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Treatment pathways, switches, and inappropriate treatment during invasive pulmonary aspergillosis: real-world experiences from a global research network study

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ABSTRACT Despite advancements in diagnosing and treating invasive pulmonary aspergillosis (IPA), there is limited knowledge of real-world treatment pathways and medication switches. We queried the TrinetX global research network database and identified 5,410 patients diagnosed with IPA. The most common initial treatments were voriconazole (49%), fluconazole (11%), and posaconazole (7%). Most patients remained on voriconazole (80%) or isavuconazole (78%) throughout the treatment duration. Switches were more frequent for those initially treated with fluconazole, echinocandins, or posaconazole.

KEYWORDS *Aspergillus*, invasive pulmonary , aspergillosis, mortality, drug therapy

Invasive pulmonary aspergillosis (IPA) is a fungal infection of the lungs caused by *Aspergillus* species. It remains a significant clinical challenge, with a higher mortality rate in immunocompromised individuals, such as those undergoing therapy for acute leukemia or lymphoma. The incidence of IPA continues to increase—affecting additional vulnerable populations—highlighting the need to improve therapeutic decision-making (1). Despite advancements in diagnosis and treatment, there remains limited knowledge of treatment pathways in IPA. We sought to characterize the treatment preferences, switches, and pathways of patients diagnosed with IPA using a "real world" international global health network database.

The TrinetX global research network database was queried to identify adult patients with IPA diagnosis based on the ICD-10 code (B44.0) in May 2023 (2). We captured treatment pathways within the TrinetX platform for all patients diagnosed with IPA. Treatment pathways were assessed within 3 months following IPA diagnosis. A line of treatment was defined as receipt of the same medication within 3 days of IPA diagnosis, and it was considered complete once absent from the patient's record for 3 consecutive days. Graphs were designed using GraphPad Prism version 8.0.0 for Windows (GraphPad Software, San Diego, CA, USA).

We identified 5,410 patients with IPA, of which 3,705 had treatment pathways available. The average age at diagnosis was 56.9 ± 16.6 years, with the majority (64%) being white men. Also,13% were Black or African American individuals, and 7% were Hispanic. The most common comorbidities were aplastic anemia (54%), chronic lower respiratory diseases (38%), malignant neoplasms of the lymphoid tissue (31%), and solid organ transplant recipients (23%). The most frequent initial treatments in patients with IPA were voriconazole (49%), fluconazole (11%), posaconazole (7%), echinocandins (5%), voriconazole combined with an echinocandin (5%) and isavuconazole (5%). Itraconazole (3%) and voriconazole combined with amphotericin B (1.4%) were used less frequently (Fig. 1). Dual azole therapy was reported in 5% of patients. The mean number of days from diagnosis to treatment onset was: voriconazole, 8.4 ± 14.5 [median = 2 (range

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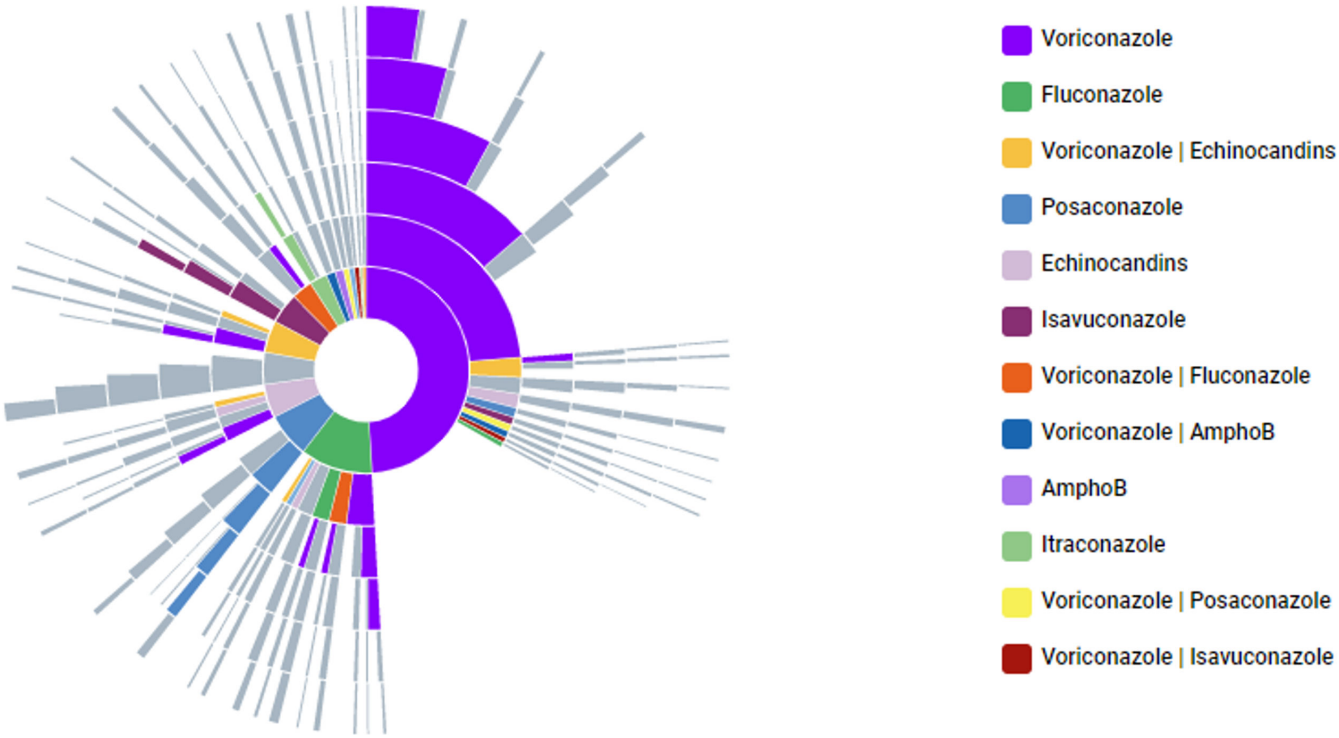

FIG 1 Treatment pathways in invasive pulmonary aspergillosis Sunburst diagram of initial treatment choices for IPA. Each ring represents a line of treatment. The inner side ring is the initial treatment choice. Subsequent rings represent switches. A ring or line of treatment was defined as receipt of the same medication within 72 h of IPA diagnosis, and it was considered complete once absent from the patient's record for 72 h. The gray color is unknown or other non-listed treatments.

0–90)]; isavuconazole, 8.6 ± 16.6 [median = 1 (0–85)]; posaconazole, 8.7 ± 15.8 [median = 1 (0–79)]; voriconazole plus an echinocandin, 5.2 ± 9.4 [median = 1 (0–68)]; fluconazole, 6.0 ± 12.1 [median = 1 (0–87)]; and echinocandins, 7.9 ± 13.4 [median = 3 (0–84)]. The average duration of treatment for voriconazole was 6.2 ± 5.2 days and 6.0 ± 12.1 days for fluconazole. Voriconazole (65% vs 25%) was used more often than fluconazole in patients with an absolute neutrophil count <500 cells/mm^3.

Switches were more frequent for fluconazole (43%), and an echinocandin (37%), followed by posaconazole (15%), voriconazole (11%), isavacunazole (10%), and the combination of voriconazole plus an echinocandin (9%). Patients on fluconazole had more rapid mortality than those treated with voriconazole, although these differences were not statistically significant (3.5 ± 0.7 days vs 8.2 ± 9.3 days; $P = 0.478$). The treatment with the greatest frequency of death was voriconazole plus an echinocandin (7.5%), followed by voriconazole (4%) and echinocandins (3%). Overall treatment duration was longer for voriconazole plus an echinocandin (10.5 ± 11.7 days). The duration of treatment switches was very similar but slightly of shorter duration for voriconazole (6.9 ± 4.9) and echinocandins (6.7 ± 6.5) and longer for the combination of voriconazole plus an echinocandin (17.8 ± 18.1). Furthermore, 80% of patients initially on voriconazole remained on the drug for the duration of their treatment course; for 4.2%, an echinocandin was added, and 2% were switched to posaconazole or isavuconazole. In contrast, for patients initially on fluconazole, 42% were switched to, or voriconazole was added (Fig. 2). Most patients on posaconazole (70%) or isavuconazole (78%) remained on the drug throughout their treatment.

Treatment of IPA includes a reduction in immunosuppression and antifungal therapy, primarily with voriconazole, posaconazole, or isavuconazole as first-line options. Voriconazole is often considered the preferred initial treatment choice for IPA (3). However, subsequent phase III clinical trials have shown isavuconazole and

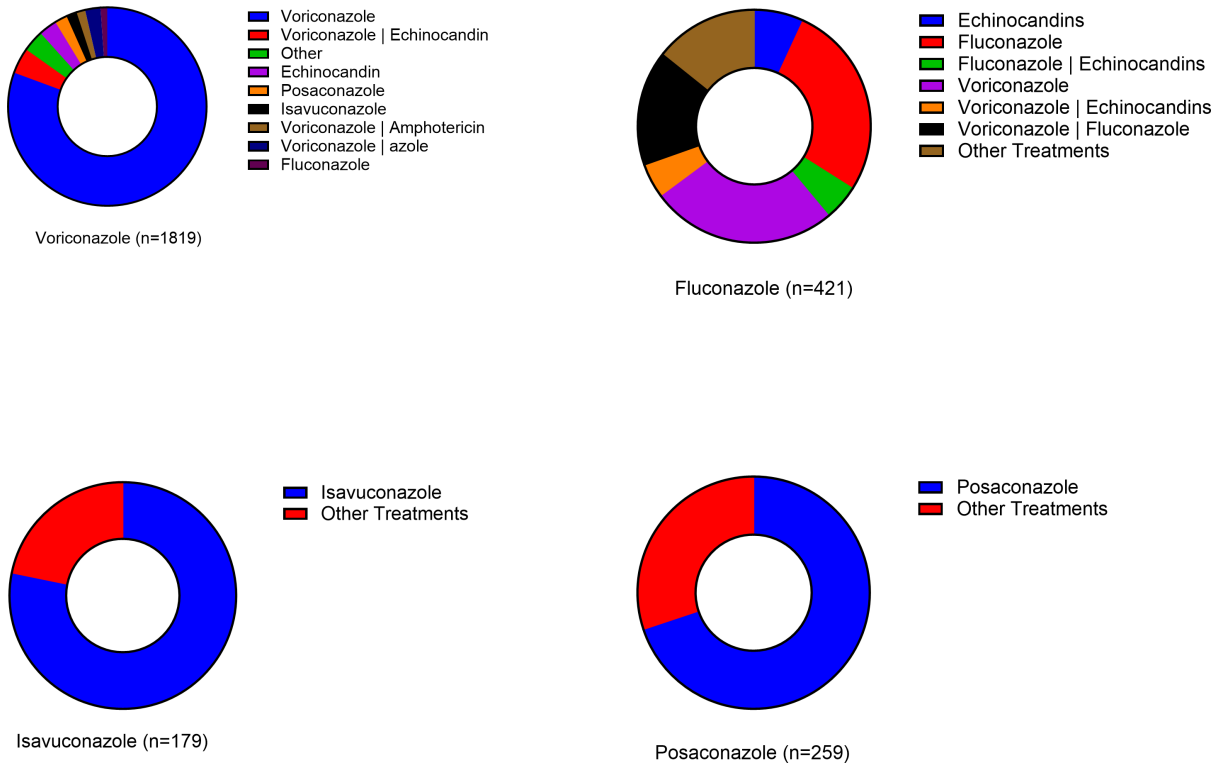

FIG 2 Frequency of initial switches for azole-based therapies in IPA whole diagrams of initial switches for patients who were placed on azole as initial therapy for invasive pulmonary aspergillosis.

posaconazole as non-inferior (4, 5). Surprisingly, we found fluconazole a frequent, albeit inappropriate, initial therapy for IPA, suggesting an area where targeted educational efforts could be focused. Patients on fluconazole had frequent switches to other antifungal therapy, suggesting intervention by providers with expertise in fungal diseases or possibly treatment failures. Also, we observed voriconazole use as the first line had a higher frequency in those patients with marked neutropenia, suggesting a more appropriate treatment for those with a known established risk factor.

Antifungal switches are common during therapy and depend on patient comorbidities, QTc findings, and drug-drug interactions. The global comparative aspergillosis study showed less frequent voriconazole switches to other licensed antifungal treatments compared to amphotericin B deoxycholate (6). However, no mold-active oral therapeutic options other than voriconazole were available then. Also, it is unclear if patients on two azoles experienced breakthrough infections while receiving triazole prophylaxis or why two triazoles were prescribed. Furthermore, despite the increased clinical experience of isavuconazole for the treatment of IPA, favorable phase III comparative data, the absence of drug monitoring requirements and decreased toxicities (7, 8), the widespread use of this antifungal was low as initial therapy or as a switch option from voriconazole or fluconazole.

Our study has several limitations. The retrospective nature of the follow-up cohort can introduce selection bias. Diagnosis of IPA was made through ICD codes, and we did not have access to culture data to confirm cases clinically, identify the *Aspergillus* species, determine antifungal susceptibility, whether the initial antifungal (fluconazole) was used for prophylaxis, or assess the type or number of adverse events with each antifungal agent. We could not distinguish cases of possible, probable, or proven aspergillosis limiting our assessment of treatment choices by the level of diagnosis certainty. The platform also prohibited us from running a subgroup survival analysis by participating centers.

Treatment pathways depend on various factors, including patient characteristics, underlying comorbidities, drug interactions, and local resistance patterns. Switches in treatment may occur due to intolerance, adverse effects, lack of response, or drug interactions. The real-world data presented here suggest considerable education efforts should be leveraged to optimize the initial and subsequent treatment of patients with IPA.

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