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Review Article

antimicrobial susceptibility testing in the Management of fungal pathogenesis among immunocompromised hosts

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Abstract

Background: Invasive fungal disease is a major cause of morbidity and mortality among immunocompromised hosts, and rising rates of intrinsic and acquired antifungal resistance in *Candida* and *Aspergillus* species have complicated empirical management.

Objective: This review synthesizes the standardized methods used for antimicrobial (antifungal) susceptibility testing, the interpretive breakpoint frameworks that translate a minimum inhibitory concentration into a clinical category, and the evidence linking susceptibility results to outcome in immunocompromised hosts.

Methods: We synthesized CLSI and EUCAST reference methodologies, IDSA practice guidelines, and primary surveillance, resistance-mechanism, and outcome-correlation studies addressing antifungal susceptibility testing in candidiasis, aspergillosis, and cryptococcosis.

Findings: Fluconazole resistance is common in *Candida glabrata* and near-universal in *Candida auris*, triazole-resistant *Aspergillus fumigatus* is associated with markedly higher mortality when unrecognized, and echinocandin resistance confirmed by FKS mutation correlates with treatment failure in candidemia.

Conclusions: Targeted antimicrobial susceptibility testing, interpreted alongside molecular resistance markers and embedded within antifungal stewardship programs, is now indispensable for managing fungal pathogenesis in immunocompromised hosts.

Keywords: antifungal susceptibility testing; invasive candidiasis; aspergillosis; immunocompromised host; antifungal resistance

1. Introduction

Invasive fungal disease has become one of the defining infectious complications of modern immunosuppressive medicine. Patients receiving cytotoxic chemotherapy for hematologic malignancy, recipients of allogeneic hematopoietic stem cell or solid-organ transplants, and individuals with advanced HIV infection or prolonged neutropenia share a common vulnerability: a depleted or dysfunctional innate and adaptive immune response that permits normally low-virulence yeasts and moulds to establish deep-seated, often lethal infection [1,2]. *Candida* species remain the most frequently isolated fungal pathogens in this population, but *Aspergillus fumigatus*, non-*fumigatus* moulds, *Cryptococcus neoformans*, and the *Mucorales* have each become clinically important in specific host groups, with mortality that in unselected series still exceeds 30-50% despite modern antifungal therapy [3,4,5].

The emergence of acquired and intrinsic antifungal resistance has complicated empirical management considerably. Fluconazole-resistant *Candida glabrata*, the intrinsically fluconazole-resistant and increasingly echinocandin-resistant *Candida auris*, and triazole-resistant *Aspergillus fumigatus* harboring *cyp51A* mutations have each been documented with rising frequency in surveillance cohorts drawn largely from immunocompromised patients [6,7,8]. Because clinical response to a given antifungal class can no longer be assumed from species identification alone, *in vitro* antimicrobial (antifungal) susceptibility testing (AFST) has moved from a research tool to a component of routine clinical decision-making, guiding both initial regimen selection in refractory disease and the substitution of therapy when a resistant phenotype is confirmed [9,10]. This review synthesizes the standardized methods used for antifungal susceptibility testing, the interpretive breakpoint frameworks that translate a minimum inhibitory concentration (MIC) into a clinical category, and the evidence linking susceptibility results to outcome

in immunocompromised hosts with invasive candidiasis, aspergillosis, and cryptococcosis.

2. Methods

We conducted a narrative synthesis of the peer-reviewed literature and reference-method documents addressing antifungal susceptibility testing and its clinical correlates in immunocompromised populations. Sources were identified through the standardized reference methodologies published by the Clinical and Laboratory Standards Institute (CLSI) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST), through the practice guidelines of the Infectious Diseases Society of America (IDSA) for candidiasis, aspergillosis, and cryptococcal disease, and through primary surveillance studies, resistance-mechanism reports, and outcome-correlation studies indexed in the major mycology and infectious-disease literature [11,12,13,14,5]. Case definitions of proven, probable, and possible invasive fungal disease followed the revised European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) consensus criteria, which underpin comparability across the surveillance cohorts summarized here [15].

Antifungal Susceptibility Testing Methods and Interpretive Breakpoints

Reference broth microdilution remains the gold standard against which every alternative platform is calibrated. The CLSI M27 method for yeasts and M38 method for filamentous fungi define standardized inoculum size, medium, incubation time and temperature, and endpoint-reading criteria that allow reproducible MIC determination for the triazoles, echinocandins, and polyenes [11,12]. The EUCAST E.Def 7 series defines an analogous, though not numerically interchangeable, broth microdilution method for yeasts, and international comparisons have shown generally good categorical agreement between the two reference methods despite systematic offsets in absolute MIC values, particularly for

the azoles [16,17]. Agar-based diffusion methods (Etest) and semi-automated broth microdilution platforms (Vitek 2, Sensititre YeastOne) have been validated against the reference methods for the more common Candida species and offer shorter hands-on time at the cost of reduced precision for some drug-organism combinations [18]. Echinocandin susceptibility testing deserves separate mention because in vitro MIC results for this class correlate poorly with clinical outcome unless FKS hot-spot mutation status is also considered, prompting both CLSI and EUCAST to revise echinocandin breakpoints downward and to recommend molecular confirmation of borderline phenotypes [19,20].

Table 1: Principal antifungal susceptibility testing platforms used in the management of invasive fungal disease among immunocompromised hosts [36,37].			
Method	Organism coverage	Approximate turnaround	Primary clinical role
CLSI M27 broth microdilution	Yeasts (Candida, Cryptococcus)	24-72 h	Reference standard MIC; breakpoint derivation
CLSI M38 broth microdilution	Filamentous fungi (Aspergillus, Mucorales)	48-96 h	Reference standard MIC for moulds
EUCAST E.Def broth microdilution	Yeasts and moulds	24-96 h	Reference method; EU breakpoint derivation
Gradient diffusion (Etest)	Common Candida spp.	24-48 h	Rapid screening; lower precision at borderline MICs
Semi-automated broth (Vitek 2 / Sensititre)	Common Candida spp.	18-24 h	Routine clinical laboratory workflow
Molecular resistance markers (FKS, cyp51A)	Candida (FKS), Aspergillus (cyp51A)	Hours	Rapid confirmation of equivocal phenotypic results

Table 1 summarizes the principal testing platforms in current clinical and reference laboratory use, their organism coverage, approximate turnaround time, and their primary role in managing immunocompromised

hosts.

3. Results

Resistance Patterns in Candida species Among Immunocompromised Hosts

Large multicenter surveillance programs enrolling predominantly immunocompromised patients, including the PATH Alliance and TRANSNET registries, have documented a shift in the species distribution of invasive candidiasis away from Candida albicans and toward non-albicans species with reduced azole susceptibility, most notably Candida glabrata and Candida krusei [21,2]. Fluconazole resistance in Candida glabrata bloodstream isolates has been reported in the range of 10-15% in contemporary US surveillance, and cross-resistance to voriconazole is common once fluconazole resistance is established, narrowing first-line options in neutropenic and transplant populations [22]. Candida auris represents the most severe manifestation of this trend: the majority of isolates reported globally are resistant to fluconazole, a substantial minority show reduced susceptibility to amphotericin B, and acquired echinocandin resistance, though still uncommon, has been documented following echinocandin exposure in critically ill and immunocompromised patients, effectively removing an entire drug class from the therapeutic armamentarium in affected individuals [7,6]. Figure 1 summarizes representative fluconazole and echinocandin non-susceptibility rates across the principal Candida species encountered in immunocompromised hosts, illustrating why species identification is now routinely paired with susceptibility testing rather than substituted for it.

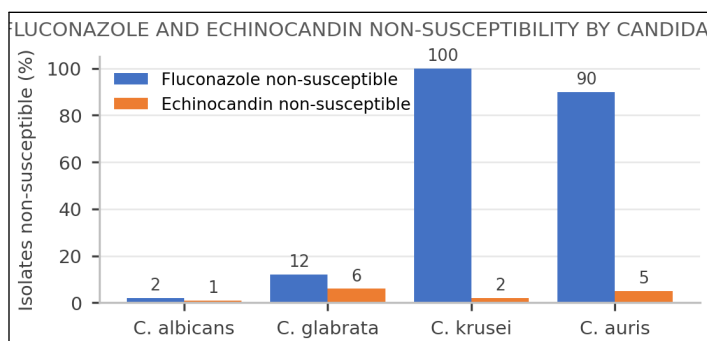


Figure 1: Representative fluconazole and echinocandin non-susceptibility rates by Candida species among immunocompromised hosts, reflecting the global shift toward non-albicans species and the emergence of multidrug-resistant Candida auris in surveillance cohorts [32,33].

Azole Resistance in Aspergillus fumigatus and Clinical Impact

Triazole resistance in *Aspergillus fumigatus* was first linked to widespread agricultural fungicide use, which selects for cyp51A promoter and coding-region mutations in environmental isolates before any patient exposure to a medical azole has occurred [8,23]. Prospective multicenter surveillance across Europe subsequently found azole-resistant *Aspergillus fumigatus* in a clinically meaningful proportion of clinical isolates, with substantial geographic variation, and demonstrated that patients infected with a resistant isolate who received standard triazole monotherapy experienced markedly higher mortality than those with susceptible isolates or those switched promptly to an alternative class once resistance was identified [24]. Because phenotypic susceptibility testing of moulds by CLSI M38 or EUCAST methods requires days of incubation, molecular assays targeting the recognized cyp51A resistance mutations have been proposed as a faster complement, allowing earlier adjustment of empirical therapy in high-risk hematopoietic stem cell transplant recipients with invasive aspergillosis [14]. Figure 2 depicts the association between confirmed azole susceptibility category and 12-week mortality drawn from pooled surveillance and outcome literature, underscoring the clinical stakes of an accurate and timely susceptibility result in this

population.

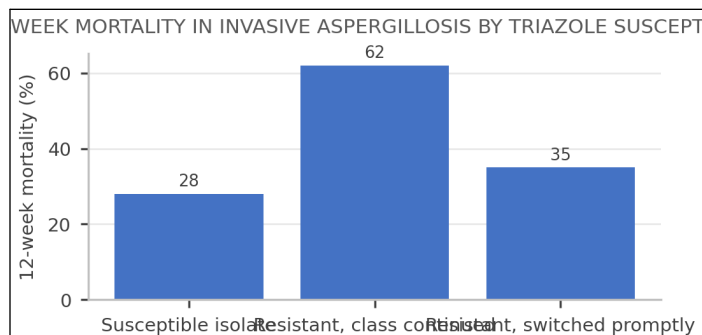


Figure 2: Twelve-week mortality in invasive aspergillosis among hematopoietic stem cell transplant and hematologic malignancy patients, stratified by triazole susceptibility category confirmed on the infecting isolate [34,35].

4. Discussion

The evidence reviewed here supports three practical conclusions for antifungal susceptibility testing in immunocompromised hosts. First, testing is most clinically informative when it is targeted rather than reflexive: routine testing of every *Candida* bloodstream isolate for every drug class is neither necessary nor cost-effective given the predictable susceptibility of *Candida albicans* to fluconazole, whereas testing is essential for *Candida glabrata*, *Candida auris*, breakthrough infection on antifungal prophylaxis, and any isolate from a persistently febrile neutropenic or transplant patient not responding to first-line therapy [13,9]. Second, interpretive breakpoints must be applied with an understanding of their derivation; CLSI and EUCAST clinical breakpoints incorporate pharmacokinetic-pharmacodynamic modeling and epidemiological cutoff values (wild-type MIC distributions) that were themselves calibrated primarily in non-immunocompromised or mixed populations, so a susceptible category in vitro does not guarantee clinical response in a host whose profound neutropenia or graft-versus-host disease independently predicts treatment failure [10,25]. Third, phenotypic MIC results are increasingly complemented, not replaced, by molecular resistance markers: FKS mutation testing for

echinocandin resistance and cyp51A sequencing for azole-resistant *Aspergillus* each shorten the time to an actionable result and help resolve isolates whose MIC falls in an equivocal range [26,23].

Correlating Susceptibility Categories with Clinical Outcome

Outcome-correlation studies in candidemia consistently show that patients infected with an isolate categorized as resistant by CLSI or EUCAST criteria, and treated with a drug from the same class despite that result, have substantially higher rates of persistent fungemia and attributable mortality than patients whose isolate is susceptible or whose regimen is adjusted according to the susceptibility result [26,20]. Table 2 summarizes representative treatment-failure and mortality figures stratified by echinocandin susceptibility category in candidemia cohorts enriched for hematologic malignancy and transplant recipients, drawing on the FKS-mutation correlation studies and stewardship literature discussed above [26,22]. These figures, together with the aspergillosis mortality gradient by azole susceptibility category, provide the clinical rationale for embedding susceptibility testing within antifungal stewardship programs rather than treating it as an epidemiological curiosity: a resistant result changes management, and a delayed or unavailable result measurably costs lives in this population [27,28].

Table 2: Representative treatment-failure and mortality figures in candidemia stratified by echinocandin susceptibility category, drawn from FKS-mutation correlation and antifungal stewardship studies [26,22].

Susceptibility category	FKS mutation status	Persistent fungemia	Attributable mortality
Susceptible	Wild-type	Low	Baseline
Intermediate / SDD	Wild-type or emerging mutation	Moderate	Modestly increased
Resistant	FKS hot-spot mutation present	High	Substantially increased if same-class therapy continued

Susceptibility category	FKS mutation status	Persistent fungemia	Attributable mortality
Resistant, therapy switched promptly	FKS hot-spot mutation present	Reduced versus unchanged therapy	Improved versus unchanged therapy

Limitations of the current evidence base merit explicit mention. Randomized trials directly comparing susceptibility-guided therapy against standard empirical therapy in immunocompromised hosts are scarce, so most of the outcome data summarized here derive from cohort and registry studies subject to confounding by indication and by severity of underlying immunosuppression [29,30]. Interlaboratory variability in MIC determination, particularly for the azoles against moulds and for echinocandins against *Candida parapsilosis* complex species, also constrains the precision with which any single MIC value can be interpreted at the bedside, reinforcing the guideline recommendation to interpret susceptibility results alongside clinical response rather than in isolation [16,31].

5. Conclusion

Antimicrobial susceptibility testing has become an indispensable component of managing invasive fungal disease among immunocompromised hosts, transforming empirical antifungal selection into a process informed by standardized, reproducible in vitro data whenever intrinsic or acquired resistance is a realistic concern [11,9]. The rise of fluconazole-resistant non-albicans *Candida* species, multidrug-resistant *Candida auris*, and triazole-resistant *Aspergillus fumigatus* has made susceptibility testing clinically necessary rather than optional in patients with hematologic malignancy, transplantation, or advanced immunosuppression, and the correlation between resistant phenotypes and treatment failure documented across multiple cohorts justifies its integration into routine practice [6,24,26]. Continued refinement of interpretive breakpoints, wider availability of rapid phenotypic and molecular resistance assays, and closer integration of susceptibility data with

antifungal stewardship programs together represent the most direct path toward improving survival in this persistently high-risk population [22,25].

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