

# CAR-T-cell Therapy

Subjects: Nursing

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Studies describing invasive fungal infections (IFIs) after chimeric antigen receptor-modified T-cell (CAR-T-cell) therapy are limited. Although post-CAR-T-cell IFIs appear to be uncommon, they are associated with significant morbidity and mortality. Specific risk factors for IFIs in CAR-T-cell recipients have not been fully characterized and are often extrapolated from variables contributing to IFIs in patients with other hematologic malignancies or those undergoing hematopoietic cell transplant. Optimal prophylaxis strategies, including the use of yeast versus mold-active azoles, also remain ill-defined. Further research should investigate key risk factors for IFIs and establish an evidence-based approach to antifungal prophylaxis in these patients in order to improve clinical outcomes.

Keywords: CAR-T-cell therapy ; risk factors ; invasive fungal infection ; prophylaxis ; mold ; yeast

## 1. Introduction

Chimeric antigen receptor-modified T-cell (CAR-T-cell) therapy targeting the B-cell antigen CD19 has drastically improved outcomes in patients with refractory B-cell malignancies [1][2][3][4][5]. However, managing the toxicities of CAR-T-cell therapies remains challenging. The two most common of these toxicities are the cytokine release syndrome (CRS) and the immune effector cell-associated neurotoxicity syndrome (ICANS) (formerly known as CAR-T-cell associated encephalopathy syndrome). These toxicities typically develop within the first 21 days of CAR-T-cell infusion during proliferation of CAR-T-cells. Treatment of CRS and ICANS may include the interleukin-6 inhibitor tocilizumab and/or corticosteroids depending on their severity (graded 1–4) [2]. Prolonged leukopenia (particularly lymphopenia) and hypogammaglobulinemia due to B-cell aplasia are also two direct CAR-T-cell toxicities and are generally thought to be mediated by “on-target, off-tumor” effects of CAR-T-cells, which occur when CAR-T-cells kill normal B-cells that express the CAR-T-cell target antigen [6]. Neutropenia may also be a direct toxicity of CAR-T-cell therapy, but its pathogenesis has not been fully defined [6][7].

Infections are among the indirect toxicities of CAR-T-cell therapy. CAR-T-cell recipients are at an increased risk of infection because of prior anti-neoplastic therapy, refractory malignancy, lymphodepleting conditioning chemotherapy (typically with fludarabine and cyclophosphamide), B-cell aplasia, the immune perturbations associated with CRS and ICANS, and their management with immunosuppressive therapies [8][9][10][11][12][13][14][15]. Nosocomial bacterial and respiratory viral infections are the most common infections after CAR-T-cell therapy. Invasive fungal infections (IFIs), in contrast, are uncommon, and studies providing detailed analyses of IFIs following CAR-T-cell therapy remain limited. Additionally, high-quality data informing antifungal prophylaxis practices are lacking.

## 2. Epidemiology of Fungal Infections after CAR-T-Cell Therapy

Seven published manuscripts and abstracts describing IFIs after CAR-T-cell therapy were identified at the time of this review [8][9][10][11][12][13][14]. Overall, IFIs after CAR-T-cell therapy are uncommon and have been reported in 1–15% of patients, with 0–10% and 0–7% of patients developing yeast and mold infections, respectively. Most IFIs occur within the first 30 days following CAR-T-cell therapy and typically represent breakthrough infections developing in patients receiving fluconazole or echinocandin prophylaxis. IFIs occurring >30 days after CAR-T-cell therapy, including invasive mold infections, have been described in patients with persistent risk factors such as prolonged neutropenia [8][9]. In one study which reported infections occurring >90 days after CAR-T-cell infusion, IFIs developed in 9% of patients and included two invasive mold infections, one yeast infection, and one endemic mycosis (*Coccidioides immitis* infection) [10]. Six studies reported infection-related deaths, of which mortality attributable to IFIs ranged from 0 to 5% [8][9][10][11][12][13].

### 2.1. Yeast Infections

Fourteen yeast infections in 13 unique patients following CAR-T-cell therapy have been reported [8][9][10][11][14][15] (Table 1). Seven of these episodes (50%) were cases of fungemia. Nine of the 14 yeast infections occurred within 30 days of CAR-T-cell infusion (early) including two *Candida glabrata* fungemias; the remainder were fungemias caused by *Candida tropicalis*, *Candida krusei*, and *Saccharomyces cerevisiae*. The additional early yeast infections described were two cases of respiratory tract infections attributed to *C. glabrata* and *Candida braccarensis*, one case of oropharyngeal candidiasis, and an intra-abdominal infection caused by *C. glabrata*. Of note, as true *Candida* respiratory tract infections are exceedingly uncommon in patients with hematological malignancies, the cases of *Candida* respiratory infections may have simply represented colonization. All patients who developed early yeast infections were receiving fluconazole

prophylaxis, with the exception of the patient who developed the *S. cerevisiae* blood stream infection, who was receiving micafungin prophylaxis. Yeast infections >30 days after CAR-T-cell therapy were *C. glabrata* fungemia, oropharyngeal candidiasis, *Candida* esophagitis, and a case of *Candida albicans* fungemia with subsequent vertebral osteomyelitis. Notably, these patients were not receiving antifungal prophylaxis, but no specific IFI risk factors were described in the studies. Infection-related mortality was attributed to the *C. krusei* and *C. tropicalis* fungemias, both of which were early infections.

**Table 1.** Published reports of invasive yeast infections following chimeric antigen receptor-modified T-cell (CAR-T-cell) therapy. Neutropenia defined as absolute neutrophil count <500 cells/ $\mu$ L. Lymphopenia defined as absolute lymphocyte count <1000 cells/ $\mu$ L. ALL = acute lymphoblastic leukemia; DLBCL = diffuse large B-cell lymphoma; CRS = cytokine release syndrome; ICANS = immune effector cell-associated neurotoxicity syndrome. Dashes indicate that the data were not reported in the studies. <sup>a</sup> As true invasive *Candida* spp. respiratory tract infections are rare in patients with hematological malignancies, it is unclear if these isolates represent invasive infections or simply colonization.

Ref.	Fungal Infection	Cancer	Prophylaxis	Neutropenia	Lymphopenia	Time of Onset of Infection	CRS	Steroids	Tocilizumab Given?	Previous Transpla
Park et al. [11]	<i>Saccharomyces cerevisiae</i> : fungemia	ALL	Micafungin	Yes	–	Day 0–30	Grade 3	–	–	–
	<i>Candida tropicalis</i> : fungemia	DLBCL	Fluconazole	Yes	Yes	Day 0–30	Grade 2	Yes	Yes (2 doses)	No
	<i>Candida glabrata</i> : intra-abdominal infection	DLBCL	Fluconazole	No	Yes	Day 0–30	Grade 1	Yes	Yes (1 dose)	Yes (autolog)
Garner et al. [8]	<i>Candida</i> esophagitis	DLBCL	Fluconazole	No	Yes	Day 0–30	Grade 2	Yes	Yes (1 dose)	Yes (autolog)
	<i>Candida albicans</i> : fungemia	DLBCL	None	No	Yes	Day 30+	Grade 2	No	Yes (1 dose)	Yes (autolog)
	<i>Candida albicans</i> : vertebral osteomyelitis	DLBCL	None	–	–	Day 30+	Grade 2	No	Yes (1 dose)	Yes (autolog)
	<i>Candida</i> esophagitis	DLBCL	None	No	Yes	Day 30+	No	No	No	No
	<i>Candida glabrata</i> : fungemia	–	Fluconazole	–	–	Day 0–30	–	–	–	–
Hill et al. [9]	<i>Candida glabrata</i> : fungemia	–	Fluconazole	–	–	Day 0–30	–	–	–	–
	<i>Candida glabrata</i> : lungs <sup>a</sup>	–	Fluconazole	–	–	Day 0–30	–	–	–	–
	<i>Candida braccarensis</i> : lungs <sup>a</sup>	–	Fluconazole	–	–	Day 0–30	–	–	–	–
Tran et al. [15]	<i>Candida glabrata</i> : fungemia	–	–	–	–	Day 30+	–	–	–	–
Cordeiro et al. [10]	Oral candidiasis	–	–	–	–	Day 30+	–	–	–	–
Louge et al. [14]	<i>Candida krusei</i> fungemia	DLBCL	Fluconazole	–	–	38 days	–	Yes, for ICANS	–	No

## 2.2. Mold Infections

Of the 15 invasive mold infections (IMIs) described after CAR-T-cell therapy, 11, 3, and 1 were proven, probable, and possible IMIs, respectively [8][9][10][11][12][13][14]. Overall, the primary site of mold infection was the lung. Eight of the 15 IMIs occurred <30 days after CAR-T-cell infusion and included two *Aspergillus* species (spp.) infections, two Mucorales infections, two *Fusarium* spp. infections, an unidentified IMI, and one case of probable pulmonary aspergillosis. Of these early IMIs, 4, 3, and 1 patients were receiving fluconazole, micafungin, and voriconazole prophylaxis, respectively. The patient receiving voriconazole prophylaxis developed a Mucorales lung infection due to *Cunninghamella* spp., but had previously been diagnosed with probable pulmonary mold infection (without a positive culture) prior to CAR-T-cell therapy; it was therefore unclear whether the *Cunninghamella* infection was present prior to CAR-T-cell infusion, or whether it developed after therapy. Both *Fusarium* spp. infections were disseminated. One involved the central nervous system, and one (caused by *Fusarium solani*) was isolated from the patient's thigh and sinuses; the latter infection developed while the patient was receiving fluconazole followed by posaconazole prophylaxis. IMIs occurring >30 days after CAR-T-cell therapy included three *Aspergillus* spp. infections, one Mucorales infection, one case each of probable and possible invasive mold infection, and a skin and soft tissue infection from which both an *Aspergillus* and *Rhizopus* spp. were identified. Four of 15

(27%) patients who developed IMI died from their infection, three of whom died within 30 days of CAR-T-cell infusion. In one study describing three IMIs, two early infections occurred in patients who developed severe CRS/ICANS requiring tocilizumab +/- corticosteroids, and the single late IMI occurred in the setting of persistent disease and prolonged neutropenia [8]. Additionally, the central nervous system *Fusarium* spp. infection occurred after the administration of a long course of steroids. Three of the studies reporting IMIs did not describe predisposing patient risk factors.

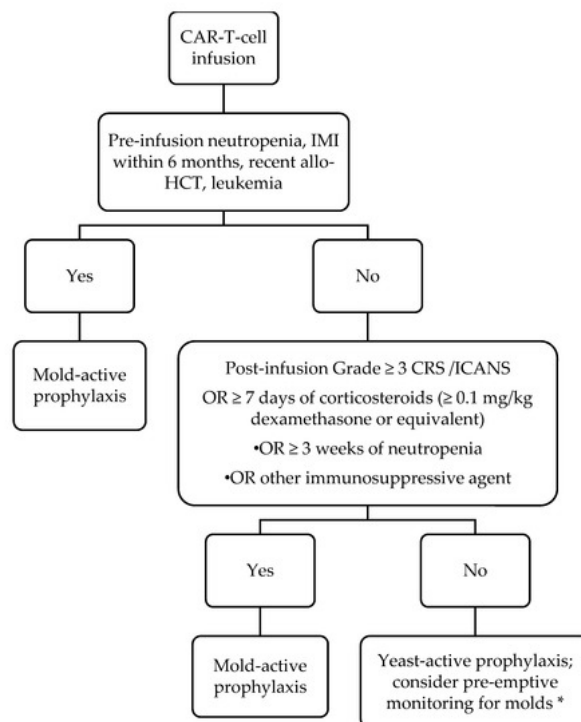
### **3. Anti-Fungal Prophylaxis Following CAR-T-Cell Therapy**

#### **3.1. Yeast Versus Mold-Active Prophylaxis**

Because risk factors for IFIs in patients receiving CAR-T-cell therapy are not well-defined, there is no consensus about the optimal choice and duration of antifungal prophylaxis after CAR-T-cell therapy. As such, clinical practice varies widely among different centers. Although anti-yeast prophylaxis during the period of neutropenia after CAR-T-cell therapy has been the most commonly used strategy in clinical trials [3][4][5][9], it is not currently known whether certain subgroups of CAR-T-cell recipients may benefit from anti-mold prophylaxis. Indeed, there is much controversy around the optimal approach of yeast-versus-mold-active prophylaxis in these patients. Proposed strategies have included universal yeast-active prophylaxis, a tiered “risk stratification” approach, universal anti-mold prophylaxis, and pre-emptive therapy using fungal biomarkers and radiographic imaging [16][17][18]. At the center of the controversy is the absence of trials demonstrating whether anti-mold prophylaxis confers any mortality benefit in this population. Thus, robust evidence-based guidelines for antifungal prophylaxis such as those outlined by the European Conference on Infections in Leukemia [19] for other hematological malignancy patients do not currently exist.

Nonetheless, in the past few years, several guidance documents have been published with provisional suggestions about the optimal approach to antifungal prophylaxis in these patients. Recent CAR-T-cell therapy expert panel guidelines suggest fluconazole or micafungin prophylaxis against *Candida* during neutropenia [1]. Another guideline from the European Society for Blood and Marrow Transplantation recommends mold-active azole prophylaxis in patients with prior allogeneic HCT, prior invasive aspergillosis, and those receiving corticosteroids [20]. Other groups have suggested that ≥4 prior anti-tumor treatment lines, CAR-T-cell dose of  $>2 \times 10^7$ /kg, prolonged neutropenia (≥3 weeks), and use of >1 dose of tocilizumab or the administration of other immunosuppressive agents (such as anakinra and siltuximab) for the management of CRS and ICANS should also warrant the use of mold-active antifungal prophylaxis [21][22].

Based on the current literature and extrapolation from risk factors for mold infections in other hematological malignancy patients, we have adopted the antifungal prophylaxis protocol described in [Figure 1](#), which generally classifies patients as “high risk” for mold infection based on whether they are “AML-like” due to the presence of prolonged neutropenia, or “graft-versus-host disease (GVHD)-like” due to the use of corticosteroids or other immunosuppressive agents. We use posaconazole as our preferred mold-active prophylactic agent because of clinical trial data supporting its use in patients with AML and GVHD [23][24]. However, until data in CAR-T-cell therapy recipients are generated, we believe that any mold-active antifungal (such as voriconazole or isavuconazole) may be acceptable, and that the specific choice of agent should be guided by history of prior mold infection, side effect profile (e.g., avoidance of voriconazole in persons with neurotoxicity), and cost. Although this is our approach, others have advocated universal mold-active prophylaxis because of the uncertainties surrounding risk factors for mold infection after CAR-T-cell therapy. Specific concerns that were cited include the risks of mold infection in treatment-experienced ALL patients and challenges predicting duration of cytopenias and extent of steroid exposure [17].



**Figure 1.** Our approach to anti-fungal prophylaxis for prevention of invasive fungal infection post-chimeric antigen receptor-modified T-cell (CAR T-cell) therapy. Abbreviations: IMI = invasive mold infection; allo-HCT = allogeneic hematopoietic cell transplantation; CRS = cytokine release syndrome; ICANS = immune effector cell-associated neurotoxicity syndrome. For our purposes, we define neutropenia as an absolute neutrophil count of  $\leq 500/\mu\text{L}$ . Duration of mold-active prophylaxis should be individualized. We maintain patients on mold-active agents until at least 1 month after discontinuation of immunosuppression AND resolution of neutropenia. Posaconazole is our preferred agent; voriconazole and isavuconazole are reasonable alternatives based on side effect profile and cost. \* Pre-emptive therapy consists of diagnostics such as fungal biomarkers (serum beta-D-glucan, galactomannan) and surveillance radiographic imaging.

There are no data to guide the duration of mold-active prophylaxis. Although the paradigm in [Figure 1](#) outlines a general framework for duration depending on the presence of neutropenia and the use of steroids, the precise duration of prophylaxis should be determined on a case-by-case basis based on the resolution of risk factors. A pre-emptive approach relying on biomarkers and imaging <sup>[25]</sup> has not been validated in these patients and may be hampered by limited testing availability and slow turnaround times. While the  $\text{CD4}^+$  T-cell cell count is an appealing marker that may help guide and individualize the duration of mold-active or other antifungal prophylaxis, further research validating this approach would need to be conducted prior to widespread inclusion of  $\text{CD4}^+$  T-cell measurements in prophylactic algorithms. Ultimately, there is a need to conduct large multicenter prospective studies, preferably randomized clinical trials similar to the pivotal trials of posaconazole in AML and GVHD <sup>[23][24]</sup>, to determine the benefit of yeast versus mold-active antifungal prophylaxis in CAR-T-cell therapy recipients.

### 3.2. Prophylaxis Against PCP

It is standard practice to administer trimethoprim-sulfamethoxazole (or alternatives, such as dapsone, atovaquone, and monthly intravenous pentamidine) for 3–6 months after CAR-T-cell therapy to prevent PCP <sup>[6][21][22]</sup>. Given that many CAR-T-cell patients are expected to experience prolonged lymphopenia due to “on-target, off-tumor” effects of CAR-T-cells, these patients may be at risk for PCP beyond 6 months. Some authors have suggested that PCP prophylaxis be continued until the  $\text{CD4}^+$  T-cell count is greater than 200 cells/ $\mu\text{L}$  <sup>[21]</sup>. Indeed, cases of PCP have been reported over 6 months after CAR-T-cell therapy in lymphopenic patients whose PCP prophylaxis had been discontinued <sup>[9][9][13]</sup>. Based on these data, we currently recommend at least 1 year of anti-PCP prophylaxis at our center, which can be stopped once the  $\text{CD4}^+$  T-cell count is greater than 200 cells/ $\mu\text{L}$ .

## References

1. Kansagra, A.J.; Frey, N.V.; Bar, M.; Laetsch, T.W.; Carpenter, P.A.; Savani, B.N.; Heslop, H.E.; Bollard, C.M.; Komanduri, K.V.; Gastineau, D.A.; et al. Clinical Utilization of Chimeric Antigen Receptor T-Cells (Car-T) in B-Cell Acute Lymphoblastic Leukemia (All)—An Expert Opinion from the European Society for Blood and Marrow Transplantation (Ebmt) and the American Society for Blood and Marrow Transplantation (Asbmt). *Bone Marrow Transplant.* 2019, 54, 1868–1880.
2. Mahadeo, K.M.; Khazal, S.J.; Abdel-Azim, H.; Fitzgerald, J.C.; Taraseviciute, A.; Bollard, C.M.; Tewari, P.; Duncan, C.; Traube, C.; McCall, D.; et al. Management guidelines for paediatric patients receiving chimeric antigen receptor T cell therapy. *Nat. Rev. Clin. Oncol.* 2019, 16, 45–63.

3. Maude, S.L.; Laetsch, T.W.; Buechner, J.; Rives, S.; Boyer, M.; Bittencourt, H.; Bader, P.; Verneris, M.R.; Stefanski, H. E.; Myers, G.D.; et al. Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia. *N. Engl. J. Med.* 2018, 378, 439–448.
4. Neelapu, S.S.; Locke, F.L.; Bartlett, N.L.; Lekakis, L.J.; Miklos, D.B.; Jacobson, C.A.; Braunschweig, I.; Oluwole, O.O.; Siddiqi, T.; Lin, Y.; et al. Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. *N. Engl. J. Med.* 2017, 377, 2531–2544.
5. June, C.H.; Sadelain, M. Chimeric Antigen Receptor Therapy. *N. Engl. J. Med.* 2018, 379, 64–73.
6. Haidar, G.; Garner, W.; Hill, J.A. Infections after Anti-Cd19 Chimeric Antigen Receptor T-Cell Therapy for Hematologic Malignancies: Timeline, Prevention, and Uncertainties. *Curr. Opin. Infect. Dis.* 2020, 33, 449–457.
7. Fried, S.; Avigdor, A.; Bielorai, B.; Meir, A.; Besser, M.J.; Schachter, J.; Shimoni, A.; Nagler, A.; Toren, A.; Jacoby, E. Early and late hematologic toxicity following CD19 CAR-T cells. *Bone Marrow Transplant.* 2019, 54, 1643–1650.
8. Garner, W.; Samanta, P.; Dorritie, K.; Sehgal, A.; Winfield, D.; Agha, M.; Boudreau, R.; Nguyen, M.H.T.; Haidar, G. 1105. The Burden of Infections Prior to Chimeric Antigen Receptor (CAR) Modified T-cell Therapy Predicts Post-CAR T-cell Infectious Complications. *Open Forum Infect. Dis.* 2020, 7, S583.
9. Hill, J.A.; Li, D.; Hay, K.A.; Green, M.L.; Cherian, S.; Chen, X.; Riddell, S.R.; Maloney, D.G.; Boeckh, M.; Turtle, C.J. Infectious complications of CD19-targeted chimeric antigen receptor–modified T-cell immunotherapy. *Blood* 2018, 131, 121–130.
10. Cordeiro, A.; Bezerra, E.D.; Hirayama, A.V.; Hill, J.A.; Wu, Q.V.; Voutsinas, J.; Sorror, M.L.; Turtle, C.J.; Maloney, D.G.; Bar, M. Late Events after Treatment with CD19-Targeted Chimeric Antigen Receptor Modified T Cells. *Biol. Blood Marrow Transplant.* 2020, 26, 26–33.
11. Park, J.H.; Romero, F.A.; Taur, Y.; Sadelain, M.; Brentjens, R.J.; Hohl, T.M.; Seo, S.K. Cytokine Release Syndrome Grade as a Predictive Marker for Infections in Patients With Relapsed or Refractory B-Cell Acute Lymphoblastic Leukemia Treated With Chimeric Antigen Receptor T Cells. *Clin. Infect. Dis.* 2018, 67, 533–540.
12. Vora, S.B.; Waghmare, A.; A Englund, J.; Qu, P.; A Gardner, R.; A Hill, J. Infectious Complications Following CD19 Chimeric Antigen Receptor T-cell Therapy for Children, Adolescents, and Young Adults. *Open Forum Infect. Dis.* 2020, 7, ofa121.
13. Wudhikarn, K.; Palomba, M.L.; Pennisi, M.; Garcia-Recio, M.; Flynn, J.R.; Devlin, S.M.; Afuye, A.; Silverberg, M.L.; Maloy, M.A.; Shah, G.L.; et al. Infection during the first year in patients treated with CD19 CAR T cells for diffuse large B cell lymphoma. *Blood Cancer J.* 2020, 10, 79.
14. Logue, J.M.; Zucchetti, E.; Bachmeier, C.A.; Krivenko, G.S.; Larson, V.; Ninh, D.; Grillo, G.; Cao, B.; Kim, J.; Chavez, J. C.; et al. Immune reconstitution and associated infections following axicabtagene ciloleucel in relapsed or refractory large B-cell lymphoma. *Haematologica* 2020.
15. Tran, N.; Eschenauer, G.; Scappaticci, G.; Frame, D.; Miceli, M.; Patel, T. Infections in Patients Treated with Chimeric Antigen Receptor T-Cells (CAR-T) Therapy. *Open Forum Infect. Dis.* 2020, 7, S354.
16. Haidar, G.; Dorritie, K.; Farah, R.; Bogdanovich, T.; Nguyen, M.H.; Samanta, P. Invasive Mold Infections After Chimeric Antigen Receptor–Modified T-Cell Therapy: A Case Series, Review of the Literature, and Implications for Prophylaxis. *Clin. Infect. Dis.* 2019, 71, 672–676.
17. E Lewis, R.; Kontoyiannis, D.P. Chimeric Antigen Receptor T-cell Immunotherapy and Need for Prophylaxis for Invasive Mold Infections. *Clin. Infect. Dis.* 2020, 71, 1802–1803.
18. Haidar, G.; Nguyen, M.H.; Samanta, P. Reply to Lewis and Kontoyiannis. *Clin. Infect. Dis.* 2020, 71, 1803–1804.
19. A Maertens, J.; Girmenia, C.; Brüggemann, R.J.; Duarte, R.F.; Kibbler, C.C.; Ljungman, P.; Racil, Z.; Ribaud, P.; A Slavina, M.; A Cornely, O.; et al. European guidelines for primary antifungal prophylaxis in adult haematology patients: Summary of the updated recommendations from the European Conference on Infections in Leukaemia. *J. Antimicrob. Chemother.* 2018, 73, 3221–3230.
20. Yakoub-Agha, I.; Chabannon, C.; Bader, P.; Basak, G.W.; Bonig, H.; Ciceri, F.; Corbacioglu, S.; Duarte, R.F.; Einsele, H.; Hudecek, M.; et al. Management of adults and children undergoing chimeric antigen receptor T-cell therapy: Best practice recommendations of the European Society for Blood and Marrow Transplantation (EBMT) and the Joint Accreditation Committee of ISCT and EBMT (JACIE). *Haematologica* 2019, 105, 297–316.
21. Los-Arcos, I.; Iacoboni, G.; Aguilar-Guisado, M.; Alsina-Manrique, L.; De Heredia, C.D.; Fortuny-Guasch, C.; García-Cadenas, I.; García-Vidal, C.; González-Vicent, M.; Hernani, R.; et al. Recommendations for screening, monitoring, prevention, and prophylaxis of infections in adult and pediatric patients receiving CAR T-cell therapy: A position paper. *Infection* 2020, 1–17.
22. Hill, J.A.; Seo, S.K. How I prevent infections in patients receiving CD19-targeted chimeric antigen receptor T cells for B-cell malignancies. *Blood* 2020, 136, 925–935.
23. Ullmann, A.J.; Lipton, J.H.; Vesole, D.H.; Chandrasekar, P.; Langston, A.; Tarantolo, S.R.; Greinix, H.; De Azevedo, W. M.; Reddy, V.; Boparai, N.; et al. Posaconazole or Fluconazole for Prophylaxis in Severe Graft-versus-Host Disease. *N. Engl. J. Med.* 2007, 356, 335–347.
24. Cornely, O.A.; Maertens, J.; Winston, D.J.; Perfect, J.; Ullmann, A.J.; Walsh, T.J.; Helfgott, D.; Holowiecki, J.; Stockelberg, D.; Goh, Y.-T.; et al. Posaconazole Vs. Fluconazole or Itraconazole Prophylaxis in Patients with Neutropenia. *N. En*

gl. J. Med. 2007, 356, 348–359.

25. Maertens, J.; Theunissen, K.; Verhoef, G.; Verschakelen, J.; Lagrou, K.; Verbeken, E.; Wilmer, A.; Verhaegen, J.; Boogaerts, M.; Van Eldere, J. Galactomannan and computed tomography-based preemptive antifungal therapy in neutropenic patients at high risk for invasive fungal infection: A prospective feasibility study. *Clin. Infect. Dis.* 2005, 41, 1242–1250.

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