OUTBREAK OF EXTENDED-SPECTRUM BETA-LACTAMASE–PRODUCING *KLEBSIELLA PNEUMONIAE* IN A NEONATAL INTENSIVE CARE UNIT LINKED TO ARTIFICIAL NAILS

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ABSTRACT

BACKGROUND: From April to June 2001, an outbreak of extended-spectrum beta-lactamase (ESBL)–producing *Klebsiella pneumoniae* infections was investigated in our neonatal intensive care unit.

METHODS: Cultures of the gastrointestinal tracts of patients, the hands of healthcare workers (HCWs), and the environment were performed to detect potential reservoirs for ESBL-producing *K. pneumoniae*. Strains of *K. pneumoniae* were typed by pulsed-field gel electrophoresis using *Xba*I. A case–control study was performed to determine risk factors for acquisition of the outbreak clone (clone A); cases were infants infected or colonized with clone A and controls (3 per case) were infants with negative surveillance cultures.

RESULTS: During the study period, 19 case-infants, of whom 13 were detected by surveillance cultures, harbored clone A. The overall attack rate for the outbreak strain was 45%; 9 of 19 infants presented with invasive disease (n = 6) or developed invasive disease (n = 3) after colonization was detected. Clone A was found on the hands of 2 HCWs, 1 of whom wore artificial nails, and on the designated stethoscope of a case-infant. Multiple logistic regression analysis revealed that length of stay per day (odds ratio [OR], 1.05; 95% confidence interval [CI_{95}], 1.02 to 1.09) and exposure to the HCW wearing artificial fingernails (OR, 7.87; CI_{95}, 1.75 to 35.36) were associated with infection or colonization with clone A.

CONCLUSION: Short, well-groomed, natural nails should be mandatory for HCWs with direct patient contact (*Infect Control Hosp Epidemiol* 2004;25:210-215).

Klebsiella pneumoniae is a well-described healthcare-associated pathogen and a cause of sepsis, urinary tract infections, pneumonia, and soft tissue infections in patients in the neonatal intensive care unit (NICU).[1,2] The emergence of extended-spectrum beta-lactamase (ESBL) production in *K. pneumoniae* was first reported in 1983,[3] but outbreaks associated with increased morbidity and mortality have been noted with increasing frequency in intensive care units (ICUs), including NICUs.[4] The most common reservoir for this pathogen appears to be the gastrointestinal tract of colonized patients,[5] and patient-to-patient transmission is facilitated by transient or persistent hand carriage of healthcare workers (HCWs).[6] Strategies to control outbreaks have included antibiotic control policies; cohorting infected and colonized patients; transmission precautions; surveillance cultures of patients, the environment, and HCWs; and improving hand hygiene.[7-10]

In April 2001, routine surveillance by the Department of Epidemiology staff of the clinical microbiology laboratory reports revealed an increase in ESBL-producing *K. pneumoniae* infections in our level III–IV, 45-bed NICU. The infection control strategies implemented to contain this outbreak and a case–control study conducted to determine possible risk factors for acquisition of ESBL-producing *K. pneumoniae* in this NICU population are described.

METHODS

Identification of the Outbreak

In April 2001, routine surveillance of computerized microbiology laboratory reports by the Department of Epidemiology indicated an increase in the number of infections caused by ESBL-producing *K. pneumoniae* in the level III–IV NICU of a university-affiliated children's hospital in New York City. An incident case was defined as an infant infected or colonized with ESBL-producing *K. pneumoniae*, and included cases identified by surveillance cultures. Incidence was expressed as the number of infected infants per 1,000 patient-days. Approval was obtained from the institutional review board to report on this outbreak.

Surveillance Cultures of Infants, the Environment, and HCWs

Surveillance cultures of the gastrointestinal tracts of all hospitalized infants were performed by obtaining

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rectal swabs. Surveillance efforts were performed once in May, weekly in June, and biweekly in July and August until August 13. Environmental cultures were performed using a swab premoistened with sterile saline to identify other potential reservoirs for ESBL-producing *K. pneumoniae*. Cultured sites included respiratory therapy equipment, sinks, tap water, designated stethoscopes, countertops, a glucometer, computer keyboards, telephones, doorknobs, diaper scales, and a breast milk pump.

Due to the ongoing transmission of ESBL-producing *K. pneumoniae* noted in mid-June, despite establishing a cohort of infected or colonized infants, all HCWs who had direct contact with infants hospitalized in the NICU from May 21 to June 14, 2001, had cultures for ESBL-producing *K. pneumoniae* during the last 2 weeks of June. Hands were cultured using a modification of the glove juice method.[11] Both hands were sequentially placed in a polyethylene bag containing 50 mL of sampling solution prepared in the microbiology laboratory (75 mM phosphate buffer, pH 7.9, with 3% polysorbate 80 and 0.1% Triton X-100) and each was thoroughly massaged by an infection control practitioner for 30 seconds through the wall of the bag. The hands of HCWs were inspected for artificial nails, nail polish, and cracked or inflamed nail beds. Specimens were processed on arrival in the microbiology laboratory. MacConkey and blood agars were inoculated and incubated at 35°C, and were examined for growth at 24 and 48 hours. Isolates were identified and stored at -70°C for further analyses.

The MicroScan semiautomated system (Dade Behring, Deerfield, IL) was used to identify isolates and to perform antimicrobial susceptibility testing. Isolates were screened for ESBL production by testing for resistance to cefpodoxime (1 µg/mL). If resistance was detected, further confirmation of ESBL production was obtained using E-test strips (AB Biodisk, Solna, Sweden) of cefotaxime and ceftazidime alone and in combination with clavulanic acid.[12] ESBL production was confirmed if the minimal inhibitory concentration of either cefotaxime or ceftazidime was decreased by 3 or more twofold dilutions with the addition of clavulanic acid.

Molecular Typing

Genomic typing of *K. pneumoniae* strains isolated from patients, HCWs, and the environment was performed by pulsed-field gel electrophoresis (PFGE) to determine the extent of clonal spread. Genomic DNA was prepared in agarose plugs and incubated with a mixture of 0.5 M EDTA, 1% wt/vol sarkosyl, and 20 mg/mL of proteinase K (Sigma, St. Louis, MO) for 18 hours at 55°C. Protein digestion products were removed by washing the plugs 5 times for 30 minutes per wash in tris–EDTA at room temperature. One plug of DNA was incubated overnight with restriction endonuclease *Xba*I (New England Biolabs, Beverly, MA). The DNA restriction fragments were separated by PFGE using a CHEF-MAPPER system (Bio-Rad Laboratories, Hercules, CA). Pulse time was ramped from 2.2 to 54.2 seconds for 22 hours.

Interpretation of the PFGE banding patterns followed established guidelines[13] (ie, isolates were considered indistinguishable if they shared every band, closely related if they differed by 1 to 3 bands, possibly related if they differed by 4 to 6 bands, and unrelated if a difference of more than 7 bands was observed). Strain types (clones) were indicated by capital letters.

Case–Control Study

A case–control study was performed to determine possible risk factors for acquisition of the outbreak clone of ESBL-producing *K. pneumoniae*. Cases were defined as infants who had a positive culture, including a surveillance culture, for the outbreak clone, identified from April to June 2001. Controls were infants who had negative surveillance cultures on admission to the NICU within 1 week of the respective case. When possible, three controls per case were selected. If more than three eligible controls were available for a given case, the controls with admission dates closest to the admission date of the case were selected. For cases, risk factors were assessed for the 2 weeks prior to case status. For controls, risk factors were assessed for the entire hospital stay or until the last negative surveillance culture was performed.

The infants' computerized medical records (Eclypsis Corp., Delray Beach, FL) and WebCIS (Clinical Information System, New York Presbyterian Healthcare; and the Department of Medical Informatics, Columbia University, New York, NY) were reviewed for possible risk factors. Data on demographics, the mode of delivery, bed location, medications, surgical procedures, instrumentation including central venous catheters, length of stay (LOS), and exposure to individual nurses were collected. For case-infants, LOS was defined as the duration of hospitalization prior to the first positive culture for ESBL-producing *K. pneumoniae*. For control-infants, LOS was the duration of hospitalization until discharge or until the last negative surveillance culture. To assess the risk of exposure to individual nurses, the nursing assignments from May 21 to June 14, 2001, were reviewed for case-infants and control-infants. This interval was chosen because, despite cohorting, transmission continued during this time.

Infection Control Measures

In addition to surveillance cultures, numerous infection control strategies were implemented to control the outbreak. Three cohorts of infants were established in May. In the first, all infants infected or colonized with ESBL-producing *K. pneumoniae* were placed on contact precautions until hospital discharge in a separate nursery. A group of designated nurses cared for these infants. A second cohort of infants with exposure to case-infants, but with negative surveillance cultures, was cared for by another group of designated nurses. A third cohort of newly admitted infants was cared for in a separate room

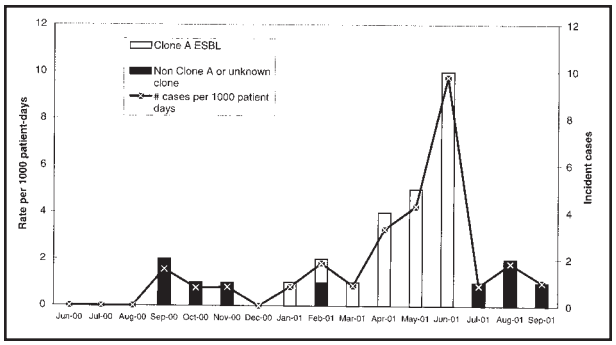

FIGURE 1. The incidence rate of extended-spectrum beta-lactamase (ESBL)–producing *Klebsiella pneumoniae* in the neonatal intensive care unit from June 2000 to September 2001. The incidence of infection per 1,000 patient-days (depicted in the left-sided y axis) peaked at 4.1 cases in April 2001. The incidence includes infants initially colonized with *K. pneumoniae* who developed active infection. The number of incident cases (either infection or colonization) is shown (depicted in the right-sided y axis). In all, 30 of 32 strains were available for typing; 2 strains from 2000 were unavailable for typing. Strains identified as clone A versus non–clone A or unknown clone are indicated. Surveillance efforts were performed on May 7, weekly in June, and biweekly in July and August until August 13, 2001.

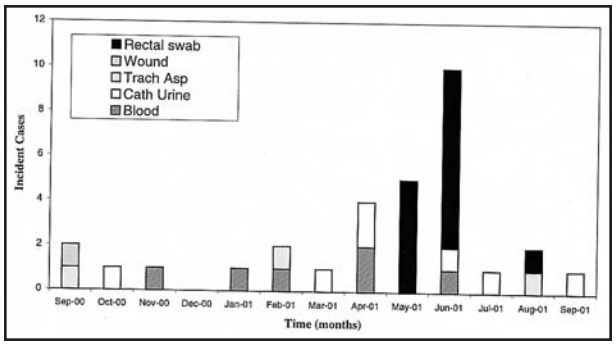

FIGURE 2. Clinical cultures versus surveillance cultures for extended-spectrum beta-lactamase–producing *Klebsiella pneumoniae* in the neonatal intensive care unit from September 2000 to September 2001. The first culture by body site from each infected or colonized infant is shown. Trach Asp = tracheal aspirates; Cath Urine = urinary tract culture obtained by catheterization.

by another group of designated nurses. Separate physician teams for the first and the third cohorts were maintained as well. Multidisciplinary meetings were held twice weekly to discuss the ongoing investigation and control measures, hand hygiene using 2% chlorhexidine gluconate was emphasized at staff meetings, the restriction of third-generation cephalosporins was enforced, and the use of imipenem for infants with suspected late-onset sepsis was suggested. Specimens for rectal and respiratory tract surveillance cultures were obtained from infants at least 48 hours old who had been transferred from other NICUs to detect possible introduction of ESBL-producing *K. pneumoniae* from a referring NICU. A cost analysis of this outbreak has been reported elsewhere.[14]

Statistical Analysis

Abstracted data were collected using Microsoft Access (Microsoft Corp., Redmond, WA). Univariate analysis of potential risk factors was performed using EpiInfo 2000 software (version 6.01; Centers for Disease Control and Prevention, Atlanta, GA). The Wilcoxon signed rank test was performed using the SPSS statistical system (version 10.0 for Windows; SPSS, Inc., Chicago, IL) to compare the LOS for case-infants versus control-infants. Multivariate analysis of risk factors found significant in the univariate analysis ($P < .1$) was performed using logistic regression analysis (SAS, version 8 for Windows; SAS Institute, Inc., Cary, NC).

RESULTS

Incidence of ESBL-Producing K. pneumoniae

The incidence of infection or colonization with ESBL-producing *K. pneumoniae* per 1,000 patient-days is shown in Figure 1. From September 2000 to September 2001, 31 infants were infected or colonized with this organism, of whom 19 (61%) were identified from April to June 2001. Seventeen of 31 (55%) were diagnosed by cultures performed for clinical purposes: blood (n = 6), urinary tract (n = 7), tracheal aspirates (n = 3), and abdominal wound (n = 1) (Fig. 2). The remaining 14 (45%) were detected by surveillance cultures in response to this outbreak.

From January to June 2001, 19 case-infants were infected or colonized with the outbreak clone, designated clone A by PFGE. The last case-infant was discharged from the NICU on November 18, 2001. In addition, one infant had a bloodstream infection caused by clone C in February 2001, and 4 infants (one in September 2000, July 2001, August 2001, and September 2001) harbored clone I.

The outbreak strain, designated clone A by PFGE (Fig. 3), caused substantial morbidity. The overall attack rate was 45%; 9 of 19 infants presented with invasive disease (n = 6) or developed invasive disease (n = 3) after colonization was detected. Overall, there were 6 cases of sepsis including 3 that developed in infants who had previously been treated for urinary tract infections. Two infants with bloodstream infections had other foci of infection including endophthalmitis and osteomyelitis. One additional infant was admitted to the NICU in March 2001, was transferred to the pediatric ICU in April, and developed bacteremia in the pediatric ICU with clone A. However, this infant was not considered an incident case or analyzed in the case–control study.

Surveillance Cultures

The surveillance efforts are listed in Table 1. Of the 158 HCWs for whom cultures were performed, 2 (1.3%) had positive cultures for clone A. Repeat hand cultures of these 2 HCWs were positive, but cultures of the gastrointestinal tract (specimens obtained by rectal swab) and urine (specimens obtained by clean catch) of these HCWs were negative for ESBL-producing *K. pneumoniae*. One of these HCWs (RN 53) wore artificial nails and the other

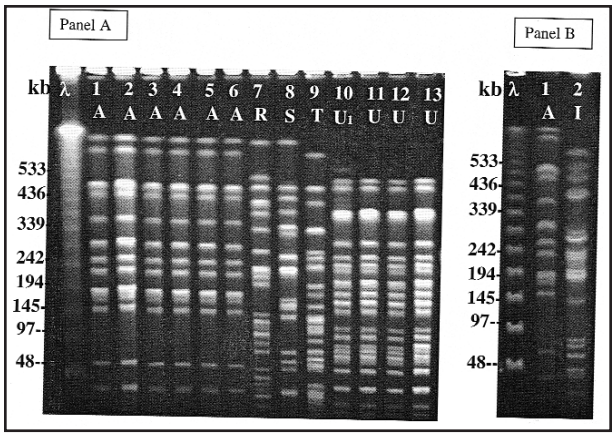

FIGURE 3. Results of pulsed-field gel electrophoresis of *Klebsiella pneumoniae* isolated in the neonatal intensive care unit. The lanes in panel A are as follows: λ = ladder DNA size marker; 1 = extended-spectrum beta-lactamase (ESBL)–producing *K. pneumoniae* isolate from the urine of infant 1; 2 to 4 = ESBL-producing *K. pneumoniae* isolates from the blood of infant 1; 5 = ESBL-producing *K. pneumoniae* isolate from the hands of RN 53; 6 = ESBL-producing *K. pneumoniae* isolate from the tracheal aspirate of infant 2 (1 to 6 are clone A); 7 = ESBL-producing *K. pneumoniae* isolate from the urine of infant 3; 8 to 13 = non–ESBL-producing *K. pneumoniae* isolates from the gastrointestinal tract surveillance cultures of 5 different infants; and 10 to 13 = isolates from a set of triplets, suggesting maternal transmission. The lanes in panel B are as follows: λ = ladder DNA size marker; 1 = ESBL-producing *K. pneumoniae* isolate, clone A; and 2 = ESBL-producing *K. pneumoniae* isolate, clone I.

(RN 23) had professional manicures weekly and a nail length of more than 1/4 in (Fig. 3). Both HCWs were furloughed in mid-June for approximately 2 weeks. RN 53 removed her artificial nails and RN 23 cut her nails to 1/8 in and subsequent hand cultures from both were negative for *K. pneumoniae*. Of the 30 environmental cultures performed, only the designated stethoscope of a case-infant was contaminated with the outbreak strain.

Risk Factors for Acquisition of ESBL-Producing K. pneumoniae

A case–control study was performed to determine possible risk factors for acquisition of the outbreak strain of ESBL-producing *K. pneumoniae*. The univariate analysis for risk factors is detailed in Table 2. Very low birth weight (less than 1,500 g), intubation, use of central venous catheters, and use of intralipids were associated with acquisition of clone A. Case-infants had a longer LOS than did control-infants (42.5 vs 14.4 days). In contrast, transfer from another institution; surgical procedures; placement of chest tubes; use of umbilical artery catheters; treatment with ampicillin, gentamicin, amikacin, or piperacillin/tazobactam; NICU bed location; and type of enteral feeding were not risk factors for ESBL-producing *K. pneumoniae* infection or colonization (data not shown). Case status was associated with care by RN 53 (odds ratio [OR], 6.24; 95% confidence interval [CI_{95}], 1.41 to 28.81) but not by RN 23 (OR, 2.29; CI_{95}, 0.46 to 11.13). Multivariate analysis revealed that LOS (OR, 1.05 per day; CI_{95}, 1.02 to 1.09) and exposure to RN 53 (OR, 7.87; CI_{95}, 1.75 to 35.36) remained risk factors for acquisition of clone A.

TABLE 1
SURVEILLANCE CULTURES FOR EXTENDED-SPECTRUM BETA-LACTAMASE–PRODUCING *KLEBSIELLA PNEUMONIAE* IN THE NEONATAL INTENSIVE CARE UNIT FROM MAY TO AUGUST 2001

Type of Surveillance Culture	No. Performed	No. Positive for Clone A
Rectal swabs from infants*	422	37 (8.8%)
Healthcare workers' hands	158	2 (1.3%)
Environment	30	1 (3.3%)

*Infants may have had more than one surveillance culture.

TABLE 2
UNIVARIATE ANALYSIS OF RISK FACTORS FOR ACQUISITION OF EXTENDED-SPECTRUM BETA-LACTAMASE–PRODUCING *KLEBSIELLA PNEUMONIAE* IN PATIENTS IN THE NEONATAL INTENSIVE CARE UNIT, APRIL TO JUNE 2001

Risk Factor	Cases (n = 19)	Controls (n = 54)	OR	CI_{95}	*P*
Birth weight, g					
< 1,500	10	15	2.89	0.87–9.79	.049
⩾ 1,500	9	39			
Male	10	27	1.11	0.35–3.58	.844
Gestational age, wk					
⩽ 32	11	19	2.53	0.77–8.46	.083
> 32	8	35			
Vaginal delivery	9	30	1.39	0.43–4.50	.538
Length of stay, d*	42.5	14.4			.003
Intubation	12	17	3.73	1.11–12.94	.015
Central venous catheters†	15	22	5.45	1.42–22.70	.004
Use of cefotaxime	1	6	0.44	0.02–4.25	.456
Hyperalimentation	18	45	3.60	0.41–81.33	.213
Intralipids	18	35	9.77	1.20–211.37	.011
Exposure to RN 53	7	5	6.24	1.41–28.81	.01
Exposure to RN 23	4	6	2.29	0.46–11.13	.43

OR = odds ratio; CI_{95} = 95% confidence interval; RN = registered nurse.
*Student's *t* test.
†Central venous catheters include umbilical venous catheters, percutaneously inserted central venous catheters, and indwelling central venous catheters.

DISCUSSION

K. pneumoniae causes approximately 4% of cases of late-onset sepsis in neonates with very low birth weights and approximately 6% of overall infections.[15-17] Common sites of colonization with *Klebsiella* species are the gastrointestinal tract, eyes, respiratory tract, and genitourinary tract.[15,18] As noted in our study, asymptomatic, colonized patients, the contaminated environment, or both can serve as reservoirs for this pathogen, which is then

spread by HCW hand carriage.[19] There have been numerous studies, largely performed on adult patients, describing the epidemiology and risk factors associated with colonization and infection with ESBL-producing organisms.[20] Risk factors have included nursing home residence,[21] central venous catheterization,[21] gastrointestinal tract colonization with ESBL-producing organisms,[22] duration of prior antibiotic use,[23] and mechanical ventilation.[24] In previous studies in NICU populations, LOS,[25] low birth weight[25,26] and younger gestational age,[25] colonization with an ESBL-producing organism,[26] central venous catheters,[26] and being female[26] were risk factors for colonization with ESBL-producing *Klebsiella* species. We used multivariate analysis and demonstrated that LOS was a risk factor for infection or colonization with ESBL-producing *K. pneumoniae* in a NICU population, suggesting that low birth weight and young gestational age were confounded by LOS. Furthermore, colonization with ESBL-producing *K. pneumoniae* can persist and be associated with infection after NICU discharge.[25]

In this study, acquisition of the outbreak strain was significantly associated with exposure to a nurse wearing artificial nails. It has been increasingly appreciated that artificial nails worn by HCWs can contribute to healthcare-associated infections particularly in the ICU population. Compared with natural nails, artificial nails have higher rates of colonization with gram-negative flora and yeast.[27-30] Reports have linked artificial nails to healthcare-associated infections with *Pseudomonas aeruginosa*,[31-33] *Serratia marcescens,*[34] and *Candida albicans*.[35] Guidelines from the Healthcare Infection Control Practices Advisory Committee for hand hygiene grade the elimination of artificial nails from HCWs with direct patient contact as "Category 1A" (ie, a strong recommendation, supported by well-designed experimental, clinical, or epidemiologic studies).[36]

This study had several limitations. The use of rectal surveillance cultures to detect colonization and the inclusion of such infants in the case definition resulted in more cases being detected than if this had not been done. Nevertheless, relatively few cases were available for the case–control study. Suitable controls were unavailable for one case-infant. We did not establish the relationship between colonization and invasive disease with certainty in all infants. Not all case-infants were cared for by RN 53, and hence other possible modes of transmission such as transient hand carriage by other HCWs or undetected environmental contamination should be considered. Finally, other risk factors such as overcrowding and understaffing were not addressed.

The gastrointestinal tracts of hospitalized patients can serve as an important reservoir for ESBL-producing *K. pneumoniae*. Patient-to-patient transmission can occur via hand carriage by HCWs, particularly those wearing artificial nails. As a result of this investigation, an institution-wide ban on the wearing of artificial nails was implemented; HCWs with direct patient contact must have well-groomed, short, natural nails.[37]

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