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Molecular Epidemiology and Antifungal Resistance of *Candida* Species in Iraq: A Review of Available Evidence and a Critical Analysis of the Genomic Gap

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Abstract: *Candida* species have become increasingly resistant to antifungals, particularly azoles. Studies in Iraq are fragmented and limited, relying almost entirely on single-center studies despite the growing body of evidence on molecular epidemiology of these species. This study reviews the published literature regarding the distribution of *Candida* species, antifungal resistance patterns, and molecular and genomic characteristics, in addition to identifying key research gaps preventing the development of a comprehensive molecular epidemiological map at the national level. I searched scientific databases (PubMed and PMC repositories, as well as indexed Iraqi and regional journals) systematically. reports lacking systematic documentation were excluded. The most common strain in Iraqi clinical samples is C.*albicans, followed by C.glabrata and C.tropicalis*, to varying degrees, depending on geographical region and sample type. As of now, most molecular characterizations are based ITS sequencing, without extending to whole-genome techniques or identifying specific resistance genes (such as ERG11 and FKS1/2). No officially documented cases of *Candida auris* in Iraq. Iraqi literature reveals a clear genomic gap. Multicenter national surveillance studies, genetic analyses of resistance mechanisms, and an effective surveillance system for *C.auris* are lacking in the country. As an essential step to understand this increasingly important pathogen's true epidemiological dynamics, the review recommends the establishment of a national surveillance network for invasive fungal infections.

Keywords: *Candida*; Iraq, Antifungal Resistance, Fluconazole, Molecular Epidemiology, *Candida Auris*, ITS Sequencing, Genomic Analysis.

Research Paper

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1. INTRODUCTION

Candida species are normal parts of the human microbiome, but when the host's bacterial balance is disrupted, they can become dangerous pathogens. As a result, infections range from common superficial forms such as oral and vaginal candidiasis to life-threatening invasive ones such as candidiasis (blood candidiasis), which is associated with a high mortality rate among critically ill patients in intensive care units [1].

A global epidemiological shift has been occurring in recent decades, marked by the increasing prevalence of non-*albicans Candida* species (NACs) such as *Candida glabrata, Candida tropicalis*, *Candida parapsilosis*, and *Candida* krusei (Pichia kudriavzevii), as well as the emergence of multidrug-resistant *Candida auris*, which has been classified as an urgent fungal threat by the World Health Organization and the Centers for Disease Control and Prevention [1, 2]. Increasing use of prophylactic and therapeutic azoles, an increasing number of immunocompromised patients, and widespread catheter and invasive medical device use are contributing to this shift [2].

At the molecular level, the mechanism of azole resistance is largely attributed to point mutations in the

ERG11 gene, which encodes lanosterol 14α-demethylase, or to the over-expression of drug-releasing pumps such as CDR1, CDR2, and MDR1. A mutation in the FKS1 or FKS2 gene hotspots is associated with echinocandin resistance [1-9].

To understand the modern epidemiological dynamics of this pathogen, we need diagnostic tools that go beyond traditional phenotypic approaches to targeted gene sequencing or whole genome sequencing. The scientific picture in Iraq remains limited in scope and heterogeneous even though there is a growing body of literature (Iranian, Kuwaiti, Jordanian, Saudi, and Lebanese) on this topic [10-12]. Most available studies (Baghdad, Duhok, Sulaimaniyah, Kirkuk) are scattered across various university centers with small sample sizes and limited phenotypic or molecular identification methods (primarily ITS sequencing) without comprehensive genomic analyses of resistance mechanisms [13-16]. The goal of this review is to identify research priorities and systematically compile the available evidence in order to bridge the knowledge gap.

2. METHODOLOGY

2.1 Search Strategy

Following the PRISMA principles, I adopted a systematic review approach. To cover Iraqi and regional journals not fully indexed in international databases (such as the Iraqi Journal of Science, the Journal of Contemporary Medical Sciences, and Bionatura), search engines were used to supplement PubMed and PMC databases, as well as general scientific search engines. The compound search terms included: "*Candida*" AND "Iraq", "antifungal resistance" AND "Iraq", "molecular identification" AND "*Candida*" AND (city names: Baghdad, Basra, Mosul, Erbil, Dohuk, Sulaimaniyah, Najaf, Kirkuk, Karbala), as well as "*Candida auris*" AND "Middle East".

2.2 Inclusion and Exclusion Criteria

I included original studies (cross-sectional, retrospective, or quasi-experimental) of Iraqi clinical or environmental isolates, which were published in peer-reviewed journals and included documentation of phenotypic or molecular identification of species. We excluded news reports, incomplete conference abstracts, and studies without a clear geographic origin.

2.3 Data Extraction

Based on each included study, the following data was extracted: study location, type of sample and target patients, number of isolates, identification method (phenotypic or molecular), isolated species and their proportions, and results of antifungal susceptibility tests, where available. I also recorded any genetic data relating to resistance mechanisms or phylogenetic analysis.

3. RESULTS

3.1Geographical and Specific Distribution of *Candida* Isolates in Iraq

There are few Iraqi studies that are geographically distributed, with most being concentrated in Baghdad and the Kurdistan Region (Duhok and Sulaymaniyah), and the central and southern governorates are underrepresented. Among these studies, Table1 and 2 summarize the most prominent ones.

Table 1: This table summarizes their basic characteristics in terms of location, type, size, and identification method. Based on the inclusion criteria, seven studies were included

Geographical location	Publication year	Samples	Sample size(n)	Identification method	Reference
Baghdad	2023	Oral and vaginal	58 samples / 31 isolates	Phenotypic +VITEK 2	[15]
Duhok/Zakho	2020	Urine (women)	620 samples / 144 isolates	ITS1/ITS4 (Molecular)	[18]
Duhok	2025	Oral and nasal (COVID-19)	100 samples / 45 isolation	ITS+Phylogeny (Molecular)	[15]
Kalar (Sulaymaniyah)	2022	skin	40 samples / 8 isolates (NAC)	ITS-PCR/RFLP (Molecular)	[22]
Sulaymaniyah and Kirkuk	2023	Oral (children)	210 samples/ 75 isolation	ITS-PCR (Molecular)	[23]
Mosul	2020	Oral (children)	63 samples / 36 isolates	Phenotypic +VITEK 2	[24]
Karbala	2026	Oral	51 samples / 2 isolates WGS	ITS + Whole Genome Sequencing (WGS)	[25]

Table 2: The total number of samples tested and the number of positive samples were provided in five studies, totaling 951 samples across Iraq.

Study	n checked	n positive	Prevalence rate	95% confidence interval
Dohuk/Zakho (urine)	620	144	23.2٪	20.1٪ – 26.7٪
Sulaymaniyah/Kirkuk (sick children)	160	62	38.8٪	31.5٪ – 46.5٪
Sulaymaniyah and Kirkuk	50	13	26.0٪	15.9٪ – 39.6٪
Mosul (Oral Pediatrics)	63	36	57.1٪	44.9٪ – 68.6٪
Baghdad (oral/vaginal)	58	31	53.4٪	40.8٪ – 65.7٪
Total	951	286	30.1٪	27.2٪ – 33.1٪

3.2 Antifungal Resistance Patterns

Iraqi *Candida* isolates remain understudied compared to those in Iran and the Gulf States in terms of drug resistance. According to multicenter Iranian studies [16], *C.glabrata* isolates have a polyazole resistance rate of 24%, while C.albicans isolates have a resistance rate of 67% in some categories [1]. Kuwaiti studies have also found fluconazole resistance of 25% in Nakaseomyces glabratus (formerly *C.glabrata*) [10]. Currently, Iraqi literature does not contain studies of similar size and methodology to characterize resistance rates across the country.

According to Iraqi studies, fungal biofilms contribute significantly to reduced antifungal sensitivity. A high level of biofilms has been observed in vaginal isolates of *C.albicans, followed by C.tropicalis, while C.parapsilosis* and *C.glabrata* were found in relatively lower quantities [17]. The observations were not supported by standardized quantitative sensitivity tests (such as MIC determinations according to CLSI or EUCAST protocols) on a national scale.

4. THE GENOMIC GAP: THE ABSENCE OF WHOLE-GENOME ANALYSIS

A major finding of this review is the wide gap between molecular epidemiology data, which are often limited to ITS sequencing for qualitative identification, and As part of genomic analysis, whole genome sequencing (WGS), single-nucleotide polymorphism (SNP) typing, multi-locus profiling (MLST), identifying specific mutations in resistance genes (ERG11, FKS1, FKS2, MRR1, TAC1, UPC2), and linking local lineages to global pedigrees stored in databases such as GenBank and NCBI are included.In addition, as far as we are aware, no whole genome sequences of Iraqi-sourced *Candida* isolates have been deposited in international databases dedicated to this purpose, unlike partial ITS sequences[15].

Table 3: Summarizes the most prominent research gaps identified in this audit and their implications

Research gap	Potential impact
Lack of national reference studies for multicenter candidemia isolates	Lack of knowledge of the true burden of invasive candidiasis at the national level
Studies on resistance (ERG11, FKS1/2, MRR1, TAC1) remain scarce.	Failure to identify the molecular mechanisms underlying azole therapy failure
The absence of full genotyping (WGS) for Iraqi isolates in global databases	It is impossible to link Iraqi lineages to global genealogies or to trace cluster transmission.
The lack of an effective surveillance system for *Candida auris* despite its spread in neighboring countries	The possibility of the strain entering undetected, with a delayed response when it appears.
The near-complete reliance on phenotypic methods in many laboratories	A documented misclassification rate of approximately 21-27% has been reported in some regional studies.

5. DISCUSSION

A general trend has been observed in the Iraqi literature that *C.albicans* remains the dominant species for superficial infections across the globe, but non-white (NAC) species like *C.glabrata and C.tropicalis* are gradually increasing, especially in the urine and respiratory samples of diabetics and immunocompromised patients [14-18]. While the sample sizes in Iraq are generally smaller, and coverage is less extensive, this trend is similar to that reported in Iran [19], Kuwait [10], and neighboring countries.

Comparing molecular characterization is more important than consistency of specificity distribution, however. Advances in regional studies have mostly remained in the early stages, whether through phenotypic methods or limited ITS sequencing, like the Iranian study involving ten hospitals that determined minimum

inhibitory concentrations (MIC90) for eight different antifungal agents [19], or the Lebanese study that used molecular profiling in combination with phylogenetic analysis [20]. The comparison thus represents a direct conflict of methodological depth between "molecular epidemiology" as it presently manifests in Iraqi literature and "molecular epidemiology" as it matures regionally.

In light of the fact that Iraq borders several countries that have reported *C.auris*, this lack of data is particularly significant: first, Iraq is geographically located near several countries that have reported this pathogen [11, 12], and In addition, Iraqi health systems have been under considerable strain for the past two decades because of population movements, a large number of critically ill patients, and widespread antibiotic and antifungal use – all known risk factors for the spread and emergence of *C.auris* throughout the world [2-11]. There is no conclusive evidence that the pathogen does not exist merely because there are no reliable, documented reports. The finding should be interpreted cautiously with respect to methodological implications and should not be regarded as a passive admission of fact, but rather as a reflection of the current diagnostic limitations, not a reflection of a confirmed epidemiological reality.

Especially noteworthy from a methodological viewpoint is the misclassification rate of the documented phenotype in the Duhok study [15], which indicates there may be some inaccuracies in qualitative classification of Iraqi epidemiological data whose classification has traditionally relied on typological methods (chromatic agar medium, conventional biochemical tests), highlighting the importance of generalizing molecular confirmation as a minimum standard in all future research and justifying a careful reevaluation of some historical findings.

RECOMMENDATIONS FOR FUTURE RESEARCH AND PRACTICE

- Implement standardized susceptibility testing protocols based on CLSI or EUCAST criteria in Baghdad and the provinces to conduct a nationwide surveillance study for invasive candidiasis (candidiasis).
- Research studies and reference clinical laboratories should make molecular confirmation (at least ITS sequencing) mandatory for phenotypic identification, given the documented rate of misclassification.
- For phenotypically resistant isolates, invest in targeted gene sequencing technologies (ERG11, FKS1/2, MRR1, TAC1) to identify molecular mechanisms.
- Create a national capacity to sequence whole genomes (WGS), or establish regional and international collaborations for the submission of epidemiologically significant isolates to advanced genomic analysis and for the deposit of the results in a global open database.
- Develop a national protocol for active surveillance of *Candida auris*, including reference laboratories capable of accurately distinguishing this species (e.g. MALDI-TOF systems calibrated for this species or specific PCR), in addition to a mandatory reporting system similar to those implemented in neighboring countries.
- Promote collaboration among Iraqi universities to standardize methodologies and maximize the statistical power of results, overriding the limitations of current studies conducted by single institutions.

6. CONCLUSION

According to this review, there is a lack of in-depth genomic characterization of *Candida* species in Iraq, despite a gradual increase in recent years. Iraq's species distribution patterns correspond to general regional and global trends, but molecular studies that link resistance patterns to their precise genetic basis or place local strains within a global evolutionary context are still behind the current generation of studies.

Considering that *Candida* otosclerosis is on the rise in Iraq, the lack of documented reports on this disease highlights the urgency of investing in national diagnostic and surveillance capabilities. In this review, the main demand remains a national infrastructure for molecular epidemiology and genomics, which will enable Iraq to move from monitoring "which" *Candida* species infects its patients to understanding "how" and "why" resistance develops, which will ultimately benefit public health as well as clinical decision-making.

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ERG11 و*CDR1*, *CDR2*, *MDR1*

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