PDA Patient identification and management pathways in preterm infants

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Domain	Recommendation [with GRADE certainty of evidence]
Prophylactic cyclo-oxygenase inhibitor therapy	• Routine prophylactic treatment of PDA with indomethacin in all preterm infants is not recommended [Strong recommendation, moderate certainty of evidence] • Selective prophylaxis with intravenous indomethacin may be considered in **extremely low birth weight infants at a high risk of severe intraventricular hemorrhage (such as lack of antenatal corticosteroids, male sex, gestational age less than 26 weeks at birth)**[conditional recommendation, moderate certainty of evidence]. *Use of prophylactic indomethacin is not recommended in conjunction with prophylactic hydrocortisone due to high risk of spontaneous gastrointestinal perforation.* • Routine or selective prophylactic treatment of patent ductus arteriosus with ibuprofen is not recommended [strong recommendation, very low certainty of evidence] • Routine or selective prophylactic treatment of patent ductus arteriosus with acetaminophen is not recommended [strong recommendation, very low certainty of evidence] ***References:***(1–3)
'Routine echocardiographic screening' vs 'echocardiography only when clinically indicated' to diagnose of hs-PDA	• Routine echocardiographic screening in the first 72 h of life may be considered in infants born <26 weeks GA, if local resources are available [conditional recommendation, low certainty of evidence] **Additional comments:** For centers considering routine echo screening in <26 wk GA infants within the first 72h, we suggest considering early treatment in the first 72h if the infant is clinically symptomatic (such as high ventilatory/oxygen requirements; pulmonary hemorrhage or hemodynamic instability) **AND** echocardiography is suggestive of a 'large PDA shunt' (such as PDA size>2.5 mm, with dilated left atrium and/or high left ventricular output and/or reversal of diastolic flow in the descending aorta). [*Please note, there are currently no well-validated combinations of clinical and echocardiographic markers to define a 'large PDA shunt' with demonstrable clinical benefit from early pharmacotherapy*] ***References:*** (4–10)

When should a PDA be treated with pharmacotherapy?	• Neonatologists may choose to conservatively manage a symptomatic PDA within the first 1-2 weeks after birth (conditional recommendation; moderate-low certainty of evidence). However, clinicians should exercise caution in applying the results of existing RCTs to clinically unstable extremely preterm infants (especially <26 weeks GA) where earlier pharmacotherapy may be considered. • There is insufficient evidence to recommend a PDA severity score based approach to aid clinicians in making the decision whether to initiate pharmacotherapy for PDA ***References:*** (11–18)
What is the pharmacotherapy of choice for treatment of hs-PDA?	**<u>Extremely preterm infants (<27 wk GA)</u>** ***<u>Within the 1st week after birth:</u>*** ➢ Standard dose ibuprofen (10 mg/kg followed by 2 doses of 5 mg/kg) may be considered as the first choice (Enteral route may be preferred in infants tolerating enteral feeds) ➢ Intravenous indomethacin may be considered as an alternative to intravenous ibuprofen [Conditional recommendation; low-certainty of evidence] ***<u>More than 1 week of age:</u>*** ➢ High dose ibuprofen (20 mg/kg followed by 2 doses of 10 mg/kg) may be considered as the first choice (Enteral route may be preferred in infants tolerating enteral feeds) ➢ Intravenous indomethacin may be considered as an alternative to intravenous ibuprofen [Conditional recommendation; low-certainty of evidence] **<u>Additional considerations:</u>** Acetaminophen may be considered as a safer treatment option for hs-PDA compared to NSAIDs (ibuprofen or indomethacin) in extremely preterm infants [Conditional recommendation; low-certainty of evidence] ***Please note,*** *effectiveness of acetaminophen in this GA group has not been demonstrated. Further, intravenous formulation of acetaminophen has been shown to have significantly lower efficacy for PDA closure compared to both indomethacin and ibuprofen in extremely preterm infants in recent RCTs.* **<u>Preterm infants >27wks GA</u>** • Adjustable dose ibuprofen (standard doses in the first 3-5 days; higher doses beyond 5 days) should be considered as the first line

	treatment [Strong recommendation; moderate-high certainty of evidence] • Acetaminophen (oral) should be considered as an alternative if there is a concern of side effects with high dose ibuprofen. [Strong recommendation; moderate-high certainty of evidence] ***References:*** (3,19–22)
Repeat courses of pharmacotherapy	• A second course of pharmacotherapy (ibuprofen or indomethacin) should be considered over procedural PDA closure for persistent hs-PDA, if there is no contraindication [Strong recommendation; low-certainty of evidence] • Prior to considering procedural closure, a 3rd course of 5-7 days of oral acetaminophen may be considered [Conditional recommendation; low-certainty of evidence] ***Additional comments:*** A third course of Indomethacin is not recommended, as it appears to increase the risk of PVL. The literature is unclear about 3rd course of ibuprofen. ***References:*** (23–28)
Feeding during treatment	• We recommend against stopping or cutting back on feeds during PDA medical treatment [conditional recommendation; low-certainty of evidence] **Additional comments:** There is insufficient evidence for or against progression of feeds during PDA medical treatment. ***References:*** (29–39)

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