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Incidence of Breakthrough Fungal Infections in Patients With Isavuconazole Prophylaxis: A Systematic Review and Meta-analysis

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Background. Isavuconazole (ISA) is a newer triazole that has activity against most mold species and has been utilized for prophylaxis as well as treatment in patients with hematologic malignancies (HM) and hematopoietic stem cell transplant (HSCT). However, several studies have documented breakthrough invasive fungal infections (bIFIs). Thus, we conducted a systematic review and meta-analysis to investigate the incidence of bIFIs among patients receiving ISA prophylaxis.

Methods. We conducted a systematic review and meta-analysis of the published literature using the concept of ISA, HSCT, and HM from 5 search engines. In patients with HSCT and HM, the pooled incidence of bIFI while undergoing ISA prophylaxis was calculated via the DerSimonian-Laird random effect model.

Results. The systematic review and meta-analysis included 35 and 19 studies, respectively. In total, 991 patients were identified as using ISA prophylaxis, and the majority had either acute myeloid leukemia or myelodysplastic syndrome (69.9%). The pooled incidence of proven/probable bIFI was 7% (95% CI, 4%–12%, $I^2 = 55\%$). The most common pathogen was *Aspergillus* species (43.1%), followed by *Candida* (22.4%) and Mucorales (12.1%). In 19 studies, mortality rates were documented and ranged between 0% and 100%; the majority of which were >50%.

Conclusions. In patients with HM or HSCT, we found a high incidence of bIFI while undergoing ISA prophylaxis, with high mortality. Given the lack of randomized clinical trials evaluating ISA in this indication, its role in prophylaxis remains unclear.

Keywords. breakthrough; hematologic malignancy; invasive fungal infections; isavuconazole; prophylaxis.

Isavuconazole (ISA) is a relatively newer triazole that has activity against most invasive mold species, including *Aspergillus* and Mucorales, although it is not generally active against *Scedosporium* species [1].

According to previous clinical studies in patients with invasive aspergillosis (IA) and invasive fungal diseases, ISA showed non-inferior clinical outcome when compared to voriconazole (VOR), as the first line therapeutic antifungal agent for IA, and showed comparable clinical response for mucormycosis when compared to Amphotericin B, as the first line therapeutic agent for mucormycosis [2–5]. In addition, ISA has in vitro activity against many yeasts, such as most *Candida*, *Cryptococcus*, and *Trichosporon* species, although ISA could not demonstrate noninferiority to echinocandin agents for treatment of invasive candidiasis in a randomized clinical trial [1, 6]. Furthermore, ISA has a more favorable adverse effect profile when compared with VOR and posaconazole (POS) [1, 2, 7–9]. Additionally, therapeutic drug monitoring, which is required for patients receiving VOR or POS, is not generally needed for patients receiving ISA [10, 11].

Although guidelines acknowledge the use of ISA for prophylaxis of invasive fungal infections (IFIs) in addition to VOR and POS, in patients with high-risk hematologic malignancies (HM), including allogeneic hematopoietic stem cell transplant (HSCT) recipients, to reduce risk of IFIs [12], however, data is limited [12, 13]. Nonetheless, breakthrough IFIs (bIFIs) have been reported in such high-risk cases despite receipt of these antifungal agents, which have good efficacy against many fungi [14].

A recent systematic review focused on bIFIs among patients receiving VOR and POS [15]. It provided detailed information

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of causative fungal pathogens of the IFIs. In contrast, our understanding regarding bIFIs among patients receiving ISA has been limited to several single-center published studies, with significant heterogeneity among patient populations and characteristics. Thus, we conducted a systematic review and meta-analysis to clarify the clinical characteristics of ISA bIFIs, including incidence of bIFIs, distributions of causative fungal pathogens, and treatment strategies among patients with HM and HSCT.

MATERIALS AND METHODS

Our review was conducted with guidance from the MECIR manual (Methodological Expectations of Cochrane Intervention Reviews) [16] and reported following the PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-analyses; Supplementary Figure 1) [17].

Search Methods

We conducted a comprehensive database search to find all relevant literature regarding use of ISA as prophylaxis among patients with HM and HSCT.

The search strategy was developed by an academic health science librarian (J. R.) in consultation with the project leaders (M. R. and Y. N.) and was reviewed by an independant librarian using the PRESS tool (Peer Review for Electronic Search Strategies) [18]. MeSH terms, EMTREE terms, and text words were used for the concepts of ISA, bone marrow and stem cell transplants, hematologic malignancies, and their synonyms. We searched Medline (Ovid, MEDLINE-ALL), Embase (Elsevier, Embase.com), Cochrane CENTRAL (Cochrane Library, Wiley), Scopus (Elsevier), and the Web of Science platform (Clarivate). The search strategy was written for Ovid Medline and translated with each database's syntax, controlled vocabulary, and search fields. The Medline search strategy was adapted for other databases in part with use of the Institute for Evidence-Based Healthcare's Polyglot Search Translator [19]. No language, date, or other limits were applied. All databases were searched 16 and 17 March 2023 and 10 September 2024. For full search strategies and database segments, see the supplementary appendix. All citation records were downloaded to EndNote 20 (EndNote Team) and uploaded to Covidence web-based software for deduplication, screening, and full-text evaluation [20]. We did not contact any study authors, manufacturers, other experts, or search study registries, nor did we review the studies included in systematic reviews on related topics. The Retraction Watch database and journal websites were checked for retractions of the included studies. Two independent reviewers (K. I. and M. H.) at first conducted title and abstract screening, followed by full-text assessment. Any discrepancies were resolved by third reviewer (M. R.). Two reviewers (K. I. and M. H.) independently assessed all studies for risk of bias.

Inclusion and Exclusion Criteria

We included all randomized clinical trials, cohort studies, and case reports that investigated the use of ISA as primary and secondary prophylaxis in patients with HM, HSCT, or chimeric antigen receptorT-cell therapy (CAR-T). All cases of ISA used for prophylaxis were included, regardless of the duration of administration or dosage. We excluded studies and cases involving patients without HM or HSCT or where ISA was used for treatment of IFIs. For meta-analysis, we included only studies with a total cohort size of $\geq$10 patients.

Data Extraction

The following variables were extracted: study design, year of publication, number of patients with ISA prophylaxis, country, age, gender, number of patients with HM and type of malignancy, number of patients with HSCT or CAR-T, duration of ISA, reason for stopping prophylaxis, number of patients with bIFIs, duration from ISA initiation to occurrence of bIFIs, sites of bIFIs, pathogen of bIFIs, criteria used by the authors for diagnosis, antifungal susceptibility of causative fungal pathogen, antifungal agents used to treat bIFIs, and mortality after bIFIs.

Definitions

To classify IFIs as possible, probable, or proven, we used EORTC/MSG criteria (European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group) or author definitions similar to EORTC/MSG criteria [21, 22]. We included all bIFIs as defined by the authors in each study.

Outcome

Primary outcome was pooled incidence of proven or probable bIFI in patients receiving any type of ISA prophylaxis (primary, secondary, and not otherwise specified) according to EORTC/MSG 2008 criteria. Secondary outcomes were as follows:

- Pooled incidence of possible, probable, or proven bIFI in patients undergoing any type of ISA prophylaxis according to EORTC/MSG 2008 criteria
- Pooled incidence of bIFI per author definition in patients using ISA as the only primary prophylaxis
- Pooled incidence of bIFI per author definition in patients receiving any type of ISA prophylaxis

Data Analysis

Meta-analysis was done in R version 4.0.1. The R packages *meta*, *metafor*, and *metasens* were used to estimate the summary effect size. Incidence of bIFIs was shown as a proportion/percentage of individuals who developed bIFIs while prescribed ISA over the total number of patients with ISA. Freeman-Tukey double-arcsine transformation was applied to

all studies to make them follow a normal distribution, which enables accurate estimation of the summary proportion. Pooled effect size was calculated per the DerSimonian-Laird random effect model. The transformed summary proportion was converted to the original proportion and reported. The forest function within the R package *meta* was used to create forest plots. Heterogeneity among studies were assessed with I^2 values. Publication bias was assessed by Doi plot and Luis Furuya-Kanamori (LFK) index. The LFK index is explained elsewhere [23], where a result between −1 and +1 is consistent with symmetry in a Doi plot (ie, no publication bias) while a result less than −1 or more than +1 is not consistent with symmetry in a Doi plot (ie, publication bias).

RESULTS

Included Studies

With this search strategy, we found 896 potential unique studies after excluding the duplicates. Of these, 787 studies were excluded during the abstract and title review as they did not meet eligibility criteria (Figure 1). As a result, we conducted a full-text review for 109 articles, of which 74 were excluded. The most common reasons for exclusion were wrong patient population/setting. Finally, 35 studies were included in the full systematic review [9, 14, 24–56], and 19 studies with ≥10 patients were included in the meta-analysis [9, 24–41]. Among all 35 studies, the total number of bIFIs was 133 among 991 patients undergoing ISA prophylaxis [9, 14, 24–56].

Demographic and Clinical Characteristics of Patients

A total of 991 patients were identified as using ISA for prophylaxis [9, 14, 24–56]. Among 691 patients for whom we could identify the indication for ISA prophylaxis, primary and secondary prophylaxis was given in 650 (94.1%) and 41 (5.9%), respectively. Twenty-six studies specified the types of HM for 674 patients, with the most common being acute myelogenous leukemia/myelodysplastic syndrome (471/674, 69.9%) [9, 24–27, 29, 30, 33, 35–38, 40, 41, 43–47, 49, 50, 52–56]. Eight studies specified underlying HSCT, with 248 allogeneic, 2 autologous, and 191 undefined [9, 26, 31, 32, 34, 38, 39, 45]. Of note, 2 studies identified a total of 3 CAR-T recipients [26, 38].

Incidence of bIFIs

For the primary outcome, we analyzed the pooled incidence of probable or proven bIFI in ISA prophylaxis utilizing EORTC/MSG 2008 criteria. The incidence was 7% (95% CI, 4%–12%; I^2 = 55%; Figure 2*A*) with an LFK index of −0.87 (Supplementary Figure 2) from 9 studies [9, 24, 26–28, 30, 33, 36, 41]. For a secondary outcome, we analyzed the pooled incidence of possible, probable, or proven bIFI utilizing EORTC/MSG 2008 criteria among ISA prophylaxis. This incidence was 9% (95% CI, 5%–14%; I^2 = 65%; Supplementary Figure 3) from 10 studies (Figure 2*B*) [9, 24, 26–28, 30, 33, 36, 39, 41]. Finally, the pooled incidence rates of bIFI in primary prophylaxis and any type of prophylaxis (primary, secondary, and unspecified) were, respectively, 9% (95% CI, 5%–14%; I^2 = 69%) [9, 24–30, 34, 36, 38, 41] and 7% (95% CI, 4%–11%; I^2 = 74%) [9, 24–41] (for forest plots, see Figure 2*C* and 2*D*; for Doi plots, see Supplementary Figures 4 and 5).

Clinical Characteristics of Breakthrough Infections

Supplementary Table 1 summarizes each study, number of patients undergoing ISA prophylaxis, number of bIFIs, and number of deaths from bIFIs. Sites of infections were identified in 79 patients across 24 studies (Table 1), which included 47 lung and 20 bloodstream infections [9, 24–26, 28–30, 32, 33, 38, 39, 42–47, 49, 50, 52–56]. The onset of bIFIs varied from study to study, and the range of time from start of ISA to bIFI was 6 to 400 days [24, 26, 28–30, 38, 39, 42, 45, 49, 50, 53, 54]. According to 3 studies, the median time from initiation of ISA to bIFI was 22, 14, and 68 days [24, 26, 38].

Table 2 shows fungal pathogens across 21 studies per the EORTC/MSG 2008 criteria. The most predominant was *Aspergillus* species (25/58), which included cases with a combination of galactomannan antigen and culture, followed by *Candida* (13/58), Mucorales (7/58), and *Fusarium* species (4/58) [9, 14, 24, 26–28, 30, 33, 36, 39, 41, 43, 45–48, 50, 53–56]. Even though some studies showed breakthrough candidemia as a primary cause [9, 28], invasive mold infections were the most common etiology for bIFIs in this systematic review. For example, in the Fontana et al study, *Aspergillus* species were the most common mold (58.3%), followed by *Fusarium* species (16.7%) and Mucorales (16.7%) [26].

ISA Serum Concentration and bIFI

Out of 35 studies in the systematic review, 4 outlined ISA serum concentrations in detail [24, 26, 38, 50]. Bose et al [24] checked serum concentrations on days 8 and 15 after initiation of prophylaxis, with median levels of 3.37 μg/mL (range, 1.81–7.65) and 3.95 μg/mL (range, 1.56–9.25 μg/mL), respectively. When ISA serum concentrations were compared between the bIFI and non-bIFI groups, there was no difference in concentrations checked on day 8. However, the authors observed a higher serum concentration in patients with bIFI vs those without when checked on day 15. Overall, Bose et al did not find any association between bIFI and low serum concentration of ISA. Of note, the median time to develop bIFI was 22 days (range, 8–57) from ISA initiation. Fontana et al [26] checked ISA serum concentrations in 5 bIFI cases, all within 72 hours after diagnosis (3.3, 3.4, 3.7, 4.3, and 6.3 μg/mL). Khatri et al [38] reported serum concentrations in 6 patients with bIFI within 7 days after diagnosis, with a median level of 3.65 μg/mL (range, 1.7–5.1).

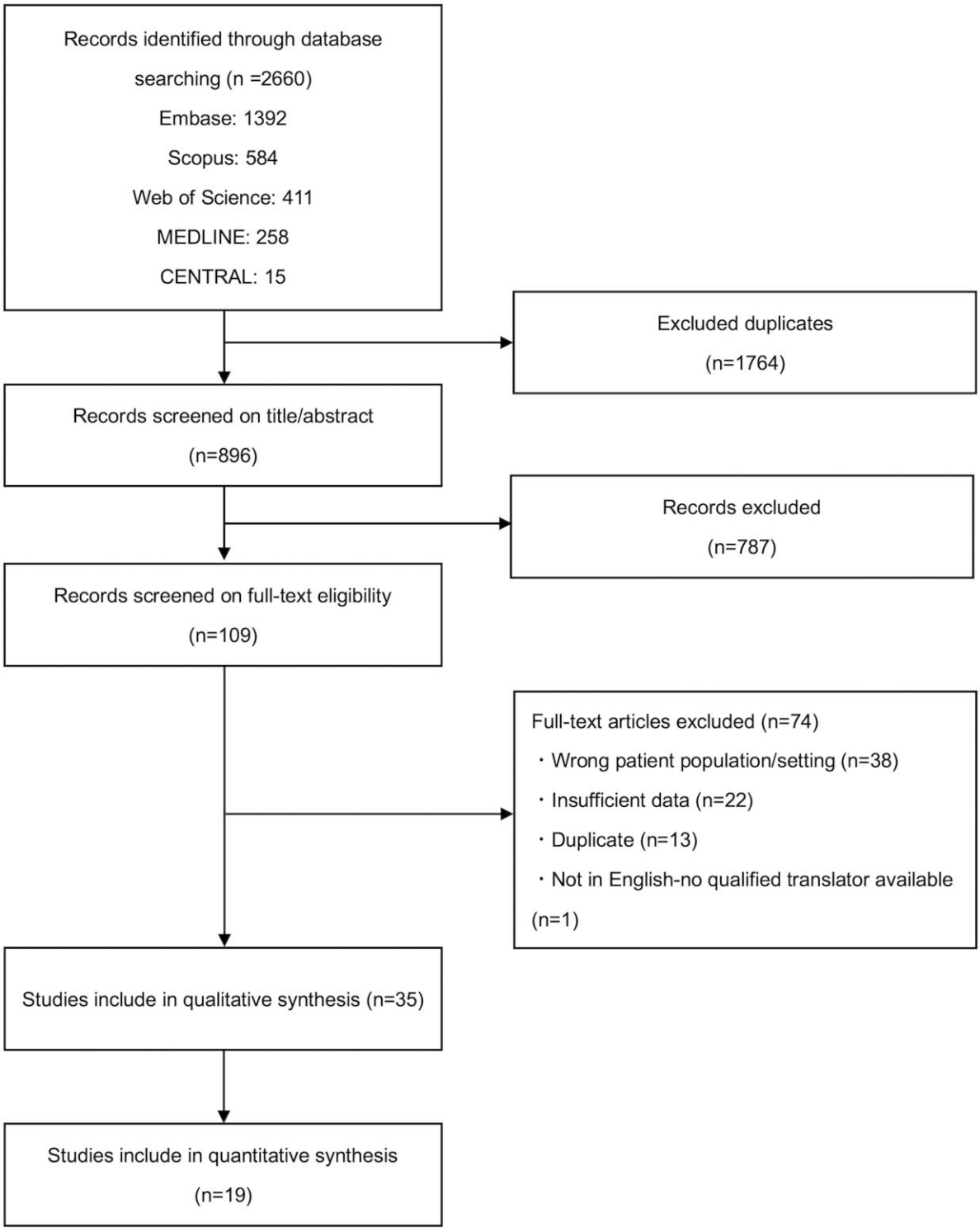

Figure 1. Study selection flow.

Treatment and Outcomes of bIFIs

Treatment regimens were recorded in 51 patients from 15 studies (Table 3) [24–26, 38, 39, 42, 43, 45–47, 50, 52–54, 56]. Out of 51 patients, 24 and 24 patients received monotherapy and combination therapy, while 3 patients had no change in treatment. Overall, the most commonly used regimen for treatment in bIFIs was a combination of liposomal amphotericin B (L-AMB) and POS (10/51), followed by L-AMB alone (8/51).

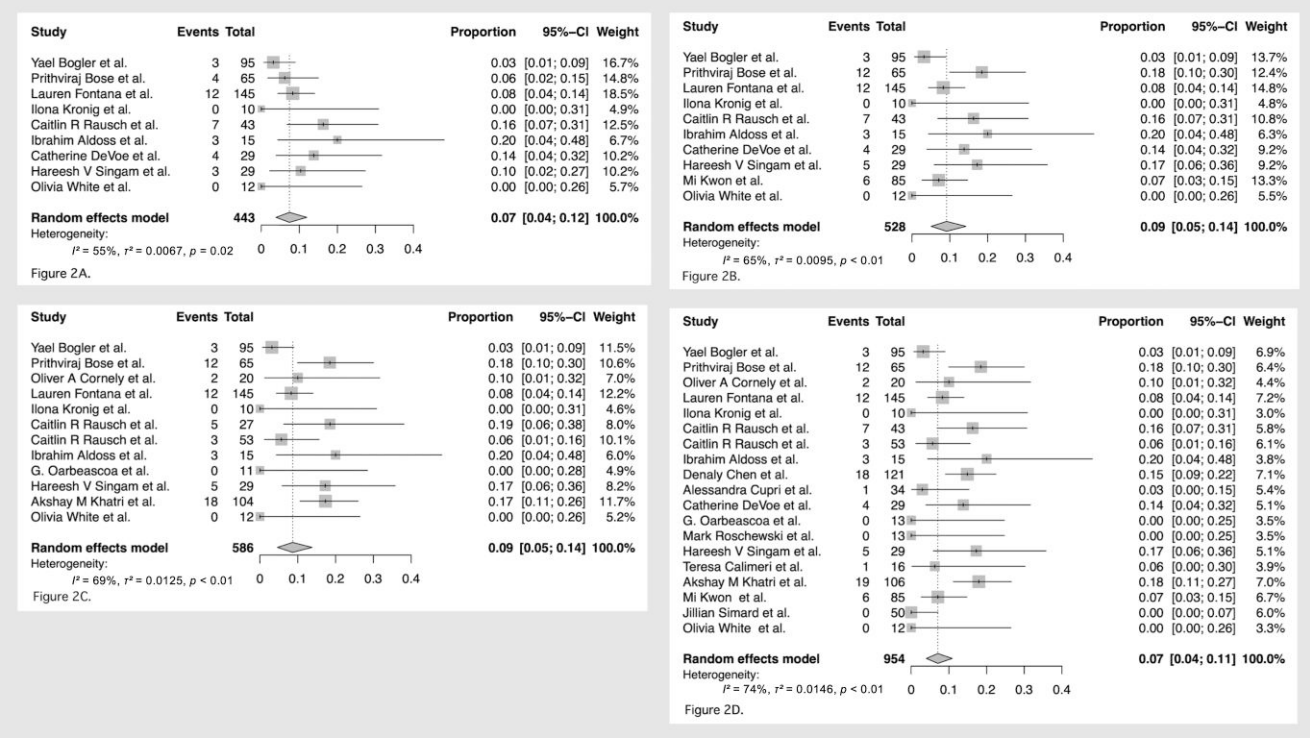

Figure 2. Pooled incidence of bIFI. *A*, Pooled incidence of proven or probable bIFI in patients receiving any type of ISA prophylaxis, according to the EORTC/MSG 2008 criteria. *B*, Pooled incidence of possible, probable, or proven bIFI in patient undergoing any type of ISA prophylaxis, according to the EORTC/MSG 2008 criteria. *C*, Pooled incidence of bIFI per author definition in patients using ISA as the only primary prophylaxis. *D*, Pooled incidence of bIFI per author definition in patients receiving any type of ISA prophylaxis. bIFI, breakthrough fungal infection; EORTC/MSG, European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group; ISA, isavuconazole.

In addition, switching from ISA prophylaxis to a regimen based on L-AMB and/or echinocandin was performed in 40 of 51 cases.

The number of patients with bIFI who died was documented in 19 studies (Supplementary Table 1) and ranged from 0% to 100% [9, 24–26, 28, 29, 33, 38, 39, 42, 43, 45–47, 50, 51, 53, 54, 56], nearly half of which at >50% [26, 28, 39, 42, 45, 47, 54]. We analyzed 4 studies that included a cohort of ≥10 patients with bIFI, finding a pooled mortality of 42% (95% CI, 25%–61%; I^2 = 47%; LFK index, −0.55; for forest and Doi plots, see Supplementary Figures 6 and 7) [24, 26, 38, 51].

DISCUSSION

To the best of our knowledge, this is the first systematic review and meta-analysis to investigate the incidence, outcomes, and most common fungal pathogens with bIFIs in patients with HM and HSCT receiving ISA solely as prophylaxis. We found a high incidence of bIFIs and a poor outcome after diagnosis of bIFI.

Antifungal prophylaxis is recommended during neutropenia in patients with HM and recipients of HSCT, as well as in patients with severe graft-vs-host disease [5, 12]. Given the significant drug-drug interactions due to cytochrome P450 inhibition by VOR and POS, as well as potential for QT prolongation, more centers, especially in the United States, opt to use ISA as their choice of agent for fungal prophylaxis, given the more favorable side effect profile and the data of treatment against IPA and mucormycosis in adults [24, 29]. However, our meta-analysis showed a 7% pooled incidence of probable or proven bIFI, which is higher than that of bIFIs in POS and/or VOR at <3.2% [57–59]. Yet, there was a similar trend when it came to sites of infection. With VOR and POS prophylaxis, lung and disseminated infections were the 2 most common bIFIs, as similarly observed with ISA prophylaxis (Table 1). In a recent systematic review by Boutin et al [15], the most common pathogens in patients with bIFIs while undergoing VOR and POS were *Aspergillus* (39.9%), Mucorales (20.0%), and *Candida* (18.4%), with *Fusarium* species being the least common (9.1%). In our systematic review, *Aspergillus* species was the most common pathogen in ISA bIFIs, followed by *Candida*, Mucorales, and *Fusarium* species. Invasive mold and *Candida* infection had poor outcomes. In our systematic review, a similarly high mortality, approximately 40%, was observed after bIFI in POS, VOR, and ISA [15].

We had 2 hypotheses to explain this high incidence of bIFI with ISA: low serum concentrations and resistant pathogens.

Table 1. Sites of Infection of Breakthrough Invasive Fungal Infection From 24 Studies

Infection	No. (%)
Total	79 (100)[a]
Lung	42 (53.2)
Sinus	7 (8.9)
Esophagus	1 (1.3)
Skin	1 (1.3)
Disseminated	28 (35.4)
Bloodstream	14
Lung + bloodstream	1
Lung + bloodstream + skin	1
Lung + brain	1
Lung + skin	2
Skin + bloodstream	2
Skin + bloodstream + bone	1
Peritoneal + bloodstream	1
Not otherwise described	5

All patients were receiving either primary or secondary isavuconazole prophylaxis.

[a]Out of 133 unique patients, site of infection was identified in 79 patients from 24 studies.

Table 2. Fungal Pathogens of 21 Studies Using EORTC/MSG 2008 Criteria

Pathogen	No. (%)
Total	58 (100)
Yeast	14 (24.1)
Proven IFI	14
Probable IFI	0
Candida spp	13 (22.4)
C albicans	1
C glabrata	5
C parapsilosis	3
C krusei	1
C gulliermondii	1
Trichosporon spp	1 (1.7)
T asahii	1
Mold	40 (69.0)
Proven IFI	11
Probable IFI	24
Proven or probable IFI	5
Aspergillus spp	25 (43.1)
A fumigatus	10
A niger	2
A calidoustus	1
Species not specified	6
Galactomannan positive	6
Mucorales	7 (12.1)
Rhizopus spp[a]	3
Mucor spp	1
Syncephalastrum spp[b]	1
Genus/species not specified	2
Fusarium spp	4 (6.9)
F dimerum	1
F fujikoroi	1
F lactis	1
Species not specified	1
Scedosporium spp	3 (5.2)
S apiospermum	2
Species not specified	1
Exserohilum spp	1 (1.7)
E rostratum	1
Fungi not otherwise described	4 (6.9)
Proven IFI	1
Probable IFI	3

Fungal pathogens fulfilling proven and probable IFIs are included. All patients were receiving either primary or secondary isavuconazole prophylaxis. Fifty-eight proven or probable IFIs occurred in 58 patients.

Abbreviations: EORTC/MSG, European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group; IFI, invasive fungal infection.

[a]One of 3 *Rhizopus* species was identified as *R microspores* or *asygosporus*.

[b]*Syncephalastrum* species was identified as *S monosporum* or *racemosum*.

Regarding serum concentration of ISA, we identified only 4 studies [24, 26, 38, 50]. The concentration of ISA was obtained before the bIFI [24] or around the time thereof [26, 38, 50]. We hypothesized that the serum concentrations of ISA in the bIFI group should be on the low side, although no study proved this to be true. In fact, one study [24] showed an even higher serum concertation of ISA in patients with bIFI when compared with patients without. Moreover, all studies reported adequate serum concentrations as shown in prior industry-sponsored clinical trials [2, 60], hence making bIFI due to subtherapeutic ISA serum concentration a low likelihood.

Regarding potential resistant pathogens, this remains to be seen. One explanation may be the potential to develop specific resistance patterns against ISA, such as overexpression of efflux pumps or alterations in the *Cyp51A* gene affecting targeted enzymes [61, 62]. However, in our systematic review, only 1 case report discussed susceptibilities and resistant genes against ISA, and no such genotypic or phenotypic resistance was found [54]. Hence, no concrete conclusions can be derived regarding resistance of fungal pathogens as a potential cause for breakthrough, nor as to why incidence of bIFI with ISA is higher compared to VOR or POS.

This study had several inherent limitations. First, the total sample size is small, and there is variation in the dose and duration of treatment among the included cases. Second, the study did not categorize the severity of graft-vs-host disease and HM, the presence or absence of recurrence, treatment regimens for HM, and the duration of neutropenia, which are important host factors that may influence the development of bIFIs. Third, the variability of definitions for IFIs among studies may have attributed to heterogeneity. To overcome this issue, we conducted an analysis only for studies based on the EORTC/MSG 2008 criteria to calculate the incidence of the IFIs. Interestingly, the subgroup analysis did not significantly change the incidence (7%–9%; Figure 2*B*–*D*). However, as expected, lower heterogeneity was observed with the EORTC/MSG 2008 criteria. In addition, some publication bias was identified for the pooled incidence of bIFI with any type of prophylaxis (primary, secondary, and unspecified). Among analyses for all types, we also find high heterogeneity. Moreover,

Table 3. Treatment of Breakthrough Invasive Fungal Infection From 15 Studies

Treatment	No. (%)
Total	51 (100)
Monotherapy	24 (47.1)
L-AMB	8
VOR	5
POS	3
MIC	6
CAS	2
Combination therapy	24 (47.1)
L-AMB–containing regimens	21
L-AMB + VOR	6
L-AMB + POS	10
L-AMB + CAS	2
L-AMB + TER	1
L-AMB + POS + MIC + TER	1
L-AMB + fosmanogepix	1
Other regimens	…
VOR + MIC	2
POS + CAS	1
No treatment[a]	3 (5.9)

All the patients were receiving either primary or secondary isavuconazole prophylaxis.

Abbreviations: CAS, caspofungin; L-AMB, liposomal amphotericin B; MIC, micafungin; POS, posaconazole; TER, terbinafine; VOR, voriconazole.

[a]Patients classified as *no treatment* continued isavuconazole after the onset of breakthrough invasive fungal infections.

duration of follow-up varied significantly among studies, hence limiting the ability to calculate a cumulative incidence of bIFIs.

In conclusion, the present study suggests a high incidence of bIFI, around 7%, when ISA is administered as prophylaxis for patients with HM and HSCT. Due to the high incidence of bIFI seen with ISA prophylaxis and the lack of randomized controlled trials to evaluate ISA in this indication, its role in antifungal prophylaxis remains unclear.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Potential conflicts of interest. All authors: No reported conflicts.

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