Clinical Oral Investigations (2022) 26:6479–6489
https://doi.org/10.1007/s00784-022-04716-2

REVIEW

Resistance profiles to antifungal agents in *Candida albicans* isolated from human oral cavities: systematic review and meta-analysis

Sarah Quadros Santos Kessler[1] · Pauline Mastella Lang[2] · Tatiane Silva Dal-Pizzol[3] · Francisco Montagner[1]

Received: 27 April 2022 / Accepted: 6 September 2022 / Published online: 27 September 2022

Abstract

Aim To identify the antifungal susceptibility profile of *Candida* spp. isolated from the human oral cavity was assessed with meta-analyses of observational studies that collected samples from the oral cavity of human subjects.

Material and methods Isolated *Candida albicans* tested by E-test®; disk diffusion test; microdilution and macrodilution; Sensititre YeastOne; and/or FungiTest. Search strategies were conducted on the MEDLINE, Embase, CINAHL, Dentistry, and Oral Sciences, Central, Scopus, and LILACS databases, and gray literature sources. Articles were initially screened by title and then their abstracts. Articles that met the conditions for inclusion were read in full, followed by data extraction. A descriptive analysis was conducted of each study, and the data were tabulated. A first meta-analysis was conducted to assess the resistance of antifungals regardless of systemic comorbidities. An additional stratified analysis was conducted by systemic comorbidity groups for the outcome "resistance" to the antifungals.

Results When not grouping *Candida albicans* isolates by systemic conditions, the lowest resistance rates to the antifungals tested were observed for amphotericin B, nystatin, flucytosine, and caspofungin. In contrast, the highest resistance rates were observed for miconazole and econazole. There was a high degree of heterogeneity and low resistance in general in all analyses, except for the "several associated comorbidities" group, which had high resistance rates.

Conclusions Clinical *C. albicans* isolates had low antifungal resistance.

Clinical relevance The presence of concomitant systemic comorbidities appears to be an essential factor that should be considered when evaluating resistance to antifungals for oral isolates.

Keywords Antifungal agent · Susceptibility · Candidiasis · Oral candidosis · Meta-analysis

Introduction

Oral candidiasis is a common fungal infection. In the majority of cases, these lesions are caused by the yeast *Candida albicans* [1]. *Candida* is an opportunistic microorganism and its growth increases in the presence of certain local and/or systemic factors [2]. The incidence of this microorganism increases as immune system function declines [3]. Individuals who have poor oral hygiene, xerostomia, removable dentures, human immunodeficiency virus (HIV) infection, or who have been exposed to radiotherapy of the head and neck are more susceptible to oral candidiasis. In 2019, Quindós et al. listed dysbiosis, poor oral hygiene, the anatomic changes linked to aging, dysplasia, smoking and excessive alcohol consumption, endocrine disorders, immunodeficiency in general (not only secondary to HIV, but also due to chemotherapy and neoplasms), and treatment with corticosteroids as potential facilitators of colonization by this microorganism. Other predisposing factors for oral candidiasis include malnutrition, malabsorption, and eating disorders. More specifically, it is said that a diet rich in carbohydrates contributes to the development of oral candidiasis. The following deficiencies have also been linked to

✉ Francisco Montagner
francisco.montagner@ufrgs.br

1 Post-Graduation Program in Biological Sciences Pharmacology and Therapeutics, Federal University of Rio Grande Do Sul, R. Sarmento Leite, n° 500 - Farroupilha, Porto Alegre, Rio Grande do Sul CEP 90050-170, Brazil

2 Brazilian Army, Cruz Alta, Rio Grande do Sul, Brazil

3 Post-Graduation Program in Epidemiology, Faculty of Medicine, Federal University of Rio Grande Do Sul, Porto Alegre, Brazil

increased risk: iron, zinc, magnesium, selenium, folic acid, and vitamins (A, B6, B12, and C) [4].

When treating, it is first necessary to identify predisposing factors and, if present, treat them. After this initial intervention, the patient's immunological status, the specific characteristics of the oral candidiasis (clinical presentation, etiology, susceptibility to antifungals, location, dissemination), and the pharmacological characteristics of the available antifungals (administration, metabolism, clearance, interactions with other drugs, and toxicity) should all be considered [4]. Topical treatment is the first choice for mild cases, which generally respond well to this approach (nystatin or miconazole) [4]. Systemic treatment should be considered if there is fungal dissemination or resistance to topical treatment [5]. A systematic review and meta-analysis conducted by Fang et al. evaluated the efficacy of antifungal drugs on oral candidosis in randomized controlled trials. The authors concluded that itraconazole (capsules or oral solution), miconazole (tablets and oral gel), clotrimazole, fluconazole, ketoconazole, nystatin, and amphotericin B can significantly improve the mycological rate, when compared to the placebo group. They also observed that fluconazole exhibited better results than the other antifungals tested [6].

A wide range of drugs are available for treatment of oral candidiasis and the resistance profiles should be analyzed before making a treatment decision. There is a large body of literature reporting on resistance, especially about azoles. Resistance can occur via the following mechanisms: activation of efflux pumps; mutation of the ERG-11 gene; dysregulation of ERG-11 gene expression; and changes affecting the ergosterol biosynthesis pathway [7, 8]. Recently, the ongoing COVID-19 pandemic elicited the discussion on the emergence of fungal infections in critically ill, mechanically ventilated COVID-19 patients. Invasive fungal infections increased mortality among coronavirus patients who are not given antifungal treatment, compared with those who are given antifungal treatment [9], immediate diagnosis and treatment are essential for clinical success. Non-albicans species appear to comprise the group of microorganisms most frequently involved in superinfection cases [10].

The objective of this systematic review and meta-analysis was to trace the antifungal resistance profile of *C. albicans* strains isolated from the oral cavity of human subjects.

Materials and methods

Population, exposure, comparator, and outcomes (PECO) question

A systematic review was conducted according to the items specified on the PRISMA 2020 checklist (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) [11]. The review protocol was registered on the PROSPERO database (Protocol number CRD42020208245). The research question formulated using the PECO strategy was as follows, "What rates of resistance to antifungal agents are reported in studies that have isolated fungi of the genus *Candida* from the oral cavities of humans?" Data were collected on April 21, 2020.

Eligibility criteria

The study included observational studies that collected samples from the oral cavities of humans and isolated *Candida albicans* fungi (the PROSPERO protocol was altered: the original registration had stated the *Candida* genus) and conducted tests for susceptibility to the antifungal agents nystatin, amphotericin b, fluconazole, ketoconazole, miconazole, itraconazole, and others (this was another change to the protocol after registration on PROSPERO: the list of antifungals analyzed was expanded to match the findings of the studies reviewed) using the E-Test®, disk diffusion, and/or microdilution and macrodilution methods (this was another change to the protocol after registration on PROSPERO: the list of laboratory tests analyzed was expanded to match the findings of the studies reviewed). Descriptive literature reviews, letters to the editor, in situ studies, animal model studies, and studies undertaken with extracted teeth or with samples from removable dentures were excluded. Additionally, the authors of studies for which the full text was not available were contacted, but the study was excluded if the full text was not forthcoming.

Search strategy and information sources

Electronic searches were run on MEDLINE (via the PubMed search engine), Embase, CINAHL, Dentistry and Oral Sciences, Central, Scopus, and LILACS databases and in the grey literature, from database inception to April 20, 2020. No publication language filters were applied. Figure 1 illustrates the search strategy used for the MEDLINE database, via the PubMed search engine. The same strategy was also used for the other databases, modified as appropriate. Free or controlled vocabulary search terms were employed (MeSH/TextWord) as appropriate for each database. The search strategies used on the other platforms are shown in the supplementary material for this study.

Study selection and data extraction

The Zotero 5.0.87 program was used to manage and organize databases constructed with the results of the database searches. The initial selection included many duplicate titles identified by the strategy, which were excluded from the analysis.

MEDLINE (PUBMED)	((((((antifungal agentes [tw]) OR antifungal agents[MeSH Terms] OR antifungal agents[Text Word] OR antifungal therapy [tw] OR antifungal therapy[MeSH Terms] OR antifungal therapy[Text Word] OR nystatin OR nystatin[Text Word] OR nystatin[MeSH Terms] OR amphotericin OR amphotericin[Text Word] OR amphotericin[MeSH Terms] OR fluconazole OR fluconazole[MeSH Terms] OR fluconazole[Text Word] OR ketoconazole OR ketoconazole[Text Word] OR ketoconazole[MeSH Terms] OR miconazole OR miconazole[Text Word] OR miconazole[MeSH Terms] OR itraconazole OR itraconazole[MeSH Terms] OR itraconazole[Text Word] OR clotrimazole OR clotrimazole[MeSH Terms] OR clotrimazole[Text Word])) AND ((((oral cavity [tw]) OR oral cavity[Text Word]) OR mouth OR mouth[Text Word] OR mouth[MeSH Terms] OR palate OR palate[MeSH Terms] OR palate[Text Word] OR tongue OR tongue[MeSH Terms] OR tongue[Text Word])) AND ((candida) OR candida[Text Word] OR candida[MeSH Terms] OR oral candidosis [tw] OR oral candidosis[MeSH Terms] OR oral candidosis[Text Word] OR oral candidiasis [tw] OR oral candidiasis[Text Word] OR oral candidiasis[MeSH Terms]))) AND Humans[Mesh])) NOT (animals NOT humans)

Fig. 1 Search strategy adopted for the study, showing MeSH keywords and the terms for antifungal activity and resistance of *Candida* spp. from the oral cavities of human subjects

In stage 1, two independent reviewers (F. M. and S. Q. S. K.) selected articles by title and, in cases of doubt as to whether an article should be included, the abstract was read. In case of disagreement, a third examiner (T. S. D. P.) decided whether the article should be included. The kappa test was used to determine the agreement between reviewers in the initial evaluation of titles and abstracts ($\alpha = 5\%$; SPSS V. 18.0.0 software, SPSS Inc., Chicago, IL, USA). According to the agreement criterion suggested by Landis and Koch (1977) [12], kappa values < 0.40 represent reasonable agreement; values from 0.41 to 0.60 reflect moderate agreement; values from 0.61 to 0.80 demonstrate substantial agreement; and kappa values from 0.81 to 1.00 are considered indicative of excellent agreement.

In stage 2, all of the articles selected in stage 1 were analyzed to check that they met the inclusion criteria established in the study protocol. Those that did not were excluded.

In stage 3, all of the articles that had not been excluded after stage 2 were assessed for study quality against the inclusion and exclusion criteria and data were extracted. The entire selection process was conducted independently by two different examiners (S. Q. S. K. and P. M. L.). Any disagreements between examiners were adjudicated by a third evaluator (T. S. D. P.), independently, who decided whether the article would be included in the review or not, and proceeded to the next stage. Reasons for exclusion of studies in stage 2 were noted. The data extracted were input to a spreadsheet (article title, author, year of publication, objective, number of study participants, prior exposure to antifungal or antibacterial agents, mean age of study participants, presence and type of underlying disease or systemic comorbidities, presence or type of localized diseases, use of removable dentures, sample collection site, estimate for sample size calculation, number of *C. albicans* isolated, method employed to determine susceptibility to antifungal agents, method employed to determine identification of *C. albicans*, antifungal agents tested, and absolute and relative values for strains resistant to each antifungal agent). Data were individually extracted by two evaluators (P. M. L. and S. Q. S. K.). Disagreements between them were adjudicated by a third evaluator (T. S. D. P. or F. M.).

The percentage of resistant strains was calculated for all of the antifungals tested in each study. Groups of microorganisms with intermediate susceptibility profiles were defined as susceptible.

Meta-analysis

Meta-analyses were performed using the meta and metafor packages in RStudio (Version 1.4.1717 © 2009–2021). Analyses were conducted with the random effects model. Combined *Candida albicans* resistance rates were estimated as percentages (number of resistant strains/total number of strains tested) * 100) with 95% confidence intervals. The generalized linear mixed model (GLMM) for proportions was used, following Schwarzer et al. [13] and the maximum likelihood method was used to estimate variance.

Resistance rate outcomes were calculated for each antifungal and illustrated with forest plots. The degree of heterogeneity was analyzed with the statistical tests I^2 and τ^2. Additionally, a subset analysis was conducted with data broken down by systemic comorbidities (acute lymphoblastic leukemia, diabetes, head and neck cancer, HIV/AIDS, cancer, more than one associated comorbidity, kidney disease, immunocompromise, oral cavity and respiratory tract infection, organ transplantation, and candida bloodstream infections).

All of the studies were included in the meta-analysis, except for subgroups for which there was only one study per comorbidity (oral cavity and respiratory tract infection, acute lymphoblastic leukemia, and immunocompromise) and cases in which an antifungal was only tested for resistance once (luliconazole, lanoconazole, fluconazole and itraconazole combined, and miconazole, itraconazole, ketoconazole, and fluconazole combined).

Analysis of study quality and risk of bias

Risk of bias quality was not assessed because no instrument was found that was applicable to this type of study since it analyzes as outcome results of laboratory analyses with standardized tests performed on *Candida albicans* collected from the oral cavities of human beings.

Results

The results of the search strategy are illustrated in Fig. 2. The final results of searches on Central, CINAHL, Dentistry and Oral Sciences, Embase, LILACS, PubMed, and Scopus yielded 92, 61, 178, 1399, 240, 785, and 1031 studies, respectively. None of the studies found in the gray literature was included. Some studies were indexed on more than one database, producing 390 duplicates. Application of the inclusion and exclusion criteria resulted in exclusion of 2713 articles during the title/abstract assessment phase and 158 articles when the full texts were read. The inter-rater reliability during study selection was moderate ($k = 0.487$ [CI 95% 0.424–0.551]; $P < 0.0001$, percentage agreement = 93.2%). The studies excluded during this stage were those that did not test *C. albicans* resistance/susceptibility; did not classify results by *C. albicans* collection sites; that only tested natural extracts; that extracted *C. albicans* samples from dentures; that did not isolate *C. albicans* from the oral cavity; that only tested 1 strain of *C. albicans*; that did not define the number of *C. albicans* strains; that obtained *C. albicans* samples from dental abscesses or root canals; that evaluated the anti-cariogenic effect of the drugs tested; that did not report the *C. albicans* resistance rates; that combined resistant *C. albicans* strains with those with intermediate resistance; that did not divide groups of healthy patients from those with systemic comorbidities; that tested subtherapeutic doses of the antifungals; that selected certain strains of *C. albicans* by convenience for laboratory tests other than susceptibility, according to the study objective; and that did not exhibit the results clearly and combined results for *C. albicans* strains with those for other species.

The authors were contacted at two points during the study. Contact details for authors of 33 articles for which the full text could not be accessed were obtained by searching the internet and used to request the full text. Only 2 of these authors replied. When there was any doubt with relation to the method used to identify *Candida albicans* in the studies, requests for clarification were sent by email. Requests were sent to 8 researchers, only 3 of whom replied. A total of 88 articles were included in the analysis of resistance. For the meta-analysis, groups of participants from each study broken down by their comorbidities were analyzed when there was also a control group.

Brazil was the country in which the highest number of studies was conducted (29 studies), followed by Iran (6 studies) and the USA (4 studies). The results for year of publication revealed a very wide date range (1984 to 2020). The

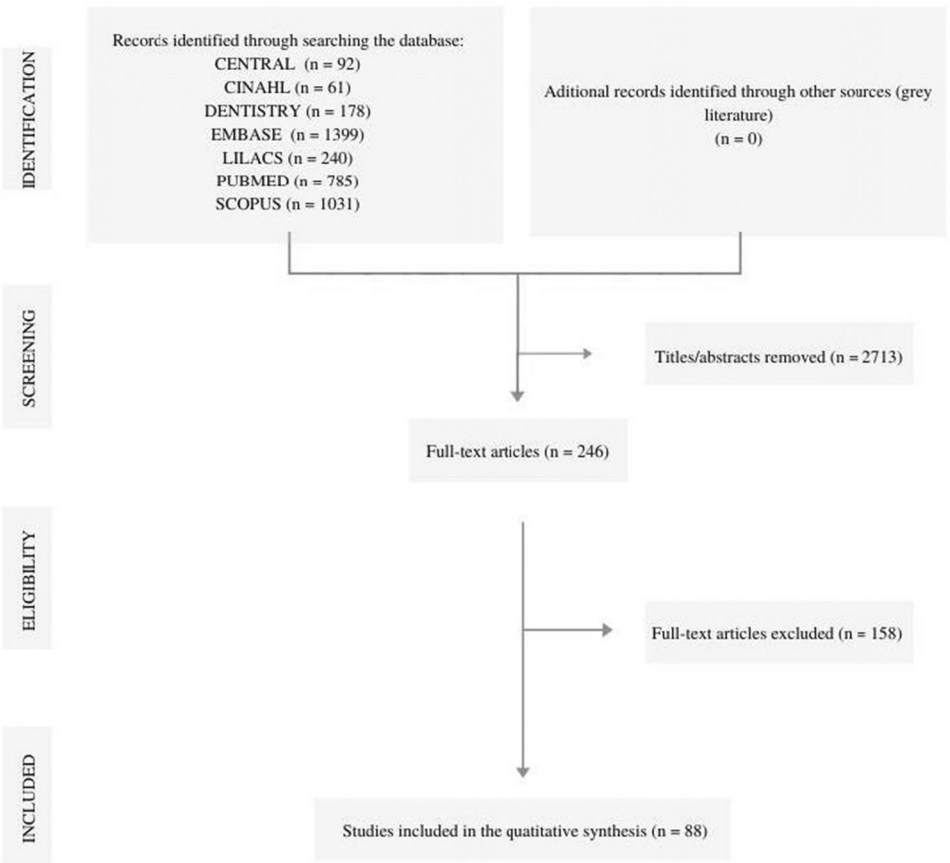

Fig. 2 PRISMA diagram illustrating the search strategy employed to identify studies related to resistance to antifungals of *C. albicans* isolated from the oral cavities of humans

year in which the largest number of studies was published was 2018 (10 studies).

Data extracted from the studies enabled analysis of 27 groups of samples from patients without systemic comorbidities and 90 groups of samples from patients with associated systemic comorbidities. It is important to point out that a given study may have been counted more than once if it analyzed a control group and a group with comorbidities or administered different treatments to different groups.

The antifungals tested appeared in the following order of frequency: fluconazole (101 groups of samples), amphotericin B (56 groups of samples), ketoconazole (38 groups of samples), voriconazol (24 groups of samples), flucytosine (18 groups of samples), nystatin (17 groups of samples), miconazole (12 groups of samples), clotrimazole (10 groups of samples), caspofungin (7 groups of samples), posaconazole (5 groups of samples), econazole (4 groups of samples), anidulafungin (3 groups of samples), micafungin (3 groups of samples), terbinafine (2 groups of samples), luliconazole (1 group of samples), and lanoconazole (1 group of samples). Combinations of the following drugs were also analyzed: miconazole and itraconazole (2 groups of samples); fluconazole and itraconazole (1 group of samples); and miconazole, itraconazole, ketoconazole, and fluconazole (1 group of samples).

The most frequently applied tests of antifungal susceptibility used in isolation were as follows: microdilution or macrodilution tests, 76; E-tests®, 15; and disk diffusion tests, 14. Two studies employed more than one analytical method, but separately, i.e., certain antifungals were tested with one method and others with another. Studies that employed more than one test of susceptibility for the same strains and did not observe agreement/report agreement between results were excluded. Some alternative tests were also used, such as Sensititre YeastOne and FungiTest (1 study each).

Table 1 lists overall rates of *Candida albicans* resistance to the antifungals studied. In general, there was a high degree of heterogeneity (illustrated by I^2). The lowest rates of resistance observed in the analysis of the antifungals tested, regardless of presence of systemic conditions, were for amphotericin B, followed by nystatin, flucytosine, and caspofungin. In contrast, the highest rates of resistance were observed for miconazole and econazole.

Table 2 lists rates of *Candida albicans* resistance to antifungals, by presence or absence of systemic comorbidities. Once more, there is a high level of heterogeneity (illustrated by I^2) in these analyses.

In the "HIV" group, the lowest rates of resistance were observed for amphotericin b, caspofungin, and nystatin, followed by ketoconazole. The highest rates of resistance in the same group were for itraconazole and fluconazole. In the "diabetes" group, the antifungal with lowest resistance was flucytosine and the highest resistance was to itraconazole. In the "head and neck cancer" group, the lowest resistance was found for amphotericin B and the highest resistance was to fluconazole. In the group "cancer, multiple sites," the lowest rates of resistance were observed to amphotericin b, nystatin, and caspofungin, and the highest resistance was observed to econazole and miconazole. Only 3 antifungals

Table 1 Rates of *C. albicans* resistance to the antifungals tested

Antifungal	*N* studies	*N*	*n*	Resistance	I^2	τ^2	*p*
NIS	17	670	36	0.16% [0.00; 5.81]	0%	13.6136	0.99
ECO	4	112	37	28.56% [7.39; 66.72]	85%	2.3739	< 0.01
MCZ	12	436	33	3.26% [0.57; 16.68]	74%	6.3333	< 0.01
FLZ	101	5539	385	2.10% [1.09; 3.98]	77%	8.7842	< 0.01
KTZ	38	1840	124	2.75% [1.14; 6.48]	72%	4.6009	< 0.01
CLO	10	182	20	2.20% [0.16; 23.17]	6%	7.9144	0.38
5-FLU	18	793	27	0.45% [0.05; 4.04]	48%	5.9107	0.01
ANF B	56	2660	143	0.00% [0; 0.04]	42%	134.7723	< 0.01
VCZ	24	1575	47	1.10% [0.29; 4.12]	60%	5.4426	< 0.01
PSZ	5	293	5	1.71% [0.71; 4.03]	0%	0	1.00
CASP	7	505	20	0.47% [0.01; 13.47]	47%	5.8724	0.08
ANI	3	124	2	1.11% [0.07; 16.20]	0%	1.4631	1.00
TER	2	93	21	2.99% [0; 100.00]	0%	56.5406	1.00
MICA	3	81	1	1.23% [0.17; 8.24]	0%	0	1.00
MCZ + ITZ	2	60	4	2.89% [0.05; 65.47]	0%	4.7963	1.00

NIS, nystatin; *ECO*, econazole; *MCZ*, miconazole; *FLZ*, fluconazole; *KTZ*, ketoconazole; *CLO*, clotrimazole; *5-FLU*, flucytosine; *ANF B*, amphotericin B; *VCZ*, voriconazole; *PSZ*, posoconazole; *CASP*, caspofungin; *ANI*, anidulafungin; *TER*, terbinafine; *MICA*, micafungin; *MCZ + ITZ*, miconazole and itraconazole

N Studies, number of studies; *N*, number of fungal strains tested for antifungal susceptibility; *n*, number of resistant fungal strains tested

Table 2 Rates of *C. albicans* resistance observed, by systemic comorbidities

Comorbidity	Antifungal	*N* studies	*N*	*n*	Resistance	I^2	τ^2	*p*
HIV/AIDS	ANF B	20	1223	11	0.00% [0.00; 85.15]	0%	180.6217	1.00
	CASP	2	85	0	0.00% [0.00; 100.00]	0%	0	1.00
	CLO	5	74	6	2.52% [0.10; 39.96]	51%	5.2927	0.08
	5-FLU	5	101	12	4.63% [0.52; 31.04]	35%	3.5848	0.19
	FLZ	46	3306	261	4.73% [2.39; 9.14]	84%	4.4997	< 0.01
	ITZ	24	1784	182	5.81% [2.25; 14.19]	90%	4.9123	< 0.01
	KTZ	15	866	39	1.01% [0.15; 6.39]	41%	6.0092	0.05
	MCZ	3	156	7	3.48% [0.08; 62.30]	90%	8.0815	< 0.01
	NIS	5	98	0	0.00% [0; 100.00]	0%	0	1.00
	VCZ	7	718	27	1.73% [0.11; 22.75]	84%	9.9744	< 0.01
Diabetes	ANF B	5	222	47	9.24% [0.03; 96.83]	91%	33.1888	< 0.01
	5-FLU	2	68	0	0.00% [0; 100.00]	0%	0	1.00
	FLZ	6	257	47	1.77% [0.01; 78.47]	87%	28.8675	< 0.01
	ITZ	2	140	32	27.77% [2.04; 87.65]	98%	4.2468	< 0.01
	KTZ	4	208	26	10.69% [2.98; 31.82]	91%	1.6104	< 0.01
	VCZ	2	140	7	1.30% [0.01; 76.08]	0%	9.6590	1.00
Head/neck cancer	ANF B	2	46	0	0.00% [0; 100.00]	0%	0	1.00
	FLZ	5	138	15	7.13% [1,78; 24.57]	58%	1.3716	0.05
	ITZ	3	69	4	4.64% [0.54; 30.49]	0%	0.3034	1.00
	KTZ	2	28	0	0.00% [0; 100.00]	0%	0	1.00
Cancer (different body sites)	ANF B	7	436	29	0.00% [0; 100.00]	0%	81.0583	1.00
	CASP	2	282	20	7.54% [2.50; 20.58]	91%	0.5780	< 0.01
	CLO	3	72	0	0.00% [0; 100.00]	0%	0	1.00
	ECO	3	72	36	48.52 [28.84; 68.66]	74%	0.3686	0.02
	5-FLU	4	272	2	0.74% [0.18; 289]	0%	0	1.00
	FLZ	6	474	23	2.73% [0.63; 11.09]	71%	2.0630	< 0.01
	ITZ	4	377	17	2.46% [0.31; 16.74]	87%	3.2100	< 0.01
	KTZ	3	304	32	7.87% [0.72; 50.03]	94%	4.3457	< 0.01
	MCZ	3	72	16	14.94% [2.50; 54.61]	0%	1.8996	0.56
	NIS	5	321	0	0.00% [0; 100.00]	0%	0	1.00
Organ transplantation	ANF B	2	56	0	0.00% [0; 100.00]	0%	0	1.00
	FLZ	2	56	4	7.14% [2.71; 17.54]	0%	0	0.94
	MICA	2	56	0	0.00% [0; 100.00]	0%	0	1.00
Kidney disorders	ANF B	2	39	0	0.00% [0; 100.00]	0%	0	1.00
	FLZ	3	40	0	0.00% [0; 100.00]	0%	0	1.00
	ITZ	2	11	1	0.00% [0; 99.93]	0%	19,740.5627	1.00
	VCZ	2	30	0	0.00% [0; 100.00]	0%	0	1.00
Candidemia	FLZ	2	84	0	0.00% [0; 100.00]	0%	0	1.00
	VCZ	2	84	1	1.19% [0.17; 7.97]	0%	0	1.00
Several comorbidities	FLZ	2	175	7	66.12% [0.01; 100.00]	0%	33.2995	1.00
	ITZ	2	175	12	71.34% [0.12; 99.98]	0%	20.2927	1.00
	KTZ	3	201	17	34.13% [1.40; 94.97]	0%	7.9121	0.48
No systemic comorbidities related	ANF B	15	555	36	0.02% [0.00; 94.49]	60%	22.0512	< 0.01
	5-FLU	7	213	0	0.00% [0; 100.00]	0%	0	1.00
	FLZ	27	937	22	0.50% [0.00; 1.86]	67%	0.0189	< 0.01
	ITZ	14	517	28	2.39% [0.39; 13.29]	30%	6.8277	0.13
	KTZ	10	223	10	2.67% [0.68; 9.91]	33%	1.7015	0.15
	MCZ	3	135	3	2.22% [0.72; 6.66]	0%	0	0.87
	NIS	4	155	19	2.47% [0.14; 32.07]	0%	4.3668	0.82
	PZS	3	151	2	1.32% [0.33; 5.14]	0%	0	1.00
	sMCZ + ITZ	2	60	4	2.89% [0.05; 65.47]	0%	4.7963	1.00

NIS, nystatin; *ECO*, econazole; *MCZ*, miconazole; *FLZ*, fluconazole; *KTZ*, ketoconazole; *CLO*, clotrimazole; *5-FLU*, flucytosine; *ANF B*, amphotericin B; *VCZ*, voriconazole; *PSZ*, posoconazole; *CASP*, caspofungin; *ANI*, anidulafungin; *TER*, terbinafine; *MICA*, micafungin; *MCZ + ITZ*, miconazole and itraconazole

Table 2 (continued)

N studies, number of studies; *N*, number of fungal strains tested for antifungal susceptibility; *n*, number of resistant fungal strains tested

were tested for the "organ transplantation" group. Resistance to amphotericin B and micafungin was lowest and resistance to fluconazole was highest. In the "kidney disorders" group, there was no resistance reported to any of antifungals tested (amphotericin b, fluconazole, itraconazole, and voriconazol). In the "candidemia" group, no resistance to fluconazole was detected but there were strains resistant to voriconazol. In the "several comorbidities" group, high rates of resistance were observed to all of the antifungals tested: ketoconazole, fluconazole, and itraconazole exhibited ascending rates of resistance in that order. Finally, rates of resistance were low in the "no systemic comorbidities reported" group, with the lowest rates observed for amphotericin b, flucytosine, and fluconazole and the highest rates for ketoconazole and a combination of miconazole with itraconazole.

Figures illustrating the meta-analyses for all of the antifungals studied and for all of the associated comorbidities are presented in full as part of the supplementary material to this article.

Discussion

Treatment of oral candidiasis requires consideration of predisposing factors, the severity of clinical status, and the patient's systemic complications, in addition to requiring pharmacological knowledge about available antifungals in order to define the type of treatment to be adopted, whether topical or systemic [4]. It is necessary to isolate strains from patients and monitor their profile of susceptibility to the antifungal agents available and compile these results by conducting systematic reviews and meta-analyses. The objective of the present study was to determine rates of *Candida albicans* resistance reported by observational studies that isolated these microorganisms from the oral cavities of humans and tested their susceptibility to antifungal agents using laboratory methods. The study also considered the presence of systemic conditions that could modulate this outcome. Topical and systemic treatments were not differentiated, to ensure the clarity of the resistance results.

In view of the volume of data retrieved from the literature by the original search strategy, it was decided to assess the susceptibility of the species *Candida albicans* only, rather than all *Candida* species, as had been proposed in the original protocol registered on the PROSPERO database. Different *Candida* species exhibit varying degrees of susceptibility to the antifungal agents most commonly administered in clinical practice. For example, while *C. krusei* is intrinsically resistant to fluconazole, *C. glabrata* exhibits reduced dose-dependent susceptibility compared with other species of *Candida* [14]. Moreover, *Candida albicans* accounts for the majority of isolates from samples from oral cavity infections. In 2016, Hertel et al. collected 958 samples from patients, in which *C. albicans* was the most prevalent species, accounting for 76.8% of isolates [15]. Wright and colleagues corroborate this statement. *Candida albicans* was clearly and significantly the microorganism with greatest colonization density when compared to the other species isolated in the study (which included: *C. glabrata*, *C. samata*, *C. parapilosis*, *C. krusei*, and *C tropicalis*, among others) [16]. In 2017, Lewis and Williams also confirmed that *C. albicans* is the pathogen most frequently isolated from human oral cavity specimens, present in 80% of samples and the most often identified in both health and disease [17]. The results of the searches for sources related to *C. albicans* conducted for the present study returned a total of 2713 studies for preliminary analysis (title/abstract), which confirms the relevance of studying *C. albicans* resistance profile. Although it is indispensable to extend research to other species of *Candida*, the volume of data produced could make interpretation difficult since many different species of the genus *Candida* can be found in the oral cavity and would be tested against the many different antifungals (19 in total, including combinations of antifungals) in patients with/without associated comorbidities (11 in total). Future studies will therefore be conducted to analyze these data.

The microdilution method is considered the gold standard for assessing fungal susceptibility [18]. In the present systematic review, there was no standardization of the methods used to assess susceptibility. The studies analyzed used microdilution or macrodilution, E-test®, disk diffusion, Sensititre YeastOne, and FungiTest, in addition to comparing tests against each other. In 2002, Silva et al. compared the broth macrodilution and E-test® methods by determining the minimum inhibitory concentrations (MICs) of four antifungal agents for 59 clinical isolates from the oral cavities of patients with AIDS and an initial diagnosis of candidiasis [19]. These authors observed agreement between methods for *C. albicans*, in contrast with other species assessed in the study, for which agreement was lower, such as itraconazole for *C. krusei* (66.7%) and fluconazole, ketoconazole, and amphotericin B for *C. tropicalis* (75%) [19]. The E-test® has been suggested as an alternative to the broth dilution method established by the Clinical and Laboratory Standards Institute (CLSI) because of its greater practicality. In 1995, Wanger et al. confirmed that the E-test® is equivalent to the method proposed by the CLSI for testing the susceptibility of

yeasts and has superior capacity for detecting resistance to amphotericin B [20]. In 2012, Junior et al. compared the disk diffusion method with the method proposed by the CLSI and observed that agreement between the methodologies exceeded 97%, albeit with a limited number of strains. These authors argue that the disk diffusion method can be employed within the laboratory routine, because it is inexpensive and is easier to conduct than macrodilution and microdilution tests, although it does not provide individual MIC values for each strain [21]. Cutoff points for *Candida albicans* have not been defined for the antifungals miconazole and ketoconazole, so studies assessing these drugs base their results on cutoff points adopted in epidemiological studies. Therefore, since this review included studies that employed different methods of susceptibility analysis, the outcome was defined as the numeric relative frequency of resistance as reported by the researchers, and crude MIC data for each antifungal agent were not employed.

Certain aspects that limited extraction of data for the systematic review and their inclusion in the subsequent meta-analysis should be considered. Silva et al. (2002) compared the E-test® and broth macrodilution methods to test the susceptibility of oral *C. albicans* isolates to a range of antifungals [19]. Only the results for resistance to itraconazole achieved agreement between the results of both tests and were included in the meta-analysis. The results for fluconazole were different for the same strains when different tests were used and were therefore excluded. The data on resistance to amphotericin B and ketoconazole were not presented clearly, introducing doubt and were also excluded. Kostiala and Kostiala (1984) investigated resistance of *C. albicans* isolated from the oral cavity to the antifungals amphotericin b, nystatin, clotrimazole, ketoconazole, miconazole, and econazole using broth microdilution [22]. They also conducted susceptibility tests for the same isolate to flucytosine using microdilution and disk diffusion. Since it was impossible to ascertain whether the results were duplicated, it was decided to exclude the data for this agent from the meta-analysis.

The quality of the studies included was not evaluated because there is no validated instrument for assessing the quality of observational studies that considers the specific aspects involved in studies with clinical and laboratory components, specifically those related to microbiology. According to the STROBE document's recommendations on how to correctly report observational studies, it is important to calculate the sample size and report it in the methodology [23]. Unfortunately, these data were not reported in the majority of the articles included since the analyses were based on laboratory results. STROBE also recommends that the characteristics of participants should be described (demographic, clinical, and/or social variables). This item was also omitted in many of the studies included in the systematic review and meta-analysis. Several studies merely stated that the samples were from the oral cavities of humans, without specifying any participant characteristics.

Oral candidiasis is related to impaired host immunity, and it is known that *C. albicans*, which is a fungal species that is highly abundant in the oral cavity, is the most frequently related to oral candidiasis, which was the reason justifying the exclusion of other species. In a literature review published in 2020, Bhattacharya et al. discussed the molecular mechanisms of action of a number of antifungals and the mechanisms of resistance of *Candida*. With relation to the antifungals studied, these authors listed two important drug classes used to treat candidiasis: azoles and polyenes. Azoles are more frequently administered to treat *Candida* infections. They target the enzyme 14α-demethylase (Erg11p), which is important in biosynthesis of ergosterol, the principal sterol component in fungal cell membranes. Polyenes also target ergosterol in the plasmatic membrane and are fungicides. These authors explain that resistance to azoles is an emerging problem that causes therapeutic failure and is the result of several different mechanisms, such as overexpression membrane transporters, altered ergosterol biosynthesis, altered sterol import, genome plasticity, and altered azole import. They also comment on resistance to other drugs [24].

In 2019, Prasad et al. also described other mechanisms of *C. albicans* resistance which, they argue, are new survival strategies developed by the microorganism and are being discovered over recent years. In their literature review, they report that these microorganisms evolved to respond to a range of environmental stresses (thermal, oxidative, osmotic, changes to pH, and nutrient limitations) [25]. The frequency with which they acquire resistance varies according to the class of antifungal. For example, in 2013, Vincent et al. reported that resistance to polyenes is extremely rare because of the consequences for fitness associated with development of resistance [26]. In contrast, in 2005, Anderson claimed that resistance to azoles is much more prevalent because of their fungistatic nature, which results in powerful selection of surviving populations [27]. In the analysis ignoring systemic conditions conducted in the present study, amphotericin B and nystatin exhibited the lowest rates of resistance. This result confirms the position of Vincent et al. since both drugs are polyenes. In turn, the highest rates of resistance were for agents in the azoles class (econazole and miconazole), which agrees with Anderson. However, the fact that there were high rates of resistance to econazole does not have major clinical implications, since this drug is not often used to treat oral candidiasis, rather it is prescribed for dermatological disorders [28]. In contrast, miconazole is often administered for topical treatment of oral candidiasis [3]. In 2012, Vasquez and Sobel pointed out that this drug

had been used to treat superficial fungal infections safely and effectively for approximately 40 years [29].

Considering the antifungals tested, it is important to point out that flucytosine is not used in any of the oral candidiasis treatment protocols, which means that the data related to its resistance profile are irrelevant to clinical applications. Besides that, the results of the present study showed that amphotericin B was the antifungal with the lowest rates of in vitro resistance to oral isolates of *Candida albicans*. The first-choice route of amphotericin B administration is intravenous. Amphotericin B is almost entirely insoluble in water and has a high molecular weight. These characteristics result in low gastrointestinal permeability and stomach instability, contributing to its low bioavailability when orally administered [30, 31]. It has a broad spectrum of action and good activity against *Candida* species, although a few non-albicans *Candida* samples may be resistant [32]. The adverse effects of intravenously administered amphotericin B are vascular, respiratory, thoracic, mediastinal, renal, and urinary disorders [33]. Xiao et al. (2022) evaluated the effectiveness of topical application of antifungals commonly used in treating oral candidiasis in a systematic review and meta-analysis. Among the studies included, the topical formulations of amphotericin B analyzed comprised oral suspension (0.5 g, three times a day, for 14 days) and lozenges (10 mg, four times a day, for 30 days). Fluconazole and amphotericin B demonstrated similar results in clinical response, mycological cure, the incidence of adverse reactions, and relapse rates. The authors also indicated that the results might be influenced by the reduced number of studies included, the differences in patient age, the dosage, the course, and the frequency of drug administration [34]. Drew and Perfect emphasized that published data regarding the administration of antifungals by alternative routes are scarce and restricted to uncontrolled case reports or studies with small sample sizes [35]. Fitchenbaum et al. reported that in a group of patients with HIV infection or CDC-defined AIDS, amphotericin B oral suspension had limited efficacy for treating fluconazole-refractory oral candidiasis. Despite the low in vitro resistance rates in *Candida albicans* oral isolates, amphotericin B would not be the first choice to treat oral candidiasis, especially through alternative routes [36].

Regardless of the drug class employed to treat candidiasis, knowledge of the mechanisms of resistance to antifungals and understanding them as an evolving problem is a prerequisite for dealing with resistance and accelerating development of new therapeutic strategies [37]. The present study also calculated rates of resistance by subsets, which has not been described in the literature previously. These subsets were formed based on studies' reporting of systemic conditions affecting the patients from whom their samples were isolated. The literature suggests that oral candidiasis is associated with use of removable dentures, based on a series of factors, such as poor hygiene, advanced age, polypharmacy, and impaired host immunity [38, 39]. This is not a systemic factor but a local one. Data related to use of removable dentures were collected and compiled in tables but were not treated as inclusion or exclusion criteria. The decision was taken to limit the bibliographic review to studies that collected samples from the oral cavity, excluding those that had tested isolates from removable dentures. There is a possibility that *C. albicans* could undergo phenotypical changes due to nutritional limitations and especially due to formation of biofilms [40, 41]. Moreover, cleaning dentures with a toothbrush has been shown to be effective for reducing palate inflammation, preventing and reducing infection by *Candida* [42].

With regard to the systemic factors, Samaranayake et al. discovered that the association of oral candidiasis with AIDS is reported before the first manifestations of AIDS in the patient [43]. In 2014, Garcia-Cuesta et al. listed the following systemic predisposing factors: hormonal disorders, immunological disorders, endocrine disorders, psychological disorders, xerostomia, drug treatments, and alcohol consumption [44]. Thompson et al. also report that oral candidiasis is one of the most common clinical complications in patients with HIV and can be observed in up to 90% of patients with this systemic condition [45].

In 2019, Quindós et al. reported that colonization by *Candida* occurs from birth and is greater at extreme ages (babies, children, and the elderly). Among adults, colonization is facilitated by use of removable dentures, on which difficult to eradicate biofilms form, or by the presence of oral changes such as xerostomia, leukoplakia, and oral lichen. They also confirmed that colonization is greater among patients who are given certain medications, such as antibiotics, corticoids, or chemotherapy, or in diabetic patients, hospitalized patients, and people infected by HIV [4].

Systemic conditions are directly linked to the proliferation of *Candida* and the development of candidiasis. This occurs because *Candida* is an opportunistic microorganism [2]. In the present study, a series of different comorbidities were analyzed. The subset that exhibited the highest rates of resistance was the subset with several associated comorbidities. In contrast, resistance rates were low in the group with "no systemic comorbidities reported." Among the other subsets, the one with the highest rate of resistance was "cancer, multiple sites," with resistance to econazole. It was not possible to perform exact comparisons between comorbidities because there was no standardization between the antifungals assessed in the different studies. Therefore, the presence of concomitant systemic comorbidities appears to be an important factor to take into consideration when assessing resistance to antifungals in patients.

Conclusion

This systematic review has shown that the majority of the drugs available is effective for treatment of oral lesions caused by *C. albicans*. It suggests that nystatin may be the topical treatment of choice if systemic comorbidities can be ruled out since it was the antifungal with the lowest rates of resistance. For cases of disseminated candidiasis and/or in patients in whom topical treatment has been ineffective, amphotericin B would be the recommended antifungal to be used via intravenous routes. Presence of concomitant systemic comorbidities appears to be an important factor that should be considered when evaluating resistance to antifungals. The subset that exhibited the highest rates of resistance, regardless of the antifungal tested, comprised people with a range of different health issues. In these cases, combinations of antifungals should be considered. The resistance assessment test most used in previous studies was microdilution (the gold standard), confirming its importance at the laboratory level. Compilation and analysis of published data by meta-analysis enables healthcare professionals to choose medications based on robust scientific evidence. Regardless, it is the responsibility of the prescribing professional to assess each case individually. The recommendations on drug selection suggested in this paper are based entirely on microbiological aspects and do not consider other important individual aspects that must be taken into account when taking prescribing decisions.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00784-022-04716-2.

Author contribution F. M., and S. Q. S. K. contributed to study conception. S. Q. S. K. and P. M. L. performed the literature search. S. Q. S. K., P. M. L., T. S. D. P., and F. M. conducted data analysis. All the authors drafted and critically revised the work. All authors read and approved the final manuscript.

Declarations

Ethical approval Not required.

Competing interests The authors declare no competing interests.

References

1. Terézhalmy GT, Huber MA (2011) Oropharyngeal candidiasis: etiology, epidemiology, clinical manifestations, diagnosis, and treatment. Pract Periodontics Aesthet Dent 9(6):635–641; quiz 642
2. Mayor AM, Gómez MA, Ríos-Olivares E, Hunter-Mellado RF (2008) AIDS defining neoplasms prevalence in a cohort of HIV infected patients, before and after highly active antiretroviral therapy. Ethn Dis 18:S2–189–94
3. Zhang L-W, Fu J-Y, Hua H, Yan Z-M (2016) Efficacy and safety of miconazole for oral candidiasis: a systematic review and meta-analysis. Oral Dis 22:185–195. https://doi.org/10.1111/odi.12380
4. Quindós G, Gil-Alonso S, Marcos-Arias C et al (2019) Therapeutic tools for oral candidiasis: current and new antifungal drugs. Med Oral Patol Oral Cir Bucal 24:e172–e180. https://doi.org/10.4317/medoral.22978
5. Pappas PG et al (2016) Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis 62(4):e1-50. https://doi.org/10.1093/cid/civ933
6. Fang J, Huang B, Ding Z (2021) Efficacy of antifungal drugs in the treatment of oral candidiasis: a Bayesian network meta-analysis. J Prosthet Dent 125:257–265. https://doi.org/10.1016/j.prosdent.2019.12.025
7. Tobudic S, Kratzer C, Presterl E (2012) Azole-resistant Candida spp. – emerging pathogens? Mycoses 55:24–32. https://doi.org/10.1111/j.1439-0507.2011.02146.x
8. Fuentefria AM, Pippi B, Lana DFD et al (2018) Antifungals discovery: an insight into new strategies to combat antifungal resistance. Lett Appl Microbiol 66:2–13. https://doi.org/10.1111/lam.12820
9. White PL, Dhillon R, Cordey A et al (2020) A national strategy to diagnose COVID-19 associated invasive fungal disease in the ICU. Clin Infect Dis 73(7):e1634–e1644. https://doi.org/10.1093/cid/ciaa1298
10. Arastehfar A, Daneshnia F, Farahyar S et al (2019) Incidence and spectrum of yeast species isolated from the oral cavity of Iranian patients suffering from hematological malignancies. J Oral Microbiol 11:1601061. https://doi.org/10.1080/20002297.2019.1601061
11. Page MJ, McKenzie JE, Bossuyt PM, et al (2021) The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ n71. https://doi.org/10.1136/bmj.n71
12. Landis JR, Koch GG (1977) The measurement of observer agreement for categorical data. Biometrics 33:159–174
13. Schwarzer G, Chemaitelly H, Abu-Raddad LJ, Rücker G (2019) Seriously misleading results using inverse of Freeman-Tukey double arcsine transformation in meta-analysis of single proportions. Res Synth Methods 10:476–483. https://doi.org/10.1002/jrsm.1348
14. Playford EG, Marriott D, Nguyen Q et al (2008) Candidemia in nonneutropenic critically ill patients: risk factors for non-albicans Candida spp. Crit Care Med 36:2034–2039. https://doi.org/10.1097/CCM.0b013e3181760f42
15. Hertel M, Schmidt-Westhausen AM, Strietzel F-P (2016) Local, systemic, demographic, and health-related factors influencing pathogenic yeast spectrum and antifungal drug administration frequency in oral candidiasis: a retrospective study. Clin Oral Investig 20:1477–1486. https://doi.org/10.1007/s00784-015-1631-0
16. Wright PS, Clark P, Hardie JM (1985) The prevalence and significance of yeasts in persons wearing complete dentures with soft-lining materials. J Dent Res 64:122–125. https://doi.org/10.1177/00220345850640020501
17. Lewis MaO, Williams DW (2017) Diagnosis and management of oral candidosis. Br Dent J 223:675–681. https://doi.org/10.1038/sj.bdj.2017.886
18. de Demitto FO, do Amaral RCR, Biasi RP et al (2012) Suscetibilidade a antifúngicos in vitro de Candida spp. em pacientes do Hospital Universitário Regional de Maringá-PR. J Bras Patol E Med Lab 48:315–322. https://doi.org/10.1590/S1676-24442012000500003
19. do Silva MRR, Costa MR, Miranda ATB et al (2002) Evaluation of Etest and macrodilution broth method for antifungal susceptibility testing of Candida sp strains isolated from oral cavities of AIDS patients. Rev Inst Med Trop São Paulo 44:121–125. https://doi.org/10.1590/S0036-46652002000300002

20. Wanger A, Mills K, Nelson PW, Rex JH (1995) Comparison of Etest and National Committee for Clinical Laboratory Standards broth macrodilution method for antifungal susceptibility testing: enhanced ability to detect amphotericin B-resistant Candida isolates. Antimicrob Agents Chemother 39:2520–2522
21. de Júnior AA, V, Menezes EA, Cunha FA, et al (2012) Comparação entre microdiluição e disco difusão para o teste de susceptibilidade aos antifúngicos contra Candida spp. Semina Ciênc Biológicas E Saúde 33:135–142. https://doi.org/10.5433/1679-0367.2012v33n1p135
22. Kostiala AA, Kostiala I (1984) Susceptibility of fungi in mouthrinse specimens from patients with haematological malignancies. J Med Microbiol 18(2):249–254. https://doi.org/10.1099/00222615-18-2-249
23. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP (2008) STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol 61(4):344–349. https://doi.org/10.1016/j.jclinepi.2007.11.008
24. Bhattacharya S, Sae-Tia S, Fries BC (2020) Candidiasis and mechanisms of antifungal resistance. Antibiotics 9:312. https://doi.org/10.3390/antibiotics9060312
25. Prasad R, Nair R, Banerjee A (2019) Emerging mechanisms of drug resistance in Candida albicans. Prog Mol Subcell Biol 58:135–153. https://doi.org/10.1007/978-3-030-13035-0_6
26. Vincent BM, Lancaster AK, Scherz-Shouval R et al (2013) Fitness trade-offs restrict the evolution of resistance to amphotericin B. PLOS Biol 11:e1001692. https://doi.org/10.1371/journal.pbio.1001692
27. Anderson JB (2005) Evolution of antifungal-drug resistance: mechanisms and pathogen fitness. Nat Rev Microbiol 3:547–556. https://doi.org/10.1038/nrmicro1179
28. Firooz A, Nafisi S, Maibach HI (2015) Novel drug delivery strategies for improving econazole antifungal action. Int J Pharm 495:599–607. https://doi.org/10.1016/j.ijpharm.2015.09.015
29. Vazquez JA, Sobel JD (2012) Miconazole mucoadhesive tablets: a novel delivery system. Clin Infect Dis Off Publ Infect Dis Soc Am 54:1480–1484. https://doi.org/10.1093/cid/cis205
30. McEvoy GK (2000) AHFS drug information 2000. American Society of Health-System Pharmacists, Bethesda, MD
31. Liu M, Chen M, Yang Z (2017) Design of amphotericin B oral formulation for antifungal therapy. Drug Deliv 24:1–9. https://doi.org/10.1080/10717544.2016.1225852
32. Gallis HA, Drew RH, Pickard WW (1990) Amphotericin B: 30 years of clinical experience. Rev Infect Dis 12:308–329. https://doi.org/10.1093/clinids/12.2.308
33. Yang Y-L, Xiang Z-J, Yang J-H et al (2021) Adverse effects associated with currently commonly used antifungal agents: a network meta-analysis and systematic review. Front Pharmacol 12:697330. https://doi.org/10.3389/fphar.2021.697330
34. Xiao Y, Yuan P, Sun Y et al (2022) Comparison of topical antifungal agents for oral candidiasis treatment: a systematic review and meta-analysis. Oral Surg Oral Med Oral Pathol Oral Radiol 133:282–291. https://doi.org/10.1016/j.oooo.2021.10.023
35. Drew RH, Perfect JR (2022) Conventional antifungals for invasive infections delivered by unconventional methods; aerosols, irrigants, directed injections and impregnated cement. J Fungi Basel Switz 8:212. https://doi.org/10.3390/jof8020212
36. Fichtenbaum CJ, Zackin R, Rajicic N et al (2000) Amphotericin B oral suspension for fluconazole-refractory oral candidiasis in persons with HIV infection. Adult AIDS Clinical Trials Group Study Team 295. AIDS Lond Engl 14:845–852. https://doi.org/10.1097/00002030-200005050-00011
37. Robbins N, Caplan T, Cowen LE (2017) Molecular evolution of antifungal drug resistance. Annu Rev Microbiol 71:753–775. https://doi.org/10.1146/annurev-micro-030117-020345
38. Moskona D, Kaplan I (1992) Oral lesions in elderly denture wearers. Clin Prev Dent 14:11–14
39. Girard B, Landry RG, Giasson L (1996) Denture stomatitis: etiology and clinical considerations. J Can Dent Assoc 62:808–812
40. Chandra J, Mukherjee PK, Leidich SD et al (2001) Antifungal resistance of candidal biofilms formed on denture acrylic in vitro. J Dent Res 80:903–908. https://doi.org/10.1177/00220345010800031101
41. Baillie GS, Douglas LJ (1998) Effect of growth rate on resistance of Candida albicans biofilms to antifungal agents. Antimicrob Agents Chemother 42:1900–1905. https://doi.org/10.1128/AAC.42.8.1900
42. de Souza RF, Khiyani MF, Chaves CAL et al (2017) Improving practice guidelines for the treatment of denture-related erythematous stomatitis: a study protocol for a randomized controlled trial. Trials 18(1):211. https://doi.org/10.1186/s13063-017-1947-y
43. Samaranayake LP, Holmstrup P (1989) Oral candidiasis and human immunodeficiency virus infection. J Oral Pathol Med Off Publ Int Assoc Oral Pathol Am Acad Oral Pathol 18:554–564. https://doi.org/10.1111/j.1600-0714.1989.tb01552.x
44. Garcia-Cuesta C, Sarrion-Pérez M-G, Bagán JV (2014) Current treatment of oral candidiasis: a literature review. J Clin Exp Dent 6:e576-582. https://doi.org/10.4317/jced.51798
45. Thompson GR, Patel PK, Kirkpatrick WR et al (2010) Oropharyngeal candidiasis in the era of antiretroviral therapy. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 109:488–495. https://doi.org/10.1016/j.tripleo.2009.11.026