High-Risk Febrile Neutropenia Protocol for Patients with Hematological Malignancy

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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.

UHN Canada's Hospital

Click orange buttons to navigate protocol.

Index: Prophylaxes & Treatment

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 x10^9/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

or

alternatives: **micafungin** 50 mg IV daily or **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

or

alternative: **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

1b. Antimicrobial Prophylaxes in Acute Lymphocytic Leukemia with Vinca Alkaloids Chemotherapy

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 x10^9/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

+

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

or

alternative: consult ID and respirology

+

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

+

acyclovir 400 mg PO BID starting day 1 of chemotherapy

or

alternative: **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

1c. Antimicrobial Prophylaxes in Acute Lymphocytic Leukemia without Vinca Alkaloids Chemotherapy

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

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**

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

+

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

or

alternative: consult ID and respirology

+

fluconazole 400 mg PO/IV daily during induction chemo

+

acyclovir 400 mg PO BID starting day 1 of chemotherapy

or

alternative: **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

1d. Antimicrobial Prophylaxes in Autologus Bone Marrow Transplant

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

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**

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

or

alternative: consult ID and respirology

+

fluconazole 400 mg PO/IV daily Day +1

or

alternatives: **micafungin** 50 mg IV daily or **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

or

alternative: **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

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**

ciprofloxacin 500 mg PO BID starting day 8 of conditioning chemotherapy

+

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

or

alternative: consult ID and respirology

+

posaconazole 200 mg PO Q8H taken with high-fat food

or

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

or

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

1f. Antimicrobial Prophylaxes in alloBMT but No Acute GVHD

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**

ciprofloxacin 500 mg PO BID starting day 8 of conditioning chemotherapy

+

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

or

alternative: consult ID and respirology

+

fluconazole 400 mg PO/IV daily during induction chemo

or

alternatives: **micafungin** 50 mg IV daily or **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

or

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

1g. Antimicrobial Prophylaxes in Aplastic Anemia

Patient has aplastic anemia:
Patient receives anti-thymocyte globulin (ATG) treatment

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

ciprofloxacin 500 mg PO BID

+

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

or

alternative:
consult ID and respirology

+

fluconazole 400 mg PO/IV daily

or

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

+

acyclovir 400 mg PO BID starting day 1 of chemotherapy

or

alternative:
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

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 x10^9/L or fewer) **neutropenia**, i.e.: **High-Risk Neutropenia**

ciprofloxacin 500 mg PO BID

+

cotrimoxazole 1 double-strength tab PO Q Mon, Wed, Fri

or

alternative: consult ID and respirology

+

fluconazole 400 mg PO/IV daily

or

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

+

acyclovir 400 mg PO BID starting day 1 of chemotherapy

or

alternative: **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

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**

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

+

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

or

alternative: consult ID and respirology

+

fluconazole 400 mg PO/IV daily

or

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

+

acyclovir 400 mg PO BID starting day 1 of chemotherapy

or

alternative: **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

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 1x10^9/L but expected to fall below 0.5x10^9/L in the next 48h **+ single oral temperature** higher than 38.3ºC or **sustained oral temperature** of 38ºC 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.

1 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**.

2 Treat with empiric therapy below:

Empiric antimicrobials:

piperacillin-tazobactam 4.5g IV Q6H **+ tobramycin** 7 mg/kg IV Q24H

or

Alternative (for penicillin-hypersensitivity): **meropenem** 1g IV Q8H (cross-reactivity <1%). Clarify allergy history when feasible and modify antibiotic accordingly.

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

3 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.

Continue to next page

2. Initial Investigations and Management of a Patient with High-Risk Febrile Neutropenia

Patient is being assessed daily

Evidence of clinical deterioration (48h)

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

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

or

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 tobramycin / other modifying antimicrobials.

Continue to Figures 3, 4, and 5

or

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.

Continue to Figures 4 and 5

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

Definition: Need for pre-emptive therapy = **Positive biomarker** (galactomannan) + **Presence of risk factor** (neutropenia).
Serial 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.

Serum GM results are:

Positive

Index value greater than or equal to 0.5

Complete the following:

- ☐ 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

Negative

Index value lower than 0.5

Continue serum GM monitoring.

CT findings are:

CT findings **are suggestive** of fungal pneumonia (e.g. cavity, nodules, halo signs) **and** repeat serm GM test is **positive** or pending

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

or

CT findings **are suggestive** of pneumonia **and** repeat serum GM test is **negative**

→ Consult Respirology and ICH ID to determine further action

or

CT findings are **not suggestive** of fungal pneumonia (e.g. no cavity, no nodules, no halo signs) **or** repeat serum GM test is **negative**

→ **Stop voriconazole** and continue to monitor serum GM

BAL findings are:

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

3b. Pulmonary Infiltrate Management

Eligible patients:

Group 1: Neutropenic patient (ANC < $0.5x10^9$/L) with oral temperature higher than or equal to 38.3^0C. 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

1 **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 → **Go to Figure 2 Initial Investigations**

or

Yes → **Follow the steps below:**

- Urgent consult Respirologist 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

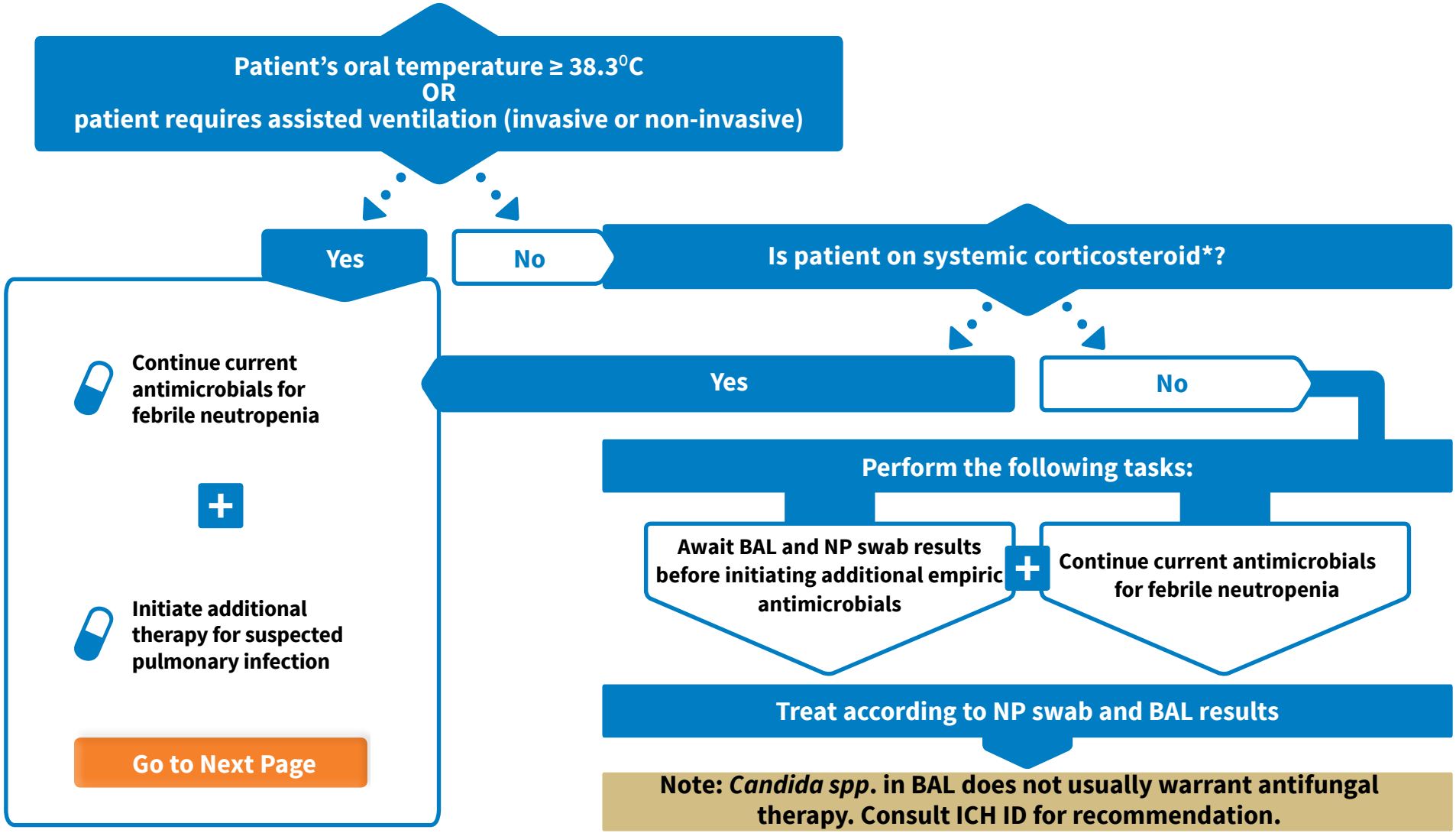
3b. Pulmonary Infiltrate Management: Further Actions

*** 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**.

Abbreviations:

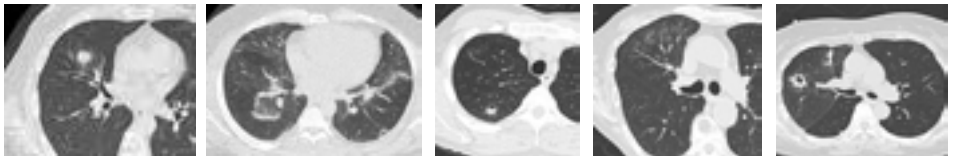
BAL: Bronchoalveolar Lavage
NP Swab: Nasopharyngeal Swab



3b. Pulmonary Infiltrate Management: Empiric Antimicrobial Therapy Based on CT Abnormalities

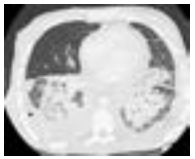
Description of abnormalities on CT (hover mouse on images to enlarge, click to close image)

Nodules



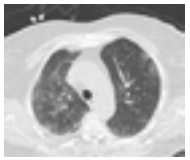
or

Consolidation



or

Ground glass opacity or interstitial pattern



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.

Great
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2
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Centrilobular Ground Glass Opacity Nodules

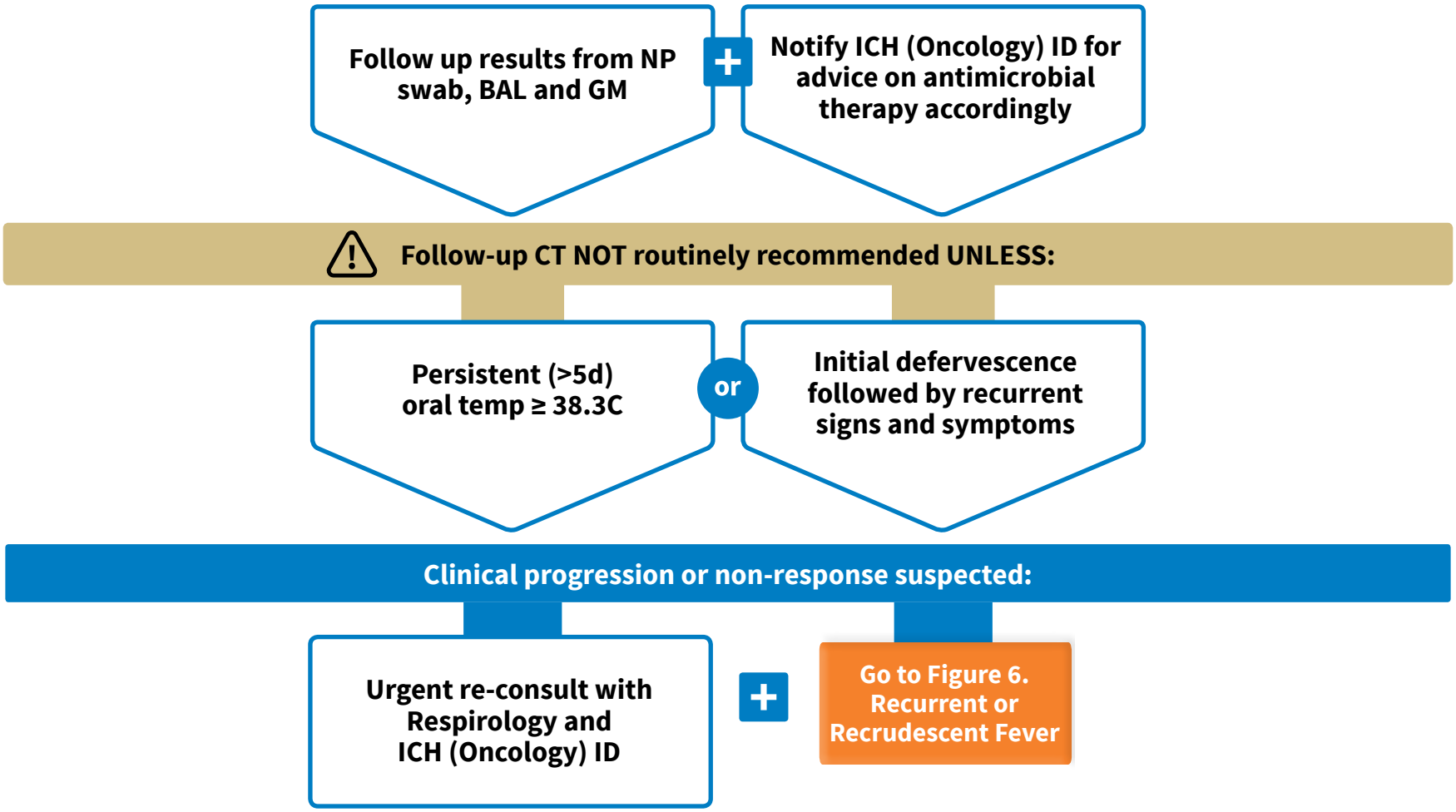
Monitor elevated transaminases or bi
ID to advise on alternative therapy if

Continue to next page a **riate empiric therapy**

3b. Pulmonary Infiltrate Management: Follow-Up Assessment

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

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

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

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

4 Cultures are:

Positive

Definitive diagnosis:

- 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

DTP can be calculated in the electronic patient record under the "audit" function in the microbiology results*

Negative at 72h

Discontinue **vancomycin**

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

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

5a. Recommended Antimicrobials by Type of Infection

Source of infection identified?

No → **Go to Figure 5c**

Yes

Causative organism identified?

Yes

No

Identify Gram stain & select below:

- **Gram-positive**
- **Gram-negative**
- **Yeast**

Continue empiric piperacillin-tazobactam or meropenem and any additions from **Figure 2**

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? → **Repeat** all investigations including **diagnostic imaging and cultures** from all possible sites → See **Figure 6** for Recommendation on Management of Recurrent or Recrudescent Fever

5a. Recommended Antimicrobials by Type of Pathogen

For all organisms, tailor therapy based on susceptibility results.

Gram stain available:

Gram-positive

1 Empiric therapy:

vancomycin 15 mg/kg IV Q12H (Max 1.5g/dose)

+

Continue piperacillin-tazobactam or meropenem **while patient is neutropenic**

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.

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.

3 Follow recommended duration of therapy by infectious syndrome

or

Gram-negative

1 Empiric therapy:

piperacillin-tazobactam 4.5g IV Q6H **+** **tobramycin** 7 mg/kg IV Q24H

2 Suggestions for specific organisms:

P. aeruginosa
If susceptible, piperacillin-tazobactam 4.5g IV Q6H preferably over 3h and stop tobramycin. If resistant to piperacillin-tazobactam, meropenem 1g IV Q8H preferably over 3h and stop tobramycin. Consider ICH ID consult.

ESBL-producing
Meropenem 1g IV Q8H and stop tobramycin.

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

3 Follow recommended duration of therapy by infectious syndrome

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 endophalmitis.
- 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

or

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

Significant mucositis?

Yes

Continue IV antimicrobials for minimum of 14d

No

or

Patient remains febrile with ANC **fewer** than 0.5x10^{9}cells/L after 5d of appropriate empiric antimicrobials

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.**

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

No

Stop antimicrobial treatment. Refer to **prophylaxes** as indicated.

Yes

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

Continue to Figure 6

6. Persistent or Recrudescent Neutropenic Fever Investigations and Management

1 5d **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** → Rule out non-infectious etiology
- **Yes** → **Follow the appropriate path below:**

Blood culture positive for bacteria	**Go to Figure 4** + **Go to Figure 5a**
or	
Blood culture positive for yeast	**Go to Figure 4** + **Go to Figure 5b**
or	
Cryptococcal serum antigen positive	Consult ICH ID
or	
Fungal pneumonia	**Go to Figure 3 for recommended antifungals**
or	
Atypical infection e.g. TB, PJP (*Pneumonosystis jiroveci pnemonia*), or viral infection	Consult ICH ID and respirology