Yorkshire & Humber Neonatal ODN (Pan) Neonatal Clinical Guideline

Title: Patent Ductus Arteriosus

Author: Updated by Dr Peirce, Dr Van Beek, Dr Stokell, Dr Bustani

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This clinical guideline has been developed to ensure appropriate evidence based standards of care throughout the Yorkshire & Humber Neonatal Network (Pan). The appropriate use and interpretation of this guideline in providing clinical care remains the responsibility of the individual clinician. If there is any doubt discuss with a senior colleague.

A Summary

1. Aim of the guideline

   Guidance for the management of a persistent ductus arteriosus (PDA) in preterm neonates.

2. Summary of recommendations

1. Echocardiography should be performed in patients with clinical signs of PDA to rule out other lesions and assess haemodynamical significance.
2. Repeat echocardiography only if clinical signs worsen or if treatment is considered
3. Repeat echocardiography at/prior to discharge if PDA>1.5mm to guide follow up
4. Decision to treat (conservative and ductal closure) and choice of agent for ductal closure is a consultant led decision
5. Generally only treatment in case of moderate-severe haemodynamically significant PDA (HSDA) using both clinical and echocardiographic findings (see table)
6. Consider intravenous fluid restriction to 120ml/kg/d if signs of left heart volume overloading or pulmonary oedema, whilst maximising nutrition
7. Chlorthiazide and spironolactone are first choice diuretics where indicated
8. Evidence suggests high dose ibuprofen is the most effective treatment option. However rational for choice of agent is included in the table below. Indomethacin not recommended.
9. If choosing to use ibuprofen, please refer to the contra-indications listed below. Oral treatment has been shown to be more effective than IV. Renal function and fluid balance need to be monitored daily.
10. If choosing to use paracetamol please note that the dosing differs from analgesic doses. Extended LFTS need to be monitored, before treatment and on D2 and D4 after commencing treatment.
11. Follow up in local neonatal cardiology clinic if duct still greater than 1.5mm at discharge
12. Referral to paediatric cardiology at Leeds is suggested if requiring diuretics at discharge or to consider for ongoing presence up to one year of age. Please refer to PDA Referral Guideline.

Treatment choice summary table (if treatment decided on):

Age in days	Consider treating if:	Treatment	Alternative treatment if CI
< 72 hours	Large duct (>3mm) on Echo with significant clinical features such as hypotension	Ibuprofen 10/5/5	Paracetamol
72 hrs – 5 days	Moderate PDA Large PDA	Ibuprofen 10/5/5 Ibuprofen 20/10/10	Paracetamol Fluid restriction of IV fluids with growth optimisation
➢ 5 days	Moderate or severe PDA	Ibuprofen 20/10/10	Paracetamol Fluid restriction of IV fluids with growth optimisation Or Diuretics and enteral feeds

This is a summarised approach to treatment choice. However, there may be individual consultant approaches when choosing the agent for a specific baby.

Features which might suggest treating the duct more aggressively include:-

- Hypotension thought to be secondary to duct
- Evidence of GI or renal steal
- Increasing respiratory support requirements thought to be in part related to presence of a PDA
- Failure to make progress on weaning respiratory support as expected for gestation of the baby

B. Full guideline

1. Background

Closure of the ductus arteriosus normally occurs soon after birth as part of a physiological process triggered by increasing PaO_2, reduction in prostaglandins from the placenta and secretion of bradykins by lung tissue. Whilst a persistent ductus arteriosus (PDA) is a common condition in the preterm infant, this will still close spontaneously in a significant proportion of cases (31-47% of those <1000grams, 67-94% of those >1000grams). (1) However, the presence of a PDA is associated with increased mortality as well as significant morbidities, including more severe respiratory distress syndrome (RDS), more prolonged assisted ventilation, pulmonary haemorrhage, chronic lung disease (CLD), necrotising enterocolitis (NEC), renal impairment, intraventricular haemorrhage (IVH) and periventricular leukomalacia (PVL). (2) Whether this is a causal relationship, or whether delayed ductal closure in preterm infants is a reflection of some underlying process also causing increased morbidity is still being debated. (2,3)

2. Aim of the guideline

Guidance for the management of a persistent ductus arteriosus (PDA) in preterm neonates.

3. Scope of the guideline

This guideline for the management of an isolated PDA in *preterm* neonates. Term infants with a PDA, particularly in the context of other congenital heart disease or syndromic anomalies, fall outside its remit.

4. Core Guideline

4.1 Pathophysiology

Antenatally the fetal circulation bypasses the lungs, as the pressures on the right are high and the blood will flow from right to left via the ductus arteriosus. In most term babies functional closure of the duct happens in the first 24hrs. In preterm gestations constriction of the ductus in the first hours after birth varies from minimal constriction to similar constriction that of term infants. As pulmonary pressures drop after delivery and systemic pressures increase in those babies where constriction is minimal the PDA leads to a left to right shunting of blood from the high pressure aorta to the lower pressure pulmonary artery. (3) Problems caused by this shunting can be divided into two pathophysiological issues:

- Increased pulmonary blood flow causing increased pulmonary venous pressures and fluid shift into the pulmonary interstitium. This can lead to pulmonary oedema, pulmonary haemorrhage and more difficult ventilation.

- Decreased systemic blood flow. Reduction of systemic blood flow has been demonstrated as early as 5 hours of age, although subsequently ventricular compensation occurs. (3) Persistence of decreased supply (“ductal steal”) has been demonstrated in cerebral, intestinal and renal blood supply.

4.2 Assessment

Clinical findings:

Clinical signs are present from day one but become more apparent as pulmonary vascular resistance falls over the next few days. Findings are nonspecific and do not always correlate well with echocardiographic findings. (2,4)

- Cardiovascular: Coarse systolic murmur at left sternal border
  Increased precordial impulse
  Prominent or bounding arterial pulses, or palpable pulses in the palms of the hands
  Low systolic and diastolic blood pressure, or low diastolic blood pressure with widened pulse pressure
- Respiratory: Increased O_2 requirement/inability to wean ventilatory support
  Signs of pulmonary congestion (crepitations, haemorrhagic oedema)
- Other: Hepatosplenomegaly
  Suggestive CXR findings
    - enlarged heart
    - increased vascular markings
    - air bronchograms
  persistent or recurrent renal impairment
  feed intolerance/NEC
  Reversed end-diastolic flow on ultrasound Doppler in either in the cerebral circulation or superior mesenteric artery

4.3 Echocardiogram

Echo assessment is used to exclude other lesions as well as to assess the haemodynamic significance of a PDA in the presence of clinical significant findings. This is done by a combination of parameters including; the size of the duct, flow velocity, left heart volume loading (mitral regurgitation, LA:Ao ratio), pressure loading and end organ diastolic flow. (5) Echo findings can be used to guide when to start treatment, which should be a consultant led decision. Generally, only moderate to severe haemodynamically significant PDAs warrant treatment. Repeat echocardiography can be considered if clinical signs worsen. All PDAs >1.5mm should be rescanned at/prior to discharge to ensure ductal closure.

Clinical and echo findings alter not only with severity, but with the progression of time. In the first 72hrs, the only findings of a significant duct may be a large diameter vessel with unrestrictive flow. Beyond this volume overload and steal may become progressively apparent.

Table 1. Clinical and echocardiographic findings depending on the magnitude of haemodynamically significant PDA (HSDA) (5)

	Clinical	Echocardiographic
Mild/ small non-significant PDA	- Oxygenation difficulty (OI<6) - Occasional (<6) episodes of bradycardias, desaturations or apnoea's - Respiratory support (CPAP or ventilation with MAP <8) - Feed intolerance - Radiologic evidence of increased pulmonary vascularity	- Diameter <1.5mm - Restrictive continuous transductal flow (Vmax>2.0m/s) - No left heart volume or pressure loading - Normal end-organ arterial diastolic flow
Moderate HSDA	- Oxygenation difficulty (OI 7-14) - Frequent bradycardias, desaturations or apnoeas - Increasing ventilation requirements (MAP 9-12) - Inability to tolerate feed due to breathlessness - Oliguria with mild creatinine rise - Systemic hypotension requiring single cardiotropic agent - Radiological evidence of cardiomegaly or pulmonary oedema - Mild metabolic acidosis (pH 7.1-7.25, base deficit -7 to -12)	- Diameter 1.5-3.0mm - Unrestrictive pulsatile ductal flow (Vmax <2.0m/s) - Mild-moderate left heart volume loading (LA:Ao ratio 1.5-2:1), bowing of atrial septum - Decreased/absent diastolic flow in SMA, MCA or RA - Mild Mitral regurgitation
Severe/Large HSDA	- Oxygenation difficulty (OI>15) - High ventilation requirements (MAP>12 or HFOV) - Profound or recurrent pulmonary haemorrhage - "NEC-like" abdominal distension - Acute renal failure - Haemodynamic instability requiring > 1 inotropic agent - Moderate – severe metabolic acidosis (pH<7.1 or base deficit > -12	- Diameter >3.0mm - Unrestrictive pulsatile ductal flow (Vmax <2.0m/s) - Severe left heart volume loading (LA:Ao ratio >2:1, moderate/severe MR jet) - Reversed end diastolic flow in SMA, MCA or RA

4.4 Treatment

Treatment of PDA can be subdivided into conservative treatment and treatment aimed at ductal closure. Although there is controversy regarding the correct strategy around ductal closure there is consensus on the risks of untreated left to right shunting. Consideration of treatment is based on both clinical and echocardiographic findings. Generally, only moderate to severe haemodynamically significant PDAs warrant treatment.

For management of hypotension and/or pulmonary haemorrhage please follow the appropriate guidelines.

4.4.1 Conservative treatment

Fluid restriction

Moderate fluid restriction has been suggested as a treatment for PDA. A Cochrane review in 2008 (updated in 2014) included 5 RCTs which found a lower incidence of PDA in patients who had a restricted fluid intake. However, there was no difference in other outcomes including death, IVH and chronic lung disease. (6) Furthermore fluid restriction may limit calorie and protein intake putting babies at increased risk of poor growth and undernutrition. Therefore, routine restriction of fluids is not recommended. For patients with pulmonary oedema or volume loading of the left heart moderate fluid restriction may be beneficial in alleviating these symptoms. Patients who are fluid restricted should be monitored closely for dehydration, systemic hypoperfusion and growth. (7)

Diuretics

Diuretics can alleviate symptoms of pulmonary oedema and volume loading of the left heart. They may be used in patients who continue to be symptomatic despite fluid restriction.

Choice of diuretic: For patients tolerating enteral feeds chlorothiazide and spironolactone should be used. Furosemide is known to stimulate renal synthesis of prostaglandins and may delay duct closure. (8) Therefore use of furosemide should be avoided where possible in the first two weeks of life whilst the duct is usually constricting, unless alternatives cannot be given or fluid overload is present. When the duct is established and unresponsive to closure, with volume overload, furosemide can be considered. Patients on diuretics should be monitored closely for signs of dehydration and hypoperfusion. If furosemide is being used long term (e.g. > 3 weeks), consideration should be made to use renal ultrasound scan to identify developing nephrocalcinosis.

Nutrition management in PDA patients

Optimising nutrition is vital in all neonates but is particularly important in patients with PDA who have been shown to take longer to achieve full enteral feeds and have poorer growth. It is important to only consider fluid restriction in patients where there is evidence of fluid overload or pulmonary oedma. It should be used for shortest period of time possible.
Where a baby in on parenteral nutrition, fluid restriction can be achieved without compromising intake by maximising the nutritional content of PN. Therefore fluid restriction may be the best form of conservative management

Where a baby is receiving predominantly enteral nutrition fluid restriction will significantly impair nutritional intake and growth therefore should be avoided in favour of diuretic treatment.

4.4.2 Medical approaches

Opinions on the correct strategies regarding management of a PDA are divided. Efficacy in ductal closure between ibuprofen, indomethacin and paracetamol is similar. (9,10) Despite achieving ductal closure, multiple RCTs and meta-analysis have not shown a benefit of treatment on long-term outcomes. Discussion is ongoing whether this is lack of evidence or evidence of lack of effect. (2,3,11–14)

Currently there are 4 different treatment strategies for ductal closure:

- Prophylactic - treating all high risk babies in the first 24 hours
- Pre-symptomatic - treating babies in first 72hrs based on ductal patency
- Symptomatic - treating once clinical features and evidence of volume loading on echo is apparent
- No treatment

Symptomatic treatment is most common despite lack of evidence in outcomes. (11) To target treatment, better understanding of the cause of delayed ductal closure, or identification of the subgroup of infants that might benefit from early treatment are needed. Ongoing studies include pre-symptomatic treatment (Baby Oscar) and early versus no treatment (Beneductus). (11,15) Therefore decision to treat and choice of agent should be a consultant led decision.

We suggest the use of ibuprofen unless there are specific GI or renal contraindications, in which case it would be appropriate to use paracetamol.

4.4.2.1 Ibuprofen

Evidence

Ibuprofen reduces prostaglandin formation by inhibiting cyclooxygenase enzymes, thus aiding closure of the PDA. Ibuprofen is significantly more effective than placebo for closing a PDA, in both IV (RR 0.62 95%CI 0.44-0.86) and oral (RR 0.26, 95%CI 0.11-0.62) administration. There was no significant difference in ductal closure compared to indomethacin (RR 1.07, 95%CI 0.92-1.24), but less risk of NEC (RR 0.68, 95% CI 0.49-0.94), oliguria (RR 0.28, 95% CI 0.14-0.54), shorter ventilatory support (MD -2.35 days, 95% CI -3.71 - -0.99) and lower creatinine following treatment. High dose treatment (20-10-10mg or 15-7.5-7.5mg) was more effective than standard dose treatment (10-5-5mg) (moderate quality evidence), with no difference in side effects (low quality evidence), and is likely to become more beneficial with postnatal age due to increasing clearance of Ibuprofen (9)

Conclusion: ibuprofen has the same efficacy, but a better side effect profile and long-term outcomes compared to indomethacin. Oral treatment appears preferential to IV treatment. High dose ibuprofen has better efficacy than standard dose ibuprofen but has not been studied below 3 days of age.

Side effects

GI bleeding, Renal impairment & oliguria. Renal impairment and oliguria are likely to be transient. Oliguria is most marked at the beginning of the course.

Contra indications

- Duct dependent heart lesions
- Thrombocytopenia (plt<50)
- Evidence of active haemorrhage (GI / intracranial)
- Renal impairment (Cr>100), unless felt secondary to ductal steal
- Active NEC
- Life threatening sepsis
- Concurrent treatment with steroids
- Pulmonary hypertension
- Unconjugated hyperbilirubinaemia at or above exchange-line
- For oral ibuprofen – Hepatic failure

Dosing
See also Ibuprofen Monograph
Can be given iv (over 15 minutes) or orally. Oral treatment has been shown to have greater efficacy.

Below five days of age:
Three day course: Day 1: 10mg/kg/day, Day 2 and Day 3: 5mg/kg/day

From five days of age or if the duct is particularly significant (e.g >3mm and evidence of steal), dose should be doubled (20/10/10mg/kg/day). See table below. (20) (21)

Monitoring
Daily platelets and U&E. If significant thrombocytopenia, consider platelet transfusion if ibuprofen is considered essential therapy.
Strict fluid balance

4.4.2.2 Paracetamol

Evidence
In high doses, paracetamol inhibits the synthesis of prostaglandins. There is no difference in ductal closure compared to standard dose ibuprofen (RR 0.95, 95%CI 0.75-1.21), or indomethacin (RR 0.96, 95%CI 0.55-1.65), and no difference in long-term outcomes. Paracetamol carries less risk of side effects compared to ibuprofen (gastrointestinal bleed) or both ibuprofen and indomethacin (creatinine levels, urine output and platelet count), but is less extensively studied compared to these agents. Paracetamol regimes used varied between 10mg/kg 6hrly for 3 days (PO), 15mg/kg 6hrly for 2 days (PO), 15mg/kg 6hrly for 3 days (PO), 15mg/kg 6hrly for 7 days (PO), 15mg/kg 6hrly for 3 days (IV) or 20mg/kg loading followed by 7.5mg/kg 6hrly for 4 days (IV). Clinical effectiveness might depend on duration of treatment and gestation of infant, and further evidence on neurodevelopmental outcomes is recommended. (10)

Side effects
Hepatotoxicity – clinical signs of liver failure develop 2-6 days following administration. Concerns have been raised about the long-term neurodevelopmental effects. There is lack of evidence regarding longterm affects and studies are ongoing.

Contra-indications
Duct dependent heart lesions.
Caution in hepatic impairment.
Do not use in combination with any other preparation containing paracetamol.

Dosing
Oral and IV dosing
15mg/kg 6 hourly for 3 days

After 3 days of either PO or IV treatment the baby should be reassessed for PDA and if still present consider continuing course for 6 days in total.

Age in days	Consider treating if:	Treatment	Alternative treatment if CI
< 72 hours	Large duct (>3mm) on Echo with significant clinical features such as hypotension	Ibuprofen 10/5/5	Paracetamol
72 hrs – 5 days	Moderate PDA Large PDA	Ibuprofen 10/5/5 Ibuprofen 20/10/10	Paracetamol Fluid restriction of IV fluids with growth optimisation
5 days	Moderate or severe PDA	Ibuprofen 20/10/10	Paracetamol Fluid restriction of IV fluids with growth optimisation Or Diuretics and enteral feeds

Liver function tests should be performed prior to commencing paracetamol, at D2 and D4 post commencing paracetamol, to confirm that there is no hepatotoxicity. Paracetamol levels are not required.

4.4.2.3 Indomethacin

Indomethacin is also a cyclo-oxygenase inhibitor which has been shown to be effective in closing a PDA. Prophylactic use has not shown any substantial benefit in mortality or neurodevelopmental outcomes, but has shown short term benefits including PDA closure and reduction in incidence of severe IVH. (14) Efficacy is similar to ibuprofen but with a worse side effect profile and poorer long-term outcomes. (9) Therefore the use of indomethacin is not recommended.

4.4.2.4 Choice of treatment agent.

High dose oral ibuprofen has been shown to be the most effective treatment option (21). This will usually be the treatment of choice.

Above is a summarised approach to treatment choice. However, there may be individual consultant approaches when choosing the agent for a specific baby.

Features which might suggest treating the duct more aggressively include

- Hypotension thought to be secondary to duct
- Evidence of GI or renal steal
- Increasing respiratory support requirements thought to be in part related to presence of a PDA
- Failure to make progress on weaning respiratory support as expected for the gestation of the baby.

The window for successful treatment is debated, but medical management becomes less effective as time passes.

4.4.2.5 Surgical ligation

Duct ligation is associated with significant risk of complications. (2,14,17) There is insufficient evidence to support prophylactic duct ligation in preterm infants. (18) Duct ligation is not a common treatment of choice and is usually reserved for where medical management has failed and it is felt that the duct is significantly contributing to a baby's lack of respiratory improvement, despite optimum respiratory strategies (including consideration of diuretics and/or steroids).

Decision to refer for duct ligation is consultant led and involves referral to Leeds cardiothoracic department (See separate guideline). Complications include intra-operative bleeding, pneumothorax, vocal cord paralysis, chylothorax, and phrenic nerve injury.

Recent changes in practise is a move toward percutaneous catheter closure, which is less invasive. This is dependant on the size of the baby and of the PDA.

4.5 Follow up

All preterm babies with a PDA at discharge >1.5mm should have a follow up scan by a paediatrician with expertise in echocardiogram.

Preterm babies with PDA less than 1.5mm do not need specific cardiology follow-up, they can be clinically assessed for a murmur as part of routine follow-up post discharge.

Referral to paediatric cardiology at Leeds is suggested if requiring diuretics at discharge where these are for PDA management, or to consider for ongoing presentce up to one year of age. Please refer to PDA Referral Guideline.

5. References:

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