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Date:

2020-06-01

Citation:

Babl, F. E., Franklin, D., Schlapbach, L. J., Oakley, E., Dalziel, S., Whitty, J. A., Neutze, J., Furyk, J., Craig, S., Fraser, J. F., Jones, M. & Schibler, A. (2020). Enteral hydration in high-flow therapy for infants with bronchiolitis: Secondary analysis of a randomised trial. *Journal of Paediatrics and Child Health*, 56 (6), pp.950-955. <https://doi.org/10.1111/jpc.14799>.

Persistent Link:

<https://hdl.handle.net/11343/275389>

Enteral Hydration in High-flow Therapy for Infants with Bronchiolitis: Secondary Analysis of a Randomized Trial

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This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: [10.1111/jpc.14799](https://doi.org/10.1111/jpc.14799)

Short Title: Hydration in High Flow

Funding

The study was funded by a project grant from the National Health and Medical Research Council (NHMRC, GNT1081736), Canberra, Australia, and the Emergency Medicine Foundation, Brisbane, Australia. Regional site funding was obtained for Ipswich Hospital from the Ipswich Hospital Foundation and the Gold Coast University Hospital (GCUH) from the GCUH Foundation. Drs Schibler and Fraser received a research fellowship from the Queensland Health Department, Australia. PREDICT sites were supported by a National Health and Medical Research Council Centre of Research Excellence grant for pediatric emergency medicine (GNT1058560). Victorian sites received infrastructure support from the Victorian Government's Infrastructure Support Program, Melbourne, Australia. Dr Babl was part funded by a Royal Children's Hospital Foundation grant, a Melbourne Campus Clinician Scientist Fellowship, Melbourne, Australia and an NHMRC Practitioner Fellowship. Dr Dalziel was part funded by a grant from the Health Research Council of New Zealand (HRC), Auckland, New Zealand. The Townsville Hospital was part funded by a SERTA grant (Study, Education and Research Trust Account). The high-flow equipment and consumables for all study sites were provided free of charge by Fisher & Paykel Healthcare (Auckland, New Zealand), who had no involvement in design, conduct, and analysis of the study.

Financial disclosure

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Conflicts of interest: none

Clinical Trial registration: The trial is registered with the Australian and New Zealand Clinical Trials Registry ACTRN12613000388718. No further data are available.

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NGT nasogastric tube
IV intravenous
RCT randomized controlled trial
CRF clinical report form

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We assessed the form of hydration in 505 infants who received high flow for hypoxic respiratory failure within a randomised trial. Enteral hydration was safe and the majority of infants on high flow were exclusively hydrated via nasogastric tube.

Contributors statement page

Ms Franklin and Drs Babl and Schibler conceptualized and designed the study, drafted the initial manuscript and reviewed and revised it.

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All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

ABSTRACT

OBJECTIVE

Nasal high-flow oxygen therapy is increasingly used in infants for supportive respiratory therapy in bronchiolitis. It is unclear whether enteral hydration is safe in children receiving high-flow.

STUDY DESIGN

We performed a planned secondary analysis of a multi-center, randomized controlled trial of infants aged <12 months with bronchiolitis and an oxygen requirement. Children were assigned to treatment with either high-flow or standard-oxygen therapy with optional rescue high-flow. We assessed adverse events based on how children on high-flow were hydrated: intravenously (IV), via bolus or continuous nasogastric tube (NGT) or orally.

RESULTS

505 patients on high-flow via primary study assignment (n=408), primary treatment (n=10) or as rescue therapy (n=87) were assessed. While on high flow 15 of 505 (3.0%) received only IV fluids on high-flow, 360 (71.3%) received only enteral fluids and 93 (18.4%) received both IV and enteral fluids. The route was unknown in 37 (7.3%). Of the 453 high-flow infants hydrated enterally patients could receive one or more methods of hydration. 80 (15.8%) received NGT bolus, 217 (43.0%) NGT continuous, 118 (23.4%) both bolus and continuous, 32 (6.3%) received only oral hydration and 171 (33.9%) a mix of NGT and oral hydration.

None of the patients receiving oral or NGT hydration on high-flow sustained pulmonary aspiration (0%; 95% CI N/A); one patient had a pneumothorax (0.2%; 95% CI 0.0 to 0.7%).

CONCLUSIONS

The vast majority of children with hypoxic respiratory failure in bronchiolitis can be safely hydrated enterally during the period when they receive high-flow.

What is already know

In infants admitted with bronchiolitis not on high flow nasogastric hydration has been shown to be effective and safe. It is unclear if children receiving high-flow in bronchiolitis can be safely hydrated enterally as well.

What this study adds

We assessed the form of hydration in 505 infants who received high flow for hypoxic respiratory failure within a randomised trial. Enteral hydration was safe and the majority of infants on high flow were exclusively hydrated via nasogastric tube.

INTRODUCTION

Bronchiolitis, an acute lower airway lung disease is the most common reason for non-elective hospital admission in infants. No interventions have shown efficacy^{1,2} and American Academy of Pediatrics and Australasian Bronchiolitis guidelines recommend only supportive therapy including oxygen therapy for hypoxia, respiratory support and the maintenance of hydration.^{3, 4}

Three methods of hydration and feeding are available for infants diagnosed with bronchiolitis including intravenous (IV), enteral hydration via nasogastric tube (NGT) or oral hydration. Enteral hydration has several theoretical advantages such as physiological benefits and allowing the additional administration of calories. In infants not requiring respiratory support, IV and NGT hydration have been shown to be equally efficacious and safe in bronchiolitis infants.^{5, 6} Oral hydration remains controversial particularly in infants with more severe disease with either inadequate intake or risk of aspiration.

Nasal high-flow oxygen therapy has emerged as a means to provide respiratory support in bronchiolitis.⁷⁻¹² We have recently conducted a multi-center randomized controlled trial (RCT) which demonstrated that high-flow oxygen therapy can be provided safely in ward settings with a lower risk of treatment failure than standard oxygen therapy but no difference in hospital length of stay or duration of oxygen therapy.¹³ It is unclear, however, if enteral hydration via

NGT or orally can be safely administered in infants on high-flow oxygen therapy. In a secondary analysis of the RCT we set out to assess if infants on high-flow oxygen therapy can safely receive enteral hydration.

METHODS

STUDY DESIGN

The parent study was an unblinded RCT comparing high-flow oxygen therapy with standard-oxygen therapy in emergency departments and general pediatric inpatient units in 17 tertiary and regional hospitals in Australia and New Zealand between October 2013 and August 2016.¹³ The human research ethics committee at each participating site approved the study. The study protocol has been published.¹⁴ The study protocol was registered with the Australian and New Zealand Clinical Trials Registry (ACTRN12613000388718).

PATIENTS

Infants less than 12 months of age were eligible for inclusion upon presentation to emergency or pediatric inpatient units with clinical signs of bronchiolitis and an oxygen requirement. Bronchiolitis was defined according to the American Academy of Pediatrics³ criteria as an infant with symptoms of respiratory distress associated with symptoms of a viral respiratory tract infection.² We excluded critically ill infants with immediate need for respiratory support and intensive care admission, infants with cyanotic heart disease, apneas, basal skull fracture,

upper airway obstruction, craniofacial malformations and infants receiving home oxygen therapy. Written informed consent was obtained from all parents or guardians.

STUDY INTERVENTION

High-flow group infants received heated and humidified high-flow oxygen therapy at a rate of 2L/kg per minute delivered via the Optiflow™ system (Fisher & Paykel Healthcare; Auckland, New Zealand) using an age-appropriate Optiflow Junior™ cannula and the Airvo2™ high-flow device. The standard-oxygen group infants were placed on subnasal oxygen via nasal cannula up to a maximum of 2 L/min. Details of the study protocol are available in a separate publication.¹⁴

For all infants who received high-flow a NGT placement was recommended for venting of the stomach at least 4 hourly to avoid gastric hyperextension. IV placement was not mandated or encouraged. Depending on the clinician's preference oral intake was allowed if tolerated, particularly during weaning of the treatment. Nursing care management was to continue NGT feeding during high-flow delivery and to stop high-flow and change to low-flow humidified oxygen via the same high-flow Airvo2 device during oral feeding. In this case the infant would remain undisturbed with the same nasal cannula for this time period and up to a maximum of 20 minutes before ceasing oral hydration and returning to previous high-flow settings via the Airvo2 device. Type of hydration during high-flow and low-flow humidified oxygen was recorded. Information as to whether or not the flow rate was turned down during enteral hydration was turned down was not collected. Data on type of hydration

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during high-flow and low-flow humidified oxygen was obtained where accurately recorded in the medical charts. This was at times difficult to adhere to and collect data on, as parents may have fed their infant when the nurse was not present.

STUDY OUTCOMES

The primary outcome of the parent study was treatment failure resulting in escalation of care during the current hospital admission. At the point of care the treating clinicians determined the presence of treatment failure if at least three of four clinical criteria were met and escalation of care was required.¹³ The clinicians were allowed to escalate therapy if they were concerned for other clinical reasons not captured in the four clinical criteria. For children in the standard-oxygen group who received escalation of care, it was suggested to use rescue high-flow in the inpatient ward environment.

For this study we assessed all infants who received high-flow oxygen therapy either as their primary commencement therapy regardless of randomized study assignment or as rescue high-flow therapy if they failed standard-oxygen therapy. Detailed hydration data were collected and included in the CRF from November 2015. Primary analysis of this study was adverse events based on how children on high-flow were hydrated, either via IV route, via bolus or continuous NGT or orally. We collected adverse events by specifically asking for certain adverse events. A serious adverse event was defined as any event that was fatal, life-threatening, permanently disabling, incapacitating or resulted in a prolonged hospital stay.

STATISTICAL ANALYSIS

Descriptive statistics were used to report on the baseline characteristics of the infants who received high-flow and their means of hydration with 95% confidence intervals for key proportions.

RESULTS

PATIENT CHARACTERISTICS

Of 1,638 infants randomized 166 parents/guardians (10%) declined consent to use data, thus 1,472 infants were included in the analyses of the parent study. Of these, 739 were primarily randomized to the high-flow group and of whom 728 actually received high-flow, and 733 were primarily randomized to the standard-oxygen group and of whom 18 actually received high-flow in the first instance and 162 received rescue high-flow for a total of 908 receiving high-flow (**Figure 1**).

Prospective hydration data were collected for 505 patients who received high-flow and represent the study cohort analyzed. Demographic and basic clinical characteristics are shown in **Table 1**. The average age of the infants was 5.8 months and 217 of 393 tested (55.2%) were RSV positive. A history of prematurity or previous hospital admission was 92 (18.2%) and 122 (24.2%) respectively. The mean peripheral oxygen saturation level on room air at enrolment was 88%.

HYDRATION ON HIGH FLOW

While on high-flow 15 of 505 (3.0%) received only IV fluids, 360 (71.3%) received only enteral feeds and 93 (18.4%) received both IV and enteral feeds (**Figure 1**). For 37 (7.3%) route of fluid administration was unknown. Of the 453 who had at least at some point been enterally fed while on high-flow 80 (15.8%) received NGT bolus, 217 (43.0%) NGT continuous, 118 (23.4%) both bolus and continuous, 32 (6.3%) received only oral feeds without NGT hydration and 171 (33.9%) received a mix of NGT and oral feeds (**Table 2**). Infants less than 3 months of age had higher IV rates than older infants.

ADVERSE EVENTS

None of the patients receiving oral or NGT feeding on high flow sustained pulmonary aspiration (0%; 95% CI N/A); 1 patient had a pneumothorax (0.2%; 95% CI 0.0 to 0.7%) which was unrelated to NGT insertion and did not require a chest tube. Of note in the parent study there was one pneumothorax noted in the standard oxygen group. No life-threatening serious adverse-events were observed, specifically no emergency intubation or cardiac arrest (**Table 2**).

DISCUSSION

In this secondary analysis of a multi-center randomized controlled trial in infants with bronchiolitis and hypoxemia we found that the vast majority of patients – 71.3% - were solely

fed and hydrated enterally during high-flow administration and that IV hydration was infrequently used. Most enteral hydration was via an NGT. None of the enterally fed children had a clinical aspiration or other adverse events attributable to enteral hydration.

There are several reasons why NGT feeding was used at a high rate in this study. In the first instance NGT insertion was recommended by the protocol to allow intermittent venting of the stomach. Furthermore, in Australia and New Zealand NGT hydration is used for a variety of conditions in preference to IV fluids, including in bronchiolitis and gastroenteritis,^{5, 6, 15,16,17} and it became obvious very quickly in this study that enteral feeding could be safely conducted during high-flow delivery. A further advantage of hydration via NGT is that fewer attempts are needed in infants with bronchiolitis to achieve successful placement compared to IV insertion.⁵ A concern in NGT placement in children in contrast to adults^{18, 19} is that there is no demonstrated means of reducing the pain and distress associated with NGT insertion.²⁰ Anecdotally, after insertion infants fed via a NGT seem less irritable than IV hydrated infants, without the caloric content provided by formula, though there are no data to support this.

Our study has some limitations. As set out in methods we started collecting feeding data only once a section of the patients had already been enrolled in the trial when the study team realized that these data would be important secondary information. While for the majority of infants only one type of hydration was provided, for some children multiple modalities were used, and sometimes alternating modalities occurred. In addition, we did not record how long

different modalities were used in children who had received more than one modality. In this group of infants it was difficult to determine the predominant feeding modality during high-flow. The protocol recommended to decrease flow rates for feeds; this was proscribed as a safety measure when no data on high flow and feeding were available prior to this study. We did not collect why clinicians chose one modality over another nor if they adhered to the study protocol in terms of reducing high-flow during NGT bolus feeds or oral feeds. We cannot comment specifically on advantages/disadvantages of bolus versus continuous feeds- neither was associated with adverse events. We did not collect details of the type of enterally used fluids.

In conclusion, we aimed to investigate how infants managed on high-flow therapy are hydrated and if enteral feeding, and NGT feeding in particular, is safe during high-flow therapy support. Our data indicates that the vast majority of children with hypoxic respiratory failure in bronchiolitis can be safely fed enterally during the period when they receive high-flow.

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LEGENDS

Figure 1.

Numbers of Infants Who Received High Flow Oxygen via Nasal Cannula and Had Hydration Status Assessed.

Table 1. Baseline Characteristics of Infants with Bronchiolitis Receiving High Flow Therapy

	N=505
Age (months)	5.77±3.59
≤ 3 months no. (%)	151 (29.9)
> 3 to 6 months no. (%)	120 (23.8)
> 6 months no. (%)	234 (46.3)
Weight (kg)	7.32±2.27
Sex female no. (%)	186 (36.8)
Ethnicity	
Caucasian no. (%)	216 (42.8)
Aboriginal/Torres Strait Islander no. (%)	15 (3.0)
Maori/Pacific Islander no. (%)	176 (34.9)
Other/unknown no. (%)	98 (19.4)
Prematurity <37 weeks no (%)	92 (18.2)
Need for neonatal respiratory support no. (%)	69 (13.7)
Oxygen only no. (%)	15 (3.0)
Non-invasive ventilation no. (%)	54 (10.7)
Invasive ventilation no. (%)	15 (3.0)
Previous hospital admissions for respiratory disease postnatal no (%)	122 (24.2)
Intensive care admission for respiratory support no. (%)	25 (5.0)
Invasive ventilation no. (%)	1 (0.2)
Non-invasive ventilation no. (%)	3 (0.6)
High-flow therapy no. (%)	21 (4.2)
Chronic Lung Disease no. (%)	10 (2.0)
Congenital Heart Disease no. (%)	7 (1.4)
Patient history of wheeze no. (%)	110 (21.8)
Family history of asthma no. (%)	227 (45.0)
Family history of allergy no. (%)	99 (19.6)
Currently attending child care no. (%)	64 (12.7)
Viral etiology*	
Respiratory syncytial virus no. (%)	217/393 (55.2)
Other viruses no. (%)	138/393 (35.1)
Multiple viruses no. (%)	99/393 (25.2)
No virus detected on nasopharyngeal aspirate no. (%)	76/393 (19.3)

Plus-minus value denotes means and $\pm$ SD, medium interquartile range (IQR).

*Viral testing was not mandated with lower number of tests overall obtained.

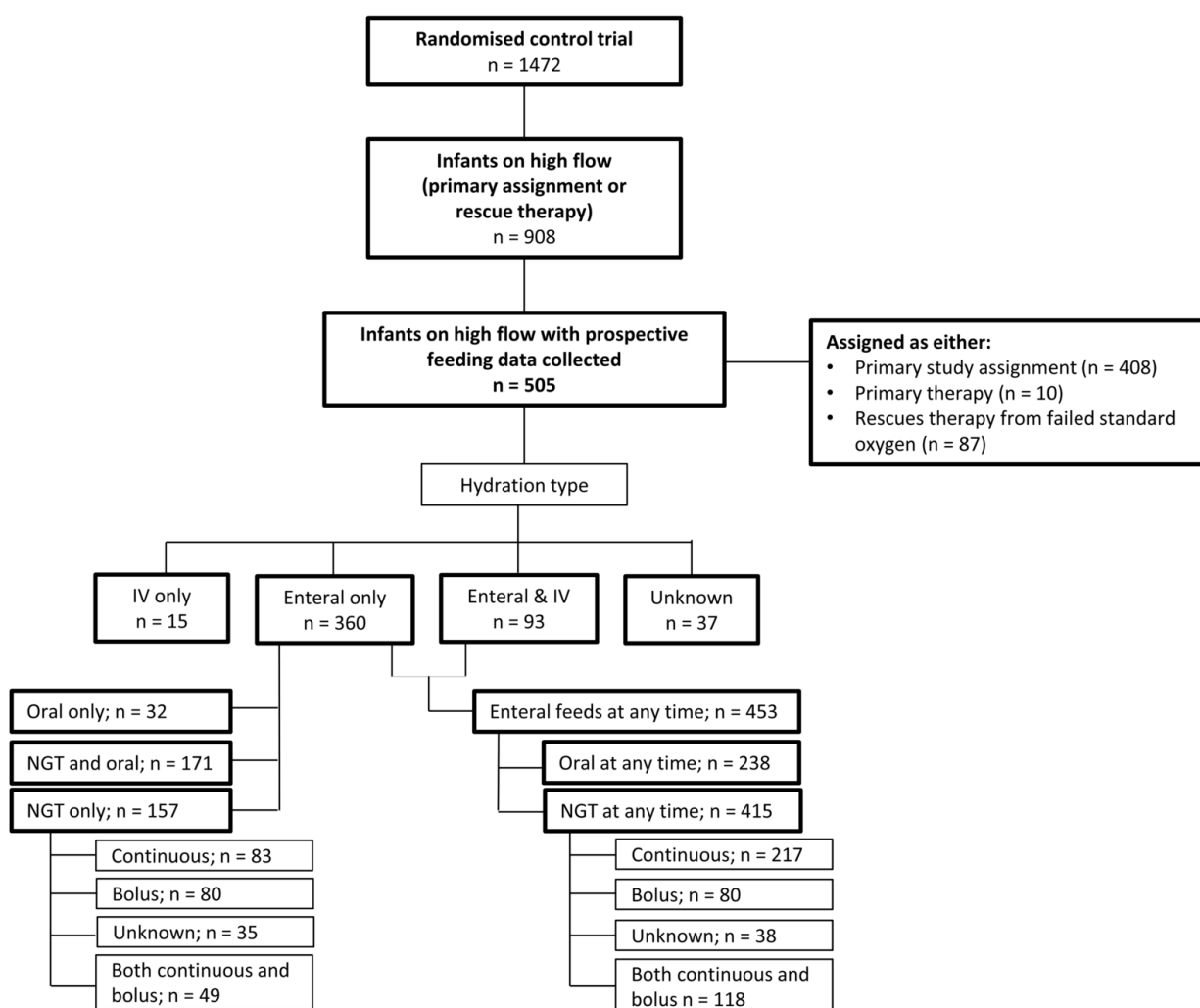
†Multiple options possible

Table 2. Modalities of Hydration in Infants with Bronchiolitis Receiving High Flow

	N=505		
IV fluids only	15 (3.0)		
Enteral fluids only	360 (71.3)		
NGT only	157 (31.1)		
Continuous	83 (16.4)		
Bolus	25 (5.0)		
Both continuous and bolus	49 (9.7)		
Unknown	35 (6.9)		
Oral only	32 (6.3)		
NGT and oral	171 (33.9)		
IV and enteral fluids	93 (18.4)		
Fluid administration unknown	37 (7.3)		
Enteral feeds at any time	453 (89.7)		
NGT at any time	415 (82.2)		
Continuous	217 (43.0)		
Bolus	80 (15.8)		
Both continuous and bolus	118 (23.4)		
Unknown	38 (7.5)		
Oral at any time	248 (49.1)		
Age	NGT only	IV only	Enteral at any time
≤ 3 months no (%)	42/151 (27.8)	8/151 (5.3)	136/151 (90.1)
> 3 to 6 months no (%)	34/120 (28.3)	5/120 (4.2)	106/120 (88.3)
> 6 months no (%)	81/234 (34.6)	2/234 (0.9)	211/234 (90.2)
Adverse events	N=157	N=15	N=453
Serious adverse events no (%)	0	0	0
Pulmonary aspiration no (%)	0	0	0
Pneumothorax no (%)	0	0	1 (0.2)
Emergency intubation no (%)	0	0	0
Cardiac arrest no (%)	0	0	0
Respiratory arrest no (%)	0	0	0
Apneas no (%)	1 (0.6)	1 (6.7)	5 (1.1)

Plus-minus values are means±SD. RSV denotes respiratory syncytial virus. ICU denotes intensive care unit.

[¶]P-value for all subgroup analyses represents test of homogeneity across the odds ratios compared between subgroups



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