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Contents

Background	3
Which babies should undergo echocardiography?	3
Diagnosis of hsPDA.....	3
Management of babies with PDA.....	4
Management strategies/therapeutic interventions (see appendix 1)	4
Expectant management.....	4
Non-pharmacological intervention	4
Diuretic therapy.....	4
Pharmacological closure	5
a. Ibuprofen.....	5
b. Paracetamol (acetaminophen) (see appendix 3 for sample drug information sheet).....	5
Surgical closure.....	5
Appendix 1	7
Appendix 2	8
Appendix 3	9
Appendix 4	12
References	16

Management of Patent Ductus Arteriosus

Background

The ductus arteriosus closes spontaneously in many preterm infants but prolonged ductal patency is a complication of extreme preterm birth [1]. A persistently patent ductus with a large ductal shunt (a 'haemodynamically significant', hsPDA) is associated with pulmonary hyper-perfusion, systemic hypo-perfusion and adverse clinical outcomes including pulmonary haemorrhage, NEC, CLD and mortality [2].

Which babies should undergo echocardiography?

An echocardiogram should be performed in any preterm baby in whom the clinical signs and/or radiological features suggest the presence of a hsPDA. These include murmur, tachycardia, full pulses, an active praecordium, hypotension, cardiomegaly, worsening respiratory status and dependence on respiratory support.

Diagnosis of hsPDA

Diagnosis of PDA can only be made using 2D and Doppler echocardiography; clinical signs are unreliable and should not be used in isolation to make the diagnosis. Early echocardiographic 'screening' for PDA is not routinely performed. Diagnostic echocardiography should include an initial assessment to exclude structural heart disease and, specifically, duct-dependent cardiac defects.

Assessment of hsPDA should include measures of ductal size and the magnitude and impact of the ductal shunt. The following echocardiographic indices and thresholds should be used to define a hsPDA [3]:

1. PDA diameter ≥ 2.0 mm (either using 2D or colour Doppler)
2. Ductal flow pattern ('growing' pattern or pulsatile with $V_{max} < 2$ m/s and $V_{max}/V_{min} \geq 2$)
3. Retrograde post ductal aortic/coeliac/SMA diastolic flow
4. $La/Ao \geq 2$
5. $LVO > 300$ ml/kg/min
6. Mitral valve E/A ratio > 1

The diagnosis of hsPDA should be made in the presence of supportive clinical signs and at least 3 of the above echo indices.

Management of babies with PDA

- a. **Babies with PDA and a small ductal shunt** (i.e. not haemodynamically significant) should be managed expectantly. A repeat echo should be performed if the baby has a cardiorespiratory deterioration or if a murmur is still present prior to discharge home. Refer to cardiology if PDA is still present at discharge.
- b. **Asymptomatic babies with echocardiographic criteria of hsPDA** should also be managed expectantly, but with a low threshold for repeating the echo if the baby develops any symptoms of hsPDA. Subsequently, management should follow (a) or (c), as appropriate.
- c. **Symptomatic babies* with a hsPDA** may be treated with diuretics, ibuprofen and/or paracetamol (see below).

**Clinical features include persistent hypotension, pulmonary haemorrhage, prolonged dependence (or increase in) invasive or non-invasive respiratory support, feed intolerance.*

Management strategies/therapeutic interventions (see appendix 1)

Expectant management

This approach is used when uncomplicated spontaneous closure of the ductus arteriosus is anticipated. Management is the same as in a baby in whom the PDA is closed.

Non-pharmacological intervention

Although there is no clear evidence of clinical efficacy, various approaches including fluid restriction, increasing PEEP, permissive hypercapnia, maintaining a high haematocrit and higher target SpO₂ (89-94%) have all been used as part of a 'conservative' approach to managing a hsPDA [4].

Action:

- Follow current unit guidelines for fluid, blood transfusion and oxygen and respiratory support;
- Give information leaflet on PDA to parents.

Diuretic therapy

There is some evidence that furosemide stimulates renal synthesis of prostaglandin E₂ (a dilator of the ductus arteriosus) and delays ductal closure. The risk of PDA is greater with furosemide compared with chlorothiazide. Furosemide is associated with nephro- and ototoxicity.

Action:

- Use chlorothiazide (and not furosemide) for management of PDA-associated left heart volume overload and pulmonary oedema.

Pharmacological closure

Although pharmacological closure of the DA is associated with decreased severe IVH and pulmonary haemorrhage, there is no convincing evidence of longer-term benefit from randomised controlled trials [5]. A conservative management approach might also be superior to early routine treatment in babies dependent on respiratory support [6].

a. **Ibuprofen**

Ibuprofen is effective in achieving ductal closure in around 70-80% of cases [7, 8]. There is some evidence that oral therapy and higher dosage regimens are associated with higher closure rates [7-9].

Action:

- Use standard dose ibuprofen (3 doses of 10, 5, 5 mg/kg at 24 hourly intervals) as routine first-line pharmacological treatment of hsPDA in babies < 21 days of age;
- Use oral (rather than IV) ibuprofen if baby is receiving full enteral feeds;
- Re-assess the ductus arteriosus and ductal shunt after 3 days;
- A second course of high dose ibuprofen (3 doses of 20, 10, 10 mg/kg at 24 hourly intervals) can be considered if baby is still under 21 days of age.

b. **Paracetamol (acetaminophen) (see appendix 3 for sample drug information sheet)**

Paracetamol has comparable efficacy to ibuprofen in ductal closure but there is limited information on long-term safety [10]. There is some evidence to support the use of paracetamol in late treatment of PDA after failure of previous NSAID therapy, although the efficacy in achieving ductal closure was only 15% [11].

Action:

- Consider using paracetamol to treat hsPDA in babies \geq 21 days of age, or in babies < 21 days in whom there are contraindications to using ibuprofen (refer to drug information folder);
- Reassess the ductus arteriosus and ductal shunt after 3 days.

Surgical closure

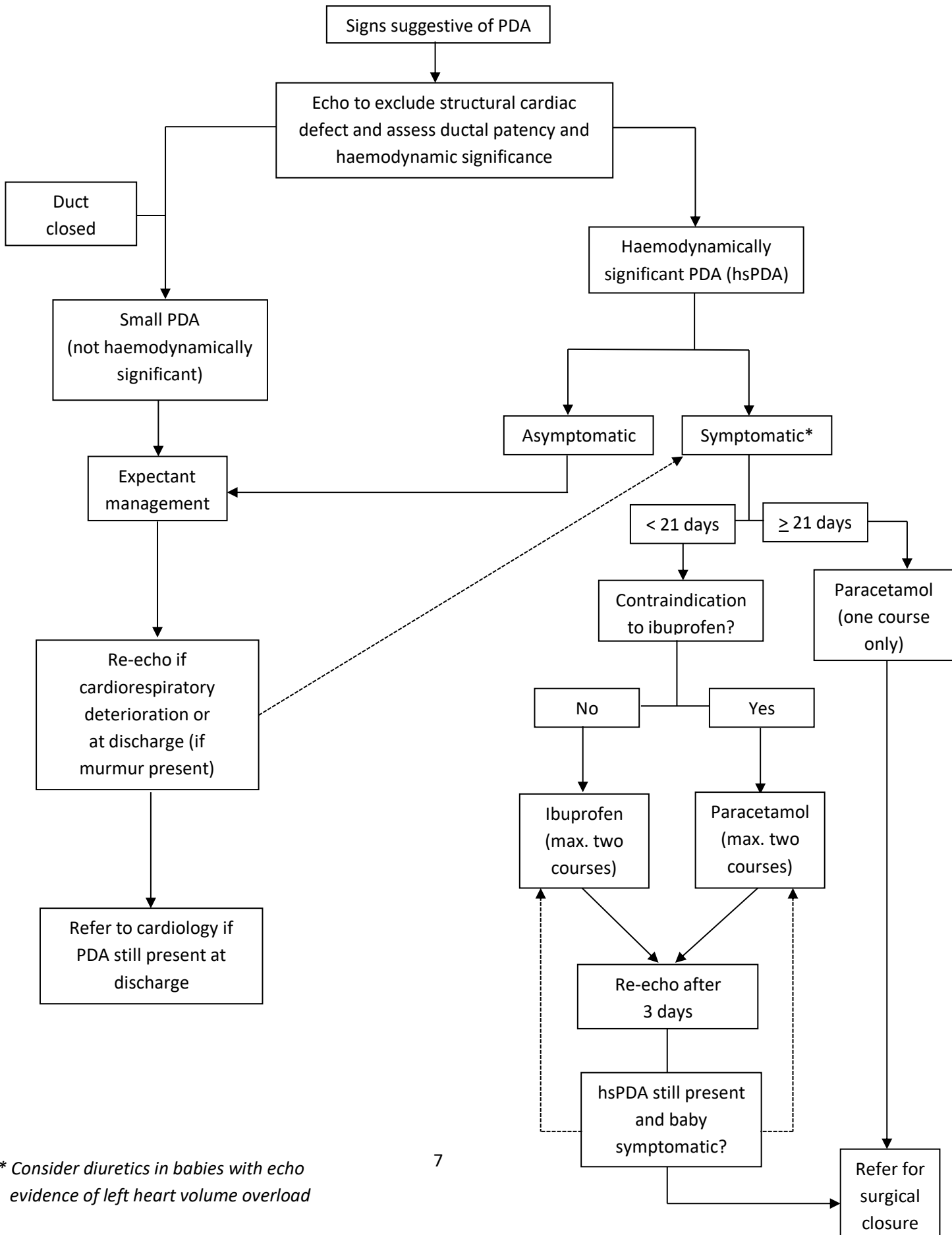
Surgical closure should be considered in babies with hsPDA despite pharmacological therapy (or in whom pharmacological therapy is contraindicated) who remain dependent on high levels of respiratory support (ventilation, CPAP or HFNC). Duct ligation carries significant risks associated with transfer, surgery and post-operative complications (such as post-ligation cardiac syndrome) [12]. Catheter closure might be appropriate in selected larger babies (> 6 kg) at the discretion of the cardiologists.

If after the above sequential assessment the baby is felt to require consideration for surgical or interventional closure of a haemodynamically significant Persistent Ductus Arteriosus (hsPDA) please refer to the *Congenital Heart Network Guidance 'Referral for management of patent ductus arteriosus (PDA) in premature babies'*.

Action:

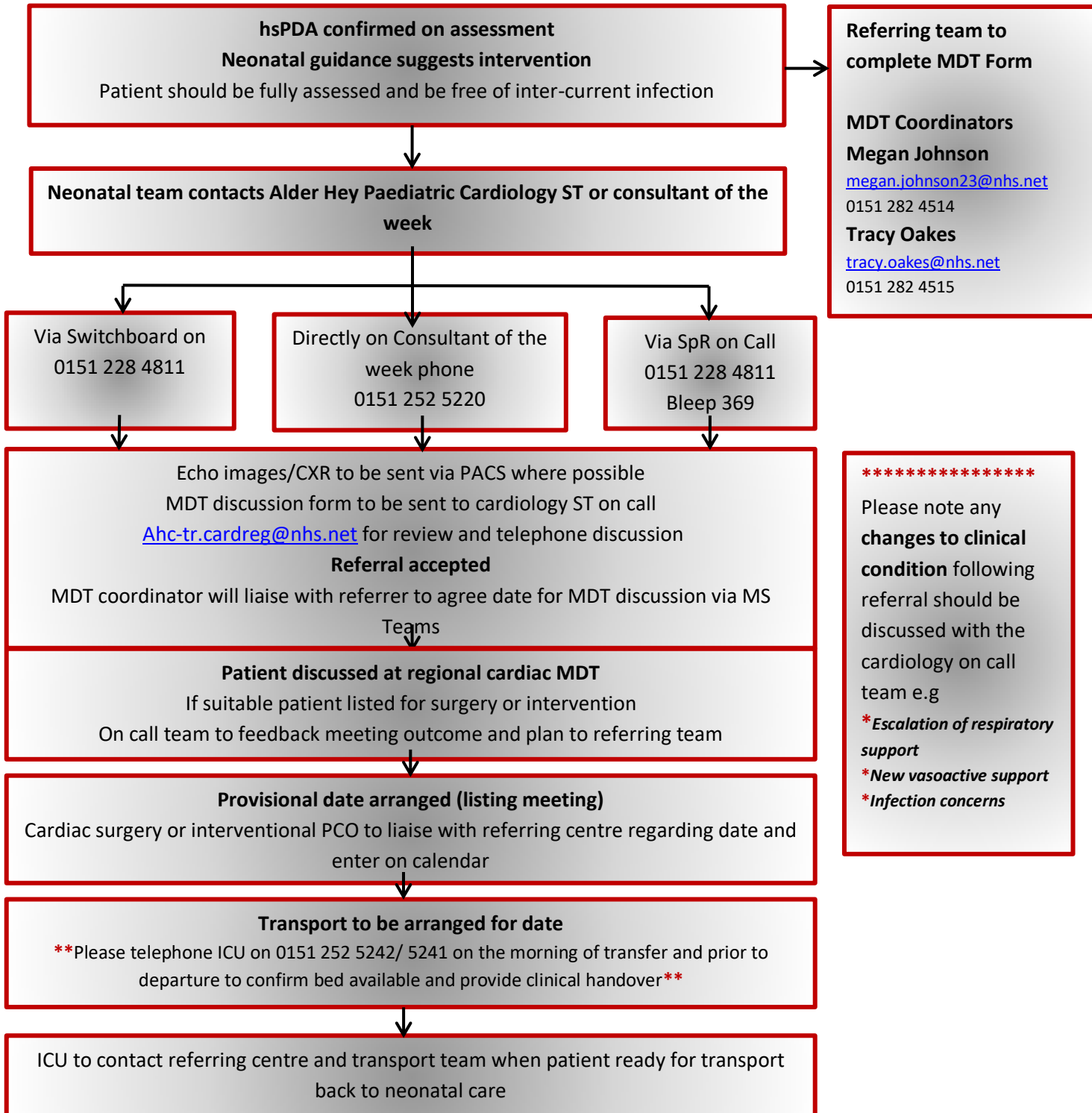
- Consider duct ligation in babies with hsPDA who are dependent on high levels of respiratory support (ventilation, CPAP or HFNC) .
- A consultant-to-consultant referral should be made to the cardiology team verbally and using the referral process outlined in the Congenital Cardiac *Congenital Heart Network Guidance 'Referral for management of patent ductus arteriosus (PDA) in premature babies'*. See Appendix 2 for flow chart of process.
- A pre-op echo should be performed within 3 days of transfer to confirm that a hsPDA is still present.

Appendix 1



* Consider diuretics in babies with echo evidence of left heart volume overload

Appendix 2: Summary of PDA Referral Pathway



Appendix 3: Sample Ibuprofen Drug Information Summary (LWH, May 2020)

IBUPROFEN

INDICATION: Treatment of haemodynamically significant patent ductus arteriosus (PDA) confirmed by ECG examination in neonates <34 weeks gestational age.

BACKGROUND

Ibuprofen is a non-steroidal anti-inflammatory drug with anti-pyretic and analgesic effects. It interferes with prostaglandin synthesis through cyclo-oxygenase inhibition. Ibuprofen has less of an effect on organ perfusion as compared to indomethacin. Ibuprofen may inhibit platelet aggregation and increase bleeding time.

PRESENTATION 2mL ampoule containing 10mg Ibuprofen Pedeo®
(5mg/mL)
pH 7.8 – 8.2

DOSE: Initial (loading) dose of **10 mg/Kg** by IV infusion over 15 minutes followed at 24 hourly intervals by two further (maintenance) doses of **5 mg/Kg** by IV infusion over 15 minutes.

A second course of high dose ibuprofen may be given if the PDA remains haemodynamically significant 48 hours after the end of the first course:

Initial (loading) dose of **20 mg/Kg** by IV infusion over 15 minutes followed at 24 hourly intervals by two further (maintenance) doses of **10 mg/Kg** by IV infusion over 15 minutes.

ADMINISTRATION: Preferably administer undiluted. However, may be diluted to a suitable volume with sodium chloride 0.9% or glucose 5% to adjust the volume to enable practical administration.

Select IBUPROFEN on GUARDRAILS system

LOADING DOSE: Infuse intravenously at a rate of 40mg/Kg/hour for 15mins to deliver a dose of 10mg/Kg **OR** 80mg/Kg/hour for 15mins to deliver a dose of 20mg/Kg

MAINTENANCE DOSE: Infuse intravenously at a rate of 20mg/Kg/hour for 15mins to deliver a dose of 5mg/Kg **OR** 40mg/Kg/hour for 15mins to deliver a dose of 10mg/Kg

DILUENTS Sodium chloride 0.9% or Glucose 5%

ROUTE OF ADMINISTRATION

Administer by INTRAVENOUS INFUSION over 15 minutes.

In order to avoid ibuprofen being in contact with any acidic solution, the infusion line should be rinsed over 15 minutes before and after administration, with 1.5-2mL sodium chloride 0.9% or glucose 5%

FLUSH

Sodium chloride 0.9% or Glucose 5%

CAUTION

Monitor for bleeding problems including upper gastrointestinal bleeding. May mask signs of infection. Avoid in severe liver disease. Avoid in moderate/severe renal impairment. If anuria or oliguria occurs after the first or second dose, the next dose should be withheld until urine output returns to normal levels.

COMPATIBILITY

Do not infuse with any other medicines.

KNOWN INCOMPATIBILITIES

Do not use chlorhexidine to disinfect ampoules as it is incompatible with ibuprofen (Pedea®) solution. For asepsis use ethanol 60% or isopropyl alcohol 70%. Ensure external surface of ampoules is dry before opening.

SIDE EFFECTS

Thrombocytopenia, neutropenia, intraventricular haemorrhage, periventricular leukomalacia, bronchopulmonary dysplasia, pulmonary haemorrhage, hypoxemia, necrotising enterocolitis, intestinal perforation, gastrointestinal haemorrhage, oliguria, acute renal failure, fluid retention, haematuria

MONITORING

Weight, urine output, urea, electrolytes, platelet function and severe hyperbilirubinaemia. Blood creatinine increase and blood sodium decrease may occur.

INTERACTIONS

Ibuprofen may decrease the clearance of aminoglycosides such as gentamicin and strict surveillance of antibiotic levels is important during co-administration with ibuprofen. Ibuprofen may reduce the effect of diuretics. It may increase the risk of gastrointestinal haemorrhage when used in combination with corticosteroids.

STORAGE

Store at room temperature in original packaging to protect from light. After first opening of an ampoule, any unused portions must be discarded.

OTHER INFORMATION

1. Licensed for closure of ductus arteriosus (premature neonate <34 weeks)
2. Excipients include: trometamol.
3. Not used for analgesia in this neonatal unit.
4. Contraindicated with duct-dependent congenital heart disease; life-threatening infections; active bleeding especially intracranial or gastrointestinal; thrombocytopenia or coagulopathy; marked unconjugated hyperbilirubinaemia; known or suspected NEC, pulmonary hypertension.

REFERENCES

BNF for Children (ONLINE), Neonatal Formulary 7th Edition, Medusa injectable medicines guide (ONLINE), Trissel Handbook on Injectable Drugs (ONLINE), SPC: Pedia 5mg/ml solution for injection (ONLINE). Online resources accessed 03/03/2019.

High dose Ibuprofen: Dani et al. High-dose ibuprofen for patent ductus arteriosus in extremely preterm infants: a randomized controlled study. [Clin Pharmacol Ther.](#) 2012 Apr;91(4):590-6

Appendix 4: Sample Paracetamol Drug Information Summary (LWH, 2019)

PARACETAMOL

INDICATION:

- For analgesia and pyrexia in babies \geq 28 weeks post-menstrual age (PMA) (See pain and sedation guideline)
- Treatment of Patent Ductus Arteriosus (PDA) (See Management of Patent Ductus Arteriosus guideline)

BACKGROUND

Paracetamol is a non-opioid analgesic with antipyretic properties. It does not cause respiratory depression and causes less irritation to the stomach than NSAIDs such as ibuprofen. Paracetamol causes ductal constriction and is used as an alternative to Ibuprofen in the management of babies with a PDA. Paracetamol can cause severe life-threatening hepatic damage in overdose. It can be given orally, rectally and intravenously. There are limited safety data on the use of paracetamol in preterm infants. Optimum pain relief occurs approximately one hour after peak serum concentration has been reached. Peak concentrations are reached almost immediately after IV administration and in 30-60 minutes following oral administration (longer with rectal administration). The reported elimination half-life varies from a median of 4 hours in term infants to 8 hours in infants <32 weeks.

PRESENTATION

100mL vial containing 1000mg Paracetamol (10mg/mL)
Already in solution
Paracetamol oral suspension 120mg/5mL
pH 5 – 7

FOR ANALGESIA AND PYREXIA

- Can be prescribed regularly or when required (PRN)
- Review prescription regularly and stop if no longer required.

INTRAVENOUS Dose	\geq 28 weeks PMA	20mg/Kg Loading Dose followed 6 hours later by Maintenance Dose of 10mg/Kg every SIX hours
ORAL/ENTERAL Dose	28 – 32 weeks PMA	20mg/Kg Loading Dose followed 12 hours later by Maintenance Dose of 10mg/Kg every TWELVE hours
	> 32 weeks PMA	20mg/Kg Loading Dose followed 6 hours later by Maintenance Dose of 10mg/Kg every SIX hours

FOR PDA CLOSURE

- Use IV route if available
- Use for 3 days initially then review clinically and by ECHO. A further 3-day course may be prescribed, if indicated (Consultant decision)

INTRAVENOUS Dose	All babies	20mg/Kg Loading Dose followed 6 hours later by Maintenance Dose of 10mg/Kg every SIX hours
ORAL/ENTERAL Dose	All babies	15mg/Kg every SIX hours (no loading dose required)

ADMINISTRATION

- INTRAVENOUS:**
1. Calculate volume needed for required dose.
 2. Withdraw the required volume from the vial into a syringe (plus extra volume to prime the administration line). Can be administered without further dilution.
 3. Administer dose by INTRAVENOUS INFUSION over **15 minutes** using GUARDRAILS.

Loading dose (select Paracetamol LOADING)	20 mg/kg over 15 minutes is equivalent to 80 mg/kg/hour
Maintenance dose (select Paracetamol MAINT)	10 mg/kg over 15 minutes is equivalent to 40 mg/kg/hour

* In smaller infants an excess will have to be drawn up and VTBI set on the pump to allow administration of small volumes or IV preparation may be diluted to a suitable volume to enable practical administration. (Diluted solution has an expiry of one hour including infusion time)

ORAL/ENTERAL: Shake bottle before use. Measure required dose and administer orally or via enteral feeding tube.

DILUENTS

Sodium Chloride 0.9%, Glucose 5%

ROUTE OF ADMINISTRATION

Administer by IV infusion over 15 minutes via peripheral or central access using GUARDRAILS.

FLUSH

Sodium Chloride 0.9% or Glucose 5%

CAUTION

Reduce intravenous dose by 50% in patients with hepatic impairment or neonates with unconjugated hyperbilirubinaemia. Drug clearance is slower in jaundiced babies. Risk of liver toxicity with overdosage. Clinical signs and symptoms of liver damage are not usually seen until 2-6 days after administration.

COMPATIBILITY

Glucose 5%, glucose 10%, sodium chloride 0.9%

KNOWN

Do not infuse with other medicines or infusions.

INCOMPATIBILITIES

SIDE EFFECTS

Hypotension, hypersensitivity reactions, flushing, tachycardia, injection site reactions. Rarely thrombocytopaenia, leucopaenia, neutropaenia.

MONITORING

Monitor pain score (NPASS), temperature, oxygenation, hepatic function, renal function and ECHO (if treating PDA)

INTERACTIONS

Increased risk of hepatotoxicity with carbamazepine, clavulanic acid, flucloxacillin, fluconazole, valproate. Decreased efficacy with phenobarbitone, phenytoin and rifampicin

STORAGE

Vials: Store at room temperature and protect from light. Each vial is single use, discard any remaining solution after use.

Oral Suspension: Store at room temperature.

Do NOT refrigerate or freeze paracetamol.

OTHER INFORMATION

1. Paracetamol is not licensed for use in children under 2 months of age.
2. Paracetamol solution for injection is isotonic.
3. Paracetamol suppositories for rectal administration are not stocked at LWH. Rectal absorption in the neonate is unpredictable and this route is rarely used.
4. Paracetamol toxicity is treated with acetylcysteine as it reduces the hepatotoxic effects of paracetamol overdose by replenishing glutathione stores, thereby enhancing production of the non-toxic metabolites.

Acetylcysteine dose and administration instructions (as per BNFC)

- 150 mg/Kg IV during the first hour and then 50 mg/Kg over the next 4 hours followed by 100 mg/Kg over 16 hours as described below:
- Initial infusion: Take one 10mL vial of acetylcysteine and dilute with 30mL of Glucose 5% to give a 50mg/mL solution. Infuse at a rate of 3mL/Kg/hour for one hour only.
- Subsequent infusion: Take one 10mL vial of acetylcysteine and dilute with 310mL of Glucose 5% to give a 6.25mg/mL solution. When the initial infusion has finished, infuse this solution at a rate of 2mL/Kg/hour for 4 hours and then at a rate of 1mL/Kg/hour for 16 hours.

REFERENCES

BNF for Children (ONLINE), Neonatal Formulary 7th Edition, Medusa injectable medicines guide (ONLINE), Trissel Handbook on Injectable Drugs (ONLINE), SPC: Paracetamol 10mg/ml solution for infusion; Paracetamol 120mg/5ml oral suspension (ONLINE). Online resources accessed 28/05/2019.

Allegaert K, Rayyan M, De Rijdt T et al. Hepatic tolerance of repeated intravenous paracetamol administration in neonates. Paediatr Anaesth. 2008 May;18(5):388-92.

Allegaert K, Van den Anker J. Pharmacokinetics and pharmacodynamics of intravenous acetaminophen in neonates. *Expert Rev Clin. Pharmacol.* 2011; 4(6):713-718.

Jasani B, Weisz D, McNamara P. Evidence-based use of acetaminophen for hemodynamically significant ductus arteriosus in preterm infants. *Semin Perinatol.* 2018 Jun;42(4):243-252.

General References

1. Semberova J, Sirc J, Miletin J, Kucera J, Berka I, Sebkova S, O'Sullivan S, Franklin O, Stranak Z. Spontaneous Closure of Patent Ductus Arteriosus in Infants ≤ 1500 g. *Pediatrics* 2017 Aug;140(2).
2. Sellmer A, Bjerre JV, Schmidt MR, McNamara PJ, Hjortdal VE, Høst B, Bech BH, Henriksen TB. Morbidity and mortality in preterm neonates with patent ductus arteriosus on day 3. *Arch Dis Child Fetal Neonatal Ed.* 2013 Nov;98(6):F505-10.
3. Van Laere D, Van Overmeire B, Gupta S, El Khuffash A, Savoia M, McNamara PJ, Schwarz CE, de Boode WP; European Special Interest Group "Neonatologist Performed Echocardiography" (NPE). Application of NPE in the assessment of a patent ductus arteriosus. *Pediatr Res.* 2018 Jul;84(Suppl 1):46-56.
4. Smith A, McNamara PJ, El-Khuffash AF. Non-pharmacological management of a hemodynamically significant patent ductus arteriosus. *Semin Fetal Neonatal Med.* 2018 Aug;23(4):245-249.
5. Benitz WE, Bhombal S. The use of non-steroidal anti-inflammatory drugs for patent ductus arteriosus closure in preterm infants. *Semin Fetal Neonatal Med.* 2017 Oct;22(5):302-307.
6. Clyman RI, Liebowitz M, Kaempf J et al. PDA-TOLERATE (PDA: TO LEave it alone or Respond And Treat Early) Trial Investigators. PDA-TOLERATE Trial: An Exploratory Randomized Controlled Trial of Treatment of Moderate-to-Large Patent Ductus Arteriosus at 1 Week of Age. *J Pediatr.* 2018 Oct 16. pii: S0022-3476(18)31283-6.
7. Ohlsson A, Walia R, Shah SS. Ibuprofen for the treatment of patent ductus arteriosus in preterm or low birth weight (or both) infants. *Cochrane Database Syst Rev.* 2018 Sep 28;9:CD003481.
8. Dani et al. High-dose ibuprofen for patent ductus arteriosus in extremely preterm infants: a randomized controlled study. *Clin Pharmacol Ther.* 2012 Apr;91(4):590-6.
9. Mitra S, Florez ID, Tamayo ME et al. Association of Placebo, Indomethacin, Ibuprofen, and Acetaminophen With Closure of Hemodynamically Significant Patent Ductus Arteriosus in Preterm Infants: A Systematic Review and Meta-analysis. *JAMA.* 2018;319(12):1221-1238.
10. Jain A, Shah PS. Diagnosis, Evaluation, and Management of Patent Ductus Arteriosus in Preterm Neonates. *JAMA Pediatr.* 2015 Sep;169(9):863-72.
11. Kluckow M, Carlisle H, Broom M, Woods P, Jeffery M, Desai D, Chen Y, Evans N. A pilot randomised blinded placebo-controlled trial of paracetamol for later treatment of a patent ductus arteriosus. *J Perinatol* 2019 Jan;39(1):102-107.
12. Weisz DE, Giesinger RE. Surgical management of a patent ductus arteriosus: Is this still an option? *Semin Fetal Neonatal Med.* 2018 Aug;23(4):255-266.