NEONATOLOGY TODAY

News and Information for BC/BE Neonatologists and Perinatologists

Volume 9 / Issue 1
January 2014

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NEONATOLOGY TODAY

ISSN: 1932-7129 (print); 1932-7137 (online).
Published monthly.

Corporate Offices:
8100 Leaward Way
PO Box 444
Manzanita, OR 97130 USA

Editorial and Subscription Offices
16 Cove Rd, Ste. 200
Westerly, RI 02891 USA
www.NeonatologyToday.net

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Very Low Birth Weight Infants (≤1500g) with Indwelling Peripherally Inserted Central Venous Catheters: Colonization and Risk of Nosocomial Bloodstream Infections

By Kamlesh Jha, MD; Tessy Joseph, MD; Norman M. Jacobs, MD; Suma Pyati, MD; and Manhal Khilfeh, MD

Abstract

Objective

The objective of this study was to delineate patterns of microbial colonization of the endotracheal tube and Peripherally Inserted Central Venous Catheter (PCVC) site in Very Low Birth Weight (VLBW) (≤1500g) infants who develop Nosocomial Bloodstream Infections (NBSIs) while hospitalized in our Neonatal Intensive Care Unit (NICU).

Hypothesis

We hypothesized that in ventilated VLBW infants the endotracheal tube is the common site for initial microbial colonization and that contamination from the colonized endotracheal tube predisposes to concordant colonization of the PCVC site, and thereby enhances the risk of NBSI. Hence, we prospectively studied colonization patterns of the endotracheal tube and PCVC sites over time in VLBW infants who subsequently developed NBSI.

Methods

This prospective study was conducted in the NICU at Stroger Hospital of Cook County, Chicago, IL, from August 2008 to February 2010. The protocol was approved by the Hospital's Institutional Review Board. Preterm infants admitted to our NICU weighing ≤1500g at birth and requiring PCVC placement were eligible for the study.

Results

During the 19-month study period, 161 infants weighing ≤1500g at birth were admitted to our NICU; of these, 131 infants survived and were assessed for eligibility. NBSIs occurred in greater proportion of infants (P <0.001) who were intubated >48 hrs (23 percent, 10 of 43) as compared to those never intubated or intubated for ≤48 hours (7 percent, 5 of 68).

Conclusion

In conclusion, in this study, the majority of NBSIs occurred in neonates with an indwelling PCVC who were intubated for >48 hr, weighed less than 1000g at birth, and were less than 29 weeks of gestation.

The use of peripherally inserted central venous catheters (PCVCs) for maintaining prolonged vascular access is common practice in neonatal intensive care units (NICUs) because they have the convenience of being placed at the bedside and remain patent for an extended period of time with minimal complications.[1,2]

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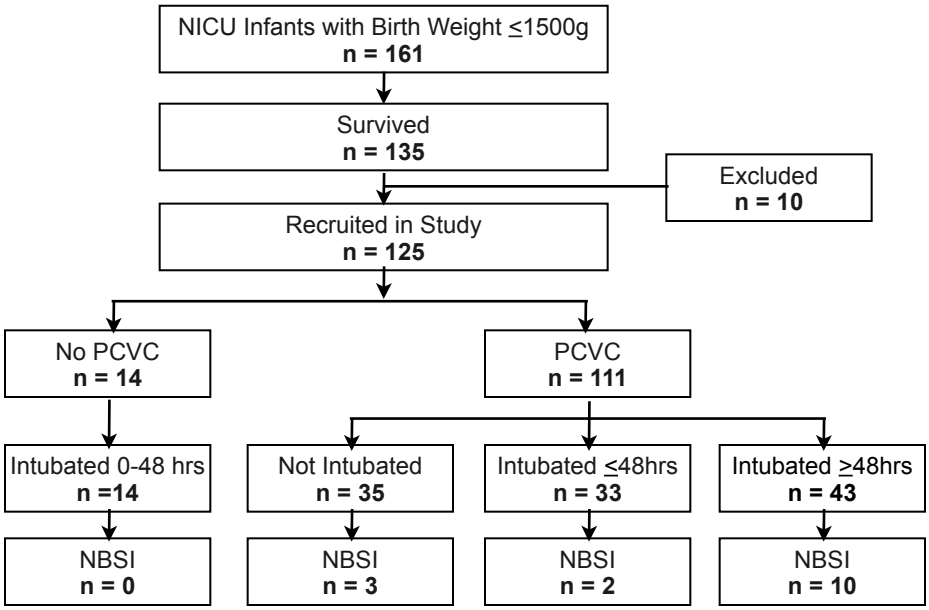

Figure 1. Flow diagram of study population.

The use of PCVCs is particularly beneficial for the management of Very Low Birth Weight (VLBW) neonates, infants with Short-Gut Syndrome, and those with chronic diseases that require long-term venous access for the delivery of parenteral nutrition. However, the presence of an indwelling PCVC increases the risk of nosocomial bloodstream infections (NBSIs), a major cause of morbidity and mortality among preterm VLBW infants.[3] In the National Hospital Safety Network (NHSN) survey, the incidence of catheter related bloodstream infections BSI ranged from 4.4 to 6.4 per 1000 catheter-days among neonates weighing less than 1000g.[4]

The most common mechanism of catheter related NBSI is colonization and migration of the infectious organism from the insertion site to the distal end of the catheter and ultimately, hematogenous dissemination.[1,2,5] Garland et al compared various surface cultures to define the pathogenesis of CRBSI in neonates; however, only the catheter hub contamination was significantly correlated with a positive blood culture.[5] The results of a prospective study in adults by Bouza et al,[6] suggest that superficial cultures of the catheter site, is an inexpensive and conservative method for the diagnosis of catheter related CR-BSI. Studies on the contamination of PCVCs, though limited, compared superficial and blood cultures to identify the mechanism of colonization in neonates.[6] Salzman et al reported that 54% of CR-BSI in neonates were preceded by or coincided with the contamination of the catheter hub with the same infecting organism found in the blood culture.[7]

Table 1. Characteristics of infants with and without Proven Nosocomial Blood Stream Infections

Characteristic	Infants with NBSI	Infants without NBSI	*P*
Total Number	15	96	
401-750g 751-1000g 1001-1250g 1251-1500g	6 6 2 1	18 23 34 21	
Birth weight, g$	827.33 (208.0)	1034.31 (255.56)	0.004
Gestational age, wks$	26.73 (3.3)	28.2 (2.7)	0.063
Gender, male	4 (26.7)	52 (54.2)	0.056
Age at PCVC placement, d$	5.4 (3.4)	4.9 (2.4)	0.468
PCVC duration, days	50 (28.5)	27.3 (14.0)	0.008
Duration of intubation, d$	25.8 (23.8)	8.8 (13.7)	0.000
Length of hospital stay, d$	94.9 (46.5)	61.9 (28.7)	0.000
Episodes of probable NBSI$	6.4 (2.8)	2.4 (1.9)	0.000
Total antibiotic days$	25 (15.5)	10.0 (6.6)	0.000
Total HAL, d$	58.93 (56.1)	29.6 (16.6)	0.000
Total IL, d$	58.87 (26.0)	29.3 (16.5)	0.000
Age at full enteral feeding, d$	60.80 (26.6)	31.2 (17.5)	0.000
$ mean + SD; NA not applicable			

"The use of peripherally inserted central venous catheters (PCVCs) for maintaining prolonged vascular access is common practice in neonatal intensive care units (NICUs) because they have the convenience of being placed at the bedside and remain patent for an extended period of time with minimal complications.[1,2]"

Methods

This prospective study was conducted in the NICU at Stroger Hospital of Cook County, Chicago, IL, from August 2008 to February 2010. The protocol was approved by the Hospital's Institutional Review Board. Preterm infants admitted to our NICU weighing ≤1500g at birth and requiring PCVC placement were eligible for the study.

Placement of the PCVC was performed under sterile conditions only by neonatal fellows, neonatal nurse practitioners, and trained nurses. All were percutaneous silicone catheters (Vygon, Aachen, Germany). A small-bore extension set was connected to the PCVC in a sterile manner and remained on the lines indefinitely. The catheter and the proximal portion of the extension set were secured to the skin by using a sterile, transparent, occlusive dressing.

PCVCs were not used for rapid medication infusions or blood product administration. Blood was not drawn from the PCVC unless sepsis was suspected and PCVC cultures were necessary. Sterile gloves were worn during all solution changes. Dressing integrity was assessed routinely and documented.

Surface cultures and cultures from the catheter access port were collected weekly for all infants without disturbing the dressing until the PCVC was discontinued or CRBSI was confirmed. All cultures were collected with a sterile cotton-tipped applicator and organized in separate containers. Surface cultures were obtained from a 1x1 cm area of skin surrounding the catheter insertion site. Cultures were also obtained from the catheter insertion site when dressings were changed due to loss of adhesiveness or drainage at the site. Use of the PCVC was discontinued at the discretion of the primary physician and cultures from the catheter insertion site and from the catheter hub were obtained after removing the dressing. In addition, the PCVC tip (approximately 3 cm) was sent for culture after disinfecting the exit site with alcohol. Endotracheal cultures were collected three times a week for all intubated infants.

Table 2. Characteristics of Infants Who Were Intubated for < 48 hr and > 48 hr

Characteristic	Infants Intubated <48hrs	Infants Intubated >48hrs	*P*
Number	68	43	
Birth weight, g$	1124.0 (192.75)	820.2 (241.31)	0.000
Gestational age, wks$	29.2 (2.2)	26.1 (2.7)	0.000
Gender, male	33 (48.2)	23 (53.5)	0.68
Age at PCVC placement, d$	4.26 (2.5)	6.05 (2.3)	0.000
PCVC duration, days	22.59 (9.9)	42.9 (21.5)	0.000
Duration of intubation, d$	0.62 (0.7)	27.7 (15.6)	0.000
Length of hospital stay, d$	48.91 (16.1)	94.1 (34.9)	0.000
Episodes of probable NBSI$	1.82 (1.3)	4.7 (2.9)	0.000
Infants with proven NBSI	5/68 (7.4)	10/43 (23.3)	0.000
Total antibiotic days$	8.29 (8.3)	18.1 (11.4)	0.04

$ mean + SD; NA not applicable

Blood cultures drawn from a peripheral vein and a complete blood count were obtained routinely as part of a partial or complete sepsis evaluation in infants with clinical findings of suspected infection (e.g., temperature instability, increased ventilator settings, increased apnea, bradycardia or desaturations, feeding intolerance, lethargy, or blood pressure instability). In addition, at each sepsis evaluation, samples of surface cultures were also obtained from the dressing and catheter access port. In the event of a positive blood culture, urine and CSF cultures were performed at the discretion of the primary physician. The blood cultures were processed in conventional 2-bottle broth blood-culture systems according to standard procedures.

For the purposes of this study, an episode of probable NBSI was diagnosed in an infant who was admitted for ≥48 hours, demonstrated clinical and/or laboratory findings suggestive of infection, and was treated with broad-spectrum antibiotics starting after blood culture collection. The NBSI episode was considered definite in such an infant when a pathogen was then isolated from one or more blood cultures. NBSI were considered catheter-related if the microorganism isolated from the peripheral blood culture was identical to that from the catheter hub, catheter tip or entry site with no other identifiable primary site of infection.

Data were collected prospectively, including total PCVC days, location of PCVC, ventilation days, sepsis evaluation, total antibiotic days, reports of cultures at all sites, and relevant demographic information, to allow

Table 3. Pathogens Recovered from Infants with an Indwelling PCVC Who Developed Nosocomial Blood Stream Infections while in the Neonatal Intensive Care Unit

Type of Organism	Proven NBSI, d	Birth Weight, g	Intubation, d	PCVC, d	Probable NBSI, n	Total Antibiotic, d	LOS, d
1. *Staph. aureus*	24	930	7	41	6	19	59
2. CONS	46	1000	26	53	8	15	88
3. CONS	48, 51	600	40	46	8	38	120
4. CONS	21	580	21	53	9	17	58
5. *Bacillus*	33	740	51	114	6	28	123
6. CONS	42	760	31	34	5	20	129
7. CONS	11, 13, 71	660	56	56	8	33	136
8. *Enterobacter*	27, 31	1070	31	39	4	18	96
9. CONS	27	670	51	97	8	47	153
10. *Enterobacter*	24, 97	520	70	134	13	59	194
11. *Enterococci*	15	860	2	32	2	17	54
12. Bacillus	37	860	2	33	4	11	71
13. CONS	27	1010	0	44	3	15	51
14. *Enterobacter*	26	880	0	38	5	41	72
15. *C. glabrata*	39	1270	0	37	7	13	48

CONS Coagulase-negative staphylococci; NA not applicable; ND not done

Table 4. Day of Life of Concordant Pathogen Isolates at Different Sites in Infants with Nosocomial Blood Stream Infections					
Organism	**Blood Culture**	**ET Culture before NBSI**	**ET Culture at NBSI**	**Hub Culture before NBSI**	**Hub Culture at NBSI**
Infants Intubated >48 hrs					
1. *Staph aureus*	24	18	24	Negative	Negative
2. CONS	46	25, 32	Extubated	ND	46
3. CONS	48, 51	16, 37	Extubated	37	48, 51
4. CONS	21	4,11,18	21	11, 18	21
5. *Bacillus*	33	Negative	33	Negative	Negative
6. CONS	42	26	Extubated	10, 24, 31, 38	ND
7. CONS	11, 13, 71	6	11, 13	11	11
8. *Enterobacter*	27, 31	ND	ND	ND	ND
9. CONS	27	7	ND	ND	ND
10. *Enterobacter*	24, 97	Negative	Negative	Negative	ND
Infants Intubated ≤48 hrs					
11. *Enterococci*	15	NA	NA	ND	ND
12. *Bacillus*	37	NA	NA	19, 26	ND
13. CONS	27	NA	NA	ND	ND
14. *Enterobacter*	26	NA	NA	Negative	Negative
15. *C. glabrata*	39	NA	NA	Negative	39
CONS Coagulase-negative staphylococci; NA: not applicable; ND not done					

analysis. Statistical analysis was conducted using SPSS 10 (SPSS, Inc, Chicago, IL). Categorical variables were analyzed by using Fisher's exact test or Pearson 2, as appropriate and the independent sample t test was used for comparison of means of continuous variables. Two-tailed P values of <0.05 were considered statistically significant for all analyses.

Results

During the 19-month study period, 161 infants weighing ≤1500g at birth were admitted to our NICU; of these, 131 infants survived and were assessed for eligibility (Figure 1). Ten infants were ineligible; of these, four infants were transferred back to the referring hospital, five had midline catheters, and one had proven early-onset infection. Fourteen infants did not require a PCVC. There were no proven or probable episodes of NBSI in the 14 infants who did not require PCVC or intubation. One hundred seventeen PCVCs were placed in the remaining 111 infants for a total of 3,388 catheter days. Forty-three of these infants required intubation and assisted ventilation for ≥48 hrs.

There were 18 proven episodes of definite NBSI in 15 of the 111 infants (13.5%) with indwelling PCVCs; of these 13 were in the 43 infants who remain intubated for ≥48 hrs, two in infants intubated for ≤48 hrs, and three in infants who were never intubated. Median time of positive blood culture was day of life 27. As shown in (Table 1), the mean birth weight of infants with definite NBSI was significantly lower 827 + 208g than infants without NBSI 1034+256g (P = 0.004). NBSI occurred in 25% of infants with a birth weight between 400g and 750g; 20% between 751 to 1000g, and in five percent of infants with a birth weight between 1001g and 1500g. As compared to infants without NBSI, infants with proven NBSI had the PCVC in-situ for greater length of time, had more episodes of probable NBSIs and antibiotic days, and stayed approximately a month longer in the NICU.

NBSI occurred in greater proportion of infants (*P* <0.001) who were intubated >48 hrs (23 percent, 10 of 43) as compared to those never intubated or intubated for <48 hours (7 percent, 5 of 68) (Table 2). Likewise, episodes of probable NBSI also occurred in a greater proportion of infants (*P* <0.001) who were intubated >48 hrs (93%) as compared to those intubated for ≤48 hours (50%). In 53% of infants the infection was successfully treated with the line in situ. Logistic regression analysis was performed to examine risk factors for NBSI. Predictors of statistical significance were hub culture, gestational age, gender, number of episodes of probable NBSIs, and total days of antibiotic therapy (Overall model, P = 0.000).

Organisms recovered from the blood culture of the fifteen infants with NBSIs are listed in (Table 3). The organism responsible for infection was coagulase-negative staphylococci in seven infants; *enterobacter* in three; *bacillus* in two; and one each due to *staphylococcus aureus, enterococci* and *candida glabrata.*

Endotracheal tube cultures were available in 9 of 10 infants with NBSI who were intubated >48 hours (Table 4). In 8 of these 9 infants the organism isolated from the blood was also isolated from endotracheal culture; in seven infants (78%) the endotracheal colonization with the concordant pathogen preceded the NBSI, and in one infant it was negative in preceding cultures, but positive at NBSI. Strikingly, in all infants with NBSI due to CONS, the endotracheal colonization preceded the NBSI. A PCVC hub culture report was available in 11 of 15 NBSI infants; of these, 7 were colonized with the concordant pathogen as the BSI and colonization preceded NBSI in 5 of 10 infants. Endotracheal tube colonization with the concordant pathogen preceded concordant hub colonization in all but one infant.

Discussion

In this study of VLBW infants with an indwelling PCVC, nosocomial blood stream infections occurred in significantly greater proportion of infants intubated >48 hours than in infants intubated ≤48 hours (23% versus 7%, *P* <0.001). Among intubated VLBW infants, the endotracheal tube was the site for initial concordant microbial colonization and preceded the onset of NBSI in 78% of cases; this concordance was 100% in infants with CONS bacteremia. Endotracheal tube colonization preceded concordant hub colonization in all but one infant. This observation

supports our hypothesis that pathogens from the endotracheal tube may increase the risk of contamination of the catheter site, and thereby predispose the occurrence of NBSI.

Among neonates with surgically placed CVCs, Salzman and colleagues[7] noted that in 10 of 28 episodes of CRBSIs, the same microorganism grown from the blood was also grown from the catheter hub before the onset of BSI symptoms. Recently, Garland and colleagues[5] used molecular epidemiology to examine the pathogenesis of neonatal catheter-related BSIs caused by CONS. Concordance between the organism grown from the catheter hub, catheter tip, and isolates from the blood was established using molecular subtyping by pulse-field gel electrophoresis. In a prospective trial[7] involving neonates with PCVCs, 54% of BSIs were associated with a catheter hub that was colonized either prior to or at the time of BSI onset.

The importance of CONS, noted in other studies, was found in these study results.[8-10] Gram-positive and Gram-negative bacteria account for 55.4 and 31.2% of microbes, respectively.[11] The most common organisms were *Staphylococci, Escherichia coli* and *Klebsiella*, and *Candida*.[11,12] In this study the most common pathogen was CONS, which accounted for 46.66% of NBSI.

In the neonatal intensive care, peripherally inserted central venous catheters are essential for optimal therapeutic management. Indwelling catheters, however, represent a major risk for NBSI in NICU infants. Authors of many recent studies recognized catheter duration as a risk factor for catheter-related BSI;[13-18] however, evidence for prevention of catheter-related BSI through routine replacement of catheters is lacking.[19-22] In our study, the duration of indwelling PCVC was statistically significant (P =0.008, 2 tailed), but on logistic regression it did not stand out as a significant predictor of NBSI.

Low birth weight and younger gestational age were strongly associated with risk of infection. In this study, infants weighing less than 1,000 g at birth and infants with a gestational age of less than 29 weeks had the highest risk of infection. These findings are reflected in the National Nosocomial Infections Surveillance System Report, which found that infants weighing less than 1,000 g at birth (9.1 infections per 1,000 catheter-days) had a higher rate of infection than infants weighing more than 2,500 g at birth (3.5 infections per 1,000 catheter-days).[23]

In our study, neonatologists generally left the catheters in place until no longer needed, or until there was reason to believe that the catheter may be infected (fever, leukocytosis, redness, or pus at the insertion site). Catheter was withdrawn only if the catheter was not absolutely essential, if the infant's clinical course did not stabilize with the institution of antimicrobial therapy, or if the infant had persistently positive blood cultures. The infection was successfully treated in 53% of infants with the line in situ. This was based on several reports that have stated that bacteremia in the presence of an indwelling PCVC in situ may be successfully treated with intravenous antimicrobials in 65% to 78% of cases.[24-27]

In conclusion, in this study, the majority of NBSI occurred in neonates with an indwelling PCVC who were intubated for >48 hr, weighed less than 1000g at birth, and were less than 29 weeks of gestation. The endotracheal tube was the site for initial microbial colonization and preceded the onset of concordant NBSI in 78% of cases; this concordance was 100% in infants with CONS bacteremia. Endotracheal tube colonization preceded concordant hub colonization in all but one infant. The endotracheal tube is the common site for initial microbial colonization; colonization of the PCVC hub by contamination from the endotracheal tube serves as the portal of entry for microorganisms leading to NBSI in ventilated VLBW infants.

"In conclusion, in this study, the majority of NBSI occurred in neonates with an indwelling PCVC who were intubated for >48 hr, weighed less than 1000g at birth, and were less than 29 weeks of gestation. The endotracheal tube was the site for initial microbial colonization and preceded the onset of concordant NBSI in 78% of cases; this concordance was 100% in infants with CONS bacteremia."

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IMPORTANT SAFETY INFORMATION

SURFAXIN (lucinactant) Intratracheal Suspension is intended for intratracheal use only. The administration of exogenous surfactants, including SURFAXIN, can rapidly affect oxygenation and lung compliance. SURFAXIN should be administered only by clinicians trained and experienced with intubation, ventilator management, and general care of premature infants in a highly supervised clinical setting. Infants receiving SURFAXIN should receive frequent clinical assessments so that oxygen and ventilatory support can be modified to respond to changes in respiratory status.

Most common adverse reactions associated with the use of SURFAXIN are endotracheal tube reflux, pallor, endotracheal tube obstruction, and need for dose interruption. During SURFAXIN administration, if bradycardia, oxygen desaturation, endotracheal tube reflux, or airway obstruction occurs, administration should be interrupted and the infant's clinical condition assessed and stabilized. Overall the incidence of administration-related adverse events did not appear to be associated with an increased incidence of serious complications or mortality relative to the comparator surfactants.

SURFAXIN is not indicated for use in acute respiratory distress syndrome (ARDS).

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INDICATIONS AND USAGE

SURFAXIN® is indicated for the prevention of respiratory distress syndrome (RDS) in premature infants at high risk for RDS.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Acute Changes in Lung Compliance

Administration of exogenous surfactants, including SURFAXIN, can rapidly affect lung compliance and oxygenation. SURFAXIN should be administered only by clinicians trained and experienced in the resuscitation, intubation, stabilization, and ventilatory management of premature infants in a clinical setting with the capacity to care for critically ill neonates. Infants receiving SURFAXIN should receive frequent clinical assessments so that oxygen and ventilatory support can be modified to respond to changes in respiratory status.

Administration-Related Adverse Reactions

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Increased Serious Adverse Reactions in Adults with Acute Respiratory Distress Syndrome (ARDS)

Adults with ARDS who received lucinactant via segmental bronchoscopic lavage had an increased incidence of death, multi-organ failure, sepsis, anoxic encephalopathy, renal failure, hypoxia, pneumothorax, hypotension, and pulmonary embolism. SURFAXIN is not indicated for use in ARDS.

Clinical Trials Experience

The efficacy and safety of SURFAXIN for the prevention of RDS in premature infants was demonstrated in a single randomized, double-blind, multicenter, active-controlled, multi-dose study involving 1294 premature infants (Study 1). Infants weighed between 600 g and 1250 g at birth and were 32 weeks or less in gestational age. Infants were randomized to received 1 of 3 surfactants, SURFAXIN (N = 524), colfosceril palmitate (N = 506), or beractant (N = 258). Co-primary endpoints were the incidence of RDS (defined as having a chest x-ray consistent with RDS and an $FiO_2 \geq 0.30$) at 24 hours and RDS-related mortality at 14 days. The primary comparison of interest was between SURFAXIN and colfosceril palmitate with the intent of demonstrating superiority. Beractant served as an additional active comparator. Compared to colfosceril palmitate, SURFAXIN demonstrated a statistically significant improvement in both RDS at 24 hours and RDS-related mortality through Day 14. A second multicenter, double-blind, active-controlled study involving 252 premature infants was also conducted to support the safety of SURFAXIN (Study 2). Infants weighed between 600 g and 1250 g and were less than 29 weeks in gestational age. Infants received 1 of 2 surfactants, SURFAXIN (N = 119) or poractant alfa (N = 124).

The safety data described below reflect exposure to SURFAXIN administered intratracheally to infants at a dose of 5.8 mL per kg (up to 4 doses) in either 4 aliquots (Study 1) or 2 aliquots (Study 2) in 643 premature infants.

Comparator surfactants colfosceril palmitate and beractant were administered at the recommended doses (5.0 and 4.0 mL per kg, respectively) while the first dose of poractant alfa administered (2.2 mL per kg) was less than the recommended dose of 2.5 mL per kg. Any subsequent doses of poractant alfa were at the recommended 1.25 mL per kg dose.

Overall, the incidence of administration-related adverse reactions was higher in infants who received SURFAXIN compared to other surfactants (Table 1) and resulted in a greater proportion of infants treated with SURFAXIN who experienced administration-related oxygen desaturation and bradycardia. For Study 1, oxygen desaturation was reported in 17%, 9%, and 13% and bradycardia for 5%, 2%, and 3% of infants treated with SURFAXIN, colfosceril palmitate, and beractant, respectively. For Study 2, oxygen desaturation was reported in 8% and 2% and bradycardia in 3% and 2% of infants treated with SURFAXIN and poractant alfa, respectively. These adverse reactions did not appear to be associated with an increased incidence of serious complications or mortality relative to the comparator surfactants (Table 2).

Table 1. Administration-Related Adverse Reactions in SURFAXIN Controlled Clinical Studies[a]

	Study 1[b]			Study 2[c]	
	SURFAXIN (N = 524)	Colfosceril palmitate (N = 506)	Beractant (N = 258)	SURFAXIN (N = 119)	Poractant alfa (N = 124)
Total Doses Administered	994	1038	444	174	160
	Total Number of Events (Events per 100 Doses)				
ETT Reflux	183 (18)	161 (16)	67 (15)	47 (27)	31 (19)
Pallor	88 (9)	46 (4)	38 (9)	18 (10)	7 (4)
Dose Interruption	87 (9)	46 (4)	30 (7)	7 (4)	2 (1)
ETT Obstruction	55 (6)	21 (2)	19 (4)	27 (16)	1 (1)

[a] Table includes only infants who received study treatment.
[b] Study 1 doses were administered in 4 aliquots.
[c] Study 2 doses were administered in 2 aliquots.

Table 2. Common Serious Complications Associated with Prematurity and RDS in SURFAXIN Controlled Clinical Studies Through 36-Weeks Post-Conceptual Age (PCA)

	Study 1			Study 2	
	SURFAXIN (N = 527) %	Colfosceril palmitate (N = 509) %	Beractant (N = 258) %	SURFAXIN (N = 119) %	Poractant alfa (N = 124) %
Apnea	52	52	46	66	75
Intraventricular hemorrhage, all grades	52	57	54	39	38
-Grade 3/4	19	18	21	13	8
Periventricular leukomalacia	10	10	12	4	9
Acquired sepsis	44	44	44	45	52
Patent ductus arteriosus	37	35	37	43	44
Retinopathy of prematurity, all grades	27	26	25	32	31
-Grade 3/4	6	7	6	5	9
Necrotizing enterocolitis, all grades	17	17	19	13	15
-Grade 2/3	6	8	14	8	8
Pulmonary air leak through Day 7, all types	15	17	14	9	7
-Pulmonary interstitial emphysema	9	10	10	3	5
-Pneumothorax	3	4	2	4	1
Pulmonary hemorrhage	10	12	14	6	9

All-cause mortality through 36-weeks PCA was similar regardless of which exogenous surfactant was administered.

Adverse reactions reported in the controlled clinical studies through 36-weeks PCA occurring in at least 10% of infants were anemia, jaundice, metabolic acidosis, oxygen desaturation, hyperglycemia, pneumonia, hyponatremia, hypotension, respiratory acidosis, and bradycardia. These reactions occurred at rates similar to the comparator surfactants.

No assessments for immunogenicity to SURFAXIN were performed in these clinical studies.

Follow-up Evaluations

Twelve-month corrected-age follow-up of 1546 infants enrolled in the 2 controlled clinical studies demonstrated no significant differences in mortality or gross neurologic findings between infants treated with SURFAXIN and those treated with the comparator surfactants (colfosceril palmitate, beractant, or poractant alfa).

OVERDOSAGE

There have been no reports of overdose following the administration of SURFAXIN.

HOW SUPPLIED/STORAGE AND HANDLING

SURFAXIN (lucinactant) Intratracheal Suspension is supplied sterile in single-use, rubber-stoppered, clear glass vials containing 8.5 mL of white suspension (NDC 68628-500-31). One vial per carton.

Store SURFAXIN in a refrigerator at 2° to 8°C (36° to 46°F) and protect from light until ready for use. Do not freeze. Vials are for single use only. Discard any unused portion of SURFAXIN. Discard warmed vials of SURFAXIN if not used within 2 hours of warming.

To report SUSPECTED ADVERSE REACTIONS, contact Discovery Laboratories, Inc. at 1-877-SURFAXN (877-787-3296) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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Understanding ICD-10-CM Chapter 17, Congenital Malformations, Deformations and Chromosomal Abnormalities

By Julie-Leah J. Harding, CPC, RMC, PCA, CCP, SCP-ED, CDIS

There is less than one year until October 1, 2014, the date the transition to ICD-10 code set goes into effect. Twenty-one chapters of the ICD-10-CM code should be reviewed with clinicians to have them familiar with the code set, but more importantly, to identify gaps in documentation that may exist. There are numerous clinical documentation improvement opportunities to implement into a clinician's documentation to better prepare for ICD-10.

Chapter 17 of ICD-10-CM, diagnosis codes, focuses on Congenital Malformations, Deformations and Chromosomal Abnormalities. Within this chapter is where you will find Hypospadias. Hypospadias refers to a congenital condition in which the urethral meatus lies on the ventral position of the penile shaft and may be located as far down as in the scrotum or perineum.

Like many of the codes within ICD-10-CM, there is much more granularity to the code set. When reporting Hypospadias the changes are vast from ICD-9-CM to ICD-10-CM.

752.61 → **ICD-9-CM** → **HYPOSPADIAS**

There is only one code option in ICD-9

Q54 Hypospadias
- **Excludes 1:** epispadias (Q64.0)
- **Q54.0 Hypospadias, balanic**
  - Hypospadias, coronal
  - Hypospadias, glandular
- **Q54.1 Hypospadias, penile**
- **Q54.2 Hypospadias, penoscrotal**
- **Q54.3 Hypospadias, perinatal**
- **Q54.4 Congenital Chordee**
  - Chordee without hypostatus
- **Q54.8 Other Hypospadias**
  - Hypospadias with intersex state
- **Q54.9 Hypospadias, unspecified**

→ **ICD-10-CM**

What does your documentation look like today?

Will the current capture move from unspecified to a more specific type of Hypospadias?

Physicians need to realize that payers are going to push back and state with this new code set, ***how could a clinician not know?*** This is a documentation improvement opportunity.

Diagnosis codes from Chapter 17 may be reported throughout the patient's lifetime. Although present at birth, malformation/deformation/or chromosomal abnormality may not be identified until later in life. Whenever the condition is diagnosed by the physician, **it is appropriate to assign a code from codes Q00-Q99.**

If a congenital malformation has been corrected, a personal history diagnosis code should be reported to identify the history of the malformation or deformity. For example, if a glandular hypospadias is repaired on a patient at 2-months-old and the patient comes in for a well child visit when they are three-years-old, the pediatrician documents as such in the patient's medical record, for ICD-10-CM; code **Z87.710** may be reported.

Z87.7 Personal history of (corrected) congenital malformations
Conditions classifiable to Q00-Q89 that have been repaired or corrected
- **Excludes 1:** congenital malformations that have been partially corrected or repaired, but which still require medical treatment - code to condition
- **Excludes 2:** Other post-procedural states (Z98-)
  Personal history of medical treatment (Z92-)
  Presence of cardiac and vascular implants and graphs (Z95-)
  Presence of other devices (Z97-)
  Presence of other functional implants (Z96-)
  Transplanted organs and tissue of other devices (Z94-)

Z87.71: Personal history of (corrected) congenital malformations of genitourinary system
→ **Z87.710: Personal history of (corrected) hyposadias**
Z87.718: Personal history of other specified (corrected) congenital malformations of genitourinary system

Z87.72: Personal history of (corrected) congenital malformations of nervous system and sense organs
Z87.720: Personal history of (corrected) congenital malformations of eye
Z87.721: Personal history of (corrected) congenital malformations of ear
Z87.728: Personal history of (corrected) congenital malformations of nervous system and sense organs

Z87.73: Personal history of (corrected) congenital malformations of digestive system
Z87.730: Personal history of (corrected) cleft lip and palate
Z87.738: Personal history of (corrected) congenital malformations of digestive system
Z87.74: Personal history of (corrected) congenital malformations of heart and circulatory system

Be sure to identify documentation improvement opportunities over the coming months. Implement these practices now to be better prepared for ICD-10 come October 1, 2014.

NT

Resource: www.cdc.gov/nchs/data/icd10/10cmguidelines_2013_final.pdf

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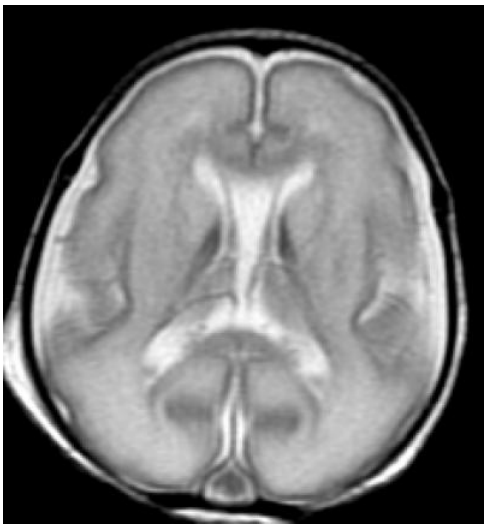
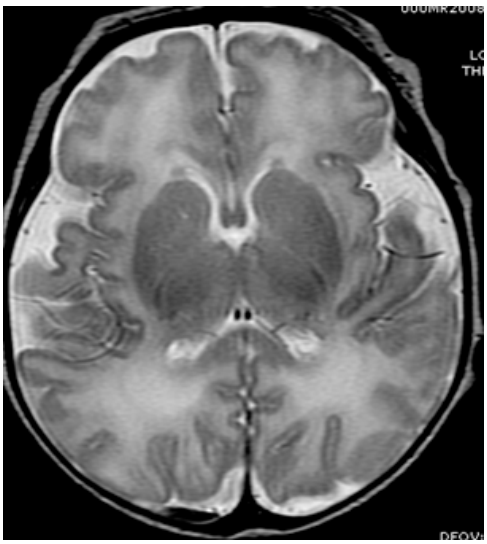


This image shows anatomy (MRI) -- 15 weeks premature.
Radiological Society of North America



This image shows anatomy (MRI) -- at term.
Radiological Society of North America

Premature birth appears to trigger developmental processes in the white matter of the brain that could put children at higher risk of problems later in life, according to a study presented at the annual meeting of the Radiological Society of North America (RSNA) in December 2013.

Preterm infants—generally those born 23 to 36 weeks after conception, as opposed to the normal 37- to 42-week gestation—face an increased risk of behavioral problems, ranging from impulsiveness and distractibility to more serious conditions like autism and attention deficit hyperactivity disorder (ADHD).

"In the United States, we have approximately 500,000 preterm births a year," said Stefan Blüml, PhD, Director of the New Imaging Technology Lab at Children's Hospital Los Angeles and Associate Professor of Research Radiology at the University of Southern California in Los Angeles. "About 60,000 of these babies are at high risk for significant long-term problems, which means that this is a significant problem with enormous costs."

Dr. Blüml and colleagues have been studying preterm infants to learn more about how premature birth might cause changes in brain structure that may be associated with clinical problems observed later in life. Much of the focus has been on the brain's white matter, which transmits signals and enables communication between different parts of the brain. While some white matter damage is readily apparent on structural magnetic resonance imaging (MRI), Dr. Blüml's group has been using magnetic resonance spectroscopy (MRS) to look at differences on a microscopic level.

In this study, the researchers compared the concentrations of certain chemicals associated with mature white matter and gray matter in 51 full-term and 30 preterm infants. The study group had normal structural MRI findings, but MRS results showed significant differences in the biochemical maturation of white matter between the term and preterm infants, suggesting a disruption in the timing and synchronization of white and gray matter maturation. Gray matter is the part of the brain that processes and sends out signals.

"The road map of brain development is disturbed in these premature kids," Dr. Blüml said. "White matter development had an early start and was 'out of sync' with gray matter development."

This false start in white matter development is triggered by events after birth, according to Dr. Blüml.

"This timeline of events might be disturbed in premature kids because there are significant physiological switches at birth, as well as stimulatory events, that happen irrespective of gestational maturity of the newborn," he said. "The most apparent change is the amount of oxygen that is carried by the blood."

Dr. Blüml said that the amount of oxygen delivered to the fetus' developing brain in utero is quite low, and our brains have evolved to optimize development in that low oxygen environment. However, when infants are born, they are quickly exposed to a much more oxygen-rich environment.

"This change may be something premature brains are not ready for," he said.

While this change may cause irregularities in white matter development, Dr. Blüml noted that the newborn brain has a remarkable capacity to adapt or even "re-wire" itself—a concept known as plasticity. Plasticity not only allows the brain to govern new skills over the course of development, like learning to walk and read, but could also make the brains of preterm infants and young children more responsive to therapeutic interventions, particularly if any abnormalities are identified early.

"Our research points to the need to better understand the impact of prematurity on the timing of critical maturational processes and to develop therapies aimed at regulating brain development," Dr. Blüml said.

Co-authors are: Ashok Panigrahy, MD; Marvin D. Nelson, MD; Lisa Paquette, MD; and Jessica L. Wisnowski, PhD.

NEONATOLOGY TODAY

© 2014 by Neonatology Today
ISSN: 1932-7129 (print); 1932-7137 (online).
Published monthly. All rights reserved.

Publication Headquarters
PO Box 444
Manzanita, OR 97130 USA
www.NeonatologyToday.net

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