CE 1.5 HOURS Continuing Education

Understanding the Pathophysiology, Implications, and Treatment Options of Patent Ductus Arteriosus in the Neonatal Population

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ABSTRACT

Background: Patent ductus arteriosus (PDA) is the persistence of a fetal shunt between the pulmonary artery and the aorta. This structure normally closes in the first 3 days after birth; however, closure is delayed in up to 80% of infants born at 25 to 28 weeks of gestation. Persistent PDA results in pulmonary overcirculation and systemic hypoperfusion.

Purpose: The purpose of this article is to review pathophysiology and treatment options for PDA.

Methods: A literature review was conducted using PubMed, CINAHL, and Google Scholar (2013-2018). Search terms included neonate, PDA, pathophysiology, pharmacotherapy, nursing, ligation, indomethacin, ibuprofen, and acetaminophen (paracetamol).

Results: Optimal treatment remains contentious. Options include conservative/medical, pharmacologic, and surgical management. Conservative/medical management includes mild fluid restriction, increased airway pressures, and supportive care. Pharmacologic treatment is accomplished using indomethacin, ibuprofen, or acetaminophen. Surgical intervention is by direct closure or by percutaneous ligation. Treatment may be prophylactic, presymptomatic, or symptomatic. Long-term morbidities associated with PDA include chronic lung disease, retinopathy of prematurity, and neurodevelopmental delay.

Implications for Research: Absence of a universal scoring system for severity of PDA limits accuracy of comparisons among research studies. Lack of a consistent definition also makes it difficult to aggregate data for meta-analyses. Adoption of a consistent scoring system for hemodynamic significance would facilitate comparisons of outcomes among research studies.

Implications for Practice: Clinicians should be aware of treatment options for PDA and their implications on neonatal outcomes. For nurses, anticipation of possible side effects is important for performance of focused assessments.

Key Words: acetaminophen (paracetamol), ibuprofen, indomethacin, ligation, neonate, patent ductus arteriosus, pathophysiology, PDA, prostaglandin

A patent ductus arteriosus (PDA) is the neonatal persistence of a conduit between the aorta and the pulmonary artery. This shunt is essential to fetal circulation and it closes by 2 to 3 days of life in full-term neonates. When the ductus persists, it can lead to problematic pulmonary overcirculation and systemic hypoperfusion.

The most significant risk factor for PDA is preterm birth, with incidence inversely related to gestational age. It is estimated that 80% of infants with gestational age between 25 and 28 weeks will experience persistence of the ductus arteriosus (DA).[1] Other risk factors include excessive fluid administration, respiratory distress, septicemia, phototherapy, and furosemide therapy.[2] Patent ductus arteriosus is associated with long-term morbidities including bronchopulmonary dysplasia, necrotizing enterocolitis (NEC), renal impairment, diastolic cardiac dysfunction, intraventricular hemorrhage, neurodevelopmental delay, and retinopathy of prematurity (ROP).[2,3] Patent ductus arteriosus is rarely a direct cause of mortality due to significant improvements in neonatal care.[2]

The role of the DA varies widely within the clinical context. During fetal life, the DA allows blood to bypass the high-resistance pulmonary circulation to provide oxygenation to the lower limbs.[2] In ductal-dependent congenital heart defects, a patent ductus is crucial for the continuation of blood flow to the lungs after birth during the period before surgical repair can be undertaken.[4]

In contrast, a persistent PDA with otherwise normal cardiac anatomy can lead to pulmonary overcirculation. This correlation was established as the transition from fetal to neonatal circulation was

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The authors declare no conflicts of interest.

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DOI: 10.1097/ANC.0000000000000590

explored in detail in the early 1900s. Even before the widespread use of echocardiography, neonates with a PDA were recognized by the presence of clinical signs including cardiomegaly on radiograph, pulmonary edema, murmur, and bounding pulses.[5] The first surgical ligation to ameliorate these symptoms was performed in 1938.[6,7] It was not until 1972 that physicians Elliot and Starling would correctly describe the role of prostaglandins in maintaining patency of the ductus, leading to the first efforts at pharmacologic treatment. In 1976, chloroquine was trialed as a prostaglandin antagonist, and by 1977, indomethacin was used in small trials for infants with evidence of a large left-to-right shunt.[5,8]

Surgical ligation and pharmacotherapy are both still used to treat PDA today. However, the ideal management option and timing of treatment remain contentious. Multiple prostaglandin antagonists are used to promote PDA closure, and less invasive surgical techniques are becoming available. In addition, both treated and untreated PDA are associated with morbidities, leading to disagreement over whether or when treatment is actually necessary. This article will review pathophysiology, clinical manifestations, diagnosis, and modalities of management of PDA in the preterm infant. The article will also explore different timing options for treatment including prophylaxis, presymptomatic treatment, and symptomatic treatment.

FETAL AND POSTNATAL CARDIOVASCULAR PHYSIOLOGY

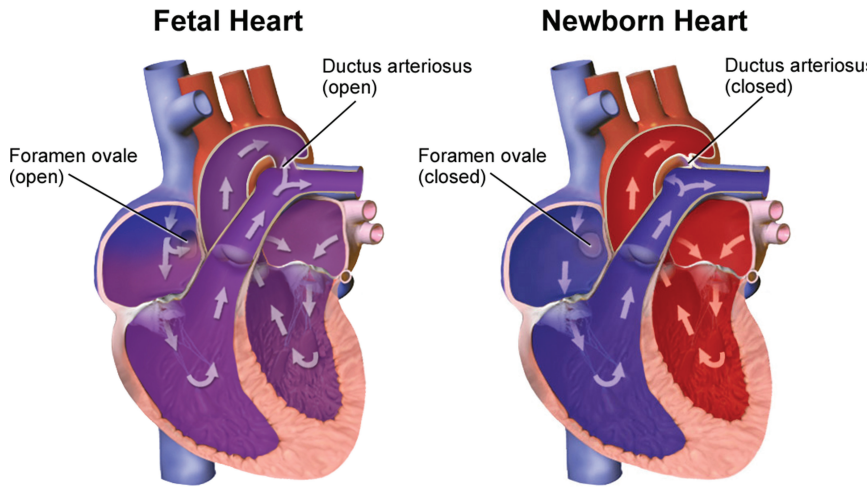
Fetal circulation is uniquely configured to meet the needs of the growing fetus. Exchange of gases and waste products occurs at the placenta, which receives approximately 40% to 50% of fetal cardiac output.[2] Normal fetal circulation is characterized by 2 parallel circuits: a high-resistance pulmonary circuit and a low-resistance systemic circuit. Oxygenated and deoxygenated blood mix at 3 different shunts that are typically present only in fetal circulation: the ductus venosus, the foramen ovale, and the DA. The ductus venosus allows blood returning from the placenta to bypass portal circulation, enter the inferior vena cava, and return directly to the right side of the heart. The foramen ovale is a shunt between the right and left atria that allows oxygenated blood from the placenta to bypass pulmonary circulation and subsequently be pumped by the fetal heart to the brain and myocardium. The remainder of blood flow in the descending aorta will mix with deoxygenated blood from the DA and will then enter systemic circulation before returning to the placenta for uptake of oxygen.[2,9] The DA is a vessel approximately the same diameter as the pulmonary artery and the descending aorta. In fetal circulation, 90% to 95% of blood flow into the pulmonary trunk is shunted across this vessel. This allows only blood flow necessary for development to reach the lungs, while the remainder of blood flow exits via the descending aorta. At birth, this circulation pattern changes and adult circulation is established.

Cardiovascular physiology changes drastically at birth because of the loss of the low-resistance placental circuit, initiation of respiration, and loss of placental prostaglandins. Loss of the placental circuit functionally closes the ductus venosus, and subsequent decreased blood flow through the inferior vena cava and inflation of lungs with the first breath initiate the cascade that leads to a drop in pulmonary vascular pressure.[2] Clamping and cutting of the umbilical cord cause accumulation of carbon dioxide (CO_2), which stimulates respiratory drive. The initiation of respiration causes a marked increase in the infant's arterial partial pressure of oxygen (Pao_2). Oxygen is a pulmonary vasodilator that also contributes to the drop in pulmonary vascular pressure. With the onset of respirations, blood flow to the lungs increases from approximately 35 mL/kg/min to approximately 160 to 200 mL/kg/min to facilitate gas exchange.[2] Pulmonary pressure will continue to decrease over the first few days of life. This drop in right atrial pressure and a corresponding increase in left atrial pressure functionally close the foramen ovale. Placental prostaglandins are lipid hormones that act as vasodilators at the DA and contribute to its patency during fetal life.[3] Loss of the placental prostaglandins, rapid metabolism of prostaglandins spurred by increased pulmonary blood flow, increased oxygen concentration, and increased blood pH facilitate ductal constriction.[2,3,9,10] Of note, functional closure of fetal shunts precedes anatomic closure. Although hemodynamic changes close the shunts so that no more blood flow occurs (functional closure), it takes longer for fibrin and other cell products to seal the holes permanently, resulting in full anatomic closure.[9] Shunts may close and reopen during the transition to normal infant circulation based on hemodynamic pressures.[2]

Normal postnatal circulation is characterized by a single circuit that works in series. Deoxygenated blood from the body is returned to the heart via the inferior vena cava and the superior vena cava. This blood enters the right atrium, then the right ventricle, and is pumped through the pulmonary artery for oxygenation within the lungs. After gas exchange takes place, oxygenated blood leaves the lungs through the pulmonary veins, returning to the left atrium. Blood is pumped out from the left ventricle into systemic circulation. See Figure 1 for a visual representation of normal fetal and postnatal cardiac circulation. Failure of fetal shunts to close can disrupt this circulation pattern.

Cardiac output after delivery is the product of heart rate and stroke volume. Stroke volume, in

FIGURE 1



Visual comparison of fetal and neonatal blood flow through the heart.

turn, is impacted by preload, afterload, and myocardial contractility.[2] Preload refers to the amount of blood in the ventricles prior to systole, while afterload is the pressure which the heart must overcome to eject the blood. Higher blood pressure results in a greater afterload.[2] Finally, myocardial contractility is the innate ability of cardiac myocytes to generate contractile force to pump blood. It is impacted by numerous factors including contractile proteins, calcium uptake, electrolyte levels, and vagal stimulus.[2]

PATHOPHYSIOLOGY

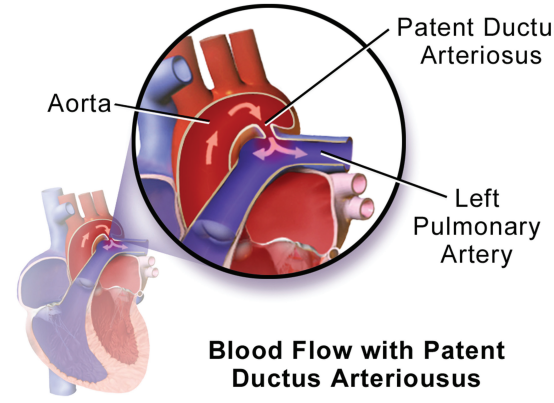
In both term and preterm neonates, spontaneous closure of the DA may fail or be delayed significantly. However, the occurrence of persistent PDA is progressively more common with decreasing gestational age. Persistence of the DA past the third day of life is considered pathologic, and this delay in normal transition is referred to as a persistent patent DA, or PDA.[1] Several factors influence continued patency and hemodynamics of the ductus.

In delayed transition, flow across the DA continues after birth but reverses in direction due to the changes in pulmonary and systemic pressures. Lung expansion causes a drop in pulmonary pressure, and loss of the (low pressure) placental circuit results in increased systemic pressures, with flow from the aorta into the pulmonary artery (a left-to-right shunt). This reversal of flow leads to pulmonary overcirculation as oxygenated blood intended to be delivered systemically through the aorta is shunted back toward the lungs. Concurrently, blood is shunted away from the systemic circulation, causing systemic hypoperfusion by a phenomenon commonly called "ductal steal."[2] The disordered circulation that results from this persistent patency can be seen in Figure 2.

Persistent PDA is encouraged by differential responses to prostaglandin and oxygen, mainly in premature infants. Prostaglandins help maintain patency of the ductus during fetal life; they may also maintain patency after birth in the case of delayed transition. Premature infants have a higher expression of prostaglandin receptors in DA walls and higher levels of circulating prostaglandin E2, which encourages patency of the ductus.[11,12] In a term infant, oxygen acts as a vasoconstrictor at the DA.[11,12] However, the DA of a preterm infant is less sensitive to increasing oxygen concentration, causing decreased constriction after birth and also encouraging patency.

The hemodynamics of a patent ductus are impacted by multiple factors. The most important factor is the size and shape of the PDA. A short, wide ductus tends to allow more blood flow. Increases in systemic vascular resistance and decreases in pulmonary vascular resistance both favor left-to-right

FIGURE 2



Shunting across a patent ductus arteriosus.

shunting. Chemical mediators including cytokines and prostaglandins also increase pulmonary blood flow.[3] Finally, viscosity of the blood is a factor; anemic infants will experience more left-to-right shunting.[3] Patency of the ductus alone does not dictate either severity of symptoms or treatment—rather, it is the hemodynamics that inform treatment decisions.

CLINICAL PRESENTATION AND ASSOCIATED COMPLICATIONS

A PDA can result in significant complications and has a recognizable pattern of clinical presentation. Although physical signs do not necessarily predict the hemodynamic significance of the ductus, they are important to recognize on assessment. The most common symptomology occurs within the cardiovascular, renal, respiratory, and gastrointestinal (GI) systems.

Cardiovascular

The most common cardiovascular signs of PDA are wide pulse pressures, a characteristic coarse systolic murmur at the left sternal border, an active precordium, and hypotension.[3] Compromised systemic perfusion during diastole causes the wide pulse pressures, while turbulent blood flow through a patent ductus causes the characteristic murmur.[3] Increased preload leads to an active precordium as pulmonary overcirculation causes increased blood return to the left side of the heart during diastole. Diversion of blood flow from the aorta to the pulmonary artery during systole causes systemic hypotension and impacts perfusion of organs.[3] Decreased perfusion pressure is especially pronounced during diastole. Of note, coronary artery perfusion is dependent on aortic diastolic pressure, which may result in a degree of myocardial ischemia.[13] This ductal steal is also responsible for symptoms in the renal and GI systems.

Renal

Renal consequences of PDA include fluid retention within the cardiopulmonary circuit, metabolic acidosis secondary to renal hypoperfusion, and oliguria (urine output <1 mL/kg/h). Associated laboratory findings may include hyponatremia and increased creatinine.[3] Doppler studies may show decreased, absent, or reversed diastolic flow to the renal arteries.[10] Renal hypoperfusion activates the compensatory renin-angiotensin-aldosterone system, which begins with the release of renin from the juxtaglomerular cells of the kidneys. Renin activates a signaling pathway that results in peripheral vasoconstriction in an attempt to retain sodium and water and expand the intravascular space.[14] In the case of large PDA with left-to-right shunting, this compensatory pathway antagonizes and further increases cardiopulmonary circulation, while renal perfusion remains supoptimal.[3,15]

Respiratory

Respiratory signs of PDA include pulmonary edema, prolonged need for assisted ventilation, pulmonary hemorrhage, and higher rates of bronchopulmonary dysplasia (BPD).[1,11] These sequelae result from pulmonary overcirculation secondary to decreased pulmonary resistance. Decreasing resistance causes increasing flow from the aorta to the pulmonary artery as transition to postnatal circulation progresses. Preterm infants have a lower threshold for developing pulmonary edema in conjunction with overcirculation due to surfactant deficiency and low serum oncotic pressures, which allow easier accumulation of interstitial fluid.[10] Prolonged ventilation and oxygen therapy impair alveolarization, as well as increase risk of prolonged hospitalization.[3]

Gastrointestinal

Gastrointestinal complications of PDA include feeding intolerance and increased risk of NEC.[3] These outcomes occur secondary to systemic hypoperfusion and shunting of blood flow away from the GI tract. It is hypothesized that the gut becomes ischemic during periods of hypoperfusion. Subsequently, the gut experiences reperfusion-reoxygenation injury and increased risk of NEC.[3] A diagnosis must be made to inform treatment decisions when clinical signs of a PDA are noted.

DIAGNOSIS

A variety of nondiagnostic clinical markers may suggest the presence of a PDA. These characteristic indicators include assessment features, laboratory markers, and chest radiograph findings. However, cardiac echocardiogram remains the criterion standard for diagnosis of PDA by illuminating the direction of shunting and pressure differences in various chambers.

Nondiagnostic Clinical Markers

A PDA may be strongly suspected in the presence of physical assessment findings including worsening respiratory status, widened pulse pressures, hypotension, feeding intolerance, and a characteristic holosystolic murmur.[1] These classic clinical signs are caused by altered blood flow as detailed previously.

Common laboratory values include metabolic acidosis, worsening blood gases, and elevated c-reactive protein.[11] In addition, elevations in several biochemical markers have been shown to correlate with presence of PDA, including B-type natriuretic peptide, cardiac troponin T, and the segment of the amino terminal B-type natriuretic peptide.[11] The clinical

utility of these markers is still under investigation, and they are not yet commonly used to determine diagnosis or treatment.

The chest radiograph of a patient with PDA may show cardiomegaly, left atrial dilation, and pulmonary congestion.[3] However, these findings are not definitively diagnostic. Similar physical and radiographic findings may be seen in infants with aortic-pulmonary collateral vessels, an aortic-pulmonary window, a right pulmonary artery that originates from the aorta, or a fistula between the coronary artery and the right ventricle.[4] Definitive diagnosis relies on Doppler echocardiogram.

Doppler Echocardiography

Doppler echocardiography is the criterion standard for assessing both patency and hemodynamics across the DA.[10] Doppler studies function through the reflection of sound waves from the myocardium and blood as it flows through the heart, creating a visual representation of both speed and direction of blood flow. This allows for assessment of relevant parameters, which include ductal diameter, patterns of ductal flow, left atrial size compared with the aorta, filling pressure of the left ventricle, and patterns of blood flow to the renal and middle cerebral arteries.[16]

Measurement of ductal diameter and blood flow velocity allows estimation of total blood flow across the DA.[16] Kluckow and Evans, as cited in Wylie[16] found that a ductal diameter greater than 1.5 mm, measured in the first 31 hours of life, was the best early predictor of hemodynamic significance in infants younger than 29 weeks. This indicator has a sensitivity of 83% (confidence interval, 71%-94%) and a specificity of 90% (confidence interval, 81%-98%).[16] Of the recent studies reviewed by Bardanzellu and colleagues,[11] the majority used echocardiographic criteria of 1.4-mm diameter or greater or 1.5 mm or greater as the cutoff for treatment. Blood flow velocity is most significant when considered together with the diameter of the ductus. Fast flow through a small ductus may indicate a relatively small shunt, while fast flow coupled with a large ductal diameter indicates more severe hemodynamic compromise.[16]

Other parameters assessed during echocardiography typically include patterns of ductal flow, left atrial size compared with the aorta, filling pressure of the left ventricle, and absence or reversal of end-diastolic flow to the middle cerebral or superior mesenteric artery.[17] The most severe hemodynamic compromise is characterized by unrestrictive, pulsatile flow across the ductus. This pattern is exemplified by a low flow during end diastole, which suggests that the pressures in the pulmonary artery and aorta are nearly equal at this point in the cardiac cycle. Dilation and filling pressure of the left atrium indicate the severity of pressure loading of the left-sided heart. The left atrium tends to be larger with significant ductal shunting, corresponding with increased pulmonary overcirculation and leading to left-sided heart dysfunction if uncorrected.[17] Absence or reversal of end-diastolic flow to the middle cerebral or superior mesenteric artery signals the most significant compromise to end-organ perfusion.[17]

MANAGEMENT OPTIONS

There is no consensus for optimal management of a PDA. The goal of management may be to close the ductus or to minimize clinical complications experienced by the infant until spontaneous closure occurs. Treatment options include conservative/medical management, pharmacologic management, and surgical management.

Conservative/Medical Management

Conservative management strategies include decreasing preload, optimizing gas exchange, and mitigating excessive pulmonary blood flow. Mild fluid restriction or a diuretic is often used to decrease preload in the heart.[18] Diuretics should be used with caution, as furosemide can prolong patency of a PDA.[19] Furosemide increases renal blood flow by increasing circulating prostaglandins, which also has a dilatory effect on the ductus.[20] Positive end-expiratory pressure is maintained at a level of at least 5-cm H_2O via mechanical ventilation or nasal continuous positive airway pressure to improve gas exchange. Positive end-expiratory pressure also minimizes demands on left ventricular function through provision of adequate oxygenation.[21] Hematocrit may be maintained at a minimum of 35% to 40% to help reduce shunting to the pulmonary artery.[18,21] Other measures that reduce pulmonary blood flow include permissive hypercapnia and avoidance of situations that lower pulmonary vascular resistance such as metabolic alkalosis and excessive supplemental oxygen.[10]

Pharmacologic Management

Pharmacotherapy has been a mainstay of DA treatment since the role of prostaglandins in ductal patency was defined. Pharmacologic inhibition of prostaglandin synthesis constricts the DA. Several nonselective cyclooxygenase inhibitors are used to decrease the production of prostaglandins, including indomethacin, ibuprofen, and acetaminophen. For an overview of the mechanism of action, indications, side effects, and contraindications of these medications, see Table 1.

Drug interactions and supply issues should also be noted when considering pharmacologic treatment of PDA. Gentamicin, a frequently used antibiotic in the very low birth-weight population, carries a risk of nephrotoxicity. Concurrent use of gentamicin and

TABLE 1. Pharmacologic Treatment Options for Patent Ductus Arteriosus

	Mechanism of Action	Indication	Side Effects	Contraindications
Indomethacin	Nonselective inhibition of cyclooxygenase (COX) enzyme Prevents conversion of arachidonic acid into prostaglandins[3]	Hemodynamically significant PDA First 24 h of life for PDA prophylaxis[31]	Renal impairment Oliguria Hyperkalemia White matter damage Necrotizing enterocolitis (NEC) Intestinal perforation Platelet dysfunction[3,8]	Thrombocytopenia Intracerebral hemorrhage Active renal or GI bleeding Pulmonary hemorrhage Sepsis NEC Intestinal perforation Liver damage with hyperbilirubinemia[3]
Ibuprofen	Nonselective COX inhibition	Hemodynamically significant PDA[19]	Oliguria Thrombocytopenia Pulmonary hypertension Hyperbilirubinemia[3,19]	Infection Active bleeding Thrombocytopenia NEC Significant renal impairment[19]
Acetaminophen	Reduces synthesis of prostaglandins by targeting peroxidase enzyme[3,18]	Alternative PDA treatment, although not currently FDA approved for this purpose[3]	Liver toxicity reported in 1 study[3] May have unpredictable absorption if given enterally[29]	None

Abbreviations: COX, cyclooxygenase; FDA, Food and Drug Administration; GI, gastrointestinal; PDA, Patent ductus arteriosus.

nonsteroidal anti-inflammatory drugs, including indomethacin and ibuprofen, increases the risk of nephrotoxicity by approximately 6%.[22] Risk of intestinal perforation with indomethacin is increased if it is given with glucocorticosteroids.[10]

Supply issues may also be a concern for pharmacologic treatment. Multiple studies in the literature noted changes in treatment protocol during the study period due to either drug shortages or recalls, such as one that affected ibuprofen from 2010 to 2012.[23,24] In cases in which pharmacologic treatment fails or is contraindicated, surgical intervention may be required to close a persistent PDA.[25]

Surgical Management

Surgical management was the first method successfully used to close a PDA.[6] This option uses physical means to occlude the ductus and stop blood flow. Surgical management of PDA can be accomplished through either direct ligation or percutaneous closure.

Ligation

Surgical ligation is performed by left lateral thoracotomy and application of a vascular clip to the ductus.[26] Ligation is typically reserved for infants with a PDA refractory to pharmacologic treatment or those with contraindications to pharmacologic management.[25] Successful closure of the ductus results in the cessation of pulmonary overcirculation and systemic hypoperfusion, with a resultant improvement in pulmonary status.[26] Ligation has a high rate of complications, including vocal cord dysfunction, BPD, ROP, chylothorax, pneumothorax, diaphragmatic paralysis, bleeding, and cardiorespiratory failure necessitating supportive intensive care.[1,11] Notably, BPD and ROP are also complications of an untreated PDA—both have been independently linked to PDA ligation.[11,26] Surgical ligation also carries a risk of impaired neurological outcome.[11] There are no specific contraindications for surgical ligation.

Percutaneous Closure

Percutaneous PDA closure is accomplished by threading a vascular occlusion device to the ductus from a peripheral site, most often the femoral vein. This strategy is gaining increasing recognition for use in the very low birth-weight population as new devices become available.[26] Although technically challenging, percutaneous closure has been accomplished successfully in an increasing number of infants; Rodríguez Ogando and colleagues[26] reported successful closure in 23 infants weighing between 1 and 2 kg. In addition, Rodríguez Ogando et al[26] reported a significantly earlier improvement in pulmonary status with percutaneous closure than with ligation, which tended to worsen pulmonary scores immediately after surgery. The pulmonary scoring system used was developed and validated in the STOP-ROP trial and includes measures of respiratory medication use, supplemental oxygen, and ventilatory support.[26] Pulmonary function scores on day 7 following surgery were significantly improved in the group that underwent percutaneous closure compared with

those that underwent ligation ($P = .007$).[26] Percutaneous closure also ameliorates systemic hypoperfusion and pulmonary overcirculation.[26] Possible complications of percutaneous closure include embolization of the device, which can migrate into the pulmonary artery after release and blood loss requiring transfusion.[26] Rodríguez Ogando et al[26] found no significant differences in mortality, BPD, or moderate to severe neurodevelopmental impairment between percutaneous closure and ligation after adjustment for other antenatal and perinatal variables (adjusted odds ratio, 0.89).[26] No specific contraindications were noted, although caution should be used with renal impairment due to the use of contrast angiography.[26] Refer to Table 2 for a summary of nursing considerations for each treatment modality.

TIMING OF TREATMENT

Although treatment options for PDA have been thoroughly explored, the optimal timing of intervention remains controversial. Treatment may be initiated in the first 12 hours of life or implemented only if the infant displays signs of hemodynamic compromise. Treatment strategies include prophylaxis, presymptomatic treatment, and symptomatic treatment.

Prophylaxis

Pharmacologic prophylaxis is characterized by treatment with indomethacin in the first 12 hours of life for infants below a certain gestational age or weight. Although parameters differ between studies, the trial of indomethacin prophylaxis in preterms included infants with birth weights from 500 to 999 g.[1] This strategy has been shown in multiple studies to significantly reduce the incidence of intraventricular hemorrhage of grade 3 or greater.[1,11,27] As a secondary outcome, indomethacin prophylaxis also decreases subsequent development of a symptomatic PDA and the necessity of surgical ligation.[11,27] However, prophylaxis has not been shown to reduce chronic lung disease or NEC, or to improve neurodevelopmental outcomes at 18 months.[28] Because of lack of impact on these important long-term outcomes, indomethacin prophylaxis is not currently recommended as a routine treatment.[1]

Presymptomatic Treatment

Presymptomatic treatment is characterized by early echocardiographic screening of high-risk infants, usually by day 3 of life.[29] This strategy aims to identify a PDA before clinical signs appear to allow for early pharmacotherapy. Early pharmacotherapy increases the probability of successful pharmacologic closure compared with delaying treatment.[11] Early treatment causes an increased rate of renal side effects by exposing a larger number of infants to the nephrotoxic effects of ibuprofen and indomethacin.[29] Future research is necessary to determine the efficacy of early treatment with acetaminophen.[11]

Symptomatic Treatment

Symptomatic treatment includes the evaluation of infants with clinical signs of PDA with echocardiography and treatment of confirmed PDA with

TABLE 2. Nursing Considerations for PDA Treatment Options

Treatment	Nursing Considerations
Medical management	May be fluid restricted or given diuretics Monitor for improvements in respiratory status Monitor blood pressure and perfusion
Indomethacin	Monitor renal function and urine output Monitor platelet count Be alert for signs of bleeding Monitor for signs of feeding intolerance
Ibuprofen	May be ordered either orally or intravenously Monitor renal function and urine output Monitor platelet count Monitor for hyperbilirubinemia
Acetaminophen	Not yet FDA approved for patent ductus arteriosus treatment Monitor liver function
Surgical ligation	Postoperatively: monitor for chylothorax, pneumothorax, diaphragmatic paralysis, and bleeding Cardiorespiratory status often worsens initially
Percutaneous closure	Technically difficult; not widely available Device may embolize and migrate to pulmonary artery Monitor for bleeding Monitor kidney function following use of contrast angiography

Abbreviation: FDA, Food and Drug Administration.

Summary of Recommendations for Practice and Research	
What we know:	• Preterm birth is the largest risk factor for PDA. • Untreated PDA is associated with BPD, NEC, renal impairment, cardiac dysfunction, IVH, ROP, and neurodevelopmental impairment. • PDA management options include medical treatment, pharmacotherapy, and surgical intervention. • Treatment may be prophylactic, early, or symptomatic.
What needs to be studied:	• Consistent use of scoring to determine hemodynamic significance and facilitate comparisons among research studies. • Consensus on optimal timing of treatment. • Additional data are needed before recommendation of acetaminophen as a treatment option. • Whether any of the current methods of treatment improves long-term outcomes.
What we can do today:	• Be aware of various management options and the evidence for each. • Choose management strategies based on infant's clinical presentation and short-term goals. • Watch for side effects based on management strategy chosen.

pharmacotherapy.[18] This approach is the most widely used and exposes the fewest infants to the risks of pharmacologic treatment by reserving the use of medication for those infants with signs of clinical compromise.[29] However, the delay in administration may decrease the effectiveness of pharmacotherapy.[11] Symptomatic treatment with nonsteroidal anti-inflammatory drugs has not been shown to improve long-term outcomes of BPD, mortality, or NEC.[1,11,24] If pharmacotherapy is not successful, these infants may receive surgical intervention.

CURRENT MANAGEMENT TRENDS

Bixler et al[30] examined patterns of treatment for PDA from 2006 to 2015 using research data from the Pediatrix Clinical Data Warehouse that included more than 60,000 infants. Bixler et al[30] found significant changes in both diagnosis and treatment over the study period. Rates of PDA diagnosis dropped from 51% to 38% ($P < .001$); indomethacin and ibuprofen use decreased from 58.8% to 36.6% (Cochran-Armitage trend test, $P < .01$) and tended to be used later rather than in the first few days of life.[6] Surgical ligations decreased from 8.4% to 2.9% ($P < .001$).[30] These data together suggest a more conservative approach to PDA management, with treatment initiated later and avoided when possible. Perhaps most significantly, this study failed to find increases in mortality or other reported morbidities, including BPD, NEC, and severe ROP. These results suggest that a more conservative approach does not result in worse neonatal outcomes.[30] Letshwiti and colleagues[18] also supported the use of a conservative approach. Letshwiti et al[18] established 3 different groups of infants and treated them for PDA by presence of clinical signs, by early targeted echocardiography in the first 48 hours of life, or by conservative management. No difference in mortality was noted among the groups.[18]

CONCLUSION

Although many studies have examined the efficacy of different treatment options for PDA, no consensus exists as to which option is best. Short-term clinical effects vary with the treatment option chosen, but meta-analyses have failed to demonstrate that any method of closing the ductus results in improved long-term outcomes.[1,3] Recent study data suggest a trend toward more conservative management overall, with no associated increases in morbidity or mortality.[30] This strengthens the conclusion that aggressive treatment of PDA may not significantly improve long-term outcomes. Patent ductus arteriosus treatment should be individualized to each infant on the basis of severity of symptoms and short-term clinical outcomes. Clinicians should be informed of the various options and cognizant of evolving research regarding treatment of PDA in the neonate.

Acknowledgments

The authors acknowledge Dr Amy Jnah, who consulted during early development of this manuscript. They appreciate your support!

References

1. Benitz WE, Committee on Fetus and Newborn American Academy of Pediatrics. Patent ductus arteriosus in preterm infants. *Pediatrics*. 2016;137(1). doi:10.1542/peds.2015-3730.
2. Hoffman J, Thompson-Bowie N, Jnah A. Cardiovascular system. In: Jnah A, Trembath A, eds. *Fetal and Neonatal Physiology for the Advanced Practice Nurse*. New York, NY: Springer Publishing; 2008.
3. Elsayed YN, Fraser D. Patent ductus arteriosus in preterm infants, part 1: understanding the pathophysiologic link between the patent ductus arteriosus and clinical complications. *Neonatal Netw*. 2017;36(5):265-272.
4. Ashwath R, Snyder C. Congenital defects of the cardiovascular system. In: Martin R, Fanaroff A, Walsh M, eds. *Fanaroff & Martin's Neonatal-Perinatal Medicine*. 10th ed. Philadelphia, PA: Elsevier Saunders; 2015:1230-1249.
5. Lucas A, Mitchell MD. Plasma-prostaglandins in pre-term neonates before and after treatment for patent ductus arteriosus. *Obstet Gynecol Surv*. 1979;34(4):293-295.
6. Breinholt JP. Cardiac Disorders. In: Eichenwald EC, Hansen AR, Martin CR, Stark AR, eds. *Cloherty and Stark's Manual of Neonatal*

Care. 8th ed. Philadelphia, PA: Wolters-Kluwer Health/Lippincott Williams & Wilkins; 2017:510-575.
7. Obladen M. History of the ductus arteriosus: 1. anatomy and spontaneous closure. *Neonatology*. 2011;99(2):83-89.
8. Collins G, Outerbridge E, Manku MS, Horrobin DF. Chloroquine as prostaglandin antagonist in treatment of patent ductus arteriosus. *Lancet*. 1976;2(7989):810.
9. Verklan MT. Adaptation to extrauterine life. In: Verklan MT, Walden M, eds. *Core Curriculum for Neonatal Intensive Care Nursing*. St Louis, MO: Elsevier Saunders; 2015:58-76.
10. Benitz WE. Patent ductus arteriosus. In: Martin RJ, Fanaroff AA, Walsh MC, eds. *Fanaroff & Martin's Neonatal-Perinatal Medicine*.10th ed. Philadelphia, PA: Elsevier Saunders; 2015:1223-1229.
11. Bardanzellu F, Neroni P, Dessì A, Fanos V. Paracetamol in patent ductus arteriosus treatment: efficacious and safe? *Biomed Res Int*. 2017;2017:1438038-25.
12. El-Mashad AE, El-Mahdy H, El Amrousy D, Elgendy M. Comparative study of the efficacy and safety of paracetamol, ibuprofen, and indomethacin in closure of patent ductus arteriosus in preterm neonates. *Eur J Pediatr*. 2017;176(2):233-240.
13. Sehgal A, McNamara PJ. Coronary artery perfusion and myocardial performance after patent ductus arteriosus ligation. *J Thorac Cardiovasc Surg*. 2012;143:1271-1278.
14. Sherman J. Renal and genitourinary disorders. In: Verklan MT, Walden M, eds. *Core Curriculum for Neonatal Intensive Care Nursing*. St Louis, MO: Elsevier Saunders; 2015:719-733.
15. Dell KM. Fluid, electrolytes, and acid-base homeostasis. In: Martin RJ, Fanaroff AA, Walsh MC, eds. *Fanaroff and Martin's Neonatal-Perinatal Medicine*. 10th ed. Philadelphia, PA: Elsevier Saunders; 2015:613-629.
16. Wyllie J. Neonatal echocardiography. *Semin Fetal Neonatal Med*. 2015;20(3):173-180.
17. Schena F, Francescato Gaia, Cappelleri A, et al. Association between hemodynamically significant patent ductus arteriosus and bronchopulmonary dysplasia. *J Pediatr*. 2015;166(6):1488-1492.
18. Letshwiti JB, Semberova J, Pichova K, Dempsey EM, Franklin OM, Miletin J. A conservative treatment of patent ductus arteriosus in very low birth weight infants. *Early Hum Dev*. 2017;104:45-49.
19. Taketomo CK, Hodding JH, Kraus DM. *Pediatric & Neonatal Dosage Handbook*. 24th ed. Wolters Kluwer; 2017.
20. van den Anker JN, Allegaert K. Renal function and excretion of drugs in the newborn. In: Yaffe SJ, Aranda JV, eds. *Neonatal and Pediatric Pharmacology: Therapeutic Principles in Practice*. 4th ed. Philadelphia, PA: Wolters-Kluwer/Lippincott Williams & Wilkins; 2011:194-209.
21. Smith VC. The high-risk newborn: anticipation, evaluation, management, and outcome. In: *Cloherty and Stark's Manual of Neonatal Care*. 8th ed. Philadelphia, PA: Wolters-Kluwer Health/Lippincott Williams & Wilkins; 2017:76-93.
22. Constance JE, Reith D, Ward RM, et al. Risk of nonsteroidal anti-inflammatory drug-associated renal dysfunction among neonates diagnosed with patent ductus arteriosus and treated with gentamicin. *J Perinatol*. 2017;37(10):1093-1102.
23. Clyman R, Wickremasinghe A, Jhaveri N, et al. Enteral feeding during indomethacin and ibuprofen treatment of a patent ductus arteriosus. *J Pediatr*. 2013;163(2):406-411.e4.
24. Slaughter JL, Reagan PB, Newman TB, Klebanoff MA. Comparative effectiveness of nonsteroidal anti-inflammatory drug treatment vs no treatment for patent ductus arteriosus in preterm infants. *JAMA Pediatr*. 2017;171(3):e164354.
25. Weisz DE, More K, McNamara PJ, Shah PS. PDA ligation and health outcomes: a meta-analysis. *Pediatrics*. 2014;133(4):e1024-e1046.
26. Rodríguez Ogando A, Planelles Asensio I, de la Blanca ARS, et al. Surgical ligation versus percutaneous closure of patent ductus arteriosus in very low-weight preterm infants: which are the real benefits of the percutaneous approach? *Pediatr Cardiol*. 2018;39(2):398-410.
27. Brandstra ES, Montalvo BM, Goldberg RN, et al. Prophylactic indomethacin for prevention of intraventricular hemorrhage in premature infants. *Pediatrics*. 1988;82(4):533-542.
28. EL-Khuffash A, James AT, Corcoran JD, et al. A patent ductus arteriosus severity score predicts chronic lung disease or death before discharge. *J Pediatr*. 2015;167(6):1354-1361. e2.
29. Evans N. Preterm patent ductus arteriosus: a continuing conundrum for the neonatologist? *Semin Fetal Neonatal Med*. 2015;20(4):272-277.
30. Bixler GM, Powers GC, Clark RH, Walker MW, Tolia VN. Changes in the diagnosis and management of patent ductus arteriosus from 2006 to 2015 in United States neonatal intensive care units. *J Pediatr*. 2017;189:105-112.
31. Chemtob S, Dorval V. Nonsteroidal anti-inflammatory drugs. In: Yaffe S, Aranda J, eds. *Neonatal and Pediatric Pharmacology: Therapeutic Principles in Practice*. 4th ed. Philadelphia, PA: Wolters-Kluwer/Lippincott Williams & Wilkins; 2011:711-721.

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DOI: 10.1097/ANC.0000000000000632