Anti-Infective Prophylaxis in SCT Recipients

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I. Autologous

	Drug	Dose -Adjustments	Initiation	Duration	Alternatives for medication allergies or intolerance
Bacterial	Levofloxacin	500mg PO q24h -renal	Day -3 (Day -1 for Auto Mel)	Until neutrophil engraftment (ANC ≥ 500/µL x3 consecutive days or ANC ≥ 1000/µL x1 day) OR initiation of febrile neutropenia treatment	Cefpodoxime 200mg PO q12h or ceftriaxone 1000mg IV q24h
Fungal[1]	Fluconazole	400mg PO q24h -renal	Day -3 (Day -1 for Auto Mel)	Until neutrophil engraftment (ANC ≥ 500/µL x3 consecutive days or ANC ≥ 1000/µL x1 day)	Micafungin 50mg IV q24h
Viral	Acyclovir	800mg PO q12h -renal	Admission	6 months post-SCT[2]	Valacyclovir 500mg PO q12h
HBV	Lamivudine	100mg PO q24h -renal	If HBcAb+ and no detectable HBV DNA or HBsAg; start on admission	6 months post-SCT	Entecavir 0.5mg PO q24h or tenofovir alafenamide 25 mg PO daily if lamivudine resistance is suspected or if HBsAg positive
PJP	Sulfamethoxazole/ Trimethoprim	1 DS tab PO TIW	Day+30 or when ANC ≥ 1000/µL and Plt ≥ $50x10^9$/L	3-6 months post-SCT	1st line: Pentamidine 4mg/kg IV q4wk 2nd line: Atovaquone 1500mg PO q24h or dapsone 100mg PO q24h
Mycobacterium Tuberculosis (TB)	Isoniazid (plus pyridoxine) or monitor for active TB	5 mg/kg/day (max: 300 mg/day) PO q24h (plus 25 mg PO q24h)	If exposed to active, infectious TB, or TST+, or IGRA+	Treat for 9 months total	May monitor on a case by case basis if prophylaxis is not warranted. Consult ID prior to initiation and if alternatives are needed

Key- PJP: *Pneumocystis jirovecii* pneumonia; HBV: Hepatitis B virus; TST: tuberculin skin tests; IGRA: interferon-gamma release assays

[1]Anti-fungal recommendations above are for primary prophylaxis. For secondary prophylaxis, consider providing prophylaxis with the same anti-fungal used for initial treatment.

[2]If history of VZV reactivation, continue viral prophylaxis for 1 year post-SCT.

II. Allogeneic

	Drug	Dose -Adjustments	Initiation	Duration	Alternatives for medication allergies or intolerance
Bacterial	Levofloxacin	500mg PO q24h -renal	Day -3	Until neutrophil engraftment (ANC ≥ 500/µL x3 consecutive days or ANC ≥ 1000/µL x1 day) OR initiation of febrile neutropenia treatment	Cefpodoxime 200mg PO q12h or ceftriaxone 1000mg IV q24h

	Drug	Dose -Adjustments	Initiation	Duration	Alternatives for medication allergies or intolerance
Fungal[1]	Fluconazole	400mg PO q24h -renal	Day -3; *voriconazole for haploidentical, UCB, delayed engraftment (ANC ≤ 0.2/μL for >2wks), active acute leukemia or prolonged neutropenia (ANC ≤ 500/μL for >2 wks) at time of transplant	Until immunosuppression/GVHD prophylaxis discontinuation	If drug interactions (e.g., busulfan, vinca alkaloids) are present may delay initiation of azole (e.g., voriconazole or posaconazole) or initiate micafungin 50mg IV q24h temporarily. Consider checking Asp GM weekly in patients not receiving anti-mold prophylaxis.
	Voriconazole*	200mg PO q12h -hepatic -trough levels			
Viral	Acyclovir	800mg PO q12h -renal	Admission	3 months after immunosuppression discontinuation and CD4≥200cell/mm3[2]	Valacyclovir 500mg PO q12h
HBV	Lamivudine	100mg PO q24h -renal	If HBcAb+ and no detectable HBV DNA or HBsAg; start on admission	12 months post-SCT or 6 months after immunosuppression discontinuation. Consider checking HBsAb titers and delay discontinuation if <10 IU/L.	Entecavir 0.5mg PO q24h or tenofovir alafenamide 25 mg PO daily if lamivudine resistance is suspected or if HBsAg positive
PJP	Sulfamethoxazole/ Trimethoprim	1 DS tab PO TIW	Day+30 or when ANC ≥ 1000/μL and Plt ≥ 50x10^9/L	Until immunosuppression/GVHD prophylaxis discontinuation and CD4 ≥200 cells/mm3	1st line: Pentamidine 4mg/kg IV q4wk[3] 2nd line: Atovaquone 1,500mg PO q24h or dapsone 100mg PO q24h[3]
Toxoplasma (Only for IgG Ab+ patients)	Sulfamethoxazole/ Trimethoprim	1 DS tab PO TIW	Pre-emptive approach from admission until day+30: Toxoplasma DNA PCR weekly then initiate sulfamethoxazole/ trimethoprim	Until immunosuppression/GVHD prophylaxis discontinuation and CD4≥200 cells/mm3	Atovaquone 1500mg PO q24h or if unable to tolerate either medication monitor DNA PCR at each visit
CMV	Pre-emptive approach		Day +10 -day+99: CMV PCR qMon/Thurs (may decrease to weekly outpatient)[4]	12 months post-SCT	If reactivation occurs, increase frequency to once weekly until off CMV active therapy
			≥day+100: at each visit (max: 2x/week) for high risk of late CMV reactivation patients[5]; otherwise only if signs or symptoms of CMV		
Strongyloides	Ivermectin	200mcg/kg PO q2wks x2 doses[6]	1st and 2nd dose 2 wks apart prior to SCT; Treat if either Ab is positive or with unexplained eosinophilia and travel or residence history to endemic areas (tropics, subtropics, southeastern US or Europe)	Check stool O&P x3 if GI symptoms/diarrhea	
Mycobacterium Tuberculosis (TB)	Isoniazid (plus pyridoxine)	5 mg/kg/day (max: 300 mg/day) PO	If exposed to active, infectious TB, or TST+, or IGRA+	Treat for 9 months total	Consult ID prior to initiation and if

	Drug	Dose -Adjustments	Initiation	Duration	Alternatives for medication allergies or intolerance
		q24h (plus 25 mg PO q24h)			alternatives are needed

Key- PJP: *Pneumocystis jirovecii* pneumonia; HBV: Hepatitis B virus; CMV: cytomegalovirus; Ab: antibody; UCB: umbilical cord blood; Asp GM: Aspergillus galactomannan; TST: tuberculin skin tests; IGRA: interferon-gamma release assays

[1]Anti-fungal recommendations above are for primary prophylaxis. For secondary prophylaxis, consider providing prophylaxis with the same anti-fungal used for initial treatment.
[2]If history of VZV reactivation, continue viral prophylaxis until all of the following criteria are met: 1 year post-SCT, immunosuppression discontinuation, and CD4≥200 cells/mm3
[3]If toxoplasmosis IgG antibody positive; atovaquone is the only alternative to sulfamethoxazole/trimethoprim
[4]High risk for CMV reactivation: T-cell depletion (e.g., ATG, alemtuzumab), receiving ≥2 immunosuppressive agents, prior CMV reactivation/disease
[5]Risk factors for late CMV reactivation: recurrent reactivations (≥2 reactivations post-SCT), mismatched or unrelated donor, UCB, CMV-seronegative graft, lymphopenia at day +100, history of a lymphoid malignancy, ongoing acute or chronic GVHD
[6]If HTLV-1 seropositive, continue ivermectin once monthly until immunosuppression discontinuation

III. GVHD Requiring Systemic Treatment

	Drug	Dose -Adjustments	Initiation	Duration	Alternatives
Bacterial	Levofloxacin	500mg PO q24h -renal	Prednisone dose ≥0.5mg/kg/day	Until prednisone dose <0.25mg/kg/day	Amoxicillin 875mg PO q12h or Penicillin VK 250mg PO q12h
Fungal[1]	Posaconazole	300mg PO q24h -trough levels	Initiation of immunosuppression	Until prednisone dose <0.25mg/kg/day	Check Asp GM weekly inpatient and then at each outpatient visit in patients not receiving anti-mold prophylaxis. If previously on voriconazole, may continue as prophylaxis.
Viral	Acyclovir	800mg PO q12h -renal	Initiation of immunosuppression	3 months after immunosuppression discontinuation and CD4≥200cell/mm3[2]	Valacyclovir 500mg PO q12h
HBV	Lamivudine	100mg PO q24h -renal	If HBcAb+ and no detectable HBV DNA or HBsAg	Until 6 months after immunosuppression discontinuation. Consider checking HBsAb titers and delay discontinuation if <10 IU/L.	Entecavir 0.5mg PO q24h or tenofovir alafenamide 25 mg PO daily if lamivudine resistance is suspected or if HBsAg positive
PJP	Sulfamethoxazole/ Trimethoprim	1 DS tab PO TIW	Initiation of immunosuppression	Until immunosuppression discontinuation and CD4 ≥200 cells/mm3	Atovaquone 1500mg PO q24h or dapsone 100mg PO q24h or Pentamidine 4mg/kg IV q4wk
Toxoplasma (Only for IgG Ab+ patients)	Sulfamethoxazole/ Trimethoprim	1 DS tab PO TIW	Initiation of immunosuppression	Until immunosuppression discontinuation and CD4 ≥200 cells/mm3	Atovaquone 1500mg PO q24h or if unable to tolerate either medication monitor DNA PCR at each visit
CMV	Pre-emptive approach		<day+100: CMV PCR qMon/Thurs (may decrease to weekly outpatient)[2] ≥day+100: at each visit (max: 2x/week)	Until immunosuppression discontinuation	If reactivation occurs, increase frequency to once weekly until off CMV active therapy.

	Drug	Dose -Adjustments	Initiation	Duration	Alternatives
Mycobacterium Tuberculosis (TB)	Isoniazid (plus pyridoxine)	5 mg/kg/day (max: 300 mg/day) PO q24h (plus 25 mg PO q24h)	If exposed to active, infectious TB, or TST+, or IGRA+	Treat for 9 months; may continue until prednisone dose <0.25mg/kg/day	Consult ID prior to initiation and if alternatives are needed

Key- PCP: *Pneumocystis jirovecii* pneumonia; HBV: Hepatitis B virus; CMV: cytomegalovirus; Ab: antibody; UCB: umbilical cord blood; Asp GM: Aspergillus galactomannan; TST: tuberculin skin tests; IGRA: interferon-gamma release assays

[1]Anti-fungal recommendations above are for primary prophylaxis. For secondary prophylaxis, consider providing prophylaxis with the same anti-fungal used for initial treatment.

[2] High risk for CMV reactivation: T-cell depletion (e.g., ATG, alemtuzumab), receiving ≥2 immunosuppressive agents, prior CMV reactivation/disease, prednisone ≥1mg/kg/day (or equivalent), acute GVHD grade 3-4

IV. Drug Appendix

DRUG	ORAL DOSE -Dose adjustments -Dosage forms	IV or INH DOSE -Dose adjustments -Rounding	WARNINGS/PRECAUTIONS	MONITORING	COMMENTS
Antibiotics					
Levofloxacin (Levaquin)	500mg PO Q24h CrCl 30-50mL/min: 250mg PO Q24h CrCl < 30mL/min & HD: 250mg PO Q48h CRRT: 250mg PO Q24h 250mg, 500mg, 750mg, 25mg/mL	500mg IV Q24h CrCl 30-50mL/min: 250mg IV Q24h CrCl < 30mL/min & HD: 250mg IV Q48h CRRT: 250mg IV Q24h N/A	QT prolongation, glucose regulation, hepatotoxicity, photosensitivity, superinfection, tendon inflammation/rupture, peripheral neuropathy, CNS effects, exacerbate myasthenia gravis	Renal function	Avoid Mg^{2+}, Ca^{2+}, Al^{3+} containing antacids, iron, zinc, and sucralfate – decrease quinolone absorption (separate administration by ≥2 hrs)
Amoxicillin (Moxatag)	875mg PO Q12h CrCl 10-30mL/min: 500mg PO Q12h CrCl <10mL/min: 500mg PO Q24h HD: 500mg PO Q24h w/ an additional dose during and after HD 500mg, 875mg Various oral susp	N/A N/A N/A	Superinfections, anaphylaxis/hypersensitivity reactions	Renal function, liver function tests, and CBC with prolonged therapy	Suspension may be mixed with formula, milk, fruit juice, water, ginger ale or cold drinks; administer immediately after mixing
Cefpodoxime (Vantin)	200mg PO Q12h CrCl< 30mL/min: 200mg PO Q24h HD: 200mg 3x/week post-dialysis 100mg, 200mg, 100mg/5mL	N/A N/A N/A	Superinfection	Renal function	Penicillin derivative
Ceftriaxone (Rocephin)	N/A N/A 1gram, 2 gram	1,000mg IV Q24h If concurrent renal and hepatic failure, max dose 2grams/day Nearest 1gram	Hypersensitivity reactions, elevated INR, hemolytic anemia, pancreatitis, superinfection,	INR	May precipitate with calcium containing solutions; do not administer concurrently
Penicillin VK (Veetids)	250mg PO Q12h N/A 250mg, 250mg/5mL	N/A N/A N/A	Superinfection, seizure risk	None	Hypersensitivity reactions
Anti-Fungals					
Fluconazole (Diflucan)	400mg PO Q24h CrCl < 30mL/min: 200mg PO Q24h 100mg, 200mg, 40mg/mL	400mg IV Q24h CrCl < 30mL/min: 200mg IV Q24h CRRT: 400mg IV Q24h Round to nearest 200mg	CNS effects, QT Prolongation, skin reactions, hepatotoxicity	Liver function tests, renal function	Inhibits CYP1A2 (weak), CYP2C19 (strong), CYP2C9 (strong), CYP3A4 (moderate) Risk of potential drug interactions
Micafungin (Mycamine)	N/A N/A N/A	50mg IV Q24h N/A N/A	Hemolytic anemia/hemoglobinuria, hepatic and renal impairment	Liver function tests	Inhibits CYP3A4 (weak)

DRUG	ORAL DOSE -Dose adjustments -Dosage forms	IV or INH DOSE -Dose adjustments -Rounding	WARNINGS/PRECAUTIONS	MONITORING	COMMENTS
Posaconazole (Noxafil)	300mg PO q24h Variability in exposure observed with CrCl <20 mL/min 100 mg DR tab	300mg IV q24h N/A 300mg/16.7mL	QT prolongation, hepatic impairment, GI disturbances	Goal trough (after 7 days of prophylaxis) for prophylaxis: >0.7 mcg/mL Treatment: >1-2 mcg/mL	Inhibits CYP3A4 (strong).Risk for potential drug interactions. Administer with food. Avoid use of suspension due to limited absorption.
Voriconazole (Vfend)	200mg PO Q12h Consider for liver dysfunction 50mg, 200mg, 200mg/5mL	200mg IV Q12h Consider for liver dysfunction N/A	QT prolongation, dermatologic reactions, hallucinations, ocular disturbances, hepatic impairment, pancreatitis	Goal trough (after 7 days of prophylaxis) for prophylaxis: >1 mcg/mL Treatment: 2-5.5 mcg/mL	Inhibits CYP2C19 (moderate), CYP2C9 (moderate), CYP3A4 (strong). Risk for potential drug interactions. Administer 1 hour before or after meals.
Anti-Virals					
Valacyclovir (Valtrex)	500mg PO Q12h CrCl < 30mL/min: 500mg PO Q24h HD: 500mg 3x/week post dialysis CRRT: 500mg PO Q24h 500mg, 1000mg	N/A N/A N/A	Renal impairment, urinary precipitation, CNS effects, thrombocytopenic purpura/hemolytic uremic syndrome (at doses of 8 grams/day)	Renal function, CBC, mental status changes	Nephrotoxic (maintain adequate hydration).
Acyclovir (Zovirax)	800mg PO Q12h CrCl 10-30mL/min: 400mg PO Q12h CrCl < 10 mL/min: 200mg PO Q12h 200mg, 800mg, 200mg/5mL	400mg IV Q12h OR 5mg/kg IV Q12h CrCl 10-30mL/min: 5mg/kg IV Q24h CrCl < 10mL/min & HD: 2.5mg/kg IV Q24h CRRT: 5mg/kg IV Q24h round to nearest 50mg	Renal impairment, thrombocytopenic purpura/hemolytic uremic syndrome	Renal function, CBC, mental status changes	Nephrotoxic with IV formulation (maintain adequate hydration). Dose based on IBW or Adjusted BW.
Anti-PJP					
Sulfamethoxazole (SMX)/ Trimethoprim (TMP) (Bactrim)	1 DS tab PO TIW (3x/week) N/A Single strength (SS): 400-80mg tab DS: 800-160mg tab Soln: 200-40mg/5mL	N/A N/A N/A	Delayed engraftment, blood dyscrasias, myelosuppression, hypersensitivity, rash, hyperkalemia, nephritis, hepatitis, pancreatitis, superinfection	Renal function, potassium, CBC	Mild to moderate hypersensitivity reactions: Desensitization protocol available. Dosage forms 5:1 ratio (SMX:TMP). Provides additional coverage for *Nocardia sp.*, *Toxoplasma gondii* and *Stenotrophomonas maltophilia* and others
Dapsone	100mg PO Q24h OR 50mg PO Q12h No 25mg, 100mg	N/A N/A N/A	Blood dyscrasias (especially with G6PD deficiency), rash, sulfonamide allergy, peripheral neuropathy, superinfection	G6PD levels prior to initiation, CBC, jaundice & hemolysis	Caution: G6PD deficiency, hemoglobin M deficiency, methemoglobin reductase deficiency
Atovaquone (Mepron)	1500mg PO Q24h with food No 750mg/5mL	N/A N/A N/A	Hepatic impairment	CNS or respiratory changes	Diarrhea/vomiting/GI GVHD (decrease absorption). Administer after a fatty meal.
Pentamidine (Nebupent, Pentam)	N/A N/A	4mg/kg IV/Inh Q4wks OR 300mg IV/Inh Q4wks N/A	Inh: bronchospasms, asthma exacerbations IV: QT prolongation, hypotension, cardiovascular disease, diabetes, pancreatitis, hypocalcemia,	Liver function tests, renal function, blood glucose, serum potassium	IV is preferred over Inh route of administration.

DRUG	ORAL DOSE -Dose adjustments -Dosage forms	IV or INH DOSE -Dose adjustments -Rounding	WARNINGS/PRECAUTIONS	MONITORING	COMMENTS
	N/A	Round to nearest 300mg	hepatic/renal/hematologic impairment	and calcium, CBC and platelets	
Anti-Virals for Hepatitis B					
Lamivudine (Epivir)	100mg PO q24h	N/A	Fat redistribution, immune reconstitution syndrome, pancreatitis, lactic acidosis/hepatomegaly,	Renal function, amylase, bilirubin, liver function tests	Concern for resistant HBV with monotherapy
	CrCl 30-49mL/min: 100mg x1day then 50mg q24h CrCl 15-29mL/min: 100mg x1day then 25mg q24h CrCl 5-14mL/min: 35mg x1day then 15mg q24h CrCl <5mL/min: 35 mg x1day then 10mg q24h	N/A			
	100, 150, 300mg 10mg/mL	N/A			
Entecavir (Baraclude)	0.5mg PO q24h	N/A	Lactic acidosis/hepatomegaly, exacerbations of chronic hepatitis B, increased HIV resistance, hepatic and renal impairment	Renal function and liver function	Lamivudine resistant HBV: 1mg PO q24h Administer on an empty stomach
	CrCl 30-49mL/min: 0.25mg PO q24h or 0.5mg PO q48h CrCl 10-29mL/min: 0.15mg PO q24h or 0.5mg PO q72h CrCl <10mL/min, HD: 0.05mg PO q24h OR 0.5mg PO q7days (after HD)	N/A			
	0.5, 1mg 0.05 mg/mL	N/A			
Tenofovir alafenamide (Vemlidy)	25mg PO q24h	N/A	Lactic acidosis/hepatomegaly, Hepatitis B acute exacerbation, Renal failure	Renal function, phosphorous, urine protein, and urine glucose prior to initiation and hepatic function	Discontinue if significant decrease in renal function or evidence of Fanconi syndrome
	CrCl<15mL/min: not recommended Child-Pugh B/C: not recommended	N/A			
	25mg	N/A			
Anti-Parasitic Agents					
Ivermectin (Stromectol)	200 mcg/kg PO Q2wks x2 doses	N/A	Cutaneous/systemic reactions	follow up stool examinations	Administer on an empty stomach
	N/A	N/A			
	3 mg	N/A			
Anti-TB agents					
Isoniazid (INH) + pyridoxine (vitamin B6)	5 mg/kg (max: 300 mg/day) PO q24h + 25 mg PO q24h	5 mg/kg (max: 300 mg/day) IM q24h + 25 mg PO q24h	Hepatitis, peripheral neuropathies, nausea/vomiting, CNS changes	AST/ALT at baseline and monthly (hold if LFTs> 3-5x ULN)	Avoid administration with food, tyramine- and/or histamine containing foods. Increase dietary intake of folate, niacin and magnesium. Hold if acute liver disease or INH-associated hepatic injury occurs.
	HD: administer dose post-HD Acute hepatic diseases: defer treatment	Acute hepatic diseases: defer treatment			
	100mg, 300mg tabs 50mg/5mL syrup	100mg injection			

References:

1. Tomblyn M, Chiller T, Einsele H, et al. Guidelines for Preventing Infectious Complications among Hematopoietic Cell Transplantation Recipients: A Global Perspective. Biology Blood Marrow Transplant 2009;15:1143-1238.
2. Wingard JR, Carter SL, Walsh TJ, et al. Randomized, double-blind trial of fluconazole versus voriconazole for prevention of invasive fungal infection after allogeneic hematopoietic cell transplantation. Blood 2010;116(24):5111-5118.
3. Ullmann AJ, Lipton JH, Vesole DH, et al. Posaconazole or Fluconazole for Prophylaxis in Severe Graft-versus-Host Disease. NEJM 2007;356(4):335-347.

4. Giaccone L, Festuccia M, Marengo A, et al. Hepatitis B Virus Reactivation and Efficacy of Prophylaxis with Lamivudine in Patients Undergoing Allogeneic Stem Cell Transplantation. Biology Blood Marrow Transplant 2010;16: 809-817.
5. Lok ASF and McMahon BJ. AASLD PRACTICE GUIDELINES: Chronic Hepatitis B. HEPATOLOGY 2007;45:507-539.
6. Jang SH, Colangelo PM and Gobburu JVS. Exposure-Response of Posaconazole Used for Prophylaxis Against Invasive Fungal Infections: Evaluating the Need to Adjust Doses Based on Drug Concentrations in Plasma. Clinical Pharmacology & Therapeutics 2010;88(1):115-119.
7. Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis. 2011;52(4):e56-93.
8. Girmenia C, Barosi G, Piciocchi A, et al. Primary Prophylaxis of Invasive Fungal Diseases in Allogeneic Stem Cell Transplantation: Revised Recommendations from a Consensus Process by Gruppo Italiano Trapianto Midollo Osseo (GITMO). BBMT 2014;20:1080-1088.