Bacterial prophylaxis in MDS (inpatient and outpatient)

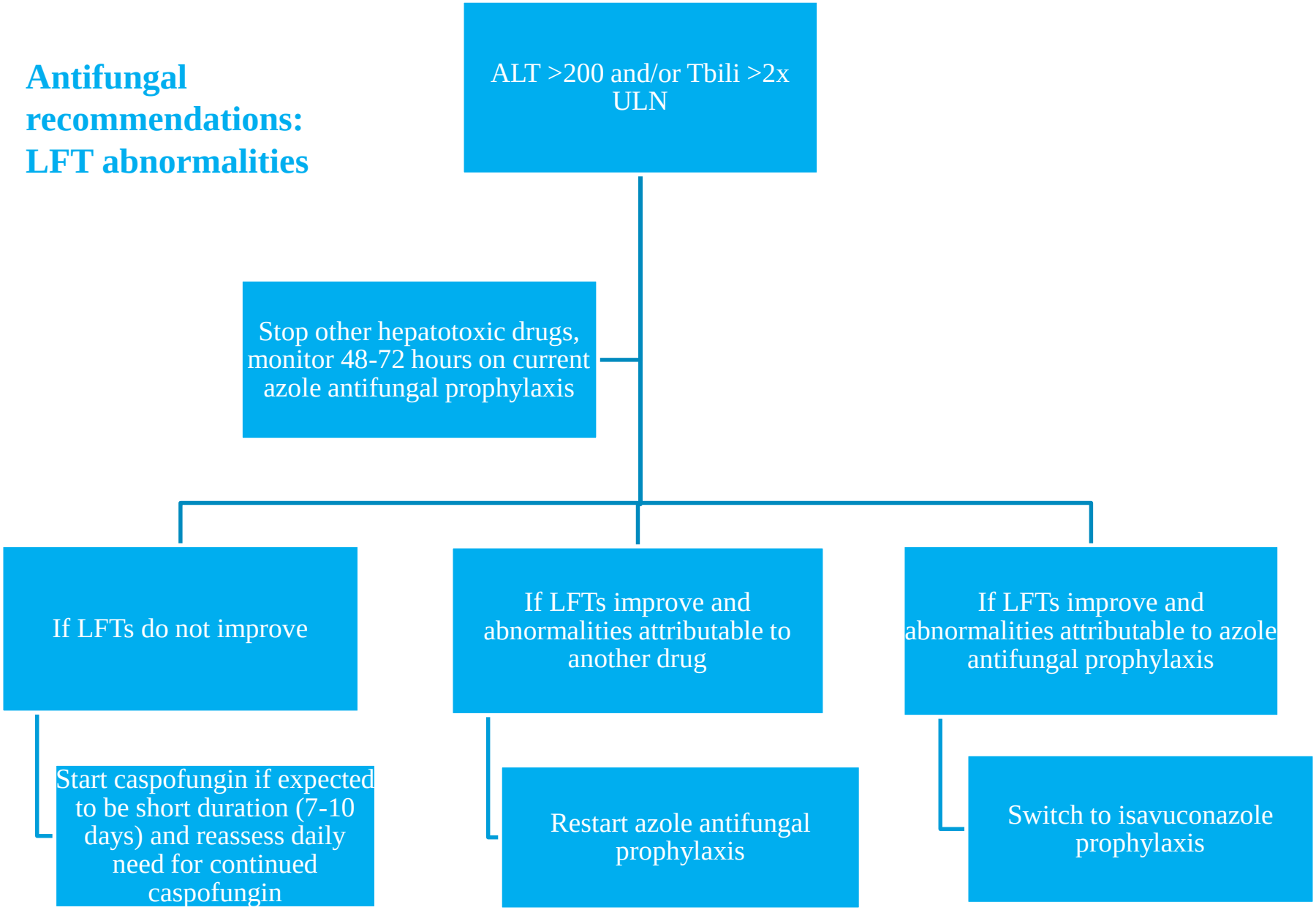
Risk Category	Agent	When to start	Duration
Chronic neutropenia irrespective of the MDS risk group in untreated patients including best supportive care	*Levofloxacin 500mg daily	ANC ≤ 250	Until ANC >250
MDS undergoing low intensity treatment		ANC ≤ 250	Until ANC >250
MDS undergoing high intensity treatment 1. If ANC <500 at baseline 2. If ANC >500 at baseline		1. ANC ≤ 250 2. ANC ≤ 500	Until ANC >250

*If history of infection with floroquinolone resistant organisms, tailor bacterial prophylaxis to prior microbiology. If patient is unable to tolerate floroquinolones due to allergy/intolerance or prolonged QTc consider amoxicillin/clavulanate or cefpodoxime prophylaxis

Malignancy	Antifungal agent*	Comments
AML	Posaconazole 300mg PO (BID on day 1, then Daily starting on Day 2)	Voriconazole** and IV caspofungin are alternative agents if patient cannot take posaconazole
MDS High-risk (undergoing intensive AML-like induction and/or HSCT)	Posaconazole 300mg PO (BID on day 1, then Daily starting on Day 2)	Voriconazole and IV caspofungin are alternative agents if patient cannot take posaconazole
MDS Low-to-intermediate risk	none	
Chronic neutropenia (aplastic anemia)	Posaconazole 300mg PO (BID on day 1, then Daily starting on Day 2) or Voriconazole 200mg PO BID	Limited data available; consider individualized approach
ALL	Fluconazole 200mg daily	Consider fluconazole 400mg daily if not receiving vincristine Consider posaconazole in patients receiving blinatumomab with prior history of HSCT and GVHD
Chronic myeloproliferative neoplasms	None	If undergoing intensive AML-like induction or HSCT → administer posaconazole when ANC < 500/µL
CLL	None	Consider in patients with prolonged neutropenia (ANC < 500/µL) >6 months, elderly, advanced/unresponsive disease

- *Administer when ANC < 500/µL for anticipated > 7 days
- **Loading dose recommended for treatment and prophylaxis

Antifungal recommendations: LFT abnormalities



Therapeutic drug monitoring

Antifungal agent	When to check a level	Therapeutic level for prophylaxis
Posaconazole	After 7 days of therapy if: 1. Receiving concomitant drugs that may alter level 2. Suspected malabsorption 3. Unable to consume high fat meals (for suspension only) 4. Suspected breakthrough fungal infection	>0.5-0.7 mg/l
Voriconazole	After 5 days of therapy if: 1. Receiving concomitant drugs that may alter level 2. Experiencing adverse events suspected to be due to voriconazole toxicity (QTc prolongation, AST/ALT 3x upper limit of normal, neurological effects such as visual hallucination, agitation, confusion) 3. Suspected malabsorption (if receiving oral formulation) 4. Moderate to severe hepatic dysfunction (Child-Pugh class B or C) 5. Suspected breakthrough fungal infection	1.0-6.0 mg/l (levels of >5-6mg/l are associated with neurotoxicity)
Isavuconazole	1. Suspected malabsorption (if receiving oral formulation) 2. Suspected breakthrough fungal infection	Not established

PCP prophylaxis

Disease Type/Therapy Examples	Antimicrobial agent	Duration
ALL	1. Trimethoprim/sulfamethoxazole (preferred) 1 DS or SS daily OR 1 DS 3 times/week 1. Dapsone 50 mg daily 2. Atovaquone 1500mg daily	From induction to end of maintenance
Alemtuzumab		≥2 months after discontinuation of alemtuzumab AND CD4 ≥200 (ECIL recommends at least 6 months of therapy after completion of treatment)
Purine analogue therapy (cladribine, fludarabine, pentostatin) **T cell depleting agents Thymoglobulin**		3-6 months after discontinuation of therapy AND CD4 ≥200
Prolonged steroid use (equivalent to prednisone 20mg daily for ≥4 weeks)		Until 4 weeks after steroids discontinued

Viral prophylaxis

Viral Prophylaxis

Acyclovir 400mg PO BID (preferred)

Acyclovir 800mg PO BID (if previous history of zoster)

Hepatitis B prophylaxis

For patients who are Hepatitis B core antibody positive, surface antigen negative (irrespective of surface antibody status) and who have undetectable viral loads at baseline:

Level of risk	Immunosuppressive condition(s)	Strategy
High	1. Chemotherapy for hematological malignancy 2. Anti-CD20 agents • Rituximab, ofatumumab, obinutuzumab 3. Anti-CD52 agents • Alemtuzumab 4. Stem cell transplant patients 5. Steroids in combination with other immunosuppressive therapy 6. Corticosteroids* • Therapy for ≥ 4 wk (moderate/high dose) 7. Anthracycline derivatives • Doxorubicin, epirubicin, daunorubicin	Prophylaxis
Low risk	1. Traditional immunosuppressive agents • Azathioprine, 6-mercaptopurine, methotrexate 2. Anti-TNF agents • Etanercept, infliximab, adalimumab, certolizumab 3. Other cytokine and integrin inhibitors • Abatacept, ustekinumab, natalizumab, vedolizumab 4. Tyrosine kinase inhibitors • Imatinib, nilotinib 5. Corticosteroids* • Therapy for ≤ 1 wk (any dose)Therapy for ≥ 4 wk (low dose) 6. Chemotherapy for solid tumor (except anthracyclines in breast cancer; see high risk section)	Preemptive

*Corticosteroids: prednisone (or equivalent): low dose, < 10 mg; moderate dose, 10 – 20 mg; high-dose, > 20 mg

Hepatitis B prophylaxis

Prophylactic strategy:
Entecavir 0.5 mg PO daily with HBV DNA monitoring every 3 months
- Rationale for entecavir as first choice: low resistance profile, lower incidence of HBV reactivation, minimal drug interactions, and well-tolerated

Pre-emptive strategy:
Check HBV DNA PCR every 3 months. If detected, check LFTs, hepatitis B serologies and start entecavir (consult Transplant ID or hepatology with questions).

Duration of prophylaxis:

- Chemotherapy patients: 12 months after the conclusion of chemotherapy
- Rituximab: consider discontinuation of prophylaxis 18 months after the last rituximab dose
- Stem cell transplant recipients: 12 months after conclusion of immunosuppression

Patients currently maintained on lamivudine should continue current therapy if:

- Lamivudine resistance is NOT identified
- HBV DNA < 2,000 IU/mL

References

- Murphy, M., Brown, A. E., Sepkowitz, K. A., Bernard, E. M., Clinical, S., Diseases, I., & Aug, N. (1997). Fluoroquinolone Prophylaxis for the Prevention of Bacterial Infections in Patients with Cancer : Is It Justified ? *Clinical Infectious Diseases*, *25*(2), 346–348.
- See, I., Freifeld, A. G., & Magill, S. S. (2016). Causative organisms and associated antimicrobial resistance in healthcare-associated, central line-associated bloodstream infections from oncology settings, 2009-2012. *Clinical Infectious Diseases*, *62*(10), 1203–1209. https://doi.org/10.1093/cid/ciw113
- Gudiol, C., Bodro, M., Simonetti, A., Tubau, F., González-Barca, E., Cisnal, M.,Carratalà, J. (2013). Changing aetiology, clinical features, antimicrobial resistance, and outcomes of bloodstream infection in neutropenic cancer patients. *Clinical Microbiology and Infection*, *19*(5), 474–479. https://doi.org/10.1111/j.1469-0691.2012.03879.x
- Ford, C. D., Lopansri, B. K., Haydoura, S., Snow, G., Dascomb, K. K., Asch, J., … Burke, J. P. (2015). Frequency, risk factors, and outcomes of vancomycin-resistant enterococcus colonization and infection in patients with newly diagnosed acute leukemia: Different patterns in patients with acute myelogenous and acute lymphoblastic leukemia. *Infection Control and Hospital Epidemiology*, *36*(1), 47–53. https://doi.org/10.1017/ice.2014.3
- Dekkers, B. G. J., Bakker, M., van der Elst, K. C. M., Sturkenboom, M. G. G., Veringa, A., Span, L. F. R., & Alffenaar, J. W. C. (2016). Therapeutic Drug Monitoring of Posaconazole: an Update. *Current Fungal Infection Reports*, *10*(2), 51–61. https://doi.org/10.1007/s12281-016-0255-4
- Luong, M. L., Al-Dabbagh, M., Groll, A. H., Racil, Z., Nannya, Y., Mitsani, D., & Husain, S. (2016). Utility of voriconazole therapeutic drug monitoring: A meta-analysis. *Journal of Antimicrobial Chemotherapy*, *71*(7), 1786–1799. https://doi.org/10.1093/jac/dkw099
- Taplitz, R. A., Kennedy, E. B., Bow, E. J., Crews, J., Gleason, C., Langston, A. A., … Strasfeld, L. (2018). Antimicrobial prophylaxis for adult patients with cancer-related immunosuppression: ASCO and IDSA clinical practice guideline update. *Journal of Clinical Oncology*, *36*(30), 3043–3054. https://doi.org/10.1200/JCO.18.00374
- Yi, W. M., Schoeppler, K. E., Jaeger, J., Mueller, S. W., MacLaren, R., Fish, D. N., & Kiser, T. H. (2017). Voriconazole and posaconazole therapeutic drug monitoring: A retrospective study. *Annals of Clinical Microbiology and Antimicrobials*, *16*(1), 1–14. https://doi.org/10.1186/s12941-017-0235-8
- Slavin, M. A., Lingaratnam, S., Mileshkin, L., Booth, D. L., Cain, M. J., Ritchie, D. S., … Thursky, K. A. (2011). Use of antibacterial prophylaxis for patients with neutropenia. *Internal Medicine Journal*, *41*(1 B), 102–109. https://doi.org/10.1111/j.1445-5994.2010.02341.x
- Mellinghoff, S. C., Panse, J., Alakel, N., Behre, G., Buchheidt, D., Christopeit, M., … Cornely, O. A. (2018). Primary prophylaxis of invasive fungal infections in patients with haematological malignancies: 2017 update of the recommendations of the Infectious Diseases Working Party (AGIHO) of the German Society for Haematology and Medical Oncology (DGHO). *Annals of Hematology*, *97*(2), 197–207. https://doi.org/10.1007/s00277-017-3196-2
- Mikulska, M., Averbuch, D., Tissot, F., Cordonnier, C., Akova, M., Calandra, T., … Witschi, A. T. (2018). Fluoroquinolone prophylaxis in haematological cancer patients with neutropenia: ECIL critical appraisal of previous guidelines. *Journal of Infection*, *76*(1), 20–37. https://doi.org/10.1016/j.jinf.2017.10.009
- Flowers, C. R., & Karten, C. (2013). Communicating safe outpatient management of fever and neutropenia. *Journal of Oncology Practice*, *9*(4), 207–210. https://doi.org/10.1200/JOP.2012.000815
- Taplitz, R. A., Kennedy, E. B., & Flowers, C. R. (2018). Antimicrobial prophylaxis for adult patients with cancer-related immunosuppression: ASCO and IDSA clinical practice guideline update summary. *Journal of Oncology Practice*, *14*(11), 692–695. https://doi.org/10.1200/JOP.18.00366
- Maertens, J., Cesaro, S., Maschmeyer, G., Einsele, H., Donnelly, J. P., Alanio, A., … Wood, C. (2016). ECIL guidelines for preventing Pneumocystis jirovecii pneumonia in patients with haematological malignancies and stem cell transplant recipients. *Journal of Antimicrobial Chemotherapy*, *71*(9), 1–8. https://doi.org/10.1093/jac/dkw157
- Baden, L. R., Bensinger, W., Casper, C., Cleveland, K. O., Dubberke, E. R., Freifeld, A. G., … Kaul, D. R. (2012). Prevention and Treatment of Cancer-Related Infections Clinical Practice Guidelines in Oncology. *Journal of the National Comprehensive Network*, *10*(11), 1412–1445.
- Maertens, J. A., Girmenia, C., Brüggemann, R. J., Duarte, R. F., Kibbler, C. C., Ljungman, P., … Cordonnier, C. (2018). European guidelines for primary antifungal prophylaxis in adult haematology patients: Summary of the updated recommendations from the European Conference on Infections in Leukaemia. *Journal of Antimicrobial Chemotherapy*, *73*(12), 3221–3230. https://doi.org/10.1093/jac/dky286
- Gafter-Gvili, A., Fraser, A., Paul, M., Vidal, L., Ta, L., Wetering, V. De, … Leibovici, L. (2012). Antibiotic prophylaxis for bacterial infections in afebrile neutropenic patients following chemotherapy. *Cochrane Database of Systematic Reviews*. https://doi.org/10.1002/14651858.CD004386.pub3.www.cochranelibrary.com
- Valdez, J. M., Scheinberg, P., Young, N. S., & Walsh, T. J. (2009). Infections in Patients With Aplastic Anemia. *Seminars in Hematology*, *46*(3), 269–276. https://doi.org/10.1053/j.seminhematol.2009.03.008
- Walsh, T. J. (2009). Advances and Challenges in Infectious Diseases Supportive Care of Patients With Hematologic Malignancies, Hematopoietic Stem Cell Transplantation, and Severe Aplastic Anemia. *Seminars in Hematology*, *46*(3), 191–197. https://doi.org/10.1053/j.seminhematol.2009.05.001
- Cuneo, A., Barosi, G., Danesi, R., Fagiuoli, S., Ghia, P., Marzano, A., … Zinzani, P. L. (2019). Management of adverse events associated with idelalisib treatment in chronic lymphocytic leukemia and follicular lymphoma: A multidisciplinary position paper. *Hematological Oncology*, *37*(1), 3–14. https://doi.org/10.1002/hon.2540
- Kantarjian, H., Stein, A., Gökbuget, N., Fielding, A. K., Schuh, A. C., Ribera, J.-M., … Topp, M. S. (2017). Blinatumomab versus Chemotherapy for Advanced Acute Lymphoblastic Leukemia. *New England Journal of Medicine*, *376*(9), 836–847. https://doi.org/10.1056/nejmoa1609783