



Antifungal hypersensitivity reactions and cross-reactivity patterns

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Purpose of review

The goal of this article is to provide an updated understanding and evidence-based approach where possible for antifungal hypersensitivity. This includes recognition of clinical phenotype, implications for cross-reactivity and diagnostic, and management strategy for immediate and delayed hypersensitivity reactions.

Recent findings

Antifungal hypersensitivity reactions can be classified according to their latency (immediate or delayed) and clinical phenotype. The majority of the cases described in the literature are delayed T-cell mediated reactions of various severities but immediate reactions consistent with non-Immunoglobulin E (IgE)-mediated mast cell activation and IgE-mediated reactions have also been described. Ancillary information such as skin testing, drug challenge and *ex vivo* experimental approaches can aid causality assessments and inform antifungal class cross-reactivity, which help optimize antifungal prescribing and stewardship.

Summary

This review will update the clinician on mechanisms of drug hypersensitivity as well as providing a structured approach to the recognition, diagnosis and management of antifungal hypersensitivity reaction.

Keywords

anaphylaxis, antifungals, azoles, delayed T-cell mediated reactions, hypersensitivity

INTRODUCTION

Antifungals are increasingly prescribed antimicrobials for invasive fungal infections (IFI) especially for the expanding immunosuppressed population in both a hospital and a community setting [1,2]. The increase in novel immunosuppressive therapies has seen a concurrent rise in the incidence of IFI requiring antifungal therapy and subsequent occurrence and recognition of immune and non-immune mediated adverse events [2,3]. Due to a limited pipeline of new antifungal therapies, in the case of a hypersensitivity reaction, ascertaining causality and which class or nonclass related drugs should be employed is imperative. This clinical decision is often undertaken by a specialized infectious disease physician or an allergy immunologist to determine cross-reactivity patterns and management options. The literature on antifungal hypersensitivity reactions is limited and there is a need to provide expert practical guidelines for clinicians on the updated diagnostic and management for these reactions.

OVERVIEW OF ANTIFUNGAL HYPERSENSITIVITY REACTIONS

The World Health Organization (WHO) has underlined the significant rise in drug-resistant antifungal infections that leads to treatment failure, increased

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KEY POINTS

- Antifungal hypersensitivity reactions can be classified according to their latency and their clinical phenotype, including the immediate reactions, consistent with non-IgE-mediated mast cell activation and IgE-mediated reactions, and the delayed T-cell mediated reactions.
- From the published literature on antifungals, we suggest an intra-dermal range of 1/1,000 to 1/10 of the intravenous drug formulation, but further studies assessing the maximal nonirritating concentration are required.
- For the most severe cases of delayed drug hypersensitivity reactions such as the Steven–Johnson Syndrome and toxic epidermal necrolysis, we recommend using patch test concentrations of 5% and/or 10%.
- As evidence is scarce regarding the sensitivity and specificity of skin testing, if the assessment is nonconclusive or negative, depending on the severity of the initial reaction (e.g. anaphylaxis or Steven–Johnson Syndrome and toxic epidermal necrolysis), we recommend avoidance of the initial culprit antifungal and its corresponding antifungal class.
- For anaphylaxis and severe delayed cutaneous adverse reactions to the azole family, this whole antifungal class should be avoided as well as all the imidazole drugs such as the antiprotozoal drugs (metronidazole), antihistamines (cimetidine), PPI (lansoprazole, omeprazole, esomeprazole), antiplatelet (ticagrelor) and antihelminthic agents (albendazole, mebendazole).
- When the criteria for desensitization are met, we advise using an initial dose that represents approximately 1/10,000 of the final dose and to double the doses at each increment or step.

healthcare consumption and costs [4,5[¶]] as well as the need for local and international antifungal stewardship programs [6]. Antifungals have wide-ranging pharmacological properties that have an impact on dosing, routes of metabolism and drug interactions [7]. There are currently 6 primary classes of antifungals FDA approved and/or in widespread clinical use: the azoles (e.g. fluconazole, itraconazole, posaconazole, voriconazole, tioconazole), the polyene antimycotic macrolides (e.g. amphotericin B, nystatin), the echinocandins (e.g. caspofungin, micafungin and anidulafungin), the allylamines (e.g. terbinafine), the cytoskeleton agents (e.g. griseofulvin) and the antimetabolites (e.g. flucytosine).

In accordance with the published literature, an immediate reaction will be defined in this review as a reported reaction within 6 h after drug

administration with less than 1 h being more consistent with an Immunoglobulin E (IgE)-mediated reaction or other immediate reaction such as an infusion reaction. The principal immediate reactions are IgE-mediated reactions such as anaphylaxis and other less severe phenotypes include urticaria, pruritus, flushing, erythema and angioedema. Non-IgE-mediated infusion reactions can also occur and are associated with hives at the site of the intravenous infusion or flushing, generalized hives and erythema that respond to slowing the infusion and/or preinfusion administration of antihistamines. The delayed reactions are suspected after a 6-h period and will be classified as Steven–Johnson Syndrome and toxic epidermal necrolysis (SJS/TEN), symmetrical drug-related intertriginous and flexural exanthema (SDRIFE), fixed drug eruption (FDE), maculopapular exanthema (MPE), acute generalized exanthematous pustulosis (AGEP) and drug rash with eosinophilia and systemic symptoms (DRESS). Isolated organ toxicity and hypersensitivity reactions can also occur with the most common being drug-induced liver injury (DILI).

As with other drug classes, the cross-reactivity patterns for antifungals relevant for immediate reactions may not be the same as for delayed reactions. As epitopes can be shared by the different azoles, IgE-mediated reactions seem to show cross-reactivity patterns, whereas the specific antigen recognition by the toll-like receptors or other mechanisms in type IV delayed reactions is likely drug specific and ill defined [8^{¶¶}]. There is currently no clinically reported evidence of cross-reactivity between the different antifungal classes.

Azoles

The most common adverse drug reactions (ADR) to the azole drug class are hepatotoxicity, skin eruptions and gastrointestinal symptoms [9]. Primarily adverse events to azoles described are pharmacologically predicted and not immune-mediated. Each individual azole carries a distinctive nonimmune mediated side-effect profile – voriconazole (e.g. neurotoxicity), fluconazole (e.g. alopecia), itraconazole (e.g. gastrointestinal intolerance) and hypersensitivity to azoles is not well described. The azole class can be divided in triazoles such as fluconazole, itraconazole, voriconazole, posaconazole, and imidazoles, including clotrimazole, ketoconazole, miconazole and tioconazole.

Immune-mediated immediate reactions

Severe immediate reactions to voriconazole were not seen with first usage of voriconazole, and urticaria was only reported in 13% of the cases in a large

French series [10]. However, since this publication, anaphylaxis (acute wheezing, facial swelling, and pruritic urticarial rash over the trunk) was described in an immunosuppressed (pre B-cell acute lymphoblastic leukemia) 13-year old patient [11]. Immediate reactions to other azole drugs have also been infrequently reported in the literature following administration of ketoconazole [12,13], fluconazole [14,15] and itraconazole [16]. Possible cross-reactivity patterns have been described between some of the azoles such as immediate reactions to fluconazole and itraconazole [17] and ketoconazole and miconazole [12].

Immune-mediated delayed reactions

Various nonsevere, self-controlled mild isolated cutaneous reactions have also been described with oral antifungals such as itraconazole [18] and fluconazole [19–21]. Contact dermatitis has also been described following tioconazole solution application [22–34] and topical miconazole [35].

Among the antifungals, fluconazole appears to be the most common cause of FDE with approximately 30 cases reported with most being single or a few lesions. Rarely fluconazole has been associated with the more severe phenotype - generalized bullous FDE [36,37]. Classified in the spectrum of non-severe delayed reactions, besides diagnostic testing with patch testing (PT) that will be discussed below, few articles have offered other management approaches. AGEP was also described following fluconazole [38,39] and itraconazole administration [40–42]. Severe reactions have been reported with azole drugs such as SJS and TEN following administration of fluconazole [43,44,45,46–49]. In these reported cases, the patients have not received any other medications and, for the majority, they had no history of autoimmune, neoplastic or infectious conditions. Indeed, when using the algorithm of drug causality for epidermal necrolysis (ALDEN), fluconazole was probably associated with SJS [50] however, given the limited number of reported cases, has not been a primary focus of severe cutaneous adverse reaction (SCAR) research [51]. These severe delayed reactions occurred from several hours to 1 week following drug administration. Even if various case reports have been described in the literature, the management or cross-reactivity patterns for these cases are not detailed.

Case reports describing nonsevere hypersensitivity reactions show a possible absence of cross-reactivity among some of the antifungal medications e.g. tolerance of itraconazole in a delayed-type fluconazole reported reaction [19,21] but also tolerance of voriconazole in a delayed-type fluconazole and itraconazole reaction [52]. However, caution

should be used when reading the various case reports as one could argue that these patients were not challenged with another azole drug but were in fact desensitized using various protocols [20] – please refer to the subsection on ‘Drug Provocation and Cross-Reactivity Patterns’. Also, studies have suggested that there is a cross-reactivity between topical tioconazole and other imidazoles [26,33,34,53,54] as well as between topical tioconazole and isoconazole [28]. Cross-reactivity has also been reported between miconazole and other agents from the imidazole family [35].

Polyene antimycotic macrolides

Although many polyene macrolide antibiotics have been produced, two major agents with antifungal properties are commonly used in a clinical setting: amphotericin B and nystatin. Side effect reported following amphotericin B use include fever, rigors, headache, nausea, emesis, bronchospasm, nephrotoxicity, phlebitis, hypokalemia, anemia, abnormal renal function, and renal tubular acidosis [55^{*}]. Some of these adverse reactions are associated with an infusion-related reaction but the differential diagnosis of anaphylaxis needs to be considered, as reported in the literature [56–58] – Table 1. IgE-mediated reactions are rarely associated with amphotericin B [59]. Liposomal formulations of amphotericin B have been associated with complement activation-related pseudoallergy (CARPA) [60]. CARPA can present very similarly to IgE-mediated anaphylaxis however it is often present on the first exposure, may become milder on subsequent infusions and may resolve spontaneously.

As for the delayed reactions following the administration of polyene antimycotic macrolides, rare cases of severe cutaneous ADRs such as DRESS have been described following liposomal amphotericin B and cases of AGEP following the administration of nystatin have been reported [61,62]. Mild and short-lived elevations in liver enzymes occur in up to 20% of patients on amphotericin B however clinically significant liver failure is rare and most likely has a toxic rather than a primary hypersensitive mechanism.

Echinocandins

In the clinical setting, 3 semi-synthetic echinocandin derivatives with similar mechanisms of action and spectrum of activity have been developed: caspofungin, micafungin, and anidulafungin. Common reactions to the echinocandin drug class include transaminitis, electrolyte imbalances, hematologic effects, cardiac toxicity and fever [63] but beyond a

Table 1. Reported adult cutaneous cases of immune-mediated hypersensitivity to antifungals

Reference	Country	Year	Patient	Antifungal	Indication	Reaction Description	Investigations	Management
Azoles – immediate reactions van Dijke <i>et al.</i> [12]	Netherlands	1983	(1) F 26 (2) M 52	Ketoconazole	(1) (2) Dermatomycosis	(1) 45 min - Severe angioedema and erythema of the face, hands and feet, collapse (2) 30 min - Severe angioedema of his face, hands, and feet, dyspnea and vomiting.	None	None
						Min - Generalized erythema, edema of the extremities, hypotension, loss consciousness 2H - fever (38.3°C) and erythematous rash on his face and body. aDelayed reaction Itraconazole	SPT (1:10) - Positive	Avoid Azoles
Neuhauser <i>et al.</i> [14]	Switzerland	1991	F 22	Fluconazole	Vulvovaginal candidiasis			
Takahashi <i>et al.</i> [17]	Japan	2001	M 53	Fluconazole	Pulmonary cryptococcosis, HIV	2H - fever (38.3°C) and erythematous rash on his face and body. aDelayed reaction Itraconazole	None	7-day Desensitization Protocol (oral) Tx duration: 3 mo
Randolph <i>et al.</i> [86]	USA	2008	F 63	Fluconazole	Oral candidiasis	Day 1-2 - Hives (2 episodes), 2 nd episode oropharyngeal and lower airway symptoms	IDT (1:1,000; 0.2 mg) Positive (tablet)	13-step 1-day Fluconazole Desensitization Protocol (oral, every 15 min)
Ensina <i>et al.</i> [13]	Brazil	2009	M 49	Ketoconazole	Prophylaxis Candidiasis	40 Min - Angioedema face, generalized urticaria	Negative SPT (1, 10, 20, 40 mg/ml) Positive OC	Avoid azoles derivatives (perform OC as needed)
Chen <i>et al.</i> [16]	China	2009	F 38	Itraconazole	Pulmonary Fungal Infection, ALL	Min - Dyspnea, low BP, nausea, vomiting, anaphylaxis (3 episodes)	None	Patient tolerated Voriconazole
Jariwala <i>et al.</i> [15]	USA	2011	M 29	Fluconazole	Cryptococcal meningitis HIV	10 Min - febrile, developed a pruritic, maculopapular rash on her face, neck, upper chest, and back	None	10-step 3-day Fluconazole Desensitization Protocol (oral, every 6 h)
Zwiener <i>et al.</i> [95]	Argentina	2013	F 37	Voriconazole	Fungal sinusitis, AML	Min - Anaphylaxis with generalized maculopapular rash and bronchospasm	None	13-step 1-day Voriconazole Desensitization Protocol (oral, every 15 min)
Azoles – Delayed Reactions								
Abbott <i>et al.</i> [97]	UK	1991	F 21	Fluconazole	Vulvovaginal candidiasis	Day 2 (6 bi-monthly prophylaxis doses) - Angioedema tongue, buccal ulceration, dyspnea (2 episodes)	None	Avoid Azoles Treatment with nystatin pessaries and cream

Table 1 (Continued)

Reference	Country	Year	Patient	Antifungal	Indication	Reaction Description	Investigations	Management
Gussenhoven <i>et al.</i> [43]	Netherlands	1991	M 30	Fluconazole	Oral candidiasis, HIV	Day 14-16 - Fever, diarrhea, vomiting, severe bullae trunk and limbs; oral mucous membrane exanthemas and superficial ulcerations, increased hepatic enzymes (SJS)	None	None
Azon-Masoliver and Vilaplana [46]	Spain	1993	M 33	Fluconazole	Oral thrush, HIV	Day n/a - Severe mucosal involvement (70% BSA, TEN)	Biopsy: TEN	None
Bittleman <i>et al.</i> [18]	USA	1994	F 67	Itraconazole	<i>Coccidiomycosis immitis</i>	Day 6 - Whole-body erythematous papules Resolution: 4 d	None	9-step 1-day Desensitization Protocol (oral, every 30 min) Tx duration: 10 mo
Heymann and Manders [40]	USA	1995	M 52	Itraconazole	Onychomycosis	Day 7 - Fever, chills, generalized erythema with superficial pustules, leukocytosis (AGEP)	Biopsy: AGEP	None
Craig <i>et al.</i> [19]	USA	1996	M 36	Fluconazole	Cryptococcal meningitis	Day 4 - Pruritic axilla rash and Eosinophilia Day 30 - Hives, dyspnea, tachycardia, oral ulceration. Resolution: a few days	None	Changed for Itraconazole 15-days Fluconazole Desensitization Protocol (oral, daily) ^a Tx duration: 4 mo
Park <i>et al.</i> [41]	Korea	1997	F 27	Itraconazole	n/a	Day 7 - Fever, pruritic, multiple plaques with overlying pustules, leukocytosis (AGEP)	Biopsy: AGEP Negative SPT and PT (100 mg/10 ml)	Positive OC (33.3 mg) - pustule formation within 2 h
Fabre <i>et al.</i> [38]	France	2002	F 65	Fluconazole	Candida infection	Day 3 - Fever, pustular eruption with erythema, neutrophilia (AGEP)	Biopsy: AGEP	None
Alsadhan <i>et al.</i> [39]	Canada	2002	M 75	Fluconazole	Oral candidiasis	Day 2 - Fever, widespread erythema with associated pustules, leukocytosis (AGEP)	Biopsy: AGEP	None
Monastirli <i>et al.</i> [44]	Greece	2008	F 50	Fluconazole	Vaginal candidiasis	Day 7 - Fever, malaise, skin and mucosal lesions, bullous pruritic skin rash, epidermal detachment 9%, severe conjunctivitis (SJS)	Biopsy: SJS	None
Pinto and Chan [20]	Australia	2009	M 65	Fluconazole	Cerebral cryptococcosis	Day 21 - Generalized Itchy erythematous maculopapular rash, increased hepatic enzymes, eosinophilia	Biopsy: drug reaction	4-days Voriconazole Desensitization Protocol (oral) Tx duration: 8 mo

Table 1 (Continued)

Reference	Country	Year	Patient	Antifungal	Indication	Reaction Description	Investigations	Management
Di Leo <i>et al.</i> [21]	Italy	2009	F 42	Fluconazole	Vaginal candidiasis	4 H – morbilliform eruption	Negative SPT (10 mg/ml) 1:100 and 1:10 Positive IDT 1:1 Negative PT	Positive OC after 12h (1/10 dose) Tolerated itraconazole (100 mg)
Ofoma and Chapnick [47]	USA	2009	F 52	Fluconazole	Esophageal candidiasis	Day 5 - Painful generalized body rash - blisters (80% BSA), lip and oral blisters (TEN) Day 5 – Fever, generalized erythematous pustular eruption (AGEP)	Biopsy: TEN	None
Cancado <i>et al.</i> [42]	Brazil	2009	M 22	Itraconazole	Pityriasis versicolor	Day 5 – Fever, generalized erythematous pustular eruption (AGEP)	Negative SPT Negative PT Positive Modified LTT	None
George <i>et al.</i> [99]	India	2012	M 28	Fluconazole	Oral thrush, HIV	Day 2 – Malaise, pruritic rash face, trunk, and extremities Day 3 – Necrotic, vesicula-bullous lesions surrounded by erythema (70% BSA), conjunctivitis, fever, increased hepatic enzymes (TEN)	Positive Nikolsky's sign	None
Keshri <i>et al.</i> [49]	India	2014	M 25	Fluconazole	Vaginal candidiasis	Day 1 (2-3H) - Fever, myalgia and erythematous papular eruptions (blisters) lips, mouth, vaginal region and swelling on the face, sub-conjunctival hemorrhage (SJS)	Biopsy: SJS	None
Lash <i>et al.</i> [52]	USA	2016	M 41	Fluconazole	Coccidioidomycosis	Day 17 – Fever, mild rash, acute renal failure, eosinophilia	None	Similar reaction 2-days following itraconazole. Tolerated 2 years of voriconazole
Morales <i>et al.</i> [98]	USA	2017	F 48	Voriconazole	Pulmonary Aspergillus	Day 11 – Swelling lips, tongue, cheeks and eyes (duration 5 days)	None	5- Day Desensitization Protocol to Isavuconazole (IV, every day)
Antony <i>et al.</i> [45*]	India	2019	M 23	Fluconazole	Tinea versicolor	Day 1 (12H) - Swelling lips, blisters, erosions buccal mucosa, genital erosions (SJS)	None	None
Macrolides – Immediate Reactions (Kemp and Lockey [58])	USA	1995	F 68	Liposomal amphotericin B	AML	1H - Bronchospasm, generalized erythema, rigors, diaphoresis, pruritus and urticaria.	None	7-step 1-day Desensitization Protocol (IV, every 10 min)

Table 1 (Continued)

Reference	Country	Year	Patient	Antifungal	Indication	Reaction Description	Investigations	Management
Dhindsa-Castaneda and Narra [57]	USA	2012	M 39	Liposomal amphotericin B	Mucormycosis AML	5 min - Dyspnea, chest pressure, hypotension and hypoxia	None	12-step 1-day Desensitization Protocol (IV, every 30 min)
(Shadur <i>et al.</i> [56])	Australia	2017	M 18	Liposomal amphotericin B	Fungal chest infection AML	15 min - Dyspnea, profuse sweating and dry retching	None	7-step 1-day Desensitization Protocol (IV, every 1-2 h)
Macrolides – delayed reactions								
Kuchler <i>et al.</i> [61]	Germany	1997	F 56 (1) F 23 (2) F 59 (3)	Nystatin	n/a	Day 1-2 – Generalized, pruritic, erythematous with pustular eruption	Biopsy: AGEP Positive delayed SPT (1:1) Positive PT (1:1) and 1/3 (10%) Positive PT	None
(Poszepczynska-Guigne <i>et al.</i> [62])	France	2003	M 29	Nystatin	n/a	Day 2 – Fever, pustular erythroderma, neutrophilia	Positive PT	None
Echinocandin – immediate reactions								
Patel <i>et al.</i> [64]	USA	2009	F 67	Micafungin	Fungal ehmold Sinusitis, HSCT	During infusion - hypotension, back pain, flushing, rigors, shortness of breath, and rash.	Positive IDT Caspofungin (0.05 mg)	Patient tolerated posaconazole
Echinocandin – delayed reactions								
Lee <i>et al.</i> [66]	Taiwan	2010	M 86	Caspofungin	Candidemia	Day 1 - extensive erythema, exfoliation, blisters, and skin erosions (50% BSA, TEN)	None	None
Allylamine – Delayed Reactions								
Kempinaire <i>et al.</i> [69]	Belgium	1997	F 63	Terbinafine	Tinea corporis	Day 14 – Pustular eruption, fever	Biopsy: AGEP Positive PT (144 h)	None
Hall and Tate [68]	Australia	2000	F 64	Terbinafine	Onychomycosis	Day 31 (3 days after 28-day treatment) - Micropustular eruption arms, back, buttocks and upper thighs	Biopsy: AGEP	None
Lombardo <i>et al.</i> [72]	Italy	2003	F 74	Terbinafine	Tinea cruris	Day 5 – Fever, generalized pustular eruption, leucocytosis	Biopsy: AGEP Negative PT	None
Beltraminelli <i>et al.</i> [70]	Switzerland	2005	M 68	Terbinafine	Onychomycosis	Day 20 - Disseminated nonfollicular small pustules on erythematous skin	Biopsy: AGEP Negative PT Positive LTT	None
Duckworth <i>et al.</i> [67]	UK	2012	M 72	Terbinafine	Tinea unguium	11 Weeks - large annular patches were with pustules and central clearing (trunk and limbs)	Biopsy: AGEP vs pustular psoriasis	None

Table 1 (Continued)

Reference	Country	Year	Patient	Antifungal	Indication	Reaction Description	Investigations	Management
Eyler <i>et al.</i> [71]	USA	2012	M 42 (1) M 38 (2)	Terbinafine	(1) Tinea unguium (2) Tinea pedis	(1) Day 14 - Generalized erythroderma with numerous small yellow pustules (2) Day 7 - Generalized pruritic and slightly tender erythematous plaques with small white pustules	Biopsy: AGEP	Avoid oral and topical terbinafine
Cytoskeleton Agent – Immediate Reactions								
Kotani <i>et al.</i> [79]	Japan	1988	M 21	Flucytosine	Oral Candidiasis AIDS	Day 1 (after a 12-day course) - fever, erythema, pruritus, hypotension, skin desquamation	None	None
Cytoskeleton Agents – Delayed Reactions								
Quero [87]	Cuba	1960	M 55	Griseofulvin	Dermatophytosis feet	Day 1 (3 rd dose) – Generalized pruritus, red macules and wheals	Negative PT Positive IDT	None
Taylor and Duffill [78]	New Zealand	1988	F 40	Griseofulvin	Tinea pedis	Day 10 – Fever, generalized patchy erythema, necrolysis	Positive Nikolsky's sign Biopsy: TEN	None
Correia <i>et al.</i> [77]	Portugal	1991	M 36	Griseofulvin	Onychomycosis	Day 6 – Fever, generalized redness and bulla, mucosal erosive lesions mouth and genital (60% BSA), conjunctivitis,	Positive Nikolsky's sign	None
Lazarov <i>et al.</i> [74]	Israel	1998	M 54	Griseofulvin	Keratosis kuchenioides chronica	12 H - Generalized pustular rash	Biopsy: AGEP	None
Maiolo <i>et al.</i> [76]	Australia	2016	F 60	Griseofulvin	Tinea interdigitale	Day 6 – Fever, generalized erythema, facial swelling, lymph nodes, eosinophilia,	RegiSCAR: DRESS Biopsy: DRESS	None

AGEP, acute generalized exanthematous pustulosis; AIDS, acquired immunodeficiency syndrome; ALL, Acute lymphoblastic leukemia; AML, acute myeloid leukemia; BP, blood pressure; BSA, body surface area; d, day; DRESS, drug reaction with eosinophilia and systemic symptoms; F, female; HIV, human immunodeficiency virus; HSCT, hematopoietic stem cell transplant; IDT, intradermal test; LTT, lymphocyte transformation test; M, male; min, minutes; mo, months; OC, oral challenge; PT, patch testing; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; tx, treatment.

Note: For the case reports where the culprit drug was unclear or where other drug classes were considered as culprit were excluded from this table.

Note 2: The case reports describing a pediatric population were excluded from this table.

Note 3: As specified in the manuscript, all cases of fixed drug eruptions and hepatitis were excluded from this table.

This desensitization protocol to fluconazole was complicated by a transient maculopapular, pruritic rash on the upper trunk and under the axilla area from day 4 to day 6 of the 15-days protocol. The protocol was successfully continued and the patient tolerated a full-course treatment (4 months duration).

handful of case reports, hypersensitivity to these agents is not well described in the literature.

Infusion-related reactions have been reported as well as possible anaphylaxis cases [11,64]. Infusion reactions may be more prevalent with caspofungin than the other echinocandins. Caspofungin has shown to significantly increase histamine concentration in whole blood and inhibit histamine N-methyltransferase activity [65]. According to the current literature available, there seems to be an evidence of cross-reactivity between micafungin and caspofungin, confirmed with intradermal skin testing [64].

Delayed immune-mediated reactions are scarcely described with no evidence of delayed mild isolated skin reactions but there have been some reported cases of TEN secondary to caspofungin [66].

Allylamines

The allylamine antifungal class is composed of 2 antifungal agents - terbinafine, available in topical and pill form and naftifine, available topically and intravenously in some countries. The most common hypersensitivity reaction is AGEP secondary to terbinafine with several reports in the literature [67–72]. Unlike AGEP associated with antibiotics, terbinafine has a long latency period up to 2 weeks versus a 24–48 h for aminopenicillin associated AGEP. Terbinafine has also been associated with DILI. The pattern of injury is often a mixed or cholestatic pattern, presents within the first 6 weeks of therapy, and leads to discontinuation of therapy in 0.31%. Despite consistent case descriptions, allergy investigations and management are scarcely described – please see ‘Skin Testing’ section below. In keeping with the acute hepatotoxicity associated with terbinafine being immunologically mediated, terbinafine DILI has been associated with HLA-A*33:01 and European patients and potentially HLA-A*33:03 in East Asian patients [73].

Cytoskeleton agents

The main agent described in this family of antifungal agents is the griseofulvin. Although elevation in transaminases can occur in up to 5% of patients, clinically apparent liver toxicity is infrequent. Hepatotoxicity is a frequent adverse reaction and the immune-mediated reactions reported secondary to the administration of this drug are rarely reported in the literature. For example, a case of AGEP following griseofulvin administration was described in a case series [74], two cases of DRESS were associated with the use of this agent [75,76], one case of SJS and two cases of TEN [77,78].

Antimetabolites

The main agent in this family is flucytosine. Anaphylaxis has been described in association with this agent [79] however the clinical case description could also correspond to a delayed type reaction.

MANAGEMENT OF IMMUNE-MEDIATED REACTIONS

The management of these hypersensitivity reactions to antifungals is based on case reports (Table 1) and clinicians do not have clear suggested management strategies. In our algorithm, we offer a phenotype-specific clinical approach to causality investigations and management (Fig. 1).

Skin testing

For the assessment of immune-mediated hypersensitivity reactions, the same systematic allergy investigations should be performed as suggested by internationally recognized societies [80,81]. Skin prick testing (SPT) and intradermal testing (IDT) are performed on the volar aspect of the forearm with, respectively, one drop and 0.02–0.05 mL of antibiotic reagent or normal 0.9% serum saline (negative control) [80,82]. The positive control normally used is a SPT with histamine [83]. A positive SPT is determined in comparison with the positive control and/or equal or greater than a 3 mm wheal. An IDT result is considered positive when the dermal induration and erythema at the injection site exceeded 5 mm from baseline [80,84]. In terms of drug concentrations, expert consensus advises the use of the highest nonirritating concentration described for immediate reactions [85]. The dilutions are performed with sterile intravenous drug formulation.

Depending on the severity of the immune-mediated reaction, careful skin testing should be performed initially with SPT, for anaphylaxis at a 1/10 concentration followed by 1/1, if negative. If skin prick is negative, low concentration should be used for IDT such as 1/1,000, followed by 1/100 if negative and, finally, 1/10 (Fig. 1). For immediate reactions other than anaphylaxis, pure concentration SPT can be performed as an initial testing followed by a 2-step IDT at 1/100 and 1/10 concentrations, if negative. Positive skin testing was described with fluconazole using 2 mg/ml for SPT and 0.2 mg/ml and 0.02 mg/ml for IDT [86]. To be noted that this positive IDT testing was performed using a dissolved tablet and the test was negative in a nonallergic control patient. IDT for fluconazole was also performed using a parenteral 10 mg/ml and a positive IDT was noted for the undiluted concentration with a confirmation by a positive oral challenge (OC) [21].

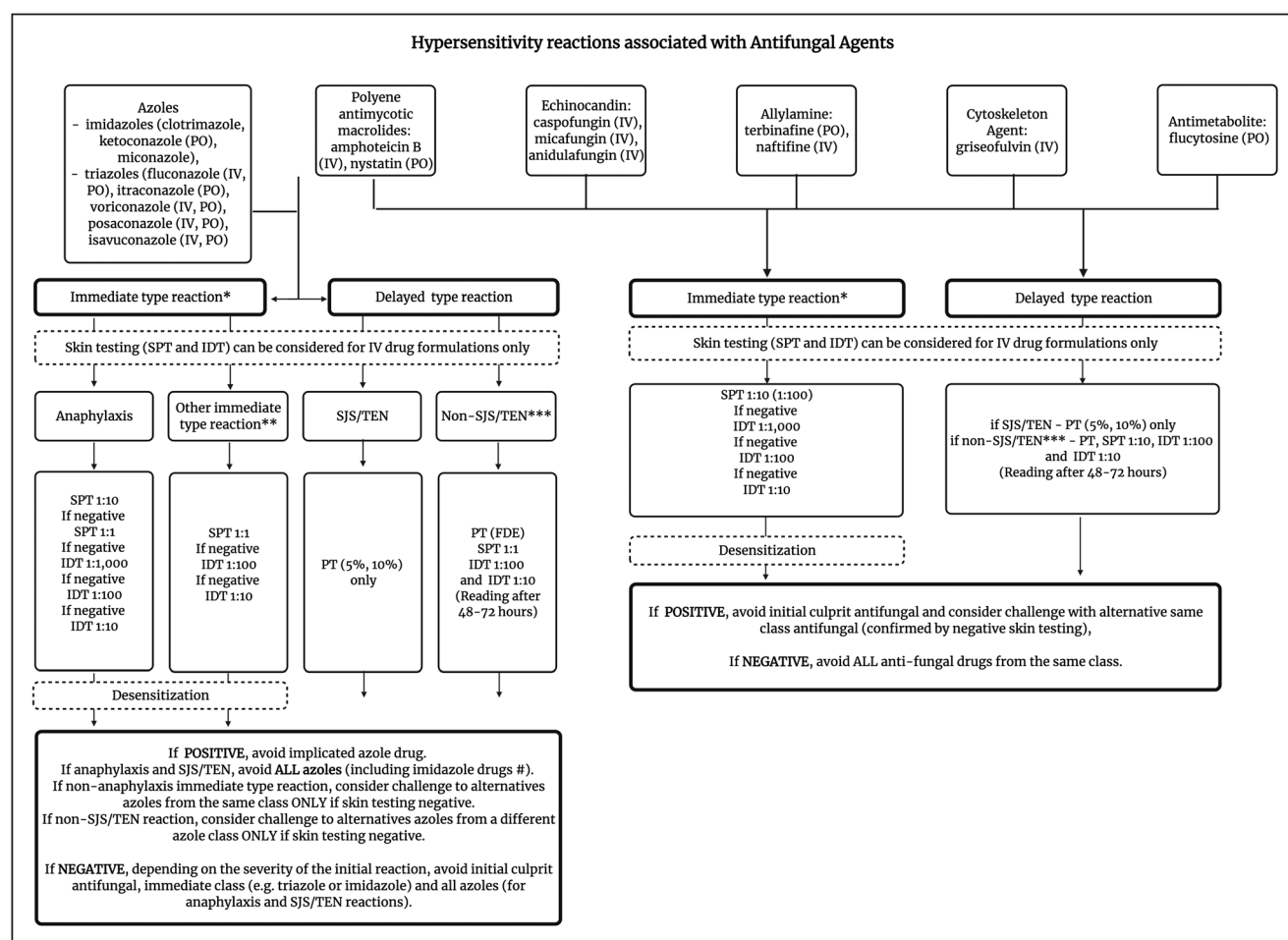


FIGURE 1. Management of hypersensitivity reactions associated with antifungal agents. AGEF, acute generalized exanthematous pustulosis; DRESS, drug rash with eosinophilia and systemic symptoms; FDE, fixed drug eruption; IDT, intradermal testing; MPE, maculopapular exanthema; PT, patch testing; SDRIFE, symmetrical drug-related intertriginous and flexural exanthema; SJS, Steven–Johnson syndrome; SPT, skin prick testing; TEN, toxic epidermal necrolysis. * Immediate reaction is defined as a reported reaction within 1 h after drug administration. ** The other immediate type reactions include urticaria, pruritus, flushing, erythema and angioedema. *** The non-SJS/TEN category includes FDE, MPE, AGEF, DRESS, SDRIFE. # Besides the antifungal imidazoles/triazoles, other imidazole-based drugs are the antiprotozoal drugs (metronidazole), antihistamines (cimetidine), PPI (lansoprazole, omeprazole, esomeprazole), antiplatelet (ticagrelor) and antihelmintic agents (albendazole, mebendazole).

Positive skin testing was also described with voriconazole using 5 mg/ml in a pediatric anaphylaxis case [11]. Positive IDT was also described (1 cm induration and 4.5 cm erythema) for caspofungin at the 0.05 mg/ml concentration in a patient that presented anaphylaxis following micafungin infusion [64]. Delayed positive SPT with undiluted concentrations was described in 3 cases of nystatin associated AGEF [61]. Finally, in a case of generalized pruritus, red macules and wheals following the 3rd dose of griseofulvin, the 1:10 IDT was positive 10 min after the procedure – 1.5 cm measured wheal with pseudopodia [87]. There are no publications concerning the maximal nonirritating concentrations of

these products and, for the majority of the cases, no controls were tested.

The clinicians are advised to discuss with their local pharmacist the composition, the solubility, the absorption and the irritation/toxic potential of the antifungal used for intra-dermal testing. As the majority of the intravenous antifungals have not been previously used in comprehensive studies describing the adequate concentrations to be administered, it is prudent to use tolerant controls or healthy controls to eliminate false positive results. A recommended IDT range from the published literature is 1/1,000 to 1/10 but further studies assessing the maximal nonirritating concentration are required.

Patch testing

For severe delayed immune-mediated reactions such as SJS/TEN, skin testing should be delayed to 6 months after the resolution of the skin reaction [88] and PT is the investigation that carries the lowest risk of disease re-activation. For non SJS/TEN reactions, negative PT can be followed by intra-dermal testing at 1/100 with delayed reading after 48–72 h and at 1/10 concentration if negative.

PT concentrations usually employed vary from 1% to 30% depending on the drug used and whether it is the trade product of the drug or reagent grade product that has been sourced [89]. The individual properties of the drug in relation to water solubility are also important. Specifically, for fluconazole, PT with 10% concentrations was positive in 3 cases of FDE [90–92] – concentration indicated in 2/3 cases [36]. Miconazole contact dermatitis was confirmed by positive PT in one case [35].

Positive PT was described for tioconazole 1% and 28% in a case of contact dermatitis [22,24–26,28–34,53,54]. Tioconazole along with undecylenic acid can be found in some antifungal nail solution and positive PT to undecylenic acid 1%, 2% and 4% have been reported [93].

For AGEP associated with itraconazole, PT was performed in one patient with a false negative result as the patient was subsequently challenged and presented pustule formation 2 h after one dose of 33.3 mg of oral itraconazole [41]. Another report of negative PT using a 100 mg itraconazole capsule was also described in the literature [42].

When nystatin was considered the culprit agent in AGEP cases, positive PT was described with undiluted nystatin preparation in 4 cases and in 1 case with nystatin 10% in petrolatum [61,62]. In one of these studies, the authors indicated that they had performed nystatin undiluted PT in 13 consecutive controls [61]. For terbinafine-related AGEP, PT concentrations described with terbinafine tablets (250 mg) and 1% cream showed negative results [70,72] and for the only positive PT, the patch concentration was not specified [69]. Considering the current lack in the literature, the recommendation is to use PT concentrations of 5% and/or 10% for the most severe cases (Fig. 1) [8^{''}].

Ex vivo testing

Lymphocyte transformation test (LTT), an *ex vivo* diagnostic method for delayed hypersensitivity reactions that measures the average proliferation of drug-exposed blood cultures based on the proliferation of negative control cultures and using a radioactive thymidine (H-thymidine) uptake [89], was used for 2 cases terbinafine-related AGEP [70]

with only one confirmed positive test [70]. Similar, dose-dependent T-cell proliferative response was demonstrated in a case of AGEP associated with itraconazole when compared to 5 healthy subjects [42]. Since LTT can be associated with false positive and negative results it is important for there to be external validation.

Drug provocation and cross-reactivity patterns

Drug challenge or provocation is the gold standard for drug allergy assessment. This includes OC as well as intravenous challenges depending on the availability of the antifungal agent. Negative skin testing should be followed by a drug challenge to validate results. In the outpatient clinic setting, this is typically an OC. In a case of ketoconazole generalized urticaria and angioedema, hypersensitivity was confirmed with an OC following negative skin testing [13].

If the pretest probability and clinical requirements are high, skin testing should be performed to the implicated antifungal and any potentially cross-reactive drugs. If the skin testing is positive in the setting of a systemic reaction, this warrants avoidance of the implicated and cross-reactive drugs. In non-severe immediate and delayed type reactions to azoles, we recommend challenge to alternative azoles previously negative on skin testing. If anaphylaxis was the reported initial reaction and the benefit of treatment is high, desensitization should be considered. If SJS/TEN were the initial reported reactions, the whole antifungal class should be avoided and, for the reactions to azoles, all the imidazole drugs. Besides the antifungal imidazoles/triazoles, other imidazole-based drugs are the antiprotozoal drugs (metronidazole), antihistamines (cimetidine), Proton pump inhibitors (PPI) (lansoprazole, omeprazole, esomeprazole), antiplatelet (ticagrelor) and antihelminthic agents (albendazole, mebendazole) [94]. As evidence is scarce regarding the sensitivity and specificity of skin testing, if the assessment is nonconclusive or negative, depending on the severity of the initial reaction, we recommend avoidance of the initial culprit antifungal and the antifungal class and, for anaphylaxis and SJS/TEN and other severe cutaneous reactions to azoles, all the imidazole drugs, as discussed.

Desensitization

When substitution with alternative antifungal medications is not an option and the initial reported reaction is an immediate reaction (other than an infusion reaction) or a delayed reaction

limited to mild-moderate rash alone (i.e. not systemic reaction or organ involvement) successful desensitization has been described with various agents such as azole – oral itraconazole [18], oral fluconazole [15,17,19,86], oral voriconazole [95], intravenous voriconazole [11] and polyene antimycotic macrolides – intravenous liposomal amphotericin B [56–58].

There is currently no consensus in the literature regarding a recommended desensitization protocol for antifungals. As immediate reactions to fluconazole are more frequently reported, one suggested protocol consists of 13-steps increasing oral doses, from 0.02 mg – 1% of the total dose [86]. A similar intravenous protocol was described for micafungin immediate reaction in a pediatric case and described 12-steps from 0.003 mg for a total cumulative dose of 150 mg [96]. To our knowledge, there are no published protocols for the fluconazole intravenous formulation. The other protocols published (Table 1) were all considered safe and successful and our recommendation would be to follow the recent desensitization guidelines in the ‘Practical Guidance for the Evaluation and Management of Drug Hypersensitivity’ that indicate that an initial dose should represent approximately 1/10,000 of the final dose and that doses should double at each increment or step [8**].

For the delayed nonsevere reactions, the duration of the desensitization varies from 1-day protocols [18,86] to multiple days protocols (up to 15 days) [17,19]. In this prolonged desensitization protocol, the initial dose of less than 1/1,000 mg was doubled daily and despite a mild cutaneous reaction, the fluconazole daily treatment was continued successfully for a 4 months period [19]. The use of a desensitization protocol for delayed hypersensitivity reactions is a debatable approach and besides published successful cases where the allergy status might not be assessed prior desensitization, there are no global recommendations.

CONCLUSION

Antifungal drugs are infrequently associated with drug hypersensitivity reactions. Although mild immediate reactions or mild to moderate delayed rash may not be a contraindication to future drug challenge, severe cutaneous reactions such as SJS/TEN, DRESS, AGEP, SDRIFE, multifocal bullous FDE and DILI have been described. Although experience with *in vivo* and *ex vivo* diagnosis is limited, skin and PT and laboratory assays have been employed with some success to aid in diagnosis and causality assessment. Although there is no inter-class cross-reactivity for antifungals, the presence of potential cross-

reactivity within class members such as the azoles is a possibility and, in the setting of SCAR, it is prudent to avoid the entire class. Currently, this remains an area reliant on expert opinion rather than a strong evidence base. Larger retrospective cohorts and prospective data will help clarify mechanisms and management of antifungal hypersensitivity.

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Conflicts of interest

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Supplement Material, <http://links.lww.com/COID/A34>

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