# RPAH Newborn Care Guideline template

<table>
<thead>
<tr>
<th><strong>Title:</strong> Patent ductus arteriosus in newborn infants</th>
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<tr>
<td><strong>TRIM Document No</strong></td>
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<td><strong>Policy Reference</strong></td>
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<td><strong>Date approved by SLHD Policy Committee</strong></td>
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<td><strong>Risk Rating</strong></td>
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**Version History**

**Current Version** V.1 – date
Patent ductus arteriosus in newborn infants

1. Introduction

Infants born at or near term gestations should be routinely examined for a cardiac murmur, hyperdynamic precordium and increased pulse volume after 72 hours age when the ductus is expected to be functionally closed.1,2
In preterm infants closure of the ductus is delayed. The ductus is likely to close without treatment in infants born at > 28 weeks’ gestation (73%)³, in those with birth weight > 1000 g (94%)⁴, and in infants born at 26-29 weeks’ gestation who do not have respiratory distress syndrome (93%)⁵. Routine treatment to induce closure of the ductus in preterm infants, either medically or surgically, in the first 2 weeks after birth does not improve long-term outcomes⁶. The optimal strategy for prevention or treatment of a hsPDA is unclear and is likely to be a balance of benefit from ductal closure and harm from toxicities or side effects of medical and surgical management.

2. **The Aims / Expected Outcome of this Guideline**

This guideline is a comprehensive review of patent ductus arteriosus in the newborn, the management of which there is no current consensus. The aim is to provide clinicians with the evidence to guide management, reduce use of interventions with limited evidence of overall benefit, and reduce the side effects of treatment.

For maintenance of ductal patency in infants with ductal dependent congenital heart disease (CHD) – see Alprostadil (Prostaglandin E1) ANMF formulary:

3. **Risk Statement**

SLHD Enterprise Risk Management System (ERMS) Risk #1 - Unwarranted Deviation from standards of clinical care:

4. **Key Performance Indicators and Service Measures**

- Patent ductus arteriosus ligation
- Serious adverse events of treatment including upper gastrointestinal haemorrhage; necrotising enterocolitis Bell’s stage ≥ 2; renal impairment (creatinine > 120 µmol/L); hepatotoxicity (ALT > 50 iU/L); otherwise unexplained cardiorespiratory deterioration post treatment.

5. **Definitions**

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tbody>
<tr>
<td><strong>hsPDA</strong></td>
<td>Clinically and/or echocardiographic haemodynamically significant patent ductus arteriosus</td>
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<tr>
<td><strong>Clinical hsPDA</strong></td>
<td>Systolic murmur associated with increased pulse volume and precordial hyperactivity</td>
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<tr>
<td><strong>Echocardiographic hsPDA</strong></td>
<td>Large patent ductus (&gt; 1.5 mm on colour Doppler) associated with:</td>
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<tr>
<td></td>
<td>- Pulsatile flow pattern (S:D velocity ratio ≥2), usually with additional measures including:</td>
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<tr>
<td></td>
<td>- LPA diastolic velocity &gt; 0.3 ms⁻¹ or LPA mean velocity ≥ 0.42 ms⁻¹; and</td>
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<td></td>
<td>- Reversed diastolic flow in the distal aorta or distal arteries (eg celiac artery)</td>
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<tr>
<td><strong>NEC, CLD, IVH, ROP</strong></td>
<td>Necrotising enterocolitis (Bell’s criteria ≥ 2), chronic lung disease (respiratory support at 36 weeks), intraventricular haemorrhage, retinopathy of prematurity</td>
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<tr>
<td><strong>Sn, Sp, PPV, NPV, +LR, -LR</strong></td>
<td>Sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, negative likelihood ratio</td>
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<tr>
<td><strong>CGA/PMA</strong></td>
<td>Corrected gestational age / postmenstrual age</td>
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</table>
6. **Summary of Practice Guidelines**

These are guidelines to clinical practice. The team caring for the infant must apply these guidelines appropriately to the infants that they are caring for.

<table>
<thead>
<tr>
<th>Prevention of a hsPDA</th>
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<tbody>
<tr>
<td><strong>Optimise antenatal corticosteroids prior to preterm birth</strong></td>
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<tr>
<td>The incidence of hsPDA was reduced by antenatal / repeat antenatal corticosteroids for women at risk of preterm birth. [LOE I GOR A]</td>
</tr>
<tr>
<td><strong>Avoid excess postnatal fluid intake</strong></td>
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<tr>
<td>Excess fluid intake in the first week in very preterm infants is associated with increased incidence of hsPDA and NEC. [LOE I GOR B]</td>
</tr>
<tr>
<td><strong>Spontaneous ductal closure</strong></td>
</tr>
<tr>
<td>The ductus is likely to close without treatment in infants born at &gt;28 weeks’ gestation (73%) [G], in those with birth weight &gt;1000 g (94%) [D], and in infants born at 26-29 weeks’ gestation who do not have respiratory distress syndrome (93%) [F]. Routine early treatment of a PDA is not indicated for these infants.</td>
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<table>
<thead>
<tr>
<th>Screening</th>
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<tbody>
<tr>
<td><strong>Clinical screening for PDA: term and late preterm infants</strong></td>
</tr>
<tr>
<td>Infants born at or near term gestations should be routinely examined for a cardiac murmur, hyperdynamic precordium and increased pulse volume after 72 hours age when the ductus is expected to be functionally closed. [G, H]</td>
</tr>
<tr>
<td><strong>Clinical screening for PDA: preterm infants &lt;32 weeks gestation</strong></td>
</tr>
<tr>
<td>Preterm infants &lt;32 weeks gestation are at higher risk of a persistent and hsPDA. [J]</td>
</tr>
<tr>
<td>Clinical examination for a systolic or continuous murmur, hyperdynamic precordium and increased pulse volume has high sensitivity (~100%) for a persistent PDA by day 7 resulting in good ‘rule out’ value. [K] However, specificity is lower (~70%) so a cardiac US should always be performed for diagnosis.</td>
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<table>
<thead>
<tr>
<th>Cardiac US screening: for preterm infants &lt;30 weeks gestation</th>
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<tr>
<td><strong>Day 1:</strong> PDA size prediction of hsPDA has reduced accuracy. For ventilated infants &lt;29 weeks gestation, 25 to 43% with a PDA &gt;1.5 mm of infants will not require treatment for a hsPDA. [L, M, N, O]</td>
</tr>
<tr>
<td><strong>Day 3 to 7:</strong> PDA size combined with measures of ductal shunt have optimal accuracy for prediction of a hsPDA. [P, Q, R, S] The following are highly predictive of a hsPDA:</td>
</tr>
<tr>
<td>- PDA diameter ≥2.0 mm [T, U]: Sn 94.7%, Sp 99.9%, PPV 90.0% NPV 91.7%</td>
</tr>
<tr>
<td>- PDA S/D ratio ≥2 [V]: ‘pulsatile pattern’ [W]: Sn 89.5%, Sp 83.3%, PPV 90.0% and NPV 83.3%. A ‘growing pattern’ is less predictive: Sn 64.5%; Sp 81.1%.</td>
</tr>
<tr>
<td>Other measures of ductal shunt that have predictive value although it is unclear if these provide additional predictive value:</td>
</tr>
<tr>
<td>- LPA diastolic velocity &gt;0.3 ms⁻¹ [X, Y] or LPA mean velocity ≥0.42 ms⁻¹ [Z]</td>
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<tr>
<td><strong>Who to treat?</strong></td>
</tr>
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</table>
| Term and late preterm infants with a persistent PDA | Term and late preterm infants with a persistent PDA after day 3 should be followed clinically to ductal closure. Infants with a clinical and echocardiographic hsPDA may be treated with a short course of diuretics with or without relative fluid restriction until asymptomatic. Continued treatment is not usually required. Infants with a persistent PDA after the first months of life should be referred to a Paediatric Cardiologist.  
| Prophylactic treatment of preterm infants | There is no indication for routine prophylactic treatment currently.  
| Early targeted treatment: infants <27 weeks gestation day 1 | There are currently insufficient data to support routine treatment of a large PDA in the first day after birth.  

**Who to treat? LOCAL CONSENSUS PRACTICE RECOMMENDATIONS** [highlighted in grey]  

| **Pre-symptomatic treatment: infants <27 weeks gestation** | Earlier pre-symptomatic treatment of infants should be considered for:  
| | • Infants with a **PDA diameter ≥ 2.0 mm** and **PDA S/D ratio ≥ 2** = *pulsatile pattern*.[17] Treatment of infants on the basis of ductal size and shunt pattern reduced exposure to cyclo-oxygenase inhibitors and reduced side effects of treatment.[28] **[LOE II GOR B]** And,  
| | • Infants with preceding low SVC flow (≤ 40 mL/kg/min) in the first day, with a PDA diameter >1.5 mm, a L-R shunt and high RVO and or LPA flow velocities who are at risk of pulmonary haemorrhage.[27, 29]  

| **Treatment of a hsPDA: infants ≥27 weeks gestation** | Infants born ≥ 27 weeks gestation should be monitored for development of a clinical and echocardiograph hsPDA. Evidence is currently insufficient to determine optimal timing of treatment although there is currently concern that early treatment may not be beneficial for infants born ≥ 27 weeks gestation.[30] **[LOE II GOR C]** Criteria for treatment:  
| | • Clinical assessment including presence of a murmur (pansystolic or continuous), hyperdynamic precordium and increased pulse volume[1, 2],  
| | • Significant respiratory support requirements clinically assessed as contributed to by ductal shunt; and  
| | • **PDA diameter ≥ 2.0 mm** and **PDA S/D ratio ≥ 2** = ‘pulsatile pattern’.[17]  
| | • And / or persistent feed intolerance clinically assessed as contributed by ductal shunt; and  

- LA:Ao ratio >1.4,[14, 18] and  
- Reversed diastolic flow in the distal aorta or distal arteries (eg celiac artery)[22, 23].
### Reversed diastolic flow in the distal aorta or distal arteries (e.g., celiac artery) \(^{22, 23}\)

### Pressor-dependent hypotension after the first day

Extremely preterm infants with pressor-dependent hypotension and a large ductal shunt may benefit from treatment. \(^{31}\) [LOE III GOR D] Before treatment with a cyclo-oxygenase inhibitor exclude [consensus]:

- Other causes of hypotension (e.g., sepsis and hypovolaemia)
- Significant pulmonary hypotension – any right to left ductal shunt on cardiac US \(^{17}\)

### Treatment options for a hSPDA [refer to ANMF formulary]

**LOCAL CONSENSUS PRACTICE RECOMMENDATIONS** [highlighted in grey]

| Infants <27 weeks gestation and ≤48 hours age | Prophylactic intravenous indomethacin is associated with oliguria but not increased creatinine or gastrointestinal side effects. \(^{24}\) However, it has not been shown to be superior to ibuprofen for prevention of hSPDA or ligation \(^{25}\), so is not recommended. [LOE I, GOR B] Its use should be restricted to extremely preterm infants considered at high risk of pulmonary haemorrhage or in whom the toxicity of late treatment would be unacceptable. [consensus] Dosage recommendation if used: Day 1: IV Indomethacin 0.2 mg/kg; day 2: IV Indomethacin 0.1 mg/kg; day 3: IV Indomethacin 0.1 mg/kg |
| Infant ≥ 72 hours Higher dose oral ibuprofen | Day 1: Oral Ibuprofen 20 mg/kg; day 2: Oral ibuprofen 10 mg/kg; day 3: Oral ibuprofen 10 mg/kg Use IV if oral contraindicated in an infant with abdominal signs. |
| Second line treatment | EITHER repeat ibuprofen: Day 1: Ibuprofen 20 mg/kg; day 2: ibuprofen 10 mg/kg; day 3: ibuprofen 10 mg/kg; OR |
| Alternative treatment – paracetamol (acetaminophen) | For infants with contraindications to a cyclo-oxygenase inhibitor or have not responded to a cyclo-oxygenase inhibitor, paracetamol is an option. Treatment course 3-7 days. \(^{32, 33}\) Recommended dosage: ≥ 28 weeks CGA/PMA and ≥ 1000 g: loading dose: 15 mg/kg then 15 mg/kg every 6 hours < 28 weeks and/or < 1000 g: loading dose 15 mg/kg then 7.5 mg/kg every 6 hours |
| Indomethacin >48 hours age | Late treatment with indomethacin for infants with a hSPDA should generally be avoided in view of increased risk of side effects including NEC \(^{32, 34, 35}\). Dosage recommendation if used: Day 1: Indomethacin 0.2 mg/kg; day 2: Indomethacin 0.2 mg/kg; day 3: Indomethacin 0.2 mg/kg |
| Surgical ligation | The role of surgical ligation in the management of the preterm persistent ductus is currently unclear. Referral for surgical ligation should be restricted to infants with a hSPDA that has failed medical therapy and has been assessed as having a significant clinical impact on respiratory and / or |
**Nutritional status with echocardiographic confirmation of haemodynamic significance. [LOE II - consensus]**

<table>
<thead>
<tr>
<th>Special comments</th>
<th>Medical treatment:</th>
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<tbody>
<tr>
<td></td>
<td>Infants with a hsPDA impacting on respiratory status may benefit from a period of relative fluid restriction and a short course of diuretic. Whilst furosemide is more potent, it is associated with increased prostaglandin excretion and ductal patency. Hydrochlorothiazide should be considered as an alternative. [LOE II GOR C]</td>
</tr>
<tr>
<td></td>
<td>Sepsis is associated with late ductus reopening and failure of ductal closure. Diagnostic work up and treatment of infection should occur before treatments to close the ductus are used. [consensus]</td>
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</table>

**Oral versus intravenous ibuprofen:** Oral ibuprofen reduced failure to close the PDA, no differences in morbidity or gastrointestinal side effects, and lower creatinine levels after treatment. [LOE I; GOR B]

**Duration of treatment:** A full course of cyclo-oxygenase inhibitor may not be necessary if ductal constriction or closure is demonstrated [LOE II GOR C]

A prolonged course (≥ 4 doses) of cyclo-oxygenase inhibitor has been associated with increased incidence of NEC and should be avoided. [LOE I]

**Contraindications to cyclo-oxygenase inhibitors include:** Serious infection, active bleeding, thrombocytopenia or coagulopathy, necrotising enterocolitis or intestinal perforation, significant renal dysfunction, ductal dependent congenital heart disease, pulmonary hypertension and significant jaundice as may displace bilirubin from albumin.

**Monitoring**

Cardiovascular status, urine output, serum biochemistry, renal function and for signs of bleeding.

Oliguria, excess weight gain, increased respiratory support requirements, hyponatraemia and increasing creatinine may be an indication of a hsPDA shunt and / or cyclo-oxygenase inhibitor toxicity.

Infants on paracetamol should have 48-hourly monitoring of liver function (abnormal ALT > 50 iU/L). [32, 33]

## 7. Overview

### 7.1 Problem – incidence / prevalence

In term infants, the ductus arteriosus (DA) normally constricts after birth and becomes functionally closed by 72 hours of age.  

The incidence of clinically evident persistent/patent DA (PDA) is about 1 in 2000 births, but may be as high as 1 in 500 for cardiac US detected PDA.

In preterm infants closure of the ductus is delayed, remaining open at 7 days of age in approximately 2% of infants born at 30-37 weeks’ gestation, 65% of those born at 25 through 28 weeks’ gestation, and 87% of those born at 24 weeks’ gestation.

The ductus is likely to close without treatment in infants born at >28 weeks’ gestation (73%), in those with birth weight >1000 g (94%), and in infants born at 26-29 weeks’ gestation who do not have respiratory distress syndrome (93%).
Rates of later spontaneous ductal closure among smaller, less mature infants with respiratory distress syndrome are difficult to estimate because of widespread use of treatments to achieve closure of the PDA. Data from placebo arms of trials demonstrate that spontaneous ductal closure among smaller, less mature infants with respiratory distress syndrome is frequent. In the Trial of Indomethacin Prophylaxis in Preterms with birth weight from 500 to 999 g, 50% of placebo recipients never developed clinical signs of a PDA. In a trial of early versus late indomethacin treatment of infants born 26-31 weeks’ gestation in which PDA was confirmed by echocardiography on day 3, the ductus closed spontaneously by 9 days of age in 78% of those randomized to late intervention. In a cohort of 842 infants, a haemodynamically significant PDA (hsPDA) occurred in 70% (106/151) of infants born at 23-24 weeks and in 59% (405/691) of infants born at 25-28 weeks of gestation.

The incidence of PDA and/or its treatment is not reported by ANZNN. In the NSW and ACT dataset 2007 to 2011, the incidence of PDA treatment and PDA surgery ranged from 81% and 12.4% for infants born at 24 weeks gestation, to 8.7% and 0.4% at 31 weeks gestation respectively.

### NSW and ACT dataset 2007 to 2011, the reported incidence of PDA treatment and PDA surgery:

<table>
<thead>
<tr>
<th>Gestation – weeks</th>
<th>Total n=4454</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>23 n=41</td>
</tr>
<tr>
<td>PDA treated %</td>
<td>61.0</td>
</tr>
<tr>
<td>PDA surgery %</td>
<td>9.8</td>
</tr>
</tbody>
</table>

### NSW and ACT dataset 2016-2018: the reported incidence of PDA treatment and PDA surgery:

<table>
<thead>
<tr>
<th>Gestation - weeks</th>
<th>Total n=2757</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>22 to 24 n=203</td>
</tr>
<tr>
<td>Not treated %</td>
<td>30</td>
</tr>
<tr>
<td>Medical treatment only %</td>
<td>65</td>
</tr>
<tr>
<td>PDA surgery %</td>
<td>5</td>
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</tbody>
</table>

#### 7.2 Aetiology and risk factors

**Patent ductus arteriosus in term infants:**

Persistent PDA is thought to relate to inherent abnormality of the ductus and/or signalling pathways that normally trigger its closure. Most cases are sporadic. PDA occurs with increased frequency in genetic syndromes including Down syndrome (trisomy 21), Wolf–Hirschhorn syndrome (4p deletion), Char syndrome (autosomal dominant), Carpenter syndrome (single gene mutation), Holt–Oram syndrome (autosomal dominant), and incontinentia pigmenti (X-linked). In a family having one sibling with a PDA, there is an approximately 3% chance of a PDA in a subsequent offspring.

**Risk factors for a PDA in preterm infants:**

- Increasing prematurity [aetiology LOE II]
- Respiratory distress syndrome and mechanical ventilation [aetiology LOE II].
- Excess fluid intake – meta-analysis of the five studies found restricted water intake increased postnatal weight loss and reduced the risks of PDA and necrotizing enterocolitis (NEC) in preterm infants. [intervention LOE I]
- Sepsis – increases late ductus reopening rates and failure of ductal closure rate. [aetiology LOE II]

**Protective factors for a PDA in preterm infants:**

- Repeated antenatal corticosteroids for women at risk of preterm birth. [intervention LOE I]
- Early postnatal corticosteroid treatment facilitates extubation and reduces risk of CLD and hsPDA. However, it causes gastrointestinal bleeding, intestinal perforation, hyperglycaemia,
hypertension, hypertrophic cardiomyopathy, growth failure, and long-term follow-up studies report increased risk of abnormal findings on neurological examination and cerebral palsy. 51 [intervention LOE I]

- Prophylactic early low-dose hydrocortisone in very preterm infants reduced PDA and survival without CLD, but was associated with an increased risk of intestinal perforation when given in association with indomethacin, and with late onset sepsis. 52 [intervention LOE I]

What has been shown to not affect the incidence of PDA in preterm infants?

- Chorioamnionitis – meta-analysis of observational studies found differences in rates of PDA correlated to gestational age and birthweight. 53 [aetiology LOE I]
- Cyclooxygenase inhibitors for preventing or treating preterm labour. 54, 55 [intervention LOE I]
- Reviews of calcium channel blockers for tocolysis or maintenance treatment of preterm labour did not report PDA. 56, 57
- Lower versus higher oxygen concentrations titrated to target oxygen saturations during resuscitation of preterm infants at birth. 58 [intervention LOE I]
- Targeting lower (SpO₂ ≤90%) versus higher (>90%) arterial oxygen saturations after admission in preterm infants. 59 [intervention LOE I]
- Although there was a concern about increased PDA with use of prophylactic protein free synthetic surfactant in preterm infants 60. Systematic reviews of early animal derived, prophylactic and repeated surfactant treatment found no association 61, 62, 63, 64. [intervention LOE I]
- Any non-invasive strategy for avoiding or minimising mechanical ventilation including nasal continuous positive pressure (nCPAP) 65, 66, non-invasive intermittent positive pressure ventilation (NIPPV) 67, and high flow nasal cannula (HFNC) 68. [intervention LOE I]

7.3 Consequences

A patent ductus arteriosus has variable roles in sick neonates. In preterm infants with an otherwise structurally normal heart, a PDA left to right shunt results in increased pulmonary blood flow and reduced distal aortic and organ diastolic blood flow.

Pulmonary hypertension of the newborn: whereas right to-left shunt may worsen hypoxia, the PDA can help unload pressure from the right ventricle and in extreme situations prevent right ventricular failure and support systemic blood flow when associated with cardiac dysfunction 69.

Neonates with ductal-dependent congenital heart disease (CHD): a PDA may be necessary for maintaining either pulmonary or systemic blood flow for 69:

- Left-sided CHD requiring PDA for systemic blood flow: including hypoplastic left heart syndrome, critical aortic stenosis, interrupted aortic arch and coarctation
- Right-sided congenital heart defects requiring PDA for pulmonary blood flow: including pulmonary atresia with intact ventricular septum, pulmonary atresia with ventricular septal defect/tetralogy of Fallot with pulmonary atresia, Tetralogy of Fallot with pulmonary stenosis, and Tetralogy of Fallot with absent pulmonary valve.
- Transposition of the great arteries: when associated with significant cyanosis a PDA may promote intracardiac mixing.

Untreated PDA outcomes and associations:

Early patent ductus arteriosus diameter (<24 hours age) on cardiac US has been associated with:

- Inconsistently with low superior vena cava flow in the first 24 hours. 70, 71 Low SVC flow has been associated with mortality, late IVH, NEC and disability in infants born very preterm. 70, 71, 72
- A ductus diameter at 5 hours age >1.5 mm was predictive of later pulmonary haemorrhage and symptomatic PDA in ventilated very preterm infants (sensitivity 81% and the specificity 85%). 29
• A right to left or bidirectional ductal shunt on day 1 was associated with increased mortality in very preterm infants. 73, 74

A PDA on cardiac US on day 2 to 7 of life has been associated with:
• Development of clinical signs of heart failure in over 90% of infants born < 1500 g. 42
• Mortality 42, 75 and severe combined morbidity (pulmonary haemorrhage, IVH, IVH grade III–IV, NEC and/or BPD) in neonates born < 28 weeks gestation. 76
• Intraventricular haemorrhage. 76
• Chronic lung disease. 42, 75, 76
• Abnormal organ blood flow velocities (renal, celiac and superior mesenteric artery resistive index and velocity) were associated with a PDA >2.0 mm and left atrial to aortic ratio (LA:Ao) > 1.4 at the time of the US. 77
• Pulmonary haemorrhage usually in the first week has been associated with a large PDA at or near the time of haemorrhage. 29, 78, 79 However, severe pulmonary haemorrhage is uncommon with a peak incidence of 0.9% at 24 weeks gestation with risk factors including extreme prematurity, respiratory distress syndrome treated with surfactant, shock and IVH. 80 Infants with pulmonary haemorrhage are more likely to have preceding low systemic blood flow (SVC flow ≤41 mL/kg/min), a large PDA and high pulmonary blood flow at the time of haemorrhage. 29
• Dopamine dependent hypotension. 31

A hsPDA has been associated with:
• Reversed diastolic flow in the distal aorta and celiac artery, were associated with PDA diameter after day 7. 81
• Necrotising enterocolitis. 47, 82
• Chronic lung disease. 47, 83 A longer duration of PDA was also associated with increased risk for CLD. 84

7.4 Diagnosis

Clinical assessment of the ductus arteriosus:

The physical signs of a PDA include systolic murmur, increased pulse volume and precordial hyperactivity. 10, 85 Murmur: In the first days after birth the ductus is frequently clinically silent. The presence of a murmur had a sensitivity of 21% on day 2 increasing to 79% on day 7 for an echocardiographically open ductus in ventilated very preterm infants. 10, 86 For detection of an echocardiographic defined hsPDA (‘wide open’ with a strong pulsed Doppler signal from a predominantly left to right ductal shunt and an LA:Ao ≥1.4), the presence of a murmur had 30% sensitivity on day 3 increasing to 100% day 7. 10 Bounding pulses: Sensitivity ranged from 40% day 2 to 100% day 7 for a hsPDA, whilst specificity remained low throughout averaging around 70%. 10

The absence of a murmur and bounding pulses has good ‘rule out’ value (ie high sensitivity) for a hsPDA after the first 7 days, although a ductus may still be present on echocardiography. 10

ECG signs of significant ductal shunting include patterns of left atrial and left ventricular enlargement. However, in infants with an echocardiographically hsPDA the ECG had only 22% sensitivity for a hsPDA, so is not useful clinically. 87 The chest x-ray is also unreliable with very low sensitivity (14% for increased cardiothoracic ratio and 27% for increased vascular markings) for a hsPDA. 85

Echocardiographic assessment of the ductus arteriosus:

Clinician performed cardiac ultrasound is dependent on the training and skill of the clinician and may not be as reliable as a cardiologist performed assessment. 88 The mean difference and the limits of agreement between the observers for PDA diameter were 0 mm and -0.8 to 0.8 mm respectively. 89
Several studies have assessed early cardiac US measures of PDA size in very preterm infants and measures of shunt severity for prediction of a clinically and/or echocardiographically hsPDA treated medically, with the exception of a single study that managed the ductus conservatively. Prediction of a hsPDA is most accurate after 72 hours, although high risk infants can be identified in the first 24 to 48 hours on the basis of extreme prematurity, need for mechanical ventilation and early PDA diameter.

**Prediction in the first 24 hours:**

- **Colour Doppler PDA diameter:** Studies of early cardiac US prediction of hsPDA requiring treatment have reported inconsistent accuracy. In ventilated infants born <30 weeks gestation, a colour Doppler PDA diameter ≥1.5 mm from 7 to 31 hours had moderate predictive value for a subsequent treated hsPDA (Sn 81%; Sp 85%; PPV 89%; PVV 75%). In a study of ventilated infants born <29 weeks gestation that managed the ductus conservatively, a PDA ≥1.5 mm diameter at 6 to 48 hours age had good predictive value (Sn 91%; Sp 100%), but symptoms resolved spontaneously without treatment in 30%.
  
  Two studies reported poor predictive value for early PDA diameter in very preterm infants who were predominately ventilated. Pereira 2018 reported a non-significant area under the receiver operator curve 0.51 (95% CI 0.36–0.66) on day 1; and Kwinta 2009 reported a positive predictive value of only 57%: Sn 94%; Sp 73; PPV 57; NPV 97; LR+ 3.4; LR– 0.09). There was slightly improved accuracy in infants with an FiO₂ > 0.3 and DA diameter>1.5 mm/kg (Sn 81; Sp 84; PPV 65; NPV 93; LR+ 5.1; LR– 0.22).

- **Other measures of ductal shunt:** Studies have not reported significant improvements in prediction from incorporation of other measures of ductal shunt in the first 24 hours.

**Prediction between 24 to 72 hours:**

- **Studies** have reported improved cardiac US diagnostic accuracy at 72 hours for hsPDA.
- **Colour Doppler PDA diameter:** In infants <32 weeks gestation (46% ventilated) a PDA diameter ≥2 mm/kg had an efficiency of diagnosis at 24 hours 71% versus 84% at 72 hours. PDA diameter was marginally more accurate than measures of ductal shunt including flow pattern (pulsatile) and LA: Ao ratio. Studies have reported variable predictive value of the PDA: LPA diameter ratio and DA diameter ≥1.5 mm/kg had better positive predictive value in infants <27 weeks gestation [Sn 80%; Sp 86%; PPV 92%; NPV 68%] than infants ≥27 weeks gestation [Sn 73%; Sp 74%; PPV 57%; NPV 85%]. However, another cohort reported PDA: LPA ≥0.5 on day 3 in infants <27 weeks gestation had a lower positive predictive value than those 27 to 30 weeks gestation [<27 weeks: PPV 60% NPV 91% Sn 92% Sp 55%; 27-30 weeks: PPV 95% NPV 73% Sn 87% Sp 89%].

- **Measures of ductal shunt:** Combining PDA: LPA ≥0.5 and LPA diastolic flow >0.3 ms-1 when PDA: LPA ratio was <0.5 improved the predictive value on day 3 cardiac US [infants <27 weeks: PPV 84% NPV 86% Sn 84% Sp 86%; +LR 6; -LR 0.19; infants 27-30 weeks: PPV 98% NPV 68% Sn 83% Sp 94%; +LR 13.8; -LR 2.81].

**Prediction between days 3 to 7:** Cardiac US measures have improved diagnostic accuracy for hsPDA receiving treatment if performed longitudinally in the first week.

- **Colour Doppler PDA diameter:** In infants <1500 g, PDA size ≥2.04 mm on day 3 or 7 had 90% positive predictive value for a treated hsPDA [Sn 94.7%, Sp 99.9%, PPV 90.0% NPV 91.7%].

- **Measures of ductal shunt:** Ductal flow pattern predicts hsPDA. A first documented growing pattern [PDA S/D ratio <2: Sn 64.5%; Sp 81.1%] was not as predictive as a first documented pulsatile pattern which had high predictive accuracy [PDA S/D ratio >2: Sn 93.5%; Sp 100%]. An RCT of clinical treatment (clinical signs plus US open ductus) versus US flow pattern guided treatment (pulsatile pattern) (n=93) reported no difference in closure rate (89.1% versus 87.2%), a reduction in doses of indomethacin (mean 3.2 versus 1.6); and reduced side effects including hypoglycaemia, impaired urine output, and gastrointestinal bleeding. [Treatment LOE II].
7.5 Prevention

The incidence of hsPDA can be reduced by the following evidence base practices:

- Antenatal corticosteroids for women at risk of preterm birth.\(^7\) [intervention LOE I]
- Avoiding excess fluid intake in the first week in very preterm infants.\(^8\) [intervention LOE I]

Although early postnatal corticosteroid treatment for facilitating extubation\(^51\) and prophylactic early low-dose hydrocortisone in very preterm infants reduce hsPDA, significant side effects preclude their routine use\(^52\).

7.6 Treatment

**Patent ductus arteriosus in term infants**

Because most term infants and children with PDA are asymptomatic, acute medical treatment before definitive closure is usually not necessary.

Indomethacin has been reported to constrict the ductus in case series of term infants with PDA (25/41; 61\%) and infants with genetic disorders and/or congenital abnormality (67/85; 79\%)\(^91,92\). However, it is not recommended as those with symptoms usually improve with a short term regimen of fluid restriction and diuretics\(^2,92\). There are no reports of use of ibuprofen for treatment of a PDA in term infants.

**Patent ductus arteriosus in preterm infants**

- The ductus is likely to close without treatment in infants born at >28 weeks’ gestation (73\%)\(^3\), in those with birth weight >1000 g (94\%)\(^4\), and in infants born at 26-29 weeks’ gestation who do not have respiratory distress syndrome (93\%)\(^5\). No study or systematic review has reported a reduction in mortality or neurodevelopmental disability from any specific strategy. The optimal strategy for prevention or treatment of a hsPDA is unclear and is likely to be a balance of benefit from ductal closure and harm from toxicities or side effects of medical and surgical management. Systematic reviews found both prophylactic indomethacin and ibuprofen reduced the incidence of PDA ligation.\(^24,25\) [LOE I] A recent trial of early (day 6 to 14) versus conservative treatment of a hsPDA in 202 infants born <28 weeks reported early treatment did not reduce PDA ligation, presence of a PDA at discharge or other neonatal morbidity.\(^30\) [LOE II]

**Prophylactic treatment (prevention of hsPDA):**

- **Prophylactic intravenous indomethacin:** systematic review of 19 trials with 2872 infants found a reduction in hsPDA, PDA surgical ligation and severe IVH. However, there was no effect on mortality or neurodevelopment. Dosage schedules varied from a single dose of 0.2 mg/kg at 24 hours age to a daily dose of 0.1 mg/kg given for six days. Safety: Prophylactic indomethacin was associated with oliguria but not an increased creatinine or gastrointestinal side effects.\(^24\) [LOE I]
- **Prophylactic ibuprofen** decreased the incidence of hsPDA, rescue treatment with cyclooxygenase inhibitors and surgical closure. Adverse effects associated with ibuprofen (IV or oral) included increased oliguria, increased serum creatinine and gastrointestinal haemorrhage. There was a reduced risk for IVH (grade III - IV) but no difference in mortality, CLD, NEC or time to reach full feeds. In the control group, the PDA closed spontaneously by day 3 or 4 in 58\% of neonates. Prophylactic treatment exposes a large proportion of infants unnecessarily to a drug that has important side effects without conferring important short-term benefits. Current evidence does not support the use of ibuprofen for prevention of hsPDA.\(^25\) [LOE I GOR B] A single small study of prophylactic indomethacin versus ibuprofen reported no differences in outcomes.\(^93\) [LOE II]

**Pre-symptomatic cardiac US targeted treatment:**

- Five trials compared indomethacin to placebo and two trials compared ibuprofen to placebo in infants born 23 to 32 weeks gestation with cardiac US detected PDA. Meta-analysis found a reduction in hsPDA (RR 0.39, 95\% CI 0.21 to 0.73; ARR -34.3\%, 95\% CI -50.8\% to -17.8\%; 3
Compliance with this Guideline is Recommended

Treatment of hsPDA

Options for treatment of a clinical and cardiac US hsPDA include medical management (fluid restriction with or without diuretics), cyclo-oxygenase inhibitors (ibuprofen or indomethacin), paracetamol, or surgical ductal ligation in selected infants.

- **Ibuprofen**: The standard dosing regimen was 10 mg/kg followed by 5 mg/kg 24 and 48 hours later. Systematic review found intravenous ibuprofen (3 doses) reduced failure to close a PDA compared with placebo (RR 0.62, 95% CI 0.44 to 0.86; RD; -0.18, 95% CI -0.30 to -0.06; NNTB 6, 95% CI 3 to 17; 2 studies, 206 infants) but was associated with oliguria (RR 39.0, 95% CI 2.40, 633.01) and increased creatinine (MD 29.17, 95% CI 12.60, 45.74 µmol/L). There was no difference in other morbidities including pulmonary hypertension, NEC and mortality. Longer term outcomes were not reported [34]. [LOE I]

- **Ibuprofen versus indomethacin**: Systematic review found 24 studies (1590 infants) that compared ibuprofen (IV or oral) with indomethacin (IV or oral) 0.2 mg/kg at 12 hour intervals for three doses. No difference was found for failure of PDA closure (RR 1.07, 95% CI 0.92 to 1.24), but use of ibuprofen reduced NEC (18 studies, 1292 infants; RR 0.68, 95% CI 0.49 to 0.94; NNTB 25, 95% CI 14 to 100), oliguria (6 studies, 576 infants; RR 0.28, 95% CI 0.14 to 0.54; NNTB 11, 95% CI 7 to 20) and was associated with lower creatinine levels 72 hours after initiation of treatment (11 studies, 918 infants; MD -8.12 µmol/L, 95% CI -10.81 to -5.43) compared to indomethacin treated infants. [34] [LOE I]

- **Higher versus lower dose of ibuprofen**: the higher dosing regimen of was 20 mg/kg/day followed by 10 mg/kg/day for two doses. Higher dose decreased failure to close a PDA (3 studies 190 infants; RR 0.37, 95% CI 0.22 to 0.61; NNTB 4, 95% CI 3 to 7). Although neonatal morbidities including gastrointestinal and renal side effects were not significantly different, the analyses were underpowered. [34] [LOE I]

- **Oral versus intravenous ibuprofen**: Oral ibuprofen reduced failure to close the PDA (5 trials, 406 infants RR 0.38, 95% CI 0.26, 0.56). There was no difference in mortality, surgical closure of the ductus, duration ventilator support, pulmonary haemorrhage, pulmonary hypertension, CLD, IVH, periventricular leukomalacia, NEC (3 trials, 236 infants; RR 0.86, 95% CI 0.35, 2.15), intestinal perforation (2 trials, 134 infants; RR 0.32, 95% CI 0.01, 7.48), gastrointestinal bleed (2 trials, 172 infants; RR 2.89, 95% CI 0.12, 69.24), ROP or neurodevelopment at 18-24 months. Oral ibuprofen was associated with lower creatinine levels after treatment (MD -22.47, 95% CI -32.40, -12.53 µmol/L). [34] [LOE I]

- **Long versus short course indomethacin**: Five trials including 431 infants compared 2 to 3 doses for the short course (total 0.3 to 0.6mg/kg) versus 6 to 8 doses (0.6 to 1.6 mg/kg) for the long course. There was no difference in PDA closure, re-treatment, re-opening, or ligation rate. However, there was an increased risk of NEC [RR 1.87, 95%CI 1.07, 3.27; RD 0.08, 95%CI 0.01, 0.15; NNH 13, 95%CI 7, 100], but decreased incidence of renal function impairment (reduced incidence of oliguria or increased serum creatinine). [35] [LOE I]

- **Paracetamol**: Two trials in 80 infants compared paracetamol to placebo. The failure of PDA closure 4 to 5 days after treatment was of borderline significance for [RR 0.49, 95% CI 0.24 to 1.00; P = 0.05]. There were insufficient data to determine effects on morbidity and safety. The use of paracetamol is largely based on comparisons with cyclo-oxygenase inhibitors. [33] [LOE I]
• **Paracetamol versus ibuprofen:** Systematic review of five studies (559 infants) found no difference in failure of PDA closure (RR 0.95, 95% CI 0.75 to 1.21; 5 trials, 559 infants), whereas ibuprofen was associated with gastrointestinal bleeding (RR 0.28, 95% CI 0.12 to 0.69; NNTB 17 95% CI 11 to 50), higher creatinine and bilirubin levels, and lower platelet counts and daily urine output. There was no difference in the neurological outcomes at 18 to 24 months (n = 61). [LOE I]

• **Paracetamol versus indomethacin:** Systematic review of 2 trials (277 infants) found no difference in failure to close a PDA (RR 0.96, 95% CI 0.55 to 1.65) but creatinine levels were lower, platelet counts and daily urine output were higher in the paracetamol group. There were insufficient data to determine effects on morbidity and safety. [LOE I]

**Surgical ligation**

• A single trial (154 infants) reported no difference in mortality, surgical ligation reduced failure of closure of the PDA but increased pneumothorax and severe retinopathy of prematurity (stage 3 and 4) (RR 3.80; 95% CI 1.12 to 12.93; RD 0.11; 95% CI 0.02 to 0.20; NNTH 9 (95% CI 5 to 50) compared to use of indomethacin. [LOE II]

• A review of 39 cohort studies and 1 RCT found nearly all cohort studies had moderate to high risk of bias mainly due to failure to adjust for survival bias and preligation confounders such as ventilator dependence, IVH, and sepsis. Compared with medical treatment, surgical ligation was associated with increases in neurodevelopmental impairment, CLD, and severe ROP but with a reduction in mortality. There was no difference in the composite outcome of death or NDI in early childhood.

• A systematic review of observational studies comparing early with delayed PDA ligation for infants with a hsPDA found 6 studies including 397 premature or VLBW infants with PDA. The early ligation group had lower FiO2 at 24 hours postoperatively, fewer intubation days (MD -19.69, 95% CI -29.31 to -10.07), earlier date of full oral feeding (MD -22.98, 95% CI -28.63 to -17.34) and heavier body weight at 36 weeks post menstrual age (MD 232.08, 95% CI 57.28 to 406.88). No difference in mortality or other complications was found. [LOE III-2]

**Summary of treatment modalities for a hsPDA in preterm infants**

A network meta-analysis of treatment modalities for a clinically or echocardiographic hsPDA in preterm infants included 68 RCTs of 4802 infants including 14 different variations of indomethacin, ibuprofen, acetaminophen and placebo. The overall PDA closure rate was 67.4% (2867 of 4256 infants).

A high dose of oral ibuprofen [20 mg/kg followed by ibuprofen 10 mg/kg for two doses] was associated with a significantly higher odds of PDA closure versus a standard dose of intravenous ibuprofen (OR 3.59; 95% CI 1.64-8.17; RD 199, 95%CI, 95-258 more per 1000 infants) and a standard dose of intravenous indomethacin (OR 2.35, 95%C1 1.08-5.31; RD 124, 95%C1 14-188 more per 1000 infants). Based on the ranking statistics, a high dose of oral ibuprofen ranked as the best pharmacotherapeutic option for PDA closure and to prevent surgical PDA ligation. Although paracetamol ranked highly for PDA closure, data were limited and estimates imprecise. Indomethacinc regimens in excess of 0.1 to 0.3 mg/kg for up to 3 doses were associated with an increase in NEC. There were no other significant differences in mortality, NEC, or IVH with use of placebo or no treatment compared with any of the other treatment modalities. For side effects, ibuprofen continuous infusion and paracetamol were associated with the lowest risk of oliguria, whereas high dose ibuprofen and indomethacin were associated with the highest risk. However, placebo or no treatment did not significantly change the likelihood of mortality, NEC, or IVH. [LOE I]

**Medical treatment of infants with a hsPDA**

• Respiratory support including increased end expiratory pressure, relative fluid restriction and diuretics are standard management strategies for infants.
with a hsPDA, although not assessed in clinical trials. However, a single trial of furosemide versus chlorothiazide\(^{36}\) in low birth weight infants with respiratory distress syndrome reported furosemide was associated with a higher incidence of hsPDA and increased urine PGE2 excretion.\(^ {92}\)

- Renal protection: For infants with a hsPDA treated with indomethacin, systematic review of 3 trials with 75 infants found dopamine infusion had a clinically unimportant effect on urine output [MD +0.68 mL/kg/hour (95% CI 0.22, 1.44)], no effect on serum creatinine (MD 2.04 \(\mu\)mol/L, CI -17.90, 21.97) or oliguria (RR 0.73, CI 0.35, 1.54) and no difference in failure to close the PDA (RR 1.11, CI 0.56, 2.19).\(^ {104}\) [LOE I]

8. **Consultation**

Clinical Associate Professor David Osborn, Neonatologist
Dr Nicholas Williams, Neonatal/Perinatal Fellow
Department of Newborn Care Guideline Committee, RPAH


- Clinical Governance Standard
- Partnering with Consumers Standard
- Medication Safety
- Recognising and Responding to Acute Deterioration

9. **Appendix**

9.1 **Colour Doppler ductus diameter:** ductal view optimised to achieve maximal diameter, colour Doppler diameter measured at point of maximal constriction with colour gain optimised.
9.2 PDA flow pattern: A: Pulmonary hypertension; B: Growing; C: Pulsatile (S:D velocity ratio ≥2): D: Closing.

A) Pulmonary Hypertension

B) Growing

C) Pulsatile

D) Closing / constricting

9.3 Left atrial to aortic ratio (LA:Ao): M-mode image from long axis view of left ventricle perpendicular to aortic valve.
9.4 Left pulmonary artery gated Doppler flow: LPA mean and end-diastolic velocity

9.5 Distal aortic flow measured beyond ductus: A: forward diastolic flow; B: retrograde diastolic flow

10. References


