© 2012 SNL All rights reserved

Should we be using high flow therapy on the neonatal unit?

High flow therapy (HFT) has become an increasingly popular alternative to continuous positive airway pressure (CPAP) within neonatal units. However, there is little uniformity in its usage reflecting the lack of evidence. This article summarises a review of the literature presenting the evidence for this therapy and data collected through a network survey and a tertiary neonatal unit audit.

Nicola Holme
BMedSci, MBBS, PGCert, MRCPCH
ST6 Neonatal Grid Trainee/Academic Clinical Fellow
nicolaholme@doctors.org.uk

Cath Harrison
BMedSci, BM BS, DTM & H, FRCPCH
Consultant in Neonatal Medicine and Transport Medicine
catherine.harrison@leedsth.nhs.uk

Peter Congdon Neonatal Unit, Leeds General Infirmary

Keywords

infant; newborn; positive pressure respiration; high flow therapy

Key points

Holme N., Harrison C. Should we be using high flow therapy on the neonatal unit? *Infant* 2012; 8(6): 172-176.

1. The published evidence for the use of high flow therapy (HFT) is limited and conflicting. Well-powered randomised controlled trials are required to determine whether HFT provides optimal treatment for babies.
2. There is no evidence of increased risk of adverse neonatal outcomes when using HFT.
3. Survey findings highlight a delay in repatriation of babies and a variable use of HFT among neonatal units within a large neonatal network.
4. Audit findings suggest HFT prolongs admission stay due to an increased number of steps in the weaning process.

To avoid ventilator-induced lung injury, neonatologists strive to wean neonates off the ventilator onto non-invasive modes of ventilation such as continuous positive airway pressure (CPAP). However, CPAP is associated with complications such as local nasal trauma, irritation of the nares, increased nasal secretions requiring frequent suctioning, and risk of infection, kinking of the nasopharyngeal prongs in the pharynx and overall perceived patient discomfort[1]. High flow therapy (HFT) has become an increasingly popular alternative to CPAP over the last few years. A blend of oxygen and air is administered to the patient via nasal cannulae at flow rates between 1L/min and 8L/min. The minimum usually administered is 2.5-3L/min. The oxygen/air mixture is typically heated and humidified. As the flow rate increases so does the positive airway pressure. HFT is used for the treatment of apnoea of prematurity, mild forms of respiratory distress syndrome and the prevention of extubation failure.

The reported advantages of HFT include fewer ventilation days, reduced nasal trauma and more frequent contact with the care giver promoting attachment[2-3].

The major disadvantage is that airway pressure is not measured, theoretically increasing the risk of pneumothoraces. Earlier reports of airway colonisation with *Ralstonia pickettii* in a small number of cases were linked to a manufacturing flaw with Vapotherm™ filter cartridges. This has since been remedied. Recommendations from the Centers for Disease Control and Prevention (CDC)[4] led to new guidelines regarding single use filter cartridges and changing filter cartridges after 60 days of cumulative use. No further cases have been reported.

HFT usage is becoming well established within paediatric intensive care and neonatal units. Paediatric respiratory wards are also embracing this modality and its usage features on some paediatric wards outside of the intensive care setting. The need for evidence of HFT's effectiveness and use has never been stronger to enable uniformity of practice within the field of neonatology.

Evaluation of current evidence

A literature search looking for studies reporting on the effectiveness of HFT in neonates was conducted, focusing on length of stay and re-intubation rates. The search strategy involved the following:

Primary sources: A search of EMBASE and MEDLINE healthcare databases via the OVID interface identified 21 articles (search performed May 2012). Five articles were relevant. Limits: Publication year 1948-current, English language and human.

The following MeSH headings were used [infant, premature/or infant, Newborn/] AND the following keywords search [high flow nasal cannula.mp OR Vapotherm.mp)]. The references of the above articles were scanned along with the linked articles, no further articles were found. For this review, papers measuring oropharyngeal and oesophageal pressures or other outcomes were excluded. The five relevant studies are summarised in **TABLE 1**.

Secondary sources: A search of the Cochrane database identified one relevant article[8].

Citation	Study group	Study type	Outcome	Key result
Campbell et al, 2006[5]	40 Intubated preterm infants **Gestation** IF-CPAP:27.6 ±1.9 HHFNC: 27.4±1.6 **Birthweight** IF-CPAP: 925±188g HHFNC: 1008±157g	RCT – unblinded but concealed allocation Pilot study HHFNC vs IF-CPAP	**Primary outcome:** Incidence of re-intubation within 7 days **Secondary outcome:** Change in O_2 requirement pre- and post-extubation, frequency of apnoea and nasal damage	Increased oxygen requirement and apnoeas with HHFNC Relative risk of re-intubation with HHFNC compared with IF-CPAP 2.1 (CI 1.3-3.0, p=0.003)
Woodhead et al, 2006[6]	30 Intubated neonates **Gestation** HHHFNC: 31±3.6 weeks HFNC: 32±3.1 weeks **Birthweight** HHHFNC: 1630±812g HFNC: 1715±880g	RCT masked crossover HFNC vs HHHFNC After 24hr device swapped over	**Primary outcome:** Success of extubation **Secondary outcomes:** Respiratory rate, nasal mucosa damage	Extubation failure rate prior to crossover: Vapotherm™: 0/15 HFNC: 2/15
Shoemaker et al, 2007[3]	101 Premature infants **Gestation** nCPAP: 28±1.4 weeks HHHFNC: 27.6±1.5 weeks **Birthweight** nCPAP: 1050±241g HHHFNC: 1017±235g	Retrospective descriptive study HHHFNC vs nCPAP	Adverse neonatal outcomes including re-intubation rate	No significant differences in major outcomes Re-intubation rate: nCPAP 14/36 (40%); HHHFNC 12/65 (18%) (OR 10.7, 95%, CI 2.6-44, p=0.02)
Holleman-Duray et al, 2007[2]	111 (total 114 – 3 infants never intubated) **Gestation** Historical cohort 27.4±1.6 weeks HFT: 27.6±1.3 weeks **Birthweight** Historical cohort: 1000±310g HFT: 1060±261g	Retrospective descriptive study HHHFNC vs nCPAP Historical control	Adverse neonatal outcomes including re-intubation rate	No significant differences in major outcomes Failed extubation: Control = 7/47 (15%) HFNC = 8/64 (13%) (No statistics provided) HHHFNC group spent fewer days on ventilator: 11.4 ±12.8 vs 18.5±21, p=0.028
Abdel-Hady et al, 2011[7]	60 ≥28 weeks gestation 30-no HFT, 30-HFT **Gestation** nCPAP 31.1±2.6 weeks HFT 31.0±2.4 weeks **Birthweight** nCPAP 1.6±0.39g HFT 1.6±0.38g	Randomised, open label, controlled trial HHHFNC vs nCPAP	**Primary end point:** Duration of oxygen therapy in days **Secondary end points:** Duration of respiratory support etc	6/30 No-HFT and 7/30-HFT failed initial weaning (p=1) Days on oxygen [median (interquartile range)] No-HFT 5 (1-8) HFT 14 (7.5-19.25) p=<0.001 No difference in length of hospitalisation

TABLE 1 Studies of the use of high-flow oxygen via nasal cannula as a mode of non-invasive respiratory support.
Terms: nCPAP – nasal continuous positive airway pressure, IF-CPAP – infant flow CPAP, HFNC – high flow nasal cannula, HHFNC – humidified high flow nasal cannula, HHHFNC – humidified heated high flow nasal cannula.

Safety and complications

The safety and effectiveness of HFT was questioned by the recent Cochrane review[8]. The review found four studies[5,6,9,10] were suitable but due to significant heterogeneity a meta-analysis was not possible. The overall conclusion was that 'there is insufficient evidence to establish the safety and effectiveness of high flow nasal cannula (HFNC)'.

The inability to measure the pressures administered theoretically increases the risk of pneumothoraces. The amount of pressure generated by HFT is determined by flow rate, size of leakage around the nasal cannula and degree of mouth opening. Kubicka et al measured oral cavity pressure using small nasal cannulae and found that only with the smallest infants, highest flow rates and mouth closed could significant but unpredictable levels of CPAP be achieved[11]. In contrast Locke et al demonstrated that even when the flow was only 2L/min, pressures of 9.8cmH_2O could be delivered[12]. None of the studies reviewed here demonstrated any increased risk of pneumothoraces. This finding is supported by Saslow et al who demonstrated no difference in end distending pressure between CPAP and HFT[13].

Nasal CPAP versus HFT

The study conducted by Campbell et al[5] is the only study to be conducted as a randomised control trial (RCT) which compares HFT with CPAP. Despite the small numbers the study demonstrates a statistically significant increase in extubation failure rates in the HFT group. An equation described by Sreenan et al[14] was used to calculate the flow rate in the

HFT group. However, the flow rates were very low (1.4-1.7L/min). The lack of a positive effect was likely to have been the result of the low flow rates adopted. Unheated gas cannot be adequately humidified even if it passes through a humidifier, resulting in high flow rates being intolerable and damaging. If heated gas had been used with greater flow rates within the HFT group extubation may have been more successful.

The above findings have been contradicted by Shoemaker et al[3] and Holleman-Duray et al[2]. These studies were retrospective descriptive studies with greater numbers. Shoemaker concluded that HFT reduces extubation failure rates when compared with CPAP and Holleman-Durary found no difference in extubation failure rates. Both studies used heated humidified gas and higher flow rates compared to Campbell et al[5].

Benefits of heated and humidified HFT

The small randomised crossover trial performed by Woodhead et al[6] simply looked at the comparison between humidified heated high flow oxygen and simple high flow oxygen. The guidelines of the American Association of Respiratory Care were used to assess when extubation was appropriate[15,16]. None of the infants on the humidified heated HFT (HHHFT) modality failed extubation and HHHFT was used to 'rescue' infants failing on simple HFT. This highlights the importance of using heated, humidified gases. It should be noted that higher pressures were used in the HHHFT group which may have explained its success. The highest flow rate with non-humidified/heated gas was a mean of 1.8L/min and for HHHFT the mean was 3.1L/min.

Different models

Miller et al[9] demonstrated no difference between the Fisher and Paykel nasal high flow (NHF™) and Vapotherm™ models in terms of the need for reintubation. This was only a small pilot study looking at 39 infants in total and was underpowered.

Duration of oxygen therapy – CPAP vs HFT

Abdel-Hady et al[7] conducted a randomised, open-label, controlled trial comparing HHHFNC and nCPAP. They looked at the duration of oxygen therapy in days as the primary outcome and the duration of respiratory support, duration of nCPAP days, length of hospitalisation, weaning success, and duration of weaning, need for intubation and mechanical ventilation and occurrence of complications as second end points. The weaning strategies used are summarised in **FIGURE 1**. Low flow rates of ≤2L/min were used. The key finding was that HFT increased the number of days premature infants required oxygen therapy ($p<0.001$) as compared with nCPAP. However, despite this there was no significant difference in duration of hospitalisation. In addition this study identified that 63% of infants weaned to HFT did not require oxygen therapy but demonstrated a need for the distending pressure generated by HFT. Another explanation for this is that the principle mechanism of action for HFT may be flushing through the dead space of the nasopharyngeal cavity decreasing the overall dead space and resulting in alveolar ventilation as a greater fraction of minute ventilation[17]. No other studies were identified for comparison.

Neonatal network survey

Anecdotally it seemed that there was no uniformity of use of HFT within the authors' region, and that it was becoming problematic transferring babies between units due to the variable availability of HFT.

To try to get a true picture of what was happening within the region, an online survey was designed and distributed to all the lead nurses within Yorkshire and North Trent Neonatal Networks in June 2011 to determine the usage and availability of HFT within a Strategic Health Authority (SHA) in Yorkshire and Humber. The region has an annual birth rate of approximately 75,000 births with 20 neonatal units in total and a dedicated transport service (Embrace), which carries out approximately 1,700 neonatal transfers per annum.

If an electronic response was not obtained, a telephone consultation was conducted. Data were collected on HFT availability, application, weaning protocols and complications. All 20 units within the SHA were included in the survey with a 100% response rate. Eight of the 20 units (40%) used HFT including all five tertiary centres. Four of the eight units used a guideline and these were all tertiary centres. The survey highlighted a delay in

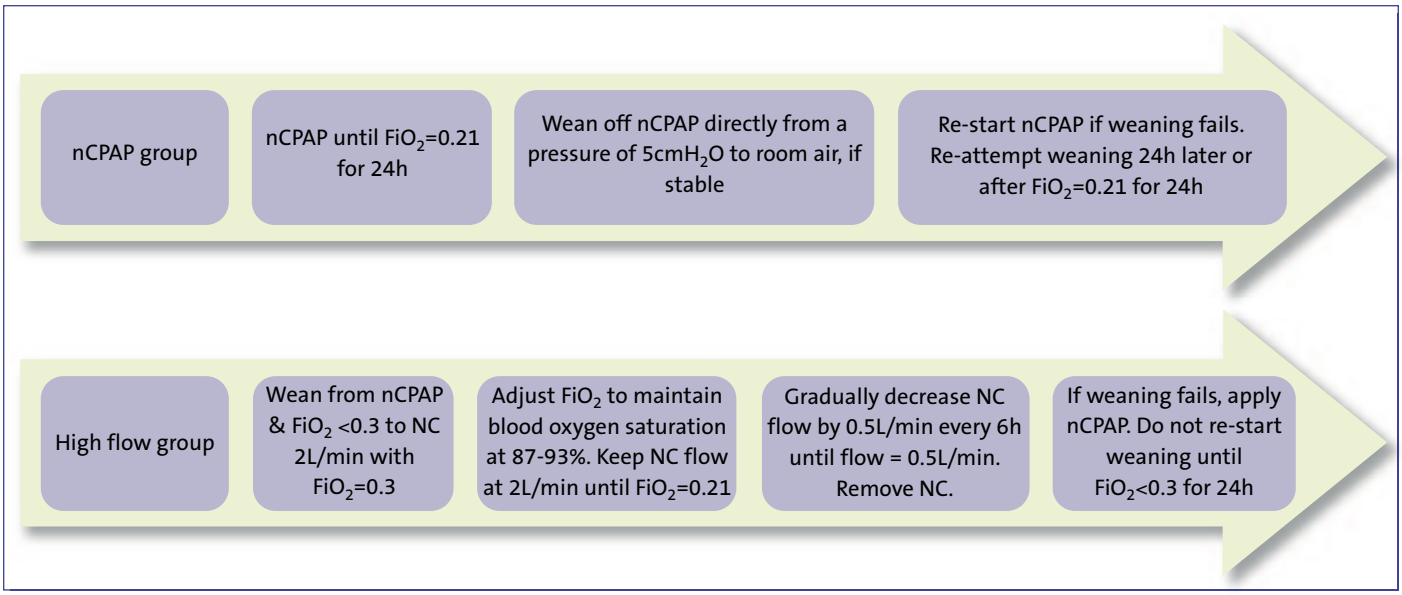

FIGURE 1 Summary of weaning regimens used by Abdel-Hady et al[7].
Key: nCPAP – nasal CPAP, NC – nasal cannulae, FiO_2 – fraction of inspired oxygen.

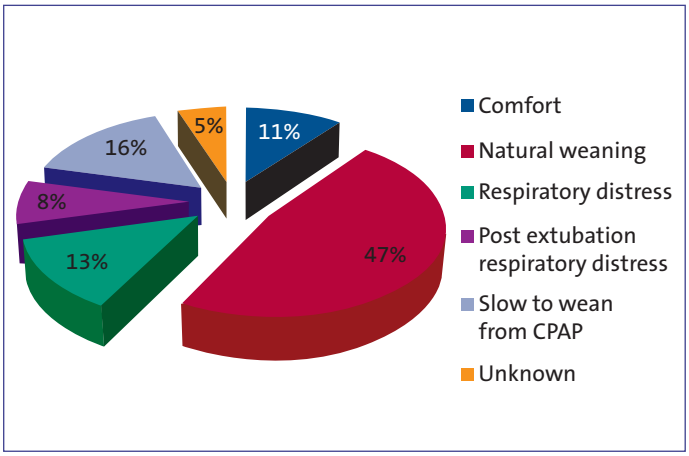

FIGURE 2 Indication for HFT within a tertiary neonatal unit.

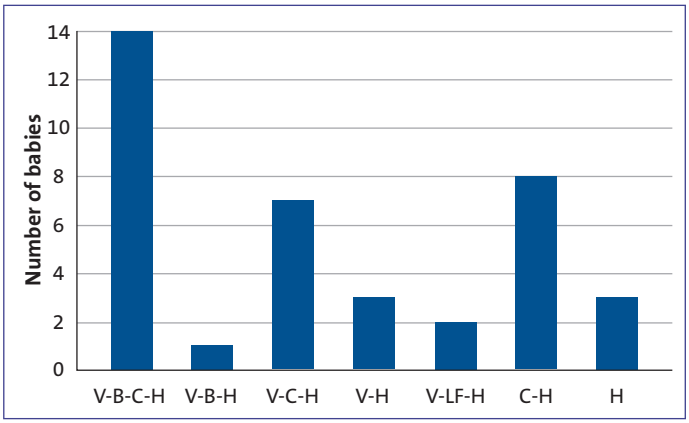

FIGURE 3 Weaning regimens used within a tertiary neonatal unit.
Key: V = ventilated, B = BiPAP, C = CPAP, H = HFT, LF = low flow.

repatriation due to lack of HFT at local units with referring units keeping babies until they had been weaned off the HFT. There seemed to be resistance to putting babies onto CPAP for transfer, as it was described as a "backward step" in their management by referring centres. This has cost implications and impacts significantly on the family waiting for repatriation transfers.

Interestingly a recent telephone survey (Steele J, June 2012) by the regional transport service showed that over the last year, use of HFT has increased with 12 units now using HFT, highlighting that despite minimal evidence this therapy is being used as routine respiratory support for many babies.

Use of HFT in a tertiary neonatal unit

An audit was conducted in January 2012 to assess the practical usage of HFT within a large tertiary unit (Leeds Teaching Hospitals NHS Trust). Thirty-eight babies were analysed retrospectively over a six-month period March-August 2011. The indications for HFT are given in **FIGURE 2** and the variable usage of HFT within the weaning process is shown in **FIGURE 3**. HFT was mainly used as a step-down therapy, after bilevel positive airway pressure (BiPAP) or CPAP following extubation (**FIGURE 2**). Only 8% of infants were weaned directly from the ventilator to HFT (**FIGURE 3**).

The initial flow rate used was 6L/min in the majority of cases, irrespective of weight or gestation. The unit guideline (**FIGURE 4**) describes the usage of 8L/min in babies weighing greater than one kilogram. Only three babies used such a high flow rate. Only 24% of babies on HFT were weaned correctly as per the guideline (**FIGURE 4**). Half of babies required no escalation of their ventilatory support once on HFT.

The mean duration of time on HFT prior to babies needing an escalation in ventilator support was 11 days; 24% required CPAP and 29% of babies required re-intubation. The reason for escalation of support was variable – 27% for simple respiratory decompensation (defined as pH <7.25, pCO_2 >8, rising oxygen requirement, apnoeas or increasing work of breathing), 55% had sepsis or necrotising enterocolitis and 18% were electively re-intubated for surgery.

Twenty-nine per cent of babies receiving HFT needed no additional oxygen therapy. The mean time using HFT in air with no oxygen therapy was 6.5 days. No complications were reported.

A CPAP cohort (2008-2009) for comparison demonstrated chronic lung disease rates of 39% compared with 19% in the HFT group analysed. It is predicted that the duration of stay is prolonged with HFT due to the increased number of steps in the weaning process. The comparison between HFT and CPAP is difficult as the findings are likely to be affected by bias as cases have not been matched between the two groups. Any analysis must be interpreted with caution and well designed trials are required.

The audit results demonstrate that despite a guideline being in place, the use of HFT is not consistent and can at times be detrimental to the baby by prolonging the length of stay on the neonatal unit due to a prolonged weaning phase of respiratory support. Anecdotally prior to the introduction of BiPAP and high flow therapy, babies were extubated on to CPAP and relatively quickly onto low flow oxygen therapy. BiPAP, and now HFT, have introduced further weaning stages post extubation (see **FIGURE 3**). The audit shows the majority of babies are extubated on to BiPAP, then CPAP, then HFT before low flow oxygen is used, if needed. The low failure rates reported within this audit are however encouraging. The use of HFT needs to be incorporated within extubation guidelines to prevent the increased number of steps in the weaning process since the adoption of this modality. Due to lack of evidence there is no consensus on the correct way to use and wean HFT.

Since carrying out this project, HFT continues to be used in the authors' unit. Nursing staff are enthusiastic about its use and how comfortable the babies are on this therapy. Work is being done to tighten criteria for use and possibly eliminate unnecessary weaning steps, by considering its use post-extubation.

Conclusions

The anecdotal evidence is that HFT is perceived to be a useful modality. It was identified from the network survey that 100% of nurses questioned preferred HFT to CPAP as it was perceived to be more comfortable for the babies and enhanced bonding with carers. However, the truth is that many neonatal units across the country have adopted this mode of respiratory support despite conflicting and insufficient evidence with a Cochrane review stating that 'there is insufficient evidence to establish the safety and effectiveness of HFNC'[8]. Adequately powered RCTs and meta-analyses with limited heterogeneity are eagerly awaited. Specifically studies addressing the questions surrounding optimal flow rates and effective weaning methods need to be undertaken. Evidence is awaited to support the use of HFT as a primary mode of non-invasive respiratory support replacing

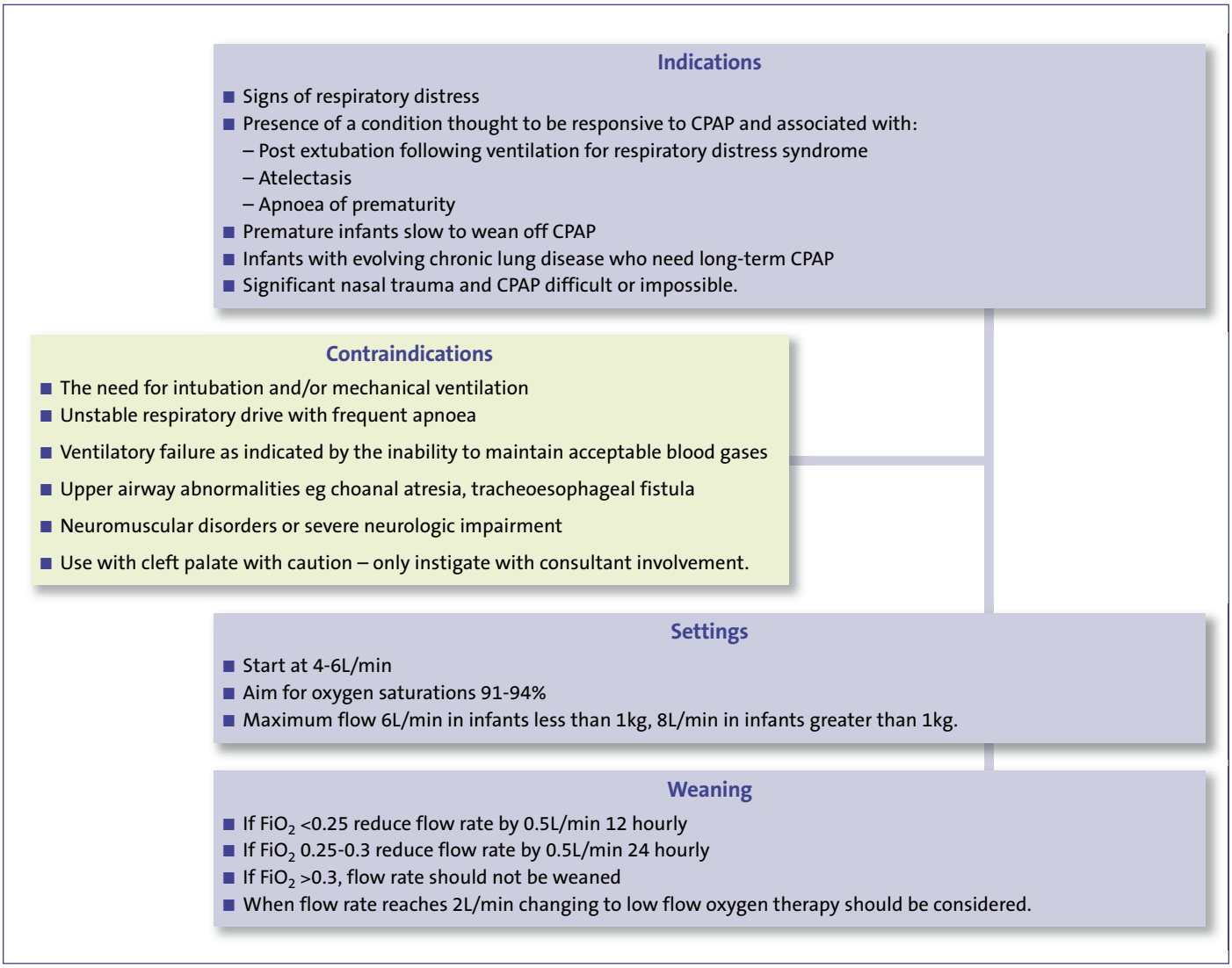

FIGURE 4 Summary of guidelines for HFT taken from the Leeds Teaching Hospitals NHS Trust 'Protocol for the Use of High Flow Therapy in the Newborn Infant' adapted from the Oxford Radcliffe Hospitals guideline.

CPAP. Ongoing studies in Australia and North America may provide this.

If HFT is considered optimal treatment for babies with respiratory compromise, it should be available within all units and in the transport setting, to prevent the delay in repatriation of babies.

References

1. **Thompson M.A.** Early nasal continuous positive airway pressure to minimise the need for endotracheal intubation and ventilation. *Neoreviews* 2005;6:e184-e188.
2. **Holleman-Duray D., Kaupie D., Weiss M.G.** Heated humidified high-flow nasal cannula: use and a neonatal early extubation protocol. *J Perinatol* 2007;27:776-81.
3. **Shoemaker M.T., Pierce M.R., Yoder B.A., DiGeronimo R.J.** High flow nasal cannula versus nasal CPAP for neonatal respiratory disease: a retrospective study. *J Perinatol* 2007;27:85-91.
4. **Centers for Disease Control and Prevention.** Ralstonia associated with Vapotherm oxygen delivery device: United States, 2005. *MMWR.* 2005;54:1052-53.
5. **Campbell D.M., Shah P.S., Shah V., Kelly E.N.** Nasal continuous positive airway pressure from high flow cannula versus infant flow for preterm infants. *J Perinatol* 2006;26:546-49.
6. **Woodhead D.D., Lambert D.K., Clark J.M., Christensen R.D.** Comparing two methods of delivering high-flow gas therapy by nasal cannula following endotracheal extubation: a prospective, randomised, masked, crossover trial. *J Perinatol* 2006;26:481-85.
7. **Abdel-Hady H., Shouman B., Aly H.** Early weaning from CPAP to high flow nasal cannula in preterm infants is associated with prolonged oxygen requirement: A randomised controlled trial. *Early Human Develop* 2011;87:205-08.
8. **Wilkinson D., Anderson C., O'Donnell C.P.F., De Paoli A.G.** High flow nasal cannula for respiratory support in preterm infants. *Cochrane Database Syst Rev* 2011 5:CD006405.
9. **Miller S.M., Dowd S.A.** High-flow nasal cannula and extubation success in the premature infant: a comparison of two modalities. *J Perinatol* 2010;30:805-08.
10. **Nair G., Karna P.** Comparison of the effects of Vapotherm and nasal CPAP in respiratory distress. *PAS* 2005:1.
11. **Kubicka Z.J., Limauro J., Darnall R.A.** Heated, humidified high-flow nasal cannula therapy: yet another way to deliver continuous positive airway pressure? *Pediatrics* 2008;121:82-88.
12. **Locke R.G., Wolfson M.R., Shaffer T.H., Rubenstein S.D., Greenspan J.S.** Inadvertent administration of positive end distending pressure during nasal cannula flow. *Pediatrics* 1993;91:135-38.
13. **Saslow J.G., Aghai Z.H., Nakhla T.A. et al.** Work of breathing using high-flow nasal cannula in preterm infants. *J Perinatol* 2006;26:476-80.
14. **Sreenan C., Lemke R.P., Hudson-Mason., Osiovich H.I.** High-flow nasal cannulae in the management of apnea of prematurity: a comparison with conventional nasal continuous positive airway pressure. *Pediatrics* 2001;107:1081-83.
15. **A collective Task Force Facilitated by the American College of Chest Physicians, the American Association for Respiratory Care, and the American College of Critical Care Medicine.** Evidence-based guidelines for weaning and discontinuing ventilatory support. *Respir Care* 2002;47:69-90.
16. **Durbin Jr C.G., Campbell R.S., Bransone R.D.** AARC clinical practice guideline. Removal of endotracheal tube. *Respir Care* 1999;44:85-90.
17. **Dysart K, Miller T.L., Wolfson M.R. et al.** Research in high flow therapy: mechanism of action. *Respir Med* 2009;103:1400-05.