SAFETY AND EFFICACY OF ISAVUCONAZOLE IN CHILDREN AND ADULT PATIENTS WITH INVASIVE FUNGAL INFECTIONS

DIMITRIOS BOULAKIS

Supervisor:
Tragiannidis Athanasios, Assistant Professor of Pediatrics - Pediatric Hematology – Oncology

Members of the examination board:
Kouvelas Dimitrios, Professor of Pharmacology – Clinical Pharmacology
Hatzipantelis Emmanuel, Associate Professor of Pediatrics - Pediatric Hematology -Oncology

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In loving memory of my father
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Abstract

Invasive Fungal Infections (IFIs) pose a major threat against the increasing immunosuppressed patients as they have high morbidity and mortality rates. Prophylaxis, empiric, pre-emptive and treatment of proven IFIs is of the utmost importance. Newly approved triazole, isavuconazole, shows activity against *Aspergillus* spp and *Mucorales* spp in the treatment of invasive aspergillosis and invasive mucormycosis respectively. Isavuconazole’s linear pharmacokinetic properties and once-daily dose makes it an appealing choice for combating IFIs. Patients treated with isavuconazole demonstrated less drug related adverse events than previous treatments with azoles like voriconazole and fluconazole. Moreover, isavuconazole can be administered in patients with renal impairment contrary to the newer and older formulations of amphotericin B. Isavuconazole proves to be well tolerated with few drug related discontinuations of treatment. Although first in pediatric trials are ongoing, case reports and case series suggest that isavuconazole could be used in pediatric patients where other antifungal treatments are contradicted or inefficacious. Also, further studies could demonstrate potential activity in patients with other IFIs due to *Candida* spp.

Keywords: isavuconazole, invasive fungal infections, invasive aspergillosis, mucormycosis, children, adults.
Περίληψη

Οι διηθητικές μυκητιάσεις (ΔΜ) είναι μία μεγάλη απειλή ανοσοκατεσταλμένων ασθενών καθώς έχουν υψηλά ποσοστά νοσηρότητας και θνητότητας. Η προφύλαξη, εμπειρική, προληπτική και θεραπεία ΔΜ είναι απαραίτητη. Μια νέα εγκεκριμένη αζόλη, η ασβουκοναζόλη, φαίνεται να είναι αποτελεσματική έναντι στελεχών Aspergillus spp και Mucorales spp για τη θεραπεία διηθητικής ασπεργίλλωσης και μουκορμύκωσης. Οι γραμμικές φαρμακοκινητικές ιδιότητες και η μία ημερήσια δόση της ασβουκοναζόλης την καθιστούν μία ελκυστική επιλογή στη μάχη εναντίων των ΔΜ. Ασθενείς που έλαβαν ασβουκοναζόλη εμφάνισαν λιγότερες ανεπιθύμητες ενέργειες, σχετικά με το φάρμακο, συγκριτικά με προηγούμενες θεραπείες με αζόλες όπως η βορικοναζόλη και η φλουκοναζόλη. Επιπροσθέτως, η ασβουκοναζόλη μπορεί να δοθεί σε ασθενείς με νεφρική ανεπάρκεια αντίθετα με παλιές και νέες μορφές της αμφοτερικίνης B. Η ασβουκοναζόλη φαίνεται να είναι καλά ανεκτή και δεν παρουσιάζονται συχνά διακοπές της θεραπείας λόγω φαρμάκου. Αν και μελέτες για χρήση σε παιδιατρικό πληθυσμό είναι ακόμα εν εξελίξει, αναφορές περιστατικών εικάζουν πως η ασβουκοναζόλη θα μπορούσε να χρησιμοποιηθεί σε ανήλικους ασθενείς όπου άλλες θεραπείες αντενδείκνυνται ή ήταν αναποτελεσματικές. Επίσης, επιπλέον έρευνες θα μπορούσαν να δείξουν πιθανή αποτελεσματικότητα έναντι άλλων ΔΜ από Candida spp.

Λέξεις-κλειδιά: ασβουκοναζόλη, διηθητικές μυκητιάσεις, διηθητική ασπεργίλλωση, μουκορμύκωση, παιδιά, ενήλικες.
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1. Introduction

Invasive fungal infections (IFIs) are a major cause of morbidity and mortality in patients with primary and secondary immunodeficiencies and those with prolonged hospitalization [1] [2]. Although invasive candidiasis and candidemia, the leading cause of IFIs in children, has decreased in incident reports, high-at-risk patients have increased in numbers [3] [4]. This is mainly due to the fact that the use of immunomodulators and the number of immunosuppressed patients, such as those undergoing intensive chemotherapy or haematopoietic or solid organ transplantation, have increased. Also, patients with extensive stay in intensive care units, HIV and patients undergoing invasive medical procedures have high risk of getting a fungal infection as well [5]. Poorly treated diabetic patients are also at risk for invasive mold infections. Critically ill children remain the most vulnerable patient group [6].

Concerning immunosuppressed patients, any fungus is potentially pathogenic. The most common organisms isolated from patients with an invasive fungal infection are *Candida* spp and *Aspergillus* spp [7] followed by *Cryptococcus* spp, *Fusarium* spp and *Mucorales* spp (Zygomycetes) [8]. When first-line barriers (the skin and mucosal surfaces) are penetrated, fungal agents can reach deep tissue causing IFIs. Additionally, medical procedures like radiotherapy, chemotherapy and surgery can break those anatomical barriers.

Mold diseases caused by *Aspergillus* spp and other filamentous fungi remain an important contributor to morbidity and mortality. Blood cultures have low sensitivity and are generally negative and the absence of diagnostic tools that give accurate and timely diagnosis is a critical factor as well. New molecular techniques may prove more helpful by providing improved diagnosis [9]. A combination of molecular tools, imaging and fungal biomarkers could lead to an optimal approach and earlier diagnosis [10]. Imaging techniques include CT scanning, high resolution CT pulmonary angiography, MRI and PET scan. Cultures, galactomannan, 1,3-β-D-glucan and PCR will eventually confirm or support the diagnosis of IFIs. Early
diagnosis and consequently early initiation of treatment is a key point in survival for patients with IFIs.

Contrary to antibacterial and antiretroviral therapies that have large numbers of drug classes in their armamentarium, antifungal therapies rely on a handful of drug classes. Antifungal arsenal consists of polyenes, nucleoside analoges, azoles and echinocandins. Polyenes are the oldest broad spectrum antifungals and are used to this day. Amphotericin B and its lipid formulations are used in the treatment of IFIs and its main mechanism of action against fungus is the extraction of membrane-lipid ergosterol from plasma membrane. Nucleoside analoges act through RNA miscoding thus inhibiting DNA synthesis. Azoles block ergosterol synthesis leading to accumulation of sterols exerting stress to cells. Finally echinocandins act by disrupting cell wall integrity.

Every antifungal class and agent exhibits both advantages and disadvantages. Amphotericin B, for instance, has an improved safety profile but also has been linked with nephrotoxicity [11]. Triazole antifungals that are a usual approach to many fungal infections including IFIs on the other hand, have drug interactions due to the fact that they usually are P450 substrates and inhibitors [12]. Combination treatment may be an option hoping for better results [13].

Invasive Mold Disease (IMD) is caused by molds like Aspergillus spp and Mucorales spp. Invasive aspergillosis (IA) and mucormycosis differ in the methods of diagnosis and prevention and patients undergo antifungal treatment in case of possible, probable and proven fungal infection. A retrospective multicenter study from years 2007 – 2017 evaluated 59 oncohematological patients with mucormycosis and 541 with IA and demonstrated that mucormycosis was developed more often in children and adolescents and its treatment usually required a greater length of stay (LOS) in hospital [14]. The Phase III Secure trial cost analysis demonstrated that isavuconazole has the potential to reduce hospital LOS of patients with IFI [15], especially those with renal impairment, and improve inpatient drug related cost savings [16].
The outcome of those fungal infections vary due to different underlying conditions, site of infection and antifungal therapy used. However, survival without the use of an antifungal agent is rare [17].
2. Aim of the review

As real world data from the use of isavuconazole begin to emerge safety and efficacy of this new antifungal is a major concern. This review aims to review safety and efficacy after the use of isavuconazole in patients, both adults and children, for the treatment of IA and mucormycosis. Pharmacokinetics, safety and efficacy of this new triazole will be assessed. Finally comparison with other antifungal agents like polyenes, echinocandins and other azoles will also be made.
3. Azoles

Azoles are synthetic compounds that inhibit ergosterol biosynthesis leading to fungal cell membrane destruction. There are two groups of azoles, imidazoles and triazoles. The basic structure unit of azoles is a five-membered azole ring attached by carbon nitrogen bonds to other aromatic rings [18]. Imidazoles, like ketoconazole and miconazole, contain 2 nitrogen atoms in the azole ring. Triazoles, on the other hand, contain three atoms of nitrogen in the azole ring.

Fluconazole

Fluconazole, a triazole antifungal, was approved by the FDA in 1990 for the treatment of fungal infections like vaginal yeast infections caused by Candida spp, systemic Candida infections as invasive candidiasis and candidemia, esophageal and oropharyngeal candidiasis, cryptococcal meningitis, urinary tract infection by Candida and peritonitis caused by Candida spp. Fluconazole was authorized in the EU via national procedures.

![Chemical structure of Fluconazole](image)

Fluconazole’s oral bioavailability is above 90%. Fluconazole is not highly bound to protein (11%) and has a volume of distribution of 39L and half-life time of 30 hours. Fluconazole’s main route of elimination is by the kidneys.

Fluconazole has fewer adverse events than the imidazoles used before. The low plasma protein affinity, long half-life and the availability in oral formulations made it widely used in fungal infections both systemic and superficial [19] [20]. Fluconazole has been the “gold standard” as primary
treatment for fungal infections. Also, fluconazole was the first azole to have both intravenous and oral formulations [21]. However, as fluconazole resistant strains emerge, mostly non albicans, new azoles should be used [22]. Concerning pediatric patients, fluconazole can be used at any age.

Itraconazole

A few years after the approval of fluconazole, another triazole gained approval by the FDA. Itraconazole was approved in 1997 for the treatment of pulmonary and extrapulmonary blastomycosis, histoplasmosis, aspergillosis and onychomycosis. Oral solution of itraconazole has been approved for fungal infections of the esophagus or the mouth (thrush).

![Itraconazole](Figure_2_Chemical_structure_of_Itraconazole.png)

Itraconazole’s oral bioavailability is 55% and is maximal (for the tablets) when taken with a full meal. Itraconazole has half-life of 21 hours, high protein binding (99.8%) and volume of distribution of 796L. Itraconazole’s is mainly metabolized by CYP3A4 cytochrome in the liver.
Although there are case reports where itraconazole was used successfully on children [23], there are no clinical trials conducted to demonstrate safety and efficacy on pediatric patients. Therefore, itraconazole is not indicated for the treatment of patients under the age of 18.

Voriconazole

Immunosuppressed patients often have to deal with fungal infections. Voriconazole is a second generation triazole that was approved by the FDA and EMA in 2002 both in oral and intravenous formulations. Voriconazole is indicated for the treatment of candidemia in non neutropenic patients, treatment of fluconazole-resistant serious invasive Candida infections, invasive pulmonary aspergillosis and serious fungal infections caused by Scedosporium apiospermum and Fusarium spp. Voriconazole can be used to treat patients over 2 years of age.

Voriconazole’s oral bioavailability is 96%, it has a medium binding to protein (58%), volume of distribution 2-4,6 L/kg and half elimination time 6 hours [24]. Due to its short half-life, voriconazole must be administered twice a day.

Voriconazole became the successor of fluconazole in treating immunosuppressed patients with IFIs. Although voriconazole has proven very efficient in treating IFIs, toxicity and interactions are a major concern [25]. Thus, therapeutic drug monitoring is often required when treating patients.
Posaconazole

Posaconazole was approved by the EMA (2005) and FDA (2006) for the treatment of IA, in patients with disease that is refractory to amphotericin B or itraconazole or in patients who are intolerant of these medicinal products; fusariosis in patients with disease that is refractory to amphotericin B or in patients who are intolerant of amphotericin B; chromoblastomycosis and mycetoma in patients with disease that is refractory to itraconazole or in patients who are intolerant of itraconazole; coccidioidomycosis in patients with disease that is refractory to amphotericin B, itraconazole or fluconazole or in patients who are intolerant of these medicinal products; and oropharyngeal candidiasis: as first-line therapy in patients who have severe disease or are immunocompromised, in whom response to topical therapy is expected to be poor. Additionally, the oral suspension is indicated for prophylaxis for patients receiving remission-induction chemotherapy for acute myeloid leukemia (AML) or myelodysplastic syndromes (MDS) expected to result in prolonged neutropenia and who are at high risk of developing invasive fungal infections; and haematopoietic stem cell transplant (HSCT) recipients who are undergoing high-dose immunosuppressive therapy for graft versus host disease and who are at high risk of developing IFIs.

Figure 4 Chemical structure of Posaconazole
Posaconazole is highly protein bound (98%), has a volume of distribution of 1774L and its half-life time is around 35 hours.

Posaconazole is structurally similar to itraconazole from which it derives. The modifications of itraconazole that led to posaconazole have made it more potent and they also have enhanced its spectrum of activity.

Prophylactic treatment with posaconazole seems to be better tolerated by patients compared to voriconazole [26] although voriconazole is the cost effective choice [27] according to literature. Similarly to voriconazole, therapeutic drug monitoring is also recommended for posaconazole since there is inter- and intra- patient variability of posaconazole’s bioavailability [28].
4. The SECURE trial

The SECURE trial aimed to assess the safety and efficacy of the new triazole isavuconazole against the current “gold standard” for IA voriconazole in patients with suspected IMD. All antifungal agents used against IFIs and more specifically for IMD have minor and major disadvantages. Polyenes have only intravenous formulations and are accused of renal toxicity and hypokalaemia [11] [29]. There is little data supporting the use of echinocandins as first-line therapy for IMD [30]. Similarly to echinocandins, posaconazole, even though it is licensed as salvage treatment, has limited data concerning use as first-line therapy [31] [32] [33]. Voriconazole, licensed for first-line therapy of IA has many drug to drug interactions and non-linear pharmacokinetics [34]. Moreover, the need for a cyclodextrin vehicle to increase water solubility raises concerns about long term safety.

SECURE was a Phase III, double blind, global multicenter, comparative group study. Adult patients (18 years of age or older) that had possible, probable, or proven IMD according to the revised definitions of IFIs from the 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 (EORTC/MSG) Consensus Group were eligible [35]. Patients with hepatic and/or renal dysfunctions were excluded from this trial. Patients were stratified by geographic region, allogeneic HSCT and active malignancy at study entry. Dosage for patients receiving isavuconazole was 372 mg of isavuconazonium sulfate 3 times a day for 2 days followed by a daily intravenous dose or oral dose of 200mg isavuconazole (the equivalent of 372 mg of isavuconazonium sulfate). Patients receiving voriconazole begun intravenous treatment with 6mg/kg every 12 hours on the first day, 4mg/kg every 12 hours for the second day and 4 mg/kg intravenously or 200mg orally twice a day for the remaining treatment period. Due to the difference of daily dosage regiment between isavuconazole and voriconazole placebo was used on isavuconazole patients from the third day onwards to simulate a second daily dose. Apart from pharmacy personnel responsible for medication preparation, all in-site and
non-site personnel were blinded. Therapeutic drug monitoring, even though it is usually required for voriconazole was not allowed by the trial’s protocol. Maximum treatment duration was set for 84 days.

Clinical symptoms and physical findings were assessed on days 0, 3, 7, 14, 28, 42, 63, 84 (or end of treatment if that occurred before day 84) and 4 weeks after the end of treatment. Radiological and mycological assessments were conducted the first week and then days 42 and 84 (or otherwise end of treatment) plus during the treatment some unexpected on demand assessments.

Patients were recruited throughout six years from 102 centers from 26 countries located across North and South America, Europe, Middle East, Southeast Asia, East Asia and Pacific regions. The intention-to-treat (ITT) population was 516 patients, 258 in each drug group. Patients with proven and probable IMD, as determined by the data review committee, the modified ITT population (mITT), consisted of 143 patients for the isavuconazole group and 129 patients for the voriconazole group, respectively. Finally, patients with proven or probable invasive aspergillosis according to the EORTC/MSG criteria, the mycological ITT population (myITT) consisted of 123 patients for the isavuconazole group and 108 patients for the voriconazole group, respectively. Of the total of 258 patients in the groups receiving isavuconazole, 118 completed and 140 discontinued treatment (39 insufficient response, 31 adverse events or intercurrent illness, 17 deaths, 53 other reasons), median duration of dosing was 45 days. Of the total of 258 patients treated with voriconazole, 120 completed and 138 discontinued treatment (23 insufficient response, 53 adverse events or intercurrent illness, 21 deaths, 41 other reasons), median duration of voriconazole dosing was 47 days.

The primary efficacy endpoint was all-cause mortality from the first dose to day 42 in the ITT population. The study showed that all-cause mortality for the ITT population was 19% for isavuconazole and 20% for voriconazole demonstrating non inferiority of isavuconazole versus voriconazole [36].
The key secondary efficacy endpoint was the overall response in the mITT population after the end of treatment. Results between the two groups were similar. Overall response showed 35% of the mITT in isavuconazole group and 36% of the mITT in voriconazole group [36].

Serious treatment-emergent adverse events were proportionally similar between the two groups. The five most common adverse events were nausea, vomiting, diarrhea, pyrexia and hypokalaemia. Drug related events that were reported by patients were less for isavuconazole (42%) than for voriconazole (60%). Treatment discontinuation due to drug related adverse events was less common for patients treated with isavuconazole (8%) versus patients receiving voriconazole (14%). Also, drug discontinuation due to treatment emergent adverse events was also less common for the isavuconazole group (14%) versus voriconazole group (23%).
5. Isavuconazole

Incidence of IA continues to increase following the rise of the immunosuppressed patients worldwide. These infections are primarily caused by yeasts like *Candida* spp, or molds like *Aspergillus* spp and *Mucorales* spp, and have a high morbidity and mortality rate. Antifungal agents currently used as treatment or prophylaxis against those IFIs include polyenes, echinocandins and newer generation azoles. All of these drug classes have advantages and disadvantages that can either lead to selection or rejection depending on the patient. Second generation triazoles like posaconazole and voriconazole may have extended spectra of activity and multiple formulations to use (intravenous and oral), however, drug-drug interactions as well as variable bioavailability and adverse events can limit their use in clinical practice.

Isavuconazole is the latest triazole approved by the FDA and EMA in 2015 with use indication for treatment in IA and invasive mucormycosis. Phase III clinical trials have shown comparable efficacy of isavuconazole to voriconazole (for the treatment of IA – SECURE trial) and liposomal amphotericin B (for the treatment of mucormycosis – VITAL trial). Isavuconazole’s extended spectrum, its pharmacokinetic profile and the fact that it has both intravenous and oral formulations makes it highly lucrative as an antifungal agent for invasive infections [37].

Similarly to other triazoles, the main mechanism of isavuconazole is the inhibition of sterol 14-α-demethylase of cytochrome P450 blocking cell membrane ergosterol synthesis thus leading to toxic precursors of ergosterol in the cytoplasm and eventual cellular death [38]. Concerning yeasts, in vitro activity of isavuconazole shows comparable efficacy to posaconazole and voriconazole while in regards of *C. glabrata* the issue of resistance remains [39] [40]. Isavuconazole showed in vitro activity against molds as well. Promising antifungal activity was demonstrated against several *Aspergillus* spp including strains that showed resistance against caspofungin, itraconazole or amphotericin B [41] [42]. Apart from posaconazole, *Mucorales*
show resistance against azoles. In vitro testing with isavuconazole resulted that it is active against many species of Mucorales [42].

Isavuconazole’s core structure is very similar to that of voriconazole, both including single triazole and difluorobenzene groups [43]. Like other triazoles, isavuconazole, due to aromatic moieties in its structure has low water solubility which makes intravenous formulations challenging. Voriconazole, for instance, requires a β-cyclodextrin-solvent as a vehicle which can be problematic when administered to patients with renal impairment. Isavuconazonium sulfate is a prodrug of isavuconazole and it is highly soluble in water thus allowing intravenous formulations without the need for a cyclodextrin vehicle [44].

Isavuconazonium sulfate comes in two formulations, intravenous where 372 mg of isavuconazonium sulfate corresponds to 200 mg of isavuconazole, and oral capsules each containing 186 mg of isavuconazonium sulfate corresponding to 100 mg of isavuconazole. The recommended dosage regimen for either formulation is 200 mg of isavuconazole every 8 hours for 2 days (600 mg per day) and 200 mg daily after the loading first 2 days. Dosages as high as 200 or 400 mg per day as prophylactic treatment in immunosuppressed patients were safe and well tolerated [45]. In general,
patients receiving isavuconazole showed few side effects and no common side effects occurring with other azoles were reported [46] [47].

5.1. Pharmacokinetics

After an intravenous infusion, isavuconazonium sulfate rapidly breaks down by plasma esterases to isavuconazole, its active component, and an inactive cleavage product. More than 99% of isavuconazonium sulfate administered is turned to isavuconazole and after 30 minutes from infusion neither the prodrug nor the cleavage product is detectable in plasma concentrations. After oral administration, maximum plasma concentrations are reached 2-3 hours at which time the prodrug and the cleavage product are not detectable. Isavuconazole’s pharmacokinetics for doses of 1.6 to 28 mg/kg appear to be linear [48]. Oral bioavailability of isavuconazole is 98% and the volume of distribution was 308 to 542 liters [49]. Due to the fact that oral isavuconazole is bioequivalent to the IV formulation no change in dosage is required when switching from IV to oral regardless food or drugs that alter gastric pH [50] [51]. Isavuconazole is highly bound to proteins (more than 99%), mostly to albumin [52], and has an elimination half-life 80-130 of hours in healthy adults [43]. Even after a single dose of 200 mg of isavuconazole, detectable serum concentrations can be observed for more than 14 days. Isavuconazole demonstrates linear pharmacokinetic properties with low inter- and intra-patient variability [48] [53].

Metabolism of isavuconazole takes place in the liver (CYP3A4, CYP3A5) and mean clearance in health volunteers was 2.5L/h. Higher clearance rate has been observed in patients with high body mass index (BMI) [53]. Even though clearance of isavuconazole in patients with mild and moderate hepatic impairment differs (1.55 L/h and 1.05 L/h respectively – mean values), no dosage adjustment is recommended [54]. However, in a study conducted to monitor pharmacokinetics of isavuconazole to patients suffering from alcohol related liver disease half-life of isavuconazole increased to 224 and 302 hours respectively for patients with mild or moderate liver impairment [55]. Therapeutic drug monitoring (TDM) for isavuconazole is not
recommended in the European Conference on Infections in Leukemia (ECIL-6) guidelines. On the contrary, voriconazole and posaconazole have a strong AI-AII recommendation for TDM to ensure efficacy (voriconazole, posaconazole) and avoid toxicity (voriconazole, posaconazole). Similarly to other azoles, metabolism of isavuconazole may be affected by race. Renal impairment or even end-stage renal disease does not seem to call for dosage changes for isavuconazole as well [56]. As no major safety concerns have emerged, using isavuconazole in clinical practice will allow better understanding of this new agent [57].

Excretion of isavuconazole occurs primarily via the feces as urine elimination is negligible and less than 1% of unchanged isavuconazole is in urine [44] [43].

Isavuconazole was excreted in the milk of lactating rats, so administration to lactating women should be avoided.

5.2. Pharmacodynamics

In vitro activity of isavuconazole presented good results against all Candida species [58]. Species of Candida like C. krusei and C. glabrata that are less susceptible to azoles like fluconazole and voriconazole, showed higher susceptibility to isavuconazole [39]. Isavuconazole showed activity against Cryptococcus spp like C. gattii and C. neoformans as well [59]. Potent activity against other rare pathogens like D. capitatus, S. cerevisiae, R. mucilaginosa and Trichosporon spp was also demonstrated in vitro [60].

Isavuconazole has demonstrated excellent activity against the most common species of Aspergillus spp. A. fumigatus, A. terreus, A. flavus and A. niger are the usual causes of aspergillosis and they seem susceptible to isavuconazole [61] [62]. Susceptibility against isavuconazole was also reported for Mucorales [63].
5.3. Drug – drug interactions

Strong inhibitors of CYP3A4 like ketoconazole and ritonavir as well as strong inducers like carbamazepine, rifampin and St John’s Wort is contradicted [64]. Co-administration of isavuconazole with atorvastatin, digoxin and metformin showed increased plasma concentrations indicating isavuconazole is a weak inhibitor of P-gp [65]. Isavuconazole is also an inhibitor of cyclosporine, mycophenolic acid, sirolimus and tacrolimus metabolism and therefore concurrent use should be monitored [66]. Interactions were also reported when isavuconazole was co-administered with bupropion, repaglinide, caffeine, dextromethorphan and methadone indicating that isavuconazole is a mild inducer of CYP2B6 but does not appear to affect metabolism mediated by CYP1A2, CYP2C8 or CYP2D6 [67].

5.4. Pediatric patients - adolescents

Although trials concerning the safety and efficacy of isavuconazole in children are ongoing, case reports or series of patients under 18 years of age being treated with isavuconazole have emerged [68] [69] [70] [71]. In these cases there was either intolerability in traditional antifungals or traditional treatment was ineffective. Use of isavuconazole on those patients showed good efficacy [68] [69] [70] [71]. Isavuconazole was well tolerated and no serious side effect or adverse event was documented. A dosing regimen to guide the design of a first-in-pediatric trial was proposed by Desai A et al during the 28th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID) in 2018. The proposed dose was 10mg/kg of isavuconazonium sulfate with a maximum dose of 372mg every 8 hours for 2 days and after that one dose daily. This regimen was extrapolated from adults and predicts safe and efficacious exposures in patients between the ages of 2 and 17 years [72].
6. Aspergillosis

Aspergillosis is an infection caused by Aspergillus spp, a filamentous, cosmopolitan and ubiquitous fungus found in nature. Aspergillus primarily affects the lungs and causes four main syndromes: allergic bronchopulmonary aspergillosis (ABPA), chronic necrotizing pulmonary aspergillosis (CNPA), aspergilloma and IA. Even though we inhale on a daily basis spores of Aspergillus spp, fungal infection and subsequent disease is rare. IA occurs more frequently in patients with prolonged neutropenia or immunosuppression, however, IA’s occurrence increases in non-neutropenic patients as well [73]. The most commonly appearing species of Aspergillus that are linked with IA are A. fumigatus, A. flavus, A. niger and A. terreus [74]. There is no “gold standard” for single testing to IA [73]. Histopathological documentation and positive result of specimen culture is required for proof of aspergillosis, otherwise clinical manifestations and microbiological evidence can only lead to probable infection. CT scans can also be used as a diagnostic tool to get the earliest possible diagnosis and start antifungal treatment.

6.1. Traditional treatment for Invasive Aspergillosis

The most important element for long term survival against IA is early diagnosis and prompt initiation of antifungal therapy [75] [76]. In cases of extrapulmonary IA surgical debridement is an additional therapeutic option in selected cases. Apart from that, however, surgery in IA is mainly an option to get a more objective diagnosis [77]. Until recently voriconazole and amphotericin B were the only antifungal agents licensed in the United States for primary treatment of IA [78]. Studies between those two antifungal agents give a slight advantage to voriconazole with better primary outcome and higher survival rate than amphotericin B along with fewer severe side effects [79] [80]. However, voriconazole needs therapeutic drug monitoring due to
variability in plasma concentrations between patients so that overexposure or underexposure, with the respective implications that implies (toxicity or subtherapeutic levels), may be avoided [81] [82] [83] [84]. Although antifungal treatment failure can be attributed to a number of factors, clinicians often think only of drug resistance. Before exploring other antifungals, all underlying conditions of the patient in hand along with immune status and pharmacological characteristics of the current therapy must be considered [85].

6.2. Treatment using isavuconazole

The European Society for Clinical Microbiology and Infectious Diseases (ESCMID) in its last guidelines recommends the use of voriconazole and isavuconazole as first-line treatment for IA [86]. While the standard first-line treatment for IA is the use of voriconazole, toxicity associated with the intravenous formulation and its cyclodextrin vehicle makes isavuconazole an appealing alternative [87]. The SECURE study concluded that isavuconazole had comparable efficacy and safety with voriconazole [88]. Moreover, isavuconazole was better tolerated by patients and with fewer drug related adverse events compared to voriconazole [36] and there was no need for dose adjustment depending on sex or age of the patient [89]. During treatment in the SECURE study, discontinuation due to drug related event was considerably lower in the isavuconazole group than among patients treated with voriconazole. However there is no sufficient data available from patients without haematological malignancies suffering from IA thus voriconazole remains a first-line treatment option. Isavuconazole has not been used as salvage therapy extensively so older antifungal agents like posaconazole, voriconazole and liposomal amphotericin B are the first choice according to literature.
Finally, multiple studies suggest that treatment of invasive aspergillosis using isavuconazole compared to voriconazole would lead to cost savings for hospitals making it the cost effective choice [90] [91] [92].

6.3. Potential use on pediatric patients

IA is a life threatening infection that affects immunocompromised children as well as adults [93]. Children with primary and secondary immunodeficiencies that are affected by a fungus differ from adults in terms of epidemiology, presentation, detection and management of the disease [94]. It is reported that children with malignancies and IA versus those without have greater length of Hospital stay, higher mortality rate and eventually higher hospitalization costs [93].

Current treatments for IA in children vary depending on the age of the patient. Voriconazole is used for patients over 2 years of age and posaconazole may be used over the age of 13 (oral administration). For younger patients liposomal amphotericin B (L-AMB) and eventually caspofungin can be used. Due to age restrictions and drug related adverse events it is clear that there are no strict guidelines concerning pediatric patients.

Recent bibliographic data reported the case of a 3 year old girl that was affected by acute lymphoblastic leukemia and developed cerebral and pulmonary aspergillosis [70]. First-line treatment with voriconazole proved inefficient as the patient was CYP2C19 cytochrome ultra rapid metabolizer. Three weeks after voriconazole’s treatment initiation, antifungal treatment was switched to a combination of L-AMB and isavuconazole. One week later liposomal amphotericin B was discontinued and isavuconazole was continued as monotherapy and after two weeks the patient was put on chemotherapy. Isavuconazole’s dose that was used was half the recommended dosage for adults (100mg every 8 hours for 2 days and
100mg daily after that). 20 weeks after initiation of isavuconazole no adverse events and side effects due to its use were reported.
7. Mucormycosis

Mucormycosis is a term used for infections caused by certain fungi of the order *Mucorales*. Mucormycosis most commonly appears in haematology, solid organ transplants and diabetic patients. Mucorales have a tendency for vascular invasion, hence a trauma is the more likely point of entry, and they release a vast number of airborne spores while growing, spores that can be found in organic matter and soil. Most common mucormycosis-causing species are *Rhizopus* spp, *Mucor* spp, *Rhizomucor* and *Leichenheimia* spp [95]. Mucormycosis infections are life threatening, especially when found in immunosuppressed or diabetic hosts. Therefore, pre-emptive treatment is usually administered when a probable and not yet proven incident occurs. Due to mucormycosis’ nature and the state of its host, mucormycosis management is a complex activity that has to take in consideration comorbidities, immunosuppression state of the host as well as the pharmacological properties of antifungals to be used [96]. Even with the use of new tools to obtain an earlier diagnosis and new drugs to fight it, mucormycosis incidence still rises and mortality rate remains still high [97].

7.1. Standard treatment for Invasive Mucormycosis

Surgery, whether it is an open surgery for extensive disease or endoscopic for an early stage of the disease, is the core of mucormycosis therapy [98] [99]. However, surgery alone does not seem to be enough for an improved overall outcome. The major cause for high morbidity, for patients with haematological malignancies, was relapsed and/or refractory malignancy and protracted neutropenia [100]. Although laboratory analysis can take some time, early diagnosis is the key for timely treatment. In a study of 70 patients with haematological malignancies during a period of 17 years, it was established that delaying antifungal treatment even for one week can result in significant increase in mortality rate [101]. Also, clinical / radiological
similarities with invasive aspergillosis make mucormycosis difficult to diagnose. However, in a retrospective analysis three years ago, researchers found that *Mucorales* DNA can be detected in serum sampling of patients with proven or probable mucormycosis [102]. Even with the less than optimal samples used the sensitivity rate was high (81%) and it was estimated that with optimal measurements it could reach even 92%. This accuracy combined with the average time needed for histological or mycological evidence could lead to an earlier start of the treatment by a week.

Amphotericin B (AMB), in its lipid formulations, is considered the drug of choice for primary treatment of mucormycosis. However, AMB when administered in high doses has been associated with nephrotoxicity which resulted in rise of serum creatinine levels [103]. Moreover, higher doses of amphotericin B did not lead to additional benefit for the patient [104]. The duration of the antifungal treatment is another issue as there are no strict guidelines concerning its length. Although some authors propose certain weeks of treatment before switching to other agents, the duration of the treatment should be based and adjusted on each individual patient.

### 7.2. Treatment using isavuconazole

Isavuconazole, a broad-spectrum antifungal and last to date triazole to be approved, is the biologically active agent of the produg isavuconazonium sulfate and is approved by the FDA for the treatment of mucormycosis. The European Medicines Agency has granted approval to isavuconazole for the treatment of mucormycosis when the use of Amphotericin B is not feasible. In VITAL study isavuconazole presented similar efficacy with AMB and was well tolerated by patients [105]. During the five years of VITAL study (April 2008 to June 2013) 37 patients with mucormycosis received isavuconazole for a median of 84 days. 21 of the patients were given isavuconazole as primary treatment, 11 patients were given isavuconazole for refractory disease and 5 patients were given isavuconazole because they were intolerant to other
antifungals. By day 42, 4 patients showed partial response, 16 had stable invasive fungal disease and 1 had disease progression. 13 patients had died by day 42. 35 patients had adverse events and 28 of them were serious. All-cause mortality through day 42 was 38% (14 patients) and through day 84 was 43% (16 patients). Nephrotoxicity may call for discontinuation of amphotericin B whereas isavuconazole can be used without a problem. Liposomal amphotericin B still remains the first choice in treating mucormycosis in Europe. However, isavuconazole may be used as primary treatment in cases of renal failure or tolerability issues associated with amphotericin B. To date, case reports or case series where the use of isavuconazole yielded good results when AMB was inefficient are being published [106] [107].

As with the treatment for invasive aspergillosis, the use of isavuconazole compared with current treatment for mucormycosis may also reduce the cost for treating mucormycosis [108].

7.3. Potential use on pediatric patients

Due to the scarcity of patients suffering from mucormycosis data for immunosuppressed pediatric patient is limited but there are a few cases reported in medical literature. Similarly to adult population, pediatric patients treated with both antifungals and surgery have lower mortality rate than those who are treated only with antifungals [109]. In an epidemiologic study in European and non-European countries, pediatric mucormycosis affects mainly children suffering from haematological malignancies [109]. Reports of a multicenter pediatric retrospective study show that despite treatment with high doses of L-AMB combined with surgical debridement, the mortality rate of the disease remains high [110]. AMB is approved for use on pediatric patients over the age of 1 month for the treatment of mucormycosis. Just, as in adult patients, early diagnosis and treatment remains a clinical challenge. While clinical trials concerning safety when administered to pediatric patients as well as pharmacokinetic properties are still ongoing, treatment for
mucormycosis on children using isavuconazole has appeared in the literature. That is because while the use of isavuconazole has been restricted to management of IA and mucormycosis in adults, adverse effects while using other antifungal agents has led to a search for an alternative. Case reports suggest that isavuconazole may be an effective and safe option for treatment [68] [71] [69].

In a case report [71], a 7 year old girl was treated with voriconazole due to suspicion of IA. Following progression of the pulmonary infection, differential diagnosis resulted in mucormycosis as the cause. Voriconazole was discontinued and antifungal therapy was switched to amphotericin B (ABLC) and caspofungin. The lesions were surgically removed and while the culture of the infective tissue was negative, the hyphae morphology pointed to a Mucorales infection. Follow up CT 2 weeks after the surgery showed progression in the right lung. Posaconazole, as salvage therapy was implemented for a short period of 3 days, as the patient could not take oral medication. Isavuconazole alongside amphotericin B and caspofungin was used after parental consent for the off label use of isavuconazole. After 147 days of intravenous and 99 days of oral use of isavuconazole no side effects were documented. Isavuconazole was used for 101 days in the combination treatment and then as monotherapy. Follow up CT showed complete regression. Throughout the antifungal therapy chemotherapy protocol was continued.

In another case [69], a 3 year old neutropenic after discontinuation of chemotherapy showed condensation in the left lower lobe associated with right pleural effusion in a chest CT. Upon suspicion of invasive aspergillosis voriconazole was administered. After 10 days MRI showed two abscess-like cerebral lesions and confirmed kidney infiltration. Disseminated mucormycosis was diagnosed and voriconazole was switched to isavuconazole. Amphotericin B was not recommended due to renal impairment. Apart from slight nausea no adverse effects were documented after a 2 month use of isavuconazole.

Three other cases of children treated for mucormycosis with isavuconazole have been documented between 2010 and 2016 [68]. All patients who
received treatment with isavuconazole, in these cases as second line, showed improvement. At the time of the report [68] patients were receiving isavuconazole for one to two years and all of them survived. However, future studies and trials are necessary to determine pharmacokinetic properties and dosage in children.
8. Candidiasis

Alongside *Aspergillus* spp and *Mucormycetes*, one of the most common fungal pathogens associated with invasive diseases is *Candida* spp. *Candida* normally lives inside the body and on the skin without causing any problems. However if candida gets out of control it can cause invasive candidiasis (IC). IC is a common infection in immunocompromised hospitalized patients. The once predominant *C. albicans* has now given way to other *Candida* species, mostly *C. glabrata* [111]. IC is considered as a major cause of morbidity and mortality in the healthcare environment and has a mortality rate around 47% [112]. As with all IFIs, increased rate of mortality is observed when treatment is delayed [113] [114]. However, diagnosis of IC can be challenging. About half of cultures of, later proven, invasive candidiasis are negative. Non-culture tests could be the key to earlier diagnosis in patients with IC [115].

8.1. Traditional treatment for Invasive Candidiasis

Echinocandines and fluconazole are the most commonly used antifungal agents in the event of IC [112]. Following the efficacy shown by echinocandins, current treatment guidelines recommend echinocandins as first-line treatment of IC. Fluconazole, due to increasing resistance that has appeared is an alternative to echinocandins and not a primary choice [111]. Amphotericin B can be used as an alternative if there is intolerance or resistance to the previous antifungals. Voriconazole has little to offer compared to fluconazole as primary therapy and is recommended mainly as a step down oral therapy due to *C. krusei*. 
8.2. Treatment using isavuconazole

Compared to the results of Echinocandines, isavuconazole has not presented strong evidence data to support its use over the alternative. Isavuconazole has been tested, in vitro, as a combination therapy against *Candida* spp demonstrating synergistic action with micafungin and indifference with amphotericin B [116]. In a Phase III, double blind, multinational clinical trial where isavuconazole was compared to caspofungin for the treatment of IC non-inferiority of isavuconazole against caspofungin was not demonstrated [117]. As a result, until further trials, in the event of IC, isavuconazole could be used only as a step down option when other azoles are limited by their spectrum of activity or by tolerability [118].

8.3. Potential use on pediatric patients

Although the efficacy of isavuconazole in vitro against *Candida* spp yielded good results [119], to the author’s knowledge, there are no reported cases in current literature where isavuconazole was administered to patients less than 18 years of age for the treatment of IC.
9. Current Guidelines

Treatment guidelines that are presented below, grade recommendations based on existing evidence to support them. A to C recommendations mean strong to weak recommendations whereas D recommendation is a recommendation against the use of the specific agent. Quality of existing data is graded I-III, I being the highest ranking. An A I recommendation means strongly recommended agent based on more than one randomized, controlled trial. An A II recommendation means strongly recommended based on a clinical trial (without randomization) or a cohort study or from multiple time series. An A III recommendation means strongly recommended based on experts with clinical experience to back this claim or reports from expert committees.

9.1. Invasive Aspergillosis

The European Conference on Infections in Leukemia (ECIL) has included in its latest guidelines ECIL-6 [98] the new triazole, isavuconazole for the treatment of IA. Since isavuconazole showed comparable efficacy to voriconazole and fewer adverse events it is graded AI similarly to voriconazole. Amphotericin B deoxycholate is recommended against since there are more effective and far less toxic agents to be used. Therapeutic drug monitoring is recommended while treating a patient with voriconazole or posaconazole.

The European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and the European Confederation of Medical Mycology (ECMM) have posted their latest guidelines for the treatment of IA (2017) in 2018. According to these guidelines isavuconazole is recommended as primary treatment of IA followed by voriconazole and L-AMB [86]. Echinocandins and combinations may also be used as alternative treatment. Concerning pediatric patients, the use of antifungals is restricted by the age of the patient. Isavuconazole is not indicated for patients under 18 years of age so
voriconazole remains the primary treatment recommended [120] followed by L-AMB.

For the treatment of IA, the Infectious Diseases Society of America (ISDA) strongly recommends the use of voriconazole as first-line therapy (2016) [121] followed, as alternative therapies, by liposomal AmB and isavuconazole. Combination treatment with voriconazole and an echinocandin is weakly recommended and use of an echinocandin alone is strongly recommended against. ISDA also recommends a minimum duration of treatment of 6-12 weeks and secondary prophylaxis to prevent recurrence.

Table 1 Recommendation for first-line treatment of Invasive Aspergillosis

<table>
<thead>
<tr>
<th>Treatment</th>
<th>ECIL-6</th>
<th>ESCMID-ECMM-ERS 2017</th>
<th>ESCMID-ECMM (pediatric)</th>
<th>IDSA (2016)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Voriconazole</td>
<td>A I</td>
<td>A I-II</td>
<td>A II</td>
<td>A I, primary treatment</td>
</tr>
<tr>
<td>Isavuconazole</td>
<td>A I</td>
<td>A I-II</td>
<td>Not indicated for pediatric patients</td>
<td>A II, alternative treatment</td>
</tr>
<tr>
<td>Liposomal amphotericin B</td>
<td>B I</td>
<td>B II</td>
<td>B II</td>
<td>A II, alternative treatment</td>
</tr>
<tr>
<td>Amphotericin B lipid complex</td>
<td>B II</td>
<td>C III</td>
<td>C III</td>
<td>C III, alternative treatment</td>
</tr>
<tr>
<td>Amphotericin B colloidal dispersion</td>
<td>C I</td>
<td>D I-II (against use)</td>
<td>D II (against use)</td>
<td>C III, alternative treatment</td>
</tr>
<tr>
<td>Caspofungin</td>
<td>C II</td>
<td>C II</td>
<td>C II</td>
<td>NOT recommended as primary, A I</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>C III</td>
<td>C II-III</td>
<td>C III</td>
<td></td>
</tr>
<tr>
<td>Combination voriconazole + anidulafungin</td>
<td>C I</td>
<td>C I-II</td>
<td>C II</td>
<td>C II</td>
</tr>
<tr>
<td>Other combinations</td>
<td>C III</td>
<td>D III (unproven efficacy)</td>
<td></td>
<td>C II</td>
</tr>
<tr>
<td>Recommendation against use</td>
<td>A I</td>
<td>D I-II (against use)</td>
<td>D II (against use)</td>
<td></td>
</tr>
<tr>
<td>Amphotericin B deoxycholate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
ECIL-6 has not included isavuconazole as salvage treatment and has made no changes to earlier guidelines.

ESCMID-ECMM recommendation for salvage therapy is a change of class and the use of a new antifungal to the patient, for example voriconazole to be used on a voriconazole-naïve patient.

IDSA recommends, as salvage therapy for invasive aspergillosis a change of antifungal class is recommended without naming a single agent. Combination therapy with agents of different classes is also recommended. Also, in case of adverse events a change of antifungal class is recommended. According to ISDA guidelines, agents used for salvage therapy include lipid formulations of amphotericin B, micafungin, caspofungin, posaconazole or itraconazole. The use of the above agents requires consideration of possible antifungal resistance.

Table 2 Recommendations for salvage therapy of Invasive Aspergillosis.

<table>
<thead>
<tr>
<th></th>
<th>ECIL-6</th>
<th>ESCMID-ECMM-ERS 2017</th>
<th>ESCMID-ECMM (pediatric)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liposomal amphotericin B</td>
<td>B II</td>
<td>B II</td>
<td>B II</td>
</tr>
<tr>
<td>Amphotericin B lipid complex</td>
<td>B II</td>
<td>C II</td>
<td>B II</td>
</tr>
<tr>
<td>Caspofungin</td>
<td>B II</td>
<td>B II</td>
<td>B II</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>C III</td>
<td>D III (against use)</td>
<td>C III</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>B II</td>
<td>B II</td>
<td>B II</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>B II</td>
<td>A II</td>
<td>A II</td>
</tr>
<tr>
<td>Combination (azole or polyene + echinocandin)</td>
<td>B II</td>
<td>C III</td>
<td>C II</td>
</tr>
</tbody>
</table>
9.1. Invasive Mucormycosis

Although indicated for invasive mucormycosis, isavuconazole has not made it yet to any published guidelines. Although ECIL states that AMB, posaconazole and isavuconazole are, in vitro, the most potent agents against mucormycosis, only amphotericin and posaconazole appear in ECIL-6.

ESCMID and ECMM joint clinical guidelines for the treatment of invasive mucormycosis recommend as a first-line antifungal treatment the use of liposomal amphotericin B followed by posaconazole [99]. Treatment of invasive mucormycosis requires surgery debridement apart from antifungal therapy and it is strongly recommended in the ESCMID ECMM guidelines. In a mucormycosis workshop during the 27th ESCMID held in Vienna (2017) Russell Lewis presented new recommendations for the guidelines for treatment of mucormycosis. One of these recommendations is that isavuconazole should be included in the ESCMID guidelines with moderate recommendation as antifungal treatment.

<table>
<thead>
<tr>
<th>Table 3 Recommendations for first-line therapy of mucormycosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ECIL-6</strong></td>
</tr>
<tr>
<td>Combination of antifungal therapy, surgery and control of underlying conditions</td>
</tr>
<tr>
<td>Antifungal therapy</td>
</tr>
<tr>
<td>Amphotericin B deoxycholate</td>
</tr>
<tr>
<td>Liposomal amphotericin B</td>
</tr>
<tr>
<td>Amphotericin B lipid complex</td>
</tr>
<tr>
<td>Amphotericin B colloidal dispersion</td>
</tr>
<tr>
<td>Posaconazole</td>
</tr>
<tr>
<td>Combination therapy</td>
</tr>
<tr>
<td>Control of underlying condition</td>
</tr>
<tr>
<td>Surgery</td>
</tr>
</tbody>
</table>
Rhino-orbito-cerebral infection | A II
Soft tissue infection | A II
Localized pulmonary lesion | B III
Disseminated infection | C III
Hyperbaric oxygen | C III
Recommendation against use Combination with deferasirox | A II

Combination treatment is recommended in ECIL-6 as salvage treatment for invasive mucormycosis. Posaconazole has a moderate recommendation when amphotericin B has proven to be ineffective.

Salvage treatment for invasive mucormycosis, as recommended by ESCMID ECMM include higher doses of posaconazole while different formulations of amphotericin B or combination of antifungals are not strongly supported.

**Table 4** Recommendations for salvage therapy of mucormycosis

<table>
<thead>
<tr>
<th>ECIL-6</th>
<th>ESCMID-ECMM (2013)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combination of antifungal therapy, surgery and control of underlying disease</td>
<td>A II</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>B II</td>
</tr>
<tr>
<td>Liposomal AmB, AmB lipid complex, AmB colloidal dispersion</td>
<td>B II</td>
</tr>
<tr>
<td>Lipid amphotericin B + caspofungin</td>
<td>B III</td>
</tr>
<tr>
<td>Lipid amphotericin B + posaconazole</td>
<td>B III</td>
</tr>
</tbody>
</table>
10. Discussion

In a retrospective cohort study at a large US transplant and cancer center real-world use of isavuconazole was monitored [122]. Each inpatient, at the said facility, that received more than 3 doses of isavuconazole as treatment or prophylaxis was included in the study. The study confirmed existing literature concerning safety using isavuconazole while observing efficacy in patient cases never tested before. Isavuconazole’s characteristics have presented physicians with a new tool to experiment with.

Isavuconazole’s linear pharmacokinetic properties, its water soluble prodrug isavuconazonium and the ability to switch from intravenous to oral formulations make this new antifungal very appealing. Dose independent properties may prove useful when isavuconazole is administered to children (officially not indicated yet - trials are ongoing). The water solubility of isavuconazonium helps avoid a cyclodextrin vehicle and a potential toxicity by it. Moreover, isavuconazonium rapidly turns to isavuconazole (approximately 30 minutes) and is no longer detected. The dosing regimen of isavuconazole is also a plus.

Two studies have mainly contributed to the current place in therapy isavuconazole holds. The SECURE study was a double-blind, multi center, non-inferiority randomized control trial that showed non inferiority of isavuconazole to voriconazole for the treatment of invasive aspergillosis (IA). On the other hand, the VITAL study was an open label, single arm trial that tested the efficacy of isavuconazole compared with amphotericin B for the treatment of invasive mucormycosis. The frequency of adverse events was similar for isavuconazole and voriconazole when used for the treatment of IA. However, isavuconazole had fewer serious adverse events compared to voriconazole, like hepatic impairment (1.6% vs 3.5%), tachycardia (4.7% vs 8.7%) and visual disturbances (1.6% vs 7.3%). Moreover, the use of voriconazole yielded more discontinuations due to drug related adverse events than isavuconazole.
The use of isavuconazole in real-world setting gives a wider view of the drug’s possibilities. Most widely accepted guidelines do not embrace the full potential of isavuconazole due to lack of data concerning its efficacy and safety. In vitro studies show activity of isavuconazole against many species yet its indications, to this day, namely invasive aspergillosis and invasive mucormycosis block the drug’s dynamic. Case reports that emerge in literature that show off label use of isavuconazole as a last resort when all other antifungal agents have proven to be ineffective isavuconazole is a viable choice. Compared to antifungals of the same class that are used today isavuconazole shows superior safety profile. However, further studies are needed to evaluate isavuconazole in roles as prophylactic treatment, salvage treatment for aspergillosis or mucormycosis as well as treatment for other mold infections and invasive fungal infections by yeasts [123].
11. Conclusion
The use of isavuconazole in patients with invasive fungal infections seems both safe and efficacious. Treatment for invasive aspergillosis using isavuconazole vs voriconazole showed comparable efficacy, however, with less drug related adverse events and therapy discontinuation. In invasive mucormycosis, isavuconazole can be safely used when underlying conditions like renal impairment prohibit the use of amphotericin B. In both cases the use of isavuconazole may lead to increased cost savings. Use in pediatric patients, although off label, showed good tolerability, few side effects and good efficacy.
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