

An Outbreak of *Candida* spp. Bloodstream Infection in a Tertiary Care Center in Bogotá, Colombia

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Several cases of *Candida* bloodstream infections were documented from June to October 2004 at a tertiary care center in Bogotá, Colombia. Since no cases of candidemia had occurred during the preceding four months, an outbreak was declared. As a result, a microbiological study, a revision of infection control practices and a case-control study were performed. In all, 18 cases of candidemia were ascertained. Parenteral nutrition ($p=0.04$), presence of a central line ($p=0.03$), and severity of illness ($p=0.03$) were associated with candidemia in bivariate analysis. Diverse *Candida* species were observed. *Candida parapsilosis* contamination was found in plastic containers used for transient intravenous (IV) medication storage at the bedside, plastic bags reused for the transportation of IV medicines and cotton used for disinfection of IV ports. Poor infection control practices were widely observed. The outbreak was controlled after elimination of plastic bags used for transportation, instauration of daily disinfection of IV medication containers, acquisition of sterile alcohol swabs for port disinfection and staff education.

It was concluded that candidemia was associated with previously-described risk factors and that poor infection-control practices were likely responsible for the outbreak.

Key-Words: *Candida*, fungemia, disease outbreaks, developing countries, Colombia, Latin America.

Candida spp. has emerged as one of the most common causes of nosocomial bloodstream infections (BSI) in many areas of the world [1-4]. These infections are difficult to diagnose and cause significant morbidity and mortality despite antifungal therapy [5,6]. The mortality associated with *Candida* spp. BSI is consistently high, with estimated figures between 40%-50% [6]. Most *Candida* spp. BSIs occur in patients with indwelling vascular devices [7]. Established risk factors for invasive candidiasis include mucosal or cutaneous barrier disruption, defects in the number and function of neutrophils or in cell-mediated immunity, metabolic dysfunction, extremes of age, use of broad-spectrum antibiotics, cytotoxic chemotherapies and transplantation [1].

Outbreaks of candidemia have been associated with contaminated milk bottles [8], parenteral nutrition [9], glycerin suppositories [10], IV medication contamination [11], syringe reutilization [12], healthcare worker (HCW) hand-colonization [13,14] and contamination of indwelling vascular devices [15]. Other outbreak investigations did not find a common source, but in many cases the outbreak was controlled after optimization of infection-control practices [16,17].

Several cases of *Candida* spp. BSI were documented at the Clínica Jorge Piñeros Corpas, a tertiary care center in the city of Bogotá, Colombia between June and October 2004. No cases of *Candida* spp. BSI had occurred during the four preceding months.

The purpose of this investigation was to determine the factors contributing to *Candida* spp. BSI in order to allow the

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development of control measures that would halt the progression of the outbreak.

Material and Methods

We performed a preliminary investigation to confirm the outbreak and a definitive investigation to determine the factors contributing to its occurrence. The preliminary investigation included establishing a case definition, performing case ascertainment, describing the clinical characteristics of cases, building an epidemic curve and performing a literature review. Cases were defined as patients with at least one blood culture (BC) positive for *Candida* spp. from January to October 2004, at the Clínica Jorge Piñeros Corpas, Bogotá, Colombia. Case ascertainment was performed by reviewing microbiology laboratory and medical records.

The definitive investigation included a case-control study, a revision of infection control practices in the hospital and a microbiological investigation. The first 13 cases were included in the case-control study. Controls were defined as patients with BC results different from *Candida* spp. (positive for other microorganisms or no growth). Patients with positive cultures for *Candida* spp. from other body sites were excluded. This was decided based on the fact that invasive candidiasis is difficult to diagnose [5,18,19] and that candida colonization of non-sterile sites, although non-specific, can be a marker of systemic disease [18,19]. Including patients with positive *Candida* spp. cultures from non-sterile sites in the control group would have created the possibility of misclassification bias of outcome, since some of the "control" patients would have potentially been classified as such when in fact they had undiagnosed invasive candidiasis. We planned to use three controls for each case, selected at random from a list provided by the microbiology laboratory that included BCs done during the outbreak period. Exposure variables collected for cases and controls included age, gender, presence of central venous catheter at time of BC, severity of illness

(American Society of Anesthesiology physical status score) at the time of BC, parenteral nutrition, enteral nutrition, blood product transfusion, medications administered, invasive procedures performed and exposure to HCW within 7 days of BC. Bivariate analysis was performed using the Wilcoxon rank-sum test for numeric exposure variables and the Chi-square or Fisher exact test for categorical variables. P-values less than 0.05 were considered significant. Statistical analyses were performed using SAS software version 8.2 (SAS Institute, Cary, NC, USA).

A revision of behaviors and infection control practices was carried out by the hospital epidemiology team through staff interviews and observations related to common practices at different hospital locations. Practices related to intravenous (IV) catheter management, and to IV medication transportation, storage, preparation and administration were particularly scrutinized.

The microbiological investigation was comprised of culturing HCW hands, ventilator tubing in the intensive care unit (ICU) and coronary care unit (CCU), latex gloves, surgical tape, bandages, cotton, IV catheters, IV solutions, IV medication containers and IV medication transportation bags. Sheep blood agar cultures and Sabouraud agar cultures were used to isolate the microorganisms. A germ tube assay was performed for speciation of *Candida albicans*. Speciation was performed on selected non-*albicans* isolates using the Vitek Yeast Biochemical Card (YBC).

Information obtained from this investigation was utilized to formulate outbreak control measures. Assessment of the impact of outbreak control strategies was performed comparing the candidemia rate (cases per 1,000 patient-days) during and after the outbreak period, using a z-score calculation.

Results

Eighteen cases of *Candida spp.* were documented between June and October 2004. No cases of *Candida spp.* BSI had been documented during the previous four months. Case patients were located at the ICU, the CCU or the pediatric ward. The mortality rate for the 18 cases was 33%. Detailed clinical characteristics for cases and controls are presented in Tables 1 and 2. Figure 1 depicts the epidemic curve for the outbreak.

Thirteen cases and 36 controls were included in the case-control study (ratio 1:2.8). Parenteral nutrition ($p=0.04$), presence of a central venous catheter ($p=0.03$) and severity of illness ($p=0.03$) were associated with *Candida spp.* BSI (Tables 1 and 2). No significant associations were observed between *Candida spp.* BSI and exposure to a particular HCW, IV medication or invasive procedure.

Poor hand hygiene practices were widely observed. IV medications were prepared at the bedside by ICU and CCU nurses and at the nurse station by pediatric ward nurses. IV medications were transported from the pharmacy to the ICU, CCU and other hospital areas in plastic bags that were reused for several weeks or months without disinfection. IV

medications were stored in plastic containers at the bedside in the ICU and CCU, which did not undergo regular disinfection. In the pediatric ward, small pieces of non-sterile cotton were prepared at the beginning of the day in non-sterile plastic cups, and an arbitrary amount of alcohol was poured on top. The cotton pieces were taken from a common source that was kept near the floor, directly exposed to the environment. The nurses used the cotton fragments to clean the IV sites and IV ports before medication injection. These practices had been initiated by the nurses during May or early June 2004.

Candida species isolated from the cases were diverse, with a predominance of *Candida albicans* and *Candida parapsilosis*. Ninety-five HCW were cultured. Personnel cultures were positive for six HCW (6.3%). More than 150 environmental cultures were made. Six environmental cultures were positive for *Candida parapsilosis*. Heavy *Candida parapsilosis* contamination was documented in plastic containers used for transient IV medication storage at the bedside, plastic bags reused for the transportation of IV medicines and cotton used for disinfection of IV sites and ports. Table 3 shows the *Candida* species for clinical, staff and environmental isolates.

Interventions included HCW education, elimination of plastic bags used for the transportation of IV medications, standardization of disinfection practices for the IV medication containers, replacement of alcohol-impregnated cotton by sterile alcohol swabs for IV site and IV port disinfection.

The rate of *Candida spp.* BSI significantly decreased from 1.13 cases per 1000 patient-days during the outbreak period, to 0.25 cases per 1000 patient-days during the post-outbreak period (z-score 2.18, $p=0.014$). Of relevance, the proportion of patient-days considered "at-risk" for *Candida spp.* BSI (the sum of number of ICU, CCU and Oncology patient-days over the total number of patient-days) significantly increased from the pre-outbreak period to the outbreak period (35.6% vs. 40.5%, z-score = -7, $p<0.0001$) and from the outbreak period to the post-outbreak period (40.5% vs. 49%, z-score = -9.3, $p<0.0001$).

The outbreak was considered controlled after a five month period, during which only one new case of *Candida spp.* BSI was ascertained each month (Figure 1).

Discussion

This is one of the largest outbreaks of candidemia described in the literature. Previous large outbreaks reported in the literature accounted for 22 cases of *Candida parapsilosis* fungemia among adults in the United States [16], 19 cases of candidemia in a neonatal ICU in the United States [20], 17 cases of *Candida parapsilosis* fungemia in a neonatal ICU in China [13] and 16 cases of *Candida tropicalis* fungemia in a neonatal ICU in India [21]. Three of these outbreaks were restricted to a single *Candida* species [13,16,21]. Similarly, three of these outbreaks [13,20,21] were restricted to single hospital areas. We included different candida species in our

Table 1. Case-control study – Bivariate analysis – Categorical variables. Frequency of clinical and demographic characteristics overall and for cases and controls.

Variable	Overall n (%) N = 49	Cases n (%) N = 13	Controls n (%) N = 36	p-value *
Male gender	28 (59.6%)	6 (46.2%)	22 (64.7%)	0.24
CVC	33 (67.4%)	12 (92.3%)	21 (58.3%)	0.03
ICU stay	21 (42.8%)	7 (53.9%)	14 (38.9%)	0.35
Enteral nutrition	7 (14.9%)	4 (33.3%)	3 (8.6%)	0.06
Parenteral Nutrition	9 (18.8%)	5 (38.5%)	4 (11.4%)	0.04

* Fisher or Chi-square. CVC: Central venous catheter; ICU: Intensive Care Unit.

Table 2. Case-control study – Bivariate analysis – Numeric variables.

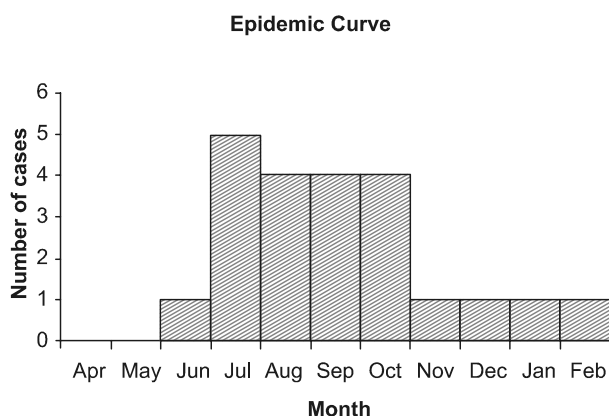
Variable	Overall Median (Range)	Cases Median (Range)	Control Median (Range)	p-value *
Age	33 (0.25–79)	21 (0.45–79)	35 (0.25–77)	0.88
Hospital stay (days)	8 (1–66)	13 (1–66)	9 (1–40)	0.14
ASA score	3 (2–5)	3 (2–5)	3 (2–5)	0.03

* Wilcoxon rank sum test. ASA: American Society of Anesthesiology.

Table 3. *Candida* species identified during the outbreak.

Type of specimen	<i>Candida</i> species	N (%)
Clinical (n=18)	<i>Candida albicans</i>	7 (38.9%)
	<i>Candida parapsilosis</i>	3 (16.7%)
	<i>Candida glabrata</i>	1 (5.5%)
	<i>Candida tropicalis</i>	1 (5.5%)
	<i>Candida</i> spp.*	6 (33.3%)
Health-care workers (n=6)	<i>Candida albicans</i>	2 (33.3%)
	<i>Candida parapsilosis</i>	2 (33.3%)
	<i>Candida tropicalis</i>	1 (16.6%)
	<i>Candida</i> spp. *	1 (16.6%)
Environmental (n=6)	<i>Candida parapsilosis</i>	6 (100%)

* No species determination made for these 7 isolates.

Figure 1. Epidemic curve. Y axis represents the number of cases. X axis represents the month of the year.

investigation because the epidemic curve indicated that any episode of candidemia, regardless of species, was an unusual phenomenon before the initiation of the outbreak. The observed number of cases of candidemia during the outbreak period clearly represented an increase over and above the expected number of cases. Additionally, we elected to study candidemia occurring in any hospital area because the preliminary investigation revealed that the condition had emerged almost simultaneously across several hospital units.

The observed crude mortality was 33% in our study, somewhat lower than the 41–63% range described in previous series [6,16]. *Candida* spp. BSI occurred more frequently in patients with severe illness, exposed to parenteral nutrition and/or central venous catheters. These conditions are previously recognized risk factors for candidemia [1,7,9, 13, 16]. Interestingly, the proportion of “at-risk” patient-days (the sum of ICU and CCU patient-days and oncology patient-days) significantly increased from the pre-outbreak period to the

outbreak period and from the outbreak period to the post-outbreak period. This suggests that a change in patient susceptibility may have facilitated the emergence of the outbreak and may also explain why the rate of candidemia did not entirely return to pre-outbreak levels. However, despite the consistent overall increase in patient susceptibility, the rate of *Candida* spp. BSI significantly decreased after the implementation of outbreak control measures. We believe this is strong evidence in favor of outbreak control as a result of the implemented measures.

Although *Candida* spp. BSI usually originates from an endogenous source [1,22], several studies have described the relevance of *Candida* spp. as a nosocomial pathogen [5]. *Candida* spp. can be transmitted to patients from hospital sources and staff skin. In the setting of patient predisposition to candidemia, poor infection control practices were the most likely culprits of this outbreak. Our documentation of hand colonization in some HCW and our observation of poor hand-hygiene practices suggest that nosocomial transmission could have been facilitated from HCW hands as transient reservoirs. Several previous studies have linked the hands of HCW with *Candida* BSI outbreaks [13-15,23,24]. Additionally, we found that devices used for IV medication storage and administration were contaminated with *Candida parapsilosis*. This is the first outbreak to suggest that contaminated non-sterile cotton, plastic transportation bags and plastic IV medication containers can facilitate the emergence of *Candida* spp. as a nosocomial bloodstream pathogen. Contaminated plastic bags were used for transportation of IV medications to all affected units (ICU, CCU and pediatric ward); contaminated plastic containers were used in the ICU and CCU for bedside medication storage; and contaminated non-sterile cotton was used in the pediatric ward for IV site and IV port disinfection. These environmental sources are more likely to be problematic in resource-limited settings, where a variety of strategies are often improvised as a result of misleading cost-oriented ("money-saving") policies. At the time of this outbreak, the hospital did not have a central pharmacy for medication preparation. Additionally, there were no medication transportation carts, and sterile alcohol preps were unavailable. Because of the lack of a central pharmacy and medication transportation carts, pharmacy and nursing personnel had to improvise methods for IV medication transportation and storage at bedside. Plastic bags and plastic containers were selected and reused without proper disinfection. Likewise, because of the lack of sterile alcohol preps, the nurses improvised alcohol impregnation of non-sterile cotton for IV site and IV port disinfection. These improvisations favored the emergence of the outbreak, resulting in significant hospital cost as well as patient morbidity and mortality. This report is therefore relevant to caution hospital and regional policy makers, particularly in settings with significant resource limitations, about the possible unanticipated and undesirable consequences of misleading cost-oriented policies. Such policies and their possible behavioral and clinical

consequences should be discussed with infection control personnel before implementation.

Our study has several limitations. Because of resource limitations, we were unable to determine the species for all candida isolates. We believe that some of the non-*albicans* isolates for which speciation was not performed could have been *C. parapsilosis*. Therefore, our reported frequency of *Candida parapsilosis* from clinical samples may represent an underestimation. Additionally, we were unable to carry out molecular testing to demonstrate a link between the presumptive environmental sources and the clinical cases. Usually, a common environmental source is suspected once the same organism is obtained from the clinical infections and the presumptive reservoirs. Further molecular testing then confirms that the clinical isolates and the environmental isolates are related. Because of limited laboratory capacity and resources, we were unable to incorporate molecular testing into our investigation. Despite a predominance of *C. albicans* in clinical isolates and *C. parapsilosis* in environmental isolates, we believe that the same infection control deficiencies and similar reservoirs may have resulted in the emergence of the outbreak. This is supported by the evidence of unprecedented clustering of candida BSI during the outbreak period as well as the significant reduction of the candida BSI rate after eradication of identified reservoirs and optimization of infection control practices. Additionally, several studies suggest that different candida species may have similar adherence properties to cotton and other fabrics [25], as well as to plastic and other synthetic materials [25-27]. It has been demonstrated in-vitro that once adhered to fabrics and synthetic materials, both *C. albicans* and *C. parapsilosis* can survive for several days [25]. The adhesion capacity of diverse candida species to different surfaces presumably plays a major role in the pathogenesis of human colonization and invasion [25] as well as in the establishment and perpetuation of infection [28]. As a result, different *Candida* species can contaminate similar environmental reservoirs and cause human infection through similar pathophysiological processes. The isolation of diverse candida species from clinical and environmental sources in our study is therefore not in disagreement with available knowledge. For at least certain synthetic materials, the survival time under dry conditions may be longer for *C. parapsilosis* than for *C. albicans*, [25], which may at least partially explain the predominance of *C. parapsilosis* in our environmental samples.

In conclusion, we believe that candida contamination of non-sterile cotton, plastic transportation bags and plastic IV medication containers, in conjunction with poor infection control practices, facilitated the occurrence of several candida BSIs, predominantly in patients with established clinical predisposition.

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