
Abstract

The ductus arteriosus (DA) connects the main pulmonary artery and the aorta in the fetus. Although the term infant DA almost always closes in the first three days of postnatal life, that of the preterm infant can be present for weeks to months. The frequency of diagnosis and rate of complications due to patent ductus arteriosus (PDA) are inversely proportional to gestational age. This vascular connection between pulmonary and systemic circulations can lead to the “stealing” of blood from systemic organs supplied by the aorta. Furthermore, with left-to-right shunting across the DA, the preterm lung is challenged with increased pulmonary blood flow. Although these complications can be serious, many infants with a PDA are asymptomatic. Despite monumental advances in neonatal care over the last 20 years, the best approach to management of PDA in preterm infants remains unclear. Clinical practice still varies widely with regard to treatment.

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Patent Ductus Arteriosus in the Premature Infant: A Clinical Dilemma

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For preterm infants, especially those less than 1000 grams, there are many complex issues involving their medical care. Diseases and their treatments often involve multiple organ systems with intertwining effects. One interesting dilemma is what to do about the presence of a patent ductus arteriosus (PDA). Should anything be done at all? Much has been written about the PDA and its associated comorbidities, but clinical practice still varies within and between institutions. With increasing survival of infants with extremely low-birth-weight (ELBW), PDA continues to be a common problem in the neonatal intensive care unit, affecting up to 60% of those infants less than 28 weeks gestation¹ and representing 10% of all congenital heart lesions.² Therefore, it is important to distinguish a hemodynamically significant PDA from one that is simply present because treatment decisions and long-term impact are based on this difference.

Fetal Cardiac Physiology

The ductus arteriosus (DA) is a vessel that connects pulmonary and systemic circulations in the fetus. It is most commonly located 5 to 10 millimeters distal to the origin of the left subclavian artery and connects the aorta to the main pulmonary artery (MPA).² In fetal life, the DA provides a critical function of diverting oxygenated blood from the placenta away from the pulmonary circulation into the systemic circulation. As oxygenation and ventilation for the fetus are provided by the placenta, the fetal lung only needs enough blood flow to support its growth. Therefore, more than 90% of the blood from the right ventricle bypasses the lungs and directly enters the systemic circulation via the DA.³ There are two exits for blood in the right atrium. A portion passes through the right atrium, across the patent foramen ovale to enter the left atrium. The remainder of the blood in the right atrium passes through the tricuspid valve, into the right ventricle, and through the pulmonary valve into the MPA. Most of the blood in the MPA moves through the DA into the aorta. The fetal pulmonary vascular resistance (PVR) is very high; hence, blood preferentially moves across the DA into the aorta where the systemic vascular resistance (SVR) is lower.

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Postnatal Cardiac Physiology

At birth, the blood flow patterns through the heart and lungs change dramatically. With aeration of the lungs and increased oxygen tension (PaO_2) in the bloodstream, PVR falls rapidly. This results in a seven- to tenfold increase in pulmonary blood flow and a fivefold decrease in pulmonary artery pressure.⁴ Blood in the right ventricle then preferentially flows through the pulmonary circulation, as now PVR is less than SVR. The patent foramen ovale is functionally closed as left atrial pressure rises with increased pulmonary venous return.

In term infants, the DA is exquisitely sensitive to oxygen and constricts when the PaO_2 rises at birth. The muscles of the DA at term are spiral in configuration and well developed, such that any constriction in the vessel yields a significant decrease in blood flow through it. In addition, there are pillow-like projections from the intimal lining of the DA that protrude into the lumen, further restricting blood flow. These muscle layers are fed by a plexus of vessels, the vasa vasorum. As the DA constricts, the vessel becomes shorter, and the muscle wall doubles in thickness. This restricts blood flow between tissue layers, causing hypoxia within the muscle.⁵ It is believed that this tissue hypoxia plays a critical role in closing the DA permanently. In most term infants, the DA functionally closes within the first 12 to 15 hours of life and in virtually all by day of life 3.⁶ Once the term DA is closed, it does not reopen. Anatomic closure of the DA occurs over the following weeks, forming a fibrous band called the ligamentum arteriosus.

In preterm infants, however, the physiology of the DA is different. The maturation of the fetal DA has not taken place in those infants born prematurely. In the third trimester of pregnancy, the DA becomes more muscular and less sensitive to circulating prostaglandins, which are produced by the placenta, the fetal lung, and locally within the DA itself. The absence of these adaptations in the preterm DA promotes ductal patency postnatally. Endogenous nitric oxide (NO) plays an important role in vascular relaxation in the lung to decrease PVR at birth. The preterm DA is also sensitive to the relaxing effect of NO. In fact, the preterm DA becomes less sensitive to circulating prostaglandins over the first few weeks of life. It is possible that NO then plays a more important role in promoting ductal patency.

When the preterm ductus does close, either spontaneously or after treatment, it is prone to reopening. Oxygen and nutrients are supplied by blood in the lumen because the vasa vasorum does not develop until the third trimester. Because the wall of the preterm DA is not very muscular, the vessel must be constricted very tightly to induce hypoxia with the muscle layers by obliterating the ductal lumen.

Physiologic Effect of PDA

In infants with a structurally and functionally normal heart, the amount of blood in the pulmonary circulation (Q_p) equals that in the systemic circulation (Q_s) after postnatal adaptation. This is often expressed as a ratio (Q_p/Q_s) and equals one under normal physiologic conditions. In the presence of a PDA, blood from one circulation can be shunted to the other. The direction of flow across the DA is dependent on the difference between PVR and SVR.

When the pulmonary artery resistance exceeds that of the aorta, blood is shunted from the pulmonary circulation to the systemic circulation across the DA. Pulmonary hypertension is not uncommon in the presence of a number of disease states in term neonates. Meconium aspiration, birth asphyxia, sepsis, pneumonia, and some malformations, such as congenital diaphragmatic hernia, are frequently associated with pulmonary hypertension in term infants. However, in preterm infants, the medial muscle layer of the pulmonary arterioles is not as well developed as that of the term infant. Even in preterm infants with lung disease, PVR generally falls below SVR shortly after birth. Therefore, blood preferentially flows across a PDA from the aorta to the pulmonary artery or from left to right.² On rare occasions, a preterm infant may have PVR that exceeds SVR, resulting in a right-to-left flow. In this state, the PDA serves as a “pop-off valve” for the right ventricle, allowing blood to cross the ductus into the lower resistance systemic circulation. The right ventricle then does not face the volume and pressure overload that it would without the aid of the PDA. In this very small subset of preterm infants, the DA should not be closed, either pharmacologically or surgically, until the pulmonary resistance normalizes.

The volume of blood shunting across the DA is determined by the difference between PVR and SVR as well as the size of the DA. The amount of blood that is shunted determines the physiologic effect, or hemodynamic significance, of the PDA. If only a small portion of oxygenated blood reenters the pulmonary circulation, then the Q_p/Q_s is likely still close to one and the shunt would be considered hemodynamically insignificant. As shunting from left to right increases, the Q_p/Q_s also increases. As a higher volume of blood in the pulmonary circulation returns to the heart, there is increased demand on the left side or systemic chambers. The left ventricular stroke volume increases proportionally to the size of the left-to-right shunt. Eventually, the left-sided chambers dilate, and hypertrophy may develop.² The lungs then become “overcirculated,” resulting in fluid shifts across the pulmonary vascular bed and into interstitial tissues. Preterm babies have low plasma oncotic pressure and

increased capillary permeability, both of which contribute to interstitial edema. Over time, this worsens oxygenation and ventilation, requiring increasing respiratory support. As ventilator settings increase, so does the risk of mechanical lung injury, which further increases inflammation and edema. This cycle of trauma can be devastating to the preterm lung that should be growing and maturing. The damaged lung then experiences inefficiency in gas exchange, cellular dysfunction, and pulmonary vascular remodeling. Over time, this can lead to pulmonary hypertension and right ventricular failure or to cor pulmonale.

With hemodynamically significant flow from left to right across the DA, there is diastolic runoff and a widening of the pulse pressure. This results in a decrease in end-organ tissue perfusion and predisposes infants to necrotizing enterocolitis (NEC), renal insufficiency, pulmonary hemorrhage, and intraventricular hemorrhage (IVH).⁷ Infants with ELBW are at risk for each of these diseases by virtue of being premature, and having a PDA further increases this risk.

Symptoms of left-to-right shunting usually do not occur in the first few days of life because of increased lymphatic clearance of fluid. However, after 7 to 10 days of increased pulmonary blood flow, the baby may exhibit worsening respiratory status with increased work of breathing, tachypnea, and/or increased oxygen requirement. It may be difficult to assess whether respiratory symptoms are related to parenchymal lung disease or PDA. Often, babies who have lung disease at birth are symptomatic beyond the first week of life. In addition, frequently, those babies with respiratory distress syndrome (RDS) also have a PDA. Therefore, defining the etiology of respiratory symptoms in premature infants can be difficult.

Diagnosis of PDA

The suspicion of PDA usually begins with physical examination. Because shunting in preterm infants is almost exclusively left to right, their symptoms result from blood flow out of the systemic circulation into the pulmonary vascular bed. The most common physical findings are harsh, continuous murmur, prominent pulses, widened pulse pressure, and increased precordial activity. These exam findings coupled with symptoms of worsening respiratory status are concerning for a symptomatic PDA. On chest radiography, there may be evidence of cardiomegaly and/or increased interstitial fluid in the lungs. However, these chest radiography findings are usually seen later in the course of disease. Abnormal interstitial markings can be attributed to underlying lung disease and are not specific to pulmonary edema seen with PDA.

For those babies with right-to-left flow across the PDA, the most common physical finding is cyanosis. As poorly saturated blood crosses the DA into the systemic circulation, the postductal saturation of the blood will be lower than the preductal saturation. The right subclavian artery branches from the aortic arch prior to the DA connection. Therefore, the blood entering the right subclavian artery should be fully saturated, coming only from the left ventricle. The right arm saturation (preductal) will be higher than the pulse oximetry reading from any other extremity (postductal). These babies exhibit cyanosis at birth or shortly after, and clinical symptoms are related to the underlying cause of pulmonary hypertension. These findings are much more common in term infants.

The definitive diagnosis of PDA is made by echocardiography. Direct visualization of the DA is the most definitive method of diagnosis, but turbulent blood flow in the MPA can be diagnostic as well. This finding indicates flow across the ductus from the higher pressure aorta. Finally, Doppler imaging with echocardiography can assess volume and direction of flow across the DA.⁸

Is This PDA Symptomatic?

Defining a PDA as hemodynamically significant can be difficult. As previously stated, the line where preexisting lung disease ends and PDA symptomatology begins is often blurred. It has been well established that babies with RDS have delayed closure of the PDA. Worsening respiratory status is often the symptom used to define the significance of left-to-right ductal flow, but confirmation with echocardiography can yield supportive information.

Certainly, the dimension of the DA, degree of shunting, and direction of blood flow can be diagnostic, but these parameters alone do not define the hemodynamic significance of a PDA. Assessment of left ventricular output and chamber size can be helpful but is not particularly sensitive, as is the left atrial-to-aortic root ratio. If it is seen on echocardiography, reversal of blood flow in the aorta during diastole is indicative of a significant ductal shunt.⁸ Echocardiographic evidence of shunting is important but must be correlated with the clinical status of the infant in making treatment decisions.

In the last few years, several studies have been published regarding the use of serum B-type natriuretic peptide (BNP) in distinguishing ductal patency from hemodynamically significant shunting across a PDA in preterm infants. BNP is a substance produced primarily in the cardiac ventricles. With increased volume or pressure on the ventricle, the level of serum BNP rises. Although there is a trend to support the use of this assay in conjunction with echocardiography in determining if

treatment is needed, the values used to demonstrate significance vary between studies. Hence, no standardized normal or abnormal BNP level has been established for preterm infants, and further studies are needed.⁹⁻¹¹

Medical Treatment for PDA

Nonpharmacologic treatment for PDA involves fluid restriction, respiratory support, and potential diuretic therapy if symptoms of heart failure are present. Excessive fluid administration has been associated with persistent ductal patency.¹² As a result, fluid restriction after diagnosis of PDA is often used. However, there is a paucity of data in the literature to support fluid restriction as an effective treatment. Most sick premature infants with symptomatic PDA require either pharmacological or surgical treatment to yield ductal closure.

Indomethacin

As stated earlier, the preterm DA remains sensitive to circulating prostaglandins that promote ductal patency. Thus, inhibiting prostaglandin synthesis should assist in DA closure. Indomethacin (Indocin IV, Ovation Pharmaceuticals, Inc, Deerfield, Ill) is a prostaglandin inhibitor that has been well studied for medical closure of PDA in preterm infants. This drug is successful in constricting the DA in 60% to 70% of babies treated.¹³ There are three pharmacologic strategies that include prophylaxis, early asymptomatic treatment, and treatment after the development of symptoms. Indomethacin works most effectively in the first one to two weeks of life. The decrease in efficacy of indomethacin with increasing postnatal age and gestational age can be explained by improved renal clearance of the medication, as well as decreasing ductal reliance on circulating prostaglandins for patency.^{14,15}

Prophylactic use of indomethacin is utilized in many centers to promote ductal closure shortly after birth. Typically, this approach is reserved for infants with ELBW who are very premature, as these babies are at highest risk of having a complication related to the PDA. The indomethacin dose given is less than the treatment dose, and the drug is administered in the first 24 hours of life. The rationale behind using indomethacin prophylactically is that the drug works best in the first few days of life and can yield closure of the DA before the baby becomes symptomatic. A recent Cochrane review showed that prophylactic indomethacin decreases the rate of symptomatic PDA, IVH, and the need for surgical ligation of PDA when compared to placebo. However, there was no effect on rates of NEC and chronic lung disease (CLD). In

addition, no changes in long-term neurodevelopmental outcomes and mortality rates were seen.¹⁶

Some centers prefer treatment of a PDA with indomethacin over prophylactic use. This method is used only in infants with evidence of PDA. This avoids unnecessary exposure to the drug in those infants who would have closed their PDA spontaneously. Two treatment strategies may be used. One involves early asymptomatic treatment, as defined by the presence of a murmur or other signs of PDA but prior to the development of clinical symptoms. The second strategy involves “late” treatment after clinical symptoms develop. Echocardiographic confirmation of PDA and follow-up imaging after treatment vary from institution to institution. Treatment may be initiated without an echocardiogram, relying only on physical exam and/or symptoms.

The doses and frequency used vary among institutions, and the optimal dosing strategy has not been clearly established. The most widely accepted regimen is 0.2 milligram per kilogram per dose given every 12 hours for three doses, but the range can be 0.1 to 0.25 milligram per kilogram per dose given every 12 to 24 hours for a total of three to seven doses.¹⁷ There are many studies that prove indomethacin’s effectiveness for ductal closure in preterm infants, but the effect of the drug is transient. Ductal patency recurs in up to 30% of infants treated.¹⁸ For babies who tolerate the drug well, a repeat course can be given. Because of the significant recurrence rate of PDA, some institutions advocate a longer course of indomethacin in the initial treatment. A recent report showed that a higher dose indomethacin given in stepwise fashion is both safe and effective. Increasing doses were given for the duration necessary to achieve ductal closure.¹⁹ This approach differs greatly from standard dosing regimens that administer the same strength and number of doses for all babies treated. A Cochrane review by Herrera et al²⁰ evaluated long-versus-short course of indomethacin for treatment of PDA. There was marginal improvement in rates of reopening of the DA but no effect on closure rate of the PDA with a longer duration of treatment.

Because the effects of this medication are not selective for the DA, vasoconstriction occurs in other vascular beds. For this reason, indomethacin should be infused for at least 30 minutes to avoid acute vasoconstriction. Some of the side effects of the drug include transient renal insufficiency, decreased intestinal perfusion, and cerebral ischemia. The most common side effect is renal impairment, which usually resolves once treatment is completed. Oliguria is common, so serum electrolytes and drug levels of other medications with renal clearance should be followed. Because of the risk of end-organ hypoperfusion, many centers will stop or decrease enteral feedings during indomethacin treatment to reduce the risk of NEC. There

has been some association between isolated intestinal perforation and indomethacin use, and this risk is increased if corticosteroids are given concomitantly.²¹ Other side effects of indomethacin include platelet dysfunction and hypoglycemia. Indomethacin is contraindicated in babies with active bleeding, thrombocytopenia, coagulopathy, NEC, and/or renal insufficiency.

The literature, old and new, continues to support the use of indomethacin as treatment for PDA in preterm infants. Specifically, prophylactic dosing and early asymptomatic treatment seem to be most effective in decreasing the incidence of symptomatic PDA and PDA ligation.^{16,22} However, there are mixed results regarding effect on mortality, CLD, IVH, and neurodevelopmental outcome with any of the three treatment strategies. A significant problem in analyzing these studies is that they differ in patient populations enrolled and dosing regimens used. Hence, too many variables between study designs make comparisons of results difficult to interpret. Thus, 20 years after indomethacin was first described for treatment of PDA, there is still no standard approach to its use.

Ibuprofen

Because of the side-effect profile of indomethacin, intravenous ibuprofen has received attention as an alternative. Ibuprofen is a prostaglandin inhibitor that appears to have fewer vasoconstrictive effects on the central nervous system, mesenteric and renal vascular beds.^{23,24} Because ibuprofen is highly protein-bound, there have been concerns that the drug could displace bilirubin from albumin and increase the risk of bilirubin encephalopathy. This was addressed in a small study of 15 preterm infants, where bilirubin levels were drawn before and after ibuprofen infusion. No change in free bilirubin levels was seen.²⁵ In a recent Cochrane review, ibuprofen was found to be as effective as indomethacin in ductal closure rates. There were no differences in outcome with regard to mortality, PDA ligation, ventilator days, IVH, periventricular leukomalacia, NEC, gastrointestinal bleeding, and length of hospital stay. The only statistically significant finding in favor of ibuprofen was an improvement in urine output during treatment. However, there was a concerning increase in the rate of CLD, as defined by oxygen requirement at 36 weeks postconceptional age.²⁶ Prophylactic dosing of ibuprofen has also been studied, although not as extensively as treatment dosing. Prophylaxis is effective in PDA closure, and most short-term outcome measures show no statistical difference when compared with indomethacin use.²⁷ However, in 2002, Gournay reported three cases of pulmonary hypertension that developed after treatment with ibuprofen.²⁸ The

pulmonary side effects related to the use of this drug are inconsistent but certainly concerning. Most studies do report improved renal function during ibuprofen treatment when compared with indomethacin, but this side effect of indomethacin therapy is transient. No long-term neurodevelopmental outcome studies after ibuprofen therapy have been published, and this information would be very helpful in distinguishing the optimal pharmacologic agent. With the current evidence, the use of ibuprofen has no clear advantage over indomethacin treatment.

The most common treatment dose of ibuprofen given is a 10 milligram per kilogram load followed by two 5 milligram per kilogram doses, each given 24 hours apart for a total of three doses.²⁹ This dose yields a PDA closure rate of 80% in infants 27 to 29 weeks gestation.³⁰ These dosing studies were performed using the intravenous form of ibuprofen, which has recently become available in the United States for neonatal use (Neoprofen, Ovation Pharmaceuticals, Inc, Deerfield, IL). Limited information is available regarding the use of the oral form of ibuprofen for PDA treatment. One small pilot study reported encouraging results both in efficacy as well as safety of the oral form.³¹ However, this study was purely observational, and no comparison to either placebo or indomethacin was made. Larger trials are required before recommendations can be made.

Surgical Treatment for PDA

For infants in whom pharmacologic treatment is contraindicated or where it has failed, surgical closure is an option. Surgical closure of a PDA should be definitive, although it is possible for the vessel to recanalize if the DA is only ligated and not divided. This complication is very rare, unlike the rate of reopening of the DA after pharmacologic treatment. Surgical PDA closure in preterm infants normally involves an open left posterior thoracotomy with either clip application across the ductus or tying of the vessel with or without separation.² Thoracoscopic techniques are used by some surgeons in small preterm infants for PDA closure to avoid an open procedure. Cardiac catheterization techniques, however, are not an option for preterm infants because of their small size. In small babies, the ductus is short and friable; hence, great caution must be taken to avoid laceration of the ductus, aorta, and/or pulmonary artery. Complications directly related to the procedure include recurrent laryngeal nerve injury and chylothorax. Other rare but reported complications include occlusion of a vessel other than the DA, infection, and pneumothorax.³²

Indirect complications are related to the degree of illness the infant had before the procedure, particularly

with regard to heart and/or lung disease. Many of these babies who require surgical closure of the DA are critically ill and may not tolerate abrupt cessation of flow across the DA. As previously mentioned, babies with CLD may be dependent on pulmonary overcirculation for adequate oxygenation and ventilation. Adaptation to a lower pulmonary blood flow may take time after surgery, and the infant may be quite ill during this adjustment period. In addition, cardiac dysfunction after PDA ligation is common. SVR acutely increases after PDA ligation. The elevation in SVR places a greater demand on an already volume-loaded and potentially dysfunctional left ventricle. However, decreased left ventricular performance is usually transient after ductal ligation.³³

There has only been one prospective, randomized study, published in 1983, comparing surgical ligation versus indomethacin as first-line treatment for PDA. In the surgical group, there was a statistically significant increase in pneumothorax and worse retinopathy of prematurity but greater success of ductal closure. However, there was no difference between the groups with regard to short-term outcomes such as mortality, CLD, NEC, creatinine values, or IVH.¹⁸ No studies reporting long-term neurodevelopmental outcomes after PDA ligation have been published. Many articles have been written supporting either surgical or pharmacological closure as first-line treatment, but no prospective randomized trials comparing the two have been published in the surfactant era. The strongest argument for surgical closure is that it is definitive, whereas recurrence of PDA is common after pharmacological treatment. In addition, timing of closure is an important component in the decision of how best to treat the PDA. Cyclooxygenase inhibitors work best in the first one to two weeks of life; hence, surgical closure after this time may be indicated. Current published information shows both techniques to be safe and effective. Therefore, treatment decisions can be individualized for the specific needs of each patient.

PDA and CLD

Because most infants with ELBW have multiple medical problems, the complications of prematurity can overlap. This makes defining direct cause-and-effect relationships difficult, particularly with regard to PDA and CLD. It is not clear whether the presence of a PDA contributes to CLD or whether CLD prevents PDA closure. This association between PDA and CLD was established in the presurfactant era of neonatology, when lung disease in preterm infants was much more severe. Even now with widespread use of surfactant and tremendous advances in ventilation strategies for infants with ELBW, CLD is a persistent problem. The presence of a

PDA remains a risk factor for the development of CLD. However, many risk factors are associated with both CLD and PDA, including infection, excessive fluid administration, and RDS.^{34,35} Because preterm infants often have multiple concurrent problems, it is virtually impossible to implicate causality in any given disease process.

There may be several explanations for the persistence of CLD. The lack of improvement in long-term outcome in ELBW infants with or without PDA may be related to an increase in survival of very small babies. As survivors are younger and smaller, they endure a greater number of complications. Another argument is that with routine use of prenatal steroids and postnatal surfactant in infants with ELBW, PVR falls more quickly with less severe lung disease. In those infants with PDA, shunting from left to right may occur more rapidly. This may then lengthen the duration of the lung's exposure to systemic blood pressure and increased pulmonary blood flow. Finally, there are some babies with relatively mild RDS who later develop CLD. It is possible that a PDA could contribute to the disease in this circumstance because treatment for PDA closure may not be pursued aggressively in a baby who was initially asymptomatic.

There have been no clinical trials to specifically address this relationship of PDA and CLD. Most of the literature reflects CLD as an outcome measure of PDA treatment. Thus, these studies were not designed to assess the effect of the PDA itself or the impact that PDA closure has on outcome. Even in placebo-controlled trials, treatment for PDA was permitted if it was clinically indicated. Although this association persists, early closure of PDA has not reduced the rate of CLD in infants with ELBW.^{22,16}

Why is the Management of a PDA So Controversial?

The nature of the DA is to remain patent until a fetus reaches term. For preterm neonates, their "third trimester" is extrauterine, and in many, the DA remains patent during that time. Delayed spontaneous closure of the DA is common in preterm infants, unlike term infants where patency of the DA is considered pathologic beyond three days of life. Some neonatologists consider the DA to be an important physiologic structure, and ductal patency can be asymptomatic; therefore, forcing the DA to close disrupts postnatal adaptation. Other neonatologists feel that the presence of a PDA is wrought with serious potential side effects, and closing the DA is a necessity. Both sides of the argument can be supported by reputable literature.

Most interventions in neonatology are now measured by a change in either mortality rates or neurodevelopmental outcome in infants with ELBW. Although the presence

of PDA is associated with hemodynamic instability and IVH, outcome data have shown no difference in these long-term outcome measures with either early or late PDA closure.^{16,36} These outcome measures are important when considering standardized treatment protocols for specific populations of preterm infants. However, because preterm infants with a PDA can be very sick, individual babies may need treatment for acute relief of symptoms even if the long-term outcome remains unchanged.

Although many studies over the last 20 years have attempted to establish guidelines for when and how the PDA should be treated, there still is not enough evidence to make universal recommendations. Study design and outcomes vary widely, making interpretation difficult. There are many different strategies ranging from no treatment to surgical ligation of the PDA. However, no single approach has improved survival, neurodevelopmental outcome, or rates of CLD in infants with ELBW.

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