

# High-flow warm humidified oxygen versus standard low-flow nasal cannula oxygen for moderate bronchiolitis (HFWHO RCT): an open, phase 4, randomised controlled trial



Elizabeth Kepreotes, Bruce Whitehead, John Attia, Christopher Oldmeadow, Adam Collison, Andrew Searles, Bernadette Goddard, Jodi Hilton, Mark Lee, Joerg Mattes

## Summary

**Background** Bronchiolitis is the most common lung infection in infants and treatment focuses on management of respiratory distress and hypoxia. High-flow warm humidified oxygen (HFWHO) is increasingly used, but has not been rigorously studied in randomised trials. We aimed to examine whether HFWHO provided enhanced respiratory support, thereby shortening time to weaning off oxygen.

**Methods** In this open, phase 4, randomised controlled trial, we recruited children aged less than 24 months with moderate bronchiolitis attending the emergency department of the John Hunter Hospital or the medical unit of the John Hunter Children's Hospital in New South Wales, Australia. Patients were randomly allocated (1:1) via opaque sealed envelopes to HFWHO (maximum flow of 1 L/kg per min to a limit of 20 L/min using 1:1 air–oxygen ratio, resulting in a maximum  $\text{FiO}_2$  of 0.6) or standard therapy (cold wall oxygen 100% via infant nasal cannulae at low flow to a maximum of 2 L/min) using a block size of four and stratifying for gestational age at birth. The primary outcome was time from randomisation to last use of oxygen therapy. All randomised children were included in the primary and secondary safety analyses. This trial is registered with the Australian New Zealand Clinical Trials Registry, number ACTRN12612000685819.

**Findings** From July 16, 2012, to May 1, 2015, we randomly assigned 202 children to either HFWHO (101 children) or standard therapy (101 children). Median time to weaning was 24 h (95% CI 18–28) for standard therapy and 20 h (95% CI 17–34) for HFWHO (hazard ratio [HR] for difference in survival distributions 0.9 [95% CI 0.7–1.2]; log rank  $p=0.61$ ). Fewer children experienced treatment failure on HFWHO (14 [14%]) compared with standard therapy (33 [33%];  $p=0.0016$ ); of these children, those on HFWHO were supported for longer than were those on standard therapy before treatment failure (HR 0.3; 95% CI 0.2–0.6;  $p<0.0001$ ). 20 (61%) of 33 children who experienced treatment failure on standard therapy were rescued with HFWHO. 12 (12%) of children on standard therapy required transfer to the intensive care unit compared with 14 (14%) of those on HFWHO (difference –1%; 95% CI –7 to 16;  $p=0.41$ ). Four adverse events occurred (oxygen desaturation and condensation inhalation in the HFWHO group, and two incidences of oxygen tubing disconnection in the standard therapy group); none resulted in withdrawal from the trial. No oxygen-related serious adverse events occurred. Secondary effectiveness outcomes are reported in the Results section.

**Interpretation** HFWHO did not significantly reduce time on oxygen compared with standard therapy, suggesting that early use of HFWHO does not modify the underlying disease process in moderately severe bronchiolitis. HFWHO might have a role as a rescue therapy to reduce the proportion of children requiring high-cost intensive care.

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## Introduction

High-flow warm humidified oxygen (HFWHO)—also known as high-flow nasal cannula oxygen—in paediatric health care has been investigated in the contexts of neonatal<sup>1</sup> and paediatric intensive care units (ICUs),<sup>2,3</sup> but its safety and efficacy in children have not been established by randomised trials.<sup>4,5</sup> In the neonatal context, a non-inferiority study<sup>1</sup> of HFWHO at 5–8 L/min found the efficacy of HFWHO to be similar to continuous positive airway pressure (CPAP), and a randomised controlled trial<sup>6</sup> showed no difference in the rate of extubation failure between HFWHO and CPAP.

Adult studies<sup>7,8</sup> of HFWHO have also found no difference in various primary outcomes. Intubation rates did not differ in a study<sup>7</sup> of HFWHO versus standard non-rebreather mask oxygen or a combination of non-invasive ventilation and HFWHO in patients with hypoxaemia, but a reduced 90-day mortality was noted in favour of HFWHO. Another study<sup>8</sup> found HFWHO to be non-inferior to bilevel positive airway pressure in prevention of treatment failure after cardiothoracic surgery.

Although observational studies<sup>9,10</sup> and retrospective audits<sup>2,3</sup> suggest promising outcomes from the use of HFWHO in paediatric care, large randomised trials are

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John Hunter Children's Hospital, Newcastle, NSW, Australia (E Kepreotes PhD, B Whitehead MD, B Goddard MAM, J Hilton BMed, M Lee BMed, Prof J Mattes PhD); Priority Research Centre GrowUpWell (E Kepreotes, A Collison PhD, Prof J Mattes) and Faculty of Health (E Kepreotes, B Whitehead, Prof J Attia MD, C Oldmeadow PhD, A Collison, A Searles PhD, B Goddard, J Hilton, M Lee, Prof J Mattes), University of Newcastle, Newcastle, NSW, Australia; John Hunter Hospital, Newcastle, NSW, Australia (Prof J Attia, C Oldmeadow, M Lee); and Hunter Medical Research Institute, Newcastle, NSW, Australia (E Kepreotes, Prof J Attia, C Oldmeadow, A Collison, A Searles, Prof J Mattes)

Correspondence to:  
Dr Elizabeth Kepreotes,  
John Hunter Children's Hospital,  
NSW 2310, Australia  
[Elizabeth.Kepreotes@hnehealth.nsw.gov.au](mailto:Elizabeth.Kepreotes@hnehealth.nsw.gov.au)

### Research in context

#### Evidence before this study

We searched PubMed and MEDLINE for clinical trials published in English between Jan 1, 2000, and July 1, 2016, using the terms “high-flow oxygen”, “infants”, “children”, “p\*ediatrics”, “bronchiolitis”, but could not find randomised trial evidence for the use of high-flow oxygen compared to standard low-flow nasal cannula oxygen. We identified a randomised trial (n=19) comparing variable flow oxygen (4–8 L/min) with headbox oxygen in bronchiolitis through Beggs and colleagues’ Cochrane review, whereas Mayfield and colleagues’ review examining high-flow oxygen in any paediatric context other than bronchiolitis found none. A recent Bangladeshi trial (n=225) compared CPAP, 2 L/kg per min high-flow oxygen, and standard therapy in children with severe pneumonia, but was stopped early because of the significant benefit of CPAP over standard therapy for mortality (three deaths vs ten deaths). Paediatric observational studies and audits suggest that high-flow oxygen is beneficial, and Manley and colleagues were able to show equivalence to CPAP post-extubation of neonates. However, other studies in neonates and adults have found no difference in their primary outcome.

#### Added value of this study

To our knowledge, this study is the first randomised trial to examine HFWHO in a paediatric, ward-based cohort. HFWHO

and standard therapy were both effective when standardised approaches to starting and weaning oxygen were used, and early use of HFWHO did not alter the overall course of the bronchiolitis. HFWHO prevented clinical deterioration in significantly more infants than standard therapy and was able to reverse deterioration in 63% (95% CI 45–77) of the 32% (23–41) of those who were not adequately supported by standard therapy.

#### Implications of all the available evidence

For children with moderate bronchiolitis, HFWHO is safe and effective at 1 L/kg per min (maximum FiO<sub>2</sub> 0.6). For children who are not supported by standard therapy, HFWHO might reduce the need for admission to ICU with substantial cost savings. Whereas observational studies have suggested that HFWHO is more beneficial compared with standard therapy, our study has not shown superiority for the primary endpoint of time on oxygen. Future research is required to test HFWHO as a rescue treatment in bronchiolitis, to test its application to other paediatric respiratory conditions, and to examine the safety and effectiveness of standardised procedures for starting and weaning of oxygen with economic outcomes.

CPAP=continuous positive airway pressure. HFWHO=high-flow warm humidified oxygen.

needed to provide evidence of superior safety and efficacy.<sup>4,5,11,12</sup> A Bangladeshi randomised trial<sup>13</sup> (n=225) compared CPAP, 2 L/kg per min high-flow oxygen, and standard therapy in children aged less than 5 years with severe pneumonia, but was stopped early due to increased mortality in the standard therapy group (ten deaths) compared with the CPAP group (three deaths).

To address the insufficiency of evidence surrounding the safety and effectiveness of high-flow oxygen in paediatric health care, we conducted a pragmatic randomised controlled trial<sup>14</sup> designed to provide clinical guidance for the care of children with moderate bronchiolitis hospitalised for supplemental oxygen therapy. Bronchiolitis is a major contributor to paediatric and intensive-care admission rates each year. With only supportive treatment options available<sup>15–17</sup> and a mortality rate in children aged under 5 years estimated at 199 000 per year globally for respiratory syncytial virus (RSV) alone,<sup>16</sup> a large proportion of children with bronchiolitis rely on the optimal delivery of supplemental oxygen as mainstay therapy.

The aim of our study was to examine whether HFWHO provided enhanced respiratory support as evidenced by a reduction in time to weaning off oxygen, hypothesising that HFWHO might increase the alveolar surface area, improve ventilation–perfusion mismatch, and reduce ventilation inhomogeneities.

## Methods

### Study design

We conducted an open, phase 4, randomised controlled trial from July 16, 2012, to May 1, 2015, in the emergency department of the John Hunter Hospital and the medical unit of the John Hunter Children’s Hospital in the Hunter New England Local Health District of New South Wales (NSW), Australia. This health district has a catchment area similar in size to England and serves approximately 900 000 people. The John Hunter Children’s Hospital is co-located with the adult John Hunter Hospital and is the only tertiary paediatric referral hospital in the Hunter New England Local Health District. The John Hunter Hospital Emergency Department assesses approximately 20 000 paediatric cases each year. The study was approved by the Human Research Ethics Committees of the Hunter New England Local Health District and the University of Newcastle, NSW. A trial steering committee comprising executive and senior members of the two clinical areas of paediatrics and emergency medicine supervised the conduct of the trial. The Trial Steering Committee and the larger Clinical Advisory Group met monthly in the first year of the trial and then quarterly or as required until the end of the trial.

An economic cost estimate has been calculated by an independent senior health economist from the Clinical Research Design, Information Technology, and Statistical

For the study protocol see [http://www.hnekidshealth.nsw.gov.au/client\\_images/1871628.pdf](http://www.hnekidshealth.nsw.gov.au/client_images/1871628.pdf)

Support (CReDITSS) Unit, Hunter Medical Research Institute (HMRI), Newcastle, NSW.

### Patients

Children aged less than 24 months presenting to the emergency department or admitted to the ward were eligible for inclusion if they had a clinical diagnosis of bronchiolitis that was assessed as being of moderate severity using the NSW Health clinical practice guideline<sup>15</sup> and required supplemental oxygen. Infants with chronic neonatal lung disease on home oxygen could be included, but they were weaned to their home oxygen rate rather than to room air. Children with severe or life-threatening bronchiolitis were excluded because low-flow oxygen is not part of standard care for these patients.

The following exclusion criteria were applied: children with mild bronchiolitis not requiring oxygen (although they could be enrolled if their condition deteriorated and oxygen was required after admission); children with severe or life-threatening bronchiolitis as defined by NSW Health<sup>15</sup> including any of the following: a witnessed apnoea, severe tachypnoea (>70 breaths per min) or bradypnoea (<30 breaths per min), moderate–severe grunting, cyanosis, or pallor; peripheral capillary oxygen saturation (SpO<sub>2</sub>) less than 90% on room air or less than 92% on 2 L/min oxygen via nasal cannulae (standard therapy), or marked tachycardia (>180 beats per min) or bradycardia (<100 beats per min); children admitted to the ward after ICU management; children transferred from other facilities if they had received supplemental oxygen prior to arrival; a known diagnosis of asthma; or the presence of pneumothorax or nasal trauma.

Written informed consent was obtained from the parents or legal guardians of all children prior to randomisation.

### Randomisation and masking

After obtaining consent either in the emergency department or the medical unit, we randomly allocated (1:1) the patients using a block size of four and stratification for gestational age at birth<sup>16,17</sup> using three strata: extreme prematurity of 28 weeks or less, premature (from 28 weeks and 1 day to 36 weeks and 6 days), and term of 37 weeks or more. Allocation was concealed in opaque sealed envelopes. The lead investigator (E Kepreotes) generated and stored the allocation sequence. Children who were medically assessed as requiring oxygen (with at least one of the following: abnormal heart rate, abnormal respiratory rate, decreased oxygen saturation, or increased work of breathing) were started on maximum standard therapy using 2 L/min cold nasal cannula wall oxygen while further clinical assessment, eligibility assessment, and written informed consent were attended. The children were then randomly assigned according to gestational age to either standard therapy or HFWHO by a member of the research team or by the medical registrar. Masking of the allocation was not possible due to obvious visual differences between the two modes of oxygen delivery.

### Procedures

Standard therapy incorporated cold wall oxygen 100% via infant nasal cannulae at low-flow to a maximum of 2 L/min. This approach has been practised in Australian hospitals for more than 20 years and is considered standard therapy in most developed countries. Estimates of standard therapy FiO<sub>2</sub> are difficult to establish in children but a range of 0.30–0.38<sup>18</sup> was reported in healthy adults. The emergency department does not add humidification to standard therapy but the wards use Aquapak (Hudson RCI301; Hudson RCI Teleflex; Temecula, CA, USA) bubble humidifiers to add moisture to the cold wall gas by bubbling it through sterile water before it reaches the patient.

In the experimental arm, HFWHO was delivered via age-appropriate Optiflow Junior nasal cannulae and the MR850 humidifier (Fisher and Paykel Healthcare; Auckland, New Zealand) using a maximum flow of 1 L/kg per min to a limit of 20 L/min using 1:1 air–oxygen ratio, resulting in a maximum FiO<sub>2</sub> of 0.6. The Optiflow Junior nasal cannulae allowed all children in the experimental arm to start on a flow of 1 L/kg per min.

The need for supplemental oxygen was identified by an infant's appearance, work of breathing, heart rate, respiratory rate, SpO<sub>2</sub>, and ability to feed. These data contributed to a holistic severity assessment (appendix p 1).

For SpO<sub>2</sub>, a reading of 94% or less indicated the need for additional oxygen, accounting for the reported range of oximeter error (>90% ± 2–3% and ≤90% ± 5%)<sup>19</sup> and the normative SpO<sub>2</sub> range for healthy infants.<sup>20</sup> Both treatment arms were started at maximum therapy, which continued for a minimum of 3 h, and children were nursed nil by mouth for the first hour on their allocated treatment. All children were monitored for heart rate and SpO<sub>2</sub> and all had a nasopharyngeal aspirate collected and nasal hygiene attended prior to starting the initial nasal cannula oxygen as per standard care.

Weaning of oxygen was permitted after 3 h on maximum therapy and was done using a novel dose-finding procedure that incorporated the track-and-trigger standard paediatric observation charts (SPOCs; appendix pp 2–3) developed by the NSW Ministry of Health Clinical Excellence Commission in 2011 for the Between the Flags<sup>21,22</sup> project. These colour-coded observation charts show trend data that prompt a clinical response when deterioration is detected by charted observations falling into a yellow zone (at risk: request a clinical review within 30 min) or red zone (critical: call a rapid response for ICU assessment within 10 min). The procedure for starting and weaning of oxygen (appendix pp 4–6) was developed for this trial to standardise clinical practice and to reduce the risk of performance bias in view of the inability to conceal the allocated therapy. Clinicians were trained in the new weaning procedure and in recognising and responding to any clinical deterioration experienced by the study

See Online for appendix

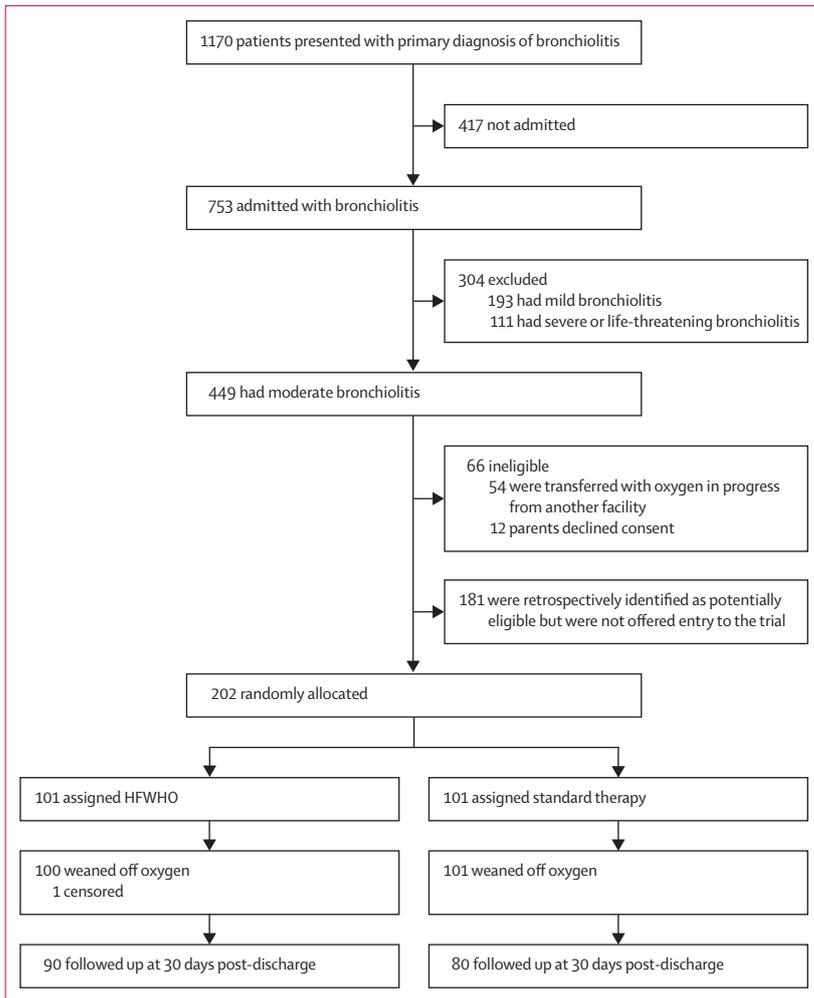


Figure 1: Trial profile

participants. This training involved a daily visit to the emergency department and ward by the lead investigator and other researchers (B Goddard, M Kepreotes, L Jenkinson, and N Lacey), and planned group education sessions with treating physicians, nurses, advanced trainees, registrars, and junior medical officers.

Escalation procedures were also developed using SPOCs and state policy.<sup>22</sup> Treatment failure was defined as critically abnormal observations that fell within the red zone on an age-appropriate SPOC for heart rate (age dependent), respiratory rate (age dependent), SpO<sub>2</sub> (<90%), or respiratory distress score (severe) while on maximum therapy, along with a clinical decision by the treating physician or medical delegate that the current treatment was insufficient to reverse the deterioration. Red zone observations required a mandated rapid response within 10 min by the ICU team.

The study protocol stated that children who deteriorated on standard therapy could trial HFWHO at

1 L/kg per min as a rescue therapy in the ward, or transfer to ICU on critical care HFWHO at 2 L/kg per min (variable FiO<sub>2</sub>), CPAP, or intermittent positive pressure ventilation depending on the clinical need. HFWHO could escalate to critical care HFWHO, CPAP, or intermittent positive pressure ventilation in the ICU.

We performed RSV direct immunofluorescence on nasopharyngeal aspirate samples from all children as standard care. We then used Multiplex10 PCR (AusDiagnostics; Beaconsfield, NSW, Australia) to screen for the respiratory viruses influenza A, influenza B, RSV, human metapneumovirus, adenovirus, picornavirus (rhinovirus), enterovirus, and parainfluenza virus type 1, 2, and 3 in children with sufficient nasopharyngeal aspirate for extended testing.

We carried out follow-up phone interviews with parents or carers 30 days after discharge.

### Outcomes

We chose time to weaning off oxygen as a pragmatic primary outcome for both clinicians and parents or carers who were invested in having children stabilised, recovered, and discharged as quickly as possible. We defined time to weaning off oxygen as the time from randomisation to the first sustained room-air observation after oxygen—ie, the first observation recorded in room air with no further need for subsequent supplemental oxygen. The protocol stated that death, transfer to another hospital, or withdrawal from the study by the consenting parent or carer would result in the infant being censored at the time of the event.

Secondary safety outcomes were time from randomisation to treatment failure, proportion of treatment failure, proportion of serious adverse events, and transfer to ICU. Secondary effectiveness outcomes were length of hospital stay, and baseline-adjusted heart rate and respiratory rate at 4 h and 24 h. Parent-reported outcomes collected through the follow-up phone interviews were assessed for any delayed serious adverse events, subsequent medical care, parental concern with the oxygen therapy, and parental rating of their child's comfort, ability to feed, and sleep quality on the allocated treatment using a five-point Likert scale.

Full outcome data were not available until the final analysis. An a-priori interim analysis of the primary and supporting safety outcomes was attended at the end of the second winter season with 93 of 202 recruitments. Stopping rules were to be applied only for significant harm, but the threshold was not reached.

### Statistical analysis

We determined that a total study sample size of 202 children would be required, randomised 1:1 to standard therapy or HFWHO, to provide 80% power to reject the null hypothesis that no difference existed between the two treatment arms in survival distributions for time to successful weaning from oxygen, with a two-sided type 1

error of 5%. This calculation assumed a median time on oxygen of 38 h for children on standard therapy (based on historical data from 160 children aged <24 months consecutively admitted to John Hunter Children's Hospital with moderate bronchiolitis requiring standard oxygen therapy in 2007) and that the HFWHO treatment would reduce this to 26 h. The sample was inflated by 5% to allow for attrition. All randomised children were included in the primary and secondary safety analyses.

Patient characteristics are presented as frequencies and percentages for categorical data and means (SD) or medians (IQR) for continuous data. The primary analysis of all outcomes followed the intention-to-treat (ITT) principle. For our primary and secondary safety outcomes, we also present results from a per-protocol analysis, from which children whose management violated protocol were excluded. For the primary outcome, Kaplan-Meier estimates of the survival distributions are graphed over the period of time on oxygen, and compared between treatment groups using the log-rank test. Median survival times are presented for each treatment group with 95% CIs (obtained using Greenwood's formula) and treatment effects are presented as hazard ratios (HRs) with 95% Wald CIs estimated from a Cox-proportional hazard model.

We analysed ten secondary outcomes selected a priori. Time to treatment failure was summarised using 24 h event-free survival and compared between groups using the same method as time to weaning off oxygen. The distributions of length of stay were compared between treatment groups using Mann-Whitney *U* tests. We compared differences in the proportion with an adverse event using Pearson's  $\chi^2$  test, with 95% (asymptotic) CIs for these differences. We compared baseline-adjusted differences in respiratory rate and heart rate between treatment groups at 4 h and 24 h post-baseline using linear mixed models, with fixed effects for the baseline value of the outcome, treatment group, time and their interaction, and random subject-level intercepts. *p* values and 95% CIs for the between-group differences are presented at each timepoint.

The 30-day follow-up of the parent-reported outcomes of comfort and ability to feed and sleep were scored on a five-point Likert scale and compared between treatment groups using Mann-Whitney *U* tests. A two-tailed *p* value less than 0.05 was considered to be statistically significant for the primary outcome, and a Bonferroni corrected threshold of 0.005 was used for the ten secondary outcomes. All statistical analyses were done by an independent senior statistician from CReDITSS, HMRI, and programmed using SAS version 9.4 (SAS Institute, Cary, NC, USA). This trial is registered with the Australian New Zealand Clinical Trials Registry, number ACTRN12612000685819.

#### Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or

writing of the report. The manufacturers of equipment used in this trial had no involvement in its design or conduct. All equipment used was purchased at market

	Standard therapy (n=101)	HFWHO (n=101)
Sex		
Male	75 (74%)	63 (62%)
Female	26 (26%)	38 (38%)
Median age (months)	5.0 (3.0-10.0)	6.0 (3.0-10.0)
Age (stratified)		
≤1 month	12 (12%)	12 (12%)
1.1-12 months	73 (72%)	72 (71%)
12.1-24 months	16 (16%)	17 (17%)
Gestational age at birth		
Extremely premature (≤28 weeks)	3 (3%)	4 (4%)
Premature (28 weeks and 1 day to 36 weeks and 6 days)	13 (13%)	17 (17%)
Term (≥37 weeks)	85 (84%)	80 (79%)
Ethnic background		
Indigenous Australian	8 (8%)	10 (10%)
Other	93 (92%)	91 (90%)
Weight (kg)	7.9 (6.1-9.3)	8.0 (5.8-10.8)
Baseline heart rate (beats per min)*	159 (17)	163 (18)
Baseline respiratory rate (breaths per min)*	55 (11)	56 (12)
Baseline SpO <sub>2</sub> *	96% (93-98)	96% (94-98)
Baseline M-WCAS*	2.6 (0.9)	2.6 (0.9)
Viral infections		
Concurrent infections		
0	3 (3%)	3 (3%)
1	68 (67%)	74 (73%)
2	26 (26%)	20 (20%)
3	3 (3%)	4 (4%)
4	1 (1%)	0
Viruses detected†		
RSV	54 (53%)	62 (61%)
Rhinovirus	55 (54%)	40 (40%)
Adenovirus	8 (8%)	12 (12%)
Human metapneumovirus	10 (10%)	8 (8%)
Parainfluenza 2	0	1 (1%)
Parainfluenza 3	3 (3%)	3 (3%)
Influenza A	2 (2%)	0
Influenza B	1 (1%)	0
Ever breastfed		
No	26 (26%)	27 (27%)
Yes	70 (69%)	64 (63%)
Data missing	5 (5%)	10 (10%)
Current tobacco smoke exposure		
No	63 (62%)	65 (64%)
Yes	35 (35%)	25 (25%)
Data missing	3 (3%)	11 (11%)

(Table 1 continues on next page)

	Standard therapy (n=101)	HFWHO (n=101)
(Continued from previous page)		
Comorbidity‡	2 (2%)	8 (8%)
Maternal asthma		
No	53 (52%)	52 (51%)
Yes	42 (42%)	34 (34%)
Data missing	6 (6%)	15 (15%)
Caesarean birth	20 (20%)	11 (11%)
Season admitted		
Winter	44 (44%)	44 (44%)
Autumn	30 (30%)	30 (30%)
Spring	14 (14%)	17 (17%)
Summer	13 (13%)	10 (10%)
Day of illness	4·0 (3·0–5·0)	4·0 (3·0–5·0)

Data are mean (SD), median (IQR), or n (%). HFWHO=high-flow warm humidified oxygen. SpO<sub>2</sub>= peripheral capillary oxygen saturation. M-WCAS=Modified Woods Clinical Asthma Score. \*Baseline observation in room air. †Detected with Multiplex10 PCR. ‡Comorbid conditions were chronic neonatal lung disease, ventricular hypertrophy, pulmonary stenosis, chromosome 5 deletion, laryngomalacia, and neurological insult from an acute life-threatening event.

**Table 1: Baseline characteristics of participants according to allocation**

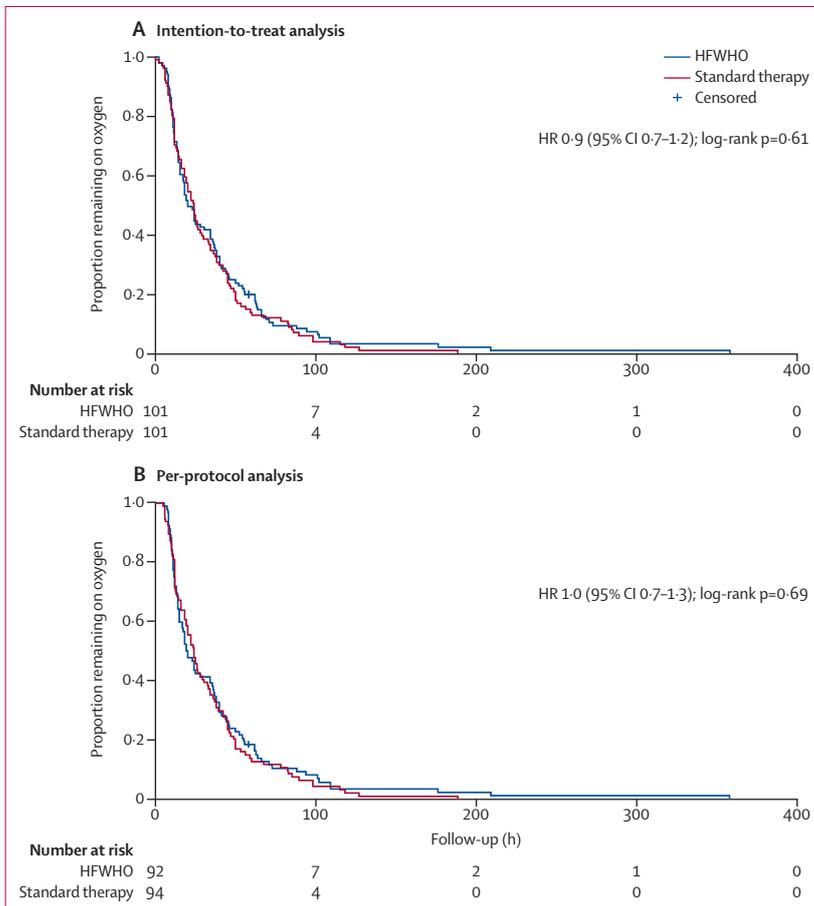
value. The corresponding author had access to all the data in the study and had final responsibility for the decision to submit for publication.

**Results**

From July 16, 2012, to May 1, 2015, 1170 children aged less than 24 months presented to the emergency department with a primary diagnosis of bronchiolitis and 753 were admitted for management (figure 1). Of those admitted, 449 had moderate bronchiolitis requiring supplemental oxygen and 395 were eligible for inclusion in the study, with 54 ineligible due to being transferred from other sites with oxygen in progress. Parents of 12 children declined consent. 202 children were randomly assigned to HFWHO or standard therapy, with 101 in each group, and all included in the primary analysis. We retrospectively identified 181 children who appeared eligible but were not offered the trial for reasons unknown—probably because of staffing or acuity pressures in the emergency department. This missed population had similar descriptive characteristics for sex, age, and month admitted to those in the trial. No infant died or was withdrawn from the study. One infant was censored for the primary outcome after being transferred to another ICU because of bed shortages, but was counted as a treatment failure for the secondary outcomes. The last patient was followed up on June 6, 2015. Baseline characteristics of the 202 children seemed balanced between groups (table 1).

Emergency department staff collected nasopharyngeal aspirate samples from all 202 children (table 1). Results ranged from no virus detected (six; 3%) to four concurrent infections (one; <1%), with RSV detected in 116 (57%) nasopharyngeal aspirate samples, rhinovirus in 95 (47%) samples, and more than one infection identified in 54 (27%) patients. Multiplex10 PCR was done in 193 (96%) children, and detected adenovirus (20; 10%), human metapneumovirus (18; 9%), parainfluenza 2 (one; <1%), parainfluenza 3 (six; 3%), influenza A (two; 1%), and influenza B (one; <1%; table 1).

Time to weaning off oxygen did not differ significantly between the standard therapy group (24·0 h [95% CI 18–28]) and the HFWHO group (20·0 h [17–34]; HR 0·93 [95% CI 0·7–1·2]; p=0·61; figure 2, table 2). Per-protocol results (n=186) were similar to those for the ITT population. At no point had 50% of the children in either group experienced treatment failure, making calculation of median time to treatment failure impossible; therefore, we used 24 h event-free survival to summarise the proportion of children who survived 24 h without experiencing treatment failure. 90% (95% CI 80–100) of the HFWHO group remained free from treatment failure at 24 h compared with 60% (50–70) of the standard therapy group. The difference in survival distributions for time to treatment failure was statistically significant and favoured the HFWHO group (HR 0·3 [95% CI 0·2–0·6]; p<0·0001). The per-protocol analysis was similar (figure 3).



**Figure 2: Comparison of time on oxygen between treatment groups using (A) intention-to-treat and (B) per-protocol analyses**

The proportion of children who experienced treatment failure was higher in the standard therapy group than in the HFWHO group (table 2). Of the 33 children who were not supported by standard therapy, one child became distressed and did not tolerate having standard therapy in place; her observations subsequently stabilised on room air while being assessed for HFWHO. The 32 remaining children trialled HFWHO as a rescue therapy following deterioration. 12 of these children required transfer to ICU after further deterioration, whereas HFWHO reversed the deterioration of the other 20 children who stayed in the ward.

Of 14 children who had treatment failure on HFWHO, 13 required transfer to the John Hunter Hospital ICU and one was transferred to a Sydney ICU where she recovered on bubble-CPAP. The ICU admission rate was therefore 13% (n=26; episodes of treatment failure described in appendix p 7).

No serious oxygen-related adverse events such as pneumothorax, pressure injuries, or bleeding occurred, and no child died. Four adverse events were recorded, with two in each group. In the HFWHO group, one infant was found to have only room air connected to the humidifier, resulting in a brief period of oxygen desaturation. Another infant inhaled condensation from the circuit during transfer from the emergency department to the ward. This infant was changed onto standard therapy at the request of the parent, but was not withdrawn from the trial and recovered without further incident on standard therapy. Two children on standard therapy experienced oxygen tubing disconnection from the wall outlet resulting in brief periods of agitation before their oxygen tubing was reconnected.

The per-protocol population for time to weaning consisted of 186 children after 16 exclusions (seven standard therapy, nine HFWHO). The following violations occurred: 13 children did not have responsive oxygen weaning as per procedure with three children not tolerating their assigned therapy (one standard therapy, two HFWHO), two had severe or life-threatening bronchiolitis at the time of randomisation (HFWHO), and one child was randomised to standard therapy but oxygen therapy was not started.

The per-protocol population for time to treatment failure consisted of 196 children after six exclusions (four standard therapy, two HFWHO). The following violations occurred: three children did not meet treatment failure criteria, two had severe bronchiolitis at randomisation (HFWHO), and one was not started on maximum standard therapy.

Of the 26 children who required admission to ICU with deterioration to severe bronchiolitis, 18 (69%) had RSV detected in their nasopharyngeal aspirate sample, suggesting that RSV continues to contribute to a more severe form of the infection, as previously reported.<sup>23</sup>

For our health economics estimate, we compared standard therapy (ITT if crossover had not been allowed)

	Standard therapy	HFWHO	p value	Hazard ratio (HR) or difference
<b>Time to oxygen weaning (h; median)</b>				
ITT (n=202)	24.0 (18.0–28.0)	20.0 (17.0–34.0)	0.61	HR 0.9 (0.7–1.2)
Per-protocol (n=186)	24.0 (19.0–30.0)	19.5 (15.0–34.0)	0.69	HR 1.0 (0.7–1.3)
<b>Time to treatment failure (proportion with 24 h event-free survival)</b>				
ITT (n=202)	0.6 (0.5–0.7)	0.9 (0.8–1.0)	<0.0001	HR 0.3 (0.2–0.6)
Per-protocol (n=196)	0.6 (0.5–0.8)	0.9 (0.9–1.0)	<0.0001	HR 0.3 (0.2–0.6)
<b>Length of stay (days; median)</b>				
ITT (n=202)	2.0 (1.0–3.0)*	2.0 (1.0–3.0)*	0.99	..
<b>Treatment failure and care escalation, ITT (n; %)</b>				
Treatment failure (ITT, n=202)	33 (33%)	14 (14%)	0.0016	19% (8–30)
Crossover†	32 (32%)	1 (1%)	<0.0001	31% (17–44)
Rescued‡	20 (20%)	..	..	..
ICU transfer†	12 (12%)	14 (14%)‡	0.41	–1% (–7 to 16)
<b>Adverse events</b>				
Any	2	2	..	..
Serious	0	0	..	..
<b>Heart rate (baseline-adjusted beats per min; mean)</b>				
4 h (n=202)	–16.8 (–21.2 to –12.4)	–21.5 (–25.5 to –17.5)	0.40	2.0 (–2.6 to 6.5)
24 h (n=202)	–23.0 (–27.1 to –19.0)	–27.0 (–31.1 to –22.9)	0.59	1.3 (–3.3 to 5.8)
<b>Respiratory rate (baseline-adjusted breaths per min; mean)</b>				
4 h (n=202)	–11.3 (–13.8 to –8.8)	–9.1 (–11.6 to –6.5)	0.0208	–3.0 (–5.5 to –0.5)
24 h (n=202)	–13.5 (–16.0 to –10.9)	–12.9 (–15.7 to –10.0)	0.28	–1.4 (–3.9 to 1.2)
<b>Comfort score (median)</b>				
mITT (n=170)	3 (3–4)*	4 (3–4)*	0.0170	..
<b>Sleep score (median)</b>				
mITT (n=170)	3 (3–4)*	4 (3–4)*	0.08	..
<b>Feeding score (median)</b>				
mITT (n=170)	3 (2–4)*	4 (3–4)*	0.0100	..

Ranges in parentheses are 95% CIs unless otherwise stated. Comfort, sleep, and feeding are scored on 5-point Likert scale. ITT=intention to treat. ICU=intensive care unit. mITT=modified ITT (ITT analysis of 170 children whose parents were available for follow-up 30 days after discharge). \*IQR. †Included in treatment failure. ‡Including the child who was transferred to another ICU.

**Table 2: Primary and secondary outcomes**

with HFWHO (ITT) and standard therapy (allowing for HFWHO crossover). The costing used the Australian National Weighted Activity Units defined by the Independent Hospitals Pricing Authority.<sup>24</sup> We assumed that emergency department, ward, and ICU care-related costs per patient were similar in both arms, given the results. The cost differential for consumables favoured standard therapy, with each HFWHO circuit and nasal cannulae costing AU\$80 per week per infant compared with \$5 per week per infant for the standard therapy nasal cannulae and Aquapak. However, in the ITT analysis, HFWHO resulted in 19 fewer treatment failures compared with standard therapy. After accounting for consumable costs and any ICU stay, standard therapy (ITT if HFWHO crossover had not been allowed) would have required additional resources valued at \$300048 (95% CI 207698–373635). By comparison, HFWHO

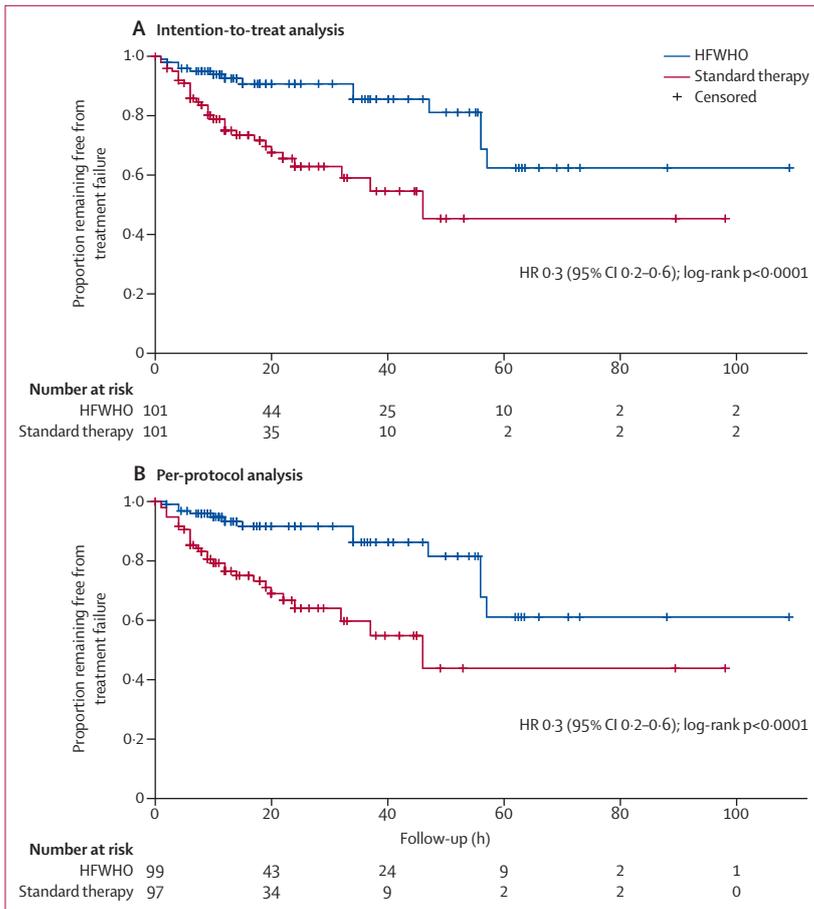


Figure 3: Comparison of time to treatment failure between treatment groups using (A) intention-to-treat and (B) per-protocol analyses

(ITT) required fewer resources at \$135 513 (73 171–196 937) as did standard therapy (allowing HFWHO crossover) at \$111 990 (52 754–170 648; appendix pp 8–9).

Other secondary outcomes are presented in table 2 and reported in the appendix (pp 10–12). Tertiary outcomes from virology, diagnostic, and detailed health economic analyses will be reported separately.

**Discussion**

In this single-centre, open, randomised controlled trial, we found no evidence of a difference in the survival distributions for time to weaning off oxygen between HFWHO and standard therapy for children aged less than 24 months with moderate bronchiolitis. This primary outcome was inclusive of treatment failure and any time spent in ICU, and crossover to HFWHO was included in both the ITT and per-protocol analyses. We found statistically significant and clinically important effects of HFWHO in delaying the time to treatment failure and reducing the number of children who experienced treatment failure. These effects were observed after the significance threshold was adjusted

to 0.005 for the ten a-priori secondary analyses to constrain the chance of false-positive results.

Treatment failure criteria were defined objectively, but the treating physician or medical delegate had to make the decision that the allocated therapy was insufficient to reverse clinical deterioration. This requirement ensured accountability of medical decision making and safeguarded a vulnerable study population randomised to an experimental treatment. It did, however, introduce the risk of performance bias in view of the study being unmasked. To mitigate this risk, we did per-protocol analyses of the primary and safety outcomes, which supported the ITT analysis.

The study protocol allowed HFWHO to be used as rescue therapy as an alternative to escalating to non-invasive ventilation and ICU transfer for those children who deteriorated and met the criteria for treatment failure on standard therapy. This decision was based on the established but untested practice of the ICU response team, who were independent of this study, to start HFWHO or critical care HFWHO on the ward while awaiting transfer to ICU. 20 (63%) of 32 children who deteriorated on standard therapy and trialled HFWHO as a rescue therapy did so successfully and avoided transfer to ICU. Although secondary outcomes need to be interpreted with caution, both the reduction in treatment failure observed in the experimental HFWHO study arm and the potential of HFWHO to rescue infants who deteriorate on standard therapy have important implications for practice. Our study suggests that, if used as a rescue therapy for children who are not adequately supported by standard therapy, HFWHO might reduce the proportion of children who require high-cost intensive care.

In our trial, the bed-day costs were equivalent in both arms, whereas the consumables cost of HFWHO was 16 times that of standard therapy. Overall, the least resources were consumed by standard therapy with crossover to HFWHO allowed, followed by HFWHO (ITT), then standard therapy (ITT) if HFWHO crossover had not been allowed.

Notably, we found a reduction in median time on oxygen in both study arms (20 h for HFWHO and 24 h for standard therapy) when compared with our historical 2007 data (38 h) when only standard therapy was available. This reduction suggests that, whether on standard therapy or HFWHO, the holistic assessment of severity and the standardised, responsive approach to oxygen administration employed in this trial might have the greatest potential for cost reduction. The safety of our oxygen procedures is also inferred by low readmission rates (two children readmitted within 24 h of discharge, four children within 72 h, and 12 children within 28 days of discharge).

The criteria for oxygen supplementation requirements and the assessment of bronchiolitis severity differ around the world.<sup>25</sup> Australian guidelines recommend

supplemental oxygen therapy for oxygen saturations of 94% or less,<sup>15</sup> in line with the Scottish Intercollegiate Guidelines Network of the UK,<sup>26</sup> whereas the American Academy of Pediatrics<sup>17</sup> recommends a threshold of less than 90%.

We used the bronchiolitis-validated Modified Woods Clinical Asthma Score<sup>27</sup> to draw a baseline comparison with the NSW consensus-based bronchiolitis assessment guideline<sup>15</sup> used in this study (appendix p 13). This comparison indicated that our study cohort fell within the moderate range on the Modified Woods Clinical Asthma Score. This result supports the assertion that oxygen saturation in isolation is a poor predictor of bronchiolitis severity,<sup>16,28,29</sup> and suggests that the higher oxygen saturation threshold used in this study does not reflect a cohort with milder bronchiolitis. In fact, this study's mean baseline (triage) SpO<sub>2</sub> measurements are lower than those reported by Schuh and colleagues<sup>29</sup> and similar to those reported by Cunningham and colleagues.<sup>30</sup>

This clinical trial is the first we know to examine HFWHO compared with standard nasal cannula oxygen in a large cohort of children with moderate bronchiolitis who were assessed as requiring oxygen in emergency department and ward settings. Its strengths include a pragmatic, inclusive design, and standardised clinical procedures that embed policy to increase the safety and effectiveness of care across multiple clinical settings. Importantly, we obtained parent-reported outcomes to capture the user experience of the different therapies and found that parents and carers favoured HFWHO for ability to feed and overall comfort. Study limitations include the trial being a single-centre study, which might reduce the generalisability of the findings, and our inability to blind the allocation of the two oxygen delivery modes, introducing the risk of performance bias. To mitigate these limitations, we developed clearly defined study procedures and conducted per-protocol analyses. We were not always able to contact parents 30 days after discharge, but parent-reported outcomes were obtained at the earliest opportunity after this date.

The study procedures, appropriate to both standard therapy and HFWHO, have translated into sustained clinical improvement in oxygen management and care in our hospital, regardless of any treatment differences. Further testing of these procedures and the role of HFWHO as a rescue therapy represent potential future research directions, along with testing of HFWHO in other paediatric populations. Our findings are applicable to other emergency department and paediatric ward-based populations of children with moderate bronchiolitis.

In conclusion, this study did not detect a difference in time on oxygen when HFWHO was compared with standard therapy, which suggests that early use of HFWHO does not modify the underlying disease process in moderately severe bronchiolitis. However, HFWHO proved to be safe at the conservative flows and FiO<sub>2</sub> used

in this study, and its use prevented intensive care admission in some children for whom standard therapy failed. We caution against the routine use of higher flows or higher FiO<sub>2</sub> in paediatric wards in the absence of trial evidence of safety and effectiveness. This study provides evidence for the use of HFWHO at a maximum of 1 L/kg per min (FiO<sub>2</sub> 0.6) in the management of children with bronchiolitis of moderate severity for whom standard therapy with oxygen at 2 L/min has failed or have used HFWHO from the outset.

#### Contributors

EK was the lead investigator and was responsible for the concept outline, study design, protocol development, ethics application, funding applications, team meetings and minutes, generation of the randomisation sequences, data collection, data interpretation, authorship of the first draft of the manuscript, and all critical reviews of the manuscript. BW supervised the trial management (John Hunter Children's Hospital) and contributed to the study design, protocol development, data interpretation, and critical reviews of the manuscript. JA advised on the study design, calculated the sample size, supervised the analysis, and provided data interpretation and critical review of the manuscript. CO performed the statistical analysis and generated the tables. AC was responsible for the processing and secure storage of re-identifiable bio-specimens and manuscript review. AS provided economic analyses and reviewed the manuscript. BG assisted with trial management, staff education, writing of the standard operating procedures, recruitment, and manuscript review. JH assisted with study design, data collection, and manuscript review. ML assisted with study design and provided trial oversight in the John Hunter Hospital Emergency Department. JM supervised laboratory staff, contributed to the study design, provided trial oversight, collected lung ultrasound data, analysed and interpreted the study data, and contributed to the authorship and all critical reviews of the manuscript.

#### Declarations of interests

We declare no competing interests.

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#### References

- 1 Manley BJ, Owen LS, Doyle LW, et al. High-flow nasal cannulae in very preterm infants after extubation. *N Engl J Med* 2013; **369**: 1425–33.
- 2 Schibler A, Pham T, Dunster K, et al. Reduced intubation rates for infants after introduction of high-flow nasal prong oxygen delivery. *Intensive Care Med* 2011; **37**: 847–52.

- 3 McKiernan C, Chua LC, Visintainer PF, Allen H. High flow nasal cannulae therapy in infants with bronchiolitis. *J Pediatr* 2010; **156**: 634–38.
- 4 Beggs S, Wong ZH, Kaul S, Ogden KJ, Walters JA. High-flow nasal cannula therapy for infants with bronchiolitis. *Cochrane Database Syst Rev* 2014; **1**: CD009609.
- 5 Mayfield S, Jauncey-Cooke J, Hough J, Schibler A, Gibbons K, Bogossian F. High-flow nasal cannula therapy for respiratory support in children. *Cochrane Database Syst Rev* 2014; **3**: CD009850.
- 6 Collins CL, Holberton JR, Barfield C, Davis PG. A randomized controlled trial to compare heated humidified high-flow nasal cannulae with nasal continuous positive airway pressure postextubation in premature infants. *J Pediatr* 2013; **162**: 949–54.
- 7 Frat J-P, Thille AW, Mercat A, et al. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. *N Engl J Med* 2015; **372**: 2185–96.
- 8 Stéphan F, Barrucand B, Petit P, et al. High-flow nasal oxygen vs noninvasive positive airway pressure in hypoxemic patients after cardiothoracic surgery: a randomized clinical trial. *JAMA* 2015; **313**: 2331–39.
- 9 Mayfield S, Bogossian F, O'Malley L, Schibler A. High-flow nasal cannula oxygen therapy for infants with bronchiolitis: pilot study. *J Pediatrics Child Health* 2014; **50**: 373–78.
- 10 Hough JL, Shearman AD, Jardine LA, Davies MW. Humidified high flow nasal cannulae: current practice in Australasian nurseries, a survey. *J Pediatr Child Health* 2012; **48**: 106–13.
- 11 Haq I, Gopalakaje S, Fenton AC, McKean MC, O'Brien CJ, Brodlie M. The evidence for high flow nasal cannula devices in infants. *Pediatr Respir Rev* 2014; **15**: 124–34.
- 12 Manley BJ, Dold SK, Davis PG, Roehr CC. High-flow nasal cannulae for respiratory support of preterm infants: a review of the evidence. *Neonatology* 2012; **102**: 300–08.
- 13 Chisti MJ, Salam MA, Smith JH, et al. Bubble continuous positive airway pressure for children with severe pneumonia and hypoxaemia in Bangladesh: an open, randomised controlled trial. *Lancet* 2015; **386**: 1057–65.
- 14 Zwarenstein M, Treweek S, Gagnier JJ, et al. Improving the reporting of pragmatic trials: an extension of the CONSORT statement. *BMJ* 2008; **337**: a2390.
- 15 NSW Health. PD2012\_004. Infants and children—acute management of bronchiolitis. North Ryde: NSW Ministry of Health, 2012.
- 16 Meissner HC. Viral bronchiolitis in children. *N Engl J Med* 2016; **374**: 10.
- 17 Ralston SL, Lieberthal AS, Meissner HC, et al. Clinical practice guideline: the diagnosis, management, and prevention of bronchiolitis. *Pediatrics* 2014; **134**: e1474–502.
- 18 Wettstein RB, Shelledy DC, Peters JI. Delivered oxygen concentrations using low-flow and high-flow nasal cannulas. *Respir Care* 2005; **50**: 604–09.
- 19 Jubran A. Pulse oximetry. *Crit Care* 1999; **3**: R11–17.
- 20 Suiter DM, Ruark-McMurtrey J. Oxygen saturation and heart rate during feeding in breast-fed infants at 1 week and 2 months of age. *Arch Phys Med Rehabil* 2007; **88**: 1681–85.
- 21 Clinical Excellence Commission. Between the flags. Keeping patients safe. 2011. <http://www.cec.health.nsw.gov.au/programs/between-the-flags> (accessed Dec 8, 2015).
- 22 NSW Health. PD2011\_077. Recognition and management of patients who are clinically deteriorating. North Ryde: NSW Ministry of Health, 2011.
- 23 Welliver RC. Review of epidemiology and clinical risk factors for severe respiratory syncytial virus (RSV) infection. *J Pediatr* 2003; **143**: 112–17.
- 24 Independent Hospital Pricing Authority. National efficient price determination 2015–16. Canberra: Commonwealth of Australia, 2015.
- 25 Cunningham S, Nair H, Campbell H. Deciphering clinical phenotypes in acute viral lower respiratory tract infection: bronchiolitis is not an island. *Thorax* 2016; **71**: 679–80.
- 26 SIGN. Bronchiolitis in children: a national clinical guideline. NHS Quality Improvement. Edinburgh: Scottish Intercollegiate Guidelines Network, 2006.
- 27 Duarte-Dorado DM, Madero-Orostegui DS, Rodriguez-Martinez CE, Nino G. Validation of a scale to assess the severity of bronchiolitis in a population of hospitalized infants. *J Asthma* 2013; **50**: 1056–61.
- 28 Piedra P, Stark A. Bronchiolitis in infants and children: treatment, outcome; and prevention. October, 2016. [http://www.uptodate.com/contents/bronchiolitis-in-infants-and-children-treatment-outcome-and-prevention?source=search\\_result&search=Bronchiolitis&selectedTitle=1%7E150](http://www.uptodate.com/contents/bronchiolitis-in-infants-and-children-treatment-outcome-and-prevention?source=search_result&search=Bronchiolitis&selectedTitle=1%7E150) (accessed July 7, 2016).
- 29 Schuh S, Freedman S, Coates A, et al. Effect of oximetry on hospitalization in bronchiolitis: a randomized clinical trial. *JAMA* 2014; **312**: 712–18.
- 30 Cunningham S, Rodriguez A, Adams T, et al. Oxygen saturation targets in infants with bronchiolitis (BIDS): a double-blind, randomised, equivalence trial. *Lancet* 2015; **368**: 1041–48.