of polymyxins, however, should not be accepted as a reason to forgo treatment with antibiotics that have better safety and efficacy outcomes. The primary goal of antimicrobial therapy and stewardship is to optimize clinical outcomes while minimizing unintended consequences of antimicrobial use, including toxicity [6]. Our patients deserve better and these novel agents are steps in the right direction. Resources should be marshalled to further substantiate the value of these antibiotics to patients and clinicians in the "real world" of challenging infections caused by multidrug-resistant bacteria.

Note

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References

1. Pogue JM, Kaye KS, Veve MP, et al. Ceftolozane/tazobactam vs polymyxin or aminoglycoside-based regimens for the treatment of drug-resistant *Pseudomonas aeruginosa* [manuscript published online ahead of print 23 September 2019]. Clin Infect Dis **2019**; 71:304–10.
2. Motsch J, Murta de Oliveira C, Stus V, et al. RESTORE-IMI 1: a multicenter, randomized, double-blind trial comparing efficacy and safety of imipenem/relebactam vs. colistin plus imipenem in patients with imipenem-nonsusceptible bacterial infections [manuscript published online ahead of print 10 August 2019]. Clin Infect Dis **2020**; 70:1799–808.
3. Shields RK, Nguyen MH, Chen L, et al. Ceftazidime-avibactam is superior to other treatment regimens against carbapenem-resistant *Klebsiella pneumoniae* bacteremia. Antimicrob Agents Chemother **2017**; 61. doi:10.1128/AAC.00883-17.
4. van Duin D, Lok JJ, Earley M, et al; Antibacterial Resistance Leadership Group. Colistin versus ceftazidime-avibactam in the treatment of infections due to carbapenem-resistant Enterobacteriaceae. Clin Infect Dis **2018**; 66:163–71.
5. Wunderink RG, Giamarellos-Bourboulis EJ, Rahav G, et al. Effect and safety of meropenem-vaborbactam versus best-available therapy in patients with carbapenem-resistant Enterobacteriaceae infections: the TANGO II randomized clinical trial. Infect Dis Ther **2018**; 7:439–55.
6. Dellit TH, Owens RC, McGowan JE Jr, et al; Infectious Diseases Society of America; Society for Healthcare Epidemiology of America. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. Clin Infect Dis **2007**; 44:159–77.

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Chimeric Antigen Receptor T-cell Immunotherapy and Need for Prophylaxis for Invasive Mold Infections

To the Editor—We read with interest the report by Haidar et al regarding invasive mold disease (IMD) in patients receiving chimeric antigen receptor modified T-cell therapy (CARTT) [1]. Because this revolutionary treatment is frequently associated with cytokine release syndrome (that requires intense glucocorticoid-based immunosuppression) and prolonged cytopenias, the concerns of excess risk for IMD are logical. However, the independent contribution of CARTT to IMD risk remains to be seen as refractory underlying lymphoid malignancy, currently the most common indication for CARTT, remains a major confounder in risk assessment. In particular, experience preceding CARTT shows that a comparably low subset of heavily pretreated adult and pediatric patients with refractory ALL, with associated cytopenias and cumulative corticosteroid use (both known IMD risk factors), developed IMD [2]. In addition, the increasing use of more intensive induction/consolidation chemotherapies for ALL make these patients acute myeloid leukemia–like in terms of IMD risk [3], even without CARTT, rekindling the discussion regarding the need for antifungal prophylaxis in these patients [4]. As CARTT is being introduced earlier in the course of these malignancies, carefully conducted case-control prospective studies/registries, paired with immunogenetic profiling [5], could give more precision of the CARTT-associated IMD risk. For now, we would recommend more caution as we do not have prediction rules to decide who would be the patients to benefit from preemptive screening vs mold-active prophylaxis following CARTT for refractory lymphoid malignancies. The authors assert that "preemptive screening," with all the limitations listed in their discussion, is an option in institutions with < 6 % IMD rate and in patients not expected to have > 3 weeks of neutropenia (pre- or post-CARTT) or > 0.1 mg/kg/day of dexamethasone for > 7 days. The problem with those criteria is that modern hospitals have very low autopsy rates [6] and a significant proportion of IMD cases is still missed premortem [7, 8], even in the era of more sensitive fungal biomarkers. In addition, it would be hard to predict a priori who will develop prolonged cytopenia or requirement of significant corticosteroid use. Furthermore, important elements of immune responses against fungi (eg, monocytopenia, lymphopenia, even hypogammaglobinemia, a common condition post-CARTT) [9]—the type, dose, and frequency of CARTT—are not accounted for in the proposed algorithm. Until there is more experience about IMD risk, perhaps it would be prudent to start all patients with refractory lymphoid malignancy who are to receive CARTT on mold-active prophylaxis and to do a comprehensive baseline

workup for occult IMD before starting on CARTT. The excess cost and risk associated with posaconazole prophylaxis are miniscule in relation to the costs of CARTT [10]. The decision of whether to use a broad-spectrum triazole or an echinocandin as prophylaxis in these patients should be influenced by the prevalence of *Aspergillus* and non-*Aspergillus* molds (eg, Mucorales) in each institution and patient-level characteristics such as comorbidities and receipt of leukemia drugs that affect QTc interval. Finally, efforts to increase autopsy rates in patients who die following CARTT would shed light on the IMD risk.

Notes

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References

1. Haidar G, Dorritie K, Farah R, Bogdanovich T, Nguyen MH, Samanta P. Invasive mold infections after chimeric antigen receptor-modified T-cell therapy: a case series, review of the literature, and implications for prophylaxis [manuscript published online ahead of print 22 November 2019]. Clin Infect Dis **2020**; 71:672–6.
2. Georgiadou SP, Pongas G, Fitzgerald NE, et al. Invasive mold infections in pediatric cancer patients reflect heterogeneity in etiology, presentation, and outcome: a 10-year, single-institution, retrospective study. J Pediatric Infect Dis Soc **2012**; 1:125–35.
3. Cattaneo C, Monte S, Algarotti A, et al. A randomized comparison of caspofungin versus antifungal prophylaxis according to investigator policy in acute leukaemia patients undergoing induction chemotherapy (PROFIL-C study). J Antimicrob Chemother **2011**; 66:2140–5.
4. Cornely OA, Kontoyiannis DP. How to prophylax against invasive fungal infections in adult ALL? An unmet need. Mycoses **2018**; 61:646–9.
5. Brunel AS, Wójtowicz A, Lamoth F, et al. Pentraxin-3 polymorphisms and invasive mold infections in acute leukemia patients receiving intensive chemotherapy. Haematologica **2018**; 103:e527–30.
6. Lewis RE, Cahyame-Zuniga L, Leventakos K, et al. Epidemiology and sites of involvement of invasive fungal infections in patients with haematological malignancies: a 20-year autopsy study. Mycoses **2013**; 56:638–45.
7. Chamilos G, Luna M, Lewis RE, et al. Invasive fungal infections in patients with hematologic malignancies in a tertiary care cancer center: an autopsy study over a 15-year period (1989–2003). Haematologica **2006**; 91:986–9.
8. Multani A, Allard LS, Wangjam T, et al. Missed diagnosis and misdiagnosis of infectious diseases in hematopoietic cell transplant recipients: an autopsy study. Blood Adv **2019**; 3:3602–12.
9. Hill JA, Li D, Hay KA, et al. Infectious complications of CD19-targeted chimeric antigen receptor-modified T-cell immunotherapy. Blood **2018**; 131:121–30.
10. Bach PB, Giralt SA, Saltz LB. FDA approval of tisagenlecleucel: promise and complexities of a $475 000 cancer drug. JAMA **2017**; 318:1861–2.

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Reply to Lewis and Kontoyiannis

To the Editor—The points Drs Lewis and Kontoyiannis raise regarding the use of antimold prophylaxis for all chimeric antigen receptor (CAR) T-cell therapy recipients are extremely well-taken. The safety and efficacy of prophylactic posaconazole, for instance, have already been demonstrated in patients with acute myeloid leukemia (AML) and hematopoietic cell transplant (HCT) recipients receiving steroids for graft-vs-host disease [1, 2]. However, while other patients may intuitively benefit from universal antimold prophylaxis, the trial data are either lacking or less compelling. Indeed, the debate of whether all CAR T-cell therapy recipients should receive antimold prophylaxis mirrors not only that of patients with acute lymphoblastic leukemia [3, 4], but also that of allogeneic HCT recipients in the preengraftment period. These are 2 neutropenic and deeply immunosuppressed patient populations in whom the administration of antimold prophylaxis appears rational. However, because of the absence of convincing efficacy data and the presence of conflicting clinical trial data [5–7], respectively, the use of fluconazole prophylaxis (and not a mold-active azole) is currently recommended [4].

The challenge we face is to assimilate what is already known about invasive mold infections (IMIs) into protocols that can be applied to a new patient population. Based on the results of 3 studies and 1 abstract, the IMI rate after CAR T-cell therapy appears to be around 1%–7% [8–11]. While at least 1 of these studies meets the 6%–8% rate at which guidelines recommend the use of antimold prophylaxis [10], the number of studies performed in CAR T-cell recipients is still low, tempering our enthusiasm for universal prophylaxis. Among the concerns regarding the use of universal antimold prophylaxis is the emergence of breakthrough IMIs, which are often caused by resistant molds [12], as was the case for patient 2 in our series [11]. Thus, while it is not possible to predict which CAR T-cell recipients will become "AML-like," institutions may still elect to avoid universal antimold prophylaxis, in part to prevent breakthrough infections with resistant molds [12]. Additionally, much of outpatient azole use is hampered by high drug costs and capricious insurance policies [13], making it difficult to justify discharging patients on mold-active azoles that may not be covered by insurance providers when the benefit of these agents is unproven. Finally, the optimal duration of prophylaxis remains unclear.

Despite the emphasis of "background rate" risk stratification by several guidelines [4, 14], we acknowledge the challenges surrounding the "critical first step" of determining the local epidemiology of IMIs. It is nonetheless imperative that we generate estimates