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


<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
</table>

**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

<table>
<thead>
<tr>
<th>Paragraph</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td>5</td>
</tr>
<tr>
<td>2.0</td>
<td>5</td>
</tr>
<tr>
<td>3.0</td>
<td>5</td>
</tr>
<tr>
<td>4.0</td>
<td>7</td>
</tr>
<tr>
<td>Table: ECHO features of haemodynamically significant PDA</td>
<td>6</td>
</tr>
</tbody>
</table>

### 1.0 Aim of Guideline

### 2.0 Scope of Guideline

### 3.0 Management Summary

| Table: ECHO features of haemodynamically significant PDA | 6 |

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

#### Rationale for treating PDAs

#### When to start treatment (with literature data and commentary)

| Figure 1: Timing of different treatment options | 8 |

#### Ligation

| 10 |

#### Conservative management

| 11 |

#### Pharmacological treatment

| 11 |

| Table: Echocardiogram features of a haemodynamically significant PDA | 12 |

| Table: Monitoring whilst treating a PDA | 13 |
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.

<table>
<thead>
<tr>
<th>Thames Valley</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Buckinghamshire Healthcare NHS Trust</td>
<td>- Stoke Mandeville Hospital, Aylesbury</td>
</tr>
<tr>
<td>Frimley Health NHS Foundation Trust</td>
<td>- Wexham Park Hospital, Slough</td>
</tr>
<tr>
<td>Milton Keynes University Hospital NHS Trust</td>
<td>- Milton Keynes General Hospital</td>
</tr>
<tr>
<td>Oxford University Hospitals NHS Foundation</td>
<td>- John Radcliffe Hospital, Oxford</td>
</tr>
<tr>
<td>Oxford University Hospitals NHS Foundation</td>
<td>- Horton General Hospital, Banbury</td>
</tr>
<tr>
<td>Royal Berkshire NHS Foundation Trust</td>
<td>- Reading</td>
</tr>
</tbody>
</table>

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: FiO₂ > 40%, Mean airway Pressure > 12 cmH₂O
        ii. infants ≤ 26+6 weeks gestational age: FiO₂ > 30%, Mean airway Pressure > 10 cmH₂O
     c. pulmonary haemorrhage
     d. radiological features of pulmonary oedema
  2. On High-flow Therapy or nCPAP:
     a. increasing FiO₂ 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

<table>
<thead>
<tr>
<th>Feature</th>
<th>Significant Values</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Size of PDA</strong></td>
<td></td>
</tr>
<tr>
<td>• Large</td>
<td>• &gt; 2.0 mm</td>
</tr>
<tr>
<td>• Moderate</td>
<td>• 1.5 – 2.0 mm</td>
</tr>
<tr>
<td><strong>Flow through PDA</strong></td>
<td>Continuous L-to-R flow with unrestrictive flow pattern</td>
</tr>
<tr>
<td></td>
<td>($V_{\text{max}} &lt; 2.0 \text{ m/s} \text{ and } V_{\text{min}} &lt; \frac{1}{2} V_{\text{max}}$)</td>
</tr>
<tr>
<td><strong>LA:Ao ratio</strong> (less sensitive when there is concurrent L-to-R shunt via PFO)</td>
<td>&gt; 1.5</td>
</tr>
<tr>
<td><strong>Descending aorta flow</strong></td>
<td>Holodiastolic flow reversal</td>
</tr>
</tbody>
</table>
| **Mean and end-diastolic velocity in Left Pulmonary Artery** | $V_{\text{Mean}} > 0.4 \text{ m/s}$  
|                                             | $V_{\text{End Dias}} > 0.2 \text{ m/s}$                |

**Conservative management:**

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

**PEEP**
Consider increasing PEEP by 1-2 cmH₂O 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 (FiO₂ > 40-50%, MAP >12-13 cmH₂O) 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 O₂ 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 leukomalacia (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](image)

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 subgroup 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 (FiO₂ ≥ 0.5, Pₕ₋ₐ ≥ 13 H₂O 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.

- **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: FiO₂ > 40%, Mean airway Pressure > 12 cmH₂O
      ii. infants ≤ 26+6 weeks gestational age: FiO₂ > 30%, Mean airway Pressure > 10 cmH₂O
    c. pulmonary haemorrhage
    d. radiological features of pulmonary oedema

  - On High-flow Therapy or nCPAP:
    a. increasing FiO₂ 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 (FiO₂ > 40%, P_{aw} >12 cmH₂O) 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 cmH₂O 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 haemodynamically significant PDA

<table>
<thead>
<tr>
<th>Feature</th>
<th>Significant Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size of PDA</td>
<td>• &gt; 2.0 mm&lt;br/&gt;• 1.5 – 2.0 mm</td>
</tr>
<tr>
<td>Flow through PDA</td>
<td>Continuous L-to-R flow with unrestrictive flow pattern (Vmax &lt; 2.0 m/s and Vmin &lt; ½ Vmax)</td>
</tr>
<tr>
<td>LA:Ao ratio (less sensitive when there is concurrent L-to-R shunt via PFO)</td>
<td>&gt; 1.5</td>
</tr>
<tr>
<td>Descending aorta flow</td>
<td>Holodiastolic flow reversal</td>
</tr>
<tr>
<td>Mean and end-diastolic velocity in Left Pulmonary Artery</td>
<td>Vmean &gt; 0.4 m/s&lt;br/&gt;VEnd Dias &gt; 0.2 m/s</td>
</tr>
</tbody>
</table>
## Monitoring whilst treating a PDA

<table>
<thead>
<tr>
<th>Usual intensive care monitoring</th>
<th>Daily serum bilirubin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine output and fluid balance</td>
<td>Cranial ultrasound scan before and after treatment</td>
</tr>
<tr>
<td>8 – 12 hourly renal function</td>
<td>Echo at end of course</td>
</tr>
<tr>
<td>Daily platelet count</td>
<td></td>
</tr>
</tbody>
</table>

### Version Control:

<table>
<thead>
<tr>
<th>Version</th>
<th>Date</th>
<th>Details</th>
<th>Author(s)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Final v1</td>
<td>14 Sep ‘15</td>
<td>OUH Guideline for Thames Valley Network</td>
<td>Dr Zoltan Molnar</td>
<td>Approved by Neonatal Consultants and Paediatric Cardiologists</td>
</tr>
<tr>
<td>Version 2</td>
<td>23 Feb ‘16</td>
<td>TV Neonatal ODN Format</td>
<td>Dr Zoltan Molnar</td>
<td>Approved by TV&amp;W Neonatal ODN Governance Group 28 April 2016 subject to agreed amendments</td>
</tr>
<tr>
<td></td>
<td>May 2016</td>
<td>Amendments completed</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Review Date:** 14 September 2018