Clinical Pathways

Oncology Patient with Fever

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MAGNET RECOGNIZED AMERICAN NURSES CREDENTIALING CENTER

BEST CHILDREN'S HOSPITAL WOMEN'S CHOICE AWARD 2023

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)
- 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, depending on level of risk

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

- Ceftriaxone
  - Strong coverage against: *Streptococcus,* common Gram negatives in gut (e.g., *E. coli, Klebsiella)*
  - Limited coverage against: MSSA
  - No coverage against: MRSA, *Enterococcus, Pseudomonas,* anaerobes
- Cefepime
  - Broadens ceftriaxone's coverage to include:
    - Gram positive: MSSA (in addition to *Streptococcus)*
    - Gram negative: *Enterobacter* and *Pseudomonas* species (including *E. coli* and *Klebsiella*)
  - No coverage against: MRSA, *Enterococcus*, anaerobes
- Ceftazidime
  - Broadens ceftriaxone's coverage for Gram negatives to include *Pseudomonas*
  - Loses much of ceftriaxone's Gram positive activity (e.g., not reliable against *Streptococcus, Staphylococcus,* or *Enterococcus species)*
- Vancomycin
  - Very strong coverage against: Gram positives (*Staphylococcus, Streptococcus,* and *Enterococcus)*
  - No coverage: Gram negatives, anaerobic
  - Often added to ceftazidime to provide strong activity against common Gram negatives and Gram positives
- Metronidazole
  - Strong coverage: anaerobes (includes *Bacteroides*)
  - Added only if patient does **not** have strong anaerobic coverage and it is needed (e.g., add to vancomycin/ceftazidime or to cefepime monotherapy)
    - It is not needed if already receiving anaerobic coverage (e.g., with piperacillin/tazobactam, ampicillin/sulbactam, or meropenem)

Vancomycin

- Early vancomycin treatment may reduce mortality in high risk patients
- However, judicious use of vancomycin is warranted as:
  - It can cause nephrotoxicity.
  - There has been a link between its overuse and the development of drug resistance in *Enterococcus* species and *S. aureus.*
- Recommend discontinuing use, after 36-48 hours of therapy, if susceptible species are not grown on culture[4]

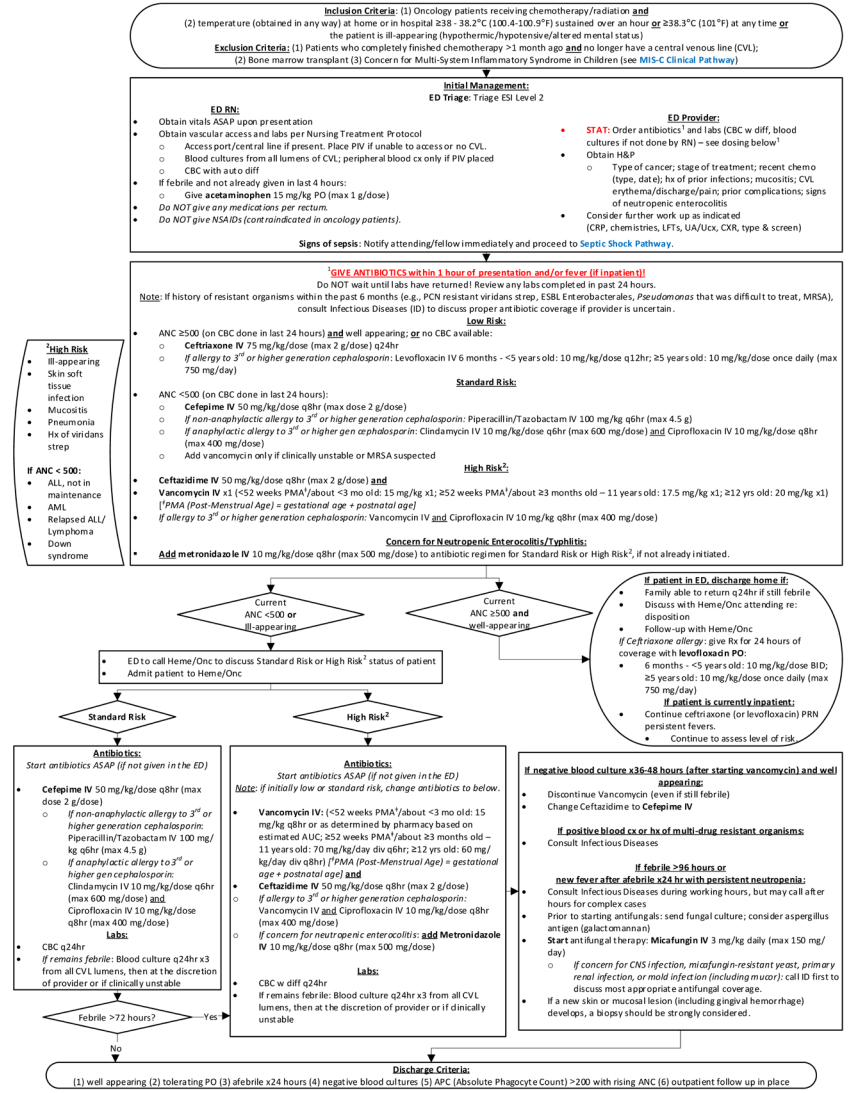
This is the Oncology Patient with Fever Clinical Pathway.

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.



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CLINICAL PATHWAY:

Oncology Patient with Fever

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Inclusion Criteria: (1) Oncology patients receiving chemotherapy/radiation **and** (2) temperature (obtained in any way) at home or in hospital ≥38 - 38.2°C (100.4-100.9°F) sustained over an hour **or** ≥38.3°C (101°F) at any time **or** the patient is ill-appearing (hypothermic/hypotensive/altered mental status)

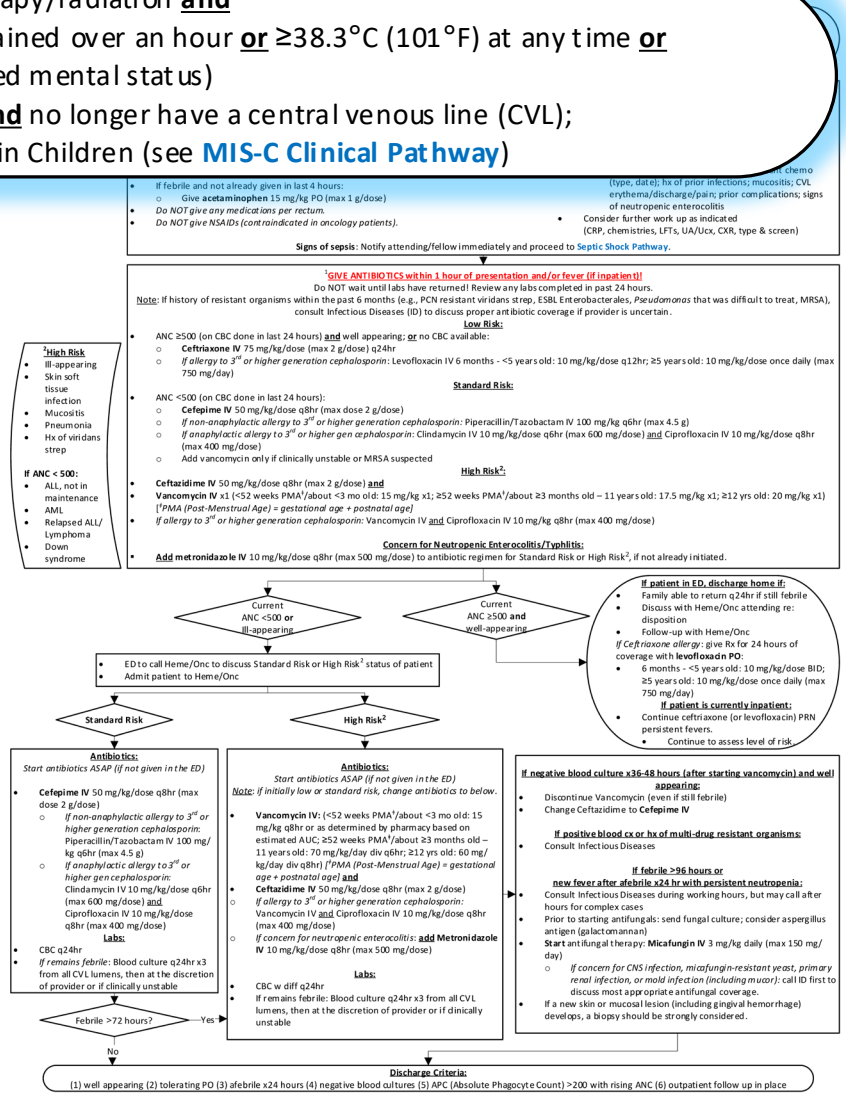
Exclusion Criteria: (1) Patients who completely finished chemotherapy >1 month ago **and** no longer have a central venous line (CVL); (2) Bone marrow transplant (3) Concern for Multi-System Inflammatory Syndrome in Children (see **MIS-C Clinical Pathway**)

Inclusion criteria:

- Oncology patients who are receiving chemotherapy/radiation
  AND
- Temperature 38-38.2°C (100.4-100.9°F) sustained for an hour OR ≥38.3°C (101°F) at anytime OR ill appearing

Exclusion criteria:

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



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Oncology Patient with Fever

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

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Initial Management:

ED Triage: Triage ESI Level 2

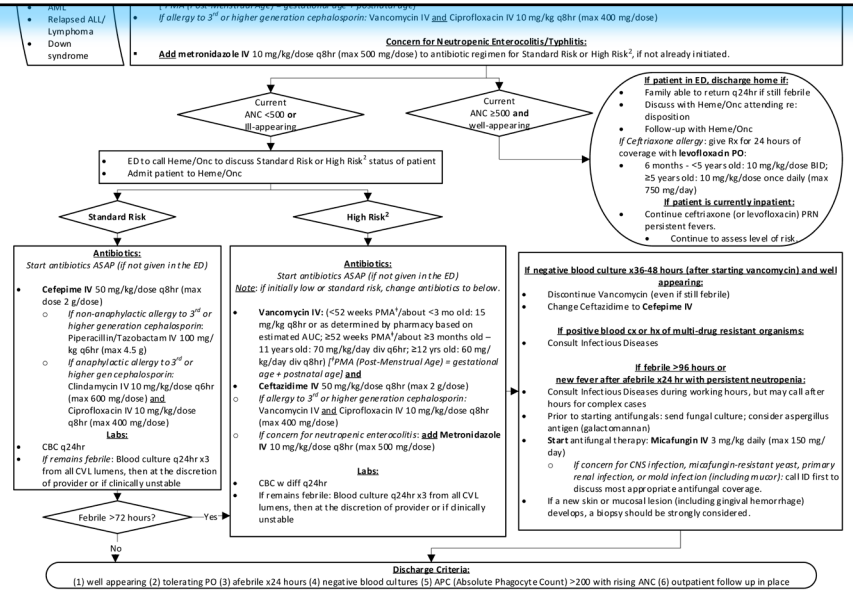
ED RN:

- 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 (max 1 g/dose)
- *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 *****

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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 = WBC * (%Neutrophils + %Bands)]

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High risk criteria

[2]High Risk

- Ill-appearing
- Skin soft tissue infection
- Mucositis
- Pneumonia
- Hx of viridans strep

If ANC < 500:

- ALL, not in maintenance
- AML
- Relapsed ALL/ Lymphoma
- Down syndrome

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

Note: If history of resistant organisms within the past 6 months (e.g., PCN resistant viridans strep, ESBL Enterobacterales, *Pseudomonas* that was difficult to treat, MRSA), consult Infectious Diseases (ID) to discuss proper antibiotic coverage if provider is uncertain.

Low Risk:

- ANC ≥500 (on CBC done in last 24 hours) **and** well appearing; **or** no CBC available:
  - **Ceftriaxone IV** 75 mg/kg/dose (max 2 g/dose) q24hr
  - *If allergy to 3rd or higher generation cephalosporin*: Levofloxacin IV 6 months - <5 years old: 10 mg/kg/dose q12hr; ≥5 years old: 10 mg/kg/dose once daily (max 750 mg/day)

Standard Risk:

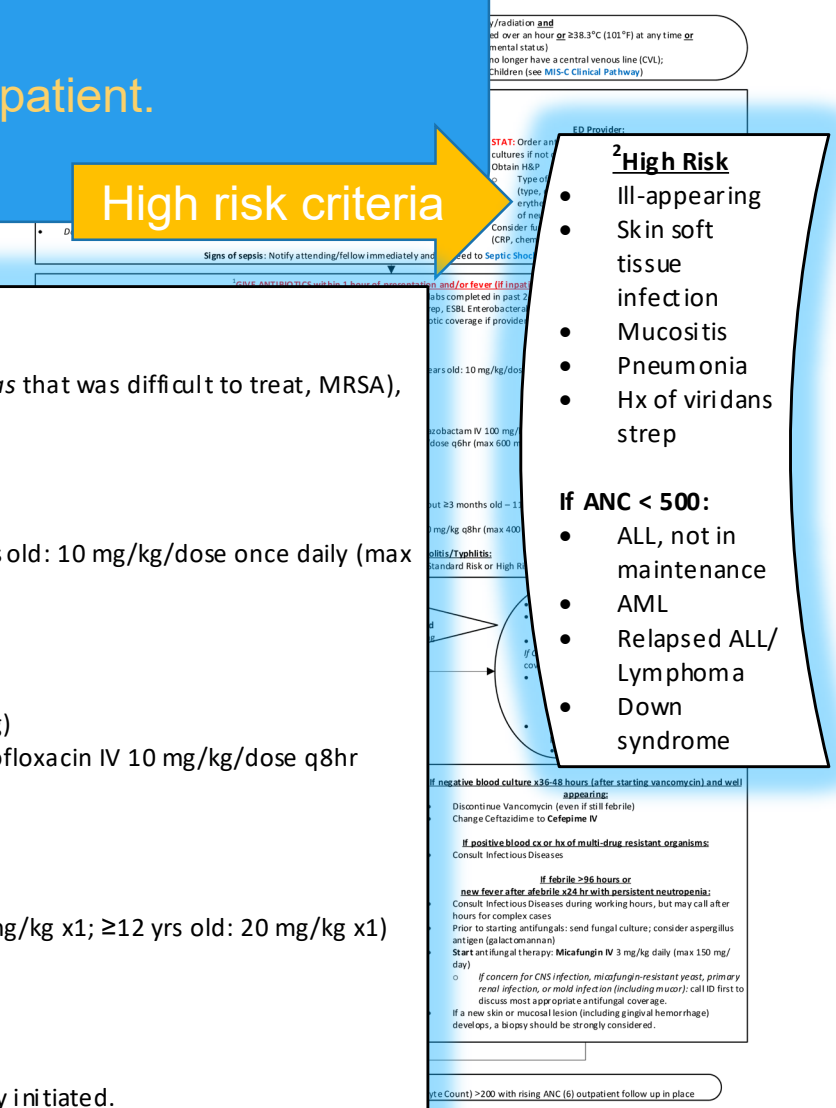
- ANC <500 (on CBC done in last 24 hours):
  - **Cefepime IV** 50 mg/kg/dose q8hr (max dose 2 g/dose)
  - *If non-anaphylactic allergy to 3rd or higher generation cephalosporin:* Piperacillin/Tazobactam IV 100 mg/kg q6hr (max 4.5 g)
  - *If anaphylactic allergy to 3rd or higher gen cephalosporin*: Clindamycin IV 10 mg/kg/dose q6hr (max 600 mg/dose) and Ciprofloxacin IV 10 mg/kg/dose q8hr (max 400 mg/dose)
  - Add vancomycin only if clinically unstable or MRSA suspected

High Risk[2]:

- **Ceftazidime IV** 50 mg/kg/dose q8hr (max 2 g/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]*
- *If allergy to 3rd or higher generation cephalosporin:* Vancomycin IV and Ciprofloxacin IV 10 mg/kg q8hr (max 400 mg/dose)

Concern for Neutropenic Enterocolitis/Typhlitis:

- **Add metronidazole IV** 10 mg/kg/dose q8hr (max 500 mg/dose) to antibiotic regimen for Standard Risk or High Risk[2], if not already initiated.



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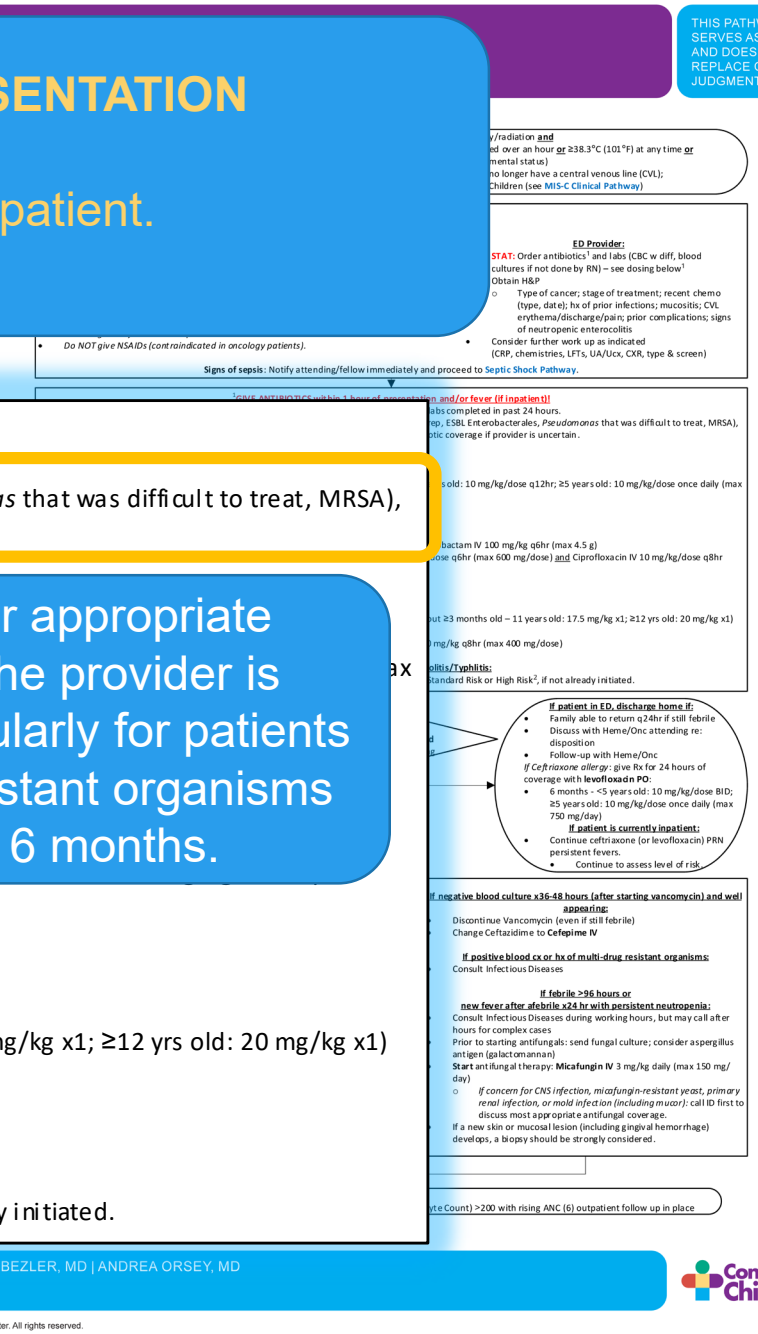
Concern for Neutropenic Enterocolitis/Typhlitis:

- **Add metronidazole IV** 10 mg/kg/dose q8hr (max 500 mg/dose) to antibiotic regimen for Standard Risk or High Risk[2], if not already initiated.

Consult ID for appropriate antibiotics if the provider is uncertain, particularly for patients with a hx of resistant organisms in the past 6 months.



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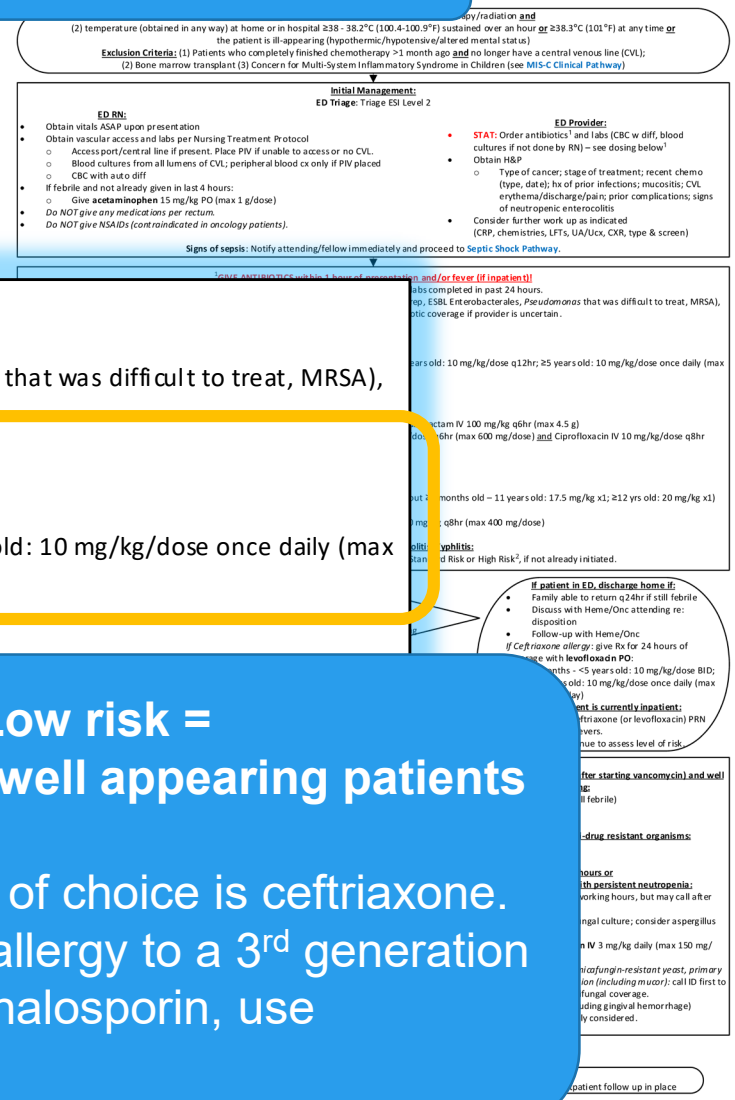

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- *If allergy to 3rd or higher generation cephalosporin:* Vancomycin IV and Ciprofloxacin IV 10 mg/kg

Concern for Neutropenic Enterocolitis/T

- **Add metronidazole IV** 10 mg/kg/dose q8hr (max 500 mg/dose) to antibiotic regimen for Standard

Low risk =
ANC ≥500 and well appearing patients

- The antibiotic of choice is ceftriaxone.
- If there is an allergy to a 3rd generation or higher cephalosporin, use levofloxacin.

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Standard Risk = ANC <500

- The antibiotic of choice is cefepime.
- Piperacillin/tazobactam is no longer recommended as first line:
  - Viridans streptococci coverage has now improved with cefepime.
  - Broad anaerobic coverage is not needed for standard risk patients.
- If there is a non-anaphylactic allergy to 3rd or higher cephalosporins, can give pip/tazo. If there is an anaphylactic allergy, clinda and cipro.
- Vancomycin coverage should only be added if the patient is clinically unstable or there is MRSA suspected.

[1]GIV

Do NOT

Note: If history of resistant organisms within the pa

consult Infe

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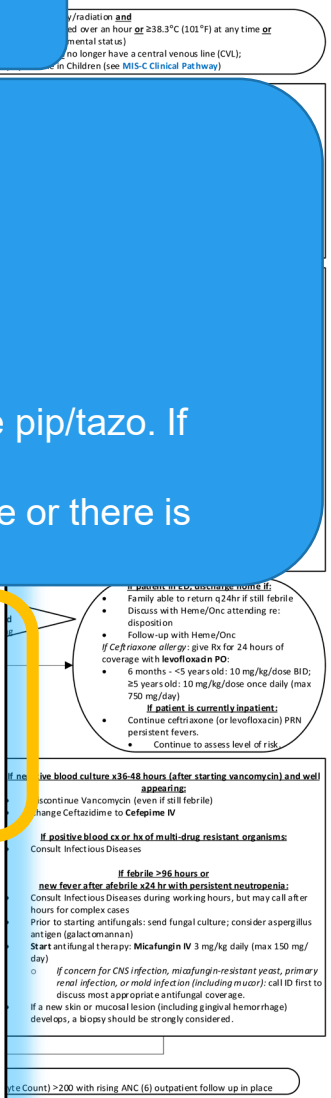

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High risk patients are listed to the right.

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 criteria)
  - Or have failed low risk therapy after 72 hours
- Broader coverage should be initiated with ceftazidime and vancomycin.
  - Ceftazidime broadens ceftriaxone's Gram negative coverage, but loses Gram positive activity
  - Vancomycin: good Gram positive coverage including MRSA
- If there is an allergy to a 3rd or higher gen cephalosporin: vancomycin and ciprofloxacin should be utilized.

High risk criteria

[2]High Risk

- Ill-appearing
- Skin soft tissue infection
- Mucositis
- Pneumonia
- Hx of viridans strep

If ANC < 500:

- ALL, not in maintenance
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  -
  -
- ANC <
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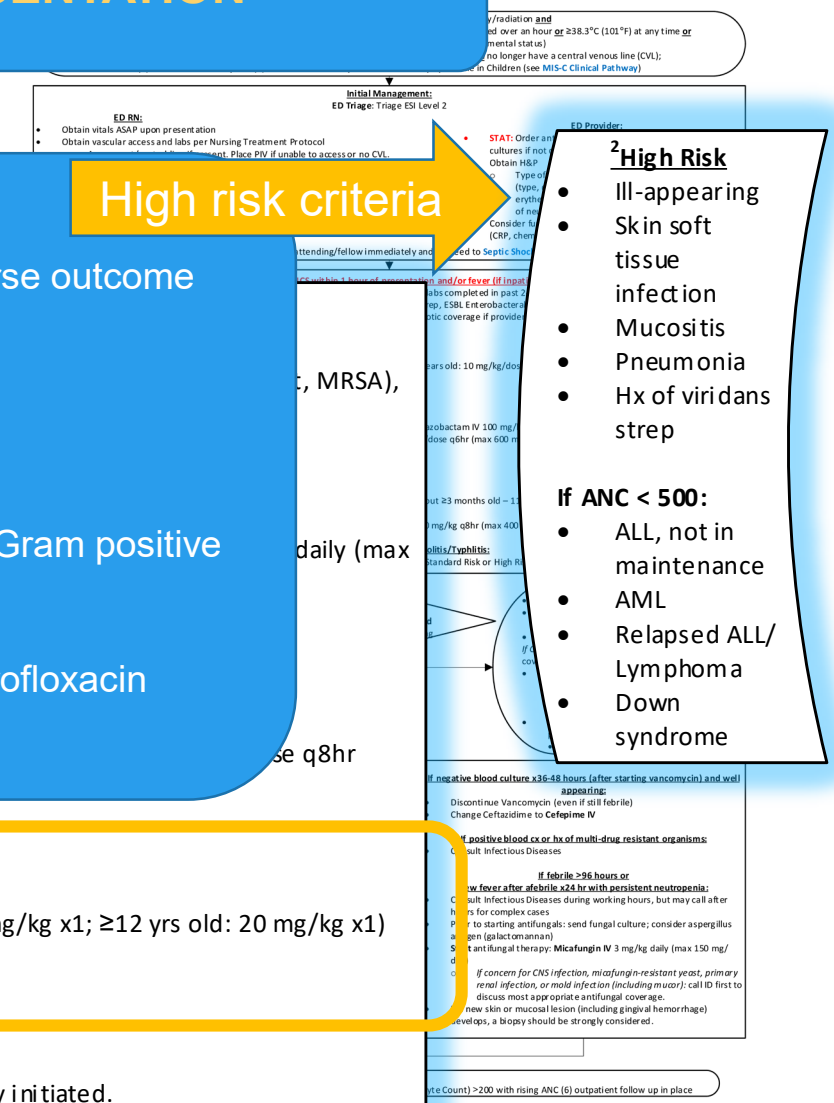

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Low Risk:

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  - **C**
  - *If*
  - *If a*
- ANC <5
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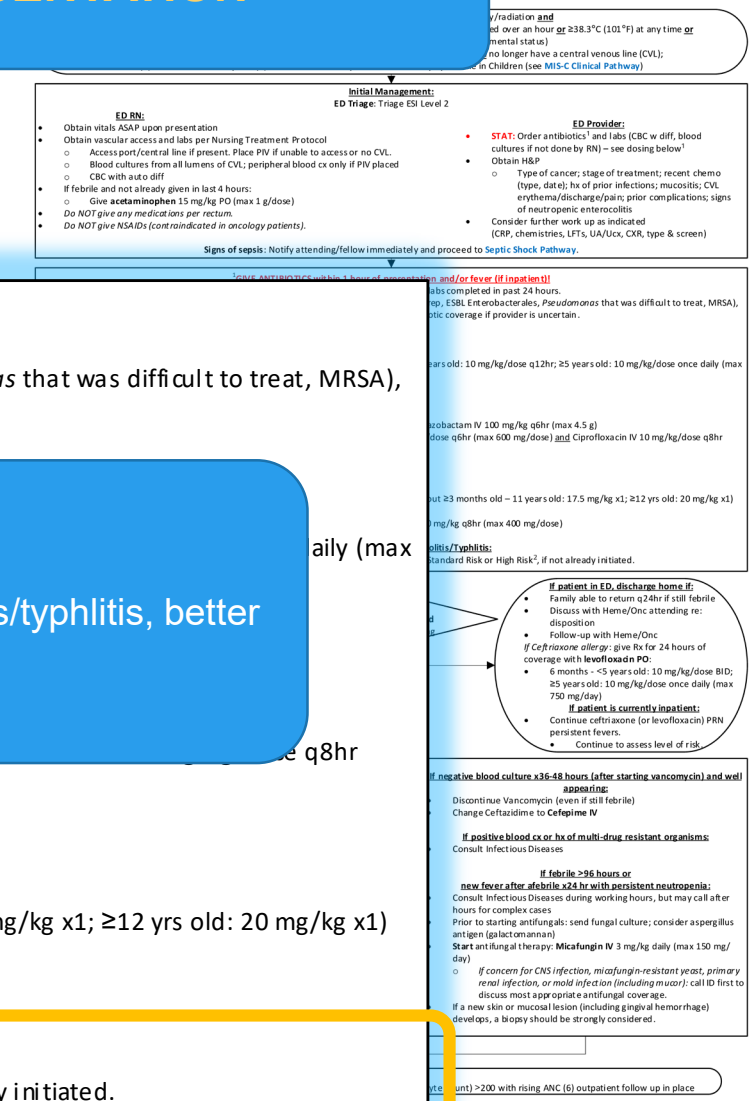
Concern for Neutropenic Enterocolitis/Typhlitis:

- **Add metronidazole IV** 10 mg/kg/dose q8hr (max 500 mg/dose) to antibiotic regimen for Standard Risk or High Risk[2], if not already initiated.

Concern for neutropenic enterocolitis/typhlitis:

For standard or high risk patients, if there is a concern for neutropenic enterocolitis/typhlitis, better anaerobic coverage is needed:

- **Add** metronidazole to the recommended antibiotics



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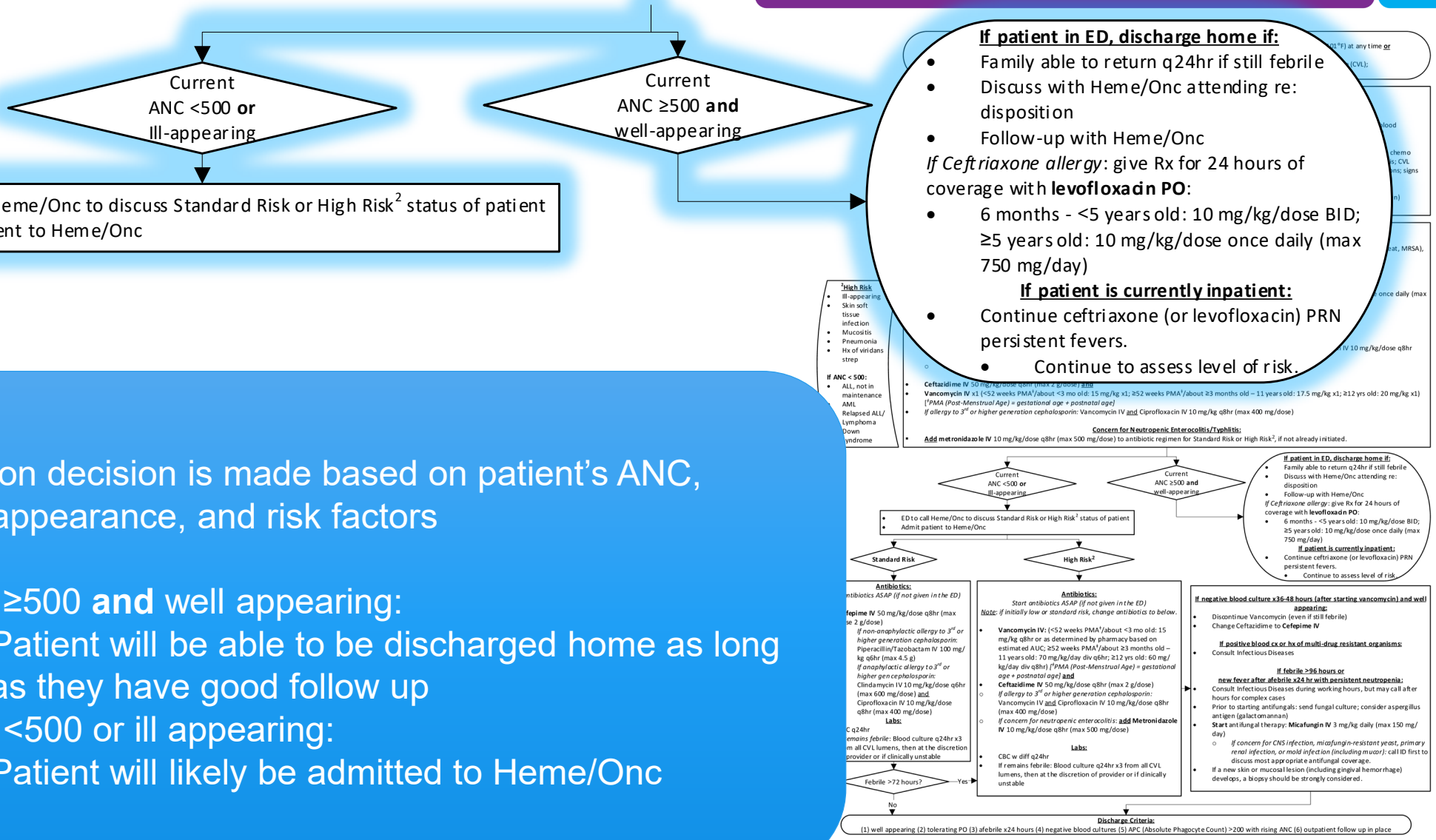

Admission decision is made based on patient's ANC, clinical appearance, and risk factors

- 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

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

- Standard Risk patients will get cefepime 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
- Pneumonia
- Hx of viridans strep

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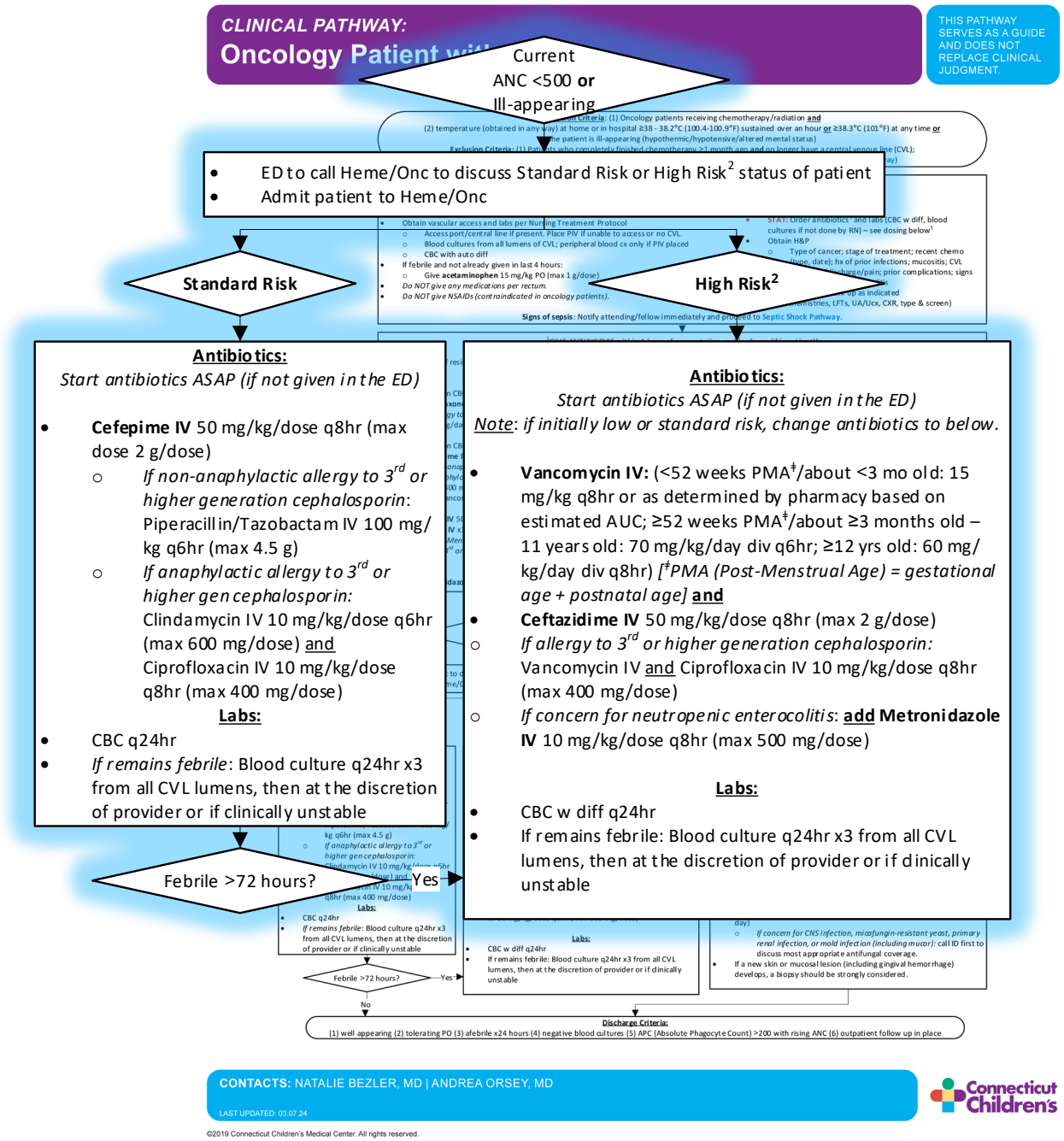

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- ED to call Heme/Onc to discuss Standard Risk or High Risk[2] status of patient
- Admit patient to Heme/Onc

Standard Risk

Antibiotics:

Start antibiotics ASAP (if not given in the ED)

- **Cefepime IV** 50 mg/kg/dose q8hr (max dose 2 g/dose)
  - *If non-anaphylactic allergy to 3rd or higher generation cephalosporin*: Piperacillin/Tazobactam IV 100 mg/kg q6hr (max 4.5 g)
  - *If anaphylactic allergy to 3rd or higher gen cephalosporin:* Clindamycin IV 10 mg/kg/dose q6hr (max 600 mg/dose) and Ciprofloxacin IV 10 mg/kg/dose q8hr (max 400 mg/dose)

Labs:

- CBC q24hr
- *If remains febrile*: Blood culture q24hr x3 from all CVL lumens, then at the discretion of provider or if clinically unstable

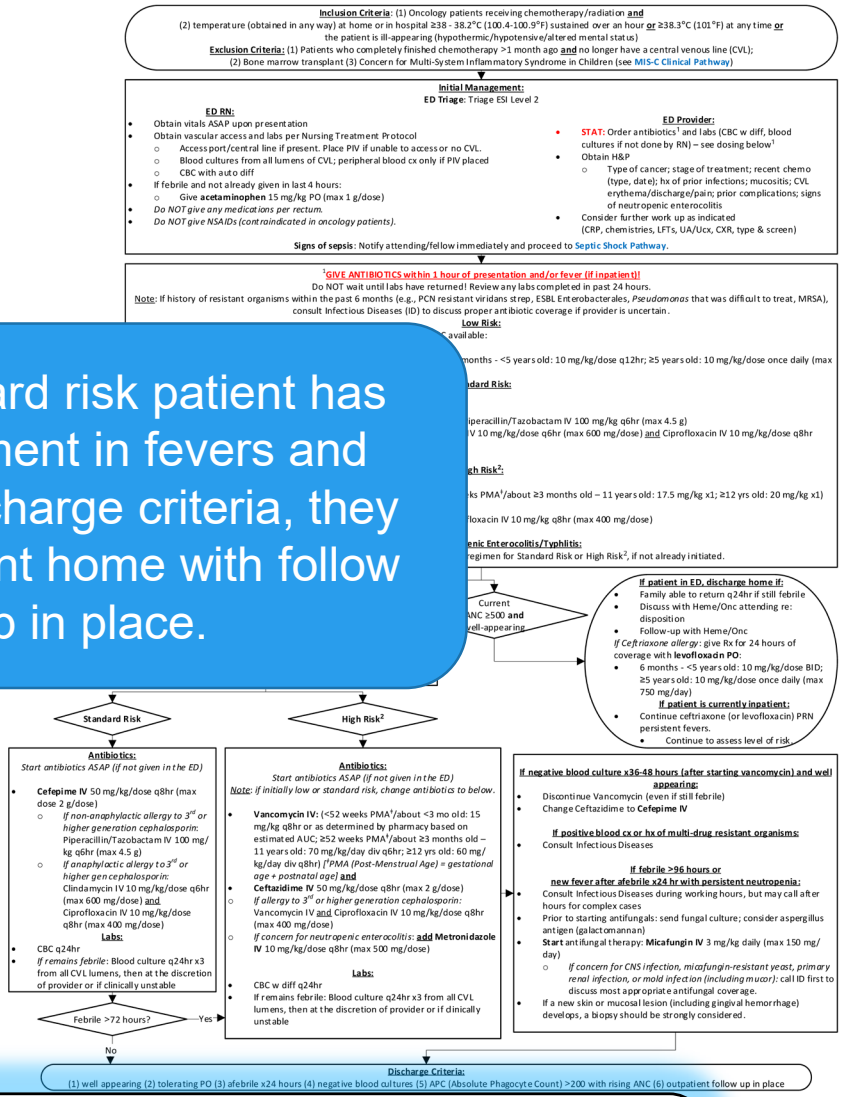
Febrile >72 hours?

No

Discharge Criteria:

(1) well appearing (2) tolerating PO (3) afebrile x24 hours (4) negative blood cultures (5) APC (Absolute Phagocyte Count) >200 with rising ANC (6) outpatient follow up in place

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



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

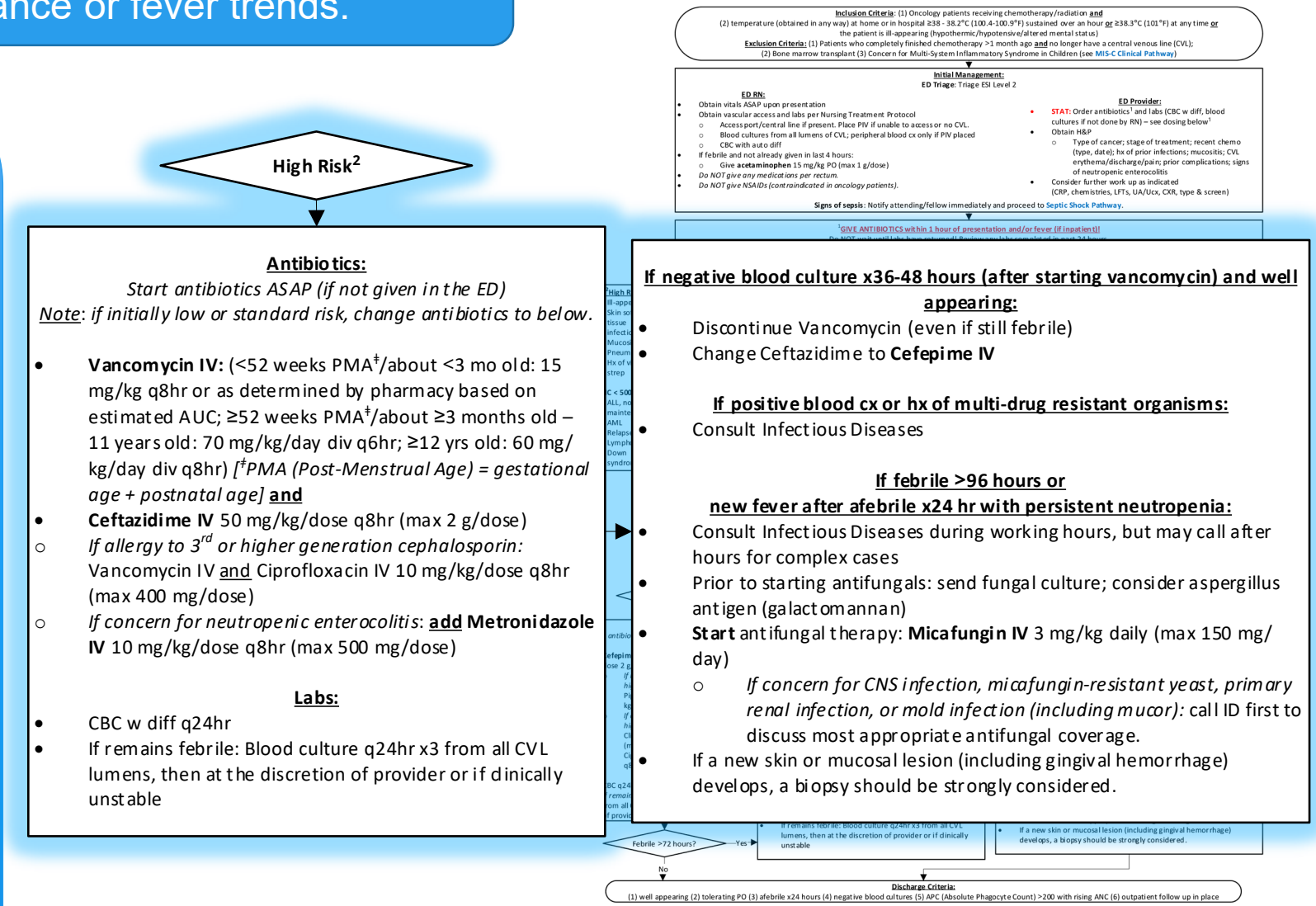
CLINICAL PATHWAY:
Oncology Patient with Fever

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

If negative blood culture x 36-48hrs and well appearing:
- Discontinue vancomycin
  - Prolonged use of vancomycin can increase rates of resistance
- Ceftazidime doesn't have reliable Gram positive coverage. So without vancomycin, ceftazidime should be changed to cefepime to better cover Gram positives.

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.



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CLINICAL PATHWAY:

Oncology Patient with Fever

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

Discharge Criteria:

(1) well appearing (2) tolerating PO (3) afebrile x24 hours (4) negative blood cultures (5) APC (Absolute Phagocyte Count) >200 with rising ANC (6) outpatient follow up in place

Discharge Criteria

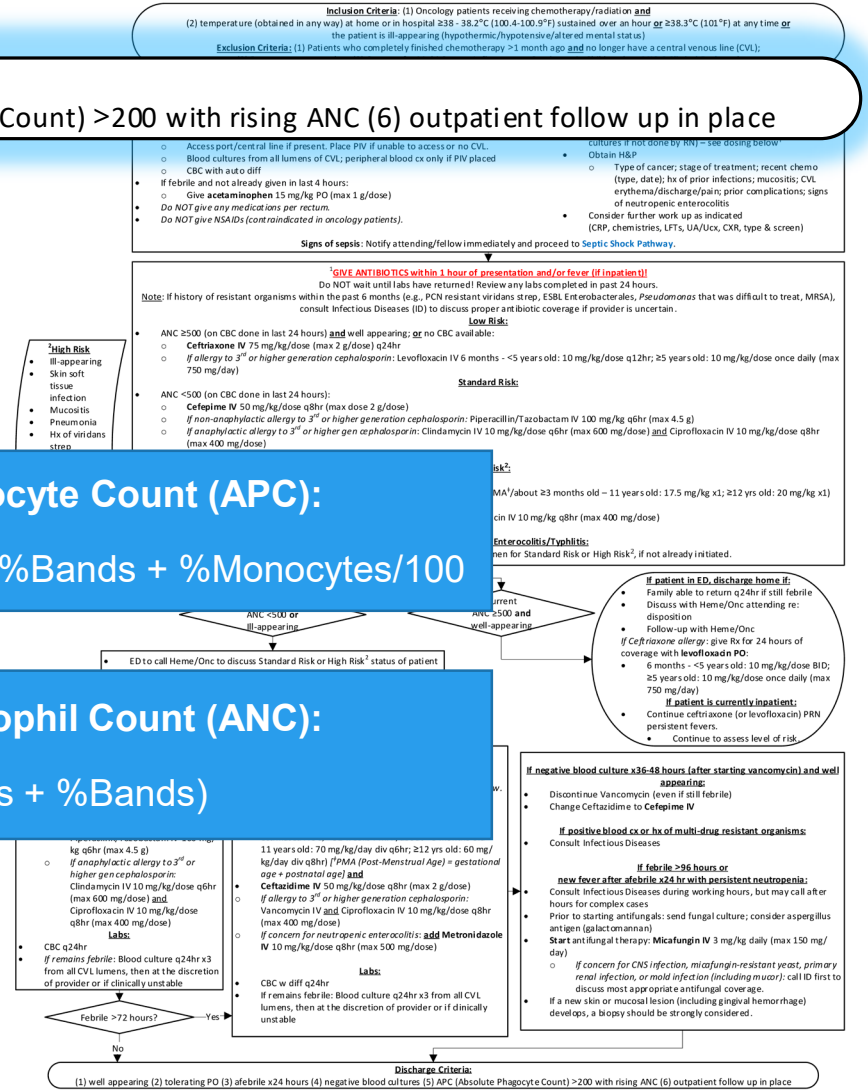
- Well appearing
- Tolerating PO
- Afebrile for 24 hours
- Negative blood cultures
- APC >200 and rising ANC
- Follow up in place

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)



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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 cefepime once Vancomycin is discontinued

Pathway Contacts

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

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Thank You!

About Connecticut Children's 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 judgment.