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# Solid Tumor or Lymphoma Febrile Neutropenia Protocol

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# Index: Management of Febrile Neutropenia in **Solid Tumor** or **Lymphoma**

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For patients receiving chemotherapy for **solid tumor** or **lymphoma**

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Recommended ongoing monitoring and follow-up assessment of empiric antimicrobials.

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Recommended investigations in persistent fever or if fever returns after initial response to antimicrobial therapy.





# 1. Initial Investigations and Management of a Febrile Neutropenic Patient with **Solid Tumor** or **Lymphoma**

## Definition of Febrile

**ANC** lower than or equal to  $0.5 \times 10^9/L$  + **oral temperature** higher than or equal to  $38.3^\circ C$  (or sustained at  $38^\circ C$  for at least one hour).

## Eligible Patients for this Protocol

**Definition as stated** (i.e. has fever + neutropenia) **and** currently receives chemotherapy for **solid tumor or lymphoma**. Neutropenic fever anticipated to be **shorter than 7 days** and **nadir ANC higher than or equal to  $0.1 \times 10^9/L$** .

## Patients NOT eligible:

If **profound or prolonged** neutropenia expected, follow **High-Risk Protocol**.



### 1 Complete initial assessments and investigations in the checklist below:

#### I. Routine (should be completed):

- CBC with differential
- Electrolytes and SCr
- Blood cultures before antibiotics from peripheral site **and** central lines
- Surveillance as per Infection (Prevention and) Control

#### II. Source-specific assessment by symptoms:


- Oral cavity for mucositis or abscess
- Respiratory symptoms for pulmonary infection
- Evidence of cellulitis
- Intravenous access site(s) for possible line-related infections
- Abdomen for focal tenderness
- Peri-rectal abscess

#### III. Source-specific investigations:


- Nasopharyngeal swab for respiratory virus
- Viral swab for mucocutaneous HSV or VZV
- Sputum culture
- LOW DOSE** CT of chest
- Urinary *Legionella* antigen
- Stool for *C. difficile* PCR
- Abdo X-ray
- Urine culture

### 2 Treat with empiric therapy below:

#### Empiric antimicrobials:

 **cefazolin** 2g IV Q8H + **gentamicin** 5 mg/kg IV Q24H

or

 alternative (for penicillin-hypersensitivity): **meropenem** 1g IV Q8H  
Clarify allergy history when feasible and modify antibiotics accordingly.

### 3 If necessary, make additions according to list below:

#### *C. difficile* suspected

Add **metronidazole** 500 mg PO Q8H **or vancomycin** 125 mg PO Q6H

#### Pneumonia suspected

Add **azithromycin** 500 mg PO/IV x 1day, then 250 mg PO daily x4 days

#### Influenza PCR positive

Add **oseltamivir 75 mg PO BID**

#### Mucocutaneous HSV infection

Add **acyclovir** 400 mg PO 5x/day **or acyclovir** 5 mg/kg IV Q8H

#### IV site infection

Add **vancomycin** 15 mg/kg IV Q12H

#### Cellulitis suspected

Consider adding **vancomycin** 15 mg/kg IV Q12H if MRSA is a concern

#### Abbreviations:

ANC = absolute neutrophil count  
CrCL = creatinine clearance  
CT = computed tomography  
HSV = Herpes Simplex Virus  
MRSA = methicillin-resistant *S. aureus*  
VZV = Varicella Zoster Virus  
SCr = serum creatinine



Consult clinical pharmacist for advice on dosing adjustment for antimicrobial (e.g. gentamicin, vancomycin) in patients with renal insufficiency (CrCL less than 50 mL/min) after the 1st dose.

Continue to next page 



# 1. Initial Investigations and Management of a Febrile Neutropenic Patient with **Solid Tumor** or **Lymphoma**

## 4 Determine disposition of patient

Currently IN-patient

Continue INPATIENT management  
Go To Section 2a

MASCC score criteria are for guidance only and do not replace clinician's judgement to admit patient.

Currently OUT-patient

The MASCC\* score may be used to identify patients at low risk of medical complication

Click on these criteria to see fuller explanation.  
Check score box from each criterion to calculate MASCC score.

### Characteristics and Weighted Score

mild or no symptoms	5
moderate symptoms	3
severe or moribund	0
No hypotension (systolic blood pressure higher than 90mmHg)	5
	4
	4
No dehydration requiring parenteral fluids	3
Currently outpatient status	3
Age younger than 60 years	2

\*Multinational Association for Supportive Care in Cancer Scoring System. Maximum 26 points. References: Frifeld et al., 2011; Flowers et al., 2013.

Calculate MASCC score for this patient:

CALCULATOR

MASCC score AT or ABOVE 21  
CONSIDER OUTPATIENT  
MANAGEMENT  
Go To Section 2b

Yes

No

MASCC score BELOW 21  
ADMIT TO IN-PATIENT  
Go to Section 2a



## 2a. **In-Patient** Management of a Febrile Neutropenic Patient with **Solid Tumor** or **Lymphoma**

### ADMIT PATIENT with ongoing assessment

24-48h

Evidence of clinical deterioration

Patient becomes hemodynamically unstable, despite 24-48h of appropriate empiric antimicrobials.

- Repeat all investigations including blood cultures and comprehensive physical exam
- Change antimicrobials to piperacillin-tazobactam 4.5g IV Q8H**
- Consult ICH ID\***

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

or

72h

Patient is stable, cultures remain **negative**

Patient is stable. Microbiology results remain **negative** at 72h, or investigations for suspected infections remain negative at 72h.

- Stop empiric gentamicin.
- Stop additional modifying antimicrobials based on results from investigations and microbiology testing.

Go to Figure 4c

or

72h

Patient is stable, cultures are **positive**

Patient is stable. Blood and/or other cultures are **positive** or source of infection is identified within 72h.

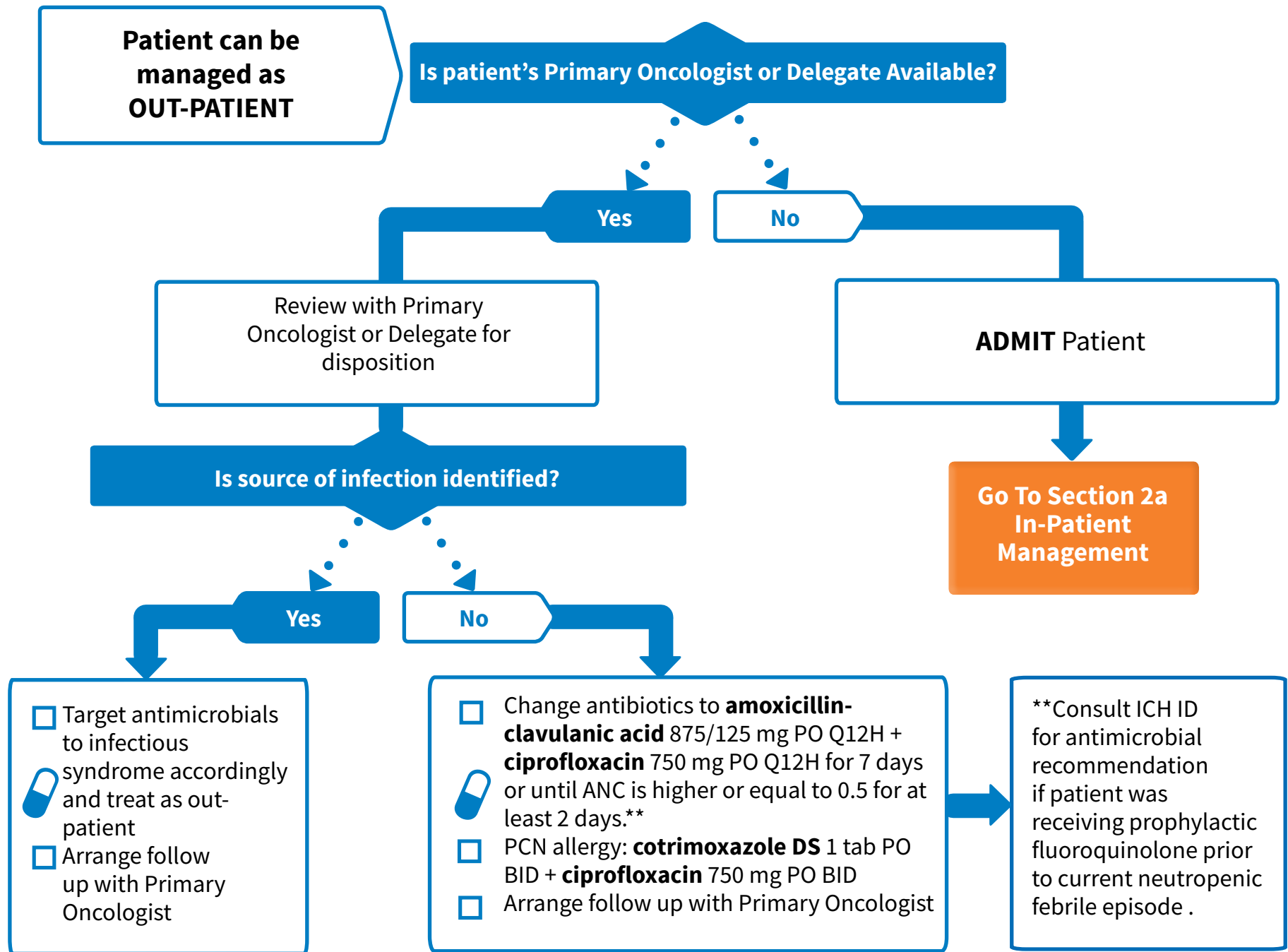
- Modify empiric antimicrobials to target infectious syndrome and microbiology results.

Go to Figures 3 and 4





## 2b. **Out-Patient** Management of a Febrile Neutropenic Patient with **Solid Tumor** or **Lymphoma**






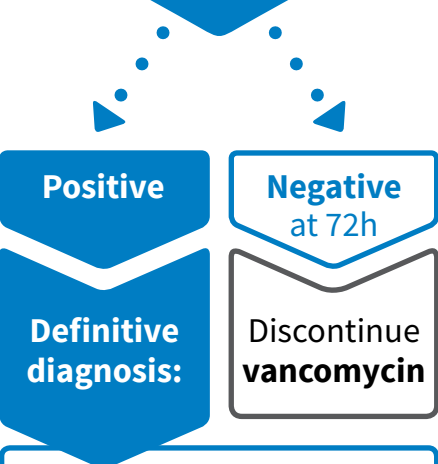
# 3. Recommended Management for Catheter-Related Blood Stream Infections

**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:



- 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

## 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 4a** 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



**ICH ID = Immunocompromised Host Infectious Diseases**






# 4a. Recommended Antimicrobials by Type of Infection

Source of infection identified?

No

Go to Figure 4c

Yes

Causative organism identified?

Yes

No

Identify Gram stain & select below:



Gram-positive



Gram-negative



Yeast



Target antimicrobial(s) to infectious syndrome. See below for duration of treatment.



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.

<b>Bacteremia</b> (duration of treatment count from day 1 of documented negative culture) <b>in the absence of complications</b> (e.g. abscess, metastatic seeding)	<ul style="list-style-type: none"> <li>▶ GNB <b>14d</b></li> <li>▶ GPC (except <i>S. aureus</i>) <b>14d</b></li> <li>▶ <i>S. aureus</i>: minimum <b>14d</b>, consult ICH ID</li> </ul>
<b>Pneumonia</b> (bacterial)	▶ <b>14d</b>
<b>Sinusitis</b> (bacterial)	▶ <b>14d</b> , consult ICH ID and ENT
<b>Dental infections</b>	▶ <b>7d</b> , as per Dentistry and ICH ID
<b>Skin and skin structure</b>	▶ <b>7d</b> , abscess: consult ICH ID
<b>Urinary tract infections</b>	▶ <b>7d</b> (lower UTI); <b>14d</b> (pyelonephritis) if prostatitis focus suspected: consult ICH ID
<b>Osteomyelitis</b>	▶ <b>6-8 wks</b> , consult ICH ID
<b>C. difficile infection</b>	▶ <b>14d</b> 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

Consult ICH ID



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# 4a. 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)



Discontinue gentamicin.  
Role of cefazolin: See Step 2

\*MRSA, MSSA, VGS, enterococci: consider transthoracic echocardiogram in work-up

### 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.
- Consult ICH ID**

#### Methicillin-resistant *S. aureus* (MRSA)\*

- Continue vancomycin.
- Consult ICH ID.**

#### 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 (VGS)\*

- Penicillin-susceptible: penicillin 4MU IV Q4H and stop vancomycin
- Penicillin non-susceptible: ceftriaxone 1g IV Q24H and stop vancomycin
- Ceftriaxone non-susceptible: continue vancomycin

#### Enterococci\*

- Ampicillin-susceptible: ampicillin 2g IV Q4H and stop vancomycin
- Ampicillin-resistant: continue vancomycin
- Vancomycin-resistant: **Consult ICH ID**

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

or

## Gram-negative

### 1 Empiric therapy:



**cefazolin** 2 g IV Q8H + **gentamicin** 5 mg/kg IV Q24H

### 2 Suggestions for specific organisms:

#### *P. aeruginosa*

- Stop cefazolin and gentamicin AND see suggestions below:
- If susceptible, piperacillin-tazobactam 4.5g IV Q6H (preferably over 3h).
- If resistant to piperacillin-tazobactam, meropenem 1g IV Q8H (preferably over 3h).
- Consider ICH ID consult.**

#### ESBL-producing Gram-negative organisms

- Ertapenem 1g IV Q24H and stop cefazolin + gentamicin

#### Other Gram-negatives

- Follow susceptibility results to tailor empiric therapy accordingly, including stopping empiric gentamicin

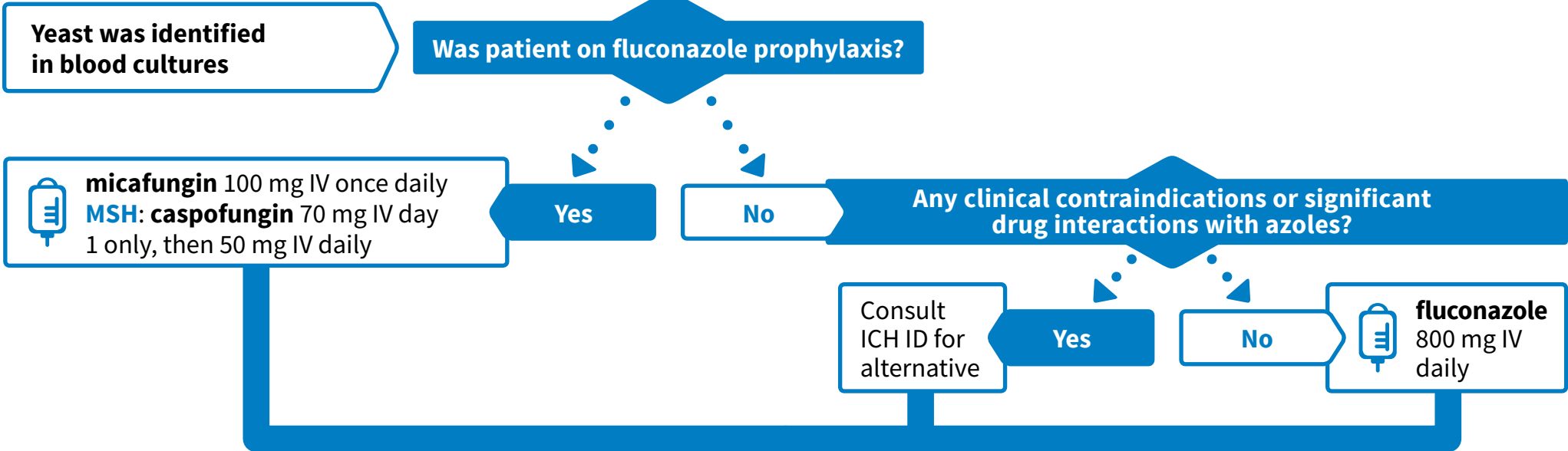
**3 Follow recommended duration of therapy by infectious syndrome**

Consult clinical pharmacist for advice on dosing adjustment for antimicrobial in patients with renal insufficiency (CrCL less than 50 mL/min) after the 1st dose.

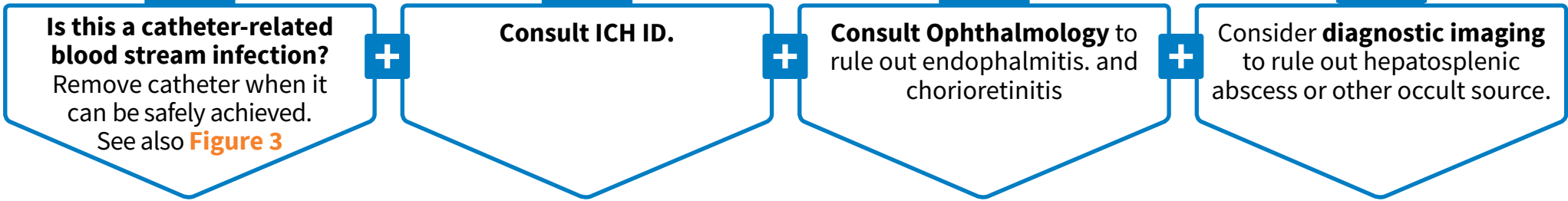
**ICH ID = Immunocompromised Host Infectious Diseases**



# 4b. Candidemia



## Perform the following tasks concurrently:



## 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.



**ICH ID = Immunocompromised Host Infectious Diseases**





# 4c. Recommended Antimicrobials if Source of Infection or Pathogen is Not Identified

If causative pathogen or source of infection is identified by 72hrs:

Go to Figure 4a

If not yet identified at 72h, assess patient's status

Patient's status is:

Patient is **afebrile** + ANC recovered to **higher** than  $0.5 \times 10^9$  cells/L for at least 48h

or

Patient is **afebrile** but ANC remains **lower** than  $0.5 \times 10^9$  cells/L

or

Patient remains **FEBRILE** with ANC remains **lower** than  $0.5 \times 10^9$  cells/L

- Stop antimicrobials
- Discuss with Primary Oncologist for disposition and arrange follow up.

Significant mucositis or cannot tolerate oral medication ?

- Review with Primary Oncologist for patient disposition
- Consider changing antibiotics to **amoxicillin-clavulanate** 875/125 mg PO BID + **ciprofloxacin** 750 mg PO BID for 7 days or until ANC is greater than  $0.5 \times 10^9$  cells/L for at least 48 hours.  
PCN allergy: **Cotrimoxazole DS** 1 tab BID + **ciprofloxacin** 750 mg PO BID



**Change IV antibiotics to piperacillin-tazobactam 4.5g IV Q8H to avoid prolonged gentamicin exposure.** Reassess in next 48hrs and consider ICH ID consult

Yes

No

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

Stop antimicrobial treatment.

No

Yes

- Repeat all investigations, blood cultures and diagnostic imaging.
- Consult ICH ID.
- Consider changing antibiotics to **piperacillin-tazobactam** 4.5 g IV Q8H

Go to Figure 5



ICH ID = Immunocompromised Host Infectious Diseases





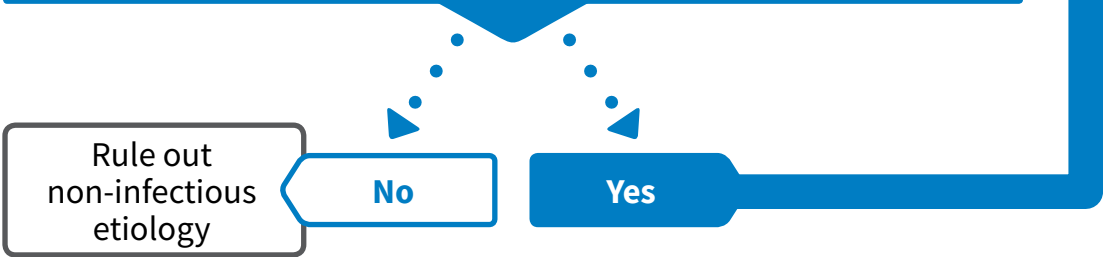
# 5. Persistent or Recrudescent Neutropenic Fever Investigations and Management

## 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), plus routine Mon, Wed testing
  - Assess risk of drug and organism mismatch

### 3 Is Infectious Etiology Identified?



### Follow the appropriate path below:

