Patent Ductus Arteriosus: A Diagnostic and Treatment Dilemma

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ABSTRACT

Ductus arteriosus is a critically important vascular structure that functions as an extracardiac shunt in fetal life between the pulmonary and systemic circulations for optimal utilization of the placenta as a gas exchange organ and fetal well-being. While morbidities and mortality are well known to be associated with persistence of patent ductus arteriosus (PDA) in postnatal life, the treatment options have concerns for adverse outcomes. Additionally, high spontaneous closure rates, lack of clear definition of hemodynamically significant PDA (hs-PDA), ideal diagnostic tools, conflicting evidence regarding timing of treatment, and lack of clear benefits of PDA treatment from randomized trial in reducing adverse outcomes continue to pose challenges for clinicians managing preterm infants with PDA. This review focuses on the pathophysiology, current diagnostic and management practices, as well as the potential of utilizing unique diagnostic tools to support precision medicine for preterm infants with hs-PDA.

Keywords: Ductus arteriosus, Neonate, Patent ductus arteriosus, Prematurity.

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INTRODUCTION

The patency of the *ductus arteriosus*, which is a critically important vascular structure, results in an extra-cardiac shunt between the pulmonary (pulmonary artery) and systemic (aorta) circulations. Galen was the first to describe a patent ductus arteriosus (PDA) and Gross to report its successful closure.[1] Although rare, premature, *in utero* closure of the PDA due to maternal medications and/or due to unknown etiology can lead to right ventricular overload, congestive heart failure, fetal hydrops, and/or intrauterine fetal demise.[2,3] In most infants, the PDA closes within 24–72 hours after birth. In term infants, a persistent PDA can account for up to 5–10% of all congenital heart disease of newborns.[4] On the contrary, the PDA is a common occurrence in preterm, very low birth weight (VLBW) infants where continuous pulmonary over circulation continues until the duct remains open. Ductal closure leads to the improvement of lung compliance and stops the "stealing" from the systemic circulation. These hemodynamic alterations have been historically known to be associated with neonatal morbidities, such as accentuated respiratory distress syndrome (RDS), pulmonary hemorrhage, bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), renal insufficiency, intraventricular hemorrhage (IVH), and/or cardiac dysfunction.[5,6] About 20–60% of preterm infants have a PDA beyond the first 72 hours of life.[7] The prevalence of PDA in preterm infants is inversely related to gestational age and birth weight with an incidence of 70% in infants <28 weeks gestation.[8] Over the last decade with advances in diagnostic modalities, awareness of natural history with spontaneous closure,[9,10] and limited benefits of treatment,[11–13] the management of PDA has posed a significant dilemma to clinicians. The objective of this review is to discuss the utilization of potential innovative diagnostic tools for identification and thereby targeted treatment of hemodynamically significant PDA (hs-PDA).

PATHOPHYSIOLOGY

The three *in utero* shunts, *ductus venosus*, *ductus arteriosus,* and foramen ovale, play a critical role in fetal hemodynamics and are

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essential for efficient utilization of the placenta for gas exchange, normal cardiovascular growth, and function. The relatively low fetal oxygen tension with partial pressure of oxygen (pO_2) ranges of 25–28 mm Hg (65% O_2 saturation),[14] and circulating prostaglandins, specifically prostaglandin E2 (PGE2), formed by the action of cyclooxygenase (COX) enzymes maintains the PDA through their vasodilatory effects.[15] The *ductus arteriosus* smooth muscle relaxation occurs due to activation of the G protein–coupled receptor EP4 by PGE2.[15,16] At birth, increasing oxygen tension and decreasing PGE2 production lead to spontaneous PDA closure by 24–48 hours of life. Fan et al. described the PDA maturation pathway in their rabbit model and demonstrated that patency of the preterm ductus is maintained by high levels of PGE2, which binds the EP4 receptors under conditions of hypoxia as opposed

to the term ductus where the EP3 receptor levels are higher and exposure to PGE2 caused vasoconstriction under normoxic conditions.[17] Once functional closure of the ductus occurs, then anatomic closure follows with intraluminal remodeling in response to hypoxemic conditions.[18] Hence, delayed ductal closure in term infants is primarily related to structural alterations, whereas the lack of spontaneous closure in preterm infants is due to immaturity.[18]

Spontaneous PDA closure rates increase with both advancing gestational age and postnatal age. In the meta-analysis by de Klerk et al., they noted that 34% of premature infants (gestational age ≤28 weeks and/or BW ≤1000 g) had spontaneous ductus closure by the 3rd day after birth (72–96 hours) and up to 41% by the 7th day.[19] Although most ductus will close spontaneously, without intervention,[20] infants with GA ≤28 weeks have the lowest chance of spontaneous PDA closure in the first week of life.[9,19] Liu et al. noted that maternal chorioamnionitis, lower gestational age and birth weight, BPD, IVH, NEC, RDS, sepsis, surfactant treatment, ventilation, and lower platelet count were all positively related to persistence of the PDA, whereas a small for gestational age (SGA) status had a converse effect among preterm infants. Additionally, premature rupture of membrane (PROM), preeclampsia, antenatal steroids, male gender, and platelet indices were not associated with PDA.[21] Our current limited knowledge about predictive factors[22] as well as processes for identification of hemodynamically significant PDA further adds a layer of complexity to successful management of PDA in these critically ill preterm infants.

Diagnosis

In making a diagnosis and determining the need for treatment, clinicians usually grapple with two issues: (a) the presence/absence of a PDA and (b) its hemodynamic significance. Clinically, PDA can be suspected based on clinical signs and confirmed with a two-dimensional (2D) echocardiography. The clinical signs include the presence of a continuous murmur, although "silent" large PDAs may exist; bounding pulses and widened pulse pressures; unexplained metabolic acidosis, due to systemic under perfusion; evidence of pulmonary over circulation manifesting as tachypnea; increased work of breathing, increased need for respiratory support; hypotension and low diastolic blood pressure; oliguria; and biochemical alterations as persistent metabolic acidosis and elevated creatinine. Once suspected, PDA is confirmed by a 2D echo wherein structural and functional measurements are made (Fig. 1).

Echocardiography reports provide information about the PDA size, left atrium (LA)-to-aorta (LA/Ao) ratio, LA and left ventricular (LV) size, and LV output. However, the presence of a PDA alone does not provide guidance for further management. Determination of hemodynamic significance if the PDA with a potential for negative impact on multiple organ systems is also considered as an indication for treatment (Fig. 2).

Defining Hemodynamically Significant PDA

The definition of an hs-PDA is controversial.[23] As reported by Zonnenberg et al., most clinical trials use clinical and ultrasound-based criteria to define an hs-PDA, but there is considerable variability in the inclusion criteria and cutoffs without a clear consensus. Of the clinical criteria, a murmur or hyperdynamic circulation is most commonly used. The LA/Ao ratio is most commonly utilized ultrasound criteria.[24] In addition, the likelihood of spontaneous closure and vulnerability to the severity of illness related to gestational or chronological age may also be considered.[25] Kluckow suggested even though echocardiography may be the mainstay of diagnosis, assessment of clinical manifestations,
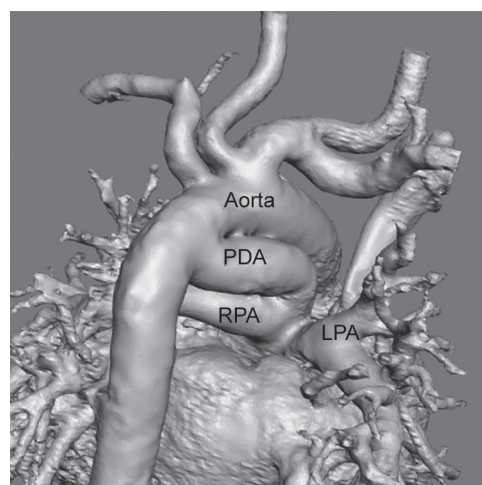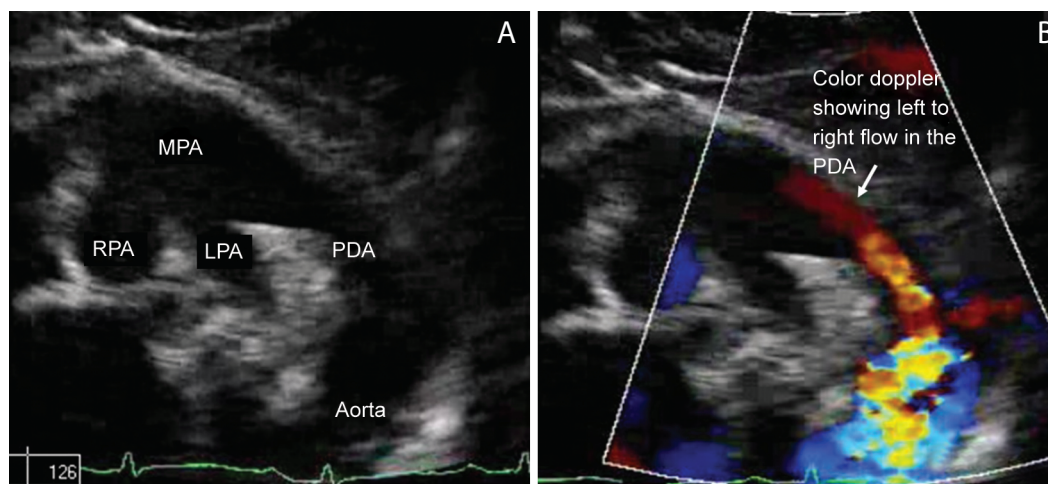

Fig. 2: 3D Volume rendered image depicting the PDA anatomy, posterior view. RPA, right pulmonary artery; LPA, left pulmonary artery; PDA, patent ductus arteriosus

Figs 1A and B: 2D Echocardiographic images of PDA shown in the "ductal view" without (A) and with color Doppler; (B) Showing left to right flow across the duct. MPA, main pulmonary artery; RPA, right pulmonary artery; LPA, left pulmonary artery; PDA, patent ductus arteriosus

biomarkers and physiological markers of the end-organ effects such as with cerebral Doppler or near infra-red spectroscopy should be considered.[26] A combination of these modalities may provide a clearer picture of hs-PDA for judicious, individualized treatment, as opposed to generalized application of therapy for all and/or none. Multiple modalities have been used to assess the hemodynamic significance of a PDA, with each having their own pros and cons:

- *Clinical scores for hs-PDA:* Initial diagnosis of an hs-PDA still relies largely on clinical parameters. Accurate clinical scoring tools can allow for better noninvasive monitoring over time, but also limit the repeated need for echocardiography and other stress-inducing procedures. One such scoring system was proposed by Kindler et al., wherein they measured eight clinical variables with each variable receiving a score of 1. A composite score ≥2 prompted further evaluation with an echocardiogram. These initial variables were further improvised to create the final scoring system composed of four significant symptoms—precordial pulsations, bounding femoral pulses, apnea/need for mechanical ventilation, and metabolic acidosis. This score demonstrated a calculated sensitivity of 84% and specificity of 80%. They further adapted the need for apnea/mechanical ventilation variable to "pulmonary deterioration," as indicated by increased oxygen supplementation, increased noninvasive or invasive respiratory support, increased apnea frequency, and mounting hypercapnia.[27] Another scoring tool utilizing 14 clinical items, the Scoring preterm Infants for PDA clinically without Echocardiographic evaluation (SIMPLE) score, warrants further evaluation in future studies. The authors identified these items based on a literature review and then weighed them by severity on an arbitrary 1–4 scale, the sum of which represented the final SIMPLE score. This objective, bedside administrable score was found to be consistently high in infants with hs-PDA as compared to infants without hs-PDA.[28] A PDA severity score (PDAsc) was developed to predict the diagnosis of chronic lung disease and/or death prior to discharge through an observational study. Using echocardiographic data from 141 infants in a prospective observational study, the PDAsc on postnatal day 2 was noted to be consistently higher in infants who either developed chronic lung disease or died prior to discharge. A PDAsc cutoff of 5 in this study had a sensitivity and specificity of 92 and 87%, respectively, and positive and negative predictive values of 92 and 82%, respectively.[29] However, these clinical scores need further validation.

- *Biomarkers for hs-PDA:* The degree of metabolic acidosis, urinary output, and the blood urea nitrogen (BUN) and creatinine (Cr) levels are the most common biochemical indicators of an hs-PDA and probably most widely used markers of end-organ insult secondary to the ductal "steal" in perfusion. Serum brain natriuretic peptide (BNP) and serum/urinary N-terminal pro-brain natriuretic peptide (NTproBNP) have also generated interest as predictors for chronic lung disease with or without associated pulmonary hypertension in preterm infants.[30,31] Given the association between hs-PDA and chronic lung disease, exploration of NTproBNP as a potential biomarker for assessment of hs-PDA is being explored, given its increased secretion by ventricular myocardium in response to volume overload.[32,33] Additionally, Olsson et al. demonstrated that high levels of BNP, interleukin (IL)-6, -8, -10, and -12, growth differentiation factor-15, and monocyte chemotactic protein-1 were associated with persistent PDA, as were low levels of platelet-derived growth factor. High levels of both inflammatory markers and erythropoietin were associated

with persistent PDA and failure to respond to pharmacological treatment.[34] However, prior to translation into clinical decision-making, further work is needed to determine the most optimal timing for testing, cutoff thresholds for treatment, and/or the role of trending these biomarkers over time to assess for severity and/or improvement.

- *Echocardiographic assessment of hs-PDA:* To date, echocardiography remains to be the gold standard for diagnosis of hs-PDA, and the determination of the anatomical characteristics of the ductus, evidence of systemic hypoperfusion and pulmonary over-circulation have been useful.[35] In the order of relevance, the most useful characteristics of hs-PDA are the presence of descending aortic diastolic flow reversal, increased LV output, isovolumic relaxation time (IVRT), PDA diameter, pulmonary vein D wave, LA:Ao ratio, and the mitral E wave (Table 1).[36,37] An E/A ratio is utilized to assess left ventricular function and is defined as the ratio of peak velocity blood flow from left ventricular relaxation during early diastole (the E wave) to the peak velocity flow during late diastole caused by atrial contraction (the A wave). In preterm infants with hs-PDA and signs of volume overloading, the E/A ratio may approach ≥1 or be reversed and can be used in conjunction with other markers, such as the isovolumic relaxation time (IVRT), which may be <40 with pulmonary over-circulation.[38] As decisions are made for medical and/or surgical treatment, defining the anatomy of the PDA becomes critical to rule out ductal-dependent cardiac lesions; the assessment for ductal length and diameter to plan type of closure; determining the directionality of the shunt not only through the PDA but also other intracardiac shunts that may exist as foramen ovale, atrial, and/or ventricular septal defects; and any other structural aberrations as sidedness of the arch and/or presence of vascular rings. While 2D echo is performed most often in clinical setting, emerging evidence supports the role of real-time 3D dimensional echocardiography (RT3DE) in clinical practice They were submitted with the original article and are begin resubmitted (Videos 1A and B). Roushdy et al. imaged 42 older postneonatal patients (mean age of 3.6 years; ranging from 2 months to 14 years) who were referred for elective percutaneous PDA closure after having been assessed with a full 2D echocardiogram, and RT3DE, and off-line analysis using Q lab software within 6 hours from their angiograms. They concluded

Table 1: 2D Echocardiographic markers of hemodynamically significant PDA (Adapted from Boradhouse KM, Price AN, Durighel G, et al. Assessment of PDA shunt and systemic blood flow in newborns using cardiac MRI. NMR Biomed 2013;26(9):1135–1141. DOI: 10.1002/nbm.2927)

Measurement	Hemodynamically significance
PDA size	>1.5 mm
LA–Ao ratio	>1.5 mm
IVRT	<50 ms
LA size	Increased ≥2 SD
LV size	Increased ≥2 SD
LV output	>1.5 × RV output
Mitral E wave	>45 cm/sec
PV D-wave	>30 cm/sec
Aortic diastolic flow	Reversed

PDA, patent ductus arteriosus; LA, left atrium; Ao, aorta; IVRT, isovolumic relaxation time; LV, Left ventricle; PV, pulmonary vein; mm, millimeter; SD, standard deviation

that RT3DE was more accurate than 2D echocardiogram in determining the length and the ampulla of the PDA, determining type A and type E PDA and correlated well with angiography.[39]

- *Magnetic resonance imaging (MRI) for hs-PDA:* The role of cardiac magnetic resonance imaging (CMR) is increasingly being explored as a complement for patients during pre- and/or postintervention for structural cardiac disease. As a noninvasive imaging technique, CMR can allow detailed visualization of cardiac anatomy and functional assessment, including wall motion analysis, quantification of chambers size and volume, systolic function, and myocardial tissue characterization, without exposure to ionizing radiation.[40] It can also provide spatial resolution and 3-dimensional (3D) multiplanar reconstruction allowing for assessment of the PDA anatomy (Fig. 2), evaluation of associated abnormalities in the aortic arch, and quantification of ductal shunt volume. While larger PDAs can be seen on spin-echo images, breath-hold magnetic resonance angiogram (MRA), the flow disturbances produced by even small PDA in the pulmonary artery can be visible as signal loss on cine MRA. Additionally, sagittal reconstructions using 3D noncontrast MRA can demonstrate the small PDA.[40] Since direct quantification of the PDA shunting can be difficult with CMR, Broadhouse et al. attempted to indirectly assess for hemodynamic shunting through the PDA with phase-contrast MRI sequences. They assessed 75 infants with median (range)-corrected gestation 33^{+6} $(26^{+4}–38^{+6})$ weeks, of whom 15 had PDA. In 60 infants without PDA, left ventricular outflow (LVO) matched total systemic flow; while in infants with PDA, ductal shunt volume was 7.9–74.2% of the LVO. Multiple linear regression analysis correcting for gestational age showed a significant association between ductal shunt volume and decreased upper and lower body flow ($p = 0.01$ and $p < 0.001$).[36] PDA is uniquely the only shunt type that gives a Qp/Qs <1, when pulmonary blood flow is increased. Since PDA causes a systemic-to-pulmonary shunt from the descending aorta to the left pulmonary artery, quantification of Qp/Qs cannot be interpreted the same way it is interpreted in an intracardiac shunt. The aorta usually has higher flow than the pulmonary artery so that one way to calculate the shunt volume is to subtract the pulmonary flow from the systemic one (Qshunt = Qs − Qp). Another possible method is MRI measurement of the relation between the flow in the superior cava, the left cardiac output, and the flow of the descending aorta in order to obtain information about the amount of flow subtracted from the inferior systemic circulation (distal to the ductus). This quantitative data about the steal to the descending aorta circulation can be relevant for the indication of PDA closure in premature infants in order to avoid complications.[41] The severity of PDA can potentially be quantified in terms of Qp/Qs and surgery is generally reserved for patients with Qp/Qs >1.5. CMR although has great potential, it also comes with logistic challenges of transporting an infant to MRI suite, obtaining detailed MRI images, need for breath-holding and spatial resolution in a small preterm infant.

- *Near-infrared spectroscopy for hs-PDA:* Persistent shunting from systemic-to-pulmonary circulation results in hypoperfusion of tissues with resultant hypoxemia, as the PDA becomes hemodynamically significant. Ability to measure tissue perfusion with near-infrared spectroscopy (NIRS) can provide further information in the assessment of hs-PDA and has been evaluated. Chock et al., in their study of 47 infants, noted that after adjusting for gestational age found that lower renal saturation (Rsat) was associated with an hs-PDA by echo (OR

0.9, 95% CI 0.83–0.98, $p = 0.01$), while there was no significant change for cerebral saturations (Csat). Using receiver-operating characteristic (ROC) curves, Rsat <66% identified an hs-PDA with a sensitivity of 81% and specificity of 77%.[42] Since the cerebral blood flow has a preductal origin, it has been assumed that if the hemodynamics are stable, then the presence of an hs-PDA does not impact cerebral tissue perfusion. However, in a prospective case–control study, mean arterial blood pressure and regional cerebral oxygen saturation were significantly lower and fractional tissue oxygen extraction significantly higher for infants with PDA when compared with the control infants during PDA (mean arterial blood pressure: 33 ± 5 vs 38 ± 6 mm Hg; regional cerebral oxygen saturation: $62 \pm 9\%$ vs $72 \pm 10\%$; and fractional tissue oxygen extraction: 0.34 ± 0.1 vs 0.25 ± 0.1, respectively). These improved after treatment with indomethacin and became similar to controls after successful closure.[43] However, in a recent prospective observational study of 49 preterm infants with a closed PDA, non-hs-PDA, and hs-PDA within 2 weeks after birth, no differences were noted for Csat and/or Rsat and fraction tissue oxygenation extraction (FTOE) within the three groups as well as with the presence of by retrograde diastolic blood flow in the descending aorta.[44] Given these conflicting reports, further evaluation of NIRS monitoring for hs-PDA is needed.

Video 1A: Real-time 3D view of the PDA

Video 1B: 3D view of PDA aneurysm

MANAGEMENT

Management of PDA continues to be controversial with no consensus regarding the need for treatment, optimal timing, and choice of treatment. As most PDAs close spontaneously, treatment of PDA has generally failed to show a decrease in adverse outcomes in preterm infants[45] and the medications may be associated with significant adverse events, like intestinal perforations; routine treatment to induce early closure of a persistent PDA in preterm infants has fallen out of favor.[46]

Timing of PDA Treatment

Historically, treatment considerations have focused on prophylactic vs therapeutic as well as conservative vs medical/surgical management plans.[22] Prophylactic indomethacin administration for prevention of intraventricular hemorrhage for infants born <1000 g and/or <28 weeks has been associated with decreased rates of hypotension, symptomatic PDA, and rates of any PDA.[47,48] Due to the reports showing high rates of spontaneous closure with increasing chronological age,[9,10] and those of complications reported with treatment and limited benefits on long-term outcomes,[11–13] there has been a shift in practice for delaying treatment until the physiological compromise becomes evident due to hs-PDA.[49,50] Based on current literature, the appropriate timing for initiation of treatment still remains an unanswered question with wide variations in practice.

Medical Management

Medical management of hs-PDA, with fluid restriction and administration of nonselective cyclooxygenase (COX) inhibitors, like indomethacin and ibuprofen, as well as prostaglandin-H_2 synthase inhibitors, like acetaminophen, are the first line of treatment before considering surgical options.[51–53]

COX inhibitors promote the constriction and eventual closure of the ductus[54] by inhibiting the synthesis and release of prostaglandins, which play a major role in maintaining ductal

patency during fetal life.[55] Although indomethacin has been the traditional "drug of choice" for treatment of PDA, the US Food and Drug Administration approved the use of ibuprofen lysine in April 2006 for closure of clinically significant PDA in premature infants <32 weeks and weighing between 500 and 1500 g. However, several adverse effects have been reported with these medications, including gastrointestinal bleeding and perforation, decreased platelet aggregation, hyperbilirubinemia, renal failure, thrombocytopenia, and hyponatremia.[52,56,57] In comparison, while acetaminophen appears as a safer alternative to indomethacin and ibuprofen with potentially fewer adverse effects,[58] it has lower efficacy, probably influenced by the gestational age and the size of the PDA.[59,60] The commonly utilized dosing protocols for all prophylactic and treatment protocols for these three medications are presented in Table 2.[52,61–66] The comparative efficacy of these medications is presented in Table 3. However, the protocols and subject selection in these studies were highly variable, making it difficult to generalize the results. Mitra et al., in their meta-analysis evaluated 68 randomized clinical trials of 4,802 infants, where 14 different variations of indomethacin, ibuprofen, or acetaminophen were used as treatment modalities. The overall PDA closure rate was 67.4% (2,867 of 4,256 infants). A high dose of oral ibuprofen was associated with a significantly higher odds of PDA closure vs a standard dose of intravenous ibuprofen [odds ratio (OR), 3.59; 95% credible interval (CrI), 1.64–8.17; absolute risk difference, 199 (95% CrI 95–258) more per 1,000 infants] and a standard dose of intravenous indomethacin [OR, 2.35 (95% CrI, 1.08–5.31); absolute risk difference, 124 (95% CrI, 14–188) more per 1,000 infants]. They concluded that a high dose of oral ibuprofen was associated with a higher likelihood of hemodynamically significant PDA closure vs standard doses of intravenous ibuprofen or intravenous indomethacin; placebo or no treatment did not significantly change the likelihood of mortality, necrotizing enterocolitis, or intraventricular hemorrhage.[67] In their Cochrane meta-analysis,

Table 2: Dosing regimen of pharmacological agents for PDA closure (Adapted from Neofax, 2021 [Accessed May 20, 2021])

Drug	Dosing regimen
Indomethacin prophylaxis[61–63]	1. 0.1–0.2 mg/kg/dose IV every 12–24 hours beginning within the first 6–24 hours of birth for a total of three doses **OR** 2. 0.1 mg/kg/dose IV every 24 hours for three doses
Indomethacin treatment[#]	• Age-based dosing: – <48 hours: first dose: 0.2 mg/kg IV; second and third doses 0.1 mg/kg IV Q 12–24 hours after first dose – 2–7 days: first dose: 0.2 mg/kg IV; second and third doses 0.2 mg/kg IV Q 12–24 hours after first dose – >7 days: first dose: 0.2 mg/kg IV; second and third doses 0.25 mg/kg IV Q 12–24 hours after first dose **OR** • Longer course 0.2 mg/kg/dose IV every 24 hours for a total of 5–7 days
Ibuprofen treatment[64,65,67]	• Loading dose of 10 mg/kg IV/PO on day 1, followed by 5 mg/kg/dose at 24 and 48 hours subsequently • A second course may be required **OR** • High dose of ibuprofen as 15–20 mg/kg followed by 7.5–10 mg/kg administered every 12–24 hours for a total of three doses
Acetaminophen treatment[52,66]	1. 15 mg/kg/dose IV/PO every 6 hours × 3 days 2. A second course may be required

[#]Product Information: Indomethacin IV injection. APP Pharmaceuticals, LLC (per Manufacturer), Schaumburg, Illinois, 2010

Table 3: Comparative efficacy of pharmacological agents for medical treatment of PDA

Study	Infants studied (N)	Study type	Diagnostic criteria for hs-PDA	Success rate (%)/OR [CrI, CI]				
				Acetaminophen	Indomethacin	Ibuprofen standard dose	Ibuprofen high dose	Placebo
Davidson et al., 2020	37	RCT	Echo only	5.9%	55%	n/a	n/a	
Mitra et al., 2018	4,802	Meta-analysis (68 RCTs)	Clinical + Echo	2.93 [1.52–5.62]	2.35 [1.08–5.31]	2.22 [1.44–3.40]	3.59 [1.64–8.17]	n/a
Overmeire et al., 2000	148	RCT	Clinical + Echo	n/a	66%	70%	n/a	n/a
Luecke et al., 2017	41	Observational	Clinical + Echo	66%	n/a	n/a	n/a	n/a
Meena et al., 2020	105	RCT	Clinical + Echo	71.43%	68%	77.14%	n/a	n/a
Kumar et al., 2020	161	RCT	Clinical + Echo	64% 1 course 89% 2 courses	n/a	78% 1 course 89% 2 courses	n/a	n/a
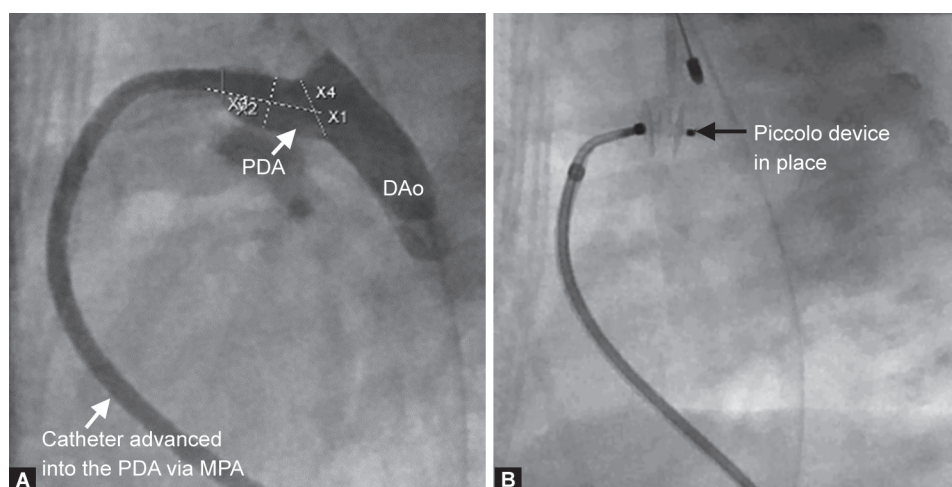
Figs 3A and B: Transcatheter closure of PDA in a preterm infant. (A) Measurements of the PDA prior to device deployment; (B) Image showing the successful deployment of the Piccolo device in the duct. PDA, patent ductus arteriosus; Dao, descending aorta; MPA, main pulmonary artery

Ohlsson et al. included 8 studies that reported on 916 infants. One study compared paracetamol to both ibuprofen and indomethacin, the other 5 compared the treatment of PDA with paracetamol (acetaminophen) vs ibuprofen and enrolled 559 infants. There was no significant difference between paracetamol and ibuprofen for failure of ductal closure after the first course of drug administration [typical risk ratio (RR) 0.95, 95% confidence interval (CI) 0.75–1.21; typical risk difference (RD) −0.02, 95% CI −0.09 to 0.09]; $I^2 = 0\%$ for RR and RD; moderate quality of evidence. They concluded that moderate-quality evidence according to GRADE suggests that paracetamol is as effective as ibuprofen; low-quality evidence suggests paracetamol to be more effective than placebo or no intervention; and low-quality evidence suggests paracetamol as effective as indomethacin in closing a PDA, but suggest need for neurodevelopmental follow-up data in future RCTs.[51]

Surgical Management

Surgical ligation of a symptomatic PDA in preterm neonates is successful in closing the ductal shunt in 98–100% of cases.[68] While surgical ligation of a hemodynamically significant PDA can improve hemodynamics, lung compliance, and reduce the duration of mechanical ventilation, complications associated with the procedure are well known, including but not limited to pneumothorax, hypothermia, intraoperative bleeding, phrenic nerve palsy, wound infection, vocal cord palsy, and thoracic scoliosis.[69–71] With increasing conservative management of hs-PDA and higher rates of morbidity and mortality with surgical treatment, the overall rates of ligation for PDA have decreased.[72,73] Ngo et al. examined the trends in a retrospective cohort study of very low birth weight infants (<1500 g) between 2008 and 2014 across 134 California hospitals. They described a trend toward lower annual rate of infants who received pharmacologic intervention (30.5 vs 15.7%) or both pharmacologic intervention and surgical ligation (6.9 vs 2.9%) as well as higher rate of infants who were not treated (60.5 vs 78.3%) or received primary ligation (2.2 vs 3.0%).[74]

In a retrospective cohort study, the cumulative mortality rates at 7 days, 30 days, and at hospital discharge were 2, 8, and 20%, respectively.[75] These concerns have led to exploration of transcatheter closure (TC) of PDA in preterm infants, based on successful and positive experiences from adults and children.[4]

Initial assessments of TC of PDA in infancy (<1 year of age) were presented by Backes et al. in their meta-analysis of 38 observational studies and noted technical success rate of 92.2% [95% confidence interval (CI) 88.8–95.0] with overall adverse event and clinically significant adverse event incidence of 23.3% (95% CI 16.5–30.8) and 10.1% (95% CI 7.8–12.5), respectively.[76] These initial reports were followed by a RCT followed by subsequent FDA approval of the Amplatzer Piccolo Occluder to treat PDA in patients ≥700 g (Fig. 3). The trial reported an implant success rate of 95.5% (191/200) overall and 99% in patients ≤2 kg (99/100). Four patients experienced a primary safety endpoint event (two transfusions, one hemolysis, and one aortic obstruction), no branch pulmonary artery obstructions were noted and five patients, all ≤2 kg, were noted to have worsening of tricuspid regurgitation (TR) after the procedure.[77] Technical feasibility in extremely low birth weight infants, potential respiratory and length of hospitalization benefits make TC of PDA an attractive option.[78–80] Additionally, there seems to be a benefit of TC vs surgical ligation of PDA in relation to the occurrence of "postligation syndrome" seen in preterm infants.[81] It is defined as cardiac dysfunction observed due to a sudden increase in afterload and decrease in left ventricular preload with resultant decreased cardiac output and hypotension.[82,83] Careful patient selection, timing, and choice of surgical intervention as well as postprocedural management practices are areas requiring further investigation.

CONCLUSION

In conclusion, while great strides have been made in understanding the natural history of PDA closure as well as the identification of many promising diagnostic and therapeutic choices there remains the need for consensus guidelines for the management of PDA. Future clinical trials need to focus not only on universal, practical diagnosis of hs-PDA but also identify optimal timing and therapeutic choices.

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Videos

Both the videos are available online on the website of www.newbornjournal.org

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