

Galactomannan Testing During Mold-Active Prophylaxis

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(See the Major Article by Duarte et al on pages 1696–702.)

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Choosing a prophylactic approach is a strategic decision impacting the choice, timing, and even the indication of in vitro diagnostic tests and antifungal treatments. In the past, clinical studies informing clinical decisions were conducted in settings without prophylaxis. One may object, that empiric antifungal treatment trials allowed enrolling patients on antifungal prophylaxis with fluconazole and itraconazole. However, prophylaxis with these older azoles cannot be considered effective in preventing mold infection in pivotal protocols [1–3].

There is a debate on how to treat patients with breakthrough infections during posaconazole or voriconazole prophylaxis. To date, no convincing trial addresses this clinically challenging question, likely

because of the very low breakthrough rates observed [4–6]. Today's diagnostic gold standard still depends on tissue sampling, a principle unchanged since the 19th century [7, 8].

In this issue of *Clinical Infectious Diseases*, Duarte et al report their experience with posaconazole prophylaxis in hematological populations at high risk. The Catalan Institute of Oncology, Barcelona, is one of the premier cancer centers in Spain and their prospective 4-year study period covers 121 patients and 262 consecutive treatment episodes. The study focuses on the effect of prophylaxis on in vitro diagnostics, namely, serum galactomannan testing in a population on active prophylaxis.

During posaconazole prophylaxis, the rate of positive galactomannan screening tests was low, which is in line with previous observations in animal models and in humans [9, 10]. Interference of the posaconazole molecule with the assay itself appears unlikely, although false-negative serum results have been reported in the past [11]. When posaconazole is used prophylactically, the performance of galactomannan screening tests is impacted by the very low pretest probability of invasive fungal infection (IFI); in other words, successful prophylaxis results in low IFI breakthrough rates. In that setting, one hardly detects a case of aspergillosis

by galactomannan testing, but false-positive results become important, as they trigger a diagnostic workup and have the potential to mislead the clinician. It is important to know that we can harm simply by applying in vitro diagnostics, if the false-positive results outnumber the true positives. Actually, galactomannan screening may not be advisable at all during effective antifungal prophylaxis. Many centers must have observed this, but none published their observation as result of a prospective study. Thanks to the very timely study of Duarte et al, we now have evidence to personalize diagnostics according to the initial strategic decision.

How do Duarte's findings affect prophylactic strategies? At the University Hospital of Cologne, galactomannan screening 3 times weekly was routine practice when posaconazole prophylaxis was introduced in January 2006 [11, 12]. In 2003–2005, we ran 6950 serum galactomannan assays on samples of 190 patients, or 35 galactomannan tests per patient. When we abandoned galactomannan screening during prophylaxis in 2009, the average number substantially decreased to 8 galactomannan tests per patient (2391 tests in 273 patients) (Cologne Cohort of Neutropenic Patients, NCT01821456).

Should we stop all galactomannan testing? There is at least one caveat: The pretest probability of the galactomannan

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test increases, if the test is not used for screening but for confirmation of IFI in symptomatic patients. Persistent fever of unknown etiology should always trigger a chest computed tomographic scan regardless of posaconazole prophylaxis, as any lung infiltrate should prompt bronchoalveolar lavage for microbiological and virological workup [13]. In Cologne we do, for example, test galactomannan on bronchoalveolar lavage fluid, although there is an ongoing debate regarding its diagnostic value [14–16]. Our infectious diseases team further advises that an investigational galactomannan test series be done over 5 consecutive days to confirm the diagnosis of invasive aspergillosis. Therefore, we quite intensely use galactomannan for the purpose of confirming disease, in a situation where the positive predictive value reaches almost 90%.

Importantly, Duarte reminds us that the result of any in vitro diagnostic assay needs to be interpreted in the clinical context. Appreciating all known uncertainties of the galactomannan assay, there are populations where galactomannan screening is considered state of the art [17]. In acute lymphoblastic leukemia, vinca alkaloids are a cornerstone of induction chemotherapy regimens, but mold-active azoles inhibit their metabolism, resulting in neuropathy [18]. Azole prophylaxis is not recommended, and alternative prophylactic regimens are currently undergoing clinical evaluation (eg, in the Ambiguard trial [NCT01259713]).

In general, it becomes apparent that we need more advanced in vitro diagnostic assays. Ideally these would detect not only *Aspergillus* species, but other unmet clinical needs, for example, in managing mucormycosis [19]. Although we may have to wait for such tests to arrive, what we can tackle immediately is education. Every large hospital treating patients with hematological malignancy should

establish multidisciplinary teams focusing on infections in these patients, because management of invasive fungal infection is far too complex to be dealt with by one specialty alone.

Note

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