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REVIEW ARTICLE

Patent Ductus Arteriosus: An Overview

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Patent ductus arteriosus (PDA) is one of the most common congenital heart defects, accounting for 5%-10% of all congenital heart disease in term infants. The occurrence of PDA is inversely related to gestational age and weight, with an even greater incidence in preterm infants. The maintenance of ductal patency is essential for the normal development of the fetus. In the neonate, however, persistent patency of the ductus arteriosus (DA) is associated with significant morbidity and mortality. Normally, at birth, the DA constricts, resulting in intraluminal ischemic hypoxia, which eventually leads to closure and remodeling of the ductus. PDA in term infants is usually associated with a functional defect, whereas in preterm infants it is associated with immaturity. Normal physiologic mechanisms contributing to closure - oxygen tension and decreased prostaglandins—are altered in prematurity. Clinical signs of ductal patency include murmur, tachycardia, bounding peripheral pulses, and congestive heart failure and associated symptoms. Symptoms are not always present; therefore, diagnostic imaging is critical if a PDA is suspected on clinical grounds. Three management strategies are currently available for PDA: fluid restriction and diuretics (as clinically appropriate), medical intervention, and surgical ligation. Pharmacologic closure can be achieved via administration of intravenous indomethacin or ibuprofen lysine. While both agents have shown similar efficacy, ibuprofen lysine has demonstrated an improved safety profile, particularly in terms of renal effects, compared to indomethacin.

KEYWORDS cyclooxygenase inhibitors, ibuprofen lysine, indomethacin, non-steroidal anti-inflammatory drugs, patent ductus arteriosus, prostaglandins

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INTRODUCTION

Patent ductus arteriosus (PDA) is one of the most common congenital heart defects. A PDA, defined as failure of the ductus arteriosus (DA) to close within 72 hours after birth,[1] may result in significant infant morbidity and mortality rates that approach 30%.[2] Potential complications of a persistently patent DA after birth include heart failure, renal dysfunction, necrotizing enterocolitis (NEC), intraventricular hemorrhage, and altered postnatal

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ABBREVIATIONS ATP, adenosine triphosphate; BNP, B-type natriuretic peptide; BPD, bronchopulmonary dysplasia; CLD, chronic lung disease; CHF, congestive heart failure; COX, cyclooxygenase; DA, ductus arteriosus; ECG, electrocardiogram; ECHO, echocardiogram; hsPDA, hemodynamically significant patent ductus arteriosus; IV, intravenous; NEC, necrotizing enterocolitis; NICHD, National Institute of Child Health and Human Development; PDA, patent ductus arteriosus; PGE_2, prostaglandins; PGI_2, prostacyclins; RDS, respiratory distress syndrome; ROP, retinopathy of prematurity; TIPP, Trial of Indomethacin Prophylaxis in Preterms

Table 1. PDA incidence by birth weight for infants born in the NICHD Neonatal Research Network by epoch (%)

Birth weight	Epoch		
	1987-1988	1993-1994	1999-2000
501-750 g	32	55	50
751-1,000 g	41	46	37
1,001-1,500 g	17	17	17

Adapted from references 9 and 10

nutrition and growth.[3,4] In addition, PDA is a risk factor for the development of chronic lung disease (CLD).[5]

This overview provides a review of the epidemiology, pathophysiology, and clinical identification of PDA. Furthermore, management options for PDA are examined, including medical therapy with the cyclooxygenase (COX) inhibitors indomethacin (Indocin IV; Ovation Pharmaceuticals Inc., Deerfield, IL) and intravenous (IV) ibuprofen lysine (Neoprofen; Ovation Pharmaceuticals Inc., Deerfield, IL).

EPIDEMIOLOGY

The reported incidence of PDA in term neonates is only 1 in 2,000 births, accounting for 5%-10% of all congenital heart disease.[6] The incidence of PDA in preterm neonates is far greater, with reports ranging from 20%-60% (depending on population and diagnostic criteria).[3] The increased incidence of PDA in the preterm infant is attributable to the lack of normal closure mechanisms due to immaturity. Gestational age and weight are intimately linked to PDA in preterm neonates. Specifically, PDA is present in 80% of infants weighing less than 1,200 g at birth, compared to 40% of infants weighing less than 2,000 g at birth.[1,7] Furthermore, symptomatic PDA is present in 48% of infants with a birth weight of less than 1,000 g.[8] This inverse relationship between birth weight and the incidence of PDA is summarized in Table 1, which reports findings from the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network.[9,10]

Approximately 80% of preterm infants presenting with respiratory distress syndrome (RDS) also have a PDA,[2] which may be due to the increased circulating prostaglandins (PGE_2) associated with RDS.[11] Several birth factors have been shown to increase the incidence of PDA, including high altitude at birth,[12] genetic factors,[13] and in utero exposure to rubella.[14] For reasons that have not been elucidated, PDA is more common among female infants than males (2:1).[2]

Hemodynamically significant PDAs have been associated with significant morbidity and mortality, which can be as high as 30%.[2] This is particularly of concern in preterm neonates, as they are already at risk for other serious complications. An understanding of the mechanisms involved, early identification of PDA, and knowledge of therapeutic options are paramount for successful outcomes.

PATHOPHYSIOLOGY

The DA is derived from the distal dorsal sixth aortic arch and is completely formed by the eighth week of gestation.[6] Its role is to shunt the blood from the nonfunctional fetal lung through its connection between the main pulmonary artery and the proximal descending aorta. This right-to-left shunt allows the blood with a relatively low oxygen concentration to be carried from the right ventricle through the descending aorta and eventually to the placenta, where gas exchange will occur. Before birth, approximately 90% of right ventricular output flows through the DA. Figure 1 illustrates the role of the DA in redirecting fetal circulation in comparison to neonatal circulation.[15] Premature closure in the fetus is associated with significant morbidities, including right-sided heart failure, which may result in fetal hydrops.[6] Normally, the DA closes within 24-72 hours after a full-term birth; if after 72 hours the ductus fails to close, a diagnosis of persistent PDA may be made.[1,16]

The patency of the DA is primarily controlled by low fetal oxygen tension and the circulation of prostanoids produced from the metabolism of arachidonic acid by COX, with PGE_2 producing the most profound ductal relaxation among the prostanoids.[16,17] Smooth muscle relaxation

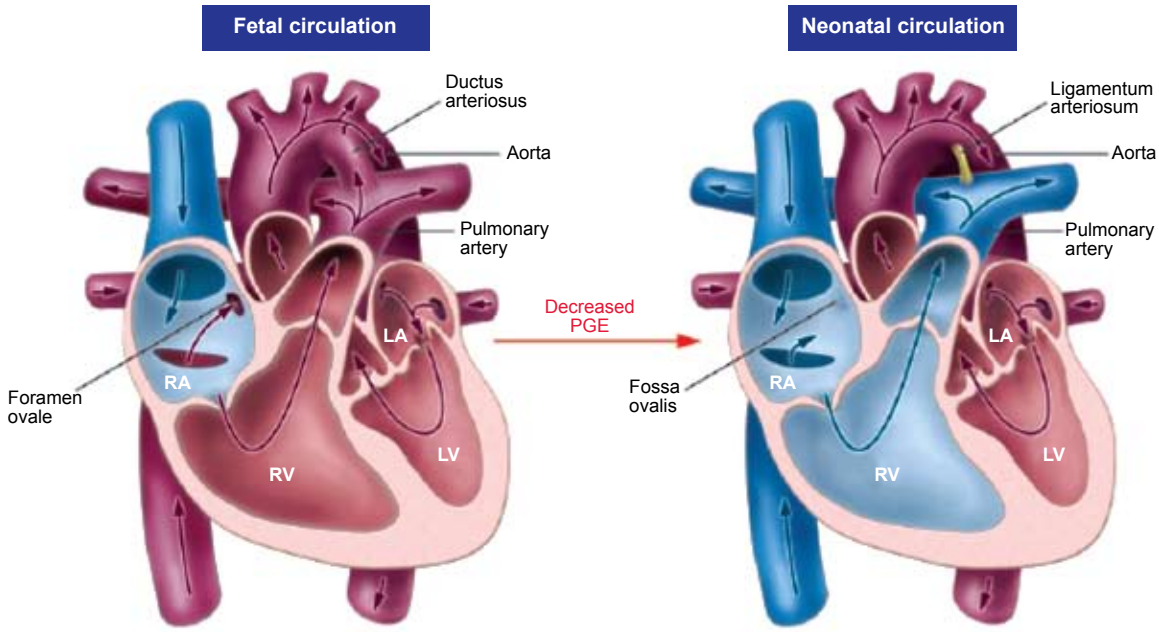

Figure 1. Left–The ductus arteriosus is an essential component of fetal circulation. It functions by shunting blood away from the nonfunctional fetal lung and into the systemic circulation through the aorta. Right–After birth, decreases in PGE_2 and oxygen tension contribute to the closure of the ductus Arteriosus, allowing gas exchange to occur in the newly functioning lungs rather than the now absent placenta. Blue = oxygen-poor blood; Red = oxygen-rich blood; LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle. The paradoxical patent ductus arteriosus. J Clin Invest 166:2863-2866 by Ivey KN, and Srivastava D. Copyright 2006 by J Clin Invest. Reproduced with permission of J Clin Invest via Copyright Clearance Center.

of the DA results from the activation of the G-coupled prostaglandin receptor EP_4 by PGE_2. Following the activation of prostaglandin receptor EP_4, a cascade of events ensues, which includes the accumulation of cyclic adenosine monophosphate, increased protein kinase A, and finally, decreased myosin light chain kinase, leading to vasodilation and ultimately DA patency.[15] The preterm ductus is especially sensitive to the vasodilatory effects of prostaglandins, contributing to the failure of ductal closure.[18] In term infants, as birth approaches, decreased sensitivity of the DA to prostaglandins and decreased circulating levels of PGE_2 contribute to DA closure.[19]

Within 24-72 hours after a full-term birth, the DA closes as a result of increased oxygen tension and decreased circulating PGE_2 and prostacyclins (PGI_2). As oxygen tension increases, smooth muscle voltage-dependent potassium channels are inhibited. Through this inhibition, an influx of calcium contributes to ductal constriction. This oxygen-induced constriction fails in preterm infants potentially due to immaturity of oxygen-sensing receptors.[20] Levels of circulating PGE_2 and PGI_2 are decreased as a result of increased metabolism in the newly functioning lung, as well as the removal of the placental source. The decreased circulating levels of these potent vasodilators allow the DA to constrict. These factors collectively contribute to smooth muscle constriction, leading to ischemic hypoxia of the inner muscle wall of the DA.

As the ductus constricts, the luminal area is diminished, resulting in a thickened vessel wall and obstructed flow through the vasa vasorum, the essential capillary network nourishing the outer cells of the vessel. This causes an increased distance of diffusion for oxygen and nutrients, including glucose, glycogen, and adenosine triphosphate (ATP), which results in nutritional deficit and oxygen starvation, leading to cell death.[21] Ductal constriction in preterm infants is not sufficiently profound. Consequently, preterm infants are resistant to smooth muscle hypoxia, which is paramount in triggering the cell death and remodeling required for permanent closure of the DA.[22] Inhibition of prostaglandin and nitric oxide re-

sulting from tissue hypoxia is not as extensive in the preterm neonate in comparison to the term infant, further contributing to resistance to DA closure in the preterm infant.[23]

The main provider of nutrients to the DA is the lumen; however, the vasa vasorum is also a substantial provider to the outer wall of the ductus. The vasa vasorum grows toward the lumen and extends 400-500 μm from the outer wall of the ductus. The distance between the lumen and the vasa vasorum (40-500 μm) is referred to as the avascular zone and represents the maximum distance allowable for effective nutrient diffusion. In full-term infants, this avascular zone is expanded beyond the effective diffusion distance, therefore contributing to cell death. In preterm infants, the avascular zone does not sufficiently expand, resulting in cell survival and maintenance of ductal patency.[24] If the levels of circulating PGE_2 and other prostaglandins are decreased through COX inhibition, closure is facilitated. The above-mentioned differences between ductal vessel wall thickness of the fetus, term neonate, and preterm neonate are illustrated in Figure 2.[16] In response to the nutritional deficit and ischemic hypoxia, vascular endothelial growth factor and transforming growth factor beta (both of which contribute to endothelial proliferation), in combination with other inflammatory mediators, contribute to the remodeling of the DA into the non-contractile ligament commonly referred to as the ligamentum arteriosum.[16,24]

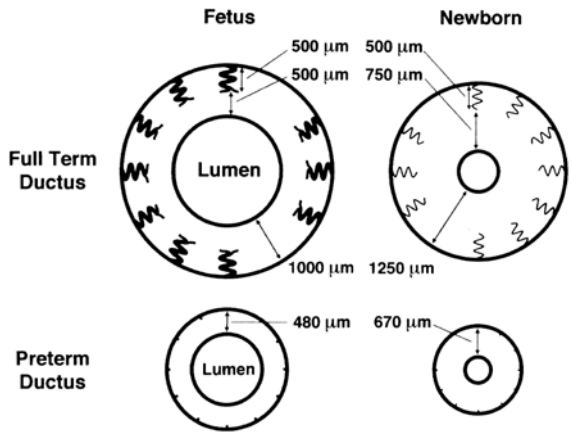

Figure 2. Comparison of fetal and both the premature and full-term newborn ductus arteriosus. The avascular zone in the preterm ductus (bottom row) does not sufficiently expand beyond the effective diffusion distance after birth (bottom right). Hermes-deSantis et al.16 Reprinted by permission from Macmillan Publishers Ltd: J Perinatol 26: s14-s18, copyright 2006.

CLINICAL PRESENTATION

Many of the consequences of a PDA result from the left-to-right shunt (aorta to the pulmonary artery). Hyperperfusion of the pulmonary vasculature causes pulmonary edema, which may contribute to respiratory failure. Symptomology of a persistently patent DA includes bounding pulses, wide pulse pressure, cardiac hypertrophy (resulting from compensation for systemic hypoperfusion), murmur (not often seen in preterm infants), and unexplained metabolic acidosis. Low diastolic pressure contributes to hypotension and systemic hypoperfusion, altering circulation to pressure-dependent organs such as the intestines, muscles, kidneys, brain, and skin. Depending on the organ affected, hypoperfusion may lead to renal dysfunction, NEC, feeding intolerance, and intraventricular hemorrhage. Additionally, this hypoperfusion may contribute to volume overload and development of congestive heart failure (CHF). Neonates may also experience multiple episodes of apnea and exhibit ventilator dependence.[25,26] Table 2 provides an overview of the clinical presentation of a symptomatic PDA.

Diagnostic and laboratory testing further enhances the clinical picture. Either left or right ventricular hypertrophy, or both, may be revealed with an electrocardiogram (ECG); however, this is dependent on the degree of left-to-right shunting, and ECG does not provide any information on ductal-dependent lesions. Additionally, cardiomegaly and increased pulmonary markings are often appreciated with chest radiography. An image of the DA can be provided through an echocardiogram (ECHO), the gold standard for diagnosis. ECHO will show the size of the opening, demonstrate the shunt, and allow estimation of mean pulmonary arterial pressure. The information provided by the ECHO is crucial for accurate diagnosis.[26] An ECHO may also help rule out ductal-dependent cardiac lesions, where closure of the ductus would result in rapid clinical deterioration and subsequent death. This is of concern in neonates where patency of the DA is critical for pulmonary blood flow, such as in

Table 2. Clinical presentation of PDA[25,26]

- Crescendo systolic murmur
- Bounding peripheral pulses with wide pulse pressure
- Hyperactive cardiac impulse at apex
- Congestive heart failure and associated signs and symptoms
- Diastolic hypotension
- Tachycardia
- Cardiomegaly
- Hepatomegaly
- Left or right ventricular hypertrophy (or both)
- Episodes of apnea
- Ventilator dependence
- Respiratory distress
- Unexplained metabolic acidosis
- Poor weight gain

severe aortic coarctation or hypoplastic left heart syndrome. B-type natriuretic peptide (BNP) levels may provide evidence of hemodynamically significant PDA (hsPDA) as well as treatment efficacy. In one study, the sensitivity and specificity of BNP were found to be 92.9% and 73.3%, respectively, at a cutoff value of 70 pg/mL, for detection of hsPDA. Normalization of BNP after treatment is indicative of a successful clinical outcome.[27] Although it is a simple test that can be done at the bedside, BNP measurement does not replace ECHO as a means of diagnosis, but rather provides additional information. Persistent elevation of BNP after treatment warrants a repeat ECHO to confirm successful closure of PDA.[28]

Symptoms are dependent on the size of the ductus, which also dictates the degree of left-to-right shunting. Infants with small PDAs may exhibit minimal or no symptoms. Large PDAs increase the risk for development of pulmonary vascular disease.[29] Justification for treatment of PDA is based on categorization of the PDA as hemodynamically significant; however, definitions vary between neonatologists.[30] Certain criteria may facilitate this determination. A ductal diameter of 1.5 mm in the first 30 hours of life in infants requiring ventilation and weighing less than 1,500 g is both sensitive (83%) and specific (90%) for PDA requiring treatment.[31] Left atrial to aortic root ratio is also an excellent measure after the first day of life; a ratio of greater than 1.5 has a high sensitivity (88%) and specificity (95%) for determining whether the PDA requires intervention.[30,32] Despite the usefulness of these measurements, there is no standardization of criteria, and therefore treatment should be based on clinical features as well as diagnostic imaging, particularly ECHO findings.

TREATMENT OF PDA

Three main strategies are currently available to neonatologists to treat PDAs in preterm infants: fluid restriction and "watchful waiting"; pharmacologic management; and surgical ligation. Each option has its advantages and disadvantages, as indicated in Table 3 and described herein. A more in-depth analysis of the pharmacology, efficacy, and safety issues are reviewed elsewhere in this supplement.

Fluid Restriction and Watchful Waiting

A conservative approach to the treatment of PDA involves fluid restriction and "watchful waiting." Diuretics lack evidence justifying routine use, but they may be useful if the neonate is exhibiting signs of CHF while waiting for spontaneous closure of the DA.[33] The loop diuretic furosemide may contribute to patency of the DA through renal stimulation of renal PGE_2.[34] There have not been sufficient studies addressing this concern; however, a meta-analysis demonstrated an increase in treatment failure by 7% with use of furosemide, although this did not reach statistical significance.[35] Advantages to the "watch-and-wait" approach include limiting the infant's exposure to a pharmacologic agent that may have significant side effects and avoiding the risk of surgery. This is a viable option in some cases, considering that approximately 34% (42 of 122 neonates) of extremely low birth weight preterm infants (≤ 1,000 g; estimated gestational age 26 ± 2 weeks) with a PDA demonstrated spontaneous closure at 4.3 ± 2 days postnatal age in a recent study by Koch et al.[4]

The major drawback to this conservative treatment modality is the potential diminished efficacy of alternate treatment options, particularly pharmacologic management with COX inhibition. In the same study cited above, 68 of 80 preterm infants with a persistent PDA were treated with indomethacin 6.2 ± 4 days postnatally. The failure rate was 41%, suggesting that earlier treatment might be associated

Table 3. Advantages and disadvantages associated with treatment choices for PDA

Treatment option	Advantage	Disadvantage
Fluid restriction and "watchful waiting"	Minimizes exposure to pharmacologic agents	Delaying treatment decreases the response rate to COX inhibition;[16,21,24] lower success rate
Pharmacologic management	High success rate[36]	Side effects associated with pharmacologic agent*† ‡
Surgical ligation	High success rate, good option when medical management is contraindicated[17,38]	Postoperative management costs; associated with complications such as ROP, BPD, and neurosensory impairment;[40] associated with development of CLD,[42] other surgery related complications

** Greater renal toxicity associated with indomethacin;*
† ibuprofen THAM has been associated with increased incidence of NEC[44] and persistent pulmonary hypertension of the newborn (PPHN).[45] There has also been 1 case report of PPHN associated with the lysine formulation of ibuprofen[46]
‡ Indomethacin and ibuprofen are highly protein-bound. They have the potential to displace bilirubin, allowing unbound bilirubin to cross the blood-brain barrier. Theoretically this displacement of bilirubin may lead to kernicterus and negative neurodevelopmental outcomes[47]

with improved outcomes in extremely low birth weight neonates.

Pharmacologic Management

Although COX-2 is intrinsic to the DA, studies have shown that PGE_2 derived from COX-1 predominates in the maintenance of patency of the DA. Based on the literature to date, nonselective COX inhibitors are the treatment of choice for pharmacologic closure of PDA.[17]

Currently, there are 2 United States Food and Drug Administration (FDA)-approved nonselective COX inhibitors indicated in the closure of PDAs. Both IV indomethacin and IV ibuprofen lysine are equally effective in the closure of PDA, achieving closure rates of 75%-93%.[36] Administration of IV ibuprofen lysine may be associated with decreased incidence of adverse events, particularly renal toxicity. Further, IV ibuprofen lysine may also have a less significant impact on cerebral blood flow[37] and mesenteric blood flow,[38] and thus may be associated with fewer effects on neurologic development and incidence of NEC, respectively. There are, however, no published data at this time to support that ibuprofen is associated with fewer effects on neurologic development or NEC than indomethacin. Ibuprofen trishydroxyaminomethane, or THAM (Pedea, Orphan Europe S.a.r.l, Paris, France), is the IV formulation currently available in Europe. Additionally, there has been limited experience with oral ibuprofen. This route is not optimal in this population because a poorly perfused gastrointestinal tract does not favor the absorption of orally administered medications.

Responsiveness to PGE_2 decreases with increased age; therefore, delaying treatment may result in diminished efficacy of COX inhibition. Several variables contribute to the decreased responsiveness of PDA to COX inhibition as time post-birth increases. These include the production of vasodilating cytokines acting independently of PGE_2 and nitric oxide, and lack of sufficient energy molecules to permit adequate contraction of the DA. The lack of nutrients affects contractibility of the ductus; however, nutrient deprivation is not prominent enough to cause the cell death necessary for remodeling.[16,21,24] The optimal timing of treatment requires further evaluation. This issue is described in greater detail in other parts of this supplement.

Surgery

Surgical repair of a PDA typically involves either ligation or a combination of ligating and dividing the DA using surgical clips or nonabsorbable sutures. Video-assisted thoracoscopic surgery permits surgeons to safely and effectively ligate the DA with minimal invasiveness. Alternatively, some patients require open ligation, which is accomplished via left posterior lateral thoracotomy.[2]

Surgical ligation is typically reserved for patients who cannot be managed pharmacologically.[17] Based on the current literature, there is no significant difference between the effect of surgical closure and pharmacologic

closure on mortality during hospital stay;[39] however, surgical ligation is associated with increased risks of bronchopulmonary dysplasia (BPD), neurosensory impairment, and severe retinopathy of prematurity (ROP).[40] These increased risks are based on an analysis of patients from the Trial of Indomethacin Prophylaxis in Preterms (TIPP) trial. The majority of preterm infants whose PDAs were treated in the TIPP trial surgically also received prophylactic indomethacin (91/110; 83%). Unlike pharmacologic closure, surgical ligation has not shown any benefit on alveolar growth.[41] Chorne and associates studied the effects of PDA and treatments used to manage PDA on neonatal and neurodevelopmental morbidity in 446 infants (less than 28 weeks gestation). Immature gestation accounted for the majority of neonatal morbidities assessed; however, the use of surgical ligation for PDA closure was significantly associated with the development of CLD. These results further contribute to dubiety regarding the risks and benefits of surgical ligation for closure of PDA.[42] In addition, postoperative management may incur additional hospital costs. Other complications of surgical ligation include pneumothorax, infection, laryngeal-nerve paralysis, erroneous closure of the phrenic nerve or major blood vessels other than the DA, and respiratory compromise.[1,43]

CONCLUSION

Preterm infants are at an increased risk of PDA compared to term neonates; incidence is inversely correlated with gestational age and weight. While the DA is an essential component of the fetal circulatory system, failure of the DA to close shortly after birth is associated with significant neonatal morbidity and mortality. Incidence is much higher in preterm infants (20%-60%) in comparison with term infants. Clinical signs of hemodynamic compromise may or may not be present, so ECHO findings are of great value. Early diagnosis is essential, as delaying treatment may decrease the chance of success. The increased sensitivity of the DA to PGE_2, in addition to high levels of circulating PGE_2, contributes to ductal patency in preterm infants.

There are three treatment options for PDA: fluid restriction while awaiting spontaneous closure, pharmacologic intervention, and surgical ligation. While conservative and surgical management strategies are effective in certain clinical scenarios, they are both associated with important risks and disadvantages not associated with medical intervention. Because the pathology involves prostaglandins, current pharmacologic treatment strategies used to close a PDA involve the use of nonselective COX inhibitors, namely IV ibuprofen lysine or IV indomethacin. IV ibuprofen lysine is associated with a decreased incidence of renal toxicity and may have less impact on neurodevelopment than IV indomethacin. The development of IV ibuprofen lysine for treatment of PDA presents an exciting addition to treatment options, as this pharmacologic agent has shown better tolerability than indomethacin, particularly in terms of renal impairment.

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