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The Patent Ductus Arteriosus Problem: Infants Who Still Need Treatment

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Persistent patency of the ductus arteriosus (PDA) remains an ongoing clinical conundrum.¹ For more than a decade, neonatologists have been asked to consider whether treatment to induce PDA closure is ever warranted.^{2–5} Yet daily rounds in the neonatal intensive care unit frequently include bedside deliberations over management of preterm infants whose PDA is considered problematic. The quandary arises from conflicting information on adverse outcomes that can be attributed to PDA, unclear determinations of whether PDA closure alleviates those outcomes, attempts to balance the risks of treatment with any potential benefit, and the poorly defined characteristics of a “significant” PDA that would trigger a decision for treatment.

One problem is deciding when to call the ductus arteriosus (DA) patent, or a PDA. The natural course of ductus closure in preterm infants has been difficult to study because physiologic derangements attributed to PDA shunting usually prompt efforts to invoke its closure. In preterm infants >30 weeks gestation or >1500 g at birth, DA closure was traditionally expected to occur by 4 days of age.^{6,7}

However, historical information also has suggested that spontaneous DA closure might eventually occur at several months of age in some moderately premature infants (reviewed in reference⁸). More recent reports have begun to map the fate of untreated PDA in the smallest preterm infants. In 2006, Rosenfeld et al noted that 42 of 122 infants (34%) with birth weight <1000 g experienced spontaneous, permanent DA closure by 8 days of age.⁹ Five neonates had persistent DA patency beyond 10 days of age; 2 were discharged home with an asymptomatic PDA. Dani et al found spontaneous DA closure in 24% of infants <27 weeks gestation; 1 infant (out of 26 with PDA) had an open ductus at the time of discharge.¹⁰

Nemerofsky et al observed spontaneous closure in 31% of infants <1000 g birth weight by day of life seven; the median time to spontaneous DA closure was 57 days. Four infants

were eventually discharged home with PDA.¹¹ Rolland et al similarly noted spontaneous DA closure at a mean of 67 days of age in 51 of 70 infants with PDA.¹² Reports such as these have made it more difficult to know when a PDA should be considered “persistently patent,” and support the concept that spontaneous DA closure may eventually occur in an appreciable number of small preterm infants. In fact, nontreatment of an open ductus may already be a widespread practice, even in infants <25 weeks gestation.¹³ On the other hand, waiting for spontaneous closure depends on understanding the long-term consequences of sending an infant home with a PDA, which have not been well described.

Two articles in this issue of *The Journal* provide new, pertinent information to help address this knowledge gap. Janz-Robinson et al examined neurodevelopmental outcomes at 2–3 years of age in preterm infants <29 weeks gestation who were treated for PDA.¹⁴ Data on cognitive and developmental delay, sensorineural impairment, and functional disability were obtained from a network of 10 Australian neonatal units. Among 2701 infants available for study, 58% did not require PDA treatment; 37% received pharmacologic therapy and 4.6% underwent ligation.

Medically- and surgically-treated infants had higher rates of moderate-to-severe functional disability, developmental delay, hearing loss, and motor impairments. Multivariate regression analysis identified both medical and surgical PDA treatment as independent risk factors associated with poor outcomes. The authors conclude that the adverse outcomes after any PDA treatment, particularly in infants less than 25 weeks gestation “may support permissive tolerance of PDAs.”

The observation that PDA ligation is associated with neurodevelopmental impairment is well recognized.^{15–20} Adoption of a delayed, selective ligation policy might reduce, but not eliminate, adverse outcomes.^{21,22} Other complications related to ligation also raise concern.²³ However, study bias can distort the impact of adverse outcomes after PDA ligation,^{20,24,25} and it is important to note that ligation is typically utilized as a last-resort measure, confounding the attribution of long-term impairments. The work of Janz-Robinson et al echoes the expanding call for neonatologists to consider avoidance of treatments designed to close the PDA and adoption of conservative management strategies until controlled trials are available to demonstrate a superior approach. In the interim, a greater understanding of the consequences of permissive tolerance and allowing long-term DA patency would be helpful.

In that vein, a related article by Weber et al describes the outcome of 68 infants who were discharged home with a persistent PDA.²⁶ Out of 321 surviving infants with PDA, 253 (78%) responded to medical or surgical treatment; the remaining 68 infants failed to respond to a course of nonsteroidal anti-inflammatory drugs. Discounting infants who died (2) or were lost to follow-up (2), a remarkable number of infants (52/64) experienced spontaneous DA closure after discharge, whereas 7 were still patent at the time of data analysis, and 5 (8%) required catheter-based intervention at 9–36 months of age. Kaplan–Maier analysis showed that nearly 50% achieved PDA closure by 9 months after birth. These are noteworthy findings when we consider our recent mindset that persistent PDA should be avoided. These data corroborate an earlier study on the natural history of DA closure in very

low birth weight (VLBW) infants by Herrman et al in which 11 of 32 infants who never received nonsteroidal anti-inflammatory drugs, and 10 of 25 infants who failed indomethacin treatment, were discharged with PDA.²⁷ Interestingly, both studies report impressive spontaneous DA closure rates after discharge: from 81% (52/64)²⁶ to 86% (18/21).²⁷ Catheter-based closure was required in only 2 (9.5%) infants at 12–14 months of age, similar to the 8% intervention rate noted by Weber et al. Both studies report final DA closure at approximately 48–49 weeks post-menstrual age.

The importance of these findings is the reassurance that most premature neonates who fail to close their PDA by the time of discharge will undergo spontaneous closure a few weeks later. However, some caution is warranted as there is a lack of information on pulmonary, neurodevelopmental, or other long-term outcomes of interest that have not been reported in this population of infants. Additionally, more information is needed on the indications for catheter-based occlusion—do these infants have worsening heart failure? Infection/endocarditis? Growth failure? Pulmonary complications? Were there multiple rehospitalizations attributable to persistent DA patency? Do infants discharged with PDA thrive without the need for extra caloric support or additional medications? Identification of clinical characteristics or echocardiographic criteria that distinguish infants who will need catheter-based intervention among those who are discharged with PDA would be a valuable contribution.

Finally, it is important to note that the PDA was considered small in the vast majority of infants who demonstrated spontaneous closure after discharge.^{26,27} Moreover, the number of VLBW infants who can be managed without PDA intervention remains unclear. Weber et al only report 68 of 321 (21%) infants with PDA who were discharged with an open ductus, of whom 52/321 (16%) had spontaneous DA closure after discharge. Similarly, Herrman et al identified 21 out of 95 (22%) infants with PDA who were discharged with an open ductus, of whom 18/95 (19%) spontaneously closed. Thus, one-fifth of all VLBW infants who are diagnosed with PDA can be expected to undergo spontaneous DA closure after discharge, and the population of infants who truly need PDA treatment appears to be shrinking. But for most neonatologists, the problem lies with those remaining infants with a moderate-to-large PDA who might require some form of intervention. It is still unclear whether these PDAs can be safely left untreated. Toward this end, Vanhaesebrouck et al reported 100% DA closure in 10 ventilated infants who were successfully managed with conservative measures.²⁸ The results of other prospective nontreatment studies are eagerly awaited. Until then, even those who suggest a moratorium on PDA treatment and advocate that ductus patency should be tolerated while we learn to manage its consequences rather than attempting to achieve its closure^{8,29} acknowledge that some infants may benefit from DA closure. Therefore, the most noteworthy outcome of the two new studies in this issue of *The Journal* might be to encourage nonintervention trials to understand better the outcomes of prolonged DA patency, while more focused therapies and refined treatment criteria are developed.

Glossary

DA Ductus arteriosus

PDA	Patency of the ductus arteriosus
VLBW	Very low birth weight

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