Chapter Three: Treatment of Infection

Purpose: To provide guidelines for the treatment of infection for patients in the BMT Unit. These guidelines may be altered as necessary and appropriate to provide appropriate individualized care for each patient.

Scope: These guidelines apply to the treatment of infection in patients undergoing hematopoietic stem cell transplantation at the University of Kentucky Markey Cancer Center.

I. Antibacterial Therapy
II. Anti-Fungal Therapy
III. Treatment of Pneumocystis
IV. Anti-Viral Therapy
V. Ganciclovir Dosing Guidelines
VI. Cidofovir Dosing Guidelines
VII. Foscarnet Dosing Guidelines
VIII. Ribavirin Dosing Guidelines
IX. References
I. ANTI-BACTERIAL THERAPY (for Adults and Children)

A. Documented Infections:
   1. **Gram negative infection** – preferably 2 effective agents should be used in neutropenic patients. Antibiotic selection will be based on culture sensitivities and hospital resistance patterns.
   2. **Gram positive infection** – appropriate coverage for gram positive organisms in neutropenic patients. Gram negative coverage may also be used in neutropenic patients. Antibiotic selection will be based on culture sensitivities and hospital resistance patterns.

B. Neutropenic fever:
   1. The criteria for the diagnosis of Neutropenic fever includes the following:
      a) Fever ≥101° or >100.4° F x 2 determinations within any 24 hour period.
      b) ANC < 500/mm³ or < predicted decline to < 500/mm³ within next 48 hours.
   2. Lab tests required for patients with Neutropenic include, but are not limited to, the following:
      a) Blood cultures from all indwelling catheter ports and 1 peripheral culture
      b) Urinalysis and urine culture
      c) Sputum culture (if available)
      d) Chest x-ray (per symptoms)
      e) Stool cultures (if diarrhea present)
      f) Electrolytes
      g) Complete Blood Count with differential.
   3. Empiric antibiotics for patients with Neutropenic fever:
      a) Tobramycin 5-7 mg/kg dosing body weight and piperacillin/tazobactam 4.5g IV every 6 hours in patients with normal renal function
      b) Both tobramycin and piperacillin/tazobactam must be adjusted for renal dysfunction. Contact BMT pharmacist for appropriate dosing guidelines.
      c) Patients with a non-anaphylactic penicillin allergy should receive cefepime 2 grams IV every 8 hours in place of piperacillin/tazobactam
      d) Patients with an anaphylactic penicillin allergy should receive aztreonam 2 grams IV every 8 hours or levofloxacin 750 mg IV/PO daily if patient is not currently receiving levofloxacin prophylaxis.
   4. Vancomycin Therapy:
      a) Will be initiated empirically in the following patients: Patients with severe mucositis, history of MRSA colonization, previous documented MRSA or MRSE infection, obvious catheter related infection, pneumonia, and patients with hypotension.
      b) Vancomycin will be discontinued after 72 hours unless the patient has positive cultures or fever resolution after addition of vancomycin therapy.
   5. For persistent fever despite antibiotics without a definite source, evaluate patient for eligibility for antifungal treatment. If not eligible for an ongoing antifungal study initiate empiric antifungal therapy as per the antimicrobial subcommittee of P&T consensus guidelines: Ambisome at 3 mg/kg/day or voriconazole at 6 mg/kg IV every 12 hours or 400mg orally twice a day for two doses followed by 4 mg/kg every 12 hours or 200mg orally twice a day. Alternatively, micafungin 100 mg IV daily may be used.

II. ANTI-FUNGAL THERAPY (for Adults and Children)

A. Evaluate patient for eligibility for antifungal protocols.
B. For suspected or documented fungal infection options include:
   1. Ambisome 3 mg/kg/day for most infections.
   2. Voriconazole 6 mg/kg IV every 12 hours for two doses followed by 4 mg/kg IV every 12 hours or 200mg orally twice a day for suspected or documented fungal infection.
   3. Micafungin 100mg IV daily
C. Itraconazole oral solution, voriconazole oral tablets, or posaconazole oral suspension may be utilized in selected settings (usually for non-candidal infections), particularly for chronic outpatient therapy.
D. For histoplasmosis, Ambisome 3 mg/kg/day IV should be used for moderate/severe infections for 1-2 weeks followed by itraconazole 200 mg po twice daily for a total of at least 12 weeks. For mild/moderate infections, itraconazole 200 mg po once or twice daily for a total of 6-12 weeks. Longer durations of
therapy may be required depending on severity of infection.

E. For toxoplasmosis, initiate pyrimethamine 200 mg po x 1 dose followed by 50 mg po daily in addition to sulfadiazine 1000 mg po four times per day and leucovorin 10-25 mg po daily. Alternatively, patients who cannot tolerate sulfadiazine should receive pyrimethamine at doses listed above plus clindamycin 600 mg IV/PO q6 hours.

III. TREATMENT OF PNEUMOCYSTIS JIROVECII PNEUMONIA (Children > 2 months and Adults)
   A. Bactrim 5mg/kg/dose IV every 6 hrs is the treatment of choice.
   B. For renal impairment call BMT pharmacist for dose adjustment.
   C. For patients intolerant or allergic to Bactrim, use clindamycin 600 mg IV every 6 hours and primaquine 15-30 mg daily, IV pentamidine 4 mg/kg/day, or atovaquone 750 mg po twice daily. Check with BMT pharmacist for dosing in renal or hepatic dysfunction.

IV. ANTI-VIRAL THERAPY
   A. HSV: Acyclovir 400 mg orally five times daily or 250 mg/m²/dose IV every 8 hours.
   B. VZV, Chicken Pox, Disseminated HSV Infections
      1. ADULTS
         a) Acyclovir 500 mg/m²/dose IV every 8 hours in all transplant patients. As soon as lesions appear to be healing, can switch to oral acyclovir 800 mg 5 times per day, to oral famciclovir 500mg 3 times per day, or oral valacyclovir 1000 mg three times per day.
         b) Host resistant HSV: Persistent HSV lesions despite appropriate therapy consider HSV resistant disease or base host deficiencies. Changing therapy to IV foscarinet may be warranted. See intravenous foscarinet dosing guidelines.
      2. CHILDREN
         a) Acyclovir 500 mg/m²/dose IV every 8 hours in children > 1 years.
   C. RSV: Check current protocol or consult with Infectious Diseases. Please refer to Hospital Policy HP10-32 regarding ribavirin administration.
      1. If patient is receiving aerosolized Ribavirin, the following guidelines are in effect for visitors and health care workers:
      2. Sealed goggles are required for both contact lens and noncontact lens wearers.
      3. Wear a DMR 2010 orange mask as Ribavirin causes pulmonary irritation and cough.
      4. Aerosolized particles are cleared from the BMT rooms in 30 minutes.
      5. PREGNANT STAFF MEMBERS MAY NOT CARE FOR THESE PATIENTS.
   D. Influenza
      1. ADULTS – Oseltamivir 75 mg by mouth BID for five days.
      2. CHILDREN
         a) For children ages >1 year oseltamivir 2 mg/kg up to a total of 75 mg by mouth twice daily for five days.
   E. Parainfluenza and Adenovirus
      1. Parainfluenza – patients with symptoms of lower respiratory tract disease consider inhaled ribavirin.
      2. Adenovirus:
         a) Patients with >1 site should be considered to have disseminated disease. Cidofovir therapy should be considered. See cidofovir dosing guidelines.
         b) Patients with isolated adenovirus pneumonia may benefit from inhaled ribavirin as per the RSV therapy; and, patients with isolated adenovirus hemorrhagic cystitis may benefit from intravenous ribavirin as per the Lassa fever protocol (JAMA 287:2391, 2002).
   F. Cytomegalovirus
      1. All allogeneic transplant patients will have a weekly CMV DNA by PCR lab drawn prior to day + 10. Weekly testing should continue through at least day +100 post-transplant.
      2. Patients who continue on immunosuppression or have chronic GvHD should continue CMV PCR surveillance beyond day +100 on an every other week schedule. While no firm guidelines exist, monitoring for these patients through day +240 post-transplant should be considered.
      3. Any positive CMV DNA by PCR will be treated with preemptive therapy:
a) CMV DNA < 2,000 copies / mL initiate valganciclovir 900 mg by mouth twice daily, or ganciclovir 5 mg/kg IV every 12 hours.
   (1) Continue induction therapy for 2-4 weeks. After induction therapy is completed, maintenance therapy consists of valganciclovir 900 mg daily or ganciclovir 5 mg/kg IV daily for a minimum of 2-4 more weeks.
   (2) For patients with renal dysfunction, contact the BMT pharmacist for appropriate dosing guidelines.

b) CMV DNA > 2000 copies / mL initiate ganciclovir 5 mg/kg IV every 12 hours.
   (1) Continue induction therapy for 2-4 weeks. After induction therapy is completed, maintenance therapy consists of ganciclovir 5 mg/kg IV daily for a minimum of 2-4 more weeks.
   (2) In patients at high-risk for recurrence oral valganciclovir at 450mg/day for prophylaxis should be considered post-maintenance therapy.
   (3) Patients intolerant of ganciclovir therapy for any reason may receive foscarnet treatment. See table below for appropriate dosing guidelines.

c) Allogeneic URD recipients with > 1 CMV infections should be considered for valganciclovir 450 mg daily prophylaxis.

d) For patients with CMV pneumonitis IVIG therapy is given in addition to fulldose ganciclovir.
   (1) IVIG 500 mg/kg every other day x 10 doses.
   (2) IVIG 500 mg/kg twice a week x 8 doses.

4. In patients developing CMV disease on therapeutic ganciclovir or in those with an ANC< 500, foscarnet should be given at a therapeutic dose x 2-4 weeks followed by a maintenance dose x 2-4 weeks.

G. BKV (Bladder-Kidney-Virus)
   1. Patients who develop hemorrhagic cystitis following hematopoietic stem cell transplant should be evaluated for viral infection – BKV and CMV PCR tests are available for this purpose.
   2. Supportive care measures according to best clinical practices for hemorrhagic cystitis should be initiated.
   3. In severe cases, treatment with cidofovir or leflutamide should be considered.

V. GANCICLOVIR DOSING GUIDELINES

| Induction Ganciclovir Dosing Guidelines in Renal Dysfunction |
|-----------------|-----------------|-----------------|
| CrCL (Ml/min)   | Dosage per Interval | Therapeutic Interval |
| ≥70             | 5 mg/kg          | Every 12 hours   |
| 50-69           | 2.5 mg/kg        | Every 12 hours   |
| 10-49           | 2.5 mg/kg        | Every 24 hours   |
| 10-24           | 1.25 mg/kg       | Every 24 hours   |
| <10             | 1.25 mg/kg       | 3 per week       |

| Maintenance Ganciclovir Dosing Guidelines in Renal Dysfunction |
|-----------------|-----------------|-----------------|
| CrCL (Ml/min)   | Dosage per Interval | Therapeutic Interval |
| ≥70             | 5 mg/kg          | Every 24 hours   |
| 50-69           | 2.5 mg/kg        | Every 24 hours   |
| 10-49           | 1.25 mg/kg       | Every 24 hours   |
| 10-24           | 0.625 mg/kg      | Every 24 hours   |
| <10             | 0.625 mg/kg      | 3 per week       |
Calculating Creatinine Clearance (CrCL)

CrCL (Men) = \frac{(140 - \text{age}) \text{ (wt in kg)}}{(72 \text{ (serum creatinine) })}

CrCL (Women) = \frac{(140 - \text{age}) \text{ (wt in kg)}}{(72 \text{ (serum creatinine) } \times 0.85)}

VI. CIDOFOVIR DOSING GUIDELINES

A. The recommended intravenous dose of induction cidofovir is 5 mg/kg once weekly for two weeks, followed by 5 mg/kg once every other week until CMV progression, resolution or therapy-limiting toxicity (Lalezari et al, 1998; Prod Info Vistide(R), 1998; Lalezari et al, 1995). See D below for alternative dosing schedule.

B. If renal function changes during cidofovir therapy, the dose should be reduced from 5 mg/kg to 3 mg/kg for an increase in serum creatinine of 0.3 to 0.4 milligrams per deciliter above baseline (Prod Info Cidofovir(R), 1998).

C. Cidofovir is contraindicated in patients with a serum creatinine level greater than 1.5 mg/dL, a calculated creatinine clearance less than or equal to 55 mL/minute, or a urine protein concentration greater than or equal to 100 mg/dL (greater than or equal to 2+ proteinuria) (Prod Info Cidofovir(R), 1998).

1. Pre and post-hydration is recommended to prevent nephrotoxicity.
2. Consider probenecid to decrease the severity of adverse renal events.

D. Alternative cidofovir dosing includes 1 mg/kg 3 times weekly in attempt to decrease renal toxicity associated with conventional dosing. (Hoffman JA et al. BB&MT 2001: 7; 388-394). Experience with this dosing has been very successful in the treatment of pediatric patients with disseminated adenovirus.

E. Doses of intravenous cidofovir are given as a 1-hour infusion in 100 milliliters normal saline (Lalezari et al, 1998; Prod Info Vistide(R), 1998; Cundy et al, 1995a; Lalezari et al, 1995a).
VII. FOSCARNET DOSING GUIDELINES

The dose of foscarnet should be adjusted according to creatinine clearance calculated as ml/min/kg. Creatinine clearance is calculated by the following formula:

\[
\text{CMV Induction Dose of Foscarnet (per kilogram)}
\]

<table>
<thead>
<tr>
<th>CrCL (Ml/min)</th>
<th>Equivalent to 60 mg/kg/dose every 8 hours</th>
<th><strong>PREFERRED REGIMEN</strong>* Equivalent to 90 mg/kg/dose every 12 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.4</td>
<td>Not recommended</td>
<td>Not recommended</td>
</tr>
<tr>
<td>≥0.4-0.5</td>
<td>50 mg every 24 hours</td>
<td>50 mg every 24 hours</td>
</tr>
<tr>
<td>≥0.5-0.6</td>
<td>60 mg every 24 hours</td>
<td>60 mg every 24 hours</td>
</tr>
<tr>
<td>≥0.6-0.8</td>
<td>40 mg every 12 hours</td>
<td>80 mg every 24 hours</td>
</tr>
<tr>
<td>≥0.8-1.0</td>
<td>50 mg every 12 hours</td>
<td>50 mg every 12 hours</td>
</tr>
<tr>
<td>≥1.0-1.4</td>
<td>45 mg every 8 hours</td>
<td>70 mg every 12 hours</td>
</tr>
<tr>
<td>≥1.4</td>
<td>60 mg every 8 hours</td>
<td>90 mg every 12 hours</td>
</tr>
</tbody>
</table>

**CMV Maintenance Dose of Foscarnet (per kilogram)**

<table>
<thead>
<tr>
<th>CrCL (Ml/min)</th>
<th>Equivalent to 90 mg/kg/day.</th>
<th><strong>PREFERRED REGIMEN</strong>* Equivalent to 120 mg/kg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.4</td>
<td>Not recommended</td>
<td>Not recommended</td>
</tr>
<tr>
<td>≥0.4-0.5</td>
<td>50 mg every 48 hours</td>
<td>65 mg every 48 hours</td>
</tr>
<tr>
<td>≥0.5-0.6</td>
<td>60 mg every 48 hours</td>
<td>80 mg every 48 hours</td>
</tr>
<tr>
<td>≥0.6-0.8</td>
<td>80 mg every 48 hours</td>
<td>105 mg every 48 hours</td>
</tr>
<tr>
<td>≥0.8-1.0</td>
<td>50 mg every 24 hours</td>
<td>65 mg every 24 hours</td>
</tr>
<tr>
<td>≥1.0-1.4</td>
<td>70 mg every 24 hours</td>
<td>90 mg every 24 hours</td>
</tr>
<tr>
<td>≥1.4</td>
<td>90 mg every 24 hours</td>
<td>120 mg every 24 hours</td>
</tr>
</tbody>
</table>
VIII. RIBAVIRIN DOSING GUIDELINES
A. An Infectious Disease consult is required. The ID service must approve the use of ribavirin by the IV route before it may be ordered for a specific patient. Intravenous Dosing Guidelines

B. Intravenous Dosing Guidelines
1. ADULTS
   a) 30 mg/kg IV loading dose (maximum 2 grams); followed by 
   b) 16 mg/kg/dose IV every 6 hours for 4 days (maximum 1 gram/dose); followed by 
   c) 8 mg/kg/dose IV every 8 hours for 6 days (maximum 500 mg/dose). 

2. CHILDREN
   a) The dose for children is the same schedule that is used in adults. 
   b) Ribavirin is mixed in 50-100 ml of NSS and infused over 30 minutes.

C. Aerosolized Dosing Guidelines
   a) Ribavirin for inhalation 600 mg/300 mL via SPAG over 18 hours per day for 7-14 days; longer treatment courses may be required.

IX. REFERENCES
1. MMWR Guidelines for Preventing Opportunistic Infections Among Hematopoietic Stem Cell Transplant Recipients. Oct 20, 2000, Vol 49 (I believe this was also published in BBMT)