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A Comprehensive Meta-Analysis of Antifungal Resistance in *Candida albicans* in Turkey

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Abstract

Aim of the study: The frequency of antifungal resistance continues to increase, complicating patient management despite the introduction of new antifungal agents. Candida albicans is a pathogenic species that is most commonly isolated from patients with fungal infections. *Material and Methods*: In this meta-analysis, we evaluated the trends in C. albicans antifungal resistance over the past 15 years. The study was planned and conducted in accordance with the declaration of PRISMA and involved a literature search, determination of inclusion criteria for, and evaluation of articles, data collection and statistical analysis. Appropriate articles were searched for in Google Scholar, Science Direct, PubMed, and Web of Science. The data obtained from the literature were assessed according to inclusion and/or exclusion criteria. Following application of appropriate criteria, a meta-analysis of 23 studies published between 2000 and 2015 was performed. *Results*: The highest rate of resistance was determined against antifungals of the triazole group. The highest mean rates of resistance to itraconazole, voriconazole and econazole were 23.2±33.1%, 14.6±26.3% and 12.7±11.6% respectively. Among the triazole antifungals, the rate of resistance to fluconazole was found low with 9.6±17.8%. No resistance to caspofungin was detected. We found no report regarding susceptibility or resistance to imidazole derivatives in Turkey published in the last 10 years. Therefore, our comments about imidazole derivatives refer only to 2000 to 2005. The mean rates of resistance to antifungals differed significantly both with time and geographically. The highest mean rate of antifungal resistance was detected between 2011 and 2015. Eastern Anatolia showed a higher mean rate of resistance to antifungals compared to Western Anatolia and Central Anatolia. Using a random-effects model, the event rates of resistance to amphotericin B, nystatin, itraconazole, fluconazole, voriconazole, econazole, miconazole, and ketoconazole were 1.6%, 8.5%, 16.8%, 5.9%, 8.8%, 10.2%, 7.2%, and 4.1%respectively. The event rates for resistance to flucytosine and caspofungin were calculated using a fixed-effects model because their I2 values were <50. The event rates for resistance to flucytosine and caspofungin were determined as 0.9% and 0.6%, respectively. *Conclusion*: To our knowledge, this study is the first meta-analysis of the resistance to antifungal agents of clinical *C. albicans* isolates. This study could enhance our knowledge of the antifungal resistance of *C. albicans* but its renovation will continue in the future. Further research about *C. albicans* should be planned in detail, and focused on antifungal resistance, the quality of life of immune-suppressed patients, and treatment costs.

1. Introduction

The incidence of Candida infections has increased recently due, at least in part, to the increasing number of patients receiving chemotherapy and other immunosuppressive therapies, developments in transplantation surgery, the use of broad-spectrum antibiotics, and the increase in the number of patients staying in intensive care units and undergoing invasive procedures [1]. Although *Candida albicans* is still the primary cause of these infections, the frequency of non-*albicans* species has been increasing in parallel with the widespread use of azole-derived drugs [2].

A rise in fungal infections has caused a greater use of antifungal drugs leading to the emergence of resistant strains. When these facts are taken into consideration, appropriate drug selection, evaluation of their clinical outcomes, determination of resistance rates and investigation of new drugs are of considerable significance [3]. The distribution of Candida species and their susceptibility to antifungal agents may vary depending on the use of antifungal agents and the strategies used to control the resulting infections [4]. Further, these infections are severe, fast-paced, difficult to diagnose and treat, and cause serious morbidity and mortality [4].

When analysed in terms of infection frequency, Candida species are the fourth-leading cause of nosocomial bloodstream infections in the United States and Europe [5]. In addition, *C. albicans* has been reported as the second most common cause of hospital-acquired urinary tract infections in intensive care units (ICU) in National Nosocomial Infection Surveillance (NNIS) reports [6].

The gradual increase in infections associated with fungal pathogens and the difficulties of treatment brought about by resistant isolates have increasingly caught the attention of researchers to this field. However, our knowledge about the antifungal resistance rates of *C. albicans* isolates causing infections in Turkey is very limited. In addition, there is no consensus about the use of antifungal drugs like antibiotics. This situation has a negative impact on the development of resistance in *C. albicans* isolates. Here, we performed a meta-analysis of all studies that discuss sensitivity and/or resistance to antifungal drugs of *C. albicans* isolated from various clinical samples between 2000 and 2015, aiming to develop knowledge associated with antifungal resistance in Turkey.

2. Materials and Methods

The study was planned and conducted in accordance with the declaration of PRISMA and involved a literature search determination of inclusion criteria for and evaluation of articles data collection and statistical analysis [7]. *C. albicans* isolates identified as the causative agent of several clinical samples in Turkey were studied and antifungal resistance or susceptibility was meticulously assessed.

2.1. Data Search

The studies to be used for the meta-analysis were identified using Google Scholar, Science Direct, PubMed and Web of Science electronic databases using the keywords "*Candida albicans*, antifungal susceptibility, Turkey", "*Candida albicans*, antifungal resistance, Turkey", "*Candida albicans*, antifungal direnç, Türkiye", "*Candida albicans*, antifungal duyarlılık, Türkiye".

2.2. Determining Acceptance and Rejection Criteria

For the determination and elimination of scientific publications used for the meta-analysis, some conformity criteria were searched. Title and summary parts of the scientific publications analysed were examined in detail for conformity by researchers. Studies deemed unsuitable according to the conformity criteria were removed from the examination (Figure 1).

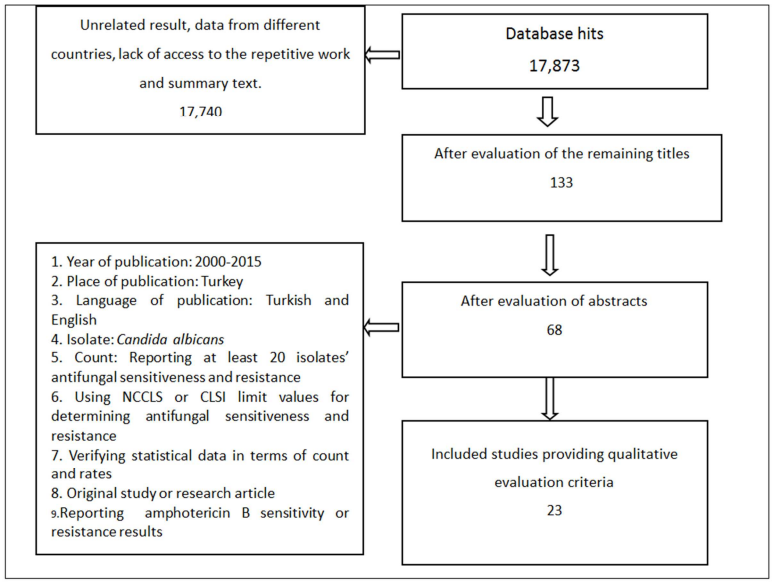

Figure 1. *Flow chart used in selecting the studies included in the meta-analysis.*

2.3. Literature Review and Data Collection

Two independent researchers performed the meta-analysis and evaluated their compliance. In accordance with the principle of objectivity publications from authors or institutions that are involved in this publication were not included. The studies that were included in the meta-analysis were graded qualitatively and quantitatively according to the following criteria: specimen type (urine and blood:2, clinical samples:1), number of specimens (above 100: 3, between 50-100: 2, below 50: 1), scope (multi-centre:3, regional: 2, single centre: 1), typology (automatic: 2, conventional: 1), determination of antifungal activity (MIK value: 3, automatic: 2, others:1), working time (≥2 years: 2, 1 year: 1).

All numerical data and data regarding sensitivity and resistance were controlled. Antifungal resistance rates were re-calculated as numerical data, and converted to a common unit (n and % resistance). Using the studies' results, the sensitivity rates (n and %resistance) were re-calculated and all values were converted to a common unit. Reviewing the collected data the following therapies were used to treat infections: amphotericin B (AMB), nystatin (N), miconazole (MIC), econazole (ECO), ketoconazole (KET), fluconazole (FLU), itraconazole (ITR), voriconazole (VOR), caspofungin (CAS), flucytosine (FLS).

2.4. Statistical Analysis

A Comprehensive Meta-Analysis (CMA) (Biostat, ABD) was performed using the program "Forest Plot" (FP). The studies were assessed using the Cochran Q test to consider the random effect; An $I^2 \geq 50$ threshold was considered to indicate homogeneity. During the study period the status of the *C. albicans* isolates was measured with MedCalc 12.3.0 (Mariakerke, Belgium) by one-way ANOVA. In the calculations, a value of $p \leq 0.05$ was considered significantly different.

3. Results

In total, 23 academic studies were considered to meet the criteria; 10 were published between 2000 and 2005, 3 between 2006 and 2010, and 10 between 2011 and 2015. These publications investigated the antifungal susceptibility of *C. albicans* isolated in Turkey. In the quantitative/qualitative assessments performed within the proposed criteria framework, the scientific studies included were given an average score of 9.69±1.63 (minimum 7, maximum 12).

From the included studies the average resistance rates calculated for AMB, FLU, VOR and ITR, whose limit values are stated in CLSI and/or EUCAST guidelines, were 2.5±5.8%, 9.6±17.8%, 14.6±26.3% and 23.2±33.1%, respectively. No resistance to CAS was reported. Average resistance rates calculated for EKO, KET, MIK, FLS and N were 12.7±11.6%, 11.8±10.0%, 8.6±9.5, 0.7±1.3% and 12.4±18.6%, respectively (For these molecules there was not any information in CLSI and/or EUCAST guidelines) [8].

When the change in *C. albicans* resistance to antifungal drugs was examined over time, the highest resistance rates, calculated during the period 2000-2005, were 30.9±13.1%, 25.4%±5.9 and 24.8±9.6% for N, AMB and KET respectively. When the findings reported in the studies published during the period 2006-2010 were combined, the highest resistance rates were for FLU and VOR and were calculated as 1.8±1% and 1.80±1%, respectively; however, these data were from one study. The studies performed in the same period also reported that all isolates were sensitive to AMB, ITR and FLS. In the studies conducted between 2011 and 2015, resistance rates were 80.4±41.6%, 66.3±28.6% and 58.9±22.9% for ITR, VOR and FLU, respectively. The highest increase in resistance rates within the specified periods were determined to be between 2011 and 2015 for ITR, VOR and FLU. Other data are summarized in Table 1.

Table 1. *Distribution of antifungal resistance during the time period studied (%± standard deviation).*

	Antifungals	2000-2005	2006-2010	2011-2015	Total	P
CLSI and or EUCAST reference method with the boundary values determined resistance they found.	AMB	2.5±8.0	0	3.2±1.6	2.5±5.8	<0.05
	FLU	8.0±8.4	1.2±1.1	12.8±22.9	9.6±17.8	<0.05
	VOR	-	2.8±0	15.9±28.7	14.6±26.3	<0.05
	ITR	10.1±9.0	0	44.7±41.5	23.2±33.1	<0.05
CLSI and or EUCAST reference method with no set limit values for resistance.	CAS	-	0	-	0	-
	ECO	12.7±11.6	-	-	12.7±11.6	-
	KET	11.8±9.9	-	-	11.8±9.9	-
	MIC	8.6± 9.5	-	-	8.6± 9.5	-
	FC	0.6±0.9	0	1.0±1.7	0.7±1.3	<0.05
	N	6.7±12.0	-	46.4±0	12.4±18.6	<0.05

References: [2, 4, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29].

In the regional assessments, 11 studies were from Central Anatolia, 9 were from Western Anatolia and 3 were from Eastern Anatolia. The resistance rate of ITR, one of the antifungal drugs in the triazole group, in Eastern Anatolia was significantly different from those in both Western Anatolia and Central Anatolia. Similarly, highly significant differences were seen among the VOR resistance rates. High resistance rates were determined in Western Anatolia for EKO, an imidazole, and the lowest resistance rate was determined for FLS in the same region. The highest resistance rate in Central Anatolia was determined for KET, and the lowest resistance rate was determined for FLS. Notably, the lowest resistance rate in all regions was against FLS. The rate of change in antifungal resistance according to

the studies analysed is summarized in Table 2.

Table 2. *Distribution of antifungal resistance according to regions in the analysed studies (% mean± standard deviation).*

	Antifungals	Western Anatolia	Central Anatolia	Eastern Anatolia	Total	P
CLSI and or EUCAST reference method with the boundary values determined resistance they found.	AMB	3.17±8.48	1.82±4.43	2.04±2.18	2.51±5.85	>0.05
	FLU	4.11±4.97	2.71±5.72	38.49±30.65	9.60±17.82	<0.05
	VOR	-	2.65±3.38	44.12±38.21	14.56±26.30	<0.001
	ITR	10.26±6.92	4.36±8.73	80.39±0.05	23.22±33.14	<0.001
	CAS	-	0	-	0	
CLSI and or EUCAST reference method with no set limit values for resistance	ECO	14.74±12.75	7.32±10.35	-	12.72±11.56	>0.05
	KET	11.64±9.32	11.98±12.44	-	11.77±9.96	>0.05
	MIC	8.13±9.46	9.55±13.51	-	8.60±9.52	>0.05
	FC	0.61±1	0.71±1.34	2.04±2.06	0.72±1.32	>0.05
	N	9.05±16.33	1.91±2.70	46.42±0	12.35±18.58	<0.05

References: [2, 4, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29].

In the FP analyses, probable resistance rates of *C. albicans* strains causing infections in Turkey for AMB, FLU, VOR and ITR within the framework of CLSI and/or EUCAST according to the random effects model (I^2>50) were calculated as 1.6%, 5.9%, 8.8% and 16.8% respectively. Since its I^2 values were <50, the probable resistance calculated for CAS according to the random effects model was observed to be 0.6%.

According to the random effects model (I^2>50), the probable resistance rates for EKO, KET, MIK, and N, which are not included in CLSI and/or EUCAST guidelines, were calculated to be 10.2%, 10.4%, 7.2% and 8.5%, respectively. Possible resistance to FC, calculated using the fixed effects model, was observed to be 0.9%.

Table 3. *Possible resistance rates of infection-causing C. albicans isolates for antifungal drugs analysed according to fixed and random effects models.*

95% Confidence Interval								
			Resistance rate (%)	Lower limit (%)	Upper limit (%)	Q	I^2	P
CLSI and or EUCAST reference method with the boundary values determined resistance they found.	AMB	Fixed effects	0.5	0.3	0.8	104.3	78.9	<0.01
		Random effects	1.6	0.6	3.1			
	FLU	Fixed effects	3.5	2.8	4.4	329.9	94.9	<0.01
		Random effects	5.9	1.8	12.2			
	VOR	Fixed effects	13.6	10.8	16.9	281.8	96.8	<0.01
		Random effects	8.8	0.3	27.2			
	ITR	Fixed effects	6.6	5.0	7.3	529.5	98.5	<0.01
		Random effects	16.8	2.9	39.7			
	CAS	Fixed effects	0.6	0.01	4.1	0.1	0.9	0.91
		Random effects	0.6	0.01	2.7			
	ECO	Fixed effects	11.9	9.0	15.4	44.7	88.8	<0.01
		Random effects	10.2	3.1	20.8			
CLSI and or EUCAST reference method with no set limit values for resistance	KET	Fixed effects	12.9	10.3	16.1	58.1	87.9	<0.01
		Random effects	10.4	4.1	18.9			
	MIC	Fixed effects	9.8	7.1	12.9	44.2	88.9	<0.01
		Random effects	7.2	1.5	16.5			
	FC	Fixed effects	0.9	0.4	1.8	10.7	1.8	0.70
		Random effects	0.9	0.4	1.7			
	N	Fixed effects	7.8	5.6	10.6	97.1	93.8	<0.01
		Random effects	8.5	1.2	21.4			

References: [2, 4, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29].

4. Discussion

Invasive fungal infections are a common, costly problem with high morbidity and mortality rates [30]. Immunosuppressive therapies increase the number of patients at risk for fungal infections. *C. albicans* in the gastrointestinal tract are responsible for 90-100% of fungal infections of the mucous membrane and in 50-70% of candidemias [31]. Therefore, monitoring of antifungal resistance and factors of *C. albicans* will determine whether new antifungal drug should be used in the clinic.

AMB, the oldest of the polyene group drugs, is the approved standard drug for the treatment of invasive fungal infections and has a broad-spectrum antifungal activity [32]. In international studies *C. albicans* are usually reported to be sensitive to AMB [33]. In this study the average resistance to AMB was found to be 2.51±5.85%. However, the highest rate of resistance to AMB was reported by Erdemoglu [28] et al. in Istanbul in 2000 as 25.5%. Acting upon the knowledge that *C. albicans* can resist antifungal drugs through mechanisms such as reduced ergosterol, altered localization of polyene-binding sterols, and masking of ergosterol [34], it is inevitable that the rate of resistance will increase if AMB is used often. Therefore, resistance should continue to be monitored.

Nystatin, another antifungal of the polyene group, is used

as a prophylactic in immunodeficiency, chemotherapy and transplant patients [35]. Resistance for N has been reported in recent years often attributed to changes in the POL gene family and the efflux pump [36, 37]. The rates for N resistance in international studies are between 0% and 4% [38]. In the studies performed in Turkey, N resistance has been reported within the range of 0% to 46.4%. The average N resistance for Turkey was shown to be 12.4±18.6% in calculations that incorporated all available data. This resistance, which is quite high compared to the literature, increased mostly in Eastern Anatolia; the source or cause of this resistance should be investigated. In addition, N resistance has significantly increase over the years ($p < 0.05$).

Triazoles are antifungals that act by inhibiting the synthesis of ergosterol, the building block of the fungal cell membrane. Triazole drugs, which are usually effective and tolerable, especially FLU, ITR and VOR, are widely used in the treatment of *Candida* infections [39]. In particular, FLU has a broad spectrum similar to AMB [40]. *C. albicans* is the *Candida* species most sensitive to FLU [41]. Reports of resistance to FLU between 0 and 3.2% have been published in international studies [42, 43]. In this study, the average resistance rate for FLU was calculated as 12.8±22.9%, which is quite high. Similarly, a high rate of resistance 23.2±33.1% for ITR was calculated. VOR resistance has been reported between 0 and 0.4% in international studies [40, 41]. In this study, the average VOR resistance was calculated as 14.6±26.3%. The high rates of resistance to triazoles calculated in this study are mostly due to isolates in Eastern Anatolia. The resistance rates of this region to FLU, ITR and VOR were found to be 38.5±30.7%, 80.4±0.1% and 44.1±38.0%, respectively (Table 2). The cause of this resistance should be determined quickly since the triazole resistance in Eastern Anatolia will soon be a common problem in other regions as people migrate.

Imidazoles, which are azole derivatives also inhibit the synthesis of ergosterol [20]. No reports of resistance or sensitivity to the imidazole derivatives EKO, MIK and KET, were found in the national and international literature search over the last 10 years. In this study, resistance rates for EKO, MIK and KET between 2000 and 2005 were calculated to be 12.7±11.6%, 8.6±9.5% and 11.8±9.9% respectively.

The mechanism for resistance for *C. albicans* to FLS relates to the loss of permease and the activity of cytosine deaminase and uracil phosphoribosyl transferase [34]. When used alone, the development of resistance is frequent. Therefore, guidelines recommend that FLS be used in combination with AMB [44]. In the meta-analysis the data from Iris et al. [45] and Hazirolan et al. [29] reported the highest FLS resistance at 6.3%. The determined average FLS resistance, 0.7±1.3% ($p < 0.05$), changed significantly over the time period studied.

No resistance to CAS, an echinocandin derivative with an antifungal effect on the cell wall components β-1-6 glucan and β-1-4 glucan was found in this search, in agreement with international and national literature.

Evaluating these 23 studies by region shows that resistance rates, especially those of N, ITR, FLU, VOR and FLS, in Eastern Anatolia are remarkably high. This may have originated from the methods used. However, in order to clarify the issue, it is necessary to verify the antifungal resistance states of the strains for which resistance was determined in Eastern Anatolia through minimal inhibitory concentration (MIC) tests and to clarify the molecular basis of the resistance, as the resistant strains in question may threaten all regions as migration rates increase.

5. Conclusion

In conclusion, the antifungal resistances of *C. albicans* strains in Turkey were studied using meta-analysis for the first time. The increases in resistance to numerous antifungals over the years and the differences between the regions in Turkey are remarkable. To help solve the problem, the antifungal resistance of *C. albicans* should be further monitored using verified resistance rates in accordance with CLSI and/or EUCAST along with clinic data and molecular epidemiological analyses of resistant strains.

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