An Outbreak of *Candida parapsilosis* Bloodstream Infections in a Community Hospital – Mississippi, 2001

by

Thomas A. Clark, M.D.

Presented to

The Department of Public Health and Preventive Medicine

Oregon Health & Science University

In partial fulfillment of the requirements of the degree of

Master of Public Health

May 1, 2002

Oregon Health & Science University

School of Medicine

CERTIFICATION OF APPROVAL

This is to certify that the M.P.H. Thesis of

Thomas A. Clark, M.D.

has been approved.

Mark O. Loveless, M.D., Committee Chair

Rana Hajjeh, M.D.

Donald Austin, M.D., M.P.H.

Maureen Phelan, M.S.

TABLE OF CONTENTS

ACKNOWLEDGEMENTS

I wish to thank the Laboratory Section of the Mycotic Diseases Branch, Centers for Disease Control and Prevention, for their contributions to this investigation: Mary Brandt, Tim Lott, Beth Skaggs, Wendy Yang, and Lynette Benjamin. For his helpful comments and suggestions on this paper, I also thank David Warnock. Special thanks are due to my CDC supervisors during the course of the investigation: Rana Hajjeh, Juliette Morgan, Scott Fridkin, and Mike Bell. In addition, I gratefully acknowledge the help of the Mississippi State Department of Health, in particular, Mary Currier and Sally Slavinski. Finally, but most importantly, I offer my thanks to the administration and staff of Hospital A for their help, their interest, and their hard work in controlling this outbreak.

Introduction

Candida organisms are yeasts, or fungi that exist primarily in single-celled form. They are small, thin-walled, oval shaped cells. Yeasts, including *Candida* species, are found widely distributed in terrestrial and aquatic habitats (1). However, the *Candida* species that cause human disease, or candidiasis, are most commonly found associated with man and other warm-blooded animals. In fact, the association of *Candida* species with man has long been recognized. Though fungus was first isolated from a lesion of oral candidiasis, or thrush, in 1839, written descriptions of thrush exist from the time of Galen and Hippocrates (2).

Infections with *Candida* species are described as superficial or deep (3). Deep infections that become widespread within the body are referred to as disseminated candidiasis. Superficial infections predominate; oral, vaginal, and cutaneous candidiasis occur, as do candida nail infections. Deep infections are more serious, however. They may be acute or chronic, and may involve almost any organ or organ system in the body. Common sites of involvement include the esophagus, urinary tract, lungs, and heart. Candida bloodstream infection, or candidemia, is considered a disseminated infection.

Among more than 150 described species of *Candida,* relatively few are of medical importance (2). *Candida albicans* is the most common cause of both superficial and deep infections, though at least eight other species commonly cause human disease. Clinically relevant *Candida* species are frequently part of normal human microbiological flora. They can be found colonizing the skin, mouth, gastrointestinal (GI) tract, and female genital tract. The proportion of normal individuals found colonized with *Candida* ranges from 2 to 80% in various studies, differing by species, subject age, site of

colonization, and yeast sampling method (1). On average, 30 to 50% of healthy persons carry *Candida* species in the mouth and GI tract, while 20% of healthy women have genital tract colonization (3). While *C. albicans* commonly colonizes these sites, it is uncommonly found on the skin, where *C. parapsilosis* and *C. guilliermondii* are more prevalent. *C. parapsilosis* is a relatively infrequent colonizer of other sites (4).

Normal host defense mechanisms that protect against Candida infection include intact skin, cellular and humoral immunity, platelets, and complement. Disruption of these normal host defenses allows such commensal organisms to become pathogenic, overgrowing or gaining access to normally sterile body sites. *Candida* species are therefore termed opportunistic pathogens.

Risk factors for candidiasis can be divided into two categories: host factors, and healthcare-associated, or iatrogenic factors. Diabetes mellitus is an example of the former, predisposing to superficial forms of candidiasis. However, the most important risk factors for candida infection, and particularly disseminated candidiasis, are related to the healthcare setting (5).

Since the advent of widespread use of antibacterial drugs, the incidence of practically all forms of candidiasis has risen, and previously unrecognized manifestations of Candida infection have been documented (2). Candida bloodstream infection (BSI), or candidemia, is one of the most important forms of candidiasis. The incidence of Candida BSI has increased over the past two decades (6). Candida BSI currently occurs with an overall incidence of 8 to 10/100,000 persons per year in the US (7). Candida species are particularly important hospital-acquired pathogens, and the proportion of hospital-acquired BSI caused by *Candida* species has increased over the past two decades.

Candida species are currently the fourth most common group of organisms isolated from the bloodstream of hospitalized patients, accounting for 8%-15% of all hospital-acquired bloodstream infections (8). While annual mortality rates due to candidiasis increased three-fold during the 1980s, from 0.2 to 0.6 deaths per 100,000 persons, they have declined in recent years (9). However, case fatality rates associated with episodes of Candida BSI remain as high as 40% (10), (11).

In addition to the widespread use of antibiotics, several factors have contributed to the emergence of *Candida* species as important hospital-acquired pathogens. Deep fungal infections tend to occur in people with impaired immunity, whether due to illness and debility, or iatrogenic factors. Advances in bone marrow and solid organ transplantation, the development of newer and more powerful chemotherapeutic agents, and the advent of human immunodeficiency virus (HIV) all have resulted in increasing numbers of immunocompromised persons (6). Improvements in medical care of severely ill persons, including the use of invasive monitoring devices, parenteral nutrition, broad-spectrum antibiotics, and mechanical ventilation, allow the survival of patients with previously fatal diseases. Application of these same technologies in neonatal intensive care units (ICUs) has improved the survival of premature infants who would previously have been considered nonviable.

While *Candida albicans* causes the majority of Candida infections in humans, the proportion of Candida infections caused by non-*albicans* species has increased in recent years (7). *Candida glabrata, C. tropicalis,* and *C. parapsilosis* all commonly cause bloodstream infection among hospitalized patients, with increasing incidence (5). Their distribution varies by patient age group, underlying risk factors, geographic location, and

location within the hospital. For example, *Candida tropicalis* has become an important cause of BSI in neutropenic cancer patients, while *C. parapsilosis* is common in neonatal ICU patients.

Most hospital-acquired Candida infections occur sporadically, as a result of endogenous acquisition. However, the epidemiology of non-*albicans Candida* species in non-outbreak settings is not well described. Bloodstream infections are most common, though cases of healthcare-associated arthritis, peritonitis, endocarditis, and endopthalmitis have been reported (12), (13), (14). Outbreaks of hospital-acquired candidemia occur, and many have been documented in the literature (15), (16), (17), (18). Outbreaks of *Candida parapsilosis* infections are most commonly associated with total parenteral nutrition (TPN), intravascular devices, or contaminated medications (5).

One difficulty posed in investigating outbreaks caused by one organism is determining if the infections were caused by the same strain of that organism, *i.e.,* did a common source population cause many or all of the cases of infection. Many laboratory methods have been employed to differentiate among isolates of individual *Candida* species, and to aid in investigating and controlling healthcare-associated outbreaks. These range from simple phenotypic studies like antiobiogram profiles, to more complex molecular studies, such as restriction enzyme analysis of chromosomal DNA (19). The hallmark of modern molecular epidemiologic techniques is the use of agarose gel electrophoresis. This process uses electrical current passed through a gel medium to separate DNA segments based on their size, allowing them to be visualized by special staining techniques. Patterns on the resulting gel are commonly referred to as the "DNA fingerprint" of the organism. These techniques may also use polymerase chain reaction

(PCR) technology to sequence microbial DNA or amplify it, allowing it to be more readily electrophoresed. While no "gold standard" exists for delineation among *Candida parapsilosis* isolates, the organism demonstrates a significant degree of genetic variability (20), (21). Both randomly amplified polymorphic DNA analysis (RAPD), which uses PCR to amplify random segments of DNA, and electrophoretic karyotyping (EK), which uses gel electrophoresis to separate whole chromosomes, have proven useful in differentiating among strains (22). Use of the latter in outbreak settings has been reported (23), (24), (18). Methods which use specially constructed strain-specific DNA probes have the greatest capacity to distinguish among isolates. Recently, a DNA probe has been developed for subtyping of *C. parapsilosis* (25).

Background

In April 2001, infection control staff at a large community hospital in Mississippi (referred to as Hospital A) first noted an increase in the number of laboratory isolates of *Candida parapsilosis* from blood and central venous catheter (CVC)-tip cultures. Preliminary investigation by the hospital and the Mississippi State Department of Health determined many of the patients with *C. parapsilosis* shared the following factors: use of CVCs and dialysis catheters, care in one of the hospital's ICUs, use of TPN, and use of hemodialysis. The Mississippi State Department of Health invited the Centers for Disease Control and Prevention (CDC) to assist in investigating this outbreak of *Candida parapsilosis* BSI in October 2001.

The objectives of this investigation were: (1) to determine the extent and characteristics of the outbreak, (2) to identify risk factors for *C. parapsilosis* BSI among this patient population, and (3) to recommend control measures.

Methods

Confirmation of the Outbreak

To determine if the observed increase in the number of *C. parapsilosis* bloodstream infections during this period represented a true increase in the rate of infection, we examined the annual catheter-related BSI rates for 1999, 2000, and the first six months of 2001. As a participant in CDC's National Nosocomial Infection Surveillance (NNIS) System, Hospital A maintains active surveillance for catheter-related bloodstream infections in the medical, surgical, and neurological ICU areas.

Case Finding and Ascertainment

To determine the extent of the outbreak, we conducted case finding and ascertainment. The outbreak period was defined as April 1, 2001 through October 31, 2001. We defined a confirmed case as a *Candida parapsilosis* bloodstream isolate obtained at least 48 hours after admission from a Hospital A inpatient during the study period. We defined a possible case as a *Candida parapsilosis* CVC tip isolate obtained at least 48 hours after admission from a Hospital A inpatient during the study period, in the absence of a bloodstream isolate. We identified potential cases by reviewing laboratory records for all *Candida* species isolated in culture from any patient source during the study period.

Case-Control Study

To determine the potential risk factors for *C. parapsilosis* BSI, we conducted a case-control study. Confirmed and possible cases were included. Two control patients

were included for each case patient, selected randomly from all inpatients at Hospital A. Control patients were matched using the following criteria: age group (18-44, 45-70, or >70 years), and length of hospitalization prior to the case culture. Potential control patients were excluded if they had been hospitalized fewer than seven days, as the minimum total length of stay for case patients was seven days.

A standardized questionnaire was used to abstract medical records of case and control patients (see Appendix A). Demographic data, admission and discharge dates, outcome of hospitalization, and underlying illnesses were recorded. Data were also collected on a number of potential risk factors, including prior bacterial or fungal BSI, surgical and non-surgical procedures, use of devices including CVCs, and medications and infusions. Data were recorded on pen-and-paper forms from the Hospital A computerized medical record system by the author and a medical student, and then entered into a Microsoft Access database by the author.

Data specific to the time of culture were recorded from the index day. For case patients, the hospital day on which *C. parapsilosis* was first isolated from a blood or CVC-tip culture represents the "index day". The index day was assigned to control patients, representing the hospital day on which *C. parapsilosis* was first isolated from the corresponding case patient. For example, laboratory values on the index day were abstracted and used to calculate an acute physiology and chronic health evaluation II (APACHE II) score (26). The APACHE II system uses 12 routine physiologic measurements, age, and previous health status to assign a severity of illness point score ranging from 0 to 71. Increasing admission APACHE II scores among ICU patients correlate with increasing risk of in-hospital death.

Observational Studies

We conducted an observational assessment of healthcare worker (HCW) hand hygiene practices in the medical, surgical, neurological, and cardiac ICUs using a standardized data collection tool. Observations were conducted over three separate days, during observation periods of 30 to 90 minutes each. Both daytime and evening shift hours were included. Healthcare workers were potentially aware that they were being observed, but were not directly informed of the observations.

We defined a HCW "hand hygiene opportunity" as the time from entry into a patient room until departure, when such episodes included direct contact with the patient or with objects in the environment. For each opportunity, we recorded whether or not hand hygiene was performed, the agent used (*i.e.* soap versus alcohol hand foam), and whether or not gloves were worn.

In addition to hand hygiene practices, we directly observed the following hospital practices and procedures: preparation of TPN by each of the two pharmacists responsible for this process, routine dressing changes of indwelling central catheters and dialysis catheters, catheter removal, medication administration through indwelling catheters, care of endotracheal tubes (ETT) in ventilated patients, and hemodialysis. We also reviewed the following procedures via interviews with appropriate hospital personnel: routine cleaning and surveillance culturing of hemodialysis machines, handling and processing of clinical specimens for culture in the microbiology laboratory, and insertion of CVCs.

Environmental Studies

Fungal hand cultures were obtained from a large convenience sample of nurses in the ICU areas using the handiwipe method (27). Briefly, a cloth towel that has been soaked in a mild detergent and sterilized is used to scrub all surfaces of both hands. Nurses from the medical-surgical, neurological, and cardiac ICU day and night shifts were included. Cultures were obtained throughout the outbreak period, and throughout the course of normal work day activities. Handiwipe cultures were also obtained from a smaller convenience sample of other HCWs who perform direct patient care activities in the ICUs, including physicians, phlebotomists, respiratory therapists, radiology technicians, and dialysis nurses.

To determine the prevalence of skin colonization with *Candida parapsilosis* among ICU patients, swabs for fungal culture were made from the insertion sites of CVCs and dialysis catheters in all patients in the medical-surgical and neurological ICUs in a single cross-sectional sample conducted on November 5, 2001. All CVC hubs from the same patients were cultured on the same day, as were EKG leads and blood pressure cuff tubing in each patient room in the medical-surgical ICU.

Laboratory Studies

All environmental samples, as well as 12 patient isolates received from Hospital A, were sent to CDC for identification. All specimens were plated on ChromAgar and Sabouraud dextrose agar with chloramphenicol. ChromAgar is a commercially available culture medium that changes color to indicate specific *Candida* species. Sabouraud dextrose agar with chloramphenicol encourages the growth of yeasts while suppressing

bacterial growth. Suspicious colonies were subcultured, and identification was made by the API-20C yeast identification system and cornmeal agar. The API-20C system comprises a series of biochemical tests, identifying most *Candida* species in 2 to 5 days. Cornmeal agar is used to grow a wide range of fungi, each producing characteristic morphology.

Molecular typing, commonly referred to as "DNA fingerprinting," was performed using three methods: randomly amplified polymorphic DNA (RAPD) analysis, electrophoretic karyotyping (EK), and a novel 15-kb DNA probe (25). Antifungal susceptibility testing was conducted on all isolates, using National Committee for Clinical Laboratory Standards (NCCLS) published guidelines (28).

Statistical Analysis

Univariate statistical analysis was performed using SAS, Version 8.2 (SAS Institute, Cary, NC, 1989-2000). Continuous data were compared with t tests, and categorical variables with Chi square tests (α=0.05). Non-parametric tests (Wilcoxon rank sum) were used when data deviated significantly from the normal distribution. Univariate odds ratios were adjusted for age group and duration of hospitalization prior to the index day. Multivariable analysis was completed with SAS using the proportional hazards regression procedure, modified to analyze matched case-control data. Variables were included in modeling where $p<0.1$ on univariate analysis, and results were considered significant on multivariable modeling where $p<0.1$.

Results

Confirmation of the Outbreak

Evaluation of the NNIS ICU data revealed a five-fold increase in the rate of CVC-associated Candida BSI in the first six months of 2001 compared to the year 2000, and an almost seven-fold increase in the CVC-associated BSI rate for *Candida parapsilosis* alone. During the same period, the rate of CVC-associated bacterial BSI did not change. The NNIS data also revealed that between 1999 and 2000 the total and bacterial CVC-associated BSI rates declined by half. These data are summarized in Table 1.

Case Finding and Ascertainment

Case ascertainment yielded 22 patients who met either of our case definitions, including 15 confirmed and 7 possible cases. Of these 22 case patients, the mean age was 58 years (range 29 to 81 years), 12 (55%) were white, and 12 (55%) were male. All case patients had CVCs, and 18 (82%) had been in an ICU prior to isolation of *Candida parapsilosis*. The mean time to *Candida parapsilosis* isolation following catheter placement was 13 days (range 3 to 29 days). The mean time from admission to isolation was 23 days (range 5 to 50 days). Median total length of stay in hospital was 38 days. Nine (41%) case patients died; the mean time to death following isolation of *C. parapsilosis* was 10 days (range 1 to 20 days). Six case patients died within seven days of the organism's isolation.

Figure 1 demonstrates the distribution of confirmed and possible *Candida parapsilosis* BSI cases by month of isolation, including cases that occurred before and after the outbreak period.

Case-Control Study

The case-control study included 20 cases (13 confirmed and 7 possible) and 40 controls. Complete medical records were not available for review for two of the original 15 confirmed cases. We also performed a subset analysis of the 13 confirmed cases and 26 controls. Clinical and demographic characteristics of confirmed and possible case patients and control patients are presented in Table 2. Case and control patients were similar with respect to gender, race, age group, and underlying illnesses.

Univariate analysis of the data for all cases and controls identified the following factors to be associated with increased risk of *Candida parapsilosis* BSI: higher APACHE II scores on the index day (mean, 19 versus mean, 13.7; p=0.007); being mechanically ventilated on the index day (OR, 10.0; 95% CI, 1.9-51.3); being in an ICU on the index day (OR, 8.9; 95% CI, 2.2-36.2); greater number of catheters placed during hospitalization (median, 2 versus median 1; p=0.02); being mechanically ventilated at any time during hospitalization (OR, 13.0; 95% CI, 2.7-61.7); receiving any TPN during hospitalization (OR, 5.9; 95% CI, 1.6-21.4); having a previous bacteremia or candidemia during the hospitalization (OR, 3.8; 95% CI, 1.2-11.6); and being on a surgical service (odds ratio [OR], 7.5; 95% confidence interval [CI], 1.4-38.4).

Univariate analysis of the data for the subset of 13 confirmed cases and 26 controls revealed similar risk factors to be associated with increased risk of *Candida parapsilosis* BSI: higher APACHE II scores on the index day (mean, 21.1 versus mean, 12.2; p=0.0001); being mechanically ventilated on the index day (OR, 19.3; 95% CI, 2.1-175.6); being in an ICU on the index day (OR, 10.7; 95% CI, 2.0-56.2); greater number

of catheters placed during hospitalization (median 3 versus median, 1; p=0.04); being mechanically ventilated at any time during the hospitalization (OR, 7.2; 95% CI, 1.4-36.1); receiving any TPN during hospitalization (OR, 5.8; 95% CI, 1.1-31.9); having a previous bacteremia or candidemia during the hospitalization (OR, 5.4; 95% CI, 1.3-22.2); and being on a surgical service (OR, 10.5; 95% CI, 1.2-95.5). Significant univariate results are summarized in Table 3.

No systematic surveillance is performed in the ICUs of Hospital A for yeast colonization. However, cultures may be obtained from patients for whom colonization is suspected, such as urine cultures from patients with indwelling urinary catheters, or sputum cultures from patients with prolonged intubation and mechanical ventilation. Among confirmed case patients who had such cultures, we found that prior colonization with *Candida* at any site other than the bloodstream was associated with infection (OR, 14.9; 95% CI, 1.7-125). However, only two confirmed case patients and no control patients had *Candida parapsilosis* isolated from non-bloodstream sites, while 5 confirmed case patients and 7 control patients had a *Candida* isolate of undetermined species. Restricting to only the 14 *Candida* isolates that were or might have been *C. parapsilosis*, the odds ratio for prior colonization was reduced to 6.9 (95% CI, 1.2-38.5).

The following factors were not significantly associated with increased risk of BSI among either confirmed cases or all cases: type of indwelling vascular catheter (*i.e.* central venous catheter, dialysis catheter, or peripherally inserted central catheter [PICC]); vessels in which the catheters were placed; number of catheter lumens; use of dialysis; major surgical procedures; non-surgical procedures; or medications. Notably,

cases and controls did not differ in the number or classes of antibiotics received, or the use of antifungal drugs, including fluconazole.

Multivariable analysis was conducted for confirmed cases. Because of the limited number of cases, it was not possible to include more than two covariates in one model simultaneously. The following variables were included in potential models: APACHEII severity of illness score (dichotomized at the 75th percentile), previous bacteremia or fungemia, any use of TPN, mechanical ventilation during hospitalization, being in an ICU on the index day, and being on a surgical service. Model evaluation criteria included the -2 log likelihood score, as well as the clinical relevance of the model (29). Table 4 presents pair-wise combinations of the selected variables, and the corresponding log likelihood score of the model containing those variables. We found that use of TPN, mechanical ventilation, and being on a surgical service were confounders of one another, as were being in an ICU, being mechanically ventilated, having a previous bloodstream infection during the hospitalization, and having an APACHE II score above the 75th percentile. Hospitalization in an ICU (OR, 16.4; 95% CI, 1.8-148.1) and receiving TPN (OR, 9.2; 95% CI, 0.9-98.1) were independently associated with increased risk of *C. parapsilosis* BSI, and were chosen as the most clinically relevant among the predictive models.

Observational Studies

We observed 79 hand hygiene opportunities during the four observation periods. Hand hygiene was performed before 30 (38%) and after 39 (49%) of all opportunities. Restricting to hand hygiene opportunities involving direct patient contact, for nurses we

observed hand hygiene before 42% and after 60% (n=43), and for physicians, before 18% and after 18% (n=11). Gloves were worn during 10 (13%) hand hygiene opportunities. In total, we observed hand hygiene being performed 64 times: 45 (70%) using an alcohol foam waterless hand hygiene agent, 16 (25%) using antibacterial soap and water, and three (5%) using both.

Preparation of TPN solutions is done with a partially automated system. The contents of large bags and bottles (holding several liters) of glucose, amino acid, and lipid-containing solutions are accessed individually, using sterile tubing that is replaced daily. A mechanical (non-vacuum) pump is used which mixes the sterile solutions into a separate bag for each patient. Additives, such as multi-vitamins, micronutrients, and insulin are added afterwards, using a separate sterile needle and syringe for each additive. Some additives come in single use vials, though multi-use vials of insulin and micronutrients are used. In practice, however, vials do not last for more than a day. The large containers of ingredient solutions generally make TPN bags for two to three patients before running out. All TPN preparation is done under a large laminar flow hood, which is cleaned with isopropyl alcohol before and after preparing all TPN orders for the day. Both pharmacists who have responsibility for TPN preparation were observed to use appropriate sterile technique throughout the process. Of note, one of the pumps on the TPN machine malfunctioned during the outbreak period. At the time of the investigation, a new machine had been in use for one month.

Beginning in 1999, dressing changes of CVCs were performed three times per week by a dedicated central line dressing change team. For personnel reasons, Hospital A was not able to maintain the teams, and after the winter of 2000-2001, dressing changes were

performed by the nurse responsible for the patient, using the same pre-packaged, commercially-available dressing change kit. In practice, however, one nurse may change dressings for several patients on their unit. Non-sterile gloves are used during dressing changes. We observed appropriate technique during 8 dressing changes performed by two nurses.

Hospital A has 8 dialysis machines, all of which are portable and may be used in the dialysis unit or taken to patient rooms. Dedicated dialysis nurses perform dialysis. Each day, the water circuits are cleaned with a bleach-containing solution and once per week with sodium hypochlorite solution according to the instructions of the machines' manufacturer. Monthly, surveillance cultures are performed on the water source, water, and dialysate from each machine. We reviewed records of these cultures for the outbreak period. Seven exceedences of maximum allowable colony counts were noted, occurring on two separate days. Following exceedences, machines are cleaned and re-cultured. All follow up cultures were negative. Cultured organisms are not identified.

The microbiology laboratory at Hospital A uses a commercially available automated system for blood cultures. Prior to March 2001, vented culture bottles were used, but the laboratory subsequently changed to non-vented bottles. Yeast species are also determined using a commercially available automated system. No irregularities with any laboratory processes were noted during the course of our investigation.

Environmental Studies

Handiwipe cultures from 18 (26%) of 68 HCWs grew *Candida parapsilosis*, including 14 (26%) of 53 nurses, 3 (43%) of 7 physicians, 1 (33%) of 3 radiology

technicians, and 0 of 2 pharmacists. No CVC hubs or insertion site cultures grew the organism (0 of 8). One (6%) of 16 cultures obtained from patient care devices (blood pressure cuff tubing) grew *C. parapsilosis*. All environmental cultures are summarized in Table 5.

Laboratory Studies

Molecular typing with both EK and RAPD analysis revealed that the predominant banding pattern was shared among all 12 patient isolates (including 5 bloodstream isolates) and 6 (33%) of 18 hand isolates. Figure 2 demonstrates representative examples of both patient and hand isolates.

Antifungal susceptibility testing showed that the MIC_{50} for the 12 patient isolates - the average concentration of fluconazole that inhibited growth in 50% of isolates - was 4μg/mL (range 0.25 to 8μg/mL). The MIC_{50} for the hand isolates was 0.5μg/mL (range 0.25 to 4μg/mL). No consistent antifungal susceptibility pattern was observed among the patient and hand isolates with similar DNA banding profiles.

Discussion

This paper describes a large hospital outbreak of *Candida parapsilosis* BSI with a high case fatality rate. Such outbreaks among adults have not commonly been reported (30), (31), (32). We found that severe illness requiring ICU care, mechanical ventilation, CVCs, and TPN were associated with *C. parapsilosis* BSI in this population. Our investigation strongly supports the hypothesize that *Candida parapsilosis* was acquired exogenously from the hands of healthcare workers, for the following reasons: (1) 26% of healthcare workers carried the organism on their hands, (2) all the patient isolates and 33% of the hand isolates share the predominant DNA banding pattern, (3) missed opportunities for hand hygiene are common, and (4), resolution of the outbreak with interventions focused on improving hand hygiene (*ed., or words to this effect*).

Bloodstream infections with *C. parapsilosis* do not typically result from endogenous acquisition (*i.e.,* infection resulting from prior colonization at other body sites, such as the GI tract) (33). In a prospective, single-center study of *Candida* acquisition among 585 bone marrow transplant patients, Marr and colleagues found that none of seven patients infected with *Candida parapsilosis* had been previously colonized, and none of 30 patients colonized with the organism developed infection (34). In outbreak settings in particular, infection is more commonly acquired exogenously, with introduction of the organism more directly into the bloodstream via extrinsically contaminated sources such as intravenous hyperalimentation fluids, blood pressure transducers, and retrograde medication administration systems (30), (4), (31), (15), (16).

Few potential common sources of exposure were found in this outbreak setting. The process by which TPN is made uses a closed pump system, with very little potential for

contamination. Hospital A uses disposable blood pressure transducers, which are not reused between patients. Of cultures obtained from reusable patient devices, only a single blood pressure cuff tube grew *C. parapsilosis.* It would be unlikely that this contaminated device could have accounted for such a large number of cases, as no patient room was common to more than a few case patients. Very few intravenous medications used in Hospital A are packaged in multi-use vials. It is unlikely that extrinsic contamination in one of these would have resulted in on ongoing outbreak in only one hospital.

Transmission of *C. parapsilosis* via the hands of healthcare workers has been implicated in a number of outbreaks (4), (35), (32), (18). Forty to 60% of HCWs may harbor *Candida* species on their hands (36). Moreover, published data indicate that *C. parapsilosis* can be grown from between 5% and 26% of hand cultures of surgical and neonatal ICU HCWs in non-outbreak settings (37). In an outbreak of prosthetic valve endocarditis, the hands of 20 (26%) of 70 HCWs cultured grew *C. parapsilosis* (14). In a large *C. parapsilosis* outbreak in a neonatal ICU, 20% of hands of unit staff were colonized with the organism (18). The proportion of hand carriage we found among HCWs at Hospital A, 26%, is consistent with these studies. However, our estimate of the prevalence of hand colonization among Hospital A HCWs should be considered a minimum one. Cultures were obtained in the typical working environment of the hospital ICUs. Some HCWs had just completed patient care prior to being cultured, while others had just performed hand hygiene. Moreover, the culture technique used in this outbreak, while simpler to administer and more acceptable to HCWs, may be less sensitive than the bag-broth method used in two of the studies described above.

Compliance with hand washing recommendations in hospitals is typically less than 50%, with proportions of non-compliance varying among physicians, nurses, and other HCWs (38). Our hand hygiene compliance observations are similar. Missed HCW hand hygiene opportunities apparently allow the transmission of *C. parapsilosis* from hands to CVCs.

Once introduced onto catheters, several factors may promote growth and introduction into the bloodstream of *C. parapsilosis*. Solutions that contain high concentrations of glucose and amino acids, such as TPN, confer a selective growth advantage to *Candida* species, including *C. parapsilosis* (39), (40), (16). Certain *Candida* species, including *C. parapsilosis*, can form extensive biofilms on bioprosthetic materials (41), (32), (42). Collections of cells and extracellular fibrinous material, these biofilms appear to correlate with pathogenicity, and to confer a relative resistance to antifungal drugs (43).

Patient clinical characteristics also increase the risk of infection. Index date APACHE II scores were higher for case patients, which may indicate more severe illness caused by, rather than resulting in, candidemia. However, other factors presented, such as any TPN use and any mechanical ventilation, indicate that cases were more severely ill than controls throughout hospitalization. While no case patients had neutropenia, or deficiency in infection fighting cells, the acute illnesses and underlying medical conditions of case patients, like diabetes and renal insufficiency, rendered them immunocompromised and susceptible to *Candida* infection. Moreover, more severe acute illnesses require greater numbers of invasive devices, physiologic support, intravenous medication use, and more frequent hands-on care. Unlike in other studies,

however, we did not find the use of broad-spectrum antibiotics to be associated with increased risk of infection, or the use of fluconazole to be protective (5), (34).

We also observed a notable susceptibility pattern among the clinical isolates to antifungal drugs. While these isolates do not exceed the cutoff value for resistance ($MIC_{50} \geq 64\mu g/mL$), it is an unusual finding that the clinical isolates demonstrate reduced susceptibility to fluconazole. *Candida parapsilosis* typically exhibits extreme susceptibility to fluconazole: in one large population-based surveillance study, the observed MIC_{50} for 83 isolates was 1.0μg/mL (range 0.25 to 4μg/mL) (7). Fluconazole is commonly used in the ICUs in Hospital A as empiric therapy for persistent fever without an obvious source, which may be contributing to the emergence of a less susceptible strain of *Candida,* in this case *C. parapsilosis,* in this setting.

Molecular epidemiologic techniques demonstrated that one-third of the hand isolates in this outbreak have the same electrophoretic pattern as the clinical isolates, and that this is the predominant pattern among the 5 patterns observed. While molecular typing techniques have been used in a number of outbreaks, it is uncommon to identify a single strain as the cause of all infections in larger outbreaks (23), (14), (24), (32), (18) *(ed., the previous placement of this paragraph seemed a bit clumsy and out of place).*

Subsequent to October 31, 2001, Hospital A began to implement expanded infection control measures; these measures are detailed in Appendix B. To summarize, recommendations focused on the choice and use of an alcohol-based waterless hand hygiene agent by Hospital A, the implementation of improved adherence to hand hygiene recommendations outlined in the Hospital Infection Control Practices Advisory Committee (HICPAC) Guidelines, and monitoring the effects of the interventions (44).

We also recommended that the hospital consider expanding hand hygiene procedures for HCWs caring for ICU patients on TPN. Cases that occurred after this date are presented in Figure 3. Hospital A has had one possible case (CVC-tip isolate only) since January 1, 2001.

Several limitations to this study should be mentioned. Because we chose to include only case-patients with *C. parapsilosis* isolated from blood, the small number of confirmed cases limited the power for multivariable modeling of risk factors for BSI in our case-control study. Additionally, we may have misclassified some cases of true bloodstream infection as possible cases due to the relatively low sensitivity of fungal blood cultures, or the masking of blood cultures due to fluconazole use in case patients (5 of 7 possible cases had been on fluconazole prior to culture). However, the similarity between results of the two univariate analyses presented suggests that the risk factors for catheter colonization do not differ appreciably from those for bloodstream infection. This is consistent with the hypothesis that *C. parapsilosis* is acquired exogenously.

Molecular typing techniques for *Candida* species, and in particular *C. parapsilosis*, have not yet been standardized. This limits interpretation of the potential relatedness among isolates. However, use of a new DNA probe (results pending) may improve discriminatory ability, and better measure relatedness among strains (25).

The cross-sectional sampling technique used for culturing of HCW hands does allow us to determine if hand carriage truly resulted from failure to perform hand hygiene, or from failure of hand hygiene technique. For example, the alcohol foam hand hygiene product dispenser used at Hospital A does not dispense a fixed amount of foam; rather, it depends on the user to dispense the recommended product amount. We did not assess

HCW hand hygiene technique or appropriate use of the use of the alcohol foam hand hygiene product.

Prior colonization with *Candida* among case patients was associated with infection in this outbreak. This finding is difficult to interpret. No systematic surveillance is conducted among patients of Hospital A for colonization with *Candida.* Moreover, only two of 26 colonizing *Candida* species were identified as *C. parapsilosis*; twelve were other species. The species of 5 case patient isolates and 7 control patient isolates were not determined. It is not known what proportion of these, if any, were *C. parapsilosis*. While endogenous acquisition is an important mechanism of infection for many *Candida* species, evidence for this mode of transmission of *C.* parapsilosis is scant. In one study among 82 consecutive neonatal ICU admissions, the development of *C. parapsilosis* BSI among four patients was significantly associated with gastrointestinal colonization. The GI tract was not among the case patient sites found colonized in this outbreak. Two control patients had GI tract *Candida* colonization - one with *C. albicans* and one with an undetermined species. The best method to understand the role of prior colonization in *Candida parapsilosis* BSI would be to obtain prospective surveillance cultures of ICU patient, which we were not able to do in this outbreak setting.

Areas for future investigation of *Candida parapsilosis* should include studies of the epidemiology of infection in the non-outbreak setting, further development of molecular typing techniques, and elucidating modifiable risk factors for hospital-acquired infection.

REFERENCES

1. Odds FC. Candida and candidosis. London: W. B. Saunders Co., 1988.

2. Edwards JE. Candida Species. In: Mandell GL, Bennett JE, Dolin R, eds. Principles and Practice of Infectious Diseases. Philadelphia, PA: Churchill Livingstone, 2000:2656-2674.

3. Richardson MD, Warnock DW. Fungal Infection: Diagnosis and Management. Oxford: Blackwell Science Ltd., 1997.

4. Weems JJ, Jr. Candida parapsilosis: epidemiology, pathogenicity, clinical manifestations, and antimicrobial susceptibility. Clin Infect Dis 1992;14:756-66.

5. Fridkin SK, Jarvis WR. Epidemiology of nosocomial fungal infections. Clin Microbiol Rev 1996;9:499-511.

6. Beck-Sague C, Jarvis WR. Secular trends in the epidemiology of nosocomial fungal infections in the United States, 1980-1990. National Nosocomial Infections Surveillance System. J Infect Dis 1993;167:1247-51.

7. Kao AS, Brandt ME, Pruitt WR, et al. The epidemiology of candidemia in two United States cities: results of a population-based active surveillance. Clin Infect Dis 1999;29:1164-70.

8. Pfaller MA, Jones RN, Messer SA, Edmond MB, Wenzel RP. National surveillance of nosocomial blood stream infection due to Candida albicans: frequency of occurrence and antifungal susceptibility in the SCOPE Program. Diagn Microbiol Infect Dis 1998;31:327-32.

9. McNeil MM, Nash SL, Hajjeh RA, et al. Trends in mortality due to invasive mycotic diseases in the United States, 1980-1997. Clin Infect Dis 2001;33:641-7.

10. Blumberg HM, Jarvis WR, Soucie JM, et al. Risk factors for candidal bloodstream infections in surgical intensive care unit patients: the NEMIS prospective multicenter study. The National Epidemiology of Mycosis Survey. Clin Infect Dis 2001;33:177-86.

11. Wenzel RP, Edmond MB. The impact of hospital-acquired bloodstream infections. Emerg Infect Dis 2001;7:174-7.

12. Greaves I, Kane K, Richards NT, Elliott TS, Adu D, Michael J. Pigeons and peritonitis? Nephrol Dial Transplant 1992;7:967-9.

13. Johnston BL, Schlech WF, 3rd, Marrie TJ. An outbreak of Candida parapsilosis prosthetic valve endocarditis following cardiac surgery. J Hosp Infect 1994;28:103-12.

14. Diekema DJ, Messer SA, Hollis RJ, Wenzel RP, Pfaller MA. An outbreak of Candida parapsilosis prosthetic valve endocarditis. Diagn Microbiol Infect Dis 1997;29:147-53.

15. Solomon SL, Alexander H, Eley JW, et al. Nosocomial fungemia in neonates associated with intravascular pressure- monitoring devices. Pediatr Infect Dis 1986;5:680-5.

16. Sherertz RJ, Gledhill KS, Hampton KD, et al. Outbreak of Candida bloodstream infections associated with retrograde medication administration in a neonatal intensive care unit. J Pediatr 1992;120:455-61.

17. Saxen H, Virtanen M, Carlson P, et al. Neonatal Candida parapsilosis outbreak with a high case fatality rate. Pediatr Infect Dis J 1995;14:776-81.

18. Huang YC, Lin TY, Leu HS, Peng HL, Wu JH, Chang HY. Outbreak of Candida parapsilosis fungemia in neonatal intensive care units: clinical implications and genotyping analysis. Infection 1999;27:97-102.

19. Sader HS, Hollis RJ, Pfaller MA. The use of molecular techniques in the epidemiology and control of infectious diseases. Clin Lab Med 1995;15:407-31.

20. Carruba G, Pontieri E, De Bernardis F, Martino P, Cassone A. DNA fingerprinting and electrophoretic karyotype of environmental and clinical isolates of Candida parapsilosis. J Clin Microbiol 1991;29:916-22.

21. Lott TJ, Kuykendall RJ, Welbel SF, Pramanik A, Lasker BA. Genomic heterogeneity in the yeast Candida parapsilosis. Curr Genet 1993;23:463-7.

22. Reiss E, Tanaka K, Bruker G, et al. Molecular diagnosis and epidemiology of fungal infections. Med Mycol 1998;36:249-57.

23. Welbel SF, McNeil MM, Kuykendall RJ, et al. Candida parapsilosis bloodstream infections in neonatal intensive care unit patients: epidemiologic and laboratory confirmation of a common source outbreak. Pediatr Infect Dis J 1996;15:998-1002.

24. Vazquez JA, Boikov D, Boikov SG, Dajani AS. Use of electrophoretic karyotyping in the evaluation of Candida infections in a neonatal intensive-care unit. Infect Control Hosp Epidemiol 1997;18:32-7.

25. Enger L, Joly S, Pujol C, Simonson P, Pfaller M, Soll DR. Cloning and characterization of a complex DNA fingerprinting probe for Candida parapsilosis. J Clin Microbiol 2001;39:658-69.

26. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med 1985;13:818-29.

27. Petersen NJ, Collins DE, Marshall JH. A microbiological assay technique for hands. Health Lab Sci 1973;10:18-22.

28. Rex JH, Pfaller MA, Galgiani JN, et al. Development of interpretive breakpoints for antifungal susceptibility testing: conceptual framework and analysis of in vitro-in vivo correlation data for fluconazole, itraconazole, and candida infections. Subcommittee on Antifungal Susceptibility Testing of the National Committee for Clinical Laboratory Standards. Clin Infect Dis 1997;24:235-47.

29. Agresti A. An Introduction to Categorical Data Analysis. New York, NY: John Wiley & Sons, Inc., 1996.

30. Plouffe JF, Brown DG, Silva J, Jr., Eck T, Stricof RL, Fekety FR, Jr. Nosocomial outbreak of Candida parapsilosis fungemia related to intravenous infusions. Arch Intern Med 1977;137:1686-9.

31. Solomon SL, Khabbaz RF, Parker RH, et al. An outbreak of Candida parapsilosis bloodstream infections in patients receiving parenteral nutrition. J Infect Dis 1984;149:98-102.

32. Levin AS, Costa SF, Mussi NS, et al. Candida parapsilosis fungemia associated with implantable and semi- implantable central venous catheters and the hands of healthcare workers. Diagn Microbiol Infect Dis 1998;30:243-9.

33. Pfaller MA. Nosocomial candidiasis: emerging species, reservoirs, and modes of transmission. Clin Infect Dis 1996;22 Suppl 2:S89-94.

34. Marr KA, Seidel K, White TC, Bowden RA. Candidemia in allogeneic blood and marrow transplant recipients: evolution of risk factors after the adoption of prophylactic fluconazole. J Infect Dis 2000;181:309-16.

35. Sanchez V, Vazquez JA, Barth-Jones D, Dembry L, Sobel JD, Zervos MJ. Nosocomial acquisition of Candida parapsilosis: an epidemiologic study. Am J Med 1993;94:577-82.

36. Strausbaugh LJ, Sewell DL, Ward TT, Pfaller MA, Heitzman T, Tjoelker R. High frequency of yeast carriage on hands of hospital personnel. J Clin Microbiol 1994;32:2299-300.

37. Rangel-Frausto M, Martin M, Saiman L, et al. High prevalence of Candida spp. on hands of health care workers in surgical and neonatal intensive care units. 34th Interscience Conference on Antimicrobial Agents and Chemotherapy. Washington, D.C., 1994:J106, p105.

38. Pittet D, Mourouga P, Perneger TV. Compliance with handwashing in a teaching hospital. Annals of Internal Medicine 1999;130:126-130.

39. Gelbart SM, Reinhardt GF, Greenlee HB. Multiplication of nosocomial pathogens in intravenous feeding solutions. Appl Microbiol 1973;26:874-9.

40. Goldmann DA, Martin WT, Worthington JW. Growth of bacteria and fungi in total parenteral nutrition solutions. Am J Surg 1973;126:314-8.

41. Branchini ML, Pfaller MA, Rhine-Chalberg J, Frempong T, Isenberg HD. Genotypic variation and slime production among blood and catheter isolates of Candida parapsilosis. J Clin Microbiol 1994;32:452-6.

42. Chandra J, Kuhn DM, Mukherjee PK, Hoyer LL, McCormick T, Ghannoum MA. Biofilm Formation by the Fungal Pathogen Candida albicans: Development, Architecture, and Drug Resistance. J. Bacteriol. 2001;183:5385-5394.

43. Kuhn DM, Chandra J, Mukherjee PK, Ghannoum MA. Comparison of Biofilms Formed by Candida albicans and Candida parapsilosis on Bioprosthetic Surfaces. Infect. Immun. 2002;70:878-888.

44. Garner JS. Guideline for isolation precautions in hospitals. The Hospital Infection Control Practices Advisory Committee. Infect Control Hosp Epidemiol 1996;17:53-80.

Table 1. Overall and organism-specific central venous catheter-associated bloodstream infection rates by year for combined medical, surgical, and neurological ICU areas, Hospital A - Mississippi, 1999-2001.

BSI rates per 1000 catheter-days	1999	2000	2001
Total	8.3	4.3	8.3
Bacterial	7.8	3.6	3.8
***Candida* species**	1.0	1.0	5.3
Candida parapsilosis	0	.7	4.5

Table 2. Demographic and clinical characteristics of confirmed and possible case patients and control patients, *Candida parapsilosis* bloodstream infection outbreak, Hospital A - Mississippi, 2001.

Characteristic	Confirmed Cases (n=13)	Possible cases (n=7)	All cases (n=20)	Controls (n=40)
Age group				
18-44	3 (23%)	1 (14%)	4 (20%)	7 (18%)
45-69	7 (53%)	1 (14%)	8 (40%)	17 (43%)
70 and above	3 (23%)	5 (71%)	8 (40%)	16 (40%)
Gender				
Male	9 (69%)	2 (29%)	11 (55%)	17 (43%)
Female	4 (31%)	5 (71%)	9 (45%)	23 (58%)
Race				
White	6 (46%)	6 (86%)	12 (60%)	23 (58%)
Black	7 (54%)	1 (14%)	8 (40%)	17 (43%)
Died	4 (31%)	5 (71%)	9 (45%)	7 (18%)
Underlying illnesses				
Hematologic cancer	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Non-hematologic cancer	2 (15%)	1 (14%)	3 (15%)	7 (18%)
HIV	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Diabetes	5 (38%)	1 (14%)	6 (30%)	17 (43%)
Immune disorders	1 (8%)	2 (29%)	3 (15%)	4 (10%)
Chronic renal insufficiency	2 (15%)	1 (14%)	3 (15%)	10 (25%)
Chronic steroid use	2 (15%)	1 (14%)	3 (15%)	6 (15%)
Hepatic insufficiency	0 (0%)	0 (0%)	0 (0%)	1 (3%)
Respiratory disease	1 (8%)	1 (14%)	2 (10%)	5 (13%)
Cardiac disease	5 (38%)	5 (71%)	10 (50%)	15 (38%)
Infectious disease	0 (0%)	0 (0%)	0 (0%)	1 (3%)
Surgical procedures	9 (69%)	4 (57%)	13 (65%)	16 (40%)
Thoracic	1 (8%)	1 (14%)	2 (10%)	3 (8%)
Pelvic	0 (0%)	0 (0%)	0 (0%)	1 (3%)
Abdominal	7 (54%)	3 (43%)	10 (50%)	11 (28%)
CNS	1 (8%)	1 (14%)	2 (10%)	2 (5%)
Vascular	0 (0%)	1 (14%)	1 (5%)	0 (0%)
Orthopedic	0 (0%)	0 (0%)	0 (0%)	1 (3%)
Mean time from line placement to index day in days +/- S.D.	9 +/- 4.1	19.7 +/- 6.8	12.8 +/- 7.2	11.9 +/- 9.8
Median time from admission to index day in days	16	24	20	20
Median length of stay in days	39	37	38	30

Table 3. Results of univariate analysis, case-control study of *Candida parapsilosis* bloodstream infection outbreak, Hospital A - Mississippi, 2001.

Risk Factor	13 confirmed cases and 26 controls		20 cases and 40 controls	
	Odds Ratio	95% Confidence Interval	Odds Ratio	95% Confidence Interval
Any mechanical ventilation during hospitalization	7.2	1.4-36.1	13	2.7-61.7
TPN use	5.8	1.1-31.9	5.9	1.6-21.4
Mechanical ventilation on index day	19.3	2.1-175.6	10	1.9-51.3
ICU on index day	10.7	2.0-56.2	8.9	2.2-36.2
Surgical service	10.5	1.2-95.5	7.5	1.4-38.4
Previous bacteremia or candidemia	5.4	1.3-22.2	3.8	1.2-11.6
Previous colonization with any *Candida*	14.9	1.7-125	3.0	0.8-11.0
Previous colonization with *C. parapsilosis* or undetermined *Candida* species	6.9	1.2-38.5	2.1	0.7-6.8

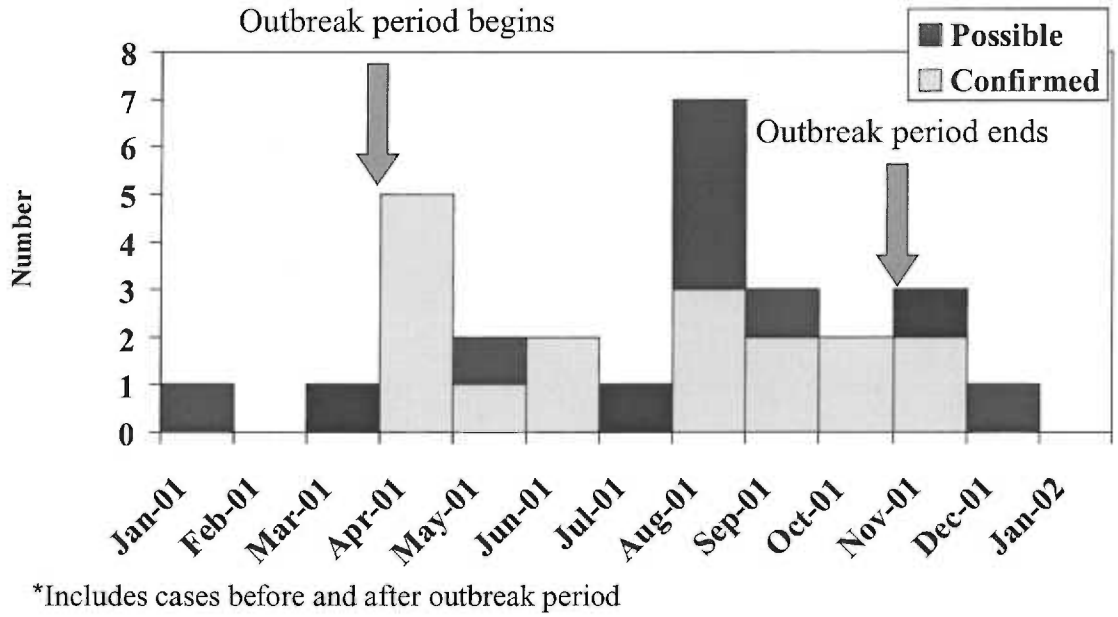
Risk Factor	Confirmed cases (n=13)	Controls (n=26)	p value	All cases (n=20)	Controls (n=40)	p value
APACHE II score	mean 21.1 median 23	mean 12.2 median 12.5	0.0001	mean 19 median 18.5	mean 13.7 median 13	0.007
Number of catheters placed during hospitalization	mean 2.7 median 3	mean 1.7 median 1	0.04	mean 2.5 median 2	mean 1.6 median 1	0.02

Table 4. Multivariable models consisting of paired combinations of variables found to be significantly associated with increased risk of *Candida parapsilosis* bloodstream infection on univariate analysis, Hospital A – Mississippi, 2001.

		Adjusted Odds Ratio (-2 log likelihood score)					
Risk Factor	**Univariate Odds Ratio**	**ICU on index day**	**Any mechanical ventilation**	**TPN**	**Previous bacteremia or candidemia**	**Severity of illness**	**Surgical service**
ICU on index day	10.7	N/A	6.3 (21.1)	16.4 (17.1)	7.2 (21.1)	5.0 (20.1)	15.2 (16.3)
Any mechanical ventilation	7.2	2.0 (21.1)	N/A	5.0 (22.7)	4.1 (23.0)	3.0 (21.4)	5.0 (20.8)
TPN	5.8	9.2 (17.1)	2.8 (22.7)	N/A	6.3 (21.1)	8.7 (18.2)	2.9 (23.9)
Previous bacteremia or candidemia	5.4	1.7 (21.1)	2.3 (23.0)	5.8 (21.1)	N/A	3.1 (20.6)	15.4 (15.3)
Severity of illness	13.7	3.2 (21.0)	6.5 (21.4)	23.3 (18.2)	8.3 (20.6)	N/A	18.9 (17.7)
Surgical service	10.5	14.1 (16.2)	6.2 (20.8)	6.3 (23.9)	34.8 (15.3)	12.2 (17.7)	N/A

Table 5. Summary of clinical, hand, and environmental cultures for *Candida parapsilosis* obtained during bloodstream infection outbreak investigation, Hospital A – Mississippi, 2001.

Cultures	Number positive	Number obtained	Proportion
All HCWs	18	68	26%
Nurses	14	53	26%
Physicians	3	7	43%
Radiology technicians	1	3	33%
Pharmacists	0	2	0%
CVC sites	0	8	0%
All Devices	1	16	6%
Blood pressure cuff tubing	1	8	13%
EKG lead	0	8	0%



*Includes cases before and after outbreak period

Figure 1. Distribution of confirmed and possible *Candida parapsilosis* cases by month of isolation, Hospital A – Mississippi, 2001.

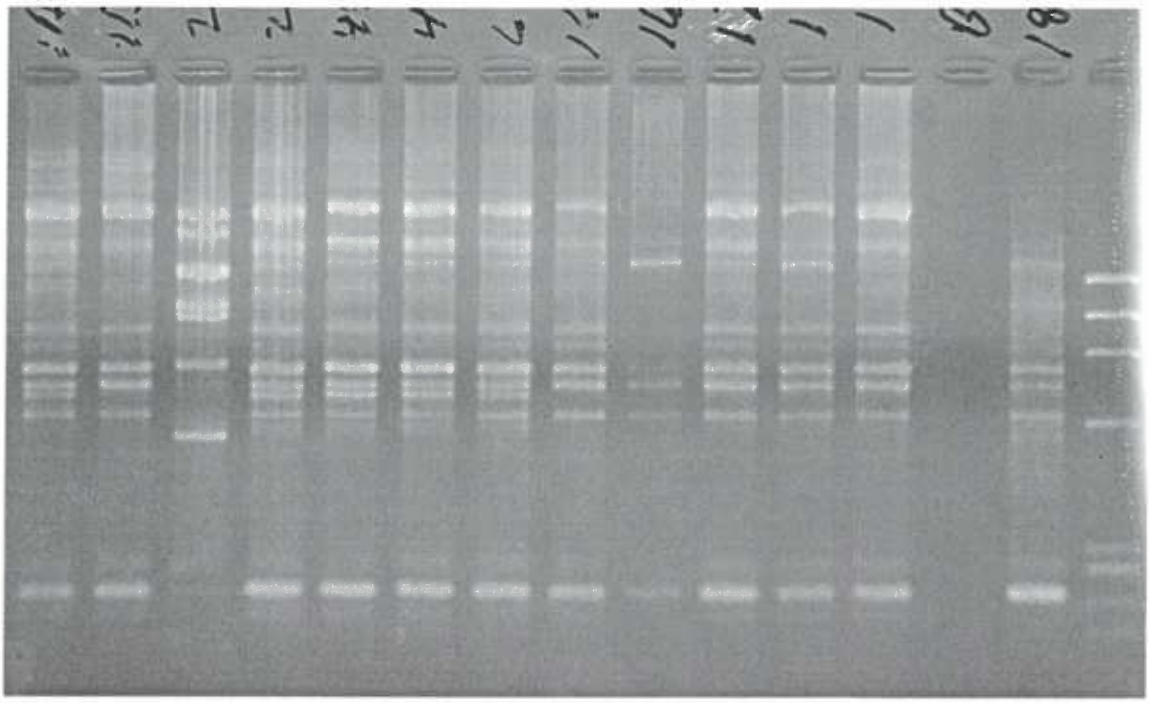


Figure 2. Representative example of hand isolates (lanes 1 through 7, from left to right) and patient isolates (lanes 8 through 12 and 14) by randomly amplified polymorphic DNA (RAPD) analysis, *Candida parapsilosis* BSI outbreak, Hospital A – Mississippi, 2001.

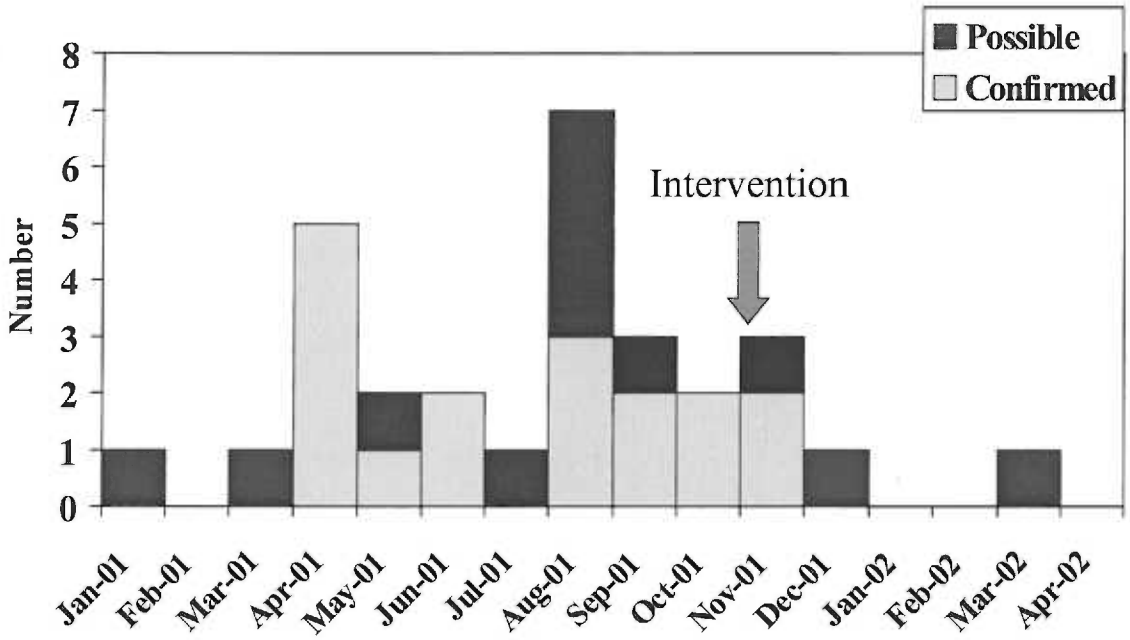


Figure 3. Distribution of confirmed and possible *Candida parapsilosis* cases (n=29), by month of isolation, including after hand hygiene intervention, Hospital A – Mississippi, 2001.

Appendix A: Case-control study medical record data abstraction tool.

CASE-CONTROL STUDY OF NOSOCOMIAL CANDIDA PARAPSILOSIS INFECTIONS

Case Control

DEMOGRAPHICS

DOB (MM/DD/YY) _____/_____/_____

Gender: Male_____ Female_____

Admit Date (MM/DD/YY) _____/_____/_____

Discharge Date _____/_____/_____

Outcome: Death_____ Discharge_____ In hospital_____

Did this patient have a positive (check one):

Blood culture only

Date of first positive blood culture _____/_____/_____

Time obtained_____

Catheter tip culture only

Date of first positive catheter tip culture _____/_____/_____

Time obtained_____

Both

Date of first positive blood culture _____/_____/_____

Time obtained_____

Date of first positive catheter tip culture _____/_____/_____

Time obtained_____

Appendix A: Case-control study medical record data abstraction tool.

CULTURE DATA

Source of blood culture: _____Peripheral venipuncture

_____Blood from line (if yes, specify which type of line)

_____PICC _____CVL _____PAL

_____Hemodialysis

_____Other (specify)_____

Source of catheter tip culture: _____PICC _____CVL _____PAL

_____Hemodialysis

_____Other (specify)_____

Reason for blood culture (check all that apply):

	Fever		Hypotension
	Increased WBC		Sepsis, deemed to be septic
	Wound drainage		Respiratory secretions
	Change in mental status		Unknown
	Surveillance/Routine culture		Other (specify):

Reason for catheter tip culture (check all that apply):

	Fever		Hypotension
	Increased WBC		Sepsis, deemed to be septic
	Catheter/site drainage		Surveillance/Routine culture
	Unknown		Other (specify):

Did this patient have *any prior* positive cultures for CP? Y N

If yes, specify site and date:

Urine date of culture _____/_____/_____ _____/_____/_____

_____/_____/_____ _____/_____/_____

Sputum date of culture _____/_____/_____ _____/_____/_____

_____/_____/_____ _____/_____/_____

BAL date of culture _____/_____/_____ _____/_____/_____

_____/_____/_____ _____/_____/_____

Wound date of culture _____/_____/_____ _____/_____/_____

Appendix A: Case-control study medical record data abstraction tool.

____/____/____ ____/____/____

Other (specify)_____

date of culture ____/____/____ ____/____/____

____/____/____ ____/____/____ ____/____/____

Did this patient have any *subsequent* positive CP cultures? Y N

If yes, specify site and date:

Blood date of culture ____/____/____ ____/____/____

____/____/____ ____/____/____

Catheter tip date of culture ____/____/____ ____/____/____

____/____/____ ____/____/____

Urine date of culture ____/____/____ ____/____/____

____/____/____ ____/____/____

Sputum date of culture ____/____/____ ____/____/____

____/____/____ ____/____/____

BAL date of culture ____/____/____ ____/____/____

____/____/____ ____/____/____

Wound date of culture ____/____/____ ____/____/____

____/____/____ ____/____/____

Other (specify)_____

date of culture ____/____/____ ____/____/____

____/____/____ ____/____/____ ____/____/____

Did this patient have any other positive *blood* cultures? Y N

If yes, specify dates and organism: ____/____/____ _____

____/____/____ _____ ____/____/____ _____

Appendix A: Case-control study medical record data abstraction tool.

____/____/____ _____ ____/____/____ _____

____/____/____ _____ ____/____/____ _____

UNDERLYING/PRE-EXISTING MEDICAL CONDITIONS

Check all that apply:

_____Hematological Cancer _____Non-Hematological Cancer

_____HIV _____Diabetes

_____Autoimmune disorder _____Chronic renal insufficiency

_____Chronic steroid use _____Hepatic insufficiency

_____Circulatory disease _____Respiratory disease

_____Cardiac disease _____Other (specify)

_____Infectious disease _____

AT THE TIME THE FIRST POSITIVE BLOOD OR CATHETER TIP CULTURE WAS DRAWN, CHECK ALL THE FOLLOWING THAT APPLY:

PATIENT LOCATION/SERVICE

Room #_____

	ICU S		2N		5N
	ICU W		2S		5S
	ICU N		3N		6N
	CVR		3S		6S
	CVSC		4N		AL
	CCU		4S		EN
	C1				WC

Service ordering culture:

	MEDICAL SERVICES		**SURGICAL SERVICES**
	General Medicine		General Surgery
	Family Practice		CT Surgery
	Pulmonary/Critical Care		Vascular Surgery
	Nephrology		Neurosurgery
	Heme/Onc		Orthopedics
	Cardiology		Urology
	Radiation Oncology		
	Infectious Disease		
	Other (specify):		Other (specify):

Appendix A: Case-control study medical record data abstraction tool.

Primary Service:

	MEDICAL SERVICES		SURGICAL SERVICES
	General Medicine		General Surgery
	Family Practice		CT Surgery
	Pulmonary/Critical Care		Vascular Surgery
	Nephrology		Neurosurgery
	Heme/Onc		Orthopedics
	Cardiology		Urology
	Radiation Oncology		
	Infectious Disease		
	Other (specify):		Other (specify):

INDWELLING CATHETERS IN PLACE

	Vascular	Date placed		Other	Date placed
	CVL - IJ			Foley/urinary catheter	
	CVL - Subclavian			PEG tube	
	CVL - Femoral			ETT/tracheostomy	
	PICC line				
	Peripheral arterial line				
	Dialysis catheter				
	Other intravascular device (specify):			Other catheter (specify):	

SINCE ADMISSION, CHECK ALL THE FOLLOWING THAT APPLY:

PROCEDURES

Did this patient have any major surgical procedure this hospitalization? Y N

If yes, specify:

		Date			Date
	Thoracic/cardiac			Pelvic/GU	
	Abdominal			CNS	
	Vascular			Orthopedic	

Appendix A: Case-control study medical record data abstraction tool.

Did this patient have any procedures (other than surgical): Y N

If yes, specify:

		Number of times performed	Date of most recent
	PEG insertion		
	LP		
	Interventional Radiology		
	Fluoroscopy/Contrast radiology		
	GI Endoscopy		
	Bronchoscopy		
	Central line/dialysis/PICC catheter placement		
	Other (specify):		

Was the patient mechanically ventilated? Y N

If yes, number of days_____

Was another form of ventilatory assistance used (CPAP, BiPAP)? Y N

CATHETER USE

Mark all that apply:

		Date of first use	Date of final use	Total doses or treatments
	TPN			
	Lipids (without other TPN)			
	Albumin			
	Dialysis			
	Blood products			
	Other (specify):			

Appendix A: Case-control study medical record data abstraction tool.

MEDICATIONS

Check all that apply:

At positive culture	Any since admit		At positive culture	Any since admit	
		Penicillins/ Cephalosporins			Aminoglycosides
		Fluoroquinolones			Macrolides
		Sulfonamides			Tetracyclines
		Insulin drip			Vancomycin
		Chemotherapy agents			Propofol
		H2-blockers			Anti-retrovirals
		Other antibiotics (specify):			

Antifungals (calculate days from start date = day 0 to index culture date):

At positive culture	Start date	Total days		At positive culture	Start date	Total days	
			Amphotericin B				Amphotericin lipid suspension (Abelcet)
			Fluconazole				Itraconazole
			Ketoconazole				

Appendix A: Case-control study medical record data abstraction tool.

SEVERITY OF ILLNESS SCORE

Parameters	**Highest**	**Lowest**
Heart Rate (beats per minute)		
Blood Pressure (mm of Hg) Record highest and lowest pressure pairs		
Temperature (^{0}C) (Rectal preferred) **Method**		
Respiratory Rate (breaths per minute)		
Arterial Blood Gas Parameters (Enter data below)		
FiO_2 (% O_2)		
pH		
PaO_2 (mm of Hg)		
PCO_2 (mm of Hg)		
Is the patient intubated?	☐No ☐Yes	
Hematocrit (%)		
White Blood Cell (cells/mm^3)		
Absolute Neutrophil Count, ANC (%Neutrophils+%Bands) x WBC		
Serum Creatinine (mg/dl)		
Does the patient have acute renal failure? **Creatinine ≥ 1.5 mg/dl** **Urine Output < 410cc/d** **Not on Chronic dialysis**	☐No ☐Yes	
Serum Sodium (Na)		
Serum Potassium (K)		
Serum HCO_3 (mEq/dl)		
Age (years)		
Glasgow Coma score-		

Appendix B: Recommendations for preventing further infections.

Preliminary, on-site discussions were held with nursing supervisory personnel, infection control practitioners, the hospital epidemiologist, and hospital administrators regarding recommendations to prevent further cases of *Candida parapsilosis* BSI. Following further data analysis and discussion after the investigation, more specific recommendations were outlined. In addition to the indications for washing hands or hand antisepsis outlined in the Hospital Infection Control Practices Advisory Committee (HICPAC) Guideline for Isolation Precautions in Hospitals (*i.e.*, Standard Precautions (44)), the following issues should be considered to reduce transmission of *C. parapsilosis*, and other organisms, between patients via contaminated HCW hands:

1. Recommend continued use of alcohol-based waterless agents by HCWs in the involved ICU areas. Several factors should be considered in the choice of the product. If the following factors were not considered, re-evaluate the choice of the agent. The choice of the product should:
    a. be based on solicited input by care givers expected to use the product,
    b. not be based on cost as the primary factor in product selection,
    c. incorporate the assurance that adequate volume of product is likely to be delivered and used by care givers during routine use (*i.e.,* the volume recommended by manufacturer),
    d. be based on ability to provide easy-access to use, such as pocket-sized packages, obvious placement in patient's rooms at bedside or the entrance.
2. Make improved hand hygiene adherence an institutional priority and provide appropriate administrative support and financial resources to do such, consider:

a. creating a multidisciplinary program, including hospital administration support, designed to improve adherence of care givers to recommended hand hygiene practices (see below).

b. As part of this program, educate personnel regarding the types of patient care activities that can result in hand contamination and the advantages and disadvantages of various methods used to clean their hands.

   i. Use the draft HICPAC Hand Hygiene Guideline as a resource,

   ii. work with CDC's Division of Healthcare Quality Promotion (Epidemiology Section) for suggestions on methods,

   iii. emphasize proper technique in using antisepsis agent chosen in (1) above (*i.e.,* cover all hand and finger surfaces with enough agent to remain wet at least 10 seconds).

c. As part of this program, develop and implement an ongoing system for measuring improvements in adherence of healthcare workers to recommended hand hygiene practices. Examples are listed:

   i. Monitor healthcare workers' adherence with recommended hand hygiene practices after implementation of this program, and provide personnel with timely information regarding their performance. (i.e., the number of hand hygiene episodes performed by personnel/number of hand hygiene opportunities, by ward or by service).

   ii. Monitor the volume of alcohol-based handrub (or detergent used for handwashing or hand antisepsis) used/1000 patient-days.

iii. Continue to monitor BSI.

3. Expand indications for handwashing and hand antisepsis from those listed under Standard Precautions, to include those outlined in the draft HICPAC Hand Hygiene Guideline, including the most relevant to this outbreak:

a. Wash with soap (any type) and water if visibly soiled.

b. Use antisepsis agent (*e.g.*, waterless agent) if not visibly soiled to decontaminate hands of care givers:

i. **after** contact with a patient's intact skin (regardless of glove use)

ii. **after** contact with body fluids, excretions, draining, or wound dressings (regardless of glove use)

iii. **after** contact with inanimate objects in the immediate vicinity of the patient.

iv. **before** donning sterile gloves when inserting a central intravascular catheter.

c. Consider using an antisepsis agent (*e.g.*, waterless agent) if not visibly soiled to decontaminate hands of care givers **before** caring for patients in the ICUs on TPN (*i.e.*, for any patient care activity, medication administration, blood draws).