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Letters to the Editor

Can We Kill Two Birds with This Stone? Anti-*Pneumocystis* Prophylaxis to Prevent *Nocardia* Infection in Hematopoietic Stem Cell Transplant Recipients

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To the Editor:

Nocardiosis is an opportunistic infection caused by *Nocardia* species (spp.), which are Gram-positive branching filamentous bacteria. In a recent issue of *Biology of Blood and Marrow Transplantation*, Molina et al. [1] studied the relationship between *Pneumocystis jirovecii* pneumonia (PJP) prophylaxis and *Nocardia* infections in allogeneic hematopoietic stem cell transplant (HSCT) recipients. Molina et al. [1] performed a retrospective study of nocardiosis among HSCT recipients at the University of California, Los Angeles (UCLA), Medical Center between 2000 and 2017. Around 1000 patients underwent allogeneic HSCT at this institution during the study period. Historically, cotrimoxazole was used to prevent PJP after transplantation, and *Nocardia* infection was very rare (only 1 case between 2000 and 2011). Importantly, the authors observed a dramatic increase in the incidence of *Nocardia* infections since 2012, when transplant physicians started to use atovaquone to prevent PJP, instead of cotrimoxazole (9 cases between 2012 and 2017). Most patients with nocardiosis (80%, n = 8) were receiving a prophylaxis other than cotrimoxazole when nocardiosis occurred; the 2 other patients were on cotrimoxazole prophylaxis (20%). All 10 patients had pulmonary nocardiosis, and all cases were culture-confirmed. It is concluded that the use of atovaquone for PJP prophylaxis in place of cotrimoxazole may be associated with an increased risk of nocardiosis in HSCT recipients. With the hope to prevent nocardiosis and other opportunistic infections, Molina et al. [1] re-emphasized the use of cotrimoxazole prophylaxis after HSCT. In response, we would like to make 3 comments.

First, most cases of nocardiosis occurred in 2015 (n = 6). Although the vast majority of *Nocardia* infections are sporadic, several reports suggested the possibility of *Nocardia* outbreaks affecting transplant units [2-4]. The fact that all the cases of nocardiosis described by Molina et al. [1] were pulmonary may suggest an airborne outbreak of *Nocardia*. Also, the fact that only 1 case was found the following year, when approximately the same number or HSCT recipients were given atovaquone to prevent PJP (37 patients in 2016 versus 34 patients in 2015) suggests that a *Nocardia* outbreak may have occurred in 2015. We would be interested to know whether this possibility has been explored, by combining microbiological and epidemiological data.

Second, the ability of laboratories to detect *Nocardia* infections depends on several factors, including incubation time and culture medium. The authors reported that in 2013—soon after atovaquone started to replace cotrimoxazole to prevent PJP—the local laboratory started to use a buffered charcoal-yeast extract medium for isolation of *Nocardia* species from clinical specimens. In our experience as well as in the literature [5-7], this culture medium has been found to be useful for the detection of *Nocardia* in clinical samples. The fact that 8 of the 10 cases (80%) of nocardiosis are reported by Molina et al. [1] to have occurred after this microbiological change may suggest that this modification increased their capacity

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to detect nocardiosis in HSCT recipients since 2013. However, we acknowledge that the absence of cases of nocardiosis in 2014 does make this hypothesis less likely.

Last, but not least, it is unclear whether cotrimoxazole (ie, the drug historically used to prevent PJP at the UCLA Medical Center) is efficient to prevent nocardiosis in transplant recipients. Despite the in vitro activity of cotrimoxazole against a vast majority of *Nocardia* spp. strains, and the undeniable efficacy of high-dose cotrimoxazole to treat nocardiosis (usually 10 to 20 mg/kg/day of trimethoprim), *Nocardia* infections may occur in transplant recipients receiving low-dose cotrimoxazole prophylaxis in the prevention of PJP [7-9]. Along the same line, 2 case-control studies concluded that the use of low-dose cotrimoxazole prophylaxis was not protective against nocardiosis in organ transplant recipients [10,11]. To our knowledge, this question has not been directly addressed in the field of HSCT. Whether the particular protocol used for cotrimoxazole prophylaxis at UCLA since the 1970s (trimethoprim 240 mg/sulfamethoxazole 1200 mg 3 times daily on 2 consecutive days of each week) is beneficial in the prevention of nocardiosis after transplantation, as compared with usual low-dose prophylaxis (eg, ≤160/800 mg 3 times weekly in the previously mentioned case-control studies), is an interesting question that has yet to be answered.

As a conclusion, we believe that cotrimoxazole has not consistently been demonstrated to prevent nocardiosis after transplantation. Given the multiple reports of *Nocardia* infections breaking through cotrimoxazole prophylaxis, and the possible severity of this opportunistic infection, it is important for clinicians to maintain a high degree of suspicion for nocardiosis in HSCT recipients, independently of the prophylaxis used to prevent PJP.

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Response

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Response: We thank the authors for their comments, which we addressed in the discussion of our article. We found no evidence of a *Nocardia* outbreak to explain the increase in nocardial infections, which occurred over a period of several years at multiple locations [1]. Furthermore, because the lung is the most common site of nocardial infection in both sporadic cases and in reported outbreaks, the occurrence of only pulmonary cases in our report does not necessarily imply a localized outbreak. We also began seeing more cases of nocardiosis before the change in culture methods for isolation of *Nocardia* species. Finally, we acknowledge in our article on several occasions that the degree to which trimethoprim-sulfamethoxazole (TMP-SMX) protects against nocardial infection after allogeneic hematopoietic stem cell transplantation (HSCT) is not entirely clear. Nonetheless, similar to our experience, most patients in previous studies of nocardiosis after HSCT were also not taking TMP-SMX prophylaxis [2-6]. Both the dose of TMP-SMX and the duration of prophylaxis may determine the effectiveness of TMP-SMX for prevention of nocardiosis. The 2 patients in our article who developed nocardiosis on TMP-SMX were either on a low dose given only 3 times weekly or had received TMP-SMX prophylaxis for only 2 weeks. Breakthrough nocardial infections reported by others have also occurred primarily on low doses of TMP-SMX [2-6]. In contrast, the high doses of TMP-SMX used at UCLA for *Pneumocystis jiroveci* pneumonia (PJP) prophylaxis, which were associated with only 1 case of nocardiosis over 11years from 2000 to 2012, may be more effective for prevention of nocardiosis and PJP than atovaquone prophylaxis.

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