Trends and variation in management and outcomes of very low-birth-weight infants with patent ductus arteriosus

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BACKGROUND: We examined recent trends and interhospital variation in use of indomethacin, ibuprofen, and surgical ligation for patent ductus arteriosus (PDA) in very-low-birth-weight (VLBW) infants.

METHODS: Included in this retrospective study of the Pediatric Hospital Information System database were 13,853 VLBW infants from 19 US children's hospitals, admitted at age < 3 d between 1 January 2005 and 31 December 2014. PDA management and in-hospital outcomes were examined for trends and variation.

RESULTS: PDA was diagnosed in 5,719 (42%) VLBW infants. Cyclooxygenase inhibitors and/or ligation were used in 74% of infants with PDA overall, however studied hospitals varied greatly in PDA management. Odds of any cyclooxygenase inhibitor or surgical treatment for PDA decreased 11% per year during the study period. This was temporally associated with improved survival but also with increasing bronchopulmonary dysplasia, periventricular leukomalacia, retinopathy of prematurity, and acute renal failure in unadjusted analyses. There was no detectable correlation between hospital-specific changes in PDA management and hospital-specific changes in outcomes of preterm birth during the study period.

CONCLUSION: Use of cyclooxygenase inhibitors and ligation for PDA in VLBW infants decreased over a 10-y period at the studied hospitals. Further evidence is needed to assess the impact of this change in PDA management.

Patent ductus arteriosus (PDA) is diagnosed in 39% of very-low-birth-weight infants (VLBW, <1,500 g birth weight), and up to 70% of infants born before 28 wk gestation (1,2). Preterm infants with PDA are at increased risk for a number of complications, including death, bronchopulmonary dysplasia (BPD), pulmonary hemorrhage, necrotizing enterocolitis (NEC), and periventricular leukomalacia (PVL) (3,4), however it is unclear whether these associations represent a causal relationship (5). While pharmacological therapy with cyclooxygenase inhibitors (COXI) and surgical ductus ligation have been common in the care of premature infants for decades (6–8), these treatments carry risks of short- and long-term complications (4,9,10), and may not reduce the risk of important morbidities such as BPD or NEC (11–14).

Recent years have seen growing calls for either more selective attempts at PDA closure (2,15–18), or abandoning routine attempts at closure altogether (4,19). Satisfactory outcomes using less aggressive management of PDA have been presented as alternatives to usual care (18,20). It is unclear whether clinical practices have changed in response to these published reassessments of the literature and, if so, whether clinical outcomes have changed as well. Accordingly, the objectives of this study were to examine trends and inter-hospital variability in pharmacological and surgical management of PDA, and to describe contemporaneous trends in outcomes for infants with PDA. We hypothesized that use of indomethacin, ibuprofen, and surgical ligation for PDA in VLBW infants changed significantly during the period studied.

RESULTS

Inclusion criteria were met by 13,853 VLBW infants from 19 US referral children's hospitals (**Figure 1**). PDA was diagnosed in 42.3% (n = 5,719) of VLBW infants overall, 49.9% in Group 1 (3,539/7,096), and 32.3% (2,180/6,757) in Group 2. No significant secular trend was detected in the VLBW cohort during the study period with respect to proportion diagnosed with PDA. No significant secular trends were found regarding proportion of Group 1 vs. Group 2 infants in either the VLBW cohort overall or in VLBW infants diagnosed with PDA.

Among VLBW infants with PDA, 5,068 were admitted on the day of birth, 544 at 1 d of age, and 107 at 2 d of age. In all, 4,209 (73.6%) infants diagnosed with PDA were treated with COXI or ligation (**Supplementary Figure S1** online). Infants with PDA treated with COXI included 3,138 (54.9%) with indomethacin, 601 (10.5%) with ibuprofen, and 150 (2.6%) with both. PDA ligation was performed for 1,580 (27.6%) infants, including 1,260 (22.0%) who received COXI

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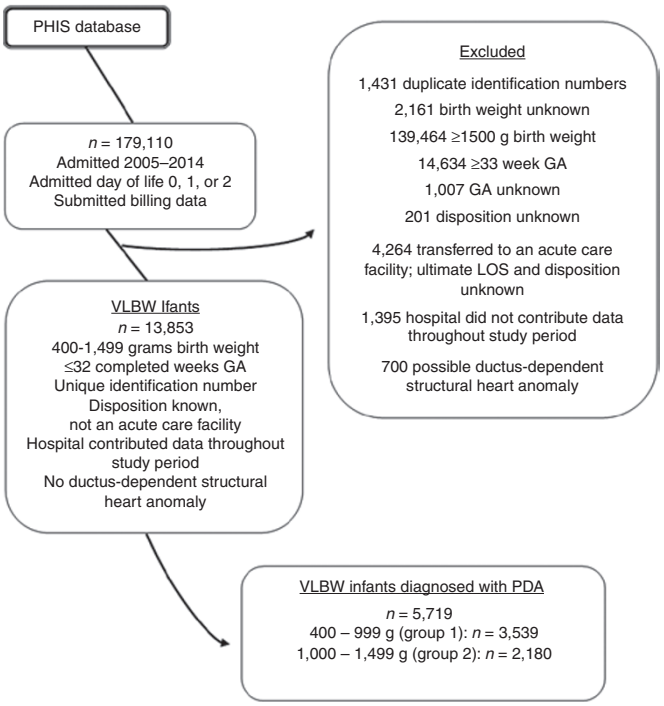

Figure 1. Derivation of study cohort.

therapy followed by ligation. For those treated, COXI therapy was started at median (25th, 75th percentile) (range) age of 2 (1, 4) (0–51) days with 3 (2, 4) (1–14) days of therapy in total. Ductus ligations were performed at 18 (10, 28) (0–219) days of age.

Secular Trends in PDA Treatment

Trends in PDA treatment for VLBW infants with PDA are shown in Table 1 and Figure 2. A general trend of decreasing frequency of treatment for PDA was evident in a variety of measures during the study period. Among VLBW infants with PDA, COXI therapy decreased significantly overall and individually for indomethacin, however odds of receiving ibuprofen increased during the study period. Odds of PDA ligation also decreased overall and as rescue therapy following COXI therapy. Also significantly decreasing with time were odds of COXI without ligation; indomethacin therapy on day 0 or day 1, and the combined outcome of any COXI or surgical ligation. Most of these trends occurred in both Group 1 and Group 2. Overall, there was a 11% decrease per year in odds of treatment with either COXI or PDA ligation during the study period, including a 11% decrease per year in Group 1 and 14% decrease per year in Group 2. An exception to this general trend was ligation as sole therapy for PDA, which showed an overall 4% increase in odds per year during the study period.

VLBW infants with PDA treated with COXI were started on therapy significantly later each year, while for those ligated chronological age at the time of the procedure increased significantly with time (Table 2). These statistical trends represented increases of less than 1 d over the 10-y study period.

Table 1. Change per year among 5,719 VLBW infants with PDA in treatment for PDA, hierarchical logistic regression, 19 US referral children's hospitals, 2005–2014

Categorical outcomes	*N* (% VLBW with PDA)	OR (95% CI)[a]	*P**
PDA, no COX inhibitor, no ligation	1,510 (26.4)	1.13 (1.11, 1.15)	<0.001
400–999 g	616	1.12 (1.09, 1.15)	<0.001
1,000–1,499 g	894	1.17 (1.13, 1.20)	<0.001
COX inhibitor	3,889 (68.0)	0.89 (0.87, 0.91)	<0.001
400–999 g	2,686	0.91 (0.80, 0.93)	<0.001
1,000–1,499 g	1,203	0.86 (0.83, 0.88)	<0.001
Any indomethacin	3,288 (57.5)	0.87 (0.86,0.89)	<0.001
400–999 g	2,292	0.89 (0.87, 0.92)	<0.001
1,000–1,499 g	996	0.83 (0.81, 0.86)	<0.001
Any ibuprofen	751 (13.1)	1.05 (1.01,1.08)	0.006
400–999 g	519	1.05 (1.01, 1.09)	0.022
1,000–1,499 g	232	1.05 (0.99, 1.11)	0.104
COX inhibitor, no ligation	2,629 (46.0)	0.96 (0.94, 0.98)	<0.001
400–999 g	1,612	1.01 (0.99, 1.04)	0.385
1,000–1,499 g	1,017	0.89 (0.86, 0.92)	<0.001
Indomethacin therapy, day 0 or day 1	1,450 (25.4)	0.94 (0.92, 0.96)	<0.001
400–999 g	1,227	0.96 (0.94, 0.99)	0.006
1,000–1,499 g	223	0.86 (0.81, 0.91)	<0.001
Ligation	1,580 (27.6)	0.93 (0.91, 0.95)	<0.001
400–999 g	1,311	0.92 (0.90, 0.94)	<0.001
1,000–1,499 g	269	0.92 (0.88, 0.97)	<0.001
Ligation without COX inhibitor	320 (5.6)	1.04 (1.01, 1.08)	0.018
400–999 g	237	1.03 (0.99, 1.07)	0.129
1,000–1,499 g	83	1.04 (0.97, 1.10)	0.287
COX inhibitor or ligation	4,209 (73.6)	0.89 (0.87, 0.90)	<0.001
400–999 g	2,923	0.89 (0.87, 0.92)	<0.001
1,000–1,499 g	1,286	0.86 (0.83, 0.89)	<0.001
COX inhibitor and ligation	1,260 (22.0)	0.91 (0.88, 0.93)	<0.001
400–999 g	1,074	0.90 (0.88, 0.93)	<0.001
1,000–1,499 g	186	0.88 (0.82, 0.93)	<0.001

[a]All trends adjusted for clustering of infants within hospitals. *Multivariate hierarchical logistic regression.
PDA, patent ductus arteriosus; VLBW, very low birth weight.

Variation in PDA-Related Treatment Among Hospitals

Trends and variation in hospital-specific rates of PDA treatment in 2005–2009 vs. 2010–2014 are provided in Table 3. For VLBW infants with PDA born 2010–2014, the more recent half of the study, hospital-specific median rates of COXI treatment ranged from 20 to 79%, while median rates of ligation ranged from 0 to 54%. Between the first and second halves of the study period, 18 of 19 studied hospitals decreased the proportion of VLBW infants with PDA who were treated with either COXI or ligation.

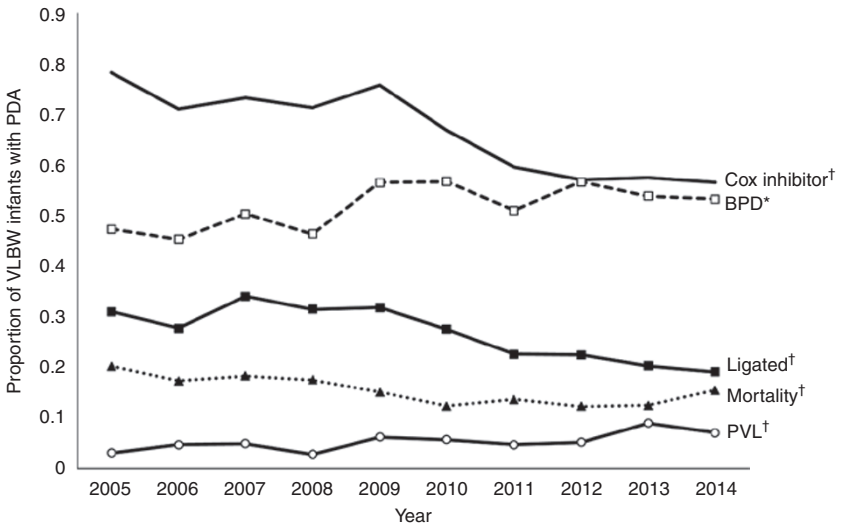

Figure 2. Trends in treatment and outcomes among 5,719 very-low-birth-weight infants with patent ductus arteriosus at 19 US referral children's hospitals, 2005–2014. *$P < 0.01$; †$P < 0.001$.

Secular Trends in Clinical Outcomes

Trends in clinical outcomes for VLBW infants with PDA are shown in Table 4. Mortality decreased in this cohort overall, driven by an 8% decrease per year in odds of mortality in Group 1 without significant change in Group 2. Also observed in Group l were increasing odds of BPD, PVL, and any stage retinopathy of prematurity (ROP), but decreasing odds of NEC stage 3 or SIP. Observed in both groups were decreasing odds per year of any diuretic therapy but increasing odds of acute renal failure (ARF) and any systemic steroid therapy.

Vocal cord paralysis occurred in about 11% of infants in the study cohort (Table 4). Among Group 1 infants this included 14.7% of infants undergoing PDA ligation vs. 11.5% not undergoing ligation, and 10.8% for those ligated vs. 8.4% not ligated in Group 2. These differences were not statistically significant. Similarly, there was no detectable trend in incidence of grade 3 or grade 4 intraventricular hemorrhage (IVH), any stage NEC, pulmonary hemorrhage, or ROP treatment with laser photocoagulation or bevacizumab in either birth weight group or the cohort overall. Duration of positive pressure respiratory support, duration of systemic steroid therapy, and length of stay among infants with PDA surviving to hospital discharge increased significantly by less than one day over the 10-y study period (Table 2).

Correlation of Hospital-Specific Rates of Treatment and Outcomes

Sixteen hospitals had at least 10 infants in Group 1 and Group 2 in each half of the study. No significant correlation was evident between hospital-specific changes in rates of COXI use and hospital-specific changes in ligation. No significant correlations were evident between hospital-specific changes in rates of PDA management and hospital-specific changes in outcomes of preterm birth in either birth weight group after controlling false discovery rate.

DISCUSSION

This study of VLBW infants from 19 US referral children's hospitals documents significant secular trends in pharmacological and surgical treatment for PDA over the past decade. Use of COX inhibitors decreased significantly during the 2005–2014 study period, and when used the likelihood of choosing ibuprofen over indomethacin increased. PDA ligation decreased with time, and became more likely to occur without preceding COXI as the study period progressed. These changes were not associated with detectable adverse trends in survival, severe IVH, pulmonary hemorrhage, NEC or severe NEC/SIP, or frequency of diuretic use at the studied hospitals.

A number of authors have highlighted the lack of evidence of long-term benefit accompanying the evident risks associated with PDA treatment. It has been suggested that routine attempts to close the ductus in preterm infants be replaced by more selective treatment (2,4,15–20). Our results indicate that, reflecting this literature, PDA management at the studied hospitals has become less aggressive in the past decade.

Significant secular trends were identified as well in outcomes of preterm birth among VLBW infants with PDA during the study period. Apparent increases in BPD, PVL, ROP, and ARF raise concerns regarding the safety of a less aggressive approach to PDA closure. However, this retrospective study cannot establish causal relationships, and the unadjusted contemporaneous trends identified here must be interpreted with caution (21). For example, decreasing use of COXI and PDA ligation during the study period was temporally associated in Group 1 with significant increases in BPD, any ROP, and PVL. However, mortality decreased in Group 1 as well. It is possible that improved survival among Group 1 infants increased the number of infants at high risk for BPD, any ROP, and PVL, thus confounding the temporal association between changes in these diagnoses and changes in PDA treatment and complicating interpretation. The temporal associations we report

Table 2. Change per year among 5,719 VLBW infants with PDA in characteristics of treatment for PDA, diuretic therapy, steroid therapy, positive pressure respiratory support, and length of stay, hierarchical linear regression, 19 US referral children's hospitals, 2005–2014

Continuous outcomes	*N*	β (95% CI)[b]	*P**
Age at ligation, days, ligated infants[a]	1,580	0.04 (0.03, 0.06)	<0.001
400–999 g	1,311	0.04 (0.03, 0.06)	<0.001
1,000–1,499 g	269	0.05 (0.02, 0.09)	0.003
Age at first treatment with COX inhibitor, days, treated infants[a]	3,889	0.026 (0.017, 0.035)	<0.001
400–999 g	2,686	0.02 (0.01, 0.03)	<0.001
1,000–1,499 g	1,203	0.04 (0.02, 0.05)	<0.001
Days of COX inhibitor therapy, treated infants[a]	3,889	0.015 (0.011, 0.02)	<0.001
400–999 g	2,686	0.014 (0.008, 0.019)	<0.001
1,000–1,499 g	1,203	0.016 (0.008, 0.024)	<0.001
Days of diuretic therapy, treated infants[a]	4,501	0 (−0.01, 0.02)	0.644
400–999 g	3,102	−0.01 (−0.03, 0)	0.101
1,000–1,499 g	1,399	0.04 (0.01, 0.06)	0.005
Days of systemic steroid therapy, treated infants[a]	2,767	0.03 (0.02, 0.05)	<0.001
400–999 g	2,209	0.03 (0.02, 0.05)	<0.001
1,000–1,499 g	558	0.04 (0.01, 0.07)	0.009
Days of positive pressure respiratory support, treated infants[a]	4,908	0.06 (0.05, 0.07)	<0.001
400–999 g	3,159	0.08 (0.06, 0.09)	<0.001
1,000–1,499 g	1,749	0.05 (0.03, 0.07)	<0.001
Length of stay, days, survivors[a,c]	3,527	0.022 (0.017, 0.027)	<0.001
400–999 g	1,991	0.012 (0.006, 0.017)	<0.001
1,000–1,499 g	1,536	0.024 (0.017, 0.031)	<0.001
Length of stay, days, nonsurvivors[a]	901	0.02 (−0.01, 0.05)	0.233
400–999 g	738	0.03 (0, 0.06)	0.056
1,000–1,499 g	163	−0.01 (−0.07, 0.06)	0.858

[a]Natural log-transformed for hierarchical linear regression analysis, reverse transformed for presentation as β (95% CI). [b]All trends adjusted for clustering of infants within hospitals. [c]Limited to infants discharged to home rather than transferred. *Hierarchical linear regression.
PDA, patent ductus arteriosus; VLBW, very low birth weight.

may be due partly or entirely to such confounding by known or unknown factors. Nonetheless, this study reports a trend of decreasing COXI and surgical PDA closure at 19 tertiary referral NICUs without evidence of increased mortality, severe IVH, NEC or severe NEC/SIP, pulmonary hemorrhage, or diuretic use.

Congestive heart failure appeared to increase among VLBW infants with PDA in our cohort during the study period, with $P = 0.04$. However, this finding was not significant after controlling false discovery rate, indicating that there is a >5% likelihood that this finding is a false positive.

This study also documents substantial variability among hospitals in use of COXI and PDA ligation. However, we found no significant correlation between hospital-specific changes in PDA management and corresponding changes in outcomes of preterm birth during the 10-y study period. This result provides some support for recommendations that routine efforts at PDA closure be moderated. Further research is needed to establish the safety of more selective PDA closure and to determine whether specific subgroups of VLBW infants are appropriate for conservative management vs. more aggressive PDA closure.

Using the Kids' Inpatient Database, Weinberg *et al.* documented wide interhospital variation in PDA ligation for infants born ≤32 wk in 2003, 2006, and 2009, with an overall ligation rate of 14% (22). They identified an increase in PDA ligation among infants born ≤28 wk of gestation from 14% in 2003 to 21% in 2009. From 2005 to 2014, we documented persistent variation in PDA management, and similarly found that the rate of ligation peaked in 2007 at studied hospitals (**Figure 2**). However, thereafter rates of ligation decreased for both birth weight subgroups. Overall, this study documented a PDA ligation rate of 28% for VLBW infants with PDA, higher than that reported by Weinberg and colleagues. This is not surprising, since children's hospitals were more likely than other centers to perform PDA ligations in their study. PDA was also diagnosed more frequently among VLBW infants in this study (42%) compared to the prior study (17%). These differences may in part reflect differences between the two studies regarding selection criteria (infants < 1,500 g at birth vs. ≤ 32 wk EGA) or age at evaluation. Further, it is possible that the tertiary referral children's hospitals we studied were more aggressive with diagnostic or screening echocardiograms than the more diverse group of hospitals contributing to the Kids' Inpatient

Table 3. Hospital-specific rates of treatment in VLBW infants with PDA, 2005–2009 vs. 2010–2014, 19 US referral children's hospitals

	2005–2009	2010–2014	*P**
PDA, no COX inhibitor, no ligation	0.23 (0.16, 0.35) (0.09–0.61)	0.40 (0.27, 0.52) (0.14–0.80)	0.001
COX inhibitor or PDA ligation	0.77 (0.65, 0.84) (0.39–0.91)	0.60 (0.48, 0.73) (0.20–0.86)	0.001
COX inhibitor	0.70 (0.46, 0.80) (0.29–0.90)	0.44 (0.34, 0.64) (0.20–0.79)	0.001
Ligation	0.30 (0.22, 0.39) (0.14–0.52)	0.21 (0.17, 0.26) (0–0.54)	0.002

Hospital-specific proportion or median values summarized as median (25th, 75th percentile) (range).
*Related-samples Wilcoxon Signed Ranks test.
PDA, patent ductus arteriosus; VLBW, very low birth weight.

Table 4. Change per year among 5,719 VLBW infants with PDA in rates of outcomes of prematurity, diuretic use and systemic steroid use, 19 US referral children's hospitals, 2005–2014

Categorical outcomes	N (% VLBW with PDA)	OR (95% CI)[a]	*P**
Mortality	901 (15.8)	0.94 (0.91, 0.96)	<0.001
400–999 g	738	0.92 (0.89, 0.94)	<0.001
1,000–1,499 g	163	0.98 (0.94, 1.03)	0.516
Bronchopulmonary dysplasia	2,934 (51.3)	1.03 (1.01, 1.05)	0.002
400–999 g	2,196	1.03 (1.01, 1.06)	0.009
1,000–1,499 g	738	1.03 (1.00,1.06)	0.068
Intraventricular hemorrhage grade 3 or 4	898 (15.7)	1.0 (0.97,1.02)	0.790
400–999 g	699	0.98 (0.95,1.01)	0.272
1,000–1,499 g	199	1.02 (0.97,1.07)	0.445
Congestive heart failure	111 (1.9)	1.06 (1.003, 1.13)	0.04[c]
400–999 g	75	1.06 (0.99, 1.13)	0.121
1,000–1,499 g	36	1.09 (0.97, 1.22)	0.153
Pulmonary hemorrhage	274 (4.8)	1.02 (0.97, 1.06)	0.414
400–999 g	216	1.0 (0.95, 1.05)	0.99
1,000–1,499 g	58	1.07 (0.98, 1.17)	0.148
NEC, any stage	823 (14.4)	1.0 (0.97, 1.02)	0.718
400–999 g	598	1.0 (0.97, 1.03)	0.934
1,000–1,499 g	225	0.98 (0.94, 1.03)	0.472
NEC stage 3 or Spontaneous Intestinal Perforation[b]	151 (2.6)	0.88 (0.80, 0.97)	0.011
400–999 g	133	0.89 (0.80, 0.98)	0.023
1,000–1,499 g	18	0.87 (0.68, 1.12)	0.274
Periventricular leukomalacia	290 (5.1)	1.09 (1.04, 1.13)	<0.001
400–999 g	208	1.13 (1.08, 1.19)	<0.001
1,000–1,499 g	82	0.98 (0.91, 1.06)	0.629
Acute renal failure	350 (6.1)	1.08 (1.039,1.12)	<0.001
400–999 g	286	1.05 (1.009,1.095)	0.018
1,000–1,499 g	64	1.18 (1.09, 1.28)	<0.001
Vocal cord paralysis	639 (11.2)	1.02 (0.99, 1.05)	0.106
400–999 g	449	1.04 (1.00, 1.07)	0.051
1,000–1,499 g	190	1.01 (0.96, 1.06)	0.770
ROP, any	2,236 (39.1)	1.06 (1.04, 1.08)	<0.001
400–999 g	1,739	1.10 (1.07, 1.12)	<0.001
1,000–1,499 g	497	1.01 (0.97, 1.05)	0.608
ROP treated with laser photocoagulation or bevacizumab	508 (8.9)	0.98 (0.94, 1.01)	0.194
400–999 g	486	0.97 (0.94,1.004)	0.086
1,000–1,499 g	22	1.06 (0.93, 1.20)	0.371
Diuretic therapy, any	4,501 (78.7)	0.93 (0.91, 0.95)	<0.001
400–999 g	3,108	0.92 (0.88, 0.95)	<0.001
1,000–1,499 g	1,393	0.93 (0.90, 0.96)	<0.001
Systemic steroid therapy, any	2,767 (48.4)	1.03 (1.01, 1.05)	0.001
400–999 g	2,209	1.03 (1.005, 1.06)	0.017
1,000–1,499 g	558	1.04 (1.005, 1.08)	0.026

[a]All trends adjusted for clustering of infants within hospitals. [b]2009–2014. [c]Not statistically significant after controlling for false discovery rate. *Multivariate hierarchical logistic regression.

NEC, necrotizing enterocolitis; PDA, patent ductus arteriosus; ROP, retinopathy of prematurity; VLBW, very low birth weight.

Database, or may have cared for sicker infants. Weinberg and colleagues did not examine pharmacological treatment for PDA, however a recent survey reported practice variation in COXI use among and within NICUs (23). We were unable to locate prior multicenter studies examining trends in use of COXI for PDA.

The Vermont Oxford Network (VON) reported decreasing mortality in the lower birth weight subgroups of VLBW infants between 2000 and 2009, similar to our findings (24). Not surprisingly, the mortality rate of 16.5% we observed in VLBW infants with PDA is slightly higher than that observed in VON NICUs for VLBW infants overall. However, we report increasing bronchopulmonary dysplasia in VLBW infants with PDA between 2005 and 2014 driven by an increase in BPD in Group 1, in contrast to VON findings of decreasing BPD in VLBW infants overall between 2000 and 2009.

Indomethacin given on the day of birth or the following day may have been intended primarily as prophylaxis against severe intraventricular hemorrhage. However, early COXI therapy reduces the incidence of hemodynamically significant PDA, so that COXI given on the day of birth or the following day may be partly or primarily intended as PDA prophylaxis (25,26). In our cohort of VLBW infants with PDA 10% (61/601) of infants treated exclusively with ibuprofen received this intervention on the day of birth or the following day, yet ibuprofen has no evidence-based role in IVH prophylaxis. Thus, speculation regarding the motivation for indomethacin use based on early timing of therapy may be problematic. Treatment with indomethacin on the first or second day of life was therefore included in our definition of PDA treatment. It is noteworthy that, as with other interventions promoting ductal closure, use of indomethacin on the first or second day of life decreased over the course of our study period. The present focus on the flaws in the literature supporting interventions to close the ductus may be prompting a reassessment of the benefits and risks of early indomethacin including its role in IVH prophylaxis.

The observed increase in PDA ligation without prior COXI therapy was an unexpected finding. There was a contemporaneous increase in the diagnosis of ARF in the cohort of VLBW infants with PDA from studied hospitals, and the numbers of infants with ARF are approximately comparable to those ligated without prior pharmacotherapy. The increase in ligation without prior pharmacotherapy may thus represent an increase among infants in the study cohort with contraindications to COXI therapy. It is possible that, rather than a COXI, some of these infants may have received acetaminophen prior to ligation, which we did not examine. While evidence from randomized trials is emerging examining acetaminophen as an intervention for ductal closure, the number of reported patients remains small (27).

Statistical analyses in this study adjusted for correlation due to clustering of infants within hospitals, reducing risk of type I error. Controlling false discovery rate to <5% further strengthened the study findings. Robust sample size reduced risk of type II error. However, we may have overlooked small but clinically important trends in treatment or outcomes. The study's retrospective design limited the scope of collected data and the ability to draw causal inferences. Also, because diagnoses were ascertained using ICD-9 codes, it was not feasible to determine whether PDA was diagnosed clinically or echocardiographically, or the criteria used to diagnose NEC or BPD. It is possible that some infants may have received indomethacin treatment at an outside referring hospital on day 0 or 1. However, only 107 infants in the study cohort were admitted after 1 d of age, making the potential impact of any resulting misclassification small. Finally, this study could not examine post-discharge mortality, morbidities, or neurodevelopmental outcomes.

Conclusion

In summary, we report significant secular trends in pharmacological and surgical PDA management and in contemporaneous outcomes of preterm birth at 19 US tertiary referral children's hospitals over the past decade. This study documents a general trend of decreasing frequency of COXI and surgical therapy for PDA, and provides new data regarding the current extent and variation in PDA treatment for VLBW infants in US tertiary referral children's hospitals. These results will be of interest to those investigating the epidemiology of PDA management and sequelae of prematurity, as well as to care providers concerned that decreasing intervention for infants with PDA may be increasing risk for adverse outcomes.

Urgent calls for further randomized trials examining management alternatives for PDA have become commonplace. A small number of such trials are underway, including some that will examine long-term neurodevelopmental outcomes (28–30). The persistent variation in PDA treatment in the most recent 5 y of our study illustrates a continued need for new studies to help guide management of this common condition in VLBW infants.

METHODS

Data for this study were obtained from the Pediatric Health Information System (PHIS), an administrative database containing inpatient data from 49 not-for-profit, tertiary care pediatric hospitals in the United States (31). These hospitals are affiliated with the Children's Hospital Association (CHA). Data quality and reliability are assured through a joint effort between the CHA and participating hospitals, while the data warehouse function for the database is managed by Truven Health Analytics. Data are deidentified but linked at the time of data submission and are subjected to reliability and validity checks before inclusion in the database.

PHIS hospitals reporting both inpatient and billing data were included in this analysis. Hospitals were omitted if they did not submit billing data for the entire duration of the study period. This study was approved by the Institutional Review Board at Connecticut Children's Medical Center.

Subjects

Included were neonates born between 1 January 2005 and 31 December 2014 with birth weight 400–1,499 g, who had initial PHIS hospital admission on day of life 0, 1, or 2. Readmission hospitalizations were excluded. As presence or absence of specific diagnoses and therapies were determined from billing data, patients with missing billing data including pharmacy or respiratory support billing data, or with $0 total billed from all sources during their inpatient stay were excluded. Data obtained from the PHIS database included demographics, date of birth, medications and dates of therapy, date of

PDA ligation if applicable, in-hospital clinical outcomes, and disposition. Birth weight was subgrouped by International Classification of Disease—Ninth Revision (ICD-9) code. Diagnoses and procedures were determined by ICD-9 code. Necrotizing enterocolitis (NEC) was coded as a general diagnosis throughout the study period but was coded by stage starting in 2009, therefore trends in severe NEC grouped with spontaneous intestinal perforation (SIP) were examined starting in that year. Infants were excluded if they had an ICD-9 code for a congenital heart anomaly that might result in ductal-dependent systemic or pulmonary blood flow or ductal-dependent oxygenation, as such lesions could require that clinicians change their usual approach to PDA management. Length of stay (LOS) was calculated. Annual and overall rates of outcomes and use of therapies were determined for each hospital and for the cohort as a whole. PDA treatment was defined as any COXI therapy with either indomethacin or ibuprofen including the day of birth or the following day, or ductus ligation.

Statistics

Analyses of independent data were performed using SPSS 18.0 (IBM Corporation, Armonk, NY). Paired 5-y hospital-specific rates of use of PDA management strategies (any COXI, any ligation, no COXI or ligation) were calculated for both Group 1 and Group 2 for the first (2005–2009) and second (2010–2014) halves of the study period. Correlations between hospital-specific changes in rates of PDA therapies and changes in rates of outcomes of preterm birth (BPD, PVL, ARF, stage 3 NEC/SIP) between the first and second halves of the study were assessed using partial correlation adjusted for hospital-specific and birth weight group-specific mortality rate. These analyses were limited to hospitals with a minimum of 10 infants in each birth weight group in each half of the study.

For some analyses data were not independent due to clustering of infants within hospitals; in such cases univariate and multivariate analyses were performed with hierarchical linear or logistic regression using HLM 7.0 (Scientific Software International, Lincolnwood, IL) (32). Secular trends were described with odds ratios and 95% confidence intervals, with year of birth as independent infant-level variable and PDA treatment or outcome of prematurity as dependent variable. Trends were examined for the cohort overall, and separately for infants with birth weight 400–999 g (Group 1) and those with birth weight 1,000–1,499 g (Group 2). Continuous outcomes were natural log-transformed where necessary to ensure normal distribution for analysis, then reverse transformed for clarity when reporting results. All statistical tests were two-tailed.

False discovery rate was controlled <5% by adjusting significance levels using the Benjamini-Hochberg method (33). False discovery rate was controlled separately for analyses performed for the entire cohort of VLBW infants, for infants diagnosed with PDA, for Group 1, for Group 2, and for hospitals to ensure that the distribution of *P* values was properly scaled among tests performed with equal sample sizes (33).

SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at http://www.nature.com/pr

AUTHOR CONTRIBUTIONS

J.I.H. conceptualized and designed the study, supervised data analysis, drafted and revised the manuscript, and approved the final manuscript as submitted. E.A.B. conceptualized and designed the study, performed data analysis, reviewed and revised the manuscript, and approved the final manuscript as submitted. J.M.T. conceptualized and designed the study, performed data analysis, reviewed and revised the manuscript, and approved the final manuscript as submitted. K.R.J. conceptualized and designed the study, performed data analysis, reviewed and revised the manuscript, and approved the final manuscript as submitted. S.L. conceptualized and designed the study, performed data analysis, reviewed and revised the manuscript, and approved the final manuscript as submitted. B.T.C. conceptualized and designed the study, reviewed and revised the manuscript, and approved the final manuscript as submitted. K.W.H. conceptualized and designed the study, performed data collection and analysis, reviewed and revised the manuscript, and approved the final manuscript as submitted.

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REFERENCES

1. Vermont Oxford Network. Nightingale Database. Network Databases 2016; (https://nightingale.vtoxford.org/home.aspx).
2. Clyman RI, Couto J, Murphy GM. Patent ductus arteriosus: are current neonatal treatment options better or worse than no treatment at all? Semin Perinatol 2012;36:123–9.
3. Benitz WE. Learning to live with patency of the ductus arteriosus in preterm infants. J Perinatol 2011;31 Suppl 1:S42–8.
4. Benitz W. Patent ductus arteriosus: to treat or not to treat? Arch Dis Child Fetal Neonatal Ed 2012;97:F80–2.
5. Clyman RI, Chorne N. Patent ductus arteriosus: evidence for and against treatment. J Pediatr 2007;150:216–9.
6. Cotton RB, Stahlman MT, Bender HW, Graham TP, Catterton WZ, Kovar I. Randomized trial of early closure of symptomatic patent ductus arteriosus in small preterm infants. J Pediatr 1978;93:647–51.
7. Cotton RB, Stahlman MT, Kovar I, Catterton WZ. Medical management of small preterm infants with symptomatic patent ductus arteriosus. J Pediatr 1978;92:467–73.
8. Kitterman JA, Edmunds LH Jr, Gregory GA, Heymann MA, Tooley WH, Rudolph AM. Patent ducts arteriosus in premature infants. Incidence, relation to pulmonary disease and management. N Engl J Med 1972;287:473–7.
9. Madan JC, Kendrick D, Hagadorn JI, Frantz ID 3rd; National Institute of Child Health and Human Development Neonatal Research Network. Patent ductus arteriosus therapy: impact on neonatal and 18-month outcome. Pediatrics 2009;123:674–81.
10. Chorne N, Leonard C, Piecuch R, Clyman RI. Patent ductus arteriosus and its treatment as risk factors for neonatal and neurodevelopmental morbidity. Pediatrics 2007;119:1165–74.
11. Jensen EA, Schmidt B. Epidemiology of bronchopulmonary dysplasia. Birth Defects Res A Clin Mol Teratol 2014;100:145–57.
12. Benitz WE. Treatment of persistent patent ductus arteriosus in preterm infants: time to accept the null hypothesis? J Perinatol 2010;30:241–52.
13. Sosenko IR, Fajardo MF, Claure N, Bancalari E. Timing of patent ductus arteriosus treatment and respiratory outcome in premature infants: a double-blind randomized controlled trial. J Pediatr 2012;160:929–35.e1.
14. Schmidt B, Roberts RS, Fanaroff A, et al.; TIPP Investigators. Indomethacin prophylaxis, patent ductus arteriosus, and the risk of bronchopulmonary dysplasia: further analyses from the Trial of Indomethacin Prophylaxis in Preterms (TIPP). J Pediatr 2006;148:730–4.
15. Bose CL, Laughon M. Treatment to prevent patency of the ductus arteriosus: beneficial or harmful? J Pediatr 2006;148:713–4.
16. Bose CL, Laughon M. Patent ductus arteriosus: lack of evidence for common treatments. Arch Dis Child Fetal Neonatal Ed 2007;92:F498-502.
17. Clyman RI. Surgical ligation of the patent ductus arteriosus: treatment or morbidity? J Pediatr 2012;161:583–4.
18. Jhaveri N, Moon-Grady A, Clyman RI. Early surgical ligation versus a conservative approach for management of patent ductus arteriosus that fails to close after indomethacin treatment. J Pediatr 2010;157:381–7, 387.e1.
19. Laughon MM, Simmons MA, Bose CL. Patency of the ductus arteriosus in the premature infant: is it pathologic? Should it be treated? Curr Opin Pediatr 2004;16:146–51.
20. Vanhaesebrouck S, Zonnenberg I, Vandervoort P, Bruneel E, Van Hoestenberghe M, Theyskens C. Conservative treatment for patent ductus arteriosus in the preterm. Arch Dis Child Fetal Neonatal Ed 2007;92:F244-7.
21. Petitti DB. Associations are not effects. Am J Epidemiol 1991;133:101–2.
22. Weinberg J, Evans F, Burns K, Pearson G, Kaltman J. Surgical ligation of patent ductus arteriosus in premature infants: trends and practice variation. Cardiol Young 2015:1–8.
23. Slaughter JL, Reagan PB, Bapat RV, Newman TB, Klebanoff MA. Nonsteroidal anti-inflammatory administration and patent ductus arteriosus ligation, a survey of practice preferences at US children's hospitals. Eur J Pediatr 2016;175:775–83.

24. Horbar JD, Carpenter JH, Badger GJ, et al. Mortality and neonatal morbidity among infants 501 to 1500 grams from 2000 to 2009. Pediatrics 2012;129:1019–26.
25. Shah S, Ohlsson A. Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants. Cochrane Database Syst Rev 2006:CD004213.
26. Cooke L, Steer P, Woodgate P. Indomethacin for asymptomatic patent ductus arteriosus in preterm infants. Cochrane Database Syst Rev 2003:CD003745.
27. Le J, Gales MA, Gales BJ. Acetaminophen for patent ductus arteriosus. Ann Pharmacother 2015;49:241–6.
28. European Medicines Agency. The European Union Clinical Trials Register. 2016; (https://www.clinicaltrialsregister.eu).
29. US National Institutes of Health. ClinicalTrials.gov. 2016; (https://clinicaltrials.gov).
30. World Health Organization. International Clinical Trials Registry Platform (ICTRP). 2016; (http://www.who.int/ictrp/en).
31. Children's Hospital Association. Pediatric Health Information System. Programs and Services: Data Analytics and Research 2015; (https://www.childrenshospitals.org/Programs-and-Services/Data-Analytics-and-Research/Pediatric-Health-Information-System).
32. Raudenbush S, Bryk A. Hierarchical Linear Models: Applications and Data Analysis Methods. 2nd edn. Thousand Oaks, CA: Sage Publications; 2002.
33. Glickman ME, Rao SR, Schultz MR. False discovery rate control is a recommended alternative to Bonferroni-type adjustments in health studies. J Clin Epidemiol 2014;67:850–7.