Journal of Perinatology (2016) 36, 1045–1048

www.nature.com/jp

ORIGINAL ARTICLE

Chorioamnionitis and subsequent bronchopulmonary dysplasia in very-low-birth weight infants: a 25-year cohort

AR Ballard[1], LH Mallett[1], JE Pruszynski[2] and JB Cantey[1]

OBJECTIVE: To determine whether chorioamnionitis (CA) or sepsis were associated with bronchopulmonary dysplasia (BPD) in a 25-year cohort of very-low-birth weight (VLBW) infants.

STUDY DESIGN: VLBW infants ⩽32 weeks gestation admitted to the neonatal intensive care unit between 1989 and 2014 were reviewed. BPD was defined using the National Institutes of Health consensus definition. CA was defined clinically. Logistic regression models were used for BPD prediction.

RESULTS: One thousand six hundred and eighty-seven infants were included; 44% ($n = 740$) had moderate or severe BPD. In multivariable analysis, lower gestational age (odds ratio (OR) 1.12 per week (95% confidence interval (CI) 1.11, 1.14)), sepsis (OR 2.03 (95% CI 1.49, 2.77)) and birth year ⩾1995 (OR 1.49 (95% CI 1.09, 2.04)) were significant predictors of BPD. CA was not associated with BPD (OR 1.18 (95% CI 0.66, 2.11)).

CONCLUSION: Sepsis, but not CA, is associated with the development of moderate or severe BPD in VLBW infants after controlling for gestational age.

Journal of Perinatology (2016) **36,** 1045–1048; doi:10.1038/jp.2016.138; published online 1 September 2016

INTRODUCTION

Bronchopulmonary dysplasia (BPD) is a sequela of premature birth and remains a significant cause of morbidity for very-low-birth weight (VLBW < 1500 g) infants, including neurodevelopmental delays, hospitalizations and mortality.[1] The 'multiple hits' hypothesis describes the pathophysiology of BPD as a complex balance between inflammatory lung injury and subsequent repair and development.[2] The intrauterine inflammation caused by chorioamnionitis (CA) contributes to preterm delivery and its attendant morbidities, including respiratory distress syndrome, mechanical ventilation, supplemental oxygen, early-onset sepsis and need for parenteral nutrition, all of which increase the risk of developing BPD.[3,4] However, whether CA is an independent risk factor for the development of BPD remains controversial.[5,6] Human and animal studies have suggested that, in the absence of proven sepsis, CA may actually accelerate lung development, reducing the need for aggressive ventilator management and supplemental oxygen and therefore protecting against BPD.[4,7] Additionally, improved practices such as antenatal steroids, early non-invasive ventilation and caffeine use may diminish the role of antenatal inflammation.[8,9] Determining whether or not CA is a risk factor for BPD in preterm infants is complicated by the difficulty of controlling for all confounders and the evolution of the pathophysiology of BPD over the past several decades. Therefore, the purpose of this study was to utilize a prospectively collected database to evaluate whether CA is independently associated with BPD among VLBW infants over the past 25 years.

MATERIALS AND METHODS

Study population

Since 1989, demographic, clinical, laboratory and outcome data have been prospectively collected for every infant admitted to the Baylor Scott & White neonatal intensive care unit. Inclusion criteria for this cohort study included all VLBW infants ⩽32 weeks gestation admitted to the neonatal intensive care unit between 1 January 1989 and 31 December 2014. Infants with major congenital anomalies or who received only comfort care were excluded. Infants who died or were transferred before 36 weeks postmenstrual age were also excluded.

Definitions

CA was defined clinically using modified Gibbs criteria.[10] Women were considered to have CA if they had fever (⩾38 °C) and at least one of the following: uterine tenderness, maternal or fetal tachycardia, or foul/purulent amniotic fluid. Placental histopathology was not available. Moderate or severe BPD was the primary outcome. BPD was defined using the consensus definition from the National Institute of Child Health and Human Development Neonatal Research Network as an oxygen requirement for ⩾28 days.[11] Severity of BPD was determined by oxygen requirement at 36 weeks postmenstrual age (none = mild; < 30% = moderate; ⩾30% = severe). Sepsis was defined as culture of a pathogen from a sterile site.[12] Coagulase-negative staphylococci were considered pathogens if recovered from ⩾2 cultures or from 1 culture if clinical signs of sepsis were present and the infant received ⩾5 days of appropriate antibiotic therapy.[13] All sepsis evaluations and episodes of sepsis that occurred before 36 weeks postmenstrual age were recorded. Birth year was analyzed both as a continuous variable and as a dichotomous categorical variable (1989–1994, before routine use of antenatal corticosteroids; ⩾1995, after routine use of antenatal corticosteroids).

Statistical analysis

Descriptive characteristics were used for the study population, including medians and interquartile range or means and s.d. where appropriate. Statistical analysis was performed using SAS 9.4 (SAS Institute, Cary, NC, USA). Bivariate analysis was performed using χ^2 test or Kruskal–Wallis test as appropriate. Logistic regression models were developed for moderate or severe BPD as well as severe BPD only. Univariate logistic regression

[1]Department of Pediatrics, Texas A&M Health Science Center, Temple, TX, USA and [2]Department of Biostatistics, Texas A&M Health Science Center, Temple, TX, USA. Correspondence: Dr JB Cantey, Department of Pediatrics, Texas A&M Health Science Center, 1901 SW H.K. Dodgen Loop, Temple, TX 76502, USA.
E-mail: jcantey@sw.org
This study was presented in part at the Pediatric Academic Society Annual Meeting, 30 April–3 May 2016, Baltimore, MD, USA.
Received 9 March 2016; revised 26 July 2016; accepted 1 August 2016; published online 1 September 2016

models were used to determine which covariates had a marginal association with the outcome ($P < 0.20$). Backwards selection procedure was then used to determine which covariates constituted the best model of fit by using Hosmer–Lemeshow test and residual plots. All tests were two-sided, with $P < 0.05$ considered to indicate significance. The study was approved by the Institutional Review Board of Baylor/Scott & White Health with a waiver of informed consent.

RESULTS

One thousand nine hundred and fifty-six VLBW infants ⩽32 weeks gestation were admitted to the NICU during the study period. Among these, 269 infants (13.7%) died ($n = 161$, 8.2%) or were transferred ($n = 108$, 5.5%) before 36 weeks postmenstrual age. The remaining 1687 infants were included (Table 1). Of these, 87 (5.2%) were exposed to CA and 740 (43.9%) had moderate (31.2%) or severe (12.7%) BPD.

In bivariate analysis, infants with moderate or severe BPD were more likely to be multiples, have lower gestational age and birth weight, lower 1 and 5 min Apgar scores, a more recent birth year, more sepsis evaluations and proven sepsis episodes and exposure to CA. Gender, race/ethnicity and mode of delivery were not associated with the risk for BPD. In multivariate analysis (Table 2), only gestational age (odds ratio (OR) 1.12 per decreasing week of gestation (95% confidence interval (CI) 1.11, 1.14)), proven sepsis (OR 2.03 per episode, (95% CI 1.49, 2.77)) and birth year ⩾1995 (OR 1.49 (95% CI 1.09, 2.04)) remained significant risk factors for BPD; there was no significant association between CA exposure and moderate or severe BPD (OR 1.17 (95% CI 0.66, 2.11)). When only severe BPD was considered, gestational age and sepsis remained significant but neither CA exposure nor birth year were risk factors.

Table 1. Demographic and clinical information for very-low-birth weight infants with and without exposure to clinical chorioamnionitis

	Exposed to chorioamnionitis	*Not exposed to chorioamnionitis*	P-*value*
N	87	1600	
Gestational age, weeks	26 (24–28)	28 (26–30)	< 0.0001
Birth weight, g	880 (738–1090)	1101 (819–1330)	< 0.0001
Male sex	53%	52%	0.46
Birth year	2004 (1996–2008)	2001 (1995–2006)	0.002
1989–1994	22%	25%	
⩾1995	78%	75%	
Race/ethnicity			0.88
White	47%	45%	
Black	35%	36%	
Hispanic	16%	18%	
Asian	2%	1%	
Multiple gestation	11%	28%	0.006
Antenatal steroids	82%	80%	0.78
Vaginal delivery	62%	41%	< 0.0001
Apgar, 1 min	5 (2–7)	6 (4–8)	0.0003
Apgar, 5 min	8 (7–8)	8 (7–9)	0.06
Sepsis evaluations	2 (1–3)	1 (1–2)	0.0006
⩾1 sepsis episode	32%	24%	0.049
Days on ventilator	15 (5–34)	5 (1–24)	< 0.0001
Days on oxygen	46 (27–68)	19 (3–52)	< 0.0001
Length of stay, days	82 (68–103)	63 (44–88)	< 0.0001
Bronchopulmonary dysplasia	63%	43%	< 0.0001
Moderate	48%	30%	< 0.0001
Severe	15%	13%	0.63

Table 2. Multivariable logistic regression model for moderate or severe bronchopulmonary dysplasia (BPD)

Variable	*Odds ratio (95% CI)*	P-*value*
Moderate or severe BPD		
Gestational age	1.12 (1.11, 1.14) per week	< 0.0001
Sepsis episode	2.03 (1.49, 2.77) per episode	< 0.0001
Birth year		
1989–1994	Reference	
⩾1995	1.413 (1.04, 1.91)	0.025
Chorioamnionitis	1.17 (0.66, 2.11)	0.59
Severe BPD only		
Gestational age	1.05 (1.04, 1.06) per week	< 0.0001
Sepsis episode	1.43 (1.04, 1.97) per episode	< 0.0001
Chorioamnionitis	0.75 (0.39, 1.41)	0.37

DISCUSSION

Our study suggests that clinical CA is not an independent risk factor for the development of moderate or severe BPD. Instead, our modeling indicates that prematurity is the primary risk factor for BPD, followed by occurrences of sepsis. CA exposure unquestionably contributes to the risk of preterm delivery[14,15] and neonatal sepsis.[16,17] However, after controlling for those factors there was no additional risk from CA exposure. These results are consistent with previous studies showing that intrauterine inflammation alone is not a risk factor for BPD.[18–20] A few studies have demonstrated a protective effect of histological CA on subsequent BPD for infants without sepsis, which is consistent with animal data.[7,18,21] However, this protective effect was not seen in the current study. Our data support the evidence that CA is not a direct risk factor for BPD.

Sepsis, in contrast, is a clear risk factor for BPD. Lahra *et al.*[18] studied risk factors for BPD in 798 infants ⩽29 weeks gestation and showed a clear association between neonatal sepsis and subsequent moderate or severe BPD (coagulase-negative staphylococcal sepsis, OR 3.17 (95% CI 2.08, 4.83); any other bacteria, OR 2.46 (95% CI 1.42, 4.27)). Similarly, Ohlin *et al.*[22] reported a cohort study of 497 infants ⩽26 weeks gestation and showed increased BPD in infants with proven sepsis (OR 1.6 (95% CI 1.6, 2.7)). A study of >7500 infants ⩽31 weeks gestation in the Canadian Neonatal Network found higher risk for BPD in infants with Gram-negative (OR 2.79 (95% CI 1.96, 3.97)) and Gram-positive (OR 1.44 (95% CI 1.21, 1.71)) sepsis compared with infants without sepsis.[23] Our findings are consistent with these reports; study infants with proven sepsis were twice as likely to develop BPD as infants without sepsis after controlling for confounders. Supportive care such as central line bundles, effective antimicrobial stewardship and standardized feeding guidelines can reduce the risk of sepsis and may also contribute to reduced risk for BPD.[24]

Birth year after 1995 was a risk factor for BPD in our study when compared with infants born between 1989 and 1994. The year 1995 was chosen because this was when antenatal corticosteroids became routine practice at our center. In logistic regression analysis, birth year rather than administration of antenatal corticosteroids produced the best model fit. This suggests that other changes over time, beyond simply antenatal corticosteroids, impacted the risk for subsequent BPD. These changes likely include improved supportive care and increased survival at lower gestational ages. Previously reported trends from the United States and Israel show a steady decline in mortality and small increases in BPD among VLBW infants over the past 15–20 years.[25,26] However, birth year was no longer significant when only severe BPD was evaluated. This suggests that the increased BPD in recent years is primarily due to mild or moderate BPD and may help to explain why BPD-associated mortality has continued to

trend down even as the incidence of BPD has risen.[27] Future studies should focus on severe BPD, as infants with severe BPD are at the highest risk for neurodevelopmental impairment and mortality.[28]

The controversy regarding whether CA exposure is a risk factor for BPD is due in part to inherent challenges involved in studying BPD. BPD has evolved over time from the fibrosis and scarring described by Northway *et al.*[29] in 1967 to the more recent arrest of alveolar development pattern seen in 'new' BPD.[2] During that time, obstetric and neonatal care (for example, antenatal corticosteroids, resuscitation practices, postnatal support) has changed dramatically.[8,30–32] Furthermore, the complex pathophysiology of BPD includes not only myriad environmental confounders but also genetic and epigenetic influences on inflammation and repair pathways, most of which are only beginning to be understood.[33,34] Finally, the definition of BPD has changed over time, from one based on histopathology, to need for $\geqslant 28$ days of oxygen support, then to need at 36 weeks postmenstrual age and currently to the complex consensus definition with physiological challenge.[11,35] BPD is a collection of clinical outcomes with variable presentation, complex pathophysiology and a shifting definition, all of which make the literature heterogeneous.

Limitations of our study include those inherent to retrospective cohort studies, although the data were collected and recorded prospectively. Our data comes from a single institution and may not be generalizable to other centers. However, the incidence of moderate or severe BPD at our center since 1996 closely approximates the median incidence in the Vermont/Oxford Network. Not all environmental exposures could be captured. Specifically, data were not available regarding patent ductus arteriosus or invasive ventilation strategies. Notably, *Ureaplasma* colonization has been clearly associated with development of BPD but is not routinely screened for at our center.[36] We attempted to control for potential demographic confounders to find the best predictive model. When models with different potential confounders forced in (for example, birth weight, gender) were analyzed, the model fit worsened. Finally, clinical CA is not an accurate predictor of histological CA, although clinical CA defined using $\geqslant 2$ findings (as in our study) was associated with the same risk for BPD as histological CA in meta-analysis.[37,38] Strengths of our study include the relatively large sample size, a robust model fit and a longitudinal database that allowed us to account for temporal trends and changes in practice.

The past 25 years have seen not only a change in care practices but a change in the nature of BPD itself. BPD is a complex condition with many inter-related risk factors, including host (demographic, clinical, and genetic), environmental (inflammation, corticosteroids, supportive care) and even microbiological factors (sepsis, airway microbiome). This complexity makes establishing specific risk factors challenging, which helps to explain the controversy regarding the role of CA on subsequent development of BPD. Our findings add to growing literature suggesting that clinical CA is not an independent risk factor for BPD. However, CA does contribute to preterm delivery and neonatal sepsis, both of which were associated with increased risk for and severity of BPD. Therefore, care practices that reduce preterm delivery and prevent neonatal sepsis—including prevention and treatment of CA—may indirectly provide some protection against the development of BPD.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

We thank C Vivek Lal, MD and Glen Cryer for their thoughtful reviews and suggestions and David R Krauss, MD for his long dedication to maintaining the Baylor Scott & White neonatal database.

REFERENCES

1 Natarajan G, Pappas A, Shankaran S, Kendrick DE, Das A, Higgins RD *et al.* Outcomes of extremely low birth weight infants with bronchopulmonary dysplasia: impact of the physiologic definition. *Early Hum Dev* 2012; **88**(7): 509–515.
2 Jobe AH. What is BPD in 2012 and what will BPD become? *Early Hum Dev* 2012; **88** (Suppl 2): S27–S28.
3 Thomas W, Speer CP. Chorioamnionitis: important risk factor or innocent bystander for neonatal outcome? *Neonatology* 2011; **99**(3): 177–187.
4 Van Marter LJ, Dammann O, Allred EN, Leviton A, Pagano M, Moore M *et al.* Chorioamnionitis, mechanical ventilation, and postnatal sepsis as modulators of chronic lung disease in preterm infants. *J Pediatr* 2002; **140**(2): 171–176.
5 Lacaze-Masmonteil T. That chorioamnionitis is a risk factor for bronchopulmonary dysplasia--the case against. *Paediatr Respir Rev* 2014; **15**(1): 53–55.
6 Thomas W, Speer CP. Chorioamnionitis is essential in the evolution of bronchopulmonary dysplasia--the case in favour. *Paediatr Respir Rev* 2014; **15**(1): 49–52.
7 Choi CW, Lee J, Oh JY, Lee SH, Lee HJ, Kim BI. Protective effect of chorioamnionitis on the development of bronchopulmonary dysplasia triggered by postnatal systemic inflammation in neonatal rats. *Pediatr Res* 2015; **79**: 287–294.
8 Schmidt B, Roberts RS, Davis P, Doyle LW, Barrington KJ, Ohlsson A *et al.* Caffeine therapy for apnea of prematurity. *N Engl J Med* 2006; **354**(20): 2112–2121.
9 Rojas-Reyes MX, Morley CJ, Soll R. Prophylactic versus selective use of surfactant in preventing morbidity and mortality in preterm infants. *Cochrane Database Syst Rev* 2012; **3**: CD000510.
10 Tita AT, Andrews WW. Diagnosis and management of clinical chorioamnionitis. *Clin Perinatol* 2010; **37**(2): 339–354.
11 Ehrenkranz RA, Walsh MC, Vohr BR, Jobe AH, Wright LL, Fanaroff AA *et al.* Validation of the National Institutes of Health consensus definition of bronchopulmonary dysplasia. *Pediatrics* 2005; **116**(6): 1353–1360.
12 Stoll BJ, Hansen NI, Sanchez PJ, Faix RG, Poindexter BB, Van Meurs KP *et al.* Early onset neonatal sepsis: the burden of group B Streptococcal and *E. coli* disease continues. *Pediatrics* 2011; **127**(5): 817–826.
13 Stoll BJ, Hansen N, Fanaroff AA, Wright LL, Carlo WA, Ehrenkranz RA *et al.* Late-onset sepsis in very low birth weight neonates: the experience of the NICHD Neonatal Research Network. *Pediatrics* 2002; **110**(2 Pt 1): 285–291.
14 Romero R, Grivel JC, Tarca AL, Chaemsaithong P, Xu Z, Fitzgerald W *et al.* Evidence of perturbations of the cytokine network in preterm labor. *Am J Obstet Gynecol* 2015; **213**(6): 836 e831–836 e818.
15 Erdemir G, Kultursay N, Calkavur S, Zekioglu O, Koroglu OA, Cakmak B *et al.* Histological chorioamnionitis: effects on premature delivery and neonatal prognosis. *Pediatr Neonatol* 2013; **54**(4): 267–274.
16 Ofman G, Vasco N, Cantey JB. Risk of early-onset sepsis following preterm, prolonged rupture of membranes with or without chorioamnionitis. *Am J Perinatol* 2015; **33**(4): 339–342.
17 Wortham JM, Hansen NI, Schrag SJ, Hale E, Van Meurs K, Sanchez PJ *et al.* Chorioamnionitis and culture-confirmed, early-onset neonatal infections. *Pediatrics* 2016; **137**(1): 1–11.
18 Lahra MM, Beeby PJ, Jeffery HE. Intrauterine inflammation, neonatal sepsis, and chronic lung disease: a 13-year hospital cohort study. *Pediatrics* 2009; **123**(5): 1314–1319.
19 Durrmeyer X, Kayem G, Sinico M, Dassieu G, Danan C, Decobert F. Perinatal risk factors for bronchopulmonary dysplasia in extremely low gestational age infants: a pregnancy disorder-based approach. *J Pediatr* 2012; **160**(4): 578–583 e572.
20 Kent A, Dahlstrom JE. Chorioamnionitis/funisitis and the development of bronchopulmonary dysplasia. *J Paediatr Child Health* 2004; **40**(7): 356–359.
21 Plakkal N, Soraisham AS, Trevenen C, Freiheit EA, Sauve R. Histological chorioamnionitis and bronchopulmonary dysplasia: a retrospective cohort study. *J Perinatol* 2013; **33**(6): 441–445.
22 Ohlin A, Bjorkman L, Serenius F, Schollin J, Kallen K. Sepsis as a risk factor for neonatal morbidity in extremely preterm infants. *Acta Paediatr* 2015; **104**(11): 1070–1076.
23 Shah J, Jefferies AL, Yoon EW, Lee SK, Shah PS, Canadian Neonatal Network. Risk factors and outcomes of late-onset bacterial sepsis in preterm neonates born at <32 weeks' gestation. *Am J Perinatol* 2015; **32** (7):675–682.
24 Cantey JB, Milstone AM. Bloodstream infections: epidemiology and resistance. *Clin Perinatol* 2015; **42**(1): 1–16, vii.
25 Stoll BJ, Hansen NI, Bell EF, Walsh MC, Carlo WA, Shankaran S *et al.* Trends in care practices, morbidity, and mortality of extremely preterm neonates, 1993-2012. *JAMA* 2015; **314**(10): 1039–1051.

26 Grisaru-Granovsky S, Reichman B, Lerner-Geva L, Boyko V, Hammerman C, Samueloff A *et al*. Population-based trends in mortality and neonatal morbidities among singleton, very preterm, very low birth weight infants over 16 years. *Early Hum Dev* 2014; **90**(12): 821–827.
27 Zysman-Colman Z, Tremblay GM, Bandeali S, Landry JS. Bronchopulmonary dysplasia - trends over three decades. *Paediatr Child Health* 2013; **18**(2): 86–90.
28 Lal CV, Ambalavanan N. Biomarkers, early diagnosis, and clinical predictors of bronchopulmonary dysplasia. *Clin Perinatol* 2015; **42**(4): 739–754.
29 Northway WH Jr., Rosan RC, Porter DY. Pulmonary disease following respirator therapy of hyaline-membrane disease. Bronchopulmonary dysplasia. *N Engl J Med* 1967; **276**(7): 357–368.
30 ACOG committee opinion. Antenatal corticosteroid therapy for fetal maturation. Number 210, October 1998 (Replaces Number 147, December 1994). Committee on Obstetric Practice. American College of Obstetricians and Gynecologists. *Int J Gynaecol Obstet* 1999; **64** (3):334–335.
31 Stevens TP, Finer NN, Carlo WA, Szilagyi PG, Phelps DL, Walsh MC *et al*. Respiratory outcomes of the surfactant positive pressure and oximetry randomized trial (SUPPORT). *J Pediatr* 2014; **165**(2): 240–249 e244.
32 Kapadia VS, Chalak LF, Sparks JE, Allen JR, Savani RC, Wyckoff MH. Resuscitation of preterm neonates with limited versus high oxygen strategy. *Pediatrics* 2013; **132** (6): e1488–e1496.
33 McEvoy CT, Aschner JL. The natural history of bronchopulmonary dysplasia: the case for primary prevention. *Clin Perinatol* 2015; **42**(4): 911–931.
34 Lal CV, Ambalavanan N. Genetic predisposition to bronchopulmonary dysplasia. *Semin Perinatol* 2015; **39**(8): 584–591.
35 Sahni R, Ammari A, Suri MS, Milisavljevic V, Ohira-Kist K, Wung JT *et al*. Is the new definition of bronchopulmonary dysplasia more useful? *J Perinatol* 2005; **25**(1): 41–46.
36 Viscardi RM, Kallapur SG. Role of ureaplasma respiratory tract colonization in bronchopulmonary dysplasia pathogenesis: current concepts and update. *Clin Perinatol* 2015; **42**(4): 719–738.
37 Hartling L, Liang Y, Lacaze-Masmonteil T. Chorioamnionitis as a risk factor for bronchopulmonary dysplasia: a systematic review and meta-analysis. *Arch Dis Child Fetal Neonatal Ed* 2012; **97**(1): F8–F17.
38 Curtin WM, Katzman PJ, Florescue H, Metlay LA. Accuracy of signs of clinical chorioamnionitis in the term parturient. *J Perinatol* 2013; **33**(6): 422–428.