Caffeine Therapy in Preterm Infants UHL Neonatal guideline

University Hospitals of Leicester NHS Trust

C12/2012

Contents

1. Introduction and Who Guideline applies to

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

Aim:

1. To prevent and treat apnoea of prematurity
2. To use caffeine effectively and safely in preterm infants.

Key Points:

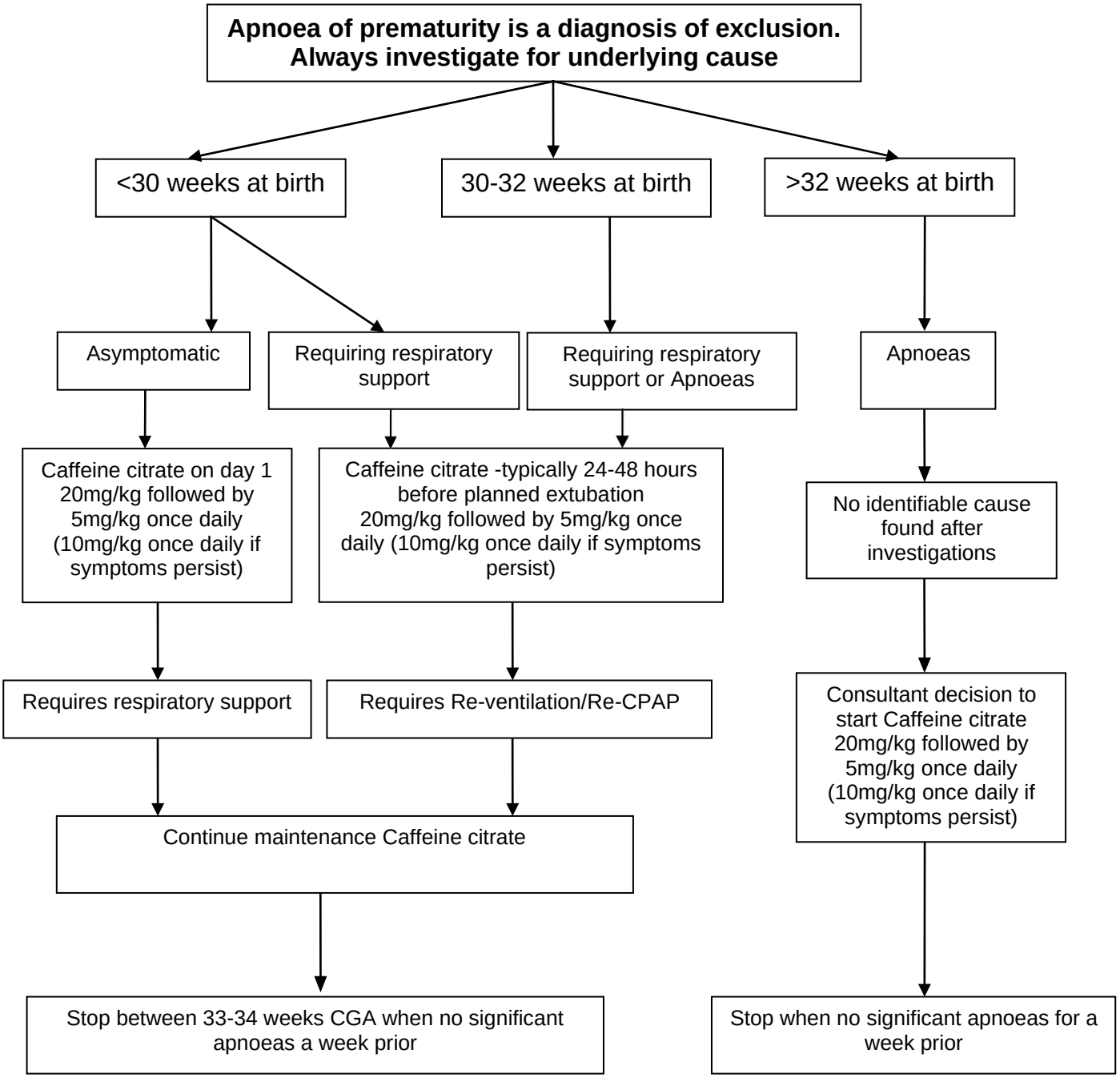
- Caffeine therapy prevents and treats apnoea of prematurity without increasing neurodisability rates (Grade A).
- Caffeine treatment in preterm VLBW (Very Low Birth Weight) is associated with improved survival without disability at 18-21 months and decreases CLD (Chronic lung Disease) and severe ROP (Retinopathy of Prematurity) (Grade A).
- Infants receiving respiratory support appeared to derive most neurodevelopmental benefits from caffeine treatment (Grade A).
- Earlier initiation of caffeine may be associated with a greater reduction in time on ventilation (Grade A)
- All infants receiving a course of caffeine require monitoring – then continued for a minimum of two days after stopping caffeine.

Related UHL documents

- Monitoring of Infants on NNU UHL Neonatal Guideline UHL Trust ref: C23/2010

Management Flow Chart:

This management applies to babies in the first 3 days of postnatal life. Primary apnoea of prematurity is always a diagnosis of exclusion and other causes must be excluded. The causes are different when apnoeas occur shortly after birth compared with later in the patient's hospital stay. Always exclude infection, upper airway obstruction, hypoglycaemia and central nervous system pathology.



2. Guideline Standards and Procedures

Background:

Caffeine is the most commonly used treatment for primary apnoea in premature newborns. Its effect has been well established in reducing the frequency of apnoea, intermittent hypoxemia, and extubation failure in mechanically ventilated preterm infants.

Although caffeine therapy is stopped once the risk of apnoea of prematurity becomes low (usually 32 weeks postconceptual age), the optimal treatment length has not been defined in carefully controlled trials.

Recent studies of caffeine therapy in preterm infants have shown decrease in the incidence of cerebral palsy, CLD, and severe ROP in very low birth weight infants[1, 2, 3]. Although, by 5 years of age, there was no significant difference in rates of cerebral palsy between both groups, there was a significant reduction of the incidence of developmental coordination disorder in the caffeine treated group (11.3% *vs* 15.2% adjusted OR: 0.70, 95%CI: 0.51-0.95) [4]. In addition preterm infants receiving respiratory support gained the most neurodevelopmental benefit from caffeine[2]. Earlier initiation of caffeine may be associated with a greater reduction in time on ventilation [5].

Dosage:

Caffeine CITRATE - Loading dose 20 mg/kg, followed by a once daily maintenance dose 5 mg/kg (10 mg/kg once daily if symptoms persist).
Refer to Neonatal Formulary for further details (the prescribed dose is twice that of **caffeine BASE**).

Mechanism of action:

In infants with apnoea, caffeine is believed to work through a combination of effects including stimulating the central respiratory centre, promoting fluid loss, decreasing the carbon dioxide threshold, increasing cardiac output and increasing the response to hypercapnea. Caffeine may also increase skeletal muscle tone and decrease diaphragmatic fatigue, aiding respiratory effort.

Caffeine Pharmacokinetics and Metabolism:

Caffeine is well absorbed by infants when given orally (bioavailability approaching 100%). Absorption does not appear to be affected by administration with feeds. Pharmacokinetic studies in premature neonates have established that the half-life of caffeine is significantly prolonged to 102.9
± 17.9 hours and remains prolonged for as long as 38 weeks' gestation.

Caffeine Toxicity and Safety Data:

The common side effects observed during caffeine therapy are tachycardia, jitteriness, feed intolerance and calcium loss. Caffeine use may reduce weight gain temporarily and may influence changes in gut blood flow and gastric emptying. Toxicity is uncommon but a ten-fold overdose can make a baby extremely ill. Tachycardia and agitation are the first signs of toxicity.

Drug interactions:

Administration of caffeine with fluconazole or ketoconazole may decrease the rate of caffeine metabolism and result in increased serum concentrations.
Drugs that induce CYP1A2 activity, including phenytoin and phenobarbitone, increase the rate of caffeine metabolism and may result in sub-therapeutic concentrations. Concomitant administration of caffeine and beta-adrenergic agonists may result in an additive increase in heart rate.

3. Education and Training

None

4. Evidence Criteria:

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

5. Audit standards:

1. Caffeine should be commenced before planned extubation in preterm infants (< 32 weeks) requiring respiratory support.
2. Caffeine should be continued even if baby subsequently require respiratory support
3. Caffeine is stopped between 33-34 weeks CGA when no significant apnoea a week prior in infants born < 32 weeks.

6. Supporting References

1. Schmidt, B., R. S. Roberts, et al. (2006). Caffeine therapy for apnea of prematurity." N Engl J Med 354(20): 2112-21.
2. Schmidt, B., R. S. Roberts, et al. (2007). Long-term effects of caffeine therapy for apnea of prematurity. N Engl J Med 357(19): 1893-902.
3. Erenberg, A., R. D. Leff, et al. (2000). Caffeine citrate for the treatment of apnea of prematurity: a double-blind, placebo-controlled study. Pharmacotherapy 20(6): 644-52.
4. Doyle LW, Schmidt B, Anderson PJ, Davis PG, Moddemann D, Grunau RE, O'Brien K, Sankaran K, Herlenius E, Roberts R. Reduction in developmental coordination disorder with neonatal caffeine therapy. J Pediatr. 2014;165:356–359.e2

5. Davis PG, Schmidt B, et al (2010). Caffeine for Apnea of Prematurity trial: benefits may vary in subgroups. J Pediatr. 2010 Mar;156(3):382-7

7. Key Words

Apnoea, Caffeine Citrate, Respiratory

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) Author: Dr Venkatesh Kairamkonda, Consultant Neonatologist Contact: Neonatal Guidelines Lead – S Mittal			**Executive Lead** Chief Medical Officer
Details of Changes made during review:			
Date	**Issue Number**	**Reviewed By**	**Description Of Changes (If Any)**
4/10/2011	**1**	Neonatal Guidelines Meeting	(new guideline)
30/12/11	**2**	(VK)	Amendments
18/9/2012	**3**	Neonatal Governance Meeting	(ratified)
8/10/2014	**4**	(REM)	Minor amendments (change dosages to caffeine citrate)
Jan 2016 - 19/4/2016	**5**	Review by audit group and by author (VK) Neonatal Guidelines Meeting Neonatal Governance Meeting	No significant change to evidence
April 2019 - May 2019	**6**	Neonatal Guidelines Meeting Neonatal Governance Meeting	
May 2022	**7**	Neonatal Guidelines Meeting Neonatal Governance Meeting	No changes