PATENT DUCTUS ARTERIOSUS
Supporting information

This guideline has been prepared with reference to the following:

Gupta MA. Do we know how to treat PDA with paracetamol? Current evidence on the pharmacokinetics and pharmacodynamics of paracetamol for hsPDA closure in extreme preterm infants. Infant. 2021;17:186-92

Does ibuprofen have advantages over indometacin?
A 2020 systematic review of RCTs identified twenty-four studies (1590 infants) comparing ibuprofen (IV or oral) with indometacin (IV or oral) found no significant differences in failure rates for PDA closure (typical RR 1.07, 95% CI 0.92 to 1.24) [Ohlsson, 2020]. A reduction in necrotising enterocolitis was noted in the ibuprofen (IV or oral) group (18 studies, 1292 infants; typical RR 0.68, 95% CI 0.49 to 0.94). There was a statistically significant reduction in the proportion of infants with oliguria in the ibuprofen group (6 studies, 576 infants; typical RR 0.28, 95% CI 0.14 to 0.54). The serum/plasma creatinine levels 72 hours after initiation of treatment were statistically significantly lower in the ibuprofen group (11 studies, 918 infants; MD -8.12 µmol/L, 95% CI -10.81 to -5.43). Therefore, of these two drugs, the authors concluded that ibuprofen appears to be the drug of choice.

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:CD003481
https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD003481.pub8/full

Evidence Level: I

In premature infants with patent ductus arteriosus (PDA), does early treatment with indometacin improve outcomes?
A randomised prospective trial in 127 infants (van Overmeire, 2001) compared early (day 3, n = 64) with late (day 7, n = 63) iv indometacin treatment (3 x 0.2 mg/kg 12 hrly). PDA closure rate was higher in the “early” group at both 6 (73% vs 44%, p = .0008) and 9 days of age (91% vs 78%, p = .047). More adverse events (including death, lower urinary output, higher serum creatinine, necrotising enterocolitis, extension of haemorrhage and cystic leukomalacia) occurred in the “early” group, however.
Evidence on the duration of indometacin therapy is unclear. A randomised trial in 61 premature infants (Tammela, 1999) compared 31 given a short course (3 doses:0.2/0.1/0.1 mg/kg in 24 hours) to 30 given a long course (0.1 mg/kg every 24 hours for 7 days). Primary PDA closure occurred more often in the short course group (94% vs 67%, p = .011), but the sustained closure rates were not significantly different (74% vs 60%). The short course patients suffered fewer adverse effects. The authors concluded that a prolonged, low-dosage regimen offered no advantage over a standard-dosage short course.
A similar conclusion was reached by a Cochrane review of 5 trials in a total of 431 infants (Herrera, 2007).
In a more recent retrospective cohort study (Quinn, 2002), 313 infants with PDA were divided, after an initial 3 doses of indometacin into “clinically closed” (n = 214), “partially closed” (n = 69) and “nonresponder” (n = 30) groups. The 69 partial responders were then investigated, using a hierarchical regression model, to identify factors associated with permanent closure. Only gestational age and duration of indometacin treatment were significantly and independently associated, with long course (6 dose rather than 3) recipients also having decreased incidence of symptomatic reopening (OR 0.19, 95% CI 0.04-0.96) and ductus ligation (OR 0.14, 95% CI 0.03-0.68).
A small retrospective study in 46 infants (Dumas de la Roque, 2002) found that omitting the initial bolus of indometacin and giving 0.1 mg/kg daily until the ductus arteriosus was closed was as effective as the standard protocol. Initial success rate was 84.7%, of which 6.5% reopened. The mean cumulative dose of indometacin was 0.35 mg/kg.
A multicentre, randomised controlled trial in 105 infants (Jegatheesan, 2008) found that increasing indometacin concentrations above the levels achieved with a conventional dosing regimen had little effect on the rate of PDA closure and was associated with higher rates of retinopathy of prematurity and renal compromise.
A Cochrane review of 19 trials in 2872 infants (Fowlie, 2010) found the incidence of symptomatic PDA [RR 0.44, 95% CI 0.38 to 0.50] and PDA surgical ligation (RR 0.51, 95% CI 0.37,0.71) was significantly lower in infants treated with prophylactic indometacin. Prophylactic indomethacin also

significantly reduced the incidence of severe intraventricular haemorrhage (RR 0.66, 95% CI 0.53 to 0.82). Meta-analyses found no evidence of an effect on mortality (RR 0.96, 95% CI 0.81 to 1.12) or on a composite of death or severe neurodevelopmental disability assessed at 18 to 36 months old (RR 1.02, 95% CI 0.90, 1.15).

Dumas de la Roque E, Fayon M, Babre F, et al. Minimal effective dose of indomethacin for the treatment of patent ductus arteriosus in preterm infants. Biol Neonate 2002;81:91-4

Fowlie PW, Davis PG, McGuire W. Prophylactic intravenous indomethacin for preventing mortality and morbidity in preterm infants. Cochrane Database of Systematic Reviews 2010, Issue 7. Art. No.: CD000174
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD000174.pub2/full

Herrera C, Holberton J, Davis P. Prolonged versus short course of indomethacin for the treatment of patent ductus arteriosus in preterm infants. Cochrane Database of Systematic Reviews 2007, Issue 2. Art. No.: CD003480
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003480.pub3/full

Jegatheesan P, Ianus V, Buchh B, et al. Increased indomethacin dosing for persistent patent ductus arteriosus in preterm infants: a multicenter, randomized, controlled trial. J Pediatr 2008;153:183-9

Quinn D, Cooper B, Clyman RI. Factors associated with permanent closure of the ductus arteriosus: a role for prolonged indomethacin therapy. Pediatrics 2002;110:e10
http://pediatrics.aappublications.org/content/110/1/e10.long

Tammela O, Ojala R, Iivainen T, et al. Short versus prolonged indomethacin therapy for patent ductus arteriosus in preterm infants. J Pediatr 1999;134:552-7

van Overmeire B. Patent ductus arteriosus: how aggressive should we be? Neonatology 2007;91:318
http://www.curoservice.com/health_professionals/22nd_international_workshop/pdf/vanovermeire.pdf

van Overmeire B, van de Broek H, van Laer P, et al. Early versus late indomethacin treatment for patent ductus arteriosus in premature infants with respiratory distress syndrome. J Pediatr 2001;138:205-11

van Overmeire B, Smets K, Lecoutere D, et al. A comparison of ibuprofen and indomethacin for closure of patent ductus arteriosus. N Engl J Med 2000;343:674-81
http://www.nejm.org/doi/full/10.1056/NEJM200009073431001#t=articleTop

van Overmeire B, Follens I, Hartmann S, et al. Treatment of patent ductus arteriosus with ibuprofen. Arch Dis Child Fetal Neonatal Ed 1997;76:F179-84
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1720646/pdf/v076p0F179.pdf

Evidence Level: I

Does the feeding regime need to be altered when the patient is on indometacin?

Early enteral nutrition has been supposed to be associated with an increased risk for necrotising enterocolitis (NEC) in preterm infants. The only study to investigate this in conjunction with indometacin treatment, however, has found no such association (Bellander, 2003). 32 infants given indometacin were matched with 32 controls; feeding volumes were the same in both groups. Two infants developed NEC in the treatment group, and two in the control group.

A cohort study by Kelleher analysed 5674 extremely low birth weight infants who survived beyond 12 hours after birth who were treated with indometacin to determine whether early feeding vs non-early feeding was associated with an increased risk of intestinal perforation. The study authors found no statistically significant difference between the two groups (adjusted relative risk 0.74, 95% CI 0.49-1.11)

Bellander M, Ley D, Polberger S, et al. Tolerance to early human milk feeding is not compromised by indomethacin in preterm infants with persistent ductus arteriosus. Acta Paediatr 2003;92:1074-8

Kelleher J, Salas A, Bhat R et al. Prophylactic indomethacin and intestinal perforation in extremely low birth weight infants. Pediatrics 2014:134:e1369.

Evidence Level: IV

If a duct fails to close after the first course of indometacin, are further courses indicated?

A study in 32 infants (Keller, 2003) showed that recurrent PDA rarely responds to further courses of indometacin if there is persistent Doppler evidence of ductus flow after completion of the initial course. All 9 of the infants in this category failed the second course of indometacin.
A prospective study in 41 infants (Kumar, 1997) Found that an initial course of indometacin therapy was successful in 90% of cases. The recurrence rate after the first course was 3%. The success rate of therapy increased to 95% following a second course of indometacin.

Keller RL, Clyman RI. Persistent Doppler flow predicts lack of response to multiple courses of indomethacin in premature infants with recurrent patent ductus arteriosus. Pediatrics 2003;112:583-7

Kumar RK, Yu VY. Prolonged low-dose indomethacin therapy for patent ductus arteriosus in very low birthweight infants. J Paediatr Child Health 1997;33:38-41

Evidence Level: IV

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