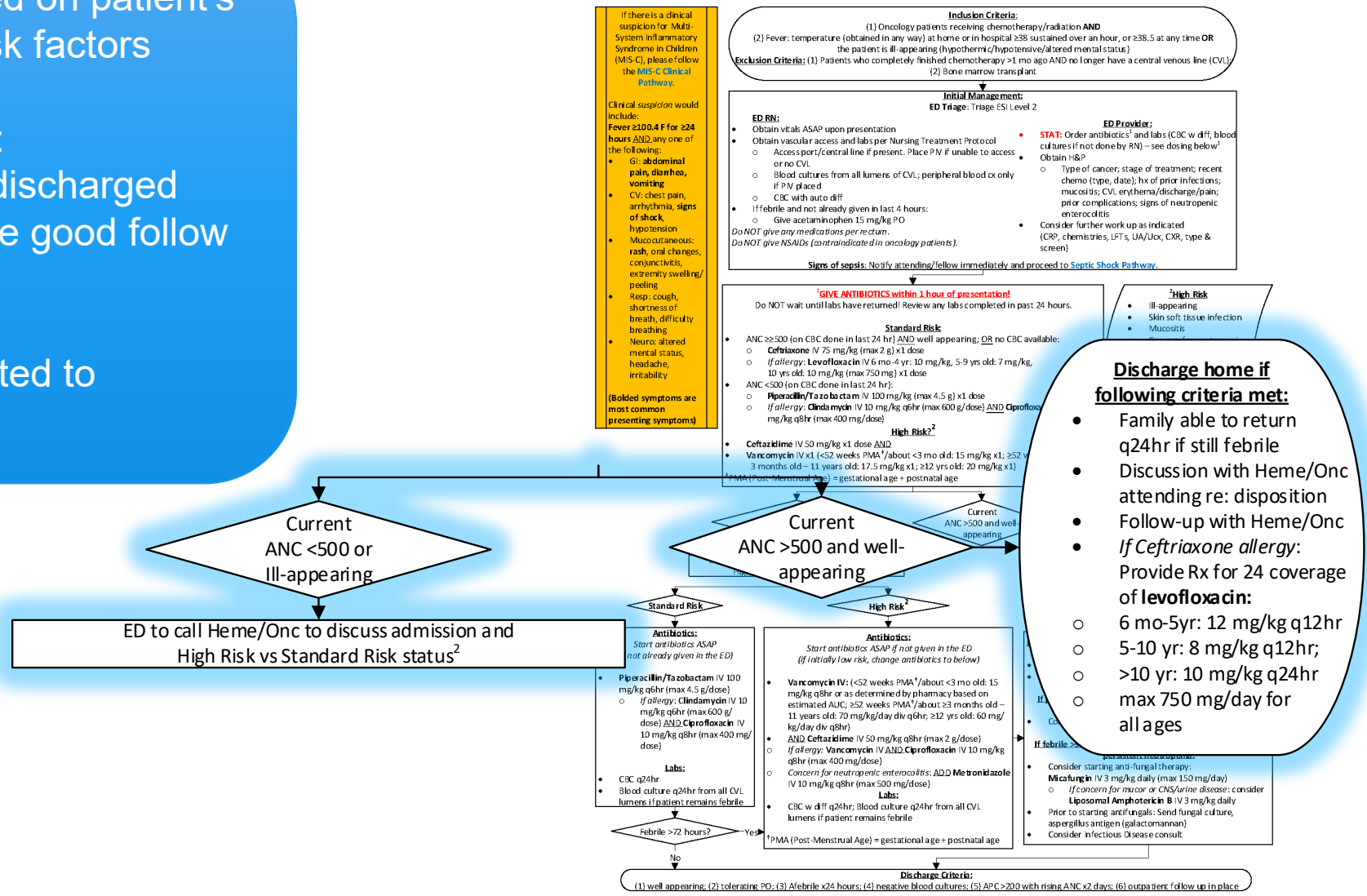
Admission decision is made based on patient's ANC, clinical appearance, and risk factors

- 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

CLINICAL PATHWAY:

Oncology Patient with Fever

THIS PATHWAY SERVES AS A GUIDE AND DOES NOT REPLACE CLINICAL JUDGMENT.



CONTACTS: NATALIE BEZLER, MD | ANDREA ORSEY, MD

LAST UPDATED: 03.15.21

Those that are admitted with receive antibiotics based on risk status.

- Standard Risk patients will get Piperacillin/Tazobactam as first line therapy
- High Risk patients will get Vancomycin AND Ceftazidime as first line

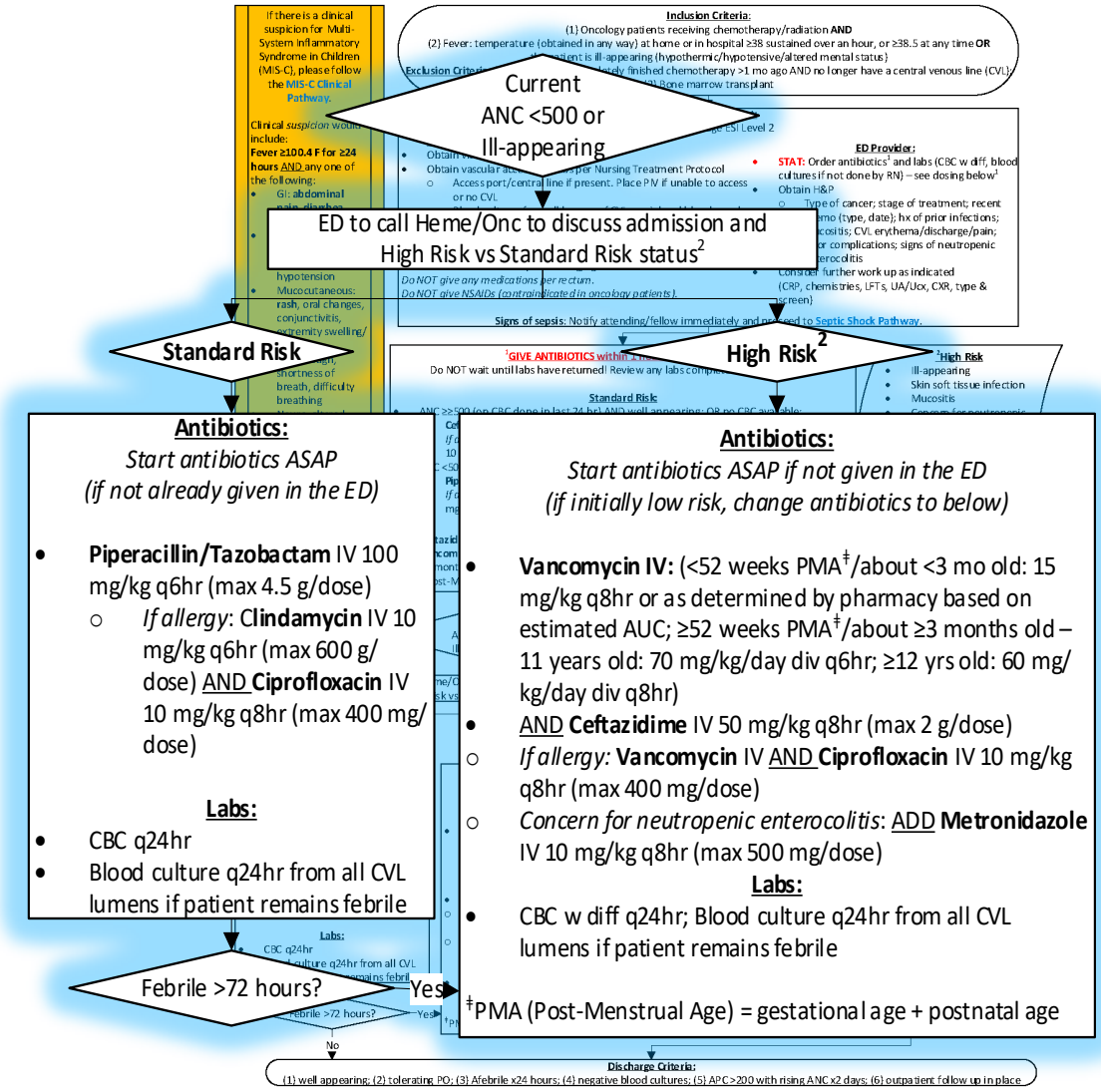
*If a Standard Risk patient remains febrile at 72 hours, proceed to the High Risk arm

[2]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

CLINICAL PATHWAY:
Oncology Patient with Fever

THIS PATHWAY SERVES AS A GUIDE AND DOES NOT REPLACE CLINICAL JUDGMENT.



CONTACTS: NATALIE BEZLER, MD | ANDREA ORSEY, MD

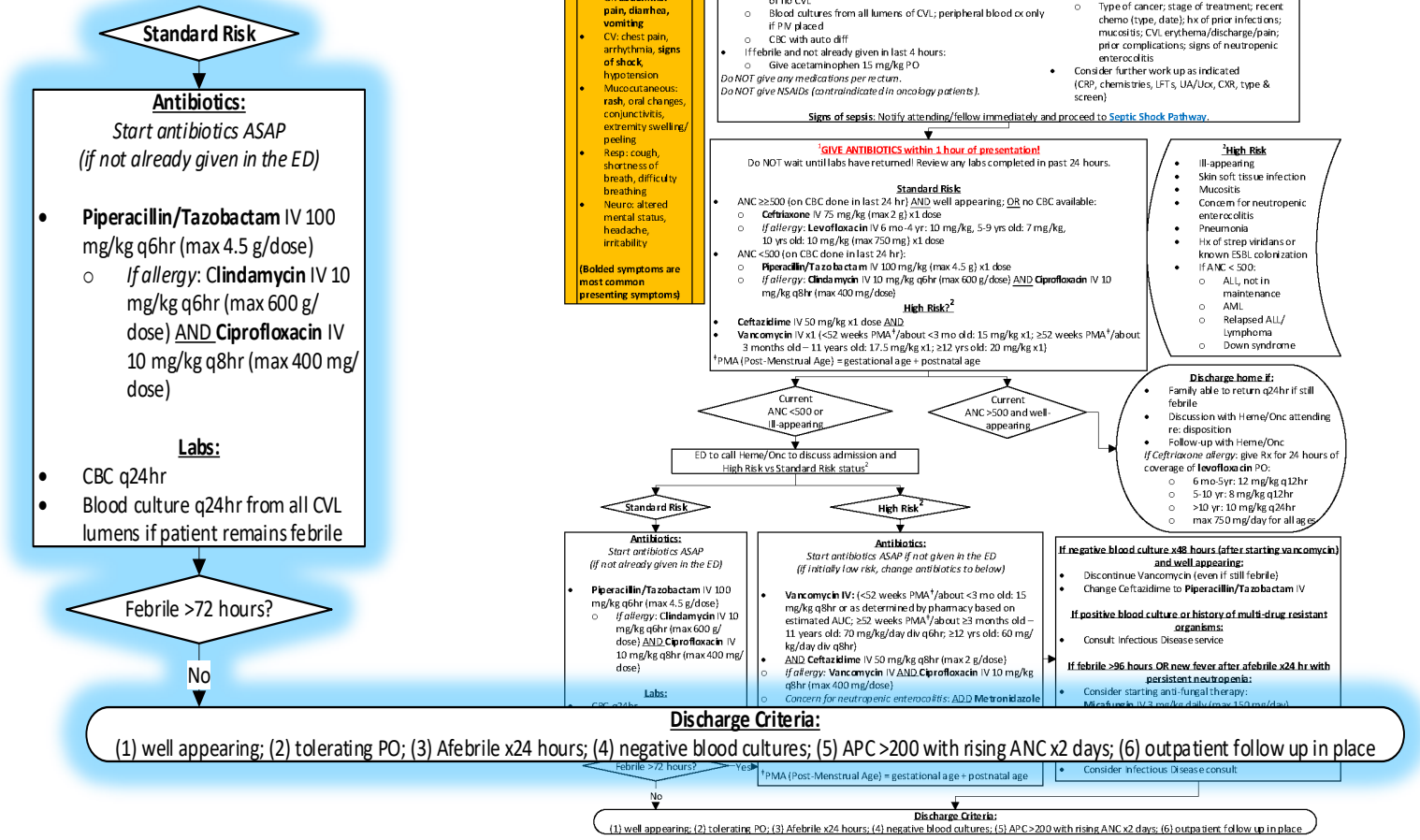
LAST UPDATED: 03.15.21

CLINICAL PATHWAY:

Oncology Patient with Fever

THIS PATHWAY SERVES AS A GUIDE AND DOES NOT REPLACE CLINICAL JUDGMENT.

If a standard risk patient has improvement in fevers in 72 hours and meets discharge criteria, they may be sent home with follow up in place.



CONTACTS: NATALIE BEZLER, MD | ANDREA ORSEY, MD

LAST UPDATED: 03.15.21

Those that are high risk have special considerations based on blood cultures, clinical appearance or fever trends.

If negative blood culture x 48hrs and well appearing:

- Remember that prolonged use of vancomycin can increase rates of resistance, and ceftazidime doesn't have adequate gram positive or anaerobic coverage that Pip/Tazo can provide.

If there is a positive blood culture, or there is a history of MDRO:

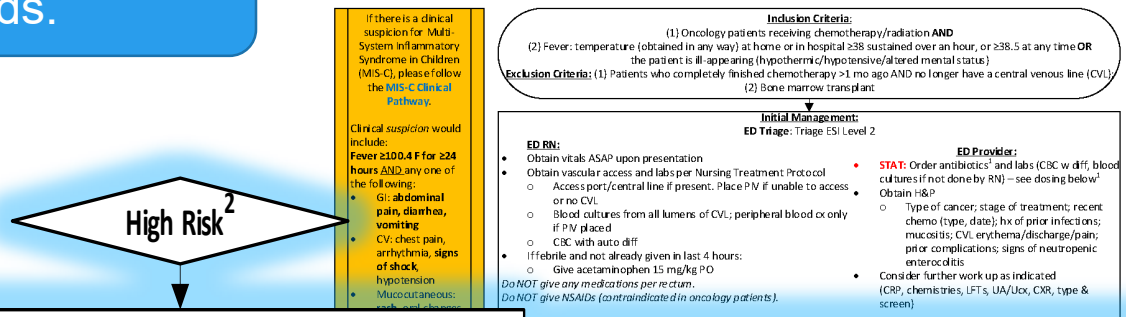
- Consult ID to help choose the most appropriate antibiotic coverage.

If the patient remains febrile >96 hours, OR there is a new fever after being afebrile for 24 hours with persistent neutropenia:

- There is a risk that a fungal infection is not being treated. Send fungal studies and start micafungin. Consider consulting ID to help determine adequate fungal coverage or further investigation and management.

CLINICAL PATHWAY:
Oncology Patient with Fever

THIS PATHWAY SERVES AS A GUIDE AND DOES NOT REPLACE CLINICAL JUDGMENT.



Antibiotics:

Start antibiotics ASAP if not given in the ED
(if initially low risk, change antibiotics to below)

- **Vancomycin IV:** (<52 weeks PMA‡/about <3 mo old: 15 mg/kg q8hr or as determined by pharmacy based on estimated AUC; ≥52 weeks PMA‡/about ≥3 months old – 11 years old: 70 mg/kg/day div q6hr; ≥12 yrs old: 60 mg/kg/day div q8hr)
- AND **Ceftazidime** IV 50 mg/kg q8hr (max 2 g/dose)
  - *If allergy:* **Vancomycin** IV AND **Ciprofloxacin** IV 10 mg/kg q8hr (max 400 mg/dose)
  - *Concern for neutropenic enterocolitis*: ADD **Metronidazole** IV 10 mg/kg q8hr (max 500 mg/dose)

Labs:

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

‡PMA (Post-Menstrual Age) = gestational age + postnatal age

If negative blood culture x48 hours (after starting vancomycin) and well appearing:

- Discontinue Vancomycin (even if still febrile)
- Change Ceftazidime to **Piperacillin/Tazobactam** IV

If positive blood culture or history of multi-drug resistant organisms:

- Consult Infectious Disease service

If febrile >96 hours OR new fever after afebrile x24 hr with persistent neutropenia:

- Consider starting anti-fungal therapy:
  Micafungin IV 3 mg/kg daily (max 150 mg/day)
  - *If concern for mucor or CNS/urine disease*: consider **Liposomal Amphotericin B** IV 3 mg/kg daily
- Prior to starting antifungals: Send fungal culture, aspergillus antigen (galactomannan)
- Consider Infectious Disease consult

CLINICAL PATHWAY:
Oncology Patient with Fever

THIS PATHWAY SERVES AS A GUIDE AND DOES NOT REPLACE CLINICAL JUDGMENT.

Discharge Criteria

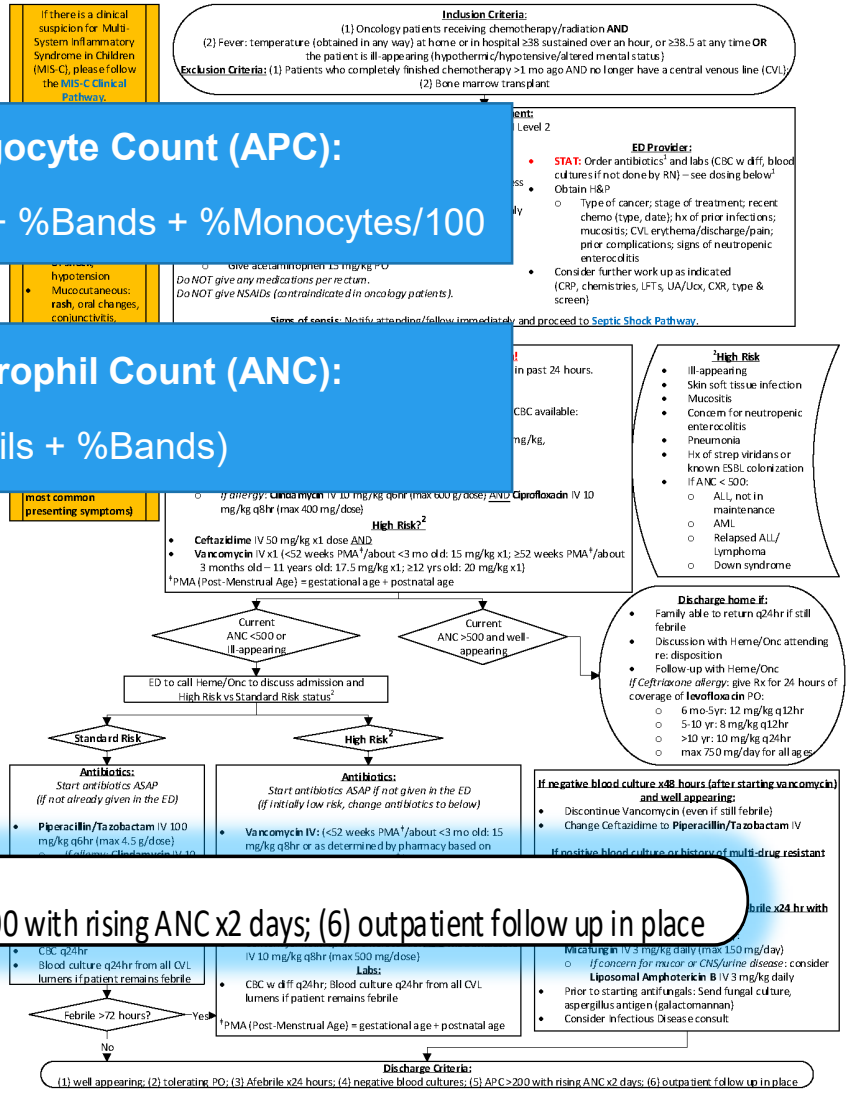
- Well appearing
- Tolerating PO
- Afebrile for 24 hours
- Negative blood cultures
- APC >200 and rising ANC for 2 days
- Follow up in place

How to calculate Absolute Phagocyte Count (APC):

APC = WBC * (%Segmented Neutrophils + %Bands + %Monocytes/100

How to calculate Absolute Neutrophil Count (ANC):

ANC = WBC * (%Neutrophils + %Bands)



Discharge Criteria:

(1) well appearing; (2) tolerating PO; (3) Afebrile x24 hours; (4) negative blood cultures; (5) APC >200 with rising ANC x2 days; (6) outpatient follow up in place

CONTACTS: NATALIE BEZLER, MD | ANDREA ORSEY, MD

LAST UPDATED: 03.15.21

Connecticut Children's

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

- Rhodes A, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. *Intensive Care Med*. 2017 Mar;43(3):304-377.
- Rosa RG, Goldani LZ. Cohort study of the impact of time to antibiotic administration on mortality in patients with febrile neutropenia. *Antimicrob Agents Chemother*. 2014 Jul;58(7):3799-803.
- Cohen C, King A, Lin CP, Friedman GK, Monroe K, Kutny M. Protocol for Reducing Time to Antibiotics in Pediatric Patients Presenting to an Emergency Department With Fever And Neutropenia: Efficacy and Barriers. *Pediatr Emerg Care*. 2016 Nov;32(11):739-745.
- Freifeld AG, Bow EJ, Sepkowitz KA, Boeckh MJ, Ito JI, Mullen CA, Raad II, Rolston KV, Young JA, Wingard JR; Infectious Diseases Society of America. Clinical Practice Guideline for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer: 2010 Update by the Infectious Diseases Society of America. *Clin Infect Dis.* 2011 Feb;52(4):e56-93.
- Brugress LD, Drew RH. Comparison of the incidence of vancomycin-induced nephrotoxicity in hospitalized patients with and without concomitant piperacillin-tazobactam. *Pharmacotherapy.* 2014;34:670-676.
- Lehrnbecher T, et al; International Pediatric Fever and Neutropenia Guideline Panel. Guideline for the management of fever and neutropenia in children with cancer and/or undergoing hematopoietic stem-cell transplantation. *J Clin Oncol.* 2012 Dec;30(35):4427-38.
- Zosyn[package insert]. Philadelphia: Pfizer Inc.; 2012

Thank You!

About Connecticut Children's Clinical Pathways Program

The Clinical Pathways Program at Connecticut Children's aims to improve the quality of care our patients receive, across both ambulatory and acute care settings. We have implemented a standardized process for clinical pathway development and maintenance to ensure meaningful improvements to patient care as well as systematic continual improvement. Development of a clinical pathway includes a multidisciplinary team, which may include doctors, advanced practitioners, nurses, pharmacists, other specialists, and even patients/families. Each clinical pathway has a flow algorithm, an educational module for end-user education, associated order set(s) in the electronic medical record, and quality metrics that are evaluated regularly to measure the pathway's effectiveness. Additionally, clinical pathways are reviewed annually and updated to ensure alignment with the most up to date evidence. These pathways serve as a guide for providers and do not replace clinical judgment.