Patent Ductus Arteriosus of the Preterm Infant

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Postnatal ductal closure is stimulated by rising oxygen tension and withdrawal of vasodilatory mediators (prostaglandins, nitric oxide, adenosine) and by vasoconstrictors (endothelin-1, catecholamines, contractile prostanoids), ion channels, calcium flux, platelets, morphologic maturity, and a favorable genetic predisposition. A persistently patent ductus arteriosus (PDA) in preterm infants can have clinical consequences. Decreasing pulmonary vascular resistance, especially in extremely low gestational age newborns, increases left-to-right shunting through the ductus and increases pulmonary blood flow further, leading to interstitial pulmonary edema and volume load to the left heart. Potential consequences of left-to-right shunting via a hemodynamically significant patent ductus arteriosus (hsPDA) include increased risk for prolonged ventilation, bronchopulmonary dysplasia, necrotizing enterocolitis or focal intestinal perforation, intraventricular hemorrhage, and death. In the last decade, there has been a trend toward less aggressive treatment of PDA in preterm infants. However, there is a subgroup of infants who will likely benefit from intervention, be it pharmacologic, interventional, or surgical: (1) prophylactic intravenous indomethacin in highly selected extremely low gestational age newborns with PDA (<26 + 0/7 weeks' gestation, <750 g birth weight), (2) early targeted therapy of PDA in selected preterm infants at particular high risk for PDA-associated complications, and (3) PDA ligation, catheter intervention, or oral paracetamol may be considered as rescue options for hsPDA closure. The impact of catheter-based closure of hsPDA on clinical outcomes should be determined in future prospective studies. Finally, we provide a novel treatment algorithm for PDA in preterm infants that integrates the several treatment modalities in a staged approach.

The fetal ductus arteriosus (DA) diverts cardiac output away from the lungs toward the placenta to support systemic oxygenation. After delivery, circulatory adaptation depends on DA closure within the first days of life. In preterm infants, DA closure frequently fails to occur because of immature structures and responses to constrictive mechanisms. A persistently patent ductus arteriosus (PDA) can have clinical consequences depending on the degree of left-to-right shunting

and ductal steal. The increase in pulmonary blood flow in the setting of prematurity can lead to pulmonary edema, respiratory deterioration, and diminished gastrointestinal, renal, and cerebral blood flow.¹ The incidence of PDA (ie, an open DA beyond the first 3 postnatal days) exceeds 50% in preterm infants ≤ 28 weeks' gestational age.² Although spontaneous closure rates in these infants are high, historical practice has led to medical or surgical therapy in 60% to 70% of preterm

abstract

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infants <28 weeks' gestational age.³ However, because of high spontaneous DA closure rates in these infants, there has been a shift toward less frequent and invasive treatment in the last decade (watchful waiting without intervention).⁴ Nevertheless, the mid- and long-term consequences of prolonged ductal patency are still unclear.⁵⁻¹⁰

BIOLOGICAL BASIS OF PDA

Embryology of DA and Genetic Syndromes Associated With PDA

During embryogenesis, paired pharyngeal arch arteries (PAAs) form and connect the heart and dorsal aorta. The DA develops from the distal portion of the left sixth PAA, which is ultimately composed of endothelium derived from the second heart field and smooth muscle derived from neural crest progenitor cells.¹¹ Abnormal PAA development can cause a variety of congenital heart defects, including PDA.

Although PDA is generally considered a sporadic defect impacted by extrinsic factors, genetic studies have identified syndromes that frequently manifest PDA (Table 1).¹² Still, only 10% of PDA cases are associated with chromosomal abnormalities.¹³ Therefore, single-nucleotide polymorphisms associated with nonsyndromic PDA may be more informative regarding genetic regulation of the more common sporadic cases of PDA^{14,15} (Table 1).

Mechanisms Underlying Postnatal Closure of the DA

The fetal DA has intrinsic tone and requires dilating factors (nitric oxide, prostaglandin E₂, adenosine, atrial natriuretic peptide, carbon monoxide, and potassium channels) to maintain its patency.¹⁶ At birth, DA closure occurs by (1) functional constriction and (2) anatomic remodeling resulting in formation of the ligamentum arteriosum. Initial DA constriction occurs as pulmonary

vascular resistance (PVR) falls, systemic vascular resistance increases, circulating prostaglandin E (PGE) levels decline, and respiration is initiated, triggering a sharp increase in arterial oxygen tension. Complete closure is achieved by a combination of physiologic, molecular, and structural factors (Fig 1A).^{1,17-21}

Mechanisms Underlying Persistent Patency of the DA in Preterm Infants

Spontaneous PDA closure occurs less frequently in preterm infants at <28 weeks' gestation. The time it takes to achieve closure is inversely proportional to gestational age at birth, with some vessels requiring months to years to close.²² PDA in preterm infants is considered the result of generalized immaturity of the smooth muscle and biochemical oxygen sensing mechanisms (Fig 1B). Indeed, the preterm ductus is transcriptionally distinct from term vessels.²³⁻²⁵

The preterm DA is also structurally different from mature vessels. The absence or rudimentary formation of intimal cushions in the preterm DA is associated with failure to close.¹³ Similarly, preterm vessels have fewer layers of contractile smooth muscle cells and lack vasa vasorum.²⁶ This can result in partial postnatal constriction without the ischemia-driven remodeling critical for permanent closure.

Preterm DAs are also subjected to extrinsic factors that make vessel closure more difficult (Fig 1B). Echocardiographic studies reveal that preterm DAs exposed to sustained bidirectional, right-to-left, or low-velocity blood flow were more likely to remain patent and were resistant to pharmacologic therapy,^{27,28} thus highlighting the role of hemodynamic forces and PVR in modulating DA tone. In addition, studies on the role of platelets have yielded conflicting results. In some, an association between low platelet number and

delayed spontaneous or pharmacologic PDA closure was identified in very preterm infants²⁹⁻³²; however, platelet transfusions failed to accelerate PDA closure in thrombocytopenic premature infants.³³ In other studies, it was argued that platelet function, not number, was the key regulator of preterm PDA status.^{34,35}

CLINICAL CONSEQUENCES OF HEMODYNAMICALLY SIGNIFICANT PATENT DUCTUS ARTERIOSUS

Multiorgan Comorbidities Associated With Patency of the DA

A left-to-right ductal shunt causes increased pulmonary blood flow and ductal steal from the systemic circulation and thus can have adverse effects on premature infants,¹ although a causal relationship is not well defined.³⁶

Pulmonary Sequelae and Chronic Lung Disease

The pathologic effects of excess left-to-right ductal shunting, namely increased lung fluid, decreased pulmonary compliance, and impaired oxygenation, is associated with increased need for respiratory support and mechanical ventilation, contributing to lung injury.³⁷

PDA poses the risk for hemorrhagic pulmonary edema due to pulmonary overcirculation, redistribution of hydraulic pressures to downstream capillary filtration sites, left-sided cardiac dysfunction, and consecutive postcapillary (venous) pulmonary hypertension.³⁷ 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. In a large hemodynamically significant patent ductus arteriosus (hsPDA) with unrestricted pulmonary artery (PA) flow, PA pressure is elevated to at least a systemic level, increasing

TABLE 1 Genetic Factors Associated With PDA

Human Syndromes (Gene)	Nonsyndromic SNPs (Accession Number)
22q11.2 deletion Char (<i>TFAP2B</i>) Cantu (<i>ABCC9</i> , <i>KCNJ8</i>) Noonan (<i>PTPN11</i>) Mowat-Wilson (<i>SMADIP1</i>) DiGeorge (<i>TBX1</i>) Holt-Oram (<i>TBX5</i>) Loeys-Dietz (<i>TGFBR1</i> and <i>TGFBR2</i>) Rubinstein-Taybi (<i>CREBP</i>) Periventricular heterotopia (<i>FLNA</i>)	Increased Risk of PDA <i>TFAP2B</i> (rs987237) <i>TRAF1</i> (rs1056567) <i>AGTR1</i> (rs5186) Decreased Risk of PDA <i>PTGIS</i> (rs493694, rs693649) <i>ESR1</i> (rs2234693) <i>IFN-γ</i> (rs2430561)

PDA is associated with several genetic syndromes. Several SNPs have also been associated with cases of nonsyndromic PDA. *ABCC9*, ATP binding cassette subfamily C member 9; *AGTR1*, angiotensin II receptor type 1; *CREBP*, cyclic adenosine monophosphate–response element binding protein; *ESR1*, estrogen receptor 1; *FLNA*, filamin A; *IFN-γ*, interferon-γ; *KCNJ8*, potassium inwardly rectifying channel subfamily J member 8; *PTGIS*, prostaglandin I2 synthase; *PTPN11*, protein tyrosine phosphatase nonreceptor type 11; *SMADIP1*, SMAD-interacting protein 1; SNP, single-nucleotide polymorphism; *TBX1*, T-box transcription factor 1; *TBX5*, T-box transcription factor 5; *TFAP2B*, transcription factor AP-2-β; *TGFBR1*, transforming growth factor-β receptor type 1; *TGFBR2*, transforming growth factor-β receptor type 1; *TRAF1*, tumor necrosis factor receptor associated factor 1.

flow and/or shear stress injury, endothelial cell dysfunction, and eventual pulmonary hypertension^{38,39} with increased PVR. In the acute phase of PDA exposure, the incidence of serious pulmonary hemorrhage in infants weighing <1000 g is 10%.⁴⁰ Prophylaxis with indomethacin reduced the risk for serious pulmonary hemorrhage by 35% over the first week of life; 80% of this beneficial effect was explained by reduced risk for PDA.⁴¹ Similarly, infants at <29 weeks' gestation who were selectively treated prophylactically by 6 hours of age had less pulmonary hemorrhage than controls (2% vs 21%).⁴²

Sustained PDA exposure may contribute to bronchopulmonary dysplasia (BPD).^{43–45} However, an association between PDA and BPD has not been found in other studies,^{8,22,46} suggesting the need for controlled studies. In the Patent Ductus Arteriosus: To Leave It Alone or Respond and Treat Early (PDA-TOLERATE) trial, early versus late PDA treatment was compared in a prospective multicenter randomized controlled trial (RCT). By prespecified secondary analysis, there was no difference in the development of BPD (relative risk [RR] 0.94; 95% confidence interval [CI] 0.70–1.3) or BPD or death before 36 weeks (RR 1.00; 95% CI 0.80–1.3) between the

early treatment arm and the conservative treatment arm.⁴⁷ However, among 137 infants screened for the trial, but not enrolled because of lack of physician equipoise, the combined outcome of home oxygen or death for treated infants was lower than that in the enrolled cohort.⁴⁸

The binary variable of PDA versus no PDA may not be as important as the duration of exposure. In infants at <28 weeks' gestation surviving for at least 7 days, the risk of BPD or death increased in infants after 7 days of exposure to a moderate-to-large PDA shunt (odds ratio 2.12; 95% CI 1.04–4.32).⁴⁹ For the singular outcome of BPD, exposure to a PDA was required for at least 14 days (odds ratio 4.09; 95% CI 2.22–7.22).⁴⁹

Neurologic Morbidities

Intraventricular hemorrhage (IVH), periventricular leukomalacia, and school-aged performance are important outcomes associated with prematurity. The role of PDA in these outcomes versus the effect of PDA treatments is hard to tease apart. The Trial of Indomethacin Prophylaxis in Preterms (TIPP) revealed decreased IVH rates after prophylactic indomethacin but without long-term benefit.⁴⁰ The data for prophylactic ibuprofen or paracetamol are less compelling.^{50,51} Prophylactic surgical

ligation provides no benefit in terms of IVH,⁵² and surgical ligation itself may be an independent risk factor for poor neurodevelopmental outcome.^{53,54}

PDA decreases regional cerebral oxygenation saturation and increases fractional tissue oxygen extraction in preterm infants.⁵⁵ Follow-up term-equivalent MRIs reveal decreased cerebellar volumes in infants requiring surgical ligation.⁵⁶

Infants treated with pharmacotherapy or ligation had worse neurodevelopmental outcomes at 2 to 3 years of age than infants without PDA or without treatment of PDA; however, no adjustments were made for postnatal confounders, such as necrotizing enterocolitis (NEC).⁵⁷ In one long-term study of preterm infants born in the 1980s, no difference in cognitive development or behavior was found between infants with and without a PDA at ages 3, 8, and 18 years.⁵⁸ This cohort was likely healthier and more mature than the infants at 22 to 26 weeks' gestation of today's NICUs; however, 18-year follow-up is unusual, and these findings should be considered in context.

NEC or Focal Intestinal Perforation

Diminished intestinal blood flow in the setting of a ductal shunt may predispose preterm infants to NEC or

Factors Promoting Postnatal DA Closure	Factors Promoting Preterm DA Patency
Molecular Factors	
Increased O_2 tension Decreased vasodilating prostaglandins Activation of cytochrome P450 Increased endothelin-1 levels Production of isoprostanes (8-iso-PGF 2α) Inhibition of potassium channels (K_{ATP} , Kv, BK_{Ca}) Activation of transient receptor potential channels Decrease in intracellular cAMP and/or cGMP levels Angiotensin II Bradykinin Acetylcholine Norepinephrine Activation of RhoA, RhoB, Rock1, and Rock2	Hypoxia Increased nitric oxide signaling Increased prostaglandin signaling
Physiologic Factors	
Decreased pulmonary vascular resistance Increased systemic vascular resistance	Prolonged bidirectional or right-to-left blood flow Low-velocity blood flow
Structural Factors	
Mature contractile smooth muscle cells Prominent intimal cushions Vasa vasorum Zone of ischemia and/or necrosis Platelet adherence to lumen	Thin layer or immature smooth muscle Insufficient intimal cushion development Thrombocytopenia or platelet dysfunction

FIGURE 1

Factors affecting postnatal DA closure and preterm PDA. A and B, Postnatal DA closure (A) and preterm DA patency (B) are regulated by a combination of molecular, physiologic, and structural factors. Of note, several studies have identified distinct variants in *CYP2C9*2* that are associated with failure of PDA closure in response to indomethacin.^{14,15} cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; O_2 , oxygen.

focal intestinal perforation (FIP). An RCT from 1989 revealed decreased NEC risk in infants undergoing prophylactic surgical ligation (8% vs 30%)⁵²; however, most RCTs on prophylactic pharmacotherapy have revealed no difference in NEC rates.^{50,51}

Simultaneous exposure to corticosteroids and indomethacin is a known risk for intestinal injury. However, indomethacin for IVH prophylaxis after antenatal steroid exposure was not associated with FIP in extremely low gestational age newborns (ELGANs), although

indomethacin for treatment of symptomatic PDA was.⁵⁹ Although there are few data on feeding practices in the presence of PDA, early feeding during indomethacin treatment may improve the time to reach full feedings,⁶⁰ may preserve postprandial mesenteric perfusion,⁶¹

and is not associated with increased risk of NEC or FIP.^{60–62}

TREATMENT OF PDA IN THE PRETERM INFANT

When Is a PDA Hemodynamically Significant?

There is no consensus on clinical or sonographic criteria that define the need for PDA closure. The determinants of risk for hsPDA we propose are shown in Fig 2. The gold standard for diagnosing a PDA and for assessing its hemodynamic significance is transthoracic echocardiography^{63,64}; it not only allows for visualization of the ductus and determination of its size but also identifies shunt direction, systolic-diastolic pattern and velocity, and ventricular and atrial volumes and function. A ductal diameter ≥ 1.5 mm during the first hours of life is predictive of development of a symptomatic DA in infants ≤ 28 weeks' gestational age^{65,66}; this finding provides a rationale to consider early targeted treatment in selected infants.^{42,67} Several other echocardiographic variables have been used to assess the significance of a PDA: an LA-to-aortic root ratio ≥ 1.4 , LV enlargement, increased mean and diastolic PA flow velocities, and a reversed mitral E/A ratio (echocardiographical PW-Doppler variable of early versus late filling as surrogate for diastolic LV function) are reported indicators for pulmonary overcirculation (high Qp/Qs [ratio of pulmonary/systemic blood flow]) and subsequent increased left heart volume load⁶⁴; however, these measurements depend on preload and have interobserver variability. In addition, retrograde diastolic flow in the descending aorta and low-antegrade or retrograde diastolic flow in systemic arteries (eg, anterior cerebral artery and renal and mesenteric arteries) indicate systemic hypoperfusion and ductal steal

(Fig 2). Additional echocardiographic markers that indicate an hsPDA shunt are reviewed elsewhere.⁶⁸ The diagnosis of hsPDA should be based on a combination of echocardiographic and clinical variables and should incorporate individual risk factors for adverse outcome, such as gestational age, chronological age, and comorbidities. Plasma and urinary biomarkers¹ and assessments of cerebral and abdominal tissue oxygenation by near-infrared spectroscopy might help identify patients with compromised hemodynamic status^{69,70} because the existing sonographic criteria cannot clearly define the need for PDA closure.

Pharmacologic Ductus Closure by Prostaglandin Inhibition: Cyclooxygenase Inhibitors (Indomethacin and Ibuprofen) and Paracetamol (Acetaminophen)

Intravenous indomethacin has been the therapeutic mainstay since pharmacotherapy for PDA was introduced to clinical practice. Over the past decade, there has been substantial interest in new regimens and pharmaceutical choices for PDA closure. RCTs from the 1980s were focused on prophylactic, early (< 24 hours), or symptomatic treatment, typically between 2 and 6 days after birth.¹ In additional studies, third and fourth treatment categories are now considered: asymptomatic infants < 72 hours after birth^{42,64} or late symptomatic treatment after watchful waiting.⁷¹ New formulations, such as oral and intravenous ibuprofen and oral and intravenous paracetamol, broaden but also complicate the landscape once dominated by indomethacin (Table 2). Additionally, use of cyclooxygenase (COX) inhibitors is declining in favor of watchful waiting.^{4,72}

Indomethacin and Ibuprofen

Pharmaceutical strategies generally are focused on inhibiting prostaglandin synthesis. COX

inhibitors, such as indomethacin or ibuprofen, are the mainstays of treatment. Although paracetamol, which is thought to act at the peroxidation site of COX, has gained attention over the past decade,⁵¹ it appears less effective than indomethacin or ibuprofen in extreme prematurity.^{73,74} COX inhibitors are less effective in severely preterm infants, likely because of maturational factors in response to prostaglandin inhibition and prevention of intimal cushion formation.¹

Ibuprofen has less detrimental effects on end-organ perfusion than indomethacin.^{1,75} A recent meta-analysis of 9 trials, comparing prophylactic ibuprofen (oral or intravenous) with a placebo or no treatment, revealed that ibuprofen decreases the risk of PDA on day 3 to 4 of life when it is given at < 24 hours of life (RR 0.39; 95% CI 0.31–0.48).⁵¹ Prophylactic ibuprofen also decreased the need for rescue treatment and surgical ligation (RR 0.17 [95% CI 0.11–0.26] and RR 0.46 [95% CI 0.22–0.96], respectively). Despite a trend toward diminished grade 3 or 4 IVH risk and a clearer risk for increased oliguria, compared with a placebo or no treatment, no difference was noted for mortality, any IVH, or chronic lung disease (CLD) with prophylactic ibuprofen.⁵¹

As a treatment strategy for symptomatic PDA, 3 doses of intravenous ibuprofen were compared with a placebo (2 studies) in a 2018 Cochrane review, and a superior rate of closure was found with ibuprofen (RR 0.62; 95% CI 0.44–0.86).⁷⁶ On the basis of 24 studies, ibuprofen in either an oral or intravenous route appears to be as effective as indomethacin, with an improved safety profile (reduced ventilator days and oliguria). Oral ibuprofen is preferable to indomethacin in terms of risk for NEC (RR 0.41; 95% CI 0.23–0.73).⁷⁶

Lower Risk	Determinants of Risk (hsPDA)	Higher Risk
No	Tachycardia	Yes
No	Tachypnea	Yes
No need for respiratory support or oxygen, stable SpO ₂ and Pao ₂	Respiratory support	Need for invasive or noninvasive respiratory support Worsening respiratory situation (eg, increasing flow and Fio ₂ on HFNC; increasing PEEP, PIP, and Fio ₂ on CPAP; NIV; MV) and frequent desaturations
Abdomen soft, not distended	Abdominal signs and symptoms	Abdominal distension, residual feeding volume (other pre-NEC signs)
Not present	Signs of organ dysfunction	Renal failure, NEC, impaired NIRS variables
<ul style="list-style-type: none"> • LA only mildly dilated LA/Ao ≤ 1.2 (PLAX) • Normal LV size • Normal systolic LV function (LVEF ≥ 55%) • Ductal diameter ≤ 1 mm (at narrowest ID) • PDA Vmax ≥ 3 m/s (CW Doppler) • Ductal systolic and diastolic left-to-right flow ≥ 2 m/s (continuous) usually indicates narrowing (closing) PDA • Normal mean and diastolic PA flow • ACA RI ≤ 0.75 • No (or only early) diastolic retrograde DAO flow 	Echocardiography, Doppler sonography (cerebral, abdominal)	<ul style="list-style-type: none"> • Severe LA dilation LA/Ao ≥ 1.4 (PLAX) • Severe LV dilation (4C view, PSAX) • Systolic LV dysfunction (LVEF < 50%) • Ductal diameter ≥ 2 to 3 mm (at narrowest ID) or ductal diameter greater than or equal to MPA diameter • PDA Vmax ≤ 2 m/s (CW, unrestrictive) • Ductal left-to-right diastolic flow ≥ 0.5 m/s • Highly elevated mean + diastolic PA flow • Severe PA dilation (eg, LPA > AAO) • ACA RI ≥ 0.9 • Holodiastolic retrograde DAO flow (steal)

FIGURE 2

Determinants of risk for preterm infants with an hsPDA. AAO, ascending aorta; ACA, anterior cerebral artery; CPAP, continuous positive airway pressure; CW, continuous wave; DAO, descending aorta; Fio₂, fraction of inspired oxygen; HFNC, high-flow nasal cannula; ID, inner diameter; LA/Ao, left atrium to aortic root diameter ratio; LPA, left pulmonary artery; LVEF, left ventricular ejection fraction; MPA, mean pulmonary artery; MV, mechanical ventilation; NIRS, near-infrared spectroscopy; NIV, noninvasive ventilation; PEEP, positive end-expiratory pressure; PIP, positive inspiratory pressure; PLAX, parasternal short axis; PSAX, parasternal short axis; RI, resistance index; SpO₂, pulse oxygen saturation; Vmax, maximum velocity.

In terms of efficacy of hsPDA closure, a 2018 network meta-analysis favored high-dose oral ibuprofen over other agents.³² However, a comparative effectiveness study of indomethacin, ibuprofen, and paracetamol in infants at <28 weeks' gestation favored indomethacin in this regard⁷³; rectal ibuprofen may also be effective.⁷⁷ Newer strategies to disrupt prostaglandin signaling include combined COX inhibitor treatments^{78,79} or the potential use of compounds that could selectively inhibit PGE receptors.⁸⁰ To summarize, on the basis of meta-analyses and the original TIPP trial,⁸¹ although intravenous ibuprofen is an effective

agent for prophylactic use, intravenous indomethacin is favored because of reduction in IVH incidence. For treatment strategies (as opposed to prophylaxis), ibuprofen and indomethacin are likely equivalent (Table 2), although the safety profile of ibuprofen is superior.

Paracetamol (Acetaminophen)

Paracetamol is an attractive option in cases in which COX inhibitors are contraindicated or ineffective. A recent systematic review of studies comparing oral paracetamol with intravenous ibuprofen (559 infants), intravenous indomethacin (277 infants), and a placebo (80 infants)

identified moderate-quality evidence suggesting that paracetamol is as effective as ibuprofen, with less gastrointestinal bleeding and lower serum creatinine levels.⁵⁰ In contrast, the initial constriction rate was only 27% with paracetamol, that is, lower than with either indomethacin and ibuprofen⁷³; of note, this trial (PDA-TOLERATE) was conducted in infants with an average gestation of 26 weeks, unlike more mature infants studied in recent meta-analyses.⁷³ Moreover, a randomized trial on the efficiency of treatment of hsPDA by using either intravenous paracetamol or intravenous indomethacin in 37 very low birth weight (VLBW) infants (<32 weeks' gestation, ≤1500 g, first

TABLE 2 Current Pharmacologic Treatment Strategies for PDA in the Preterm Infant

	Drug(s) of Choice	Dosing	Comments	Pros	Cons
Targeted prophylaxis in at-risk infants (6–24 h after birth)	Indomethacin ^a	3 × 0.1 mg/kg per dose IV every 12 h ^b (single-dose prophylaxis may be considered)	Do not start treatment within the first 6 h of life. It is recommended not to use ibuprofen (IV) in the first 24 h of life (increased risks for renal failure, gastrointestinal hemorrhage, and possibly PPHN)	Prevention of IVH (prophylaxis); risk reduction of pulmonary hemorrhage; association with beneficial neurodevelopmental outcome in boys	Unnecessary treatment of many infants without an hsPDA
Early targeted treatment of infants with PDA (<6 d after birth)	Indomethacin ^a	1 × 0.2 mg/kg per dose IV, followed by 2 × 0.1 mg/kg per dose every 12 h ^b	It is recommended not to use ibuprofen (IV) in the first 24 h of life (increased risks for renal failure, gastrointestinal hemorrhage, and possibly PPHN).	Risk reduction of pulmonary hemorrhage; possible risk reduction of in-hospital mortality	Unnecessary treatment of some infants who have a small PDA that is hemodynamically not significant; unclear effects on outcome
	Ibuprofen ^c	10 mg/kg per dose PO or IV, followed by 5 mg/kg at 24 and 48 h of treatment start	—	—	—
Treatment in symptomatic infants with hsPDA (≥6 d after birth)	Ibuprofen ^c	10 mg/kg per dose PO or IV, followed by 5 mg/kg at 24 and 48 h of treatment start	Higher doses might be considered.	Treatment only in infants with hsPDA	No evidence for beneficial long-term outcome if administered late (>6–14 d); might still be associated with adverse outcome (eg, BPD) due to a longer duration of a significant shunt
Rescue treatment	Paracetamol	15 mg/kg per dose PO or IV every 6 h for 3–7 d	Might be attempted in selected infants after failed standard COX inhibitor treatment; can also be applied earlier if contraindications for standard COX inhibitor use are present	Might prevent the use of more invasive measures, such as ligation or catheter intervention; no known renal or gastrointestinal side effects	Unclear effect on neurodevelopmental outcome

IV, intravenously; PO, per os (orally); PPHN, persistent pulmonary hypertension of the neonate; —, not applicable.

^a Infuse over at least 30 min.

^b Last indomethacin dose might be omitted if echocardiography suggests pressure restrictive (closing) PDA.

^c Oral ibuprofen should be followed by 2 mL/kg water or milk (hyperosmolarity).

21 postnatal days) confirmed the aforementioned findings: the primary hsPDA closure rate with intravenous paracetamol was much lower (5.9%; 1 of 17) than the success rate with intravenous indomethacin (55%; 11 of 20), so more patients treated with paracetamol underwent transcatheter PDA closure (47% vs 15%).⁸²

Timing of Pharmacologic Treatment

The TIPP trial revealed a reduction in IVH incidence with the use of indomethacin as prophylaxis but failed to confirm a benefit on a composite outcome of survival and neurodevelopment at 18 months.⁴⁰ A longer follow-up study at 3 to 8 years

revealed a modest sex effect favoring prophylactic treatment in boys.⁸³ Spontaneous closure rate varies substantially by center and is an important factor when deciding to use prophylaxis.⁴⁷ Given that prophylactic ibuprofen is less efficient in preventing grades 3 and 4 IVH, indomethacin is usually considered the drug of choice for prophylaxis in selected infants.⁵¹ Additionally, longer prophylactic indomethacin courses decreased moderate-to-severe white matter injury in a prospective brain MRI study.⁸⁴ However, given the high spontaneous closure rate, prophylaxis may only be justifiable for certain subgroups (see

below). There are insufficient data on paracetamol use for hsPDA prophylaxis and risk of IVH (a small prospective study did not reveal a benefit on severe IVH).⁸⁵ Prophylactic use of indomethacin, ibuprofen, or paracetamol has no effect on NEC,^{40,50,86} and studies on the according BPD risk had ambiguous results.

In the PDA-TOLERATE trial, researchers examined the effect of prolonged exposure to a moderate-to-large PDA shunt in infants <28 weeks' gestational age, an important distinction to previous trials because enrollment of infants who would

spontaneously close their PDA (41% of those screened) was avoided.⁴⁷

The PDA-TOLERATE trial suggests that early (<6 days) targeted pharmacologic treatment of infants <28 weeks' gestational age with a significant shunt and need for respiratory support is of benefit, but in the absence of these characteristics, conservative management is acceptable.

In an Italian retrospective multicenter study, ELGANs born at 23 to 24 weeks' gestation had the highest risk of developing hsPDA refractory to pharmacologic treatment requiring surgical closure (562 of 842 [67%]),⁷⁴ highlighting the need for individualized strategies for timely hsPDA management in this very immature population.

Catheter-Based Interventional Closure of the DA in Preterm Infants

Transcatheter device closure of the PDA has recently become more widely available. The Amplatzer Piccolo Occluder device (Amplatzer Duct Occluder II Additional Sizes, Abbott Medical Devices, Abbott Park, IL) recently received US Food and Drug Administration approval for PDA closure in premature infants weighing ≥ 700 g. In a multicenter trial of 200 patients, the Amplatzer Duct Occluder II Additional Sizes implant success rate was 95.5% (191 of 200) overall and 99% in those weighing 700 to 2000g (99 of 100; age 1.25 ± 0.60 months).⁸⁷ The effective closure rate at the 6-month follow-up echocardiogram, defined as no or trivial residual PDA shunt, was 100% in patients ≤ 2000 g and 98.8% >2000 g. Four patients experienced a primary safety end point event (2 transfusions, 1 hemolysis, and 1 aortic obstruction).⁸⁷ Additionally, 5 patients <2000 g (5%) developed new-onset moderate tricuspid regurgitation post procedure, likely related to tricuspid valve trauma during the procedure. This complication was not seen in patients

>2000 g. There were no instances of left PA obstruction at the 6-month follow-up. Vascular complications are rare because the procedure is performed by using venous access only. The device is delivered entirely inside the PDA to avoid obstruction of the left PA and/or the aortic arch. Although fluoroscopy is necessary, device position and effect on adjacent structures is primarily assessed by using intraprocedural echocardiography, reducing exposure to iodinated contrast and radiation. The procedure can be performed in the catheterization laboratory or at the bedside (by using a mobile C-arm). Although there has not been an RCT comparing device closure with surgical ligation, early experience suggests that post ligation cardiac syndrome^{88,89} may be less common and that improvement in respiratory status may be faster after device closure.⁹⁰ Although these types of catheter devices provide the health care community with a nonsurgical alternative to achieve definitive ductal closure, important questions on the optimal use of the device, such as long-term outcome, timing, and setting of the catheter intervention, need to be answered by future studies.

Surgical Ligation of the DA

The PDA ligation rate in a US cohort of infants at 23 to 30 weeks' gestation decreased from 8.4% in 2006 to 2.9% in 2015 with an accompanying shift in the age at ligation (8 days in 2006 vs 22 days in 2015).⁹¹ This trend is consistent with those of other large cohort studies.^{72,92-94} Prophylactic and early ligation approaches are no longer indicated,⁹⁵ but there remains uncertainty about when and for whom ligation has clinical benefit.

In a meta-analysis of 39 cohort studies and 1 RCT, ligation compared with medical treatment was found to be associated with increased odds of neurodevelopmental impairment, CLD, and severe retinopathy of

prematurity (ROP) but decreased odds of death.⁹⁶ Comparing pharmacotherapy plus ligation versus conservative treatment revealed a decrease in mortality with pharmacotherapy plus surgical ligation but increased odds of CLD and severe ROP.⁹⁶

As surgical ligation rates decline, clinicians must still respect the complications of this procedure, which may be present in up to 44% of infants.⁹⁷ The major complications include postligation cardiac syndrome,⁹⁸⁻¹⁰⁰ acute kidney injury,¹⁰¹ vocal cord paralysis, prolonged mechanical ventilation, and BPD.¹⁰²

Conservative Treatment of PDA

The specifics of conservative management are not well defined. The spectrum extends from PDA nontreatment^{2,103} to intentional use of fluid restriction, targeted ventilation strategies, and diuretic therapy to counteract the effects of PDA shunt while waiting for spontaneous closure.^{1,8,104} In 2 Cochrane reviews in which the comparisons were placebo or no treatment versus ibuprofen or paracetamol, there was no increase in death, duration of mechanical ventilation, or incidence of CLD, NEC, periventricular leukomalacia, or all grades of IVH in the placebo or no treatment group.^{50,51} The PDA-TOLERATE trial provides evidence that conservative management is no worse and may be more beneficial compared to active treatment⁴⁷ in select settings.

In an observational study of the natural history of hsPDA in preterm infants at <28 weeks' gestation who were managed with fluid restriction, 111 of 195 infants developed hsPDA beyond the first week of life.² No infant received pharmacotherapy or surgical ligation before discharge. There was no difference in hospital mortality or incidence of IVH, ROP, BPD, NEC, or sepsis in those with and

without a hsPDA. The duration of PDA exposure by weekly increments did not affect outcomes. Only 2 infants required device closure after hospital discharge.²

In a recent South Korean single-center, double-blind, placebo-controlled, noninferiority RCT, 146 preterm infants (23–30 weeks' gestation) diagnosed with hsPDA between postnatal days 6 and 14 were studied. In contrast to the aforementioned 2018 network meta-analysis,³² in this RCT, the authors report nonintervention to be noninferior versus oral ibuprofen treatment in closing hsPDA and reducing the rate of BPD or death, probably because of the low efficacy of oral ibuprofen, especially in the 41 of 83 total infants born at 23 to 26 weeks' gestation.¹⁰⁵

The California Perinatal Quality Care Collaborative data were recently interrogated to evaluate the effect on mortality in declining COX inhibitor usage from 2008 to 2015. Mortality improvement was slowed in the 400- to 749-g birth weight cohort in NICUs with reduced COX inhibitor use,¹⁰⁶ suggesting an overlooked treatment benefit in this group. Conversely, in infants 1000 to 1499 g, a decreasing ligation rate was associated with a reduction in BPD rates.¹⁰⁶

In summary, as for many aspects of PDA care, conservative management is likely appropriate for subgroups of preterm infants but not all.

Comprehensive Approach to Preterm Infants With PDA

Several different strategies exist to manage infants with PDA. As discussed earlier, if PDA-targeted treatment is attempted, 4 main approaches can be differentiated: (1) early targeted prophylaxis (<24 hours), (2) targeted therapy of asymptomatic infants (<6 days after birth), (3) symptomatic treatment when the PDA becomes hemodynamically relevant (≥ 6 days after birth), and (4) late symptomatic

treatment after watchful waiting or rescue treatment after previously failed treatment. In Fig 3, we present a treatment algorithm that incorporates these 4 main treatment categories into a stepwise approach; the details on drug therapy are summarized in Table 2. However, it should be noted that these recommendations are based primarily on expert opinion and only provide a framework that needs to be adapted and modified to local practices:

1. Targeted early prophylaxis of PDA (indomethacin): Because of the high risk of exposing infants to adverse drug effects without clear benefit, targeted early prophylaxis should only be attempted in units with a low rate of spontaneous closure in carefully selected infants (eg, infants <26 weeks' gestation, <750 g). Indomethacin is usually considered the agent of choice for prophylactic treatment⁴² (Table 2). Paracetamol may have fewer side effects than indomethacin or ibuprofen, but there is insufficient evidence on neurodevelopmental implications to recommend it for prophylaxis.
2. Early targeted treatment of PDA: Pharmacologic treatment is recommended at <6 days for infants <28 weeks' gestational age with a moderate-to-large hemodynamically significant shunt (Fig 2) and greater than minimal respiratory support (eg, >2 L nasal cannula flow, >0.25 fraction of inspired oxygen). This recommendation implies echocardiographic screening of all infants <28 weeks' gestational age who are on any respiratory support before 6 days of postnatal life. In the absence of significant respiratory support (asymptomatic infants) or a moderate-to-large hemodynamically significant

shunt (small PDA), a conservative approach may be justified.

3. Treatment of symptomatic infants with hsPDA: All VLBW infants ≥ 6 days of age with greater than minimal respiratory support should be echocardiographically screened for PDA. In the presence of a moderate-to-large hsPDA and additional risk factors, such as failure of ventilator weaning and fraction of inspired oxygen > 0.25 (Fig 2), treatment may be considered (Table 2, Fig 3), although positive effects on long-term outcome have not been established. Ibuprofen is usually considered as the first drug of choice (favorable safety profile versus indomethacin).
4. Late and rescue treatment of symptomatic infants with PDA: For infants with a moderate-to-large PDA shunt and more than minimal respiratory support, there are no RCTs evaluating pharmacologic closure versus catheter-based closure versus surgical ligation. Common sense would suggest a trial of pharmacologic closure first. After failed COX inhibitor treatment, rescue use of paracetamol might be attempted, although the success rate may be low.^{107,108} Recommendations for either catheter-based closure or surgical ligation post discharge vary among tertiary institutions and depend on the local experience (Table 2).

Discharge of the Preterm Infant With PDA

The majority of infants discharged with a PDA will still experience closure by 1 year of age; current best evidence suggests that it is safe to leave a small PDA untreated at discharge but with appropriate follow-up.^{5–7} There is a need for prospective research on rates of spontaneous postdischarge closure rates of infants with and without cardiorespiratory sequelae (BPD and

FIGURE 3

Treatment algorithm of PDA in the preterm infant. The proposed treatment algorithm incorporates the following 4 main treatment categories into a stepwise approach: (1) early targeted prophylaxis, (2) targeted therapy of asymptomatic infants (<6 days after birth), (3) symptomatic treatment of hsPDA (≥6 days after birth), and (4) late symptomatic treatment after watchful waiting or rescue treatment (for details, see main text). The details on drug therapy are summarized in Table 2. Of note, these recommendations are mostly based on expert opinion and only provide a framework that needs to be adopted and modified to local practices. For example, given the wide variance in spontaneous constriction (8%–78% in screened PDA-TOLERATE infants <28 weeks' GA in first week of life), it is first important to know your unit's spontaneous closure rate. There may be unrecognized factors (eg, genetics, altitude, echo interpretation, fluid, or respiratory management) that determine unit variability. In addition, the optimal indication and timing of catheter-based interventions (especially in comparison to surgical ligation) have not yet been clearly defined, and thus there is a large variability of its use among different neonatal units. ^a Some units attempt for early catheter intervention (eg, after the first failed pharmacologic treatment cycle). ELBW, extremely low birth weight (<1000 g); FiO₂, fraction of inspired oxygen; GA, gestational age.

pulmonary hypertension) of prematurity (Table 3).⁷

CONCLUSIONS

In the last decade, there has been a trend for less aggressive treatment of PDA in preterm infants. However, a subgroup of infants will likely benefit from intervention, be it pharmacologic, interventional, or surgical: (1) prophylactic intravenous indomethacin in highly selected ELGANS with PDA (<26 + 0/7 weeks' gestation, <750 g birth

weight; NICUs with low spontaneous closure rate); (2) early targeted therapy of PDA in selected preterm infants at particular high risk for PDA-associated complications; and (3) PDA ligation, catheter intervention, or oral paracetamol may be considered as rescue options for hsPDA closure. The impact of catheter-based interventional closure of hsPDA on clinical outcomes should be determined in prospective studies. We provide a novel treatment algorithm for PDA in preterm infants that integrates several treatment

modalities in a staged approach. Our approach is somewhat limited by the lack of sufficient clinical trial data in all areas of PDA closure (expert opinion only) but is still useful for clinical guidance and for opening a debate. The recommendations of hsPDA management in the preterm infant made in this article may be adapted to local practices, and this in turn may help inform future recommendations. Comparative validation studies on the different treatment options in clearly defined at-risk populations are required.

TABLE 3 Areas of Uncertainty and Future Research Directions

Areas of Uncertainty and Future Research Directions
Molecular and cellular mechanisms during initial and permanent DA closure and pathologic DA reopening (eg, during sepsis)
Further refinement of standardized protocols for the diagnosis of PDA and grading of its hemodynamic significance
Identification of high-risk infants who still require PDA-targeted therapy
Relationship between duration of significant DA patency and outcome (eg, BPD, neurodevelopment)
Impact of shunt magnitude and duration on the developing pulmonary vasculature
Association between hsPDA (and its treatment) and long-term outcome
Pharmacologic data on paracetamol in preterm newborn infants with PDA (pharmacokinetics, safety and efficacy as compared with ibuprofen and/or indomethacin), including combination therapy
Development of new pharmacologic approaches, such as PGE receptor blockers
Impact of individual risk assessment by biomarker and pharmacogenetics approaches
Further data on safety and benefits of fluoroscopy or echo-guided catheter interventions in comparison with surgical treatment of hsPDA

ABBREVIATIONS

BPD: bronchopulmonary dysplasia

CI: confidence interval

CLD: chronic lung disease

COX: cyclooxygenase

DA: ductus arteriosus

ELGAN: extremely low gestational age newborn

FIP: focal intestinal perforation

hsPDA: hemodynamically significant patent ductus arteriosus

IVH: intraventricular hemorrhage

LA: left atrium

LV: left ventricle

NEC: necrotizing enterocolitis

PA: pulmonary artery

PAA: pharyngeal arch artery

PDA: patent ductus arteriosus

PDA-TOLERATE: Patent Ductus Arteriosus: To Leave It Alone or Respond and Treat Early

PGE: prostaglandin E

PVR: pulmonary vascular resistance

RCT: randomized controlled trial

ROP: retinopathy of prematurity

RR: relative risk

TIPP: Trial of Indomethacin Prophylaxis in Preterms

VLBW: very low birth weight

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