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Patent Ductus Arteriosus in Preterm Infants

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Despite extensive research in basic science and in clinical settings with thousands of infants over decades, uncertainty and controversy persist regarding the significance, assessment, and management of the patent ductus arteriosus (PDA) in preterm infants, resulting in substantial variability in clinical approach. This clinical report aims to succinctly review the available evidence to guide evaluation and treatment of preterm infants with prolonged ductal patency. Delayed closure of the PDA is common in preterm infants, particularly at more extreme immaturity. Echocardiography is essential for confirming the presence of a PDA and assessing hemodynamic significance. Medical closure of a PDA using ibuprofen or acetaminophen is an option for a hemodynamically significant PDA (hsPDA). Recent data from multiple clinical trials indicate the lack of benefits of prophylactic or early (<2 weeks of age) medical closure of PDA as compared with expectant management, and they are, therefore, not recommended. There are insufficient data to support firm recommendations on management of infants with an hsPDA beyond 2 weeks of age as relative benefits and risks of expectant management with close monitoring, attempted pharmacologic closure, or procedural (transcatheter/surgical) closure have not been adequately defined. Many clinicians attempt medical closure of an hsPDA beyond 2 weeks of age. If the hsPDA persists despite medical therapy (or if medical therapy is contraindicated), such infants may be considered for either transcatheter closure or surgical ligation. In recent years, surgical closure of the PDA has become less frequent, and transcatheter closure is more common in many centers. Although there are known adverse effects of an hsPDA, there is a lack of evidence to guide management, necessitating equipoise regarding treatment options and timing and a need for trials that can expand the available body of evidence, especially regarding long-term cardiopulmonary and neurodevelopmental outcomes.

abstract

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CLINICAL EPIDEMIOLOGY, PHYSIOLOGY, AND NATURAL HISTORY OF THE PATENT DUCTUS ARTERIOSUS

In term infants, the ductus arteriosus normally constricts after birth and becomes functionally closed in 90% by 48 hours of age, in nearly all by 96 hours of age, and further delayed in preterm infants.[1] More immature infants have a more pronounced delay, with the ductus remaining open at 4 days of age in approximately 10% of infants born at 30 through 37 weeks' gestation, 80% of those born at 25 through 28 weeks' gestation, and >90% of those born at 24 weeks' gestation.[2] By day 7 after birth, those rates decline to approximately 2%, 65%, and 87%, respectively.

Spontaneous closure is likely in infants born at >28 weeks' gestation (73%),[3] in those with birth weight >1000 g (94%),[4] and in the few infants born at 26 to 29 weeks' gestation who do not have respiratory distress syndrome (RDS; 93%).[5] In the PDA-TOLERATE study, 40% of infants born at less than 28 weeks' gestation had no PDA or minimal respiratory impact from their PDA in the first 2 weeks of life.[6] Rates of later spontaneous ductal closure among smaller, less mature infants with RDS from placebo arms of controlled trials demonstrate that spontaneous ductal closure in these infants is quite frequent. In the Trial of Indomethacin Prophylaxis in Preterms (TIPP), which included infants with birth weight from 500 to 999 g, 50% of placebo recipients never developed clinical signs of a PDA.[7] In a trial of early vs late indomethacin treatment of infants born at 26 through 31 weeks' gestation in whom PDA was confirmed by echocardiography on day 3, the ductus closed spontaneously by 9 days of age in 78% of those randomized to late intervention.[8] As conservative management has become more prevalent, the majority of infants (90%) born at less than 26 weeks' gestation have been found to have spontaneous closure of the ductus, with closure occurring at a median of 36 weeks' postmenstrual age (PMA).[9] Of infants discharged home with persistent patent ductus, 50% will go on to close spontaneously by 9 months of age (approximately 49 weeks' PMA) and 80% will close by 2 years of age.[10] The hemodynamic significance of the PDA during that time is unclear and has not been well studied.

While the ductus remains open, blood typically flows left-to-right from the aorta into the pulmonary arteries. As pulmonary vascular resistance declines in the initial days after birth, there is an augmented diversion of aortic blood flow into the pulmonary circulation, known as the "ductal steal." This phenomenon results in additional blood flow through the lungs, predisposing to the development of pulmonary congestion, pulmonary edema, and exacerbated respiratory failure. The diversion of blood flow from the systemic circulation may surpass compensatory increases in total cardiac output, resulting in compromised perfusion of vital organs such as the bowel, kidney, and brain. Prolonged patency is associated with numerous adverse outcomes, including prolonged assisted ventilation and higher rates of death, bronchopulmonary dysplasia (BPD), pulmonary hemorrhage, necrotizing enterocolitis (NEC), impaired renal function, intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), and cerebral palsy (CP).[11] However, the precise extent to which these adverse outcomes are attributable to the hemodynamic consequences of ductal patency vs comorbid conditions resulting from extreme prematurity has not been defined. These associations prompted the hypothesis that intervention to close the ductus might prevent or reduce the severity of these complications seen more commonly in prematurity. The widespread adoption of interventions designed to achieve early closure of the ductus in preterm infants ensued with the anticipation that this hypothesis would be substantiated. The efficacy of these interventions is discussed subsequently.

ASSESSMENT OF HEMODYNAMIC SIGNIFICANCE

To date, an accurate and precise definition of a "hemodynamically significant" PDA (hsPDA) remains elusive. The hemodynamic effects of a large left-to-right shunt associated with a PDA may be evident by physical examination, echocardiography, or serum biomarkers.

In addition to the presence of a classic continuous murmur at the left sternal border, affected infants may have an increased precordial impulse and clinical signs of a widened pulse pressure, such as prominent or bounding arterial pulses, or palpable pulses in the palms of the hands. Nevertheless, these findings are nonspecific and have been found to be unreliable predictors of the presence of an hsPDA. Some infants may present with clinical evidence of pulmonary overflow (persistent or increased need for respiratory support) or systemic hypoperfusion (hypotension, renal dysfunction, feeding intolerance). These clinical features usually prompt clinicians to perform echocardiography to evaluate for a PDA.

Neonatal echocardiography has a critical role for PDA diagnosis and evaluation of therapeutic responses.[12] Defining an hsPDA involves careful determination of: (1) PDA shunt assessment and its impact on the systemic and pulmonary circulations; (2) myocardial and mitral valve function evaluation, especially in the context of the potential for myocardial ischemia secondary to impaired coronary artery perfusion; and (3) clinically relevant characteristics that modify the effects a shunt may have to an already compromised milieu.[13]

Pulmonary overcirculation, systemic hypoperfusion, and characterization of the duct itself, including diameter and Doppler flow pattern, are typically evaluated and considered when examining the ductus. Echocardiographic measurements that are indicative of pulmonary overcirculation and left heart volume overload include left atrial-to-aortic root ratio (LA:Ao), left ventricular end-diastolic diameter, mitral valve E/A (early passive filling to late

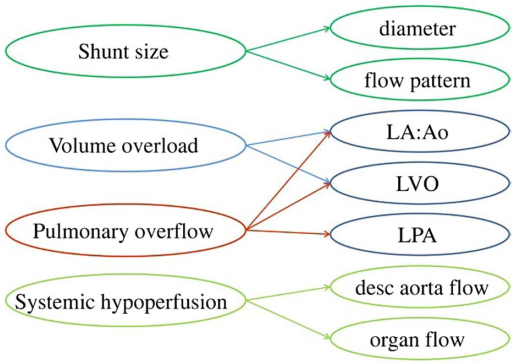

Figure 1.
Echocardiographic indicators of an hsPDA. For each echocardiogram, consider evaluating the size of the shunt, the extent of volume overload, the degree of pulmonary overflow, and the magnitude of systemic hypoperfusion. PDA shunt size can be estimated using the diameter and flow pattern through the PDA. Volume overload can be determined by calculating the left atrial (LA) to aortic (Ao) ratio (LA:Ao) and the left ventricular output (LVO). Pulmonary overflow can be evaluated by the LA:Ao, LVO, and by the end-diastolic velocity in the left pulmonary artery (LPA). Systemic hypoperfusion can be assessed by flow in the descending aorta (desc aorta flow) and flow to organs, such as in the cerebral, renal, or splanchnic arteries. Copyright © 2019 Shepherd JL, Noori S.[12] Published by Tech Science Press. This work is licensed under a Creative Commons Attribution 4.0 International License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Table 1. A Suggested Definition of a Hemodynamically Significant PDA (hsPDA): a Combination of Clinical and Echocardiographic Parameters

Clinical criteria (should fulfill 2 of 4 criteria)	1. High CPAP/NIMV with high FiO_2 or moderate or high ventilator settings at any FiO_2
	2. Hypotension needing a vasopressor
	3. Persistent oliguria or renal dysfunction
	4. Abdominal distension, feeding intolerance, poor growth despite optimization of nutrition, or history of NEC
AND	
Echocardiographic criteria (should fulfill at least one criterion)	1. Minimum PDA diameter >1.5 mm
	2. Unrestrictive left to right transductal flow (PDA Vmax <2 m/s)
	3. Left sided volume overload (≥moderate LA or LV enlargement)
	4. Decreased, absent, or reversed end-diastolic flow in abdominal descending aorta

CPAP indicates continuous positive airway pressure; FiO_2, fraction of inspired oxygen; LA, left articular; LV, left ventricular; NIMV, noninvasive mechanical ventilation; Vmax, maximum velocity.

active phase velocities), and isovolumic relaxation time (IVRT).[13] Mitral regurgitation may occur in some infants with a large PDA shunt.

Echocardiography and color Doppler ultrasonography can be used to assess the effect of hsPDA on end-organ perfusion and function (Figure 1). In the presence of a PDA in very low birth weight infants, the superior mesenteric artery has been associated with a smaller diameter, greater systolic velocity, lower diastolic velocity, and higher resistivity and pulsatility indices, as compared with those without a PDA.[14] Some infants with a PDA may also have absent or reversed end-diastolic flow in the superior mesenteric artery consistent with a steal effect and lower values of portal vein diameter and flow.[14] It was previously thought that the PDA would only exert negative effects on the blood flow of post-ductal vessels; however, a persistent PDA was also associated with reversed diastolic flow in the brachiocephalic artery[15] and with reduced middle cerebral artery blood flow velocity[16] indicating that preductal flow may also be impaired.

Myocardial performance is an essential component of assessing hsPDA. The diastolic dysfunction that is common in preterm infants with a PDA may increase adverse effects of increased pulmonary blood flow, emphasizing the importance of considering LV diastolic function in the definition of hemodynamic significance.[13,17]

Antenatal and perinatal clinical factors, such as lower gestational ages, growth restriction, lack of antenatal steroids, and other adverse perinatal events may contribute to adverse effects associated with a PDA. Therefore, determination of an hsPDA must not only include echocardiographic markers of shunt volume and right ventricular and left ventricular function but must also incorporate important clinical characteristics such as gestational age, postnatal age, and clinical evidence of pulmonary overflow or systemic hypoperfusion.

Table 1 provides a definition of an hsPDA that may be appropriate for most preterm infants.

Biomarkers have been used alone and in combination with echocardiography to diagnose ductal significance. B-type natriuretic peptide (BNP) and amino-terminal pro-B-type natriuretic peptide (NT-proBNP) have moderate accuracy in identifying hemodynamic significance of a PDA and may possibly be helpful in selecting infants for echocardiography, although nonspecific.[18] However, studies evaluating the diagnostic accuracy of BNP and NT-proBNP vary by assay characteristics and infant characteristics, and local validation of these tests is required before routine use.[18]

EVIDENCE FOR BENEFITS AND RISKS OF TREATMENT

Since the early reports of feasibility of surgical closure[19] and efficacy of nonsteroidal anti-inflammatory drugs (NSAIDs) for medical treatment of PDA,[20,21] results have been reported from multiple randomized trials of various medical and surgical therapies for PDA. A recent overview of 16 Cochrane Systematic Reviews combined data from

138 randomized clinical trials and 11 856 preterm infants.[22] Of the 16 Cochrane Reviews, 6 reported on prophylactic interventions, including pharmacological prophylaxis, prophylactic surgical ligation, and nonpharmacologic interventions (chest shielding during phototherapy and fluid restriction), and 9 reported on intervention for symptomatic PDA, including pharmacotherapy, surgical ligation, and adjunct therapies (use of furosemide and dopamine in combination with indomethacin).[22] The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach[23] which is a systematic process of grading the quality of evidence and strength of recommendations was used to assess the quality of evidence in Cochrane Reviews, which will be discussed further in this section.

Prophylactic Interventions

Prophylactic interventions (those not guided by knowledge of PDA status) have included the use of indomethacin,[24] ibuprofen,[25] and acetaminophen[26] in preterm infants during the first 3 days after birth, and prophylactic surgical ligation in 1 study.[27,28] The Cochrane Review of prophylactic intravenous indomethacin reports on 19 trials with 2872 infants.[24] Indomethacin reduced symptomatic PDA (typical relative risk [RR], 0.44; 95% confidence interval [CI], 0.38–0.50), PDA surgical ligation (RR, 0.51; 95% CI, 0.37–0.71), and severe IVH (RR, 0.66; 95% CI, 0.53–0.82) but did not significantly change mortality (RR, 0.96; 95% CI, 0.81–1.12), BPD (RR, 1.06; 95% CI, 0.92–1.22), NEC (RR, 1.09; 95% CI, 0.82–1.46), or death/severe neurodevelopmental disability at 18 months to 3 years of age (RR, 1.02; 95% CI, 0.90–1.15)[24] (level of evidence: 1A).[29] For ibuprofen, there have been 9 trials (n = 1070) comparing prophylactic ibuprofen (intravenous or oral) with placebo/no intervention or indomethacin. It was noted that ibuprofen reduced the risk of a PDA by day 3 or 4 (RR, 0.39; 95% CI, 0.31–0.48), rescue treatment with cyclooxygenase-2 (COX) inhibitors (RR, 0.17; 95% CI, 0.11–0.26), and surgical ligation (RR, 0.46; 95% CI, 0.22–0.96), and possibly the risk of severe IVH (RR, 0.67; 95% CI, 0.45–1.00) (moderate-quality evidence), but with increased risk of oliguria (RR, 1.45; 95% CI, 1.04–2.02) (high-quality evidence).[25] No differences were noted for mortality or BPD.[25] Acetaminophen (paracetamol) has been evaluated in 27 studies enrolling 2278 infants, with acetaminophen (either alone or in combination) compared with no intervention, placebo, or other agents (indomethacin or ibuprofen).[26] Acetaminophen was more effective than placebo (RR, 0.27; 95% CI, 0.18–0.42; low certainty evidence) but has little to no difference compared with indomethacin or ibuprofen in failure of ductal closure after a single course (moderate certainty), or on all-cause mortality during hospital stay.[26] The single randomized trial of prophylactic PDA ligation was performed in the presurfactant and preantenatal steroid era, and had a limited sample size (44 extremely low birth weight infants randomly assigned to receive standard treatment and 40 randomly assigned to undergo prophylactic ligation).[28] It was found that infants in the prophylactic PDA ligation group had a lower risk of severe NEC, but no differences in mortality, BPD, severe IVH, or retinopathy of prematurity (ROP) were noted.[28]

In summary, these results suggest that the use of prophylactic indomethacin, ibuprofen, or acetaminophen is associated with a lower risk of a symptomatic PDA and with less severe IVH (for indomethacin and ibuprofen) but with no effects on mortality or BPD (level of evidence: 1A).[29]

Pharmacologic Therapy for Symptomatic PDA

Overall, all available prostaglandin inhibitor drugs (indomethacin, ibuprofen, and acetaminophen) are very effective in symptomatic PDA closure compared with no therapy (indomethacin: RR, 0.30; 95% CI, 0.23–0.38; 10 randomized controlled trials [RCTs], 654 infants; high-certainty evidence; ibuprofen: RR, 0.62; 95% CI, 0.44–0.86; 2 RCTs, 206 infants; moderate-certainty evidence; acetaminophen: RR, 0.35; 95% CI, 0.23–0.53; 2 RCTs, 127 infants; low-certainty evidence)[22] (level of evidence: 1A).[29] Ibuprofen used intravenously at the standard dose of 10 mg/kg followed by 2 doses of 5 mg/kg at 24-hour intervals may be preferred as it is as effective as indomethacin for PDA closure (typical failure rate, 1.07; 95% CI, 0.92–1.24; moderate quality evidence) and has a significantly better safety profile than indomethacin with lower risk of NEC (RR, 0.68; 95% CI, 0.49–0.94; number needed to benefit, 25; moderate quality evidence), trend toward less intestinal perforation (RR, 0.48 95% CI, 0.20–1.14), and less oliguria (RR, 0.28; 95% CI, 0.14–0.54; NNTB 11; moderate quality evidence).[30] A systematic review and meta-analysis of placebo, indomethacin, ibuprofen, and acetaminophen for closure of a hemodynamically significant PDA evaluated 68 RCTs of 4802 infants comparing 14 different variations of indomethacin, ibuprofen, or acetaminophen.[31] The overall PDA closure rate was 67.4%, and a high dose of oral ibuprofen (15 mg/kg to 20 mg/kg followed by 2 doses of 7.5 mg/kg to 10 mg/kg at 24-hour intervals) was associated with a higher odds of PDA closure compared with standard dose of intravenous ibuprofen (odds ratio [OR], 3.59; 95% credible interval 1.64–8.17; absolute risk difference, 199; 95–258 more per 1000 infants) or standard indomethacin (RR, 2.35; 95% CI, 1.08–53.1; absolute risk difference, 124; 14–188 more per 1000 infants). However, this high-dose regimen has not been adequately evaluated in extremely preterm infants (<29 weeks' gestation) as the sample size of such infants has been very limited and its efficacy and safety in this population is not known.[30,32]

A recent Cochrane Review assessed the effectiveness and safety of early treatment (defined as treatment initiated by 7 days of age) or very early treatment (treatment initiated

by 72 hours of age) vs expectant management for a hemodynamically significant PDA and found that early or very early treatment did not decrease mortality and did not impact the rates of BPD, severe IVH, NEC, or surgical ligation while increasing exposure to NSAIDs.[33]

The efficacy and safety of repeat courses of medications if the initial course fails to close the PDA has not been adequately investigated in RCTs. Observational studies suggest that a second course may increase the closure rate, but a third course is less likely to lead to closure, and that adverse effects are rare with additional courses[34,35] (level of evidence: 2B).[29] There is no evidence to indicate that dual medication (combination) therapy improves the rate of successful PDA closure or clinical outcomes[36] (level of evidence: 1A).[29]

However, even though these medical therapies are frequently effective in closing the PDA, improvements in hospital and longer-term outcomes including all-cause mortality, BPD, NEC, or moderate/severe neurodevelopmental impairment have not been demonstrated[22] (level of evidence: 1A).[29] Although the reasons are not clear, it is possible that some of the benefits in improved hemodynamics with a closed PDA may be balanced by adverse effects of NSAIDs on the lung.[37–40] It is also possible that closing the PDA only affects specific outcomes and endotypes of neonatal disease, which may not have been the ones evaluated in studies or may not be able to be fully captured. For example, prolonged PDA exposure was associated with pulmonary hypertension in infants with BPD,[41] but such clinical phenotyping and endotyping of neonatal disorders has not been performed for PDA management. Adverse effects may also potentially occur in other organs such as the brain, although these effects may be more relevant to prenatal exposure[42] and not with postnatal exposure or in preterm infants.[43,44] A single center retrospective cohort study suggests that a highly targeted approach to PDA using very early hemodynamic screening, a comprehensive scoring system, and a physiology-based approach is associated with survival free of severe IVH,[45] but this approach has to be evaluated further.

Conservative (Expectant) Management

With increasing concerns of exposure to these medications without clear benefit, conservative or expectant management, defined as the practice of tolerating the presence of a persistent PDA that does not appear to be hemodynamically significant and allowing a delayed spontaneous closure, has become common. Numerous reports after this change in management suggest that this approach is safe[46–48] but are retrospective, and do not address the question of which infants may most benefit from this strategy and which infants could benefit from intervention. A retrospective review of a California Perinatal Quality Care Collaborative (CPQCC) found that neonatal intensive care unit (NICU)-specific reduced use of COX inhibitors was associated with lower rates of BPD in infants weighing more than 1000 g but not in those weighing less than 750 g in whom there was an association of reduced use of COX inhibitors with increased mortality.[49] A similar retrospective multicenter study in the Pediatrix Clinical Data Warehouse at 259 NICUs summarized data on 78 105 infants. The between-year reductions in the NICU-specific proportion treated with indomethacin or ibuprofen/ligation were associated with concurrent increases in local mortality but with reduced BPD among infants weighing 400–749 g and decreased pulmonary hemorrhage in larger infants.[50] A recent systematic review by Hundscheid et al[51] compared conservative management with any other active treatment (either prophylactic or nonprophylactic pharmacological or surgical therapy), in 12 cohort studies and 4 RCTs, encompassing 41 804 and 720 patients, respectively. It was noted that the cohort studies demonstrated a higher risk of mortality (RR, 1.34; 95% CI, 1.12–1.62) but lower BPD (RR, 0.85; 95% CI, 0.77–0.93), IVH (RR, 0.88; 95% CI, 0.83–0.95), and ROP (RR, 0.47; 95% CI, 0.28–0.79) with conservative management, while the meta-analysis of the RCTs did not reveal any significant differences between conservative and active treatment.[51]

To address the question prospectively, there have been some recent randomized trials. The PDA-TOLERATE Trial[6] randomly assigned 202 preterm infants born at <28 weeks' gestation with a moderate-to-large PDA between 6 and 14 days of age to early routine treatment (ERT) with either indomethacin, ibuprofen, or acetaminophen (with indomethacin backup if the PDA failed to constrict after the initial treatment) or conservative treatment(CT), with open-label (rescue) treatment for those infants in either group with hemodynamically significant PDA. Although infants in the conservative management arm were more likely to receive open-label therapy, especially in those infants born at <26 weeks' gestation, no significant differences were noted in the primary outcome of ligation or presence of a PDA at discharge (ERT 32% vs conservative treatment 39%) or any of the secondary outcomes of NEC (ERT 16% vs conservative treatment 19%), BPD (ERT 49% vs conservative treatment 53%) or BPD/death (ERT 58% vs conservative treatment 57%).[6] A trend for higher death was noted in the early routine therapy group (ERT 19% vs conservative treatment 10%; RR, 1.9; 95% CI, 0.92–3.8). In addition, among infants who were born at ≥26 weeks' gestational age, those receiving ERT took significantly longer to achieve enteral feeding of 120 mL/kg/d (ERT 14 days vs CT 6 days) and had significantly higher incidence of late-onset non-coagulase-negative *Staphylococcus* bacteremia (ERT 24% vs CT 6%) and death (ERT 16% vs CT 2%).[6]

The BeNeDuctus Trial[52] randomly assigned 273 infants born at <28 weeks' gestational age with PDA (>1.5 mm with left to right shunting at 24–72 hours of age) to receive either

expectant management or early ibuprofen therapy received at a median postnatal age of 63 hours (range, 55–70 hours), with the primary outcome being a composite of NEC, moderate/severe BPD, and/or death at 36 weeks' PMA. Open-label treatment was considered if prespecified criteria were met for clinical or echocardiogram findings of heart failure associated with a clinically significant left-to-right shunt. The primary outcome occurred in 63 of 136 infants (46.3%) in the expectant management group and in 87 of 137 (63.5%) in the early ibuprofen group (absolute risk difference, −17.2 percentage points; upper boundary of the one-sided 95% CI, −7.4; $P < .001$ for noninferiority). No significant differences were noted in rates of NEC (17.6% expectant vs 15.3% ibuprofen) and death (14.0% expectant vs 18.2% ibuprofen) although there was an increase in BPD in the ibuprofen group (33.3% expectant vs 50.9% ibuprofen; absolute risk difference, −17.6%; 95% CI, −30.2 to −5.0).[52]

The Baby-OSCAR trial evaluated early treatment (≤72 hours after birth) with ibuprofen for a large PDA (≥1.5 mm diameter with pulsatile flow) in extremely preterm infants (23 weeks' to 28 weeks, 6 days' gestational age) and randomly assigned 326 infants to receive ibuprofen and 327 to receive placebo.[53] Death or moderate/severe BPD occurred in 69.2% of the ibuprofen group and 63.5% of the placebo group (adjusted risk ratio, 1.09; 95% CI, 0.98–1.20; $P = .1$), with death occurring in 13.6% of the ibuprofen group and 10.3% of the placebo group (adjusted risk ratio, 1.32; 95% CI, 0.92–1.90), demonstrating no reduction in death or BPD in infants.[53]

Studies on this topic have left several unanswered questions. First, hemodynamic significance has not been fully evaluated in most RCTs to date. Second, most RCTs enrolled infants soon after birth (when spontaneous closure is more likely), and it is not known whether a more selective approach enrolling only infants at later time points would show different results. It is possible that the PDA trial (NCT03456336) currently under way in the Eunice Kennedy Shriver NICHD Neonatal Research Network with a planned enrollment of 836 infants would provide important data in this regard. With these important limitations not yet accounted for, there has not been clear evidence that early (1–2 weeks of age) pharmacologic closure of PDA helps to improve outcomes of extreme prematurity.

Therefore, selective treatment of infants born at or before 28 weeks' gestation, who are at highest risk of PDA, may remain an option beyond 2 weeks' postnatal age. Deferral of early treatment in infants without hemodynamic compromise may allow avoidance of treatment of those in whom spontaneous closure occurs without compromising the potential efficacy of future medical treatment. Deferring early procedural closure in the PDA that is not hemodynamically significant may have similar advantages, avoiding a procedure in many infants in whom the ductus closes without treatment. The duration of such watchful expectancy needs to be determined and more evidence is needed to determine an optimal treatment strategy.

Surgical Closure

Surgical closure of the PDA is accomplished very predictably either by a clip application or by ligation and has had low morbidity and mortality even in very preterm infants for many decades.[54,55] There have been no recent randomized studies comparing surgical closure to medical therapies, with the Cochrane Review[56] including only 1 study from 1983.[57] In this trial, Gersony et al[57] compared surgical ligation to indomethacin, and found that surgical closure was more effective at closing the ductus (1% failure vs 30% failure with indomethacin), but with no differences in mortality or BPD, NEC, or IVH, although pneumothorax and ROP were more common in the surgical ligation group.

Although surgical closure is effective in achieving rapid and complete ductal closure, it may sometimes be followed by severe hemodynamic and respiratory collapse, requiring marked escalation in supportive intensive care.[58] The risk of this complication appears to decline substantially over the first 6 weeks after birth.[59] Complications of surgical closure include pneumothorax,[60] wound infection,[60] paresis of the left vocal cord[61,62] or diaphragm,[63] chylothorax,[64] and risk of scoliosis.[65] In addition, infants who undergo surgical ligation have been found to be more likely to develop BPD,[66,67] ROP,[67] and neurodevelopmental impairment.[67–69] Because of these risks and the risks of anesthesia and transfer from the NICU to the operating room, surgical closure is often reserved for infants who have a persistent PDA despite medical therapy (usually after 2 or more failed courses) or in whom medical therapy is contraindicated. From 2006 to 2015 in a large multicenter database evaluating 61 250 infants born between 23 and 30 weeks' gestation from 280 NICUs in the United States, the rates of surgical closure of PDA decreased from 8.4% to 2.9% ($P < .001$), accompanied by a decrease in the diagnosis of PDA (79% of sites), use of indomethacin or ibuprofen from 32% to 18% ($P < .001$) and a decrease in overall mortality without increases in any measured morbidity.[70] In another large multicenter database study from 2014 to 2021, evaluating 64 580 infants born between 22 and 30 weeks' gestation, 24 028 (37.2%) were diagnosed with a PDA.[71] The percentage of infants receiving any procedural closure of the PDA decreased from 4.4% in 2014 (4.36% surgical; 0.02% transcatheter closure) to 1.9% (0.84% surgical; 1.05% transcatheter closure) in 2021 ($P < .001$ for all comparisons), with transcatheter occlusion surpassing surgical ligation in 2021.[71] These data suggest that many centers had shifted to a more conservative approach in recent years, with fewer evaluations for PDA and subsequent decreases in medical and surgical management and with more frequent transcatheter as compared with surgical closure.

Transcatheter Closure of PDA

In 1966, Portsmann was the first to successfully close a PDA by a transcatheter method and reported subsequently that this approach was successfully used in 56 of 62 patients with no mortality and minimal morbidity.[72] Since then, there has been a constant pursuit to perform PDA closure at a younger age and smaller size to treat presumed associated deleterious physiologic effects. Transcatheter closure has classically been the procedure of choice for definitive PDA occlusion in adults, children, and infants weighing >6 kg and has become a first-line intervention for much smaller patients in many institutions as devices and techniques have improved and developed. In a recent large multicenter study, the number of sites offering transcatheter closure increased from 5 of 274 (1.8%) in 2014–2015 to 35 of 276 (12.7%) in 2020–2021, while centers offering surgical ligation decreased from 112/274 (40.9%) to 54/276 (19.6%) ($P < .0001$).[71]

In a meta-analyses of percutaneous PDA closure during infancy that included 38 studies through 2015, Backes et al[73] reported a technical success of percutaneous PDA closure of 92% (95% CI, 89–95), with clinically significant adverse event incidence of 10% (95% CI, 7.8–12.5).[73] Patients specifically <6 kg in weight who had a PDA device closure were studied from the IMPACT (Improving Pediatric and Adult Congenital Treatments) NCDR Registry and had a 94.3% procedural success rate among 73 hospitals during 2011–2015.[74] There was a 2.4% incidence of device embolization requiring retrieval and 3.5% incidence of acute arterial occlusion in that study. A meta-analysis of percutaneous PDA closure through 2020 in 373 infants weighing ≤1.5 kg by Bischoff et al[75] found that technical success was 96% (93–98), with overall adverse effect incidence of 27% (17–38) and major adverse event of 8% (5–10), with 5 deaths related to the procedure (4 in infants weighing <0.8 kg). Importantly, experience has grown exponentially since that time in smaller and more preterm infants and with that has come greater procedural success and safety.[76] The above study periods included limited percutaneous device choices and there has since been an increase in the availability of devices to address the unique ductal morphology of preterm infants, and there have been increasing levels of expertise in such procedures by interventional teams in smaller and less mature infants.[76] The successful technique of solely utilizing femoral venous access for PDA device closure and with echocardiographic guidance was described by Zahn et al,[77] thus eliminating the risk of arterial occlusion and even potentially eliminating the need for contrast administration in a small pilot group of preterm infants with off-label use of the Amplatzer Vascular Plug II (AVP II [Abbott Structural Heart, Plymouth, MN]) device. This was followed by a single-institution report of this approach of implanting the AVP II device with 88% success rate in 24 patients.[78] With the prior device limitations, several uncommon but important challenges of left pulmonary artery (LPA) and aortic obstruction occurred, emphasizing the need for tools designed for the extremely low weight and preterm population.

The Amplatzer Piccolo Occluder received FDA approval in 2019 and became the first device approved for PDA closure in patients weighing ≥700 g.[79] A single-arm, prospective, multicenter, nonrandomized study to evaluate the Amplatzer Piccolo Occluder in patients weighing ≥700 g evaluated 200 patients in 9 centers, with 100 patients weighing ≤2 kg (and 33 weighing ≤1 kg).[79] The implant success rate was 95.5% (191/200) overall, and 99% in those weighing ≤2 kg.[79] The primary effectiveness endpoint of PDA closure at 6-month follow-up was achieved in 99.4% of implanted patients, but 4 patients had a primary safety endpoint (2 transfusions, 1 hemolysis, and 1 aortic obstruction), and 5 patients (all weighing ≤2 kg) had worsening nonclinically evident tricuspid regurgitation. There was one instance of device-related aortic obstruction. Intraprocedural device embolization occurred in 5 patients (3 weighing <2 kg), all of which were successfully retrieved and replaced during the same procedure. There was no branch pulmonary artery obstruction. The 3-year follow-up of this study showed no new complications and no device or procedure-related deaths.[80] Although 2 patients had elevated LPA velocity by echocardiography of >2.5 m/s, both resolved with somatic growth and without intervention. Of the 5 patients with worsened tricuspid regurgitation, one had a nonprocedure-related mortality, one was withdrawn from the study for a device not being placed following initial device retrieval, and the other 3 have not required interventions on their tricuspid valves. All successfully closed PDAs that were followed to completion remained closed.

A recent cohort study using the IMPACT Registry of 1587 attempted PDA closures in infants weighing ≤2 kg (nearly all weighing >700 g) from 2016–2021, showing a significant increase in the distribution of percutaneous PDA device closures during the 2019–2021 time period, as compared with 2016–2019.[81] This study reported a 3% incidence of technical failure with a 5.5% incidence of the composite outcome of technical failure and/or major adverse event.[81] The most common major adverse event included device embolization requiring retrieval (1.3%) and unplanned cardiac or vascular surgery (1.3%).[81] The incidence of the composite outcome was associated with the use of arterial access (OR, 5.25; 95% CI, 2.3–12.01; $P < .001$), which has been largely abandoned by most institutions for this weight range; in addition, the composite outcome was associated with annual hospital volume of percutaneous PDA closures in infants weighing ≤2 kg (for higher volume: OR, 0.51; 95% CI, 0.28–0.93; $P = .03$), with similar rates of procedural failure across weight categories.[81]

A recent C3PO (Congenital Cardiac Catheterization Project on Outcomes) Registry study focusing on PDA device closure in infants weighing <2.5 kg from 2019–2020 showed a 98.7% success rate among 300 cases with a median weight of 1.0 kg (0.7–2.4) at 13 institutions.[82] There was a 1.7% incidence of level 4/5 adverse events (AEs), including device malposition causing aortic obstruction (n = 2) and respiratory arrest (n = 2). There was 1 death 12 hours postprocedure in the setting of urosepsis and "postligation syndrome." The 5.6% incidence of level 3 AEs include a 1.3% (n = 4) incidence of device embolization; these were all retrieved successfully during the same procedure. Age and weight at the time of catheterization were not significantly associated with AEs. This study's timeframe corresponds with the approval of the Piccolo Occluder, although an off-label device (Micro Vascular Plug [Medtronic, Minneapolis, MN]) was used first in 20% of cases and showed that patients who had the Micro Vascular Plug as the first device had a higher likelihood of failed device placement (OR, 12.9; $P = .028$).

The challenges to using transcatheter or surgical closure strategies are establishing the appropriate timing, the selection of patients, and the experience and expertise within each center. Although there are no randomized trials comparing transcatheter and surgical closure, there are some data from observational studies, although data from the most immature infants (born at 22–23 weeks' gestational age) are very limited. Ogando et al[83] in Spain performed a retrospective cohort study of 25 very low weight preterm infants undergoing percutaneous closure using the Piccolo Occluder (then named the Amplatzer Duct Occluder-II-Additional Sizes [ADO-II-AS]) to 28 matched infants (for gestational age, birth weight, and procedure weight) with surgical closure from 2011–2016. There was quicker improvement in the pulmonary status in the percutaneous closure group and a higher morbidity in the surgical closure group with a high rate of recurrent laryngeal nerve palsy (17%).[83] There were 2 device embolizations, which were successfully retrieved and replaced during the same procedure. Unfortunately, the majority of the remainder of studies comparing percutaneous to surgical treatment were performed prior to the availability and approval of the Amplatzer Piccolo Occluder as well as widespread use of a sole transvenous approach with echocardiographic guidance. Kim et al[84] compared 33 infants receiving device closure to 39 infants with surgical closure during 2014–2017 period and noted that infants undergoing surgical ligation were younger and smaller and required more preoperative support, but the procedure time was shorter for surgical ligation, with fewer complications. The procedural charges were higher for percutaneous closure, driven by device charge and catheterization room utilization.[84] Regan et al[85] compared 64 infants undergoing transcatheter closure to 83 matched surgical cases. PDA closure was successful in all cases, with 4 deaths in catheter group (6.3%) vs 10 (12%) in the surgical group ($P = .24$), and with a shorter duration of mechanical ventilation after catheterization (median 3 vs 5 days, $P = .04$).[85] Kuntz et al[86] compared trends and outcomes for surgical (n = 175) vs transcatheter (n = 503) PDA closure at US Children's Hospitals. Surgical patients were younger (0.1 vs 0.53 years; $P < .001$) and more premature (60% vs 20.3%; $P < .001$), with higher rates of comorbidity. When only preterm infants (n = 102 for catheter vs 105 for surgical ligation) were compared, infants surgically ligated were more likely to be mechanically ventilated, and for longer, with a longer hospital stay (adjusted difference in medians, 4 days; 95% CI, 1.7–6.3 days; $P < .001$) and postoperative length of stay (adjusted difference in medians, 3 days; 95% CI, 1.1–4.9 days; $P = .002$).[86]

Advances in the percutaneous device closure of the PDA have led to its widespread adoption among many institutions with a congenital interventional cardiology team as a viable treatment option for preterm infants. With the approval of the Amplatzer Piccolo Occluder and advanced technical approaches, safety and efficacy have improved. If there is no transcatheter or surgical closure available at a center, decisive treatment of hsPDAs failing medical therapy (or in whom it is contraindicated) requires transfer to centers with expertise in such procedures. Development of collaborative, multidisciplinary teams who can assess the regional availability of procedural closure along with the risks and benefits of patient transfer may be required to best determine the timing and eligibility of intervention. It is likely that the availability of such specialized care and procedures may not be easily accessible or available, resulting in potential inequities in health care delivery. Although procedural outcomes have been shown in registry-based and multicenter clinical studies, it is important to determine whether closing the PDA by transcatheter approaches improves short-term clinical outcomes (initial hospital mortality, BPD, NEC, ROP, etc) or longer-term outcomes (neurodevelopmental impairment). The ongoing Percutaneous Intervention Vs Observational Trial of Arterial Ductus in Low Birth Weight Infants (PIVOTAL) (NCT05547165) will yield useful data in this regard.

Adjunct and Other Medical Nonpharmacological Therapies

Expectant management of the PDA includes management of fluid, electrolyte, and nutrition status, and support of the cardiac, circulatory, and respiratory systems that may be impacted by the PDA. These frequently include restriction of fluid intake, diuresis, and use of higher end-expiratory pressures and permissive hypercapnia.[87]

Restricted water intake in preterm infants has been shown to increase postnatal weight loss (overall weighted mean difference, 1.94% of birth weight; 95% CI, 0.82–3.07)

and significantly reduce the risks of PDA (RR, 0.52; 95% CI, 0.37–0.73; number needed to treat, 7; range, 5–14) and NEC (RR, 0.43; 95% CI, 0.21–0.87; NNT, 20; range, 11–100), with trends for reduction in BPD (RR, 0.85; 95% CI, 9.63–1.14), IVH (RR, 0.74; 95% CI, 0.48–1.14), and death (RR, 0.81; 95% CI, 0.54–1.23).[88] Hence, there is some evidence that early fluid restriction may reduce the incidence of a PDA; however, this evidence is based on trials that are from several decades ago and may not be generalizable to current practices and more immature infants. There is no evidence that fluid restriction is helpful following the diagnosis of a hemodynamically significant PDA. Fluid restriction after diagnosis negatively affects energy intake and growth.[89] A reduction of fluid intake from 145 ± 15 to 108 ± 10 mL/kg/d did not change respiratory variables, FiO_2, blood gas values, PDA diameter, blood flow velocities (in the PDA, left pulmonary artery, or descending aorta), or LA/Ao ratio but reduced flow in the superior vena cava significantly (105 ± 40 to 61 ± 25 mL/kg/min, $P < .001$) and lowered blood flow velocity in the superior mesenteric artery.[90] It may be optimal to limit fluid restriction to a minimum of 120 to 130 mL/kg/d after the first week, to limit such adverse effects of over-restricted fluid intake.

Diuresis is often induced with furosemide in an attempt to reduce pulmonary edema associated with a hemodynamically significant PDA. However, loop diuretics such as furosemide (but not thiazides) also increase renal prostaglandin E_2 production in vitro[91] and cause PDA dilatation in vivo in neonatal rats.[92] Early prophylactic use of furosemide in a small randomized trial led to more rapid postnatal weight loss and a higher heart rate but with a trend toward a higher prevalence of PDA (40% in furosemide group with PDA vs 24% in placebo group; $P = .09$).[93] Hence, there is a concern over the use of loop diuretics in PDA and a lack of consensus.[94] However, the use of concomitant furosemide did not reduce the efficacy of acetaminophen in closing the PDA,[95] and a recent large retrospective cohort study showed that exposure to furosemide was actually associated with decreased odds of PDA treatment (OR, 0.72; 95% CI, 0.65–0.79),[96] suggesting that although prophylactic use of furosemide may not be appropriate, it may be useful in management in the setting of pulmonary edema.

Respiratory management using higher end-expiratory pressures and permissive hypercapnia may potentially reduce left-to-right shunting in the setting of a PDA.[87] However, these management strategies based on respiratory physiology have not been adequately studied.

CLINICAL TRIAL OPPORTUNITIES

Additional research is needed to address 2 broad questions related to prolonged ductal patency in preterm infants. First, the relationship between measures of hemodynamic significance and increased risks for both very prolonged patency and adverse clinical outcomes, such as BPD, pulmonary hypertension, or neurodevelopmental impairment, needs to be established, with additional focus on the optimal timing and method of achieving closure. Second, well-designed and meticulously executed intervention trials, for which the endpoints are clinically important long-term outcomes in addition to short-term physiologic changes, and not simply rates of ductal closure and adverse procedural events, are essential. In these trials, both treatment arms must be unambiguously defined so that the superior strategy can be replicated in clinical practice and evaluated against alternatives in future trials. If it is not feasible to forego use of rescue treatment in the control (placebo or late-treatment) arm, strict criteria for both a required time interval and diagnostic thresholds for such treatment are essential. Long-term follow up with assessment of neurodevelopmental outcomes would further guide treatment. Without clear demonstration that adverse outcomes can be averted by medical, surgical, or transcatheter closure of the ductus, the hypothesis that ductal patency is causal with respect to those outcomes remains unproven.

RECOMMENDATIONS

For Clinical Practice

1. Prophylactic medical interventions (those not guided by knowledge of PDA status) are not recommended at any age or birth weight for the purpose of reducing the risk of a symptomatic PDA, as there are no effects on mortality, BPD, or neurodevelopmental impairment (level of evidence: 1A).[29]
2. Early fluid restriction may reduce the incidence of a PDA (level of evidence: 1A).[29] However, such data are from several decades ago and may not be generalizable to current practices and extremely preterm infants. There is no evidence that fluid restriction is helpful following diagnosis of a hemodynamically significant PDA (level of evidence: 2B).[29] Furosemide may be useful as an adjunct in management (level of evidence: 2B).[29] Ventilator management strategies have not been adequately studied for firm recommendations.
3. Very early (<72 hours of age) or early (<7 to 14 days of age) routine treatment to induce PDA closure (regardless of hemodynamic significance) in preterm infants, either medically, via transcatheter, or surgically, is able to close the ductus but does not improve outcomes and is not recommended (level of evidence: 1A).[29] Conservative management in this age group may let infants avoid medical therapy or procedural exposure (either surgical or transcatheter closure), allowing spontaneous delayed closure without risk of increased adverse outcomes. It is likely that the presence of a

PDA is a marker for more extreme immaturity and a biomarker for worse outcomes, but treatments to close the PDA may not significantly impact such outcomes.

4. There are insufficient data for recommendations on management of infants with a hemodynamically significant PDA beyond 2 weeks of age. Benefits and risks of watchful expectancy with close monitoring, attempted medical closure, transcatheter closure, or surgical ligation of the hemodynamically significant PDA have not been adequately defined. The duration of watchful expectancy needs to be determined and more evidence is needed to determine an optimal treatment strategy.
5. It is considered reasonable to attempt pharmacologic closure of a hemodynamically significant PDA beyond 2 weeks of age (ibuprofen as a preferred agent, although acetaminophen or indomethacin are acceptable alternatives) (level of evidence: 5).[29]
6. If the hsPDA persists beyond 2 weeks of age despite pharmacologic therapy of up to 2 courses (or if medical therapy is contraindicated), such infants may be considered for either transcatheter closure or surgical ligation (level of evidence: 4).[29]

For Further Study

1. The role of more selective use of medical therapies for inducing PDA closure, both for defined higher-risk infants in the first 2 postnatal weeks (perhaps by early hemodynamic screening or other targeting), or for older infants in whom the PDA remains patent (whether hemodynamically significant or not), remains uncertain and is currently the subject of ongoing studies. There is a lack of evidence to guide management, necessitating equipoise regarding treatment options and support for parents to permit enrollment of their infants in trials that can expand the available body of evidence, especially regarding long-term cardiopulmonary and neurodevelopmental outcomes.
2. Increasing numbers of infants currently undergo transcatheter closure while surgical ligation of PDA has declined in recent years. Transcatheter closure is very effective in closing the PDA but the risks, benefits, and longer term outcomes need to be adequately defined, and the eligibility and optimal timing for transcatheter interventions need to be better understood before firm recommendations can be developed (level of evidence: 4).[29]

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ABBREVIATIONS

BPD: bronchopulmonary dysplasia
COX: cyclooxygenase-2
ERT: early routine treatment
hsPDA: hemodynamically significant patent ductus arteriosus
NT-proBNP: amino-terminal pro-B-type natriuretic peptide
PDA: patent ductus arteriosus
RCT: randomized controlled trial
RDS: respiratory distress syndrome
ROP: retinopathy of prematurity

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