Article:
Morris, JV, Kapetanstrataki, M, Parslow, RC orcid.org/0000-0002-3945-5294 et al. (2 more authors) (2019) Patterns of Use of Heated Humidified High-Flow Nasal Cannula Therapy in PICUs in the United Kingdom and Republic of Ireland*. Pediatric Critical Care Medicine, 20 (3). pp. 223-232. ISSN 1529-7535

https://doi.org/10.1097/pcc.0000000000001805

Patterns of use of heated humidified high flow nasal cannula therapy in paediatric intensive care units in the United Kingdom and Republic of Ireland

Jenny V Morris, MSc[1]; Melpo Kapetanstrataki, PhD[1]; Roger C Parslow, PhD[1]; Peter J Davis, FRCPCH[2]; Padmanabhan Ramnarayan, FRCPCH[3,4]

[1] School of Medicine, University of Leeds, Leeds, United Kingdom

[2] Paediatric Intensive Care Unit, University Hospitals Bristol NHS Foundation Trust, Bristol, United Kingdom

[3] Children's Acute Transport Service, Division of Critical Care, Great Ormond Street Hospital, London, United Kingdom

[4] Paediatric Intensive Care Unit, St Mary's Hospital, Imperial College Healthcare NHS Trust, London, United Kingdom

Corresponding author:
Dr Padmanabhan Ramnarayan
Children's Acute Transport Service
26-27 Boswell Street, London, UK, WC1N 3JZ
Telephone: +44 (0)207 4305850
Email: p.ramnarayan@gosh.nhs.uk

Keywords: high flow nasal cannula; non-invasive respiratory support; pediatric; non-invasive ventilation

Copyright form disclosure: Dr. Parslow's institution received funding from Healthcare Quality Improvement Partnership. Dr. Ramnarayan received travel support from Fisher and Paykel Healthcare to lead a research symposium in Nov 2017. The

remaining authors have disclosed that they do not have any potential conflicts of interest.

Abstract

Objectives: To: 1) describe patterns of use of high flow nasal cannula therapy (HFNC); 2) examine differences between patients started on HFNC and those started on non-invasive ventilation (NIV); and 3) explore whether patients who failed HFNC therapy were different from those who did not.

Design: Retrospective analysis of data collected prospectively by the Paediatric Intensive Care Audit Network (PICANet).

Setting: All paediatric intensive care units (PICUs) in the United Kingdom and Republic of Ireland (n=34).

Patients: Admissions to study PICUs (2015-16) receiving any form of respiratory support at any time during PICU stay.

Interventions: None.

Measurements and Main Results: Eligible admissions were classified into nine groups based on the combination of the first-line and second-line respiratory support modes. Uni- and multivariate analyses were performed to test the association between PICU and patient characteristics and two outcomes: a) use of HFNC versus NIV as first-line mode, and b) HFNC failure, requiring escalation to NIV and/or invasive ventilation (IV). We analysed data from 26,423 admissions; HFNC was used in 5,951 (22.5%) at some point during the PICU stay. HFNC was used for first-line support in 2,080 (7.9%) and post-extubation support in 978 admissions (4.5% of patients extubated after first-line IV). HFNC failure occurred in 559/2080 admissions (26.9%) when used for first-line support. Uni- and multivariate analyses showed that PICU characteristics as well as patient age, primary diagnostic group

and admission type had a significant influence on the choice of first-line mode (HFNC or NIV). Younger age, unplanned admission and higher admission severity of illness were independent predictors of HFNC failure.

Conclusions: The use of HFNC is common in PICUs in the UK and Republic of Ireland. Variation in the choice of first-line respiratory support mode (HFNC or NIV) between PICUs reflects the need for clinical trial evidence to guide future practice.

Introduction

Greater recognition of the risks of invasive ventilation (IV) have led to increased adoption of non-invasive modes of ventilation such as continuous or bi-level positive airway pressure (CPAP and BiPAP) in paediatric intensive care units (PICUs) in the United Kingdom (UK) and Republic of Ireland (ROI) as well as internationally.(1-3) Over the past decade, an alternate mode of non-invasive respiratory support, heated humidified high flow nasal cannula (HFNC) therapy, has become popular in critically ill newborns, children and adults, mainly due to its advantages of greater comfort and therefore better tolerance by patients, easier nursing care and potential cost savings.(4-6)

Despite the lack of convincing evidence of its effectiveness from rigorous randomised trials in children,(7, 8) national surveys of practice reveal that many clinicians now consider HFNC as their first-line choice for non-invasive respiratory support (NRS), both inside and outside the critical care environment.(9-11) Observational studies, mainly from single centres, demonstrate that there is considerable practice variation in terms of when, why and how clinicians use HFNC in the PICU setting, with the therapy being used in a range of conditions such as asthma, bronchiolitis, pneumonia, cardiac failure, neuromuscular weakness and recurrent apnoeas as well as for post-extubation respiratory support.(12-15) There is however little published data describing the patterns of HFNC use at a national or international level.

We aimed to address this evidence gap by analysing a high quality international clinical database of paediatric intensive care admissions in the UK & ROI to: 1) describe the patterns of use of HFNC (timing, indications for use and flow rates); 2) examine PICU- and patient-level differences between patients started on HFNC as the first-line mode of NRS and those started on non-invasive ventilation (NIV); and 3) explore whether patients who failed HFNC therapy as first-line NRS were different from those who did not.

Methods

We analysed anonymised data prospectively collected by the Paediatric Intensive Care Audit Network (PICANet) clinical audit database. PICANet collects an admission dataset containing clinical and demographic data, as well as information on daily interventions as part of the Paediatric Critical Care Minimum Dataset (PCCMDS), from all PICUs in the UK & ROI. HFNC was included as a daily intervention in PICANet from January 2015. Data quality is ensured by regular training of staff and by local and central validation checks. PICANet has approval to collect personally identifiable data under special circumstances from the Health Research Authority Confidentiality Advisory Group (ref: PIAG 4-07(c)/2002) and approval from the Trent Medical Research Ethics Committee (ref: 05/MRE04/17).

Data

We identified all children (<16 years of age) admitted to study PICUs during a 2-year study period (January 2015 to December 2016) who received any form of respiratory support (IV; NIV such as CPAP, pressure support or BIPAP; or HFNC) at any point

during their admission. We extracted data on the details and timing of each mode of respiratory support used, demographic data (age, gender and weight), clinical features (primary diagnostic group, main reason for admission and physiological parameters recorded at admission as part of the Paediatric Index of Mortality 2 score)(16) and key outcomes (length of PICU stay, total length of ventilation and vital status at PICU discharge).

To fulfil our study aims, we created a restricted dataset in which we included data regarding the first-line respiratory support mode (IV, NIV or HFNC) and the second-line mode (only if it was started within two calendar days of stopping the first). Admissions were classified into one of nine groups based on a combination of the first and the second respiratory support mode as shown in Figure 1 (IV-no support, IV-NIV, IV-HFNC, NIV-no support, NIV-IV, NIV-HFNC, HFNC-no support, HFNC-NIV and HFNC-IV). In cases where more than one mode of support was recorded on the same day, we checked the next calendar day to identify the first subsequent form of support to be received alone (e.g. if both IV and NIV were recorded on the day of admission and only IV was recorded on the next calendar day, patients were classified as NIV-IV). Where it was not possible to determine the order in which respiratory support was provided, we excluded those records from further analysis.

Data analysis

We calculated the number of discrete episodes of HFNC recorded during the entire PICU admission. An episode was defined as a continuous period of HFNC usage followed by at least one calendar day of no receipt of HFNC, irrespective of whether

other modes of respiratory support were used. We calculated the median length of time spent on HFNC. We also analysed the timing of the first recorded respiratory support mode (IV, NIV and HFNC) in relation to the day of PICU admission.

Using the restricted dataset, we performed three analyses to fulfil our objectives:

Analysis 1: We studied the timing of HFNC use (*primary respiratory support*: to include the groups HFNC-no support, HFNC-NIV and HFNC-IV; *post-extubation respiratory support*: IV-HFNC group), clinical indications (*primary diagnostic group*: respiratory, cardiovascular, neurological, infection, oncology, other; *main primary diagnosis*: asthma, bronchiolitis, upper airway obstruction, post-operative, other; *source of admission*: same hospital, other hospital, other; *type of admission*: planned following surgery, unplanned following surgery, planned other, unplanned other; *physiological variables at PICU admission*: systolic blood pressure, base excess and serum lactate) and HFNC flow rates (starting flow rate in litres per minute for all patients, and litres per minute per kilogram body weight for children weighing <10 kilograms).

Analysis 2: To identify possible differences in the use of HFNC or NIV as the first-line NRS mode, we examined PICU characteristics (*unit type*: general, cardiac, mixed; *unit size*: <400, 400-800 and >800 admissions/year; *emergency admissions rate*: low and high, based on the national mean cut-off of 60.6%) as well as patient characteristics (age, gender, weight, primary diagnostic group, main primary diagnosis, source and type of admission, and admission physiological variables) of children who received HFNC-first versus NIV-first. We also compared their outcomes (length of PICU stay, total length of respiratory support and PICU mortality). To test the association

between the patient characteristics (exposure) and use of HFNC or NIV as first-line NRS mode (outcome) we developed mixed-effects logistic regression models, with the admitting PICU as a random effect. Similarly, to test the association between PICU characteristics (exposure) and use of HFNC or NIV as first-line NRS mode (outcome) we developed logistic regression models. We entered into the models all characteristics that were significantly associated with the outcome in univariate analyses.

Analysis 3: We compared patient characteristics and outcomes of children who were commenced on first-line HFNC and failed the therapy (HFNC-NIV and HFNC-IV groups) with those who did not fail HFNC therapy within two calendar days (HFNC-no support) to identify risk factors for HFNC failure. We developed regular as well as mixed-effects logistic regression models to study the association between patient characteristics (exposure) and HFNC failure (outcome) to account for any clustering of data within the admitting PICUs.

Categorical data are reported as number and percentages, and continuous data as means or medians as appropriate. P values of <0.05 were considered significant. All analyses were performed using Stata version 15 (StataCorp, College Station, Texas, USA).

Results

During the study period, there were 41,388 admissions recorded in PICANet from 34 PICUs in the UK & ROI. Our study cohort consisted of 26,423 admissions (63.8%) after we excluded admissions where a tracheostomy was in place (n=146, 0.4%) or

no respiratory support was provided during the admission (n=10,281, 24.8%), where information on daily interventions was not available (n=956, 2.3%), where PICUs did not submit HFNC data during the study period (n=3,334, 8.1%) and admissions unable to be classified by the order in which respiratory support was provided (n=248, 0.6%). The 26,423 admissions included in the analysis occurred in 20,689 patients. Figure 1 illustrates that a majority of children who received respiratory support received IV as their first recorded mode (n=21,663, 82.0%) while a smaller proportion received NIV (n=2,680, 10.1%) and HFNC (n=2,080, 7.9%).

The first-line respiratory support mode (IV, NIV or HFNC) was started on the day of PICU admission in the vast majority of admissions (95.1%) as shown in Supplementary Table 1. In total, 5,951 out of 26,423 study subjects (22.5%) received at least one discrete episode of HFNC during their PICU stay (this proportion was 16.1% when all admissions with complete information regarding daily interventions including HFNC and excluding those with a tracheostomy were considered in the denominator [5951/36952 admissions]). The majority received just one episode (5,182, 19.6%); some received two episodes (597, 2.3%) and a small proportion received more than two episodes (172, 0.7%). The median length of HFNC use was 2 days (IQR 1-3) for admissions where only one episode of HFNC was used, 4 days (IQR 3-6) for those where two episodes of HFNC were used, and 10 days (IQR 6-20) when over 2 HFNC episodes were recorded.

Analysis 1: patterns of HFNC use

HFNC was started for first-line respiratory support in 2,080 admissions (7.9%) and for post-extubation support in 978 out of 21,663 admissions (4.5%) where IV was used as first-line mode. Table 1 illustrates the differences in age, primary diagnostic group and main primary diagnosis between these two groups: where HFNC was used as primary respiratory support, respiratory conditions accounted for nearly two-thirds of cases, nearly a quarter had bronchiolitis, and over three-quarters of admissions were unplanned medical admissions. In contrast, cardiovascular conditions predominated in the post-extubation support group, over half of the group were post-operative patients and nearly one-half of admissions were planned post-surgical admissions. The median starting flow rate when HFNC was used as primary respiratory support was 8 L/min (IQR 0-15); in children with a weight of <10 kg the median starting flow rate was 2 L/kg/min (IQR 1.7-2.5). In the post-extubation support group median starting flow rate was 10 L/min (IQR 8-16); in children <10 kg, it was 2 L/kg/min (IQR 1.6-2.6). Weight was available only in 709 (34.1%) and 330 (33.7%) admissions respectively.

Analysis 2: Children who received HFNC versus those who received NIV

NIV was started for primary respiratory support in 2680 admissions (10.1%) and for post-extubation support in 722 admissions (3.3% of 21,663 admissions where IV was used as first-line mode) as shown in Table 1.

Primary respiratory support: Patients who were started on HFNC were significantly younger than those started on NIV (median age: 40 weeks, IQR 12-168 versus 58 weeks, IQR 11-377, $p<0.001$), more likely to have a main primary diagnosis of asthma

or bronchiolitis and were more likely to be admitted from within the same hospital. As shown in Table 2, the total duration of respiratory support differed between the two groups (median 3 days, IQR 2-6 vs. 4 days, IQR 2-8, p<0.001) as did length of PICU stay (median 4 days, IQR 3-7 vs. 5 days, IQR 3-10). Patients started on HFNC as first-line therapy had a lower crude mortality rate than those started on NIV (2.2% v 3.8%, p <0.001).

Post-extubation support: Patients started on HFNC after extubation compared to those started on NIV were more likely to have a cardiovascular diagnosis (45.9% versus 38.4%, p<0.001), more likely to be post-operative cases (54.7% versus 49.9%, p<0.001), and were more likely to have been admitted to PICU following planned surgery (49.2% vs 45.0%, p<0.001). There was a significant difference between the groups in terms of mortality (HFNC: 0.5% vs. NIV: 1.7%, p=0.02), total duration of respiratory support (p=0.02) and length of PICU stay (p<0.001).

Choice of first-line NRS: There was significant variation in the choice of HFNC as the first-line mode of NRS based on the admitting PICU (Supplementary Table 2). As shown in Supplementary Table 3, in a logistic regression model, unit type (odds ratio for choice of HFNC as first-line NRS mode in a cardiac unit compared to a general unit 0.55, 95% CI 0.41-0.75) and emergency admissions rate (odds ratio for high rate unit compared to low rate unit 0.40, 95% CI 0.35-0.45) were significant factors. Results of the mixed-effects logistic regression analysis with the PICU as the random effect are shown in Table 3. The likelihood ratio test calculated by the final model showed that the random effect was statistically significant (p<0.001).

Analysis 3: Failure of HFNC treatment

In 559 out of 2,080 (26.9%) of admissions where HFNC was used for first-line respiratory support, the therapy failed requiring commencement of NIV or IV within 2 calendar days. As shown in Tables 4 and 5, patients who failed HFNC were likely to be younger (median age: 25 [IQR 7, 188] versus 48 weeks [IQR 16, 183], p<0.001), sicker at admission (median PIM-2 risk of mortality 1.3% [IQR 0.5, 2.8] versus 1.0% [IQR 0.3, 1.7], p<0.001), have cardiovascular diagnoses (21% versus 13%), were less likely to have asthma as the main primary diagnosis, more likely to have an unplanned medical admission, and have a lower median systolic blood pressure at admission (95 mm Hg [IQR 82, 108] versus 100 mm Hg [IQR 86, 112], p<0.001). HFNC failure was also more likely when started on the day of PICU admission (493/1703, 28.9%) rather than on subsequent days (66/377, 17.5%). As shown in Table 5, HFNC failure was associated with longer overall length of respiratory support (median 7 days [IQR 4, 13] versus 2 days [IQR 2, 4], p<0.001), longer PICU stay (median 8 [IQR 5, 14] versus 4 days [IQR 2, 5], p<0.001), and a higher crude mortality (4% versus 1%, p<0.001). There was no difference in terms of the starting HFNC flow rate (median 12 L/min in both groups, p=0.31). Since there was minimal clustering of data within admitting PICU (intraclass correlation coefficient 0.07), regular logistic regression analysis was used, which showed that independent risk factors for HFNC failure were younger age, primary diagnostic group, unplanned admission and higher PIM-2 score (Supplementary Table 4).

Discussion

In this retrospective cohort study, we analysed data from a high quality clinical database of admissions to PICUs in the UK and Republic of Ireland and found that HFNC is used frequently, to provide primary respiratory support as well as support following extubation. We found significant differences between patients in whom HFNC was started for primary respiratory support and those in whom NIV was started, although this practice also varied depending on the characteristics of the admitting PICU, reflecting potential differences in clinician preferences and/or PICU admission thresholds. Nearly a quarter of admissions where HFNC was started for primary respiratory support required to be escalated to other forms of support within two calendar days.

Despite the absence of evidence from randomised trials to support its clinical and cost effectiveness, HFNC has become a popular means of providing NRS to children, inside and outside the critical care unit.(7, 17) A single-centre study from the USA reported that 27% of PICU admissions from a two-year period (2011-13) were managed with HFNC, for conditions ranging from asthma, pneumonia and bronchiolitis to congenital heart disease. HFNC was used most frequently for primary support (73%), although post-extubation support was a common indication (16%).(13) Similarly, experience from one Canadian PICU over a 12-month period suggested that 16% of admissions received HFNC. Congenital heart disease, especially in the post-operative period, was the main patient group in this cohort, and post-extubation support was the main indication for HFNC (36%) rather than

primary support (31%). Escalation to NIV and/or IV was required in 22% of cases.(14) Our analysis of international data provides roughly similar findings: 22% of study subjects received HFNC, primary respiratory support accounted for 68% of HFNC use, and the rate of escalation to NIV and/or IV was 27%. As a multicentre study, we were also able to demonstrate a significant influence of the admitting PICU characteristics on the patterns of HFNC/NIV use. This finding may have been influenced by differences in unit or clinician preferences resulting from the lack of strong evidence to guide clinical practice, or by unit-wise differences in the threshold for PICU admission, which we did not have information on (for example, NIV-first may appear artificially higher in hospitals where HFNC can be delivered on the wards, but NIV can only be delivered in the PICU).

Our study provides several important findings that may be relevant for future research in this area.(18) First, HFNC has become a common intervention in contemporary PICU practice, being used in nearly a quarter of admissions, and at least as frequently as NIV. Second, there are important differences in the patient groups where HFNC is used for primary support and for post-extubation support: respiratory disease, especially bronchiolitis and other respiratory illnesses, is the most common indication for primary support, while post-operative cardiac surgery is the most common population in which post-extubation support is provided. Third, the median starting flow rate for HFNC is 2 L/kg/min for infants weighing <10 kg, indicating that clinicians are potentially choosing to use HFNC as an alternative for CPAP, based on physiological evidence that a CPAP-effect may be generated at these flow rates.(19, 20) Fourth, in a population of critically ill children with diverse

pathologies, the failure rate for HFNC when used as first-line NRS was 27%, with the majority escalating directly to IV (17%), not dissimilar to the failure rate of NIV when used as first-line NRS (28%).

To our knowledge, this is the first detailed international report of clinical practice related to the use of HFNC in the PICU setting. A key strength of our study was the use of a high-quality clinical database covering daily interventions from all PICUs in the UK and ROI. PICANet uses strict data definitions and trained data collectors to ensure the integrity of data; in addition to real-time validation during data entry, data are subject to independent verification by a trained research nurse during site visits and audit of a random sample of patients. Another key strength of this study was the large sample size and multicentre nature of the dataset that allowed us to confidently explore associations between the use of HFNC and factors relating to the patient and the organisation. Limitations to this study include the retrospective analysis, although this may have been ameliorated by high data quality and prospective nature of data collection. Missing data may also have affected our analyses, although the frequency of missing data was generally low, except for admission weight and blood gas parameters. We did not include co-morbidities in our analysis since missing data were common for this field in the PICANet data. Since PICANet does not collect detailed physiological data, we were unable to describe the physiological profile of the groups in terms of respiratory rate, heart rate and oxygen saturations prior to and after starting NRS, or to explore the reasons for failure in more detail. Similarly, the reasons for clinicians choosing one mode of NRS over another were not available from this dataset. Finally, we analysed multiple

admissions for the same child during the study period as individual admissions, which may have potentially introduced bias due to clustering of data.

Conclusions

We have shown that the use of high flow nasal cannula therapy is common in PICUs in the UK and Republic of Ireland and that patients started on HFNC for primary respiratory support differ from those started on HFNC for post-extubation support. Differences between PICUs in the choice of first-line respiratory support mode (HFNC or NIV) reflect the poor evidence base in this area. Randomised trial evidence is urgently required to guide future intensive care practice.

Acknowledgements

The PICANet Audit is commissioned by the Healthcare Quality Improvement Partnership (HQIP) as part of the National Clinical Audit Programme (NCA). HQIP is led by a consortium of the Academy of Medical Royal Colleges, the Royal College of Nursing and National Voices. Its aim is to promote quality improvement and in particular to increase the impact that clinical audit has on healthcare quality in England and Wales. HQIP holds the contract to manage and develop the NCA Programme, comprising more than 30 clinical audits that cover care provided to people with a wide range of medical, surgical and mental health conditions. The PICANet Audit is funded by NHS England, the Welsh Government, NHS Lothian/National Service Division NHS Scotland, the Royal Belfast Hospital for Sick Children, The National Office of Clinical Audit (NOCA), Republic of Ireland and HCA Healthcare.

Figures

Figure 1: Study flow diagram showing the classification of nine groups based on the first-line and second-line respiratory support modes

References

1. Paediatric Intensive Care Network (PICANet). National report of the Paediatric Intensive Care Audit Network, January 2011–December 2013. Leeds: Universities of Leeds and Leicester; 2014.

2. Wolfler A, Calderini E, Iannella E, et al. Evolution of Noninvasive Mechanical Ventilation Use: A Cohort Study Among Italian PICUs. Pediatr Crit Care Med 2015;16(5):418-427.

3. Emeriaud G, Essouri S, Tucci M. Noninvasive Ventilation in the PICU: One Step Closer. Crit Care Med 2017;45(6):1103-1104.

4. Ramnarayan P, Schibler A. Glass half empty or half full? The story of high-flow nasal cannula therapy in critically ill children. Intensive Care Med 2017;43(2):246-249.

5. Lee JH, Rehder KJ, Williford L, et al. Use of high flow nasal cannula in critically ill infants, children, and adults: a critical review of the literature. Intensive Care Med 2013;39(2):247-257.

6. Manley BJ. Nasal High-Flow Therapy for Preterm Infants: Review of Neonatal Trial Data. Clin Perinatol 2016;43(4):673-691.

7. Mayfield S, Jauncey-Cooke J, Hough JL, et al. High-flow nasal cannula therapy for respiratory support in children. The Cochrane database of systematic reviews 2014(3):CD009850.

8. Beggs S, Wong ZH, Kaul S, et al. High-flow nasal cannula therapy for infants with bronchiolitis. The Cochrane database of systematic reviews 2014(1):CD009609.

9. Turnham H, Agbeko RS, Furness J, et al. Non-invasive respiratory support for infants with bronchiolitis: a national survey of practice. BMC pediatrics 2017;17(1):20.

10. Schmid F, Olbertz DM, Ballmann M. The use of high-flow nasal cannula (HFNC) as respiratory support in neonatal and pediatric intensive care units in Germany - A nationwide survey. Respiratory medicine 2017;131:210-214.

11. Jones AJ, Mathew S, Wong SW, et al. A regional audit of high-flow nasal cannula therapy use for bronchiolitis in London district general hospitals. Arch Dis Child 2017;102(3):296-297.

12. Kawaguchi A, Yasui Y, deCaen A, et al. The Clinical Impact of Heated Humidified High-Flow Nasal Cannula on Pediatric Respiratory Distress. Pediatr Crit Care Med 2017;18(2):112-119.

13. Coletti KD, Bagdure DN, Walker LK, et al. High-Flow Nasal Cannula Utilization in Pediatric Critical Care. Respiratory care 2017;62(8):1023-1029.

14. Baudin F, Gagnon S, Crulli B, et al. Modalities and Complications Associated With the Use of High-Flow Nasal Cannula: Experience in a Pediatric ICU. Respiratory care 2016;61(10):1305-1310.

15. Maul CP, Franklin D, Williams T, et al. Nasal High-Flow Therapy in Children: A Survey of Current Practice in Australia. Journal of paediatrics and child health 2017;53(10):1031-1032.

16. Slater A, Shann F, Pearson G, et al. PIM2: a revised version of the Paediatric Index of Mortality. Intensive Care Med 2003;29(2):278-285.

17. Milesi C, Essouri S, Pouyau R, et al. High flow nasal cannula (HFNC) versus nasal continuous positive airway pressure (nCPAP) for the initial respiratory management of acute viral bronchiolitis in young infants: a multicenter randomized controlled trial (TRAMONTANE study). Intensive Care Med 2017;43(2):209-216.

18. Ramnarayan P, Lister P, Dominguez T, et al. FIRST-line support for Assistance in Breathing in Children (FIRST-ABC): protocol for a multicentre randomised feasibility trial of non-invasive respiratory support in critically ill children. BMJ open 2017;7(6):e016181.

19. Milesi C, Baleine J, Matecki S, et al. Is treatment with a high flow nasal cannula effective in acute viral bronchiolitis? A physiologic study. Intensive Care Med 2013;39(6):1088-1094.

20. Weiler T, Kamerkar A, Hotz J, et al. The Relationship between High Flow Nasal Cannula Flow Rate and Effort of Breathing in Children. J Pediatr 2017;189:66-71 e63.