# Patent Ductus Arteriosus Management

This Local Guideline applies to:

1. **Adults** - No
2. **Children up to 16 years** - No
3. **Neonates – less than 29 days** - Yes

**Target audience**

All clinicians caring for infants in NICU with a patent ductus arteriosus.

**Description**

Guideline for the management a patent ductus arteriosus.

**National Standard**

Comprehensive Care

## Keywords

- NICU, PDA, NSAID, ECHO, Duct, Indomethacin, Ibuprofen

## Document registration number

JHCH_NICU_13.03

## Replaces existing document?

Yes

## Registration number and dates of superseded documents

- Patent Ductus Arteriosus Management in NICU
- JHCH_NICU_13.03

## Related Legislation, Australian Standard, NSW Ministry of Health Policy Directive or Guideline, National Safety and Quality Health Service Standard (NSQHSS) and/or other, HNE Health Document, Professional Guideline, Code of Practice or Ethics:

- [Medication Safety in HNE Health PD2013_043:PCP31](#)

## Prerequisites (if required)

This document reflects what is currently regarded as safe and appropriate practice. The guideline section does not replace the need for the application of clinical judgment in respect to each individual patient but the procedure(s) require mandatory compliance. If staff believe that the procedure(s) should not apply in a particular clinical situation they must seek advice from their unit manager/delegate and document the variance in the patient’s health record.

## Position responsible for the Local Guideline and authorised by

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PURPOSE AND RISKS

This local clinical procedure has been developed to provide instruction to the health clinician and to ensure that the risks of harm to the infant associated with patent ductus arteriosus are prevented, identified and managed.

The risks are:
- Patent ductus arteriosus can lead to blood shunting
- Increased pulmonary circulation and interstitial oedema contribute to apnoea, increased need for respiratory support and oxygen, increased risk of pulmonary haemorrhage and chronic lung disease
- Patent ductus arteriosus treatments are associated with many adverse effects

The risks are minimised by:
- Clinicians having knowledge of a patent ductus arteriosus and recognising when treatment is required
- Clinicians seeking assistance if caring for infants is outside their scope of practice
- Following the instructions set out in the clinical procedure

Risk Category: Clinical Care & Patient Safety

GLOSSARY

<table>
<thead>
<tr>
<th>Acronym or Term</th>
<th>Definition</th>
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<tbody>
<tr>
<td>A</td>
<td>Peak late diastolic transmitral flow velocity</td>
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<tr>
<td>BPD</td>
<td>Bronchopulmonary dysplasia</td>
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<tr>
<td>CPAP</td>
<td>Continuous positive airway pressure</td>
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<tr>
<td>CPU</td>
<td>Cardio-pulmonary ultrasound</td>
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<tr>
<td>e′</td>
<td>Peak early diastolic mitral annular velocity</td>
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<tr>
<td>E</td>
<td>Peak early diastolic transmitral flow velocity</td>
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<tr>
<td>E/A</td>
<td>Ratio of early to late diastolic transmitral flow velocities</td>
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<tr>
<td>E/e′</td>
<td>Ratio of early diastolic transmitral flow velocity to early diastolic mitral annular velocity</td>
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<tr>
<td>EF</td>
<td>Ejection fraction</td>
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<tr>
<td>JHCH</td>
<td>John Hunter Children’s Hospital</td>
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<tr>
<td>LA</td>
<td>Left atrium</td>
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<tr>
<td>LAvol</td>
<td>Left atrial volume</td>
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<tr>
<td>LPAd</td>
<td>Left pulmonary artery diastolic flow velocity</td>
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LV | Left ventricle
LVO | Left ventricular outflow
NICU | Neonatal Intensive Care Unit
NSAID | Non-steroidal anti-inflammatory drug
PDA | Patent ductus arteriosus
PEEP | Positive end-expiratory pressure
Qp:Qs | Ratio of pulmonary to systemic blood flow
ROP | Retinopathy of prematurity
RVO | Right ventricular outflow
TDI | Tissue Doppler imaging
TR | Tricuspid regurgitation
VLBW | Very low birth weight

GUIDELINE
This Guideline does not replace the need for the application of clinical judgment in respect to each individual patient.

Staff Preparation
It is mandatory for staff to follow relevant: “Five moments of hand hygiene”, infection control, moving safely/safe manual handling, documentation practices and to use HAIDET for patient/carer communication: Hand hygiene Acknowledge, Introduce, Duration, Explanation, Thank you or closing comment.

Background
The ductus arteriosus is an artery joining the aorta and pulmonary artery that normally functionally closes soon after birth. Closure of the ductus arteriosus is due to constriction of ductal smooth muscle in response to increased arterial oxygen tension and falling concentrations of circulating prostaglandins, which is followed by fibrotic remodelling in the vessel wall. These processes are impaired in extremely preterm infants and early spontaneous ductus arteriosus closure occurs only about half of the time. A patent ductus arteriosus (PDA) typically leads to a progressive shunt of blood flowing from the aorta back into the pulmonary circulation, leading to volume loading of the lungs and the left heart. A PDA lowers afterload for the left ventricle and lowers blood pressure with the possibility of reduced organ perfusion pressure.¹
Incidence of PDA
The incidence of PDA is dependent on gestational age and postnatal age. In the John Hunter Children’s Hospital, 49% of preterm infants <29 weeks gestation had a PDA >1.5 mm at 48–72 hours of age, and 20% >2.0 mm. The natural history of a PDA is not completely known, as many would receive treatment. Semberova et al. collected data on 280 VLBW infants with a PDA who received conservative management, and found that it takes 6, 8, 13 and 71 days for half of the infants at >30 wk, 28–29 wk, 26–27 wk and <26 wk to close their PDA without active treatments. Younger gestational age is the only clinical factor associated with prolonged (>14 days) exposure to a PDA, treated or not treated.

Clinical consequences of a PDA
The clinical impact of a PDA is dependent on the magnitude of the shunt and the ability of the infant to initiate compensatory mechanisms. Shunt magnitude is mainly dependent on PDA diameter, but also on the pressure difference between the pulmonary and systemic ends. Increased pulmonary circulation and interstitial oedema contribute to apnoea, increased need for respiratory support and oxygen, and increased risk of pulmonary haemorrhage and chronic lung disease. A PDA is also associated with reduced afterload, perfusion pressure and diastolic blood flow to key organs, including the kidneys, intestine and brain, and may contribute to acute and chronic ischaemia. Heart failure with reduced ejection fraction (systolic heart failure) is not very common in preterm infants with a PDA, but the risk of diastolic dysfunction increases with each week of exposure to a PDA. Diastolic heart failure was found in 4% of preterm infants with a PDA.

Diagnosis of a PDA
The clinical diagnosis can be considered based on a systolic or continuous murmur, hyperactive precordium and increased pulse volume resulting in a widened pulse pressure. More commonly, respiratory signs (apnoeas, increased need for respiratory support, unable to wean off respiratory support) will be the trigger for an echocardiogram to diagnose a PDA. Overt heart failure with hypotension and shock is a rare sign of a PDA,
but low systemic blood flow during the first 24 hours after birth is more common in mechanically ventilated preterm infants with a large PDA. Clinical signs can be minimal in the first days of life and screening echocardiograms can be performed in high risk infants (e.g. <29 weeks gestation) at 24–72 hours of life.

A PDA echocardiogram report includes details on PDA diameter, flow pattern, pulmonary volume load, systolic and diastolic cardiac function and structural concerns. In general, a PDA between 1.5 to 2.0 mm is considered moderate and >2.0 mm as large. A PDA >3.0 mm is rare and should be followed closely. Pulmonary volume load is assessed by the changes in LA shape (LAV) and Qp:Qs and cardiac function by measuring cardiac output (EF, LVO) and diastolic blood flow parameters ($E/A$, $E/e'$).

**NSAID treatment**
Current first line treatment for a PDA is administration of non-steroidal anti-inflammatory drugs (NSAIDs) which inhibit prostaglandin synthesis. Both indomethacin (indomethacin) and ibuprofen are used in neonates and appear to be equally effective for PDA closure. Despite the strong association between a PDA and neonatal morbidity, randomised trials have failed to demonstrate a clear benefit from accelerated ductal closure with NSAIDs. A recent meta-analysis with over 50 randomised, controlled trials in over 5000 preterm infants found that reduced PDA patency did not lead to medium or long term benefits, except reduced IVH with prophylactic indomethacin (not ibuprofen), and, in one study, prevention of pulmonary haemorrhage.

The existing evidence cannot tell us whether NSAID treatment is either safe or best practice for preterm infants with a PDA. This is reflected in wide variation of practice in management of PDA between, and even within, neonatal units worldwide. One-fifth of neonatologists in Australia and New Zealand report that they do not base their practice on the trial literature because the quality of the evidence is too poor.

It is possible that the current NSAID treatment is causing harm. Indomethacin is a potent unselective vasoconstrictor. Adverse effects include a transient decrease in cerebral, cardiac, mesenteric and renal perfusion, and increased risk of gastrointestinal perforation, necrotising enterocolitis and renal impairment. Ibuprofen appears to have fewer adverse effects on organ blood flow, but may increase the risk of chronic lung disease. Both NSAIDs can induce early cessation of kidney development and may alter the number of nephrons and glomeruli in adulthood. Inhibition of the prostaglandin E2 receptor by NSAIDs may attenuate ductus arteriosus remodelling required for anatomical closure, especially in extremely premature infants in which the ductus arteriosus is not fully remodelled. This recent finding might explain the high NSAID failure rate (up to 70%) in infants of very young gestation. NSAID-induced vasoconstriction at a critical period during the intensive care stay without the benefits of PDA closure is associated with a greater risk of adverse neurodevelopmental outcome at age 2–3 years, particularly among infants born at <25 weeks’ gestation.

**Conservative management**
Because most randomised trials have failed to demonstrate a clear benefit from NSAID treatment, some clinicians have now adopted a conservative approach not primarily
intended to achieve PDA closure. With this approach, PDA associated volume overload is managed with supportive care such as optimising positive pressure settings, careful fluid management and sometimes with the addition of diuretics until spontaneous closure occurs. This is also common practice after failed NSAID treatment. Potential adverse effects of a conservative approach are prolonged exposure of the heart and pulmonary artery system to higher pressures and increased blood flow that could lead to heart failure or irreversible pulmonary vascular disease as found in children and adults with a PDA.\textsuperscript{14} Uncertainty remains about how long a newborn can be exposed to such physiology before any adverse changes take place. We found that reversed remodelling was quick after PDA closure, with shape and function as expected at 36 weeks’ corrected gestational age.\textsuperscript{15} Most PDAs close during the NICU stay, and 75–85\% in the first year of life.

Surgical ligation
If medical management fails and the PDA remains significantly symptomatic then surgical ligation is the last line of treatment. Surgical ligation provides definite PDA closure and reduces neonatal mortality. However, among survivors, PDA ligation is associated with an increased incidence of chronic lung disease, retinopathy of prematurity and neurosensory disability, although the extent to which this is related to the procedure per se or confounding from the underlying PDA pathophysiology is unclear.\textsuperscript{16}

Treatment, the bottom line…
After 5 decades of research, it is still unknown how best to manage the PDA. This has led to large variations in PDA management between and within neonatal units, and reluctance to participate in new trials. To date, supportive management of a PDA in preterm infants has not been attempted in a placebo-controlled trial as all trials allowed open label treatment in the placebo group. Our unit is currently running the uPDA pilot trial that randomises preterm infants <29 weeks’ gestation with a PDA >1.5 mm <72 hours after birth to standard NSAID treatment versus supportive care. No open label NSAID treatment is allowed after the randomisation period. The primary endpoint is willingness of clinicians to recruit patients (consent rates) and ability to avoid open label treatments. Secondary clinical outcomes include chronic lung disease and/or death.
Treatment, clinical guideline
JHCH has no directive guideline on PDA management. Management is determined individually for each patient. Suggestions are described below.

Indications for a diagnostic PDA echocardiogram
Screening CPU in all infants <29 week <72 hours, and on clinical indication.

Indications for treatment (supportive or pharmacological)
All preterm infants with an open PDA are exposed to unrestricted left-to-right shunt with increased pulmonary blood flow and volume load of the left heart until closure occurs. The diagnosis of volume overload is complex and consists of assessment of shunt volume, system response to volume load, system response to hypoperfusion and cardiac function. As a general rule, a PDA >1.5 mm with significant volume overload on ultrasound should be considered for treatment. The following ultrasound parameters are associated with volume overload or steal:3, 17, 18

- Pulsatile flow pattern in the PDA
- Left atrium dilatation (LAvol index >1.20 mL/kg in the first week, >1.50 thereafter)
  - Increased diastolic flow velocity in the left pulmonary artery (LPAd >25 cm/s)
  - Increased LVO:RVO ratio (Qp:Qs >1.20)
  - Increased LV ejection fraction (EF >65%)
  - Diastolic heart failure (2 or more out of the following; LAvol >1.50 mL/kg, E/A >0.90, TDI septal e' velocity <2.7 cm/s, E/e' >18 and a TR velocity >3.2 m/s)
- Reverse flow in the descending aorta

Systolic heart failure with myocardial dysfunction and low systemic blood flow is rare in infants with a PDA.

Treatment goal
The primary goal in PDA management is to manage the signs and symptoms of the PDA until PDA closure.

Treatment options
Several treatment options are available to manage PDA-related clinical signs and symptoms. Besides NSAID treatment, most are not founded on rigorous, randomised controlled trials but rely on the current understanding of the pathophysiology of PDA fluid loading to guide treatments. Serial ultrasounds provide insight into the actual pathophysiology of fluid overload and response to treatments.15

1. Optimal distending pressure
Appropriate level of PEEP (usually 8 cm H2O), either with nasal CPAP or mechanical ventilation can reduce pulmonary blood flow or limit clinical signs of pulmonary volume overload.19, 20 Consider continuing CPAP until PDA closure.21

2. Careful fluid management
High fluid strategies in the first days of life in preterm infants are associated with increased risk of a PDA.22 Hypernatraemia occurs in 70% of very preterm infants but is not associated with significant morbidity and should not prompt increasing fluid intake.23, 24
Infants with a PDA increase their LA and LV size by over 30% in the first 72 hours suggesting hypervolaemia, not hypovolaemia, during this phase.\(^5,25\)

If pulmonary oedema is present, fluid restriction to 80% of the current intake could be considered.\(^26\) Severe fluid restriction will reduce systemic blood flow and is not recommended.\(^27\)

3. Diuretics
Persistent fluid overload can lead to heart failure, mostly diastolic heart failure, diagnosed in up to 18% of preterm infants with a PDA after the first week of life.\(^28\) The heart has difficulty filling at normal pressure and the infant develops signs of pulmonary oedema. Loop diuretics can alleviate acute volume overload by reducing LV filling pressure and reduce lung water content.\(^29\) The beneficial effects of loop diuretics are short lasting and only 1 or 2 doses of furosemide (frusemide), 1 mg/kg, 12–24 hours apart is recommended in infants with a PDA and diastolic dysfunction. The use of diuretics in preterm infants with a PDA without diastolic dysfunction is controversial and the safety and efficacy of long-term diuretic use is not well studied.\(^30,31\) Please refer to NeoMed for dose, duration and monitoring of long-term diuretic use.

4. NSAID treatment
NSAIDs (indomethacin, ibuprofen) inhibit fatty acid cyclooxygenase (COX) which converts arachidonic acid to prostaglandin H\(_2\) (PGH\(_2\)), from which further prostanoids, including prostaglandin E\(_2\) (PGE\(_2\)), are enzymatically derived. Prostaglandin E\(_2\) is needed to maintain ductal patency. PDA closure rates with up to 6 doses of NSAID are 70% in 26–28 week gestation infants and 30% in 23–25 week gestation infants. Indomethacin has a higher risk of renal side effects compared to ibuprofen. Both drugs can lead to fluid retention and hyponatraemia and appropriate adjustments need to be made to the fluid intake.\(^10\) There is no definite evidence of improved efficacy of one over the other. Oral preparations are equally effective as intravenous ones, possibly even more so.\(^32\) Prolonged NSAID courses (>6 doses) are not recommended as they increase the risk of complications without increasing efficacy.

NSAID efficacy is significantly reduced if used after 4 weeks’ postnatal age.

5. Paracetamol
Paracetamol facilitates ductal closure via inhibition of COX by a different mechanism to the NSAIDs. Increasing number of studies have shown that paracetamol is as effective as NSAIDs in PDA closure.\(^33\) Evidence from clinical studies of limited quality supports paracetamol treatment as rescue therapy for infants with persistent PDA after unsuccessful NSAID treatment, including those being considered for surgical ligation.

6. Feeding during PDA and treatment
Routinely stopping of enteral feeds during NSAID treatment leads to increased time to reach full enteral feeding and increased risk of late-onset sepsis.\(^34,35\) Blood flow velocity in the mesenteric artery shows an appropriate response with feeding, suggesting there is no reason to adjust the infant’s feeding regimen, only when clinical food intolerance is present.\(^36\)

7. Dexamethasone
Exogenous corticosteroids reduce lung inflammation and clinical respiratory signs, but are also effective inhibitors of endogenous steroid synthesis.\(^37\) Dexamethasone increases LV wall thickness and wall stress, increasing the ability of the LV to cope with increased LV
filling pressure.\textsuperscript{15} Postnatal steroids in an infant with evolving BPD and a PDA should be considered before surgical ligation.

8. Surgical ligation
Surgical ligation should be considered when significant clinical signs due to PDA volume load cannot be controlled with any of the above treatments. The clinical signs and symptoms must outweigh the increased risk of BPD, ROP and neurodevelopmental impairment with surgical ligation.\textsuperscript{38}

Follow up
Each treatment should be monitored according to its efficacy. The therapeutic goal is to reduce and control clinical signs associated with pulmonary oedema and fluid overload. Most treatments will take a few days to show a (sustained) effect. Clinical and ultrasound follow up is recommended after active pharmacological treatments (NSAIDs, paracetamol, dexamethasone) and after 1–2 weeks of supportive care.

IMPLEMENTATION, MONITORING COMPLIANCE AND AUDIT

1. Approved clinical guideline will be uploaded to the PPG and communication of updated ‘Patent Ductus Arteriosus Management in NICU’ clinical guideline to NICU staff will be via email and message on the HUB.
2. Incident investigations associated with this Guideline and Procedure will include a review of process.
3. The Guideline and Procedure will be amended in line with the recommendations.
4. The person or leadership team who has approved the Guideline and Procedure is responsible for ensuring timely and effective review of the Guideline and Procedure.
5. Evaluation will include a review of the most current evidence as well as a consideration of the experience of Neonatal staff at JHCH in the implementation of the Guideline and Procedure.
REFERENCES


5. de Waal K, Phad N, Collins N, Boyle A. Cardiac remodeling in preterm infants with prolonged exposure to a patent ductus arteriosus. *Congenital Heart Disease.* 2017;00:1-9.


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FEEDBACK
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