High-Risk Febrile Neutropenia Protocol for Patients with Hematological Malignancy

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Last updated: October, 2014.
Approved by Pharmacy & Therapeutics at UHN and MSH in October 2014
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Approved by UHN and MSH Medical Advisory Committee December 2014.
1. **Antimicrobial Prophylaxis for High-Risk Febrile Neutropenia**

1a. **Acute Myeloid Leukemia** (AML)

1b. **Acute Lymphocytic Leukemia** (ALL) with Vinca Alkaloids chemotherapy: In patients exposed to high-dose corticosteroid with Vinca Alkaloid chemotherapy.

1c. **Acute Lymphocytic Leukemia** (ALL) without Vinca Alkaloids chemotherapy: In patients exposed to high-dose corticosteroid but no Vinca Alkaloid chemotherapy.

1d. **Autologous Bone Marrow Transplant**

1e. **Allogeneic Bone Marrow Transplant** but has acute GVHD: In patients exposed to high-dose corticosteroid and have Grade 2-4 Graft vs. Host Disease (GVHD) or Chronic GVHD.

1f. **Allogeneic Bone Marrow Transplant** but no acute GVHD: In patients exposed to high-dose corticosteroid but no Graft vs. Host Disease.

1g. **Aplastic Anemia**: In patients receiving anti-thymocyte globulin (ATG) or alemtuzumab.

1h. **Chronic Lymphocytic Leukemia or Lymphoma** (fludarabine chemotherapy): In patients receiving fludarabine.

1i. **Myelodysplastic Syndrome** (MDS): In patients with transformed MDS.

2. **Initial Investigation and Management of a Patient with Febrile Neutropenia**

Initial assessments and management in a patient presenting with high-risk febrile neutropenia.

3a. **Pre-Emptive Antifungal Therapy in Patients with Hematological Malignancies**

Patient has positive biomarker (serum galactomannan) and has risk factor (neutropenia) which meet criteria for pre-emptive antifungal therapy.

3b. **Management of Pulmonary Infiltrate in Patients with Hematological Malignancies**

Patient with abnormal CT chest who requires further investigations and antimicrobial therapy.

4. **Recommended Management for Catheter-Related Blood Stream Infections**

Investigations and management for suspected or confirmed central-line related infections.

5a. **Recommended Antimicrobials by Type of Infection**

Recommended antimicrobial regimens for patients in whom a source of infection (+/- organisms) has been identified.

5b. **Candidemia**

Recommended management for candidemia.

5c. **Recommended Antimicrobials if Source of Infection or Pathogen is Not Identified**

Recommended antimicrobial therapy management if source of infection is unknown.

6. **Persistent or Recrudescent Neutropenic Fever Investigations and Management**

Investigations and recommended antimicrobial therapy in patients with persistent fever after 5d (or more) of appropriate antimicrobials, or recurrent fever after initial response to antimicrobial therapy.
1. Antimicrobial Prophylaxes for High-Risk Febrile Neutropenia

Identify **Eligible** Patients

Neutropenia **anticipated** to be **prolonged** (7d or more) and **profound** due to hematological malignancies and associated chemotherapy

Select 1 of the indications below:

- **1a.** Acute Myeloid Leukemia (AML)
- **1b.** Acute Lymphocytic Leukemia (ALL) and is to receive chemo **with** Vinca Alkaloids (e.g. vincristine)
- **1c.** Acute Lymphocytic Leukemia (ALL) and is to receive chemo **without** Vinca Alkaloids (e.g. vincristine)
- **1d.** Autologus Bone Marrow Transplant
- **1e.** Allogeneic Bone Marrow Transplant but **has** Acute Grade 2-4 Graft vs. Host Disease (GVHD) or Chronic GVHD
- **1f.** Allogeneic Bone Marrow Transplant but **no** Acute Graft vs. Host Disease (GVHD)
- **1g.** Aplastic Anemia
- **1h.** Chronic Lymphocytic Leukemia or Lymphoma
- **1i.** Myelodysplastic Syndrome (transformed)
1a. Antimicrobial Prophylaxes in Acute Myeloid Leukemia (AML)

Patient has Acute Myeloid Leukemia (AML)

Patient has hematological malignancy + is at risk of prolonged (7d or more) and profound (ANC 0.1 x10⁹/L or fewer) neutropenia, i.e.: High-Risk Neutropenia

- ciprofloxacin 500 mg PO BID starting day 8 of re-induction (in-patient) or consolidation (out-patient) chemotherapy
- fluconazole 400 mg PO/IV daily during induction chemo
  - alternatives: 
    - micafungin 50 mg IV daily
    - caspofungin 70 mg IV day 1 then 50 mg IV daily if drug interactions or intolerance
- acyclovir 400 mg PO BID starting day 1 of chemotherapy
  - alternative: acyclovir 5 mg/kg IV Q12H if unable to tolerate PO

Continue until ANC greater than 0.5 x10⁹/L for at least 48h

Patient presents with Febrile Neutropenia, go to Figure 2
Patient has Acute Lymphocytic Leukemia (ALL) and is to receive: chemo with Vinca Alkaloids (e.g. vincristine)

Patient has hematological malignancy

is at risk of prolonged (7d or more) and profound (ANC 0.1 x10⁹/L or fewer) neutropenia, i.e.: High-Risk Neutropenia

**cotrimoxazole** 1 double-strength tab PO Q Mon, Wed, Fri starting day 4 of chemotherapy

**micafungin** 50 mg IV daily or **caspofungin** 70 mg IV day 1 then 50 mg IV daily during induction

**alternative:** consult ID and respirology

**acyclovir** 400 mg PO BID starting day 1 of chemotherapy

**alternative:** **acyclovir** 5 mg/kg IV Q12H if unable to tolerate PO

**ciprofloxacin** 500 mg PO BID starting day 8 of re-induction (in-patient) or consolidation (out-patient) chemotherapy

Continue until ANC greater than 0.5 x10⁹/L for at least 48h

Patient presents with Febrile Neutropenia, go to Figure 2
1c. Antimicrobial Prophylaxes in Acute Lymphocytic Leukemia without Vinca Alkaloids Chemotherapy

**Patient has Acute Lymphocytic Leukemia (ALL) and is to receive:** chemotherapy **without Vinca Alkaloids (e.g. vincristine)**

**Patient has hematological malignancy**

- **cotrimoxazole** 1 double-strength tab PO Q Mon, Wed, Fri starting day 4 of chemotherapy
- alternative: consult ID and respirology

- **fluconazole** 400 mg PO/IV daily during induction chemo

**Patient is at risk of prolonged (7d or more) and profound (ANC 0.1 x10⁹/L or fewer) neutropenia, i.e.: High-Risk Neutropenia**

- **acyclovir** 400 mg PO BID starting day 1 of chemotherapy
- alternative: **acyclovir** 5 mg/kg IV Q12H if unable to tolerate PO

**ciprofloxacin** 500 mg PO BID starting day 8 of re-induction (in-patient) or consolidation (out-patient) chemotherapy

Continue until ANC greater than 0.5 x10⁹/L for at least 48h

Patient presents with Febrile Neutropenia, go to Figure 2
Antimicrobial Prophylaxes in Autologus Bone Marrow Transplant

**Patient has hematological malignancy** + is at risk of **prolonged** (7d or more) and **profound** (ANC 0.1 x10⁹/L or fewer) **neutropenia**, i.e.: High-Risk Neutropenia

**Autologus Bone Marrow Transplant and is to receive:** chemotherapy likely to cause mucositis, but **no** prior exposure to fludarabine

**ciprofloxacin** 500 mg PO BID or 400 mg IV BID

**cotrimoxazole** 1 double-strength tab PO Q Mon, Wed, Fri starting day 4 of chemotherapy

**alternative:** consult ID and respirology

**fluconazole** 400 mg PO/IV daily Day +1

**alternatives:**
- **micafungin** 50 mg IV daily
- **caspofungin** 70 mg IV day 1 then 50 mg IV daily if drug interactions or intolerance

**acyclovir** 400 mg PO BID starting day 1 of chemotherapy

**alternative:**
- **acyclovir** 5 mg/kg IV Q12H if unable to tolerate PO

Continue until ANC greater than 0.5 x10⁹/L for at least 48h

**Patient presents with Febrile Neutropenia, go to Figure 2**
1e. Antimicrobial Prophylaxes in alloBMT but Has Acute GVHD

**Allogeneic Bone Marrow Transplant:** but has Acute Grade 2-4 Graft vs. Host Disease (GVHD) or Chronic GVHD

**Patient has hematological malignancy** + **is at risk of prolonged** (7d or more) and **profound** (ANC 0.1 x10^9/L or fewer) **neutropenia**, i.e.: **High-Risk Neutropenia**

- **cotrimoxazole** 1 double-strength tab PO Q Mon, Wed, Fri starting day 4 of chemotherapy
  - alternative: consult ID and respirology

- **posaconazole** 200 mg PO Q8H taken with high-fat food
  - alternative: **voriconazole** 6 mg/kg PO/IV Q12H x2 doses then 4 mg/kg PO/IV Q12H

- **acyclovir** 400 mg PO BID starting day 1 of chemotherapy
  - alternative: **acyclovir** 5 mg/kg IV Q12H if unable to tolerate PO

**Continue until day 180+ if on immunosuppressant for GVHD**

Patient presents with Febrile Neutropenia, go to Figure 2
Allogeneic Bone Marrow Transplant: but no Acute Graft vs. Host Disease (GVHD)

Patient has hematological malignancy + is at risk of prolonged (7d or more) and profound (ANC 0.1 x10^9/L or fewer) neutropenia, i.e.: High-Risk Neutropenia

- **cotrimoxazole** 1 double-strength tab PO Q Mon, Wed, Fri starting day 4 of chemotherapy
- alternative: consult ID and respirology
- or
- **fluconazole** 400 mg PO/IV daily during induction chemo
- alternatives: 
  - **micafungin** 50 mg IV daily
  - **caspofungin** 70 mg IV day 1 then 50 mg IV daily if drug interactions or intolerance
- or
- **acyclovir** 400 mg PO BID starting day 1 of chemotherapy
- alternative: 
  - **acyclovir** 5 mg/kg IV Q12H if unable to tolerate PO

Continue to day 100+ and ANC greater than 0.5 x10^9/L for at least 48h

Patient presents with Febrile Neutropenia, go to Figure 2
Patient has aplastic anemia: Patient receives anti-thymocyte globulin (ATG) treatment

Patient has hematological malignancy

Patient is at risk of **prolonged** (7d or more) and **profound** (ANC 0.1 x10⁹/L or fewer) neutropenia, i.e.: High-Risk Neutropenia

- **Fluconazole** 400 mg PO/IV daily
  - alternative: **micafungin** 50 mg IV daily or **caspofungin** 70 mg IV day 1 then 50 mg IV daily

- **Cotrimoxazole** 1 double-strength tab PO Q Mon, Wed, Fri starting day 4 of chemotherapy
  - alternative: consult ID and respirology

- **Ciprofloxacin** 500 mg PO BID
  - alternative: **acyclovir** 400 mg PO BID starting day 1 of chemotherapy

Continue until ANC greater than 0.5 x10⁹/L for at least 48h

Patient presents with Febrile Neutropenia, go to Figure 2
1h. Antimicrobial Prophylaxes in Chronic Lymphocytic Leukemia or Lymphoma (fludarabine chemotherapy)

**Patient has Chronic Lymphocytic Leukemia or Lymphoma and is receiving:** fludarabine

**Patient has hematological malignancy** + is at risk of **prolonged** (7d or more) and **profound** (ANC 0.1 x10⁹/L or fewer) **neutropenia**, i.e.: **High-Risk Neutropenia**

- **cotrimoxazole** 1 double-strength tab PO Q Mon, Wed, Fri
- **fluconazole** 400 mg PO/IV daily
- **acyclovir** 400 mg PO BID starting day 1 of chemotherapy

Alternatives:
- **micafungin** 50 mg IV daily
- **caspofungin** 70 mg IV day 1 then 50 mg IV daily
- alternative: **acyclovir** 5 mg/kg IV Q12H if unable to tolerate PO

Continue until ANC greater than 0.5 x10⁹/L for at least 48h

Patient presents with Febrile Neutropenia, go to Figure 2
1i. Antimicrobial Prophylaxes in Myelodysplastic Syndrome (transformed)

Patient has Myelodysplastic Syndrome (transformed)

Patient has hematological malignancy

is at risk of prolonged (7d or more) and profound (ANC 0.1 x10^9/L or fewer) neutropenia, i.e.: High-Risk Neutropenia

**cotrimoxazole** 1 double-strength tab PO Q Mon, Wed, Fri starting day 4 of chemotherapy

**fluconazole** 400 mg PO/IV daily

**acyclovir** 400 mg PO BID starting day 1 of chemotherapy

**ciprofloxacin** 500 mg PO BID starting day 8 of re-induction (in-patient) or consolidation (out-patient) chemotherapy

**alternative:** consult ID and respirology

alternatives:
- **micafungin** 50 mg IV daily
- **caspofungin** 70 mg IV day 1 then 50 mg IV daily

**acyclovir** 5 mg/kg IV Q12H if unable to tolerate PO

Continue until ANC greater than 0.5 x10^9/L for at least 48h

Patient presents with Febrile Neutropenia, go to Figure 2

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**Legend:**
- PO: Oral
- IV: Intravenous
- BID: Twice daily
- Q: Every
- Q12H: Every 12 hours
2. Initial Investigations and Management of a Patient with High-Risk Febrile Neutropenia

**Definition of Febrile Neutropenia:**
ANC fewer than or equal to 0.5 \(x10^9\)/L, or fewer than or equal to 1\(x10^9\)/L but expected to fall below 0.5\(x10^9\)/L in the next 48h + single oral temperature higher than 38.3°C or sustained oral temperature of 38°C for more than 1h.

**Definition of High-Risk Febrile Neutropenia:**
All qualifications as stated to the left (i.e. has fever + neutropenia) + neutropenia anticipated to be prolonged (7d or more) and profound (with ANC fewer than 0.1 \(x10^9\) cells/L). E.g. Febrile neutropenia in patients with hematological malignancies.

### Complete initial assessments and investigations in the checklist below:
- **Blood cultures:**
  - From each CVC lumen (if present) and one peripheral site, 10 mL into an aerobic bottle, and 10 mL into an anaerobic bottle.
  - Screening for multi-resistant organisms as per Infection Prevention (and Control) policies.
- **Symptom or source-directed assessment:**
  - Central nervous system: signs and symptoms, imaging studies as appropriate
  - Chest CT (LOW DOSE)
  - BAL (bronchoalveolar lavage) including galactomannan if CT chest abnormal
  - Sputum culture
  - NP swab for respiratory viral panel (RSV, influenza, parainfluenza)
  - Legionella urinary antigen
  - Skin and integumentary system for lesions, cellulitis
  - All IV line sites if exudate or evidence of infection present
  - Mouth ulcers swab (for gram stain, viral, fungal cultures)
  - Abdominal CT if abdominal symptoms present to rule out neutropenic enterocolitis or collections
  - C. difficile PCR as appropriate

### Ongoing:
- Serum galactomannan every Mon, Wed in in-patients.
  - With results, go to Figure 3.

### Treat with empiric therapy below:
- **Empiric antimicrobials:**
  - **piperacillin-tazobactam**
    - 4.5g IV Q8H + **gentamicin**
    - 5 mg/kg IV Q24H
  - **Alternative (for penicillin-hypersensitivity):**
    - **meropenem** 1g IV Q8H (cross-reactivity <1%). Clarify allergy history when feasible and modify antibiotic accordingly.

### If necessary, make additions according to list below:
- **CNS infections**
  - Consult ICH ID
- **Sinusitis or bacterial pneumonia**
  - Add azithromycin 500 mg PO/IV x1d, then 250 mg PO daily
- **Skin and skin structure infections or suspected central line infections**
  - Add vancomycin 15 mg/kg IV Q12H (max 1.5g per dose)
- **Suspected or documented C. difficile infection**
  - Add metronidazole 500 mg PO Q8H or vancomycin 125 mg PO Q6H
- **Mucocutaneous HSV infection**
  - Add acyclovir 5 mg/kg IV Q8H or famciclovir PO 500 mg BID. Consult ICH ID if disseminated infection suspected.
- **Suspected VZV infection**
  - Add acyclovir IV 10 mg/kg Q8H. Consult ICH ID.

**Consult clinical pharmacist for advice on dose adjustment of antimicrobials (e.g. gentamicin, vancomycin) in patients with renal insufficiency after the first dose.**

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**Blood cultures:**
- From each CVC lumen (if present) and one peripheral site, 10 mL into an aerobic bottle, and 10 mL into an anaerobic bottle.
- Screening for multi-resistant organisms as per Infection Prevention (and Control) policies.

**Symptom or source-directed assessment:**
- Central nervous system: signs and symptoms, imaging studies as appropriate
- Chest CT (LOW DOSE)
- BAL (bronchoalveolar lavage) including galactomannan if CT chest abnormal
- Sputum culture
- NP swab for respiratory viral panel (RSV, influenza, parainfluenza)
- Legionella urinary antigen
- Skin and integumentary system for lesions, cellulitis
- All IV line sites if exudate or evidence of infection present
- Mouth ulcers swab (for gram stain, viral, fungal cultures)
- Abdominal CT if abdominal symptoms present to rule out neutropenic enterocolitis or collections
- C. difficile PCR as appropriate

**Ongoing:**
- Serum galactomannan every Mon, Wed in in-patients.
  - With results, go to Figure 3.
Evidence of clinical deterioration

24-48h

- Example: hemodynamic instability, despite at least 48h of appropriate empiric antimicrobials.

Patient is stable, cultures remain negative

72h

- Patient is stable. Blood and/or other cultures remain negative at 72h or if investigations for suspected infections remain negative at 72h.

Discontinue gentamicin / other modifying antimicrobials.

Patient is stable, cultures are positive

72h

- Patient is stable. Blood and/or other cultures are positive at 72h or if investigations for suspected infections are positive at 72h.

Repeat all investigations including blood cultures and comprehensive physical exam and change antimicrobials to meropenem 1g IV Q8H + vancomycin 15 mg/kg IV Q12H (if not already on) and consult ICH ID*.  

*ICH ID: immunocompromised host infectious disease service, via locating

Continue to Figures 3, 4, and 5

Patient is being assessed daily
CT findings are suggestive of fungal pneumonia (e.g. cavity, nodules, halo signs) and repeat serum GM test is positive or pending.

Respirology consult, BAL (bronchoalveolar lavage) ideally within 72h of starting voriconazole or report of positive CT findings.

Consult Respirology and ICH ID to determine further action.

Positive BAL findings for fungal pneumonia (e.g. positive BAL GM) — Continue voriconazole x12wks.

Negative BAL findings — Consult Respirology and ICH ID to determine if voriconazole should be continued.

Chest CT (low dose) — Repeat serum GM test — Start voriconazole 6 mg/kg IV/PO Q12H x2 doses then 4 mg/kg IV/PO Q12H — Baseline liver function tests — Consult ICH ID.

Positive serum galactomannan (GM) every Monday and Wednesday, while patient is neutropenic and as an in-patient.

Consult clinical pharmacist to rule out drug interactions or contraindications with voriconazole.

Definition: Need for pre-emptive therapy = Positive biomarker (galactomannan) + Presence of risk factor (neutropenia).
3b. Pulmonary Infiltrate Management

Eligible patients:

**Group 1:** Neutropenic patient (ANC < 0.5x10^9/L) with oral temperature higher than or equal to 38.3°C. and is suspected to have respiratory tract infection.

**Group 2:** Patient is on systemic corticosteroid* and is suspected to have respiratory tract infection.

* Systemic corticosteroid:

**Increased risk of fungal infections** are associated with greater than or equal to 20mg prednisone daily, or another steroid at equivalent dose, for greater than or equal to 21 days.

**Abbreviations:**

ANC: Absolute Neutrophil Count

FN: Febrile Neutropenia

ICH-ID: Immunocompromised Host Infectious Diseases team

NP Swab: Nasopharyngeal Swab

**Order low-dose chest CT**

2. **Presence of at least one of the following NEW findings:**

- [ ] Nodules
- [ ] Ground glass opacity
- [ ] Interstitial pattern
- [ ] Consolidation

**New findings?**

- [ ] No
- [ ] Yes

**Go to Figure 2**

Initial Investigations

**Go to Figure 6**

Recrudescent Fever

**Follow the steps below:**

- Urgent consult Respiriologist for bronchoscopy within 72 hours of clinical presentation

**Send for these microbiological tests in EPR (click to open)**

- AND

**Consult PMH (Oncology) ICH ID**

AND

**NP Swab sent for respiratory viruses**

**Go to Next Page for further actions**
3b. Pulmonary Infiltrate Management: Further Actions

* Systemic corticosteroid:

**Increased risk of fungal infections** are associated with greater than or equal to 20mg **prednisone** daily, or another steroid at equivalent dose, for greater than or equal to **21 days**.

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**Patient’s oral temperature ≥ 38.3°C**

**OR**

**patient requires assisted ventilation (invasive or non-invasive)**

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**Is patient on systemic corticosteroid?**

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**Yes**

**Perform the following tasks:**

- **Await BAL and NP swab results before initiating additional empiric antimicrobials**
- **Continue current antimicrobials for febrile neutropenia**

**Treat according to NP swab and BAL results**

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**Note:** *Candida spp.* in BAL does not usually warrant antifungal therapy. Consult ICH ID for recommendation.
3b. Pulmonary Infiltrate Management: Empiric Antimicrobial Therapy Based on CT Abnormalities

**Description of abnormalities on CT (hover mouse on images to enlarge, click to close image)**

**Nodules**

- 10 or fewer nodules reported:
  - As empiric therapy for invasive aspergillosis:
    - Voriconazole 6mg/kg IV or PO Q12H x2 doses, then 4 mg/kg IV or PO Q12H thereafter
  - If patient is on mould-active prophylaxis (e.g. posaconazole), consult ICH (Oncology) ID for advice on empiric regimen.

- Greater than 10 nodules or reverse halo-sign AND pleural effusion reported:
  - As empiric therapy for mucormycosis:
    - Amphotericin B deoxycholate (Fungizone) 1.5 mg/kg IV daily
    - OR
    - Liposomal Amphotericin B (Ambisome) 5 mg/kg IV daily if patient older than 50 yrs

**Consolidation**

**Ground glass opacity or interstitial pattern**

**Go to Figure 2 empiric antibiotics for suspected bacterial pneumonia**

- Monitor elevated transaminases or bilirubin. ICH (Oncology) ID to advise on alternative therapy if adverse effects occur

Continue to next page after identifying abnormalities and initiating appropriate empiric therapy

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3b. Pulmonary Infiltrate Management: Follow-Up Assessment

Follow up results from NP swab, BAL and GM

Notify ICH (Oncology) ID for advice on antimicrobial therapy accordingly

Follow-up CT NOT routinely recommended UNLESS:

- Persistent (>5d) oral temp ≥ 38.3C
- Initial defervescence followed by recurrent signs and symptoms

Clinical progression or non-response suspected:

- Urgent re-consult with Respirology and ICH (Oncology) ID
- Go to Figure 6. Recurrent or Recrudescent Fever

Abbreviations:
- BAL: Bronchoalveolar Lavage
- GM: Galactomannan test
- ICH-ID: Immunocompromised Host Infectious Diseases team
- NP Swab: Nasopharyngeal Swab
4. Recommended Management for Catheter-Related Blood Stream Infections

**Obtain blood cultures before initiation of antimicrobials:**
Paired specimens from central venous catheters + peripheral vein

**Culture exudates at exit sites,**
insertion sites, tunnel catheter tract, or pocket of implanted cardiovascular device if present

**Empiric therapy for suspected CRBSI:**
vancomycin 15 mg/kg IV Q12H

**Culture are:**
- Positive
  - Bacteremia or fungemia with no other source except catheter
  - Concordant organisms from catheter and peripheral vein
  - DTP* (differential time to positivity): organism growth detected in catheter specimen at least 2h before peripheral specimen
- Negative at 72h
  - Discontinue vancomycin

**Definitive diagnosis:**
- Persistent bacteremia/fungemia or ongoing signs of infection:
  - Reassess antimicrobials to ensure no drug and organism mismatch
  - Rule out complications and or metastatic infections
  - Catheter removal if not already done
  - Consult ICH ID

**Indications for Catheter Removal:**
- CRBSI due to Candida spp., Mycobacteria spp., Staphylococcus aureus, Pseudomonas aeruginosa, and other Gram-negative organisms
- Persistent **positive blood culture 72h after initiation of antimicrobials** irrespective of pathogens isolated (e.g. coagulase negative staphylococci, enterococci, viridans group Streptococcus, Corynebacterium spp., Bacillus spp.) with no other source of infections identified
- Ongoing or worsening **signs of infection due to suspected CRBSI** despite 48-72h of appropriate antimicrobials
- **Complicated CRBSI** (septic thrombosis, endocarditis, possible metastatic seeding e.g. osteomyelitis)
- Extensive **cellulitis** around IV sites (greater than 2 cm), from catheter exit site, along the subcutaneous tract of tunneled catheter
- Relapse or recurrent **CRBSI after antimicrobial course** is completed

**Follow Figure 5a** for recommendations on specific antimicrobial

**Repeat blood cultures 72h after initiation of antimicrobials**

* DTP can be calculated in the electronic patient record under the “audit” function in the microbiology results
5a. Recommended Antimicrobials by Type of Infection

Source of infection identified?
- No: Go to Figure 5c
- Yes: Continue empiric piperacillin-tazobactam or meropenem and any additions from Figure 2

Causative organism identified?
- No: Repeat all investigations including diagnostic imaging and cultures from all possible sites
- Yes: Continue

Identify Gram stain & select below:
- Gram-positive
- Gram-negative
- Yeast

**Recommended duration of therapy by infection.** Average time to defervescence is 5d. Duration of antimicrobials depend on nature of infection, severity and response to treatment.

- **Bacteremia** (duration of treatment count from day 1 of documented negative culture) **in the absence of complications** (e.g. abscess, metastatic seeding):
  - GNB: 14d
  - GPC (except S. aureus): 14d
  - S. aureus: minimum 14d, consult ICH ID

- **Pneumonia** (bacterial):
  - 14d

- **Sinusitis** (bacterial):
  - 14d, consult ICH ID and ENT

- **Dental infections**:
  - 7d, as per Dentistry and ICH ID

- **Skin and skin structure**:
  - 7d, abscess: consult ICH ID

- **Urinary tract infections**:
  - 7d (lower UTI); 14d (pyelonephritis)
    - if prostatitis focus suspected: consult ICH ID

- **Osteomyelitis**:
  - 6-8 wks, consult ICH ID

- **C. difficile infection**:
  - 14d without complications; if concomitant antibiotic cannot be stopped, or complications present: consult ICH ID

**Recurrent fever after initial response to antimicrobials?**
- Yes: See Figure 6 for Recommendation on Management of Recurrent or Recrudescent Fever
5a. Recommended Antimicrobials by Type of Pathogen

**Gram-positive**

1 **Empiric therapy:**
   - **vancomycin** 15 mg/kg IV Q12H (Max 1.5g/dose)

2 **Suggestions for specific organisms:**
   - **Methicillin-susceptible S. aureus** (MSSA)
     - Cloxacillin 2g IV Q4H or cefazolin 2g IV Q8H and stop vancomycin. If penicillin allergy, continue vancomycin.
   - **Methicillin-resistant S. aureus** (MRSA)
     - Continue vancomycin. Consult ICH ID for alternative.
   - **Coagulase negative staphylococci**
     - Continue vancomycin if penicillin-resistant. If susceptible, cloxacillin 2g IV Q6H or cefazolin 1g IV Q8H and stop vancomycin.

3 **Follow recommended duration of therapy by infectious syndrome**

**Gram-negative**

1 **Empiric therapy:**
   - **piperacillin-tazobactam** 4.5g IV Q8H + **gentamicin** 5 mg/kg IV Q24H

2 **Suggestions for specific organisms:**
   - **P. aeruginosa**
     - If susceptible, piperacillin-tazobactam 4.5g IV Q6H preferably over 3h and stop gentamicin.
     - If resistant to piperacillin-tazobactam, meropenem 1g IV Q8H preferably over 3h and stop gentamicin. Consider ICH ID consult.
   - **ESBL-producing**
     - Meropenem 1g IV Q8H and stop gentamicin.

3 **Follow recommended duration of therapy by infectious syndrome**

**Viridans group streptococci**
- If ampicillin-sensitive, continue piperacillin-tazobactam or meropenem and stop vancomycin. Otherwise, continue vancomycin.

**Enterococci**
- If ampicillin-sensitive, continue piperacillin-tazobactam or meropenem and stop vancomycin. Continue vancomycin if ampicillin-resistant but vancomycin-sensitive. If vancomycin-resistant, stop vancomycin, start linezolid 600 mg PO/IV Q12H and contact ICH ID.

For all organisms, tailor therapy based on susceptibility results.

*Order an echocardiogram if organism is S. aureus (Staphylococcus aureus)
5b. Candidemia

Yeast was identified in blood cultures

Was patient on fluconazole prophylaxis?

- Yes
  - Micafungin 100 mg IV once daily
  - MSH: Caspofungin 70 mg IV day 1 only, then 50 mg IV daily

- No
  - Any contraindications or clinically significant drug interactions with azoles?
    - Yes
      - Consult ICH ID for alternative
    - No
      - Fluconazole 800 mg IV daily

Perform the following tasks concurrently:

- Is this a catheter-related blood stream infection? Remove catheter when it can be safely achieved. See also Figure 4
- Consult ICH ID.
- Consult Ophthalmology to rule out endophthalmitis.
- Consider diagnostic imaging to rule out hepatosplenic abscess or other occult source.

Modify antifungal based on speciation and susceptibility

Duration of therapy: minimum 14d counting from day 1 of documented clearance of Candida from blood stream, in the absence of complications (abscess, endophthalmitis). Consider switching to PO once blood culture is negative to complete full course of therapy.
5c. Recommended Antimicrobials if Source of Infection or Pathogen is Not Identified

If causative pathogen or source of infection is identified: Go to Figure 5a

If not, assess patient’s status

Patient’s status is:

Patient is afebrile + ANC recovered to greater than 0.5x10^9 cells/L for at least 48h and received minimum of 7d of antimicrobials

Stop antimicrobials

Fever is resolved but ANC remains fewer than 0.5x10^9 cells/L after 7d of antimicrobials

Significant mucositis?

Yes

Consider switching to PO route to complete minimum 14d of antimicrobials (e.g. amoxicillin-clavulanate 875 mg PO BID + ciprofloxacin 750 mg PO BID as step down from empiric piperacillin-tazobactam). Maintain ongoing assessment of patient.

No

Reciprocal fever after initial response, or after completing a course of antimicrobial therapy?

Repeat all investigations and diagnostic imaging. Adjust antimicrobials or consult ICH ID as appropriate. Respiratory consult and bronchoscopy as appropriate.

No

Stop antimicrobial treatment. Refer to prophylaxes as indicated.

Yes

Continue IV antimicrobials for minimum of 14d

Continue to Figure 6
6. Persistent or Recrudescent Neutropenic Fever Investigations and Management

1. Persistent fever after 5d of appropriate antimicrobials or recurrent/recrudescent fever after initial response to antimicrobial therapy

2. Complete investigations in the checklist below:
   - Rule out non-infectious causes of fever
   - Comprehensive physical exam
     - Repeat all investigations and other tests as clinically indicated:
       - Blood cultures from all IV sites
       - Bronchoscopy
       - Cryptococcal serum antigen to rule out disseminated cryptococcal disease
       - CT chest to rule out pneumonia, tuberculosis
       - Other diagnostic imaging as appropriate to rule out occult infections such as abscess, sinusitis, dental or central nervous system infections
       - Respiratory viral test panel (RSV, influenza, parainfluenza)
       - Serum galactomannan (GM), one additional to routine Mon, Wed testing
   - Assess risk of drug and organism mismatch

3. Is Infectious Etiology Identified?
   - No
   - Yes

Go to Figure 3 for recommended antifungals
Consult ICH ID and respirology

Blood culture positive for bacteria
Go to Figure 4

Blood culture positive for yeast
Go to Figure 4

Cryptococcal serum antigen positive
Go to Figure 5a

Fungal pneumonia
Go to Figure 5b

Atypical infection e.g. TB, PJP (*Pneumonosystis jiroveci pneumonia*), or viral infection
Consult ICH ID