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INFECTION PROPHYLAXIS AND TREATMENT FOR ADULT AND PEDIATRIC BONE MARROW TRANSPLANT RECIPIENTS

I. **Purpose:** BMT patients are at risk for infections in the post-transplant period.

II. **Scope:** This guideline outlines the routine infection prophylaxis for at risk patients.

III. **Guideline:**

	Phase I, Pre-engraftment, <30 days	Phase II, Post-engraftment, 30-100 days	Phase III, Late phase, >100 days
	Neutropenia, mucositis and acute GVHD	**Impaired cellular immunity and acute and chronic GVHD**	**Impaired cellular and humoral immunity and chronic GVHD**
Reactivation	Herpes Simplex Virus+	Cytomegalovirus+	
		BK Virus	
		Epstein-Barr Virus Lymphoproliferative Disease	
		HHV-6	
		HHV-7	
			Varicella-Zoster Virus
Community Aquired	HHV-6		
		Parvo B-19	
	Respiratory and Enteric Viurses		
Environmentally Aquired	Facultative Gram- Bacilli		
	GI Tract Streptococci Species		
	Staphylococcus Epidermidis		
			Encapsulated Bacteria (e.g.pneumococcus)
	All Candida Species		
	Aspergillus Species		
			Pneumocystis Carinii
		Toxoplasma Gondii	

+ Primarily among persons who are seropositive before transplant.

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<table>
<tr><th colspan="3">Table 1. Prevention of PJP and Toxoplasma</th></tr>
<tr><th colspan="3">Pathogens: Pneumocystis jiroveci and Toxoplasma*</th></tr>
<tr><th>Indication</th><th>First choice</th><th>Alternatives</th></tr>
<tr><td>All allogeneic and autologous patients

<u>Time:</u>
Start once ANC >1,000 and PLT >50,000 but no earlier than day 30.

<u>Duration (Allo):</u>
Stop at 6mo or until off IS^

<u>Duration (Auto):</u>
3-6 months</td><td><u>Adult, PJP only:</u>
TMP-SMX 1 DS tab PO BID, 2 days per week (i.e., M & Th)

<u>Adult, PJP and Toxoplasma IgG positive:</u>
TMP-SMX 1 DS tab PO BID, 3 x/week

<u>Peds:</u>
TMP-SMX 2.5 mg/kg TMP PO BID, 2 days per week (max: 160 mg TMP/dose)</td><td><u>Preferred alternative for PCP prophylaxis AND IgG Positive for Toxoplasma:</u>
Adult:
Atovaquone (Mepron) 1500 mg PO daily – take with food
Pediatric:
Atovaquone – take with food
1-3 mo or >24 mo: 30 mg/kg/day PO Daily;
4-24 mo: 45 mg/kg/day
(max: 1500 mg/dose)</td></tr>
<tr><td colspan="2" rowspan="2">*All candidates for allogeneic HSCT recipients should have a screening Toxoplasma IgG prior to transplantation.

^Patients with GvHD should be restarted or continue to receive PJP/ Toxoplasma prophylaxis

TMP-SMX : Trimethoprim-sulfamethoxazole (Bactrim)
DS tab: double strength tablet (Trimethoprim 160 mg-sulfamethoxazole 800 mg)</td><td><u>Alternative for PCP prophylaxis AND IgG Negative for Toxoplasma:</u>
Adult:
Pentamidine 300 mg inh once monthly
OR
Pentamidine 4 mg/kg IV once monthly (if unable to tolerate inhaled; dosed using actual body weight)

Pediatric:
<5 years:
Pentamidine 9 mg/kg inh once monthly (max: 300 mg)
OR
Pentamidine 4 mg/kg IV once monthly (if unable to tolerate inhaled; dosed using actual body weight)

≥5 years:
Pentamidine 300 mg inh once monthly
OR
Pentamidine 4 mg/kg IV once monthly (if unable to tolerate inhaled; dosed using actual body weight)</td></tr>
<tr><td><u>Alternative for PJP prophylaxis AND IgG Negative for Toxoplasma:</u>
Adult:
Dapsone 100 mg PO daily (G6PD screening recommended for all patients; contraindicated in patients with hypersensitivity to sulfa)

Pediatric:
Dapsone 2 mg/kg/dose PO daily (max: 100 mg/dose) (G6PD screening recommended for all patients; contraindicated in patients with hypersensitivity to sulfa)

*Be aware of increased risk of methemoglobinemia</td></tr>
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Table 2. Prevention of Fungal (Yeast and Mold) Infections			
Indication	**First Choice**	**Alternative**	**Duration**
All patients (except cord, haplo, or mismatched) **Starting on admission**	Adults: **Fluconazole** 200 mg PO/IV Daily Pediatric: **Fluconazole** 3 mg/kg PO/IV Daily (max: 200 mg)	If AST/ALT/T. Bili >3x ULN or otherwise deemed clinically significant, consider: *Adults:* **Micafungin** 50 mg IV q24h *Pediatric:* **Micafungin** 3-4 mg/kg IV q24h (max: 50 mg)	Auto: Until ANC >1000 x3 days Allo: Until day +100, off immunosuppression or on broader antifungal
Scenario 1: All cord, haplo, mismatched transplant recipients or ATG, thymoglobulin, and alemtuzumab conditioning regimens Scenario 2: Patients with prolonged neutropenia (≥30 days) entering transplant **Starting on admission**	Adults: **Micafungin** 100 mg IV q24h, then **Voriconazole** 200 mg PO/IV◆ BID starting day +5-10[α] Pediatric: **Micafungin** 5 mg/kg IV q24h, then **Voriconazole** 8 mg/kg PO/IV◆ BID (TID if ≤8 years old) starting day +5-10 [α] [α]Transition to voriconazole can be delayed if AST/ALT/T. Bili >3x ULN or otherwise deemed clinically significant	If intolerance to voriconazole** OR insurance does not cover voriconazole: *Adults:* **Posaconazole** delayed-release tabs 300 mg PO/IV◆ daily *Pediatric:* **Posaconazole** delayed-release tabs: <40 kg: 100 mg PO BID; 40-60 kg: 200 mg BID; >60 kg: 300 mg BID Isavuconazole is not recommended at this time due to reports of breakthrough infection. May be considered if >15 years AND >50 kg AND either QTc>500, hepatotoxicity to vori/posa, or insurance does not cover vori/posa: **Isavuconazole** 372 mg PO/IV◆ daily Sickle Cell Pts: avoid voriconazole	Scenario 1: Continue until day +100 or on broader fungal coverage Note: If still on immunosuppression when mold-active agent discontinued, will switch to Fluconazole (same dosing as above) until off immunosuppression. Scenario 2: Until ANC >1000 x3 days
Allogeneic patients with GvHD or engraftment syndrome receiving additional immunosuppression (systemic steroids ≥0.25 mg/kg, infliximab, ruxolitinib, etc.)	Adults: **Voriconazole** 200 mg PO/IV◆ BID Pediatric: **Voriconazole** 8 mg/kg PO/IV◆ BID (TID if ≤8 years old)	If concern for liver GvHD (AST/ALT/T. Bili >3x ULN): *Adults:* **Micafungin** 100 mg IV q24h *Pediatric:* **Micafungin** 5 mg/kg IV q24h (max: 100 mg) If intolerance to voriconazole** OR insurance does not cover voriconazole: *Adults:* **Posaconazole** delayed-release tabs 300 mg PO/IV◆ daily *Pediatric:* **Posaconazole** delayed-release tabs: <40 kg: 100 mg PO BID; 40-60 kg: 200 mg BID; >60 kg: 300 mg BID Isavuconazole is not recommended at this time due to reports of breakthrough infection. May be considered if >15 y/o AND >50 kg AND either QTc>500, hepatotoxicity to vori/posa, or insurance does not cover vori/posa. **Isavuconazole** 372 mg PO/IV◆ daily	Discontinue when off additional GvHD-related immunosuppression (or <10 mg/day prednisone (adults) or 0.15 mg/kg/day (pediatric) for >30 days). See footnote^ for prophylaxis duration after other GvHD-related immunosuppression.

***Trough levels of voriconazole, isavuconazole, and posaconazole should be drawn after 5-7 days. Refer to guideline on therapeutic drug monitoring of antifungal agents

^ Alemtuzumab and Anti-thymocyte globulin (6 months);
Infliximab, Tocilizumab, Etanercept, Adalimumab, Basiliximab, Vedolizumab (3 months)
ECP, Ruxolitinib (1 month)

**Intolerance to voriconazole is defined as presence of visual hallucinations despite normal levels or hepatotoxicity attributed to voriconazole

◆IV azole preferred over micafungin in high risk patients who are NPO with an expected duration of treatment >5 days. Change to PO azole when appropriate.

Table 3. Prevention of Bacterial Infections			
Pathogen	**Indications**	**First choice**	**Duration**
Bacterial prophylaxis	All Autologous and Allogeneic transplant recipients <u>starting D+1</u>	<u>Adult:</u> **Levofloxacin** 500 mg PO/IV daily <u>Pediatric:</u> *<5 years:* **Levofloxacin** 10 mg/kg PO/IV BID (max: 375 mg/dose) *≥5 years:* **Levofloxacin** 10 mg/kg PO/IV daily (max: 500 mg/dose) <u>Alternative for FQ Allergy/Intolerance:</u> *Adult:* **Cefpodoxime** 200 mg PO BID *Pediatric:* **Cefpodoxime** 5 mg/kg PO BID (max: 200 mg/dose)	Pre-engraftment prophylaxis, continue until: 1. Fever and Neutropenia (i.e., broader antimicrobial such as cefepime, etc.) 2. Engraftment◆
	Patients to be started on levofloxacin as prophylaxis post-transplant for the following indications: 1. Acute GvHD with <u>GI involvement</u> 2. Pancytopenia 2/2 graft failure		GI GvHD: Continue until normal PO intake Pancytopenia: Until count recovery
Encapsulated organisms	Recipients with chronic GvHD, s/p splenectomy, functionally asplenic, or sickle cell disease	<u>Adults:</u> **Penicillin VK** 500 mg PO BID <u>Pediatric:</u> *≥10 years:* **Penicillin VK** 500 mg PO BID *3-10 years:* **Penicillin VK** 250 mg PO BID *<3 years* **Penicillin VK** 125 mg PO BID <u>Alternative (Penicillin allergy):</u> *Adults:* **Azithromycin** 250 mg PO daily OR **TMP-SMX** 1 DS PO daily *Peds:* **Azithromycin** 5 mg/kg PO daily (max: 250 mg) OR **TMP-SMX** 2.5 mg TMP/kg BID, 2 days per week (max: 160 mg TMP/dose)	1. Off Immunosuppression for 1 month and asymptomatic 2. <u>Hold while on levofloxacin</u> <u>Lifelong if:</u> 1. s/p splenectomy 2. extensive cGvHD
Immunoglobulin Supplementation	IgG <400 mg/dL	**IVIG** 0.4 g/kg/dose based on ideal body wt	Monitor monthly until IgG >400 for 2 months
◆Absolute neutrophil count ≥1000/mm^3 for 3 consecutive days			

Table 4. Prevention of Viral Infections			
Pathogen	**Indication**	**First Choice**	**Duration**
Herpes Simplex Virus (HSV)	All seropositive recipients <u>(starting day 0)</u>	<u>Adult:</u> **Acyclovir*** 400 mg PO BID or 200 mg IV q12h <u>Pediatric:</u> *≥6 years:* **Acyclovir*** 400 mg PO BID or 200 mg IV q12h or 2.5 mg/kg IV q12h *<6 years:* **Acyclovir*** 200 mg PO BID or 2.5 mg/kg IV q12h <u>Alternative (Acyclovir allergy) - Famciclovir</u> *Adults:* **Famciclovir** 250 mg PO BID	1. Stop day +30 if only HSV 2. Stop at 1-year if VZV+ and HSV+ (recipient)
Cytomegalovirus (CMV)	Monitoring	Weekly quantitative CMV plasma PCR Starting day +7 for patients meeting 'additional risk factors' identified below or with conditioning for high risk pediatric pts (i.e., intermediate or distal alemtuzumab) OR At day +21 for all patients less than 18 years and adults not meeting high-risk criteria below.	1. Off immunosuppression or minimal immunosuppression (low dose tacro, etc.)
	Seropositive allogeneic recipient with additional risk factors: • Cord blood transplant recipient, Receipt of T-cell depleting agent (alemtuzumab, thymoglobulin, ATG), T-cell depleted stem cell sources (i.e., haploidentical transplants, in-vivo or ex-vivo depletion) • **Letermovir** starting Day +10 **Seropositive** allogeneic recipient without additional risk factors: • **Letermovir** to start at Day 21/discharge unless additional immunosuppression added (i.e., engraftment syndrome, aGVHD, etc)	<u>Adult:</u> **Letermovir**^ 480 mg PO/IV daily (240 mg daily with cyclosporine) *CONTINUE ACYCLOVIR WHILE ON LETERMOVIR FOR HSV COVERAGE.* Outpatient insurance coverage for letermovir should be verified prior to initiation. *All other uses of letermovir require approval by transplant infectious diseases.* *Letermovir is not approved for pediatric patients (<18 years)*	1. Continue for 3 months after initiation 2. On broader antiviral (**ganciclovir**, **valganciclovir**, **foscarnet**, full dose **cidofovir**) 3. In patients who develop GvHD within 100 days, may consider extending duration to 3 months from GvHD diagnosis.
Varicella-Zoster Virus (VZV)	All recipients with a history of chickenpox, zoster, or positive serology, <u>starting day +30</u> Pediatric patients with a history of VZV vaccine who are seropositive pre-transplant <u>DO NOT</u> need therapy.	See above HSV section	1. Until +1 year and off immunosuppression

*(Val)Acyclovir/Famciclovir should be held if patient is on ganciclovir, valganciclovir, foscarnet or full dose cidofovir but should continue if patient is on Letermovir
^Letermovir should be held if patient is being treated for CMV (see flowchart); Letermovir should be stopped after 2 separate CMV reactivations (PCR >3000) requiring treatment.

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EBV Reactivation Screening Guidelines for Stem Cell Transplant Recipients

- Guidelines to be followed for high risk patients only

Screening Guidelines

- Send quantitative EBV PCR every other week (plasma assay)
- Start testing on day +7 (adults) or with conditioning for high risk pediatric pts (i.e., recent alemtuzumab) and continue through D+100

Reactivation Guidelines

- *Consider* starting treatment with rituximab if EBV copy number >1000 IU/mL on 2 consecutive tests or if symptomatic (fever, lymphadenopathy)
- If copy number >1000 IU/mL
    - Consider CT of chest/abdomen/pelvis
    - Request EBV serostatus on the donor
    - Start **Rituximab** (dose for all patients = 375 mg/m^2); *additional doses should be given if EBV PCR remains positive 1 week after Rituximab is given (i.e., continue rituximab until PCR negative and asymptomatic)*
    - Recommend reduction in immunosuppression if clinical situation allows
    - Ganciclovir treatment is not recommended
- If EBV reactivation leads to PTLD
    - Continue **Rituximab** weekly with consideration for additional chemotherapeutic agents (CHOP based therapy)
    - If donor is seropositive, consideration should be given to donor lymphocyte infusion
    - CNS disease, consideration can be given to intrathecal **Rituximab** (Dose = 12-50 mg)
    - Recommend reduction in immunosuppression if clinical situation allows

Treatment of Toxoplasmosis

If a patient develops new CNS or new neurologic symptoms concerning for infection, recommend sending *Toxoplasma* PCR at that time. If PCR positive, treat as listed below.

Indication	First Choice	Alternative for sulfa allergy
* Positive *Toxoplasma* quantitative plasma PCR	Adult: **Pyrimethamine** 200 mg PO loading dose then 75 mg PO daily + **Sulfadiazine** 1 g PO QID + **Leucovorin** 25 mg daily† Pediatric: **Pyrimethamine** 1 mg/kg/dose PO BID (max: 50 mg/dose) x2 days, then 1 mg/kg daily (max: 75 mg/dose) + **Sulfadiazine** 50 mg/kg/dose PO QID (max: 1 g/dose) + **leucovorin** 25 mg daily†	**Pyrimethamine** + **Leucovorin** as per first choice + one of the following: **Clindamycin** IV/PO 1,800 – 2,700 mg/day divided q6-8h OR **Dapsone** 100 mg PO daily OR **Azithromycin** 1,250 mg PO daily†

† Treat for minimum of 7 days after PCR has become negative

* Consider infectious disease consultation

IV. **Diagnostic Testing Guidelines**

a. In general, quantitative viral PCR testing (e.g., CMV) does not provides clinically usefully information when repeated more frequently than weekly. In patients with low positive HHV-6 plasma PCR assays (<2500 copies/mL), more frequent repeat testing is indicated as a rising titer may result in earlier institution of treatment. In patients for whom viral monitoring is required, recommend serial testing on Mondays.
b. While case reports have demonstrated rare disease associated with HHV-7 (e.g., encephalitis), the significance of HHV-7 viremia (5%-57% of patients at least one-time point) is unknown. Measurement of HHV-7 for undifferentiated fever is unlikely to be clinically useful.
c. HHV-8 is primarily associated with Kaposi's sarcoma (0.5% of post HSCT patients) and should not be measured routinely.
d. Limited studies on the use of quantitative PCR for CMV on stool have been conducted, the assay is not standardized, and clinical utility is unknown.
e. Weekly screening galactomannan levels in patients on prophylaxis with voriconazole, posaconazole, isavuconazole, or micafungin will <u>not</u> be sent. Symptom based testing would be appropriate.

V. HHV-6 Guidelines

a. HHV-6 infection may result in encephalitis after allogeneic stem cell transplant and has been associated with delayed engraftment, pneumonitis, fever and rash. Asymptomatic reactivation occurs in about 50% of patients. The following principles guide our approach to HHV-6.
    i. HHV-6 viremia should not be routinely monitored
    ii. In patients in which there is clinical suspicion for HHV-6 related disease (e.g., encephalitis early after transplant, delayed engraftment, rash and fever without other explanation) a quantitative plasma PCR for HHV-6 should be obtained.
    iii. Treatment with foscarnet, ganciclovir (post-engraftment with adequate blood counts) or cidofovir should be considered if:
        1. Single value >5,000 copies/mL
        2. Doubling of HHV-6 PCR on serial measurement and >2500 copies/mL (serial measurement should be performed as soon as positive titer received)
        3. Transplant ID consultation recommended if treatment considered
        4. Patients at high risk for graft failure or delayed engraftment (cord blood transplants, low dose grafts, HLA mismatched grafts) may benefit most from treatment.

VI. Adenovirus Guidelines

a. Adenovirus infection may result in severe respiratory disease, hepatitis, and colitis after allogeneic stem cell transplant and disease has been associated with high rates of mortality. The incidence of adenovirus infections is higher in pediatric patients (20-26%) undergoing HSCT than in adults (9%). <u>The following principles guide our approach to Adenovirus:</u>
b. Adenovirus serum PCR should be monitored weekly in high risk patients starting on day +7 (adults) or with conditioning for high risk pediatric pts (i.e., intermediate or distal alemtuzumab)
    i. Routine monitoring is not recommended in all other patients
c. In patients in which there is a clinical suspicion for adenovirus related disease (e.g., severe diarrhea or pneumonia, delayed engraftment, etc.) or RPAN or GI PCR positive for adenovirus, a quantitative plasma PCR for adenovirus should be obtained.
    i. Note: RPAN and GI PCR test for different subtypes of adenovirus and may produce discordant results
d. Treatment should be considered if:

i. Single positive PCR value or doubling of adenovirus PCR on serial measurements
ii. Diarrhea with GI PCR positive for adenovirus in the absence of alternative etiology
iii. Pneumonia with RPAN PCR positive for adenovirus in the absence of alternative etiology

e. *Consultation to transplant ID* is highly recommended to assist in treatment decision
f. Patients at high risk for graft failure or delayed engraftment (cord blood transplants, low dose grafts, HLA mismatched grafts) may benefit most from treatment.
g. Treatment:
   i. Adult: **Cidofovir** 5 mg/kg IV weekly x2 doses then every other week with prehydration and oral **probenecid** 2 g, 2 hours prior to cidofovir, and 1 g 1 & 4 hours after completion of cidofovir.
   ii. Pediatric: **Cidofovir** 5 mg/kg IV weekly x2 doses then every other week with prehydration and oral **probenecid** 30 mg/kg (min: 250 mg; max: 2 g) 2 hours prior to cidofovir dose and 15 mg/kg (min: 250 mg, max: 1 g) 1 & 4 hours after completion of cidofovir. OK to crush tablet and mix with food or water prior to administration if needed.

VII. References

a. Guidelines for Preventing Infectious Complications among Hematopoietic Cell Transplant Recipients: A Global Perspective. Biology of blood and marrow transplantation: journal of the American Society for Blood and Marrow Transplantation. 2009;15(10):1143-1238.
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Authors:
Gianni Scappaticci, PharmD
David Frame, PharmD
Twisha Patel, PharmD
Gregory Eschenauer, PharmD
Reviewers:
Bone Marrow Transplant
Transplant Infectious Diseases
Additional approvers:
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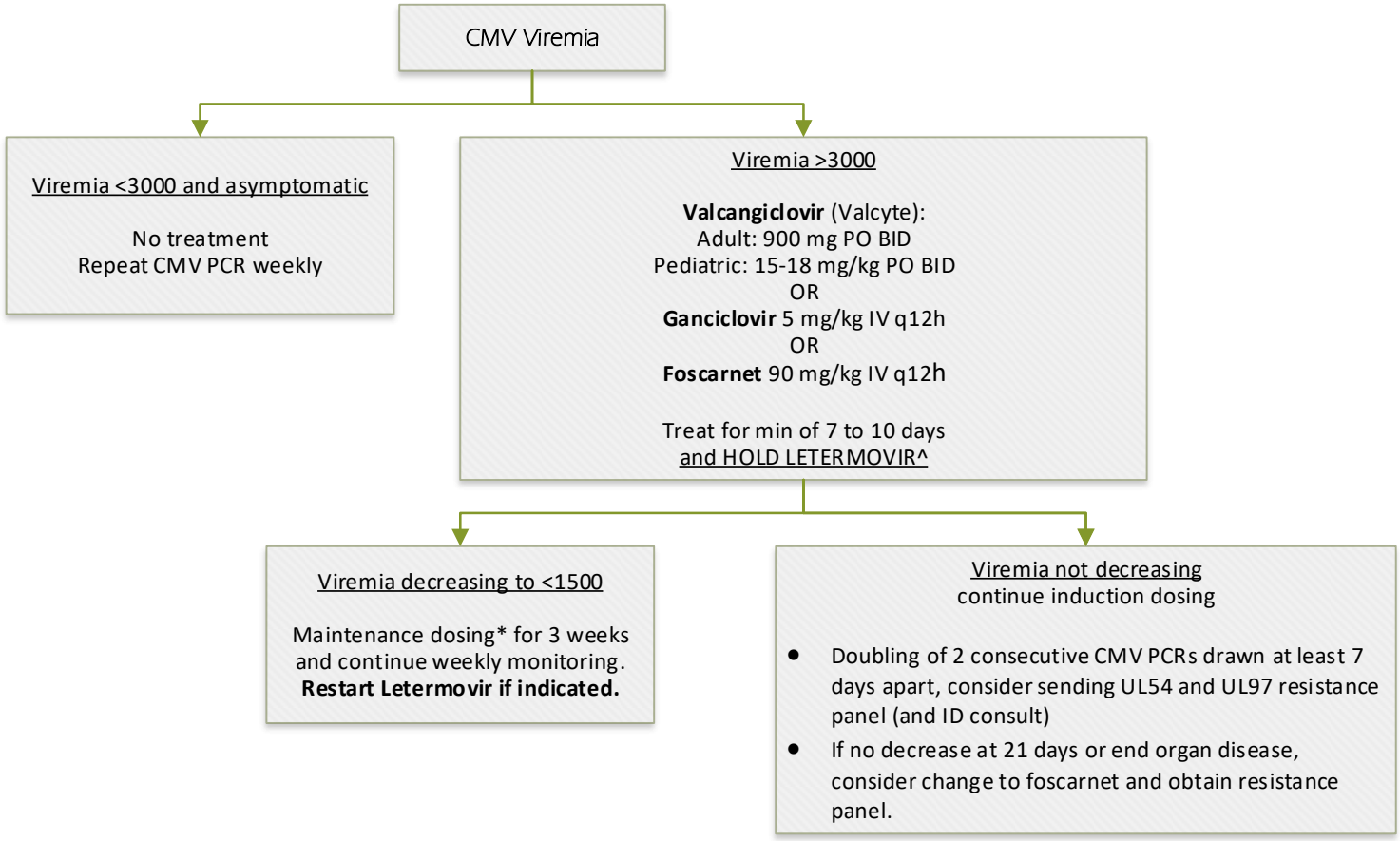
Figure 1: CMV Viremia detected in patient undergoing preemptive monitoring



* Maintenance dosing- **Valganciclovir** 900 mg PO daily, **Ganciclovir** 5 mg/kg IV q24h, **Foscarnet** 90 mg/kg IV daily
Acyclovir should be held if patient is on ganciclovir, valganciclovir, foscarnet, or full dose cidofovir but should continue if patient is on Letermovir

^ Letermovir should be stopped after 2 separate CMV reactivations (PCR >3000) requiring treatment. In patients on letermovir who do not develop GvHD, letermovir should be stopped at day +100.

Table 6. Goal trough levels for voriconazole, isavuconazole, and posaconazole (ordered 5-7 days after starting)

Antifungal	Prophylaxis	Treatment
Voriconazole	>1 mcg/mL	>1 mcg/mL
Isavuconazole	>1 mcg/mL	>1 mcg/mL
Posaconazole	>700 ng/mL	>1,250 ng/mL

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Revision History: 02/21: Adjusted letermovir criteria 01/22: Adjusted pediatric acyclovir dosing	