THE JOHNS HOPKINS HOSPITAL
SIDNEY KIMMEL COMPREHENSIVE CANCER CENTER
Guidelines for the Prevention and Treatment of Infections in the Neutropenic Patient

ALL doses are for patients with normal renal and hepatic function. Dose adjustments may be required for patients with renal and/or hepatic impairment.

Treatment of Neutropenic Fever

Definitions

Neutropenia: ANC < 500
Fever: Temp > 38.0° C times two at least 2 hours apart OR Temp >38.3° C times one

Always tailor antibiotics based on sensitivity profiles!

If the patient is hypotensive or otherwise unstable see below under "Clinically unstable"

Initial fever:

- Piperacillin/tazobactam 3.375 gm IV Q4H
  OR
- Cefepime 2 gm IV Q8H WITH or WITHOUT Metronidazole 500mg IV Q8H
- Serious allergy to PCN defined as anaphylaxis or Stevens-Johnson syndrome: (Strongly consider allergy consult to verify allergy in patients with unclear histories, see section on penicillin allergy).
  - Start with: Ciprofloxacin 400 mg IV Q12H PLUS Tobramycin 2mg/kg IV Q8h **(See "Treatment notes" below)** PLUS Vancomycin 15 mg/kg Q12H (minimum 1 g IV Q12H) WITH or WITHOUT Metronidazole 500 mg IV Q8H

NOTES

1. Discontinue mucositis prophylaxis (ampicillin or vancomycin) when antibiotics are started to treat fevers. BUT continue norfloxacin for GI decontamination.
2. Consider adding vancomycin in non-PCN allergic patients if a serious catheter related infection is suspected (e.g. there is warmth and redness at the catheter site).

Second fever: For patients who remain febrile or develop a new fever after 48-72 hours on antibiotics above but are not hypotensive:

- Continue antibacterial antibiotics above and ADD
  - Amphotericin B 1 mg/kg IV Q24H

NOTE: Discontinue fluconazole if amphotericin is started.

Third fever: For patients who remain febrile or develop a new fever after 48-72 hours on antibacterial agents AND amphotericin but are not hypotensive:

- Consider adding trimethoprim/sulfamethoxazole 5mg/kg IV Q8H (for *Stenotrophomonas maltophila*) to any of the following regimens:

Option 1:

- Add Vancomycin 15 mg/kg IV Q12H (minimum 1 g IV Q12H) - IF and ONLY IF the patient has a documented gram-positive infection that is sensitive only to Vancomycin.

Option 2:

- Continue current regimen (some patients will take longer to defervesce)

Option 3:

- No PCN allergy
  - STOP Cefepime and START Meropenem 1 gm IV Q8H.
- PCN allergy
  - STOP Tobramycin and START Amikacin **(See "Treatment notes" below)**

Clinically unstable: For patients who are clinically unstable due to a possible infectious cause at ANY time during neutropenia:

- Amphotericin B 1 mg/kg IV Q24H PLUS
- Vancomycin 15 mg/kg IV Q12H (minimum 1 g IV Q12H) PLUS
- Amikacin 8 mg/kg IV Q8H **(See "Treatment notes" below)** PLUS
- Meropenem 1 g IV Q8H OR

For patients with severe PCN allergy, replace meropenem with:

- Ciprofloxacin* 400 mg IV Q12H PLUS Metronidazole 500 mg IV Q8H

*PO norfloxacin prophylaxis should be continued even if ciprofloxacin is started.

TREATMENT NOTES

- Antibiotics should ALWAYS be adjusted based on positive cultures.
- It is recommended that all patients receiving aminoglycosides have levels obtained around the 3rd dose:
  - A **trough** level should be drawn just prior to administration of the 3rd dose.
  - A **peak** level should be drawn 30 minutes after the infusion of the 3rd dose.
- If the patient is critically ill and has an unclear volume status, some advocate obtaining a peak level after the 1st dose to ensure efficacy.

Prophylactic antibiotics for patients with expected prolonged neutropenia

1. Bone marrow transplant patients

Indication	Agent and dose	Duration
GI decontamination	Norfloxacin 400 mg PO BID	Day zero until ANC > 500
Candida prophylaxis	Fluconazole 400 mg PO QD	Day zero until ANC > 500
Anti-viral prophylaxis	Valacyclovir 500 mg PO TID [If unable to take PO then: Acyclovir 250 mg/m^2 Q12H]	Day zero until day 28
Streptococcal prophylaxis for patients at risk for mucositis*	Ampicillin 2 g IV Q6H [If severe PCN allergy then: Vancomycin 1 g IV Q12H]	Day zero to day 7 OR until mucositis is less than grade 2 (whichever is longer)

* For outpatients: Amoxicillin 500 mg PO TID (if PO tolerated) OR Vancomycin 1 g IV Q12H OR No prophylaxis **(See "Treatment notes" below)**

2. Leukemia patients

Indication	Agent and dose	Duration
GI decontamination	Norfloxacin 400 mg PO BID	Day one until ANC > 100
Anti-viral prophylaxis	Valacyclovir 500 mg PO TID [If unable to take PO then: Acyclovir 250 mg/m^2 Q12H]	Day one until ANC > 100
Streptococcal prophylaxis for patients with mucositis*	Ampicillin 2 g IV Q6H [If severe PCN allergy then: Vancomycin 1 g IV Q12H]	When ANC <500 on the way down, until ANC > 100 on the way up
PCP prophylaxis (ALL, CLL, lymphoma and myeloma pts only)	Bactrim 1 SS QD OR [If Sulfa allergy then: Dapsone 100 mg QD]	Until immunosuppression resolves

* For outpatients: Amoxicillin 500 mg PO TID (if PO tolerated) OR Vancomycin 1 g IV Q12H OR No prophylaxis (see treatment notes below)

3. Solid tumor patients

The use of prophylactic antibiotics in neutropenic patients who have solid tumors has not been studied formally and is not routinely recommended.

TREATMENT NOTES

- There is some controversy surrounding the utility of anti-streptococcal prophylaxis in patients with mucositis.

Surveillance cultures in leukemia patients with neutropenia

- Surveillance cultures can be helpful in guiding empiric therapy in patients who may have long periods of neutropenia. If surveillance cultures are to be done, the working group recommends that the following cultures be obtained in neutropenic patients until the ANC is more than 500.
- Routine surveillance cultures are NOT recommended for most BMT patients (except for weekly VRE peri-rectal cultures) but may be considered when a long period of neutropenia is anticipated.

Surveillance culture type	Frequency
Stool surveillance cultures	TWICE per week (Mon/Thurs if possible)
Peri-rectal swab for VRE surveillance	ONCE per week
Throat bacteriology cultures	TWICE per week (Mon/Thurs if possible)
Urine virology cultures (BK and adenovirus)	ONCE per week
Urine bacteriology cultures	NOT recommended

Notes on the use of surveillance cultures

- In general, surveillance culture results should not be treated but should be used to guide empiric therapy.
- *Pseudomonas spp., Enterobacter spp*. and *Serratia spp*. have the highest risk of dissemination of organisms routinely recovered in stool surveillance cultures. If these organisms are recovered in the stool, and the patient later becomes febrile, antibiotic therapy must cover the specific strain that was recovered. If a highly resistant strain is recovered, antibiotic susceptibility should be discussed with Infectious Diseases (3-8026) to determine an optimal regimen in advance.