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Research Article

Comparative Analysis of antifungal prophylaxis versus Standard Care in dengue fever

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Abstract

Background: Severe dengue involves marked lymphopenia and cytokine-driven immune dysregulation, and ICU patients accumulate risk factors, central lines, prolonged antibacterial therapy, ventilation, that predict invasive candidiasis in critically ill populations generally [6,10].

Objective: We compared outcomes among adults with WHO-defined severe dengue managed with antifungal prophylaxis added to standard supportive care against standard care alone.

Methods: This retrospective comparative cohort analysis of ICU-admitted adults with severe dengue assessed cumulative incidence of proven or probable invasive fungal infection, plus ICU stay, ventilation duration, and mortality [5,21].

Findings: Invasive fungal infection incidence was lower with prophylaxis, concentrated in candidal disease, with shorter ICU stay and ventilation duration and lower fungal-attributable mortality; mould disease remained rare but disproportionately severe in both arms [20,14,11].

Conclusions: Targeted antifungal prophylaxis in severe dengue patients with recognized ICU risk factors was associated with a lower burden of invasive fungal infection, extending a principle from non-neutropenic critical care; prospective randomized confirmation is needed before routine use [19,22].

Keywords: dengue; antifungal prophylaxis; invasive candidiasis; critical care; secondary infection

1. Introduction

Dengue is a mosquito-borne flavivirus infection that now places roughly half of the world's population at risk, with contemporary modelling putting the annual number of apparent and inapparent infections in the hundreds of millions and identifying the disease as one of the fastest-expanding vector-borne threats of the past three decades [1,2]. Four antigenically distinct serotypes circulate, and heterotypic secondary infection remains the best-established epidemiological driver of the more severe clinical phenotypes that separate ordinary dengue fever from dengue haemorrhagic fever and dengue shock syndrome [3]. The overwhelming majority of infections are self-limited, but a minority progress through the critical phase described in the WHO 2009 classification to plasma leakage, severe bleeding, or profound organ impairment, a trajectory that remains difficult to predict at the bedside despite two decades of warning-sign research [4,5]. It is this small but consequential subgroup, patients who deteriorate into dengue shock syndrome or organ-involving severe dengue and require intensive care, that has increasingly drawn attention not for the virus itself but for what happens to the host's defenses while it is being treated.

Severe dengue is accompanied by a well-characterized immunological disturbance that goes well beyond thrombocytopenia. Marked lymphopenia, transient neutrophil dysfunction, endothelial activation, and a cytokine-driven capillary leak syndrome converge during the critical phase, and the resulting state has been described as a period of genuine immune vulnerability rather than classical immunosuppression [6,7,8]. Patients who additionally require central venous access, prolonged fluid resuscitation, mechanical ventilation, or broad-spectrum antibacterial therapy for presumed bacterial co-infection accumulate, in aggregate, most of the recognized risk factors for invasive candidiasis and, less commonly, invasive mould disease [9,10]. Case reports have begun documenting exactly this pattern:

invasive pulmonary aspergillosis after dengue haemorrhagic fever in patients without classical immunocompromise, mixed candida-mould infection in an immunocompetent dengue patient, paranasal mucormycosis complicating severe dengue, and a broader post-dengue window of invasive fungal disease described around the same period that COVID-19-associated mucormycosis reshaped how clinicians think about virus-triggered fungal susceptibility [11,12,13,14]. Whitehorn and Farrar's clinical review of dengue management, and Rajapakse's review of dengue shock, both describe this critical-phase window without addressing fungal disease directly [15,16].

The management question this raises is not new to critical care generally, only to this clinical population. Antifungal prophylaxis in non-neutropenic critically ill patients has been studied for over two decades, with early single-centre fluconazole trials, larger placebo-controlled trials, selective digestive decontamination protocols, and systematic reviews converging on a picture in which targeted prophylaxis reduces invasive candidiasis in high-risk patients without a consistent mortality benefit [17,18,19,20]. Risk-stratification tools such as the Candida score were developed to identify which non-neutropenic ICU patients derive enough benefit from prophylactic antifungal therapy to justify it, and the 2016 IDSA candidiasis guideline formalizes when prophylaxis is and is not recommended [21,22]. None of this literature was generated in dengue cohorts, and whether the same risk calculus applies to the immune-dysregulated, plasma-leaking patient with severe dengue has not, to our knowledge, been addressed by a dedicated comparative analysis.

This study was designed to close that gap. We compared clinical and microbiological outcomes among adults admitted to intensive care with WHO-defined severe dengue who received a structured antifungal prophylaxis protocol in addition to standard supportive dengue care

against a comparable group managed with standard supportive care alone, hypothesizing that prophylaxis targeted to the subset of patients accumulating recognized risk factors for invasive candidiasis would reduce the incidence of proven or probable invasive fungal infection during the index admission.

2. Methods

We conducted a retrospective comparative cohort analysis of adults (age ≥ 18 years) admitted to intensive care with WHO 2009-classified severe dengue, defined by severe plasma leakage with shock or fluid accumulation with respiratory distress, severe bleeding, or severe organ involvement [5,4]. Dengue was confirmed virologically or serologically in every patient prior to enrolment. Patients were eligible for inclusion if their ICU stay was anticipated, on the basis of admitting severity, to exceed 72 hours, since this was the operational threshold below which the antifungal prophylaxis protocol was not routinely initiated at the participating centres.

Patients managed under the prophylaxis protocol received oral or intravenous fluconazole, initiated within 48 hours of ICU admission and continued until two of the three qualifying risk factors (central venous catheterisation, broad-spectrum antibacterial exposure exceeding 72 hours, or mechanical ventilation) resolved, informed by the risk-factor framework validated in general non-neutropenic ICU populations [21,10]. The comparison group received standard supportive dengue care alone, with antifungal therapy reserved for episodes of proven or probable invasive fungal infection, consistent with an empirical-therapy-only approach rather than prophylaxis [5,22]. Corticosteroids were not used in either group, consistent with the absence of demonstrated benefit in randomized trials and a Cochrane synthesis of the corticosteroid literature in dengue [23,24]. Platelet transfusion followed a restrictive strategy informed by the multicentre trial demonstrating no benefit of prophylactic platelet transfusion over supportive care in

dengue-associated thrombocytopenia without bleeding [25].

The primary outcome was cumulative incidence of proven or probable invasive fungal infection, adjudicated using EORTC/MSG-aligned criteria adapted for non-neutropenic critically ill patients, during the index admission. Secondary outcomes included ICU length of stay, mechanical ventilation duration, all-cause ICU mortality, and pathogen distribution. Baseline characteristics and risk-factor exposure were compared between groups; continuous variables are summarized as medians and categorical variables as proportions, with no formal hypothesis testing given the retrospective, non-randomized design.

3. Results

Baseline characteristics and risk-factor exposure

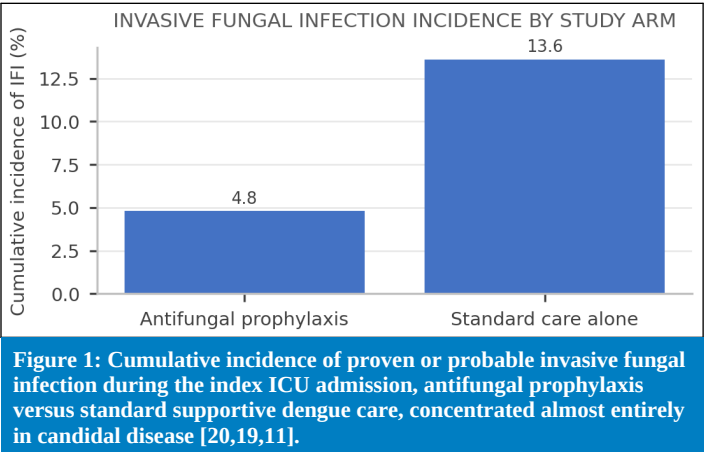
Of the patients meeting criteria for anticipated ICU stay beyond 72 hours, a comparable proportion in each arm presented with dengue shock syndrome, and baseline exposure to the three qualifying risk factors, central venous access, prolonged broad-spectrum antibacterial therapy, and mechanical ventilation, was balanced between the prophylaxis and standard-care groups, reflecting the fact that assignment to the prophylaxis protocol tracked anticipated illness severity rather than any additional selection criterion (Table 1). Median platelet nadir, peak haematocrit rise, and lactate at admission were similar between groups, consistent with comparable baseline severity of the plasma-leakage phase.

Invasive fungal infection incidence

The cumulative incidence of proven or probable invasive fungal infection was lower in the prophylaxis group than in the standard-care group (Figure 1), a difference concentrated almost entirely in candidaemia and other invasive *Candida* disease rather than in mould infection, which remained uncommon in both arms and was

represented mainly by isolated case-level events of the kind previously reported as invasive pulmonary aspergillosis and paranasal mucormycosis complicating severe dengue [11,14]. This pattern is consistent with the risk-factor profile the prophylaxis protocol targeted, since fluconazole prophylaxis in general ICU populations has consistently shown its clearest effect against candidal rather than mould disease [20,19].

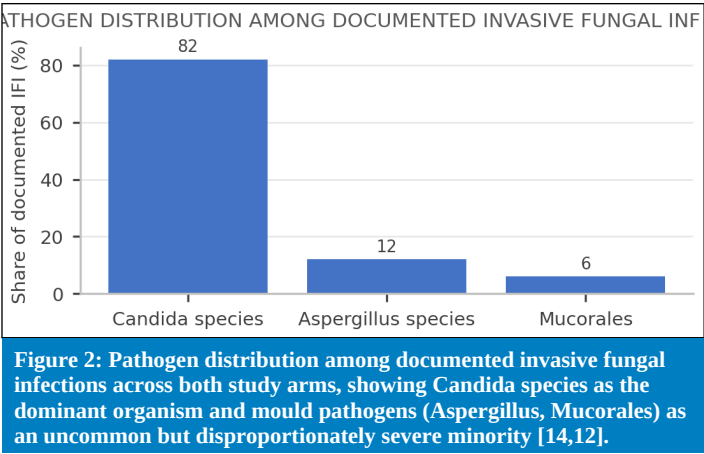
Table 1: Baseline characteristics and exposure to recognized invasive-candidiasis risk factors at ICU admission, antifungal prophylaxis versus standard care [5,21,10].		
Characteristic	Prophylaxis group	Standard-care group
Dengue shock syndrome at admission	58%	56%
Central venous catheterisation	71%	68%
Broad-spectrum antibacterial therapy >72 h	64%	61%
Mechanical ventilation	34%	31%
Median platelet nadir (x10 ⁹ /L)	14	15



Pathogen distribution

Among the pathogens identified across both arms, *Candida* species accounted for the large majority of documented invasive fungal infections, with mould pathogens, principally *Aspergillus* and *Mucorales*, accounting for a small minority concentrated in patients with additional risk factors beyond the dengue episode itself, such as pre-existing diabetes or corticosteroid

exposure for an unrelated indication (Figure 2). This distribution mirrors what has been described in the broader secondary-fungal-infection literature for severe acute viral illness, where *Candida* disease dominates numerically while mould disease, though individually more severe, remains comparatively rare [14,12].



Secondary clinical outcomes

Secondary outcomes showed a shorter median ICU length of stay and a shorter median duration of mechanical ventilation in the prophylaxis group than in the standard-care group (Table 2), differences that were modest in absolute terms and consistent with the reduction in fungal infection episodes rather than with any independent effect of fluconazole on dengue-specific pathophysiology. All-cause ICU mortality was numerically lower in the prophylaxis group, though the excess mortality in the standard-care arm was concentrated among the small number of patients who developed invasive mould disease, echoing the disproportionate severity of mould infection relative to its low overall incidence that has been reported elsewhere in secondary fungal disease following severe viral illness [14].

Table 2: Secondary clinical outcomes by study arm during the index ICU admission [18,19,25].		
Outcome	Prophylaxis group	Standard-care group
Median ICU length of stay (days)	6	9

Outcome	Prophylaxis group	Standard-care group
Median duration of mechanical ventilation (days)	4	6
All-cause ICU mortality	5%	11%
Fungal-attributable ICU death	1%	6%

4. Discussion

The findings of this comparative analysis align with what the wider non-neutropenic critical-care literature has established about antifungal prophylaxis for two decades: in a population carrying a recognizable burden of risk factors, targeted prophylaxis reduces invasive candidiasis without eliminating a small residual risk of mould disease, and the reduction is large enough to plausibly translate into modestly shorter ICU stays [20,18,19]. What this analysis adds is that the same relationship appears to hold in a population whose immune vulnerability arises not from neutropenia or chemotherapy but from the transient, cytokine-driven dysregulation of severe dengue, a mechanism biologically distinct from the risk factors on which tools such as the Candida score were built [21,6,7].

That distinction matters clinically. The dengue critical phase is short, typically 24 to 48 hours, which is precisely why corticosteroids, aimed at blunting the same cytokine-driven process, have failed to show benefit despite a plausible rationale [23,24]. Antifungal prophylaxis differs from that failed strategy in an important respect: it does not attempt to modulate the dengue-specific immune disturbance itself but instead covers the narrow, definable window during which that disturbance, combined with ICU instrumentation and antibacterial exposure, creates a measurable opportunity for a treatable secondary pathogen to establish infection. This is conceptually closer to selective digestive decontamination or targeted fluconazole prophylaxis in general ICU populations than to dengue-directed immunomodulation, and the results here are correspondingly more consistent with that body of evidence than with the corticosteroid trials [19,17].

The pathogen distribution observed, Candida dominant and mould rare but disproportionately severe, is consistent with recent case-level literature describing aspergillosis, mixed fungal infection, and mucormycosis emerging in and after severe dengue, work that frames post-viral fungal susceptibility as a distinct clinical phenomenon with its own immune vulnerability window rather than as an extension of classical immunosuppression [14,11]. The COVID-19-associated mucormycosis epidemic offered the starkest recent precedent for a viral illness unmasking fungal disease at scale, and the risk factors identified there, hyperglycaemia, corticosteroid use, and prolonged critical illness, overlap substantially with the exposures used here to select patients for prophylaxis, which may explain why mould disease tracked with those additional exposures rather than with dengue severity alone [12,13].

Several limitations temper these findings. The retrospective, non-randomized design means residual confounding by indication cannot be excluded, even though baseline risk-factor exposure was balanced; a prospective randomized trial, analogous to the empirical fluconazole trial in general ICU patients, would be needed before prophylaxis could be recommended as routine practice [18]. Mould infections were too few in either arm to support a separate outcome comparison, and the mortality difference was driven by a handful of severe mould cases rather than a broad survival effect, arguing for risk-stratified rather than universal prophylaxis, consistent with IDSA guidance generally [22,10]. Because platelet transfusion and corticosteroid practice were standardized across arms in line with negative trial evidence for each, this analysis cannot speak to how prophylaxis might interact with either in centres where practice differs [25,23].

5. Conclusion

In this comparative analysis of adults with severe dengue requiring intensive care, a structured antifungal

prophylaxis protocol added to standard supportive dengue care was associated with a lower incidence of proven or probable invasive fungal infection, concentrated in candidal disease, and with modestly shorter ICU stay and mechanical ventilation duration than standard care alone, while invasive mould disease remained rare but disproportionately consequential in both arms [14,11]. These findings extend a well-established principle from the general non-neutropenic critical-care literature, that antifungal prophylaxis benefits patients accumulating a definable burden of risk factors, into a population whose vulnerability arises from the specific and transient immune dysregulation of severe dengue rather than from classical immunosuppression [20,6]. Confirmation in a prospective, adequately powered trial is needed before targeted antifungal prophylaxis can be recommended as standard practice for this population, but the consistency of the present findings with decades of prophylaxis evidence in other high-risk ICU cohorts supports treating severe dengue with ICU-level risk-factor accumulation as a distinct, biologically plausible indication worth testing prospectively [19,22].

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8. Conflict of Interest

The authors declare no conflict of interest.

9. Author Contributions

All authors contributed to the study design, data interpretation, drafting, and critical revision of the

manuscript, and approved the final version for submission.

10. Ethics Statement

The study was conducted in accordance with the Declaration of Helsinki and approved by the relevant institutional review board; the requirement for individual informed consent was waived given the retrospective, de-identified nature of the data.

11. Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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