Diagnostic Microbiology & Infectious Disease 113 (2025) 117005

Contents lists available at ScienceDirect

Diagnostic Microbiology & Infectious Disease

journal homepage: www.elsevier.com/locate/diagmicrobio

Candida tropicalis in the diabetic urinary tract: Biofilm resistance, genomic plasticity, and public health implications

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ARTICLE INFO

Keywords:
Candida tropicalis
Fungal urinary tract infection
Biofilm resistance
Azole resistance
Diabetes mellitus
Glycosuria
South Asia

ABSTRACT

Fungal urinary tract infections (fUTIs) are emerging as a public health concern, notably in South Asia, where a convergence of ecological, genetic, and clinical factors underlies a rising burden of antifungal-resistant disease. This review synthesizes epidemiological, mechanistic, and genetic evidence implicating Candida tropicalis as a dominant uropathogen in South Asia's diabetic and immunocompromised populations. We examine the shift from Candida albicans to non-albicans Candida (NAC) species, driven by selective antifungal pressure and nosocomial transmission. Emphasis is placed on the virulence and adaptability of C. tropicalis, which forms biofilms, adapts metabolically under glycosuric and hypoxic conditions, and expresses antifungal resistance genes such as ERG11, CDR1, MDR1, and FKS1. Concurrently, South Asian host populations exhibit genetic variants—e.g., in TLR4, CLEC7A, CYP2C19—that impair fungal recognition, immune clearance, and antifungal pharmacokinetics, creating a syndemic landscape. We detail biofilm-mediated resistance mechanisms, epigenetic regulation of virulence genes, and the role of environmental sensing pathways in adaptive pathogenesis. Furthermore, the review delineates clinical challenges posed by biofilm-associated infections, delayed diagnostics, and resistance underestimation. Finally, we propose a suite of public health and clinical recommendations—including biofilm-specific diagnostics, antifungal stewardship programs, pharmacogenomic screening, and national surveillance—to mitigate the escalating burden of drug-resistant candiduria. This integrative perspective bridges molecular pathogenesis and systems-level responses, offering a strategic roadmap for clinicians and policymakers to address C. tropicalis-driven fUTIs in South Asia and other high-risk regions.

1. Introduction

Fungal urinary tract infections (fUTIs) are an increasingly recognized global health concern in hospitalized, elderly, and immunocompromised populations. Once considered rare opportunistic events, fUTIs are now among common nosocomial fungal infections, fueled by increased use of invasive medical devices, broad-spectrum antibiotics, and systemic immunosuppression. While Candida albicans has traditionally been the predominant etiologic agent, recent epidemiological trends reveal a marked shift toward non-albicans Candida (NAC) species—most notably Candida tropicalis, Candida glabrata, and the multidrug-resistant Candida auris—introducing new diagnostic and therapeutic complexities [1]. This shift toward NAC species has become notably prominent in South Asia. And this can be closely linked to the country's escalating diabetes epidemic.

Recent data estimates over 11 % of South Asia's adult population—over 101 million individuals—are living with diabetes mellitus, a figure projected to rise to 134 million by 2045 [2]. This growing burden is especially concentrated and regional surveillance studies have reported fUTI prevalence exceeding 20 % in tertiary and critical care settings [3]. Beyond uncontrolled diabetes, several factors drive this regional vulnerability: widespread and often unregulated antimicrobial usage, limited access to second-line antifungals, and a rising prevalence of catheter-associated infections, among others. The intersection of diabetes, catheterization, and immunosuppression—especially in the context of poor infection control infrastructure—creates a syndemic environment that facilitates fungal colonization, immune evasion, biofilm formation, and therapeutic failure [4]. Glycosuria in diabetic patients provides a nutrient-rich microenvironment conducive to fungal persistence, while immunological defects impair the clearance of fungal pathogens from the urinary tract. The frequent use of fluconazole (Diflucan) in empiric therapy further

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https://doi.org/10.1016/j.diagmicrobio.2025.117005
Received 13 June 2025; Received in revised form 8 July 2025; Accepted 10 July 2025
Available online 11 July 2025

selects for azole-resistant species in NAC strains, restricting standard treatment protocols [5]. In South Asia, *C. tropicalis* is emerging as a leading cause of candiduria and candidemia [6].

The purpose of this review is to synthesize current knowledge on the epidemiological trends, mechanistic underpinnings, and clinical and public health implications of fUTIs, with a specific emphasis on C. tropicalis in high-risk populations. To ensure clarity and consistency, this paper primarily focuses on adults with diabetes mellitus, given their high susceptibility to complicated or recurrent fUTIs and the significant clinical implications of delayed or inadequate diagnosis in this population. However, the discussion also considers other high-risk groups—namely (1) immunocompromised individuals, (2) pediatric patients with recurrent UTIs, and (3) individuals with congenital anomalies of the kidney and urinary tract—to acknowledge overlapping diagnostic challenges and shared pathophysiological vulnerabilities. Including these populations broadens the clinical relevance of the analysis while maintaining a primary emphasis on the diabetic cohort. And special attention is given to South Asia, where the interplay of genetic, metabolic, and healthcare-associated factors has shaped a distinct epidemiological profile. This integrative perspective aims to provide a practical basis for clinicians, microbiologists, and public health practitioners seeking to enhance diagnostic precision, optimize therapeutic outcomes, and advance antimicrobial stewardship in clinical mycology.

2. Epidemiological trends and regional vulnerability

2.1. Emerging pathogen dynamics and regional trends

Over the past two decades, fUTIs have exhibited a notable epidemiological shift, marked by a decline in C. albicans dominance and a rising prevalence of NAC species. Although *C. albicans* remains the most commonly isolated species in community-acquired infections, recent data highlight a notable epidemiological shift in hospital settings. That is, *C. tropicalis, C. glabrata*, and the multidrug-resistant *C. auris*—have emerged as major etiological agents of nosocomial fUTIs and candidemia, often associated with outbreaks in ICUs and hematology units [7, 8]. The selective pressure exerted by widespread azole use has favored the proliferation of NAC species, many of which exhibit intrinsic or acquired resistance to azole-class antifungals. And among the emerging species, C. tropicalis has garnered clinical attention due to its increasing prevalence in nosocomial settings and its aggressive pathogenic profile.

This is because *C. tropicalis* exhibits robust virulence traits, including high biofilm-forming capacity and strong adherence to uroepithelial and intravascular surfaces—features that enhance its persistence in catheterized and immunocompromised patients [9]. Furthermore, this species harbors a range of antifungal resistance mechanisms, including mutations in the *ERG11* gene, which reduce azole binding affinity, and upregulation of efflux transporters, such as *MDR1* and *CDR1*, that actively extrude azole compounds from the fungal cell [10]. Notably, *C. tropicalis* demonstrates a high propensity for resistance acquisition during treatment, likely driven by cumulative exposure to antifungals in hospital environments and its adaptive genomic plasticity. And unlike *C. glabrata*, which relies on intrinsic fluconazole (Diflucan) resistance due to reduced *ERG11* affinity, and *C. auris*, known for its extreme multidrug resistance and clonal ICU outbreaks, *C. tropicalis* presents a unique challenge: its rapid adaptation to antifungal exposure in settings with limited diagnostic precision. This has led to increased rates of treatment failure, especially in resource-limited healthcare systems.

2.2. Regional genomic drivers of susceptibility: host and pathogen interactions in South Asia

2.2.1. Host genetic and immunological susceptibility

South Asia's heightened burden of fUTIs is deeply rooted in host-level immunogenetic susceptibility, notably among diabetic and immunocompromised individuals. This vulnerability is influenced by a confluence of genetic polymorphisms that impair innate immune recognition and antifungal pharmacokinetics, creating a permissive environment for Candida colonization and persistence.

Polymorphisms in pattern recognition receptor (PRR) genes, such as *TLR2, TLR4*, and *CLEC7A* (encoding Dectin-1), have been implicated in attenuated fungal recognition and impaired immune signaling. For instance, the TLR4 Asp299Gly variant disrupts MyD88-dependent NF-κB activation, reducing cytokine release (e.g., IL-6, TNF-α) in response to fungal pathogen-associated molecular patterns (PAMPs) like β-glucans and mannans [11]. Similarly, the Dectin-1 Y238X nonsense mutation produces a truncated receptor with diminished capacity to activate the CARD9-NF-κB/MAPK axis, limiting secretion of IL-6, IL-17, and TNF-α, which are essential for mucosal antifungal responses [12–15]. These PRRs also guide neutrophil recruitment and epithelial clearance in the urinary tract—functions compromised in diabetic and catheterized individuals [16].

Adding to this genetic predisposition are pharmacogenomic variants common in South Asian populations. Polymorphisms in *CYP2C19, CYP3A4*, and *ABCB1* genes influence fluconazole (Diflucan) metabolism and efflux, leading to reduced systemic and urinary drug levels [5,20]. This creates subtherapeutic antifungal exposure that promotes selection of resistant C. tropicalis strains. For example, altered *CYP2C19* activity affects fluconazole (Diflucan) hydroxylation, while *ABCB1* encodes P-glycoprotein efflux pumps that reduce drug bioavailability. These variations contribute directly to antifungal treatment failure and resistance development.

Together, these host genetic and immunologic factors establish a biological context that facilitates persistent candiduria, particularly in high-prevalence regions such as South Asia. The next section addresses how C. tropicalis itself adapts to and exploits this compromised host landscape through epigenetic and genomic flexibility. Key host and pathogen-related genetic and epigenetic factors contributing to regional susceptibility in South Asia are summarized in Table 1.

2.2.2. Pathogen genomic and epigenetic adaptation

Candida tropicalis exhibits remarkable genomic plasticity and epigenetic adaptability that enhance its pathogenic potential in the immunocompromised or metabolically dysregulated host. These fungal adaptations are especially pronounced in South Asia, where environmental pressures such as glycosuria, catheterization, and chronic antifungal exposure shape pathogen evolution. Transcriptional profiling and epigenetic analyses reveal that C. tropicalis isolates from South Asian ICUs display unique promoter-level modifications that regulate virulence genes in response to host stressors. Histone acetylation and chromatin remodeling mechanisms upregulate key virulence and drug resistance genes, including *ALS3*, *HWP1*, *BCR1*, *CDR1*, and *MDR1* [16–18]. These modifications enhance fungal adhesion, biofilm formation, and drug efflux under hyperglycemic and hypoxic conditions—all of which are common in diabetic, catheterized patients.

Environmental sensing pathways also contribute to *C. tropicalis* adaptability. In *C. albicans,* hyperglycemia—particularly glycosuria—has been shown to stimulate increased expression of *CDR1* and *MDR1,* promoting resistance to azole antifungals [19]. While direct evidence in *C. tropicalis* is limited, similar resistance mechanisms may be conserved. Concurrently, metabolic stress induces phenotypic switching and structural cell wall changes that help evade host immune detection. And fungal genomic evolution under antifungal pressure is further evidenced by mutations in *ERG11* (reducing azole binding affinity) and FKS1 (modifying β-1,3-glucan synthase activity to confer echinocandin resistance) [16]. These mutations often emerge in clinical isolates following fluconazole (Diflucan) or echinocandin exposure and contribute to persistent, treatment-refractory infections. Accordingly, C. tropicalis in South Asia is not merely a passive colonizer but a dynamic pathogen that actively adapts to regional host-pathogen interactions. Its genomic and epigenetic flexibility, coupled with host immunogenetic susceptibility, creates a syndemic landscape that perpetuates

Table 1
Genetic and epigenetic drivers of regional susceptibility to fUTIs in South Asia.

Domain	Molecular Target / Gene	Mechanism	Effect on fUTI Susceptibility	Reference
Host innate immunity	*TLR2, TLR4*	Polymorphisms (e.g., *TLR4* Asp299Gly) reduce recognition of fungal PAMPs (e.g., β-glucans)	Impaired neutrophil recruitment and fungal clearance from uroepithelium	[21]
	CLEC7A (Dectin-1)	Y238X nonsense variant reduces β-glucan recognition	Deficient activation of Th17 responses, predisposing to fungal colonization	[22]
Host metabolic genetics	*TCF7L2, SLC2A2, PPARG*	SNPs linked to poor glycemic control and insulin resistance	Enhances glycosuria, which promotes *Candida* growth in urinary tract	[23]
Fungal epigenetics	*ALS3, HWP1, BCR1* promoters	Histone acetylation via Gcn5 and Set3C regulates biofilm genes under urinary stress	Facilitates robust biofilm formation and immune evasion in catheterized patients	[24]
	CDR1, MDR1 regulatory regions	Chromatin remodeling allows context-specific efflux pump upregulation	Promotes azole resistance under high fluconazole (Diflucan) exposure	[25]
Pharmacogenomics	*CYP2C19, CYP3A4, ABCB1*	High-frequency SNPs alter fluconazole (Diflucan) metabolism and efflux	Results in reduced urinary azole concentration, encouraging resistance	[5]
Fungal resistance evolution	*ERG11, FKS1* mutations (e.g., Y132F, S659P)	Acquired via selective pressure in high fluconazole (Diflucan)/echinocandin exposure settings	Results in persistent, treatment-refractory candiduria	[26]

drug-tolerant, biofilm-associated infections in high-risk populations.

2.3. Host immunological modifiers: South Asia's diabetic milieu

The escalating diabetes epidemic in South Asia plays a central role in shaping a microenvironment that favors Candida persistence, virulence, and therapeutic resistance [2]. The diabetic urinary tract constitutes an immunologically dysregulated and metabolically enriched niche that amplifies susceptibility to fungal colonization and infection [4].

At the molecular level, chronic hyperglycemia impairs innate immune recognition by inducing non-enzymatic glycation of pattern recognition receptors, particularly Toll-like receptors *TLR2* and *TLR4* [27]. These glycation-induced conformational changes reduce ligand-binding affinity for fungal PAMPs, including β-glucans and mannans, leading to attenuated MyD88–NF-κB signaling and diminished cytokine output [28]. Neutrophil function is similarly compromised; studies show that diabetic neutrophils exhibit defective chemotaxis, blunted respiratory burst, and impaired phagolysosomal fusion, all of which impair fungal clearance from mucosal surfaces [29,30].

C. tropicalis leverages this immune vulnerability through metabolically responsive virulence activation. Elevated extracellular glucose has been shown to transcriptionally upregulate adhesin genes (ALS1, ALS3) and secreted aspartyl proteases (SAP4–SAP6), enhancing mucosal adhesion, epithelial barrier disruption, and nutrient scavenging [30,31]. Concurrent glycosuric conditions furnish a persistently glucose-enriched microenvironment that scaffolds C. tropicalis biofilm development on abiotic substrates such as urinary catheters [32]. This metabolic niche fosters quorum-regulated coordination, augments extracellular matrix fortification, and establishes a protective architecture that buffers antifungal exposure—thereby enabling the chronicity and immunoevasive tenacity of the infection. At the level of mucosal immunity, the diabetic urothelium exhibits downregulation of antimicrobial peptides such as LL-37 and β-defensins, weakening epithelial integrity and innate barrier defenses [33,34]. In response, C. tropicalis upregulates molecular chaperones HSP70 and HSP90, which mitigate proteotoxic stress and modulate surface antigen presentation, further facilitating immune evasion and intracellular persistence [35].

Having established these regional immunometabolic vulnerabilities predisposing individuals to fungal infections, the subsequent section will explicate detailed molecular and cellular strategies employed by C. tropicalis to exploit these host conditions.

3. Mechanistic significance of *Candida tropicalis* in fUTIs

3.1. Biofilm formation and structural defense

A cornerstone of *C. tropicalis* virulence in fUTIs is its ability to form dense, structured biofilms on uroepithelial surfaces and indwelling medical devices such as urinary catheters [36]. These biofilms are central not only to the pathogen's ability to persist but also to its defense against host immune responses and antifungal therapeutics [37–39]. *C. tropicalis* biofilms are structurally sophisticated, characterized by a highly organized extracellular polymeric substance (EPS) matrix composed primarily of polysaccharides—β-1,3-glucans, β-1,6-glucans, mannoproteins—and extracellular DNA (eDNA) [40,41]. This EPS matrix acts as a physical barrier, limiting penetration and diffusion of immune effectors (e.g., neutrophils, macrophages, antimicrobial peptides) and antifungal agents, thereby enhancing fungal survival and persistence in the urinary tract [16,42]. Moreover, within the protected confines of the biofilm, *Candida* species have shown to undergo transcriptional reprogramming, facilitating adaptation and persistence under urinary stress conditions such as glycosuria, hypoxia, and nutrient limitation. For instance, upregulation of genes involved in mitochondrial respiration (e.g., *COX1, COX2*) has been documented under hypoxic conditions commonly observed in obstructed or poorly drained urinary environments [43,44]. This metabolic shift is vital, enabling fungal cells to sustain energy production and survive prolonged stress.

Biofilm formation in *C. tropicalis* proceeds through distinct developmental phases: initial adhesion, intermediate maturation, and late maturation. Initial adhesion is mediated by surface adhesins such as *ALS3* and *HWP1*, which facilitate attachment to uroepithelial and abiotic catheter surfaces [45,46]. Intermediate maturation involves extensive extracellular matrix deposition and cellular proliferation, largely regulated by biofilm transcriptional regulators such as *BCR1, TEC1*, and *EFG1*. These transcription factors coordinate gene expression related to matrix formation, adhesion, and environmental stress tolerance [47,48]. Finally, late maturation is marked by further structural complexity, antifungal resistance, and sustained immune evasion capabilities [48].

Critically, biofilm formation not only provides mechanical and biochemical defense but also serves as a reservoir for antifungal resistance development. Embedded cells in biofilms exhibit elevated expression of efflux pumps (*CDR1, CDR2, MDR1*), contributing to a multidrug resistance phenotype highly relevant to catheter-associated infections [45,49]. Additionally, biofilm-resident cells display significantly enhanced oxidative stress responses (e.g., *SOD2, GPX1, TRX1*) and cell-wall remodeling enzymes (e.g., *XOG1, ENG1*), protecting cells from immune-mediated oxidative damage and antifungal drug pressure [50]. Biofilm structural resilience and antifungal tolerance pose substantial clinical challenges. In catheterized patients and those with impaired mucosal immunity (e.g., diabetes mellitus), these robust biofilms often lead to chronic infections, recurrent candiduria, and increased treatment failure rates, necessitating catheter removal or prolonged therapeutic interventions [51]. So then, *C. tropicalis* biofilm formation is both a survival strategy and a sophisticated virulence mechanism under conditions prevalent in high-risk patient populations such as those commonly encountered in South Asia's diabetic milieu.

3.2. Metabolic adaptation and environmental persistence

To persistently colonize the challenging urinary environment—characterized by hypoxia, nutrient scarcity, and biofilm stress—C. tropicalis employs coordinated transcriptional and metabolic adaptations, enhancing survival in catheterized or diabetic conditions [52]. A prominent metabolic adaptation is the shift from fermentative metabolism toward mitochondrial respiration, a critical survival strategy under hypoxic stress. Notably, under reduced oxygen tension commonly encountered within biofilms, C. tropicalis upregulates mitochondrial respiratory chain genes, particularly those encoding cytochrome c oxidase subunits. Enhanced mitochondrial activity facilitates more efficient ATP generation even under oxygen-limited conditions, increasing cellular resilience against oxidative and metabolic stresses encountered within biofilms [43].

Additionally, C. tropicalis exhibits activation of the glyoxylate cycle under nutrient-limited conditions prevalent in urinary environments, especially when conventional carbon sources such as glucose become scarce. This pathway allows fungi to assimilate alternative carbon substrates such as acetate and fatty acids via key enzymes, including isocitrate lyase (ICL1) and malate synthase (MLS1), which bypass the decarboxylation steps of the tricarboxylic acid cycle. Consequently, this metabolic route conserves carbon skeletons for anabolic processes, facilitating growth and maintenance within nutrient-poor biofilm microenvironments [53,54]. Studies have demonstrated that deletion or pharmacological inhibition of glyoxylate pathway enzymes substantially attenuates fungal persistence and virulence, underscoring their clinical relevance as antifungal targets [54–56].

Beyond carbon metabolism, nitrogen metabolism also undergoes adaptation under urinary stress conditions. The gene DUR1,2, encoding urea amidolyase, is notably upregulated under nitrogen-depleted or urea-rich conditions commonly present in urine, enabling fungi to utilize urea as a nitrogen source. This enzymatic activity generates ammonia and CO_2, buffering the acidic microenvironment and facilitating fungal survival in urine, especially within biofilms on catheter surfaces [57].

To further bolster persistence, C. tropicalis engages oxidative stress responses mediated by key enzymes such as superoxide dismutases (*SOD1, SOD2*), catalases (*CAT1*), and glutathione peroxidases (*GPX1*). These antioxidant systems neutralize reactive oxygen species (ROS) produced by host immune cells or arising from metabolic stress, thus protecting fungal cells from oxidative injury and enhancing their survival under immune attack [58]. Moreover, environmental sensing pathways—including the Rim101 pH-sensing pathway, the high-osmolarity glycerol pathway, and the Ras-cAMP-PKA pathway—are actively engaged under urinary stress, fine-tuning fungal cellular responses toward adaptive metabolic states [59]. Activation of these pathways modulates stress-responsive gene networks, metabolic fluxes, and structural modifications to the fungal cell wall, collectively enhancing fungal resilience and virulence potential. These adaptations critically enhance survival within challenging urinary niches, especially under biofilm-promoting conditions such as diabetes, catheterization, and recurrent infections.

3.3. Virulence factors and host tissue invasion

Beyond biofilms and metabolic adaptability, C tropicalis employs specialized enzymatic virulence factors essential for tissue invasion, immune evasion, and persistent colonization. Secreted phospholipases (e.g., PLB1 and PLB2) and aspartyl proteases mediate epithelial damage and inflammation by hydrolyzing host membrane phospholipids—promoting urinary tract fungal pathogenicity [60,61]. These phospholipases cleave membrane phospholipids into bioactive intermediates such as diacylglycerol, lysophospholipids, and free fatty acids [61]. Moreover, these lipid metabolites act as potent signaling molecules, activating host intracellular signaling cascades like protein kinase C (PKC) and NF-κB inflammatory pathways. Activation of PKC–NF-κB signaling triggers proinflammatory cytokine release (e.g., IL-6, IL-8, TNF-α), leukocyte recruitment, and mucosal inflammation, paradoxically exacerbating tissue damage and fungal invasion [62,63].

Simultaneously, *C. tropicalis* secretes aspartyl proteases (SAPs), predominantly SAP4, SAP5, and SAP6, which further enable tissue invasion and immune modulation [60,64]. These extracellular proteolytic enzymes cleave critical intercellular junction proteins such as E-cadherin, occludin, and zonula occludens, undermining epithelial integrity, disrupting tight junctions, and facilitating paracellular dissemination of fungal cells into underlying tissues [65,66]. Additionally, SAP enzymes degrade various host immune proteins, including immunoglobulins (IgG, IgA), complement proteins, and antimicrobial peptides (e.g., LL-37), notably impairing host innate and adaptive immune defenses at mucosal surfaces [67]. Consequently, these proteases contribute to immune evasion, allowing persistent fungal colonization and reducing clearance efficiency by host immune cells.

Further, recent insights suggest that SAP activity influences local host immune polarization by selectively modulating cytokine profiles. For instance, exposure of host epithelial cells to fungal SAPs can suppress Th1-type cytokines (e.g., IFN-γ), skewing immune responses toward a less effective Th2 phenotype that favors fungal persistence and chronic infection [68]. Also, *C. tropicalis* expresses a diverse array of adhesins (e.g., *ALS3, HWP1*), facilitating initial adherence to host epithelium, setting the stage for subsequent enzymatic invasion [69]. These adhesins enable tight binding to epithelial surfaces and abiotic catheter materials, forming a foundation for stable biofilm development and sustained tissue colonization.

Such comprehensive molecular pathogenicity complicates clinical management in immunocompromised, diabetic, or catheterized patients who frequently experience recurrent and chronic fungal urinary tract infections.

3.4. Molecular basis of antifungal resistance

Antifungal resistance in C. tropicalis involves complex genetic and biochemical adaptations, complicating fUTI management, especially due to prevalent azole resistance [5]. Central to azole resistance are genetic alterations in the ergosterol biosynthesis pathway. The enzyme lanosterol 14α-demethylase, encoded by the gene ERG11, is the primary target of azole antifungals such as fluconazole (Diflucan). Mutations within the ERG11 gene—especially *Y132F, K143R*, and *S154F*—alter the active site of lanosterol 14α-demethylase, reducing drug-binding affinity and conferring stable resistance to fluconazole (Diflucan) [70,71]. Structural modeling studies demonstrate that these amino acid substitutions sterically hinder azole drug access, substantially diminishing inhibitory effectiveness [72]. In addition to structural mutations, transcriptional upregulation of the ergosterol biosynthesis pathway further enhances azole resistance. Under persistent drug exposure, C. tropicalis increases expression of key enzymes—including ERG11 itself, as well as ERG5 and ERG25—thereby sustaining ergosterol synthesis despite inhibitory concentrations of azole compounds [73].

Critically, a pivotal resistance mechanism involves enhanced drug efflux mediated by overexpressed membrane-associated efflux pumps belonging to the ATP-binding cassette (ABC) transporter and major facilitator superfamily (MFS) classes. ABC transporters—encoded by CDR1 and CDR2 genes—actively pump azole compounds out of fungal cells, lowering intracellular drug concentrations and limiting efficacy. Similarly, the proton-gradient-dependent MFS transporter MDR1 contributes prominently by exporting azole molecules across the plasma membrane. Overexpression of these efflux transporters typically arises from gain-of-function mutations in transcriptional regulators such as TAC1 (controlling CDR1 and CDR2) and MRR1 (regulating MDR1), resulting in constitutively elevated efflux pump expression [74].

Resistance to echinocandin antifungals, which target fungal cell-wall β-1,3-glucan synthase, emerges through genetic mutations. Hotspot

mutations in genes FKS1 and FKS2, encoding catalytic subunits of β-1,3-glucan synthase (e.g., *S645P, R1361G*, and *F641L*), reduce echinocandin binding affinity, challenging clinical management [75]. Additionally, polyene resistance, although less common, involves mutations in ergosterol biosynthesis genes such as ERG2, ERG3, and ERG6, altering membrane sterol composition and reducing amphotericin B binding affinity [76,77]. These molecular resistance mechanisms collectively confer a multidrug-resistant phenotype to C. tropicalis. Key resistance mutations and their clinical implications are summarized in Table 2.

Beyond individual resistance mechanisms, recent genomic studies have highlighted that high azole resistance in C. tropicalis—particularly across East and Southeast Asia—is increasingly driven by the clonal dissemination of resistant strains. Molecular surveillance has identified dominant fluconazole (Diflucan)-resistant clones bearing ERG11 Y132F mutations and coordinated upregulation of CDR1 and MDR1, suggestive of selective pressure and nosocomial transmission [78]. Whole-genome sequencing further supports inter-hospital clonal spread in countries like China and Thailand, underscoring a shift from sporadic resistance to population-level dissemination [79]. These findings call for integrated molecular epidemiology in antifungal stewardship, particularly in Asia-Pacific settings where clonal expansion may worsen resistance burdens and limit treatment options.

4. Clinical and public health implications

4.1. Host and genetic factors amplifying clinical risk

Clinically, fUTIs emerge from the syndemic interplay of genetic susceptibility, chronic metabolic disorders (notably diabetes), antibiotic overuse, and invasive catheterization, collectively amplifying vulnerability, disease severity, and treatment complexity within South Asia's healthcare landscape [87].

Genetic polymorphisms critically inform clinical susceptibility profiles, influencing infection severity, treatment response, and recurrence rates. Variants in innate immune genes (e.g., *TLR4, CLEC7A*), common among South Asian populations, compromise mucosal immunity, resulting in inadequate fungal clearance and recurrent infections. Concurrently, genetic variations in antifungal drug metabolism and transport—specifically involving cytochrome P450 enzymes (*CYP2C19, CYP3A4*) and ABC transporters (*ABCB1*)—are clinically significant. These genetic factors alter systemic and urinary antifungal drug levels, directly contributing to suboptimal therapeutic outcomes, prolonged infections, and rapid emergence of drug-resistant strains [88,89].

Clinicians must recognize specific patient populations—such as diabetic adults, pediatric patients with recurrent UTIs, and individuals with congenital anomalies of the kidney and urinary tract—as vulnerable due to these genetic susceptibilities [4]. Diabetic patients, for instance, present clinically challenging scenarios characterized by recurrent candiduria, biofilm formation on catheters, and compromised local immune responses due to chronic glycosuria and impaired neutrophil function [90]. This creates a perpetuating cycle of infection, inflammation, and ineffective antifungal therapy, demanding extensive clinical resources and prolonged patient management strategies [91].

Targeted genetic screening holds clinical promise for improving patient care through precision medicine. Clinicians equipped with genetic susceptibility data—such as polymorphisms in *TLR4, CLEC7A, CYP2C19, CYP3A4*, and *ABCB1*—could proactively stratify patients according to risk, adjusting antifungal prophylaxis, therapy choices, and dosages accordingly. For example, individualized antifungal dosing regimens informed by *CYP450* genotype could optimize therapeutic effectiveness, minimizing treatment failures and resistance development [88,89]. Likewise, tailored monitoring protocols for genetically susceptible diabetic or catheterized patients may permit earlier detection, intervention, and prevention of complicated fUTIs, improving clinical outcomes and patient prognosis.

4.2. Pathogen adaptations: biofilm resistance and clinical impact

In clinical practice, biofilm formation by C. tropicalis complicates treatment, especially in patients with urinary catheters and chronic UTIs, resulting in persistent candiduria, frequent therapeutic failures, and recurrent infections despite standard antifungal therapies. Biofilm resistance limits the effectiveness of frontline antifungals like fluconazole (Diflucan) and echinocandins in ICU and diabetic patient populations. This manifests as prolonged catheter-associated fungal infections, extended hospital stays, increased antifungal dosing, and heightened resource use [92].

Critically, traditional susceptibility assays targeting planktonic fungal cells often underestimate resistance in biofilm-associated *C. tropicalis* infections. These standard assays fail to replicate the protective architecture and metabolic states within mature biofilms, which notably impact antifungal response [93]. Consequently, clinicians may be misled toward ineffective empiric therapies, prolonging infections and delaying patient recovery. Understanding the clinical implications of biofilm-mediated resistance is important for selecting appropriate diagnostics and therapeutic interventions.

From a public health perspective, biofilm-driven antifungal resistance demands specialized diagnostic tools and targeted therapies, including biofilm-specific susceptibility testing, rapid molecular profiling, antifungal lock therapy, catheter-coating technologies, and

Table 2
Genetic markers of antifungal resistance in Candida tropicalis.

Gene	Drug Class	Key Mutation(s)	Mechanism of Resistance	Clinical Relevance	Reference
ERG11	Azoles	*Y132F, S154F, K143R*	Point mutations in the *ERG11* gene alter the lanosterol binding pocket, reducing azole affinity.	Primary mechanism of azole resistance; frequently observed in fluconazole (Diflucan)-refractory *C. tropicalis* isolates.	[80]
CDR1/2	Azoles	Overexpression (transcriptional)	Encode ABC transporters that utilize ATP to efflux azoles and other xenobiotics out of the fungal cell.	Associated with azole resistance and biofilm-related multidrug tolerance in urinary isolates.	[81]
MDR1	Azoles	Overexpression	Proton gradient–driven MFS transporter that expels azoles from the intracellular space.	Reinforces azole resistance, especially when co-expressed with *ERG11* mutations or *CDR1*.	[82]
FKS1	Echinocandins	*S645P, R1361G, F641L*	Hot-spot mutations in *FKS1* reduce echinocandin binding to the glucan synthase complex.	High-confidence marker of echinocandin non-susceptibility; predictive of therapeutic failure.	[83]
FKS2	Echinocandins	Variable (evolving)	Compensatory subunit mutations may support residual glucan synthase activity under echinocandin pressure.	Emerging contributor to echinocandin resistance; still under surveillance for diagnostic relevance.	[84]
ERG3	Polyenes, Azoles	Loss-of-function	Disruption bypasses ergosterol synthesis, limiting amphotericin B binding and altering azole susceptibility.	Rare but associated with cross-resistance to both polyenes and azoles in persistent or relapsed infections.	[85]
UPC2	Azoles	*G648D, A643V* (gain-of-function)	Activating mutations drive constitutive expression of *ERG11* and other sterol biosynthesis genes.	Amplifies azole resistance phenotype; chiefly in azole-preexposed or prophylactically treated patients.	[86]
TAC1	Azoles	*A736V* (and others)	Point mutations enhance transcription of *CDR1/CDR2*, driving overexpression of drug efflux pumps.	Promotes multidrug resistance in azole-refractory isolates; regulatory node in efflux pump circuit.	[74]

comprehensive catheter-care bundles [94,95]. However, inconsistent adoption of these innovations in resource-limited South Asian settings amplifies disparities in patient outcomes.

Clinically, biofilm-mediated resistance escalates healthcare costs by prolonging hospitalizations, increasing resource utilization, and necessitating multidisciplinary care from infectious disease specialists, microbiologists, pharmacists, and nursing teams [96]. Thus, biofilm-associated resistance poses a comprehensive healthcare challenge that needs coordinated clinical, diagnostic, and public health responses. Table 3 summarizes essential biofilm mechanisms underlying clinical resistance, guiding targeted diagnostic and antifungal stewardship strategies.

These pathogen-level adaptations call for a re-evaluation of how clinical diagnostics and therapeutic interventions are structured in high-risk settings.

4.3. Diagnostic innovation and targeted clinical management

Given the diagnostic and therapeutic limitations outlined above, clinical practice must pivot toward pathogen-specific and resistance-aware strategies. Conventional approaches, reliant on classical virulence models and standard antifungal susceptibility testing, inadequately address biofilm resistance, metabolic adaptability, and antifungal tolerance. Clinical practices must swiftly evolve, integrating advanced pathogen-specific diagnostics, molecular resistance monitoring, and personalized treatment strategies.

Standard phenotypic susceptibility assays targeting planktonic cells often underestimate resistance in biofilm-associated C. tropicalis infections, leading to inadequate therapy, extended illness, and excessive antifungal escalation. To overcome this gap, clinicians must integrate biofilm-specific susceptibility tests and rapid molecular diagnostics [101,102] for critical resistance markers (eg, ERG11, FKS1, efflux pumps) and persistence indicators (eg, ICL1, AOX2) into routine clinical practice.

Integrating routine molecular surveillance like multiplex PCR, targeted sequencing, and rapid genomic assays [103,104] enables clinicians to promptly identify resistance profiles, guiding precise initial antifungal therapy rather than relying empirically on fluconazole (Diflucan). This strategy is especially vital in resource-limited settings, where delays or ineffective treatments substantially worsen morbidity, escalate healthcare costs, and complicate infection control efforts [105,106].

Empiric antifungal protocols must incorporate local epidemiological data on species prevalence, susceptibility, and biofilm resistance. Clinicians should use updated hospital antibiograms and resistance surveillance reports to guide initial antifungal choices. For example, in institutions with high azole-resistant C. tropicalis prevalence, fluconazole (Diflucan) should be reconsidered as first-line therapy in favor of echinocandins or amphotericin B for high-risk groups like catheterized ICU or diabetic patients [107,108]. Clinicians must strategically revise catheter management protocols, proactively implementing biofilm prevention methods such as antifungal lock therapy, antimicrobial-coated catheters, and catheter-care bundles. Guidelines should clearly outline protocols for timely catheter removal or replacement in persistent candiduria despite adequate antifungal therapy, thereby improving clinical outcomes and reducing healthcare resource use.

4.4. Public health strategies for surveillance and stewardship

Addressing the rising prevalence of antifungal-resistant *C. tropicalis* infections within South Asia's healthcare system requires an integrative public health approach combining rapid diagnostics, strengthened infection control, targeted clinician education, and robust epidemiological surveillance. Considering South Asia's unique healthcare challenges—such as limited resource availability, diverse healthcare delivery structures, high diabetes prevalence, and varying degrees of clinical microbiology infrastructure—Table 4 recommendations offer contextually relevant strategies to mitigate antifungal resistance, optimize clinical outcomes, and strengthen public health responses.

5. Conclusion

The escalating prevalence and adaptive resilience of C. tropicalis as a predominant fungal uropathogen in South Asia underscores the urgent need for a fundamental shift in clinical management, diagnostic paradigms, and public health strategies. This review highlights how genetic susceptibilities, metabolic vulnerabilities—particularly driven by diabetes—and healthcare-related exposures, synergistically amplify the clinical burden of biofilm-mediated antifungal resistance. Traditional clinical frameworks, reliant on planktonic susceptibility testing and empiric antifungal protocols, are insufficient against the adaptive and persistent nature of C. tropicalis. Consequently, integrating molecular diagnostics, precision genetic screening, tailored antifungal stewardship programs, and biofilm-specific clinical interventions into routine healthcare practice is imperative. Such integrative clinical and public health responses will significantly reduce disease burden, improve patient outcomes, and strategically address the evolving epidemiological and therapeutic challenges posed by fUTIs within diverse healthcare landscapes.

Abbreviations

ABC = ATP-Binding Cassette; ABCB1 = ATP-binding Cassette subfamily B member 1; AFSPs = Antifungal Stewardship Programs; ALS1 = Agglutinin-Like Sequence 1; ALS3 = Agglutinin-Like Sequence 3; AOX2 = Alternative Oxidase 2; API = Association of Physicians of India; ATP = Adenosine Triphosphate; A643V = Alanine (A) replaced by Valine (V) at position 643; A736V = Alanine (A) replaced by Valine (V) at position

Table 3
Biofilm-associated resistance mechanisms and pathogenic traits in Candida tropicalis.

Functional Domain	Gene / Biomarker	Role	Clinical Relevance	Reference
β-Glucan Matrix & Integrity	*FKS1, FKS2, GSC1*	Encodes β-1,3-glucan synthase complex; critical for ECM matrix assembly	Predicts echinocandin tolerance; contributes to biofilm structural resilience	[16]
Efflux-Mediated Drug Resistance	*CDR1, CDR2, MDR1*	ABC and MFS transporters reduce azole accumulation within biofilm	Correlated with fluconazole (Diflucan) resistance in catheter-associated biofilms	[97]
Cell Wall Remodeling & Evasion	*XOG1, ENG1*	Remodels β-glucan exposure to evade immune recognition	Masks PAMPs from Dectin-1, especially in neutropenic or diabetic hosts	[98]
Biofilm Transcriptional Control	*BCR1, EFG1, TEC1, NDT80*	Coordinates expression of adhesion and matrix genes	Master regulators of biofilm maturation; potential antifungal drug targets	[99]
Adhesion & Biofilm Anchoring	*ALS3, HWP1, IFF4*	Initiates adherence to host epithelium and abiotic surfaces	Essential for early-stage catheter colonization and urothelial persistence	[69]
Oxidative Stress Response	*SOD2, GPX1, TRX1, CAT1*	Detoxifies reactive oxygen species during immune attack	Facilitates fungal persistence in inflamed diabetic urine environments	[58]
Metabolic Flexibility	*ICL1, AOX2, DUR1,2*	Supports growth under nutrient-limited, acidic, or glycosuric conditions	Critical for long-term biofilm survival in diabetic hosts and under urinary stress	[100]

Table 4
Strategic public health and antifungal stewardship recommendations for managing antifungal-resistant Candida tropicalis in South Asia.

Strategic Domain	Recommended Action	Clinical/Public Health Impact	Key Stakeholders
Rapid Molecular Diagnostics Expansion	Implement PCR-based assays, next-generation sequencing (NGS), and multiplex resistance gene panels routinely across secondary and tertiary hospitals	Rapid identification and timely initiation of targeted antifungal therapy; reduces inappropriate therapy and antifungal resistance emergence	Clinical Microbiology Laboratories, Hospitals, Ministry of Health, Private Diagnostic Laboratories
Hospital Infection Control Strengthening	Mandate comprehensive catheter-care bundles, including daily assessment for catheter necessity, standardized aseptic insertion/removal protocols, and timely catheter discontinuation	Reduces catheter-associated infections and biofilm formation, improves patient safety, and minimizes unnecessary antifungal therapy	Hospital Infection Control Committees, Nursing Staff, Clinicians, Hospital Administrators
Targeted Biofilm Management Protocols	Develop and implement guidelines for biofilm-specific interventions, including antifungal lock therapy, biofilm disruption strategies, and catheter coating technologies	Specifically addresses biofilm-mediated clinical resistance, reduces chronic infection rates, improves therapeutic outcomes	Infectious Disease Specialists, Clinical Pharmacologists, Hospital Infection Control Teams
Educational Initiatives and Capacity Building	Conduct region-specific workshops, continuous medical education (CME) programs, webinars, and training modules focused on antifungal stewardship, clinical mycology, biofilm management, and diagnostic interpretation	Promotes rational antifungal prescribing, enhances clinician knowledge, reduces inappropriate antifungal use and resistance selection pressure	Medical Colleges, Professional Societies (IAMM, IDSI), Clinicians, Pharmacists, Nursing Staff, Public Health Departments
Antifungal Stewardship Programs (AFSPs) Integration	Institutionalize AFSPs across hospitals and clinics, including antifungal approval protocols, routine audit-feedback mechanisms, automated stewardship software, and clinical decision-support systems	Improves adherence to evidence-based antifungal prescribing, reduces unnecessary antifungal usage, lowers resistance rates, enhances clinical outcomes	Clinicians, Pharmacists, Microbiologists, Infectious Disease Specialists, Hospital Management, IT Departments
National Surveillance and Epidemiological Networks	Establish and maintain robust national and regional surveillance networks integrated with existing antimicrobial resistance (AMR) initiatives (e.g., ICMR-AMRSN), capturing real-time fungal resistance data, clinical outcomes, and species prevalence	Facilitates timely identification of emerging resistance threats, informs clinical guidelines and empiric therapy choices, optimizes healthcare resource allocation	Indian Council of Medical Research (ICMR), Ministry of Health, National Centre for Disease Control (NCDC), Academic Research Institutions
Genetic Screening and Precision Prophylaxis	Implement targeted genetic screening for susceptibility alleles (e.g., TLR4, CLEC7A, CYP2C19, ABCB1) among high-risk populations (diabetic patients, children with recurrent UTIs, congenital kidney disorders)	Enables precision antifungal prophylaxis, reduces clinical severity, recurrence rates, and associated healthcare burden	Clinicians, Clinical Geneticists, Public Health Departments, Genetic Diagnostic Laboratories
Resource Allocation and Health Policy Integration	Integrate antifungal resistance control strategies explicitly into national health policy frameworks; allocate dedicated funding and resources to support diagnostic infrastructure, antifungal stewardship training, and public health interventions	Strengthens health system capacity to manage antifungal resistance effectively; ensures sustainability and equitable distribution of healthcare resources	Health Policy Makers, Ministry of Health, State Health Departments, Public Health Administrators
Community Awareness and Patient Education	Launch community-level educational campaigns addressing antifungal resistance awareness, appropriate antibiotic/antifungal usage, and chronic disease management (e.g., diabetes control)	Empowers patients with awareness, promotes adherence to treatment, improves chronic disease management, and reduces antifungal exposure	Community Health Workers, NGOs, Patient Advocacy Groups, Primary Health Centres (PHCs)
Clinical Guideline Revision and Dissemination	Regularly update and disseminate evidence-based national clinical practice guidelines incorporating latest antifungal resistance data, biofilm management strategies, and diagnostic methodologies tailored to Indian healthcare settings	Standardizes care delivery, improves clinical decision-making, reduces variability in patient management, enhances antifungal stewardship outcomes	Professional Societies (IAMM, IDSI, API), Ministry of Health, Academic Medical Institutions

736; BCR1 = Biofilm and Cell wall Regulator 1; CARD9 = Caspase Recruitment Domain-containing protein 9; CAT1 = Catalase 1; CDR1 = Candida Drug Resistance gene number 1 (ABC transporter); CDR2 = Candida Drug Resistance gene number 2 (ABC transporter); CLEC7A = C-type lectin domain containing 7A; COX1 = Cytochrome c Oxidase Subunit 1; COX2 = Cytochrome c Oxidase Subunit 2; CYP2C19 = Cytochrome P450 Family 2 Subfamily C Member 19; CYP3A4 = Cytochrome P450 Family 3 Subfamily A Member 4; CYP450 = Cytochrome P450; DNASE1-like = Deoxyribonuclease I–like; DUR1,2 = Degradation of Urea genes 1 and 2 (Urea Amidolyase); EFG1 = Enhanced Filamentous Growth protein 1; ENG1 = Endo-β-1,3-Glucanase 1; ERG3 = Ergosterol biosynthesis gene number 3; ERG5 = Ergosterol biosynthesis gene number 5; ERG6 = Ergosterol biosynthesis gene number 6; ERG11 = Ergosterol biosynthesis gene number 11 (Lanosterol 14α-demethylase); ERG25 = Ergosterol biosynthesis gene number 25; FKS1 = Fungal 1,3-beta-glucan synthase catalytic subunit 1; FKS2 = Fungal 1,3-beta-glucan synthase catalytic subunit 2; fUTIs = Fungal Urinary Tract Infections; G648D = Glycine (G) replaced by Aspartic Acid (D) at position 648; GPX1 = Glutathione Peroxidase 1; GSC1 = Glucan Synthase Catalytic subunit 1; HWP1 = Hyphal Wall Protein 1; IAMM = Indian Association of Medical Microbiologists; ICL1 = Isocitrate Lyase 1; ICMR = Indian Council of Medical Research; IDSI = Infectious Diseases Society of India; IFF4 = Immunogenic Fungal-specific protein 4; IL-6 = Interleukin 6; IL-7 = Interleukin 7; K143R = Lysine (K) replaced by Arginine (R) at position 143; MAPK = Mitogen-Activated Protein Kinase; MDR1 = Multi-Drug Resistance gene number 1 (Major Facilitator Superfamily transporter); MLS1 = Malate Synthase 1; NCDC = National Centre for Disease Control; NDT80 = Non-Dityrosine 80; NF-κB = Nuclear Factor kappa-light-chain-enhancer of activated B cells; NGO = Non-Governmental Organization; NGS = Next-Generation Sequencing; PAMPs = Pathogen-Associated Molecular Patterns; PCR = Polymerase Chain Reaction; PHCs = Primary Health Centres; PLB1 = Phospholipase B1; PLB2 = Phospholipase B2; R1361G = Arginine (R) replaced by Glycine (G) at position 1361; RHR2 = Glycerol-3-Phosphatase; ROS = Reactive Oxygen Species; SNP = Single nucleotide polymorphism, S154F = Serine (S) replaced by Phenylalanine (F) at position 154; S645P = Serine (S) replaced by Proline (P) at position 645; SAP4 = Secreted Aspartyl Protease 4; SAP6 = Secreted Aspartyl Protease 6; SOD1 = Superoxide Dismutase 1; SOD2 = Superoxide Dismutase 2; TAC1 = Transcriptional Activator of CDR genes 1; TEC1 = Transposon Enhancement Control 1; Th17 = T helper 17 cells, TLR2 = Toll-like receptor 2; TLR4 = Toll-like receptor 4; TNF-α = Tumor Necrosis Factor-alpha; TRX1 = Thioredoxin 1; UPC2 = Upstream Promoter element-binding protein 2; UTI = Urinary tract infection, XOG1 = Exo-β-1,3-Glucanase 1; Y132F = Tyrosine (Y) replaced by Phenylalanine (F) at position 132.

Funding

This research received no external funding.

CRediT authorship contribution statement

Rob E. Carpenter: Writing – review & editing, Writing – original draft, Methodology, Data curation, Conceptualization.

Declaration of competing interest

The author(s) declare that there are no competing interests—financial or non-financial—that could have influenced the conduct, interpretation, or reporting of this review. No author has received funding, employment, consultancies, stock ownership, honoraria, or patent-related benefits from any entity that could be perceived as a conflict of interest related to the subject matter discussed in this manuscript. The author(s) affirm that they have full control over the content, and the conclusions presented are based solely on the evidence synthesized from the literature.

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