Characteristics and management of hepatotoxicity in hospitalized patients treated with triazoles: a systematic review

Características e manejo da hepatotoxicidade em pacientes hospitalizados tratados com triazóis: uma revisão sistemática

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ABSTRACT

Introduction: Fungal infections are the main causes of morbidity and mortality in immunocompromised and severely hospitalized patients. Triazole antifungal drugs are used on a large scale in the treatment of hospital's fungal infections and there is concern about their adverse events, particularly hepatotoxicity. **Objectives:** Considering the frequency of triazoles use in hospitalized patients, the aim of this systematic review was to assess the overall certainty of evidence for the hepatotoxicity caused by triazoles in hospitalized patients. **Methods**: This is a systematic literature review, using the Pubmed/Medline and Scopus databases. Data collection was carried out in July – August 2020 and March – April 2021. The inclusion criteria for the study were: articles in English, Portuguese and Spanish; patients older than 18 years who used triazole antifungals (fluconazole, voriconazole, itraconazole or posaconazole). To characterize hepatotoxicity, criteria established by Hy's Law were used. **Results***:* We found 71 articles on the occurrence of hepatotoxicity, a total of 1.033 patients. Regarding the indication for the use of triazoles, the main one was invasive fungal diseases (52.7%). The duration of treatment with triazoles ranged from 24 to 53 days. Fluconazole was the drug associated with the greatest severity. Five studies detected mutations in cytochrome P450 CYP3A4 and CYP2C19. **Conclusions***:* There are a considerable number of publications in the literature on hepatotoxicity with triazole antifungals. This review showed that its incidence is higher in the male and young population. Posaconazole and voriconazole had a higher frequency of hepatotoxicity.

Keyword: Antifungal; Pharmacovigilance; Fungal infection; Hepatotoxicity.

RESUMO

Introdução: As infecções fúngicas são as principais causas de morbidade e mortalidade em pacientes imunocomprometidos e gravemente hospitalizados. Os antifúngicos triazólicos são utilizados em larga escala no tratamento de infecções fúngicas hospitalares e há preocupação com seus eventos adversos, particularmente hepatotoxicidade. **Objetivos:** Considerando a frequência do uso de triazóis em pacientes hospitalizados, o objetivo desta revisão sistemática foi avaliar a certeza global das evidências para a hepatotoxicidade causada por antifúngicos triazóis em pacientes hospitalizados. **Métodos:** Trata-se de uma revisão sistemática da literatura, utilizando as bases de dados Pubmed/Medline e Scopus. A coleta de dados foi realizada nos meses de julho – agosto de 2020 e março – abril de 2021. Os critérios de inclusão para o estudo foram: artigos em inglês, português e espanhol; pacientes maiores de 18 anos que fizeram uso de antifúngicos triazólicos (fluconazol, voriconazol, itraconazol ou posaconazol). Para caracterizar a hepatotoxicidade, foram utilizados critérios estabelecidos pela Lei de Hy. **Resultados:** Foram encontrados 71 artigos sobre a ocorrência de hepatotoxicidade, totalizando 1.033 pacientes. Quanto à indicação do uso de triazóis, a principal foi a das doenças fúngicas invasivas (52,7%). A duração do tratamento com triazóis variou de 24 a 53 dias. O fluconazol foi a droga associada à maior gravidade. Cinco estudos detectaram mutações no citocromo P450, CYP3A4 e CYP2C19. **Conclusão:** Há um número considerável de publicações na literatura sobre hepatotoxicidade com antifúngicos triazólicos. Esta revisão mostrou que sua incidência é maior na população masculina e jovem. Posaconazol e voriconazol apresentaram maior frequência de hepatotoxicidade.

Palavra chave: Antifúngicos; Farmacovigilância; Infecção fúngica; Hepatotoxicidade.

Introduction

The incidence of fungal infections can reach 24% among immunocompromised patients and severely hospitalized patients. These represent an important cause of morbidity and mortality.[1,2] Triazole agents, such as fluconazole and voriconazole, have important antifungal activity in this context.[3]

The approval of triazoles was a breakthrough in the ability to treat local and systemic fungal infections safely and effectively. The high safety profile of triazoles, in particular fluconazole, has led to their extensive use. By the year 1999, fluconazole had already been used to treat more than 16 million patients, including more than 300,000 patients with AIDS since the approval of this drug by health agencies worldwide.[4]

Azoles have high selectivity due to their higher affinity for fungal P450 enzymes than mammals.[5] However, azoles also affect human cytochrome P450 (CYP) enzymes, resulting in significant drug interactions.[6] Curiously, the human CYP isoforms affected vary depending on azole, emphasizing the importance of evaluating each patient for potential drug interactions prior to azole use.[7]

Hepatotoxicity are the main adverse reactions published in the literature and in the package leaflet of triazoles. Drug-induced liver injury (DILI) is a serious complication that can be potentially fatal among affected individuals.[8]

The incidence rate of hepatotoxicity estimates leading to hospital referral range from 2.4 per 100,000 person-years (in a retrospective study of 1.64 million UK individuals)[9] at 13.9 per 100,000 inhabitants (in a prospective analysis in France).[10] Due to the low incidence, hepatotoxicity often may not be identified during clinical trials and may come to light only after the suspected drug has obtained market approval and many patients have been exposed.[11]

Considering the frequency of triazoles use in hospitalized patients, the aim of this systematic review was to assess the overall certainty of evidence for the hepatotoxicity caused by triazoles in hospitalized patients.

The study question was: What the frequency of hepatotoxicity by triazoles among hospitalized patients?

Material and Methods

This is a systematic review.

Protocol

The study question and evidence-based search occurred through the acronym PICO (P: hospitalized patients; I: triazole antifungal, itraconazole, fluconazole, posaconazole, voriconazole; antifungal; C: Drug-induced liver disease; O: hepatotoxicity).

The databases used were the Medical Literature Analysis and Retrieval System Online (MEDLINE, via Pubmed) and Scopus/Elsevier using the keywords: triazole antifungals, DILI, liver failure, fluconazole, voriconazole, itraconazole, posaconazole. The development of the review protocol was conducted following the Preferred Reporting Items for Systematic Review and Meta Analysis Protocol (PRISMA).[12] Given the nature of the question posed by the acronym PICO, report articles and case series, clinical trials, cohort studies, and case control were included in the review. We also included pertinent articles found in the references of the reviewed articles. Data collection was carried out in July – August 2020 and March – April 2021.

Risk of bias

The risk assessment of bias was performed according to the tools of the *Cochrane Risk of Bias Tool,* used to evaluate the methodological quality of the studies. Rob 2 which is a revised tool for analysis of randomized trials, ROBINS, a tool for non-randomized studies and Robvis which is a web application designed to view bias risk assessments and graph the results found in the RoB 2 and ROBINS tools. The Joanna Briggs Institute (JBI) Critical Evaluation Checklist for Case Reports was used.

Search strategy

The search strategy combined the terms in English: "Chemically-Induced Liver Toxicity" OR "Chemically Induced Liver Toxicity" OR "Chemically-Induced Liver Toxicities" OR "Liver Toxicities, Chemically-Induced" OR "Liver Toxicity,

Chemically-Induced" OR "Toxicities, Chemically-Induced Liver" OR "Toxicity, Chemically-Induced Liver" OR "Drug-Induced Acute Liver Injury" OR "Liver Injury, Drug-Induced, Acute" OR "Acute Liver Injury, Drug-Induced" OR "Hepatitis, Toxic" OR " Toxic Hepatitis" OR "Hepatitis, Toxic" OR "Drug-Induced Liver Disease" OR "Disease, Drug-Induced Liver" OR "Induced Liver Disease" OR "Liver Disease, Drug-Induced" OR "Drug-Induced Liver Injury" OR "Drug-Induced Liver Injuries" OR "Injuries, Drug-Induced Liver" OR "Injury, Drug-Induced Liver" OR "Liver Injuries, Drug-Induced" OR "Liver Injury, Drug-Induced Liver Injury, Drug Induced" OR "Hepatitis, Drug-Induced" OR "Drug-Induced Hepatitis" OR "Drug-Induced Hepatitis" OR hepatotoxicity AND "triazole antifungals" OR fluconazole OR posaconazole OR itraconazole OR voriconazole.

Selection of articles

The selection of studies was carried out by two independent reviewers who developed the research process in the databases and evaluation of the title and abstract of the pre-selected articles. Next, the selected articles were read in full and included after the eligibility criteria were met.

Eligibility criteria

The inclusion criteria for the study were: articles in English, Portuguese and Spanish, patients over 18 years old admitted to the hospital who used triazole antifungals (fluconazole, voriconazole, itraconazole or posaconazole). Articles on other classes of antifungals, publications on pediatric or neonatal patients and experimental studies were excluded. There was no time or origin restriction of the articles. Studies focusing on drug resistance, renal toxicity and liver toxicity that did not demonstrate a relationship with antifungals were excluded.

We analyzed biochemical test data, prescribed antifungal drugs, drug dose, clinical outcome, sex and ethnicity of patients, diagnosis, treatment time, and time to reaction. The data extracted from the studies were stored in a table for analysis of the results.

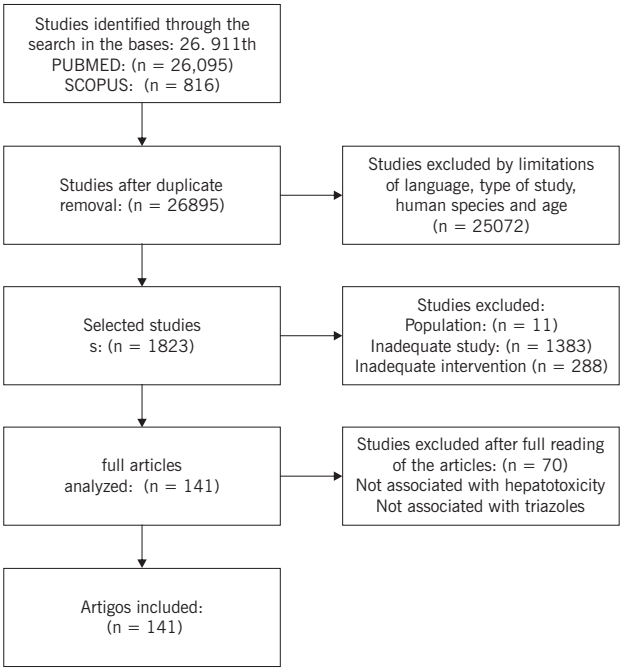
Outcome measure

To characterize hepatotoxicity, the criteria established by "Hy's Law" were used, in increased levels of alanine aminotransferase (ALT) greater than 3 × upper limit of normal (ULN) and total bilirubin levels greater than 2 × the ULN after excluding other potential causes.[13]

Ethics

The study was approved by the Research Ethics Committee of the Professor Edgard Santos University Hospital, under CAAE n° 23782919.1.0000.0049 with exemption from the Free and Informed Consent Form (ICF) because it is a review.

Flowchart 1. Identification and selection of studies in databases



Results

A total of 26.911 articles were identified, of which 71 articles filled the inclusion criteria. Those that were not suitable for the selected languages, studies that included children under 18 years old, *in vitro* trials, articles that addressed other drugs were excluded. Data on the selection of studies are shown in flowchart 1.

From the 71 articles selected, 45 articles were retrieved from Medline/PUBMED and 26 from SCOPUS/Elsevier. It was found 1.033 cases of hepatotoxicity secondary to the use of triazoles in this review. Most of the publications were from the USA, accounting for 38% (27/71) of the studies (**Table 2**), which was equivalent to 54 % (554/1,033) of the patients who developed hepatotoxicity. The average age of the patients was 49 years (standard deviation $\sigma=14$), and as for gender there was a predominance of male 70% (50/71) (**Table 2**). Regarding the indication for use, triazoles were used for treatment (52.7%) and prophylaxis (5.9%) of invasive fungal diseases, prophylaxis (11.1%) and in the treatment (18.05%) of opportunistic HIV/TB infections, prophylaxis (4.2%) and treatment (4.2%) of opportunistic infection of hematological diseases and studies that evaluated the safety of triazoles (4.2%) (**Table 2**).

The duration of treatment with triazoles ranged from 24 to 53 days, and the time to onset of symptoms related to hepatotoxicity was 10 to 52 days (**Table 2**). The data on each study are set out in Table 2. Posaconazole and voriconazole had the highest frequency of hepatotoxicity cases. The most common clinical features of hepatotoxicity were jaundice (31/69), nausea (23/69), and dermatitis (21/69). Regarding the biochemical profile, from the analysis of the articles that documented this information, itraconazole was associated with the highest average elevations of ALT (2,391 IU/L) and total bilirubin (109 mmol/L) (**Table 1**).

Table 1. Clinical and biochemical characteristics of patients being treated with triazole antifungals.

Variable (N = Studies)	Voriconazole (31)	Fluconazole (22)	Itraconazole (21)	Posaconazole (9)
Number of patients with hepatotoxicity/total number of patients (%)	293/1,345 (22%) 922/1,345 (68%)	584/162,727 (0,4%) 24,100/16,272 7 (15%)	125/10,681 (1,2%) 4,479/10,681 (42%)	100/350 (29%)
	200 – 400	150 – 400	100 – 400	
Gender (male/total) (9%)	257 (15/31)*	3,826 (10/22)*	2,274	160/350 (46%)
Daily dose (mg) AST (IU/L)				300 – 600 132 (6/9)*
			(10/21)*	
ALT (IU/L)	291 (14/31)*	1,773 (11/22)*	2,391	197 (6/9)*
			(11/21)*	
ALP (IU/L)	399 (6/31)*	659 (7/22)*	376 (7/21)*	143 (1/9)*
GGT (IU/L)	432 (5/31)*	540 (3/22)*	482 (4/21)*	327 (1/9)*
Bt (mmol/L)	97 (11/31)*	59 (7/22)*	109 (8/21)*	24 (9/9)*
Duration of treatment in days (average)	40(21/311)*	38 (20/22)*	53 (18/21)*	24 (9/9)*
Time of symptoms appearance in days (average)	15 (21/31)*	19 (20/22)*	52 (13/21)(*	10 (7/9)*

* Number of studies that provided the information. AST – aspartate aminotransferase, ALT – alanine aminotransferase, ALP – alkaline phosphatase, GGT – gamma glutamyl transferase, Bt – total bilirubin. The values presented represent the mean for each variable.

Genotypic tests were performed in 9 studies. In three articles, the investigation of gene mutation in cytochrome P450 in CYP3A4, CYP2C19 and CYP3A5 showed that mutation occurred only in CYP2C19, while five articles detected mutations in CYP3A4 and CYP2C19 and in only one article mutations in CYP2C19 and CYP3A5 were observed (Table 2). Testing results for mutations revealed interindividual variability, homozygous extensive metabolizer, heterozygous extensive metabolizer, intermediary and river metabolizer, weak metabolizer and slow metabolizers.

It was possible to analyze the effects of triazoles when used concomitantly with other medicinal products, detecting interference with their metabolism due to the inhibition action of enzymes and consequent reduction in their metabolism. These effects have been documented for the following drugs: zidovudine, haloperidol, proton pump inhibitors – omeprazole, pantoprazole, esomeprazole, lansoprazole. An increase or decrease in serum triazole concentration may occur according to co-administrations.

Reexposure to the drug suspected of hepatotoxicity was reported in patients from 8 out of 71 studies (11%) who only 1 patient in a case report did not tolerate the reintroduction of the drug and resulted in death (**Table 2**). In 64 of the 71 studies (90%) the patients' liver enzymes returned to normal after drug withdrawal, with complete recovery of hepatotoxicity after discontinuation of the suspected drug in all of them (**Table 2**). In 7 of the 71 studies (10%), deaths attributed to severe acute liver failure after the use of triazoles were reported, with 10 deaths after the use of fluconazole, 1 death after the use of voriconazole and 1 death after the use of itraconazole. In addition, 2 of the 1,033 patients who developed hepatotoxicity and made liver transplantation due to treatment with itraconazole (**Table 2**).

Regarding the risk of bias, according to the criteria of Rob 2, in general it was of low risk in relation to the process of randomization, intervention, selection of results and results in general. (**Chart 1**). The evaluation of bias by ROBINS was low risk in the analyzed criteria (**Graph 2**). The analysis of the Joanna Briggs Institute's Critical Evaluation Checklist found a low risk of bias in case reports (**Table 3**).

Discussion

The main findings of this systematic review are that the incidence of hepatotoxicity caused by triazoles in hospitalized patients was higher in the male and young population. Voriconazole and posaconazol are the triazoles most associated with the appearance of hepatotoxicity.

Triazoles are a well-known class of antifungals for clinical use. The hepatotoxicity of these drugs is an event already evidenced and reported in the package insert, however, data on post-marketing effects are limited in some populations, for example Latin Americans, particularly in hospitalized patients. Perhaps because they are safe drugs and, therefore, with a low frequency of hepatotoxicity, or the scarcity of publications on the subject based on the established criteria.

A greater number of hepatotoxicity cases was verified in the North American population, this can be attributed to the number of scientific publications coming from the USA and not necessarily, there is a greater susceptibility to hepatotoxicity development. For Fontana et al. (2014)[14] the effect of race/ethnicity on hepatotoxicity is unclear, as European Registries are composed almost universally of Caucasians. Information is limited in the U.S. DILIN (DILI Network - a consortium of several academic centers that collect data on patients with DILI) that there is a more heterogeneous population.

Association of DILI with the use of triazoles seems to be higher in the young population, similar to the study by Kao et al. (2014) where there was a higher proportion of hepatotoxicity among patients (86.3% aged <60 years).[15,16] As for gender, male is predominant, which can be explained by the clinical indications for the use of the antifungal; a higher frequency of invasive fungal diseases and HIV was observed. According to UNAIDS (Joint United Nations Programme on HIV/AIDS) almost half of the individuals living with HIV are men.[18]

The use of posaconazole and voriconazole was associated with a higher frequency of liver injury, corroborating to what was found in the study of Lo Re (2015), and fluconazole was associated with greater severity. As for the time of the reaction onset, in patients who used voriconazole and posaconazole the

reaction appeared at the beginning of treatment. Of the clinical manifestations, rash, jaundice and nausea seems to be the most common and require interruption of treatment due to toxicity, as has been reported in other studies.[19] Regarding the results of biochemical evaluation of patients, hepatotoxicity is more common with the use of voriconazole in relation to other triazoles. On the other hand, posaconazole was the antifungal that presented less alteration of transaminases of the patients, since it can be already supported by the pharmacokinetics of this drug.[7,20,21]

From the studies that performed the analysis of genetic polymorphism to cytochrome P450 the CYP3A4 and CYP2C19, it was observed that in Asians there were greater genetic changes. These changes interfere with the metabolism of drugs that have been used concomitantly with triazoles such as zidovudine, proton pump inhibitors and haloperidol, which can be interpreted as drug interactions may contribute to greater toxicity. Perhaps polymorphism in CYP2C19 should be studied in certain subjects with voriconazole-refractory aspergillosis invasive for further elucidation. Mutations in CYP2C19 are more common in Asians (60% to 70% of Asians *vs.* 30% of Caucasians and Afro-Africans).[22]

Regarding the recovery from hepatotoxicity, most individuals recovered liver function caused by triazoles after withdrawal of the drug. The idiosyncratic manifestations of outcome such as death and cases of acute liver failure caused were infrequent. The cases evidenced in this review were attributed to the use of fluconazole. Although there is no clarity in the literature about the mechanisms that lead to the most severe forms of hepatotoxicity, intrinsic susceptibility characteristics of the patient, environmental factors and drug dose, seem to be risk factors for more severe cases. In this review, it was found that a greater number of patients used this drug, so the chance of more severe outcomes is increased.[16,23]

Each study performed the management according to the patient's evolution. The treatment of hepatotoxicity is essentially supportive. The suspension of the suspected drug is the first measure to be adopted and is fundamental to prevent or minimize progressive damage. Followed by an accurate assessment of causality between the event and the suspected drug. Patients with hepatotoxicity need to be carefully evaluated for their prognosis.[24]

The present review has limitations, since the research was performed only in the Pubmed/MEDLINE and Scopus/Elsevier databases and the low methodological quality of some of the included studies contributes to the low certainty of evidence.

Implication for practice

The identification of hepatotoxicity caused by this class of drugs can help in the elaboration of proposals for therapeutic monitoring, as well as allows to know the characteristics of the hepatotoxicity phenotype.

Conclusion

In this study, the incidence of hepatotoxicity was higher in the male and young patients. Voriconazole and Posaconazole are the triazoles most associated with the appearance of hepatotoxicity. Regarding the severity criterion, fluconazole was considered as the drug that promoted hepatotoxicity of greater severity. The evaluation of genetic polymorphism does not seem to be used for decision-making in clinical practice.

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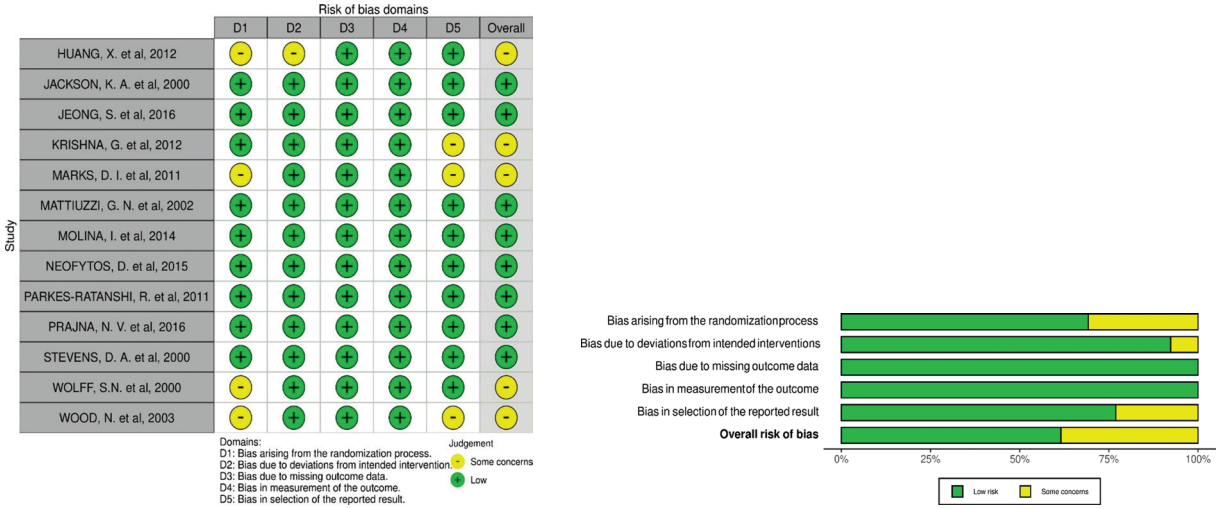
Anexo

Tabela 02. Demographics and clinical findings in patients with triazole antifungals liver injury.

Author/Year	Patient				Treatment				Treatment of DILI	Outcome
	n/N	Age (mean)	Gender (Male/total) (%)	Etnicity	Culprit Drug	Clinical indication	Duration (mean)	Genetic Polimorfism		
GIL, A. et al/199120	17/36	28	25/36 (69%)	Europan	Fluconazole	Candidal Infection	10	NA	Discontinuation the culprit drug (2%) Spontaneous recovery (98%)	Resolved
MUNOZ, P. et al/199125	3/3	29	3/3 (100%)	North American	Fluconazole	Candidal Infection	14	N	Discontinuation the culprit drug (100%)	Resolved / death (1)
WELLS; LEVER/ 199226	1/1	46	1/1 (100%)	Noth American	Fluconazole	Candidal Infection	90	NA	Rechallenge, and Discontinuation the culprit drug	Death
LAVRIJSEN, A. P. et al/ 199227	1/3	65	1/3 (33,3%)		Itraconazole	Onychomycosis infection	39	NA	Discontinuation the culprit drug (33%)	Resolved
HANN et al./199328	1/1	51	0/1 (0%)	Asiatic	Itraconazole	Onychomycosis infection	11	NA	Discontinuation the culprit drug (100%)	olved
GEARHART, M. O./ 199429	1/4	50	0/1 (0%)	North American	Fluconazole	Candidal Infection	4	NA	Reduce dose of culprit drug and Discontinuation	Resolved
JACOBSON; HANKS; FERREL/ 199430	1/1	32	1/1 (100%)	North American	Fluconazole	Opportunistic infection in oncohemat ology disease	21	NA	Spontaneous recovery	Death'
BRONSTEIN, J. A. et al./ 199731	1/1	85	1/1 (100%)	European	Fluconazole	Candidal Infection	10	NA	Discontinuation the culprit drug	Death
CRERAR-GILBERT, A./199932	1/1	45	0/1 (0%)	Oceanian	Fluconazole	Onychomycosis infection	35	NA	Discontinuation the culprit drug and Rechallenge	Resolved
GARCÍA-RODRÍGUEZ, L. A. et al. / 1999[33]	2/194 88	41	1/2 (50%)	European	Itraconazole	Candidal Infection	-	NA	Discontinuation the culprit drug	Resolved
WOLFF, S.N. et al/2000[34]	1/196	43	119/196 (61%)	North American	Fluconazole	Prophylaxis in HIV	13	NA	Discontinuation the culprit drug	Resolved
JACKSON, K. A. et al/2000[35]	2/23	37	16/23 (70%)	North American	Fluconazole	Prophylaxis in HIV	-	CYP3A4 CYP2C19	Spontaneous recovery	Resolved
STEVENS, D. A. et al/2000[36]	2/28	48	18/28 (64%)	North American	Itraconazole	Aspergillosis infection	112	NA	Discontinuation the culprit drug	Resolved
BOOGAERTS, M. A. et al/2001[37]	4/17	41	9/17 (53%)	European	Itraconazole	Prophylaxis in HIV	14	NA	Spontaneous recovery	Resolved
ADRIAENSSENS, B. et al/ 2001[38]	3/3	70	1/3 (33,3%)	European	Itraconazole	Aspergillosis infection	49	NA	Rechallenge	Resolved
LEGRAS, A. et al./ 2002[39]	1/1	68	0/1 (0%)	North American	Itraconazole	Aspergillosis and candidal infection	60	NA	Spontaneous recovery	Death
MATTIUZZI, G. N. et al/2003[40]	15/67	57	41/67 (61%)	North American	Fluconazoel + Itraconazole	Prophylaxis in HIV	12	NA	Discontinuation the culprit drug	Resolved
WOOD, N. et al/200341	1/18	26	18/18 (100%)	European	Voriconazole	Safety analysis	10	CYP3A4 CYP2C19	Discontinuation the culprit drug	Resolved
SU, F. W.; PERUMALSWAMI, P.; GRAMMER, L. C./ 2003[42]	1/1	39	1/1 (100%)	North American	Fluconazole	Candidal Infection	7	NA	Discontinuation the culprit drug and corticosteroids use	Resolved
GRIGG, A. P., et al. /2004[43]	2/44	45	31/44 (70%)	Oceanian	Itraconazole	Aspergillosis infection	56	NA	Culprit drug reduce dose	Resolved
JIMENEZ-SAENZ, M. et al./2004[44]	1/1	39	1/1 (100%)	North American	Itraconazole	Candidal Infectio	7	NA	Spontaneous recovery	Resolved
LINNEBUR, S. A.; BENETT, L. P./2004[45]	1/1	73	1/1 (100%)	North American	Fluconazole	Onychomycosis infection	21	NA	Discontinuation the culprit drug	Resolved
FISCHER, M. A., et al./2005[46]	39/11 9	43	59/119 (50%)	North American	Fluconazole	Opportunistic infection in oncohemat ology diseasea	-	NA	Rechallenge and Spontaneous recovery	Resolved
SREBRNIK, A., et al. /2005[47]	1/1	25	0/1 (0%)	Asiatic	Itraconazole	Onychomycosis infection	7	NA	Discontinuation the culprit drug	Transplant
MAERTENS, J. et al/2006[48]	5/37	55	23/37 (62%)	European	Itraconazole, Voriconazole	Aspergillosis infection	28	NA	Discontinuation the culprit drug and change the antifungal therapy	Resolved
PARK, S. H. et al/2006[49]	10/48	35	31/48 (65%)	Asiatic	Itraconazole	Prophylaxis in HIV	10	NA	Discontinuation the culprit drug	Resolved
LEVIN, M. D. et al./ 2007[50]	18/86	56	54/86 (63%)	European	Voriconazole	Aspergillosis infection	7	CYP2C19/ CYP3A5	Spontaneous recovery	Resolved
GARZONI, C. et al/2008[51]	1/1	60	0/1 (0%)	European	Voriconazole	*Cladophial ophora bantiana* infection	6	NA	Discontinuation the culprit drug and change the antifungal therapy	Resolved
TUCCORI, M., et al./ 2008[52]	1/1	61	0/1 (0%)	European	Itraconazole	Onychomycosis infection	168	NA	Discontinuation the culprit drug and corticosteroids use	Transplant
ALFFENAAR, J. W. C. et al/2010[53]	1/1	58	1/1 (100%)	European	Voriconazole	Prophylaxis in HIV	56	NA	Rechallenge, Discontinuation the culprit drug change the antifungal therapy	Resolved
AMIGUES, I. et al./2010[54]	68/20 0	42	43/68 (63%)	North American	Voriconazole	Aspergillosis and candidal infection	25	NA	Rechallenge, Discontinuation the culprit drug	Resolved
CORDONNIER, C. et al/2010[55]	4/45	48	28/45 (62%)	European	Voriconazole	Aspergillosis and candidal infection	94	NA	Discontinuation the culprit drug	Resolved
BELAICHE, S., et al./ 2011[56]	1/1	46	0/1 (0%)	European	Voriconazole	Aspergillosis infection	60	NA	Culprit drug reduce dose	Resolved
GORSKI, E. et al./2011[57]	18/10 9	55	44/109 (40%)	North American	Voriconazole	Aspergillosis infection	187	NA	Discontinuation the culprit drug	Resolved
ILLMER, T., et al/ 2011[58]	3/8	32	6/8 (75%)	European	Posaconazole	Aspergillosis infection	36	NA	Rechallenge Culprit drug reduce dose	Resolved
MARKS, D. I. et al/2011[59]	41/24 1	43	146/241 (61%)	European	Voriconazole, Itraconazole	Prophylaxis in HIV	100	NA	Discontinuation the culprit drug change the antifungal therapy	Resolved
PARKES-RATANSHI, R. et al/ 2011[60]	58/76 0	35	474/760 (62%)	African	Fluconazole	Prophylaxis in HIV	210	NA	Discontinuation the culprit drug	Resolved
KIM, S. H. et al/ 2011[61]	5/25	45	12/25 (48%)	Asiatic	Voriconazole	Prophylaxis in HIV	8	CYP3A4 CYP2C19	Discontinuation the culprit drug	Death (1) Resolved
KRISHNA, G. et al/ 2012[62]	6/24	45	14/24 (58%)	North American	Posaconazole	Safety analysis	25	NA	Discontinuation the culprit drug	Resolved
HUANG, X. et al/ 2012[63]	9/147	33	94/147 (64%)	Asiatic	Itraconazole	Prophylaxis in HIV	22	NA	Spontaneous recovery	Resolved
SOLÍS-MUÑOZ, P. et al/ 2013[64]	20/29	48	16/29 (55%)	European	Voriconazole	Aspergillosis infection	39	NA	Discontinuation the culprit drug change the antifungal therapy	Resolved

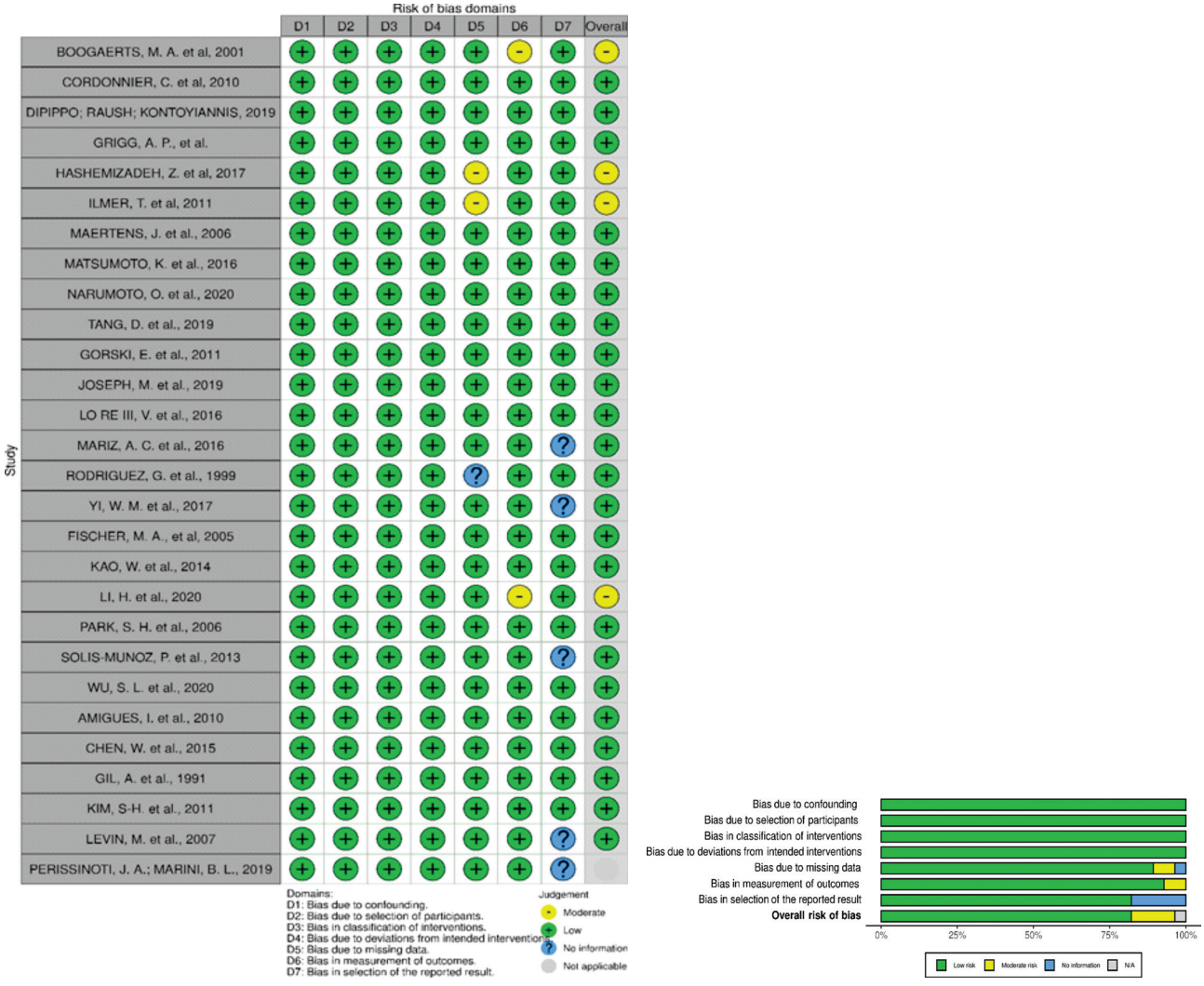
Author/Year	Patient				Treatment				Treatment of DILI	Outcome
	n/N	Age (mean)	Gender (Male/total) (%)	Etnicity	Culprit Drug	Clinical indication	Duration (mean)	Genetic Polimorfism		
ESGIN, H.; BULUT, E.; ÖRÜM, Ç./ 2014[65]	1/1	57	1/1 (100%)	Asiatic	Fluconazole	Prophylaxis in HIV	5	NA	Rechallenge change the antifungal therapy	Resolved
KAO, W. Y. et al/ 2014[66]	Fluconazol 15/37 9 Itraconazol 3/836 8	56	Fluconazol (1411/3793) (37%) Itraconazol (4030/8368) (48%)	Asiatic	Fluconazole and Itraconazole	Safety analysis	46	NA	Discontinuation the culprit drug	Resolved Death-fluconazole (6)
MOLINA, I. et al/2014[67]	30/62	39	30/62 (48%)	European	Posaconazole	Prophylaxis in HIV	60	NA	Spontaneous recovery	Recuperado
MOTTA, I. et al/ 2016[68]	1/1	43	1/1 (100%)	European	Voriconazole	Aspergillosis infection	25	CYP3A4 CYP2C19	Reduce dose Discontinuation the culprit drug change the antifungal therapy	Resolved
CHEN, W. et al/ 2015[69]	15/62	59	42/62 (68%)	Asiatic	Voriconazole	Aspergillosis and candidal infection	86	CYP3A4 CYP2C19	Spontaneous recovery	Resolved
NEOFYTOS, D. et al/ 2015[70]	3/29	59	24/29 (83%)	North American	Voriconazole	Prophylaxis in HIV	40	NA	Discontinuation the culprit drug	Resolved
ATAYA, A. et al/ 2016[71]	1/1	48	1/1 (100%)	North American	Voriconazole	Prophylaxis in HIV	28	NA	Discontinuation the culprit drug	Resolved
JEONG, S. H. et al/ 2016[2]	19/75	49	40/75 (53%)	Asiátic	Itraconazole	Aspergillosis and candidal infection	8	NA	Discontinuation the culprit drug	Resolved
LO RE, V. et al/ 2016[21]	296/ 181038 - F: 178879; I: 1653; V: 478; P:28	41	162249/18 1038 (90%)	North American	Voriconazole, Fluconazoel, Itraconazole, Posaconazol	Prophylaxis in HIV	30	NA	Discontinuation the culprit drug	Resolved
ARAÚJO-MARIZ, C. et al./ 2016[72]	29/53	27	32/53 (60%)	North American	Fluconazole	Prophylaxis in tuberculosis	180	NA	Spontaneous recovery	Resolved
MATSUMOTO, K. et al./ 2016[73]	15/29	59	17/29 (59%)	Asiatic	Voriconazole	Aspergillosis and candidal infection	22	NA	Reduce dose	Resolved
LOPEZ, J. L.; TAYEK, J. A./ 2016[74]	1/1	44	1/1 (100%)	North American	Voriconazole	Aspergillosis infection	-	NA	Rechallenge Discontinuation the culprit drug	Resolved
PRAJNA, N. V. et al./ 2016[75]	10/11 9	54	65/119 (55%)	North American	Voriconazole	Prophylaxis in HIV	20	NA	Spontaneous recovery	Resolved
PETTIT, N. et al./2016[76]	1/1	65	0/1 (0%)	North American	Itraconazole	histoplasmosis infection	180	NA	Discontinuation the culprit drug	Resolved
HASHEMIZADEH, Z. et al./ 2017[77]	14/10 4	36	60/104 (58%)	Asiatic	Voriconazole	Aspergillosis and candidal infection	54	CYP2C19	Spontaneous recovery	Resolved
YI, W. M. et al/ 2017[78]	4/151	50	79/151 (52%)	North American	Voriconazole, Posaconazole	Aspergillosis and candidal infection	18	NA	Spontaneous recovery e Reduce dose	Resolved
BEATA, S. et al/ 2017[79]	1/4	59	2/4 (50%)	European	Voriconazole	Prophylaxis in HIV	-	CYP2C19	Discontinuation the culprit drug and change the antifungal therapy	Resolved
HOENIGL, M. et al/ 2018[80]	1/1	23	1/1 (100%)	European	Voriconazole	Prophylaxis in HIV	10	NA	Discontinuation the culprit drug and change the antifungal therapy	Resolved
LIU, X. et al/ 2017[81]	1/1	21	1/1 (100%)	Asiátic	Voriconazole	Aspergillosis and candidal infection	60	NA	Rechallenge Reduce dose Discontinuation the culprit drug	Resolved
GAYAM, V. ET AL./ 2018[82]	1/1	45	1/1 (100%)	North American	Fluconazole	Candidal infection	7	NA	Discontinuation the culprit drug	Resolved
JOSEPH, M. et al/ 2019[83]	133/24 8	56	171/248 (69%)	European	Fluconazole	Candidal Infection	8	NA	Change the antifungal therapy	Resolved
PERISSINOTI, A. J.; MARINI, B. L./ 2019[84]	27/15 7	58	15/27 (55%)	North American	Posaconazole	Prophylaxis in Oncohema tology	19	NA	Spontaneous recovery	Resolved
BLANCO-DORADO, S. et al. 2019[85]	1/1	82	0/1 (0%)	European	Voriconazole	Aspergillosis infection	58	NA	Discontinuation the culprit drug	Resolved
DIPIPPO, A. J.; RAUSCH, C. R.; KONTOYIANNIS, D. P/ 2019[86]	20/23	67	15/23 (65%)	North American	Posaconazole	Prophylaxis in Oncohematology	16	NA	Discontinuation the culprit drug Change the antifungal therapy	Resolved
TANG, D. et al/ 2019[87]	-/57	48	48/57 (84%)	Asiátic	Voriconazole	Aspergillosis infection	-	CYP2C19	Spontaneous recovery	Resolved
MAKINO, K. et al/ 2019[88]	1/1	66	0/1 (0%)	Asiátic	Fluconazole	Prophylaxis in HIV	17	NA	Discontinuation the culprit drug Change the antifungal therapy	Resolved
Li, H. et al/2020[89]	3/125	62	93/125 (74%)	Asiática	Voriconazole	Aspergillosis infection	14	NA	Reduce dose	Resolved
WU, S. L. et al/2020[90]	12/65	64	37/65 (57%)	Asiátic	Voriconazole	Prophylaxis in Oncohema tology	24	NA	Spontaneous recovery	Resolved
NARUMOTO, O. et al/2020[91]	4/4	65	3/4 (75%)	Asiátic	Voriconazole	Aspergillosis infection	19	NA	Rechallenge Reduce dose	Resolved
ALSHAYA, O. A.; SALEN, R. A.; ALSHERI, S. D./2021[92]	1/1	38	0/1 (0%)	Asiátic	Voriconazole	Fusarium dimerum infection	3	NA	Discontinuation the culprit drug Change the antifungal therapy	Resolved

Graphic 1. Assessing the risk of bias in randomized studies (RoB 2).



Fonte: STERNE, J. A. C. et al. **RoB 2: a revised tool for assessing risk of bias in randomised trials.** BMJ 2019; 366: l4898.[93]

Graphic 2. ROBINS-I (Risk of bias in non-randomized studies – of interventions)



Fonte: STERNE, J. A. C. et al. ROBINS-I: a tool for assessing risk of bias in non-randomized studies of interventions. BMJ 2016; 355.

Table 3. Joanna Briggs Institute (JBI) Critical Assessment Checklist for Case Reports

Study	1	2	3	4	5	6	7	8	All
ADRIAENSSENS et al, 2001[38]	YES	YES	YES	YES	YES	YES	YES	NA	ADD
SU; PERUMALSWAMI; GRAMMER, 2003[42]	YES	YES	YES	YES	YES	YES	YES	YES	ADD
SREBRNIK, A., et al, 2005[47]	YES	YES	YES	YES	YES	YES	YES	NA	ADD
TUCCORI, M. et al., 2008[52]	YES	YES	YES	YES	YES	YES	YES	YES	ADD
BELAICHE, S., et al., 2011[56]	YES	YES	YES	YES	YES	YES	YES	YES	ADD
ATAYA et al., 2016[71]	YES	YES	YES	YES	YES	YES	YES	YES	ADD
LOPEZ, J. L. TAYEK, J. A., 2016[74]	YES	YES	YES	YES	YES	YES	YES	YES	ADD
GAYAM, V., et al. 2018[82]	YES	YES	YES	YES	YES	YES	YES	YES	ADD
ALSHAYA, O. A.; SALEN, R. A.; ALSHEHRI, S. D.[92]	YES	YES	YES	YES	YES	YES	YES	YES	ADD
MUNOZ, P. et al, 1991[25]	YES	YES	YES	YES	YES	YES	YES	YES	ADD
WELLS, C.; LEVER, A. M. L., 1992[26]	YES	YES	YES	YES	YES	YES	YES	YES	ADD
JACOBSON, M. A.; HANKS, D. K.; FERREL, L. D., 1994[30]	YES	YES	YES	YES	YES	YES	YES	YES	ADD
LAVRIJSEN, A. P. et al., 1992[27]	YES	YES	YES	YES	YES	YES	YES	YES	ADD
HANN, S. K. et al., 1993[28]	YES	YES	YES	YES	YES	YES	YES	YES	ADD
GEARHART, M. O., 1994[29]	YES	YES	YES	YES	YES	YES	YES	YES	ADD
BRONSTEIN, J. A. et al., 1997[31]	YES	YES	YES	YES	YES	YES	YES	YES	ADD
CRERAR-GILBER T, A. et al., 1999[33]	YES	YES	YES	YES	YES	YES	YES	YES	ADD
LEGRAS, A. et al., 2002[39]	YES	YES	YES	YES	YES	YES	YES	YES	ADD
JIMENEZ-SAENZ, M. et al., 2004[44]	YES	YES	YES	YES	YES	YES	YES	YES	ADD
LINNEBUR, S. A.; PARNES, B. L., 2004[45]	YES	YES	YES	YES	YES	YES	YES	YES	ADD
GARZONI, C. et al., 2008[51]	YES	YES	YES	YES	YES	YES	YES	YES	ADD
ALFFENAAR, J. W. C. et al., 2010[53]	YES	YES	YES	YES	YES	YES	YES	NA	ADD
ESGIN, H.; BULUT, E.; ÖRÜM, Ç., 2014[65]	YES	YES	YES	YES	YES	YES	YES	NA	ADD
MOTTA, I. et al., 2015[68]	YES	YES	YES	YES	YES	YES	YES	YES	ADD
PETTIT, N. et al., 2016[76]	YES	YES	YES	YES	YES	YES	YES	YES	ADD
HOENIGL, M. et al., 2017[80]	YES	YES	YES	YES	YES	YES	YES	YES	ADD
LIU, X. et al., 2017[81]	YES	YES	YES	YES	YES	YES	YES	YES	ADD
MAKINO, K. et al., 2019[88]	YES	YES	YES	YES	YES	YES	YES	NA	ADD
BLANCO-DORAD O, S. et al., 2019[85]	YES	YES	YES	YES	YES	YES	YES	YES	ADD

Legende: 1. Were the patient's demographic characteristics clearly described? 2. Was the patient's history clearly described and presented as a timeline? 3. Was the patient's current clinical condition at presentation clearly described? 4. Were diagnostic tests or assessment methods performed and were the results clearly described? 5. Was the intervention or treatment procedure clearly described? 6. Was the post-intervention clinical condition clearly described? 7. Were adverse events (damages) or unforeseen events identified and described? 8. Does the case report provide lessons?

Fonte: MOOLA, S. et al. Chapter 7: Systematic reviews of etiology and risk. In: Aromataris E, Munn Z (Editors). **Joanna Briggs Institute Reviewer's Manual**. The Joanna Briggs Institute, 2017.[95] Disponível em https://reviewersmanual.joannabriggs.org/