JOHNS HOPKINS ALL CHILDREN'S HOSPITAL

Diagnosis and Management of Patent Ductus Arteriosus in Preterm Neonates Clinical Pathway

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Rationale

A. To provide guidance for the management of a Patent Ductus Arteriosus (PDA) in neonates born at < 28 weeks gestational age (GA).

B. To provide clinical and echocardiographic parameters which can be used to guide the medical treatment of a PDA.

C. To provide clinical and echocardiographic parameters which can be used to guide the surgical or transcatheter closure of a PDA.

Background / Published Data and Levels of Evidence

Background

Before birth the ductus arteriosus (DA) is responsible for shunting blood away from the high-resistance pulmonary vascular bed into the systemic circulation. At the time of birth, the placental circulation is removed, pulmonary vascular resistance decreases, and the pulmonary circulation becomes the sole source of oxygenated blood. Shunting through the DA is no longer necessary and may become detrimental. In >95% of neonates exceeding 1500 g in birth weight (BW), DA closure generally occurs within 96 hours and is permanent soon thereafter[1]. In contrast, neonates <1500 g in BW are at increased risk of having a patent DA (PDA) beyond 96 hours postnatally[2]. Persistence of the PDA may result in a left-to-right shunt and hyperperfusion of the pulmonary vascular bed, often resulting in decreased lung compliance[3], increased need for mechanical ventilation[4], and altered postnatal nutrition and growth[5]. Thus, a PDA may adversely affect morbidity and mortality in an already high-risk population. Spontaneous PDA closure occurs in >34% of extremely low birth weight infants (ELBW) but may occurs after more than 14 days[6].

The persistence of a hemodynamically significant PDA (hsPDA) in the ELBW population may be associated with several long-term complications such as bronchopulmonary dysplasia (BPD)[7] and intraventricular hemorrhage[8]. However, the medical and surgical treatment of a PDA has also been associated with serious complications such as intestinal perforation, vocal cord paralysis, and post ligation cardiac failure[9-11]. Over the years, there has been a long-standing controversy concerning the optimal approach to the management of a hsPDA in this preterm population, with literature available to support both expectant management and medical/surgical closure. This clinical pathway aims to provide guidance to which patients are the possible best candidates for PDA closure and the optimal timing and specific therapy.

While the long-term effects of a hsPDA and its treatment remain controversial, it is our goal to standardize our unit management of hsPDAs. Guidelines have been shown to reduce patient harm through improved standardization and communication[12]. In the absence of an evidenced-based consensus for a given clinical decision, development of these guidelines sometimes may be challenging. However, the use of guidelines has been clearly demonstrated to improve outcomes and for that reason we are proposing this guideline.

Published Data and Levels of Evidence

1. Does exposure to a PDA lead to adverse outcomes in premature neonates?

Physiological aspects:

The presence of a PDA in a preterm infant can result in pulmonary over circulation and systemic hypoperfusion. The downstream cardiopulmonary effects of a large PDA include left atrium (LA) and left ventricle (LV) overload leading to LA and LV dilation. Initial hyperdynamic systolic function later develops into decreased LV systolic function[1].

In the case of a large hemodynamically significant (hsPDA)with unrestrictive pulmonary artery (PA) flow, PA pressure is elevated and increasing flow and shear stress injury, endothelial cell dysfunction, and, in some cases, it may progress to pulmonary hypertension[13]. Left to right blood shunting through the PDA increases pulmonary blood flow and pressure and decreases lung compliance via pulmonary edema[3]. These mechanisms may predispose ELBW with hsPDAs to the develop BPD. BPD is associated with the persistence of hsPDA, and each week of exposure represents an added risk for BPD (OR, 1.67)[7]. Presence of a PDA shunt was associated with an increased risk of BPD when it persisted beyond 10 days and required prolonged intubation (≥ 10 days)[4].

Association Studies:

Several studies have described an association between hsPDA and necrotizing enterocolitis (NEC), acute kidney injury (AKI), BPD, pulmonary hypertension, pulmonary hemorrhage, intraventricular hemorrhage, and death[8,13-16]. Preterm infants with moderate to large left-to-right shunts have an up to 8-fold greater mortality rate than those without a PDA[17-18].

Randomized clinical trials:

1. PDA TOLERATE[19]
    a. In this large international, multicenter, randomized controlled trial infants born before 28 weeks of gestation were randomized to routine pharmacologic treatment of PDA at the end of the first postnatal week or delayed for at least another 7 to 10 days.
    b. The study demonstrated that infants surviving for at least 7 days had increased risk of BPD or death after 7 days of exposure to a moderate to large PDA. (OR 2.12;95% CI 1.04-4.32).
    c. A statistically significant association between the singular outcome of BPD was demonstrated for exposures to PDA for 14 days or more. (OR 4.09; 95% CI 2.22-7.22).

d. In addition, this study also showed and increased risk of BPD among infants who required intubation and mechanical ventilation beyond 10 days and the presence of a PDA with left to right hemodynamic shunt[4]. (Figure 1)

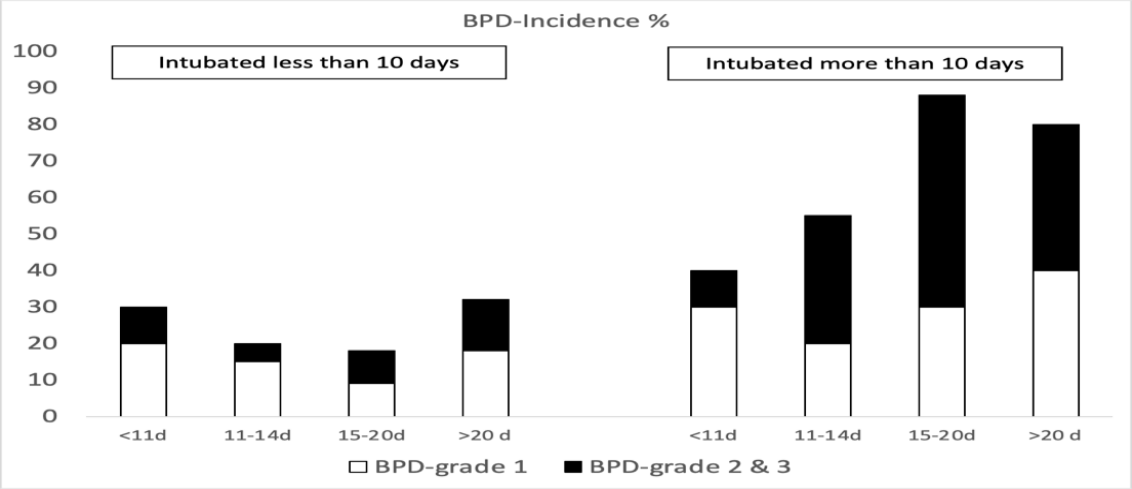


Figure 1: BPD incidence and length of exposure to hs PDA (adapted from Clyman et al, J Pediatr. 2021 Feb; 229:283)

2. BeNeDuctus Trial[20]
    a. In this international, multicenter, noninferiority trial, infants less than 28 weeks with echocardiographically confirmed PDA (diameter, >1.5 mm, with left-to-right shunting) were randomly assigned to receive either expectant management or early ibuprofen treatment (after 72 hrs).
    b. A total of 273 infants underwent randomization. A composite of NEC, moderate-to-severe BPD, or death occurred in 63 of 136 infants (46.3%) in the expectant-management group and in 87 of 137 (63.5%) in the early-ibuprofen group (absolute risk difference, −17.2 percentage points; upper boundary of the one-sided 95% confidence interval [CI], −7.4; P<0.001 for noninferiority). NEC occurred in 24 of 136 infants (17.6%) in the expectant-management group and in 21 of 137 (15.3%) in the early-ibuprofen group (absolute risk difference, 2.3 percentage points; two-sided 95% CI, −6.5 to 11.1); BPD occurred in 39 of 117 infants (33.3%) and in 57 of 112 (50.9%), respectively (absolute risk difference, −17.6 percentage points; two-sided 95% CI, −30.2 to −5.0). Death occurred in 19 of 136 infants (14.0%) and in 25 of 137 (18.2%), respectively (absolute risk difference, −4.3 percentage points; two-sided 95% CI, −13.0 to 4.4). Rates of other adverse outcomes were similar in the two groups.
    c. The frequency of adverse events and serious adverse events were similar in the two groups.
    d. In this study, expectant management for PDA in extremely premature infants was noninferior to early ibuprofen treatment with respect to NEC, BPD, or death at 36 weeks' postmenstrual age.

2. Defining a hemodynamically significant PDA

The challenge of defining a hsPDA that needs to be treated has been the subject of debate. The simple presence of a PDA does not necessarily imply there are physiological effects leading to

hemodynamic instability. Clinical trials and other studies that have reported on PDA showed heterogeneity in the definition of a hsPDA, using both clinical and echocardiographic parameters[21].

Kluckow and Lemmers recommended considering the infant's risk factors, clinical condition, radiographic and laboratory findings to diagnose a hsPDA[21].

a. **Risk factors for hsPDA**:
    1. gestational age less than 26 weeks
    2. low birth weight <1000 g
    3. birth weight <10th percentile for gestational age
    4. female gender
    5. lack of receipt of antenatal steroids
    6. maternal chorioamnionitis

b. Clinical signs of a hsPDA:
    1. continuous or systolic murmur, "silent murmur" occurs when shunt is large enough.
    2. a low diastolic blood pressure
    3. wide pulse pressure
    4. bounding pulses with an active precordium
    5. hyperdynamic precordium
    6. refractory hypotension and systemic steal
    7. oliguria
    8. hepatomegaly
    9. active pulmonary hemorrhage or decreased lung compliance or increased respiratory support needs.

c. **Chest x-ray:** pulmonary edema due to excessive blood flow and enlarged heart (especially left atrium)

d. Laboratorial findings:
    1. low platelet count within 24 hours of birth (< 100,000)
    2. elevated nucleated red blood cells at birth (>3750/mm3; 88% specificity, 57% sensitivity)
    3. increased creatinine
    4. metabolic acidosis

Echocardiogram: The gold standard for diagnosing a PDA and for assessing its hemodynamic significance is transthoracic echocardiogram. Traditional assessment of the hemodynamic significance of a PDA has relied on ductal diameter alone, however the concordance between PDA diameter and indices of shunt volume is weak. Although diameter is one of the most important determinants, the use of it in isolation to determine the hemodynamic significance of the ductal shunt should be avoided due to the potential for measurement error and the poor outcome-predictive ability of diameter alone. A comprehensive echocardiographic evaluation provides a more holistic picture with redundancies to mitigate measurement error within the individual echo parameters[22].

Standard definition of a hsPDA is lacking, therefore van Laere, et al proposed a standardized echocardiographic assessment of hemodynamic significance of a PDA. This echocardiographic assessment includes the following PDA characteristics:[23]

1. diameter
2. flow direction
3. systolic and diastolic flow velocities
4. indices of pulmonary over circulation

5. left ventricular output
6. one parameter of left sided volume loading or left heart pressure loading
7. systemic shunt effect
8. doppler flow patterns in the systemic circulation.

The Neonatologist Performed Echocardiography Group (NPE) described early predictive echocardiographic variables of a hemodynamic hsPDA (Table1). Echocardiogram studies reveal that ductus arteriosus exposed to sustained bidirectional shunt, or low velocity blood flow were more likely to remain patent and were resistant to pharmacologic therapy[23].

Early predictive echocardiographic variables for the development of hemodynamic significant PDA				
Author	GA/BW included	Timing first echo	Endpoint	Parameters
Kluckow and Evans, 1995	<1500g ventilated	<31 h	Diagnosis of a significant PDA meeting clinical and echocardiographic criteria (1-15d)	PDA diameter >1.5mm DADF absent/retrograde LA:A0 ≥1.5 LVO ≥300 ml/kg/min
Su et al	<1500g ventilated	Daily echo for 7 days	hsPDA >2 clinical, radiological signs and echocardiographic signs of L-R shunt	First growing pattern First pulsatile pattern
Kwinta et al	GA 24-32 weeks	12-48 hrs after birth	Significant PDA requiring surgical ligation	PDA diameter >1.5 mm/kg fE > 36 cm/s Cl Ao > 2.5 L/min/m^2 PDA diameter > 1.5 mm/kg + FiO2 >0.3
Ramos et al	BW < 1000g	Echo before 4 days of age	Need for subsequent treatment based on clinical and echocardiographic signs	PDA:LPA≥0.5
Harling et al	GA < 32 weeks	Echo at 24 hrs of age	Need for subsequent treatment based on clinical and echocardiographic signs	PDA diameter ≥ 2 mm/kg Pulsatile flow pattern LA:Ao ≥ 1.4 Green pixel on color doppler
Thakavel et al	GA < 30 weeks	Echo at 3 days of life	Spontaneous PDA closure on late echocardiography without treatment	PDA:LPA≥0.5 PDA diameter >1.5 mm LA:Ao ≥ 1.4 E/A ratio >1

Smith et al	GA < 32 weeks	Echo with 48 hrs	PDA ≥ 2 mm on echocardiography at 1 month of age	PDA diameter ≥ 2.1 mm Systolic flow velocity ≤ 131 m/s Diastolic flow ≤ 75 m/s Ratio systolic to diastolic flow velocity > 1.9
Ao aorta, BW birth weight, CI Ao cardiac index across aortic valve, DADF descending aorta diastolic flow, E/A ratio mitral valve early filling to atrial contraction ratio, fE early filling peak velocity, GA gestational age, La left atrium, La:Ao left atrium to aortic root ratio, LPA left pulmonary artery, PDA patent ductus arteriosus				

Table 1: Early predictive echocardiographic variables of a hemodynamic hs PDA (adapted from van Laere D, van Overmeire B, Gupta S, et al. Application of NPE in the assessment of a patent ductus arteriosus. *Pediatr Res*. 2018)

3. Does treatment of a PDA improve neonatal outcomes?

There is some evidence for no improvement in long term neonatal outcomes from controlled clinical trials that compared infants who received treatment for ductal closure versus no treatment for closure. More than 40 randomized clinical trials using standard management strategies to close PDAs and meta-analyses of PDA treatment trials have failed to show improvements in outcomes, prompting calls against treating PDAs in preterm infants.[24-25] Interpretation of these studies is limited by the co-linearity between each of these outcomes, persistent PDA despite treatment, differences in response to treatment based on immaturity, and the wide range of ways in which PDA was defined clinically and with echocardiograms[26].

Whether exposure to a PDA shunt increases the risks of later neonatal morbidity such as BPD is still unclear. None of the RCT performed has found a relationship between therapies intended to close the PDA and the risk of developing BPD. Recent single-center observational studies have shown small PDA shunts do not appear to increase risk for developing BPD in preterm infants. Instead, an association between PDA and BPD is apparent only when moderate and large shunts persist beyond 7 days[4].

According to Clyman, the “treatment” versus “no treatment” trials do not really tell us about the long-term effects of a hsPDA. They simply tell us about two different treatment choices: one designed to close the ductus and one designed to deal with its hemodynamic consequences[27]. Therefore, if treatment makes no difference in reducing adverse outcomes, then preterm PDA may not be pathological. However, lack of evidence of effect is not the same as evidence of lack of effect.

4. Prophylactic closure of PDA

Nine trials (N = 1070 infants) comparing prophylactic ibuprofen (IV or oral) with placebo/no intervention showed a decrease in the incidence of patent ductus arteriosus, the need for rescue treatment with cyclo-oxygenase inhibitors and need for surgical ductal closure. Adverse

effects associated with ibuprofen use included increased risks for oliguria, increase in serum creatinine levels, and increased risk of gastrointestinal hemorrhage. There was a reduced risk for intraventricular hemorrhage (grade III - IV) but no evidence of a difference in mortality, chronic lung disease, necrotizing enterocolitis, or time to reach full feeds. In a study by Ohlsson et al, in the control group, the patent ductus arteriosus had closed spontaneously by day 3 or 4 in 58% of neonates. Given significant side effects, the possibility of spontaneous closure and lack of significant benefit, ibuprofen should not be used for IVH/PDA prophylaxis[28].

Nineteen trials (N=2872 infants) compared prophylactic indomethacin versus placebo preterm infants for PDA closure. Most participants were very low birth weight, but the largest single trial restricted participation to extremely low birth weight infants (N = 1202). The incidence of symptomatic PDA [typical relative risk (RR) 0.44, 95% confidence interval (CI) 0.38 to 0.50] and PDA surgical ligation (typical RR 0.51, 95% CI 0.37,0.71) was significantly lower in treated infants. Prophylactic indomethacin also significantly reduced the incidence of severe intraventricular hemorrhage (typical RR 0.66, 95% CI 0.53 to 0.82). Prophylactic indomethacin has short-term benefits for preterm infants including a reduction in the incidence of symptomatic PDA, PDA surgical ligation, and severe intraventricular hemorrhage[29]. However, in a meta-analysis there is no evidence of effect on mortality or neurodevelopment although, in most studies, neurodevelopment was not a primary outcome and studies therefore often lacked sufficient power to detect a difference in neurodevelopmental outcomes[30].

Clinical Management

There are no unequivocal data to determine the optimal management of PDA in preterm infants. As a result, there is variability in the treatment of PDAs among neonatologists and pediatric cardiologists. Standardization of care within institutions has led to the development of clinical tools assessing the risk of a hemodynamically significant PDA based on clinical and echocardiographic scoring systems[31].

1. Diagnosis:

Clinical assessment:

Patients born at or before 28 weeks of gestation, who are **mechanically ventilated** between 4 to 7 days of age and have the presence of any combination of the following signs or laboratory or radiographic findings, should undergo echocardiographic evaluation to determine if a hsPDA is present.

Cardiovascular:

1. systolic murmur at the left sternal border, sometimes radiating to the back
2. active precordium
3. widened pulse pressures and prominent or bounding peripheral pulses
4. left sided cardiac dysfunction and/or hypotension and hypoxia
5. poor perfusion

Respiratory:

1. increasing respiratory support (increasing FiO2, increasing pressure support, increasing tidal volume, need for high frequency respiratory support)
2. CXR with worsening aeration, pulmonary edema
3. pulmonary hemorrhage

Gastrointestinal:

1. Feeding intolerance - abdominal distension, emesis, residuals

Renal:

1. Oliguria or anuria with or without hyponatremia.

Timing of assessment:

All the major clinical signs of a PDA have been assessed against ultrasound diagnosis and have been found to be non-specific on DOL 1. Its until day 4 of life that the clinical signs start to correlate more closely on cardiac echocardiogram[21], although assessing hemodynamic significance using clinical signs remains problematic as sensitivity is poor. Since significant risk for morbidity (BPD) is associated with exposure of a PDA greater than 7 days it is recommended that if a hsPDA is suspected to be present by clinical assessment, an echocardiogram be obtained for confirmation between 4 to 7 days of life.

Echocardiogram assessment:

If clinical symptoms as described above are present by DOL #4 to 7 and if clinically indicated, obtain echocardiogram.

The initial scan should be a comprehensive appraisal of cardiac anatomy, sufficient to confirm structural normality of the heart and avoid inadvertent PDA treatment in the presence of a duct dependent lesion.

Echocardiogram parameters to be reported include PDA characteristics:

1. diameter
2. flow direction
3. systolic and diastolic flow velocities
4. indices of pulmonary over circulation
5. left ventricular output
6. plus one parameter of left sided volume loading or left heart pressure loading, systemic shunt effect, doppler flow patterns in the systemic circulation.

A scoring system agreed by the Heart Institute at JHACH will be used and determination of hemodynamic significance of PDA and the score will be added to the report by the cardiologists.

Report requirements:

Include a statement on hemodynamic significance based on 5 criteria:

1. LA dilation: Is LA/AO ratio > 1.5? (yes/no)

2. LV dilation Is LVID z-score > 2.0? (yes/no)

3. LV function (only one needed for “yes”):

- Biplane EF < 50%? (yes/no)
- Fractional shortening < 25%? (yes/no)

4. PDA size (only one needed for “yes”):

- PDA > 2mm diameter at narrowest point? (yes/no)
- PDA/LPA ratio > 0.5? (yes/no)

5. PDA velocity/flow (only one needed for “yes”):

- PDA Vmax in diastole < 2.0 m/s? (yes/no)
- Holodiastolic flow reversal in the descending Ao? (yes/no)
- LPA Vmax in diastole < 0.3 m/s? (yes/no)

Scoring criteria for hsPDA:

▪ 0 - 1 “yes” - not hemodynamically significant

▪ 2 “yes” - undetermined hemodynamic significance

▪ 3 - 5 “yes” - hemodynamically significant

2. Management of a diagnosed PDA

An isolated PDA without significant risk factors and that is not hemodynamically significant or showing clinical impact, especially on end-organ perfusion, may be left untreated.

Conservative management for a non-hemodynamically significant PDA

Conservative treatment is defined as a management approach that does not involve medication, invasive or operative procedures.

For infants with a PDA that does not appear to be hemodynamically significant, an initial conservative approach with supportive general measures is acceptable. If a conservative approach is initially selected, this does not preclude intervention later. Subsequent directed pharmacologic therapy for PDA closure is suggested to be administered to infants with persistent PDAs who remain dependent on mechanical ventilation after one week of age.

Conservative approach may include:

- Daily moderate fluid intake awareness: excessive fluid administration is associated with an increased incidence of PDA and BPD. Although evidence for efficacy is lacking, moderate daily fluid intake (suggested by this panel 120-130 ml/kg/day, no specific literature recommendation) is a reasonable approach to limit pulmonary edema in infants with hemodynamically significant.
- Neutral thermal environment: to minimize demands on left ventricular function and to allow for restrictions in daily fluid intake. Refer to Thermoregulation CPG for ELBW
- Gentle ventilation: decrease lung injury associated with mechanical ventilation. Please refer to guidelines on invasive mechanical ventilation for premature infants with RDS as a reference.
- Diuretics: A thiazide diuretic may be considered to treat infants who become fluid-overloaded or with signs of increased interstitial pulmonary fluid. Furosemide or any other loop diuretic is not recommended in the first week or two after birth, as this stimulates renal synthesis of prostaglandin E_2,a potent vasodilator that maintains ductus arteriosus patency[32] . There are some data suggesting that the use of furosemide in combination with indomethacin increases the incidence of acute renal failure[33]
- Enteral Feeding: There is a lack of consensus and prospective randomized controlled trials regarding feeding infants with hsPDAs. Although the hemodynamic mechanisms through which a PDA can affect mesenteric perfusion have been theoretically established, the real impact on the hemodynamic response to enteral feeds are unclear due to significant methodologic heterogeneity amongst the few available trials studying this question. A small study in Journal of Maternal Fetal Neonatal Medicine found higher rates of NEC and feeding intolerance in the 'large' PDA group[34]. A study in the Journal Pediatric Gastroenterology and Nutrition, conversely found no such increase rates of gut complications in preterm infants with PDAs of variable sizes[35]. The PDA TOLERATE trial, which was not statistically powered for secondary outcomes such as NEC, did still note that negligible differences were seen in this outcome between neonates with PDAs that were and were not treated early[19]. Decisions regarding feedings and advancements will need to be made on an **individual basis**, weighing the risks of delaying enteral feedings in preterm infants and the potential risks of feeding infants with PDAs. Enteral feedings (20ml/kg/day) with breast milk in infants with asymptomatic or "mild" PDAs appear to be safe and should be started or continued if there are no other contraindications to feeding, with close attention to symptoms of intolerance.

Pharmacological treatment for PDA

When there is evidence of clinical effects of hsPDA, especially in the most vulnerable infants born <28 weeks of gestation, with echocardiographic confirmation of a hsPDA, pharmacological treatment may be indicated.

In a recent review, 16 Cochrane reviews were included corresponding to 138 randomized clinical trials and 11,856 preterm infants, on the prevention and treatment of PDA in preterm infants. Six reviews reported on prophylactic interventions for the prevention of PDA and included pharmacological prophylaxis with prostaglandin inhibitor drugs, prophylactic surgical ligation, and non-pharmacological interventions. One review reported on the use of indomethacin for the management of asymptomatic PDA; nine reviews reported on interventions

for the management of symptomatic PDA and included pharmacotherapy with prostaglandins inhibitor drugs in various routes and dosages, surgical ligation, and adjunct therapies[36].

Prevention of hsPDA

Prophylactic indomethacin reduces severe intraventricular hemorrhage (IVH; relative risk (RR) 0.66, 95% confidence interval (CI) 0.53 to 0.82; 14 RCTs, 2588 infants), and the need for invasive PDA closure (RR 0.51, 95% CI 0.37 to 0.71; 8 RCTs, 1791 infants), but it does not appear to affect the composite outcome of death or moderate/severe neurodevelopmental disability (RR 1.02, 95% CI 0.90 to 1.15; 3 RCTs, 1491 infants)[36].

Prophylactic ibuprofen probably marginally reduces severe IVH (RR 0.67, 95% CI 0.45 to 1.00; 7 RCTs, 925 infants; moderate-certainty evidence), and the need for invasive PDA closure (RR 0.46, 95% CI 0.22 to 0.96; 7 RCTs, 925 infants; moderate-certainty evidence). The evidence is very uncertain on the effect of prophylactic acetaminophen on severe IVH (RR 1.09, 95% CI 0.07 to 16.39; 1 RCT, 48 infants)[36].

Treatment of symptomatic PDA

All available prostaglandin inhibitor drugs appear to be more effective in closing a PDA than placebo or no treatment (indomethacin: RR 0.30, 95% CI 0.23 to 0.38; 10 RCTs, 654 infants; high-certainty evidence; ibuprofen: RR 0.62, 95% CI 0.44 to 0.86; 2 RCTs, 206 infants; moderate-certainty evidence; early administration of acetaminophen: RR 0.35, 95% CI 0.23 to 0.53; 2 RCTs, 127 infants; low-certainty evidence). Oral ibuprofen appears to be more effective in PDA closure than intravenous (IV) ibuprofen (RR 0.38, 95% CI 0.26 to 0.56; 5 RCTs, 406 infants; moderate-certainty evidence). High-dose ibuprofen appears to be more effective in PDA closure than standard-dose ibuprofen (RR 0.37, 95% CI 0.22 to 0.61; 3 RCTs, 190 infants; moderate-certainty evidence)[36].

With respect to adverse outcomes, compared to indomethacin administration, NEC appears to be lower with ibuprofen (any route; RR 0.68, 95% CI 0.49 to 0.94; 18 RCTs, 1292 infants; moderate-certainty evidence), oral ibuprofen (RR 0.41, 95% CI 0.23 to 0.73; 7 RCTs, 249 infants; low-certainty evidence), and with acetaminophen (RR 0.42, 95% CI 0.19 to 0.96; 4 RCTs, 384 infants; low-certainty evidence). However, NEC appears to be increased with a prolonged course of indomethacin versus a shorter course (RR 1.87, 95% CI 1.07 to 3.27; 4 RCTs, 310 infants)[36].

Table 2 shows dosing for medications used for PDA treatment. We recommend using birth weight for dosing during the first 2 weeks of post-natal life. If the baby's age is greater than 2 weeks, we recommend using the best estimate of dry weight.

Contraindications to Indomethacin or Ibuprofen Use

- Structural heart disease (seek cardiology consult advice)
- Known or suspected structural renal disease
- Significant renal impairment (anuria, severe oliguria or creatinine > 1.5)
- Suspected or active necrotizing enterocolitis
- Thrombocytopenia (<100,000) or coagulation defects
- Active bleeding

PDA Closure Dose (mg/kg)			
Indomethacin			
Age at 1st dose	1st	2nd	3rd
<48 hrs	0.2	0.1	0.1
2 to 7 days	0.2	0.2	0.2
>7 days	0.2	0.25	0.25
Usual doses, 0.1 to 0.2 mg/kg/dose IV every 12 to 24 hrs beginning within the first 6 to 24 hrs of birth for a total of 3 doses. The optimal dose is unknown, but 0.1 mg/kg/dose IV every 24 hrs for 3 doses may attenuate potential reduction in urinary output.			
Ibuprofen			
Standard dose	10 mg/kg orally or IV, followed by 5 mg/kg/dose at 24 hrs and 48 hrs		
High dose	15-20 mg/kg orally followed by 7.5 to 10 mg/kg orally per day for a total of 3 doses		
High doses of oral ibuprofen were more likely to be associated with hsPDA closure compared with standard-dose IV ibuprofen. There were not significant differences between IV or PO ibuprofen and necrotizing enterocolitis.			
Acetaminophen			
PO or IV: 15 mg/kg/dose orally every 6 hrs for 3 days; a second course may be required			
NSAIDs are the standard drugs for PDA closure. However, there are risks to NSAIDS and there is a high rate of spontaneous closure; therefore, treatment should be limited to select preterm with symptomatic PDA. Acetaminophen may be a treatment option in those having NSAIDs failure or contraindications to NSAIDs.			

Table 2 Pharmacological agents for PDA closure (adapted from Micromedex-NeoFax)

Enteral Feeding Considerations During Pharmacologic Treatment of a PDA:

Martini et al, compiled studies examining the effects of pharmacologic agents for PDA closure on splanchnic hemodynamic responses to enteral feeds as well as the association between presence of a PDA/PDA treatment and GI outcomes in preterm infants[37]. The authors found many flaws in the research and could not make a recommendation based on the evidence. While waiting for further data, the feeding management of this population with PDA should be carefully evaluated and possibly individualized based on the infants' hemodynamic and clinical characteristics. It is important to note that there are published articles including study arms who have receive feedings (both trophic and >60 ml/kg/day) during PDA treatment. Feeding infants during treatment of PDAs with trophic feeds (20 mg/kg/d) may be **considered on an individual basis .**

There is no data regarding feeding advances in the presence of a PDA. Decisions for feeding advances are **made individually**. Failure to tolerate feeds is considered criteria for moderate/severe PDA.

Percutaneous Transcatheter PDA closure

Percutaneous closure of the PDA was first described in 1968[38]. The small and extremely low birth weight premature infant has historically been excluded from the percutaneous approach due to small size, lack of appropriate devices and assumed higher risk. These infants, however, are subject to much higher incidence of PDA. More recently new devices have become available and current commercially available devices in the US have been used for trans catheter PDA (TC-PDA) closure in preterm and small infants as small as 490 grams[39].

Following a recent multicenter trial, the Amplatzer Piccolo Occluder device (Abbott, MN, USA) was approved in the USA for closure of PDA in ELBW>700 grams and 3 days of age[40]. A recent meta-analysis described younger age, not weight, at time of TC PDA closure to be associated with higher technical failure. Additionally, centers performing the procedure in fewer than 10 infants ≤1.5kg experienced higher incidence of both major and minor adverse events[41].

Some process and technique considerations should be taken when performing TC PDA:

1. Centers with the most experience with TC-PDA recommend development of a dedicated team of individuals to optimize procedural outcomes: a small cohort of neonatologists, cardiologists, anesthesiologists, catheterization lab staff and sonographers[42].

1. Contraindications for TC PDA: Ductal shunts with a right-to-left component may be indicative of either severe pulmonary hypertension or ductal dependent cardiac lesion. Suspicion of aortic coarctation or LPA stenosis that could worsen with device placement are additional contraindications.

2. Relative contraindications include acute sepsis, requirement for high frequency oscillatory ventilation during the procedure or significant hemodynamic instability.
3. To avoid intraventricular hemorrhage intraprocedural systemic heparinization should be avoided.

Post-Percutaneous Transcatheter PDA Closure Management

There are three potential post-procedure events that warrant attention by the medical team, including the cardiology service [43]:

1. device embolization (rare outside of the catheterization laboratory),
2. obstruction to the left pulmonary artery (LPA)
3. obstruction to the aorta.

Obstruction to the LPA

Many patients experience at least some narrowing of the LPA after device placement, as the ductus tends to run immediately superior to the origin of the LPA. Mild, and even moderate degrees of flow acceleration into the LPA tend not to cause problems and resolve over time;

however, rare severe forms of obstruction may require intervention. This is usually recognized near the procedure (within 24 hours or less). Evidence of device embolization or severe obstruction to the LPA can cause either the return of the ductal murmur or an accentuated systolic ejection murmur radiating to the left axilla. The patient may experience desaturations and hemodynamic instability.

Obstruction to the aorta

Aortic obstruction can occur at the time of the procedure and is typically recognized, and the device repositioned. However, there are times when there is the appearance of late obstruction thought to be related to migration of the distal disc of the device further into the aortic lumen as the duct contracts and the device lengthens. Aortic obstruction can result in a murmur over the precordium, left axilla and back. It can cause diminished or absent pulses, a blood pressure gradient from upper extremity (UE) to lower extremity (LE) (with LE being lower) and/or hypertension. There can also be decreased urine output and abdominal distension if there is diminished flow of blood past the area of obstruction ultimately resulting in renal failure and/or necrotizing enterocolitis. Laboratory changes may include increasing creatinine and a lactic acidosis.

Post Device Implantation:

Echocardiogram

1. All patients will undergo echocardiography on post-op day (POD)#1 after the implant, sooner if there are concerns.
2. Following echocardiogram will be done on POD#2 and one week later and then in POD#28-30.
3. Patients at higher risk of obstruction to the aorta as determined by cardiology team (subsequently referred to as **"high risk"**) should get daily echocardiograms until POD#3, then weekly x 3 and then monthly.

Cardiology

1. The cardiology team will assess the patients on POD#1, POD #7 then POD#28-30.
2. **High risk** patients will be assessed daily x 3 and thereafter as warranted by the clinical condition of the infant.
3. Cardiology will notify the NICU team when the patient is no longer deemed "high risk."

NICU:

1. Physical assessment to be performed by APP/Neonatal fellow/attending post-piccolo placement (baseline). Physical assessment changes that need to be brought immediately to the attention of attending and provider:
    a. Increased respiratory rate above baseline.
    b. New onset tachycardia or bradycardia
    c. New onset of a heart murmur
    d. Edema
    e. New onset desaturations or increased oxygen need
    f. Emesis and increased abdominal girth.
    g. Diminished peripheral pulses.

2. Patients should have UE/LE pulse checks q3hours for 24 hours, then daily. Blood pressure should be documented q6hrs on all 4 extremities and providers should be notified if a difference between upper and lower blood pressures is present (systolic difference of more than 10 mm Hg). **High risk** patients should have peripheral pulses (via palpation) checks Q6 hours until cleared by cardiology.
3. Urine output should be strictly charted (every 3-4 hrs) and trended by 12-hour time periods. **High risk** patients should have UOP trended Q3 hours and graphed to look for changes until cleared by cardiology. Nursing to notify providers if UOP is less than 2 ml/kg/hr
4. Abdominal girths should be checked Q6hours (with hands on care) as standard of care in the unit. Babygram may be obtained in POD#1 to evaluate for any ileus or dilated bowel loops. **High risk** patients should be checked Q24 hours until cleared by cardiology.
5. **High risk** patients should have lactate and creatine drawn on POD 1, 2, 3 and weekly until cleared by cardiology. If evidence of acidosis is present, lactate should be trended every 8 to 12 hrs. If NICU staff thinks the patient is higher risk from excessive blood draws, this should be discussed as a team and appropriate lab draw schedule determined based on risk/benefit.
6. If patients are a low-risk candidate for NIRS (per Braden QD score) abdominal and brain NIRS should be trended for one week. Longer for high-risk patients until cleared by cardiology.
    a. Normal renal tissue oxygenation values in preterm infants have not been fully established but a down trending value could provide evidence of decreased renal perfusion in high-risk patients.
    b. Harer provided theorical normal values of renal tissue oxygenation in preterm infants during the first 21 days of life[44]. Figure 2

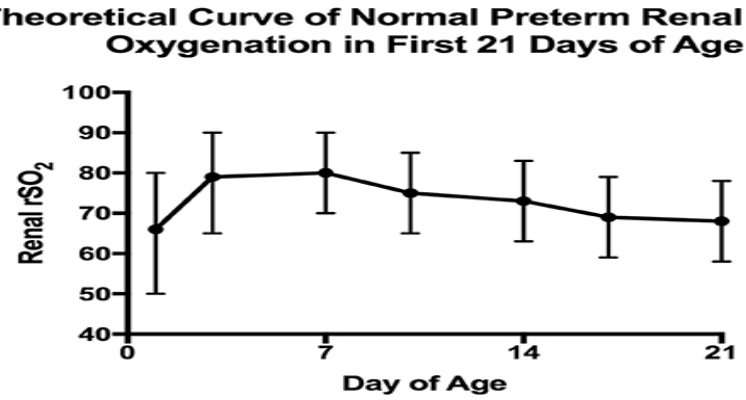


Figure 2. Renal Tissue Oxygenation in Preterm Infants (modified from Harer et al.)

If there are any clinical concerns by the NICU team that may be related to the Piccolo closure, cardiology should be contacted **immediately** for discussion and potential urgent echocardiogram.

Surgical Ligation

Surgical ligation of the PDA is rarely performed. It has been previously associated with adverse neonatal and neurodevelopmental outcomes[45-46]. A secondary analysis from the TIPP trial demonstrated an increased risk for retinopathy of prematurity (ROP) and BPD among infants treated with surgical ligation[46].

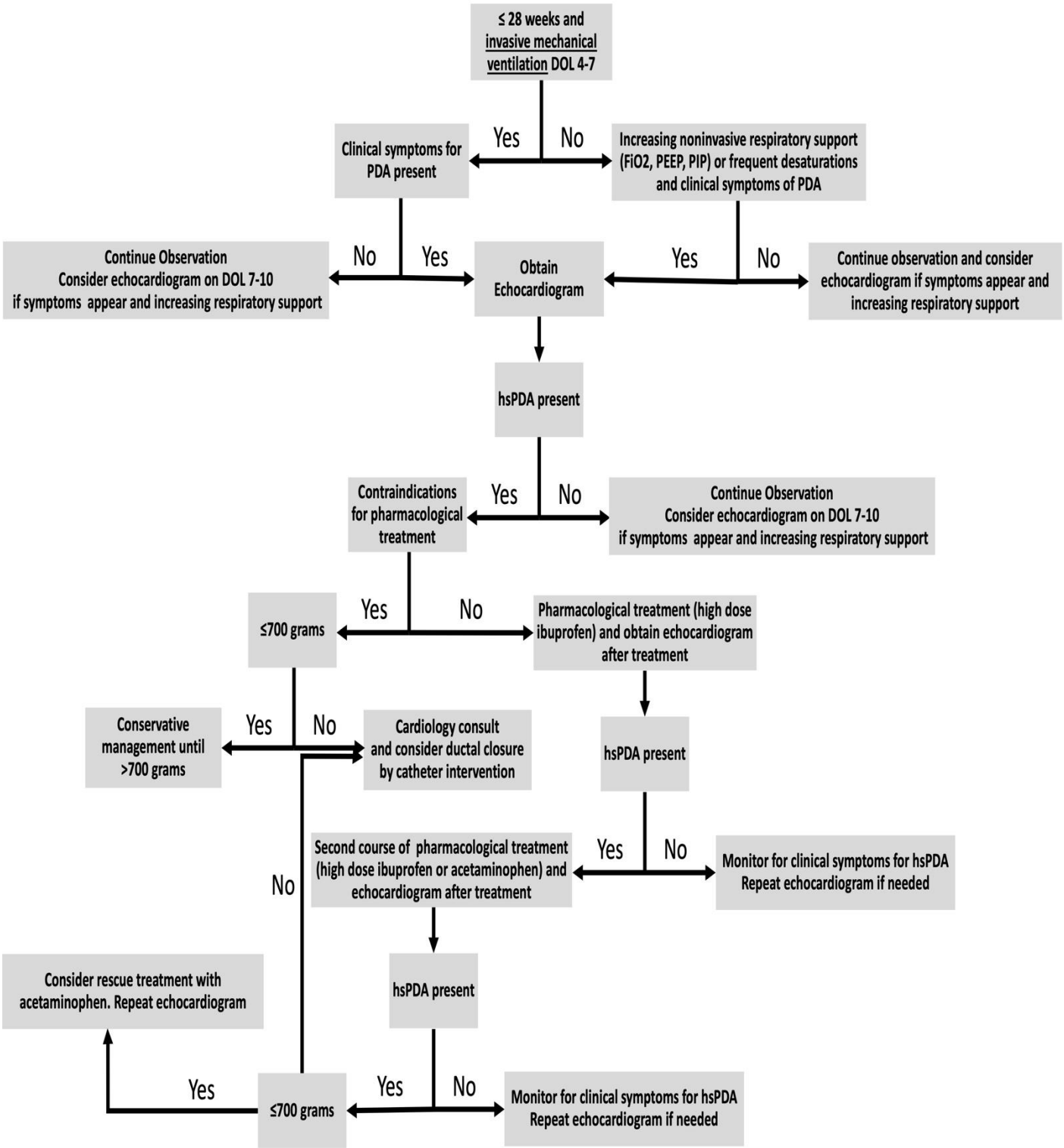
Surgical ligation may be reserved for infants with large PDAs who have failed medical therapy and remain on maximal ventilator support. Maximal ventilator support is defined as positive inspiratory pressure >25 mmHg and/or fractional inspired oxygen (FiO_2) >70 percent. More recently, therapy with closure of a PDA utilizing cardiac catheterization has become possible and safe for small neonates and should also be considered. Ogando et al. demonstrated that ductal closure (either percutaneous and surgical) resulted in improved respiratory status. However, the percutaneous group achieved faster respiratory improvement, while the surgical closure group had higher associated morbidity among survivors[47].

Summary

A. Despite the short- and long-term complications associated with both an untreated PDA and the treatments of a PDA, there are not published, universally accepted national guidelines for the management of a PDA in patients less than 28 weeks gestational age.
B. Treatment, whether expectant, pharmacological, or interventional, should be based on the age, weight, clinical findings, and echo findings.
C. Having a consistent approach to evaluation and treatment of a PDA will lead to staff satisfaction, parent satisfaction, and improved outcomes.
D. Post percutaneous PDA closure management will pro-actively assess for potential complications after transcatheter closure of the arterial duct in ELBW babies.

Diagnosis and Management of Patent Ductus Arteriosus in Preterm Neonates Algorithm / Pathway

Figure 3 PDA Management Algorithm



Glossary

BPD: bronchopulmonary dysplasia
BW: birth weight
DA: ductus arteriosus
DOL: day of life
ELBW: extremely low birth weight
GA: gestational age
hs: hemodynamically significant
LA: left atrium
LV: left ventricle
NEC: necrotizing enterocolitis
PA: pulmonary artery
PDA: patent ductus arteriosus

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Outcome Measures

- PDA incidence
- Medical treatment of PDA
- PDA treatment by catheter intervention and complications

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