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MAJOR ARTICLE

Antimicrobial Stewardship Review of Automated Candidemia Alerts Using the Epic Stewardship Module Improves Bundle-of-Care Adherence

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Background. Antimicrobial stewardship interventions utilizing real-time alerting through the electronic medical record enable timely implementation of the bundle of care (BOC) for patients with severe infections, such as candidemia. Automated alerting for candidemia using the Epic stewardship module has been in place since July 2015 at our medical center. We sought to assess the impact of these alerts.

Methods. All adult inpatients with candidemia between April 1, 2011, and March 31, 2012 (pre-intervention), and June 30, 2016, and July 1, 2017 (post-intervention), were evaluated for BOC adherence. We also evaluated the impact on timeliness to initiate targeted therapy, length of stay (LOS), and 30-day mortality.

Results. Eighty-four patients were included, 42 in the pre- and 42 in the post-intervention group. Adherence to BOC was significantly improved, from 48% (pre-intervention) to 83% (post-intervention; $P = .001$). The median time to initiation of therapy was 4.8 hours vs 3.3 hours ($P = .58$), the median LOS was 24 and 18 days ($P = .28$), and 30-day mortality was 19% and 26% ($P = .60$) in the pre- and post-intervention groups, respectively.

Conclusions. Antimicrobial stewardship program review of automated alerts identifying patients with candidemia resulted in significantly improved BOC adherence and was associated with a 1.5-hour reduction in time to initiation of antifungal therapy. No significant change was observed with 30-day mortality or LOS.

Keywords. antimicrobial stewardship; candidemia; electronic medical record.

Candidemia is associated with high rates of morbidity and mortality, and it is well recognized that delays in initiation of optimal antifungal therapy can result in poor clinical outcomes [1–4]. Strategies to improve adherence to guideline recommendations, including optimized management and timely initiation of antifungals for candidemia, are important targets for antimicrobial stewardship programs (ASPs) to reduce poor patient outcomes. Previous studies have shown that stewardship review and implementation of bundle of care (BOC) interventions that ensure consistency in the management of candidemia with national guidelines can improve bundle adherence and patient outcomes [5–7].

Timely identification of patients with candidemia is the first step to implementing effective stewardship interventions to improve BOC adherence and timely initiation of optimal antifungal therapy. In a study evaluating the impact of stewardship review and interventions for candidemia, the notification process involved the use of a separate clinical decision support system that communicated data reported in the electronic medical record, which was then reviewed by an antimicrobial stewardship pharmacist [6] Another study utilized the method of paging the primary physician and stewardship program team for review [7]. Antimicrobial stewardship interventions utilizing real-time alerting through the electronic health record can improve timeliness to initiation of appropriate management and enable more consistent implementation of the BOC for patients with severe infections [6–9]. Automated alerting identifying patients with yeast present in blood cultures (candidemia) using the Epic stewardship module (ESM) was implemented at our medical center in July 2015. We sought to assess the impact of ASP pharmacist review of these alerts on adherence to the guideline-recommended bundle of care, timeliness to antifungal initiation, timeliness to targeted antifungal therapy (modification in therapy based on availability of antifungal susceptibility data), and clinical outcomes (length of stay and 30-day mortality).

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METHODS

This study was a retrospective quasi-experimental pre- vs post-intervention analysis to evaluate the impact of stewardship pharmacist review of automated alerts for all adult inpatients with candidemia within the ESM, a clinical decision support platform in the electronic health record. This project was formally determined to be quality improvement, not human subject research, and was therefore not overseen by the institutional review board, per institutional policy. Only adult (≥18 years old) inpatients with yeast identified in blood culture who received at least 48 hours of antifungal treatment between April 1, 2011, and March 31, 2012 (pre-intervention), and June 30, 2016, and July 1, 2017 (post-intervention), were included. Patients were excluded if they did not receive at least 48 hours of antifungal therapy or if they were culture positive at an outside hospital before admission. The study site, an 811-bed acute care academic medical center, has had an antimicrobial stewardship program (ASP) since August 2010. The ASP performs stewardship review Monday through Friday, and interventions are performed by 1 of 2 adult inpatient stewardship pharmacists a second-year infectious diseases (ID)/ASP pharmacy resident.

The ESM, which provides a real-time list of alerts to identify patients requiring review by an ASP pharmacist, was implemented at our hospital in July 2015. We created an alert that "triggers" whenever a patient is growing yeast in a blood culture, signaling the need to review the patient profile to ensure consistency with guideline recommendations. Review of patients with yeast present in blood cultures occurs daily between 0700 to 1900. Of note, during both time periods included in the study, primary providers were notified of positive cultures with yeast after gram stain was performed, as per protocol with all critical lab results. Before April 2012, the ASP pharmacists did not review patients with candidemia unless they were consulted by ID or identified through other stewardship activities, as there was no mechanism in place to be notified of positive blood cultures with yeast. Starting in April 2012, notifications were sent via an "in-basket" feature to alert ASP pharmacists to patients with yeast in a blood culture. For the purposes of this study, we chose to compare the time frame in which no direct ASP review of patients with candidemia was occurring with our current optimized model in which the real-time alerts trigger within the ESM and are reviewed between 0700 and 1900. The primary end point was BOC adherence before and after the implementation of ASP review of the automated alerts for candidemia. Secondary end points included assessing timeliness to initiate antifungal therapy relative to the culture result, time to modify therapy to targeted therapy (following availability of susceptibility data), length of stay, and 30-day mortality.

The bundle of care for patients with candidemia included the following elements [10]:

Appropriate initial empiric antifungal
- Based on internal candidemia/candidiasis treatment pathway recommending the consideration of micafungin over fluconazole for patients at risk for azole resistance—critically ill patients, those with recent azole exposure, those with a history of azole-resistant *Candida* infections, and immune-compromised patients; all others could have received fluconazole or micafungin as "appropriate" initial therapy)

Consult to ID
- At our medical center (pre- and post-intervention) we routinely recommend ID consultation to ensure appropriate workup of patients with candidemia

Consult to ophthalmology

Removal of lines/prosthetic material if applicable

Echocardiography (TEE and/or TTE)

Repeat blood culture
- At least every 24–48 hours from time of initial gram stain until culture-negative, at least 48 hours

Correct duration of therapy
- 14 days from first negative culture, unless disseminated infection and longer duration implemented accordingly—eg, if endovascular, then 4+ weeks, for osteomyelitis 6+ weeks, or as recommended by ID consult service

Abbreviations: ID, infectious diseases; TEE, Transesophagral echocardiogram; TTE, Transthoracic echocardiogram.

Of note, even when the ID consult service was consulted, the stewardship pharmacist continued to review the patient and make recommendations (via page and verbal communication with providers) on all components of the bundle of care. The ID consult service physicians did not receive the automated alerts. We collected data on patient demographics (age, gender, and primary service at the time of blood culture). Data pertaining to antifungal therapy that were collected included specific agent (micafungin, fluconazole, amphotericin, other), dose in mg, dose in mg/kg if fluconazole (appropriate dosing defined as 8 mg/kg +/- for the load and 6 mg/kg +/- 1 mg/kg for maintenance dose for those with normal renal function; 50% dose reduction was deemed appropriate if the patients was receiving dialysis or if the estimated creatinine clearance was <50 mL/min) or amphotericin, date/time initial antifungal initiated, date/time antifungal changed to another agent (eg, if changed from micafungin to fluconazole after susceptibilities known). Culture-specific data reviewed included time to blood culture clearance and source of candidemia (intra-abdominal, intravenous catheter, genitourinary, other).

STATISTICAL ANALYSIS

All statistical analyses were performed using Stata Statistical Software (Version 15, College Station, TX: StataCorp LLC). To evaluate categorical data, the χ^2 test and Fisher exact tests were performed. The Mann-Whitney *U* test was used to evaluate nonparametric continuous data, and the *t* test was used to assess parametric continuous data.

Table 1. Baseline Characteristics

	Pre-intervention (n = 42)	Post-intervention (n = 42)	*P*
Age, average (±SD), y	57 (±19.8)	60 (±15.3)	.31
Male, No. (%)	22 (49)	21 (50)	.92
Hospital service at time of initial culture, No. (%)			
General medicine/cardiology	10 (24)	15 (36)	.34
Hematology/oncology	8 (19)	6 (14)	.50
Surgery	3 (7)	5 (12)	.30
Urology	2 (4)	1 (2)	.67
Intensive care unit	19 (42)	15 (36)	.53
Source of infection, No. (%)			
Line	29 (64)	26 (62)	.65
Intra-abdominal	7 (16)	11 (26)	.43
Urinary	2 (4)	2 (4)	1.0
Wound, skin/soft tissue, ulcers	1 (2)	1 (2)	1.0
Endovascular (LVAD, thrombus, endocarditis)	2 (4)	2 (4)	1.0
Unknown	6 (13)	0 (0)	.03
Candida species, No. (%)			
C. albicans	20 (44)	17 (40)	.66
C. parapsilosis	19 (42)	6 (14)	.003
C. tropicalis	6 (13)	2 (4)	.26
C. glabrata	8 (18)	15 (36)	.14
C. krusei	1 (2)	1 (2)	1.0
C. auris[a]	0 (0)	1 (2)	1.0
Initial antifungal, No. (%)			
Fluconazole	8 (19)	13 (31)	.31
Micafungin	32 (76)	27 (64)	.34
Amphotericin	0 (0)	2 (4)	.49
Posaconazole	0 (0)	0 (0)	1.0
Voriconazole	2 (5)	0 (0)	.49
Correct mg/kg fluconazole dose			
(if applicable, including if changed to fluconazole during course of therapy)	29 (85) (n = 34)	29 (91) (n = 32)	.18

Abbreviation: LVAD, Left ventricular assist device.

[a]*C. auris* may not have been identified by the methods in the lab during the pre-intervention time frame.

RESULTS

Ninety-six patients with candidemia were screened for inclusion. A total of 12 patients were excluded from the analysis (10 patients did not receive at least 48 hours of antifungals to treat the candidemia, and 2 patients were culture positive at an outside hospital before admission). Eighty-four patients were included, 42 in the pre-intervention group and 42 in the post-intervention group. Baseline characteristics, fungal pathogens isolated, and antifungal dosing information are shown in Table 1. All patients received appropriate initial antifungals with primarily either fluconazole or micafungin. More patients in the pre-intervention group had an unknown source

Table 2. Bundle-of-Care Adherence, Pre- and Post-intervention

	Pre-intervention (n = 42)	Post-intervention (n = 42)	*P*
Composite bundle adherence	20 (48)	35 (83)	.001
ID consultation	36 (86)	41 (98)	.11
Ophthalmology consultation	29 (69)	37 (88)	.03
Echocardiography	28 (65)	36 (86)	.04
Lines removed (if applicable)	34 (89) (n = 38)	32 (94) (n = 34)	.67
Repeat blood cultures	41 (98)	42 (100)	1.0
Appropriate initial antifungal	42 (100)	42 (100)	1.0
Correct duration of therapy (if evaluable)	31 (94) (n = 33)	30 (100) (n = 30)	.5

Abbreviation: ID, infectious diseases.

Table 3. Secondary Outcomes, Pre- and Post-intervention

	Pre-intervention (n = 42)	Post-intervention (n = 42)	*P*
Length of stay, median (IQR), d	24 (14–34)	18 (11–28)	.28
30-d mortality, No. (%)	8 (19)	11 (26)	.81
Time to antifungal initiation, median (IQR), h[a]	4.8 (2.2–7.3) (n = 33)	3.3 (2.4–6.5) (n = 28)	.58
Time to targeted antifungals, median (IQR), d[b]	3.1 (2.3–4.8) (n = 22)	3.6 (2.1–4.4) (n = 20)	.63

Abbreviation: IQR, interquartile range.

[a]Some patients were already on antifungals before the culture result, so time to initiate was not included/assessed.

[b]Some patients were already receiving targeted antifungal therapy before susceptibility data were available and were not included in the time to modify therapy based on susceptibility information (time to targeted therapy), as their regimen did not require modification.

of candidemia (13% vs 0%; *P* = .03). Adherence to the bundle of care for the management of candidemia is shown in Table 2 as the composite outcome and each individual component of the bundle of care. Composite bundle adherence was significantly improved (48% vs 83%; *P* = .001). Secondary outcomes evaluated are shown in Table 3. The median time to initiation of antifungal therapy was 4.8 hours vs 3.3 hours (*P* = .58) in the pre- and post-intervention groups, respectively. The median length of stay was 24 and 18 days (*P* = .28), and 30-day mortality was 19% and 26% (*P* = .60) in the pre- and post-intervention groups, respectively. Average time to blood culture clearance was 3.7 days in the pre-intervention group and 4.1 days in the post-intervention group (*P* = .7).

DISCUSSION

The implementation of real-time alerting of positive blood culture results to identify patients with candidemia using the ESM significantly improved BOC adherence, primarily related to more patients getting ophthalmologic exams and undergoing recommended echocardiography. Time to initiate antifungal therapy was 1.5 hours shorter (*P* = .58) in the post-intervention group, and time to modify antifungal therapy following susceptibility data if necessary was similar between groups (*P* = .63). The length of stay was a median of 6 days shorter among patients in the post-intervention group. We did not observe a difference in the mortality rate at 30 days.

Previous studies evaluating the impact of ASP interventions using culture-based alerting (real-time notification of yeast present in a blood culture) to facilitate guideline-based bundle of care for patients with candidemia found similar results with respect to bundle adherence and clinical outcomes [6, 7, 11]. Although overall rates of adherence to the BOC improved, a significant impact on clinical outcomes was not observed. Antworth et al. evaluated the impact of an antimicrobial stewardship–led intervention of providing BOC recommendations for patients with candidemia. Patients were identified though a clinical decision support program separate from the electronic medical record (EMR; Theradoc) with a page notification from 0700 to 1700 Monday through Friday and email notification during other times [6]. Although bundle adherence was significantly improved from 40.5% to 78% (*P* = .0016), length of stay was similar between groups (20 vs 21 days). Another study evaluating an antimicrobial stewardship intervention to provide recommendations on guideline-supported management of candidemia utilizing page notification from the microbiology laboratory found that time to effective therapy was significantly improved (13.5 hours vs 1.3 hours; *P* = .04). However, there was no impact on length of stay (10 days vs 11 days; *P* = .68) or mortality (19% vs 30%; *P* = .11) [7]. This study also looked at durations of therapy, whether ID was consulted, whether ophthalmology was consulted, and performance of echocardiography. There was no statistical difference between groups with respect to these components of the BOC. Another study evaluating 1-time stewardship review followed by ID consult to follow thereafter, using real-time alerting to identify patients, found improved time to initiation of adequate therapy in their overall patient population (3.5 hours vs 2 hours; *P* < .021); however, they did not look specifically at components of the BOC [11]. Upon receipt of the alert, stewardship pharmacists would review each case and provide recommendations on not only antifungal therapy but other elements of the bundle of care BOC as well, leaving the remainder of review and care to ID consult service. This strategy did not result in improved length of stay (18 days vs 27 days; *P* = .07) or mortality (17% vs 21%; *P* = .76). The limitation of all of these previous studies in evaluating clinical outcomes, similar to ours, is the smaller sample size, which precludes the ability to detect significant differences in outcomes such as length of stay and mortality. The studies reviewed included 78, 173, and 117 patients, respectively. With respect to the mortality outcome, it is known that delays beyond 12 hours (from the time a blood culture is drawn) in initiation of antifungal therapy are associated with increased mortality [12]. These alerts are based on the presence of yeast on gram stain and the usual time by standard laboratory procedures for yeast to be identified, which often exceeds 12 hours, likely contributing to these analyses failing to show mortality benefit.

The primary benefit of our intervention was improved BOC adherence, namely with respect to obtaining echocardiography and an ophthalmology consult, which potentially led to source identification and subsequent optimized disease management. Although the utility of screening for endopthalmitis and endocarditis on the basis of candidemia alone as recommended by guidelines has been questioned, both can occur while patients are asymptomatic, which makes their diagnosis important for cure of infection. The availability of echocardiography and ophthalmologic exam also helps to ensure implementation of appropriate durations of therapy and other relevant interventions. We also observed an increase in the number of patients appropriately started on fluconazole over micafungin based on our hospital-specific guidelines, 18% in the pre-intervention group vs 31% in the post-intervention group. Although not statistically significant, this is a pertinent change from an antimicrobial stewardship perspective. Pre-intervention, the most common organisms, comprising 86% of isolates, were *C. albicans* and *C. parapsilosis*. Based on our antibiogram at the time, fluconazole would provide more than adequate coverage; however, 71% of patients still received micafungin initially. Before stewardship review of candidemia alerts, the majority of patients received a more costly antifungal that provided broader than necessary coverage. In the post-intervention group, 40% of isolates were *C. albicans* and 36% were *C. glabrata*. Our antibiogram during the post-intervention time frame showed that the majority of *C. albicans* were susceptible to fluconazole, whereas most *C. glabrata* isolates (particularly those from cultures obtained from patients admitted to the intensive care unit) were more reliably susceptible to micafungin. Based on this, the initial antifungal selection was more appropriate in terms of coverage in the post-intervention group. We observed more *C. glabrata* in the post-intervention group, so the 64% who received micafungin received appropriate therapy initially.

Our study has several limitations to consider. As there was no randomization of patient inclusion in either group, showing a true causality relationship between intervention and outcomes was not possible. There are also confounding factors to consider with respect to identifying a true correlation between the availability of automated alerts and improved BOC adherence. One such confounding factor would be microbiology laboratory process changes that may have occurred during the study period; however, no changes in microbiology processes with respect to blood cultures positive for *Candida* spp. occurred during the time periods reviewed. Another possible confounding factor would be the availability of an institution-specific candidemia/candidiasis pathway beginning November 2011, which was 7 months into the pre-intervention time frame. With no mechanism of providing oversight for candidemia management before the automated alerts, adherence to the pathway could not be enforced or monitored in a consistent way. With the retrospective nature of data collection, there were also limitations in the availability of data or documentation of certain BOC components that were difficult to assess, for example, identifying if it was thought that the source of infection was line related and whether that line was removed or not. Additionally, although the groups were well matched in terms of baseline characteristics, a larger proportion of patients in the pre-intervention group had an "unknown" source (13% vs 0%), which is possibly due to poor documentation in the medical record but could also be reflective of situations where the appropriate workup was not or could not be completed to definitively identify a source. There is also a potential limitation with respect to whether the automated alerting process alone influenced the observed improvement in BOC adherence given that a majority of the patients were also seen by the ID consult service. We did observe an increase in the number of patients with ID consult from 86% to 98% (P = .11); therefore, improved adherence in the BOC may have been influenced by this. Last, the Infectious Diseases Society of America guidelines for the management of candidiasis were updated in 2015, recommending echinocandins as first-line empiric therapy, with the caveat that non-ICU patients who are unlikely to have azole-resistant *Candida* species may alternatively receive fluconazole up front [10]. The previous version of the guidelines, published in 2009, recommended fluconazole or an echinocandin initially but still noted preference for an echinocandin in cases of moderate to severe illness or recent azole exposure [13]. The initial antifungal selected was assessed for appropriateness based on our hospital-specific antibiogram in conjunction with the guideline recommendations for favoring an echinocandin in critically ill patients and those with recent azole exposure or other risks for azole-resistant *Candida* species. This general approach was applied consistently in both time periods to assess the appropriateness of initial antifungal agent selection.

Although others have evaluated the impact of antimicrobial stewardship–led interventions to facilitate optimized management of candidemia, ours still contributes to the literature and offers some level of uniqueness in how our real-time alerting is accomplished, as well as our review schedule. Our ASP alerts trigger within our EMR, we do not have to use a separate program, nor do we require that the page be sent to ASP from the microbiology lab. The result is immediately visible on an active list within our EMR, enabling potentially immediate notification and review. Additionally, we only reviewed this list during the time frame included, Monday through Friday from 0700 to 1900. Therefore, our observed results help to highlight what can be accomplished following this process. The other studies reviewed above implemented varying versions of this strategy using pages or separate programs and performed the reviews on different schedules (Monday through Friday 0800–1700 or 0600–1800, email notifications overnight and on weekends).

We have shown in this study that antimicrobial stewardship review of patients with candidemia using real-time alerting within an EMR can significantly improve BOC adherence and optimize management. It was also evident that we had an impact on initial antifungal agent selection, in terms of echinocandin usage being congruent with our hospital antibiogram data and clinical guidelines at the time.

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