



# Patent Ductus Arteriosus in Preterm Infants

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Despite a large body of basic science and clinical research and clinical experience with thousands of infants over nearly 6 decades,<sup>1</sup> there is still uncertainty and controversy about the significance, evaluation, and management of patent ductus arteriosus in preterm infants, resulting in substantial heterogeneity in clinical practice. The purpose of this clinical report is to summarize the evidence available to guide evaluation and treatment of preterm infants with prolonged ductal patency in the first few weeks after birth.

## abstract

### CLINICAL EPIDEMIOLOGY AND NATURAL HISTORY OF PATENT DUCTUS ARTERIOSUS

In term infants, the ductus arteriosus normally constricts after birth and becomes functionally closed by 72 hours of age.<sup>2</sup> In preterm infants, however, closure is delayed, remaining open at 4 days of age in approximately 10% of infants born at 30 through 37 weeks' gestation, 80% of those born at 25 through 28 weeks' gestation, and 90% of those born at 24 weeks' gestation.<sup>3</sup> By day 7 after birth, those rates decline to approximately 2%, 65%, and 87%, respectively. The ductus is likely to close without treatment in infants born at >28 weeks' gestation (73%),<sup>4</sup> in those with birth weight >1000 g (94%),<sup>5</sup> and in infants born at 26 through 29 weeks' gestation who do not have respiratory distress syndrome (93%).<sup>6</sup> Rates of later spontaneous ductal closure among smaller, less mature infants with respiratory distress syndrome are not known because of widespread use of treatments to achieve closure of the patent ductus arteriosus (PDA) in such infants. Data from placebo arms of controlled trials demonstrate that spontaneous ductal closure in these infants is frequent, however. In the Trial of Indomethacin Prophylaxis in Preterms, for example, which included infants with birth weight from 500 to 999 g, 50% of placebo recipients never developed clinical signs of a PDA.<sup>7</sup> In a trial of early versus late indomethacin treatment of infants born at 26 through 31 weeks' gestation in whom PDA was confirmed by echocardiography on day 3, the ductus closed spontaneously by 9 days of age in 78% of those randomized to late intervention.<sup>8</sup>

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While the ductus remains open, blood typically flows left-to-right from the aorta into the pulmonary arteries. As pulmonary vascular resistance declines over the first several days after birth, the proportion of aortic blood flow that is diverted into the pulmonary circulation correspondingly increases. This “ductal steal” results in excessive blood flow through the lungs, predisposing to development of pulmonary congestion, pulmonary edema, and worsening respiratory failure. Diversion of blood flow from the systemic circulation may exceed capabilities for compensatory increases in total cardiac output, resulting in compromised perfusion of vital organs, including bowel, kidney, and brain. Prolonged patency is associated with numerous adverse outcomes, including prolongation of assisted ventilation and higher rates of death, bronchopulmonary dysplasia (BPD), pulmonary hemorrhage, necrotizing enterocolitis, impaired renal function, intraventricular hemorrhage (IVH), periventricular leukomalacia, and cerebral palsy.<sup>9</sup> The extent to which these adverse outcomes are attributable to the hemodynamic consequences of ductal patency, if at all, has not been established. The strength of these associations led to the hypothesis that intervention to close the ductus might prevent or reduce the severity of these common complications of prematurity. The expectation that this hypothesis would be confirmed, in turn, resulted in widespread adoption of interventions designed to achieve early closure of the ductus in preterm infants.

### **ASSESSMENT OF HEMODYNAMIC SIGNIFICANCE**

The hemodynamic effects of a large left-to-right shunt associated with a PDA may be evident by physical examination, echocardiography, or measurement of serum biomarkers.

In addition to the presence of a classic coarse systolic murmur at the left sternal border, affected infants may have an increased precordial impulse, prominent or bounding arterial pulses, palpable pulses in the palms of the hands, and either low systolic and diastolic blood pressure or low diastolic blood pressure with a widened pulse pressure. Nevertheless, these findings are nonspecific, do not correlate well with echocardiographic findings,<sup>10</sup> and have not been shown to reliably predict responses to treatment or sequelae. In many instances, the presence of a large ductal shunt is suspected only on the basis of respiratory findings, such as radiographic signs of pulmonary congestion, increasing requirements for supplemental oxygen, or inability to reduce mechanical ventilator support. The presence of a PDA is most definitively demonstrated by color Doppler echocardiography, which permits confirmation of ductal patency, measurement of ductal dimensions, and assessment of the direction and velocity of ductal blood flow throughout the cardiac cycle. Substantial ductal shunting may be associated with an increased ratio of left atrial to aortic root dimensions  $\geq 1.5:1$ , ductal diameter  $\geq 1.5$  mm, left ventricular volume and pressure loading, and reversal of diastolic flow in the descending aorta or in cerebral or renal arteries.<sup>11,12</sup> Serum concentrations of natriuretic peptides (BNP or N-terminal of the prohormone BNP) are elevated in preterm infants with PDA,<sup>13,14</sup> correlate with echocardiographic measures of shunt volume,<sup>14-16</sup> and decrease after ductal closure.<sup>14,16</sup> Concentrations of troponin T at 48 hours of age are higher in infants with PDA.<sup>17</sup>

The term “hemodynamically significant” is frequently used to differentiate consequential from inconsequential PDA. Neither the best tool nor the optimal thresholds

for identification of infants at greatest risk for adverse sequelae have been delineated. The predictive values of individual echocardiographic measurements are low, but some progress has been made toward correlation of composite scores with risks of adverse long-term outcome, including BPD<sup>18</sup> or neurodevelopmental outcome at 2 years of age.<sup>12</sup> Exploratory studies suggest that elevated concentrations of either N-terminal of the prohormone BNP or troponin T at 48 hours of age may help predict death or severe IVH<sup>19</sup> as well as neurodevelopment at 2 years of age.<sup>12</sup> The presence of a “hemodynamically significant” PDA has been correlated with lower regional cerebral oxygen saturation and higher fractional oxygen extraction<sup>20</sup> and with reduced celiac artery flow,<sup>21</sup> supporting the hypothesis that prolonged ductal patency may have a causal role in substantial and enduring adverse outcomes. Development of an integrated definition of “hemodynamic significance” of PDA will be essential to risk stratification for clinical trials of PDA treatment, but this goal remains elusive.

### **EVIDENCE FOR BENEFITS OF TREATMENT**

Since the early reports of feasibility of surgical closure<sup>22</sup> and efficacy of nonsteroidal antiinflammatory drugs for medical treatment<sup>23,24</sup> of PDA, results have been reported for 50 randomized controlled trials enrolling 4878 preterm infants.<sup>9,25</sup> Although medical and surgical treatments are efficacious in closing the PDA in a large proportion of infants, neither individual clinical trials nor meta-analyses have demonstrated that closing the ductus results in improved long-term outcomes. Odds ratios for the most important outcomes (BPD, necrotizing enterocolitis, neurosensory impairment, death,

the combined outcomes of death or BPD and death or neurosensory impairment) indicate that early, routine treatment has no effect, with narrow confidence intervals, so it is unlikely that substantial differences have gone undetected.<sup>9</sup> When given as prophylaxis for IVH beginning within 12 hours of birth, treatment with indomethacin reduces rates of IVH, IVH greater than grade II, and early, severe pulmonary hemorrhage but does not improve long-term neurodevelopmental or respiratory outcomes.<sup>7,26–28</sup> The early neuroprotective effects of indomethacin may not depend on effects on ductal patency and are not replicated with similar use of ibuprofen.<sup>29</sup> In all published trials of prophylaxis or treatment, interventions were initiated within 2 weeks after birth for almost all subjects in the treatment arms, and later backup treatment to achieve ductal closure was common among control subjects.<sup>30,31</sup> The available evidence is therefore insufficient to permit assessment of potential benefits of treatments initiated after 2 weeks of age. The cumulative evidence supports the conclusion that early (in the first 2 weeks after birth), routine (as prophylaxis or for infants with echocardiographic confirmation of ductal patency with or without clinical signs) treatment to close the ductus arteriosus does not improve long-term outcomes for preterm infants. There is insufficient evidence to determine whether there are preterm infants who might benefit from early treatment or that later treatment has no potential benefit. These data also cannot be extrapolated to novel treatments (such as acetaminophen, recently reported to promote ductal closure<sup>32,33</sup>) because the balance between beneficial and adverse effects of new treatments may differ substantially from that for previously studied treatments.

Although surgical ligation is effective for achievement of rapid, complete ductal closure, it is often followed by severe hemodynamic and respiratory collapse, requiring marked escalation in supportive intensive care.<sup>34</sup> The risk of this complication appears to decline substantially over the first 6 weeks after birth.<sup>35</sup> Long-term complications of surgical ligation include paresis of the left vocal cord<sup>36,37</sup> or diaphragm,<sup>38</sup> chylothorax,<sup>38–40</sup> and scoliosis,<sup>41,42</sup> and infants who undergo surgical ligation are more likely to develop BPD,<sup>43–45</sup> retinopathy of prematurity,<sup>45</sup> and neurodevelopmental impairment.<sup>45,46</sup> Treatment with cyclooxygenase inhibitors may lead to impaired renal function,<sup>47</sup> intestinal perforation,<sup>48,49</sup> and altered cerebrovascular regulation.<sup>50</sup> In contrast to prophylactic use, treatment of confirmed PDA with indomethacin is associated with an increased risk of IVH.<sup>9</sup> Treatment to close a patent ductus may therefore not be entirely benign.

Clinical experience with less aggressive strategies for PDA management suggests that a more permissive approach does not result in worse outcomes. Strategies avoiding use of indomethacin or ibuprofen yield outcomes comparable to contemporaneous external benchmarks.<sup>51,52</sup> Less frequent use of surgical ligation in infants with PDA after failure of indomethacin prophylaxis was associated with a lower rate of necrotizing enterocolitis and no increase in rates of other adverse outcomes.<sup>53</sup> Reduced use of indomethacin and ligation at 1 center was associated with an increased rate of the combined outcome of death or chronic lung disease but no increase in rates of individual morbidities or mortality.<sup>54</sup> These experiences indicate that longer periods of exposure to left-to-right ductal shunting may not result in

significantly compromised outcomes, supporting equipoise regarding enrollment of preterm infants into randomized trials designed to assess treatment strategies for preterm infants with PDA.

## CLINICAL TRIAL OPPORTUNITIES

As previously noted, evidence-based abandonment of early routine treatment to close the PDA does not preclude other options for management of infants with this condition. First, deciding not to intervene routinely to achieve earlier closure of the ductus should not imply that consequences of ductal patency can be completely ignored.<sup>55</sup> Although many strategies for management of the consequences of PDA have been proposed, none have been subjected to systematic evaluation in clinical trials, which are urgently needed to guide management of these infants. Studies of interventions designed to limit excessive pulmonary blood flow (red cell transfusion, increased positive airway pressure, correction of alkalosis, avoidance of pulmonary vasodilators such as oxygen or nitric oxide), to increase systemic cardiac output (dopamine, captopril, avoidance of hypovolemia), to ameliorate pulmonary edema (fluid restriction, diuretics, correction of hypoproteinemia), or to minimize confounding insults (nephrotoxic drugs, systemic infection/inflammation, hypoxemia, hypocarbia) may be appropriate. Second, early identification of a subset of infants with PDA who are at particular risk on the basis of echocardiographic, serum biomarker, or hemodynamic monitoring (such as measurement of cerebral oxygen saturation or fractional oxygen extraction) may allow more selective treatment in the first 2 weeks after birth. Because few extremely preterm infants (those born at  $\leq 25$  weeks, for example) were included in extant

trials, they may constitute a high-risk group with potential benefit from early, universal treatment. Similarly, criteria for intervention after the second postnatal week need to be developed. Although early experience suggested that infants more than 10 to 14 days of age are unlikely to respond to medical treatment with ductal closure,<sup>56,57</sup> other analyses have suggested that postmenstrual, not postnatal, age is the critical determinant, with efficacy declining sharply after approximately 33 to 34 weeks' postmenstrual age.<sup>58,59</sup> Therefore, selective treatment of infants born at or before 28 weeks' gestation, who are at highest risk of PDA, may remain an option well beyond 2 weeks' postnatal age. Deferral of treatment may allow avoidance of treatment of those in whom spontaneous closure occurs without seriously compromising the potential efficacy of medical treatment. Delaying ligation may have similar advantages, avoiding surgery in many infants in whom the ductus closes without treatment and reducing the risk of postoperative hemodynamic compromise in those who do require surgery, particularly if surgery can be deferred until after 30 days of age.

Additional research is needed to address 2 broad questions related to prolonged ductal patency in preterm infants. First, the relationship between measures of hemodynamic significance and increased risks for both prolonged patency and adverse clinical outcomes, such as chronic lung disease or neurodevelopmental impairment, needs to be established. Preliminary work using echocardiographic scores and serum biomarkers, described previously, provides a promising foundation for these studies. That information is extremely important for selection of appropriate subjects for enrollment in intervention trials. Second, well-designed and meticulously executed intervention trials, for which the

end points are clinically important long-term outcomes and not simply rates of ductal closure or measures of short-term physiologic changes, are essential. In these trials, both treatment arms must be explicitly defined so that the superior strategy can be replicated in clinical practice and evaluated against alternatives in future trials. If it is not feasible to forgo use of rescue treatment in the control (placebo or late-treatment) arm, strict criteria for both a required time interval and diagnostic thresholds for such treatment are desirable. Without clear demonstration that adverse outcomes can be averted by medical or surgical closure of the ductus, the hypothesis that ductal patency is causal with respect to those outcomes remains unproven.

## CONCLUSIONS

A large body of evidence now exists demonstrating that early, routine treatment to induce closure of the ductus in preterm infants, either medically or surgically, in the first 2 weeks after birth does not improve long-term outcomes (level of evidence: 1A<sup>60</sup>). The role of more selective use of medical methods for induction of ductal closure, either for defined high-risk infants in the first 2 postnatal weeks, or more generally, for older infants in whom the ductus remains patent, remains uncertain and requires further study. Prophylactic use of indomethacin may be appropriate in settings where rates of IVH are high or if early, severe pulmonary hemorrhage is common, but may not be justified by expected effects on PDA or by an expectation of better long-term outcomes. There is a lack of evidence to guide management of PDA, necessitating equipoise regarding treatment options and support for parents to permit enrollment of their infants in trials that can expand the available body of evidence.

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## ABBREVIATIONS

BPD: bronchopulmonary dysplasia  
IVH: intraventricular hemorrhage  
PDA: patent ductus arteriosus

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William E. Benitz and COMMITTEE ON FETUS AND NEWBORN

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