Treatment of Patent Ductus Arteriosus in Preterm Babies

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Contents

Key Points

- The recently performed Baby OSCAR study did not show benefit in the routine use of prophylactic ibuprofen. (in press)
- We recommend medical treatment for **symptomatic PDA's** with clinical or echocardiographic features of significant shunt.
- There are a number of European trials (including the TREOCAPA trial) looking at the use of paracetamol for PDA including developmental follow up. We do not recommend routine use until the long term outcomes are clearer.
- The guidance given here regarding the treatment of a Patent Ductus Arteriosus (PDA) with ibuprofen only applies to those babies of less than 30 weeks gestation.
- Contra-indications to ibuprofen treatment are listed below
- The management of the patent duct in congenital heart disease is not covered in this guideline

Treatment of PDA – Summary

1	Routine prophylaxis with Non-Steroidal Anti- Inflammatory drugs is not recommended.
2	Following the Baby OSCAR study, routine early echocardiography with targeted ibuprofen prophylaxis is no longer recommended.
3	Babies that are thought to have a symptomatic PDA should have an echo performed. Echo criteria are shown in Appendix A. A clinically significant duct should be treated with ibuprofen (Grade C) – The recommended dose (BNFc) is 10mg/kg as a single dose I.V followed at 24 hourly intervals by 2 further doses of 5mg/kg – Echocardiography should be repeated after treatment and if the duct remains significant a further course may be considered 48 hours after the first course (Grade B)
4	PDA ligation may be considered in a significantly symptomatic babies where a PDA has failed to respond to medical treatment or in cases where medical treatment is contra-indicated (Grade B) The decision to treat a baby with ibuprofen, or to refer a baby for a PDA ligation is not always clear-cut. Early input should be sought from the attending consultant neonatologist before embarking on a treatment course
5	Aggressive fluid restriction is not recommended- it seems sensible to avoid excessive fluid treatment and moderate fluid restriction (by around 30%) may be helpful. Calorific intake should be maintained and milk intake should not be restricted. Non-steroidal drugs reduce the GFR and consideration should be given to relative fluid restriction during therapy, with close monitoring of fluid status. Monitoring should include daily weight, close monitoring of urine output and frequent measurement of serum electrolytes (at least daily) whilst receiving treatment
6	There is no evidence to support the use of diuretics- their use should be restricted to individual babies where there is thought to be heart failure and fluid overload (Grade B)

1. Introduction and who this guideline applies to:

Patent ductus arteriosus remains a significant cause of morbidity amongst preterm babies.

After birth, a PDA leads to left to right shunting, and results in increased blood flow through the lungs. This can be associated with pulmonary haemorrhage, and contributes towards the development of

chronic lung disease. The presence of a PDA can also lead to decreased gut perfusion and increases the risk of necrotising enterocolitis.

About a third of babies with a gestation of less than 30 weeks develop clinical signs of a patent ductus arteriosus [(1)]

A PDA can present with clinical signs:

- Active precordium
- A systolic or continuous heart murmur
- Bounding peripheral pulses
- Hepatomegaly

Babies may have increasing apnoea, difficulty weaning from the ventilator, poor feed tolerance, or pulmonary haemorrhage.

The clinical signs of a PDA are a poor predictor of duct size, and correlate poorly with the degree of ductal blood flow [(2)]. Echocardiography is usually performed, and allows confirmation of the presence of a duct with measurement of the ductal size.

Management of a PDA involves close attention to the early fluid status of preterm babies, particularly in the first few days of life, with care taken to avoid fluid overload.

Medical treatment of a PDA has traditionally consisted of fluid restriction, diuretic use and non-steroidal medications (indometacin and ibuprofen). The latter drugs are cyclo-oxygenase inhibitors. They lead to a decrease in the production of prostaglandins which encourages ductal closure. Ibuprofen is the current non-steroidal medication in use in Leicester.

If medical management is contraindicated, or fails and the duct is felt to be significantly contributing to the babies clinical state, referral to the East Midlands Congenital Heart Centre for duct ligation should be considered (this decision should be made with the attending consultant neonatologist).

This guideline is aimed at all Health care professionals involved in the care of infants within the Neonatal Service.

2. Management

When reviewing studies looking at the management of PDA, it is important to be clear about the differences between, prophylactic treatment (treating all preterm babies), targeted treatment (treating babies that have a significant sized duct on echo) and treatment of a symptomatic PDA

In this section, the following will be considered:

- Prophylactic treatment
- The role of fluid restriction and diuretics
- Echocardiography and ‘Targeted’ treatment
- Repeated courses of non-steroidal anti-inflammatory drugs
- Surgical ligation

2.1 Prophylactic treatment

TIPP trial (Prophylactic Indometacin)

A large randomised controlled trial (the TIPP trial [(3)]) looked at the use of 3 doses of indometacin, given to all babies with a birth weight between 500 and 999g.1202 babies were recruited and the

study demonstrated a decrease in the number of babies with PDA and a decrease in the number of babies with severe IVH in the indometacin treatment group.

There was however, no change in the long-term survival data, or the risk of long term neurological problems. There was no difference in the rates of NEC or gastric perforation. This study was included in a recent Cochrane Review [4]

Prophylactic Ibuprofen

Prophylactic ibuprofen does not decrease the rates of IVH and 2 large trials looking at prophylactic ibuprofen were stopped early because of concerns about hypoxaemia [5]. A Cochrane review in 2010 concluded that prophylactic treatment of preterm babies with ibuprofen was not recommended due to lack of short and long term benefits [6].

Prophylactic treatment is NOT CURRENTLY RECOMMENDED in Leicester because of the lack of evidence of long term benefit [Grade A]

2.2 The Role of Fluid Restriction and Diuretics

Careful fluid management in the first few days of life may decrease the incidence of PDA.

Studies looking at fluid restriction to treat PDA show variable results. Bell [7] showed that restricting water intake reduced the risk of developing a PDA, but a further randomised controlled trial [8] showed no difference in outcomes.

There is very little evidence concerning the use of diuretics. Studies from the 1980's, show that if anything furosemide use may increase the incidence of PDA [9].

Babies with a PDA have increased metabolic demands, and their nutrition should be maximised wherever possible.

Aggressive fluid restriction is not recommended- it seems sensible to avoid excessive fluid treatment and moderate fluid restriction (by around 30%) may be helpful. Calorific intake should be maintained and milk intake should not be restricted. Non-Steroidal Anti Inflammatory drugs reduce the GFR and consideration should be given to relative fluid restriction during therapy, with close monitoring of fluid status. Monitoring should include daily weight, close monitoring of urine output and frequent measurement of serum electrolytes (at least daily) whilst receiving treatment

There is no evidence to support the use of diuretics- their use should be restricted to individual babies where there is thought to be heart failure and fluid overload [Grade B].

2.2 Echocardiography and 'Targeted Treatment'

PDA can contribute to significant morbidity in some smallest preterm babies.

Echocardiography to assess the presence and size of a PDA, performed by neonatologists has been shown to be reliable. [10] If any doubt exists as to the presence of structural congenital heart disease, a formal cardiology echo should be requested. Evans et al [11] have demonstrated that an early measurement of ductal size can be used to predict the likelihood of closure.

Most ducts are clinically closing by around 48 hours of age in both term and preterm babies. [11] There is evidence that early treatment with indomethacin or ibuprofen is more likely to result in duct closure and decreases the need for surgical ligation. Early indomethacin (given in the first 3 days of life) appears to be safer than later indomethacin, with less risk of NEC [12].

A Cochrane review concluded that ibuprofen is at least as effective as indomethacin for the treatment of PDA in preterm babies [13,16].

The Baby OSCAR study (in press) did not show any benefit in short term outcomes when comparing ibuprofen with placebo for early targeted treatment

Targeted treatment of a PDA with ibuprofen based on echo criteria in the first 72 hours is no longer recommended

2.3 Treating the Symptomatic duct

A PDA with left to right shunt is a common cause of heart failure in preterm babies.

Symptoms suggesting a clinically significant PDA include:

- Difficulty weaning from the ventilator or failure to extubate
- Failure to gain weight
- Problems with end organ perfusion: acute kidney injury and difficulty with enteral feeds
- Apnoeas
- Pulmonary Haemorrhage

Signs include:

- Tachycardia
- Cardiomegaly on X-ray
- Bounding pulses
- Active precordium
- Signs of heart failure: pulmonary oedema and palpable liver edge
- Low diastolic blood pressure

Echocardiographic features of a significant shunt include:

- Increased Left Atrium to Aortic ratio (>1.5:1)
- Left ventricular volume loading with deviated septum
- Signs of ductal steal (decreased or reversed diastolic flow in the aorta, mesenteric or cranial arteries

(see Appendix A)

Babies with a symptomatic PDA and signs of significant shunt on echocardiography should be treated with a 3 day course of ibuprofen.

Ibuprofen

There is little evidence as to the most effective dose of ibuprofen. Most studies use a dosing regimen of 10 mg / kg I.V for the first dose, followed by 2 doses of 5mg/ kg I.V given 24 hourly. Other studies have shown good results with higher dosing regimens.

Ibuprofen causes a transient decrease in the glomerular filtration rate, and oliguria. Care should be taken to avoid fluid overload during its use. Fluids should be relatively restricted during treatment, to minimise flow through the duct and avoid fluid retention, secondary to the expected fall in GFR.

Babies receiving treatment should have daily electrolytes and platelet counts monitored.

Contraindications to treatment use would include:

- Low platelet count (<50)
- Radiological NEC, or high clinical suspicion of NEC
- Intraventricular haemorrhage (Grade 3-4)
- Established renal failure (e.g. creatinine >120 with oliguria <0.5ml/kg/hr)
- Concurrent treatment with hydrocortisone should be avoided as this may increase the risk of perforation

The recommended dose is 10mg/kg I.V as a single dose followed at 24 hourly intervals by 2 further doses of 5mg/kg I.V

- Echocardiography should be repeated after treatment and if the duct remains significant a further course may be considered 48 hours after the first course (Grade B)

- *A Cochrane review from 2020 suggested that IV ibuprofen has the same effectiveness as the oral form for duct closure. Our mainstay should still be to use the IV route. Oral route may be used as per consultant discretion in some case like, on full feeds without IV access [20], The dose for the oral route is the same as the IV ibuprofen.*
- *There is no evidence to support the stopping of enteral feeds during ibuprofen use- feeds should be continued, and increased in the usual way, unless there are clinical concerns with the abdomen.*

Repeated courses of Ibuprofen

Medical treatment is successful in closing a PDA in about 70% of babies. If the first course is not successful, a later second course can be useful- some studies report closure rates of 82% [14]. The earlier a second course is given, the higher the chance of successful duct closure. Symptomatic babies are likely to benefit from a second course of ibuprofen.

What constitutes ‘symptomatic’ remains controversial: most neonatologists would treat a baby that has a significant PDA and remains ventilated.

Treatment for a baby who requires CPAP may be considered for individual babies if the benefits are thought to outweigh the risks

If following an early course of ibuprofen, the duct reopens, and the baby is symptomatic, a second course of treatment should be considered (Grade B)

Paracetamol for Ductal Closure

Paracetamol has been used for the closure of a PDA in preterm infants. This is currently an unlicenced use, but there are a number of studies and a Cochrane review in 2020 showing paracetamol to be as effective as ibuprofen in closing a PDA [19]

The long term neurodevelopmental data is from one study and of low quality. There are some case reports suggesting an increase in autism rates in infants treated with paracetamol (low quality evidence).
There are a number of paracetamol trials running and the outcomes of these are awaited.

Paracetamol should not be routinely used for the closure of PDA. There may be specific cases where ibuprofen is contraindicated. The use of paracetamol should be a consultant decision and a discussion with the family should be documented in the notes. Should paracetamol be considered, an appropriate dosing regimen would be:

20mg/kg paracetamol loading dose followed by:

7.5mg/kg 6 hourly for a total of 5 days

There are a number of different dosing regimens: This is the regimen used in the TREOCAPA study currently running in Europe.

Surgical Ligation

Surgical ligation of a PDA may decrease mortality [17] but there is a relative lack of evidence. One randomised trial [18] in the early 1980's showed an increased risk of air leak and ROP and no difference in other outcomes.

The mortality of duct ligation is low, but there is significant morbidity - pneumothoraces, chylothoraces, recurrent laryngeal nerve damage and pulmonary oedema. Locally the ligations are performed at the East Midlands Congenital Heart Centre.

The GiRFT review in 2021 showed Leicester to have an increased rate of PDA ligation when compared to similar units.

PDA ligation may be considered in symptomatic babies where a PDA has failed to respond to medical treatment or in cases where medical treatment is contra-indicated (Grade B)

The decision to treat a baby with Ibuprofen, or to refer a baby for a PDA ligation is not always clear-cut.

Early input should be sought from the attending consultant neonatologist before embarking on a treatment course.

The decision to refer a baby for duct ligation should be made by the attending service consultant and discussed with a second consultant colleague to improve service consistency.

3. Further Reading

Information on Baby-OSCAR trial http://www.npeu.ox.ac.uk/baby-oscar/information-for-hospitals

Philips JB. Management if patent ductus arteriosus in preterm infants. UpToDate . (Eds Garcia-Prats JA, Fulton DR) accessed 10th May 2016

Gien J. Controversies in the Management of Patent Ductus Arteriosus. Neoreviews 2008; 9(10):e477-e482.

4. Education and Training

None

5. Monitoring Compliance

What will be measured to monitor compliance	How will compliance be monitored	Monitoring Lead	Frequency	Reporting arrangements
Babies with a significant duct on echo should receive targeted medical treatment unless contraindicated (80%)	Review the compliance with OSCAR study results (when available). Audit to make sure we are compliant. If the results are not in line with our current practice, the guideline will be reviewed and amended.	Guideline Lead	When OSCAR results are available	Neonatal governance
Babies receiving treatment should have daily electrolytes and platelet counts measured (100%)	Review the compliance with OSCAR study results (when available). Audit to make sure we are compliant. If the results are not in line with our current practice, the guideline will be reviewed and amended.	Guideline Lead	When OSCAR results are available	Neonatal governance

6. Evidence Criteria

Evidence according to RCPCH

Grade A	At least 1 randomised controlled trial addressing specific recommendation
Grade B	Well conducted clinical trials but no randomised trial on specific topic
Grade C	Expert committee report or opinions

7. Supporting References

1. Klucklow M, Evans N. Ductal shunting, high pulmonary blood flow, pulmonary haemorrhage. *J Pediatr.* 2000; 137: 68-72
2. Davis P, Turner-Gromes S, Cunningham K, Way C, Roberts R et al. Precision and accuracy of clinical and radiological signs in premature infants at risk of patent ductus arteriosus. *Arch Pediatr Adolesc Med.* 1995;149: 1136-1141
3. Schmidt B, Davis P, Moddemann D, Ohlsson A et al with the TIPP investigators. Long term effects of indomethacin prophylaxis in extremely low birth weight infants. *New Engl J Med* 2001; 344:1966-1972

4. Fowlie PW, Davis PG. Prophylactic intravenous indomethacin for preventing mortality and morbidity in preterm infants. *Cochrane database of Systematic Reviews. 2002*, Issue 3 Art No CD000174

5. Gournay V, Savagner C, Thiriez G, Kuster A, Roze J-C. Pulmonary hypertension after ibuprofen prophylaxis in very preterm infants. *Lancet* 2002; **359**: 1486-1488

6. Ohlsson A, Shah SS. Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants. *Cochrane Database of Systematic Reviews* 2006, Issue 1. Art. No.: CD004213. DOI: 10.1002/14651858.CD004213.pub2.

7. Bell EF, Warburton D, Stonestreet BS, Oh W. Effects of fluid administration on the development of symptomatic patent ductus arteriosus and congestive heart failure in premature infants, *N Engl J Med* 1980; 302: 598-604

8. Reller MD, Lorenz JM, Kotagal UR, Meyer RA, Kaplan S. Hemodynamically significant PDA: an echocardiographic and clinical assessment of incidence, natural history, and outcome in very low birth weight infants maintained in negative fluid balance. *Pediatr Cardiol* 1985;6:17-23.

9. Green TP, Thompson TR, Johnson DE, Lock JE. Furosemide promotes patent ductus arteriosus in premature infants with the respiratory-distress syndrome. *N Engl J Med* 1983;308: 743-748

10. Moss S, Kitchiner DJ, Yoxall CW, Subhedar NV and Wren C. Evaluation of echocardiography on the neonatal unit. *Arch Dis.Child. Fetal Neonatal Ed. 2003*: 88; 287-291

11. Evans N. Patent ductus arteriosus in the neonate. *Current Paediatrics* 2005; 15: 381-389

12. Clyman RI. Recommendations for the postnatal use of indomethacin: an analysis of four separate treatment strategies*. J Pediatr* 1996;128: 601-607

13. Ohlsson A, Walia R, Shah SS. Ibuprofen for the treatment of patent ductus arteriosus in preterm and/or low birth weight infants. *Cochrane Database of Systematic Reviews* 2010, Issue 4. Art. No.: CD003481. DOI: 10.1002/14651858.CD003481.pub4

14. Van Overmeire B, Van de Broek H, Van Laer P, Weyler J,Vanhaesebrouck P. Early versus late indomethacin treatment for patent ductus arteriosus in premature infants with respiratory distress syndrome. *J Pediatr* 2001;138:205–11.

15. Gournay C, Savagner G, Thiriez A et al. Pulmonary hypertension after ibuprofen prophylaxis in very preterm infants. *Lancet* 2002; **359**:1486-1488

16. Lago P, Bettiol T, Silvadori S, Pitassi S Safety and efficacy of ibuprofen vs indomethacin in treatment of patent ductus arteriosus – a randomised controlled trail. *Eur Jour Pediatr 2002:* 161; (4) 202-207

17. Brooks JM, Travadi JN, Patole SK et al. Is surgical ligation of patent ductus arteriosus necessary? The Western Australian experience of conservative management. *Arch Dis Child. Fetal Neonatal Ed.* 2005;90: 235-239

18. Gersony WM, Peckham GF, Ellison RC et al. Effects of Indomethacin in premature infants with patent ductus arteriosus: the results of a national collaborative trial. *J Pediatr* 1983; 102: 895- 906

19. Ohlsson A, Shah PS. Paracetamol (acetaminophen) for patent ductus arteriosus in preterm or low birth weight infants. Cochrane Database of Systematic Reviews 2020, Issue 1. Art. No.: CD010061. DOI: 10.1002/14651858.CD010061.pub4. Accessed 01 March 2022.

20. 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 of Systematic Reviews 2020, Issue 2. Art. No.: CD003481. DOI: 10.1002/14651858.CD003481.pub8. Accessed 05 April 2022.

8. Key Words

PDA, neonates, neonatal unit, Patent ductus arteriosus, Paracetamol, Ibuprofen

The Trust recognises the diversity of the local community it serves. Our aim therefore is to provide a safe environment free from discrimination and treat all individuals fairly with dignity and appropriately according to their needs.
As part of its development, this policy and its impact on equality have been reviewed and no detriment was identified.

Contact and review details

Guideline Lead (Name and Title) Sumit Mittal – Consultant Neonatal guidelines lead **Author:** Dr Jonathan Cusack - Consultant Neonatologist Muhammad Ali	**Executive Lead** Chief Medical Officer

Details of Changes made during review:

Date	Issue Number	Reviewed By	Description Of Changes (If Any)
2000	**1**		**Original guideline**
April 2011	**2**	author JMC	ratified
May 2016	**3**	by guidelines lead (REM author (JMC) circulated to consultants	– reflects current practice ratified for 1 year – pending further review – may be superseded by Baby-Oscar trial protocol
May 2017	**4**		Recruitment to Baby-OSCAR trial commenced
Jun 2017			Trial information included – no change in practice for those infants not recruited to the trial
Jan 2020	**5**	Neonatal Guidelines	agreement to ratify for a further year (no amendments made) – to be reviewed after the results of Baby OSCAR
April 2021	**6**	Jonathan Cusack Neonatal Guideline Neonatal Governance	No changes made as awaiting OSCAR trial results and outcome of new Trapioca study
April 2022	**7**	Jonathan Cusack Neonatal Guideline Neonatal Governance	Evidence Review and guideline update Ratified

Appendix A: Performing an echocardiogram for Patent Ductus Arteriosus

Echocardiography should be performed by appropriately trained and experienced personnel.

Echocardiography for a PDA should be performed by a neonatologist to help assess the degree of shunt and clinical significance of the duct.

If there is concern that the baby has congenital heart disease, input from a paediatric cardiologist should be sought.

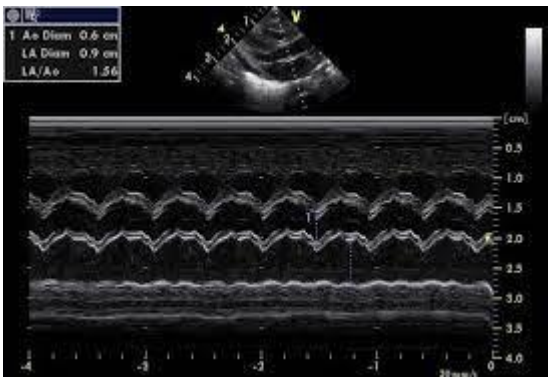
Referral should be made to the East Midlands Congenital Heart Centre if a duct ligation is recommended by the neonatal team.

Echo reports should be recorded on Badger, images saved to the Excelera database and echo images should be regularly reviewed by the cardiology team as part of a quality control peer review process.

The following echo views should be obtained:

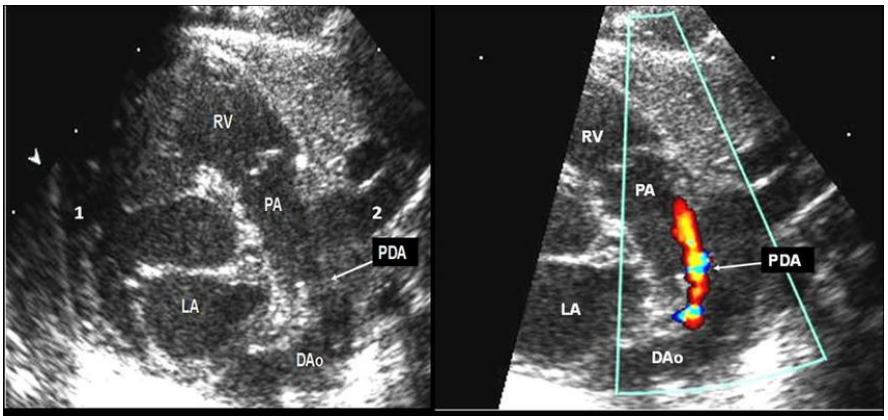
!) Situs view

2) Long axis view and assessment of LA:Ao ratio



M Mode showing LA;AO ratio measurement

3) Short axis view including a 'ductal cut'- the duct should be measured from a colour Doppler view at the narrowest point outside of the pulmonary artery



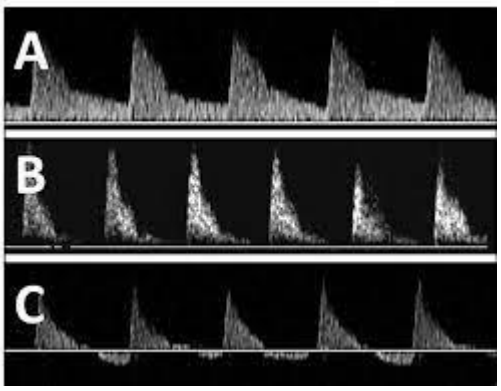
Short axis ductal cut showing ductal flow using colour Doppler

4) Subcostal and Apical 4 chamber views to assess for atrial communication, VSD, atrioventricular connections and ventriculo-arterial connections. This view is useful for assessing LV volume loading.

5) Suprasternal views to demonstrate the aortic arch (including assessment of the descending aorta flow using Doppler.

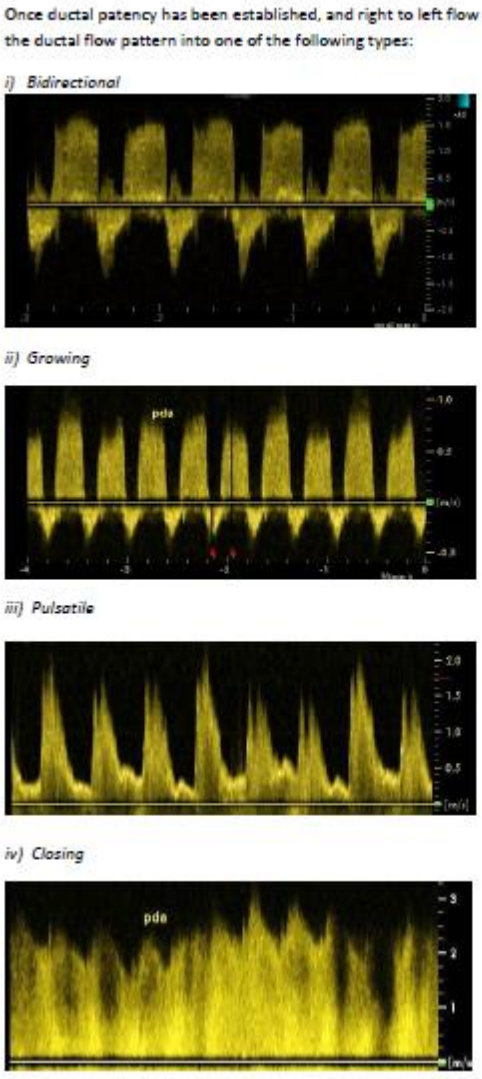
6) Visualisation of the pulmonary veins entering the left atrium

7) Doppler flow in the mesenteric vessels, descending aorta may show ductal steal:



Doppler showing steal: A shows normal Doppler, B shows absent end diastolic flow, C shows reversed end diastolic flow

8) Ductal flow pattern can be used to predict closure:



Images taken from OSCAR Trial echo workbook: available at: https://www.npeu.ox.ac.uk/assets/downloads/baby-oscar/echo/20161209%20Baby-OSCAR%20ECHO%20Workbook%20V2.pdf