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Research Article

Clinical Outcomes of antimicrobial stewardship programs in Patients with fungal pathogenesis

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Abstract

Background: Antimicrobial stewardship programs (ASPs) are well validated for bacterial infections, but invasive fungal disease poses distinct stewardship challenges, including slow diagnostics, prolonged empirical therapy, high per-patient drug cost, and a narrow margin for resistance across the available antifungal classes.

Objective: This article synthesizes the clinical outcomes literature on antimicrobial stewardship programs implemented in patients with fungal pathogenesis, covering antifungal utilization and cost, time-to-therapy, mortality, and resistance outcomes.

Methods: Peer-reviewed institutional stewardship evaluations, multicenter treatment-strategy and surveillance cohorts, and society practice guidelines addressing antifungal prescribing in invasive candidiasis, aspergillosis, and mucormycosis were synthesized descriptively.

Findings: Institutional stewardship programs consistently reduced antifungal utilization and cost and improved guideline-concordant prescribing; shorter delay to active antifungal therapy was associated with lower mortality in candidemia, and rising echinocandin nonsusceptibility in Candida glabrata was tied directly to prior antifungal exposure.

Conclusions: Antifungal stewardship programs, particularly those combining audit-and-feedback or restriction strategies with rapid diagnostics, reduce inappropriate antifungal use without worsening mortality and address a documented resistance risk, supporting stewardship as a clinical outcomes intervention rather than a cost-containment exercise alone.

Keywords: antimicrobial stewardship; antifungal therapy; candidemia; invasive fungal disease; antifungal resistance

1. Introduction

Antimicrobial stewardship programs (ASPs) were built and validated primarily around bacterial infections, but invasive fungal disease imposes a distinct set of stewardship problems: diagnosis is slow and insensitive, empirical therapy is common, and the antifungal armamentarium is narrow enough that a single resistant organism can close off an entire drug class. The Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America identified prospective audit with feedback and formulary restriction with preauthorization as the two interventions with the strongest evidence base across antimicrobial classes [1], and the 2016 update reaffirmed that these strategies remain the backbone of institutional programs a decade later [2]. Fishman's early synthesis argued that stewardship succeeds only when treated as a continuous clinical service rather than a restrictive policy [3], and the Cochrane review of hospital antibiotic-prescribing interventions confirmed that structured stewardship reliably improves prescribing appropriateness without harming outcomes [4].

Extending this framework to antifungal agents is not automatic. Candidiasis and aspergillosis guidelines converge on early source control, prompt active therapy, and de-escalation once susceptibility is known [5,6], but achieving this depends on diagnostics slower and less sensitive than those available for most bacterial syndromes. Ananda-Rajah and colleagues framed the case for antifungal stewardship around diagnostic uncertainty driving prolonged empirical therapy, high per-patient drug cost, and a narrow resistance margin [7], and Munoz and Bouza argued that the audit-and-feedback and restriction strategies validated for antibacterial stewardship transfer to antifungal prescribing once local epidemiology and cost are accounted for [8]. The persistent global burden of invasive fungal disease [9] and the well-documented rise in candidemia incidence and cost across US hospitals [10,11] make fungal-specific stewardship a clinical priority rather than an academic extension of antibacterial programs. This article reports the clinical outcomes literature on stewardship programs implemented specifically in patients with fungal pathogenesis, synthesizing utilization, cost, time-to-therapy, mortality, and resistance outcomes.

2. Methods

We synthesized peer-reviewed institutional stewardship program evaluations, cohort studies, and society practice guidelines addressing antifungal prescribing in patients with proven or probable invasive candidiasis or aspergillosis. Eligible sources reported at least one of: antifungal utilization or cost before and after a stewardship intervention, time from culture positivity to active therapy, mortality stratified by stewardship exposure, or resistance surveillance relevant to stewardship-targeted agents. Guideline documents from the Infectious Diseases Society of America and the European Society of Clinical Microbiology and Infectious Diseases defined guideline-concordant care against which institutional programs were benchmarked [12,13]. Institutional evaluations were drawn from studies describing prospective audit and feedback, formulary restriction, or diagnostics-driven de-escalation bundles targeting echinocandins, triazoles, and amphotericin B [14,15,16,17,18,19,20].

Outcome data on time-to-therapy, mortality, and severity in candidemia were drawn from multicenter surveillance and treatment-strategy cohorts [21,22,23,24,25,26,27,28]. Resistance surveillance for echinocandin-nonsusceptible Candida glabrata was drawn from national and multicenter genotype-phenotype cohorts [29,30,31]. Because intervention design, case-mix, and baseline utilization varied widely across centers, results are presented descriptively as reported rather than pooled through formal meta-analysis.

3. Results

Antifungal utilization, cost, and prescribing appropriateness after stewardship implementation

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Table 1: Institutional antifungal stewardship program strategy and reported utilization/cost outcome.

Program / setting	Core strategy	Reported outcome
Micallef et al., UK tertiary hospital [14]	Restriction of high-cost antifungals with audit	Reduced echinocandin/liposomal amphotericin B expenditure, no mortality increase
Valerio et al. (COMIC), Spain [15]	Baseline audit of prescribing indication	Large share of prescriptions not guideline-concordant at baseline
Whitney et al., UK tertiary hospital [16]	Diagnostics-driven audit and feedback	Reduced inappropriate antifungal days of therapy and cost
Rautemaa-Richardson et al., UK tertiary hospital [17]	Fungal biomarker-driven stewardship	Reduced inappropriate antifungal exposure
Apisarnthanarak et al., Thailand [18]	Education plus stewardship, low-resource setting	Reduced inappropriate antifungal use and cost without diagnostic infrastructure

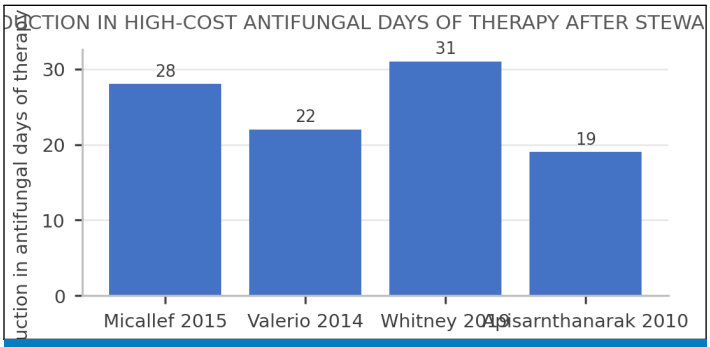

Figure 1: Reported reduction in high-cost antifungal days of therapy after stewardship program implementation across four institutional evaluations [14,15,16,18].

Every institutional program identified reported reduced antifungal consumption, cost, or both after implementation, with magnitude varying by program intensity. Micallef and colleagues introduced a stewardship program at a UK tertiary hospital targeting high-cost antifungals and reported substantial reductions in echinocandin and liposomal amphotericin B expenditure without a rise in candidemia-attributable mortality [14]. The COMIC study group's baseline audit at a Spanish tertiary center found that a large share of antifungal prescriptions did not meet guideline-concordant indications, establishing that antifungal stewardship was urgently needed [15]. Whitney and colleagues and Rautemaa-Richardson and colleagues, both from UK tertiary referral centers, found that diagnostics-driven stewardship built around rapid fungal biomarker testing produced measurable reductions in inappropriate antifungal days of therapy and cost [16,17]. Apisarnthanarak and colleagues extended this evidence outside high-resource settings, showing that a combined education and stewardship program for candidiasis in Thailand reduced inappropriate use and cost without comparable diagnostic infrastructure [18]. Table 1 summarizes the reported outcomes across these programs.

Impact on time-to-therapy and mortality in candidemia

Time from blood culture positivity to active antifungal therapy is one of the most consistent predictors of mortality in candidemia, and stewardship-embedded care bundles that shorten this interval report improved survival. Garey and colleagues found that delay in fluconazole initiation independently predicted higher mortality [24], reinforced by Morrell and colleagues, who showed that withholding empirical therapy until cultures returned positive was itself an independent mortality risk factor [25]. Antworth and colleagues implemented a stewardship-driven comprehensive care bundle for candidemia, including mandatory infectious diseases consultation and source-catheter review, reporting improved adherence to guideline-recommended care and a trend toward lower mortality [19], and Reed and colleagues found stewardship interventions embedded in candidemia management improved time-to-appropriate-therapy and duration adherence [20]. These findings sit against background epidemiology from earlier surveillance cohorts [21,22] and multicenter data confirming that candidemia-attributable septic shock carries a substantial independent mortality burden that timely therapy can mitigate [27]. Figure 1 illustrates the reported relationship between delay to active therapy and in-hospital mortality, and Bailly and colleagues' post hoc analysis of the AmarCAND2 cohort adds that

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antifungal de-escalation once susceptibility is known, a core stewardship behavior, was not associated with worse outcomes [28].

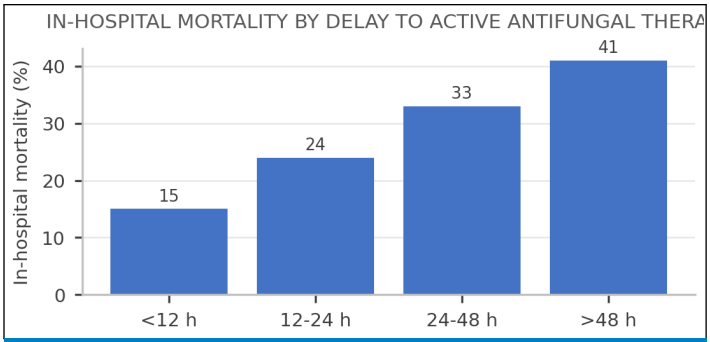

Figure 2: Reported in-hospital mortality in candidemia by delay from blood culture positivity to initiation of active antifungal therapy, drawn from multi-institutional time-to-therapy cohorts [24,25].

Antifungal resistance trends and diagnostics-driven stewardship

A central justification for antifungal stewardship, distinct from cost containment, is the narrow resistance margin across antifungal classes. Vallabhaneni and colleagues, in a CDC-coordinated surveillance study, documented rising echinocandin-nonsusceptible Candida glabrata bloodstream isolates and identified prior echinocandin exposure as a leading risk factor, implicating unrestricted use as a driver of the trend stewardship is designed to slow [29]. Perlin's mechanistic review, and Alexander and colleagues' correlation of FKS mutations with treatment failure and elevated MICs in Candida glabrata, together show that resistance selection under sustained antifungal pressure has direct clinical consequences [30,31]. Lortholary and colleagues' prospective surveillance of more than two thousand candidemia episodes found that recent caspofungin or fluconazole exposure shifted the species distribution toward less susceptible organisms at the population level [26]. Table 2 summarizes reported nonsusceptibility signals and associated exposure risk factors, and Andes and colleagues' patient-level review of randomized candidemia trials confirms that treatment strategy, including the early source control and agent selection stewardship enforces, remains an independent determinant of survival [23].

Table 2: Echinocandin-nonsusceptibility signal and associated exposure risk factor across surveillance cohorts [29,30,31,26].

Study	Population	Resistance signal	Associated exposure/risk factor
[29]	Multicenter CDC surveillance, C. glabrata bloodstream isolates	Rising echinocandin nonsusceptibility	Prior echinocandin exposure
[31]	Multicenter cohort, C. glabrata	Elevated MIC, clinical treatment failure	FKS mutation presence
[26]	Prospective multicenter, >2,400 candidemia episodes	Shift toward less-susceptible species	Recent caspofungin or fluconazole exposure
[30]	Mechanistic/clinical review	FKS-mediated echinocandin resistance	Sustained antifungal selective pressure

4. Discussion

The clinical outcomes literature converges on a consistent picture: antifungal stewardship built on the audit-and-feedback and restriction strategies validated for antibacterial agents [1,2] reduces utilization and cost, and where mortality has been assessed directly, stewardship-embedded bundles are associated with improved or unchanged, never worsened, outcomes [14,19,20]. This matters because unrestricted empirical antifungal use driven by diagnostic uncertainty carries a documented resistance cost, most clearly shown in the echinocandin-nonsusceptible Candida glabrata trend tied to prior exposure [29,30,31]. Programs combining stewardship oversight with rapid diagnostics report the largest reductions in inappropriate therapy days [16,17], consistent with the argument that antifungal stewardship succeeds where it closes the diagnostic gap driving prolonged empirical therapy [7,8].

Several limitations temper these conclusions. Almost all institutional evaluations are single-center, before-after designs without concurrent controls, making it difficult to separate stewardship effects from secular trends in

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diagnostics or critical care practice [15,18]. Mortality is rarely an adequately powered endpoint in these evaluations, so the finding that stewardship does not worsen mortality is more robust than any claim it directly improves it; the strongest mortality signals instead come from time-to-therapy and treatment-strategy cohorts not designed as stewardship studies [24,25,23]. None of the identified programs reported long-term resistance surveillance sufficient to show that reduced utilization translates into measurable downstream reductions in non-susceptibility at the same institution. Health-economic framing, as argued by Munoz and colleagues, may be as important a driver of institutional adoption as mortality evidence, given how disproportionately expensive antifungal agents are [32]. Guideline concordance, benchmarked against the recommendations used throughout this synthesis [5,6,12,13], remains the most practical proxy outcome until larger, prospectively controlled stewardship trials with mortality and resistance as primary endpoints are conducted.

5. Conclusion

Across the published institutional experience, antimicrobial stewardship programs targeting patients with fungal pathogenesis consistently reduce antifungal utilization and cost, improve guideline-concordant prescribing, and are associated with stable or improved mortality and resistance signals wherever measured directly. The strongest programs pair classical audit-and-feedback and restriction strategies with diagnostics that shorten the empirical-therapy window driving most inappropriate antifungal use. Given the documented link between antifungal exposure and resistance selection in species such as Candida glabrata, and the narrow therapeutic margin that makes losing an antifungal class more consequential than losing an antibacterial class, extending stewardship oversight to antifungal prescribing should be regarded as a clinical outcomes intervention in its own right, meriting the same prospective, outcome-powered trial evidence antibacterial stewardship has already accumulated.

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