Standard Operating Procedure for Empiric Treatment of Neutropenic Fever

Purpose:

To standardize the management of neutropenic fever and associated empiric anti-fungal treatment at DHMC, including autologous and allogeneic Hematopoietic Stem Cell Transplant (HSCT) patients.

Scope:

Hematology, Oncology, and Infectious Disease staff. All other personnel providing care for neutropenic patients.

Objectives:

1. To describe the process for evaluation of persons with febrile neutropenia.
2. To describe a standard for risk stratification of persons with febrile neutropenia that will help to direct appropriate antimicrobial therapy (outpatient vs. inpatient).
3. To describe the indications for adjunct antimicrobials in the treatment of febrile neutropenia (ie. vancomycin, aminoglycosides).
4. To clarify a stepwise approach to the antimicrobial treatment of patients with febrile neutropenia, including the addition of antifungals and the eventual discontinuation of antimicrobials.

Materials/Resources:

The attached protocol is also available on the DHMC intranet site listed below.
http://intranet.hitchcock.org/oncology/hemoncweb/PDF%20files/neutropenic%20fever.pdf

Description/Protocol:

The recommended algorithm for neutropenic fever is attached. References below.

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Definitions:

- Fever:
  - Core Body temperature $\geq 38.3^\circ\text{C} (101^\circ\text{F})$ once or $\geq 38.0 (100.4^\circ\text{F})$ for $\geq 1$ hour or on 2 separate measurements over an hour apart.
Neutropenia: Absolute Neutrophil Count (ANC) [calculated ANC = WBC * (%neutrophils+Bands)/100]
  o ANC <500 or,
  o ANC<1000 and expected to be <500 soon
  ▪ Note: Gran# (in CIS) is based on automated diff. which can be misleading in certain patients.

Initial Evaluation: The initial evaluation of a patient with febrile neutropenia should include a complete routine history and physical exam in search of a potential source which should include attention to the following components:

<table>
<thead>
<tr>
<th>Review of symptoms</th>
<th>Physical Exam</th>
<th>Laboratory/radiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>URI sx (rhinorrhea, etc.)</td>
<td>Orthostatic BP</td>
<td>CBC with diff</td>
</tr>
<tr>
<td>Sinus tenderness/drainage</td>
<td>Sinus/nasopharynx</td>
<td>Chemistries</td>
</tr>
<tr>
<td>Odynophagia, nausea, vomiting</td>
<td>Oropharynx (mucositis?)</td>
<td>Liver function tests</td>
</tr>
<tr>
<td>Cough, SOB</td>
<td>Lungs, pulse ox</td>
<td>Blood cultures x 2</td>
</tr>
<tr>
<td>Abdominal pain, diarrhea</td>
<td>Abdomen</td>
<td>Urinalysis</td>
</tr>
<tr>
<td>Perirectal tenderness</td>
<td>Perineum (no routine digital rectal exam)</td>
<td>Chest x-ray</td>
</tr>
<tr>
<td>New skin lesions</td>
<td>Skin (nodules, rash)</td>
<td>Review previous cultures</td>
</tr>
<tr>
<td>Tenderness at catheter site</td>
<td>Catheter, IV sites</td>
<td>Sputum, only with sx</td>
</tr>
<tr>
<td></td>
<td>Lymph nodes</td>
<td>Viral studies as indicated.</td>
</tr>
<tr>
<td>Stiff neck, altered mentation</td>
<td>Mental status</td>
<td></td>
</tr>
</tbody>
</table>

Evaluation of and specific therapies for abnormalities found during this initial evaluation is beyond the scope of this document. For these cases, Infectious Disease consultation is encouraged to help guide decision making. Specifically, treatment for particular infections is guided by the clinical and test findings in addition to consideration of the patients’ immunocompromised state.
Inpatient vs. Outpatient care

**Adults who may qualify for Outpatient Care or Oral Inpatient Care:**
(Pediatric patients should be admitted to the hospital)

Several studies have shown that selected adult patients at low risk for complications from febrile neutropenia treated with oral antimicrobials have similar outcomes to patients treated with intravenous antimicrobials. Oral antimicrobials decrease hospital stay, costs, and avoid catheter use. The MASCC (Multinational Association for Supportive Care in Cancer) predictive model has been used as a decision tool to identify patients that may qualify for outpatient oral antimicrobial therapy for febrile neutropenia. Patients with high scores (≥21) on the prediction model have low rates of complications from febrile neutropenia. In addition to a high score (≥21) on the MASCC predictive model, patients who are given outpatient therapy for febrile neutropenia must have significant support and aid in the home and also be able to quickly obtain medical care if necessary (for example, persons living alone and those in remote areas should be admitted for observation). This predictive model is not a substitute for clinical judgment, which supersedes any algorithm.

**MASCC predictive model: calculate total score**

<table>
<thead>
<tr>
<th>Burden of illness</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>No or mild symptoms</td>
<td>5</td>
</tr>
<tr>
<td>Moderate symptoms</td>
<td>3</td>
</tr>
<tr>
<td>No hypotension</td>
<td>5</td>
</tr>
<tr>
<td>No COPD</td>
<td>4</td>
</tr>
<tr>
<td>Solid tumor or no previous fungal infection in hematologic tumor</td>
<td>4</td>
</tr>
<tr>
<td>Outpatient status</td>
<td>3</td>
</tr>
<tr>
<td>No Dehydration</td>
<td>3</td>
</tr>
<tr>
<td>Age&lt;60 years</td>
<td>2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
</tr>
</tbody>
</table>

Persons who may be candidates for outpatient oral therapy:

- MASCC score ≥21
- Will be closely observed in the home (ie. does not live alone)
- Have prompt access to appropriate medical care
- No identified focus of bacterial infection
- No signs or symptoms suggestive of systemic infection (e.g. rigors, hypotension)
- Easy outpatient follow-up in 3-5 days
- Not taking other oral antimicrobials
**Additional factors that predict low risk for severe infection**

ANC>100
Absolute monocyte count>100
Normal chest x-ray
Nearly normal results of hepatic and renal tests
Duration of neutropenia <7 days
Resolution of neutropenia expected in < 10 days
No intravenous catheter-site infection
Early evidence of marrow recovery
Malignancy in remission
Peak temp <39.0°C
No neurologic or mental changes
No appearance of illness
No abdominal pain
No comorbidity complications (e.g. shock, hypoxia, pneumonia or other deep organ infection, vomiting, diarrhea)

**Oral Therapeutic regimen:** for persons deemed appropriate for outpatient oral antimicrobial therapy based upon initial evaluation, testing and clinical judgment.

Ciprofloxacin 750 mg orally  BID; and
Amoxicillin-clavulanate (Augmentin®) 875mg 1 tab orally BID

Quinolone allergy: admit to hospital
ß-Lactam allergy (PCN, cephalosporin): admit to hospital

If the patient is seen outside of clinic, please call the patient’s provider or coverage during working hours. After hours, please contact the on call Hematology/Oncology Fellow or other coverage depending on the service to discuss the patient and ensure that the plan is appropriate and that follow-up is arranged.

Finally, as an alternative to outpatient care, low-risk or questionable patients may be admitted and observed for 24-48 hours on IV or oral antimicrobials, and if infection is excluded by initial testing and cultures, the low-risk patient can be transitioned to outpatient care with oral therapy.

Follow-up in outpatient clinic within 5 days.
Empiric Inpatient Therapy for Febrile Neutropenia in Adult and Pediatric Patients

Initial empiric regimen is based upon several factors, including signs and symptoms, previous therapy or infections, duration of neutropenia or the presence of significant mucositis. All patients should receive a single broad-spectrum agent and the decision to add additional agents is based upon specific factors discussed below.

For patients on fluoroquinolone prophylaxis at the time fevers begin, the fluoroquinolone should be discontinued upon initiation of empiric therapy.

After obtaining the history, physical and appropriate tests and cultures, empiric antimicrobial therapy should be started:

**Fever**
Core Body temperature ≥ 38.3°C (101°F) once or ≥ 38.0 (100.4°F) for ≥ 1 hour or on 2 measurements >1 hour apart

**Suspected or proven intraabdominal or perineal infection?**

Yes

**Clinically Unstable‡**

Yes

Meropenem + Tobramycin

No

Meropenem

No

Ceftazidime + Tobramycin

**Clinically Unstable‡**

Yes

Ceftazidime + Tobramycin

No

Ceftazidime

† Intra-abdominal infection is defined as abdominal tenderness, rebound or guarding and/or a suspicion of pathology related to an abdominal viscus. Diarrhea does not qualify in the absence of other symptoms or signs.

‡ Clinically unstable is defined as signs of Gram negative sepsis, hypotension, tachycardia, tachypnea, etc. Recommend Infectious Disease consultation.
Other Antibiotic Issues

Penicillin Allergy (minor reaction: e.g. rash)
Use Ceftazidime (do not use with cephalosporin allergy, see PCN allergy: Type 1 hypersensitivity)
if abdominal pathology, add Metronidazole

Penicillin Allergy: Type 1-immediate hypersensitivity (anaphylaxis) or unknown:
Clinically stable: Aztreonam + Vancomycin
Clinically Unstable Aztreonam + Vancomycin + tobramycin
Abdominal pathology: Add Metronidazole

Duotherapy:
“Double coverage” for Gram negative organisms – see above criteria for addition of Tobramycin.
If known Gram negative organism, use duotherapy until susceptibility is known. Infectious Disease consultation is recommended.

In known renal dysfunction, decision about the addition of aminoglycoside should be made on clinical grounds after weighing the risks and benefits. If no recent treatment with a quinolone, addition of Ciprofloxacin may be considered. Infectious Disease consultation is recommended.

Vancomycin: criteria for addition
Known colonization or previous infection with MRSA
Obvious catheter-related or tunnel infection
Positive blood culture with gram positive organism
Severe hypotension
Viridans streptococci bacteremia – until susceptibility is known

Vancomycin: criteria for removal: Vancomycin therapy should be discontinued after 72 hours if:
No evidence of clinical response
No evidence for catheter-related or tunnel infection
Negative cultures for gram positive organisms or MRSA

Other initial Empiric antibiotic Considerations
- Potential or witnessed aspiration:
  Consider using pip/tazo, meropenem, or adding clindamycin
- Possible atypical community acquired pneumonia (patient not on moxifloxacin, levofloxacin):
  Consider adding azithromycin
- Concern for C. difficile colitis (based on history)
  Consider adding metronidazole

Preservation of gut flora: The use of antibiotics with activity against anaerobes is associated with reduced colonization and risk of translocation and bacteremia.
Risks of multiple antibiotics: include drug fevers, allergic reactions, rash and development of resistance
**Subsequent Care**

Afebrile within 3-5 days of treatment

- **No etiology identified**
  - Low Risk
    - Change to Outpatient Oral Regimen
  - High Risk
    - Continue same antibiotics

- **Etiology identified**
  - Adjust to most appropriate treatment (Infectious Disease consult is recommended)

Persistent Fever during first 3-5 days of treatment: No Etiology

  - Reassess patient on Days 3-5
    - If no change in patient’s condition
      - Continue initial antibiotics (consider stopping vancomycin)
    - If progressive disease
      - Infectious Disease consultation
    - If febrile through days 5-7 and resolution of neutropenia is not imminent
      - Antifungal drug with or without antibiotic change†

† See Antifungal Therapy Algorithm, next page
Antifungal Therapy Algorithm

Low Risk for Mould Infection
- No Allogeneic HSCT
- No Neutropenia >20 days
- Not Colonized with *Aspergillus*
- Low dose steroids (short duration)

On azole prophylaxis
- Risk for nephrotoxicities

High
- High Cr (>2.0) or 2x baseline Cr
- Disease Myeloma
- Concomitant nephrotoxic drugs (cyclosporine, aminoglycosides, etc.)
- History of prior renal failure

Low (all others)
- Ambisome

Micafungin

NOT on azole prophylaxis
- Fluconazole

High Risk for Mould Infection
- Allogeneic HSCT
- Neutropenia >20 days
- Colonized with *Aspergillus*
- Steroids > 1 mg/kg/day

Received long courses of triazole antifungals

IV Micafungin or Ambisome (use nephrotoxicity risk above)

No prolonged azole exposure

Tolerating oral Rx: Voriconazole
- Not tolerating oral Rx: IV Voriconazole, Micafungin or Ambisome depending on risk for nephrotoxicity† or drug interactions

† IV Voriconazole contraindicated for GFR < 50
-azole antifungals should be used with caution in persons with hepatic impairment
It is important to note that this recommendation is only to be used for the empiric regimen, if a specific diagnosis is made, therapy for that entity should follow usual clinical practice.

† A thorough evaluation should be conducted, Infectious Disease Service Consultation is advised.
Medication dosing for adults with normal renal function and normal weight:
Please refer to manufacturer’s guidelines and/or pharmacy for Pediatric dosing and for dosing in patients with renal dysfunction or abnormal weight:

Ambisome:
3 mg/kg i.v. daily
Pre-hydrate with 500 cc of NS if clinically able to tolerate.

Azithromycin:
500 mg i.v. daily

Aztreonam:
2 grams i.v. q 8 hrs.

Ceftazidime:
2 grams i.v. q 8 hrs

Ciprofloxacin:
750 mg p.o. q 12 hrs or 400mg IV q 12 hrs

Clindamycin:
900 mg i.v. q 8 hrs

Fluconazole:
200 mg p.o. daily

Meropenem:
1 gram i.v. q 8 hrs.

Micafungin:
150 mg i.v. daily

Moxifloxacin:
400 mg p.o or i.v. daily

Tobramycin
7 mg/kg i.v. q 24 hours. Check AG level 8-12 hours after the first dose and adjust dosing as needed. Check creatinine daily.

Vancomycin:
1 gram i.v. q 12 hrs

Voriconazole
GFR>50: 6 mg/kg i.v. q 12 hrs on day 1, then 4 mg/kg i.v. q 12 hrs
If able to take p.o., use similar dose orally if Gl integrity and function are normal
GFR<50: consider alternative agent.
Use with caution in hepatic impairment and with medications metabolized by CYP450.
In Transplant recipients – monitor for drug interactions (e.g. cyclosporine)