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Effect of a closed drug-delivery system on the incidence of nosocomial and catheter-related bloodstream infections in infants

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SUMMARY

We conducted a prospective, cohort study at two affiliated level III neonatal intensive care units to evaluate the effect of a closed drug-delivery system on the incidence of nosocomial and catheter-related bloodstream infections (CRBSI) in infants. A total of 300 infants ($n=150$ at each site) were enrolled over a 4-year study period. There was no difference in the rate of CRBSI per 1000 catheter days between the two sites ($16{\cdot}2\pm39$ *vs.* $8{\cdot}9\pm24$, $P=0{\cdot}054$, 95% CI $-14{\cdot}8$ to $0{\cdot}13$). Infants at site A (closed drug-delivery system) had a higher rate of infectious nosocomial respiratory complications per 100 hospital days than infants at site B (open delivery system) ($1{\cdot}1\pm2{\cdot}2$ *vs.* $0{\cdot}5\pm1{\cdot}5$, $P=0{\cdot}009$), however, there was no difference in the overall number of confirmed or suspected nosocomial infection events per patient between study sites. Logistic regression revealed that the number of additional peripheral catheters, gestational age and duration of parenteral nutrition all significantly contributed to the risk of developing one or more CRSBI. The closed drug-delivery system failed to reduce the incidence of CRBSI or overall rate of nosocomial infections in premature infants.

INTRODUCTION

Intravascular devices are indispensable tools in the care of critically ill premature infants. However, these devices are associated with high rates of nosocomial and catheter-related bloodstream infections (CRBSI). This association has lead researchers to study preventative measures, including: antiseptic-impregnated catheters [1, 2], strict catheter maintenance policies [3], low-dose daily vancomycin infusions [4–8], and antibiotic flushes [9]. Due to concerns regarding chronic use of antimicrobial agents and the risk of promoting antibiotic resistance, a drug-free prevention strategy was developed at the University of Colorado Hospital (UCH). For more than 5 years, the neonatal intensive care unit (NICU) at UCH has used a unique drug-delivery system for infants requiring medications through a central venous catheter. The intent of this closed system was to substantially reduce the number of daily catheter manipulations – a known risk factor for CRBSI [10]. This system requires the assembly and placement of a 24-h supply of medications and intravenous nutrition/maintenance fluids into the central catheter at a single time. Medications and fluids are aseptically connected together under a laminar flow hood, using microbore extension tubing and connector sets. Preparation of the catheter hub/insertion site is

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performed at the bedside, over a sterile field. The drug-delivery system is then connected to the central catheter, requiring only one line violation in a 24-h period.

In 1998, a retrospective pilot study revealed that UCH had fewer reported coagulase-negative staphylococci (CoNS) infections per central catheter placed than an affiliated NICU (10·9% *vs.* 14·5%). While these data were not collected with a clinically appropriate denominator (events per 1000 catheter days), it suggested an overall lower infection rate at UCH because CoNS is the most common microorganism isolated in neonatal catheter infections [11, 12]. A notable difference between the two sites was the process of central line access/violation and the use of the closed drug-delivery system at UCH. Therefore, the specific aim of this study was to evaluate the impact of this closed drug-delivery system on the incidence of nosocomial and CRBSI in premature infants.

METHODS

This was a prospective cohort study performed between 1999 and 2003 at two affiliated NICUs within the Denver Metro Area. Each NICU was a level III facility, operating between 42 and 50 beds per site. Site A (The University of Colorado) used a closed drug-delivery system and site B (The Children's Hospital, Denver) used a traditional open system. The study protocol was approved by the investigational review board at each site. Informed consent was not required for this exempt-status protocol.

Infants were eligible for inclusion if they were older than 7 days and had an indwelling central venous catheter [Broviac® (Bard Inc., Murray Hill, NJ, USA) or percutaneous central catheter]. Infants with umbilical lines or peripheral venous lines were not considered for inclusion unless they also had a Broviac® or percutaneous central line. Infants were excluded if they were <48 h post an outborn transfer, were pre- or post-cardiac transplant patients, or had a documented infection upon arrival at the study site.

To ensure consistency with septic event documentation, criteria and definitions from The Centers for Disease Control and Prevention and the National Nosocomial Infection Surveillance were used. To meet a definition of a 'confirmed septic event' an infant must have had *one* of the following clinical signs/symptoms: temperature instability (<37 °C or >38 °C) or apnoea or bradycardia *and* one of the following three must have occurred: (1) common skin contaminant (e.g. diptheroids, *Bacillus* spp., *Propionibacterium* spp., CoNS, or micrococci) was cultured from at least one blood culture in a patient with a (central) intravenous line, and the physician instituted appropriate antimicrobial therapy, (2) a positive antigen test (on blood) was detected, or (3) a positive blood, urine, tracheal or 'other' (e.g. stool, wound, cerebral spinal fluid, eye) culture of a recognized pathogen from one or more sites was detected. To meet the definition of a 'suspected septic event' (without a positive culture), an infant must have had three of the following five clinical signs/symptoms: (1) temperature instability (<37 °C or >38 °C), (2) 50% increase in frequency of apnoea and bradycardia events, (3) glucose instability (<40 or >150 mg/dl), (4) hypotension/hypoperfusion requiring pressor support or (5) metabolic acidosis (base excess greater than −5) *and* a complete blood cell count with an immature:total neutrophil ratio of ⩾0·2, thrombocytopenia (platelets <100 mg/dl) *or* a significantly elevated serum C-reactive protein (>2 mg/dl) [13], *and* the physician instituted antimicrobial therapy.

A perinatal clinical research centre nurse identified infants eligible for study inclusion through weekly inquiries at each site. Catheter type, duration of central catheter, use of parenteral nutrition, number of additional peripheral intravenous catheters, and length of hospital stay were recorded. Urine, tracheal and blood culture data were collected from readily available microbiology databases. Source of infection and microorganisms isolated were also recorded. When counting a central-line infection, we included those positive cultures obtained within 48 h after a central venous catheter was removed (due to potential 'shower effect'). CRBSIs were reported as 'events per 1000 catheter days' and calculated as number of confirmed bloodstream infections divided by duration of catheter days multiplied by 1000. The rates of nosocomial pneumonia, urinary tract infections and miscellaneous infections were expressed per 100 hospital days and were calculated by using number of specified infections divided by length of stay (days) and multiplied by 100.

Statistical analysis

It was estimated that to detect a 25% reduction in overall CRBSI, over 1000 infants would be required at each study site to yield a power of 80% and an

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Table 1. *Mean (± S.D.) infection rates and clinical characteristics of subjects by study site*

	Site A	Site B	95% CI*	*P* value
Number of overall confirmed septic events per subject	1·3 ± 2·2	1·2 ± 2·6	−0·72 to 0·39	0·55
Number of overall suspected septic events per subject	3 ± 3·5	3·8 ± 6·3	−0·39 to 1·95	0·19
Number of nosocomial respiratory complications per 100 hospital days	1·1 ± 2·2	0·5 ± 1·5	−0·99 to -0·14	0·009
Number of nosocomial urinary tract infections per 100 hospital days	0·13 ± 0·5	0·23 ± 1·1	−0·88 to 0·30	0·29
Number of miscellaneous nosocomial infections per 100 hospital days	0·10 ± 0·6	0·21 ± 1·0	−0·08 to 0·29	0·27
Duration of parenteral nutrition (days)	18 ± 13·8	23 ± 27·1	−0·44 to 9·8	0·052
Number of additional peripheral access devices required per subject	3·1 ± 3·2	3·3 ± 2·9	−0·48 to 0·92	0·54
Length of hospital stay (days)	57 ± 35·8	56 ± 46·4	−10·69 to 8·18	0·79

* 95% Confidence interval (CI) of the difference in the mean of each variable between site A and site B; any such 95% CI including zero in the interval is statistically not significant.

alpha error of 0·05. This large population was not practical, therefore, on parameters that were not statistically significant, we reported 95% confidence intervals (CIs) of the observed difference between the two groups (sites) as an indicator of the precision of the results. Based on pilot data from 1998 when site A admitted 426 patients and placed 82 central catheters and site B admitted 557 patients and placed 92 central catheters, we expected that a 4-year study period would yield adequate numbers of subjects for comparison. Baseline differences between study sites on numerical variables were analysed using the Student's *t* test. The independent *t* test (with Levene's test for equality of variance) was used to compare rate of CRBSI per 1000 catheter days and rate of nosocomial infections per 100 hospital days. Significance was set at a *P* value of $<0·05$ and all tests were two-tailed. Odds ratios (ORs) and 95% CI were determined with logistic regression analyses to determine which factors predicted infection risk. Power calculation and statistical analyses were performed using industry standard statistical software programs [nQuery Advisor v. 5.05 (SPSS Inc., Chicago, IL, USA) and SPSS v. 12.0 (Saugus, MA, USA), respectively].

RESULTS

A total of 300 infants were enrolled ($n=150$ at each site). The mean (± S.D.) gestational age and weight of infants at site A was lower than those infants at site B (gestational age = 29·7 ± 4·3 weeks *vs.* 32 ± 5·3 weeks, birthweight = 1418 ± 895 g *vs.* 1867 ± 1022 g; $P<0·001$). Infants were well matched in terms of catheter duration for percutaneously placed lines (16 ± 10 days *vs.* 18 ± 17 days, $P=0·29$; observed difference = 2 days, 95% CI of the difference −1·63 to 5·48 days). However, infants at site A had surgically placed Broviac® lines for a significantly shorter period of time, compared to infants at site B (28 ± 16 days *vs.* 58 ± 56 days, $P=0·003$). The overall duration of any indwelling central venous catheter was also shorter at site A (18·6 ± 14) than site B (29·4 ± 38) ($P=0·001$). Differences in catheter duration were mitigated when data regarding CRBSI were expressed in terms of events per 1000 catheter days.

The overall number of suspected and confirmed septic events per patient was not different between study sites (Table 1). However, infants at site A did have more infectious nosocomial respiratory complications per 100 hospital days than infants at site B. No difference in the duration of parenteral nutrition, number of peripheral intravascular devices or length of hospital stay was detected between the study sites (Table 1). The rate of CRBSI per 1000 central venous catheter days was 16·2 ± 39 at site A and 8·9 ± 24 at site B ($P=0·054$; observed difference = 7·3, 95% CI of the difference −14·8 to 0·13). Infants with a surgically placed Broviac® catheter had 21 ± 33 and 16 ± 27 CRBSI per 1000 catheter days at sites A and B respectively ($P=0·44$; observed difference = 5, 95% CI of the difference −19·88 to 8·76). Infants with a percutaneously placed catheter had 21 ± 57 and

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Table 2. *Logistic regression model to predict the risk of having one or more catheter-related bloodstream infections*

Parameter	OR	95% CI*	*P* value
Use of a closed drug-delivery system	1·85	0·92–3·74	0·087
Number of peripheral intravascular devices	1·19	1·06–1·34	0·004
Duration of indwelling central venous catheter (days)	0·993	0·97–1·02	0·61
Birthweight (g)	1·001	1·00–1·00	0·16
Gestational age (weeks)	0·85	0·73–1·00	0·044
Duration of parenteral nutrition (days)	1·043	1·01–1·08	0·022

* 95% confidence Interval (CI) of each respective odds ratio (OR) estimate; any such 95% CI including 1·0 in the interval is statistically not significant.

12 ± 36 CRBSI per 1000 catheter days at sites A and B respectively ($P = 0{\cdot}173$; observed difference = 9, 95% CI of the difference −20·25 to 3·6). Seventy five percent (113/150) of infants at site A did not have any CRBSI compared to 80% (121/150) at site B. The total number of positive cultures at sites A and B was 175 (28% blood, 6·8% urine, 61% respiratory, 4% other) and 142 (34% blood, 18% urine, 37% respiratory, 11% other) respectively. Results of the logistic regression model predicting the risk of having one or more CRBSI are shown in Table 2. In this analysis, the number of peripheral intravascular devices, gestational age and duration of parenteral nutrition had significant odds ratios that affected the outcome of having one or more CRBSI. The vast majority of infections were caused by Gram-positive bacteria, with CoNS being the most prevalent (Fig.).

DISCUSSION

This study described the impact of a closed drug-delivery system on the incidence of CRBSI and overall nosocomial infections in premature infants. While attempts were made to match infants based on age and birthweight, there remained significant differences in these variables between study sites. These differences may have biased the results from site A towards a higher infection rate because both gestational age and weight are inversely proportional to risk of infection [14]. Despite these differences in baseline characteristics, there was no statistical difference between the CRBSI rate per 1000 catheter days between study sites. However, there was a higher rate of culture-positive nosocomial respiratory complications (per 100 hospital days) at study site A, perhaps related to the relative pulmonary immaturity of infants at that site. No difference was detected in overall confirmed or suspected septic events per patient between the study sites. The rates and microbiology of events reported in this study are consistent with those previously reported in the literature [15–18]. We chose to study both confirmed and suspected septic events because the latter are much more common in the NICU and often drive the use of broad-spectrum antibiotics. The comparison of both confirmed and suspected septic events was made possible, in part, because the same group of neonatologists practice at both sites and had similar criteria for initiating therapy for suspected events.

Premature infants are at increased risk for infection by virtue of their immature immunological response to microorganism invasion. While risk factors for early-onset sepsis are related primarily to maternal factors (e.g. prolonged rupture of membranes, chorioamnionitis, etc.), risk factors for late-onset or nosocomial sepsis are primarily related to gestational age, birthweight and invasive procedures/therapies (e.g. mechanical ventilation, intravenous/arterial catheters, urinary catheters and parenteral nutrition) [11, 14, 15]. Central venous catheters (percutaneously and surgically placed) are common devices in the NICU and are used for long-term parenteral nutrition and medication administration. However, these devices are associated with 13·5–21·2 infections per 1000 catheter days – or a 19–31% catheter-related sepsis rate [16–20].

The pathogenesis of these nosocomial infections is multi-factorial, but contamination at the catheter hub (a portal for infection) is gaining attention [10]. While catheter care and maintenance procedures are paramount in controlling sepsis rates, there is little

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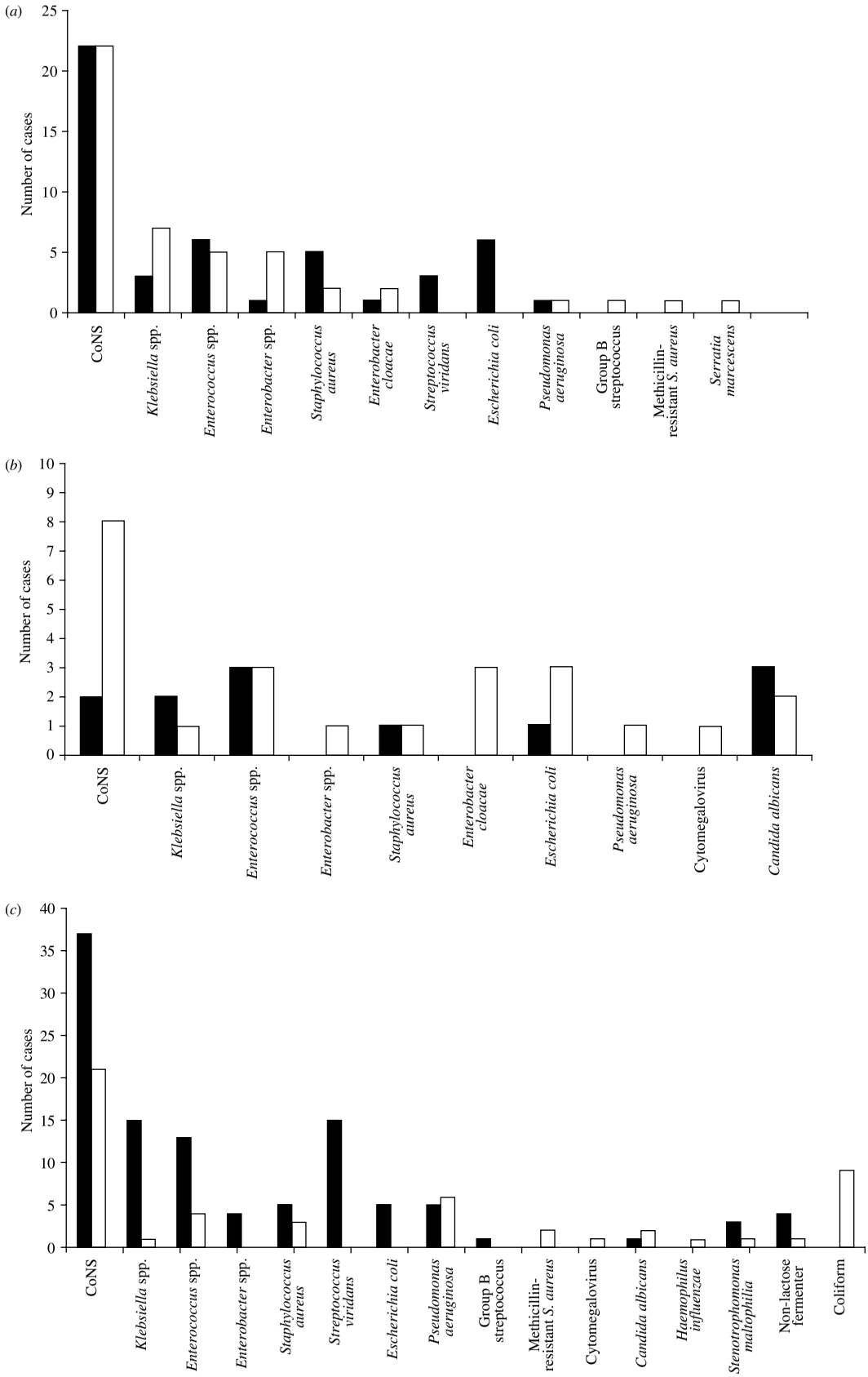

Fig. Incidence and distribution of microorganisms isolated from blood (a), urine (*b*) and respiratory (*c*) cultures of infants at site A (■) and site B (□). CoNS, Coagulase-negative staphylococci.

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consensus among practitioners regarding protocols [21]. We had hoped that a closed drug-delivery system, where a 24-h supply of medication and intravenous fluids are aseptically connected to the infant's central catheter hub site, would make an impact on the incidence of infection by reducing the number of daily line violations. However, the results from this study failed to support any reduction in infection rate associated with the closed drug-delivery system. These findings are important because this closed drug-delivery system required increased expenditures in both nursing time and medical equipment. Without evidence of a clear advantage to the closed drug-delivery system, the continuation of this novel practice cannot be advocated. In fact, although not significant, there was a trend towards a higher CRBSI rate at site A where the closed drug-delivery system was used. It seems unlikely that this trend was fully explained by the smaller and younger patient population at that site and it may point to the possibility that the cumbersome and complicated technical assembly of the closed drug-delivery system itself may have introduced an unexpected infection risk.

There are important limitations to our study that should be noted. Comparison of CRBSI rates between institutions is difficult because many confounding variables exist. We studied two affiliated institutions that used the same catheter maintenance procedures, except for a closed drug-delivery system at site A. However, it is possible that undetected variations in catheter care may have occurred between sites over the 4-year study period. Additionally, in order to detect a clinically relevant reduction (25%) in CRBSI, we needed to enrol over 1000 subjects per study site. Since this level of enrolment was not practical, we reported 95% CI data all with insignificant results. Observed 'non-differences' may require further investigation, in that larger samples may have yielded non-overlapping CIs and more significant results.

Our results suggest that the use of a closed drug-delivery system, as a preventative strategy to reduce CRBSI and nosocomial infections in premature infants, does not offer any significant advantage over current traditional open drug-delivery systems. This study confirms the high prevalence of nosocomial and CRBSI in this population of infants with central venous catheters. Novel approaches need to continue to be investigated to diminish the source of potentially preventable infectious morbidity in the NICU.

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