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Epidemiology and Resource Utilization in Pediatric Invasive Candidiasis

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Abstract

Background: This retrospective observational study was conducted to gain insight into epidemiology, treatment, length of stay (LOS) and costs for hospitalized neonate and pediatric patients with invasive candidiasis (IC).

Methods: The Cerner Health Facts Database, a multicenter US electronic health record database, was used to assess the clinical and economic impact of pediatric IC in inpatients (2005–2014). Patient encounters were identified by positive blood/cerebrospinal fluid (CSF) cultures for *Candida*, and encounter characteristics were evaluated. The impact of multiple factors on (log-transformed) LOS and cost was examined in patients with candidemia only (n = 191) using multivariable linear regression. Model parameter uncertainty was evaluated with bootstrap analysis.

Results: From 2005 to 2014, 202 patients had a positive culture (blood: n = 192; CSF: n = 12). The most prevalent species at index culture was *C. parapsilosis* (n = 70, 34.7%), followed by *C. albicans* (n = 66, 32.7%). Mean (SD) age was 5 (5.5) years, with 30 patients (14.9%) < 4 months of age. Common comorbidities included sepsis (n = 85, 42.1%), coagulation disorders (n = 57, 28.2%), cancer (n = 64, 31.7%), and low birthweight (n = 26, 12.9%). Antifungal exposure included azoles (57.4%), polyenes (28.7%), and echinocandins (35.1%); 20.8% of patients had no record of receiving an antifungal during their index encounter. The mean cost per encounter was $97,392 ($149,253), with a mean LOS of 45.6 (59.5) days and 9.9% mortality at discharge. Results did not differ greatly across *Candida* species. In regression analysis, intensive care unit (ICU) exposure, central catheter, sepsis, receipt of an antifungal > 48 hours prior to index culture, and age < 4 months were significantly associated with increased LOS, while treatment at a non-teaching hospital was associated with reduced LOS (P < 0.05). Antifungal use > 48 hours before index, alive at discharge, Midwest/West region and ventricular shunt were significantly associated with increased cost ($P \leq 0.05$).

Conclusions: While limited by small sample size, this analysis confirms the association between neonatal and pediatric candidemia and increased resource utilization. However, given high observed rates of potential under-treatment, an opportunity may exist to improve antifungal therapy in this population.

Background

- *Candida* infections pose a serious health risk and a significant burden on outcomes and resource utilization in all populations. However, most available data are derived from adults, while limited data exist for the neonatal and pediatric populations.
- Risk factors in neonates and pediatric patients are known to be different from those in adults.[1] *Candida* infections in pediatric patients may be associated with significant morbidity and mortality.
- The shifting epidemiology of candidemia in pediatric populations, associated with an increase in *C. glabrata* and *C. krusei* isolates,[2,3] has recently been recognized by the Infectious Diseases Society of America (IDSA), which has issued updated guidelines on treatment, recommending an echinocandin or fluconazole as initial therapy in most adult and pediatric patients.[4]

Objective

- This retrospective observational study was conducted to gain insight into epidemiology, treatment, length of stay (LOS) and costs for hospitalized neonate and pediatric patients with invasive candidiasis (IC).

Data Source

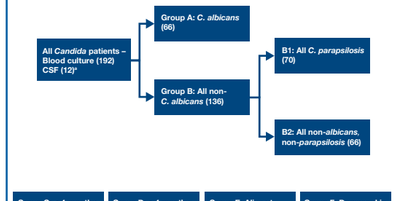
- This study used the Cerner Health Facts Database (Cerner Corporation, Kansas City, MO), a proprietary database built from participating United States hospitals' comprehensive clinical records, including time-stamped medication orders, clinical and microbiology laboratory tests, and billing information.
- Participating hospitals included a mix of urban, rural, teaching and non-teaching facilities, averaging > 200,000 neonate and pediatric admissions annually during the study period.
- Data are de-identified and fully comply with the Health Insurance Portability and Accountability Act (HIPAA) to maintain patient confidentiality.

Methods

Population selection

- Inpatient encounters, < 18 years old, with a blood or CSF culture positive for *Candida* species were identified from 2,089,778 encounters in the database; for patients with multiple eligible encounters, the first encounter in the database was included in the analysis, while data from 30 days prior to index culture were included for timing variables (see below).
- Patients admitted through the emergency department (ED) were classified as inpatients, with time spent in the ED counted towards LOS, and both their ED and inpatient data were included as part of their encounter record.
- Based on the *Candida* species present at index culture, age and in-hospital mortality, 8 study groups were formed (**Figure 1**).

Figure 1. Study groups and patient numbers



[a]Positive blood culture (n = 192), positive CSF culture (n = 10), fungal blood culture with isolates in addition to *Candida* (n = 2).

Study variables

- Patient demographics, encounter characteristics, comorbidities (defined by ICD-9-CM and Healthcare Cost and Utilization Project Clinical Classifications Software [HCUP CCS][5]), laboratory and microbiology data, antifungal therapies (AFT), and outcomes were assessed in the study cohort.
- Other relevant variables:
  - Timing variables, including: time to the index culture; time to any AFT following the index culture; time from start of first AFT to the time of index culture (for patients whose first AFT occurred within 30 days prior to their index culture).
  - Culture clearance (by drug class) in patients who survived at least 7 days post-index culture, and had ≥ 3 blood cultures during this 7-day follow-up period with at least 1 culture falling ≥ 48 hours after index culture.
  - Breakthrough of prophylaxis, defined as patients who received AFT prior to a window of –2 to +5 days from (positive) index culture.
- Group A and Group B were compared for each variable, as were Group A, B1 and B2 in a 3-way evaluation. Group C and Group D were compared for treatment patterns and outcomes (**Figure 1**).
- Group E and Group F were compared for an assessment of culture species, treatment patterns and outcomes.

Statistical analyses

- Continuous variables (reported as mean, SD) were compared using Student's t-test or Wilcoxon two-sample test (for comparisons with small sample sizes, a Wilcoxon rank sum test), while categorical variables (reported as proportions) were compared using Chi square or Fisher's exact tests.
- 3-way comparisons conducted with ANOVA.
- Multivariate analyses were conducted to determine the most predictive risk factors for hospital LOS (n = 191) and cost (n = 135).
- Statistical significance was identified as an alpha < 0.5.

Results

- A total of 202 patients with a qualifying *Candida* culture were identified. The *Candida* species distribution is shown in **Table 1**.
- Patient demographics and encounter characteristics are described in **Table 2**.
- No significant difference in mean and median Charlson Comorbidity Index (CCI) was observed between *C. albicans*, non-*C. albicans* groups. Comorbid conditions are summarized in **Table 3**.
- Overall, 58.9% of patients received their index culture > 48 hours post-admission.
- 28.2% of overall patients had bacteremia prior to the index fungal culture, and 19.3% had bacteremia following the index culture.

Antifungal therapy (AFT)

- During the index encounter, 79.2% of overall patients used at least 1 antifungal agent: azole (57.4%), amphotericin B (28.7%), and echinocandins (35.1%) (**Table 4**).
- Mean time to AFT following the index culture and mean time from the first AFT within 30 days of index culture is shown in **Table 4**. *C. parapsilosis* group had a longer mean time to AFT than *C. albicans* group (not significant).
- Time to AFT for *C. albicans* group was significantly shorter than for all non-*C. albicans* (P = 0.031). Time from first AFT to index culture was also significantly shorter for patients alive at discharge compared with those deceased in hospital (P = 0.048).

Healthcare resource utilization

- Mean (SD) cost of the index inpatient encounter was $97,392 ($149,253), and mean (SD) LOS was 45.6 (59.5) days (**Table 5**).
- Mean costs were lower in the *C. albicans* group compared with the non-*C. albicans* group, but not statistically significant.
- Both LOS (not significant) and mean cost (significant), were lower in survivors, compared with patients who died in hospital.

Multivariate analysis

- A multivariate regression analysis was conducted for log-transformed LOS (n = 191) and cost (n = 135).
- Significant drivers of increased LOS were age < 4 months, ICU exposure, central catheter, breakthrough of prophylaxis, and sepsis, while treatment at a non-teaching hospital was associated with a reduced LOS.
- Factors affecting cost were Midwest/West region, breakthrough of prophylaxis, and survival at discharge. AFT was not associated with cost.
- Higher overall costs were observed in the deceased group (descriptive analysis). However, in multivariate regression analysis, surviving was an independent predictor of increased cost.

Table 1. *Candida* species distribution

	Patients with index *Candida* culture from either blood or CSF		Patients with index *Candida* culture from blood		Patients with index *Candida* culture from CSF		Group E alive at discharge		Group F deceased in hospital	
	N = 202		*n* = 192		*n* = 10		*n* = 180		*n* = 20	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%
All	202	100%	192	100%	10	100%	180	100%	20	100%
Candida albicans	69	34.2%	65	33.9%	4	40%	63	35%	6	30%
Non-*C. albicans*	136	67.3%	130	67.7%	6	60%	120	66.7%	14	70%
C. dubliniensis	4	2%	3	1.6%	1	10%	3	1.7%	0	0%
C. glabrata	13	6.4%	13	6.8%	0	0%	10	5.6%	3	15%
C. guillermondii	3	1.5%	3	1.6%	0	0%	3	1.7%	0	0%
C. krusei	8	4%	8	4.2%	0	0%	7	3.9%	1	5%
C. lusitaniae	15	7.4%	15	7.8%	0	0%	15	8.3%	0	0%
C. parapsilosis	70	34.7%	65	33.9%	5	50%	63	35%	6	30%
C. tropicalis	19	9.4%	19	9.9%	0	0%	16	8.9%	3	15.0%
Candida other/ unknown	7	3.5%	7	3.6%	0	0%	6	3.3%	1	5.0%

Species categories are not mutually exclusive. Two patients in the study cohort had an unspecified hospital mortality and were excluded from the Alive at Discharge/Deceased in Hospital subanalysis.

Table 2. Patient demographics and encounter characteristics

	Overall study encounters *N* = 202	
Age at admission (continuous), years		
Mean (SD)	5 (5.5)	
	n	%
Age at admission (categorical), years		
< 4 months	30	14.9%
≥ 4 months – < 2 years	57	28.2%
≥ 2 years – < 12 years	77	38.1%
≥ 12 years – < 18 years	42	20.8%
Gender		
Male	116	57.4%
Female	86	42.6%
Race		
Caucasian	101	50.0%
African American	70	34.7%
Asian	2	1.0%
Other	29	14.4%
Payer		
Commercial	36	17.8%
Medicare	1	0.5%
Medicaid	67	33.2%
Self-paid	1	0.5%
Other/unknown	97	48.0%
Any hospital exposure within 90 days prior[a]	162	80.2%
Inpatient admission within 90 days prior	114	56.4%
Surgical procedure within 90 days prior	39	19.3%
Admission source		
Hospital/other care facility	0	0.0%
SNF/LTC/NH	4	2.0%
Emergency department	85	42.1%
Physician or clinic referral	97	48.0%
Other/unknown	16	7.9%
Urgent/emergent admission	126	62.4%
Surgical procedure during index encounter	86	42.6%
Discharge disposition		
Acute care facility	10	5.0%
Died	20	9.9%
SNF/NH	2	1.0%
Home	162	80.2%
Other/unknown	8	4.0%

[a]Includes other care settings, such as SNF/LTC/NH, ED, or other, as well as inpatient stays.
SNF, Skilled Nursing Facility; LTC, Long-Term Care; NH, Nursing Home.

Table 4. Antifungal agents

	Overall study encounters *N* = 202	
Categorical variables	***n***	**%**
Antifungal agents, any	160	79.2%
Azoles, any	116	57.4%
Fluconazole	110	54.5%
Itraconazole	2	1.0%
Posaconazole	0	0.0%
Voriconazole	9	4.5%
Amphotericin B compounds, any	58	28.7%
Amphotericin B	13	6.4%
Amphotericin B cholesteryl sulfate	0	0.0%
Amphotericin B lipid complex	23	11.4%
Amphotericin B liposomal	32	15.8%
Echinocandins, any	71	35.1%
Caspofungin	33	16.3%
Micafungin	42	20.8%
Anidulafungin	1	0.5%
Flucytosine	3	1.5%
Antifungal therapy within 30 days prior to admission	10	5.0%
Continuous variables		
Time to any antifungal order following index culture, days		
n	109	
Mean (SD)	2.48 (4.44)	
Time from antifungal to index culture, days[a]		
n	37	
Mean (SD)	6.36 (7.97)	

[a]Among patients whose first antifungal therapy occurred within 30 days prior to their index culture, the time from their first antifungal start time to the index culture. SD, standard deviation.

Table 3. Clinical characteristics and comorbidities

	Overall study encounters *N* = 202	
Charlson Comorbidity Index (CCI) score, continuous		
Mean (SD)	1.491 (2.033)	
	n	%
Charlson Comorbidity Index (CCI) score, categorical		
0	97	48.0%
1	25	12.4%
2	40	19.8%
3	15	7.4%
4–6	18	8.9%
7–9	7	3.5%
Neoplasms		
Cancer, any	64	31.7%
GI cancer	6	3.0%
Cancer of the lymphatic and hematopoietic tissue	31	15.3%
Cancer, other primary	35	17.3%
Secondary malignancies	17	8.4%
Malignant neoplasm without specification of site	4	2.0%
Maintenance chemotherapy; radiotherapy	42	20.8%
Hematologic malignancy	33	16.3%
Endocrine and metabolic diseases		
Obesity	6	3.0%
Conditions of birth		
Congenital anomaly	9	4.5%
Low birthweight/short gestation	26	12.9%
Respiratory distress syndrome of newborn	9	4.5%
Respiratory conditions of fetus and newborn, other than respiratory distress	10	5.0%
Diseases of the circulatory system		
Hypertension	26	12.9%
Heart valve disorders	11	5.4%
Peri-, endo-, and myocarditis; cardiomyopathy (except that caused by TB or STD)	15	7.4%
Pulmonary heart disease	5	2.5%
Cardiac dysrhythmias, any	32	15.8%
Congestive heart failure	7	3.5%
Cerebrovascular disease	13	6.4%
Peripheral and visceral atherosclerosis	11	5.4%
Diseases of the respiratory system		
Asthma	27	13.4%
Diseases of the digestive system		
Esophageal disorders	36	17.8%
Gastritis and duodenitis	9	4.5%
Liver disease	53	26.2%
Pancreatic disorders (not diabetes)	6	3.0%
Diseases of the blood and blood-forming organs		
Coagulation and hemorrhagic disorders	57	28.2%
Mental illness		
Mood disorders	10	5.0%
Schizophrenia and other psychotic disorders	6	3.0%
Alcohol and substance disorders, any	9	4.5%
Substance-related disorders	9	4.5%
Other conditions of interest		
Stem cell transplant	6	3.0%
Solid organ transplant	14	6.9%
Neutropenia		
Neutropenia, any	19	9.4%
Diseases of the circulatory system		
Acute stroke/cerebrovascular insufficiency	7	3.5%
Cardiac arrest and ventricular fibrillation	5	2.5%
Diseases of the respiratory system		
Pneumonia	20	9.9%
Aspiration pneumonitis	5	2.5%
Respiratory failure, insufficiency, arrest (adult)	44	21.8%
Diseases of the urinary system		
Acute and unspecified renal failure	18	8.9%
Diseases of the digestive system		
Gastrointestinal hemorrhage	14	6.9%
Intestinal obstruction without hernia	21	10.4%
Symptoms, signs, and ill-defined conditions		
Sepsis/septic shock	85	42.1%

This list includes all comorbidities present in ≥ 2% of the study cohort. STD, sexually transmitted diseases; TB, tuberculosis.

Table 5. Healthcare resource utilization

	Overall study encounters *N* = 202	Group A *C. albicans* *n* = 66	Group B All non-*C. albicans* *n* = 136	*P* (A vs B)
Total costs for encounter ($2014)				
n	142	49	93	
Mean (SD)	97,392 (149,253)	76,184 (112,016)	108,567 (165,011)	1
LOS, days				
n	202	66	136	
Mean (SD)	45.6 (59.5)	50.4 (67.9)	43.2 (55.2)	0.421
LOS, survivors, days				
n	182	60	122	
Mean (SD)	45.2 (60.2)	49.8 (67.6)	42.9 (56.5)	0.471
LOS, post-index fungal culture, days				
n	202	66	136	
Mean (SD)	29.3 (43.0)			
Hospital mortality				
Alive at discharge (%)	180 (89.1)	60 (90.9)	120 (88.2)	1.000
Dead at discharge (%)	20 (9.9)	6 (9.1)	14 (10.3)	
Not specified (%)	2 (1.0)	0 (0.0)	2 (1.5)	
Readmission within 30 days after encounter discharge (among survivors) (%)				
No	106 (52.5)	38 (57.6)	68 (50.0)	0.343
Yes	76 (37.6)	22 (33.3)	54 (39.7)	

LOS, length of stay.

Conclusions

- This study provides insight into real-world patterns of candidemia and IC in hospitalized pediatric patients, and confirms the association between pediatric candidemia and high levels of resource utilization, although the small sample size may impact outcome assessments.
- *C. parapsilosis* and *C. albicans* were the most prevalent species at index culture, in agreement with recent research[3,6]
- Total costs were lower in *C. albicans* than all non-*C. albicans* (not significant), while LOS was higher in *C. albicans* group than any of the comparative species subgroups. Costs were higher for neonates, who had significantly longer LOS than older children.
- Results of regression analysis may help identify patients with risk factors predisposing them to have increased LOS or associated costs, and provide an opportunity to improve AFT in this population.
- Given high observed rates of potential under-treatment, an opportunity may exist to improve AFT in the pediatric population.

References

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Disclosures

RH is a full-time employee of Astellas Pharma Global Development, Inc. NA was a full-time employee of Astellas Pharma Global Development, Inc. at the time of the study. SK, QH, RT are full-time employees of Cerner Corporation, contracted by Astellas Pharma Inc. for this project. DH receives consulting fees from Astellas Pharma Global Development, Inc.

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