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Pharmacological closure of the patent ductus arteriosus: when treatment still makes sense

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Management decisions regarding patent ductus arteriosus (PDA) have become a hand-wringing exercise during daily rounds in the neonatal ICU. Rigorous re-evaluation of the evidence beginning 20 years ago called into question the benefit of PDA treatments long considered standard care [1]. As a result, pervasive use of pharmacological agents to treat PDA decreased during the last decade in favor of more selective management, including decreased prophylactic use of cyclooxygenase inhibitor (COX-I) therapy to prevent PDA, longer periods of expectant management, and fewer infants treated [2–5]. The consequences of this trend are unclear, and an evidence basis for therapeutic decisions is lacking in an era where infants born as early as 22 weeks gestation are surviving. Neonatologists are left wondering which PDAs should we treat? Which medication should we use?

The widespread concern that pharmacological treatments for PDA may pose more harm than good is reflected in significant declines in COX-I use reported in a number of multicenter observational studies (Fig. 1, top panel). A first glance at the associated outcomes could provide reassurance, as several of these reports found no association between declining COX-I therapy and evident changes in unadjusted mortality or morbidities [3, 5, 6]. Indeed, in two single-center studies investigators withheld active treatment for PDA closure entirely and reported reassuring outcomes compared with historical controls [7, 8]. In other multicenter studies, however, selective pharmacological approaches were associated with increased unadjusted mortality or bronchopulmonary dysplasia (BPD) rates [9–13]. Data from the Pediatric Hospital Information System showed a temporal association between declining COX-I use and unadjusted increases in BPD, retinopathy of prematurity, and periventricular leukomalacia among infants < 1000 g at birth (extremely low birth weight, ELBW) [4].

These unadjusted observational studies cannot ascertain the true relationship between changing PDA treatment and changes in outcomes and therefore offer no relief to the daily consternation over PDA decision-making in the NICU. Their conflicting results underscore

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our uncertainty on this topic and preserve equipoise for future clinical trials comparing alternative PDA management strategies. Moreover, the number of studies reporting increased adverse outcomes temporally associated with decreasing COX-I use suggests that foregoing treatment for PDA closure altogether should be approached cautiously. Current best evidence supports the possibility that PDA closure may benefit some extremely preterm infants. In particular, a recent study from the California Perinatal Quality Care Collaborative (CPQCC) reported that COX-I treatment may benefit infants 400–749 g birth weight [14]. In the context of improving mortality for these infants in California NICUs, this multivariable multilevel analysis found that improvement in NICU-level mortality was significantly slowed in NICUs in direct proportion to their reduction in COX-I use in this weight subgroup (Fig. 1, bottom panel). While we await definitive clinical trials, the observational literature suggests gestational ages, chronological ages, and shunt sizes where treatment may be beneficial.

Recent pharmacotherapeutic trends include increased use of acetaminophen, a prostaglandin inhibitor with a favorable safety profile. A 2018 Cochrane review found moderate quality evidence to suggest that treatment with acetaminophen resulted in a similar ductus closure rate to ibuprofen. Most studies reviewed, however, enrolled patients up to 32–34 weeks' gestation [15]. Published subsequently, the PDA-TOLERATE trial found that indomethacin was three times as effective and ibuprofen twice as effective as acetaminophen, which had a lackluster 27% initial constriction rate [16]. Importantly, PDA-TOLERATE enrolled patients < 28 weeks with a mean gestational age of 25.8 weeks and thus focused on those most at risk for hemodynamically significant PDA (hsPDA). Infants born at 23–24 weeks gestation have a higher incidence of hsPDA than those born at 25–28 weeks (70 versus 59%), a higher rate of first course treatment failure, and twice the odds of first course treatment failure with acetaminophen compared with ibuprofen [17].

Does prophylactic indomethacin (PINDO) have a role in current PDA management? The TIPP trial found that PINDO reduced severe IVH and symptomatic PDA, but did not improve survival or neurodevelopmental impairment in ELBW infants and may increase BPD in those without PDA [18]. However, in a similar population PINDO was associated with reduced risk of BPD and death/BPD compared with deferring treatment beyond 7 days in a single-center before-and-after study [19]. Analysis of data from the multicenter Neonatal Research Network (NRN) found PINDO associated with no difference in BPD but with reduced mortality among ELBW infants with birth weight 10th percentile and those not receiving subsequent pharmacologic PDA treatment. A secondary analysis comparing NRN centers that used PINDO in more than 60% of ELBW infants to those not using PINDO identified potential reductions in BPD and death/BPD rates [20]. Thus, efforts to optimize PINDO strategies may benefit at-risk ELBW infants.

The timing of *indicated* PDA treatment also appears important. While the PDA-TOLERATE trial found no benefit to routine COX-I treatment at 7 days of life for moderate-to-large PDA in infants < 28 weeks, lack of physician equipoise resulted in exclusion of 18% of otherwise-eligible patients because providers chose to treat immediately with COX-I instead of risking randomization to conservative management [21]. When compared with enrolled patients, the early-treated, non-enrolled infants had lower rates of death, BPD, and home oxygen use,

despite being sicker and less mature. Thus, in symptomatic extremely preterm infants with a moderate-to-large hsPDA an early treatment strategy may offer the best chance for improving outcomes until more rigorous data from larger randomized trials become available.

So what is a neonatologist to do? Infants < 30 weeks at birth seldom require treatment for ductus closure [22]. We lack clear criteria defining which ductus warrants active closure, and *primum non nocere* requires no treatment if there is no evidence basis for benefit. However, first principles justify effective pharmacotherapy if known risks of medication are less than the imminent harm of ongoing severe PDA-related physiological disarray. If a ductus must be treated, current best evidence favors pharmacological treatment before 7 days for infants < 28 weeks with a moderate-to-large hsPDA, with consideration for PINDO in extremely preterm infants at highest risk for death, BPD, and treatment failure. An echocardiogram-based selective-prophylaxis strategy may optimize outcomes and reduce unnecessary drug exposures [23]. In infants < 25 weeks, acetaminophen has a low rate of success and indomethacin or ibuprofen appear preferable. For those between 26 and 28 weeks, PDA-TOLERATE justifies a conservative approach for asymptomatic infants and those with a small PDA but evidence supports pharmacological treatment of the hsPDA, particularly prior to consideration of an invasive interventional strategy. A focus on infants < 28 weeks will be helpful in future recommendations and studies of PDA pharmacotherapy, ideally with differing strategies tailored to the specific needs and risks of infants < 25 weeks versus those who are somewhat more mature.

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Fig. 1.

Superimposed trends in treatment with cyclooxygenase inhibitors (COX-I) in preterm infants, 2008–2015, and potential impact on survival in infants 400–749 g birth weight [14]. ‘Observed’ = observed average of 55 NICU-specific unadjusted mortality rates, infants born 400–749 g, CPQCC. ‘Estimated’ = estimated average NICU-specific unadjusted mortality rate, infants born 400–749 g, with COX-I use sustained at 2008–2009 baseline (data sub-analysis derived from [14]). *Treatment rate among infants diagnosed with PDA converted to all infants meeting study inclusion criteria using reported yearly rate of PDA diagnosis