Antimicrobial Prophylaxis

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Abstract During the period of neutropenia (ANC < 500 cells/mm^3) following cytotoxic chemotherapy and hematopoietic stem cell transplantation (HSCT) oncology patients are at a significant risk for infections (Freifeld et al., Clin Infect Dis 52(4):e56–e93, 2011). Patients with profound neutropenia, defined as ANC < 100 cells/mm^3 are at greatest risk with bacteremia rates reported as high as 20%, often with septic shock and multi-system organ failure (Freifeld et al., Clin Infect Dis 52(4):e56–e93, 2011; Horton et al., Curr Hematol Malig Rep13:59, 2018).

A number of modalities have been evaluated to mitigate the risk of infections in vulnerable oncology patients with neutropenia. Among the most widely utilized has been the use of antimicrobial prophylaxis during the time of afebrile neutropenia. Recommendations for prophylaxis vary based on overall risk of infections as determined by disease state and treatment received. Low risk patients are typically those with solid tumors receiving standard chemotherapy with anticipated neutropenia less than 7 days (Freifeld et al., Clin Infect Dis 52(4):e56–e93, 2011; National Comprehensive Cancer Network. Prevention and treatment of cancer-related infections (Version 1.2018). https://www.nccn.org/professionals/physician_gls/pdf/infections.pdf. Accessed 11 Apr 2018). Such patients do not routinely require bacterial, fungal or viral prophylaxis (Freifeld et al., Clin Infect Dis 52(4):e56–e93, 2011; National Comprehensive Cancer Network. Prevention and treatment of cancer-related infections (Version 1.2018). https://www.nccn.org/professionals/physician_gls/pdf/infections.pdf. Accessed 11 Apr 2018). On the other hand patients undergoing HSCT or those receiving treatment for acute leukemia are considered high risk for infections and thus typically received bacterial, fungal and viral prophylaxis (Freifeld et al., Clin Infect Dis 52(4):e56–e93, 2011; National Comprehensive Cancer Network. Prevention and treatment of cancer-related infections (Version 1.2018). https://www.nccn.org/professionals/physician_gls/pdf/infections.pdf. Accessed 11 Apr 2018).

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Antibacterial Prophylaxis

Patients with profound neutropenia, defined as ANC < 100 cells/mm^3 are at the greatest infectious risk, with bacteremia rates reported as high as 20%, often with septic shock and multi-system organ failure [1, 2]. Numerous studies, some as early as the 1980's, have demonstrated that the use of prophylactic antibiotics during the period of neutropenia can decrease febrile episodes and documented infections [1]. However, more recent meta-analyses have demonstrated risk reduction in all-cause and infection-related mortality in high risk patients receiving fluoroquinolone prophylaxis compared to placebo [4, 5].

.As a result a number of guidelines including those from American Society for Blood and Marrow Transplantation (ASBMT), Infectious Disease Society of America (IDSA), the National Comprehensive Cancer Network (NCCN), and European Society for Blood and Marrow Transplantation (EBMT) endorse this practice in high risk oncology patients with hematologic malignancies undergoing both induction chemotherapy and HCST [1, 3, 6, 7]. Emergence of resistance to fluoroquinolones, concern for superinfections with *Clostridium difficile* and alteration in the microbiome have brought this practice to question.

Who [1, 3, 6, 7]

High risk patients

- Anticipated prolonged profound neutropenia (ANC ≤ 100 cells/mm^3 for >7 days)
- Anticipated prolonged neutropenia (ANC ≤ 500 cells/mm^3 for >10 days)
- Allogeneic HSCT
- Acute leukemia
  - Induction
  - Consolidation/maintenance

What [1, 3, 8]

- Fluoroquinolone
  - Ciprofloxacin 500 mg PO/IV BID

  - Levofloxacin 500 mg PO/IV Daily
    - Preferred when additional viridans group streptococcal coverage indicated
- Oral third generation cephalosporin
  - Patients not able to receive a fluoroquinolone (i.e. intolerance, drug interactions, resistance)

When [1, 3, 6, 7]

- Start of neutropenia
  - Some protocols will start at time of chemotherapy
- Continue until resolution of neutropenia

Antifungal Prophylaxis

Neutropenic oncology patients are at risk of fungal infections, both from yeast and mold. Similar to antibacterial prophylaxis, primary antifungal prophylaxis will be guided by patient's risk for developing such infections. Patients with solid tumors and anticipated neutropenia duration of less than 7 days are considered low risk for fungal infections and routinely do not receive antifungal prophylaxis [3]. Widespread use of antifungal prophylaxis with fluconazole has been linked to increasing rates of infections with fluconazole resistant yeasts and therefore is only recommended in oncology patients with invasive *Candida* infection rates of 6–10% [1]. Patients who fall into this category are those with acute leukemia and oral or gastrointestinal mucositis secondary to chemotherapy, pre-engraftment allogeneic HSCT recipients and autologous HSCT recipients with mucositis [1, 3].

Similar to anti-*Candida* prophylaxis, the need for prophylaxis against Aspergillus varies according to patient's disease and chemotherapy used for treatment of the disease [1]. In general patients with a baseline risk of greater than 6% for invasive aspergillosis appear to benefit from primary prophylaxis with a mold active agent [1]. This includes patients with acute myeloid leukemia (AML) receiving induction chemotherapy and patients with advanced myelodysplastic syndromes (MDS) undergoing intensive treatment [1, 3]. In allogeneic HSCT recipients prophylaxis with a mold active agent should be considered in patients with graft-versus-host disease (GVHD) on high dose steroids($\geq$1 mg per kg prednisone equivalent) with or without antithymocyte globulin (ATG) or TNF blockade (infliximab), anticipated prolonged neutropenia of 2 weeks or greater or those with longstanding neutropenia immediately prior to HSCT [1, 3, 7, 9]. For details on specific agents and secondary antifungal prophylaxis please refer to chapter on antifungals and invasive fungal infections.

Pneumocystis jiroveci (PCP) is a life-threatening fungal infection that affects immunocompromised oncology and non-oncology patients. Patients with hematologic malignancies and those undergoing a HSCT are at greatest risk [3, 10]. Prophylaxis has been recommended in patients with baseline risk of PCP greater than or equal to 6.2%, with a number needed to treat is 19 to prevent a singe case of PCP [11]. This includes patients with acute lymphoblastic leukemia (ALL), allogeneic HSCT recipients, patients receiving alemtuzumab, corticosteroids (≥20 mg per day prednisone or equivalent for ≥4 weeks), purine analog therapy (fludarabine) and temozolomide in combination with radiation therapy [3, 7, 10].

Who [1, 3, 7, 9, 10]

- Yeast
  - Acute leukemia
  - Allogeneic HSCT
    - Pre-engraftment phase
  - Autologous HSCT recipients with mucositis
    - Pre-engraftment phase
- Mold
  - AML
    - Induction
  - Allogeneic HSCT
    - Graft-versus-host disease (GVHD)
      - On high doses of steroids (≥1 mg per kg prednisone equivalent)
    - Anticipated prolonged neutropenia of 2 weeks or greater
    - Longstanding neutropenia immediately prior to HSCT
- PCP
  - ALL
  - Alemtuzumab
  - Allogeneic HSCT recipients
  - Corticosteroids (≥20 mg per day prednisone or equivalent for ≥4 weeks)
  - Purine analog therapy (fludarabine)
  - Temozolomide + radiation therapy

What [1, 3, 7, 10, 12]

- Yeast
  - Fluconazole 200–400 mg PO/IV Daily
  - Micafungin 50–100 mg IV Daily
  - Amphotericin B products
- Mold
  - Posaconazole suspension 200 mg PO TID
  - Posaconazole tablets 300 mg PO/IV BID x 1 day then daily
  - Voriconazole 200 mg PO/IV BID
  - Amphotericin B products
  - Isavuconazonium
- PCP
  - First-line: Trimethoprim/ sulfamethoxazole 1 SS (80/400 mg) PO Daily or 1 DS (160/800 mg) PO TIW
  - Second-line: dapsone, atovaquone, pentamidine aerosol or intravenous

When [1, 3, 7, 10]

- Yeast and mold
  - Start of neutropenia
  - Continue until resolution of neutropenia
    - In patients with GVHD, until resolution of GVHD
- PCP
  - ALL
    - Throughout anti-leukemic therapy
  - Alemtuzumab
    - Minimum of 2 months after drug discontinuation and until CD4 ≥ 200 cells/moL
  - Allogeneic HSCT recipients
    - At least 6 months and while on immunosuppression
  - Corticosteroids (≥20 mg per day prednisone or equivalent for ≥4 weeks)
    - At least while on therapy

- Purine analog therapy (fludarabine)
  - Until CD4 ≥ 200 cells/moL
- Temozolomide + radiation therapy
  - At least while on therapy

Antiviral Prophylaxis (Herpes Viruses)

Herpes viruses are large encapsulated deoxyribose nucleic acid (DNA) viruses that can cause acute primary infections and then persist within the host in non-infectious form [13]. Under appropriate conditions herpes viruses have the ability to reactivate and cause latent infections, which may be clinically very different than the primary infection [13]. There are eight types of human herpes virus, and all have been implicated to some extent in human disease. The purpose of this section is to review prophylaxis in neutropenic oncology patients against three of the human herpes viruses; herpes simplex virus 1 (HSV-1), herpes simplex virus 2 (HSV-2) and varicella zoster virus (VZV) [13].

.Similar to antibacterial prophylaxis, antiviral prophylaxis against HSV 1/2 and VZV is only warranted in high risk, seropositive neutropenic oncology patients [1, 3]. However, risk factors other than neutropenia have been linked to reactivation of HSV and VZV, thus even in absence of neutropenia patients receiving therapy with proteasome inhibitors, alemtuzumab, corticosteroids for GVHD and purine analog therapy should receive prophylaxis [1, 3].

Who [1, 3]

- Acute leukemia (seropositive for HSV or VZV or history of chicken pox)
- Alemtuzumab
- Allogeneic HSCT (seropositive donor or recipient for HSV or VZV)
- Allogeneic HSCT with GVHD receiving corticosteroids
- Autologous HSCT (seropositive for HSV or VZV)
- Proteasome inhibitors (bortezomib, carfilzomib, ixazomib)
- Purine analog therapy (fludarabine)

What [3]

- Acyclovir 400–800 mg PO BID
- Famciclovir 250 mg PO BID
- Valaciclovir 500 mg PO BID-TID

When [1, 3]

- Acute leukemia
  - HSV
    - Continue until resolution of neutropenia or mucositis, whichever occurs later
- Alemtuzumab
  - HSV
    - Minimum of 2 months after drug discontinuation and until CD4 ≥ 200 cells/moL
- Allogeneic HSCT
  - HSV
    - Continue until resolution of neutropenia or mucositis, whichever occurs later
  - VZV
    - For at least 1 year after HSCT
- Autologous HSCT
  - HSV
    - Continue until resolution of neutropenia or mucositis, whichever occurs later
  - VZV
    - 6–12 months after HSCT
- Proteasome inhibitors (bortezomib, carfilzomib, ixazomib)
  - VZV
    - During active therapy
- Purine analog therapy (fludarabine)
  - HSV and VZV
    - During active therapy or longer depending on degree of immunosuppression

Key Points

	Who	What	When
Antibacterial	Anticipated prolonged profound neutropenia (ANC ≤ 100 cells/mm3 for >7 days) Anticipated prolonged neutropenia (ANC ≤ 500 cells/mm3 for >10 days) Allogeneic HSCT Acute leukemia Induction Consolidation/maintenance	Fluoroquinolone Ciprofloxacin 500 mg PO/IV BID Levofloxacin 500 mg PO/IV Daily (Preferred when additional viridans group streptococcal coverage indicated) Oral third generation cephalosporin Patients not able to receive a fluoroquinolone (i.e. intolerance, drug interactions, resistance)	Start of neutropenia Some protocols will start at time of chemotherapy Continue until resolution of neutropenia
Antifungal: yeast	Acute leukemia Allogeneic HSCT Pre-engraftment phase Autologous HSCT recipients with mucositis Pre-engraftment phase	Fluconazole 200–400 mg PO/IV Daily Micafungin 50–100 mg IV Daily Amphotericin B products	Start of neutropenia Continue until resolution of neutropenia

(continued)

	Who	What	When
Antifungal: mold	AML Induction Allogeneic HSCT Graft-versus-host disease (GVHD) Anticipated prolonged neutropenia of 2 weeks or greater Longstanding neutropenia immediately prior to HSCT	Posaconazole suspension 200 mg PO TID Posaconazole tablets 300 mg PO/IV BID x 1 day then daily Voriconazole 200 mg PO/IV BID Amphotericin B products Isavuconazonium	Start of neutropenia Continue until resolution of neutropenia In patients with GVHD, until resolution of GVHD
Antifungal: PCP	ALL Alemtuzumab Allogeneic HSCT recipients Corticosteroids (≥20 mg per day prednisone or equivalent for ≥4 weeks) Purine analog therapy (fludarabine) Temozolomide + radiation therapy	First-line Trimethoprim/sulfamethoxazole 1 SS (80/400 mg) PO Daily or 1 DS (160/800 mg) PO TIW Second-line Dapsone, atovaquone, pentamidine aerosol or intravenous	ALL Throughout anti-leukemic therapy Alemtuzumab Minimum of 2 months after drug discontinuation and until CD4 ≥ 200 cells/moL Allogeneic HSCT recipients At least 6 months and while on immunosuppression Corticosteroids (≥20 mg per day prednisone or equivalent for ≥4 weeks) At least while on therapy Purine analog therapy (fludarabine) Until CD4 ≥200 cells/moL Temozolomide + radiation therapy At least while on therapy

(continued)

	Who	What	When
Antiviral	Acute leukemia (seropositive for HSV or VZV or history of chicken pox) Alemtuzumab Allogeneic HSCT (seropositive donor or recipient for HSV or VZV) Allogeneic HSCT with GVHD receiving corticosteroids Autologous HSCT (seropositive for HSV or VZV) Proteasome inhibitors (bortezomib, carfilzomib, ixazomib) Purine analog therapy (fludarabine)	Acyclovir 400–800 mg PO BID Famciclovir 250 mg PO BID Valaciclovir 500 mg PO BID-TID	Acute leukemia HSV (Continue until resolution of neutropenia or mucositis, whichever occurs later) Alemtuzumab HSV (Minimum of 2 months after drug discontinuation and until CD4 $\geq$ 200 cells/moL) Allogeneic HSCT HSV (Continue until resolution of neutropenia or mucositis, whichever occurs later) VZV (For at least 1 year after HSCT) Autologous HSCT HSV (Continue until resolution of neutropenia or mucositis, whichever occurs later) VZV (6–12 months after HSCT) Proteasome inhibitors (bortezomib, carfilzomib, ixazomib) VZV (During active therapy) Purine analog therapy (fludarabine) HSV and VZV (During active therapy or longer depending on degree of immunosuppression)

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