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Empirical versus pre-emptive antifungal therapies for invasive fungal infections in critically ill patients

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Abstract

Background The initiation strategy of antifungal therapy (AT) is among the most discussed practices for patients vulnerable to invasive fungal infections (IFI). In low-resource countries, there are also no appropriate consensus or guidelines for this issue. Given this clinical gap, we aimed to investigate the use of empirical and pre-emptive therapy in an Asian intensive care setting.

Methods We conducted a retrospective cohort study (timeframe 2019–2020) on critically ill adults receiving systemic antifungals for ≥ 3 days. The exposure was empirical or pre-emptive therapy of systemic antifungals. The primary outcome was IFI-related mortality (in percentage, including in-hospital death or discharge/transfer with death prognosis). The secondary outcomes included overall rationale of AT (in percentage) and length of AT (LoAT, in days). We used logistic and linear regression to investigate the outcomes and reported the estimates with the 95% confidence interval (95% CI).

Results During a median follow-up of 27 days, among 157 included patients (median age 68, 48.4% being female), we recorded 77 deaths (49.0% [95% CI 41.0–57.1%]) that were related to IFI (60 [51.7%] in the empirical group; 17 [41.5%] in the pre-emptive group; adjusted odds ratio of IFI-related mortality 1.86 [95% CI 0.74 to 4.63; $p = 0.184$]). The overall rationale of AT was at 45.2% (95% CI 37.2–53.4%; 41.4% [95% CI 32.3–50.9%] in the empirical group; 56.1% [95% CI 40.0–71.5%] in the pre-emptive group; adjusted odds ratio of receiving rational AT: 0.75 [95% CI 0.31 to 1.87]). The median LoAT was 8 days (IQR 6–14; 8 days [IQR 6–13.3] in the empirical group; 9 days [IQR 6–14] in the pre-emptive group; adjusted mean difference − 1.1 days [95% CI -3.2 to 1.0]).

Conclusion Among critically ill patients on systemic antifungals for ≥ 3 days, the proportion of IFI-related mortality was high. The overall rationale of AT was at a low level, with the median LoAT lower than the generally recommended duration of at least 14 days. There were no significant differences in IFI-related mortality, overall rationale of AT, and LoAT between those receiving empirical and pre-emptive therapy.

Clinical trial number Not applicable.

Keywords Antifungal, Empirical therapy, Pre-emptive therapy, Mycoses, Invasive fungal infections, Intensive care

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Introduction

Invasive fungal infections (IFI) are serious and potentially fatal diseases, especially in low-middle-income countries (LMIC) [1]. Timely and accurate IFI diagnosis is a critical challenge that is likely associated with difficulties in treatment and therapeutic optimisation [2]. Susceptibility of the fungal pathogens to antifungals is another major determinant of IFI treatment and prognosis [3], which is frequently unknown due to the high false negative rate of culture tests [2]. With many IFI-related uncertainties in clinical settings, the use of antifungal therapy (AT) has remained controversial [4, 5]. The initiation strategy of AT (empirical [treatment at the first clinical suspicion of fungal infections] or pre-emptive [treatment after detecting fungal infections] therapy) is among the most discussed practices for patients who are at higher risk (neutropenia, immunosuppression, or haematological malignancy [6]) or more vulnerable (critical illness [7]) to IFI.

In the intensive care unit (ICU) settings, whether empirical or pre-emptive therapy should be the standard strategy for antifungal initiation is an ongoing debate [6, 8]. Current evidence does not provide a consistent set of specific criteria to define pre-emptive or empirical AT [6]. In low-resource countries with limited access to newer antifungals or diagnostic tools, there are also no appropriate consensus or guidelines for this issue. This can lead to irrational or unnecessary AT (for the empirical approach) or significantly delayed AT (for the pre-emptive approach), which may impact patient outcomes, antimicrobial stewardship plans, and antifungal usage [7]. Given this clinical gap, we aimed to investigate these 2 strategies for critically ill patients in the ICU within a low-resource Asian setting.

Methods

Design and subjects

We conducted a retrospective cohort study at Nhan Dan Gia Dinh Hospital (Ho Chi Minh City, Vietnam) using retrospective data from 1st January 2019 to 31st December 2020. We pre-screened and included the medical records of patients who: (1) were ≥ 18 years old; (2) could afford the standard treatment of the hospital (not having the code Z59 of the International Classification of Diseases, 10th Revision); (3) were admitted to the ICU or having critical illness; and (4) were prescribed systemic antifungals for ≥ 3 days. We excluded records of those who: (1) were pregnant or gave birth within the last 1 month; (2) were breastfeeding; (3) had been taking systemic antifungals prior to hospitalisation; or (4) received antifungals for prophylactic purposes (not for a suspected or confirmed IFI).

We followed the Declaration of Helsinki to conduct this study. We reported our findings in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement (**Table S1**, **Supplementary File**). The study was approved by the Ethics Committee of Nhan Dan Gia Dinh Hospital under approval number 52/NDGD-HDDD. As we only used retrospective data from medical records while strictly maintaining patient confidentiality, the Ethics Committee declared that no separate informed consent was required, except for the consent to data sharing for research purposes upon hospitalisation.

Exposure

All patients received standard of care with systemic antifungals. The exposure was the strategy to initiate systemic antifungals, including empirical and pre-emptive therapy. Pre-emptive therapy was initiated based on positive results of fungal screening/detecting laboratory tests, whereas systemic antifungal use without confirmed laboratory evidence was considered empirical therapy. Fungal screening or detecting laboratory tests, per local availability, generally include radiologic methods (computed tomography, magnetic resonance imaging), cultures (chromogenic agar, brain-heart infusion agar with blood), antigen/serologic tests ((1,3)-β-d-glucan, galactomannan, cryptococcal antigen, enzyme-linked immunosorbent assay for antifungal antibodies), molecular tests (polymerase chain reaction, sequencing), and mass spectrometry (matrix-assisted laser desorption/ionisation-time of flight) [9–11]. The decisions about the antifungal strategy were at the discretion of the attending physicians, in consultation with the infectious disease specialists and pharmacists.

Outcomes

The primary outcome was IFI-related mortality (measured in percentage), which counted in-hospital death or discharge/transfer with critical illness and poor prognosis. This included cases that were related to IFI or IFI treatment (severe adverse events of AT). IFI cases were detected on the classification of the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium, which included "proven", "probable", and "possible" IFI [12]. The secondary outcomes included overall rationale of AT (in percentage) and length of AT (LoAT, in days). The overall rationale of AT was defined as meeting all 3 criteria: (1) rational indication (having a reliable laboratory-based diagnosis for pre-emptive group; having ≥ 3 risk factors of IFI, meeting Ostrosky-Zeichner rule, or having Candida score ≥ 3 for empirical group); (2) rational choice of antifungal (targeting the confirmed, suspected, or highly prevalent fungal pathogens); and (3) rational dosage (adjusting for loading/maintenance dose, liver/kidney function, and dialysis status). The duration

of therapy was not evaluated for medical and logistical reasons.

Risk factors of IFI, per local protocol, included but were not limited to: admission to the ICU for ≥7 days, invasive ventilation for ≥48 h, use of broad-spectrum antibiotics for ≥4 days, severe bacteraemia, central venous catheter, total parenteral nutrition, abdominal surgery, dialysis, JJ stent, candiduria or *Candida* urinary tract infection, severe neutropenia (<500/mm^3) for ≥10 days, pancreatitis, secondary or recurrent peritonitis, diabetes, being immunocompromised or using immunosuppressants, transplants, etc. The Ostrosky-Zeichner rule includes (1a) any systemic antibiotic (days 1 to 3) OR (1b) presence of a central venous catheter (days 1 to 3) AND (2) at least 2 of the following: (2a) total parenteral nutrition (days 1 to 3); (2b) any dialysis (days 1 to 3); (2c) any major surgery (days −7 to 0); (2d) pancreatitis (days −7 to 0); (2e) any use of steroids (days −7 to 3); or (2f) use of other immunosuppressive agents (days −7 to 0) [13]. The Candida score includes severe sepsis (2 points), total parenteral nutrition (1 point), initial surgery (1 point), and multifocal *Candida* colonisation (1 point) [14].

Covariates

We investigated the following covariates: sex (female or male), age (years; <65 or ≥65), body mass index (kg/m^2; <23 or ≥23, per classification for Asians [15]), Charlson Comorbidity Index and comorbidities (cardiovascular diseases; gastrointestinal diseases; kidney diseases; respiratory diseases; and neoplasms), kidney function (estimated glomerular filtration rate), time from admission to initiation of antifungals (days), and clinical features. The clinical features included persistent fever, central venous catheter, admission to the ICU for ≥7 days, total parenteral nutrition, abdominal surgery, ventilator for ≥48 h, JJ stent, dialysis, systemic antibiotics for ≥4 days, pancreatitis, acute kidney injury, neutropenia/immunosuppression, Ostrosky-Zeichner rule, and Candida score. We also investigated the antifungal susceptibility of the isolated fungal strains (from the pre-emptive group, using broth microdilution or gradient diffusion methods for susceptibility testing).

Statistical analysis

We included all eligible medical records for analysis (n = 157). Cases with unmeasurable outcomes were excluded. Data were summarised using descriptive statistics. We reported frequency (with percentage) for categorical variables and median (with interquartile range, IQR, without normal distribution) for quantitative variables. We used logistic and linear regression to investigate the outcomes and reported the estimates with the 95% confidence interval (95% CI). All the assumptions of the regression models were satisfied. To control the type I error rate (5%) from inflation due to multiplicity, we only conducted a 2-tailed hypothesis test for the primary outcome and considered other results as exploratory findings. We attempted to mitigate the impact of immortal time bias by adjusting for the time from admission to initiation of antifungals. The control group for comparison was pre-emptive therapy. We conducted all statistical analyses using R (version 4.2.1, R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient characteristics

The patient characteristics of the included and excluded records were comparable. We included 116 records with empirical therapy and 41 records with pre-emptive therapy for analysis (Fig. 1). Among these 157 patients (median age of 68 [IQR 58–79], 48.4% being female, all being Vietnamese-origin Asians, 34.4% being overweight-to-obese, 59.2% having chronic kidney disease, median Charlson Comorbidity Index of 5 [IQR 3–6]), 74 (47.1%) met the Ostrosky-Zeichner rule while 103 (65.6%) had a Candida score ≥3. The 3 most common risk factors of IFI were having systemic broad-spectrum antibiotics for ≥4 days (97.5%), having JJ stent (93.6%), and admitting to the ICU for ≥7 days (65.6%). Further details of the empirical and pre-emptive groups were summarised in Table 1.

Fungal characteristics in the pre-emptive group

A total of 120 samples from normally sterile sites (e.g., blood, cerebrospinal fluid, brain, pleural fluid, bone, joint fluid, lymph nodes, heart, liver, etc.) were positive for pathogenic fungi. All fungal pathogens being isolated from the specimens were found to have yeast or dimorphic yeast-mold forms, of which 99 (82.5%) were *Candida* spp. and 21 (17.5%) were unidentified. The predominant species in blood and urine cultures was *C. tropicalis*, accounting for 44.1% and 46.0%, respectively. The most isolated pathogen from peritoneal fluid cultures was *C. albicans* (50.0%). For respiratory cultures, most pathogens were monomorphic yeast-form fungi (70.0%). Among 120 fungal cultures, 84 Candidal cases were provided with antifungal susceptibility results. Most strains remained sensitive to the commonly used antifungals (Table 2).

Outcomes

IFI-related mortality During a median follow-up of 27 days (IQR 17–46), we recorded 77 deaths (49.0% [95% CI 41.0–57.1%]) that were related to IFI (60 [51.7%] in the empirical group, 17 [41.5%] in the pre-emptive group). Among these, 22 cases were identified as in-hospital death (17 [14.7%] in the empirical group, 5 [12.2%] in the pre-emptive group), and 55 were discharged with a mortality prognosis (43 [37.1%] in the empirical group, 12

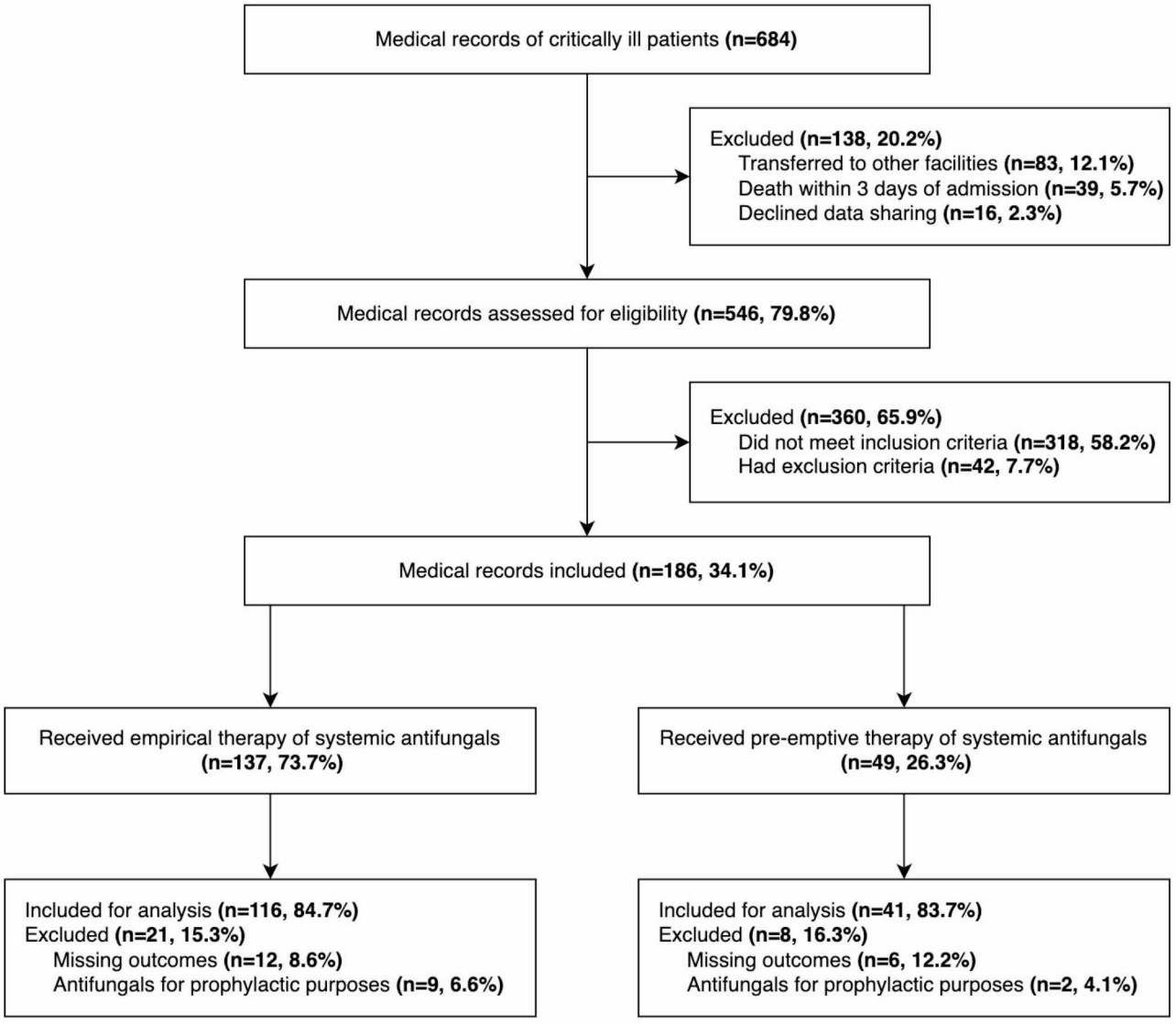

Fig. 1 Flowchart of the study subjects. *Note*. Some percentages may not equate to 100 due to rounding. Initial screening of medical records could not detect antifungal prophylaxis; thus we could only exclude patients receiving prophylactic therapy after data collection

[29.3%] in the pre-emptive group). The risk of IFI-related mortality did not differ significantly between the 2 groups (adjusted odds ratio of 1.86; 95% CI 0.74 to 4.63; $p = 0.184$; Table 3).

Overall rationale of AT We estimated that the overall rationale of AT was at 45.2%, with the 95% CI ranging from 37.2 to 53.4% (41.4% [95% CI 32.3–50.9%] in the empirical group, 56.1% [95% CI 40.0–71.5%] in the pre-emptive group). The proportions of appropriate indication, choice of antifungal, and dosage in the empirical group appeared to be lower than those in the pre-emptive group, but the odds of receiving rational AT, in general, were not statistically different between the 2 groups (adjusted odds ratio of 0.75; 95% CI 0.31 to 1.87; Table 3). The most common reasons for inappropriate indication were not meeting the Ostrosky-Zeichner rule or having a Candida score below 3 (in the empirical group) and acquiring potentially contaminated specimens (in the pre-emptive group). The general explanation for inappropriate choice of antifungal in both groups was prescribing an alternative option instead of a protocol-recommended first-line agent without compelling reasons. For medical orders with inappropriate dosage, most of these cases were due to the lack of a loading dose for antifungals that need significant amounts of time to reach the steady-state concentrations.

LoAT The median LoAT in our setting was 8 days, IQR 6–14 (8 days [IQR 6–13.3] in the empirical group; 9 days [IQR 6–14] in the pre-emptive group). The difference in LoAT between the 2 groups was not statistically significant (adjusted mean difference of -1.1 days; 95% CI -3.2

Table 1 Patient characteristics at initiation of antifungals

Characteristics	Empirical therapy (*n* = 116)	Pre-emptive therapy (*n* = 41)	Total (*n* = 157)
Being female, n (%)	55 (47.4)	21 (51.2)	76 (48.4)
Age (year), median (IQR)	66.5 (55–79)	71 (61–80)	68 (58–79)
Age category, n (%)			
< 65 year	47 (40.5)	14 (34.1)	61 (38.9)
≥ 65 year	69 (59.5)	27 (65.9)	96 (61.1)
Body mass index (kg/m^2), median (IQR)[a]	21.1 (18.6–23.6)	21.6 (19.0–23.8)	21.5 (18.7–23.6)
Underweight-to-normal (< 23 kg/m^2), n (%)	77 (66.4)	26 (63.4)	103 (65.6)
Overweight-to-obese (≥ 23 kg/m^2), n (%)	39 (33.6)	15 (36.6)	54 (34.4)
Charlson Comorbidity Index, median (IQR)	4 (3–6)	5 (3–8)	5 (3–6)
Comorbidities, n (%)			
Cardiovascular diseases	74 (63.8)	25 (61.0)	99 (63.1)
Gastrointestinal diseases	48 (41.4)	16 (39.0)	64 (40.8)
Kidney diseases	67 (57.8)	26 (63.4)	93 (59.2)
Neoplasms	19 (16.4)	9 (22.0)	28 (17.8)
Respiratory diseases	7 (6.1)	3 (7.3)	10 (6.4)
eGFR (mL/min/1.73 m^2), median (IQR)	45.1 (28.0–66.4)	39.5 (22.8–74.0)	44.9 (26.7–67.2)
Time from admission to initiation of antifungals (days), median (IQR)	9 (16.5–34.3)	10 (17–27)	9 (17–34)
Clinical features, n (%)			
Persistent fever	84 (72.4)	29 (72.5)	113 (72.4)
Central venous catheter	60 (51.7)	26 (63.4)	86 (54.8)
ICU stay for ≥ 7 days	76 (65.5)	27 (65.9)	103 (65.6)
Total parenteral nutrition	60 (51.7)	22 (53.7)	82 (52.2)
Abdominal surgery	18 (15.5)	15 (36.6)	33 (21.0)
Ventilator for ≥ 48 h	76 (65.5)	22 (53.7)	98 (62.4)
JJ stent	109 (94.0)	38 (92.7)	147 (93.6)
Dialysis, including CRRT and IHD	30 (25.9)	11 (27.5)	41 (26.3)
Broad-spectrum antibiotics for ≥ 4 days	113 (97.4)	40 (97.6)	153 (97.5)
Pancreatitis	8 (6.9)	1 (2.4)	9 (5.7)
Acute kidney injury	68 (58.6)	26 (63.4)	94 (59.9)
Neutropenia or immunosuppression	10 (8.6)	2 (4.9)	12 (7.6)
Meeting Ostrosky-Zeichner rule, n (%)[b]	54 (46.6)	20 (48.8)	74 (47.1)
Candida score ≥ 3 points, n (%)[c]	76 (65.5)	27 (65.9)	103 (65.6)

Abbreviations: CRRT, continuous renal replacement therapy; eGFR, estimated glomerular filtration rate; ICU, intensive care unit; IHD, intermittent haemodialysis; IQR, interquartile range

[a] Body mass index was categorised based on the classification for Asians [15]

[b] Ostrosky-Zeichner rule includes (1a) any systemic antibiotic (days 1 to 3) OR (1b) presence of a central venous catheter (days 1 to 3) AND (2) at least 2 of the following: (2a) total parenteral nutrition (days 1 to 3); (2b) any dialysis (days 1 to 3); (2c) any major surgery (days − 7 to 0); (2d) pancreatitis (days − 7 to 0); (2e) any use of steroids (days − 7 to 3); or (2f) use of other immunosuppressive agents (days − 7 to 0) [13]

[c] Candida score includes severe sepsis (2 points), total parenteral nutrition (1 point), initial surgery (1 point), and multifocal *Candida* colonisation (1 point) [14]

to 1.0; Table 3). Early discontinuation of AT (LoAT less than 14 days without compelling reasons) was frequently documented (115 cases out of 157 [73.2%]; 87 [75.0%] in the empirical group; 28 [60.1%] in the pre-emptive group), primarily due to drug shortages, in-hospital death, or family requests for discharge/transfer without further treatment.

Discussion

In general, we did not find any significant differences in IFI-related mortality, overall rationale of AT, and LoAT between patients receiving empirical and pre-emptive therapy. The most frequent reasons for inappropriate indications were failing to meet the Ostrosky-Zeichner rule or having a Candida score below 3 in the empirical group, and obtaining potentially contaminated specimens in the pre-emptive group. The primary explanation for inappropriate antifungal selection was prescribing an alternative/non-prioritised agent without sufficient justification. Most cases of inappropriate dosing were due to the absence of a loading dose for certain antifungals. Early discontinuation of AT was primarily due to drug shortages, in-hospital death, or family requests for discharge/transfer without further treatment.

Our results about IFI-related mortality were consistent with prior reports [7, 16], suggesting a similar prognosis

Table 2 Antifungal susceptibility of the isolated fungal strains

Susceptibility[a]	C. albicans[b]	C. tropicalis[c]	C. glabrata[d]	C. parapsilosis[e]	Candida spp.[f]	Total[g]
	(*n* = 27)	(*n* = 38)	(*n* = 8)	(*n* = 6)	(*n* = 5)	(*n* = 84)
Polyene, n (%)						
Amphotericin B	25 (92.6)	38 (100)	8 (100)	6 (100)	4 (80.0)	81 (96.4)
Triazole, n (%)						
Fluconazole	27 (100)	34 (89.5)	8 (100)	5 (83.3)	4 (80.0)	78 (92.9)
Voriconazole	27 (100)	37 (97.4)	8 (100)	6 (100)	4 (80.0)	82 (97.6)
Echinocandin, n (%)						
Caspofungin	27 (100)	38 (100)	7 (87.5)	6 (100)	5 (100)	83 (98.8)
Micafungin	27 (100)	38 (100)	8 (100)	6 (100)	5 (100)	84 (100)
Pyrimidine, n (%)						
Flucytosine	27 (100)	38 (100)	8 (100)	6 (100)	5 (100)	84 (100)

Abbreviations: *C. albicans*, *Candida albicans; C. glabrata*, *Candida glabrata; C. parapsilosis*, *Candida parapsilosis; C. tropicalis*, *Candida tropicalis*

[a] Susceptibility tests were conducted using broth microdilution or gradient diffusion methods

[b] *C. albicans* was found in 12 blood cultures, 14 urine cultures, 5 peritoneal fluid cultures, and 5 respiratory cultures

[c] *C. tropicalis* was found in 15 blood cultures, 23 urine cultures, 3 peritoneal fluid cultures, and 1 respiratory culture

[d] *C. glabrata* was found in 2 blood cultures, 4 urine cultures, and 2 peritoneal fluid cultures

[e] *C. parapsilosis* was found in 5 blood cultures and 2 urine cultures

[f] *Candida* spp. was found in 4 blood cultures and 1 urine culture

[g] Excluding yeast-form species that were unidentified

Table 3 Study outcomes

Outcomes	Empirical therapy	Pre-emptive therapy	Estimated effect[a]
	(*n* = 116)	(*n* = 41)	(95% CI)
IFI-related mortality, n (%)	60 (51.7)	17 (41.5)	1.86 (0.74 to 4.63)[b, c]
Overall rationale of AT, n (%)	48 (41.4)	23 (56.1)	0.75 (0.31 to 1.87)[b]
Indication, n (%)	85 (73.3)	33 (80.5)	
Choice of antifungal, n/total (%)[d]	66/85 (77.6)	27/33 (81.8)	
Dosage, n/total (%)[e]	48/66 (72.7)	23/27 (85.2)	
LoAT (days), median (IQR)	8 (6–13.3)	9 (6–14)	-1.1 (-3.2 to 1.0)[f]

Abbreviations: 95% CI, 95% confidence interval; AT, antifungal therapy; IFI, invasive fungal infection; IQR, interquartile range; LoAT, length of antifungal therapy; LoS, length of stay

[a] Adjusted for sex, age, body mass index, Charlson Comorbidity Index and comorbidities, kidney function, and clinical features; reference value was pre-emptive therapy

[b] Estimated using logistic regression and reported as odds ratio. All assumptions of the logistic regression were satisfied

[c] $p = 0.184$

[d] Cases with irrational indications for AT were excluded

[e] Cases with irrational choices of antifungal were excluded

[f] Estimated using linear regression and reported as mean difference. All assumptions of the logistic regression were satisfied

in both groups after AT initiation. Akin to previous guidelines [17, 18], these findings could not facilitate a recommendation for either empirical or pre-emptive therapy in the intensive care setting, at least not until more effective diagnostic methods or therapeutically optimising models are available. However, this uncertainty did allow us to create a flexible framework for tailoring antifungal treatments to individual patients, while still adhering to the best available evidence and resource limitations. With this framework, we could ethically and economically manage critically ill patients with IFI in challenging scenarios in our ICU setting, such as drug shortages, financial difficulties, patient preferences, and terminal illnesses.

To the best of our knowledge, this is the first study in a low-resource Asian country to investigate AT initiating strategies in critically ill patients with IFI. Our findings can provide evidence to refine clinical guidelines in LMIC, emphasising that physicians may have flexibility in choosing between empirical or pre-emptive approaches depending on individual patient circumstances, clinical judgment, and available resources. These results can also support the development of specific protocols for empirical/pre-emptive therapy that balance clinical efficacy with the practical challenges faced in resource-limited environments. Additionally, we highlight the need for ongoing evaluation of the antifungal stewardship program, which aims to maximise treatment outcomes while minimising unnecessary drug use and associated costs.

However, our study has some limitations. First, we only had a limited single-centre sample size that could have resulted in potentially underpowered analyses and low generalisability. Second, our sample might not be large enough to reflect an important sub-population of patients with neutropenia or haematological malignancies. Third, the limited sample size did not facilitate us to accurately estimate the prevalence of suspected (possible/probable) or proven IFI in this study. Fourth, the retrospective cohort design could lead to misclassification of exposure or outcome status. Fifth, we could not include and investigate patients who died of IFI before initiating AT, which could have introduced selection bias into this study. Finally, we could not address how the rationale of AT could affect the treatment outcomes. Given the relatively high rate of inappropriate antifungal use, antimicrobial stewardships should be further tailored for IFI, especially with the choice and dosage of AT.

Conclusion

The proportion of IFI-related mortality was high in critically ill patients on systemic antifungals. The overall rationale of AT was at a low level, with the median LoAT lower than the generally recommended duration of at least 14 days. There were no significant differences in IFI-related mortality, overall rationale of AT, and LoAT between those receiving empirical and pre-emptive therapy.

Abbreviations

AT	Antifungal therapy
CI	Confidence interval
ICU	Intensive care unit
IFI	Invasive fungal infection
IQR	Interquartile range
LMIC	Low-middle-income countries
LoAT	Length of antifungal therapy
STROBE	Strengthening the reporting of observational studies in epidemiology

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12879-025-10816-7.

Supplementary Material 1

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Author contributions

Conceptualisation: HTP and M-HT. Study design and methods: HTP and M-HT. Data collection: HTP, K-HT-N, and M-HT. Data analysis and interpretation: HTP, RLC, THK, and M-HT. Manuscript drafting and revision: all authors. Supervision: M-HT. All authors read and agreed to the final manuscript.

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Data availability

The datasets used and/or analysed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Nhan Dan Gia Dinh Hospital under approval number 52/NDGD-HDDD. All participants gave their written informed consent prior to participation.

Consent for publication

Not applicable.

Competing interests

HTP reported receiving speaking fees and travel reimbursement from Servier Vietnam Ltd and Pfizer Vietnam Ltd, grants from Servier Vietnam Ltd, and speaking fees from Aguettant Asia Pacific Pte Ltd outside the submitted work. M-HT reported receiving travel reimbursement from Pfizer Vietnam Ltd and Viatris Vietnam Ltd, speaking fees and grants from Servier Vietnam Ltd, and speaking fees from Aguettant Asia Pacific Pte Ltd outside the submitted work. The other authors declare no competing interest.

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