Yorkshire Neonatal Network and Yorkshire Paediatric Cardiology Network

Yorkshire Neonatal Network and Yorkshire Paediatric Cardiology Network regional guideline on use of Alprostadil in duct dependent congenital heart conditions in neonates

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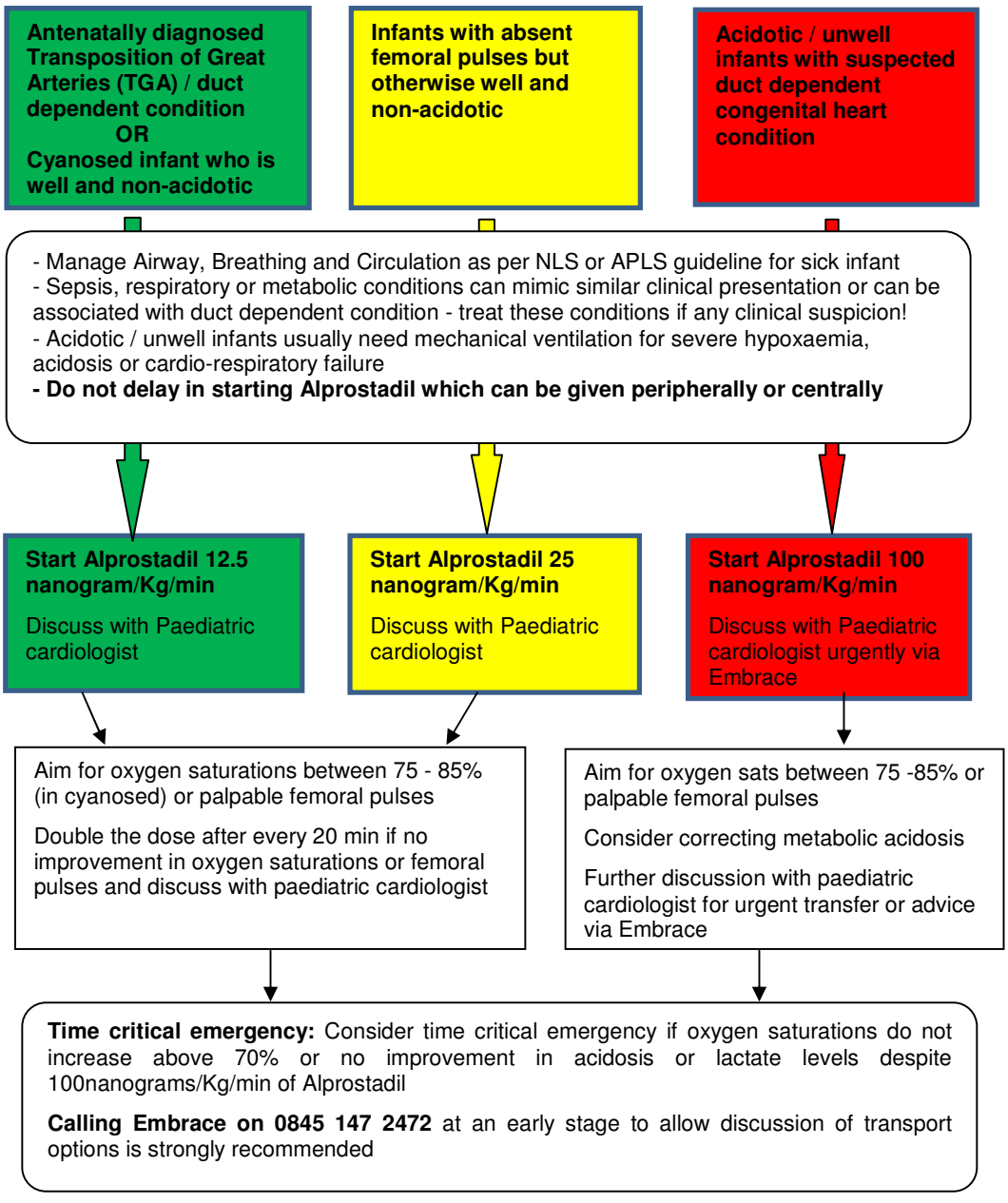
Publication date: Jan 2012
Next Review date: Jan 2015
Status

Summary: Use of Alprostadil 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 Alprostadil 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 Neonatal Network (YNN) and Yorkshire Paediatric Cardiology Network.

Background:

Infants with suspected duct dependent congenital heart disease (CHD) require Alprostadil infusion to promote patency of the ductus arteriosus. Alprostadil is a Prostaglandin E1 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 Alprostadil:

Alprostadil 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 Alprostadil 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 Alprostadil ranges from 10 to 100 nanograms/Kg/min.
Higher doses, up to 200 nanograms/kg/min, can be used on advice of the paediatric cardiologist, neonatologist or intensivist.

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 12.5 nanograms/Kg/min and monitor for the response (see section 4 below).

- **Cyanotic infant who is non-acidotic and well with suspected duct dependent CHD:** Start on 12.5 nanograms/Kg/min. If there is poor response (no improvement in oxygen saturation and/ or acidosis), increase the dose stepwise (double the dose up to a maximum of 100 nanograms/Kg/min) every 20 minutes aiming to achieve a clinical improvement of oxygen saturation levels to between 75-85%. Accept saturations > 70% if lactate remains below 2 mmol/L.

- **Infant with poorly palpable femoral pulses who is non-acidotic and otherwise well:** Start on 25 nanograms/Kg/min. These infants may take longer to respond respond. Increase dose every 20 minutes (double the dose up to a maximum of 100 nanograms/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 nanograms/Kg/min and consider mechanical ventilation. These infants usually need mechanical ventilation for severe hypoxaemia, acidosis or cardiorespiratory failure. If not ventilated there is clearly a higher risk of apnoeas in non-ventilated infants on high doses of Alprostadil (>25nanogram/Kg/min).

  Rarely some of these infants may need a much higher dose (up to 200 nanograms/kg/min) which should be used after urgent discussion with the paediatric cardiologist or intensivist. The infusion rate can be reduced to 50 nanograms/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 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 Alprostadil:

1. **DO NOT DELAY IN STARTING Alprostadil if there is clinical suspicion of duct dependent CHD** while waiting for paediatric cardiology opinion or for echocardiogram even when in-house echocardiogram facilities are present
2. **Alprostadil infusion can be given via peripheral or central line.**
3. 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 Alprostadil.
4. If likely transfer to Leeds use of the Embrace (0845 147 2472) number when calling the Paediatric Cardiologist will allow discussion of transport options at an early stage.

Desired response to Alprostadil :

In absence of echocardiographic diagnosis aim for palpable pulses, resolving acidosis and improving oxygen saturation (75 - 85%). 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 nanograms/Kg/min of Alprostadil 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 Alprostadil 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 Alprostadil:

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

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

Monitoring while on Alprostadil:

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 Alprostadil**:** 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: Alprostadil infusion MUST not be stopped and complications should be dealt with by providing intensive care support.

Transfer of infants on Alprostadil:

- Infants with severe hypoxaemia, acidosis and cardiorespiratory failure will need mechanical ventilation.
- Alprostadil is the drug of choice for transfer of duct dependant infants because of the lower incidence of apnoeas (compared to Dinoprostone) and is used by the Embrace transport service.
- Elective intubation and ventilation may be required if the infant is to be transferred immediately after starting Alprostadil infusion. This will be agreed with the Embrace team
- 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.
- An infant on Alprostadil should have 2 routes of intravenous access.

Indications of mechanical ventilation:

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

Audit and monitoring compliance:

Guideline will be audited 6 months after implementation. Audit criteria will include dosing of Alprostadil in different conditions, time taken to start the infusion and apneas following starting infusion. Dr. Cath Harrison will be responsible for auditing the guideline.

"Audit results will be presented to the neonatal clinical governance audit meeting, which will agree actions arising from the recommendations, and monitor the progress of the actions."

Provenance:

Author name (s)/ Post and address (es)

1. Dr Yoginder Singh – Neonatal specialty registrar with expertise in cardiology, Leeds Teaching Hospitals NHS trust
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Clinical condition:	**Duct dependent congenital heart conditions**
Target patient group:	**Neonates across the Yorkshire Neonatal Network (YNN) and Yorkshire Paediatric Cardiology Network**
Target group:	**Doctors, nurses and pharmacists involved in the care of neonates across YNN 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. Moulaert 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 Cadiol 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 2010-2011 page 168-169

Appendix 1

Prescription and administration of Alprostadil

Important notes on Prescription and administration:

1. **Always prescribe as ALPROSTADIL.** Never prescribe as Prostaglandin E1 or Prostin.

2. **The continuous infusion should NOT be stopped.** An infant on Alprostadil should have 2 routes of intravenous access. One for the Alprostadil and the other as spare or other IV infusions.

Alprostadil (Prostin VR): Ampoule presentation 500 micrograms in 1ml

Standard Alprostadil infusion: 300 micrograms in 50 ml final concentration
(This equates to 6000 nanograms/ml)

To make this up:
Take 0.6 ml of Alprostadil (Prostin VR) ampoule and transfer to syringe containing 49.4 ml of suitable diluent (Glucose 5% OR Sodium Chloride 0.9%). Mix well.

Rate of infusion:
0.5 ml/Kg/hour of standard Alprostadil infusion will give 50 nanograms/Kg/min.

Stability of prepared infusion: Each syringe will be stable for 24hours

Continuous infusion: Can be given centrally or peripherally

Compatibility Y- connection site:
No information available use a designated line where possible
Practical experience only - Dobutamine, dopamine and Morphine