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Nonsteroidal Anti-inflammatory Administration and Patent Ductus Arteriosus Ligation, A Survey of Practice Preferences at US Children's Hospitals

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Abstract

We surveyed neonatal leadership at 46 US children's hospitals via web-based survey to identify local preferences and concerns regarding indomethacin prophylaxis, non-steroidal anti-inflammatory drug (NSAID) treatment, and patent ductus arteriosus (PDA) ligation. We received a 100% survey response (*N*=46). Practice guidelines for prophylactic indomethacin were reported at 28% of NICUs, for NSAID treatment of PDA at 39%, and for surgical ligation at 27%.

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Ethical Oversight: The Nationwide Children's Hospital Institutional Review Board approved the study.

Conflict of Interest: Jonathan Slaughter declares that he has no conflict of interest. Patricia Reagan declares that she has no conflict of interest. Roopali Bapat declares that she has no conflict of interest. Thomas Newman declares that he has no conflict of interest. Mark Klebanoff declares that he has no conflict of interest.

Informed consent: Informed consent was obtained from all individual participants included in the study. The Nationwide Children's Hospital Institutional Review Board approved the study. The introductory page of the survey explained the purpose of the voluntary survey and informed the respondent that completing the survey would signify consent to participate. The Nationwide Children's Hospital Institutional Review Board determined that evaluation of the PHIS database was not human subjects' research, because it was an analysis of a pre-existing, de-identified dataset and involved no patient contact.

Respondents noted intra-institutional practice variation for indomethacin prophylaxis (33%), NSAID treatment (70%), and PDA ligation (73%). The majority of institutions did not prescribe indomethacin prophylaxis (72%). For PDA treatment, indomethacin was preferred over ibuprofen (80%). We validated our survey results via comparison with billing data as documented in the Pediatric Health Information System (PHIS) database, finding that survey responses directly correlated with local billing data ($p<0.0001$). At institutions that did not typically administer NSAIDs for PDA closure or surgical PDA ligation, a lack of evidence for their effectiveness in improving long-term outcomes and the risk of treatment-associated adverse effects were the most often cited reasons.

Conclusion—No consensus exists among providers at U.S. children's hospitals regarding prophylactic indomethacin, NSAID treatment, or PDA ligation. Lack of evidence and safety concerns play a prominent role.

Keywords

drug utilization; ibuprofen; indomethacin; intraventricular hemorrhage; non-steroidal anti-inflammatory drugs; patent ductus arteriosus; pharmacoepidemiology; practice preference; practice survey; practice variation; prematurity

INTRODUCTION

Nonsteroidal anti-inflammatory drug (NSAID) administration to preterm neonates, for intraventricular hemorrhage (IVH) prophylaxis and patent ductus arteriosus (PDA) closure, and surgical PDA ligation have become controversial in recent years [1, 3, 5]. These therapies are efficacious in preventing IVH and closing PDA, respectively, but have not been shown to improve long term respiratory, neurodevelopmental, or mortality outcomes [8, 10, 15, 19, 23, 25]. In addition, the risk for long-term adverse effects following treatment of developing preterm infants with NSAIDs has not been fully evaluated [31, 33] and surgical ligation of PDA has been associated with increased bronchopulmonary dysplasia (BPD) and neurodevelopmental delay [4, 5, 16, 18, 22].

Given these uncertainties, we surveyed NICU directors at freestanding US children's hospitals to: 1) determine the prevalence of clinical guidelines for prophylactic indomethacin administration, NSAID administration for existing PDA, and surgical PDA ligation, 2) determine the NICU director's perception of intra-institutional practice variation, and 3) compare survey responses with billed NSAID usage in the Pediatric Health Information System (PHIS) database to investigate the reliability of survey responses.

METHODS

Survey distribution

We surveyed NICU directors at the 46 tertiary care, children's hospitals with a history of affiliation with the Pediatric Health Information System (PHIS) database (Children's Hospital Association; Overland Park, KS). This provided us with a national sample of 46 US children's hospitals and allowed comparison of survey responses with billed NSAID usage in PHIS.

We conducted the survey electronically using Research Electronic Data Capture (REDCap) [11] hosted by The Ohio State University Center for Clinical and Translational Research. Prior to distribution, the survey was pilot-tested by three neonatologists at Nationwide Children's Hospital. We contacted the NICU director by email with a link to the online survey. A unique survey link was assigned to each institution to track survey completion and to ensure only one response per center. If the NICU director was unavailable or preferred to delegate survey completion, an attending neonatologist knowledgeable in local NSAID administration and PDA surgical ligation practices was permitted to complete the survey. A reminder was emailed weekly for 3-weeks. Initial non-responders were then contacted by a personalized email and/or phone call

The Nationwide Children's Hospital Institutional Review Board approved the study. The introductory page of the survey explained the purpose of the voluntary survey and informed the respondent that completing the survey would signify consent to participate.

Survey format

For each of the three treatments, (prophylactic indomethacin, NSAID treatment of PDA, and surgical ligation), we asked if there was a treatment guideline for its use. If so, we surveyed the clinical factors employed within the guideline to determine the need for treatment. For questions on PDA management, we focused on those factors that prompted neonatologists to designate a PDA "significant" enough to treat if discovered.

We also asked the survey respondents if they perceived variation in practice for each of the three treatments (prophylactic indomethacin, NSAID treatment of PDA, and surgical PDA ligation) by neonatal practitioners within their institution. Respondents were asked whether indomethacin or ibuprofen was used more often for treatment of diagnosed PDA or if both were used about equally.

For each of the three treatments (prophylactic indomethacin, NSAID treatment of PDA, and surgical PDA ligation), if the respondents indicated that their institutions did not typically administer that treatment, we surveyed the reasons why the treatment was avoided.

When answering questions about the clinical factors used to determine the need for treatment or questions about why a given treatment was avoided, respondents were allowed to choose multiple responses if more than one was applicable. A copy of the survey questions is available as online *Supplement 1*.

Comparison of survey results with billing data

To validate survey responses we compared them with billed NSAID usage and surgical ligations in the 2006-2013 Pediatric Health Information System (PHIS) database. PHIS, an administrative database inclusive of most major US freestanding children's hospitals, contains records used to file patient claims for payment. Medication administration and procedures including surgical PDA ligation are recorded daily for each patient. Diagnoses are recorded once per hospital stay via International Classification of Diseases Ninth Revision Code (ICD-9). Participating hospitals provide discharge/encounter data including demographics, ICD-9 diagnoses, procedures, and resource utilization data (e.g.

pharmaceutical, imaging, and laboratory billing data). Thompson-Reuters Healthcare (Ann Arbor, MI), the PHIS data processing partner, maps each hospital's daily charge codes to a common classification system, the Clinical Transaction Classification (CTC) codes, to ensure comparability of charge-level data between institutions. PHIS data quality and reliability are assured through a joint effort between CHA and participating hospitals. Data are de-identified at the time of data submission, and data are subjected to several reliability and validity checks before being included in the database.

To ensure we included only those infants most eligible to receive prophylactic indomethacin or to be diagnosed with PDA, [29] we restricted the PHIS dataset to infants with birth weight <1500 grams and gestational age of ≤ 32 weeks. We only included infants who were admitted on their birth date (postnatal day 0), to minimize exposure to unmeasured NSAID treatment at outside hospitals and to reduce selection bias by excluding neonates that are often transferred from birth to tertiary care children's hospitals at older ages for surgical or imaging procedures due to significant morbidity (i.e. severe necrotizing enterocolitis, severe intraventricular hemorrhage with obstructive hydrocephalus, etc.). We excluded patients with a <1-day length of stay since they most likely represent severely ill infants who died shortly after birth.

When evaluating prophylactic indomethacin administration, we did not restrict the dataset to patients with a diagnosis of PDA since dosing is typically conducted shortly after birth without regard to PDA status [10]. However, for questions regarding NSAID or surgical treatment of PDA, we further restricted the dataset to infants with an ICD-9 diagnosis (747.0) of PDA. We used ICD-9 procedure code 38.85 (other surgical occlusion of vessels, thoracic vessels to identify billed surgical ligation of PDA.

When evaluating each patient's NSAID treatment, we only included indomethacin (CTC code 112264) and ibuprofen (CTC code 112260) doses recorded in the first 30 postnatal days since PDA treatment with NSAIDs is most common in the first postnatal month and ibuprofen may be given to older infants as a pain reliever [8, 25]. Historically, prophylactic indomethacin for intraventricular hemorrhage (IVH) prevention has been initiated on postnatal day 0 [20, 32]. Thus, we designated billed indomethacin administration beginning on postnatal day 0 as prophylactic indomethacin therapy.

For 3 of the 46 surveyed institutions, no patients within the 2006-2013 PHIS dataset met our inclusion criteria. We note that two of these hospitals were only recently added to PHIS in 2014 just prior to the start of our investigation, but were included in the survey a priori should their billing data from prior years become incorporated into PHIS prior to our analysis. Thus, 43 of the 46 surveyed hospitals were included in our comparison of survey responses to PHIS billing data.

Statistical analysis

We used Stata 12.1 (StataCorp, College Station, TX) to conduct all analyses. We used descriptive statistics to evaluate survey responses and calculated relative risks to determine the magnitude of association between survey responses and hospital-specific NSAID

administration or surgical ligation, as recorded in the PHIS database. The statistical significance of each association was assessed using chi-squared tests.

RESULTS

We received a 100% survey response (*N*=46 centers) over the 7-week survey period. Respondents at 37 institutions (80%) were neonatal medical or division directors. Neonatologists knowledgeable in local NSAID administration and PDA surgical ligation practices provided responses at the remaining nine.

Institution-specific clinical practice guidelines for prophylactic indomethacin use were reported by 29% (*n*=13; one answer missing). Clinical practice guidelines for NSAID treatment of PDA were present at 39% (*n*=18) of 46 institutions and for surgical PDA ligation in 27% (*n*=12 of 45). Respondents noted intra-institutional practice variation for NSAID treatment of PDA at 70% (*n*=32) of centers, for prophylactic indomethacin at 33% (*n*=15), and for PDA ligation at 73% (*n*=33). One respondent noted that their consensus document supports both approaches to each intervention since the “evidence is not so compellingly in favor of any of these interventions.”

Indomethacin prophylaxis

Among the 13 responding institutions with a prophylactic indomethacin guideline, 7 used birth weight as a criterion to determine whether prophylactic indomethacin is administered, 2 used gestational age, and 3 used both. The respondent at the remaining institution with clinical practice guidelines reported they “do not use it with the rare exception of an ELBW [extremely low birth weight; <1000 grams birth weight] boy who did not receive steroids.” Of those 10 institutions reporting birth weight as a factor in the decision to administer indomethacin prophylaxis, two institutions used <1250 grams birth weight as their criterion to administer indomethacin, 5 used <1000 grams, one used <850 grams, and two used <750 grams. One of the institutions treating <1000 gram infants also noted that neonates with birth weight between 1000 and 1250 grams may receive indomethacin prophylaxis at attending discretion. Four of the five institutions that reported using gestational age as a treatment criterion provided their gestational age cutoff. One institutional guideline recommended the drug at <34 weeks, two others at <28 weeks, and the fourth reported a gestational age criterion of 23-25 weeks gestational age.

Only 13 of 46 respondents reported that the majority of providers at their institution administer indomethacin prophylaxis. The leading reasons for not administering prophylactic indomethacin were lack of evidence for improvement in neurodevelopmental outcomes (*n*=25) and the risk of adverse effects versus proven benefit (*n*=13). None of these institutions indicated that the cost of indomethacin is a factor in their decision not to administer prophylaxis. Four institutions cited other reasons for not providing indomethacin prophylaxis.

NSAID treatment of PDA

Indomethacin was indicated as the preferred institutional NSAID for PDA closure by 37 of 46 of respondents, ibuprofen by six, and three indicated that their institution used both about equally.

Among the 18 centers with clinical practice guidelines for NSAID administration to treat PDA, the leading factors influencing clinicians to use NSAIDs were respiratory settings (inclusive of oxygen settings-FiO2, positive pressure requirement, and/or specific ventilator settings) (n=14) and specific echocardiographic parameters (n=14). Text responses detailing these specific respiratory settings and/or echocardiographic parameters are included in Table 1. Other considered factors included chest x-ray findings (n=9), widened/split blood pressure or palmar pulses (n=8), hypotension (n=7), and murmur on clinical exam (n=4). Respondents at three institutions with clinical practice guidelines noted other factors that are considered in the decision to treat PDA with NSAIDs. These include 1) a baby that cannot tolerate feeds or one with renal dysfunction that may be due to PDA, 2) a clinically significant PDA as determined by a combination of respiratory support, clinical signs, and echo parameters, and 3) using indomethacin unless it is not available due to drug shortages.

Respondents at 78% of centers reported NSAID treatment of PDA by the majority of providers (n=35). Reasons for not administering NSAIDs for closure of PDA at those institutions that typically do not use them, included findings that many PDAs close spontaneously without treatment (n=11) and concern that the risks of adverse effects from NSAID treatment outweigh the proven benefits of ductal closure (n=5). Three respondents cited a lack of randomized trial evidence showing improved outcomes following closure of the PDA with NSAIDs as a reason for not treating with NSAIDs. None of these institutions indicated that the cost of NSAID treatment is a factor in their decision not to treat.

Surgical ligation of PDA

Among the 12 institutions with surgical ligation guidelines for PDA, the leading indications were failure of NSAID treatment (n=9), specific echocardiographic parameters (n=6), specific respiratory settings (n=6), and congestive heart failure (n=4). Other considered factors included chest x-ray findings (n=2), hypotension (n=2), persistent murmur on clinical exam (n=1), specific physiologic measurements or echocardiogram finding (n=1), and widened/split blood pressure or palmar pulses (n=2). Two other reasons influencing the decision to ligate were provided by text response including “concomitant high dose steroid use due to concern for perforation,” and “consider surgery only if the baby remains ventilator dependent, has echocardiographic findings of hemodynamically significant PDA or persistent PDA, clinical correlation requested and medical treatment has failed (usually after two courses) or if medical treatment is contraindicated.”

Nine institutions with guidelines provided text responses indicating the number of NSAID treatment courses given prior to consideration of ligation. Four institutions considered ligation after two NSAID courses, two institutions after three courses, and one institution after one NSAID treatment course. One respondent indicated that their institution considers

ligation after 2-3 courses and another indicated ligation after three courses, but that one of those courses was a prophylactic indomethacin administration shortly after birth.

Among the 19 institutions that indicated they typically do not perform surgical ligation, the leading reasons were lack of randomized trial evidence (n=9), the risk of vocal cord paralysis during PDA ligation (n=7), and increased risk of neurodevelopment impairment following surgical ligation (n=5). Other reasons for not ligating included an increased risk of bronchopulmonary dysplasia (BPD) (n=4) and increased risk of retinopathy of prematurity (ROP) (n=1) following ligation. One respondent noted that, “the use of surgical ligation is very attending specific, based on whether they believe it helps or not. This belief is often driven by the location where the individual attending trained.”

Comparison of survey responses with PHIS billing data

For the 43 surveyed institutions in the 2006-2013 PHIS database, we compared survey responses with billing data from PHIS (*Table 2*). Infants were more likely to have received indomethacin prophylaxis if the survey respondent indicated that most providers at their institution administered prophylaxis (p<0.0001). Similarly, NSAID treatment for PDA was more likely if the respondent noted that most providers used NSAIDs to close PDAs (p<0.0001). There was also a significant association between the survey response, preferred institutional NSAID, and billed administration in PHIS, whether respondents indicated that most providers at their institution administer indomethacin treatment for PDA rather than ibuprofen (p<0.0001), or conversely that most providers administer ibuprofen treatment for PDA in lieu of indomethacin (p<0.0001).

A survey response noting the presence of a surgical PDA treatment guideline was significantly associated with an increased probability of an infant at that institution receiving PDA ligation (p<0.0001) (*Table 2*). Using our original cohort, including only infants admitted to the NICU on their date of birth, we did not find a significant increase in billed surgical ligation when respondents noted that their institution typically performs PDA ligation (relative risk: 0.98 [95% CI: 0.92 - 1.05] [p=0.579]). Since infants are often transferred to children’s hospitals later in their neonatal course for surgical evaluation of PDA, we relaxed our inclusion criteria to permit admission at any time. When these later transfers were included, the probability of ligation was higher among infants hospitalized in institutions where respondents noted they typically perform PDA ligation (relative risk: 1.19 [95% CI: 1.14-1.25] [p<0.0001]). All other results in *Table 1* remained similar when these relaxed age of admission criteria were applied.

DISCUSSION

Our survey shows that provider preferences regarding indomethacin prophylaxis, PDA treatment with NSAIDs, and surgical ligation vary markedly between and within U.S. Children’s Hospital NICUs. There is clearly no consensus on the proper utilization of these treatments. Other important findings were that: 1) the majority of the 46 surveyed US children’s hospitals indicated they do not administer prophylactic indomethacin, 2) the majority used treatment with indomethacin over ibuprofen for most infants with PDA, 3) the majority of respondents noted that respiratory settings and echocardiographic findings play

an important role in clinicians' decisions both to administer NSAIDs for PDA closure and to surgically ligate PDAs, and that 4) a high spontaneous PDA closure rate without NSAID treatment, and a lack of evidence for treatment effectiveness in improving longer-term outcomes and risks of adverse effects following NSAID use or surgical PDA ligation, are major concerns at institutions that choose not to administer these therapies.

Our investigation carries all of the limitations of survey measurement including inaccuracy of responses. We evaluated this by comparison with recorded billing data within the PHIS database. We found that survey respondent reports regarding prophylactic indomethacin administration and NSAID treatment for PDA were directly correlated with billed NSAID usage as recorded in the PHIS database, thus demonstrating convergent validity between the survey and real-world prescribing. Although our survey was limited to leadership at 46 US Children's Hospitals, the variability in treatment preferences found by the survey is likely generalizable to other US NICUs, since most of the surveyed sites serve as major neonatal training centers. If anything, including only US children's hospitals would likely lead to a bias towards greater homogeneity of responses, so our conclusion that no consensus exists among neonatal providers regarding prophylactic indomethacin, NSAID treatment, or PDA ligation is strengthened, rather than weakened by this limitation.

Indomethacin prophylaxis

Postnatal administration of prophylactic indomethacin to at-risk preterm infants within 24 hours of birth has short-term effects including decreased grade 3 and 4 IVH, decreased PDA incidence, and a decreased number of infants that subsequently receive surgical ligation [10]. However, it has not been shown to improve long-term outcomes including neurodevelopment at 18-36 months, respiratory outcomes, and mortality [10, 32] and there are concerns about the potential adverse effects of indomethacin in preterm neonates including nephrotoxicity, acute renal failure [31, 33], and decreased cerebral and intestinal blood flow [26, 27]. Our survey demonstrated the lack of evidence for improved neurodevelopmental outcomes and concern for adverse effects as leading reasons for avoiding indomethacin prophylaxis. Prophylactic indomethacin use peaked in the academic neonatal institutions in the NICHD neonatal research network following a randomized trial in 1994 by *Ment et al* [20] showing it reduced IVH, but began to decline in the early 2000's after a much larger trial by *Schmidt et al* [32] found no long-term benefit to treatment [6]. Follow-up investigations by Ment *et al* showed some improvement in IQ and vocabulary skills at 4.5-years in those infants that had received indomethacin, but no effect on overall neurodevelopment at 4.5 and 12-years [17, 21]. In our survey, only 28% of 46 surveyed children's hospital NICUs reported prophylactic indomethacin administration by most neonatologists, providing evidence that prophylaxis remains unpopular at most US children's hospital NICUs.

NSAID treatment of PDA

Respondents at 78% of centers reported that the majority of their providers administer NSAID treatment to close PDAs. However, 70% also noted intra-institutional practice variation in NSAID treatment of PDA among their colleagues. We suspect this variation within institutions is likely due to recent controversy regarding PDA closure [3], as

spontaneous PDA closure and concern for NSAID-associated adverse effects were the leading survey responses for avoiding treatment. Although PDA in preterm infants, is associated with increased mortality and respiratory morbidity [5, 24], clinical trials have historically focused on the efficacy of NSAIDs to close the ductus instead of the reduction of adverse patient outcomes following NSAID treatment [5]. PDAs close spontaneously in many infants [13] and meta-analyses of the trials show no improvement in mortality, respiratory outcomes, or neurodevelopment following NSAID treatment of PDA [1, 8, 15, 25].

Ibuprofen versus indomethacin

If a clinician decides to attempt PDA closure with an NSAID, the closure rate between ibuprofen and indomethacin is not statistically different [25]. However, relative to indomethacin, ibuprofen has decreased vasoconstrictive effects upon mesenteric, renal and cerebral blood vessels [26, 27] and lower rates of oliguria and transient renal insufficiency [25]. None of the many small, heterogeneous trials comparing the drugs have shown lower rates of NEC with ibuprofen compared with indomethacin, but meta-analysis favors ibuprofen [25]. Surprisingly, we found that an overwhelming majority of surveyed hospitals (80%) preferred treatment with indomethacin over ibuprofen for most infants with PDA, despite intensive marketing efforts for neonatal ibuprofen [9]. We speculate that a recent, lengthy ibuprofen lysine shortage may have also played a role [12].

Surgical ligation of PDA

Surgical ligation of PDA is another controversial topic. Surgical ligation is generally performed in patients in whom medical therapy to close the ductus arteriosus has failed or is contraindicated [19]. Infants subjected to surgical ligation of the PDA usually obtain definitive closure, but are exposed to anesthesia and may endure adverse effects such as vocal cord injury [2], scoliosis [30], and post-operative hypotension [7] and increased risk for adverse outcomes including neurodevelopmental delay [16], bronchopulmonary dysplasia [4], and ROP [19]. Respondents at 41% of centers indicated they typically do not perform surgical ligation with noted practice variation between providers at 73%.

Inter-institutional and intra-institutional variation in practice

We did find some similarities among institutions. At the majority, respiratory settings and echocardiographic findings play an important role in the clinicians' decision to close PDAs. At institutions that do not typically administer NSAIDs for PDA closure or surgical PDA ligation, a lack of evidence for their effectiveness in improving long-term outcomes and the risk of treatment-associated adverse effects were most often cited as reasons. Another interesting uniformity among these hospitals was that treatment cost did not appear to be a source of practice variation for NSAID use even though the price of NSAID treatment has soared in recent years, ranging between $1458 to $1875 per three-dose treatment course [9, 14, 28].

However, when it comes to treatment decisions regarding whether to administer prophylactic indomethacin or close PDAs there is little national consensus. Survey responses also indicated a large degree of within-hospital variation in treatment. Since we only surveyed

one representative per institution our investigation was not designed to detect the reasons for disagreement between neonatologists at the same NICU. However, we speculate that disagreement regarding treatment effectiveness and adverse-effects, as well as where neonatologists trained also likely play a large role at the institutional level.

Conclusions

Institutional practice preferences for prophylactic indomethacin, NSAID treatment, and surgical ligation of PDA vary both between and within institutions, likely due to a lack of proven effectiveness in improving longer-term outcomes. The majority of surveyed children's hospitals do not administer prophylactic indomethacin, while the majority treat PDA with NSAIDS and perform surgical PDA ligation. However, most hospitals report variation among their providers in the application of these therapies. A lack of evidence for treatment effectiveness in improving longer-term outcomes and the risk of adverse effects following NSAID use or surgical PDA ligation are major concerns at institutions that choose not to administer these therapies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

CHA	Children's Hospital Association
CTC	clinical transaction code
COX	cyclooxygenase
ICD-9	International Classification of Diseases, Ninth Revision
IVH	intraventricular hemorrhage
NICU	neonatal intensive care unit
NSAID	nonsteroidal anti-inflammatory drug
PDA	patent ductus arteriosus
PHIS	Pediatric Health Information System
RR	relative risk

ROP retinopathy of prematurity

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What is Known

- NSAIDs and surgical PDA ligation are efficacious in preventing IVH and closing PDA in preterm infants, but have not been shown to improve long term respiratory, neurodevelopmental, or mortality outcomes.

What is New

- Practice preferences for indomethacin prophylaxis, and NSAID and surgical PDA treatment, vary both among and within institutions. Lack of treatment effectiveness and the risk of adverse effects are major concerns.

Table 1

Respiratory settings and echocardiographic parameters used to inform clinicians' decisions to administer NSAIDs for PDA closure

Respiratory Settings (*n*=14 text responses)[a]
1. Escalation in respiratory support (*n*=8)
2. Failure to wean respiratory support (*n*=3)
3. Need for 'significant' respiratory support defined as mechanical ventilation or CPAP (*n*=4)
4. Mechanical ventilation requirement; cannot extubate to CPAP (*n*=5)
5. Fraction of inspired oxygen (FiO2) (*n*=7)
Echocardiographic Parameters (*n*=14 text responses)[a]
Size of PDA:
Size of PDA as reported by echocardiogram read (subjective) (moderate, large) (*n*=7)
Ratio of smallest duct diameter to the ostium of the left pulmonary artery (PDA: LPA ratio) (*n*=1)
Ductal diameter in millimeters (>1.5 mm at one institution and >2 mm at another) (*n*=2)
Flow Velocity:
Transductal flow in the ductus arteriosus (*n*=3)
Low resistance across the ductus (non-restrictive); mean diastolic velocity in left pulmonary artery (*n*=2)
Mean Doppler gradient (*n*=1)
Flow Direction:
Diastolic retrograde Doppler flow in the postductal descending aorta (*n*=5)
Bidirectional shunting (*n*=2)
Cardiac Load and Functional Changes
Left atrial to aortic root ratio (LA/Ao ratio) (left atrial enlargement) (*n*=10)
Left-ventricular end-diastolic dimension to aortic root ratio (LVEDD/Ao ratio) (left ventricular enlargement) (*n*=4)
Evidence of left ventricular dysfunction; impaired cardiac function (*n*=2)

[a]Created from text responses by respondents at centers with clinical practice guidelines for NSAID administration to treat PDA. Respondents who selected respiratory settings (*n*=14) and/or echocardiographic parameters (*n*=14), respectively, as leading factors used by clinicians at their institution in determining whether to administer NSAIDs for PDA were asked to detail those institution-specific parameters in text form.

Table 2

Comparison of survey responses with institution-specific billing data as reported in the PHIS database

	Respondents (*N*)	Infants with Billed Treatment (%)	RR	95% CI	P-value
Prophylactic Indomethacin[a]					
Most providers administer	13	22.3	4.37	(4.02 - 4.75)	<0.0001
Most providers do not administer	33	5.11	-	-	-
Prophylaxis guideline reported	13	22.4	3.89	(3.58 - 4.22)	<0.0001
Prophylaxis guideline not reported	32	5.8	-	-	-
NSAID Treatment of PDA[a] ***(Among infants with a PDA diagnosis)***					
Most providers administer	35	49.9	1.52	(1.43 - 1.61)	<0.0001
Most providers do not administer	10	33.0	-	-	-
Treatment guideline reported	18	44.1	0.95	(0.91 - 1.00)	0.07
Treatment guideline not reported	28	46.2	-	-	-
Preferred NSAID Treatment ***(Among infants with PDA treated with NSAIDs at ≤30 postnatal days)***					
Most providers prescribe indomethacin	37	77.2	1.28	(1.22 - 1.34)	<0.0001
Most providers prescribe ibuprofen	6	42.8	3.06	(2.71 - 3.46)	<0.0001
Surgical Ligation of PDA ***(Among infants with a PDA diagnosis)***					
Institution typically performs ligation	27	26.5	0.98	(0.92 - 1.05)	0.579[b]
Institution typically does not ligate	19	27.0	-	-	-
Surgical ligation guideline reported	12	34.6	1.33	(1.21 - 1.48)	<0.0001
Surgical ligation guideline not reported	33	25.9	-	-	-

Abbreviations: confidence interval (CI), relative risk (RR)

[a] Prophylactic indomethacin doses (defined as any indomethacin dose beginning on postnatal day 0 with ≤ 3 total days of indomethacin administration) are not counted as indomethacin treatment for PDA

[b] This original analysis was restricted to infants admitted to the NICU on their date of birth to avoid missing prophylactic indomethacin and NSAID PDA treatment doses administered prior to transfer. When we reran the analysis without an age of admission restriction, we obtained relative risk: 1.19 [95% CI: 1.14-1.25][p<0.0001]).”