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Improved Outcomes Associated with Limiting Identification of *Candida* spp. in Respiratory Secretions

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Pneumonia due to infection with *Candida* spp. is extremely rare even though these yeasts are commonly cultured from respiratory secretions. The diagnosis of pneumonia due to *Candida* spp. should be made only by demonstrating tissue invasion of a biopsy specimen. Physicians might misinterpret the presence of *Candida* spp. in respiratory secretions as being the etiological agent of pneumonia. This study describes the practice of limiting identification (ID) of rapidly growing yeasts (i.e., *Candida* spp.) in respiratory secretions and its impact on patients. Before November 2001, rapidly growing yeasts found in respiratory secretions were identified to the species level. After November, rapidly growing yeasts were reported as "yeasts, not *Cryptococcus*." The group of patients with respiratory secretions processed before November 2001 is called the full ID group ($n = 267$); the group with samples processed after that date is called the limited ID group ($n = 77$). Full ID patients had an average length of hospital stay of 12.1 days/patient; that of limited ID patients was 10.1 days/patient, a decrease of 2 days/patient ($P = 0.02$). The full ID patients had an average cost of $9,407/patient; that of limited ID patients was $6,973/patient, a decrease of $2,434/patient ($P = 0.03$). Antifungal medications were used in 103 of 267 (39%) full ID patients and in 16 of 77 (21%) limited ID patients, a decrease of 18% ($P = 0.004$). Limited ID patients had a mortality rate of 14.3%; that of full ID patients was 18.7%, a decrease of 4.4% ($P = 0.37$). This policy of limiting yeast ID did not impair the diagnosis of pneumonia. Rather, decreases in lengths of stay, costs, and administration of unnecessary antifungal therapy were observed after instituting this policy.

Pneumonia due to infection with *Candida* spp. is extremely rare, but because of contamination with oral flora, these organisms are frequently cultured from respiratory secretions. The diagnosis of pneumonia due to *Candida* spp. is made not by culturing respiratory secretions but by demonstrating tissue invasion of a biopsy specimen by histopathological studies (2, 4, 9, 17, 18, 20). The microbiology laboratory has no role in the diagnosis of this disease. However, fungal cultures are frequently requested for respiratory secretions, and physicians might interpret the presence of *Candida* spp. as being the etiological agent of pneumonia. This misinterpretation may result in treatment with antifungal agents for a disease which is most likely not present. Other problems caused by treating *Candida* spp. in respiratory specimens include the potential risk of adverse drug reactions and increased selective pressure for the development of antimicrobial resistance.

In the past, fungal cultures of respiratory secretions at Memorial Medical Center were conducted in the manner chosen by many laboratories, resulting in a full identification (ID) of all fungi detected. However, because many think that this ID encourages physicians to overtreat pneumonia that is due to *Candida* spp., we initiated a policy of performing only limited ID of fungi in respiratory secretions (3, 10, 16). This study describes the practice of eliminating ID of rapidly growing yeasts (i.e., *Candida* spp.) to the species level in respiratory secretions and its subsequent impact on practices and patient outcomes.

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MATERIALS AND METHODS

Study design. The study was conducted at Memorial Medical Center, a 450-bed community teaching hospital for the Southern Illinois University School of Medicine. The study involved hospitalized patients who had respiratory secretions submitted for fungal cultures from 1 March 2001 to 1 March 2002. Approval from an institutional review board was obtained. Prior to 5 November 2001, all yeasts and fungi in respiratory secretions were identified to the genus or species level if fungal cultures were requested. In addition, when *Candida albicans* was present in specimens with requisitions for bacterial cultures, it was identified by a rapid method and reported as presumptive *C. albicans*. After the endorsements of the infectious disease physicians and pulmonologists, the policy was changed to one of not identifying *Candida* spp. in respiratory secretions, even if fungal cultures were requested. If rapidly growing yeasts (i.e., suspected *Candida* spp.) were present, a urease test was done to rule out *Cryptococcus neoformans*; they were then reported as "yeasts, not *Cryptococcus*." If a yeast was urease positive, additional testing was performed to identify the yeast. The group of patients with respiratory secretions processed prior to 5 November 2001 is called the full ID group; the group of patients with respiratory secretions processed after that date is called the limited ID group. There were 22 patients for whom *Candida* spp. had, in fact, been identified to the species level after this date. This was because the technologists did not initially adhere to the new policy. These 22 patients with full ID were placed in the full ID group. Except for the duration of hospitalization, essentially the only difference between the two groups is that *Candida* spp. were not specifically named in the limited ID report. *Cryptococcus neoformans* and all filamentous fungi, such as *Histoplasma capsulatum, Sporothrix schenckii*, and *Blastomyces dermatitidis*, were reported identically in both time periods (i.e., there was no change in the level of ID for these organisms in the two time periods).

TABLE 1. Characteristics derived from medical records of patients with yeasts in respiratory cultures

Characteristic[a]	No. (%) of patients in:	
	Full ID group	Limited ID group
No. of patients	267 (100)	77 (100)
Age >60 yr	148 (55.4)	46 (60.0)
Female	126 (47.2)	41 (53.2)
Coexisting conditions		
COPD	97 (36.3)	35 (45.5)
CAD	67 (25.1)	32 (41.6)
HTN	85 (31.8)	23 (29.9)
DM	47 (17.6)	15 (19.5)
Immunocompromised state	23 (8.6)	11 (14.3)
HIV or AIDS	9 (3.4)	4 (5.2)
Immunosuppressive therapy	6 (2.2)	2 (2.6)
Transplantation	4 (1.5)	0 (0)
Neutropenia	4 (1.5)	4 (5.2)
Diagnosis upon admission		
Pneumonia	139 (52.1)	42 (54.5)
Other than pneumonia	128 (47.9)	35 (45.5)
Nosocomial pneumonia	33 (12.4)	11 (14.3)
Specimen type		
Sputum (self-expectorated)	164 (61.4)	44 (57.1)
PBS	7 (2.6)	3 (3.9)
BAL	65 (24.3)	28 (36.4)
Induced sputum	2 (0.7)	1 (1.3)
Mechanical ventilation	80 (30.0)	20 (26.0)
Side effects of antifungal agents	7 (2.6)	2 (2.6)
Candidemia	7 (2.6)	0 (0)
Outcome		
Recovery	217 (81.3)	66 (85.7)
Death[b]	50 (18.7)	11 (14.3)
Cause of death		
Pneumonia	19/50 (38.0)	6/11 (54.5)
Other than pneumonia	31/50 (62)	5/11 (45.4)

[a] Abbreviations: COPD, chronic obstructive pulmonary disease; CAD, coronary artery disease; HTN, hypertension; DM, diabetes mellitus; HIV, human immunodeficiency virus; PBS, phosphate-buffered saline; BAL, bronchoalveolar lavage.

[b] Difference in mortality between the two groups ($P = 0.37$).

Data collection. The data in Table 3 were supplied electronically by the Clinical Data Management Department, but the clinical data (Tables 1 and 2) were collected by physicians performing the chart reviews. To ensure uniformity in the methods of data collection, a standard written protocol was used by each physician examining the medical records. Residents in internal medicine (R. Dela Cruz and A. Imran) as well as the infectious disease fellow (P. Arakere) reviewed the charts of the patients in the full ID group. The charts of patients in the limited ID group were reviewed solely by the infectious diseases fellow. The rationale for having the infectious diseases fellow review the patients in the limited ID group was to determine whether a negative impact occurred by limiting information on the ID of respiratory yeasts. It was thought that the infectious diseases fellow, with more experience and expertise in diagnosing infections, would be able to detect subtle findings in the charts that may have been missed by the residents.

As shown in Table 1, patient demographics and variables were analyzed by the chi-square test. As shown in Table 3, the lengths of stay and costs were analyzed by the Wilcoxon ranked sum test, the antifungal use was analyzed by the two-by-two chi-square test, and mortality was analyzed by the chi-square test. Confidence intervals for the lengths of stay and costs were for mean values; those for use of antifungal agents and mortality were for percentages.

TABLE 2. Clinicians' interpretation of the significance of *Candida* spp. in respiratory specimens

Physicians' opinion or action	No. (%) of patients in:	
	Full ID group	Limited ID group
Pathogen	45 (16.9)	7 (9.1)
Colonization	8 (3.0)	4 (5.2)
Contamination	7 (2.6)	4 (5.2)
No mention	207 (77.5)	62 (80.5)
Initiation of empiric antifungal agent in response to microbiology report	38 (14.2)	6 (7.8)
Obtain tissue diagnosis	0	0

RESULTS

Initially, there were 313 patients in the full ID group and 90 patients in the limited ID group. However, in order to better detect trends and patterns, our hospital (like most hospitals) excludes Health Care Financial Authority length-of-stay outliers, as defined by Explore (HBSI, Seattle, Wash.), a computer software program involving diagnosis-related group information derived from a large number of hospitals in the Volunteer Hospitals of America system. Outliers are defined by this system as those patients whose length of stay was greater than two standard deviations for a given diagnosis-related group. From the full ID group, 46 outliers of 313 patients (14.7%) were excluded; 13 outliers of 90 patients (14.4%) were excluded from the limited ID group. After excluding these outliers, there were 267 patients in the full ID group and 77 patients in the limited ID group.

Medical chart reviews. (i) Clinical data and demographics. The major characteristics derived from the chart reviews are presented in Table 1; the two groups were quite similar except in the area of antifungal therapy.

(ii) Antifungal therapy. When patients had severe illness and/or did not respond to initial treatment with antibacterial agents, physicians often chose to treat with empirical antifungal agents. None of the patients in either group who received antifungal agents for pneumonia had tissue obtained for the histopathological diagnosis of *Candida* pneumonia. Of the full ID group, 38 of 267 (14.2%) patients received antifungal therapy for presumed pneumonia due to *Candida* spp., whereas 6 of 77 (7.8%) patients received such therapy in the limited ID group (Table 2).

The most common systemic antifungal agent used was fluconazole. None of the amphotericin B formulations was used for the treatment of pneumonia. The duration of antifungal treatment ranged from 7 to 10 days. None of the patients in either group was treated solely with antifungal agents for pneumonia. Antifungal agents were used in conjunction with various antibacterial agents. At the end of 7 to 10 days of empirical treatment with agents, the patients had recovered or died.

The most common side effect noted from the antifungal therapy was mild to moderate elevation of levels of hepatic enzymes. None of the side effects warranted termination of

TABLE 3. Comparisons of data between full ID and limited ID patient groups

Group of patients or differences between groups	No. of patients	Mean length of stay in days (95% CI) or difference[a]	Mean actual variable cost in dollars (95% CI) or difference	No. of patients receiving antifungal therapy (% [95% CI]) or difference	% Mortality (95% CI) or difference
Full ID	267	12.1 (10.9–13.2)	9,407 (7,870–10,945)	103 (38.6 [32.8–44.4])	18.7 (14.0–23.4)
Limited ID	77	10.1 (8.1–12.1)	6,973 (5,042–8,905)	16 (20.8 [11.7–29.9])	14.3 (6.5–22.1)
Differences between full ID and limited ID groups		−2[b]	−2,434[b]	−17.8[b]	−4.4[b]
Differences between all other patients in the time periods of full ID and limited ID groups		0.2	87	0.06	−0.04

[a] CI, confidence interval.
[b] −, decrease in the limited ID group. *P* values were 0.02 for length of stay, 0.03 for actual variable cost, 0.004 for use of antifungal therapy, and 0.37 for mortality.

treatment with the antifungal agent. One patient in the limited ID group had a morbilliform papular skin rash with fever, which was attributed to fluconazole. The patient was also taking β-lactam antibiotics, but she did not have a documented allergy to penicillin or to the β-lactam group of antibiotics, which she had received in the past.

(iii) Candidemia. *Candida* spp. were present in the bloodstream of 7 of 267 (2.6%) patients in the full ID group and 0 of 77 in the limited ID group (Table 1). Of the seven patients in the full ID group, five were infected with *C. albicans*, and the infections were attributed to indwelling central catheters; one patient was thought to be infected with *C. albicans* from a skin contaminant, and no treatment was initiated for him. His condition was monitored by the use of multiple repeat blood cultures, which showed no further candidemia; the patient made an uneventful clinical recovery. The seventh patient was infected with *Candida tropicalis* and was thought to have indwelling central catheter-related infection. It was the opinion of the infectious diseases fellow as well as of the attending physician that *C. albicans* was a contaminant in one patient. The remaining patients with candidemia were treated with an antifungal agent.

The source of candidemia was thought not to originate from a pulmonary source because there were other identifiable sources of candidemia. In most cases, prompt resolution of candidemia occurred with removal of the catheter and treatment with antifungal agents.

(iv) Interpretation of *Candida* spp. in respiratory secretions. In the full ID group, *C. albicans* was found in 85.0% of the respiratory secretions, *Candida glabrata* was found in 9.4%, *Candida parapsilosis* was found in 3.0%, *C. tropicalis* was found in 1.9%, and *Candida krusei* was found in 0.4% of the respiratory secretions. By reviewing the medical records, an attempt was made to determine whether the attending physician thought that the presence of *Candida* spp. was significant. In 8 of 267 (3.0%) of the charts in the full ID group and in 4 of 77 (5.2%) of the charts in the limited ID groups, the notes indicate that the physicians thought that the presence of yeast represented colonization of the respiratory tract as a result of antibacterial therapy (Table 2). For the full ID group, the physicians made no mention of *Candida* spp. being present in the respiratory secretions in 207 of 267 (77.5%) patients, while for the limited ID group, 62 of 77 (80.5%) physicians made no mention of this potential colonization (Table 2). However, 38 of 267 (14.2%) physicians initiated antifungal therapy shortly after seeing the results of the microbiology report for the full ID group, while only 6 of 77 (7.8%) did so for the limited ID group. In spite of the fact that physicians said that they considered the *Candida* spp. to be pathogenic in 45 patients in the full ID group, only 38 of the patients received antifungal therapy. Similarly, in the limited ID group, physicians considered the yeasts to be pathogens in seven patients, but only six received antifungal therapy.

(v) Mortality. The mortality rate for patients in the full ID group was 50 of 267 (18.7%) compared to 11 of 50 (14.3%) in the limited ID group ($P = 0.37$) (Tables 1 and 3). The rate of death directly related to underlying pneumonia and respiratory failure was 19 of 50 (38.0%) in the full ID group and 6 of 11 (54.5%) in the limited ID group. None of the deaths were thought to be related to side effects of antifungal agents or to the lack of antifungal therapy.

Two patients in the full ID group died of *Candida* bloodstream infection. Both patients had catheter-related candidemia as well as serious underlying diseases. Autopsies were performed for 3 out of 50 deaths in the full ID group and for 1 out of 11 deaths in the limited ID group. None of the patients for whom autopsies were performed showed any evidence of invasive fungal infection of the respiratory tract.

Nonclinical outcomes. Major benefits were seen in the limited ID patients (Table 3). The full ID patients had an average length of stay of 12.1 days per patient; that of the limited ID patients was 10.1 days per patient, a decrease of 2 days per patient ($P = 0.02$). The full ID group had an average actual variable cost of $9,407 per patient; that of the limited ID patients was $6,973 per patient, a decrease of $2,434 per patient ($P = 0.03$). Antifungal agents administered at any time during their hospitalization (not just in response to the microbiology report as cited earlier) were used in 103 of 267 (38.6%) full ID patients and in 16 of 77 (20.8%) limited ID patients, a decrease of 18% ($P = 0.004$). During this same year, all patients hospitalized after 5 November 2001 (excluding those in this study) actually had an increased length of stay (by 0.2 days) and increased actual variable costs (by $87); the rates of their antifungal medication use and mortality were essentially identical to those of patients hospitalized between 1 March 2001 and 5 November 2001.

DISCUSSION

Full ID of *Candida* spp. (rather than limited ID as simply "yeasts") in respiratory specimens is not only of little relevance to the diagnosis of pneumonia due to *Candida* but is also

associated with statistically significant increased use of unnecessary antifungal agents, a higher cost of hospitalization, and a prolonged hospital stay.

Although the concept of performing only limited ID of yeasts in respiratory secretions was introduced several years ago, its practice is not yet standard procedure (10). Actually, many good laboratories are performing limited ID of yeasts as described here, but there has been no documentation of the approach's impact. This study documents that patients with respiratory specimens with a limited ID of rapidly growing yeasts (excluding *Cryptococcus neoformans*) have statistically significant differences from those of the full ID group, with shorter lengths of stay in the hospital, decreased actual variable costs, and decreased use of antifungal agents. This has occurred in spite of a trend for all other patients hospitalized at this time to have slightly increasing lengths of stay and increasing costs.

Memorial Medical Center has over 400 patients per year who have respiratory secretions submitted for fungal culture. If $2,434 is saved per patient, then the hospital could expect to save more than $973,600 (400 × $2,434) annually by limiting the ID of *Candida* spp. in respiratory cultures. In fact, this estimate vastly underestimates the impact of this policy because prior to its implementation, the presence of *C. albicans* was also reported for respiratory secretions with orders only for bacterial cultures. Approximately 20% of the respiratory secretions are positive for *C. albicans*, and >11,000 bacterial cultures for respiratory secretions are done annually.

A theoretical concern was that withholding the species ID of the respiratory yeasts might lead to underdiagnosis of pneumonia due to *Candida* spp., in spite of the precedents set by many good laboratories and the recommendations of experts. However, the alternative (i.e., full ID) may result in overdiagnosis of pneumonia due to *Candida* spp. A side benefit of limiting ID encourages physicians to diagnose the extremely rare entity of pneumonia due to *Candida* spp. in the correct manner (by obtaining tissue for diagnosis). Furthermore, it is probable that the patients in the full ID group were treated not for what they had but for something they did not have; what they actually had was not being appropriately diagnosed and treated.

In addition to financial and clinical benefits for individual patients, fewer cases are mistaken for pneumonia due to *Candida* spp.; thus, overuse of antifungal therapy is discouraged and better institutional antibiotic stewardship occurs. In both time periods, a comment was put on the reports indicating that since yeasts (or *Candida* spp.) were isolated from respiratory secretions, evaluation of the clinical significance was indicated before treatment and that pneumonia due to *Candida* spp. was extremely rare. Our opinion is that this comment made little impact on physicians' actions. With the introduction of azoles for treatment of fungal infections, physicians are more comfortable using them presumptively or empirically because they are relatively safer than amphotericin B. In fact, azoles have drug interactions with extremely common medications, including statins and antihistamines. Since the majority of elderly patients are generally on multiple medications, there is ample opportunity for adverse drug reactions to occur. Although no adverse drug reactions with the antifungal agents were documented in this study, underrecognition and underreporting of adverse drug reactions common (1, 5–7, 12). In fact, adverse drug reactions are recognized as being present in at least 6% of hospitalized patients and have been documented as causing increased lengths of stay (12, 13, 19). Fluconazole and ketoconazole have similar mechanisms of action, and so they share similar drug-drug interactions (R. Polk, Program Abstr. 40th Ann. Meet. Infect. Dis. Soc. Am., p. 4, 2002). Interestingly, while these interactions are noted in the package insert for ketoconazole, the package insert (which is frequently the main source of drug information for physicians) for fluconazole has no mention whatsoever of these shared interactions (R. Polk, Program Abstr. 40th Ann. Meet. Infect. Dis. Soc. Am.).

In addition, with routine use of antifungal agents, development of resistant *Candida* spp. and increasing infections with non-*C. albicans* species is of growing concern. A potential benefit of not reporting *Candida* spp. in respiratory secretions is the decrease in selective pressure for fungi to develop resistance to antimicrobial agents (8). It has been documented that 10% of *C. albicans* bloodstream isolates from hospitalized patients were resistant to fluconazole (14). Further, 48% of bloodstream infections due to *Candida* spp. were caused by non-*C. albicans* species, which are more likely to be resistant to fluconazole (11, 15).

Clinical microbiologists must accept the responsibility of educating physicians on the appropriate use of diagnostic tests in microbiology. They must supply clinically useful information so that clinicians can practice evidence-based medicine. By limiting specific data on *Candida* spp. in respiratory secretions, the laboratory report becomes an essential component of the appropriate treatment of patients. If indeed pneumonia due to *Candida* spp. is diagnosed on the basis of the tissue biopsy specimen, this occurs generally within the same time frame that *Candida* spp. will grow. In this setting, the yeast can be identified as a result of a special request. The surgical pathologist should be instructed to notify the microbiology laboratory if tissue invasion with small yeasts in a nongranulomatous pulmonary lesion is seen. In that setting only, full ID of the suspected *Candida* spp. may be appropriate in order to help with the management of pneumonia due to *Candida* spp.

In conclusion, our findings indicate that limiting the ID of the *Candida* spp. in respiratory secretions does not have a negative impact on patient outcome. Rather, we found statistically significant decreased lengths of stay in the hospital, decreased costs, and decreased use of unnecessary antifungal agents to be associated with this policy.

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