Treatments and Outcomes of Critically Ill Patients with *Candida* spp. Colonization of the Lower Respiratory Tract in Regina, Saskatchewan

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ABSTRACT

Background: Among critically ill patients receiving mechanical ventilation, *Candida* spp. are commonly detected in the lower respiratory tract (LRT). This is generally considered to represent colonization.

Objective: To evaluate the use of antifungal treatments and the clinical outcomes of patients with *Candida* colonization of the LRT.

Methods: This retrospective analysis involved consecutive patients admitted to the intensive care unit between April 2016 and May 2021with positive results on *Candida* spp. testing of LRT samples. Data related to antifungal treatment and clinical outcomes were analyzed descriptively, and multivariable logistic regression was performed.

Results: Of 200 patients initially identified, 160 (80%) died in hospital. Antifungal therapy was given to 103 (51.5%) of the patients, with treatment being more likely among those with shock and those who received parenteral nutrition. Mortality was high among patients with positive *Candida* results on LRT culture, regardless of treatment. Multivariable logistic regression, with adjustment for age, sex, comorbidities, and sequential organ failure assessment (SOFA) score, showed that antifungal treatment was associated with lower odds of death (odds ratio 0.39, 95% confidence interval 0.17–0.87) compared with no treatment ($p = 0.021$).

Conclusions: This study showed higher mortality rates than have been reported previously. Further investigation into the role of antifungal therapy among critically ill patients with *Candida* spp. colonization is required.

Keywords: *Candida*, critical care, antifungal

RÉSUMÉ

Contexte : Chez les patients gravement malades recevant une ventilation mécanique, les *Candida* spp. sont fréquemment détectées dans les voies respiratoires inférieures (VRI) – une situation généralement considérée comme une colonisation.

Objectif : Évaluer l'utilisation d'un traitement antifongique et les résultats cliniques chez les patients présentant une colonisation par *Candida* dans les VRI.

Méthodes : Cette analyse rétrospective portait sur des patients consécutifs de l'unité de soins intensifs ayant obtenu un résultat positif au test de *Candida* sur les isolats des VRI entre avril 2016 et mai 2021. Les données relatives au traitement antifongique et aux résultats cliniques ont été analysées de manière descriptive, et une régression logistique multivariable a été effectuée.

Résultats : Parmi les 200 patients initialement recensés, 160 (80 %) sont décédés à l'hôpital. Une thérapie antifongique a été administrée à 103 (51,5 %) des patients, et le traitement était plus probable chez ceux en état de choc et ceux ayant reçu une nutrition parentérale. Les patients ayant été déclarés positifs pour la *Candida* dans la culture des VRI présentaient un taux de mortalité élevé, indépendamment du traitement. Une régression logistique multivariable, avec ajustement pour l'âge, le sexe, les comorbidités et le score SOFA (*sequential organ failure assessment*), a montré que le traitement antifongique était associé à une probabilité de décès réduite (rapport de cotes 0,39; intervalle de confiance à 95 % 0,17-0,87), par rapport à l'absence de traitement ($p = 0,021$).

Conclusions : Cette étude a révélé des taux de mortalité plus élevés que ce qui avait été rapporté précédemment. Une enquête plus approfondie sur le rôle de la thérapie antifongique chez les patients gravement malades présentant une colonisation par *Candida* spp. est nécessaire.

Mots-clés : *Candida*, soins intensifs, traitement antifongique

INTRODUCTION

Critically ill patients in the intensive care unit (ICU) who are receiving mechanical ventilation are at increased risk of nosocomial infections, such as ventilator-associated pneumonia, which in turn increases their risk of morbidity and mortality.[1] Although *Candida* spp. are commonly detected in the lower respiratory tract (LRT), they are generally considered colonizers rather than a pathogenic cause of infection; therefore, empiric antifungal treatment is not recommended.[2-4] It is estimated that *Candida* spp. colonization of the respiratory tract may be present in more than half of critically ill patients undergoing mechanical ventilation.[5] In a Canadian study of ICU patients with suspected ventilator-associated pneumonia, those with *Candida* spp. in LRT samples had higher in-hospital mortality than those

without yeast (34.2% versus 21%) and almost double the hospital length of stay (59.9 versus 38.6 days).[6] A European study evaluating ICU patients with *Candida* spp. pulmonary colonization reported in-hospital mortality of 40%: 52% for those who received antifungal therapy and 35% for those who did not.[7]

The objectives of our study were to examine the use of antifungals in ICU patients with LRT samples testing positive for *Candida* spp. and to investigate their clinical outcomes.

METHODS

We performed a retrospective analysis for a cohort of all adult patients (at least 18 years of age) admitted consecutively, between April 2016 and May 2021, to a medical or surgical ICU in Regina, Saskatchewan, with *Candida* spp. identified in LRT samples (i.e., sputum, endotracheal tube aspirate, bronchoalveolar lavage, or mini–bronchoalveolar lavage, as labelled in the laboratory database). We collected demographic data, risk factors for invasive infection,[8] and antifungal treatment choice. Continuous variables are presented as means or medians, dependent on normality, as assessed by skewness and kurtosis. We compared patients with and without treatment for *Candida* spp. using the *t* test or Wilcoxon rank-sum test, dependent on normality. Categorical variables are presented as counts (with percentages), with comparisons using the χ^2 test.

We conducted a propensity score matching analysis for in-hospital mortality using matched cohorts, with 1:1 nearest-neighbour matching for age, sex, Charlson comorbidity index, sequential organ failure assessment (SOFA) score, and the *Candida* score (defined as multifocal *Candida* spp. colonization, use of parenteral nutrition, surgery on ICU admission, and severe sepsis)[9,10] using a caliper of 0.2, the standard deviation of the logit of the propensity score.

All statistical analyses were performed using Stata 15.1/MP (StataCorp), with a 2-sided p value less than 0.05 considered statistically significant.

RESULTS

A total of 200 patients admitted to the ICU between April 2016 and May 2021 met the study's inclusion criteria. The median age was 64 (interquartile range [IQR] 55–74) years, and 100 (50%) of the patients were female (Table 1). The mean SOFA score on admission to the ICU was 10 (standard deviation 3), and the median duration of intubation was 21.5 (IQR 5–37) days. Median length of stay in the ICU was 12 (IQR 4–14) days, and median hospital stay was 24 (IQR 8–29) days. Nearly 94% of patients (n = 187) received antibiotic therapy before a positive result on fungal LRT culture, whereas only 51.5% (n = 103) received antifungal treatment. Patients were more likely to be given antifungal therapy if they had experienced shock or received parenteral nutrition.

In total, 160 (80%) of the patients died in hospital (Table 1). Univariable logistic regression comparing antifungal-treated patients with untreated patients yielded an odds ratio (OR) for death of 0.44 (95% confidence interval [CI] 0.21–0.90) (Table 2). In the multivariable logistic

TABLE 1 (Part 1 of 2). Patient Demographic Characteristics and Outcomes

Characteristic	Patient Group; No. (%) of Patients[a]	
	Treated with Antifungal (n = 103)	Untreated (n = 97)
Age (years) (median and IQR)	63 (53–72)	65 (56–74)
Sex, female	50 (48.5)	50 (51.5)
Diagnosis on admission to ICU		
Respiratory failure	32 (31.1)	31 (33.0)
Sepsis	26 (25.2)	18 (18.6)
Postsurgery	8 (7.8)	4 (4.1)
Neurology	7 (6.8)	3 (3.1)
Post-arrest	3 (2.9)	6 (6.2)
Cancer complications	1 (1.0)	6 (6.2)
Other	26 (25.2)	28 (28.9)
Charlson comorbidity index (median and IQR)	1 (1–2)	1 (1–3)
COVID-19 infection	14 (13.6)	16 (16.5)
SOFA score (mean ± SD)	10 ± 4	10 ± 3
Candida score (mean ± SD)	2.2 ± 1.4	1.2 ± 1.2
CPIS on day of first fungal culture (mean ± SD)	4 ± 2	4 ± 2

TABLE 1 (Part 2 of 2). Patient Demographic Characteristics and Outcomes

Characteristic	Patient Group; No. (%) of Patients[a]	
	Treated with Antifungal (*n* = 103)	Untreated (*n* = 97)
Resource intensity weight (mean ± SD)	11 ± 7.4	6.2 ± 5.8
Risk factors for invasive candidiasis		
Systemic antibiotic	98 (95.1)	89 (91.8)
Septic shock	74 (71.8)	46 (47.4)
Parenteral nutrition	20 (19.4)	2 (2.1)
Surgery	14 (13.6)	7 (7.2)
Immunosuppression	10 (9.7)	7 (7.2)
Central venous catheter	3 (2.9)	1 (1.0)
Yeast identified		
Yeast not specified[b]	60 (58.2)	70 (72.1)
Candida albicans	27 (26.2)	23 (23.7)
Candida glabrata	6 (5.8)	1 (1.0)
Candida tropicalis	8 (7.8)	2 (2.1)
Candida krusei	1 (1.0)	1 (1.0)
Other *Candida* spp.	6 (5.8)	1 (1.0)
Aspergillus spp.	1 (1.0)	1 (1.0)
Primary location of respiratory yeast as identified in laboratory labelling		
Sputum	26 (25.2)	24 (24.7)
Endotracheal tube aspirate	47 (45.6)	50 (51.5)
Bronchoalveolar lavage	23 (22.3)	10 (10.3)
Mini–bronchoalveolar lavage	7 (6.8)	13 (13.4)
Yeast identified at second site	43 (41.7)	11 (11.3)
Urine	29	10
Blood	2	1
Ascites	2	0
Skin or soft-tissue swab	6	0
Line[c]	2	0
Other[d]	2	0
Lung imaging on day before or after the day of sampling with positive result on LRT culture[e]		
No infiltrate	29 (28.2)	32 (33.0)
Diffuse or patchy infiltrate	68 (66.0)	58 (60.0)
Distinct infiltrates	6 (5.8)	7 (7.2)
Antifungal, terminal therapy		
Fluconazole	61 (59.2)	NA
Caspofungin/micafungin	40 (38.8)	NA
Amphotericin B	1 (1.0)	NA
Voriconazole	1 (1.0)	NA
In-hospital death	76 (73.8)	84 (86.6)
Hospital length of stay (days) (median and IQR)	22 (12–40)	10 (4–14)
ICU length of stay (days) (median and IQR)	12 (6–20)	5 (3–10)

CPIS = clinical pulmonary infection score, ICU = intensive care unit, IQR = interquartile range, LRT = lower respiratory tract, NA = not applicable, SD = standard deviation, SOFA = sequential organ failure assessment.

[a]Except where indicated otherwise.

[b]In 2018, the institution's Medical Microbiology department stopped differentiating yeast identified on respiratory culture unless the treating physician makes a specific request.

[c]Femoral central line (*n* = 1) and hemodialysis line (*n* = 1) after the line was removed.

[d]Hernia mesh following removal (*n* = 1) and hepatic drain (*n* = 1).

[e]Computed tomography was used if available; otherwise, chest radiography was used.

TABLE 2. Effect of Antifungal Therapy on In-Hospital Mortality among ICU Patients with Yeast Identified In Lower Respiratory Tract Samples

Analysis	Odds Ratio (95% CI)	*p* Value
Univariable analysis	0.44 (0.21–0.90)	0.026
Multivariable logistic regression[a]	0.39 (0.17–0.87)	0.021
Propensity score–matched logistic regression (n = 61 each group)	0.41 (0.17–1.01)	0.053
Sensitivity analyses		
Effect of fluconazole	0.31 (0.13–0.77)	0.011
Effect of caspofungin/micafungin	0.59 (0.21–1.70)	0.33
Multivariable logistic regression[a] after excluding all patients with secondary sites except urine and wound swab source (n = 191)	0.39 (0.17–0.87)	0.024

CI = confidence interval, ICU = intensive care unit, SOFA = sequential organ failure assessment.
[a]With adjustment for age, sex, comorbidities, and SOFA score.

regression, after adjustment for age, sex, Charlson comorbidity index, and SOFA score, antifungal treatment was associated with OR for death of 0.39 (95% CI 0.17–0.87). In sensitivity analyses, fluconazole was associated with reduced odds of death (OR 0.31, 95% CI 0.13–0.77), whereas the results with caspofungin/micafungin were nonsignificant (OR 0.59, 95% CI 0.21–1.70). In a further sensitivity analysis with exclusion of patients who had secondary sites (excluding urine and wound swabs) that were positive for *Candida* spp. at any time in their ICU admission, the results were similar to our primary analysis. Antifungal treatment was associated with lower odds for death after multivariable logistic regression (OR 0.39, 95% CI 0.17–0.87). However, this difference was not evident after propensity score matching (OR 0.41, 95% CI 0.17–1.01).

DISCUSSION

Current guidelines recommend against exposing patients to antifungal therapy when *Candida* spp. are identified on LRT culture, as therapy may not confer benefit in this situation.[3] However, there is a lack of high-quality studies evaluating antifungal therapy in such cases. There is also evidence suggesting that *Candida* spp. isolated through high-quality sampling, such as bronchoalveolar lavage, may represent contamination and thus antifungal therapy is not required.[11] In our study, we found that a high proportion of patients with *Candida* spp. isolated from the LRT were treated with antifungal therapy, despite these recommendations. Treated patients were more likely to have presented with sepsis, to have had surgery, to have received parenteral nutrition, and/or to have a higher *Candida* score. It is possible that the clinicians at our centre perceived a higher risk for these patients and chose to initiate antifungal therapy, despite the recommendations noted above. However, only a small proportion of these patients (n = 15) had a *Candida* score above 3, which indicates that most patients did not have a higher risk of invasive infection.[10]

Notably, we found a potential association between antifungal treatment and reduced mortality; however, we cannot rule out the possibility that residual confounding, time-varying exposures, and selection bias influenced the results. Our findings are discordant with previous work suggesting that exposure to antifungal treatment does not offer additional benefit to patients.[7,12] Interestingly, there were differences between patients who received azole and those who received echinocandin antifungal treatment. However, our work was exploratory in nature and suggests the need for high-quality studies to evaluate the role of antifungal therapy in relation to *Candida* spp. colonization.

With a lack of high-quality studies to guide decision-making, clinicians are left to decide on antifungal treatment for *Candida* spp. colonization on a case-by-case basis. No drug is benign, and any exposure to therapy may lead to an adverse event. Although clinicians may definitively initiate antifungal therapy in the setting of candidemia or a histopathologic diagnosis of multifocal *Candida* spp. infection, there are also several common situations in which a clinician may choose to treat (e.g., if the patient is immunocompromised, if the patient has a high *Candida* score or colonization of multiple sites, or if a line cannot be readily removed). There are also some very limited data pointing toward a potential additive cross-kingdom interaction between *Candida* spp. and bacterial respiratory infection, whereby treatment may confer benefit.[13]

Our study had some important limitations. Because of the retrospective nature of the study and its small sample size, we were unable to completely control for residual confounding, time-varying covariates, and/or selection bias, despite multivariable modelling and propensity score matching. Of note, this cohort of patients had a higher-than-expected mortality rate (80%), which is greater than our centre's overall reported ICU mortality rate (about 20%) and mortality rates previously described in the literature on *Candida* spp. colonization.[6,14] Given that ICU patients accrue *Candida* spp. colonization over time or after exposure

to broad-spectrum antibiotics, this cohort's high mortality rate may reflect underlying population selection bias and/or severity of illness.[15-17] Time-varying exposures and immortal time bias may also play a role, as patients who have survived longer may be more likely to be exposed to antifungal therapy. An additional limitation is that several types of respiratory samples are labelled as "sputum" in our institution's laboratory's database, regardless of how the sample was collected. Despite this labelling, 97% of samples were collected while patients were intubated. A sensitivity analysis that removed the 3% of patients who were not intubated did not yield a significant change in the statistical findings. Additionally, many of the fungal respiratory isolates were labelled as "yeast (not specified)" because of changes in the laboratory's procedures. Previous work showed decreases in exposure to antifungal therapy by half when fungal respiratory cultures were labelled in this way[18]; however, when this change was made at our centre halfway through our data collection period, there was a decrease of only 6%. Our dataset tracked diagnosis of bacterial infections but did not track the pathogens isolated; thus, we were unable to assess specific bacterial contributions to our results. Our centre is unable to test for β-D-glucan levels without sending samples to a third-party laboratory, which delays assessment. Consequently, this test is not ordered routinely at our institution. Finally, no patients in our study had histopathologic sampling to confirm the presence of true fungal infection.

CONCLUSION

The findings of this study suggest the need for further high-quality investigation into the utility of antifungal therapy for critically ill patients with *Candida* spp. isolates in the LRT.

References

1. Muscedere JG, Martin CM, Heyland DK. The impact of ventilator-associated pneumonia on the Canadian health care system. *J Crit Care*. 2008;23(1):5-10.
2. Bow EJ, Evans G, Fuller J, Laverdière M, Rotstein C, Rennie R, et al. Canadian clinical practice guidelines for invasive candidiasis in adults. *Can J Infect Dis Med Microbiol*. 2010;21(4):e122-e150.
3. Pappas PG, Kauffman CA, Andes DR, Clancy CJ, Marr KA, Ostrosky-Zeichner L, et al. Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2016;62(4):e1-e50.
4. Martin-Loeches I, Antonelli M, Cuenca-Estrella M, Dimopoulos G, Einav S, De Waele JJ, et al. ESICM/ESCMID task force on practical management of invasive candidiasis in critically ill patients. *Intensive Care Med*. 2019;45(6):789-805.
5. Pendleton KM, Huffnagle GB, Dickson RP. The significance of *Candida* in the human respiratory tract: our evolving understanding. *Pathog Dis*. 2017;75(3):ftx029.
6. Delisle MS, Williamson DR, Perreault MM, Albert M, Jiang X, Heyland DK. The clinical significance of *Candida* colonization of respiratory tract secretions in critically ill patients. *J Crit Care*. 2008;23(1):11-7.
7. Lindau S, Nadermann M, Ackermann H, Bingold TM, Stephan C, Kempf VA, et al. Antifungal therapy in patients with pulmonary *Candida* spp. colonization may have no beneficial effects. *J Intensive Care*. 2015;3(1):31.
8. Thomas-Rüddel DO, Schlattmann P, Pletz M, Kurzai O, Bloos F. Risk factors for invasive *Candida* infection in critically ill patients, a systematic review and meta-analysis. *Chest*. 2022;161(2):345-55.
9. León C, Ruiz-Santana S, Saavedra P, Almirante B, Nolla-Salas J, Alvarez-Lermaet F, et al. A bedside scoring system ("*Candida* score") for early antifungal treatment in nonneutropenic critically ill patients with *Candida* colonization. *Crit Care Med*. 2006;34(3):730-7.
10. León C, Ruiz-Santana S, Saavedra P, Galván B, Blanco A, Castro C, et al. Usefulness of the "*Candida* score" for discriminating between *Candida* colonization and invasive candidiasis in non-neutropenic critically ill patients: a prospective multicenter study. *Crit Care Med*. 2009;37(5):1624-33.
11. Wood GC, Mueller EW, Croce MA, Boucher BA, Fabian TC. *Candida* sp. isolated from bronchoalveolar lavage: clinical significance in critically ill trauma patients. *Intensive Care Med*. 2006;32(4):599-603.
12. Ioannou P, Vouidaski A, Spernovasilis N, Alexopoulou C, Papazachariou A, Paraschou E, et al. *Candida* spp. isolation from critically ill patients' respiratory tract. Does antifungal treatment affect survival? *Germs*. 2021;11(4):536-43.
13. Meena DS, Kumar D. *Candida* pneumonia: an innocent bystander or a silent killer? *Med Princ Pract*. 2022;31(1):98-102.
14. Sy E, Gupta C, Shahab Z, Fortin N, Kassir S, Mailman J, et al. Long-term safety of directly discharging patients home from the ICU compared to ward transfer. *J Intensive Care Med*. 2022;37(10):1344-52.
15. Huang D, Qi M, Hu Y, Yu M, Liang Z. The impact of *Candida* spp. airway colonization on clinical outcomes in patients with ventilator-associated pneumonia: a systematic review and meta-analysis. *Am J Infect Control*. 2020;48(6):695-701.
16. Samonis G, Anastassiadou H, Dassiou M, Tselentis Y, Bodey GP. Effects of broad-spectrum antibiotics on colonization of gastrointestinal tracts of mice by *Candida albicans*. *Antimicrob Agents Chemother*. 1994;38(3):602-3.
17. Schulte DM, Sethi A, Gangnon R, Duster M, Maki DG, Safdar N. Risk factors for *Candida* colonization and co-colonization with multi-drug resistant organisms at admission. *Antimicrob Resist Infect Control*. 2015;4:46.
18. Barenfanger J, Arakere P, Dela Cruz R, Imran A, Drake C, Lawhorn J, et al. Improved outcomes associated with limiting identification of *Candida* spp. in respiratory secretions. *J Clin Microbiol*. 2003;41(12):5645-9.

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