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Letter to the Editor

Clinical significance of nosocomial *Cryptococcus laurentii* in urine: A case series

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To the Editor—The genus *Cryptococcus* spp comprises ~70 species,[1] of which the *C. neoformans–C. gattii* complex are considered pathogenic. However, non-*neoformans* cryptococci, such as *Cryptococcus laurentii* and *Cryptococcus albidus*, are emerging as opportunistic pathogens, causing disease in patients with impaired cell-mediated immunity (eg, HIV-infected patients or those with hematologic malignancies), in those using steroids or chemotherapeutic agents, and in those with invasive devices.[2] *Cryptococcus laurentii* has been isolated from several sources such as Norway spruce trees (*Picea abies*) and trembling aspen trees (*Populus tremuloides*), bird droppings, and perihospital areas.[3] Human infections due to *C. laurentii* have been described as causing fungemia, central nervous system infection, skin and soft-tissue infections, and pneumonia, among others.[2] The finding of yeasts in a urine culture of asymptomatic patients is considered colonization. Recent guidelines suggest that the treatment of asymptomatic candiduria consists of eliminating risk factors such as indwelling catheters and witholding treatment except in patients with risk factors for dissemination (eg, neutropenic patients, very-low-birth-weight infants, and prior to urologic procedures).[4] Regarding non-*neoformans* cryptococcuria, the information is lacking; therefore, we aimed to describe a case series about the clinical characteristics and outcomes of hospitalized patients with in-hospital isolation of *C. laurentii* from urine cultures.

We performed a retrospective case series in Dr. Alfredo Badallo General Hospital in Mexico. We included all hospitalized patients with at least a urine culture positive for *C. laurentii* from 2015 to 2018, identified by Vitek 2 and phenotypic tests. Clinical data and outcomes were extracted from the medical records. The follow-up after the isolation of *C. laurentii* was between 7 and 210 days, and the data were reported with descriptive statistics. The study was approved by our institutional review board.

In total, 10 patients were identified with cryptococcuria by *C. laurentii*, of which 4 were men and 6 were women. Half of these patients were older than 70 years. The patients had several comorbidities, with a median Charlson index of 3 (range, 1–5) (Table 1).

Six patients had a history of previous hospitalizations within the prior year. During their last hospitalization, the average length of stay was 9 days (range, 3–18), and these prior admissions were associated with their underlying comorbidities. An infectious diagnosis was the reason for admission in all 10 patients (100%), and the patients received antibiotic therapy with a range of 2–3 antibiotics per patient, with an average of 8 days of use (range, 4–13 days) (Table 1). The antibiotics mainly used were levofloxacin, imipenem, ciprofloxacin, ceftriaxone, and metronidazole.

Six patients were cultured from other areas; 2 had negative blood cultures, and 1 had a *S. epidermidis* blood isolate. Three patients with skin and soft-tissue cultures had *S. epidermidis*, *Escherichia coli*, and *Acinetobacter baumanni*, respectively. No other microorganisms were found in urine or blood with *C. laurentii*.

Clinicians started treatment with fluconazole in 4 patients; urine cultures were negative in 2 of these patients after treatment. Recurrent funguria with *C. laurentii* occurred in 1 patient, and therapy with itraconazole was started without follow-up urine cultures. Of the 4 patients treated with fluconazole, 3 survived free of symptoms, and 1 died of complications of liver cirrhosis in a subsequent hospitalization 7 months later. The other 6 patients did not receive treatment for *C. laurentii*; 2 of these died during the same admission, and another died within the first 30 days during a subsequent hospitalization. The other 3 patients survived.

This case series includes patients with urinary *C. laurentii* of nosocomial origin, and our patients had had antecedent hospitalizations. Remarkably, a high proportion were older patients, and all had received broad-spectrum antimicrobial therapy before the isolation of *C. laurentii*.

Isolates of *C. laurentii* of nosocomial origin have been reported in a recent molecular study, in which 26% were of common origin showing the same haplotype.[3] *C. laurentii*, as a nosocomial infection, has already been described. A systematic review of non-*neoformans* cryptococci demonstrated a significant association between the use of invasive devices and *C. laurentii* bloodstream infection (aOR, 8.7; 95% CI, 1.48–82.9).[2] A recent case report of a patient requiring invasive mechanical ventilation with a long hospital stay, central venous catheter use, and prolonged duration of broad-spectrum antibiotics including echinocandin, developed a *C. laurenttii* bloodstream infection.[1] Another case report described a cystic fibrosis patient with a prior *C. laurentii* paranasal sinus colonization who developed pneumonia and disseminated cryptococcosis after sinus surgery.[5]

In our case series, the clinicians considered treating the cryptococcuria in some patients; however, the sample size did not allow us to reach conclusions regarding whether treatment of asymptomatic urinary *C. laurentii* was beneficial; none of these patients developed cryptococcal disease without treatment. On the other hand, the treatment of *C. laurentii* infection (eg, fungemia or central nervous system infection) does require urgent treatment, mainly with amphotericin B because since *C. laurenti* has shown resistance to azoles in up to 50% of tested strains.[6,7]

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Table 1. Demographic Data, Clinical Characteristics, and Outcomes of Patients With Urinary *Cryptococcus laurentii*

Patient	Age, y	Sex	Charlson Index	Admission Diagnosis	Days of In-Hospital Stay Prior to the Isolation of *C. laurentii*	Invasive Devices	Antibiotic Treatment	Average Days of Antibiotic Treatment	Treatment for Crypto-coccuria	Death in the 1st 30 d
1	71	F	3	Infectious diarrhea/ Infected venous ulcer	13	PVC	Ciprofloxacin/Metronidazole	12	No	No
2	79	M	3	Abdominal sepsis secondary to intestinal perforation	21	CVC/Urinary catheter/ Nasogastric tube/Penrose	Cefotaxime/Metronidazole Ciprofloxacin/Imipenem	6	No	No
3	48	M	3	Surgical wound infection	14	CVP/ Urinary catheter/ Hemodialysis catheter	Meropenem/Vancomycin	10	No	Yes[a]
4	47	M	5	VAP	25	CVP Mechanical ventilation/ Peritoneal dialysis catheter	Levofloxacin/Ceftazidim Vancomycin/Imipenem	4	No	Yes[b]
5	70	F	1	Sepsis of abdominal origin secondary to intestinal perforation	17	CVC	Imipenem/Amikacin Levofloxacin	5	No	Yes[c]
6	23	M	1	Anxiety crisis/UTI[d]	6	PVC	Levofloxacin	5	No	No
7	55	F	2	CAP	10	PVC	Ceftriaxone/Clarithromycin Levofloxacin/Ceftazidime/ Amikacin	4	Fluconazole	No
8	77	F	5	DM /UTI[d]	4	PVC/Urinary catheter	Ceftriaxone	7*	Fluconazole	No
9	88	F	5	Infectious diarrhea	20	PVC/Urinary catheter	Ceftriaxone/Metronidazole Levofloxacin/Imipenem	13**	Fluconazole	No
10	67	F	5	Infectious diarrhea	9	CVC	Ciprofloxacin	12*	Fluconazole	No

Note. M, male; F, female; PVC, peripheral venous catheter; CVC, central venous catheter; UTI, urinary tract infection; DM2, type-2 diabetes mellitus 2; CAP, community-acquired pneumonia; VAP; ventilator-associated pneumonia.
*Patients with negative controls after treatment.
**Patient with change of treatment after a new positive culture for *C. laurentii* after treatment, with negative control after second treatment.
[a]Death at 30 d in a subsequent hospitalization due to septic shock secondary to community-associated pneumonia.
[b]Death after 7 d in the same hospitalization due to septic shock secondary to Pneumonia associated with mechanical ventilation.
[c]Death at 7 d in the same hospitalization due to septic shock secondary to sepsis of abdominal origin.
[d]Patients who were admitted with a clinical data of urinary tract infection without positive cultures.

In conclusion, *C. laurentii* is an opportunistic pathogen of immunosuppressed or severely ill hospitalized patients, and a critical risk factor is the previous use of antibiotic therapy. However, the isolation of urinary *C. laurentii* in the correct clinical setting may be nonsignificant. What to do in patients at risk, such as neutropenic patients, and patients before urologic instrumentation who have a urine culture positive for *C. laurentii*, has not yet been determined.

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Age: A variable whose definition we should not ignore

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To the Editor—The age of included patients is described as a demographic patient characteristic in many research articles, and handled as a continuous variable, expressed as a mean with standard deviation or median with interquartile range, or as a categorical variable. However, in the methods section of articles, how the age of patients was calculated was almost never explained. The starting point is obvious: the birth date of the included patient. However, the second date is not always that obvious; especially when dealing with different follow-up and inclusion times, it can become difficult. What should one do—calculate age at time of inclusion in the study, calculate age at time of the outcome measure, or maybe calculate age at time of hospital admission? Additionally, should age be considered a discrete value or a continuous value including months? To gain insight into how authors handled the demographic variable age, I considered the original articles in the latest issue of *Infection Control and Hospital Epidemiology*, volume 40, issue 8 (August 2019).

Of 8 original articles in this issue, 6 (75%) described age as a demographic patient characteristic. Fridkin et al[1] classified age as a categorical value. In their article, age was described as the average age of residents followed by a median, but the point in the study at which the age was calculated was not stated. Dyer et al[2] were more clear: age was classified as a continuous variable and described as mean age. A footnote of their table 3 states that pediatric admission was defined as 0–17 years of age at hospital admission. Asundi et al[3] conducted a cohort study including 2,059 patients with a median age of 71.7 years, but how was age determined? In the methods section, they stated that age was part of the prospectively collected data; however, for the variable age, was age considered at the moment of the procedure considered or age at admission? Elman et al[4] classified age as a categorical variable, and they described 4 different age groups, but was age taken at time of detecting the outcome measure (ie, urinary tract infection) or at admission? Jiang et al[5] calculated a median age; however, which dates were taken into account when calculating age, such as age at time of enrollment, was not stated. Nesher et al[6] presented age as a mean in their table 2; however, its definition was not described in the methods section of the article. Was age taken as age at the time of diagnosis? In the methods section, they stated that all data were collected prospectively, but similar to Asundi et al, it is unclear how the age of patients was handled in this study.

None of the articles stated whether age was considered a discrete value from the start, or whether months were taken into account for individual patients during analyses. In only 1 of these 6 articles was it somewhat clear that age at admission was used. One might think, what is the problem with being a few months off, or when dealing with discrete values, possibly a year off? This is the reason: Our goal is to conduct research in the best way we can. Even small things matter because when data are combined, they may reveal something larger. Therefore, I feel that age of patients should be described in a more specific and consistent manner. Future studies should investigate which definition is best and should propose which measurement should be used.

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