



Vanessa Gow-Lee, M.D.<sup>1</sup>, Supavit Chesdachai, M.D.<sup>2</sup>, Jennifer Gile, M.D.<sup>1</sup>, Nadia Akhiyat, M.D.<sup>1</sup>, Courtney Harris, M.D.<sup>3</sup>, Omar Abu Saleh, M.B.B.S.<sup>2</sup>  
<sup>1</sup>Mayo Clinic Dept of Internal Medicine, <sup>2</sup>Mayo Clinic Division of Infectious Diseases, <sup>3</sup>Massachusetts General Hospital / Brigham & Women's Hospital Division of Infectious Diseases

## BACKGROUND

The treatment of invasive fungal infections is often complicated by both drug and host factors.

Unpredictable pharmacokinetics of the anti-fungals, drug-drug interactions, and drug toxicities is a common challenge with oral azoles.

Novel anti-fungals with the allure of fewer toxicities and side effects are of particular interest.

Isavuconazole, has various qualities that make it attractive for use. These include excellent oral bioavailability<sup>1</sup> that is not affected by food,<sup>2</sup> more predictable pharmacokinetics,<sup>3</sup> potential for fewer drug-drug interactions compared to other azoles,<sup>4</sup> and shortening of the cardiac QTc interval.<sup>5</sup> Especially because the patient population who contract invasive fungal infections are very likely to be on medications with a high potential for drug-drug interactions, the issue of Isavuconazole efficacy and use is a highly relevant question.

Isavuconazole has been found to be effective in the treatment of primary invasive aspergillosis and of invasive mucormycosis,<sup>6,7</sup> which are the two indications for which it carries FDA approval. But both because of the more limited clinical experience with Isavuconazole and because of the high likelihood of drug-drug interactions in the patient population who contract invasive fungal infections, the issue of its use for off-label indications is a highly relevant question.

To that end, we conducted a retrospective study of patients with probable or proven IFI treated with Isavuconazole at Mayo Clinic sites from 1/1/2015 to 4/1/2020 to examine temporal trends and characteristics of ISA use.

## METHODS

- Retrospective descriptive study of patients with invasive fungal disease treated with ISAV as primary, secondary, or salvage therapy at the Mayo Clinic Enterprise (Rochester, Arizona, and Florida) between January 1, 2010 and March 31, 2020.
- Included were patients who had definite or probable invasive fungal infection as defined by the 2019 European Organization for Research & Treatment of Cancer & the Mycoses (EORTC).<sup>8</sup>
- Excluded were patients receiving Isavuconazole as prophylaxis.
- Demographics including clinical history, transplant status, immunosuppression status, previous antifungal therapy, fungal species and site of infection were collected.
- We examined how often Isavuconazole was used as the initial versus as the secondary antifungal agent, why it was chosen for treatment, and then why Isavuconazole was discontinued.

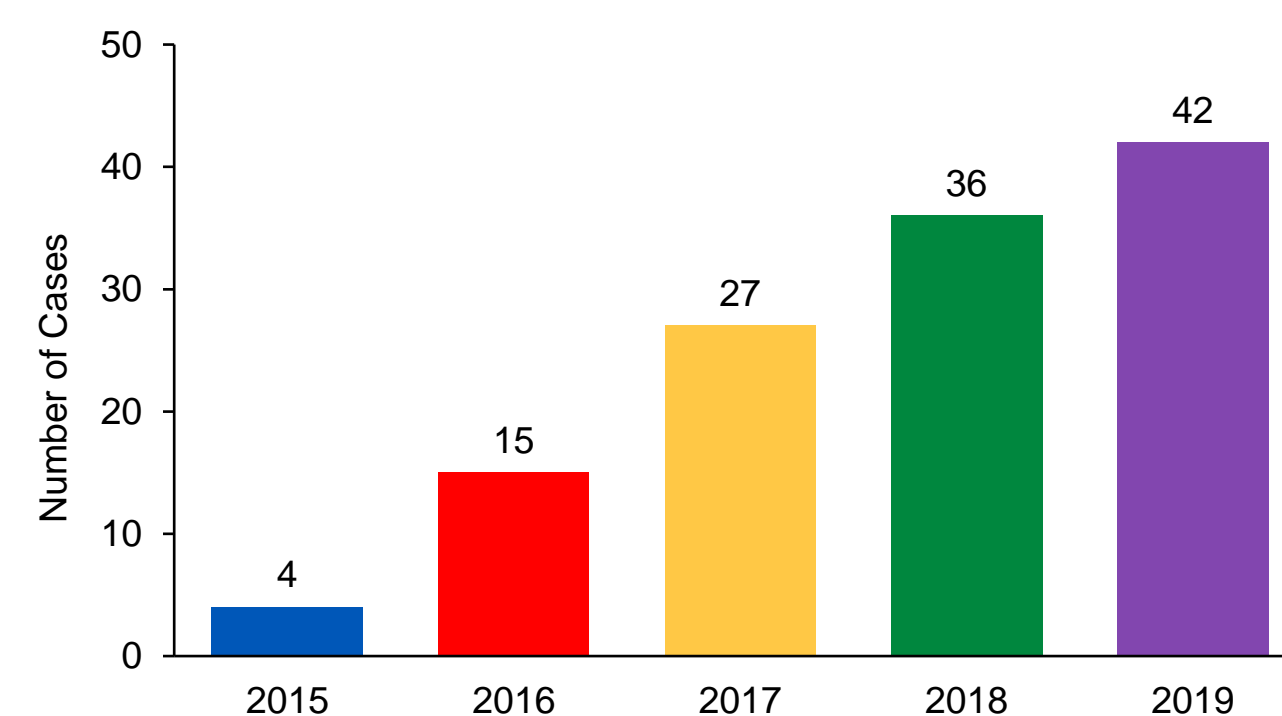
## FINDINGS

In the period January 2015–March 2020, Isavuconazole was used as treatment for definite or probable invasive fungal infection in 131 cases. Unsurprisingly, the use rose over this period, from four cases in 2015 to 42 cases in 2019. Of these 131 cases, Isavuconazole was the initial antifungal used in 15 (11.5%) and as a secondary agent in 116 (88.5%), although this later group included those who were initially on an IV antifungal first such as Amphotericin for induction therapy.

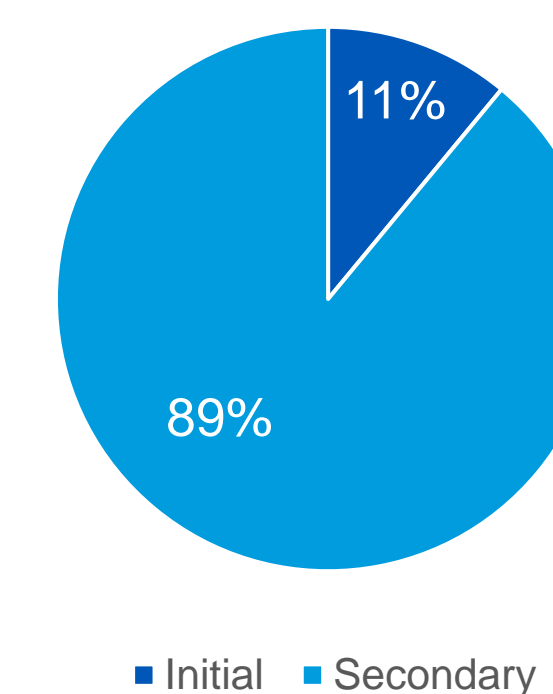
## FINDINGS (con.)

- The most common reasons that Isavuconazole was used as the initial antifungal were drug-drug interactions (5 of the 15 relevant cases or 33%) and baseline QTc prolongation (n: 3, 20%).
- When used as a secondary agent, reasons that Isavuconazole was chosen included various organ toxicities with the first agent (34 of the 116 cases or 29%, not QTc / cardiac concerns), QTc prolongation (n: 22, 19%), judged failure of the primary therapy (n: 20, 17%), drug-drug interactions (n: 12, 10%), fungal resistance to initial anti-fungal (n: 10, 9%), inadequate drug levels (n: 4, 3%), and cost/access (n: 1, 0.9%), with the remainder unclear from chart review.
- Isavuconazole was discontinued earlier than originally planned in 81 cases (62% of the total 131 cases). The most common reason for early discontinuation was patient death or transition to comfort care (27 of the 81 cases or 33%), followed by intolerance (n: 18, 22%), judged failure of therapy (n: 17, 21%), cost or access (n: 6, 7%), drug-drug interactions (n: 3, 4%), issues with absorption or drug delivery (n: 3, 4%), and microbe susceptibility (n: 1, 1%). In the remaining 50 cases, Isavuconazole was used as definitive treatment and judged successful. Of note, 30 patients took >1 year of Isavuconazole and had no major adverse effects from long-term therapy.

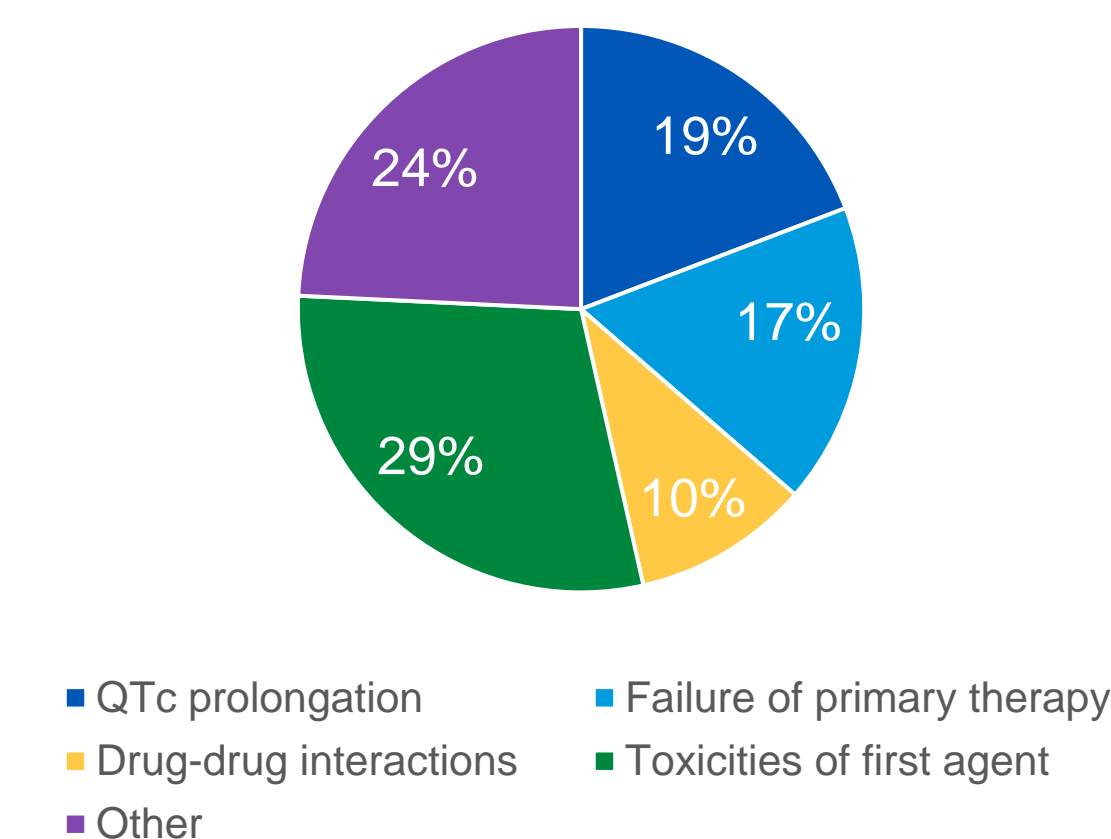
Use of Isavuconazole for Treatment of Invasive Fungal Infections



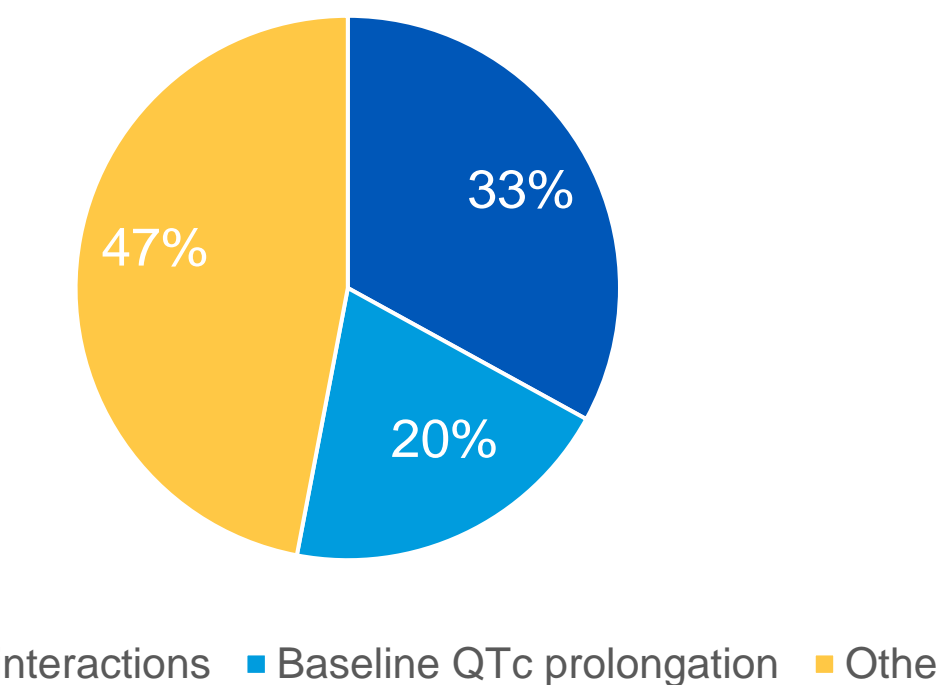
Isavuconazole Use as Initial vs Secondary Anti-Fungal



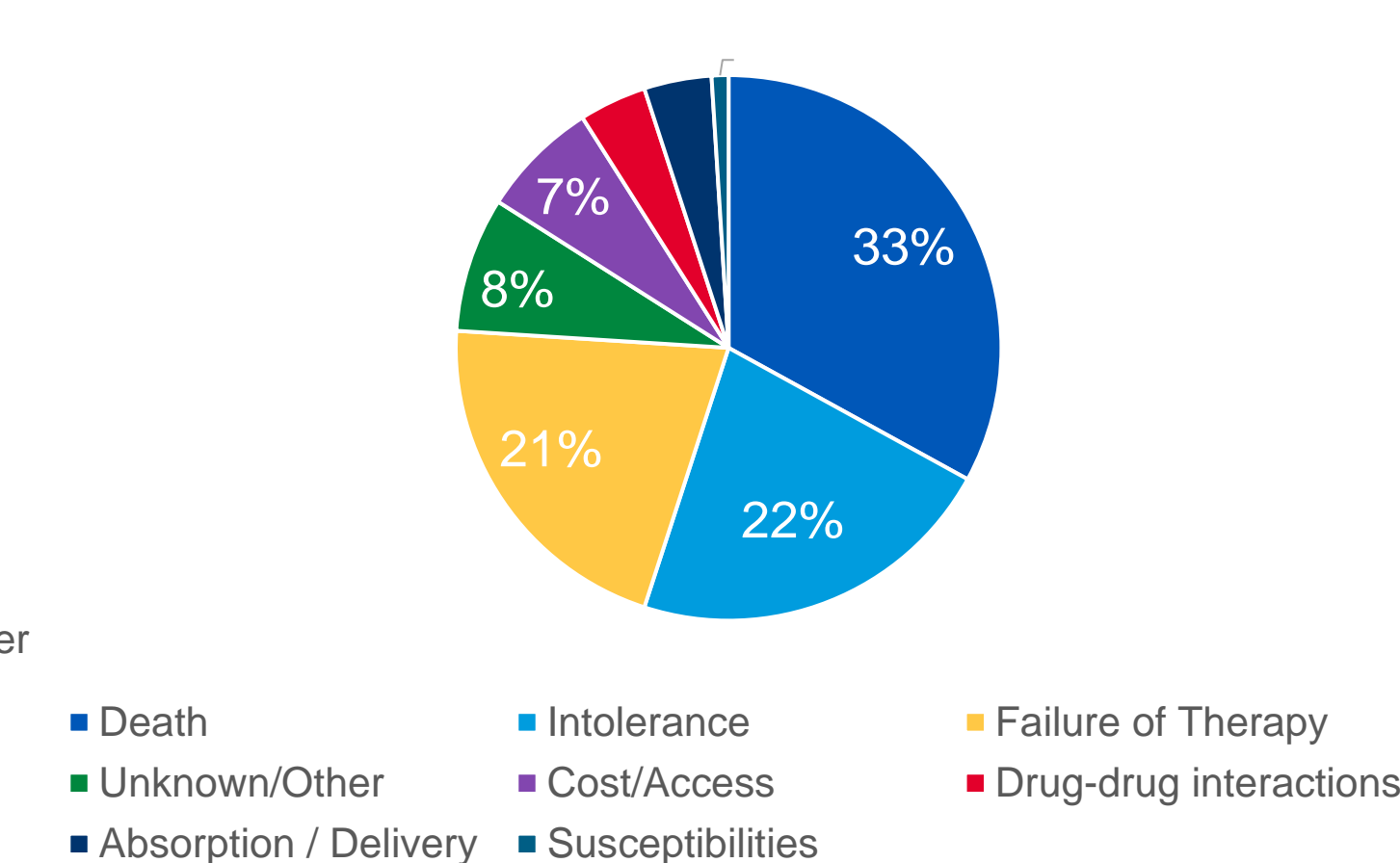
Reasons Isavuconazole Used as Secondary Anti-Fungal



Reasons Isavuconazole Used as Initial Anti-Fungal



Why Isavuconazole was Discontinued Early



## DISCUSSION

Since its approval for invasive aspergillosis and mucormycosis in 2015, the use of Isavuconazole steadily rose in our institution's network, although it was still primarily used as secondary treatment. The oft-touted benefits of Isavuconazole were well-recognized by the prescribing clinicians, but there was also a high rate of discontinuation of Isavuconazole due to either patient death or judged failure of therapy. Especially in the setting of the concern for breakthrough fungal infections when Isavuconazole is used as prophylaxis,<sup>9</sup> it is difficult to attribute these observations to the drug, the patient population, or the infections they face.

Future areas of study of importance include deeper investigation into tolerance from long-term use and the efficacy of Isavuconazole for off-label indications.

## CONCLUSIONS

- Although Isavuconazole carries FDA-approval for invasive aspergillosis and mucormycosis, relatively few patients were treated with Isavuconazole for either primary or secondary therapy.
- Avoidance of QTc prolongation and fewer drug-drug interactions were the most attractive qualities to prescribing clinicians.
- Given the morbidity common with other azoles, more studies to elucidate the efficacy of Isavuconazole – especially for off-label use – are needed.

## REFERENCES

- Schmitt-Hoffmann A, Roos B, Heep M, et al. Single-ascending-dose pharmacokinetics and safety of the novel broad-spectrum antifungal triazole BAL4815 after intravenous infusions (50, 100, and 200 milligrams) and oral administrations (100, 200, and 400 milligrams) of its prodrug, BAL8557, in healthy volunteers. *Antimicrob Agents Chemother.* 2006;50(1):279-285.
- Shirley M, Scott LJ. Isavuconazole: A Review in Invasive Aspergillosis and Mucormycosis. *Drugs.* 2016;76(17):1647-1657.
- Falci DR, Pasquotto AC. Profile of isavuconazole and its potential in the treatment of severe invasive fungal infections. *Infect Drug Resist.* 2013;6:163-174. Published 2013 Oct 22.
- Miceli MH, Kauffman CA. Isavuconazole: A New Broad-Spectrum Triazole Antifungal Agent. *Clin Infect Dis.* 2015;61:1558-65.
- Mellinghoff SC, Bassetti M, Dorfel D, et al. Isavuconazole shortens the QTc interval. *Mycoses.* 2018;61:256-60.
- Maertens JA, Raad II, Marr KA, et al. Isavuconazole versus voriconazole for primary treatment of invasive mould disease caused by Aspergillus and other filamentous fungi (SECURE): a phase 3, randomized-controlled, non-inferiority trial. *Lancet.* 2016;387(10020):760-769.
- Marty FM, Ostrosky-Zeichner L, Cornely OA, et al. Isavuconazole treatment for mucormycosis: a single-arm open-label trial and case-control analysis. *Lancet Infect Dis.* 2016;16(7):828-837.
- Donnelly JP, Chen SC, Kauffman CA, et al. Revision and Update of the Consensus Definitions of Invasive Fungal Disease From the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium. *Clin Infect Dis.* 2020;71(6):1367-1376.
- Fung M, Schwartz BS, Doernberg SB, et al. Breakthrough Invasive Fungal Infections on Isavuconazole Prophylaxis and Treatment: What is Happening in the Real-World Setting?. *Clin Infect Dis.* 2018;67(7):1142-1143.