SYNOPSIS

Large Outbreaks of Fungal and Bacterial Bloodstream Infections in a Neonatal Unit, South Africa, 2012–2016

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Learning Objectives

Upon completion of this activity, participants will be able to:

- Describe the background of *Candida krusei* infection among neonates
- Assess the clinical picture and prognosis of *C. krusei* candidemia among neonates
- Distinguish risk factors for *C. krusei* candidemia among neonates
- Analyze results of an environmental study in the neonatal intensive care unit (NICU) to find the source of *C. krusei*

CME Editor

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Candidemia is a major cause of healthcare-associated infections. We describe a large outbreak of *Candida krusei* bloodstream infections among infants in Gauteng Province, South Africa, during a 4-month period; a series of candidemia and bacteremia outbreaks in the neonatal unit followed. We detected cases by using enhanced laboratory surveillance and audited hospital wards by environmental sampling and epidemiologic studies. During July–October 2014, among 589 patients, 48 unique cases of *C. krusei* candidemia occurred (8.2% incidence). Risk factors for candidemia on multivariable analyses were necrotizing enterocolitis, birthweight <1,500 g, receipt of parenteral nutrition, and receipt of blood transfusion. Despite initial interventions, outbreaks of bloodstream infection caused by *C. krusei*, rarer fungal species, and bacterial pathogens continued in the neonatal unit through July 29, 2016. Multiple factors contributed to these outbreaks; the most functional response is to fortify infection prevention and control.

On August 4, 2014, the National Institute for Communicable Diseases (NICD) received a report of 11 neonates infected with candidemia from a university-affiliated hospital in Gauteng Province, South Africa. A large outbreak of candidemia caused by *Candida krusei* ensued over 4 months in the neonatal unit. We investigated to identify the possible source and mode of transmission of the outbreak, to identify risk factors for the development of candidemia, and to recommend control measures. After this outbreak, and despite the initial interventions, a series of ≥4 outbreaks of bacterial and fungal bloodstream infections (BSI) lasting until July 29, 2016, occurred. We investigated the first outbreak extensively; we report the results of this and subsequent investigations.

Candidemia may result in substantial long-term illness among hospitalized premature neonates, and reported crude mortality rates are 32%–46% (*1*–*3*). In a recent point prevalence survey among hospitalized adults and children in the United States, *Candida* was the leading pathogen causing BSI (*4*). *C. krusei*, a less common cause of BSI, is intrinsically resistant to fluconazole, a first-line antifungal agent (*5*).

Known risk factors for candidemia among neonates include very low birthweight (VLBW), prematurity, central venous catheter use, necrotizing enterocolitis (NEC), total parenteral nutrition (TPN), and prior or prolonged broad-spectrum antibacterial drug use, among others (*1*,*2*,*6*–*10*). Worldwide, outbreaks of candidemia in neonatal intensive care units (NICUs) are often caused by *C. parapsilosis* and associated with suboptimal adherence to infection prevention and control practices (*5*,*11*–*13*). In South Africa, *C. parapsilosis* is the most common *Candida* species among neonates; 2% of candidemia case-patients among all age groups test positive for *C. krusei* (*14*).

Methods

Outbreak Setting

Hospital A is a 1,500-bed public-sector hospital in a semi-urban area of South Africa that serves as a referral center for 9 hospitals in 3 provinces in the region. The metropolitan area had a population of ≈3.1 million in 2014 (*15*). The infant mortality rate was estimated at 19.3/1,000 live births in Gauteng in 2014 (*16*), and the antenatal HIV prevalence was 28% (*17*).

The neonatal unit at hospital A has 55 beds, comprising 14 intensive-care beds, 20 high-care beds, and a nursery area that has 15 cots and 6 beds for surgical patients. The ward is largely of open-plan design: it has areas not fully separated by floor-to-ceiling divisions. An average of 154 patients are admitted to the unit every month. The unit is often overcrowded, and infants share cots when capacity is exceeded. Fluconazole is not routinely used as prophylaxis but was used as first-line treatment for suspected or confirmed fungemia and other invasive fungal infections before this outbreak. Amphotericin B deoxycholate was the other systemic antifungal agent available for therapeutic use; penicillin G and amikacin were used as empiric therapy for suspected bacteremia. The unit protocol requires that blood culture samples be collected for every admitted neonate at birth and for all infants in whom sepsis is suspected. A confirmatory blood culture specimen is completed before appropriate treatment is initiated. All specimens are referred to an onsite hospital laboratory with a full microbiology service.

First Outbreak

Case Definition

For the outbreak investigation, we defined a case-patient as any neonate admitted to the neonatal unit during July 1–October 31, 2014, whose blood sample was positive for *C. krusei*. Any specimen positive for *C. krusei* from the same patient within 30 days of the first positive specimen was considered to be part of a single case. We defined a neonate as an infant ≤28 days of age; however, infants remaining in the unit or whose sample tested positive for candidemia beyond the 28th day of life were also included in this investigation.

Baseline Data Extraction, Confirmation of the Outbreak, and Identification of Cases

We extracted data for all cases of laboratory-confirmed candidemia during January 2012–December 2013 from the National Health Laboratory Service (NHLS) Corporate Data Warehouse (CDW), which archives demographic and laboratory data from patients whose diagnostic laboratory tests are performed by any NHLS laboratory. NICD began conducting active, laboratory-based surveillance for

candidemia at enhanced surveillance sites in South Africa in 2012. Hospital A became an enhanced site in January 2014, which meant that a nurse surveillance officer at the hospital collected clinical data on a standardized case report form (including age, gestational age, gender, birthweight, mode of delivery, feeding method, and HIV exposure status and outcome) and isolates were submitted to a reference laboratory at NICD. We extracted demographic, clinical, and laboratory data for cases of candidemia from January–June 2014 from the surveillance database. We used the C2-CUSUM method (*18*) to establish a baseline of expected cases, by *Candida* species, in the unit. We detected outbreak cases through ongoing surveillance.

Reference Laboratory Methods

We confirmed identification and susceptibility testing of bloodstream *Candida* isolates, as previously described, with modifications (*14*). This included the use of matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (Bruker Daltonics, Bremen, Germany) and sequencing of the internal transcribed spacer region of the ribosomal gene to confirm species-level identification. We did not genotype specimens.

Epidemiologic Studies

To determine risk factors for *C. krusei* candidemia, we conducted a retrospective cohort study. All neonates admitted for ≥72 hours to the neonatal unit during July 1–October 31, 2014, were included. We analyzed data from an existing ward database containing clinical data on all admitted patients and their mothers.

We collected and analyzed additional data (unavailable in the ward database) for a subset of patients by using a nested matched case–control design. We retrospectively reviewed patient and laboratory records for data pertaining to antibacterial and antifungal treatment, other medication administered (with emphasis on medication from multidose vials), intravenous fluids, TPN, blood transfusions, and laboratory parameters. Data for the presence, sites, and duration of insertion of peripheral and central venous catheters were not available. We selected 41 control-patients and 41 case-patients from the same neonatal unit who were admitted during a similar time period (±1 week) and matched by gender and birthweight (±500 g).

Statistical Analysis

By dividing the number of new cases by the total number of admissions to the neonatal unit during the 4-month outbreak period, we calculated the incidence of *C. krusei* and other fungal and bacterial BSI. Data on patient-days were not available.

We compared clinical and demographic characteristics of case-patients and non–case-patients in the cohort by using the Pearson χ^2 and Fisher exact tests or Student *t*-test and Wilcoxon rank-sum test, as appropriate. We evaluated exposure variables as risk factors for candidemia by univariate analysis. Variables with p values <0.2 were included in a multivariable logistic regression model. We used conditional logistic regression to determine additional risk factors for candidemia in matched case-control pairs. We conducted all statistical analyses in Stata version 13 (StataCorp LLC, College Park, TX, USA).

Infection Prevention and Control Interventions

Upon recognition of the outbreak, the hospital infection control department conducted a hand hygiene campaign, and infection prevention and control (IPC) was intensified. We recommended the use of amphotericin B as the empiric antifungal agent of choice, instead of fluconazole, for all neonates with suspected candidemia. We conducted 2 IPC audits (initial, December 2014, and follow-up, March 2015), to determine whether suboptimal practices had contributed to the outbreak and to encourage improvement in IPC. We describe details of the audits in the online Technical Appendix (https://wwwnc.cdc.gov/EID/article/24/7/17-1087-Techapp1.pdf).

We conducted 4 types of surveys during 2 IPC audit periods: during the first period, administration of IPC knowledge and perception questionnaires and targeted environmental sampling with submission of samples for fungal culture; and in both periods, a cross-sectional observational audit and observation of hand hygiene behavior. We sampled high-touch surfaces (such as procedure trolleys, intravenous fluid stands, computer monitor touchscreens and keyboards, and incubator door handles), fluids (such as TPN, a container of communal hand cream shared by staff, and a tube of water-based lubricant), contents of multidose vials (such as heparin), staff member hands, and stethoscopes.

Subsequent Outbreaks

Ongoing surveillance identified ≥4 subsequent outbreaks. We performed a 1-time retrospective audit of the NHLS CDW for 2014–2015 for 3 common bacterial pathogens: *Klebsiella pneumoniae*, *Escherichia coli*, and *Enterobacter cloacae*. We compared these data with candidemia surveillance data (beginning on January 1, 2014, and ending on December 31, 2016). Results are shown in the online Technical Appendix Figure.

Ethics

NICD acquired approval for retrospective data collection for surveillance purposes and outbreak investigation activities from the Human Research Ethics Committee (Medical) of the University of Witwatersrand (reference numbers M140159 and M160667). In addition, an epidemiologic study protocol was approved (M1411112). We obtained permission to conduct the investigation from hospital A.

The hospital Department of Paediatrics and Child Health granted permission for secondary data use.

Results

First Outbreak

In a 5-year period (January 2012–December 2016) before, during, and after the first outbreak, 262 cases of candidemia (caused by numerous *Candida* species) were detected in the neonatal unit at hospital A (Figure 1). We identified 10 different species of *Candida*; the most common was *C. krusei* (91/262; 35% of cases), followed by *C. albicans* (75/262; 29%) and *C. parapsilosis* (41/388; 16%). Cases of candidemia caused by *C. albicans* were diagnosed continually through the 5-year period; other species were identified intermittently. Before onset of the outbreak in July 2014, a single case of *C. krusei* candidemia was recorded in October 2012. During July–October 2014, of 589 neonatal admissions, 48 cases of *C. krusei* candidemia occurred, an incidence of 8.2/100 admissions. During July (n = 14), August (n = 18), and September 2014 (n = 11), *C. krusei* was the only *Candida* species detected from blood cultures in the neonatal unit. This represented a total species replacement and was above the expected baseline of 0 cases for the unit.

The *C. krusei* index case sample was collected on July 5, 2014. Overlapping collection dates suggested a propagated outbreak with horizontal transmission of *C. krusei* among case-patients (Figure 2). The last outbreak case was confirmed from a sample collected on October 20, 2014. In samples from 48 case-patients, C. krusei was isolated >1 time in 29 (60%) case-patients (mean 2.5 positive isolates/case-patient). All 118 C. krusei isolates had amphotericin B MICs<2 µg/mL.

Characteristics of Outbreak Case-Patients

Among the cohort of 589 infants admitted to the neonatal unit during the 4-month outbreak period, the mean gestational age of infants with *C. krusei* candidemia (33 wk) was lower than that of infants whose samples tested negative (35 wk; p<0.001) (Table 1). Mean birthweight was also lower among positive (1,356 g) than negative (2,300 g) infants (p<0.001). Among case-patients, 26 infants (54%) had a very low birthweight and 8 infants had an extremely low birthweight (<1,000 g). Median chronological age at onset of candidemia was 13 days (interquartile range [IQR] 7.5–17.5 days). Of 35 case-patients for whom HIV exposure status data were available, 16 (46%) had antenatal exposure to HIV; not all infants who were treated for candidemia had been tested for HIV at birth. Infants in whom candidemia was diagnosed had a longer duration of hospitalization (median 39 days, IQR 25–55 days) than did infants who tested negative (median 7 days, IQR 1–17 days; p<0.001). Of 48 infants who tested positive for candidemia, 7 died (crude case-fatality ratio 15%), compared

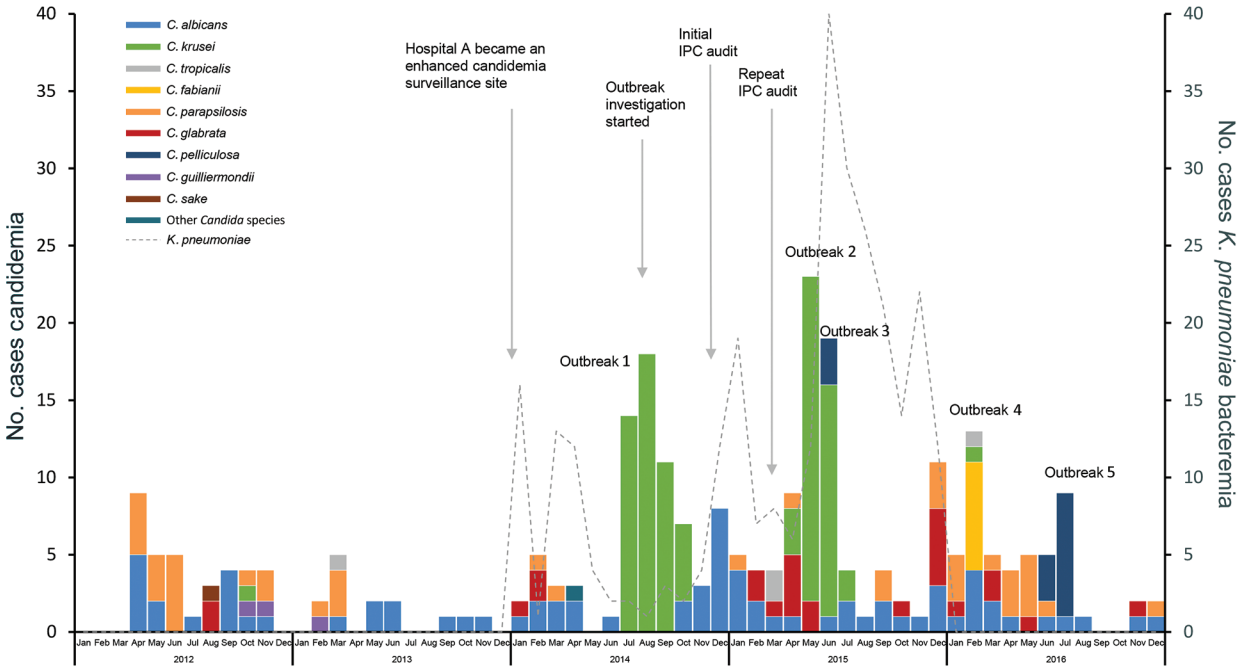

Figure 1. Cases of candidemia (n = 262), by *Candida* species, and bacteremia caused by *Klebsiella pneumoniae* (n = 298) in the neonatal unit at hospital A, Gauteng, South Africa, January 2012–December 2016. Individual outbreaks caused by the following *Candida* species: outbreak 1, *C. krusei*; outbreak 2, *C. krusei*; outbreak 3, *C. pelliculosa*, outbreak 4, *C. fabianii*; outbreak 5, *C. pelliculosa*. Specific points during the outbreak investigation are labeled. IPC, infection prevention and control.

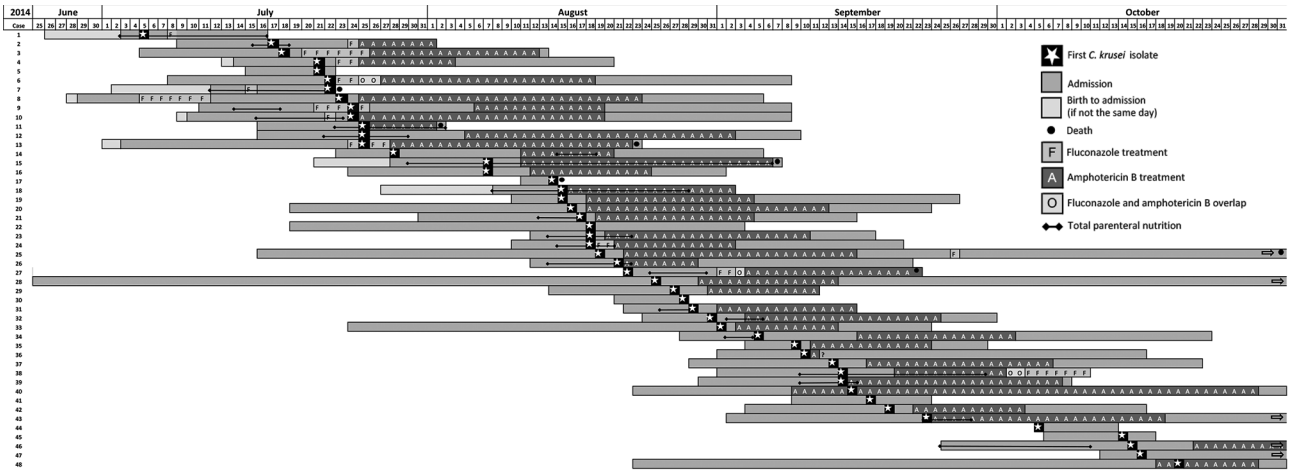

Figure 2. Gantt chart illustrating the timeline of an outbreak of 48 cases of *Candida krusei* bloodstream infection among neonates admitted to the neonatal unit at hospital A, Gauteng, South Africa, July 1–October 31, 2014.

to 62 of 538 infants who tested negative (crude case-fatality ratio 12%) (p = 0.5).

Risk Factors for C. krusei Candidemia

After adjustment for possible confounders in the multivariable regression model, infants diagnosed with NEC were 3 times more likely to develop candidemia than those who tested negative (adjusted odds ratio [aOR] 3.1, 95% CI 1.4–6.7) (Table 2). Neonates weighing 1,000–1,500 g at birth were 6 times more likely to have candidemia than those who had a birthweight >2,500 g (aOR 6.1, 95% CI 2.1–17.2). Infants who had extremely low birthweight also had a higher risk for candidemia (aOR 6.5, 95% CI 1.9–21.6). In addition, having been admitted to the unit during July and August was associated with positive test results for candidemia (Table 2).

Case-patients and controls received a median of 3 (IQR 2–5) antibacterial drugs during their entire hospital stay. During the first 13 days after admission (a censored time-point corresponding to the median age of onset of candidemia), case-patients received a median of 3 (IQR 2–3) antibacterial drugs, whereas controls received a median of 2 (IQR 0–3) antibacterial drugs (p = 0.001). Of 41 case-patients, 37 (90%) received courses of antifungal therapy; 6 of these occurred before the first positive culture of *C. krusei* (fluconazole, n = 4; amphotericin B, n = 2). Of the 4 case-patients who received fluconazole, 3 were subsequently given amphotericin B, and 1 case-patient

Table 1. Characteristics of a cohort of 589 neonates, with and without *Candida krusei* candidemia, admitted to the neonatal unit at hospital A, Gauteng, South Africa, July 2014–October 2014*

Patient characteristics	*C. krusei* candidemia, n = 48	No *C. krusei* candidemia, n = 541	Total	p value
Sex				
M	28/48 (58.3)	309/539 (57.3)	337/587 (57.4)	0.878
F	20/48 (41.7)	230/539 (42.7)	250/587 (42.6)	
Median chronological age at onset of candidemia, d (IQR)	13 (7.5–17)	NA	NA	NA
Mean gestational age at birth, wk (±SD)	33 (±3.8)	35 (±4.1)	35 (±4.1)	**<0.001**
Median birthweight, g (IQR)	1,365 (1,130–1,970)	2,300 (1,635–3,070)	2,225 (1,580–3,030)	**<0.001**
Median length of hospital stay, d (IQR)	39 (25–55)	7 (1–17)	8 (2–20)	**<0.001**
Twin infants or triplets	4/48 (8.3)	54/541 (10)	58/589 (9.8)	1.000
Born in hospital A	42/46 (91.3)	490/541 (90.6)	532/587 (90.6)	1.000
Died	7/48 (14.6)	62/538 (11.5)	69/586 (11.8)	0.468
Received antibacterial drugs during hospital stay	40/41 (97.6)	28/41 (68.3)	68/82 (82.9)	**0.001**
Median no. (IQR) antibacterial drugs received in first 13 d	3 (2–3)	2 (0–3)	2 (0–3)	**0.001**
Received TPN during hospital stay	24/40 (60)	5/41 (12.2)	29/81 (35.8)	**<0.001**
Received ≥1 blood transfusion during hospital stay	38/41 (92.7)	18/41 (43.9)	56/82 (68.3)	**<0.001**

*Values are no. in category/total no. (%) except as indicated. Bold indicates statistically significant values. In the No *C. krusei* candidemia group, data were unavailable for the following variables: sex (n = 2), gestational age (n = 22), birthweight (n = 1), length of hospital stay (n = 3) and death (n = 3). In the *C. krusei* candidemia group, data was unavailable for the following variables: gestational age (n = 3), birthweight (n = 2), length of hospital stay (n = 4), place of birth (n = 2). Data for the following variables were only available for a subset of patients from the nested case-control study (cases: n = 41, controls: n = 41): antibacterial drugs during hospital stay, number of antibacterial drugs in first 13 d, TPN during hospital stay and blood transfusions. IQR, interquartile range; NA, not applicable; TPN, total parenteral nutrition.

Table 2. Univariate and multivariable logistic regression analysis of factors associated with candidemia caused by *Candida krusei* among infants admitted to the neonatal unit at hospital A, Gauteng, South Africa, July 1–October 31, 2014*

Characteristics	Candidemia positive, no. in category/total no. (%)	Univariate analysis		Multivariable analysis	
		OR (95% CI)	p value	aOR (95% CI)	p value
Sex					
M	27/336 (58.7)	Reference		Reference	
F	19/249 (41.3)	0.9 (0.5–1.8)	0.857	0.9 (0.4–1.7)	0.671
Gestational age at birth, wks†					
<28	3/27 (6.7)	3.1 (0.7–12.1)	0.111	ND	ND
28–31	18/99 (40.0)	5.4 (2.3–12.6)	**<0.001**	ND	ND
32–36	15/209 (33.3)	1.9 (0.8–4.5)	0.141	ND	ND
≥37	9/229 (20.0)	Reference		ND	ND
Birthweight, g					
<1,000	8/44 (17.4)	8.7 (2.8–26.7)	**<0.001**	6.5 (1.9–21.6)	**0.002**
1,000–1,499	16/87 (34.8)	8.9 (3.3–23.5)	**<0.001**	6.1 (2.1–17.2)	**0.001**
1,500–1,999	11/120 (23.9)	4.0 (1.4–11.1)	**0.008**	3.4 (1.1–10.0)	**0.023**
2,000–2,499	5/93 (10.9)	2.2 (0.6–7.6)	0.193	2.5 (0.7–8.8)	0.139
≥2,500	6/242 (13.0)	Reference		Reference	
Necrotizing enterocolitis					
No	31/521 (67.4)	Reference		Reference	
Yes	15/65 (32.6)	4.8 (2.3–9.4)	**<0.001**	3.1 (1.4–6.7)	**0.005**
HIV exposed					
No	19/314 (54.3)	Reference		ND	ND
Yes	16/178 (45.7)	1.5 (0.7–3.1)	0.226	ND	ND
Month admitted					
July	21/152 (45.7)	8.9 (2.6–30.6)	**<0.001**	9.3 (2.5–33.1)	**0.001**
August	15/128 (32.6)	7.4 (2.0–26.2)	**0.002**	8.6 (2.3–31.5)	**0.001**
September	7/137 (15.2)	3.0 (0.7–11.9)	0.117	3.5 (0.8–14.4)	0.080
October	3/170 (6.5)	Reference		ND	ND
Underlying conditions					
Respiratory					
No	9/195 (19.6)	Reference		ND	ND
Yes	37/390 (80.4)	2.2 (1.0–4.6)	0.043	ND	ND
Cardiovascular					
No	25/387 (58.1)	Reference		ND	ND
Yes	18/149 (41.9)	2.0 (1.0–3.8)	0.035	ND	ND
Jaundice				ND	ND
No	17/313 (37.0)	Reference		ND	ND
Yes	29/274 (63.0)	2.1 (1.0–3.9)	0.023	ND	ND
Mother's antenatal care					
None	13/76 (28.2)	Reference		ND	ND
1–5 visits	26/392 (56.5)	0.3 (0.1–0.8)	**0.004**	ND	ND
6–10 visits	7/116 (15.2)	0.3 (0.1–0.9)	**0.018**	ND	ND
>10 visits	0/3 (0)	1		ND	ND
Mother's educational level					
<Grade 10	7/134 (16.7)	Reference		ND	ND
≥Grade 10	35/426 (83.3)	1.6 (0.7–3.8)	0.255	ND	ND

*Bold typeface indicates statistically significant values. Variables with a p value of <0.2 in the univariate analysis were added to a multivariable model and only variables that remained in the final model are displayed in the last 2 columns. Sex was included in the multivariable model as an *a priori* confounder. OR, odds ratio; aOR, adjusted OR; NA, not applicable; ND, no data (variables were not included in the final multivariable model).
†World Health Organization classification.

received 1 dose of fluconazole as prophylaxis on the day of surgery, 7 days before she had positive *C. krusei* culture results.

Among 40 case-patients for whom nutritional source data were available, 24 received TPN during their hospital stay; 19 had started TPN before the first positive culture for *C. krusei* (median 4 days, IQR 3–7 days). Having received TPN at any point during hospitalization (aOR 14.1, 95% CI 1.3–143.6) and having received furosemide after blood transfusion (aOR 12.0, 95% CI 1.1–139.5) were associated with having candidemia. The number of antibacterial drugs received was not associated with candidemia in the regression model. We found no difference in median duration of TPN between cases (6 days, IQR 4–9.5 days) and controls (3 days, IQR 2–11 days) (p = 0.6).

Evaluation of IPC Interventions

At the time of the audit, conducted almost 2 months after the first outbreak ended, the patient census was 12% above the unit's capacity. General cleanliness and handwashing facilities were adequate, but ventilation was poor. Isolation facilities were inadequate. A period of interrupted municipal water supply reportedly occurred in June 2014. Staff hand hygiene compliance was 76% (72 actions performed/95 opportunities). Although we isolated other bacterial and fungal species from surfaces, solutions, and staff

hand samples, we were unable to find a source of *C. krusei* in the environment.

Subsequent Outbreaks

During April–July 2015, another large outbreak consisting of 41 identified cases of *C. krusei* candidemia occurred (Figure 1, outbreak 2). Three cases of candidemia caused by *Candida pelliculosa* were retrospectively identified; these cases occurred during the second *C. krusei* outbreak in June 2015 (Figure 1, outbreak 3). Because this species had not been identified in the neonatal unit before, this cluster constituted an outbreak. Similarly, in February 2016, 7 cases of candidemia caused by *Candida* (*Cyberlindnera*) *fabianii* were detected (Figure 1, outbreak 4). In June 2016, another 8 cases of candidemia caused by *C. pelliculosa* occurred (Figure 1, outbreak 5). During January 2014–December 2015, a total of 298 cases of *K. pneumoniae* bacteremia occurred in the neonatal unit, with an overall incidence of 8/100 admissions. We retrospectively identified ≥3 outbreaks of *K. pneumoniae* bacteremia that appeared to closely precede or follow outbreaks of candidemia.

Discussion

We have documented a large outbreak of *C. krusei* candidemia in a neonatal unit, reporting 48 cases occurring during 4 months. Candidemia-positive infants had a lower gestational age and birthweight than did infants negative for candidemia. NEC, birthweight <1500 g, administration of TPN, and blood transfusion were identified as risk factors. An environmental source of the outbreak was not identified, but infection was likely transmitted among infants by contact with healthcare workers and fomites.

Nosocomial outbreaks caused by other *Candida* species (mostly *C. parapsilosis*) have been reported in NICU settings in the United States, Mexico, Taiwan, and Brazil (*5*,*11*–*13*,*19*,*20*). However, none of these outbreaks was as large as the outbreak we describe. The root causes of an outbreak spanning a 4-month period are likely multifactorial; delayed recognition of the outbreak and a slow response in implementing control measures were probable contributing factors, as were broader issues such as interrupted water supply, structural problems of the building that precluded appropriate isolation of infected infants, and overcrowding in the unit. Suboptimal IPC practices, however, are usually a major contributing factor in outbreaks of this nature. In an outbreak of *C. parapsilosis* among 3 patients in a Mexico NICU, molecular testing confirmed that the hands of a healthcare worker were a source of infection (*12*). A point source from a bottle of intravenous multielectrolyte solution was identified in a 7-case outbreak of *C. krusei* fungemia in a NICU in India (*21*). Often, the sources of such outbreaks are not found.

Of neonates infected with *C. krusei* candidemia in this outbreak, >50% had very low birthweights and were born earlier than neonates who tested negative for candidemia. This finding is in agreement with other reports highlighting prematurity and low birthweight as well-recognized risk factors for candidemia (*2*,*3*,*7*). Host factors such as an immature immune system and a fragile skin barrier predispose neonates to invasive infection. Disruption of the intestinal lining, as seen in conditions like NEC, may also facilitate invasion of *Candida* into the bloodstream (*8*,*10*). We found a clear association between NEC and candidemia in this outbreak; however, we could not establish the order of onset. We used the modified Bell's staging criteria (*22*) to diagnose and stage NEC in this unit, but the date of onset of symptoms or diagnosis was not routinely recorded. Therefore, we were unable to determine whether NEC preceded candidemia.

Administration of TPN likely represents a critical event during which *Candida* entered the bloodstream, in addition to suboptimal adherence to IPC protocols. The possibility of contaminated TPN could not be ruled out, but is unlikely in view of the propagated nature of the outbreak. Previous studies have found a longer duration of TPN to be associated with an increased risk for candidemia in older patient populations, hypothesized to be associated with prolonged exposure to glucose and lipid-rich solution, and subsequent *Candida* biofilm formation (*23*,*24*). We did not, however, find such an association, possibly because of the low number of patients who received TPN.

It is standard practice in this neonatal unit to administer a dose of furosemide after blood is administered. As with TPN, blood transfusion is not a risk factor in itself but more likely indicates exposure to an invasive procedure or a breach in IPC.

Source of the Outbreak

Although the source of this outbreak could not be definitively established, overcrowding and suboptimal IPC practices likely contributed to transmission of *C. krusei* (online Technical Appendix). This assumption is supported by the overlap of collection dates for the first positive specimen, suggesting a propagated outbreak, as well as subsequent outbreaks of bacterial and fungal pathogens in the unit, for which similar findings were documented. *C. krusei* has been isolated from healthcare workers' hands, hospital surfaces, and medical devices in previous studies (*25*,*26*). Although *C. krusei* was not isolated from the environment in our investigation, propagation on hands or fomites was the probable mode of transmission in this outbreak.

Limitations

This outbreak investigation had several limitations. First, delayed recognition and initiation of a response limited the

team's ability to intervene in a timely manner. The outbreak response team had limited jurisdiction to become involved without appropriate permission from the hospital authorities; such permission to conduct an investigation was not obtained until October 2014. Second, our secondary analysis of routine ward clinical data was limited by the variables originally collected. Although we obtained additional data from patient and laboratory records, the retrospective nature of data collection meant that data were inevitably incomplete. Nonetheless, we were able to assess associations between well-established risk factors and candidemia in both epidemiologic studies. Third, because the investigation involved a closed population with a limited number of appropriately matched controls admitted to the unit during the outbreak period, the case–control study was statistically underpowered to detect true differences between the 2 groups. In addition, because identification of laboratory-confirmed cases is dependent on specimen collection practices and blood cultures have low sensitivity as a diagnostic test method, we may have misclassified potential case-patients as controls and therefore underestimated associations between risk factors and the development of candidemia. Fourth, we compiled the IPC audit after the outbreak was over, thereby reducing the probability of isolating the causative pathogen in the environment or identifying the source of the outbreak. Information on the exact location and relocation of infants within the ward was not available. We were also not able to assess staff allocations and determine which staff members were allocated to care of infants. Although we assessed the action of performing hand hygiene, we did not measure the effectiveness of those actions. We did not evaluate invasive procedures, such as administration of TPN or blood transfusions and practices around central or peripheral intravenous line maintenance.

Recommendations Made after the Outbreak Investigation

As a result of the outbreak investigation, we re-emphasized adherence to IPC protocols at all opportunities and made further detailed recommendations (online Technical Appendix). Active surveillance for candidemia has continued at this hospital. Although there were recurrent outbreaks, response has improved.

Conclusions

Multiple factors contributed to this outbreak of *C. krusei* candidemia and the series of subsequent outbreaks, the most critical being suboptimal adherence to IPC practices at the point of patient care. This investigation highlights the need for early detection and timely interventions in outbreaks of this nature. We did not attempt to report the resolution of a single outbreak, because contributing factors have been and are still present in this neonatal unit. Like many healthcare facilities in low- and middle-income countries, hospital infrastructure and maintenance, access to reliable water and sanitation services, and broader healthcare system and socioeconomic issues contribute to a scenario ripe for outbreaks of this magnitude to occur. A proactive approach to prevention of neonatal sepsis, with a focus on IPC and antimicrobial stewardship, is needed in this unit.

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Large Outbreaks of Fungal and Bacterial Bloodstream Infections in a Neonatal Unit, South Africa, 2012–2016

Technical Appendix

Infection Prevention and Control Audit

Methods

We conducted an infection prevention and control audit to determine if suboptimal practices had contributed to the outbreak and to improve Infection Prevention and Control (IPC) knowledge and practices in the neonatal unit. The audit was done on 2 consecutive days in December 2014 and was comprised of 4 components: 1) cross-sectional ward audit by using an observational checklist; 2) observation of hand hygiene behavior by using a World Health Organization (WHO) tool (*1*); 3) completion of IPC knowledge and perception questionnaires by a convenient sample of healthcare workers; and 4) targeted environmental sampling, and submission of samples for fungal culture. We conducted a follow-up audit in March 2015.

The cross-sectional audit was conducted by using a checklist, which was based on an existing National Health Laboratory Service standard operating procedure for conducting IPC audits. The checklist included the following sections: patient care equipment and procedures, handwashing facilities, toilet facilities, sluice room and waste disposal, medication and infusates, feeds, common use products, staff tea room or kitchen facilities, isolation facilities, and general equipment and facilities. On 2 different days, 3 checklists were completed by independent observers. The observers completed the checklist by direct observations and questions posed to unit staff.

Observation of hand hygiene practice was performed using the WHO hand hygiene observation tool included in the My Five Moments for Hand Hygiene (*1*). Independent observers conducted 5 observation sessions lasting 20 minutes each, including 1 session during a

nightshift. Observers were assigned different times during the day of the audit and each observed 3–4 healthcare workers in the ward during performance of their routine duties. Opportunities for hand hygiene (actions which require either handwashing or using an alcohol-based hand rub) were recorded with a corresponding action (i.e., handwashing, hand rubbing or a missed opportunity).

A standardized WHO "Hand Hygiene Knowledge Questionnaire for Healthcare Workers" was administered to a convenient sample of staff on duty in the ward during the 2 audit days. A WHO hand hygiene perception survey was also administered to staff during the audit period (*1*).

Targeted environmental sampling was performed by applying sterile dry cotton swabs (without transport medium) to "high-touch surfaces" or visibly dirty areas in the unit (such as procedure trolleys, IV fluid stands, touchscreens and buttons of monitors, handles of incubator doors). We evaluated 14 areas in the unit. Hand imprints of staff, and imprints of doctors' stethoscopes and stethoscopes on the ward trolleys were taken. Samples of medication from different multi-dose vials were collected. Samples of common-use products were collected, such as total parenteral nutrition (TPN), a container of communal hand cream shared by staff and a tube of water-based lubricant. All samples were submitted to the National Institute for Communicable Diseases for fungal culture.

We compiled data from the IPC checklists using a structured questionnaire. Hand hygiene observation forms were analyzed and compliance calculations performed as recommended by the tool guidelines. Compliance (%) was calculated as the number of hand hygiene actions performed divided by the number of hand hygiene opportunities observed ×100 and stratified by professional category and indication. Completed hand hygiene knowledge and perception surveys were entered into an electronic database using Epi Info version 7 (Centers for Disease Control and Prevention, Atlanta, GA, USA) and described accordingly.

Results

At the time of the audit, conducted almost 2 months after the outbreak was over, there was noticeable commitment to improve IPC practices in the ward. General cleanliness and handwashing facilities appeared adequate. Handwashing facilities were adequate with elbow-

operated taps at sinks in each cubicle. Povidone iodine (7.5%) solution was available at every sink. Posters displaying hand hygiene techniques were visible on the walls. Examination gloves were available at the entrance to each cubicle and each incubator had a dedicated container of 70% alcohol-based hand rub.

A total of 62 infants (112% bed occupancy) were admitted in the neonatal unit on the day of the audit. We observed the unit to be hot and the ventilation system was not functional. Thermometers monitoring ambient temperature in the ward were not functional. The distance between incubators/cots ranged from 45–145 cm. Procedure trolleys and other surfaces were cleaned using a chlorine-based solution. Adequate personal protective equipment (PPE) was donned by majority of staff. A doctor was observed not wearing gloves or practicing hand hygiene between collecting blood samples from infants.

Several medications from multi-dose vials were used in the ward. A new needle and syringe were used every time the solution was drawn up for a new patient. Multi-dose vials were fitted with vial access devices.

The unit had a milk kitchen with separate “clean” and “unclean” areas. Cleanliness was good. Formula feeds were ordered from the central milk kitchen where it was prepared under sterile conditions and stored in a dedicated milk fridge in the milk kitchen. Donor milk was sterilized and stored in sterile containers in the milk fridge. Mothers expressed breast milk into plastic sterilized cups in a different ward. Expressed milk was not stored. TPN was ordered from the pharmacy and stored in the medication fridge. Sterile procedures were observed when administering the TPN and there was no sharing of feeds.

We observed 95 hand hygiene opportunities; 24 handwashing actions, and 48 hand rub opportunities. Overall, hand hygiene compliance was 76% (72 actions/95 opportunities), with professional nurses performing the best of the 4 observed staff categories (92%) and doctors performing the poorest (60%). Indication-related hand hygiene compliance was the best after touching patient surroundings (100%, n = 2), before touching a patient (82%, n = 22) and after touching a patient (82%, n = 18). The total follow-up hand hygiene compliance was 74%.

Thirteen healthcare workers were interviewed after training: 10 professional nurses (77%), 2 nursing students (15%), and 1 medical doctor (8%). IPC training had been attended by 92% (12/13) of the surveyed healthcare workers. Hand hygiene knowledge was scored at 58%.

No isolates resembling *C. krusei* were cultured from the environmental dry swabs and hand or stethoscope imprints. There was scanty bacterial and fungal growth from the multi-use vial and TPN specimen, but no growth from the water-based lubricant or hand cream samples.

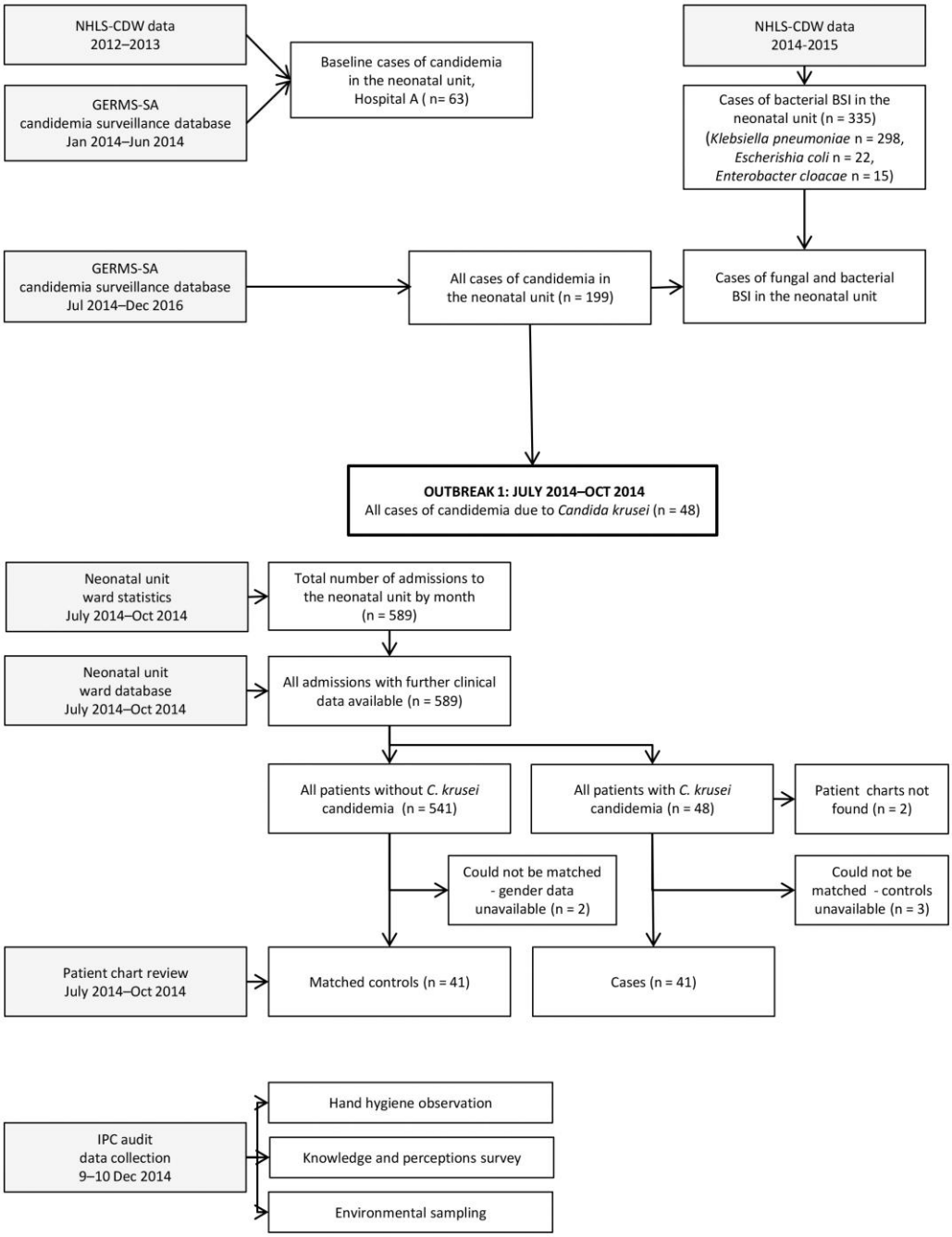
Reference

1. World Health Organization. WHO Guidelines on Hand Hygiene in Health Care—tools for evaluation and feedback 2009 [updated 2009; cited December 3, 2014]. http://www.who.int/gpsc/5may/tools/evaluation_feedback/en/

Technical Appendix Table. Recommendations made after the investigation of an outbreak of candidemia caused by *Candida krusei*, followed by a series of candidemia and bacteremia outbreaks in the neonatal unit of Hospital A, Gauteng, South Africa*

Area to be addressed	Short-term recommendations	Short-to-long-term recommendations
Infection prevention and control	Adherence to local, national and international IPC protocols Intensive training of staff on the importance of consistent and effective practice of IPC, in particular hand hygiene among doctors	Hospital IPC team to conduct more frequent hand hygiene observations and unannounced spot checks, with feedback to clinicians and neonatal unit staff IPC incentive programs and positive reinforcement
Clinical	Implementation of IPC care bundles, such as a central line-associated BSI (CLA-BSI) care bundle if central lines are used Judicious use of antimicrobial agents in the neonatal unit (both antifungal and antibacterial drugs) Clinicians reminded to maintain a high index of suspicion of candidemia in premature neonates with low birthweight and concomitant NEC and those exposed to invasive procedures	Development or adoption of a formal antimicrobial stewardship program
Administrative	Diversion of mothers in pre-term labor, to reduce referrals to the neonatal unit and therefore minimizing overcrowding (this was attempted, but due to a lack of district hospitals in the area that can share the patient load, diversion was achieved for a few hours only) Increasing the staff complement	Strengthening of neonatal services at surrounding hospitals
Infrastructural	Repair of ventilation system	Structural problems to be addressed to ensure more bed space Construction of an adequate isolation area

*IPC, infection prevention and control; BSI, bloodstream infections.



Technical Appendix Figure. Flowchart of sources and combination of data used in the investigation of an outbreak of candidemia caused by *Candida krusei* at Hospital A, Gauteng, South Africa, 2014–2016. Shaded boxes indicate data sources. NHLS-CDW, National Health Laboratory Service Corporate Data Warehouse; BSI, bloodstream infection; IPC, infection prevention and control.