Managing the patent ductus arteriosus: current treatment options

Anne Marie Heuchan,1 Ronald I Clyman2

ABSTRACT
Optimal management of the patent ductus arteriosus (PDA) in the premature infant remains controversial. Despite considerable historical and physiological data indicating that a persistent PDA may be harmful, robust evidence of long-term benefits or harms from treatment is lacking. This has been equated to a lack of benefit but is also a reflection of the fact that most clinical trials were designed to assess the effects of short-term (2–8 days) rather than prolonged exposure to a PDA. No clinical trials have been designed to assess the effects of prolonged exposure of persistent PDA on morbidity and mortality of very premature infants in the era of antenatal corticosteroids, surfactant and non-invasive respiratory support. Further research is required, but new insights and novel therapies are evolving, which will allow greater support. Further research is required, but new insights and novel therapies are evolving, which will allow greater support. Further research is required, but new insights and novel therapies are evolving, which will allow greater support. Further research is required, but new insights and novel therapies are evolving, which will allow greater support.

BACKGROUND
Optimal management of the PDA in the premature infant is a controversial issue.1 2 The ductus arteriosus in normal term infants constricts rapidly after birth, resulting in ductal intimal hypoxia, remodelling and permanent closure.3 In most term infants, this process is well established within 72 h of birth.9 Most well preterm infants >29 weeks’ gestational age (GA) achieve ductal constriction by day 4; however, in extremely premature infants, failure of constriction is common, affecting 70% <28 weeks6 and 80% at 24–25 weeks.7 Early postnatal constriction is driven by changes in circulatory haemodynamics, increasing oxygen levels and a decrease in circulating prostaglandin concentrations.3 Failure of early constriction is associated with gestational immaturity, lack of antenatal corticosteroids and respiratory disease.8 9 Early spontaneous ductal constriction usually occurs by day 8; when it fails, the median time to closure is 56 days.10 Problems associated with failure of early PDA constriction include cardiac failure, prolonged ventilator dependence,11 12 hypotension (beyond the first 48 h of life),13 pulmonary haemorrhage,14 15 periventricular haemorrhage (PVH),16 necrotising enterocolitis (NEC)17 and abnormalities of cerebral perfusion.18 ‘Ductal steal’, by reducing organ blood flow and producing excessive pulmonary blood flow, contributes to the pathophysiology of these conditions.15 Where a left-to-right shunt persists beyond the first few days of life, the pulmonary lymphatic vasculature is overloaded and pulmonary oedema develops.1 In non-human primates, prolonged exposure to a ductal shunt results in increased ventilation requirements and a reduction in alveolar surface area.19 Pharmacological closure of the PDA arrests this process and improves lung compliance.19 Reductions in pulmonary morbidity and the incidence of NEC have been demonstrated following closure of symptomatic PDA,20–22 but these trials are old and may not be relevant in the current neonatal setting. More recent observational data demonstrate a higher mortality rate associated with failure of ductal closure,23 but causality has not been proven. Most randomised controlled trials (RCTs) have focused on the timing of early treatment rather than on the risks of PDA closure versus prolonged PDA exposure.24 25 These studies and their meta-analysis could be misinterpreted as demonstrating no benefit from any PDA treatment. However, even proponents of no specific PDA treatment (and supportive therapy alone) acknowledge that it would be wrong to assume that there might not be some very low birth weight babies who would benefit from PDA closure.2 In the absence of clear data, potential side effects of treatment must be balanced against the likelihood of eventual spontaneous duct constriction. Therefore, any treatment must be targeted to infants with the greatest likelihood of benefit and should be designed to optimise efficacy and minimise side effects. Given the high incidence of spontaneous duct closure ≥28 weeks’ GA,19 treatment strategies should be aimed specifically at the population <28 weeks with evidence of or at high risk of a significant PDA shunt.

PATENT DUCTUS ARTERIOSUS ASSESSMENT
Early clinical signs associated with PDA are subtle, evolving as pulmonary pressures fall, and are unreliable before day 3. In unrestrictive PDA, a murmur may not be detectable for several weeks.26 Clinical trials have not been rigorous in defining the size and systemic impact of the PDA. Echocardiography can be used to predict persistent patency and assess shunt size. A left atrial:aortic root (La:Ao) ratio ≥1.4 is a marker of established left ventricular overload but, due to the relative lack of distensibility of the preterm myocardium, is a poor marker of early increases in cardiac output.3 Early ductal colour Doppler measurements ≥1.5 mm diameter in the first day of life (7–31 h) predicted the development of a symptomatic duct in infants <29 weeks’ GA (sensitivity 83%, specificity 90%).27 These findings are supported by other studies,27–28 including longitudinal data demonstrating a direct relationship between early duct diameter, later surgical PDA ligation or death.29 A systematic approach to the echocardiographic assessment of PDA includes assessment of shunt size by demonstrating pulmonary overcirculation.
(eg, LA:Ao ratio, elevated flow in the left pulmonary artery [LPA] in diastole, elevated mean PA flow and reversed mitral E/A ratio), systemic hypoperfusion (eg, retrograde flow in the descending aorta, left ventricular output:superior vena cava flow ratio >4.0) and characteristics of the ductus arteriosus (eg, diameter and velocity).28 29 The use of these parameters to grade PDA into small, moderate or large shunts (figure 1) is logical29 but has not been validated against postnatal age and clinical course. These measures should be considered in individual patient assessment and incorporated into future clinical trials. Additional measures of systemic impact include near infrared spectroscopy (NIRS), since as significant reductions in cerebral saturations have been observed with PDA.18 Substantial increases in the plasma concentrations of brain natriuretic peptide (BNP) have been demonstrated in infants with clinically significant PDA; however, the levels that achieve diagnostic significance vary widely between studies.30

**TREATMENT STRATEGIES**

Established treatments for PDA are prostaglandin H$_2$ synthetase (PGHS) inhibitors (indomethacin and ibuprofen), surgical PDA ligation and delayed closure using interventional catheterisation. More recently, the effects of paracetamol (acetaminophen) and enteral ibuprofen have been studied. Supportive therapy alone has been advocated in infants who appear to tolerate PDA, while awaiting spontaneous ductal closure.1 2

![Figure 1](image-url)  
**Figure 1**  Echocardiographic assessment of haemodynamic significance of the ductus arteriosus (HSDA).29 (A) Transductal diameter: 3.0 mm=large patent ductus arteriosus (PDA) (small <1.5, moderate 1.5–3.0, large >3.0 mm). (B) Ductal velocity Vmax: 1.5–2.0 m/s=moderate PDA (small >2.0, moderate 1.5–2.0, large <1.5 m/s). (C) Antegrade left pulmonary artery (PA) diastolic flow: 0.3–0.5 m/s=moderate PDA (small <0.3, moderate 0.3–0.5, large >0.5 m/s). (D) Transmitral Doppler E/A wave ratio: approaching 1.0=moderate PDA (small <1, moderate 1–1.5, large >1.5). (E) Left atrial:aortic (LA:Ao) ratio: 1.7=large PDA (small <1.4:1, moderate 1.4±1.6:1, large >1.6:1). (F) Retrograde diastolic flow (%) in descending aorta: >50% =large PDA (grading: small <30%, moderate 30–50%, large >50%).
PROSTAGLANDIN H2 SYNTHETASE INHIBITORS

Indomethacin and ibuprofen reduce prostaglandin-mediated vasodilatation by inhibition of the cyclo-oxygenase (COX) and peroxidase (POX) sites on PGHS. Efficacy decreases postnatally as the balance of vasodilators changes from a system regulated predominantly by prostaglandins to one regulated by other vasodilators. Intravenous indomethacin and ibuprofen appear to have similar efficacy when used prophylactically, but only indomethacin significantly reduces the risk of PVH. Early symptomatic treatment at <29 weeks’ GA achieves closure in 75% of infants. At <27 weeks’ GA, there is reduced efficacy, with a probability of success of only 30.6% for treatment of a symptomatic PDA with standard courses of ibuprofen (10, 5 and 5 mg/kg). A recent Cochrane review reports equivalent efficacy with indomethacin with reduced incidence of NEC, but this may be related to heterogeneity of gestation, dosage and administration route in the meta-analysis. Greater efficacy with higher ibuprofen doses (20, 10, and 10 mg/kg) has been reported at low GA. The optimal age-appropriate dosing schedule is still under consideration, since the effects of ibuprofen on total and free serum bilirubin concentrations raise concerns about the safety of some of the higher dose options. Enteral ibuprofen may offer benefits, possibly because of its longer half-life, even at lower GAs and birth weights. There is biological variability in response to all therapies; longer courses of treatment may be required in some infants, but exposure to PGHS can be minimised by echocardiographic evaluation of individual treatment response.

Major concerns with indomethacin and ibuprofen are their detrimental effects on the gastrointestinal tract and kidneys. Detrimental effects on renal function include oliguria and decreased creatinine clearance. Usually, these can be managed with anticipatory fluid restriction, but PGHS inhibitors should be avoided in patients with hypotension or renal impairment. Epidemiological data suggest an association between PDA, PDA treatment and NEC, but this is not supported by recent studies. The meta-analysis of RCTs that compared oral ibuprofen to indomethacin suggests that oral ibuprofen treatment may be associated with a lower incidence of NEC than indomethacin. Spontaneous intestinal perforation has been associated with both indomethacin and ibuprofen, particularly if given in the first week or with comorbid hypotension or glucocorticoids.

Paracetamol (acetaminophen) has been less extensively studied but appears to have similar efficacy without side effects. PDA closure is probably mediated by inhibition at the POX site of PGHS. Further work is required on optimal dosage regimes, but paracetamol has a wide therapeutic margin, so the risk of hepatotoxicity is low. Although not currently licensed for PDA closure, paracetamol is a promising therapy and should be incorporated into future clinical studies.

CYCLO-OXYGENASE INHIBITORS: TREATMENT STRATEGIES

Different treatment strategies for use of PGHS include prophylaxis, asymptomatic targeted, early symptomatic, late symptomatic and supportive±late rescue. ‘Early’ and ‘late’ symptomatic strategies usually differ by only a few days; studies reporting ‘late symptomatic’ treatment are based on treatment by 10–14 days of age. The evidence for different strategies for a very premature population (<29 weeks’ GA) is summarised below. Consideration should be given to individual patient risk and the NICU’s current strategy and outcomes, including referral for PDA ligation. Suggested treatment doses and schedules are given in table 1.

Prophylactic treatment

Prophylactic treatment has been studied extensively, mostly examining whether treating on day 1 is better or worse than waiting several days before starting treatment in infants who develop symptoms. This approach, with indomethacin, significantly increases efficacy and reduces the incidence of symptomatic PDA, surgical ligation, major PVH, periventricular leucomalacia (PVL) and pulmonary haemorrhage at lower gestational ages, with no significant adverse effects. The benefits

### Table 1 PGHS treatment regimes for PDA

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Prophylaxis: 10 mg/kg followed by 5 mg/kg at 24 and 48 h</th>
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<tbody>
<tr>
<td></td>
<td>Symptomatic: 10 mg/kg followed by 5 mg/kg at 24 and 48 h</td>
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<tr>
<td>Ibuprofen IV</td>
<td>Administer after the first 6 h of life. The final dose need not be given if the duct is closed on echocardiographic review after the second dose.</td>
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<tr>
<td></td>
<td>Should the duct remain open after the third dose, continue with fourth and fifth doses of 5 mg/kg to be given 24 and 48 h after the third dose. If there is absolutely no response after one course, or failure to close after an extended course, further PGHS treatment is frequently ineffective.</td>
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<tr>
<th>Treatment</th>
<th>Symptomatic: 10 mg/kg followed by 5 mg/kg at 24 and 48 h</th>
</tr>
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<tbody>
<tr>
<td>Ibuprofen enteral (20 mg/mL) *</td>
<td>Should the duct remain open after the third dose, continue with fourth and fifth doses of 5 mg/kg to be given 24 and 48 h after the third dose. If there is absolutely no response after one course, or failure to close after an extended course, further PGHS treatment is frequently ineffective.</td>
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<table>
<thead>
<tr>
<th>Treatment</th>
<th>Prophylaxis: 0.2 mg/kg followed by 0.1 mg/kg at 12, 24 and 48 h</th>
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<tr>
<td></td>
<td>Early symptomatic: (2–6 days) 0.2 mg/kg followed by 0.1 mg/kg at 12, 24 and 48 h</td>
</tr>
<tr>
<td>Indomethacin IV†</td>
<td>The final dose need not be given if the duct is closed on echocardiographic review after the second dose.</td>
</tr>
<tr>
<td></td>
<td>Should the duct remain open after the fourth dose, continue with fifth and sixth doses of 0.1 mg/kg to be given 24 and 48 h after the fourth dose. If there is absolutely no response after one course, or failure to close after an extended course, further PGHS treatment is frequently ineffective.</td>
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<table>
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<tr>
<th>Treatment</th>
<th>Late symptomatic: (&gt;7 days) 0.2 mg/kg at 0, 12, 24 and 48 h</th>
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<td></td>
<td>Should the duct reopen after one course, a further course may be worthwhile and would be recommended before referral for PDA ligation. If there is absolutely no response after one course, or failure to close after an extended course, further PGHS treatment is frequently ineffective.</td>
</tr>
</tbody>
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Neither drug should be administered in the presence of renal impairment, thrombocytopenia and/or active bleeding problems. Caution should be exercised in infants with postnatal corticosteroid treatment or hypotension.

*†As per enteral ibuprofen trials. Commercial preparations are hyperosmolar and should be followed by 2 mL/kg of water or milk. This is not a licensed indication.

†Indomethacin should always be infused over at least 30 min.

PDA, patent ductus arteriosus; PGHS, prostaglandin H2 synthetase.
do not extend to late morbidity, mortality or neurosensory impairment, despite the decrease in frequency of major PVH.43 However, in the largest indomethacin prophylaxis trial,42 neurodevelopmental outcomes were defined at 18 months, potentially missing more subtle differences. Importantly, rates of PVH in both treatment arms were so low that it is unlikely that any significant differences in developmental outcomes due to differences in PVH rates would be demonstrable. On the other hand, trials that have followed infants to 8 years of age have found significant improvement in results of neurodevelopmental testing when comparing boys treated with indomethacin prophylaxis versus saline.43 Similar data have been demonstrated for ibuprofen, although with no effect on rates of IVH. In view of concerns about unnecessary exposure of 30–40% of babies to PGHS, prophylactic treatment has not been advocated. However, for individuals at high risk of PVH, pulmonary haemorrhage or PDA ligation, particularly when echocardiography is not readily available, this approach cannot be discounted.

**Early asymptomatic treatment based on echocardiographic findings**

Targeting treatment at babies with early echocardiographic evidence of failure of duct constriction, before symptoms develop, optimises efficacy and avoids universal exposure associated with prophylaxis. A meta-analysis of three small studies demonstrated a reduction in symptomatic PDA and reduced duration of supplemental oxygen, particularly at the lowest birth weights.44 A recent Australian study (DETECT) demonstrated a significant reduction in pulmonary haemorrhage in infants treated with indomethacin compared with a symptomatically managed control group.45 There is no contraindication to this approach in high-risk infants and further study is desirable, particularly at lower GAs.

**Early symptomatic (days 2–5) and late symptomatic (days 10–14) treatment**

Older studies (1982–87), comparing early and late symptomatic treatment,20 suggest early treatment may reduce the duration of mechanical ventilation and bronchopulmonary dysplasia (BPD). However, these findings need to be re-examined now that antenatal betamethasone, surfactant, shorter intubation times and non-invasive respiratory support have become standard. Two recent studies suggest that moderately delayed PDA closure at 11–14 days of life, with modest fluid restriction, can be tolerated and significantly reduces the need for PGHS inhibitors and/ or PDA ligation.46 47 However, since an increase in the combined outcome of chronic lung disease (CLD) and death in the delayed treatment group was reported in one trial,46 and the sickest infants with ‘haemodynamically significant’ PDA were treated in week 1 and thus excluded from recruitment in the other,47 it is difficult to draw conclusions from these studies. Therefore, whilst a modestly delayed treatment approach may be well tolerated by many babies, the impact on long-term outcome in the most fragile babies with early symptomatic PDA is unknown. The effects of further treatment delays beyond 14 days have not been studied, but are likely to result in higher rates of failure to close the PDA.

**SURGICAL LIGATION**

Surgical ligation generally is well tolerated and facilitates extubation in babies with established left ventricular overload.48 Improvements in lung compliance have been demonstrated,49 but transient left ventricular dysfunction,50 51 most likely due to changes in ventricular filling, and a profound, catecholamine-resistant hypotension, due to a low cortisol state, with loss of vaso-motor tone,52 can occur in the 24 h following ligation. In addition, a transient reduction in cerebral blood flow demonstrated by NIRS53 has been described postoperatively, particularly in the least mature infants. Higher incidences of neurosensory impairment,54 and CLD48 have been reported following ligation. These may reflect the degree of illness and immaturity of the infants referred for PDA ligation and highlight the need for illness severity scoring systems to be included in future studies.55 However, surgery may also directly contribute to lung morbidities56 57 and therefore should be avoided where possible. When deemed necessary, there are few studies to determine the optimal timing of PDA ligation. Increasing preoperative inspired oxygen >40% has been associated with late death from BPD,48 but a recent study comparing the effects of early versus moderately delayed ligation for specified criteria (ie, failure to extubate or persistent inotrope support) in infants <28 weeks’ GA demonstrated that delaying ligation for several days (median age at ligation 23 days), or until respiratory and hemodynamic signs become more marked, allowed significant reductions in ligations and the frequency of NEC.58 When this strategy was followed, the incidence of mortality and CLD were low (9% and 40%, respectively). There was also no increase in abnormal neurodevelopment in the ‘selectively’ managed infants. Therefore, provided there has been early prior PGHS inhibitor treatment,48 58 this treatment strategy of modest delay and re-evaluation appears to be appropriate. More urgent ligation should be considered where there are associated comorbidities or contraindications to medical treatment, for example, NEC, gastrointestinal perforation, severe pulmonary haemorrhage, hypotension and inotrope dependency or renal impairment.

**CLOSURE BY INTERVENTIONAL CATHETERISATION**

PDA closure is generally advised by 2 years of age to prevent bacterial endocarditis and pulmonary hypertension. Closure by device in infants with persistent PDA is considered to be a safe alternative, but complications, such as limb ischaemia and misplaced devices, are not infrequent in small infants.59 Although possible at around 2 kg body weight,60 most catheter closures are deferred until patients are considerably older. The effects of prolonged exposure to a PDA on outcome are unknown.

**SUPPORTIVE MANAGEMENT**

This approach has not been evaluated in clinical trials. Antenatal corticosteroids, careful resuscitation, meticulous fluid management and respiratory care are required while awaiting natural, gradual constriction of the ductus arteriosus. This may be a reasonable strategy for the more mature infant (>28 weeks’ GA), provided the infant is thriving, tolerating feeds and requiring minimal respiratory support. Where doubt exists, cardiology review is vital. For less mature infants, particularly those who are ventilator dependent, case series data reporting increased mortality without PDA closure23 26 are of concern. Recent studies suggest that, with modest fluid restriction, PDA may be tolerated for 1–2 weeks without adverse outcome, but the effect of prolonged exposure to PDA and the effect of large PDA shunts on the most vulnerable babies have not been assessed. Further clinical trials are required if we are to understand the effects of increased exposure to the PDA and develop greater certainty about the most appropriate PDA treatments.

**CONCLUSION**

There is evidence that closure of the PDA in the first few weeks of life may provide short-term benefits. There are no studies assessing the effect of either shunt size or the long-term effects...
of untreated PDA in extremely premature infants. Significant changes in management, that is, less PDA treatment, have evolved in recent years, but there is no evidence to support these changes. Carefully constructed clinical trials are required to compare the effects of present treatment strategies (including the use of ligation during the neonatal stay) with more conservative approaches. Future clinical trials involving infants <28 weeks’ GA that examine the risks and benefits of less aggressive treatments should include clinical and echocardiographic PDA scoring systems and novel treatment options. They should also include outcomes that can evaluate the effects of a prolonged period of PDA exposure, such as days of respiratory support, days of gavage feeds, diuretic therapy, growth, need for continuing outpatient cardiology review, late neurodevelopmental follow-up and need for late PDA closure.

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