THAMES VALLEY & WESSEX NEONATAL OPERATIONAL DELIVERY NETWORK

THAMES VALLEY GUIDELINE FOR PATENT DUCTUS ARTERIOSUS (PDA) IN PRETERM INFANTS	
Approved by /on:	**Thames Valley & Wessex Neonatal ODN Governance Group** **28 April 2016**
Date of publication	**OUH 14 September 2015**
Last Reviewed	**May 2019**
Review date *(Max 3 years)*	**May 2022**
Authors	**Dr Zoltan Molnar, Neonatal Consultant, OUH**
Distribution	**Thames Valley Neonatal Clinical Forums** **Thames Valley and Wessex Neonatal Network website** **Thames Valley and Wessex Neonatal Network e-bulletin**
Related documents	**References**

1. Benitz WE. Treatment of persistent Patent Ductus Arteriosus in preterm infants: time to accept the null hypothesis? J Perinatol. 2010 Apr; 30(4):241-52. Review
2. Heuchan AM, Clyman RI. Managing the Patent Ductus Arteriosus: current treatment options. Arch Dis Child Fetal Neonatal Ed. 2014 Sep; 99(5):F431-6. Review
3. Ohlsson A, Walia R, Shah SS. Ibuprofen for the treatment of Patent Ductus Arteriosus in preterm and/or low birth weight infants. Cochrane Database Syst Rev. 2013 Apr 30; 4. Review
4. Evans N. http://www.sswahs.nsw.gov.au/rpa/neonatal/content/pdf/guidelines/2013 Guideline
5. Clyman RI, Couto J, Murphy GM. Patent Ductus Arteriosus: are current neonatal treatment options better or worse than no treatment at all? Semin Perinatol. 2012 Apr;36(2):123-9. Review.
6. Schmidt B, Davis P, Moddemann D, Ohlsson A, Roberts RS, Saigal S, Solimano A, Vincer M, Wright LL; Trial of Indomethacin Prophylaxis in Preterms Investigators. Long-term effects of indomethacin prophylaxis in extremely-low-birth-weight infants. N Engl J Med. 2001 Jun 28; 344(26):1966-72.
7. Alfaleh K, Smyth JA, Roberts RS, Solimano A, Asztalos EV, Schmidt B; Trial of Indomethacin Prophylaxis in Preterms Investigators. Prevention

and 18-month outcomes of serious pulmonary hemorrhage in extremely low birth weight infants: results from the trial of indomethacin prophylaxis in preterms. Pediatrics 2008 Feb; 121(2):233-8.

8. Van Overmeire B, Allegaert K, Casaer A, Debauche C, Decaluwé W, Jespers A, Weyler J, Harrewijn I, Langhendries JP. Prophylactic ibuprofen in premature infants: a multicentre, randomised, double-blind, placebo-controlled trial. Lancet.2004 Nov 27-Dec 3; 364(9449):1945-9.
9. Dani C, Bertini G, Pezzati M, Poggi C, Guerrini P, Martano C, Rubaltelli FF; ItraVentricularIbuprofen Study Group. Prophylactic ibuprofen for the prevention of intraventricular hemorrhage among preterm infants: a multicenter, randomized study. Pediatrics. 2005 Jun; 115(6):1529-35.
10. Kluckow M, Jeffery M, Gill A, Evans N. A randomised placebo-controlled trial of early treatment of the Patent Ductus Arteriosus. Arch Dis Child Fetal Neonatal Ed. 2014 Mar; 99(2):F99-F104.
11. Aranda JV, Clyman R, Cox B, Van Overmeire B, Wozniak P, Sosenko I, Carlo WA, Ward RM, Shalwitz R, Baggs G, Seth A, Darko L. A randomized, double-blind, placebo-controlled trial on intravenous ibuprofen L-lysine for the early closure of nonsymptomatic Patent Ductus Arteriosus within 72 hours of birth in extremely low-birth-weight infants. Am J Perinatol. 2009 Mar; 26(3):235-45.
12. Van Overmeire B, Van de Broek H, Van Laer P, Weyler J, Vanhaesebrouck P. J Early versus late indomethacin treatment for Patent Ductus Arteriosus in premature infants with respiratory distress syndrome. Pediatr. 2001 Feb; 138(2):205-11.
13. Sosenko IR, Fajardo MF, Claure N, Bancalari E. Timing of Patent Ductus Arteriosus treatment and respiratory outcome in premature infants: a double-blind randomized controlled trial. J Pediatr. 2012 Jun; 160(6):929-35.
14. Kaempf JW, Wu YX, Kaempf AJ, Kaempf AM, Wang L, Grunkemeier G. What happens when the Patent Ductus Arteriosus is treated less aggressively in very low birth weight infants? J Perinatol. 2012 May; 32(5):344-8.
15. Clyman R and Noori S. The very low birth weight neonate with haemodynamically significant Ductus Arteriosus in the first postnatal week. Section C Chapter 13. Neonatology Questions and Controversies: Hemodynamics and Cardiology. Edited by Kleinman CS and Seri I, Second Edition, Elsevier Saunders. 2012
16. Heuchan AM, Young D. Early colour Doppler duct diameter and symptomatic Patent Ductus Arteriosus in a cyclo-oxygenase inhibitor naïve population. Acta Paediatr. 2013 Mar; 102(3):254-7.
17. Rolland A, Shankar-Aguilera S, Diomandé D, Zupan-Simunek V, Boileau P. Natural evolution of Patent Ductus Arteriosus in the extremely preterm infant. Arch Dis Child Fetal Neonatal Ed. 2014 Aug 28. Epub ahead of print

	18. Weisz DE, McNamara PJ. J Patent Ductus Arteriosus ligation and adverse outcomes: causality or bias? J Clin Neonatol. 2014 Apr;3(2):67-75. Review 19. Jhaveri N, Moon-Grady A, Clyman RI. Early surgical ligation versus a conservative approach for management of Patent Ductus Arteriosus that fails to close after indomethacin treatment. J Pediatr. 2010 Sep; 157(3):381-7. 20. Hammerman C, Bin-Nun A, Markovitch E, Schimmel MS, Kaplan M, Fink D. Ductal closure with paracetamol: a surprising new approach to Patent Ductus Arteriosus treatment. Pediatrics. 2011 Dec; 128(6):e1618-21. 21. El-Khuffash A, Jain A, Corcoran D, Shah PS, Hooper CW, Brown N, Poole SD, Shelton EL, Milne GL, Reese J, McNamara PJ. Efficacy of paracetamol on Patent Ductus Arteriosus closure may be dose dependent: evidence from human and murine studies. Pediatr Res. 2014 Sep;76(3):238-44. 22. Nadir E, Kassem E, Foldi S, Hochberg A, Feldman M. Paracetamol treatment of Patent Ductus Arteriosus in preterm infants. J Perinatol. 2014 Oct; 34(10):748-9. 23. Allegaert K, Anderson B, Simons S, van Overmeire B. Paracetamol to induce Ductus Arteriosus closure: is it valid? Arch Dis Child. 2013 Jun; 98(6):462-6. Review. 24. Clyman R, Wickremasinghe A, Jhaveri N, Hassinger DC, Attridge JT, Sanocka U, Polin R, Gillam-Krakauer M, Reese J, Mammel M, Couser R, Mulrooney N, Yanowitz TD, Derrick M, Jegatheesan P, Walsh M, Fujii A, Porta N, Carey WA, Swanson JR; Ductus Arteriosus Feed or Fast with Indomethacin or Ibuprofen (DAFFII) Investigators. Enteral feeding during indomethacin and ibuprofen treatment of a Patent Ductus Arteriosus. J Pediatr. 2013 Aug; 163(2):406-11. 25. Richards J, Johnson A, Fox G, Campbell M. A second course of ibuprofen is effective in the closure of a clinically significant PDA in ELBW infants. Pediatrics. 2009 Aug; 124(2):e287-93. 26. Lago P, Salvadori S, Opocher F, Ricato S, Chiandetti L, Frigo AC. Continuous infusion of ibuprofen for treatment of Patent Ductus Arteriosus in very low birth weight infants. Neonatology. 2014; 105(1):46-54.
Implications of race, equality & other diversity duties for this document	**This guideline must be implemented fairly and without prejudice whether on the grounds of race, gender, sexual orientation or religion.**

Thames Valley Guideline for Patent Ductus Arteriosus (PDA) in Preterm Infants		
Contents		
Paragraph		**Page**

1.0 Aim of Guideline

A guideline framework to manage the treatment of Patent Ductus Arteriosus (PDA) with Ibuprofen. This is only indicated in the presence of one or more definite clinical symptoms **and** ECHO evidence of haemodynamically significant PDA

2.0 Scope of Guideline

This guideline applies to all Neonatal Units covered by Thames Valley Neonatal ODN. This includes the following hospitals.

Thames Valley	
Buckinghamshire Healthcare NHS Trust	- Stoke Mandeville Hospital, Aylesbury
Frimley Health NHS Foundation Trust	- Wexham Park Hospital, Slough
Milton Keynes University Hospital NHS Foundation Trust	- Milton Keynes General Hospital
Oxford University Hospitals NHS Foundation Trust	- John Radcliffe Hospital, Oxford
Oxford University Hospitals NHS Foundation Trust	- Horton General Hospital, Banbury
Royal Berkshire NHS Foundation Trust	- Reading

3.0 Management Summary

Routine ECHO screening for PDA in ventilated preterm infants is not indicated.
Consider ECHO if **clinical symptoms** and physical signs (murmur, hyperactive praecordium, bounding pulses, wide pulse pressure) suggest pulmonary problems or ductal steal as defined below:

- **Pulmonary problems** due to large left-to-right shunt volume, such as:

    1. In ventilated preterms:
        a. persistent ventilator dependence
        b. deteriorating respiratory status without other obvious explanation
            i. infants ≥ 27^{+0} weeks gestational age: FiO_2 > 40%, Mean airway Pressure > 12 cmH_2O
            ii. infants ≤ 26^{+6} weeks gestational age: FiO_2 > 30%, Mean airway Pressure > 10 cmH_2O
        c. pulmonary haemorrhage
        d. radiological features of pulmonary oedema

    2. On High-flow Therapy or nCPAP:
        a. increasing FiO_2 requirement (especially with radiological features of pulmonary oedema)
        b. increasing work of breathing, dyspnoea and recurrent apnoea

- **Ductal steal** from systemic circulation, such as:
    a. hypotension without other explanation
    b. unable to wean from inotropes
    c. persistent metabolic acidosis

The sensitivity of physical signs can be low in the first week of life, therefore if clinical symptoms are suggestive of a PDA request an ECHO.

ECHO features of a haemodynamically significant PDA

Feature	Significant Values
Size of PDA • **Large** • **Moderate**	 • **> 2.0 mm** • **1.5 − 2.0 mm**
Flow through PDA	**Continuous L-to-R flow with unrestrictive flow pattern (V_{max} < 2.0 m/s and V_{min} < ½ V_{max})**
LA:Ao ratio (less sensitive when there is concurrent L-to-R shunt via PFO)	**> 1.5**
Descending aorta flow	**Holodiastolic flow reversal**
Mean and end-diastolic velocity in Left Pulmonary Artery	**V_{Mean} > 0.4 m/s** **$V_{End\ Dias}$ > 0.2 m/s**

Conservative management:

Fluid restriction
Consider fluid restriction and diuretic therapy in infants with haemodynamically significant PDA.

PEEP
Consider increasing PEEP by 1-2 cmH_2O if ventilated or on nCPAP.

Correct anaemia
Transfuse with co-administration of diuretics.

Pharmacological treatment:

Ibuprofen
A course of 3 doses, at 24-hour intervals by slow iv injection over 15 minutes or continuous infusion, as follows:
Day 1 of treatment: Ibuprofen **10 mg/kg** iv
Day 2 of treatment: Ibuprofen **5 mg/kg** iv
Day 3 of treatment: Ibuprofen **5 mg/kg** iv

A second course of 3 doses of Ibuprofen may be given if the PDA has not closed 24-48 hours after the last dose or if it re-opens.

Contraindications
Life-threatening infection; active bleeding; thrombocytopenia (platelets <50); coagulation defects; significant renal impairment; known/suspected NEC; pulmonary hypertension; duct-dependent circulation; recent grade 3-4 IVH (within 24 hours).

Feeding

Cautious enteral feeding can usually be continued during treatment.

Paracetamol

Current literature suggests that Paracetamol (15 mg/kg, QDS, iv or oral) for 3-7 days can be effective in selected cases. It should be considered when medical treatment with ibuprofen has failed or there are definite contraindications to Ibuprofen (usually due to medical or surgical NEC). Discuss with consultant and/or cardiologist and monitor liver function during treatment.

Ligation:

If medical treatment has failed, refer for a paediatric cardiology opinion.
Ligation is usually only indicated in cases of symptomatic PDA when there is no other explanation for symptoms such as:

1. Increasing ventilatory requirement over several days (FiO_2 > 40-50%, MAP >12-13 cmH_2O) with signs of pulmonary hyperaemia on the CXR
2. Persistent hypotension requiring inotropic support
3. Persistent oliguria/renal failure

In selected cases, paracetamol (15 mg/kg, QDS, iv or oral for 3-7 days) could be an alternative approach to ligation.

4.0 Full Guideline for Management of the Patent Ductus Arteriosus (PDA)

Rationale for treating PDAs

Left-to-right shunt from the systemic to the pulmonary circulation via the PDA can lead to

1. Increased pulmonary blood flow with resultant
   - pulmonary oedema
   - increased O_2 requirement
   - inability to wean from ventilator
   - pulmonary haemorrhage
   - Chronic lung disease (CLD)

2. Systemic hypoperfusion with resultant
   - tachycardia
   - hypotension
   - persistent lactic acidosis
   - inability to wean from inotropes
   - compromised end-organ perfusion
     - GI system: feeding intolerance and increased incidence of necrotising enterocolitis (NEC)
     - Kidneys: oliguria, anuria
     - Brain: periventricular luekomalacia (PVL) (hypoperfusion) and intraventricular haemorrhage (IVH) (hypoperfusion-reperfusion injury)

Despite these potential complications, clear evidence is lacking from randomised controlled trials (RCT), as to whether active management of the PDA influences survival and other important long term outcomes (1, 2, 3). In view of the recent debate in the relevant literature it is hard to establish an evidence-based treatment approach.

Terminology (adapted from Reference 4)

Haemodynamically significant PDA: when **ultrasound** findings are consistent with a moderate-to-large ductal diameter with a range of indirect ultrasound markers of large shunt volume.

Symptomatic PDA: PDA **plus clinical symptoms** due to large shunt volume, such as persistent ventilator dependence, deteriorating respiratory status, increasing recurrent apnoea, pulmonary haemorrhage and signs of ductal steal from the systemic circulation (hypotension, unable to wean from inotropes, persistent metabolic acidosis). Unfortunately, these symptoms are **not specific** for PDA.

Clinically apparent PDA: when physical signs are consistent with a PDA (murmur, active praecordium or full pulses, wide pulse pressure)

Which infants should be considered for treatment
An empiric cut-off of 1000 g is used as this will include all extremely preterm infants. It will also include those less preterm infants who are growth restricted and therefore more at risk of complications attributable to a PDA. Infants less than 1000 g are more likely to have a significant PDA, and these are less likely to close spontaneously (5).

When to start treatment (with literature data and commentary)

Figure 1: Timing of different treatment options

Treatment approach can be:

1. **Prophylactic**: within 6-24 hours of birth without selection.
   Advantage: treatment is provided before the evolution of clinical symptoms and potential consequences.
   Disadvantage: unnecessary exposure to potential side effects of cyclooxygenase (COX) inhibitors of infants with spontaneous closure.
   - **Indomethacin** can decrease the incidence of symptomatic PDA, surgical ligation, pulmonary haemorrhage, major IVH and periventricular leukomalacia (6, 7), but no benefit has been shown with respect to long term neurodevelopmental outcome (6).
   - Unlike prophylactic indomethacin, prophylactic **Ibuprofen** has no effect on clinically important outcome measures (8, 9).

2. **Pre-symptomatic**: Two alternatives depending on the time of echo screening.
   1. **Echo screening** in the **first 12 hours** to assess ductal diameter → Treatment given if PDA > 1.3 – 1.8 mm (without considering echo signs of haemodynamic significance)
      Advantage: treatment is given before the evolution of clinical symptoms, but only to those infants whose PDA would not close spontaneously (as predicted from size measurement).

Disadvantage: every preterm infant < 1000 g (or GA < 29 weeks) would need echo screening after admission

- According to a recent RCT **Indomethacin** treatment administered according to this protocol reduced the incidence of early pulmonary haemorrhage (2% vs 21%) and there was a trend towards less IVH/PVH (4.5% vs 12%) (10).
- No literature data on **Ibuprofen**.

2. **Echo screening** in the **first 3 days** of life of infants receiving ventilatory assistance to assess ductal size and haemodynamic significance → Treatment given if PDA > (1.5-) 2 mm **with** echo signs of haemodynamic significance

   Advantage: treatment is given before the evolution of clinical symptoms, but only to infants with haemodynamically significant PDA.

   Disadvantage: unnecessary exposure to potential side effects of COX inhibitors of the sub-group on infants with positive echo findings who would not have gone on to develop clinical symptoms.

   - According to a recent RCT **Ibuprofen** treatment administered according to this protocol can reduce the composite outcome of 'death, study drop out and the need for later ductal treatment' (31% vs 53%), but has no effect on other parameters, such as pulmonary haemorrhage, IVH, PVL, NEC, ROP, BPD or death (11).

3. **Early and Late symptomatic**: Only babies with symptomatic PDA (please see clinical symptoms above) would undergo echo assessment usually within the first 3 - 7 days of life (Early) or after 7 days of life (Late) → Treatment given if echo demonstrates haemodynamically significant PDA responsible for clinical symptoms.
   - Widespread treatment approach. No convincing literature evidence on the long-term benefits of Early versus Late treatment (12, 13, 1). However, 'rescuing' infants with open-label drug administration in most studies in the 'Late' treatment arm needs to be considered, before drawing any conclusion. Therefore, it is more appropriate to say, that 'Late' treatment is probably safe, provided babies with definite, severe clinical signs of pulmonary overcirculation (such as pulmonary haemorrhage, escalating ventilatory requirement (FiO_2 ≥ 0.5, P_{aw}≥ 13 H_20 cm)) and/or systemic hypoperfusion (such as inability to wean from inotropes) are 'rescued' (12, 13, 2). One recent study found higher combined incidence of CLD and death in the 'Late treatment' group (14).

4. **No, or very restricted, use of COX inhibitors:** only conservative treatment provided (fluid restriction, diuretics, high PEEP). Medical or surgical intervention only in those with very severe symptoms.
   - Hardly any literature data on this approach (1, 15). Two recent papers (retrospective cohort studies) raise concerns about the safety of this approach (16, 17).

On one hand, there is a recent trend among neonatologists towards expectant management due to the lack of evidence from RCTs demonstrating a clear benefit from early, aggressive management on long-term outcome measures. On the other hand, open-label rescue treatment in the non-interventional arm in numerous RCTs makes it hard to draw a conclusion about the 'real' mid- and long-term effects of untreated left-to-right ductal shunt.

Selecting the most suitable treatment approach is further complicated by the fact that **Indomethacin** is currently **not available** in Europe.

- Prophylactic treatment **(1.1.)** with Ibuprofen is not supported by literature data.
- No data is available, as to whether very early (first 12 hours of life) Pre-symptomatic echo-targeted treatment **(2.1.)** with Ibuprofen would yield the same results as have recently been demonstrated with Indomethacin. This approach would also require echo screening within a relatively short time-frame after every admission.
- Pre-symptomatic treatment with Ibuprofen in the first 3 days **(2.2.)** showed a difference only in the combined outcome (death, study drop out and the need for later ductal treatment), but had

no statistically significant effect on other parameters, such as pulmonary haemorrhage, IVH, PVL, NEC, ROP, BPD or death.

- No, or very restricted use, of COX inhibitors **(4.)** might not be safe.

- **Late Symptomatic treatment (3.) would be preferable**, provided babies with definite clinical signs of pulmonary overcirculation or systemic hypoperfusion are 'rescued'.

Clinical symptoms indicating treatment can be summarised, as below:

- **Pulmonary problems** due to large left-to-right shunt volume, such as:

- In ventilated preterm infants:
  a. persistent ventilator dependence
  b. deteriorating respiratory status without other obvious explanation
     i. infants ≥ 27^{+0} weeks gestational age: FiO_2 > 40%, Mean airway Pressure > 12 cmH_2O
     ii. infants ≤ 26^{+6} weeks gestational age: FiO_2 > 30%, Mean airway Pressure > 10 cmH_2O
  c. pulmonary haemorrhage
  d. radiological features of pulmonary oedema

- On High-flow Therapy or nCPAP:
  a. increasing FiO_2 requirement (especially with radiological features of pulmonary oedema)
  b. increasing work of breathing, dyspnoea and recurrent apnoea

- **Ductal steal** from systemic circulation, such as:

  a. hypotension without other explanation
  b. unable to wean from inotropes
  c. persistent metabolic acidosis

Ligation

Infants with symptomatic PDA who have not responded to 2 courses of ibuprofen or in whom COX treatment is contraindicated should be referred for a paediatric cardiology opinion with regard to surgical ligation.

There is no evidence to support ligation as first line therapy and ligation is associated with increased rate of CLD, retinopathy of prematurity and long term neurodevelopmental impairment. On the other hand, there is a current debate in the literature, as to whether this association represents causality or is only a consequence of the 'sicker' preterm population referred for ligation (18).

Expectant management after no response to medical treatment versus early, aggressive ligation (i.e within 2 days if no response to Indomethacin) was reported to be a safe approach with even lower incidence of NEC (19).

Therefore, ligation should be considered only in those cases of symptomatic PDA and when there is no other explanation for symptoms such as (19):

1. Increasing ventilatory requirement over several days (FiO_2 > 40%, P_{aw} >12 cmH_2O) with signs of pulmonary hyperaemia on the CXR
2. Persistent hypotension requiring inotropic support
3. Persistent oliguria/renal failure or metabolic acidosis

In selected cases, an alternative approach to ligation could be the commencement of Paracetamol (15 mg/kg, QDS, iv or oral for 3-7 days) in view of very recent literature data (20, 21, 22, 23).

Conservative management:

Fluid restriction

Infants with haemodynamically significant PDA can have increased pulmonary blood and lymphatic flow and may develop volume overload and cardiac failure. They should therefore be fluid restricted by ~30%, except if serum sodium is high indicative of dehydration. Restriction should continue until echo demonstrates no significant left-to-right shunt or serum sodium is >147 mmol/l. Once full enteral feeding has been established, fluid intake can be increased in order to reach adequate energy and protein intake with the concurrent administration of diuretics.

PEEP

Increase PEEP by 1-2 cmH_2O if ventilated or on nCPAP. No data on High-flow therapy.

Correct anaemia
Keep Hb > 12 g/L in ventilated preterm infants with significant PDA. Transfuse with co-administration of diuretics.

Feeding

Ductal steal associated with a large PDA may result in altered gut perfusion, however cautious enteral feeding can usually be continued during treatment in view of current literature data (19, 24).

Pharmacological treatment:

Which drug?

Indomethacin is currently unavailable. Ibuprofen is as effective as Indomethacin in closing a PDA and reduces the risk of NEC and transient renal insufficiency (3).

Ibuprofen for treatment of Patent Ductus Arteriosus

Indication

Licensed for closure of Patent Ductus Arteriosus in premature neonates less than 34 weeks gestational age.

Dose

A course of 3 doses, at 24-hour intervals by slow iv injection over 15 minutes or continuous infusion, as follows:
Day 1 of treatment: Ibuprofen **10 mg/kg** iv
Day 2 of treatment: Ibuprofen **5 mg/kg** iv
Day 3 of treatment: Ibuprofen **5 mg/kg** iv

A second course of 3 doses of Ibuprofen may be given if the PDA has not closed 24-48 hours after the last dose or if it re-opens. Success rate largely depends on gestational age. Lower gestational age is usually associated with lower efficacy (efficacy is < 50% in preterms < 26 weeks) (25). Continuous

infusion has been demonstrated to improve closure, especially in the extremely preterm population (80% versus 34%, (26)).

Contraindications

Life-threatening infection; active bleeding; thrombocytopenia (platelets <50); coagulation defects; significant renal impairment; known/suspected NEC; pulmonary hypertension; duct-dependent circulation, recent IVH (within 24 hours).

Side effects

GI perforation (consider Ibuprofen carefully in IUGR and after hydrocortisone administration due to pressor-resistant hypotension); increased serum creatinine; hyponatraemia; oliguria; fluid retention; acute renal failure, platelet dysfunction and thrombocytopenia; neutropenia; haematuria; pulmonary haemorrhage; IVH; PVL. Less common: GI haemorrhage; hypoxaemia.

Monitor/Caution

Watch for signs of bleeding; may mask symptoms of infection; monitor renal function. Ibuprofen may decrease clearance of aminoglycosides so strict surveillance of serum levels is recommended. In cases of oliguria or rising creatinine, doses of aminoglycosides should be held until levels are available. Ibuprofen interferes with bilirubin-albumin binding increasing unbound bilirubin and should not be used in infants with hyperbilirubinaemia approaching exchange transfusion levels.

Paracetamol for treatment of Patent Ductus Arteriosus

Current literature data suggest that Paracetamol (15 mg/kg, QDS, iv or oral) for 3-7 days is effective in selected cases when medical treatment failed with Ibuprofen or there are contraindications to Ibuprofen (usually due to medical or surgical NEC) (20, 21, 22 , 23).

Discuss with consultant and/or cardiologist before commencing Paracetamol and monitor liver function during treatment. There is not enough evidence to support Paracetamol as the first line treatment.

Echocardiogram features of a haemodinamically significant PDA

Feature	Significant Values
Size of PDA • **Large** • **Moderate**	• **> 2.0 mm** • **1.5 − 2.0 mm**
Flow through PDA	**Continuous L-to-R flow with unrestrictive flow pattern (Vmax < 2.0 m/s and Vmin < ½ Vmax)**
LA:Ao ratio (less sensitive when there is concurrent L-to-R shunt via PFO)	**> 1.5**
Descending aorta flow	**Holodiastolic flow reversal**
Mean and end-diastolic velocity in Left Pulmonary Artery	**V_{Mean} > 0.4 m/s** **$V_{End\ Dias}$ > 0.2 m/s**

Monitoring whilst treating a PDA

Usual intensive care monitoring	**Daily serum bilirubin**
Urine output and fluid balance	**Cranial ultrasound scan before and after treatment**
8 – 12 hourly renal function	**Echo at end of course**
Daily platelet count	

Version Control:

Version	Date	Details	Author(s)	Comments
Final v1	14 Sep '15	OUH Guideline for Thames Valley Network	Dr Zoltan Molnar	Approved by Neonatal Consultants and Paediatric Cardiologists
Version 2	23 Feb '16	TV Neonatal ODN Format	Dr Zoltan Molnar	Approved by TV&W Neonatal ODN Governance Group 28 April 2016 subject to agreed amendments
	May 2016	Amendments completed		
Review Date:	**14 September 2018**			