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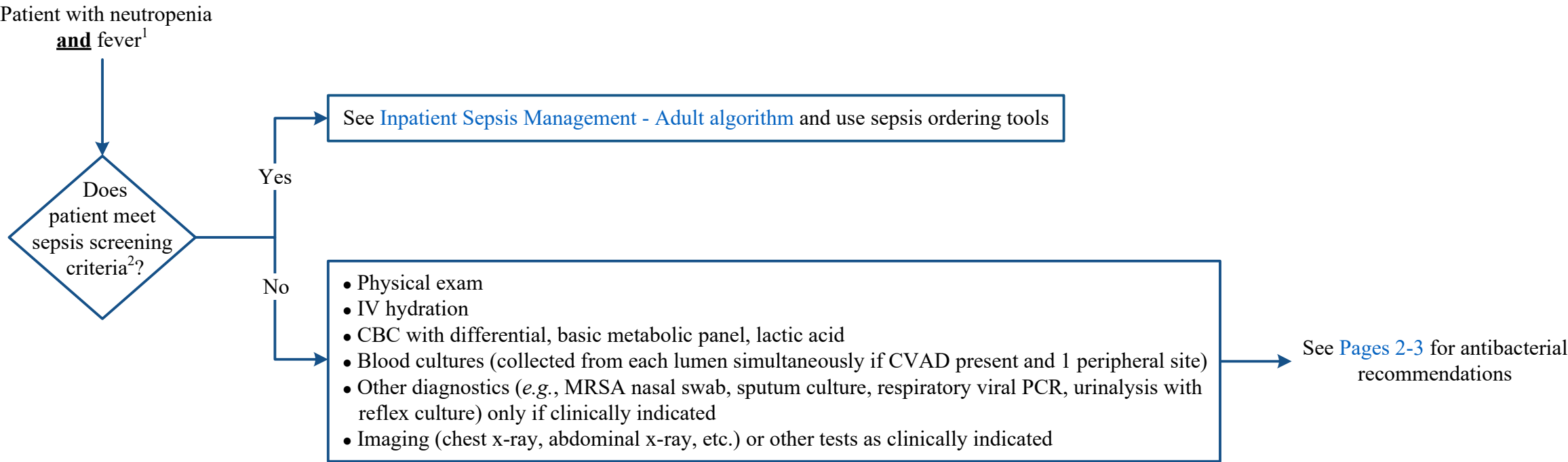**MD Anderson Cancer Center**
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Note: This algorithm can also be used for patients receiving stem cell transplantation or immune effector cell (IEC) therapy.

PRESENTATION	ASSESSMENT	TREATMENT

Patient with neutropenia **and** fever[1]

Does patient meet sepsis screening criteria[2]?

Yes → See Inpatient Sepsis Management - Adult algorithm and use sepsis ordering tools

No →
- Physical exam
- IV hydration
- CBC with differential, basic metabolic panel, lactic acid
- Blood cultures (collected from each lumen simultaneously if CVAD present and 1 peripheral site)
- Other diagnostics (*e.g.*, MRSA nasal swab, sputum culture, respiratory viral PCR, urinalysis with reflex culture) only if clinically indicated
- Imaging (chest x-ray, abdominal x-ray, etc.) or other tests as clinically indicated

See Pages 2-3 for antibacterial recommendations

CVAD = central venous access device
PCR = polymerase chain reaction
MRSA = methicillin-resistant *Staphylococcus aureus*

[1] Criteria:
- Absolute neutrophil count (ANC) ≤ 0.5 K/microliter **and** temperature either ≥ 38.3°C or equal to 38°C for 1 hour or longer **or**
- ANC ≤ 1 K/microliter and an expected decline to ≤ 0.5 K/microliter over 48 hours **and** temperature either ≥ 38.3°C or equal to 38°C for 1 hour or longer

[2] See Inpatient Sepsis Management - Adult algorithm for sepsis screening criteria

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ASSESSMENT

ANTIBACTERIAL RECOMMENDATIONS[1]
(Adjust dose for patients with renal/hepatic dysfunction)
Gram negative coverage antibiotics should be given first. Antibiotics should be given within 1 hour.

- **For serious documented beta-lactam allergy[2], see Page 3**
- **For selecting antibacterial therapy consider the following:**
  - Recent culture and sensitivity results
  - History of resistant gram negative organism[3] infection or colonization
  - Recent antibiotic history and prophylaxis
  - Source of infection, if identified
  - Organ dysfunction
  - Drug interactions
  - Local/institutional antibiogram[4]
- Consider the use of therapeutic G-CSF if risk factors are present (see Appendix A)

G-CSF = granulocyte colony stimulating factor
VRE = vancomycin-resistant enterococcus

Select one:
- **Cefepime**
  - **If mucositis ≥ grade 2, suspected intra-abdominal or perirectal infection, or other indication for anaerobic coverage consider adding:**
    - Metronidazole
- **Piperacillin-tazobactam**
- **Meropenem[5]**

If septic shock on vasopressors, complicated tissue-based infections, neutropenic enterocolitis, perirectal infections or other indication for double gram negative coverage consider adding:
- **Amikacin**

Is expanded gram positive coverage needed?

Yes →

No → See Page 4 for re-assessment

If suspected line infection[6] and/or bacteremia add:
- Vancomycin **or**
- Daptomycin (if no evidence of pneumonia)

If MRSA colonization or skin and soft tissue infection or pneumonia[7] add:
- Vancomycin **or**
- Linezolid (not preferred for MRSA blood stream infection) **or**
- Daptomycin (if no evidence of pneumonia)

If VRE colonization or infection add:
- Linezolid **or**
- Daptomycin (if no evidence of pneumonia)

See Page 4 for re-assessment

[1] Refer to institutional antimicrobial dosing guide (internal only) or tertiary dosing references (*e.g.,* Lexicomp) for dosing recommendations

[2] Serious documented beta-lactam allergy includes anaphylaxis, hives, or serious non-IgE mediated drug reactions [*e.g.*, Stevens-Johnson syndrome, toxic epidermal necrolysis, and drug reaction with eosinophilia and systemic symptoms (DRESS)]

[3] Resistant gram negative organisms include:
- *Stenotrophomonas maltophilia*
- Any extended spectrum beta-lactamase (ESBL)-producing gram negative bacilli
- Any carbapenem resistant gram negative bacilli
- All other gram negative bacilli that are resistant to usual recommended first-line agents

[4] Refer to gram negative and gram positive antibiograms (internal only)

[5] Consider meropenem if patient has any of the following: ● Non-IgE-mediated allergy to alternative agents ● Recent treatment (≥ 3 days duration) with cefepime or piperacillin-tazobactam within past 30 days ● Infection with ESBL organism ● Infection with organism only susceptible to carbapenems

[6] Chills, rigors with infusion through catheter, cellulitis or discharge around the catheter entry site

[7] If patient was not previously on fluoroquinolone prophylaxis, consider adding a fluoroquinolone, azithromycin, or doxycycline for atypical pathogen coverage

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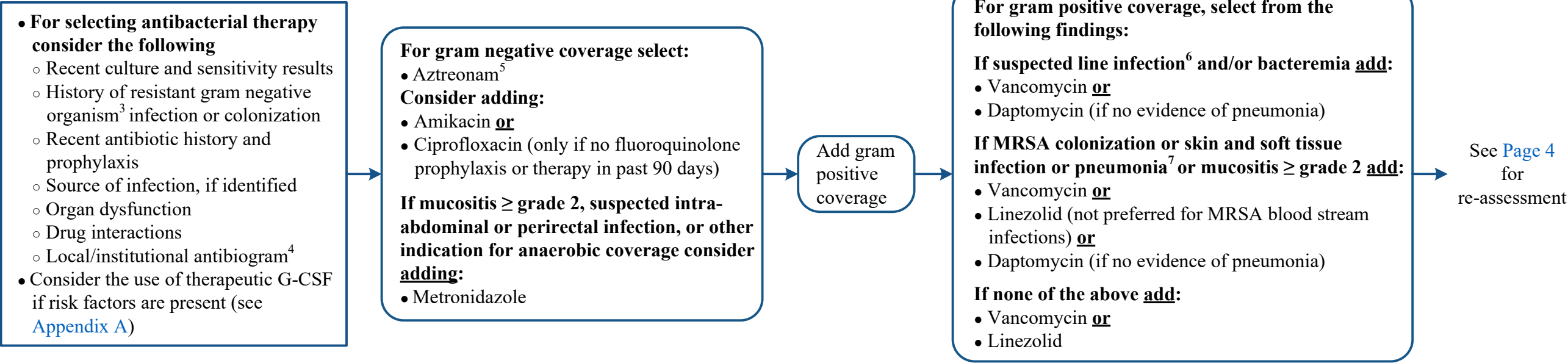MD Anderson Cancer Center
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SERIOUS DOCUMENTED BETA-LACTAM ALLERGY
(anaphylaxis, hives, or serious non-IgE mediated drug reactions[1])

ASSESSMENT

ANTIBACTERIAL RECOMMENDATIONS[2]
(Adjust dose for patients with renal/hepatic dysfunction)
Gram negative coverage antibiotics should be given first. Antibiotics should be given within 1 hour.

- **For selecting antibacterial therapy consider the following**
  - Recent culture and sensitivity results
  - History of resistant gram negative organism[3] infection or colonization
  - Recent antibiotic history and prophylaxis
  - Source of infection, if identified
  - Organ dysfunction
  - Drug interactions
  - Local/institutional antibiogram[4]
- Consider the use of therapeutic G-CSF if risk factors are present (see Appendix A)

→

For gram negative coverage select:
- Aztreonam[5]

Consider adding:
- Amikacin **or**
- Ciprofloxacin (only if no fluoroquinolone prophylaxis or therapy in past 90 days)

If mucositis ≥ grade 2, suspected intra-abdominal or perirectal infection, or other indication for anaerobic coverage consider adding:
- Metronidazole

→

Add gram positive coverage

→

For gram positive coverage, select from the following findings:

If suspected line infection[6] and/or bacteremia add:
- Vancomycin **or**
- Daptomycin (if no evidence of pneumonia)

If MRSA colonization or skin and soft tissue infection or pneumonia[7] or mucositis ≥ grade 2 add:
- Vancomycin **or**
- Linezolid (not preferred for MRSA blood stream infections) **or**
- Daptomycin (if no evidence of pneumonia)

If none of the above add:
- Vancomycin **or**
- Linezolid

→

See Page 4 for re-assessment

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[1] Examples of non-IgE mediated drug reactions include Stevens-Johnson syndrome, toxic epidermal necrolysis, and drug reaction with eosinophilia and systemic symptoms (DRESS)
[2] Refer to institutional antimicrobial dosing guide (internal only) or tertiary dosing references (*e.g.,* Lexicomp) for dosing recommendations
[3] Resistant gram negative organisms include:
- *Stenotrophomonas maltophilia*
- Any extended spectrum beta-lactamase (ESBL)-producing gram negative bacilli
- Any carbapenem resistant gram negative bacilli
- All other gram negative bacilli that are resistant to usual recommended first-line agents

[4] Refer to gram negative and gram positive antibiograms (internal only)
[5] Double gram negative coverage recommended due to reduced gram negative pathogen susceptibility to aztreonam according to local antibiograms
[6] Chills, rigors with infusion through catheter, cellulitis or discharge around the catheter entry site
[7] If patient was not previously on fluoroquinolone prophylaxis, consider adding a fluoroquinolone, azithromycin, or doxycycline for atypical pathogen coverage
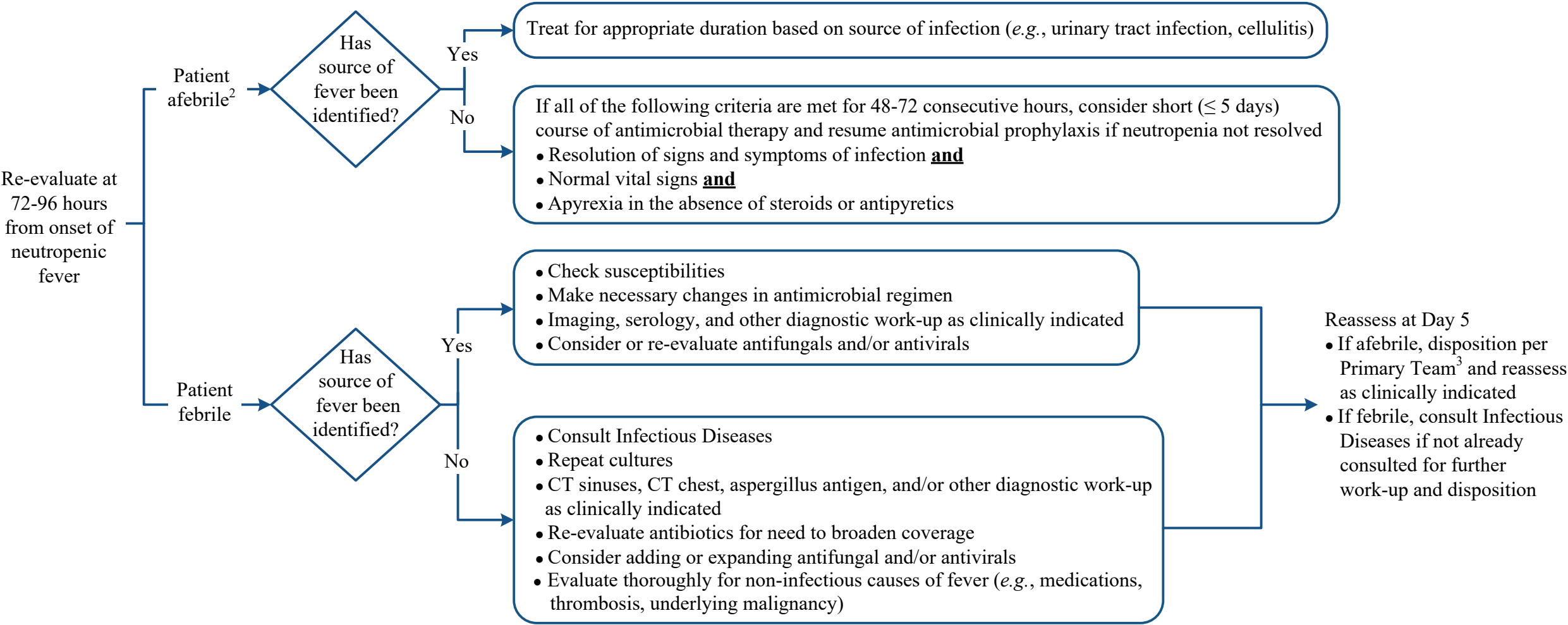
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RE-ASSESSMENT **TREATMENT[1]** **EVALUATION**

Re-evaluate at 72-96 hours from onset of neutropenic fever

Patient afebrile[2] → Has source of fever been identified?

- **Yes** → Treat for appropriate duration based on source of infection (*e.g.*, urinary tract infection, cellulitis)

- **No** → If all of the following criteria are met for 48-72 consecutive hours, consider short (≤ 5 days) course of antimicrobial therapy and resume antimicrobial prophylaxis if neutropenia not resolved
  - Resolution of signs and symptoms of infection **and**
  - Normal vital signs **and**
  - Apyrexia in the absence of steroids or antipyretics

Patient febrile → Has source of fever been identified?

- **Yes** →
  - Check susceptibilities
  - Make necessary changes in antimicrobial regimen
  - Imaging, serology, and other diagnostic work-up as clinically indicated
  - Consider or re-evaluate antifungals and/or antivirals

- **No** →
  - Consult Infectious Diseases
  - Repeat cultures
  - CT sinuses, CT chest, aspergillus antigen, and/or other diagnostic work-up as clinically indicated
  - Re-evaluate antibiotics for need to broaden coverage
  - Consider adding or expanding antifungal and/or antivirals
  - Evaluate thoroughly for non-infectious causes of fever (*e.g.*, medications, thrombosis, underlying malignancy)

Reassess at Day 5
- If afebrile, disposition per Primary Team[3] and reassess as clinically indicated
- If febrile, consult Infectious Diseases if not already consulted for further work-up and disposition

[1] Refer to institutional antimicrobial dosing guide (internal only) or tertiary dosing references (*e.g.,* Lexicomp) for dosing recommendations
[2] Consider narrowing therapy based on cultures and sensitivities (*e.g.*, discontinue anti-MRSA or anti-VRE agents if no gram positive organisms are identified, negative MRSA nares swab, and/or no active cellulitis)
[3] Consider transition to antimicrobial prophylaxis if otherwise indicated and no clear infectious source of fever is identified

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APPENDIX A: Potential Indications for use of Therapeutic G-CSF

Consider therapeutic use if the following risk factor(s) are present:
- Sepsis
- Age > 65 years old
- Pneumonia or other documented infection
- Invasive fungal infection
- ANC < 100 K/microliter
- Expected neutropenia duration > 10 days
- Hospitalization at the time of fever or prior episode of neutropenic fever

Note: Continue G-CSF if patient was receiving as daily prophylaxis.

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SUGGESTED READINGS

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DEVELOPMENT CREDITS

This practice consensus statement is based on majority expert opinion of the Neutropenic Fever experts at the University of Texas MD Anderson Cancer Center for the patient population. These experts included:

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