JOURNAL OF CLINICAL MICROBIOLOGY, July 2003, p. 3354–3357 Vol. 41, No. 7
0095-1137/03/$08.00+0 DOI: 10.1128/JCM.41.7.3354–3357.2003

Candida dubliniensis Infections in a Pediatric Population: Retrospective Identification from Clinical Laboratory Isolates of *Candida albicans*

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Received 23 December 2002/Returned for modification 26 February 2003/Accepted 4 April 2003

***Candida dubliniensis* is a recently described species that shares many phenotypic and morphological features with *Candida albicans*. The clinical significance of isolating *C. dubliniensis* from the pediatric population is not clear, as most clinical isolates have been recovered from the oral cavities or bloodstreams of adults infected with human immunodeficiency virus. In order to understand further the epidemiology of *C. dubliniensis* in our pediatric population, we identified *C. dubliniensis* isolates from clinical isolates previously identified in the laboratory as *C. albicans* and conducted a retrospective chart review of cases of *C. dubliniensis* infections. A total of 205 isolates from 183 patients were tested, and only 14 (6.8%) were identified as *C. dubliniensis*. In 5 of the 14 positive cultures, *C. dubliniensis* was the sole organism isolated (two respiratory tract specimens, one tongue specimen, one vaginal specimen, and one skin specimen). A case review showed that there were no adverse outcomes for any of the patients, and only one of the patients with cultures positive for *C. dubliniensis* was immunocompromised. In our pediatric population, the distinction of *C. dubliniensis* from *C. albicans* did not prove to have significant clinical relevance. Data from further investigations may help to define better the role of *C. dubliniensis* as a potential pathogen in children.**

Fungal infections have become increasingly prevalent among immunocompromised patients with both primary and acquired immunodeficiencies, including human immunodeficiency virus (HIV) infection (17). *Candida dubliniensis* has emerged as a new pathogen prevalent mostly in the adult HIV patient population, causing oral lesions and bloodstream infections (1–8, 16, 19). This organism may not be identified through routine fungal identification, as it shares many phenotypic and morphological features with the more commonly isolated species *Candida albicans* (8, 14, 16, 18). Notably, both species are identified by germ tube formation, chlamydospore formation, similar morphology on corn meal agar, appearance on CHROMagar Candida, and the formation of "feet" on blood and chocolate agar in ≤48 h.

In our clinical microbiology laboratory, we have not routinely screened for *C. dubliniensis* isolation, as this organism has not been known to be a significant pathogen in the pediatric population until recently. However, fungal infections have been increasing in frequency in the immunocompromised patient population, as has the number of different species isolated. There are a few short reports of pediatric infections caused by *C. dubliniensis* in the literature, primarily in severely immunocompromised patients (2, 3, 9). In order to understand further the epidemiology of *C. dubliniensis* in pediatrics, we identified *C. dubliniensis* isolates from clinical isolates previously identified in the laboratory as *C. albicans* and conducted a retrospective chart review of cases of *C. dubliniensis* infections.

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Clinical isolates were obtained from specimens submitted for either bacterial or fungal culture performed in the microbiology laboratory of the Children's Hospital of Philadelphia from December 2000 through July 2002. All of these isolates had been previously identified as *C. albicans* to treating physicians. One isolate from each specimen site per patient was included in this study. Frozen isolates were subcultured at least twice prior to testing for growth at 45°C. Prepared isolates were subcultured to sheep blood agar and incubated aerobically at 45°C for a total of 48 h. Plates were examined for growth at both 24 and 48 h of incubation. Isolates that were negative for growth at 45°C after 48 h of incubation were confirmed as *C. dubliniensis* with API 20C (bioMérieux).

There were a total of 205 isolates from specimens including 42 blood specimens, 52 urine specimens, 44 respiratory tract specimens, 16 surface wound specimens, 16 vaginal specimens, 15 deep-wound specimens, 14 ear and tympanic fluid specimens, 2 central venous catheter tip specimens, 1 stool specimen, 2 pleural fluid specimens, and 1 eye specimen. These specimens represented 183 patients who ranged in age from 6 weeks to 19 years (mean, 6.6 years). These patients represented both immunocompetent and immunocompromised hosts. A total of 14 isolates were identified as *C. dubliniensis* (6.8%). These isolates had been obtained from 14 different patients with cultures from various anatomical sites, as listed in Table 1.

A retrospective chart review was performed on the patients identified with a *C. dubliniensis* isolate. Local Institutional Review Board approval with waiver of informed consent was obtained as patient identifiers were not included in the final study. Data collected included outpatient visit or inpatient hospitalization, patient's age and gender, diagnosis, underlying morbidity, concomitant infections, antifungal therapy, and out-

TABLE 1. Clinical data on the patients examined in this study

Patient no.	Age	Gender	Specimen	Concomitant infections and organisms	Diagnosis	Underlying comorbidity	Antibiotic exposure	Patient status	Antifungal treatment
1	11 yr	M	Bronchoalveolar lavage	Alpha-hemolytic streptococci	Bronchiolitis obliterans, organizing pneumonia	Bronchiectasis	Ampicillin, azithromycin, cefotaxime, primethoprim-sulfamethoxazole	Inpatient	No
2	15 yr	F	Tracheal aspirate	None	Acute respiratory failure	Down syndrome, CHF[b]	Cefotaxime, vancomycin, erythromycin	Inpatient	No
3	17 yr	F	Sputum	Coagulase-negative, staphylococcus, bloodstream infection	Hypoxia, megacolon, necrotizing enterocolitis	Spina bifida, ventriculoatrial shunt	Trimethoprim-sulfamethoxazole, ciprofloxacin, gentamicin, oxacillin	Inpatient	No
4	19 yr	F	Sputum	Nonmucoid *Pseudomonas aeruginosa,* mucoid *P. aeruginosa, Aspergillus fumigatus*	Pseudomonas pneumonia	Cystic fibrosis, allergic broncho-pulmonary aspergillosis	Tobramycin, ceftazidime, meropenem, itraconazole	Inpatient	No
5	16 yr	M	Sputum	None	Pulmonary fibrosis	HIV infection, chronic renal failure, cardio-myopathy	Ampicillin-sulbactam, metronidazole, gentamicin, azithromycin, ticarcillin-clavulanate	Inpatient	Yes (fluconazole)
6	5 yr	M	Blood	*Staphylococcus epidermidis*	Port infection	Factor VIII, deficiency	Vancomycin, gentamicin, oxacillin, clindamycin	Inpatient	Yes (amphotericin B, fluconazole)
7	2 wk	M	Tongue	None	Thrush	None	None	Outpatient	NA[f]
8	14 yr	F	Vagina	None	Vaginitis	None	None	Outpatient	NA
9	15 yr	F	Vagina	*Staphylococcus aureus*	Vaginitis	None	None	Outpatient	NA
10	2 yr	F	Skin	None	Diaper rash	None	None	Outpatient	NA
11	16 yr	M	Abscess	Abscess, Cx + normal skin flora	Renal perirenal abscess, inpatient rehabilitation	Status post gunshot wound, resection of left kidney, spleen, and pancreatic tail; open abdominal wound, colostomy	None	Inpatient	Yes (fluconazole)
12	18 yr	F	Urine	*Neisseria gonorrhoeae, Chlamydia trachomatis Trichomonas vaginalis*	Gonococcal salpingitis	Asthma fibromyalgia	Gentamicin, clindamycin	Inpatient	Yes (fluconazole)
13	19 yr	F	Urine	*Escherichia coli,* coagulase-negative staphylococci	Urinary tract infection	None	Trimethoprim-sulfamethoxazole	Outpatient, (ED)[e]	No
14	14 yr	F	Urine	*Enterococcus* sp., *Corynebacterium* sp.	Nephrolithiasis	Arnold-Chiari malformation VP[d] shunt, neurogenic bladder	Gentamicin, ampicillin	Inpatient	Yes (amphotericin B)

[a] M, male; F, female.
[b] CHF, congestive heart failure.
[c] Cx^+, culture positive.
[d] VP, ventriculoperitoneal.
[e] ED, emergency department.
[f] NA, not available.

come (Table 1). The ages ranged from 2 weeks to 19 years, and nine patients were female (64.3%). Nine patients (64.3%) were hospitalized at the time of positive culture. In 5 (35.7%) of the 14 patients, *C. dubliniensis* was the only organism isolated. All blood and urine cultures were polymicrobial, including bacteria and one parasite, *Trichomonas vaginalis*, in one urine culture together with *C. dubliniensis*. The only immunocompromised patient was one with HIV infection with concurrent chronic renal failure and cardiomyopathy who underwent bronchoscopy for diagnosis of respiratory difficulty and was found to have pulmonary fibrosis and candidal plaques in the nose and epiglottis. A pure culture of *C. dubliniensis* was obtained from a sputum sample from him, and he was treated with fluconazole and recovered fully. There were no oncology or solid-organ transplant patients. Another patient with pulmonary disease had an underlying diagnosis of cystic fibrosis. The one patient with a blood culture positive for *C. dubliniensis* had a central venous port in place. Two of three blood cultures obtained from this patient were also positive for *Staphylococcus epidermidis* at the same time. The central line was removed, and subsequent blood cultures were negative. The patient received antifungal therapy, both intravenously and enterally, and was discharged to home without complications. Of the five pure cultures, three were from body sites that are commonly infected with *C. albicans* and are often diagnosed by appearance alone: thrush in the mouth, vaginitis, and diaper dermatitis. Only five patients were known to have received antifungal therapy directed toward *C. albicans*. No patients had subsequent cultures positive for *C. dubliniensis*. There were no deaths. All inpatients were discharged, and no outpatients were admitted to the hospital with diagnoses related to their fungal infections.

There have been several small case series reports of pediatric *C. dubliniensis* infections, particularly in immunocompromised hosts. These patients are often undergoing chemotherapy for underlying malignancy or are infected with HIV (9, 15). The data in the immunocompromised-adult literature is substantial in recognizing this organism as a significant pathogen, but as is the case with other infectious diseases, such as common opportunistic infections in HIV-infected hosts, pediatric data are often dissimilar and currently lacking. To date, the data on pediatric populations is sparse and consists of mainly case reports within immunocompromised patient groups or studies of colonization rather than infection (2, 3). Although our hospital cares for a large pediatric population, the total number of *C. dubliniensis* cases was admittedly very small. We found only one immunocompromised patient, who was not an oncology patient, in our series infected with this organism who recovered fully. Also, in contrast to the existing literature, our patients were not primarily infected in the oral cavities but rather at various sites, particularly the respiratory tract. It was likely that the three patients with other organisms present were merely colonized with *C. dubliniensis*. Most of the patients with respiratory tract cultures also had significant underlying pulmonary disease diagnosed prior to their infections and received multiple antibiotics during their relevant hospitalizations, which may have contributed to their developing fungal overgrowth.

One recent publication suggests that *C. dubliniensis* is less virulent than *C. albicans*, finding that healthy mice are better able to survive *C. dubliniensis* infection and that *C. dubliniensis* isolates are more susceptible to the fungicidal effect of human neutrophils (20). This may explain why the overall incidence of *C. dubliniensis* infection is lower than that of *C. albicans* infections, even among susceptible hosts. It is likely that HIV-infected patients are not the only hosts susceptible to these infections, as there is an increasing number of reports of various other patient populations with *C. dubliniensis* infections. In our series, we had one patient with an underlying diagnosis of cystic fibrosis. A recent article reported a relatively high rate of colonization in a population of cystic fibrosis patients (13). Our patients clearly reflected a diverse group of patients even without known immunodeficiencies, suggesting that this organism is finding its biological niche where *C. albicans* has traditionally been the pathogenic species.

In addition, more recent studies have suggested that *C. dubliniensis* becomes resistant to fluconazole during a course of therapy, making it a relatively more resistant pathogen and possibly more difficult to treat (7, 10, 11). Our case series showed that patients who received therapy directed toward *C. albicans* had no recurrence of their infections and that most of the patients did not receive any antifungal therapy but recovered fully. We did not perform antifungal susceptibility testing on these isolates, which may have supported other findings of increased resistance to fluconazole. When treating patients who are more susceptible to invasive fungal disease, the isolation of *C. dubliniensis* could potentially prompt the choice of a therapeutic agent other than fluconazole, which is often used to treat *C. albicans*, if resistance patterns prove to be more prevalent in the future. However, in our study, it did not appear that the differentiation between species contributed negatively to the patient's infection or outcome.

Although the current method of distinguishing between *C. albicans* and *C. dubliniensis* involves a 48-h incubation, in our laboratory, we showed that growing isolates at 45°C with 24 h of incubation was sufficient testing to distinguish between the two species, as all *C. albicans* isolates displayed luxuriant growth after 18 to 24 h of incubation. A relatively small percentage of presumed *C. albicans* isolates, 6.8%, were ultimately determined to be *C. dubliniensis*. This number was comparable to that described in other studies that distinguished between the two species, ranging from 4.3 to 14.4%, varying among different parts of the world (12). Given the lack of clinical significance and reliability of simpler laboratory tests, the additional time and effort required to distinguish all *C. albicans* isolates from *C. dubliniensis* may not be warranted. Larger epidemiological studies are needed to understand better the pathogenic nature of *C. dubliniensis* in pediatric patients.

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