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### Evaluation of standard dose ibuprofen in combination with acetaminophen for patent ductus arteriosus (PDA) treatment in preterm neonates

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## Background

- The ductus arteriosus is a physiologic blood vessel present before birth that connects the aorta and pulmonary artery, allowing oxygenated blood to flow into the body without passing through the lungs.
- The ductus arteriosus will often close within days after birth, but in some cases, it remains open and becomes a patent ductus arteriosus (PDA).
- Current regimens that have demonstrated efficacy for PDA closure include non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen and indomethacin, with or without acetaminophen.
- Efficacy rates following monotherapy of these agents can range from 27-80%, while combination therapy efficacy rates range from 41-100%.
- Combination therapy of ibuprofen and acetaminophen has been studied as a new strategy for PDA as it may facilitate higher ductal closure rates via additive action on two separate pathways inhibiting prostaglandin production.

## Objectives

### •Primary outcome

- Rate of hemodynamically stable and complete ductal closure following a course of standard dose ibuprofen in combination with acetaminophen, evaluated by echocardiography

### •Secondary outcomes

- Efficacy of a second pharmacological course
- Patients requiring surgical or procedural intervention
- Adverse events associated with ibuprofen and acetaminophen combination pharmacotherapy

## Methods

### •Study design

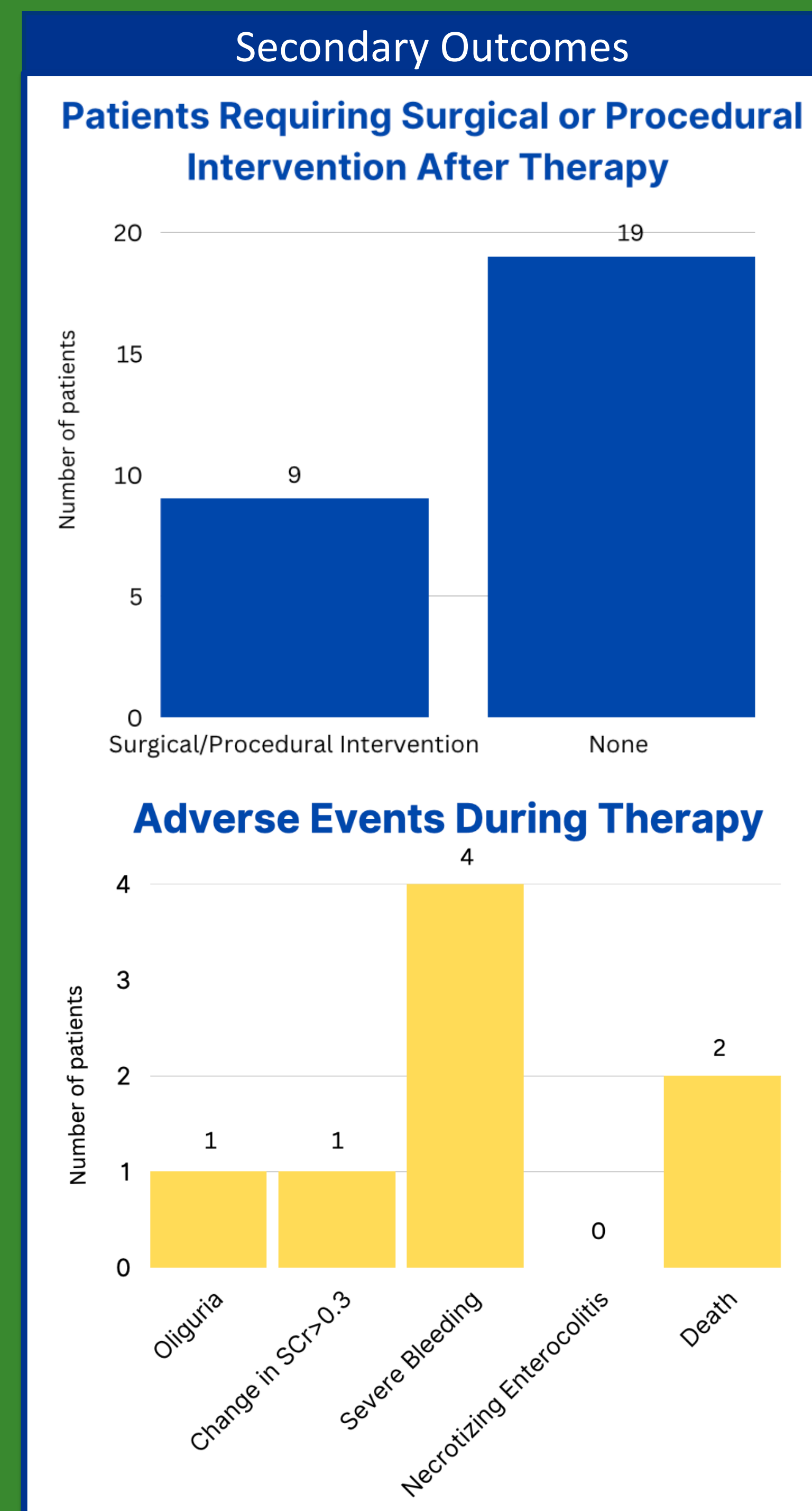
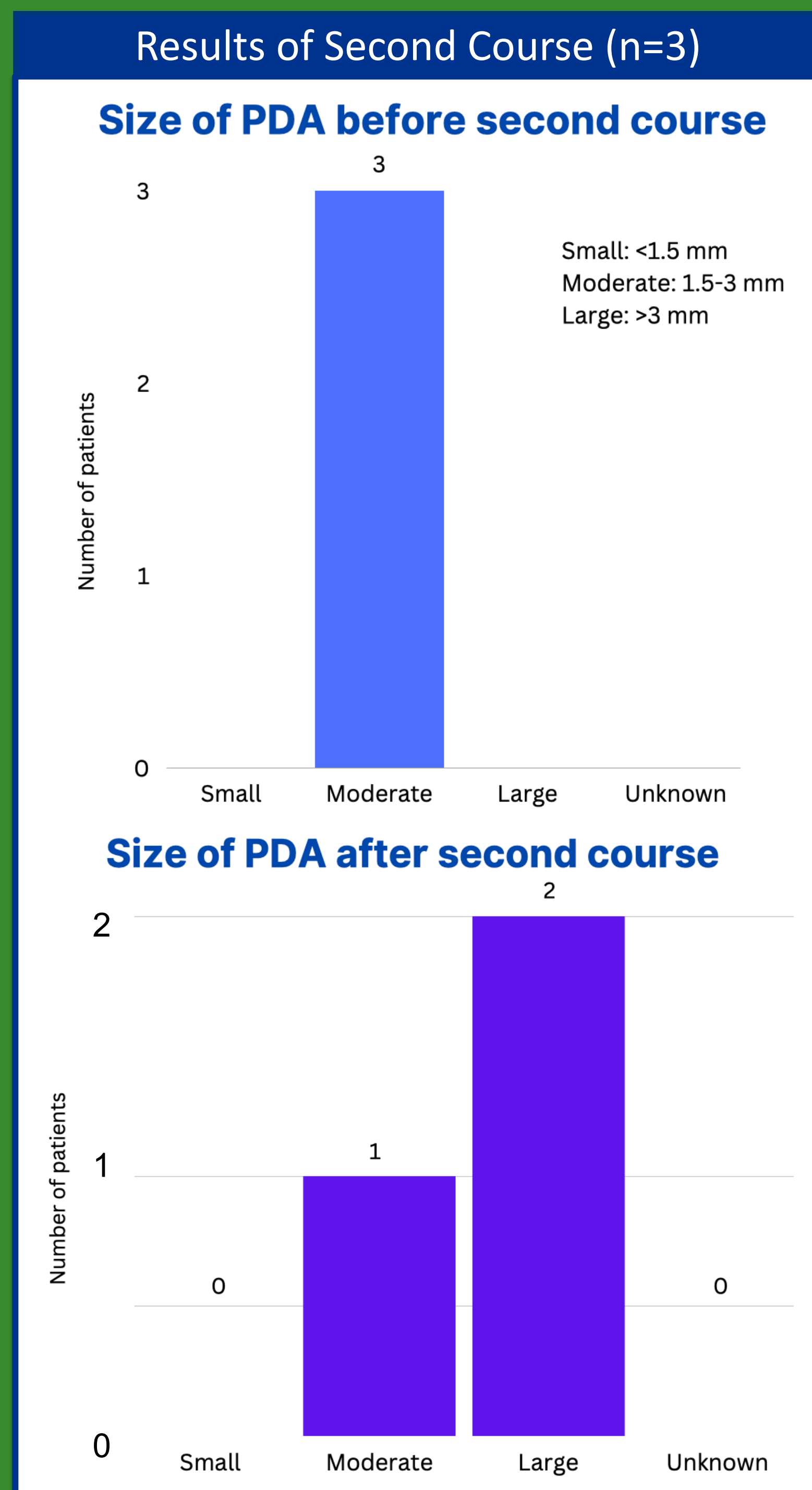
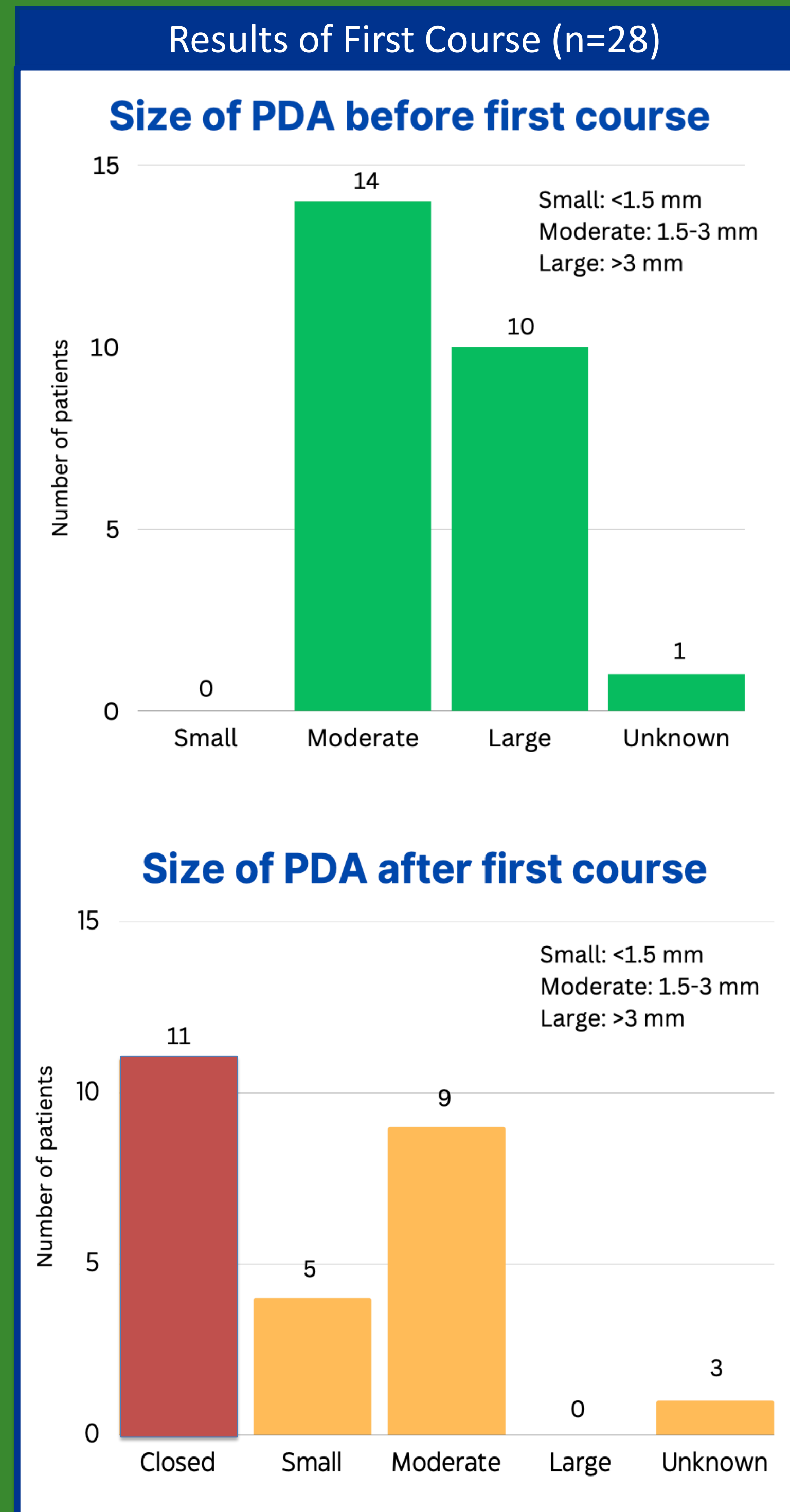
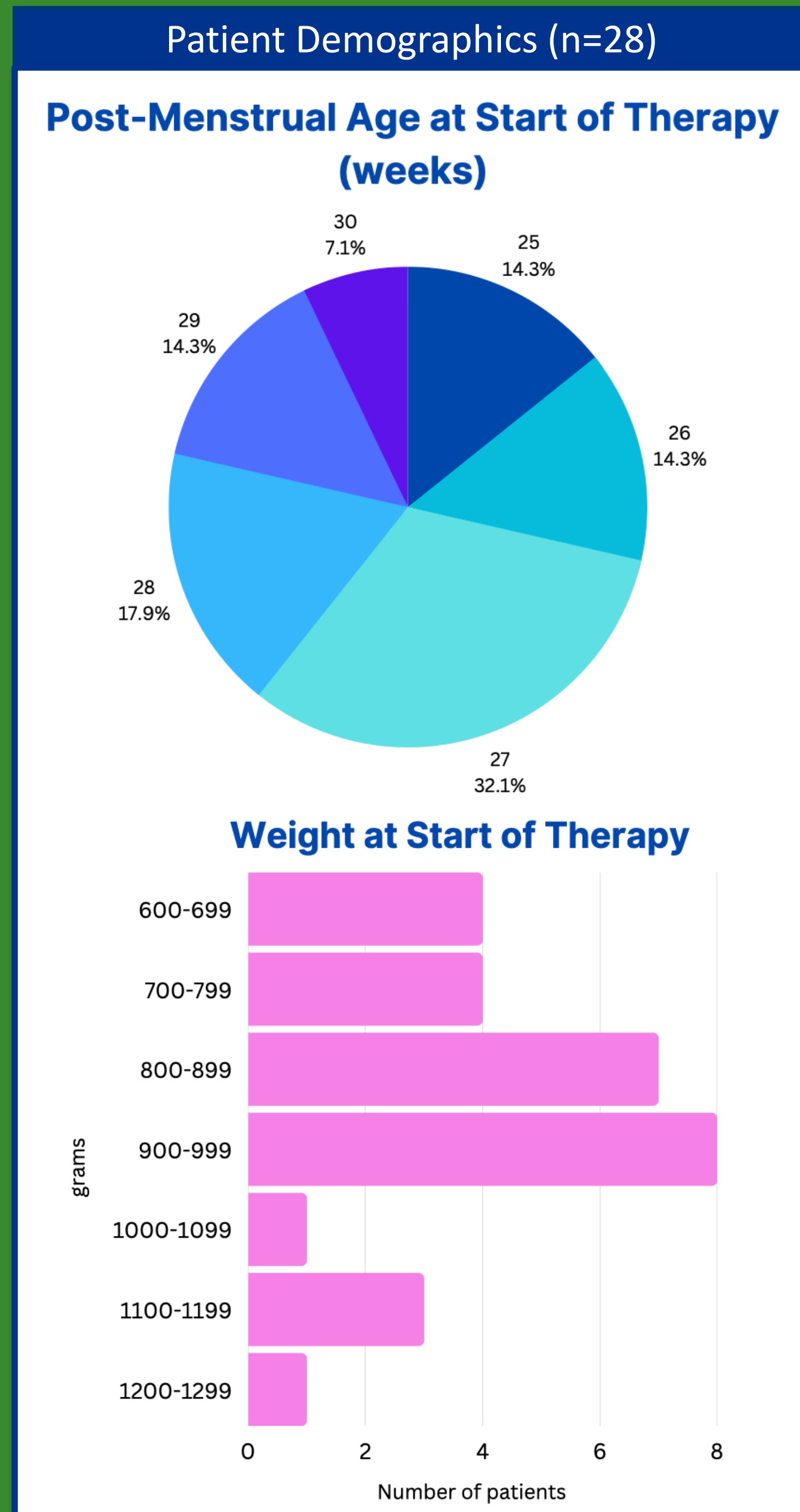
- Multicenter retrospective chart review

### •Inclusion criteria

- Neonates of gestational age  $\geq 23$  weeks
- Diagnosed with PDA on echocardiogram
- Received standard dose ibuprofen IV/PO regimen (10 mg/kg x1 dose, then 5 mg/kg x 4 doses) in combination with acetaminophen IV/PO (dose based on protocol)

### •Exclusion criteria

- Neonates of gestational age  $> 29$  weeks, 6 days
- Ibuprofen or acetaminophen indicated for pain
- Tylenol and/or ibuprofen monotherapy prior to combination therapy for PDA
- Major congenital anomalies
- Congenital heart defects
- Persistent pulmonary hypertension
- Life-threatening infections
- Severe bleeding
- Decreased urine output of  $<1$  ml/kg/hour
- Impaired renal function (SCr  $>1.8$  mg/dL)
- Platelets  $\leq 50 \times 10^9/L$
- Intraventricular hemorrhage (grade 3 or 4)
- Necrotizing enterocolitis



## Results

### •Primary outcome

- 11 patients (39%) had PDA closure after one course of combination therapy.

### •Secondary outcomes

- 3 patients underwent a second course of combination therapy and 0 had successful closure of PDA.
- 9 patients (32.13%) required surgical or procedural intervention.
- 3 patients (10.71%) had severe bleeding.
- 1 patient (3.57%) had oliguria.
- 1 patient (3.57%) had a change in SCr  $>0.3$  mg/dL.
- 2 patients (7.14%) died during the first course of therapy.

## Discussion

- Out of a total of 58 patients screened, 28 patients met inclusion criteria and were included for review.
- All patients had at least one course of standard dose ibuprofen in combination with acetaminophen.
- Though only 11 patients met the primary outcome, 3 patients were hemodynamically stable with partial closure of PDA and did not require further treatment.
- Only 3 patients underwent a second course of therapy.
- Our study of combination therapy showed a lower efficacy rate of 39% compared to those reported in current literature. Undergoing a second course of therapy was not found to be efficacious for PDA closure in this study.
- The most common adverse event reported during therapy was severe bleeding. 4 events, which occurred in 3 patients, included grade 3 subependymal hemorrhage, bilateral grade 3 germinal matrix hemorrhage, grade 4 right subependymal hemorrhage, and pulmonary hemorrhage.
- Main limitation of this study was that it was a retrospective cohort study with a small patient population.
- Given the lack of conclusive data, adequately powered studies of standard dose ibuprofen and acetaminophen combination therapy for PDA closure are necessary for future research.
- Our next steps will be to study the efficacy and safety rates of a practice change to *high* dose ibuprofen and acetaminophen combination therapy for PDA closure. The results will be compared to the standard dose ibuprofen and acetaminophen combination therapy.

## References

- Nemri AM. Patent ductus arteriosus in preterm infant: Basic pathology and when to treat. *Sudan J Paediatr.* 2014;14(1):25-30.
- Ohlsson A, Walia R, Shah SS. Ibuprofen for the treatment of patent ductus arteriosus in preterm or low birth weight (or both) infants. *Cochrane Database Syst Rev.* 2020;2(2):CD003481. Published 2020 Feb 11. doi:10.1002/14651858.CD003481.pub8
- Dani C, Vangi V, Bertini G, et al. High-dose ibuprofen for patent ductus arteriosus in extremely preterm infants: a randomized controlled study. *Clin Pharmacol Ther.* 2012;91(4):590-596. doi:10.1038/clpt.2011.284
- Pourarian S, Rezaie M, Amoozgar H, Shakiba AM, Edraki MR, Mehdizadegan N. High-Dose Oral Ibuprofen in Treatment of Patent Ductus Arteriosus in Full-Term Neonates. *Iran J Pediatr.* 2015;25(4):e2005. doi:10.5812/ijp.2005
- Jasani B, Weisz DE, Reese J, Jain A. Combination pharmacotherapy for patent ductus arteriosus: Rationale and evidence. *Semin Perinatol.* 2023;47(2):151720. doi:10.1016/j.semperi.2023.151720
- Shah SD, Makker K, Zhang M, Harnett S, Aziz KB, Hudak ML. Dual medication therapy (acetaminophen and ibuprofen) for the management of patent ductus arteriosus in preterm infants: a systematic review and meta-analysis. *J Perinatol.* 2022;42(12):1654-1661. doi:10.1038/s41372-022-01500-8