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Use of isavuconazole in mucormycosis: a systematic review

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Abstract

Background Mucormycosis is an opportunistic fungal infection which is associated with poor prognosis. Only a few antifungals are available in the arsenal against mucormycosis. The global guidelines for diagnosing and managing mucormycosis recommend high doses of liposomal amphotericin B (LAmB) as the first-line treatment. Isavuconazole is another potential treatment option for mucormycosis.

Main body This systematic review aims to consolidate and analyse existing evidence concerning the efficacy and safety of isavuconazole in treating mucormycosis alone or in combination with LAmB. For data aggregation, comprehensive searches were conducted across various electronic databases, such as PubMed, Science Direct, Trip, Google Scholar, the Cochrane Library, and Open-Gray. Furthermore, we explored the gray literature, employing tailored keywords. The reference lists of the selected articles were scrutinized to identify additional pertinent publications. Articles reporting any studies, case series, or case reports on any form of mucormycosis exclusively involving human subjects published in English were included. There were no time restrictions involved. We extracted crucial data, such as publication year, country, disease form, isavuconazole dosage, frequency, duration, overall outcomes, and reported adverse effects. A total of 31 articles, which included four case series, 24 case reports, one open-label trial, one randomized controlled trial, and one non-interventional registry study, were included in the final analysis. 135 adult patients and 14 children were treated with isavuconazole as primary monotherapy, primary combination therapy, nonprimary monotherapy, or nonprimary combination therapy. The mortality rate following LAmB monotherapy, amphotericin B plus azole, amphotericin B followed with azole, posaconazole only and isavuconazole only was 32%, 6.6%, 13.7%, 17.2% and 24.6%, respectively. The heterogeneity of the studies did not allow for a comparison of the different treatment strategies (primary mono- vs. primary combination, etc.).

Short conclusion The use of isavuconazole in combination therapies during the acute phase via intravenous administration alongside LAmB or other triazoles, followed by long-term monotherapy via the oral route, has yielded promising recovery rates. Adverse events associated with the use of isavuconazole are infrequently reported.

Keywords Antifungals, Isavuconazole, Mucormycosis

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Background

Mucormycosis is an opportunistic fungal infection with limited available treatment options. Among these options, liposomal amphotericin B is widely used and recommended [1]. Triazoles, which inhibit the ergosterol synthesis pathway, represent another class of antifungal agents. Isavuconazole, a broad-spectrum triazole, has recently gained approval for the management of mucormycosis when amphotericin B is either insufficient or considered a primary treatment choice. Notably, isavuconazole offers several advantages over other triazoles, including fewer potential drug interactions, reduced potential organ toxicity, and the convenience of both intravenous and oral formulations [2, 3].

Patients with mucormycosis face a daunting prognosis, with mortality rates ranging from 52 to 91% [2–5]. Current clinical guidelines advocate a comprehensive approach to mucormycosis management, involving antifungal therapy, surgical debridement, and addressing underlying predisposing conditions [3]. Nonetheless, the actual clinical efficacy of amphotericin B (LAmB) and triazoles such as isavuconazole and posaconazole, despite their promising in vitro efficacy against Mucorales, is often constrained [4]. Conventional Amphotericin B, in particular, is known for its nephrotoxic effects, while posaconazole has mainly been explored in salvage therapy contexts [5].

Isavuconazole has been proposed as prophylaxis for invasive fungal infections by some researchers. Isavuconazole was commonly used as a prophylactic agent among patients with acute myeloid leukemia (AML) and those who underwent allogeneic hematopoietic stem cell transplantation (HSCT) [3–5]. Isavuconazonium sulfate, a water-soluble prodrug, rapidly undergoes hydrolysis upon oral or intravenous administration and is transformed into isavuconazole, a potent triazole compound [5]. Compared with other triazoles, isavuconium sulfate has high oral bioavailability, consistent pharmacokinetics, and favourable activity against a broad spectrum of clinically significant fungi, including Mucorales. Isavuconium sulfate inhibits CYP51 or sterol 14α -demethylase, which is essential for the biosynthesis of ergosterol, the major sterol of fungal plasma membranes [4]. Following the inhibition of ergosterol biosynthesis, detrimental sterols accumulate within fungal cells and, consequently, die [5].

The current treatment standards, as stated in the global guidelines for diagnosing and managing mucormycosis, recommend high doses of LAmB as the first-line treatment [3]. In contrast, isavuconazole and posaconazole are recommended with moderate strength [3].

This systematic review aims to compile and synthesize existing evidence on the efficacy and safety of isavuconazole in treating various manifestations of mucormycosis, whether it is used as a primary treatment or as part of combination regimens.

Main text

The search was conducted over one year, commencing in October 2022. We searched electronic databases and explored gray literature to identify pertinent literature, employing appropriate keywords. Electronic searches were performed on PubMed (via an advanced search), Science Direct (via an advanced search), Trip (via a PICO search), Google Scholar (via an advanced search), the Cochrane Library (via an advanced search), and OpenGray, the gray literature database. Additionally, we scrutinized the reference lists of the included articles to identify further relevant publications. This systematic review was prospectively registered in the PROSPERO (International Prospective Register of Systematic Reviews) [6] under the registration number CRD42022344986.

Search strategy

Our search strategy involved the use of MeSH terms and other related keywords to ensure comprehensive coverage. We devised the search strategy following the guidelines outlined in the Preferred Reporting Items for Systematic Reviews (PRISMA) framework [7]. (Fig. 1)

Inclusion criteria

Our inclusion criteria encompassed all studies in which isavuconazole was administered to patients confirmed to have mucormycosis. This included both randomized and nonrandomized clinical trials, observational studies and case series, and case reports involving human subjects to assess the adverse effects and the dosage. We considered studies regardless of the dosage or duration of isavuconazole treatment, whether it was used as a standalone therapy or in combination with other interventions, and whether it was used as primary or adjunctive therapy.

Exclusion criteria

For this study, we excluded articles published in languages other than English. In vitro and animal studies were also excluded. The review articles and the secondary analysis of trials were also excluded to prevent data duplication.

Outcome measures

The review included all-cause mortality at 42 and 84 days of therapy. The dosage regimens and durations are summarized. The adverse effects arising from the therapy were also recorded. Furthermore, computations were performed to establish the mean values for the duration and dosage of isavuconazole administered during the maintenance phase.

1. **Pubmed Search: 203**
   ((((((Mucormycoses)) OR (Mucormycose)) OR ("Mucorales Infection")) OR ("Mucorales Infections")) OR ("Infection, Mucorales")) AND ((((((BAL 8557) OR (BAL8557)) OR (BAL-8557)) OR (isavuconazonium sulfate)) OR (Cresemba)) OR (Isavuconazole))

In title or abstract

Filters : From 2012 to 2022 , Language : English

2. **Science Direct: 401**

Mucormycosis AND Isavuconazole

Filters: From 2012 to 2022, Language: English

3. **Trip (PICO):14**

Population: Mucormycosis

Intervention: Isavuconazole

4. **Google Scholar:48**

allintitle: mucormycosis "Isavuconazole"

Custom range 2012-2022

5. **Cochrane Library: 8**

Trials matching mucormycosis in Title Abstract Keyword AND Isavuconazole in Title Abstract Keyword –
Limits – Publication date January 2012 to December 2022, English language

6. **Open grey : 0**

mucormycosis" AND Isavuconazole type: article

7. **Manual search: 5**

Total articles resulted from search: 679

Fig. 1 Search strategy and number of results retrieved from each database

Study selection

Four authors independently carried out the process of study selection. Each author conducted individual searches for relevant studies, downloaded the search results as .csv/PubMed-txt files, and then input them into the Rayyan Intelligence System [8]. Each author independently screened the abstracts of these studies. In cases where abstracts were unclear, lacked the necessary details, or were entirely unavailable, full articles were retrieved and reviewed. Articles were categorized into three groups: excluded, included, and those with uncertain eligibility were labelled 'may be.' Any discrepancies in selection between the four authors were resolved through further discussions involving the other co-reviewers' input.

Data extraction

We performed data extraction via a Microsoft Excel spreadsheet. The data extracted from these studies encompassed several vital elements, including the publication year and country of publication of the disease, i.e., rhinocerebral mucormycosis (RCM), pulmonary mucormycosis (PM), cutaneous mucormycosis (CM), gastrointestinal mucormycosis (GIM) and disseminated mucormycosis (DM). Isavuconazole dosages in the loading and maintenance phases, the frequency and duration of each phase, and the overall outcome reported adverse effects. The data analysis was conducted separately for the children and adults, considering the differences in dosing and context.

Definitions

Infections which was mycologically proven as mucormycosis was considered as confirmed mucormycosis. Primary therapy was operationally defined as the initial antifungal treatment (AFT) administered to treat mucormycosis. Therapy was designated 'primary' if, within seven days before starting systemic AFT, the patient had received four or fewer cumulative days of alternative treatments specifically targeting mould infections. Non-primary therapy was categorized on the basis of the rationale behind the treatment, namely, refractory infection, AFT intolerance, or transition to oral step-down/maintenance therapy. Refractory infection was defined as the necessity for additional or alternate systemic AFT due to disease advancement, characterized by worsening or emergence of new clinical indications or radiological findings associated with IFD because of inadequate response to primary mould-targeting therapy. Intolerance refers to the shift to alternative systemic AFT prompted by a patient's inability to endure mould-active therapy. Continuation therapy was defined as when the patient was given the drug after discharge from the hospital. Salvage treatment- antifungals are given when mucormycosis does not respond to other appropriate antifungal treatments [9].

Quality assessment

We used the NIH quality assessment tools for randomized trials, observational studies, and case reports/case series to assess the risk of bias.

Results

The search strategies used in each database and the number of results of each search are given in Fig. 2. The PRISMA flow chart in Fig. 1 shows the sequence of events in the selection procedure, with numbers in each step.

There were 31 articles, which included one multicentre non-interventional registry study; one randomized

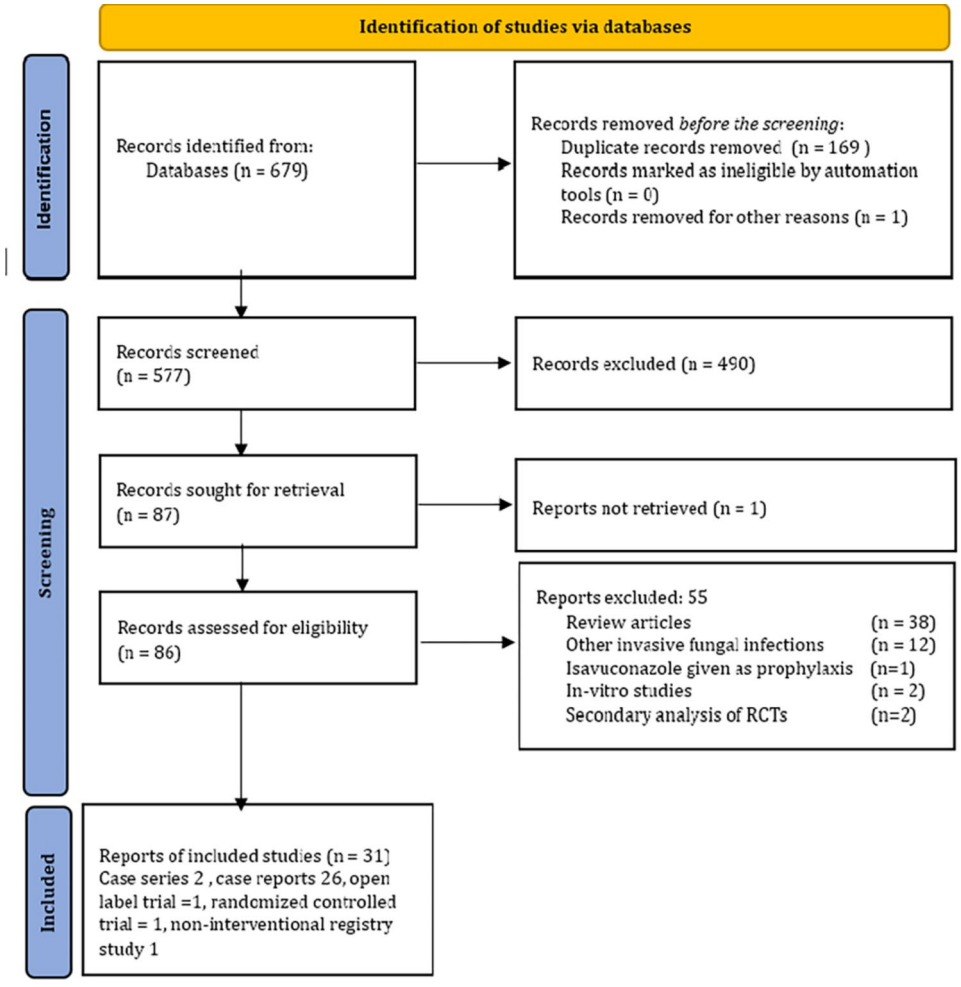

Fig. 2 PRISMA flow chart. From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. https://doi.org/10.1136/bmj.n71

controlled trial; one phase three study; a double-blinded, global, multicentre, comparative-group study; and 4 case series and 24 case reports. The articles by the year of publication are given in Fig. 3. The highest number of reported articles on the successful treatment of mucormycosis were from the USA, accounting for 19/31. In these reports, the total number of patients with mucormycosis treated with isavuconazole was 135. Among them, 14 were children (younger than 15 years). The child and adult cases were analysed separately in the final analysis.

Adult patients treated with isavuconazole for mucormycosis

One hundred thirty-five patients were treated with isavuconazole, as reported in 21 case reports, one case series, and three other types of studies.

Isavuconazole dosage

Two hundred milligrams of isavuconazole intravenously, at 8-hour intervals for two days, is the most common regimen. A total of 372 mg of isavuconium sulfate, in which 200 mg of isavuconazole is contained, was used. The maintenance dose was the same but was the same as that used for the oral and once-daily regimens. The same maintenance dose was continued as continuation therapy in most patients. In two case reports, information was not available on combined drugs. The patients had been on isavuconazole monotherapy most of the time during the maintenance phase. Thompson et al. have not described the doses of isavuconazole used [10]. Maertens et al. have given isavuconazonium sulfate 372 mg (prodrug; equivalent to 200 mg isavuconazole; intravenously three times a day on days 1 and 2, then either intravenously or orally once daily) [11]. In Marty et al., 200 mg isavuconazole (as an intravenous or oral water-soluble prodrug, isavuconazonium sulfate) was given three times daily for six doses, followed by 200 mg/day until invasive fungal disease resolution, failure, or 180 days or more [12] (Table 1).

Treatment strategies

Surgical debridement was combined in 14 of the 21 adult patients reported in case reports. In case series and other types of studies, data on surgical debridement could not be obtained. Topical washes or irrigation with amphotericin were also performed in 3 of the 21 cases (Table 2).

The outcome following antifungal therapy

The all-cause mortality rate at 42 days in adults was 27.4% (37/135 died), and at 84 days, it was 31.1% (42/135 died).

The adverse effects

The adverse effects of these drugs are rarely reported in case series and case reports. Even if they are reported, there is a reasonable difficulty in differentiating them, whether they are due to isavuconazole or other drugs, as they are used in combination in almost all cases except one. Therefore, it is more appropriate to consider them as adverse effects that occur during treatment, not as adverse effects of isavuconazole (Table 3).

Pediatric patients were treated with isavuconazole for mucormycosis

Isavuconazole dosage

Table 4 summarizes children treated with isavuconazole for any form of mucormycosis. There were eight female

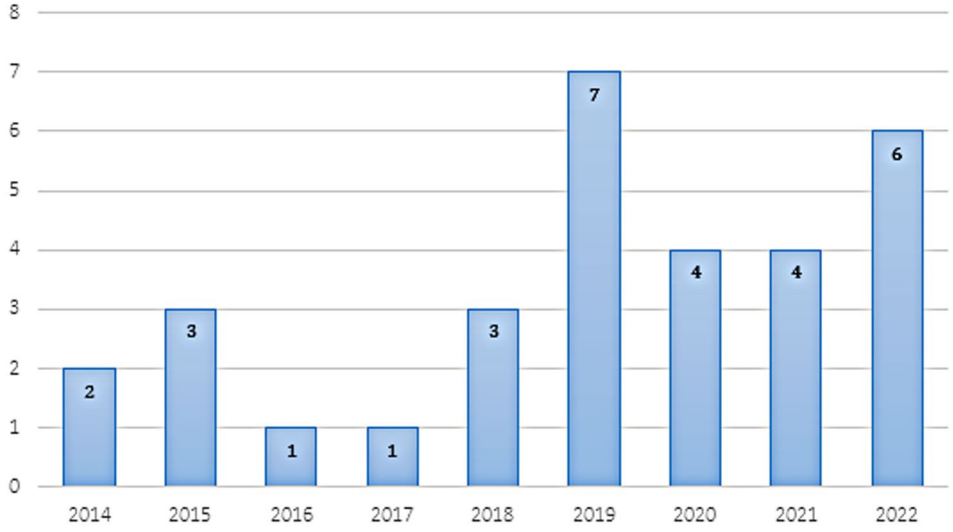

Fig. 3 Number of articles reported each year

Table 1 Different treatment strategies used for adult patients treated with isavuconazole

Type of Study	Number of mucormycosis patients	Primary isavuconazole treated		Non primary isavuconazole treated		Number of reported deaths due to mucormycosis (%)	
		Monotherapy	Combined with other antifungal therapy	Monotherapy	Combined with other antifungal therapy	Day 42	Day 84
Multicentre, noninterventional registry study [11]	62	9	33	9	11	17/62 (27%)	22/62 (35.4%)
Single-arm, open-label trial [14]	45[≠]	21	0	16	0	15 [ß]/45 (33.3%)	19/45 (42.2%)
Phase 3, double-blind, global multicentre, comparative-group study [15]	3	3	0	0	0	0	0
Case series	12	4	2	2	4	6 /12[#] (50%)	6 /12[#] (50%)
Case reports*	21	6	3	8	4	0[ß]	0[ß]
Total	135	43	38	35	19	37/135 (27.4%)	42/135 (31.1%)

[≠ Eight] patients were coinfected with other molds

*In one case report, the date of the addition of isavuconazole was not mentioned clearly. Therefore, categorizing it into primary therapy or nonprimary therapy is not possible. In any case, it was given as a combination therapy

[#]The exact date of death after the disease is not given; thus, 42-day mortality and 84-day mortality could not be assessed in case series and case reports

[ß] One lost to follow-up

children and six male children. In 5/14 case reports, the loading dose was not available. According to the available data, the minimum dosage per kg body weight was 4.6 mg, and the maximum dosage was 10.9 mg. The mean dose of isavuconazole used for the loading dose was 7. 9 mg/kg (SD=2.54). Most loading doses were given via the IV route at a frequency of three times per day (except in one case [35]) for two days.

All patients were treated with a combination of isavuconazole with LAmB with or without posaconazole. The duration of maintenance plus continuation therapy with oral isavuconazole was unavailable in two patients. The daily dose was followed in all patients. The maintenance and continuation regimens were mainly given via the oral route, with the exception of one occasion where the patient continued IV once daily for some time during the maintenance phase. However, in both cases, the duration of intravenous maintenance of isavuconazole was not mentioned, but ultimately, it was converted to oral therapy for continuation.

The outcome following antifungal therapy

A minimum of eleven children who were cured with isavuconazole therapy in combination with other drugs were cured from the reported cases of mucormycosis, accounting for 78.6% of the success. For the cured children, the minimum duration of oral isavuconazole was two months, and the maximum duration was 24 months. The mean duration of isavuconazole maintenance was 9.15 months. The all-cause mortality on day 42 was 7.1% (1/14 died), and on day 84, the all-cause mortality was 21.4% (3/14 died) (Table 4). Among pediatric population the age ranged from 1.3 to 12 years with a median of high success of 7 years. Only three children died were 11, 8 and 1.5 years.

The adverse effects

Only in one case series an adverse effect of renal insufficiency, electrolyte disturbances, and transaminitis [35] was mentioned. However, attribution was confounded following haemopoietic stem cell transplantation [HSCT]. In other case series and case reports, the adverse effects were not mentioned.

Quality assessment of the studies

Additional files 1, 2, and 3 summarize the risk of bias assessed via the NIH quality assessment tool for randomized trials, observational studies, case series, and case reports, respectively (See additional files 1, 2 and 3).

Discussion

In our analysis, both paediatric and adult patients were included, with separate data analyses conducted due to dosage variations. Children typically receive a dosage of 10 mg/kg isavuconazole, whereas adults receive a fixed dose of approximately 200 mg. The loading dose was administered intravenously 8 hourly for first 48 h (six doses), after which patients transitioned to daily oral administration once stable. In most cases, the same maintenance dose was continued for continuation therapy after discharge.

Table 2 Summary of case reports/case series reporting the use of isavuconazole in the treatment of adults with mucormycosis [13–34]

Care report/ case series	Country of the report	Form of disease	No.of cases treated with ISAvuconazole	Gender	Age in years	Comorbid conditions	Loading dose of isavuconazole mg	Route of the loading dose	Frequency of loading dose	Duration of loading dose	Maintenance dose	Frequency of maintenance	Route of maintenance	Duration of treatment	Other antifungals given to the patient	Other treatment modalities followed	Outcome
RSomana et al., 2022 [23]	India	RCM	12#	*	*	*	200	IV	8 hrly	48 h	200 mg	OD	Oral	*	Posaconazole = 4, Both Posaconazole and LAMB = 4	Surgical debridement	6 died ##
Y. Ahmed et al., 2016 [24]	USA	RCM	1	M	53	Diabetes Mellitus/HIV	372**	IV	8 hrly	48 h	372 mg**	OD	Oral	3 months cont.	NA	Surgical debridement	Improved
Brigmon MM, 2021 [25]	USA	RCM	1	M	55	Diabetes Mellitus	NA	NA	NA	NA	NA	NA	NA	10months	LAMB, Macafungin	None	Improved
Tran D; Schmit B, 2020 [26]	USA	RCM	1	M	24	Diabetes Mellitus, Dental extraction	372**	IV	8 hrly	48 h	372 mg**	OD	Oral	2 months	LAMB	Surgical debridement	Cured
Ilharco M, 2019 [27]	Portugal	RCM	1	M	61	Chronic sinusitis	200 mg	IV	8 hrly	48 h	200 mg	OD	IV – till D24, then Oral	12months	LAMB, Posaconazole	Surgical debridement	
Durà-Miralles X, 2020 [28]	Spain	RCM	1	M	46	None	200 mg	IV	8 hrly	48 h	200 mg	OD	IV – till D24, then Oral	11 months lost follow up	LAMB,	Surgical debridement	Improved, lost follow up
Shafiq M, 2018 [29]	USA	RCM	1	M	67	Diabetes Mellitus	372**	IV	8 hrly	48 h	372 mg**	OD	Oral	4 M	LAMB	Surgical debridement	Cured
Thielen BK, 2019 [30]	USA	CM	1	M	63	Diabetes Mellitus, Burn injury	NA	IV	NA	NA	NA	NA	NA	3months + 20D	LAMB – topical, Posaconazole	Surgical debridement	Improved
Gani I, 2019 [31]	USA	GIM	1	M	79	Diabetes Mellitus, Kidney transplant	372**	IV	8 hrly	48 h	372 mg**	OD	Oral	6 months cont.	NA	None	Cured
Beaver R, 2021 [32]	USA	RCM	1	M	47	Trauma	372**	IV	8 hrly	24 h	372 mg**	OD	Oral	16month	LAMB topical	Surgical debridement	Improved
Ponce-Rosas L, 2022 [33]	Peru	RCM	1	M	66	Diabetes Mellitus, Covid19	200	IV	8 hrly	NA	200	OD	Oral	10months	None	Surgical debridement	Cured
Kou C, 2019 [34]	USA	GIM	1	F	62	AML, HSCT	375**	IV	8 hrly	24 h	375 mg**	OD	Oral	7month	LAMB, Posaconazole, Micafungin	Surgical debridement	Cured
Peixoto D [35]	USA	Disseminated mucormycosis	1	M	59	AML, HSCT	200	Oral	8 hrly	48 h	200	OD	Oral	7Months and 1 week	LAMB	None	Cured
Ervens ,2014 [36]	Germany	RCM	1	M	45	ulcerative colitis	200	IV	8 hrly	48 h	200	OD	Oral	18months	LAMB	Surgical debridement	Cured
Duarte M, 2022 [37]	Portugal	PM	1	M	49	Diabetes Mellitus, Influenza B	200	NA	8 hrly	48 h	200	OD	Oral	Lost follow up	LAMB	None	Lost follow up
Sanku 2022 [38]	USA	RCM	1	M	46	Granulomatosis with polyangiitis	372 mg*	IV	8 hrly	48 h	NA	OD	Oral	6months	LAMB	None	Cured
Hoang K [39]	USA	PM	1	M	66	Diabetes Mellitus	200 mg	IV	8 hrly	NA	200	OD	Oral	16 months		Surgical debridement	Cured
Huggins, 2019 [40]	USA	PM	1	M	62	sarcoidosis, NAS cirrhosis, Diabetes Mellitus	200 mg	IV	8 hrly	NA	200	OD	Oral	6 months	LAMB	None	Cured

Table 2 (continued)

Care report/ case series	Country of the report	Form of disease	No.of cases treated with ISAvuconazole	Gender	Age in years	Comorbid conditions	Loading dose of isavuconazole mg	Route of the loading dose	Frequency of loading dose	Duration of loading dose	Maintenance dose	Frequency of maintenance	Route of maintenance	Duration of treatment	Other antifungals given to the patient	Other treatment modalities followed	Outcome
Izaguirre-Anariba [41]	USA	GIM	1	M	57	Sarcoidosis	372 mg**	IV	8 hrly	48 h	NA	OD	Oral	7 months	LAMB	None	
Zuglian [42]	Italy	CM	1	M	67	idiopathic granulocytic aplasia, trauma	200 mg	IV	8 hrly	48 h	200	OD	Oral	3 months	None	Surgical debridement	Cured
Hammoudi [43]	USA	CM	1	F	60	DM, trauma, Covid 19	186	NA	NA	NA	186 mg	OD	Oral	1.5 months	Posaconazole	Surgical debridement	Cured
Martin MS [44]	USA	PM	1	M	18	congenital renal agenesis	372*	NA	NA	NA	372 mg*	OD	Oral	7 months	LAMB	Surgical debridement	Cured

** 372 mg of *isavuconazonium sulfate* is equivalent to 200 mg of *isavuconazole*;* Not given in the article, # out of 25 proven Covid-associated mucormycosis patients, ## It is not extractable from the report whether all six patients *who* died had received *isavuconazole*. (RCM=Rhino Cerebral Mucormycosis, PM=Pulmonary Mucormycosis, Dm=Dessiminated Mucormycosis, *GIM*=Gastro-Intestinal Mucormycosis, CM=Cutaneous Mucormycosis, M=Male, F=Female, IV=Intravenous, OD=Once *daily*, NA=Not Available, LAmB=Liposomal *Amphotericin* B, RCM=Rhino-Cerebral Mucormycosis, PM=Pulmonary Mucormycosis, CM=Cutaneous Mucormycosis, DM=Disseminated Mucormycosis, OD=Once daily, NA=Not Available

Table 3 Adverse effects that occurred during treatment

Reported adverse effects
Abdominal pain
Back pain
Constipation
Decreased appetite
Diarrhoea
Dyspnoea
Elevation of liver function tests
Headache
Hypoesthesia/Paraesthesia
Hypoglycaemia
Insomnia
Nausea
Neutropenia
Noncardiac chest pain
Peripheral oedema
Pneumonia
Pyrexia
QTc segment shortening
Renal failure
Restlessness
Supra ventricular tachycardia

Compared to adults the mortality rate was lower in children at 42 days. However, the diverse study types and nonstandardized reporting of data across studies hindered a comparative analysis of mortality between different treatment strategies involving isavuconazole. The authors hypothesize that the discrepancy in treatment success rates between children and adults is primarily due to pharmacokinetic differences, specifically higher drug metabolism and clearance in children, leading to lower systemic drug exposure and reduced efficacy. Additional factors, such as immature immune response, weight-based dosing issues, and severe comorbidities, may also contributed to this discrepancy [2–4, 10–42, 43, 40].

Nevertheless, overall mortality rates in adults were comparable to those of amphotericin B monotherapy, as reported by Sigera et al. (2024) [44]. The majority of patients ($n=3749$, mortality 31.5%) receiving amphotericin B alone was followed by those receiving amphotericin B in addition to azole ($n=843$, mortality 6.6%; $P<.0001$), amphotericin B followed with azole ($n=357$, mortality 13.7%; $P<.0001$), posaconazole only ($n=250$, mortality 17.2%; $P<.0001$), and isavuconazole only ($n=65$, mortality 24.6%; $P=.24$).

Although the literature reports numerous side effects, detailed patient experiences are often lacking, particularly in case reports. Determining whether reported adverse effects are solely attributable to isavuconazole or other concurrently administered drugs is often challenging. Therefore, the reported side effects should be

Table 4 Summary of case reports/case series reporting the use of isavuconazole in the treatment of children (younger than 15 years) [35, 36, 37–41]

Case report/series	Country of the report	Form of disease	Age of the child years	Gender	Comorbidities	Loading dose of Isavuconazole	Route of the loading dose	Frequency of loading dose	Duration of loading dose	Maintenance dose	Frequency of maintenance	Route of maintenance	Duration of treatment	Other antifungals given to the patient	Other treatment modalities followed	Outcome
Asmaa Ferdjallah et al., 2021 [16]	USA	RCM	2	F	HSCT	15 mg/kg	IV	12 hrly	48 h	15 mg/kg	OD	Oral	6 M	LAMB	NA	Cured
		RCM	11	F	HSCT	10 mg/kg	IV	8 h	48 h	10 mg/kg	OD	Oral	NA	LAMB	Surgical debridement	Death (day 43+)
		PM	8	M	HSCT	7 mg/kg	IV	8 hrly	48 h	7 mg/kg	OD	Oral	1 M	LAMB	Surgical debridement	Death (day 22)
		CM	1.5	M	Huler syndrome	10 mg/kg	IV	8 hrly	48 h	10 mg/kg	OD	IV	2 M	LAMB	Surgical debridement	Death after (day 67)
Ashkenazi-Hoffnung L et al., 2020 [45]	Israel	RCM	14	M	ALL	NA	NA	NA	NA	4.5 mg/kg	NA	NA	3 M	LAMB	Surgical debridement	Cured
		RCM	13	F	ALL	NA	NA	NA	NA	3.5 mg/kg	NA	NA	2 M	LAMB	Surgical resection	Cured
		CM	8	F	Fragile x	NA	NA	NA	NA	5.mg/kg	NA	NA	3.5 M	LAMB	Surgical debridement	Cured
		GIM	7	M	Trauma	NA	NA	NA	NA	5.4 mg/kg	NA	NA	2 M	LAMB	Hyperbaric oxygen treatment Surgical debridement	Cured
Barg AA, 2018 [46]	Israel	RCM	4.5	M	ALL	200 mg	NA	NA	NA	9.3 mg/kg	OD	Oral	7 M	LAMB, Caspofungin	Surgical debridement	Cured
		RCM	5	M	ALL	200 mg	NA	NA	NA	NA			12 M	LAMB		Cured
		RCM	15	F	HL	NA	NA	NA	NA	NA	NG	NG	24 M	LAMB, Caspofungin	Surgical debridement	Cured
Pomorska A, 2019 [47]	Poland	PM	7	F	ALL	200 mg	IV	8 hrly	48 h	200 mg	OD	Oral	8 M	LAMB	Surgical debridement	Cured
Cornu M, 2015 [48]	France	Disseminated mucormycosis	3	F	ALL	70 mg	IV	8 hrly	48 h	70 mg	OD	IV	24 M	LAMB	None	Cured
Sosnowska-Sienkiewicz P [49]	Poland	Disseminated mucormycosis	1 4/12	F	ALL	10 mg/kg	IV	8 hrly	48 h	10 mg/kg	OD	Oral	6 M	LAMB	Surgical removal of abscess	Cured

RCM=Rhinocerebral Mucormycosis, PM=Pulmonary Mucormycosis, CM=Cutaneous Mucormycosis, HSCT=Haemopoietic Stem Cell Transplantation, ALL=Acute Lymphocytic Leukaemia, LAMB=Liposomal Ampicillin B, HL=Hodgkin Lymphoma
OD=Once daily, NA=Not Available

regarded as adverse events occurring during the treatment of mucormycosis. Case reports, by their nature, provide anecdotal evidence and do not establish causality in many instances, contributing to a risk of bias across the literature. However, the literature suggests that isavuconazole has a better safety profile than voriconazole and amphotericin B-based regimens in the treatment of invasive fungal infections in patients with malignancies and those undergoing transplants [45].

Furthermore, surgical debridement in conjunction with antifungal therapy is always required for the cure following mucormycosis. Surgical debridement is a critical component of effective mucormycosis management, as it helps to physically remove fungal reservoirs and reduce the source of infection, enhancing the overall efficacy of antifungal treatments. The integration of debridement with isavuconazole therapy underscores a comprehensive approach to controlling and mitigating mucormycosis, although precise data on the impact of combined treatments remain limited.

Despite inherent limitations in the available data and the anecdotal nature of case reports, our systematic review highlights the increasing importance of isavuconazole for mucormycosis treatment with potential benefits. However, the variability of mucormycosis presentation, treatment regimens, and patient characteristics, combined with a lack of specific pathogen identification in case reports, precludes the generalization of findings. Therefore, further research is warranted to conduct comparative analyses of the efficacy of isavuconazole across different forms of infection and pathogens. Another limitation of our review is the exclusion of in vitro studies, which were not incorporated because of the challenges in harmonizing and analysing disparate data from various experimental conditions. Owing to the paucity of comparative clinical trials with other antifungals used for the management of mucormycosis, we were not able to compare the effects and outcomes following isavuconazole therapy. Isavuconazole has been shown to be noninferior to voriconazole for the primary treatment of suspected invasive mould disease, demonstrating comparable efficacy while being better tolerated and associated with fewer adverse events. The literature primarily compares isavuconazole with voriconazole, and findings suggest that isavuconazole may also help reduce hospital length of stay for specific patient subgroups, particularly those with moderate-to-severe renal impairment. These results support the use of isavuconazole as an effective and well-tolerated alternative to voriconazole in managing invasive mould disease [46, 47].

Recent studies by Malene Risum et al. (2021) and Parikshit Shirish Prayag et al. (2023) emphasized the importance of therapeutic drug monitoring (TDM) for isavuconazole [47, 48]. Isavuconazole generally has more stable serum concentrations than other antifungals do, making it easier to manage. Although their findings indicate minimal significant drug–drug interactions, TDM should be performed when adding or discontinuing CYP3A4-metabolized drugs or adjusting isavuconazole doses to ensure optimal therapeutic levels [43, 47, 48].

Conclusion

In conclusion, isavuconazole has shown significant efficacy in treating mucormycosis, with a high success rate of 78.6% among children and promising results in adults. Despite this, the all-cause mortality rates remain substantial, with 27.4% of adults experiencing mortality at 42 days and 31.1% at 84 days, underscoring the severity of the infection. The most common treatment regimen involves a loading dose of 200 mg of intravenous isavuconazole every 8 h for 2 days, followed by daily intravenous or oral maintenance. The combination of isavuconazole with surgical debridement seems to improve outcomes, but the variability in treatment protocols and incomplete data on adverse effects highlight the need for further research to optimize treatment strategies and increase patient survival.

Abbreviations

RCM	Rhino Cerebral Mucormycosis
PM	Pulmonary Mucormycosis
CM	Cutaneous Mucormycosis
GIM	Gastrointestinal Mucormycosis
HSCT	Haemopoietic stem cell transplantation
ALL	Acute lymphocytic leukemia
LAMB	Liposomal Ampicillin B
HL	Hodgkin lymphoma
OD	Once daily
NA	Not available
TDM	Therapeutic drug monitoring
PROSPERO	International Prospective Register of Systematic Reviews

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

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Author contributions

SG conceived the idea. SG and RK designed the review. SG, RK, KM, and SW were involved in data collection and analysis. RK, SG, and KM performed a comprehensive literature search. SG, RK, SW and KM independently screened the titles and abstracts of all the identified studies for selection, according to the inclusion criteria. SB and SJ independently reviewed the selected studies to confirm their eligibility. SG drafted the manuscript, SG, SW, RK and SJ critically revised it. All the authors read and approved the final manuscript.

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References

1. Gupta I, Baranwal P, Singh G, Gupta V. Mucormycosis, past and present: a comprehensive review. Future Microbiol. 2023;18(3):217–34.
2. Mahalaxmi I, Jayaramayya K, Venkatesan D, Subramaniam MD, Renu K, Vijayakumar P, et al. Mucormycosis: an opportunistic pathogen during COVID-19. Environ Res. 2021;201:111643.
3. Cornely OA, Alastruey-Izquierdo A, Arenz D, Chen SCA, Dannaoui E, Hochhegger B, et al. Global guideline for the diagnosis and management of mucormycosis: an initiative of the European Confederation of Medical Mycology in cooperation with the Mycoses Study Group Education and Research Consortium. Lancet Infect Dis. 2019;19(12):e405–21.
4. Spellberg B, Walsh TJ, Kontoyiannis DP, Edwards J Jr., Ibrahim AS. Recent advances in the management of mucormycosis: from bench to Bedside. Clin Infect Dis. 2009;48(12):1743–51.
5. Smith C, Lee SC. Current treatments against mucormycosis and future directions. Chowdhary A, editor. PLOS Pathog. 2022;18(10):e1010858.
6. PROSPERO- International prospective register of systematic reviews. Available from: https://www.crd.york.ac.uk/prospero/
7. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Available from: http://www.prisma-statement.org/
8. Z AE, I I FHH. Rayyan: a systematic reviews web app for exploring and filtering searches for eligible studies for Cochrane Reviews. Abstracts of the 22nd Cochrane Colloquium. Wiley; 2014. 9.
9. Egger M, Bellmann R, Krause R, Boyer J, Jakšić D, Hoenigl M. Salvage Treatment for Invasive Aspergillosis and Mucormycosis: Challenges, Recommendations and Future Considerations. Infect Drug Resist. 2023; 16:2167–78. Available from: https://www.dovepress.com/salvage-treatment-for-invasive-aspergillosis-and-mucormycosis-challeng-peer-reviewed-fulltext-article-IDR
10. Thompson GR 3rd, Garcia-Diaz J, Miceli MH, Nguyen MH, Ostrosky-Zeichner L, Young J-AH, et al. Systemic antifungal therapy with isavuconazonium sulfate or other agents in adults with invasive mucormycosis or invasive aspergillosis (non-fumigatus): a multicentre, non-interventional registry study. Mycoses. 2022;65(2):186–98.
11. Maertens JA, Rahav G, Lee D-G, Ponce-de-León A, Ramírez Sánchez IC, Klimko N, et al. Posaconazole versus Voriconazole for primary treatment of invasive aspergillosis: a phase 3, randomised, controlled, non-inferiority trial. Lancet. 2021;397(10273):499–509.
12. Marty FM, Perfect JR, Cornely OA, Mullane KM, Rahav G, Lee M, et al. An open-label phase 3 study of isavuconazole (VITAL): focus on mucormycosis. Risk. 2014;8:21–6.
13. Soman R, Chakraborty S, Joe G. Posaconazole or isavuconazole as sole or predominant antifungal therapy for COVID-19-associated mucormycosis. A retrospective observational case series. Int J Infect Dis [Internet]. 2022;120:177–8.
14. Ahmed Y, Delaney S, Markarian A. Successful isavuconazole therapy in a patient with acute invasive fungal rhinosinusitis and acquired immune deficiency syndrome. Am J Otolaryngol. 2016;37(2):152–5.
15. Brigmon B MM, Ochoa, Brust K. Successful long-term therapy of mucormycosis with isavuconazole. Proc (Baylor Univ Med Center). 2021;34:703–4.
16. Tran D, Schmit B. An aggressive case of Mucormycosis. Cureus. 2020;12. e9610.
17. Ilharco M, Pereira CM, Moreira L, Proença AL, do Carmo Fevereiro M, Lampreia F et al. Rhinoorbital mucormycosis in the immunocompetent: Experience with Isavuconazole. Vol. 18, IDCases. 2019. e00591.
18. Durà-Miralles X, Escolà-Vergé L, Moreno D, Martínez-Ricarte F, Lung M, Fernández-Hidalgo N, et al. Isolated cerebral mucormycosis associated with intravenous drug use. J Mycol Med. 2020;30(4):101046.
19. Shafiq M, Ali Z, Ukani R, Brewer J. Isavuconazole: a promising salvage therapy for Invasive Mucormycosis. Cureus. 2018;10:e2547.
20. Thielen BK, Barnes AMT, Sabin AP, Huebner B, Nelson S, Wesenberg E, et al. Widespread lichtheimia infection in a patient with extensive Burns: opportunities for Novel Antifungal agents. Mycopathologia. 2019;184(1):121–8.
21. Gani I, Doroodchi A, Falkenstrom K, Berry H, Lee W, Mulloy L et al. Gastric Mucormycosis in a Renal Transplant Patient Treated with Isavuconazole Monotherapy. Vol. 2019, Case reports in transplantation. 2019. p. 9839780.
22. Beaver R, Garza B, Vallabhaneni H, Cahuayme-Zuniga L, Midturi J, LaDow T. Use of topical amphotericin in a case of refractory sino-orbital angioinvasive mucormycosis. 33, Medical mycology case reports. 2021. pp. 21–5.
23. Ponce-Rosas L, Gonzales-Zamora J, Diaz-Reyes N, Alarco-Cadillo O, Alave-Rosas J. Rhino-Orbital-Cerebral Mucormycosis in a Post-COVID-19 patient from Peru. Case Rep Infect Dis. 2022;2022:2537186.
24. Kou C, Rendo M, Kline D, Bishop B, Yun HC. An unusual cause of bowel obstruction: Rhizopus Arrhizus diverticulitis. 25, Medical mycology case reports. 2019. pp. 15–8.
25. Peixoto D, Gagne LS, Hammond SP, Gilmore ET, Joyce AC, Soiffer RJ, et al. Isavuconazole treatment of a patient with disseminated mucormycosis. J Clin Microbiol. 2014;52(3):1016–9.
26. Ervens J, Ghannoum M, Graf B, Schwartz S. Successful isavuconazole salvage therapy in a patient with invasive mucormycosis. Infection. 2014;42(2):429–32.
27. Duarte M, Tiago V, Camble A, Sousa R, Aldomiro F. Pulmonary mucormycosis in a poorly controlled Diabetic Patient. Cureus. 2022;14:e24932.
28. Sanku K, Youssef D. Coexistence of Mucormycosis and Granulomatosis With Polyangiitis: A Diagnostic and Therapeutic Challenge. Vol. 14, Cureus. 2022. p. e25124.
29. Hoang K, Abdo T, Reinersman JM, Lu R, Higuita NIA. A case of invasive pulmonary mucormycosis resulting from short courses of corticosteroids in a well-controlled diabetic patient. 29, Medical mycology case reports. 2020. pp. 22–4.
30. Huggins J, Al Jurdi A, Gupta R. Breaking the mold: a case of pulmonary mucormycosis treated with isavuconazole. 23, Medical mycology case reports. 2019. pp. 34–6.
31. Izaguirre-Anariba DE, Chee F, Thet Z, Lanza J. An Interesting Case of a 57-Year-Old Male with an Upper Gastrointestinal Bleeding and Obstructive Uropathy with Bilateral Hydronephrosis Diagnosed with Systemic Mucormycosis. Vol. 2018, Case reports in infectious diseases. 2018. p. 6283701.
32. Zuglian G, Ripamonti D, Tebaldi A, Rizzi M. Cutaneous mucormycosis by Rhizopus arrhizus treated with isavuconazole as first line therapy: a case report. 26, Medical mycology case reports. 2019. pp. 42–3.
33. Hammoudi DAS, Morar MM, Garbuzov A, Urias D, Katira KM. Lower extremity salvage in a Diabetic patient with cutaneous mucormycosis and COVID-19 after Open Patella fracture. Ochsner J. 2022;22:163–8.
34. Martin MS, Smith AA, Lobo M, Paramesh AS. Successful Treatment of Recurrent Pulmonary Mucormycosis in a Renal Transplant Patient: A Case Report and Literature Review. Vol. 2017, Case reports in transplantation. 2017. p. 1925070.
35. Ferdjallah A, Nelson KM, Meyer K, Jennissen CA, Ebens CL. Isavuconazonium Sulfate Use in Multi-modal Management of Invasive Mucormycosis in Four Pediatric Allogeneic hematopoietic cell transplant patients. J Pediatr Pharmacol Ther JPPT off J PPAG. 2021;26(8):863–7.
36. Vu CA, Rana MM, Jacobs SE, Saunders-Hao P. Isavuconazole for the prophylaxis and treatment of invasive fungal disease: a single-center experience. Transpl Infect Dis [Internet]. 2021;23(2).
37. Ashkenazi-Hoffnung L, Bilavsky E, Levy I, Grisaru G, Sadot E, Ben-Ami R, et al. Isavuconazole as successful salvage therapy for Mucormycosis in Pediatric patients. Pediatr Infect Dis J. 2020;39(8):718–24.
38. Barg AA, Malkiel S, Bartuv M, Greenberg G, Toren A, Keller N. Successful treatment of invasive mucormycosis with isavuconazole in pediatric patients. Pediatr Blood Cancer. 2018;65(10):e27281.

39. Pomorska A, Malecka A, Jaworski R, Radon-Proskura J, Hare RK, Nielsen HV, et al. Isavuconazole in a successful combination treatment of disseminated mucormycosis in a child with Acute Lymphoblastic Leukaemia and generalized haemochromatosis: a Case Report and Review of the literature. Mycopathologia. 2019;184(1):81–8.
40. Cornu M, Bruno B, Loridant S, Navarin P, François N, Lanternier F, et al. Successful outcome of disseminated mucormycosis in a 3-year-old child suffering from acute leukaemia: the role of isavuconazole? A case report. BMC Pharmacol Toxicol. 2018;19(1):81.
41. Sosnowska-Sienkiewicz P, Błaszczyk K, Kubisiak-Rzepczyk H, Mańkowski P, Januszkiewicz-Lewandowska D. How to treat a child with a concurrent diagnosis of leukemia and generalized mucormycosis? Case Report. Front Med. 2022;9:844880.
42. Marty FM, Ostrosky-Zeichner L, Cornely OA, Mullane KM, Perfect JR, Thompson GR 3rd, et al. Isavuconazole treatment for mucormycosis: a single-arm open-label trial and case-control analysis. Lancet Infect Dis. 2016;16(7):828–37.
43. Risum M, Vestergaard M-B, Weinreich UM, Helleberg M, Vissing NH, Jørgensen R. Therapeutic drug monitoring of Isavuconazole: serum concentration variability and success rates for reaching target in comparison with Voriconazole. Antibiot [Internet]. 2021;10(5):487.
44. Sigera LSM, Denning DW. A systematic review of the therapeutic outcome of Mucormycosis. Open Forum Infect Dis [Internet]. 2024;11(1).
45. Batista MV, Ussetti MP, Jiang Y, Neofytos D, Cortez AC, Feriani D, et al. Comparing the real-world use of Isavuconazole to other anti-fungal therapy for invasive fungal infections in patients with and without underlying disparities: a Multi-center Retrospective Study. J Fungi. 2023;9(2):166.
46. Maertens JA, Raad II, Marr KA, Patterson TF, Kontoyiannis DP, Cornely OA, et al. Isavuconazole versus Voriconazole for primary treatment of invasive mould disease caused by aspergillus and other filamentous fungi (SECURE): a phase 3, randomised-controlled, non-inferiority trial. Lancet [Internet]. 2016;387(10020):760–9.
47. Horn D, Goff D, Khandelwal N, Spalding J, Azie N, Shi F, et al. Hospital resource use of patients receiving isavuconazole vs voriconazole for invasive mold infections in the phase III SECURE trial. J Med Econ. 2016;19(7):728–34.
48. Saseedharan S, Prayag PS, Soman RN, Panchakshari SP, Ajapuje PS, Mahale NP, et al. Therapeutic drug monitoring of Isavuconazole: lessons Learnt from a real-life setting in a Tertiary Care Center in India. Indian J Crit Care Med [Internet]. 2023;27(4):260–4.

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