UWTASP

tele-antimicrobial stewardship program

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Neutropenic Fever

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Case

63 yo M with AML s/p chemotherapy presents with new fever during platelet transfusion. No other associated symptoms.

38.6˚C 110/78 92 22 98% RA
Severe mucositis
Hickman catheter site w/o erythema

Prophylaxis: levofloxacin, fluconazole, acyclovir

Absolute neutrophil count < 100 (x 10 days)

What is Neutropenic Fever?

Fever

- Single temperature equivalent to 38.3˚C orally **OR**
- Equivalent to ≥ 38.0˚C orally over 1-h period

Neutropenia

- <500 neutrophils/mcL **OR**
- <1000 neutrophils/ mCL and predicted decline to ≤ 500/mcL over the next 48h

ANC = WBCcount X [(PMNs/100) + (Bands/100)]

Who is at risk for NF?

LOW	INTERMEDIATE	HIGH
• Anticipated duration of neutropenia **< 7 days**	• Anticipated duration of neutropenia **7-10 days**	• Anticipated duration of neutropenia **> 10 days**
• Standard chemotherapy regimens for most solid tumors	• Autologus HCT • Lymphoma • CLL • Multiple myeloma	• Allogeneic HCT and cord blood • AML • GVHD, high dose steroids

HCT: hematopoietic Stem Cell Transplant; CLL: chronic lymphocytic leukemia;
AML: Acute Myeloid Leukemia; GVHD: Graft vs Host Disease

NCCN Guidelines Prevention and Treatment of Cancer Related Infections v1. 2018

Causes of Fever in a Cancer Patient

Infectious etiologies

- **Bacterial:**
  - Bloodstream infection (catheter-related or 2˚ mucosal barrier injury)
  - Site/ organ specific infections
  - Infections related to tumor obstruction (e.g. post-obstructive PNA, cholangitis, intraabdominal abscess)
- **Viral:** respiratory viruses, CMV
- **Fungal:** candidemia, invasive mold infections (aspergillus, mucor)

- **Non-infectious**
- Underlying malignancy (e.g. Hodgkin's, renal cell, hepatocellular CA, AML, CNS)
- Medications (e.g. chemo, antibiotics)
- Venous thrombosis/ thrombophlebitis
- Transfusion reactions

Infectious etiology identified in 20-30% of episodes

General Principles

- Neutropenic patients may have **more than one infectious process**
- Neutropenic patients **may lack classic signs/ symptoms,** present with unusual manifestations
- **Pay attention to antimicrobial prophylaxis….**
  - Dictate types of breakthrough infections

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Diagnostics of Neutropenic Fever

Assess potential sites of infection (careful H&P, ROS)

- Vascular access device
- Skin
- Lung and sinuses
- GI tract (oral cavity, abdomen, perirectal)
- Urologic
- Neurologic

Other information:

- Major comorbidities
- Time since last chemo
- Duration of neutropenia, anticipated time to count recovery
- Prior infections
- Exposures: Marijuana use, gardening, construction, household contacts, travel, pets, TB

Diagnostics of Neutropenic Fever

- **All patients:** Obtain **2 sets of blood cultures** (1 set = 1 aerobic/ 1 anaerobic bottle) **PRIOR** to antibiotics
  - If CVC: 1 peripheral and 1 central OR 2 central cultures
- **Symptom/ exam directed evaluation:**
  - Respiratory symptoms: multiplex respiratory viral panel, chest CT
  - Diarrhea: C. difficile and/or other enteric pathogens
  - Urinary symptoms: U/A and urine culture
  - Vesicular lesions, ulcerated mucosal lesions: HSV culture/ PCR, VZV PCR
  - Skin lesions: biopsy for microbiology and pathology

Empiric therapy

Initial antibiotic therapy should be based on:

- Broad-spectrum coverage including
- antipseudomonal activity
- Potential infecting organisms, including
- multidrug-resistant organisms (MDROs)
- colonization with or prior infection with MRSA)
- Site of infection
- Local antibiotic susceptibility patterns
- Organ dysfunction/drug allergy
- Previous antibiotic therapy
- Bactericidal nature of the antibiotic
- IV antibiotic therapy

Options:

Typically monotherapy

- **Cefepime (category 1)**
- Imipenem/cilastatin (category 1)
- Meropenem (category 1)
- Piperacillin/tazobactam (category 1)
- Ceftazidime (category 2B)

You recommend cefepime!

What about Vancomycin?

- IDSA and NCCN Guidelines **do not** recommend initial vancomycin w/ exception of selected situations
  - IDSA – **AI** level recommendation
  - NCCN – *"strongly recommends that vancomycin not be routinely added…"*

- IDSA and NCCN Guidelines recommend **discontinuation after 48-72 hours** if cultures are negative for resistant gram positive agent

Freifeld CID 2011;52 (4): e56-393; NCCN Guidelines Prevention and Treatment of Cancer Related Infections v1. 2018

Indications for Empiric Use of Vancomycin

	IDSA (2011)	ECIL (2013)	NCCN (2018)
Clinically apparent serious catheter related infection	✓	✓	✓
Hemodynamic instability	✓	✓	✓
MRSA colonization	✓	✓	✓
Skin or soft tissue infection	✓	✓	✓
Positive blood cultures for gram + bacteria (before ID & susceptibilities)	✓		✓
Pneumonia	✓	✓	
Severe mucositis **(if FQ prophylaxis AND ceftazidime used empirically)**	✓		

Back to the case

Day 4, pt remains on cefepime. Pt is afebrile, but no source found…

ANC is 150 mm/cells

What is your next step?

Daily monitoring

RESULTS OF DAILY MONITORING

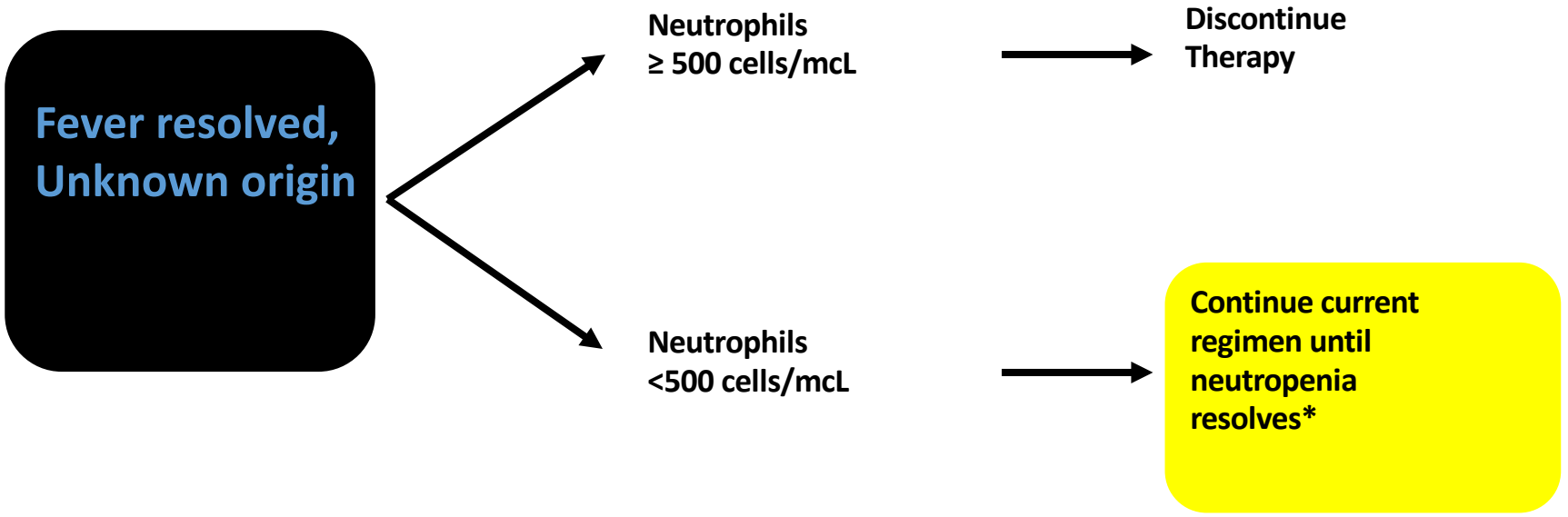
FOLLOW-UP THERAPY

- **Consider antifungal therapy with activity against molds for fever continuing ≥4 days of empiric antibiotic therapy[x]**
- **Duration of therapy depends on clinical course, neutropenia recovery, toxicity, and opinions of ID consultants**

[v] In the case of prolonged neutropenia (>14 days), consider judicious assessment of empiric therapy.
[w] In patients who defervesce, it may be appropriate in some cases to de-escalate to fluoroquinolone. The choice will depend on particular patient details; see Discussion for additional information.
[x] The timing to add empiric antifungal therapy varies with the risk of invasive mold infection but generally ranges between 4–7 days of neutropenic fever. In patients at high risk for mold infection (ie, neutropenia >10 days, allogeneic HCT recipients, high-dose corticosteroids), the panel recommends adding empiric antifungal therapy after the fourth day unless patient is receiving prophylaxis directed against molds.

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.

Febrile Neutropenia, Unknown Source: How Long to Treat?



*In the case of prolonged neutropenia > 14 days, consider judicious assessment of empiric therapy.
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Antibiotic De-escalation for Neutropenic Patients: When?

IDSA Guidelines NCCN Guidelines	European (ECIL-4) Guidelines	German (AGIHO) Guidelines
Continue **until there are clear signs of marrow recovery** (ANC > 500) **(BII)** **OR** If appropriate treatment course completed, signs/ sx of infections resolved, resume oral FQ ppx until marrow recovery **(CIII)**	Discontinue **after ≥ 72 h** if hemodynamically stable and afebrile for ≥ 48 h, **irrespective of neutrophil count or expected duration of neutropenia (BII)**	Discontinue **after 7 days** if stable defervescence without clinical signs or symptoms of infection **(BIII)**

Freifeld CID 2011; 52: e56-e93; NCCN Guidelines V2. 2017; Averbach Hematologica 2013; 98:1826-1835; Heinz Ann Hematology epub 2017 Aug 30

Febrile Neutropenia, Documented Infection: How Long to Treat?

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2019
Prevention and Treatment of Cancer-Related Infections

NCCN Guidelines Index
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FOLLOW-UP THERAPY FOR RESPONDING DISEASE

SUGGESTED MINIMUM DURATION OF THERAPY FOR DOCUMENTED INFECTION[h,l,m]

These are general guidelines and may need to be revised for individual patients.

Documented infection →

- Targeted treatment of documented infections should be done
- Reassessment of empiric Gram-negative therapy should be considered
- De-escalation and duration of antimicrobial therapy may be individualized based on:
  - Neutrophil recovery
  - Rapidity of defervescence
  - Specific site of infection
  - Infecting pathogen
  - Patient's underlying illness

→

- Skin/soft tissue: 7–14 d
- Bloodstream infection
  - Gram-negative: 10–14 d[y]
  - Gram-positive: 7–14 d[y]
  - *S. aureus*: typically requires 4 weeks after first negative blood culture; treatment may need to be prolonged in cases of endovascular involvement; encourage ID consult
  - Yeast: ≥2 wks after first negative blood culture
  - Catheter removal favored for bloodstream infections with *Candida*, *S. aureus*, *Pseudomonas aeruginosa*, *Corynebacterium jeikeium*, *Acinetobacter*, *Bacillus* organisms, atypical mycobacteria, yeasts, molds, vancomycin-resistant enterococci (VRE), *Stenotrophomonas maltophilia*, and other multidrug-resistant organisms (MDROs)
- Bacterial sinusitis: 7–14 d
- Catheter removal for septic phlebitis, tunnel infection, or port pocket infection
- Bacterial pneumonia: 7–14 d
- Fungal (mold and yeast):
  - *Candida*: minimum of 2 wks after first negative blood culture
  - Mold (eg, *Aspergillus*): minimum of 12 wks
- Viral:
  - HSV/VZV: 7–10 d (category 1); acyclovir, valacyclovir, or famciclovir (uncomplicated, localized disease to the skin)
  - Influenza: A minimum 5 d course of oseltamivir is standard based on data from ambulatory and otherwise healthy individuals with intact immune systems; some centers consider longer courses for the highly immunocompromised,[z] but there is no proven benefit to prolonged therapy

Summary

- Neutropenic patients often have subtle signs of infections
- Empiric therapy should consist of therapy against Pseudomonas
- Vancomycin is only added is select circumstances
- Duration of therapy is based on presence of fever and recovery of neutrophil count but an active area of research