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Major article

Validation of nosocomial infection in neonatology: A new method for standardized surveillance

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Background: Nosocomial infections (NIs) are a leading cause of mortality and morbidity in premature infants. We present a new method for detecting and confirming NIs in a neonatal intensive care unit.
Methods: Newborns with birth weight < 1,500 g or gestational age (GA) < 33 weeks were included prospectively over 2 years in a single-center tertiary neonatal intensive care unit. The computerized physician order entry system (CPOE) generated alerts when antibiotics were prescribed for at least 5 consecutive days and these cases were reviewed by an expert group following international recommendations.
Results: Four hundred sixty-one neonates were included, with a mean GA of 30 weeks (range, 26-32 weeks) and mean birth weight 1,270 g (range, 950-1600 g). The CPOE flagged 158 cases of potential NI, 85.1% of which were classified as true NI and 14.9% of which were false positive. Incidence and device-associated nosocomial bloodstream infection rates were 21.9% and 10.8 per 1,000 central venous catheter days, respectively. GA ≤ 28 weeks (odds ratio, 2.18; 95% confidence interval, 1.2-4) and > 7 central venous catheter days (odds ratio, 1.47; 95% confidence interval, 1.3-1.7) were independently associated with the risk of nosocomial bloodstream infection.
Conclusion: Combining CPOE and interdisciplinary review may improve the accuracy of NI recording in a neonatal intensive care unit.

Nosocomial infection (NI) or late-onset sepsis are leading causes of mortality and morbidity, especially cerebral palsy, in neonatal intensive care units (NICUs).[1,2] Nosocomial bloodstream infections (NBIs) are the most common NIs and are frequently related to central venous catheter (CVC) use. The incidence of catheter-related NBIs in neonates ranges from 3%-28% in North America and Europe,[3,4] reflecting broad differences in both NICU recourse to CVCs and population characteristics.[1,5] Validation of infection is the cornerstone of NBI monitoring, although confirming an NBI, particularly in preterm neonates, is a difficult task for clinicians. NBIs in these patients are frequently caused by coagulase-negative staphylococci (CoNS), with clinical manifestations that are subtle and laboratory results that may suggest the diagnosis but have poor predictive value. Furthermore, blood cultures are often falsely positive or the positive findings may be due to skin contamination. To address this difficulty, we developed a protocol for monitoring NBIs that combines information from a computerized physician order entry system (CPOE) with a validation process from a multidisciplinary team. The aim of our study was to present this new method to track and confirm NIs in an NICU.

METHODS

Population

Our study was conducted in a 14-bed, level-3 NICU of a French university hospital. All newborn infants admitted to our NICU with birth weight (BW) < 1,500 g and/or gestational age (GA) < 33 weeks were considered for inclusion.

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Study design

The patients were prospectively enrolled over a 2-year period. Potential NIs were tracked from alerts generated by a CPOE and were then individually reviewed by an expert group to consensually confirm or withdraw the diagnosis. Data on all potential NIs were collected to specify the infection type and the pathogen distribution. More than 150 variables covering the antenatal history and the neonatal period were compared between cases and controls to identify the risk factors for NBI.

These variables have been systematically and prospectively collected since 2003 using a standard, detailed form and then stored in the database of our neonatal unit. Data encoding and quality control were performed by the same investigator (GC). Approval of the protocol was obtained from the local ethics committee.

NI identification process

The CPOE issued alerts for potential NIs. When a physician had prescribed ≥ 1 antibiotics for at least 5 consecutive days, a nominative file was automatically generated by the software, and the clinician had to respond to 4 questions before the daily order could be validated. These questions concerned the age at the start of antibiotic treatment; the use of devices like endotracheal tubes, urinary catheters, or CVCs; and the probable site and type of infection (ie, early onset sepsis [EOS] or late onset sepsis).

The file was immediately transmitted to the bacteriology laboratory so that the bacteriologist could systematically check all cultures taken from the newborn. A list of the nominative files was also automatically generated and edited before the weekly meeting to ensure that the multidisciplinary group examined every case issued by the CPOE. The group was composed of attending neonatologists and pediatricians, a physician from the Infection Control Department, the nurse-manager, and the referent bacteriologist. The group used the Centers for Disease Control and Prevention criteria for septicemia from pathogenic germs and for urinary tract and lower respiratory tract infections,[6] as well as the Vermont Oxford Network recommendations for the definition of CoNS septicemia[7] to confirm NI and validate the type of NI, the final site, the causal germ, and the antibiotic resistance profile.

Data analysis

To calculate the number of subjects needed, we assumed that the sensitivity of a CPOE to track NI would be adequate at 70%. Given an α risk of 5% and a power of 90%, 196 patients were needed. On the basis of the number of premature infants to be recruited and the estimated NI incidence in our NICU, 1 year of inclusion was sufficient to perform the study. We decided to extend the inclusion period to 2 years to improve our understanding of the epidemiologic profile of NBIs in very–low-BW neonates. We were convinced that this would help the team to develop more effective strategies to reduce the incidence of these infections and the related complications.

We performed descriptive analysis using classical methods. If quantitative variables followed a Gaussian distribution, they were expressed as means followed by standard deviations and compared using the Student t test. If not, they were expressed as medians followed by the 25th and 75th quartiles and compared using the nonparametric Mann and Whitney U test. Qualitative variables were expressed as percentages followed by the associated 95% confidence interval (CI) and compared using either the χ^2 test or the Fisher exact test as appropriate.

A multiple logistic regression model with stepwise forward variable selection was performed to identify significant independent risk factors for NBI.

The significance level for entering a variable in the model was $P < .05$. Data were analyzed using SAS version 9.1 (SAS Institute Inc, Cary, NC).

RESULTS

Four hundred sixty-one patients born before 33 weeks GA and/or with BW < 1,500 g were admitted from January 2009-December 2010. The NICU occupancy rate was 93.5% (range, 90%-105.5%) during the study period. The median GA and BW were, respectively, 30 weeks (range, 26-32 weeks) and 1,270 g (range, 950-1600 g).

NI identification process

One hundred sixty-eight alerts were sent by the CPOE, classified as NI in 158 cases and EOS in 10 by the expert group. The multidisciplinary team did not confirm 23 NIs and 2 cases of EOS, corresponding to a false positive rate of 14.9%.

The causes for false positive NI alerts were multiple validations of the same NI in 19 cases, and the confusion between NI and EOS in 4 cases.

In 6 cases (3.8% of all NIs), the NI was detected by the multidisciplinary team, particularly the referent bacteriologist, although no alert had been sent by the CPOE. In these 6 cases, 2 rounds of antibiotic treatment, each shorter than 5 days, had been prescribed for a neonate with true NI.

Features of NBI

The multidisciplinary team identified 101 NBIs (71.6% of all NIs) (Fig 1) in 78 infants, because 15 of these infants (20%) had > 1 episode. The rate of CVC use was 0.41 during the study period. The CVC duration was 13 days (range, 9-25 days) for the cohort and 26 days (range, 15-39 days) for the 116 neonates born before GA 28 weeks versus 11 days (range, 8-19 days) for the neonates born between GA 28^{+0} and 32^{+6} weeks ($P < .0001$). All patients who developed an NBI had a CVC and no other site of infection, indicating the strong likelihood of CVC-related NBI. In 85% of cases, the CVC in place when the NBI was diagnosed was a peripherally inserted central catheter. The incidence and incidence density rate were, respectively, 21.9% and 10.8 per 1,000 catheter days.

Pathogen distribution

In 97% of NBIs, a single microorganism was isolated in the blood cultures. The most common was CoNS (80.1%; 81 cases), but we found *Staphylococcus aureus* in 10 cases (9.9%), *Enterococcus* in 2 cases (2%), *Candida albicans* in 2 cases (2%), and gram-negative bacilli (*Escherichia coli* or *Enterobacter cloacae)* in 3 cases (3%). An NBI was also validated in 3 patients, although no pathogenic germ was isolated in the bloodstream cultures, because these infants had clinical and biologic signs (ie, serum concentrations of C-reactive protein and procalcitonin higher than 10 mg/L and 0.6 ng/mL, respectively) consistent with the diagnosis and had improved following antibiotic treatment.

Risk factors for NBI

The neonates with NBI had lower GA and BW. Unsurprisingly, the duration of invasive and noninvasive ventilation and NICU stay were also longer in these neonates, and they required CVC and parenteral nutrition for longer periods. Although NBIs were directly responsible for 2 deaths (due to resistant *S aureus* and *C albicans*), the mortality rate was comparable between the 2 groups.