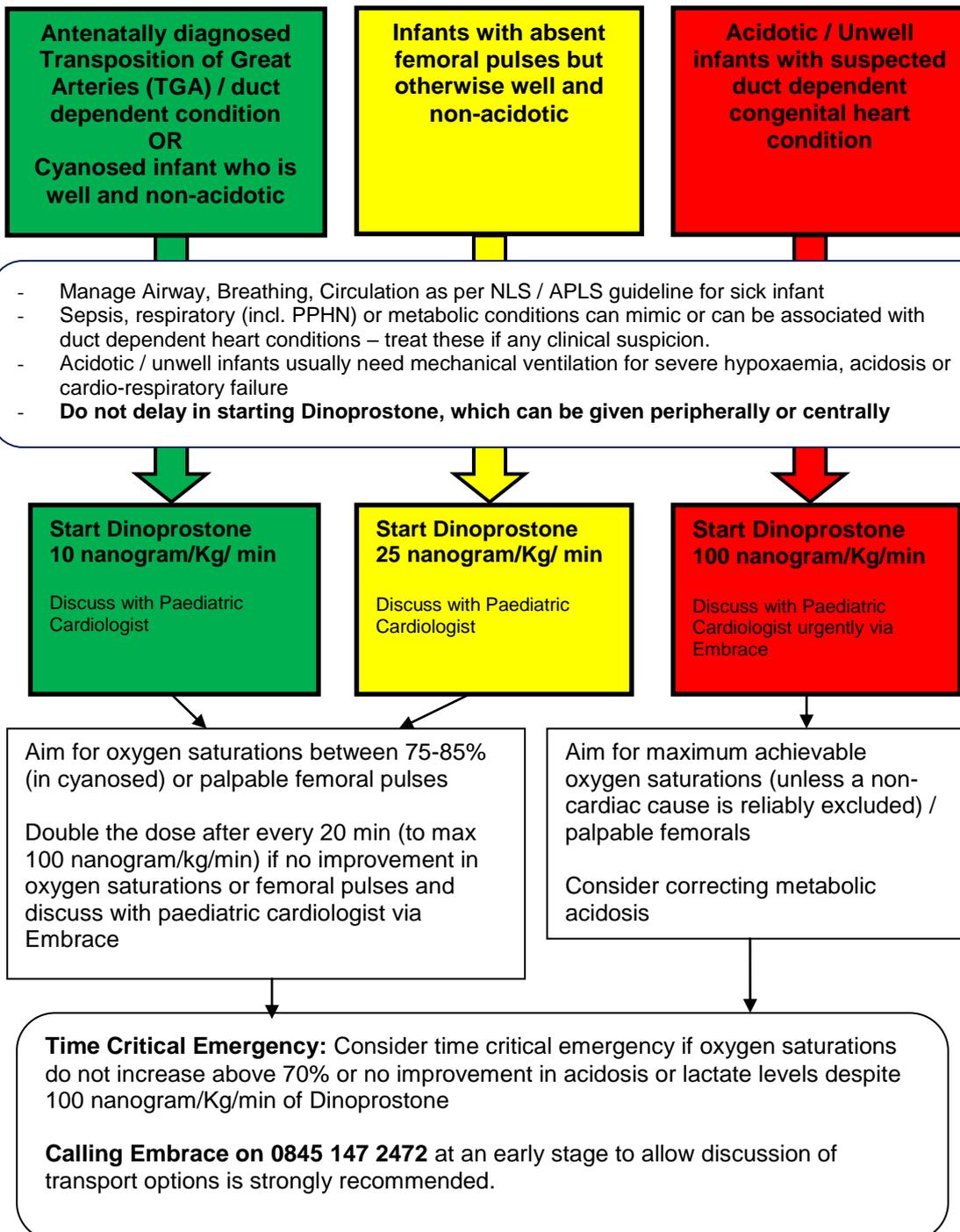




## Regional Guideline on use of Dinoprostone in duct dependent congenital heart conditions in neonates

Ownership: Adapted by Ms Teresa Brooks – Advanced Clinical Pharmacist for paediatric cardiology at Leeds Teaching Hospitals NHS Trust from the guideline adapted by Dr Sam Wallis, Consultant Neonatologist, from original by Dr Yoginder Singh et al  
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### Summary: Use of Dinoprostone in duct dependent congenital heart conditions



## Aims

To improve the management of duct dependent congenital heart conditions.

## Objectives

1. To provide evidence-based recommendations for starting the appropriate dose of Dinoprostone depending upon the clinical presentation of duct dependent or suspected duct dependent congenital heart conditions.
2. To provide guidance on management of duct dependent or suspected duct dependent congenital heart conditions.
3. To enhance the uniformity of practice in management of duct dependent congenital heart conditions across the Yorkshire and Humber Neonatal ODN and Yorkshire Paediatric Congenital Cardiac Network.

## Background:

Infants with suspected duct dependent congenital heart disease (CHD) require Dinoprostone infusion to promote patency of the ductus arteriosus.

Dinoprostone is a Prostaglandin E2 and paediatric preparation is marketed as: *Prostin VR*.

Duct dependent conditions include:

1. Left ventricular outflow obstruction: Coarctation of aorta, critical aortic stenosis, severe hypoplastic / interrupted arch of aorta
2. Right ventricular outflow tract obstruction: Pulmonary atresia, critical pulmonary stenosis, tricuspid atresia
3. Transposition of great arteries (TGA). May require urgent transfer for atrial septostomy

**Sepsis, respiratory or metabolic conditions are far more common than duct dependent CHD in neonatal period and these can mimic similar clinical presentation or can be associated with duct dependent CHD - Treat these conditions if any clinical suspicion!**

## Indications of Dinoprostone:

Dinoprostone is a potent vasodilator which is effective in maintaining the patency of the ductus arteriosus in duct dependent congenital heart conditions. The common indications for starting Dinoprostone are:

1. Antenatally diagnosed left ventricular (LV) or right ventricular (RV) outflow tract obstruction or TGA
2. High suspicion of CHD with poor pulses or significant cyanosis
3. Confirmed or suspected duct dependent congenital heart condition on echocardiogram

## Dosing regimen:

The dose of Dinoprostone ranges from 5 to 100 nanogram/Kg/min.

Higher doses, up to 200 nanogram/Kg/min, can be used on advice of the paediatric cardiologist, neonatologist or intensivist.

## Dosing regimen:

### Dosing Regimen:

An open duct (e.g. shortly after birth, in antenatally diagnosed duct dependent cases) requires a small dose to keep it patent. A closing or closed duct requires higher dose to open and maintain it. However, echocardiogram facilities may not be available in emergency situations or out of hours.

### Clinical presentation and dose regimen

- **Antenatally diagnosed TGA or duct dependent circulation (LV or RV obstruction):** Start on 10 nanogram/Kg/min and monitor for the response.
- **Cyanotic infant who is non-acidotic and well with suspected duct dependent CHD:** Start on 10 nanogram/Kg/min. If there is poor response (no improvement in oxygen saturation), increase the dose stepwise (double the dose up to a maximum of 100 nanogram/Kg/min) every 20 minutes aiming to achieve a clinical improvement of oxygen saturation levels (to between 75-85% providing infant remains well). Remember to consider alternative non-cardiac diagnoses.
- **Infant with poorly palpable femoral pulses who is non-acidotic and otherwise well:** Start on 25 nanogram/Kg/min. These infants may take longer to respond. Increase dose every 20 minutes (double the dose up to a maximum of 100 nanogram/Kg/min) to achieve a clinical improvement of palpable pulses with lactate maintained below 2 mmol/L.
- **Acidotic / unwell infants and suspected duct dependent CHD:** Start on 100 nanogram/Kg/min and consider mechanical ventilation. These infants usually need mechanical ventilation for severe hypoxaemia, acidosis or cardio-respiratory failure.

If not ventilated there is clearly a higher risk of apnoea in non-ventilated infants on high doses of Dinoprostone (>25 nanogram/Kg/min).

Rarely some of these infants may need a much higher dose (up to 200 nanogram/kg/min) which should be used after urgent discussion with the paediatric cardiologist or intensivist. The infusion rate can be reduced to 50 nanogram/Kg/min if there is rapid improvement but this is usually done after cardiology assessment.

### General management of acidotic / unwell infants with suspected duct dependent CHD:

- **DO NOT FORGET common differential diagnosis like Sepsis, Respiratory / PPHN and Metabolic conditions. These conditions are far more common than duct dependent CHD and can mimic similar clinical presentation.**
- Manage as per newborn life support (NLS) or advanced paediatric life support (APLS) guideline for sick infant
- Correcting severe acidosis may help in improving cardiac function.
- Discuss with neonatologist or PICU intensivist via Embrace for further support.

### Important notes on starting Dinoprostone:

1. **DO NOT DELAY IN STARTING Dinoprostone if there is clinical suspicion of duct dependent CHD** while waiting for paediatric cardiology opinion or echocardiogram, even when in-house echo facilities are present.
2. **Dinoprostone infusion can be given via peripheral or central line.**
3. Infusion rates, particularly for small babies can be low. This may cause a delay between starting Dinoprostone and it reaching the patient. In these instances, giving Dinoprostone alongside a continuous maintenance dextrose infusion can improve flow rate and allow quicker recognition if the line tissues. Other drugs such as antibiotics or fluid boluses need to be given through a separate line and a second line should be available so that Dinoprostone can be quickly switched if the first line fails
4. Remember to **prime the giving set** to minimise delay in Dinoprostone reaching the patient. Ideally the infusion should be connected via a Y connector close to the cannula with an anti-syphon valve to prevent backtracking up the line.
5. All cases suspected to have duct dependent congenital heart condition should be discussed with the on-call paediatric cardiologist at the first opportunity but collapsed or sick infants will need immediate stabilisation, including starting Dinoprostone.
6. If likely transfer to Leeds, use of the Embrace (0845 147 2472) number when calling the Paediatric Cardiologist will allow discussion of transport

### Desired response to Dinoprostone:

In absence of echocardiographic diagnosis aim for palpable pulses, resolving acidosis and improving oxygen saturation.  
If PPHN remains a differential diagnosis then appropriate respiratory support should be provided with an aim to maximise oxygenation.

**After** confirming diagnosis monitor for response as:

1. Suspected LV obstruction with acidosis: aim for palpable pulses and resolving acidosis.
2. Cyanotic heart disease with restricted pulmonary blood flow (PBF): aim for saturations 75-85%. Accept saturations down to 70% if lactate is maintained below 2mmol/L.

### Time critical emergency:

Some infants with TGA will have restrictive mixing despite opening of the duct. These infants constitute a time critical emergency and are at significant risk of death

without a balloon septostomy. Arrange for urgent transfer (Embrace) and discuss with the paediatric cardiologist.

Consider this diagnosis in any infant whose saturations do not increase above 70% or do not show improvement in their acidosis or lactate levels despite 100 nanogram/Kg/min of Dinoprostone for at least 20 minutes duration.

### Antenatally diagnosed or suspected TGA:

Infants known to have a TGA antenatally should be delivered wherever possible in a centre able to carry out a septostomy (Leeds General Infirmary for Yorkshire). **Acute in-utero transfers can be organised by calling Embrace (0845 147 2472).**

### Side effects:

The common side effects are apnoea, hypotension, fever, tachycardia and looking flushed. Other known side effects include hypothermia, cardiac arrest; bradycardia, convulsions, diarrhoea and disseminated intravascular coagulation.

Side effects after prolonged Dinoprostone infusion therapy include gastric outlet obstruction secondary to antral hyperplasia and hypertrophic osteoarthropathy

**In practice the major complication on starting therapy is apnoea requiring ventilator support. Apnoea after starting Dinoprostone:**

- Apnoea after starting Dinoprostone is the most common side effect.
- Apnoea is a less likely a complication on a dose of <15 nanogram/kg/min of Dinoprostone<sup>1-2</sup>.
- Apnoea as a side effect normally occurs within 1 hour after starting Dinoprostone unless dose is being increased.

In acidotic or collapsed infants the recommended dose of Dinoprostone is much higher and likely to cause apnoea needing mechanical ventilation.

### Monitoring while on Dinoprostone

During the infusion the newborn requires the normal close physiological monitoring of heart rate, oxygen saturation, blood pressure, respiratory rate, and core body temperature.

a) Stable infants on Dinoprostone: Side effects like apnoea, profound bradycardia, or severe hypotension may warrant more intensive care support. Recurrent or prolonged apnoea may require ventilatory support in order for the infusion to be continued.

b) Critically sick infants: Dinoprostone infusion MUST NOT be stopped and complications should be dealt with by providing intensive care support.

### Transfer of infants on Dinoprostone

- Infants with severe hypoxaemia, acidosis and cardiorespiratory failure will need mechanical ventilation.
- Collapsed babies / those on higher doses of Dinoprostone (e.g. 100nanogram/kg/min) will need intubation and ventilation. However at lower doses, if the infant is not suffering apnoeas after 1 hour of fixed dose infusion then ventilation is not necessary. However, it is recommended that these infants are transferred by a person who is competent to manage the airway if it becomes necessary.
- Elective intubation and ventilation may be required if the infant is to be transferred immediately after starting Dinoprostone infusion. This will be agreed with the Embrace team.
- An infant on Dinoprostone should have 2 routes of intravenous access.

## Indications for mechanical ventilation

1. Severe hypoxemia, acidosis or cardio respiratory failure
2. Apnoea following the introduction of Dinoprostone
3. Elective ventilation may be required for transfer, especially if dose > 25 nanogram/Kg/min or has recently been increased.

## Audit and monitoring compliance

Guideline will be audited yearly. Audit criteria will include dosing of Dinoprostone in different conditions, time taken to start the infusion and apnoeas following starting infusion. Dr Fatemah Rajah will be responsible for auditing the guideline.

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Clinical condition: **Duct dependent congenital heart conditions**

Target patient group: **Neonates across the Yorkshire and Humber Neonatal Operational Delivery Network and Yorkshire Paediatric Congenital Cardiac Network**

Target group: **Doctors, nurses and pharmacists involved in the care of neonates across Yorkshire and Humber Neonatal Operational Delivery Network and Yorkshire Paediatric Cardiology Network**

## Evidence Base

Evidence: B Robust experimental and observational studies

References and evidence levels:

- A. Meta-analyses, randomised controlled trials/systematic reviews of RCTs
- B. Robust experimental or observational studies
- C. Expert consensus.
- D. Leeds consensus. (where no national guidance exists or there is wide disagreement with a level C recommendation or where national guidance documents contradict each other)

### References:

1. Carmo KAB, Barr P, West M, Hopper NW, White JP, Badawi N. Transporting newborn infants with suspected duct dependent congenital heart disease on low-dose prostaglandin E1 without routine mechanical ventilation. *Arch Dis Child Fetal Neonatal Ed* 2007; 92; F117-9
2. Y Singh, C Watt, S Clark. Need of mechanical ventilation of infants on prostaglandin E1 during transport. *Acta Paediatrica* 2009; 98 (S): 235.
3. Kramer HH, Sommer M, Rammos et al. Evaluation of low dose prostaglandin E1 treatment of ductus dependent congenital heart disease. *Eur J Paediatr* 1995; 154: 700-7.
4. Lewis AB, Takahashi M, Lurie PR. Administration of prostaglandin E1 in neonates with critical congenital cardiac defects. *J Pediatr* 1978; 93(3):481-5.
5. Moolaert A, Senders R, VanErtbruggen I, Huysmans H, Harinck E. Effect of E1 type Prostaglandin on hypoxemia in the cyanotic congenital cardiac malformation. *Eur J Cardiol* 1978;5 (4):321-5.
6. Peled N, Dagan O, Babyn P. Gastric-outlet obstruction induced by prostaglandin therapy in neonates. *N Engl J Med* 1992; 327: 505-10.
7. Mills PJ. Gastric-outlet obstruction in children. *N Engl J Med* 1992; 327: 558-60.
8. Olley PM, Coceani F, Rowe RD. Role of prostaglandin E1 and E2 in the management of neonatal heart disease. *Adv Prostaglandin Thromboxane Res* 1978;4: 345-53.
9. Noah ML. Use of prostaglandin E1 for maintaining the patency of the ductus arteriosus. *Adv Prostaglandin Thromboxane Res* 1978;4:355 -62.
10. Penny DJ, Shekerdemian LS. Management of the neonate with symptomatic congenital heart disease. *Arch Dis Child Fetal Neonatal Ed* 2001; 84: 141-5.
11. Heymann MA, Rudolph AM. Ductus arteriosus dilatation by prostaglandin E1 in infants with pulmonary atresia. *Pediatrics* 1977; 59: 325-9.
12. Fariello R, Olley PM, Coceani F. Neurological and electroencephalographic changes in newborns treated with prostaglandins E1 and E2. *Prostaglandins* 1977;13 (5): 901-7.
13. Sone K, Tashiro M, Fujinaga T, Tomomasa T, Tokuyama K, Kuroume T. Long-term low dose prostaglandin E1 administration. *Pediatr* 1980; 97:86-7.
14. Ueda K, Saito A, Nakano H, Aoshima M, Yokata M, Muruoha R, Iwaya T. Cortical hyperostosis following long-term administration of prostaglandin E1 in infants with cyanotic congenital heart disease. *J Pediatr* 1980; 97: 834-6.
15. Hellstram-Westas L, Hanseus K, Jogi P et al. Long distance transports of newborn infants with congenital heart disease. *Pediatr Cardiol* 2001; 22: 380-4.
16. Singh GK, Fong LV, Salmon AP, et al. Study of low dosage prostaglandin usages and complications. *Eur Heart J* 1994; 15: 377-81.
17. Drugs database and US national library of medicine
18. BNF for children 2017 (and see neonatal e-formulary <http://www.leedsformulary.nhs.uk/chaptersSubDetails.asp?FormularySectionID=24&SubSectionRef=24.16&SubSectionID=A100> )

19. Paediatric Formulary Committee. *BNF for Children* [Online]. London: BMJ Group, Pharmaceutical Press, and RCPCH Publications. [Accessed on 30/4/19]. Available from: <https://bnfc.nice.org.uk/drug/dinoprostone.html#indicationsAndDoses>.
20. Paediatric Formulary Committee. *BNF for Children* [Online]. London: BMJ Group, Pharmaceutical Press, and RCPCH Publications. [Accessed on 30/4/19]. Available from: <https://bnfc.nice.org.uk/drug/alprostadiil.html>
21. Singh Y, Mikrou P. 2017. Use of prostaglandins in duct-dependent congenital heart conditions. *Archives of Disease in Childhood - Education and Practice*. **103**:137-140.
22. Zainal Abidin1, F. Khalid and R. MSaid. Abstract 577: Evaluation of infusion prostagland (PGE2) versus infusion prostaglandin E1 (PGE1) in management of duct-dependent pulmonary circulation congenital heart disease. *Paediatric Critical Care Medicine*. **15**(4). pp. 131
23. Thanopoulos, BD., Andreou, A. and Frimas, C. 1987. Prostaglandin E2 administration in infants with ductus-dependent cyanotic congenital heart disease. *European Journal of Paediatrics*. **146**(3). pp. 279-82

# Dinoprostone

|                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|--------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Indication</b>              | To maintain or restore patency of the ductus arteriosus<br><i>Only to be used in infants who are ventilated or where ventilation is immediately available</i><br><br>Vasodilator with specific action on the tissues of the ductus arteriosus. Inhibitor of platelet aggregation.                                                                                                                                                                                                                                    |
| <b>Dose</b>                    | Varying initial doses depending on diagnosis – please see regional guideline – between 10 and 100nanogram/kg/min<br><i>(Doses of up to 200nanogram/kg/min may be required to re-open the ductus arteriosus in certain circumstances as guided based on patient presentation and medical advice and a dose of 5nanogram/kg/min may be required at the discretion of the paediatric cardiologists)</i>                                                                                                                 |
| <b>Route of administration</b> | Intravenous infusion (central or peripheral)                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| <b>To prepare an infusion</b>  | 1mg/mL ampoules<br><br><b>Preferred diluent: glucose 5%</b><br>Other diluent: sodium chloride 0.9%<br><br><b>300micrograms in 50mL:</b> draw up 0.3mL of 1mg/mL dinoprostone (300 micrograms) and add to 49.7mL of diluent                                                                                                                                                                                                                                                                                           |
| <b>Compatibilities</b>         | No compatibility information is known. Do not infuse with any other medicines                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| <b>Notes</b>                   | Always use a separate line for infusion. Always prescribe as DINOPROSTONE. Never prescribe as prostaglandin E2 or prostin. Patients should have 2 routes of intravenous access to allow other infusions to be given. Do not stop the infusion suddenly. Prime the giving set prior to administration to minimise the delay in delivery of dinoprostone to the patient. Running dinoprostone alongside a continuous glucose 5% infusion allows quicker delivery to the patient. Use diluted solution within 24 hours. |
| <b>References</b>              | Medusa (paediatric) accessed online 28/01/2020 v. 7, , BNFC accessed online 28/01/2020, Guy's and St. Thomas', King's college and university Lewisham hospital's Paediatric Formulary 9th edition, Lexicomp accessed online 28/01/2020, Paediatrics with Expertise in Cardiology Specialist Interest Group 'Prostaglandin Guideline' accessed online 28/01/2020                                                                                                                                                      |