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Original Article

Clinical impact of the combination of rapid species identification and antifungal stewardship intervention in adults with candidemia

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Abstract *Background:* Candidemia is associated with a high mortality rate. This study aimed to evaluate the clinical impact of a diagnostic intervention and antifungal stewardship in adults with candidemia, including effectiveness in facilitating appropriate antifungals and improving patient outcomes.
Methods: A pre-post quasi-experimental study was conducted to analyze the impact of the integrated workflow of rapid species identification and antifungal stewardship intervention provided by infectious disease specialists for adults with candidemia at a medical center in southern Taiwan from March 1st, 2014 to February 29th, 2016. The primary endpoint was 30-day crude mortality, and secondary outcomes included the time to species identification, time to initial antifungal modification, and length of hospital stay.
Results: Total 303 patients with candidemia were included, including 152 adults in the pre-intervention period (Mar. 1st, 2014–Feb. 28th, 2015; control group) and 151 in the intervention period (Mar. 1st, 2015–Feb. 29th, 2016; case group). Demographic and clinical characteristics of patients in two groups were similar. The case group had a shorter time to species identification (72 *vs.* 96 h, $P < 0.001$) and earlier receipt of antifungals (47 *vs.* 59 h, $P < 0.001$) than the control group. Of note, the 30-day mortality rate (27.2% *vs.* 39.5%, $P = 0.028$) was lower

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and the hospital stay (43.5 *vs.* 46.0 days, $P = 0.006$) was shorter in the case group.
Conclusion: Rapid diagnostic workflow and antifungal stewardship provided by infectious disease specialists can promote early initiation of antifungal therapy and improve outcome for adults with candidemia.

Introduction

Candida species have become common pathogens in nosocomial bloodstream infections (BSIs) in United States since the beginning of 21st century.[1] In several population-based studies, *Candida* species have been found to cause 3.88—122 episodes of BSIs per 100,000 individuals.[2–5] The distribution of *Candida* species has changed over the past decades. While *Candida albicans* still is the dominating pathogen, it only accounts for half of clinical *Candida* isolates.[2,5,6] The rise in candidemia and azole resistance, particularly among non-*albicans Candida* isolates, posed a new threat to public health.[7–10] Candidemia is associated with a high attributable mortality rate, ranging from 36% to 47%.[11] Delay in the administration of optimal antifungal therapy can lead to unfavorable clinical outcomes.[12–14] Therefore, precise antifungal stewardship in candidemia can play a crucial role in directly impacting the prognosis of infected patients.

Several studies have shown that antifungal stewardship interventions (ASI) have resulted in a significant reduction in the time to administer appropriate antifungal therapy and have improved adherence to bundled care protocols.[15] However, limited impact on mortality and length of hospital stays were noted.[15–17] The matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF-MS) has been integrated into routine laboratory procedures for both bacteria and yeast species identification.[18–20] This technique has the potential to facilitate early customization of appropriate antifungal therapy.[21–23] The aim of our study was to evaluate the effects of an antifungal stewardship intervention, coupled with a rapid diagnostic workflow utilizing MALDI-TOF-MS, on the outcomes of adult patients with candidemia.

Materials & methods

Study population and data collection

A pre-post quasi-experimental study was conducted at National Cheng Kung University Hospital (NCKUH), which is a tertiary academic medical center with 1343 licensed beds, providing comprehensive health services to patients in southern Taiwan. The study received Institutional Review Board approval (B-ER-103-345). The patients aged ≥20 years with candidemia were identified utilizing the electronic medical record and clinical microbiology reports of the institution. MALDI-TOF-MS was introduced to assess microbiological workflow of organism identification since March 1st, 2015. The results were compared with a historical pre-intervention, control group, in which conventional methods were used for organism identification in the previous year during the same calendar months, from March 1st, 2014 to February 28th, 2015. Thirteen patients, including 7 in the control group and 6 in the case group, were excluded for the analysis of the time to initial antifungals because of their early death before the administration of antifungal therapy. Additionally, the patients with yeast-like organisms other than *Candida* species in blood or organisms not validated for identification by MALDI-TOF-MS requiring other methods at the time of this study was excluded in both groups.

Microbiology and antifungal stewardship intervention workflow

The workflow of microbiology and antifungal stewardship interventions (ASI), which followed those of Weng et al.,[24] was summarized at Fig. 1. For both groups, Gram staining and subculture were routinely performed for positive blood cultures, and the preliminary results would be reported to the electronic medical recording system from 8 AM to 11 PM. As for reports between 11 PM and 8 AM, Gram stain results were reviewed in the following morning. Primary care physicians would be informed for the Gram stain result of a yeast-like pathogen in blood culture through the medical recording system via a text message. The VITEK 2 system (bioMe'rieux, Durham, NC, USA) was performed for species identification using VITEK® 2 Yeast identification card during preintervention period, and MALDI-TOF-MS (bioMérieux, Marcy l'Etoile, France) for identification during intervention period. Regardless of identification methodology, final results were reported to the electronic medical record system on the early morning shift. The prescription of antifungal agents, indication of treatment, and dosage would be approved by the ASI team. The antifungal susceptibility testing was recommended individually.

The team of intervention program of candidemia consists of two infectious diseases (ID) specialists, clinical microbiologists and pharmacists. The ID specialist reviewed notification for the patients with positive blood cultures and provided prescribers with pre-established, evidence-based recommendations, in accordance with institutional guidelines at the time of yeast-like Gram stain, organism identification and antifungal susceptibility testing results. ID specialists of the ASI team monitored a positive blood culture list at least once daily, providing feedbacks to providers during business hours from Monday to Friday as a part of ASI workflow. The prescription of antifungal agents,

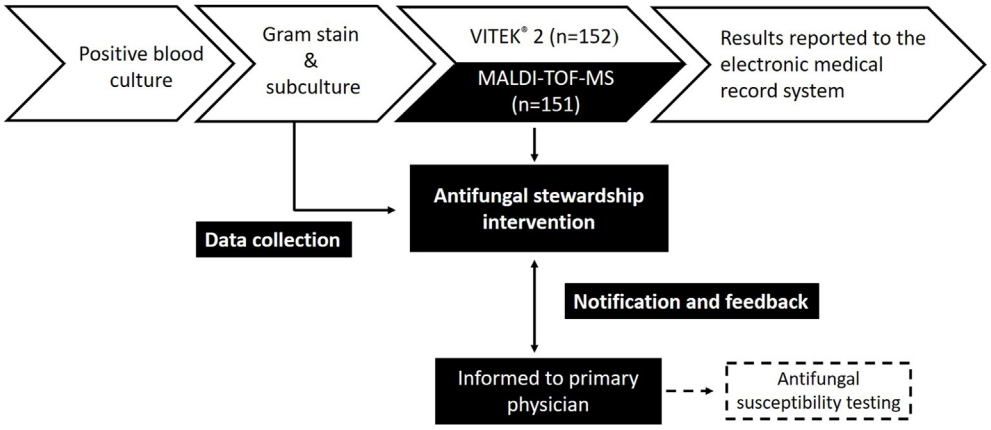

Figure 1. Antifungal stewardship intervention and microbiology workflow in candidemia. Footnote: White boxes represent both pre-intervention and intervention workflow. Black boxes and lines represent additional steps to the antifungal stewardship intervention workflow for the intervention group, including whether to examine the microbial susceptibility test.

indication of treatment, and dosage would be approved by the ASI team, who would provide further information, including antifungal susceptibility testing, reminding follow-up blood cultures, source control, and optimal duration, to the primary care physicians.

Detailed strategies implemented as a part of ASI in patients with candidemia based on the risk strategy. Once blood culture yielded yeast-like microorganism, the ASI team forwardly informed clinical physicians to prescribe antifungals, mostly fluconazole or micafungin. Anidulafungin was introduced to NCKUH since 2017. For high-risk patients, including those with hemodynamic instability, neutropenia, or azole exposure within the past 30 days, initial antifungal agent was an echinocandin. Otherwise, for non-high-risk patients, initial fluconazole at loading dosage 800 mg (or 12 mg/kg) was administered. The interventional therapeutic strategies were described as follows and shown in Supplementary Fig. 1.

1. If the pathogen was identified *C. albicans or Candida parapsilosis*, fluconazole at the daily dosage of 400 mg (or 6 mg/kg) was recommended firstly. For those with empirical echinocandin therapy, we suggested switching to fluconazole.
2. If *C. tropicalis was* identified, based on the fluconazole susceptibility rate in our hospital, fluconazole therapy was optimized to the high-dose regimen 800 mg (or 10—12 mg/kg) daily. Switching to an echinocandin would be recommended, if general condition of the affected patients deteriorated. The antifungal susceptibility testing was recommended for the causative *C. tropicalis* isolate.
3. If the pathogen was identified as *Candida glabrata*, we suggested an echinocandin as the first choice. High-dose fluconazole was only considered for a hemodynamically stable patient.
4. Further antifungal choices and dosages were based on the result of minimum inhibitory concentration (MIC) of fluconazole. If the isolate was susceptible to fluconazole, the standard dose of fluconazole, 400 mg or 6 mg/kg daily, was suggested. If the isolate was susceptible-dose dependent to fluconazole, a high dose fluconazole, 800 mg or 10—12 mg/kg daily, was preferred. For fluconazole resistance, echinocandin therapy was the recommended regimen.
5. If the patient was intolerant to echinocandin therapy in the above clinical settings, amphotericin B or other antifungals would be recommended.

Definitions and outcome

Demographic data was retrieved from medical charts and recorded in a standard record form. Candidemia was defined as the isolation of *Candida* species from at least one blood culture with compatible sepsis syndrome. *Polymicrobial bloodstream infection was defined as the presence of more than one pathogen, including bacteria or fungi, isolated from blood.* Infection source was defined as being pneumonia, if there were radiographic and laboratory evidences for pulmonary infection with no growth of significant pathogens other than the same *Candida* species in bronchoalveolar lavage fluid, and no recognized sources of candidemia. The antifungal regimens administered within 72 h of the onset of candidemia was regarded as empiric therapy, and the regimens administered afterward as definite therapy. Appropriate antifungal therapy was defined as the receipt of antifungal regimens in the optimal dose, according to *in vitro* susceptibility testing or clinical improvement by ID specialists' evaluation for the patients without susceptibility testing. The latter were often infected by *C. albicans* isolates, which were rarely resistant to fluconazole. The time to initial antifungal agents was the interval between the discovery of yeast-like pathogens in Gram stain for blood samples with a positive signature and the initiation of appropriate antifungal therapy. The primary outcome measure was the 30-day crude mortality, and the secondary outcomes included cumulative time of identification, length of hospital stay (LOS) of survivors, and the time to initial antifungal agents. A critical illness classified by the Pitt bacteremia score on the day of candidemia onset, which has been used to predict 30-day mortality in candidemia, according to a published research.[25] The prescription amount of antifungal agents was presented as DID (defined daily dose [DDD] per 1000 inhabitant-days).

Table 1 Demographics of clinical characters of patients with candidemia.

Characteristics	Pre-intervention group, n = 152	Intervention group, n = 151	*p* values
Age, median (IQR), years	66 (55–77)	66 (52–78)	0.65
Gender, male	100 (65.8)	98 (64.9)	0.9
Comorbidity			
Cancer	90 (59.2)	77 (51.0)	0.166
Diabetes mellitus	58 (38.2)	43 (28.5)	0.088
Chronic kidney disease	48 (31.6)	37 (24.5)	0.2
Cancer	90 (59.2)	77 (51.0)	0.166
Chronic hepatitis	24 (15.8)	12 (7.9)	0.5
Coronary artery disease	17 (11.2)	13 (8.6)	0.565
Cerebral vascular accident	9 (5.9)	10 (6.6)	0.818
None	8 (5.3)	9 (6.0)	0.8
Critical illness (Pitt bacteremia score ≥4 points)	48 (31.6)	57 (37.7)	0.279
Polymicrobial bloodstream infection	38 (25)	33 (21.9)	0.588
Candida species			
Candida albicans	84 (55.3)	54 (35.8)	0.001
Non-albicans Candida	68 (44.7)	97 (64.2)	0.001
Candida parapsilosis	20 (13.2)	39 (25.8)	0.006
Candida tropicalis	32 (21.1)	29 (19.2)	0.775
Candida glabrata	19 (12.5)	22 (14.6)	0.618
Source of bloodstream infection			
Vascular catheter-related infection	61 (40.1)	45 (29.8)	0.07
Primary bloodstream infection	60 (39.2)	79 (52.3)	0.03
Pneumonia	16 (10.5)	6 (4.0)	0.04
Skin soft-tissue infection	6 (3.9)	11 (7.3)	0.22
Urinary tract infection	4 (2.6)	5 (3.3)	0.75
Intra-abdominal infection	3 (2.0)	2 (1.3)	1.0
Time to initial antifungals, median (IQR), hours	59 (40–81)	47 (26–66)	0.001
30-day crude mortality	0 (39.5)	1 (27.2)	0.028
In-hospital crude mortality	70 (46.1)	59 (39.1)	0.246
Hospital stay of survivors, median (IQR), days	46 (28.8–77.8)	43.5 (31.0–71.8)	0.006

Data are given as numbers (percentages), unless otherwise specified.
Abbreviation: IQR, interquartile range.

Statistical analysis

The data were analyzed by the SPSS software version 22.0 for the Windows (SPSS Inc., Chicago, IL, USA). The continuous variables were expressed as mean values with standard deviation and were compared by the Mann–Whitney U or Student T test. The categorical variables expressed as the percentages of case numbers were analyzed and compared by the Fisher's exact or Chi-square test. The 30-day survival analysis and cumulative time of *Candida* identification between the pre-intervention control and the intervened case group were compared with a Cox proportional hazard model, adjusted for confounding variables. Besides, the independent predictors for the 30-day crude mortality were identified by means of the logistic regression analysis. Regarding multiple variable interference, we defined a strict cut-off value ($P \leqq 0.05$) among univariate analysis for the further multivariate logistic regression analysis. If the *p*-value was 0.05 or less, the variable was trumpeted as statistically significant. All of the tests were two-tailed.

Results

Total 303 patients with candidemia were included, and their demographic and clinical characteristics were summarized at Table 1. One hundred and fifty-one patients in the intervened cases and 152 patients in the control group were included for final analysis. Demographic characteristics, including age, gender, co-morbidities, clinical status (disease severity) at the time of BSIs onset, and infectious sources were similar in both groups.

All included patients received empiric antifungals with primarily either fluconazole or micafungin. The median time to initial antifungal agents was significantly shorter in the intervened case group (47 h *vs.* 59 h, $P < 0.001$) (Table 1). Besides, the case group had shorter median time of *Candida* species identification (72 h *vs.* 96 h, $P < 0.001$, Fig. 2). Of note, the 30-day crude mortality rate was lower in the case group (27.2% *vs.* 39.5%, $P = 0.028$), and even with the exclusion of these 13 cases of early death, such an outcome variable remained to be more favorable in the case group (25.5% *vs* 37.9%, $P = 0.032$). The Kaplan–Meier

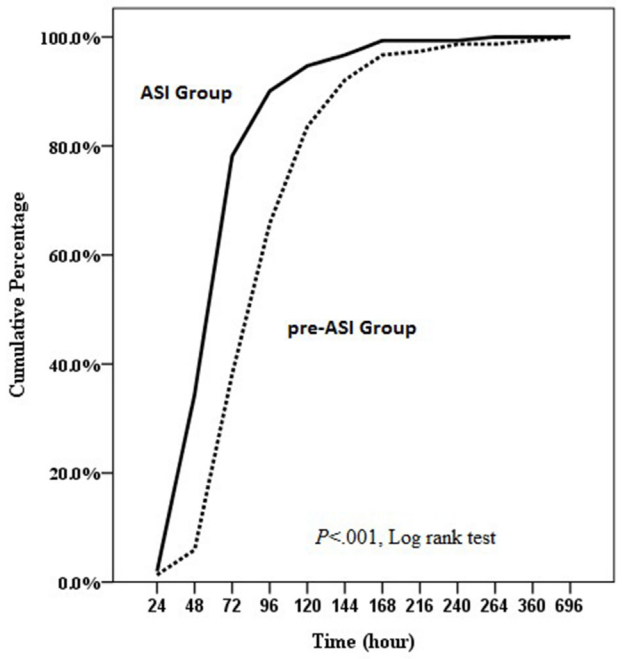

Figure 2. Cumulative time to species identification probability of the interventional case group (solid line) compared with the pre-intervention control group (dot line). Median time to species identification (interquartile range): 72 (48–72) hours *vs.* 96 (72–120) hours ($P < 0.001$, Log rank test).

survival analysis also demonstrated that the case group showed a better clinical outcome at 30 days ($P = 0.008$, Fig. 3). Among the study participants, 57 patients, including three patients in the control group and 54 patients in the case group, had received empiric antifungals before the preliminary result of Gram stain for blood culture and were more likely to be critically ill (*i.e.*, Pitt bacteremia score ≥4 points) than the others (49.1% *vs.* 31.3%). With the exclusion of these 57 cases, the 30-day crude mortality rate remained to be lower in the case group (21/97, 21.6% *vs.* 59/149, 39.6%, $P = 0.003$).

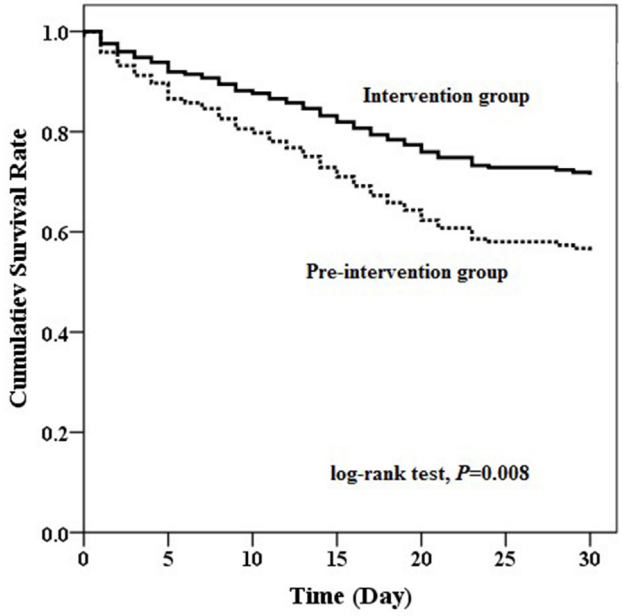

Figure 3. The survival analysis curves in the intervention case group (solid line) associated with a favorable 30-day mortality than pre-intervention control group (dot line) (log-rank test, $P = 0.008$).

In the multivariable analysis for the variables associated with the 30-day crude mortality, ASI (OR: 0.55; 95% confidence interval [CI]: 0.31–0.96; $P = 0.03$) and appropriate antifungal therapy (OR: 0.27; 95% CI: 0.08–0.67; $P = 0.04$) were associated with a favorable outcome. In contrast, those with pneumonia (OR: 6.55; 95% CI: 2.18–19.71; $P = 0.01$) or a critical illness (OR: 3.63; 95% CI: 2.08–6.32; $P < 0.001$) heralded a poor prognosis (Table 2).

As for the causative *Candida* species, the most common species was *C. albicans* (45.5%, n = 138), followed by *Candida tropicalis* (20.1%, n = 61), *C. parapsilosis* (19.5%, n = 59), and *C. glabrata* (13.5%, n = 41). None of *Candida* species was associated with the clinical outcome within 30 days after the onset of candidemia (Table 2).

As the ASI was implemented, there were some changes of annual antifungal consumption. There was a reduction in intravenous fluconazole use, with median DID of 25.21 (25.11–26.76) in the control group *vs.* 20.54 (18.99–23.23) in the case group ($P = 0.023$). But the micafungin usage was similar in two groups, with median DID of 2.32 (2.06–2.84) in the control group and 3.57 (2.63–5.52) in the case group ($P = 0.143$) (Supplementary Figure 2).

Discussion

This study demonstrated that species identification workflow using MALDI-TOF in conjunction with antifungal stewardship by ID specialists could not only shorten the time to identify the species causing candidemia and LOS, decrease the time to appropriate antifungal therapy, but also improve clinical outcome at 30-day. Compared to the period without the above interventions, ID specialists forwardly informed precise management of candidemia to primary physicians could lead to a positive prognostic impact on candidemia patients, which was different from the study findings of earlier studies, which presented no significant improvement in terms of short-term survival.[15–17,26,27] Previous studies have revealed the importance of appropriateness of antifungals and the improvement of appropriateness and duration of antifungal therapy by the pharmacist-driven antifungal stewardship program.[27,28] Moreover, our ASI team integrated not only the pharmacists, but also ID specialists and clinical microbiologists. Delayed empiric antifungals beyond 12 h after having the first positive blood sample has been linked to greater mortality.[29] In our study, 57 patients have been empirically treated with antifungal agents before the preliminary microbiological result, and were more likely to be critically ill, as defined by the presence of a high Pitt bacteremia score (≥4 points). The majority (54, 94.7%) of these 57 patients were the intervened cases, and would be likely to adversely affect the patient outcome. With the exclusion of 57 patients with empirical antifungal therapy, the intervened group still had a

Table 2 Multivariate logistic regression analysis of the variables associated with the 30-day crude mortality.

Variables	Survivors (n = 202)	Non-survivors (n = 101)	Univariate analysis		Multivariate analysis	
			OR (95% CI)	*p* values	OR (95% CI)	*p* values
Age; median (IQR), year	65 (52–77)	69 (58–79)	-	0.05	1.00 (0.99–1.02)	0.81
Male gender	136 (67.3)	62 (61.4)	0.77 (0.47–1.27)	0.31		
Diabetes mellitus	59 (29.2)	42 (41.6)	1.73 (1.05–2.84	0.038	1.61 (0.92–2.81)	0.09
Chronic kidney disease	44 (21.8)	41 (40.6)	2.45 (1.46–4.12)	0.01	1.44 (0.80–2.61)	0.23
Candida parapsilosis	46 (22.8)	13 (12.9)	0.5 (0.26–0.98)	0.046	0.75 (0.36–1.56)	0.43
ICU onset	83 (41.1)	56 (55.4)	1.78 (1.10–2.89)	0.02	1.12 (0.61–2.06)	0.71
Pneumonia	5 (2.5)	17 (16.8)	7.97 (2.85–22.32)	<0.001	6.55 (2.18–19.71)	0.001
Critical illness (Pitt score ≥4 points)	50 (24.8)	55 (54.5)	3.64 (2.19–6.02)	<0.001	3.63 (2.08–6.32)	<0.001
Antifungal stewardship intervention	110 (54.5)	41 (40.6)	0.57 (0.35–0.93)	0.028	0.55 (0.31–0.96)	0.03
Appropriate antifungal therapy	198 (98.0)	92 (91.1)	0.21 (0.06–0.69)	0.012	0.27 (0.08–0.67)	0.04

Data are given as the numbers (percentages) unless otherwise specified. Ellipses indicate "not available".
Abbreviation: ICU: intensive care unit; OR, odds ratio; CI, confidence interval; IQR, interquartile range.

favorable clinical outcome (21.6% *vs.* 39.6%, $P = 0.003$), echoing our finding in the multivariate logistic regression analysis that antifungal stewardship intervention, which would be not needed for these 57 patients, was an independent prognostic factor. Therefore, our study suggests a prognostic benefit of early antifungal therapy for the cases of candidemia, and supports the crucial role of ID specialists in an ASI program.

Though treatment options and guideline have been revised in 2016, our strategies including treatment options, following the latest guidelines at that time, were unchanged throughout entire study period. There was also no remarkable change of antifungal resistance in our hospital. With the same commonly used antifungal agents, azoles and echinocandins, in the past study period and in the current time, we consider the outcome data of the antifungal stewardship bundle to be clinically significant, irrespective of the study time.

Several studies demonstrated rapid identification technology with the integration of antimicrobial stewardship intervention decreased fatality and LOS of patients with gram-negative bacteria bloodstream infections.[24,30,31] However, the clinical value of ID specialists in directing antifungal stewardship program on candidemia patients remains controversial. Several studies have reported the possible effect of ASI on antifungal consumption and expenditure,[32,33] but few studies evaluated the association of ASI and patient safety. The responsibility of ASI varies among hospitals, but the overall goal should be to improve health outcomes and minimize morbidities. Previous studies with limited sample sizes may underestimate the outcome impact.[15–17,25]

Farmakiotis et al. have reported that early consultation for ID specialists could improve outcome and the benefit of early initiation of appropriate antifungal treatment was more prominent in the cases of non-catheter-related candidemia.[34] Of note, rapid organism identification using MALDI-TOF-MS without ASI did not reduce the time to initiate effective therapies or lower the mortality rate.[35] Such a finding suggests that the implementing new rapid testing modalities alone without ASI may increase diagnostic costs without improving outcomes in the cases of candidemia.[36]

Antifungal stewardship is a crucial component of the broader antimicrobial stewardship programs that aim to optimize the use of antifungal agents, including ensuring antifungal medications used appropriately, safely, and effectively and minimizing the risks of adverse effects and resistance development. However, there is lack of evidences supporting the scenario of prevention of antifungal resistance by antifungal stewardship. After the implement of ASI, fluconazole consumption decreased, but no significant increase of micafungin usage was noted. The trend in non-susceptible fluconazole rate from 2012 to 2017 was steady in the study hospital ($P = 0.224$). We reputed it as the consequence of appropriate and rational antifungal usage. ASI could impact the selection of antifungals and prevent unnecessary use. Appropriate antifungal agents are crucial for the treatment of candidemia, and fine tuning the class of antifungal therapy is an essential component of antifungal stewardship programs, if the result of antifungal susceptibility testing is available.[37] DID can be one of the

parameters monitoring antifungal burdens in healthcare facilities or countries. However, the association between antifungal DID, antifungal resistance and subsequent outcomes of candidemia patients is controversial. The studies have reported conflicting results,[38,39] indicating that the association of DID and candidemia outcomes appears to be complex and multifactorial. Further investigations are warranted to clarify the interaction.

The proportion of non-*albicans Candida,* esp. *Candida parapsiliosis,* increased in the intervention period, and the relevant factor related to the species shift among the candidemia isolates was not elucidated in the present study. However, we found that the bloodstream infections due to *C. parapsilosis* were not linked to the 30-day crude *mortality.*

There were several limitations in our study. First, our intervention discontinued during off-business hours, up to two days on weekends. No full-time intervention may decrease the power of beneficial effect. However, there was still a favorable outcome in the intervened cases. Second, we didn't take the expenditure or labor of ASI team into account. However, such a team work could avoid miserable consequences, and warranted comprehensive p*harmacoeconomic* analyses to justify clinical implementations of ASI. Third, the definition of appropriateness of antifungal was not objective at all, since subjective judgment of clinical improvement by ASI members was regarded as being appropriate, if susceptibility testing was not available. However, only 10% of the included patients had no antifungal susceptibility data for the causative isolate. In brief, in our hospital the susceptible rate to fluconazole among all *Candida* isolates, *C. albicans, C. parapsilosis and C. tropicalis* isolates from 2012 to 2017 was 75%, 98%, 90% and 60%, respectively. The detailed susceptibility data will be presented in another ongoing study. Owing to the steady azole-susceptible rate of *Candida* isolates, a small number of the cases without antifungal susceptibility result may trivially affect the overall appropriateness of antifungal therapy and thereafter the 30-day mortality. Source control was one of our essential strategies and all candidemia patients with intravascular catheters were suggested to remove intravascular indwelling catheters. However, the clinical details and timing of catheter removal or source control were not available in the present work. Last, the participating staffs of ASI may vary among hospitals, and the favorable clinical outcomes may not be guaranteed in other healthcare facilities or hospitals.

Conclusion

The implementation of rapid species identification and antifungal stewardship intervention could result in early initiation of appropriate antifungal therapy with optimal class and dosage, and a favorable clinical outcome for adults with candidemia.

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Author contributions

N.Y.L. and W.C.K. conceived the study. H.E.J., C.L.L., W.L.L., J.C.L., and M.C.L. provided data collection, statistical and analytic support. N.Y.L. and H.E.J. analyzed the data. N.Y.L. and H.E.J. prepared the manuscript. All authors reviewed and edited the manuscript.

Declaration of competing interest

All authors: no conflicts.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmii.2023.08.014.