# OUTBREAK OF *ENTEROBACTER CLOACAE* RELATED TO UNDERSTAFFING, OVERCROWDING, AND POOR HYGIENE PRACTICES

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## ABSTRACT

**OBJECTIVE:** To determine the cause and mode of transmission of a cluster of infections due to *Enterobacter cloacae.*

**DESIGN AND SETTING:** Retrospective cohort study in a neonatal intensive-care unit (NICU) from December 1996 to January 1997; environmental and laboratory investigations.

**SUBJECTS:** 60 infants hospitalized in the NICU during the outbreak period.

**MAIN OUTCOME MEASURES:** Odds ratios (OR) linking *E cloacae* colonization or infection and various exposures. All available *E cloacae* isolates were typed and characterized by contour-clamped homogenous electric-field electrophoresis to confirm possible cross-transmission.

**RESULTS:** Of eight case-patients, two had bacteremia; one, pneumonia; one, soft-tissue infection; and four, respiratory colonization. Infants weighing <2,000 g and born before week 33 of gestation were more likely to become cases ($P$<.001). Multivariate analysis indicated that the use of multidose vials was independently associated with *E cloacae* carriage (OR, 16.3; 95% confidence interval [$CI_{95}$], 1.8-∞; $P$=.011). Molecular studies demonstrated three epidemic clones. Cross-transmission was facilitated by understaffing and overcrowding (up to 25 neonates in a unit designed for 15), with an increased risk of *E cloacae* carriage during the outbreak compared to periods without understaffing and overcrowding (relative risk, 5.97; $CI_{95}$, 2.2-16.4). Concurrent observation of healthcare worker (HCW) handwashing practices indicated poor compliance. The outbreak was terminated after decrease of work load, increase of hand antisepsis, and reinforcement of single-dose medication.

**CONCLUSIONS:** Several factors caused and aggravated this outbreak: (1) introduction of *E cloacae* into the NICU, likely by two previously colonized infants; (2) further transmission by HCWs' hands, facilitated by substantial overcrowding and understaffing in the unit; (3) possible contamination of multidose vials with *E cloacae.* Overcrowding and understaffing in periods of increased work load may result in outbreaks of nosocomial infections and should be avoided (*Infect Control Hosp Epidemiol* 1999;20:598-603).

In recent years, *Enterobacter cloacae* has emerged as an important nosocomial pathogen.[1] Outbreaks of infection have been reported in neonatal intensive-care units (NICU),[2] surgical wards,[3] and burn units,[4] caused by cross-transmission,[4,5] contaminated intravenous fluids[6] or total parenteral nutrition solutions,[7] and other contaminated pharmaceutical products or medical equipment.[8]

Common endogenous reservoirs for *E cloacae* include the gastrointestinal tract in healthy adults and, in sick patients, the urinary and respiratory tract, as well as surgical-site and burn wounds.[9] *E cloacae* is isolated from feces of neonates with a frequency varying from 10% to 70%.[2,10-12] Bacteremia due to *E cloacae* has become an important nosocomial infection in neonatal and pediatric wards, accounting for approximately 1 episode per 1,000 admissions and causing substantial illness, especially among immunocompromised infants.[13,14]

On January 20, 1997, an NICU staff physician at the University Hospitals of Geneva (HUG) notified the Infection Control Program of a possible cluster of infections due to *E cloacae* in preterm neonates. To investigate the outbreak, we conducted (1) a cohort study to identify risk factors for nosocomial *E cloacae* infection or colonization; (2) environmental cultures and typing of isolates by contour-clamped homogeneous electric field (CHEF) electrophoresis to establish epidemiological links; and (3) an assessment of infection control procedures to stop the outbreak.

## METHODS

### *Setting*

The HUG is a 1,500-bed healthcare center providing primary and tertiary care for Geneva, Switzerland, and the surrounding areas (population, 800,000). The NICU is a 15-

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bed unit with 350 admissions per year, including approximately 100 preterm infants (<33 gestational weeks). The unit is composed of a 7-bed critical-care facility and an 8-bed intermediate-care nursery that accounted for 4,566 and 2,411 patient-days in 1996, respectively. Premature neonates with severe organ dysfunction are transferred to the 8-bed pediatric intensive-care unit (PICU) for life-support treatment and are returned to the NICU after stabilization of medical conditions. First-line therapy for suspected sepsis is amoxicillin plus gentamicin, pending microbiological results.

### *Case Definition and Diagnostic Criteria*

A case was defined as an infant admitted to the NICU between December 11, 1996, and January 20, 1997, who had *E cloacae* identified in a clinical isolate from any site. Eight preterm infants born between October 10, 1996, and January 6, 1997, were identified as case-infants by review of microbiology results, nursing charts, and medical records. The remaining 52 infants hospitalized in the NICU during the outbreak period constituted the cohort of noncase patients.

Criteria for infections were as defined by the Centers for Disease Control (CDC).[15] Characteristics of the infection, including site, duration of symptoms, and outcome, were noted. Isolates from clinically indicated specimens not associated with infection were classified as colonization.

### *Epidemiological Studies*

Among 52 noncases, 29 had stayed at least 72 hours in the unit and were selected as controls. The medical records of these 29 control-patients and of 8 case-patients were reviewed for demographic and clinical data, including gestational age, birth weight, gender, length of stay in the NICU until discharge or detection of *E cloacae*, exposure to indwelling devices, medication, nutrition, length of stay in the incubator, and antibiotic use.

Additional information was collected concerning the occupancy rate, and the real and required staffing of the NICU as measured by the Project Research in Nursing (PRN) system, which is a Canadian information system for managing nursing staff.[16,17] The instrument lists 214 indicators or tasks that nurses complete on behalf of patients during a 24-hour period and has had extensive testing, with excellent content and construct validity.[18,19]

Moreover, during 2 weeks in December 1996, an observational study was conducted throughout the institution to monitor handwashing practices of healthcare workers (HCWs). Details of the methodology and definitions have been published recently.[20]

### *Patient and Environmental Cultures*

Samples from the throat, rectum, and umbilical region were obtained on January 23, 1997, from all 21 infants present in the NICU. Incubators, disinfectants, soaps, sinks, hand basins, parenteral nutrition solutions, different topical medications, and open vials of different pharmaceutics also were sampled. Standard methods and media were used for isolation of organisms. Isolates were identified using the API 20 E system (bioMérieux, Marcy l'Etoile, France). Susceptibility testing for 14 selected antibiotics was performed by the disk-diffusion method on Mueller-Hinton agar using National Committee for Clinical Laboratory Standards endpoints for susceptibility.[21]

All available *E cloacae* isolates were typed and characterized by CHEF electrophoresis, a modification of the pulsed-field gel electrophoresis method.[22,23] Epidemiologically linked strains were considered genotypically different if they differed by at least three bands, according to the CHEF patterns.[24]

### *Infection Control Measures*

Infection control measures in the unit were reviewed and personnel urged to comply with these measures. In particular, optimal handwashing practices were reinforced. Cohorting of infected and colonized patients and work reorganization were proposed and performed in part.

### *Statistical Analysis*

The association between *E cloacae* infection or colonization and various risk factors was compared between case and noncase patients by means of the chi-square test for proportions or Fisher's Exact Test for expected cell frequencies less than five. The crude magnitude of the association between risk factors and disease was measured with the odds ratio (OR). Because in some instances a possible risk factor was not present among controls, a logistic regression model based on Fisher's Exact method was used to compute the estimated OR and its 95% lower limit, using LogXact-Turbo (CYTEL Inc, Cambridge, MA).[25] A similar multivariate logistic regression model was used to measure the independent effect of risk factors statistically associated with the disease in the univariate analysis. Variables included in the univariate analysis were gender, birth weight, gestational age, length of stay in the NICU, and important exposure factors such as indwelling devices, medication, or nutrition. Variables with a $P$ value less than .10 were entered into the multivariable analysis: exposure to central venous catheters, multidose vials, and birth weight. The explanatory variable "gestational age" was highly colinear with birth weight but had a weaker relationship with the outcome variable and therefore was not considered for inclusion in the model. Statistical analysis was performed using Epi Info (version 6.0; CDC, Atlanta, GA) and SPSS software (SPSS Inc, Chicago, IL).

## RESULTS

### *Outbreak Description*

Eight cases met the case definition during the outbreak period (attack rate, 13%). Figure 1 shows the number of NICU infants colonized or infected with *E cloacae* between April 1996 and March 1997. The incidence of *E cloacae* detection in this unit markedly increased during December 1996 and January 1997, to 5.73 episodes per 1,000 patient-days, compared to 0.86 episodes per 1,000 patient-days during the 23 preceding months (January 1995 to November 1996).

The peak of the outbreak occurred between January 12 and 16, 1997, with two cases of bacteremia and one infant with *E cloacae* tracheal colonization. Four neonates

TABLE
PATIENT CHARACTERISTICS AND INDIVIDUAL RISK FACTORS FOR *ENTEROBACTER CLOACAE* COLONIZATION OR INFECTION, NEONATAL INTENSIVE-CARE UNIT, GENEVA UNIVERSITY HOSPITALS, DECEMBER 1996 TO JANUARY 1997

| Characteristics | Cases (%) | Noncases (%) | OR | $CI_{95}$ |
|---|---|---|---|---|
| Number | 8 | 29 | | |
| Male gender | 5 (63) | 19 (66) | 0.88 | 0.17-4.45 |
| Birth weight <2,000 g | 7 (88) | 11 (38) | 11.45 | 1.23-106.1 |
| Gestational age (w) | | | | |
| ⩾36 | 0 | 8 (28) | Reference | |
| 31-35 | 2 (25) | 15 (52) | 1.17 | 0.09-∞ |
| ⩽30 | 6 (75) | 6 (21) | 8.76 | 1.02-∞ |
| LOS* in NICU >15 d | 6 (75) | 13 (45) | 3.57 | 0.52-41.9 |
| Important exposure factors | | | | |
| Central venous catheter | 4 (50) | 0 | 29.25 | 3.20-∞ |
| Umbilical catheter | 1 (12) | 3 (10) | 1.24 | 0.03-18.01 |
| Peripheral line | 5 (63) | 22 (76) | 0.53 | 0.10-2.80 |
| Nasogastric tube | 6 (75) | 10 (35) | 5.42 | 0.78-64.6 |
| Intubation >7 d | 3 (38) | 4 (14) | 3.75 | 0.63-22.2 |
| CPAP | 6 (75) | 11 (38) | 4.91 | 0.84-28.7 |
| Incubator >7 d | 7 (88) | 13 (44) | 8.18 | 0.87-412.0 |
| Amoxicillin-gentamicin therapy prior to *Enterobacter cloacae* isolation | 7 (88) | 19 (66) | 3.68 | 0.39-34.3 |
| Multidose vials† | 8(100) | 6 (21) | 34.65 | 4.59-∞ |
| Breast feeding | 4 (50) | 21 (72) | 0.38 | 0.08-1.9 |

Abbreviations: $CI_{95}$, 95% confidence interval; CPAP, continuous positive airway pressure; LOS, length of stay; NICU, neonatal intensive-care unit; OR, odds ratio.
* LOS refers to length of stay in NICU from admission to *Enterobacter cloacae* isolation among cases or until discharge for noncases.
† Multidose vials refer to the use of caffeine and budesonide inhalation spray from such vials.

had respiratory colonization or infection, and one had soft-tissue infection with *E cloacae*. One case-infant died due to necrotizing enterocolitis, but this death was not directly attributed to *E cloacae* infection. All infected patients received a third-generation cephalosporin for treatment without changing the standard antibiotic regimen for confirmed gram-negative infections in this unit.

### *Epidemiological Investigation*

Comparison of characteristics of infants colonized or infected with *E cloacae* to those of 29 noncases indicated that infants with *E cloacae* isolation were of lower birth weight (mean±SD, 1,014±404 g vs 2,224±853 g; $P$=.001), were more premature (mean gestational age±SD; 27.6±2.4 weeks vs 34.1±3.9 weeks; $P$=.005), and had stayed longer in the NICU (mean±SD, 45±39 days vs 21±18 days; $P$=.13). Case-infants had a mean length of stay of 22 (±20) days from admission to *E cloacae* isolation. They required more invasive procedures and devices, and were exposed more often to multidose vials of caffeine and budesonide inhalation spray compared to noncase patients (Table). Multivariate logistic regression analysis identified only the use of multidose vials as an independent risk factor for *E cloacae* isolation (OR, 16.3; 95% confidence interval [$CI_{95}$], 1.8-∞; $P$=.011).

Observation of NICU handwashing practices on December 18, 1996, showed a 37% noncompliance rate with handwashing or hand disinfection recommendations within the unit. Hand washing or antisepsis was not systematically performed between patient contacts. Strikingly, 75% of the staff did not wash hands before contact with an infant's intravenous (IV) line. As documented by two follow-up studies in April and June 1997, noncompliance decreased to 25% after reinforcement of handwashing practices. Importantly, noncompliance with hand antisepsis before contact with an IV line decreased to 30%.

### *Microbiological Investigation*

No sample yielded *E cloacae* from the initial, extensive environmental sampling performed January 23, 1997, and no exogenous source for the outbreak could be identified.

A total of 20 isolates of *E cloacae* from 16 patients recovered between October 1995 and February 1997 were available for genotypic characterization. In seven of the eight case-patients, *E cloacae* isolates were recovered from stored clinical specimens (3) or rectal swabs (4; sampled on January 23 to substitute for discarded clinical specimens). No *E cloacae* isolate was available for one deceased case-patient for whom the clinical isolate had been discarded before the investigation.

Antibiograms of the *E cloacae* isolates showed similar susceptibility patterns, without resistance to third-generation cephalosporins. According to molecular typing, three different strains of *E cloacae* were present during the outbreak period in the NICU, thereby suggesting cross-transmission. Strain I involved a total of five children, including two infants hospitalized previously in the PICU.

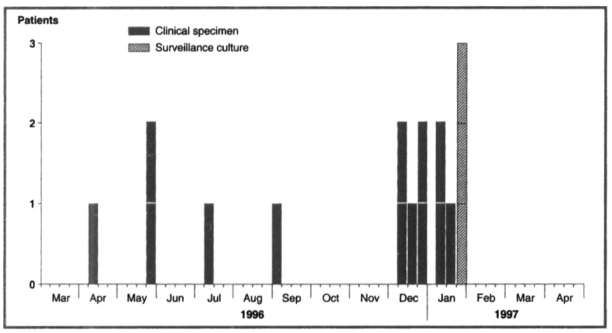


**FIGURE 1.** Infants colonized or infected with *Enterobacter cloacae* in the neonatal intensive-care unit at the University Hospitals of Geneva between March 1996 and April 1997. Three patients were detected on January 23, 1997, by screening (surveillance) cultures.

Strains II and III involved four and two infants, respectively. One of the patients was simultaneously infected with two strains. Figure 2 shows the seven-bed critical-care room of the NICU, as of January 11, 1997, with the locations of five involved and two uninvolved infants.

### *Overcrowding and Understaffing*

During the 6-week outbreak period, substantial overcrowding of the NICU was recorded. The daily occupation rate regularly exceeded the standard maximum of 15 infants per day by an average of 5 (±2.5). The mean occupation rate from mid-December to mid-January exceeded the standard by 50%. The peak of overcrowding was observed on December 19, 1996, when 25 infants were hospitalized in the unit (Figure 3). In addition, understaffing in the unit became dramatic during the last 2 weeks of December and January, when 20 staff members were on daily duty in three shifts, whereas more than 35 staff would have been required, as calculated by the PRN system (Figure 3). This figure also shows the daily occupancy of the NICU in relation to the detected *E cloacae* isolates and the staffing of the unit. Based on the contention that each instance of serious overcrowding (more than 20 infants in the NICU) and understaffing (lack of more than 8 nursing staff per shift) might result in increased cross-transmission and *E cloacae* detection in the following 3 days, we could observe an increased attack rate at Christmastime 1996 and at the end of the second week in January 1997. During these periods, more than 20 infants were hospitalized in the unit with a substantial lack of nursing staff (Figure 3).

Between August 1995 and July 1997, the incidence of *E cloacae* infection was significantly higher in periods with serious overcrowding and understaffing (more than 20 infants in the unit and lack of more than eight nursing staff per shift: 5.31 episodes per 1,000 patient-days) compared to periods with a better staffing and occupancy situation (fewer than 8 missing staff per shift and fewer than 20 infants in the unit: 0.89 episodes per 1,000 patient-days). In those periods of serious understaffing and overcrowding, the risk ratio for *E cloacae* infection was markedly higher (relative risk [RR], 5.97; $CI_{95}$, 2.2-16.4). Furthermore, surveillance of nosocomial bloodstream infections revealed an increased incidence of NICU-acquired infection caused by

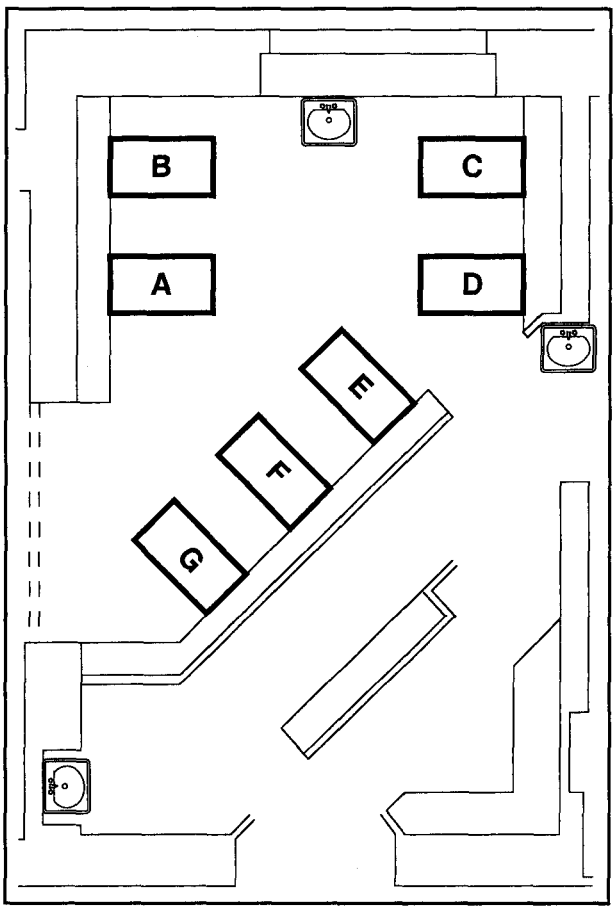


**FIGURE 2.** Schematic diagram of the seven-bed critical-care room of the neonatal intensive-care unit, showing locations on January 11, 1997, of five infants involved in *Enterobacter cloacae* cross-transmission. Three infants were colonized or infected with outbreak strain I (while housed in beds D, E, and F, respectively), and two infants were infected with strain II (beds C and G). The twin infants located in adjacent beds (A and B) were not involved in the outbreak.

any type of organism in the above-mentioned periods (from 1.06 to 4.49 episodes per 1,000 patient-days; RR, 4.2; $CI_{95}$, 1.4-13.1), thus revealing another epidemiological hint pointing at the lack of good patient-care practices during that time.

## DISCUSSION

The identification of a cluster of eight premature neonates infected or colonized with *E cloacae* between December 1996 and January 1997 prompted this investigation. Several concomitant factors may have contributed to this outbreak. Colonization may have arisen endogenously in two neonates transferred from the PICU. Once introduced into the NICU, possible contamination of multidose vials with *E cloacae* and further cross-transmission via HCWs' hands occurred, facilitated by substantial overcrowding and understaffing of the unit. The outbreak terminated after compliance with handwashing practices had improved, Universal Precautions and the use of single-dose vials were strictly enforced, and infant census decreased.

A central concept in preventing cross-transmission has been the practice of hand washing by HCWs between

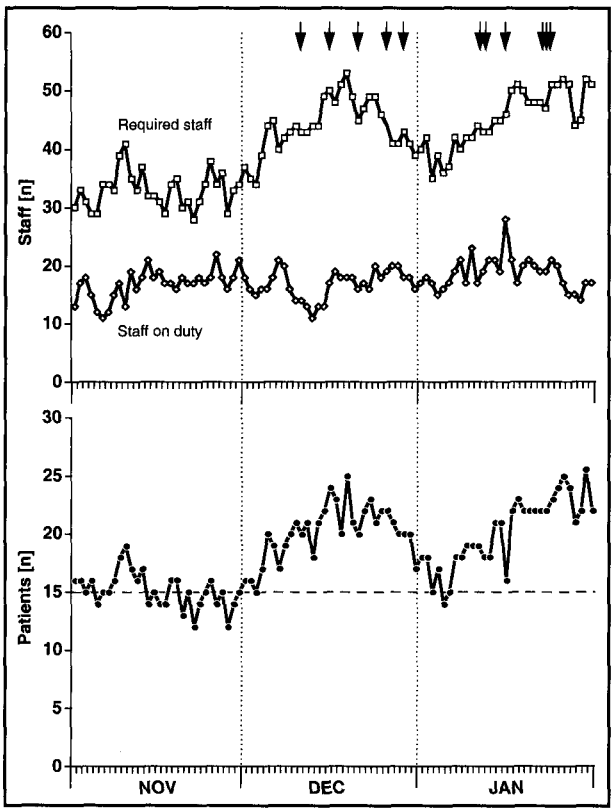


**FIGURE 3.** Staffing of the unit (staff on duty [diamonds] versus required staff [squares], upper part of the figure) and daily number of infants (circles, lower part of the figure) in the neonatal intensive-care unit; arrows indicate *Enterobacter cloacae* isolates. The horizontal dotted line in the lower part of the figure indicates the supposed maximum capacity (15 infants) of the unit.

patient contacts.[26] Besides endemic transmission of staphylococci,[27] hands have been implicated in nursery outbreaks caused by various other pathogens.[28-32] Goldmann and coworkers[10] documented the presence of gram-negative bacilli on the hands of 75% of NICU personnel. Usually, hands are transiently contaminated, and hand washing removes the organisms and interrupts transmission.[33] A unique feature of this outbreak is that, by pure coincidence, a hospitalwide survey of handwashing compliance had been conducted in the week before the outbreak, revealing a lack of compliance in several areas. Noncompliance of HCWs was the highest in the PICU (55%), followed by the NICU (37%) and other pediatric wards (28%).

Although initial colonization with *E cloacae* may arise endogenously and may persist for a long time,[5,9] our data clearly suggest further cross-transmission in the NICU. Interestingly, in parallel to this outbreak, a cluster of four cases of necrotizing enterocolitis occurred in the same ward, which may have been caused by an unidentified pathogen also transmitted by cross-infection. Further studies are necessary to demonstrate if the *E cloacae* outbreak had any causal relationship with this cluster, as suggested by a previously described outbreak.[34]

Once introduced into the NICU environment, multidose vials may have become contaminated with the pathogen during the process of care. The use of contaminated multidose vials might have facilitated further transmission of *E cloacae* in this unit, as indicated by its independent association with the outbreak. Despite obtaining cultures of several specimens, we could not demonstrate that vials of caffeine or budesonide sprays were contaminated. However, none of the vials used in the week before the investigation of the outbreak were available for microbiological investigation. Detailed questioning of the medical staff indicated that use of multidose vials was common, an observation described in other NICU outbreaks.[7,35,36] Therefore, the use of single-dose vials should be re-emphasized, and scrupulous hand antisepsis should be performed before preparing any kind of medication for premature infants.

Reduced compliance with aseptic techniques due to overcrowding and understaffing was an important contributing factor to the observed NICU outbreak. During the outbreak period, the available space in both rooms of the NICU varied between 3.5 and 6.0 $m^2$ per infant, far below the Association of Practitioners in Infection Control recommendation of 7.4 to 9.3 $m^2$.[37] As shown by Haley et al,[38,39] overcrowding and understaffing of neonatal nurseries are significantly associated with cross-infection, making frequent hand washing between infants almost impossible. In another carefully designed epidemiological study, the authors concluded that nursing staff reductions below a critical level contributed to the increased incidence of catheter-related nosocomial bloodstream infections.[40]

Our results must be interpreted in the context of the study design. First, we must acknowledge that the small number of cases limited the precision of the calculated OR and confidence intervals. Second, our case definition was based on clinical specimens and may not have allowed the inclusion of all cases. Therefore, the number of infants with *E cloacae* may have been underestimated, and the peak of *E cloacae* colonization may have been earlier than the "peak" of the clinically manifested epidemic. Third, the evidence of a relation between overcrowding and understaffing of the NICU and occurrence of *E cloacae* cross-transmission does not prove causality. Finally, we used the Project Research in Nursing work-load measurement system, which has been calculated prospectively at HUG since 1992 and has been validated extensively.[18,19] Nevertheless, it may be possible that this instrument overestimates the required additional nursing staff that was necessary in the unit during the outbreak.[17] Whether or not those estimates can be applied to other NICUs remains to be studied.

Understaffing and overcrowding appeared to play an important role in several outbreaks reported in the literature.[4,36,38-41] Our study confirms and extends these findings, and supports the view that understaffing in periods of increased work load may result in additional nosocomial infections and costs, as surrogate markers of poor quality of care.[42] In the current era of downsizing, additional studies are needed to evaluate the effects of varying work-load and staffing levels on endemic nosocomial infection rates and quality of patient care.

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