University Hospitals of Derby and Burton
NHS Foundation Trust

Patent Ductus Arteriosus (PDA) - NICU
Paediatric Full Clinical Guideline UHDB

Reference no.: NIC RC 15/May 2023/v004

1. Introduction

Patent ductus arteriosus (PDA) is the failure of the ductus arteriosus to spontaneously close in early extra-uterine life. Prostaglandins contribute to maintainingductal patency [1]. PDA is particularly common in babies born at less than 29weeks gestation or with a birth weight below 1000g. PDA remains a significant cause of or associated with morbidity and mortality amongst preterm babies.

Background In intra-uterine life, the PDA diverts majority of ventricular output away from the lungs [2], allowing blood to shunt between the descending aorta and pulmonary artery either as increased flow of oxygenated blood to the pulmonary circulation (left to right shunt) or of deoxygenated blood to the systemic circulation (right to left shunt). Most ducts clinically close around 48 hours of age in both term and preterm babies [3].

2. Aim and Purpose

Ensure standardized approach to the management of babies with PDA and to improve our understanding of PDA and its medical management, by establishing:

a. Uniform evidence-based approach to managing PDA on the unit
b. Strategies to identify and manage risk factors to reduce incidence of PDA.
c. Awareness of, and managing short and long-term complications of PDA
d. Improved understanding of risk and benefit of different treatment options

3. Definitions, keywords

PDA: Patent Ductus Arteriosus
RDS: Respiratory Distress Syndrome
IVH: Intraventricular Haemorrhage
CLD: Chronic Lung Disease
PPHN: Persistent Pulmonary Hypertension of the Newborn
V
V

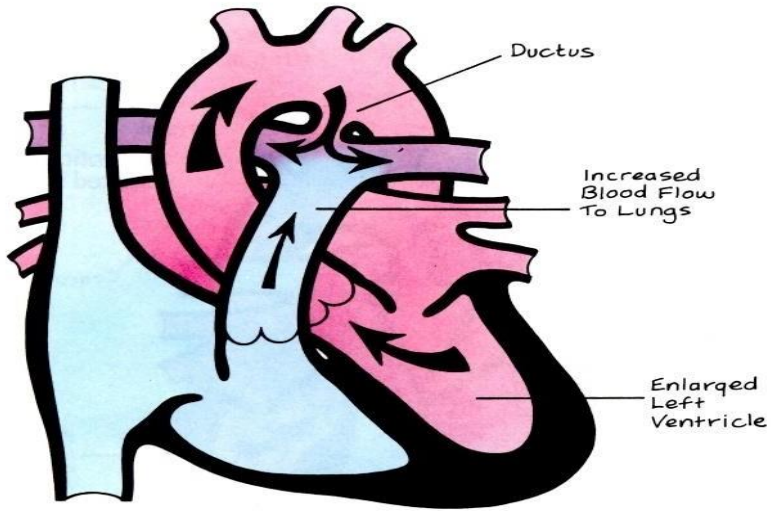

Figure 1: Normal heart with apatent ductus

4. Main body of Guidelines

a. The development of **PDA is multifactorial;** examples include

- **i.** prematurity,
- **ii.** RDS,
- **iii.** lack of antenatal steroids,
- **iv.** ongoing mechanical ventilatory support,
- **v.** infection or
- **vi.** increased pulmonary blood flow.

b. The **clinical consequence**s of a PDA in premature babies include

- **i.** increasing apnoeas,
- **ii.** difficulty weaning from the ventilator,
- **iii.** poor feed tolerance, or
- **iv.** pulmonary haemorrhage.

c. The **clinical signs of a PDA** include *active precordium, systolic or continuous heart murmur, bounding peripheral pulses and hepatomegaly.* Clinical signs are a poor predictor of duct size, and degree of ductal blood flow [4] and should not be used in deciding if to treat the PDA. Management and treatment of PDA should be based on **transthoracic echocardiography,** to confirm the **presence** of a duct, its **size** and assessing **haemodynamic significance.**

d. Pathophysiology of PDA and the preterm baby

- **i. Right to left shunt (pulmonary artery to aorta*):*** raised pulmonary pressure cause deoxygenated blood to move into the systemic circulation, in PPHN.
- **ii. Left to right shunt (aorta to pulmonary artery):** potentially more oxygenated blood volume moves to pulmonary circulation with reduced systemic circulation. Increased pulmonary blood flow is associated with:
  1. Pulmonary haemorrhage, Worsening respiratory distress
  2. Increased mechanical ventilatory support, CLD.
- **iii.** ***Congenital heart defects:*** attention to the early diagnosis of duct dependent cardiac defects before ductal closure is important.

e. Reduced systemic blood flow may result in:

- **i.** Severe IVH, poor cerebral perfusion/ischaemia, hypotension
- **ii.** Poor gut perfusion and ischaemia, Necrotizing enterocolitis (NEC)

f. General principles on how to manage the preterm with a PDA:

- **i. High index of suspicion in at risk groups:** Regularly assess at-risk group (< 30weeks gestation or birth weight < 1500g) for clinical signs of PDA, especially in the first week of life. The clinical signs are a consequence of one or a combination of the following physiological changes:
  - Increased blood to the lungs more than the baby can physiologically handle.
  - Increased left heart volume overload and heart failure if left untreated.
  - Reduced cardiac output with potential for end organ hypoperfusion.
- ii. **Managing risk factors contributing to PDA:** being multifactorial, no single

measure is superior, but a combination of these may help influence the development of PDA.

1. **Respiratory Distress Syndrome (RDS):**
    - **a.** Effective and timely use of antenatal steroids.
    - **b.** Careful attention to prophylactic or rescue surfactant
    - **c.** Effective and appropriate ventilatory modality or support

2. **Treatment of suspected infection:** Early identification and treatment of sepsis

3. **Fluid management in the 1st 72hours of life:** Avoid aggressive intravenous fluid administration or boluses except there is evidence of fluid loss. Intravenous fluid should not exceed 120mls/kg/day, except clinically justified eg excessive fluid loss, dehydration

g. Prophylaxis and prevention of PDA: *pre diagnosis or symptomatic*
The TIPP trial [7] looked at prophylactic indomethacin for babies withbirth weight 500-999g; it showed a decrease in the incidence of PDA and severe IVH but no change in the long-term survival, neurological problems, and no difference in the rates of NEC or gastric perforation [8]. There are no long-term data on prophylactic Ibuprofen, but some reports have shown similar short-term outcomes to indomethacin; some have reported significant decrease in the incidence of PDA on day 3 compared with controls [9].

h. Treating asymptomatic PDA: *targeted echocardiographic diagnosis and pre-symptomatic treatment of PDA between 6-72hrs of age in all high-risk babies.* The result of Baby OSCAR study [14] which looked at the outcome of selective early medical closure of PDA in extremely preterm babies, may guide future practice.

i. Treating haemodynamically symptomatic PDA, *following echocardiographic confirmation;* Ibuprofen or Indomethacin can close the duct in symptomatic babies compared to placebo. Treatment aims to reduce significant short-term morbidities eg CLD, IVH, NEC, mortality or need for surgical ligation [10, 11, 12, 13]. There is no difference in mortality, IVH, or CLD between indomethacin and Ibuprofen, but Ibuprofen significantly reduced NEC incidence [10] and had a less adverse effect on renal function.

j. Treating haemodynamically significant PDA with left heart volume overload: Follow general principles of management of heart failure or pulmonary oedema.

Recommendation

1. Have a high index of suspicion of a clinically apparent PDA in the at-risk group.
2. Careful attention to and management of risk factors.
3. Prophylaxis with Indomethacin or Ibuprofen is not currently recommended.
4. There is no indication to routinely treat PDA in the first 72hrs of life.
5. Universal echocardiography screening of at-risk group is not currently recommended.

k. Echocardiographic assessment of PDA: At risk babies with clinically apparent PDA should have a heart scan before treatment to assess accurately, its haemodynamic significance. Echocardiogram should be performed by appropriately skilled operator.

i. **Timing of echocardiography:** Early ductal size can predict likelihood of closure [15] but not long-term outcome. Consider early (1st 72hrs) echocardiography in at risk babies with **clinically apparent PDA** it alters management.

ii. **Findings on echocardiography [14, 16]:** ascertain cardiac function, haemodynamic significance and exclude significant structural abnormalities of the aorta and arch, before treatment to close the ductus.

iii. **Determine Left atrium to Aortic root ratio (LA/Ao):** by m-mode to assess left atrial dilatation secondary to volume overload of the left heart.
   1. <1.5: no volume overload (NVO)
   2. 1.5-2.0: no significant volume overload (NSVO)
   3. >2.0: significant volume overload (SVO)

iv. **Determine ductal size into:**
   1. <1.5mm(small),
   2. 1.5-2.0mm (moderate) or
   3. >2.0mm(large)

v. **Determine pulsatile pattern.** Determine if the flow is left to right, right to left or bi-directional. Then describe the pulsatility pattern:
   1. Growing
   2. Pulsatile
   3. Closing

vi. **Pulsatility ratio**
Ratio of Max to lowest ductal velocities, > 2.0 is significant.

vii. **It is also useful to determine or comment on:**
   1. Structural Anatomy including pulmonary arteries and aortic arch
   2. Function (gross or formal Left ventricular function)
   3. Ductal steal (retrograde post-ductal aortic flow, Coeliac or SMA)
   4. Exclude PPHN

viii. **Haemodynamically Significant duct –** need at least 3 of these criteria
   1. Moderate to large PDA
   2. LA:Ao ratio ≥ 2
   3. Ductal steal
   4. Unrestricted Pulsatile ductal flow

Recommendation:

1. No routine pre-emptive echocardiogram
2. Early echocardiogram only if clinically apparent PDA in at risk group
3. Echocardiogram should give guidance if the PDA is haemodynamically significant or not

l. **Treating a baby with haemodynamically significant and symptomatic PDA**:
Medical treatment with prostaglandin inhibitors, indomethacin and ibuprofen and recently paracetamol [5] is the treatment of choice; in a Canadian cohort study of very lowbirth-weight infants, 28% required treatment for a PDA; 75% with indomethacin alone, 8% surgical ligation alone, and 17% required both indomethacin and surgical ligation [6]. Haemodynamic significance should be considered with the baby's clinical status before deciding on treatment. There is evidence for and against treating PDA [16, 17-21]; what constitutes 'symptomatic' PDA is controversial but a symptomatic baby with PDA may:

i. Be ventilator dependent beyond 72hours of age
ii. Be unstable on CPAP.
iii. Have unexplained increase in ventilatory or oxygen requirements.
iv. Have significant hypotension with no other obvious cause.
v. Have significant pulmonary haemorrhage
vi. Have significant abdominal distension or suspected NEC or feed intolerance.

Symptomatic baby with significant PDA may be considered for treatment if the benefits outweigh the risks; however, waiting for clinical symptoms from the PDA before treatment may result in complications. Some babies with significant PDA may have no symptoms; a PDA may be a sign of other problems not the cause or majority will **close spontaneously**.

i. **Fluid Management:** fluid restriction does not help to close PDA. PDA may result in circulatory overload, left heart failure and pulmonary oedema [27]; if clinically suspected, we recommend echocardiography before considering fluid restriction [28].
ii. **Oral feeds** to 135-150mls/kg/day if compromised and breathless. Maximize nutrition, monitor weight and liberalize feeds with clinical progress.
iii. **Intravenous fluids** to 120mls/kg/day and maximize parenteral nutrition.
iv. **Diuretics treatment:** consider short term use of diuretics for symptomatic relief if there is echocardiographic or clinical evidence of left heart failure**.** Frusemide and Spironolactone: see BNFc
v. **Prostaglandin inhibitors:** Inhibiting prostaglandin synthesis with ibuprofen, non-selective cyclooxygenase (COX) 1 and 2 non-steroidal anti- inflammatory drugs (NSAID), is effective in closing PDA [2]. Mefenamic acid, has been reported to close PDA [22], but no reported randomised controlled trials [23, 24].
    1. **Indomethacin:** use is associated with NEC, gastrointestinal haemorrhage, alteration of platelet function and impairment of cerebral blood flow or flow velocity [25, 26]. **It is not used in our trust for PDA.**
    2. **Ibuprofen:** a non-selective COX inhibitor is as effective as indomethacin to close PDA, with reduced risk of NEC [24] even in babies <26 weeks gestation, with previous NEC or high creatinine with no other contraindications.
        a. Early treatment in the 1st 72hours of life is most effective.
        b. Delayed treatment (up to 14 days) is less effective.
        c. Ibuprofen is not effective after four weeks of age.
        d. Consider 2nd course after 72hrs if symptomatic and abnormal scan
        e. **Dosage Regime for ibuprofen:** Three IV doses 24 hours apart,

- 10mg/kg first dose
- followed 2 further doses of 5mg/kg**.**

f. **Intravenous infusion:** over 15 minutes usually undiluted (or diluted with 0.9% saline or 5% glucose solution).

- **Relative Contraindications**
- Thrombocytopaenia (platelet count <50)
- Evidence of significant GI/ pulmonary/ IVH (grade 3-4) haemorrhage
- Significant renal impairment (creatinine >100)
- PPHN - Ibuprofen may cause or exacerbate pulmonary hypertension
- Other congenital heart lesions which may be duct dependent.

3. **Paracetamol:** A recent study with infants treated with paracetamol resulted in ductal closure in all within three days and no side effects were observed. The authors suggest that paracetamol may offer therapeutic advantages over NSAIDs as it has no peripheral vasoconstrictive effect, can be given to infants with clinical contraindications to NSAIDs, and appears to be effective even after ibuprofen treatment [5]. Studies are being conducted to validate this observation.

   a. **Dosage regime for paracetamol:** oral paracetamol 15 mg/kg per dose every 6 hours

m. **Post treatment echocardiogram:** should be requested if there is a clinically apparent PDA and baby still symptomatic.

Recommendation:

1. Ibuprofen should be used as medical treatment of symptomatic PDA
2. If baby is in heart failure, consider short term fluid restriction and diuretics.
3. For the duration of treatment, do 12 hourly fluid balance, daily weight, monitor platelets and U&E

n. **Surgical Ligation or device closure of a clinically significant PDA:** Consider duct ligation if medical treatment has failed and the PDA is felt to be significantly contributing to a baby's problems and the baby is beyond 4 weeks of age. The mortality of duct ligation is low but evidence of long-term benefit is lacking [29]; surgical ligation exposes the infant to anaesthetic risk, or associated with significant morbidity- pneumothoraces, chylothoraces, recurrent laryngeal nerve damage and pulmonary oedema. Device closure is not without its risk especially in the small babies.

   i. **Referral** for ligation must be a multi-disciplinary team decision (See EMNODN/EMCHC pathway)

   ii. obtain up to date echocardiogram and send by Echo PACS to paediatric cardiology surgical centre to facilitate network pathway discussion and transfer.

o. Cardiology Follow up on discharge:

Asymptomatic clinically apparent PDA at discharge from the neonatal unit

- local paediatric cardiology follow up 3-4 months in Burton or Derby PEC clinics,
- neonatal follow up clinic with named neonatal or paediatric consultant if required.

- surgically ligated or device closed PDA: as per post-surgical plan.

Recommendation:

1. Consider surgical ligation in symptomatic babies where medical and specific measures have failed or contraindicated. Refer to the EMNODN/EMCHC pathways)
2. Babies diagnosed with PDA should have appropriate follow up on discharge

5. References

1. Mathew Development of the pulmonary circulation: metabolic aspects. In: Polin RA, Fox WW editor(s). *Fetal and Neonatal Physiology*. Vol. 1, Philadelphia: W.B. Saunders, 1998:924–9.

2. Clyman R. Ibuprofen and patent ductus arteriosus. *The New England Journal of Medicine* 2000;343(10):728–30.

3. Rojas MA, Gonzalez A, Bancalari E, et al. Changing trends in the epidemiology and pathogenesis ofneonatal chronic lung disease. J Pediatr 1995; 126:605–10.

4. Davis P, Turner-Gromes S, Cunningham K, et al. Precision and accuracy of clinical and radiologicalsigns in premature infants at risk of patent ductus arteriosus. Arch Pediatr Adolesc Med. 1995;149: 1136-1141

5. Hammerman C, Bin-Nun A, Markovitch E, et al. Ductal closure with paracetamol: a surprising newapproach to patent ductus arteriosus treatment. *Pediatrics* 2011;128(6):e1618–21

6. Lee SK, McMillan DD, Ohlsson A, et al. Variations in practice and outcomes in the Canadian NICUnetwork 1996-1997. *Pediatrics* 2000;106 (5):1070–9

7. Schmidt B, Davis P, Moddemann D, Ohlsson A et al with the TIPP investigators. Long term effects of indomethacin prophylaxis in extremely low birth weight infants. New Engl J Med 2001; 344:1966-1972

8. Fowlie PW, Davis PG. Prophylactic intravenous indomethacin for preventing mortality and morbidity inpreterm infants. Cochrane Database Syst Rev 2010 Jul 7;(7):CD000174.doi:10. 1002/14651858. CD000174.pub2

9. Lago P, Bettiol T, Silvadori S, Pitassi S Safety and efficacy of ibuprofen vs indomethacin in treatment ofpatent ductus arteriosus – a randomised controlled trail. Eur Jour Pediatr 2002: 161; (4) 202-207

10. Ohlsson A, Walia R, Shah SS. Ibuprofen for the treatment of patent ductus arteriosus in preterm and/orlow birth weight infants. Cochrane Database of Systematic Reviews 2013

11. Dollberg S, Lusky A, Reichman B. Patent ductus arteriosus, indomethacin and necrotizing enterocolitisin very low birth weight infants: a population-based study. J Pediatr Gastroenterol Nutr 2005;40:184–8

12. Fowlie PW, Davis PG, McGuire W. Prophylactic intravenous indomethacin for preventing mortality andmorbidity in preterm infants. Cochrane Database of Systematic Reviews 2010;7:CD000174

13. Kluckow M, Jeffery M, Gill A, et al. A randomised placebo-controlled trial of early treatment of the patentductus arteriosus Arch Dis Child Fetal Neonatal Ed 2014;99:F99–F104

14. Outcome after Selective Early Treatment for Closure of Patent Ductus ARteriosus in Pre-term Babies,(OSCAR)

15. Evans N. Patent ductus arteriosus in the neonate. Current Paediatrics 2005; 15: 381-389

16. Evans N: PDA 2013 *www.slhd.nsw.gov.au/rpa/neonatal/html/docs/pda.pdf*

17. Noori S. Patent ductus arteriosus in the preterm infant: to treat or not to treat? J Perinatol 2010;30 Suppl:S31-7

18. Clyman RI, Chorne N. Patent ductus arteriosus: evidence for and against treatment. J Pediatr2007;150(3):216-9

19. Bose CL, Laughon MM. Patent ductus arteriosus: lack of evidence for common treatments. Arch DisChild Fetal Neonatal Ed 2007;92(6):F498-502

20. Benitz WE. Patent Ductus Arteriosus: to treat or not to treat? Arch Dis Child Fetal Neonatal Ed

21. Heuchan AM, Clyman RI. Managing the patent ductus arteriosus: current treatment options. Arch DisChild Fetal Neonatal Ed fetalneonatal-2014-306176 doi:10.1136/archdischild-2014-306176

22. Sakhalkar VS, Merchant RH. Therapy of symptomatic patent ductus arteriosus in preterms withmefenemic acid and indomethacin. *Indian Pediatrics* 1992;29(3):313–8

23. Ohlsson A, Shah SS. Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birthweight infants. *Cochrane Database of Systematic Reviews* 2011, Issue 7. [DOI: 10.1002/14651858. CD004213.pub3]

24. Ohlsson A, Walia R, Shah SS. Ibuprofen for the treatment of patent ductus arteriosus in preterm or lowbirth weight (or both) infants. *Cochrane Database of Systematic Reviews* 2015, Issue 2. [DOI: 10. 1002/14651858.CD003481.pub6; PUBMED: 23633310]

25. Edwards AD, Wyatt JS, Richardson C, et al Effects of indomethacin on cerebral haemodynamics in verypreterm infants. *Lancet* 1990;335 (8704):1491–5.

26. Ohlsson A, Bottu J, Govan J, et al Effect of indomethacin on cerebral blood flow velocities in very lowbirth weight neonates with patent ductus arteriosus. *Developmental Pharmacology and Therapeutics*1993;20(1-2):100–6.

27. Bell EF, Warburton D, Stonestreet BS, Oh W. Effects of fluid administration on the development of symptomatic patent ductus arteriosus and congestive heart failure in premature infants, N Engl J Med1980; 302: 598-604

28. Bell EF, Acarregui MJ. Restricted vs liberal water intake for preventing morbidity and mortality in preterminfants. Cochrane Database Syst Rev. 2008;(1):CD00503

29. Brooks JM, Travadi JN, Patole SK et al. Is surgical ligation of patent ductus arteriosus necessary? TheWestern Australian experience of conservative management. Arch Dis Child. Fetal Neonatal Ed. 2005;90: 235-239

Documentation Controls

Reference Number NIC RC 15	**Version:** V004		**Status** Final	
Version / Amendment History	Version	Date	Author	Reason
	V004	May 2023	Dr B Etuwewe	Renewal of guideline
Intended Recipients:				
Training and Dissemination:.				
Development of Guideline: Dr Bemigho Etuwewe **Job Title: Paediatric Consultant**				
In Consultation with: Obstetric, Neonatal and Paediatric (QHB) **consultants**				
Linked Documents: None				
Keywords: Ibuprofen, fluid regime, ductal ligation, patent ductus arteriosus, PDA				
Business Unit Sign Off	**Group:** Paediatric Guidelines Group **Date: 17/07/23**			
Divisional Sign Off	**Group:** Divisional Performance & Quality Meeting **Date:** 20th July 2023			
Date of Upload	July 2023			
Review Date	May 2026			
Contact for Review	Dr Bemigho ETUWEWE bemighoetuwewe@nhs.net			

Audit standards: to be carried out at least once every 3 years

a. Prior to medical treatment, 100% of babies must have haemodynamic significant PDA evidenced by 3 of 4 echocardiographic criteria.
b. 100% of babies with PDA treated with NSAIDs must have:
    i. Platelets >50 before each dose
    ii. Serum creatinine <100 before each dose
    iii. 12 hourly fluid balance and daily weight for the duration of their treatment
c. Other information:
    i. How many babies with clinical and echocardiographic evidence of left heartfailure were fluid restricted and or given diuretics.
    ii. How many babies with PDA were treated paracetamol
    iii. How many PDAs were successfully closed by NSAIDs
    iv. How many PDAs were sent for device closure or surgical ligation
    v. How many babies treated for PDA (medical or surgical) have CLD at 36weeks gestational age.
    vi. How many babies developed side effects attributable to NSAID