JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Early High-Flow Nasal Oxygen vs Standard Oxygen Therapy on Length of Hospital Stay in Hospitalized Children With Acute Hypoxemic Respiratory Failure

The PARIS-2 Randomized Clinical Trial

Donna Franklin, PhD, MBA, BN; Franz E. Babl, MD; Shane George, MBBS, MPH, BSc; Ed Oakley, MBBS; Meredith L. Borland, MBBS; Jocelyn Neutze, MBChB; Jason Acworth, MBBS; Simon Craig, MBBS, MHPE, MPH; Mark Jones, PhD; Brenda Gannon, PhD; Deborah Shellshear, MBBS; Hamish McCay, MBChB; Alexandra Wallace, PhD, DCH, MBChB, BHB; Tobias Hoeppner, MBBS; Mark Wildman, PhD, MBBS, BSc (Hons); Joerg Mattes, MD, PhD; Trang M. T. Pham, MEng, BEng; Letitia Miller, BN; Amanda Williams, BN; Sharon O'Brien, BN; Shirley Lawrence, BN; Megan Bonisch, BN; Kristen Gibbons, PhD; Susan Moloney, MBBS; John Waugh, MBBS; Sue Hobbins, MB, ChB, BSc (Med Sci); Simon Grew, MBBS; Rose Fahy, MBBS; Stuart R. Dalziel, PhD, MBChB; Andreas Schibler, MD

IMPORTANCE Nasal high-flow oxygen therapy in infants with bronchiolitis and hypoxia has been shown to reduce the requirement to escalate care. The efficacy of high-flow oxygen therapy in children aged 1 to 4 years with acute hypoxemic respiratory failure without bronchiolitis is unknown.

OBJECTIVE To determine the effect of early high-flow oxygen therapy vs standard oxygen therapy in children with acute hypoxemic respiratory failure.

DESIGN, SETTING, AND PARTICIPANTS A multicenter, randomized clinical trial was conducted at 14 metropolitan and tertiary hospitals in Australia and New Zealand, including 1567 children aged 1 to 4 years (randomized between December 18, 2017, and March 18, 2020) requiring hospital admission for acute hypoxemic respiratory failure. The last participant follow-up was completed on March 22, 2020.

INTERVENTIONS Enrolled children were randomly allocated 1:1 to high-flow oxygen therapy (n = 753) or standard oxygen therapy (n = 764). The type of oxygen therapy could not be masked, but the investigators remained blinded until the outcome data were locked.

MAIN OUTCOMES AND MEASURES The primary outcome was length of hospital stay with the hypothesis that high-flow oxygen therapy reduces length of stay. There were 9 secondary outcomes, including length of oxygen therapy and admission to the intensive care unit. Children were analyzed according to their randomization group.

RESULTS Of the 1567 children who were randomized, 1517 (97%) were included in the primary analysis (median age, 1.9 years [IQR, 1.4-3.0 years]; 732 [46.7%] were female) and all children completed the trial. The length of hospital stay was significantly longer in the high-flow oxygen group with a median of 1.77 days (IQR, 1.03-2.80 days) vs 1.50 days (IQR, 0.85-2.44 days) in the standard oxygen group (adjusted hazard ratio, 0.83 [95% CI, 0.75-0.92]; $P < .001$). Of the 9 prespecified secondary outcomes, 4 showed no significant difference. The median length of oxygen therapy was 1.07 days (IQR, 0.50-2.06 days) in the high-flow oxygen group vs 0.75 days (IQR, 0.35-1.61 days) in the standard oxygen therapy group (adjusted hazard ratio, 0.78 [95% CI, 0.70-0.86]). In the high-flow oxygen group, there were 94 admissions (12.5%) to the intensive care unit compared with 53 admissions (6.9%) in the standard oxygen group (adjusted odds ratio, 1.93 [95% CI, 1.35-2.75]). There was only 1 death and it occurred in the high-flow oxygen group.

CONCLUSIONS AND RELEVANCE Nasal high-flow oxygen used as the initial primary therapy in children aged 1 to 4 years with acute hypoxemic respiratory failure did not significantly reduce the length of hospital stay compared with standard oxygen therapy.

TRIAL REGISTRATION anzctr.org.au Identifier: ACTRN12618000210279

JAMA. 2023;329(3):224-234. doi:10.1001/jama.2022.21805

Visual Abstract

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Andreas Schibler, MD, Critical Care Research Group, St Andrew's War Memorial Hospital, 457 Wickham Terr, Spring Hill, Brisbane, QLD 4000, Australia (andreas.schibler@wesleyresearch.org.au).

Section Editor: Christopher Seymour, MD, Associate Editor, *JAMA* (christopher.seymour@jamanetwork.org).

© 2023 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ by a University of Toronto Libraries User on 02/16/2023

Respiratory illnesses are the most frequent reason for nonelective hospital admissions in children younger than 5 years of age, with a high global health burden.[1-3] Acute hypoxemic respiratory failure is the common end point for many underlying specific diagnoses such as bronchiolitis, asthma, and pneumonia.[4] In Australia and New Zealand in 2018, 38% of nonelective admissions to the intensive care unit (ICU) for children were due to acute hypoxemic respiratory failure.[5] Although mortality due to acute hypoxemic respiratory failure improved in high-income countries, mortality remained between 13% in 2011 and 20% in 2017 in underresourced settings.[6,7]

There is an emerging trend to support respiration with methods other than standard oxygen therapy, particularly initially during the course of hospitalization with the aim of reducing the work of breathing and to potentially prevent progression of disease.[8,9] Nasal high-flow oxygen therapy has evolved as a potential alternative to noninvasive ventilation.[10,11] High-flow oxygen therapy can be used early in the disease process outside the ICU and requires little cooperation of the child.

A study performed between 2013 and 2016 in infants with hypoxia and bronchiolitis who were younger than 1 year of age showed that high-flow oxygen therapy demonstrated a lower rate for escalation of care compared with standard oxygen therapy, but there was no statistically significant difference in ICU admissions or length of hospital stay.[12] Similarly, a pilot study conducted in 2016 and 2017 demonstrated that children and adolescents aged 0 to 16 years with acute hypoxemic respiratory failure managed with high-flow oxygen therapy had a lower rate of escalation of care compared with those receiving standard oxygen therapy, but there was no statistically significant difference in ICU admissions or length of hospital stay.[13]

Based on an absence of definitive evidence on the efficacy of high-flow oxygen therapy in children with hypoxemia without bronchiolitis, the Paediatric Acute Respiratory Studies 2 (PARIS 2) multicenter, randomized clinical trial was conducted to test the hypothesis that use of high-flow oxygen therapy in children with acute hypoxemic respiratory failure would reduce the length of hospital stay compared with standard oxygen therapy.

Key Points

Question Does the early use of nasal high-flow oxygen therapy in children aged 1 to 4 years with acute hypoxemic respiratory failure reduce the length of hospital stay compared with standard oxygen therapy?

Findings In this randomized clinical trial that included 1567 children with acute hypoxemic respiratory failure, use of nasal high-flow oxygen therapy resulted in a median hospital stay of 1.77 days compared with 1.50 days in the standard oxygen therapy group, a difference that was statistically significant.

Meaning Early use of nasal high-flow oxygen therapy in children aged 1 to 4 years with acute hypoxemic respiratory failure did not reduce the length of hospital stay compared with standard oxygen therapy.

Methods

Study Design and Oversight

The PARIS 2 trial was an investigator-initiated randomized clinical trial to evaluate the role of high-flow oxygen therapy compared with standard oxygen therapy at 14 metropolitan and tertiary hospitals in Australia and New Zealand. The trial protocol was approved by the ethics committee at each hospital. The trial was overseen by a steering committee and an independent data and safety monitoring board. The trial protocol was published[14] before enrollment was completed and appears in Supplement 1. The statistical analysis plan was uploaded on GitHub prior to completion of enrollment and appears in Supplement 2.

Participants

Children aged 1 to 4 years with acute hypoxemic respiratory failure were eligible if they presented to the emergency department and were subsequently admitted to an inpatient unit. Children were included in the trial if they fulfilled all 4 inclusion criteria: (1) were experiencing increased work in breathing due to acute respiratory disease, (2) had an ongoing oxygen requirement to maintain a prespecified oxygen saturation level, (3) had an increased respiratory rate of 35/min or higher, and (4) required admission to the hospital.

The majority of hospitals had an oxygen saturation as measured by pulse oximetry (Spo_2) threshold set at 92% or greater; 1 hospital had a lower Spo_2 threshold set at 90% or greater. Diagnoses leading to acute hypoxemic respiratory failure included pneumonia, pneumonitis, acute lower respiratory tract infection, reactive airway disease, and bronchiolitis (in children >12 months of age). Patients were classified into 2 groups using a pragmatic point-of-care definition: by presence of audible wheeze on auscultation (classified as obstructive airway disease) or by absence of wheeze (classified as nonobstructive airway disease).

Children with craniofacial abnormalities, upper airway obstruction, cyanotic heart disease, and those who required immediate higher-level care in the ICU or required noninvasive or invasive mechanical ventilation were excluded (the full list of exclusions appears in Supplement 1). As required by the Australian and New Zealand ethics committees, race and ethnicity were collected for each participant based on the patient registration form at admission to the hospital, generally based on fixed categories determined by the hospital. Written informed consent was obtained from all parents or guardians using either a prospective process or a retrospective deferred process (details appear in Supplement 1).

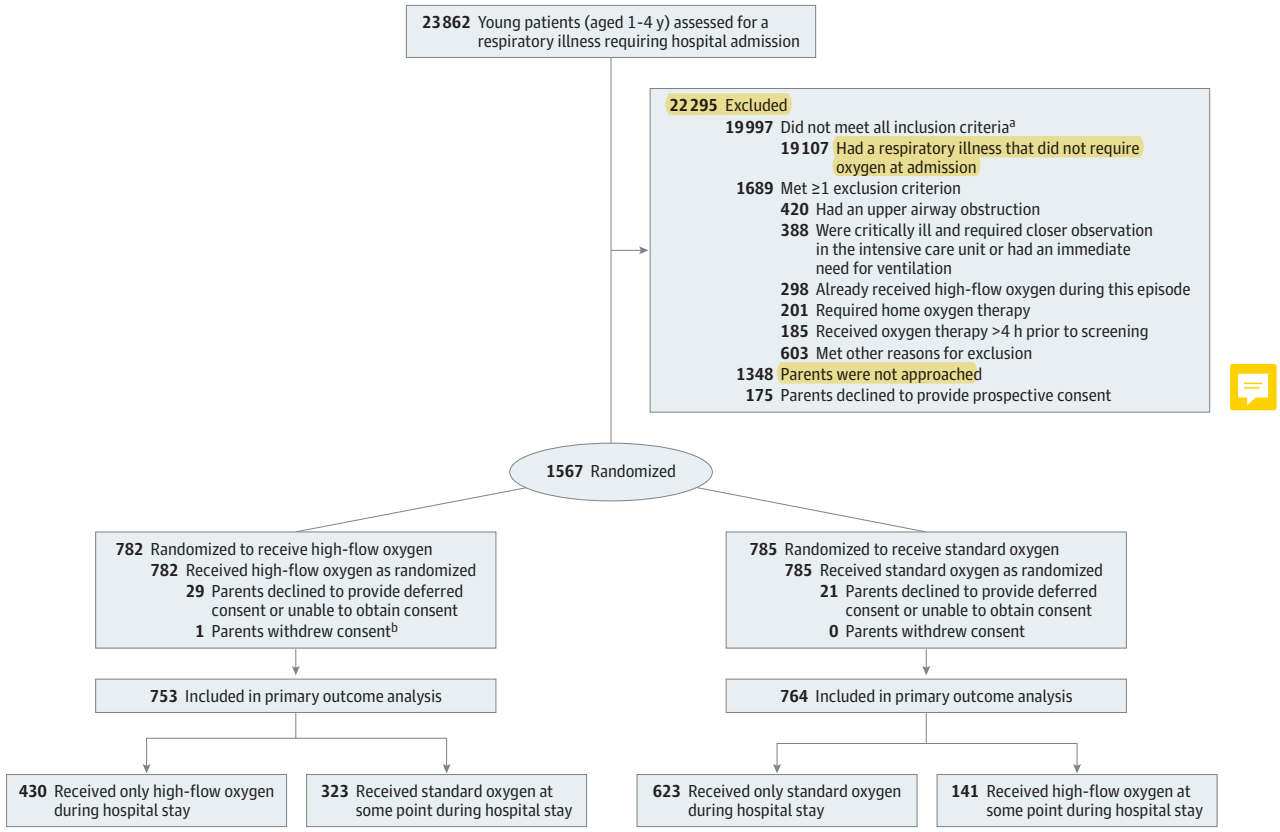
Randomization and Blinding

Children requiring hospital admission for acute hypoxemic respiratory failure were randomly allocated 1:1 to high-flow oxygen therapy or standard oxygen therapy (**Figure 1**). An online computer-generated randomization process with a sequence block size of 10 was used with stratification for each participating center and classification by presence of obstructive or

© 2023 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ by a University of Toronto Libraries User on 02/16/2023

Figure 1. Participant Flow Through the PARIS 2 Trial



PARIS 2 indicates Paediatric Acute Respiratory Studies 2.

[a] There were 4: (1) were experiencing increased work in breathing due to acute respiratory disease, (2) had an ongoing oxygen requirement to maintain a prespecified oxygen saturation level, (3) had an increased respiratory rate of 35/min or higher, and (4) required admission to the hospital.

[b] Even though consent was withdrawn, the data for this child remained in the study and analysis.

nonobstructive disease. There was 1 center that used opaque and sealed envelopes.

Blinding of the assigned treatment was not possible, given the visually obvious differences between the interventions. All investigators remained blinded and unaware of the trial outcome until the recruitment of all patients was completed and the outcome data were locked.

Trial Interventions

Prior to enrollment, children were initially treated with the hospital's standard emergency department management for acute hypoxemic respiratory failure. This included burst-inhalation bronchodilator therapy for reactive airways, fluid bolus, and other medications. A child was eligible for enrollment if acute hypoxemic respiratory failure (Spo_2 <90% or Spo_2 <92% in room air) persisted, and a decision was made to admit the patient to the hospital.

The high-flow oxygen group received therapy using the AIRVO-2 high-flow system (Fisher & Paykel Healthcare) with nasal cannulas (OptiFlow Junior /2/2+[OJR41x/OJR520]). The applied flows were 2 L/kg/min for a body weight 0 kg to 12 kg, 30 L/min for 13 kg to 15 kg, 35 L/min for 16 kg to 30 kg, and 40 L/min for 31 kg to 50 kg.

The fraction of inspired oxygen (FIo_2) for high-flow oxygen therapy was titrated to obtain an Spo_2 in the range of 92% to 98% or an Spo_2 in the range of 90% to 98% (for hospitals with lower saturation targets; additional information appears in eTable 1 in Supplement 3). During bronchodilator administration, high-flow oxygen therapy was stopped and standard oxygen therapy was provided.[15] The flows remained unchanged until cessation of high-flow oxygen (no weaning of flows). Weaning of FIo_2 to room air was permitted once the child was stable (as determined by the treating clinical team) to provide the lowest oxygen percentage to maintain an Spo_2 of 90% or greater or an Spo_2 of 92% or greater. High-flow oxygen therapy was stopped if FIo_2 was equal to 0.21 and oxygen levels were in the expected range. Length of therapy in the high-flow oxygen group was defined as the time until high-flow oxygen therapy was ceased.

The standard oxygen group was placed on oxygen using subnasal cannula with flows up to 2 L/min to maintain an Spo_2 of 90% to 98% or using a Hudson face mask (maximum of 8 L/min) or to maintain an Spo_2 of 92% to 98%. Weaning of oxygen was permitted once the child was stable to provide the lowest oxygen percentage to maintain an Spo_2 of 90% or greater or an Spo_2 of 92% or greater.

© 2023 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ by a University of Toronto Libraries User on 02/16/2023

Use of the alternative oxygen therapy from that assigned was permitted on clinical grounds of intolerance or the need to escalate therapy (decision made by the clinical team). Escalation of care was recommended if the oxygen requirement in the high-flow therapy group exceeded an Fio_2 of 0.40 or 0.50 or the oxygen requirement in the standard oxygen group exceeded 2 L/min by nasal prong to maintain an Spo_2 of 90% or greater or exceeded 8 L/min by face mask to maintain an Spo_2 of 92% or greater. Tolerance of therapy was assessed using an unmarked 100-mm visual analog scale with both the parents and nursing staff recording the intensity of patient discomfort (range, no discomfort to maximal discomfort) at 2 separate intervals: at 1 hour and between 4 hours and 48 hours after starting the intervention.

Outcomes

The primary outcome was length of hospital stay (defined as the time from randomization to the time of hospital discharge or the time of death). There were 9 secondary outcomes, including length of oxygen therapy after randomization, the total length of hospital stay since presentation to the emergency department, the proportion of children receiving a change in oxygen therapy in general ward settings, the proportion of children requiring ICU admission or transfer to a hospital with pediatric ICU facilities, the proportion of children requiring care escalation to noninvasive or invasive ventilation, and adverse events. Further secondary outcomes were collected covering tolerance of the intervention with the visual analog scale and the clinical triggers that resulted in a therapy change.

A serious adverse event was defined as any event that was fatal, life-threatening, permanently disabling, incapacitating, or resulted in a prolonged hospital stay. We plan to report the secondary outcome of health care costs in an economic evaluation.

Sample Size Calculation

The primary hypothesis was that high-flow oxygen therapy reduces the length of hospital stay by 0.4 days. Because there is a relatively short median length of hospital stay for acute hypoxemic respiratory failure (2 days) in children,[13] a mean difference of 9.6 hours (SD, 0.4 days) was chosen because it is both clinically meaningful to children and their families and it is meaningful to the health care system. Accordingly, a sample size of 1209 children was required to achieve a 2-tailed significance level of 5% and a power of 90%, assuming a median length of stay of 2.0 days and 1.6 days, and survival analysis as the primary method of analysis. To allow up to 20% nonadherence, 1512 children were required.

Statistical Analysis

The statistical analysis plan was reported and the full preliminary Stata analysis code (StataCorp) was uploaded on GitHub before completion of enrollment (also appears in Supplement 2). Patients were analyzed according to their randomization group.

The between-group difference with respect to the primary outcome measure (length of hospital stay) was assessed using a Cox proportional hazards model (the proportionality assumption was inspected visually using Kaplan-Meier plots and a log-log plot without clear evidence of divergence), and visually presented using a Kaplan-Meier plot. Both unadjusted and adjusted models were constructed; both models incorporated the treatment group as a fixed effect, with the adjusted model additionally including a stratification variable (obstructive vs nonobstructive airway disease) as a fixed effect and site as a random effect (ie, using a shared frailty model).

In addition, quantile regression with treatment group as a fixed effect was used to calculate the between-group difference and is presented alongside the 95% CIs. The adjusted model was used for the primary analysis. The hazard ratios (HRs) and 95% CIs are presented as an estimate of treatment effect and *P* values are reported for the adjusted model. Multiple imputation was preplanned for the primary outcome in the case of missing data; however, imputation was not done because there were no missing data related to hospital length of stay.

The secondary outcomes were analyzed using logistic regression (binary outcomes), linear regression (continuous normally distributed outcomes), and Cox regression (time-to-event outcomes). Unadjusted and adjusted effect estimates (site as a random effect and the stratification variable as a fixed effect) and the associated 95% CIs are provided. Because of the potential for type I error due to multiple comparisons, the findings for the analyses of the secondary outcomes should be interpreted as exploratory.

Preplanned subgroup analyses were undertaken to determine if the subgroups responded differently for children by presence vs absence of wheeze at hospital admission, presence vs absence of an obstructive airway disease diagnosis at hospital discharge, and by age of 1 year, 2 years, 3 years, and 4 years. Subgroup × treatment group interaction effects are reported for these subgroup analyses.

In addition, 2 preplanned sensitivity analyses addressing potentially subjective outcomes were undertaken. The outcomes investigated were: (1) the composite outcome of ICU admission or high-dependency care with presence of 3 or more of the aforementioned care escalation criteria present; and (2) the composite outcome of transfer to a tertiary hospital with presence of 3 or more of the care escalation criteria present.

A per-protocol analysis also was undertaken for the patients who remained on the initially allocated oxygen therapy (additional information appears in Supplement 2).

Statistical significance for the primary outcome was indicated by $P = .05$ and was determined with use of a 2-sided hypothesis test. No correction for multiple comparisons was applied in the evaluation of the secondary outcomes or for any of the other outcomes.

Results

Trial Sites and Participants

From December 18, 2017, to March 18, 2020, there were 3030 children who were screened and were eligible for the trial at

© 2023 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ by a University of Toronto Libraries User on 02/16/2023

Table 1. Characteristics of the Children, Their Families, and the Hospitals Involved in the PARIS 2 Trial

Characteristic	No. (%)[a]	
	High-flow oxygen (n = 753)	Standard oxygen (n = 764)
Age at randomization, median (IQR), y	1.9 (1.4-3.0)	1.9 (1.4-2.9)
Weight, median (IQR), kg	12.7 (11.0-14.9)	12.5 (10.9-14.9)
Sex		
Female	378 (50.2)	354 (46.3)
Male	375 (49.8)	410 (53.7)
Race and ethnicity[b]		
Aboriginal or Torres Strait Islander	18 (2.4)	21 (2.8)
Asian	48 (6.4)	47 (6.2)
Māori	43 (5.7)	43 (5.6)
Other[c]	72 (9.6)	67 (8.8)
Pacific Islander	44 (5.8)	44 (5.8)
White	249 (33.1)	258 (33.8)
Unknown[d]	279 (37.1)	284 (37.2)
Medical history		
Premature birth, No./total (%)	121/718 (16.9)	135/721 (18.7)
Neonatal respiratory support, No./total (%)	104/699 (14.9)	117/702 (16.7)
Noninvasive ventilation when the patient received neonatal respiratory support	80 (10.6)	92 (12.0)
Invasive ventilation when the patient received neonatal respiratory support	34 (4.5)	30 (3.9)
High-flow oxygen therapy when the patient received neonatal respiratory support	25 (3.3)	25 (3.3)
Hospital admission for respiratory disease	410 (54.7)	416 (54.8)
Intensive care unit admission for respiratory support	93 (12.4)	82 (10.8)
High-flow oxygen therapy during a prior hospital admission	77 (10.3)	72 (9.5)
Noninvasive ventilation during a prior hospital admission	26 (3.5)	19 (2.5)
Invasive ventilation during a prior hospital admission	14 (1.9)	14 (1.9)
Extracorporeal membrane oxygenation	0	2 (2.4)
Chronic lung disease	36 (4.8)	29 (3.8)
Congenital heart disease	11 (1.5)	15 (2.0)
Wheeze	482 (64.9)	482 (63.1)
Family history of asthma, No./total (%)	451/688 (65.6)	417/688 (60.6)
Family history of allergy, No./total (%)	288/649 (44.4)	263/641 (41.0)
Viral testing and data collected at randomization		
Attend childcare	401 (53.3)	396 (51.8)
Viral testing performed[e]	358 (47.5)	364 (47.6)
No virus detected on nasopharyngeal aspirate	133 (17.7)	132 (17.3)
Had respiratory syncytial virus	115 (15.3)	109 (14.3)
Had >2 viruses	42 (5.6)	51 (6.7)
Had metapneumovirus	33 (4.4)	30 (3.9)
Had adenovirus	21 (2.8)	27 (3.5)
Had influenza	22 (2.9)	14 (1.8)
Stratification variable		
Obstructive airway disease (wheeze present)[f]	531 (70.5)	535 (70.0)
Nonobstructive airway disease (wheeze absent)	222 (29.5)	229 (30.0)
Clinical diagnosis group		
Asthma or reactive airways disease	236 (31.3)	255 (33.4)
Viral-induced wheeze	177 (23.5)	177 (23.2)
Pneumonia (bacterial or viral)	108 (14.3)	103 (13.5)
Pneumonitis	95 (12.6)	83 (10.9)
Bronchiolitis	70 (9.3)	72 (9.4)
Acute lower respiratory tract infection[g]	50 (6.6)	51 (6.7)
Other nonobstructive airway disease	3 (0.4)	5 (0.7)
Acute respiratory distress syndrome[h]	3 (0.4)	2 (0.3)
Other obstructive airway disease	2 (0.3)	1 (0.1)
Aspiration	1 (0.1)	0
Bronchiectasis	0	0
Other diagnosis group	8 (1.1)	15 (19.6)

(continued)

© 2023 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ by a University of Toronto Libraries User on 02/16/2023

Table 1. Characteristics of the Children, Their Families, and the Hospitals Involved in the PARIS 2 Trial (continued)

Characteristic	No. (%)[a]	
	High-flow oxygen (n = 753)	Standard oxygen (n = 764)
Vital signs before enrollment		
Heart rate, mean (SD), /min	152 (21)	152 (21)
Respiratory rate, mean (SD), /min	48 (11)	46 (10)
Spo_2, median (IQR), %	88 (86-89)	88 (86-89)
Patients with an Spo_2 <90%	589 (78.2)	586 (76.7)
Time from presentation to randomization, median (IQR), h	2.88 (1.44-5.76)	3.12 (1.44-5.52)
Time from onset of illness to presentation, median (IQR), h	14.4 (7.2-28.8)	14.4 (7.2-28.8)
Hospital characteristics		
Had onsite intensive care unit	667 (88.6)	674 (88.2)
Location		
Australia	623 (82.7)	632 (82.7)
New Zealand	130 (17.3)	132 (17.3)

Abbreviations: PARIS 2, Paediatric Acute Respiratory Studies 2; Spo_2, oxygen saturation as measured by pulse oximetry.

[a] Unless otherwise indicated.

[b] Reported by parents and recorded in the medical record.

[c] African, Indian, and Japanese.

[d] None recorded in the medical record.

[e] Patients may have had 2 or more viruses that were detected.

[f] Defined with the presence of a clinically audible wheeze on auscultation.

[g] Diagnosed based on clinical suspicion without an x-ray or pathology measures.

[h] Defined by the Australian and New Zealand Paediatric Intensive Care registry.[5]

the 14 participating emergency departments, of whom 1348 were not approached and 175 parents did not provide consent (eTable 1 in Supplement 3). A total of 1567 children (51% of eligible patients) were enrolled. Deferred consent after randomization was not provided by 29 parents in the high-flow oxygen group and 21 parents in the standard oxygen group, which left 753 children in the high-flow oxygen group and 764 in the standard oxygen group (Figure 1 and eFigure 1 in Supplement 3). The groups had similar baseline characteristics (**Table 1**). None of the children were lost to follow-up for assessment of the primary outcome. The last participant follow-up was completed on March 22, 2020.

Primary Outcome

The median length of hospital stay after randomization was significantly longer at 1.77 days (IQR, 1.03-2.80 days) in the high-flow oxygen group compared with 1.50 days (IQR, 0.85-2.44 days) in the standard oxygen group (adjusted HR, 0.83 [95% CI, 0.75-0.92]; $P < .001$) (**Table 2**, **Figure 2**, and eFigure 2 in Supplement 3). There was no significant difference in the effect in those with the presence vs absence of wheeze or by age groups (Table 2).

Secondary Outcomes

Of the 9 prespecified secondary outcomes, 4 showed no significant difference. The median length of total hospital stay since presentation to the emergency department was 1.93 days (IQR, 1.21-2.94 days) in the high-flow oxygen group compared with 1.72 days (IQR, 1.03 to 2.68 days) in the standard oxygen group (adjusted HR, 0.82 [95% CI, 0.74 to 0.91]; **Table 3**). The median length of oxygen therapy after randomization was 1.07 days (IQR, 0.50-2.06 days) in the high-flow oxygen group compared with 0.75 days (IQR, 0.35-1.61 days) in the standard oxygen group (adjusted HR, 0.78 [95% CI, 0.70-0.86]; Table 3). There were 94 ICU admissions (12.5%) in the high-flow oxygen group compared with 53 ICU admissions (6.9%) in the standard oxygen group (adjusted odds ratio, 1.93 [95% CI, 1.35-2.75]; Table 3). A sensitivity analysis showed more ICU admissions in the high-flow oxygen group than in the standard oxygen group when ICU admissions were combined with 3 of 4 predetermined escalation criteria (adjusted odds ratio, 1.87 [95% CI, 1.20-2.90]; eTable 2 in Supplement 3).

Tolerance of therapy, which was determined by the parents and the nursing staff, was measured at 1 hour and between 4 hours and 48 hours after starting the assigned oxygen therapy and did not show any significant between-group difference (eTable 3 in Supplement 3).

The per-protocol population included 834 children (336 in the high-flow oxygen group and 498 in the standard oxygen group) and showed similar results to the primary analysis with a longer length of hospital stay, longer length of oxygen therapy, and a greater proportion of ICU admissions in the high-flow oxygen group compared with the standard oxygen group (eFigure 3 and eTables 4-6 in Supplement 3).

Four adverse events were noted. There was 1 death in the high-flow oxygen group that was unrelated to treatment. None of these events were attributed to the interventions (Table 3).

The recruitment rate, hospital length of stay, and the results of sensitivity analysis for the per-protocol cohort appear in eTables 7-9 in Supplement 3. The physiological parameters prior to change in oxygen therapy for both trial groups and the time to crossover of oxygen therapy appear in eTable 10 in Supplement 3.

Clinical Management

Prior to enrollment of the 1567 children, 1467 (93.6%) received inhaled bronchodilators, 994 (63.4%) received steroids, and 631 (40.2%) were given antibiotics. In both groups, most children were started with the allocated treatment (714/753 [94.8%] in the high-flow oxygen group and 735/764

© 2023 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ by a University of Toronto Libraries User on 02/16/2023

Table 2. Primary Outcome in All Patients and by Patient Subgroups

	Median (IQR), d		Estimate of difference (95% CI)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	*P* value
	High-flow oxygen	Standard oxygen				
Primary outcome: length of hospital stay						
All patients for time since randomization	(n = 753) 1.77 (1.03 to 2.80)	(n = 764) 1.50 (0.85 to 2.44)	0.27 (0.13 to 0.41)	0.85 (0.77 to 0.94)	0.83 (0.75 to 0.92)	<.001[a]
By wheeze						
Present (n = 1066)[b]	1.62 (0.92 to 2.58)	1.43 (0.82 to 2.12)	0.19 (0.03 to 0.34)	0.86 (0.77 to 0.97)	0.85 (0.75 to 0.96)	.71[c]
Absent (n = 451)	2.20 (1.31 to 3.47)	1.86 (0.93 to 2.97)	0.340 (−0.003 to 0.690)	0.82 (0.68 to 0.98)	0.81 (0.67 to 0.98)	
By obstructive disease[d]						
Present (n = 958)[b]	1.53 (0.90 to 2.34)	1.28 (0.77 to 2.02)	0.24 (0.08 to 0.40)	0.90 (0.80 to 1.03)	0.87 (0.76 to 0.99)	.38[c]
Absent (n = 559)	2.31 (1.29 to 3.79)	1.93 (1.28 to 2.95)	0.37 (0.03 to 0.70)	0.82 (0.70 to 0.97)	0.81 (0.68 to 0.96)	
By age at randomization, median (IQR)[e]						
1 y (n = 777)[b]	1.87 (1.12 to 2.80)	1.53 (0.95 to 2.61)	0.33 (0.14 to 0.53)	0.90 (0.78 to 1.04)	0.84 (0.72 to 0.97)	.08[f]
2 y (n = 372)	1.62 (0.82 to 2.82)	1.45 (0.73 to 2.30)	0.17 (−0.15 to 0.48)	0.90 (0.74 to 1.11)	0.90 (0.73 to 1.11)	
3 y (n = 189)	1.74 (1.21 to 2.77)	1.60 (0.77 to 2.30)	0.15 (−0.26 to 0.56)	0.79 (0.60 to 1.06)	0.84 (0.62 to 1.14)	
4 y (n = 149)	1.47 (1.11 to 2.47)	1.49 (0.68 to 2.25)	−0.009 (−0.490 to 0.470)	0.56 (0.40 to 0.79)	0.60 (0.42 to 0.85)	

Abbreviation: HR, hazard ratio.

[a] Adjusted for presence or absence of obstructive airway disease at randomization and study site.

[b] Sample sizes larger than original group sizes because patients could switch treatment and receive high-flow oxygen or standard oxygen.

[c] Associated with an interaction term and derived from an adjusted model.

[d] Defined as a discharge diagnosis of reactive airway disease, asthma, or bronchiolitis.

[e] Restricted to children aged 1 to 4 years (n = 1487).

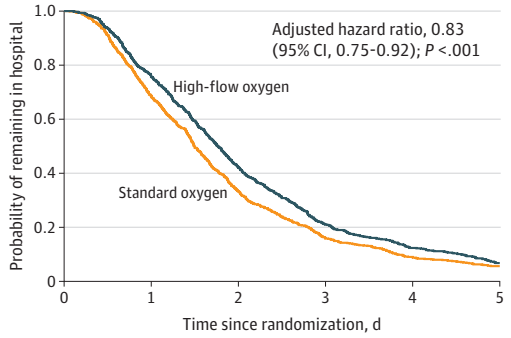
[f] Derived from the Wald test and an adjusted model.

© 2023 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ by a University of Toronto Libraries User on 02/16/2023

[96.2%] in the standard oxygen group), which occurred at a median time of 3.1 hours after presentation to the emergency department. There were 323 children (42.9%) in the high-flow oxygen group who crossed over and received standard oxygen therapy compared with 141 children (18.5%) in the standard oxygen group who crossed over and received high-flow oxygen therapy (adjusted odds ratio, 3.42 [95% CI, 2.70-4.34]; Table 3). The intervention crossovers were driven by triggers of an early-warning tool and clinician-directed treatment switches similarly in both groups, by intolerance of the allocated treatment more frequently in the high-flow oxygen group, and by increased work of breathing more frequently in the standard oxygen group (Table 3).

Figure 2. Time to Discharge From Hospital Since Randomization



No. at risk

High-flow oxygen	753	571	318	158	93	51
Standard oxygen	764	525	255	122	69	43

The median length of the hospital stay and the median length of observation time was 1.77 days (IQR, 1.03-2.80 days) for the high-flow oxygen group and 1.50 days (IQR, 0.85-2.44 days) for the standard oxygen group in the intention-to-treat analysis.

Discussion

In this multicenter, randomized clinical trial, children who received early high-flow oxygen therapy for mild to moderate acute hypoxemic respiratory failure had a significant longer stay in the hospital compared with children who received standard oxygen therapy. This significant difference was consistent for children presenting with obstructive airways disease (wheeze) and nonobstructive airways disease (no wheeze). A greater proportion of children in the high-flow oxygen group were admitted to the ICU and did not tolerate the assigned treatment compared with children in the standard oxygen group.

Consistent with the findings of a 2-center pilot study using the same intervention protocol, high-flow oxygen therapy yielded a longer length of stay by 0.2 days and a larger proportion of patients admitted to the ICU.[13] However, the pilot study found significantly greater treatment failure in the standard oxygen group. The reason for this difference between the 2 studies is uncertain. Although the 2 studies had different recruitment ages, with the pilot study recruiting children aged 0 years to 16 years with acute hypoxemic respiratory failure (excluding infants <12 months of age with viral bronchiolitis), 82% of the children in the pilot study were in the same age range as the children in the current trial. Even though there were no significant differences in mean parental or staff comfort scores (as measured on a 100-mm visual analog scale, which this trial assessed at 1 hour and between 4 hours and 48 hours after starting the trial interventions), intolerance of treatment was more frequently cited for treatment failure in the high-flow oxygen group.

This multicenter trial does not explain why the length of oxygen therapy and hospital stay were prolonged in children allocated to high-flow oxygen therapy. There was a greater number of patients in the high-flow oxygen group who crossed over to standard oxygen therapy and this change to a second form of oxygen therapy may have prolonged time receiving oxygen therapy and thus a longer stay in the hospital. However, it seems unlikely that this factor accounts for these findings because the significant between-group differences in length of oxygen therapy and hospital stay were still apparent in the per-protocol analysis, which excluded all participants who switched oxygen therapies.

Slow weaning of oxygen therapy in pediatric patients, prolonging the length of the hospital stay, is well documented.[16] Although the weaning protocol of oxygen therapy targeting an Spo_2 of 92% to 98% (Supplement 1) was the same for both intervention groups, it is possible that greater familiarity with the weaning of standard oxygen resulted in the differences demonstrated. Alternatively, children randomized to high-flow oxygen therapy may have been unconsciously perceived by clinicians to be sicker by virtue of receiving a perceived higher level of respiratory support. This may have influenced the clinical team to be less aggressive with regard to weaning and thus artificially prolonging oxygen therapy, and ultimately length of stay. Similarly, the clinical team may have had a lower threshold for escalation of care to ICU admission. Regardless of the reason, the trial failed to find any benefit of starting high-flow oxygen therapy early during hospital management.

The trial was performed at 7 tertiary and 7 regional hospitals in Australia and New Zealand for a wide range of causes of acute hypoxemic respiratory failure, allowing generalizability of the study outcomes. It is unlikely that a learning effect contributed to the longer length of hospital stay because the participating hospitals were familiar with high-flow oxygen therapy after the previous high-flow oxygen trial in infants with bronchiolitis.

Limitations

This study has several limitations. First, the allocated oxygen therapy could not be blinded, which may have led to a bias in clinical decision-making to switch from the allocated oxygen therapy to the alternative oxygen therapy.

Second, a greater proportion of the children in the high-flow oxygen group were switched to standard oxygen than the children in the standard oxygen group who were switched to high-flow oxygen. The main reason for a switch in oxygen therapy in the high-flow oxygen group was intolerance of the

© 2023 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ by a University of Toronto Libraries User on 02/16/2023

Table 3. Secondary Outcomes, Complications, and Adverse Events

Secondary outcomes	No. (%)[a]		Estimate of difference (95% CI), %[a]	Unadjusted OR (95% CI)[a]	Adjusted OR (95% CI)[a,b]
	High-flow oxygen (n = 753)	Standard oxygen (n = 764)			
Total length of hospital stay since presentation to the emergency department, median (IQR), d	1.93 (1.21 to 2.94)	1.72 (1.03 to 2.68)	0.22 (0.09 to 0.35)	HR, 0.85 (0.77 to 0.94)	HR, 0.82 (0.74 to 0.91)
Length of oxygen therapy after randomization, median (IQR), d	1.07 (0.50 to 2.06)	0.75 (0.35 to 1.61)	0.33 (0.20 to 0.46)	HR, 0.79 (0.71 to 0.87)	HR, 0.78 (0.70 to 0.86)
Escalation of care to an ICU	94 (12.5)	53 (6.9)	5.5 (2.6 to 8.5)	1.91 (1.34 to 2.72)	1.93 (1.35 to 2.75)
Required noninvasive ventilation	7 (7.4)	6 (11.3)			
Required invasive ventilation	4 (4.3)	0			
Required transfer to a tertiary hospital with onsite PICU, No./total (%)[c]	2/85 (2.3)	2/90 (2.2)	0.1 (−4.3 to 4.5)	1.05 (0.14 to 7.61)	0.92 (0.13 to 6.75)
Change of allocated therapy and reason for the change[d]					
Change in oxygen therapy in general ward or emergency department	323 (42.9)	141 (18.5)	24.4 (20.0 to 28.9)	3.32 (2.63 to 4.19)	3.42 (2.70 to 4.34)
Trigger of early-warning tool	117 (15.5)	111 (14.5)	1.0 (−2.6 to 4.6)	1.08 (0.82 to 1.43)	1.09 (0.82 to 0.24)
Increased work of breathing	33 (4.4)	98 (12.8)	−8.4 (−11.2 to −5.6)	0.31 (0.21 to 0.47)	0.30 (0.20 to 0.46)
Decreased level of consciousness	2 (0.3)	2 (0.3)	0 (−0.5 to 0.5)	1.01 (0.14 to 7.22)	1.01 (0.14 to 7.21)
Deterioration of cardiovascular function with impaired peripheral perfusion	0	2 (0.3)			
Clinician-directed treatment switch	136 (18.1)	123 (16.1)	2.0 (−1.8 to 5.7)	1.15 (0.88 to 1.50)	1.15 (0.88 to 1.51)
Based on review by ICU team	12 (1.6)	27 (3.5)	−1.9 (−3.5 to 0.4)	0.44 (0.22 to 0.88)	0.43 (0.21 to 0.86)
Intolerance of allocated oxygen therapy	92 (12.2)	0			
Complications and adverse events					
Death	1 (0.1)	0			
Air leak syndrome, emergency intubation, cardiac arrest, or respiratory arrest	0	0			
Nosebleed	2 (0.3)	0			

Abbreviations: HR, hazard ratio; ICU, intensive care unit; OR, odds ratio; PICU, pediatric intensive care unit.

[a] Unless otherwise indicated.

[b] Adjusted for presence or absence of obstructive airway disease at randomization and study site.

[c] Only includes those who were admitted to hospitals without onsite PICUs.

[d] Multiple clinical reasons may have been recorded.

© 2023 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ by a University of Toronto Libraries User on 02/16/2023

high-flow oxygen therapy. The clinical triggers indicate that children were escalated from standard oxygen to high-flow oxygen based on progression of the disease, whereas a switch in the high-flow oxygen group to standard oxygen therapy occurred more often due to intolerance of the high-flow oxygen therapy. The comfort score measured at fixed intervals after randomization did not reflect the higher intolerance of the high-flow oxygen therapy because the measurement points did not align with the time of crossover.

Third, no clinical data during the weaning process were captured in the study. The same weaning process was used in infants with bronchiolitis in the previous randomized clinical trial,[12] which did not show any significant difference in hospital length of stay. All of the staff working at the participating hospitals were familiar with the weaning process as per the previous randomized clinical trial and hence it is unlikely that a learning curve with the high-flow oxygen therapy contributed to an increased length of hospital stay.

Conclusions

Nasal high-flow oxygen used as the initial primary therapy in children aged 1 to 4 years with acute hypoxemic respiratory failure did not significantly reduce the length of hospital stay compared with standard oxygen therapy.

ARTICLE INFORMATION

Accepted for Publication: November 8, 2022.

Author Affiliations: Children's Emergency and Critical Care Research, Gold Coast University Hospital, Southport, Australia (Franklin, George); Emergency Department, Gold Coast University Hospital, Southport, Australia (Franklin, George); Faculty of Medicine, University of Queensland, Brisbane, Australia (Franklin, George, Pham, Miller, Gibbons); Menzies Health Institute Queensland, Griffith University, Southport, Australia (Franklin, George); Paediatric Research in Emergency Departments International Collaborative, Melbourne, Australia (Franklin, Babl, George, Oakley, Borland, Neutze, Acworth, Craig, Shellshear, Williams, O'Brien, Lawrence, Bonisch, Dalziel, Schibler); Emergency Department, Royal Children's Hospital, Melbourne, Australia (Babl, Oakley, Williams); Murdoch Children's Research Institute, Melbourne, Australia (Babl, Oakley, Williams); Department of Paediatrics, Faculty of Medicine, Dentistry, and Health Sciences, University of Melbourne, Melbourne, Australia (Babl, Oakley); Emergency Medicine, Perth Children's Hospital, Nedlands, Australia (Borland, Hoeppner, O'Brien); Divisions of Emergency Medicine and Paediatrics, School of Medicine, University of Western Australia, Crawley (Borland); Departments of Surgery and Paediatrics: Child and Youth Health, University of Auckland, Auckland, New Zealand (Neutze, Wallace, Dalziel); KidzFirst Middlemore Hospital, Auckland, New Zealand (Neutze, Lawrence); Emergency Department, Queensland Children's Hospital, South Brisbane, Australia (Acworth, Shellshear); Department of Paediatrics, School of Clinical Sciences, Monash University, Clayton, Australia (Craig); Emergency Department, Monash Medical Centre, Melbourne, Australia (Craig); Faculty of Health Sciences and Medicine, Bond University, Gold Coast, Australia (Jones); Centre for the Business and Economics of Health, University of Queensland, Brisbane, Australia (Gannon); Department of Paediatrics, Waikato Hospital, Hamilton, New Zealand (McCay, Wallace); Emergency Department, Townsville University Hospital, Douglas, Australia (Wildman); Paediatric Respiratory and Sleep Medicine, John Hunter Children's Hospital, New Lambton Heights, Australia (Mattes); Priority Research Centre GrowUpWell, University of Newcastle, Callaghan, Australia (Mattes); Children's Emergency Department, Starship Children's Hospital, Auckland, New Zealand (Bonisch, Dalziel); Paediatric Department, Gold Coast University Hospital, Griffith University School of Medicine, Southport, Australia (Moloney); Paediatric Department, Ipswich General Hospital, Ipswich, Australia (Waugh); Paediatric Department, Caboolture Hospital, Caboolture, Australia (Waugh); Paediatric and Emergency Departments, Prince Charles Hospital, Chermside, Australia (Hobbins, Fahy); Paediatric Department, Redcliffe Hospital, Redcliffe, Australia (Grew); University of Auckland, Auckland, New Zealand (Dalziel); St Andrew's War Memorial Hospital, Brisbane, Australia (Schibler); Critical Care Research Group, St Andrew's War Memorial Hospital, Brisbane, Australia (Schibler); Wesley Medical Research, Wesley Hospital, Auchenflower, Australia (Schibler).

Author Contributions: Drs Franklin and Schibler had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Franklin, Babl, George, Oakley, Neutze, Acworth, Craig, Jones, Gannon, Mattes, Gibbons, Hobbins, Dalziel, Schibler.
Acquisition, analysis, or interpretation of data: Franklin, Babl, George, Oakley, Borland, Neutze, Craig, Jones, Shellshear, McCay, Wallace, Hoeppner, Wildman, Mattes, Pham, Miller, Williams, O'Brien, Lawrence, Bonisch, Gibbons, Moloney, Waugh, Grew, Fahy, Dalziel.
Drafting of the manuscript: Franklin, Gannon, Shellshear, Pham, Miller, Gibbons, Schibler.
Critical revision of the manuscript for important intellectual content: Franklin, Babl, George, Oakley, Borland, Neutze, Acworth, Craig, Jones, Shellshear, McCay, Wallace, Hoeppner, Wildman, Mattes, Williams, O'Brien, Lawrence, Bonisch, Gibbons, Moloney, Waugh, Hobbins, Grew, Fahy, Dalziel.
Statistical analysis: Franklin, Jones, Gibbons, Schibler.
Obtained funding: Franklin, Babl, Craig, Gannon, Hoeppner, Wildman, Mattes, O'Brien, Moloney.
Administrative, technical, or material support: Franklin, George, Oakley, Borland, McCay, Wallace, Pham, Miller, O'Brien, Bonisch, Moloney, Waugh, Grew.
Supervision: Franklin, Babl, George, Neutze, Acworth, McCay, Wallace, Moloney, Grew, Dalziel.

Conflict of Interest Disclosures: Dr Franklin reported receiving grants from the National Health and Medical Research Council (NHMRC) in Australia, the Thrasher Research Fund, the Children's Health Foundation, and the Emergency Medicine Foundation; receiving travel reimbursement from Fisher & Paykel Healthcare; and receiving nonfinancial support from Fisher & Paykel Healthcare. Dr Babl reported receiving grants from the NHMRC. Dr George reported receiving grants from the NHMRC, the Thrasher Research Fund, and the Emergency Medicine Foundation and receiving nonfinancial support from Fisher & Paykel Healthcare. Dr Oakley reported receiving grants from the NHMRC and receiving nonfinancial support from Fisher & Paykel Healthcare. Dr Neutze reported receiving grants from the NHMRC and receiving nonfinancial support from Fisher & Paykel Healthcare. Dr Acworth reported receiving grants from the NHMRC and receiving nonfinancial support from Fisher & Paykel Healthcare. Dr Craig reported receiving grants from the NHMRC. Dr McCay reported receiving grants from the NHMRC, the Thrasher Research Fund, the Children's Health Foundation, and the Emergency Medicine Foundation and receiving nonfinancial support from Fisher & Paykel Healthcare. Dr Wallace reported receiving grants from the NHMRC and receiving nonfinancial support from Fisher & Paykel Healthcare. Dr Hoeppner reported receiving grants from the Children's Hospital Foundation and the NHMRC and receiving nonfinancial support from Fisher & Paykel Healthcare. Dr Wildman reported receiving grants from the NHMRC and the Education and Research Trust Account and receiving nonfinancial support from Fisher & Paykel Healthcare. Dr Mattes reported receiving grants from the NHMRC. Ms Pham reported receiving grants from the NHMRC and receiving nonfinancial support from Fisher & Paykel Healthcare Equipment. Ms O'Brien reported receiving grants from the NHMRC and Children's Hospital Foundation and receiving nonfinancial support from Fisher & Paykel Healthcare. Ms Lawrence reported receiving grants from the NHMRC and receiving nonfinancial support from Fisher & Paykel Healthcare. Dr Gibbons reported receiving grants from the NHMRC and the Thrasher Research Fund and receiving nonfinancial support from Fisher & Paykel Healthcare. Dr Moloney reported receiving grants from the NHMRC and Fisher & Paykel Healthcare. Dr Waugh reported receiving grants from the NHMRC, the Thrasher Research Fund, the Children's Health Foundation, and the Emergency Medicine Foundation and receiving nonfinancial support from Fisher & Paykel Healthcare. Dr Grew reported receiving grants from the NHMRC and receiving nonfinancial support from Fisher & Paykel Healthcare. Dr Fahy reported receiving grants from the NHMRC and receiving nonfinancial support from Fisher & Paykel Healthcare. Dr Dalziel reported receiving grants from the NHMRC and

© 2023 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ by a University of Toronto Libraries User on 02/16/2023

Cure Kids New Zealand; receiving nonfinancial support from Fisher & Paykel Healthcare; and receiving travel reimbursement from Fisher & Paykel Healthcare. Dr Schibler reported receiving grants from the NHMRC, the Children's Health Foundation, the Thrasher Research Fund, and the Emergency Medicine Foundation; receiving nonfinancial support from Fisher & Paykel Healthcare; receiving travel reimbursement from Fisher & Paykel Healthcare; and receiving consulting fees from Fisher & Paykel Healthcare. No other disclosures were reported.

Funding/Support: This research was supported by grant 1139903 from the National Health and Medical Research Council in Australia and funding from the Thrasher Research Fund in the US, the Children's Hospital Foundation in Australia, the Perth Children's Hospital Foundation in Australia, and the Emergency Medicine Foundation in Australia. The OptiFlow equipment and consumables were supplied free of charge for this study by Fisher & Paykel Healthcare.

Role of the Funder/Sponsor: The funders/sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Data Sharing Statement: See Supplement 4.

Additional Contributions: We thank the parents and children for participating in this trial and the medical, nursing, and research teams at the participating sites for their help in study setup, recruitment, data collection, and monitoring of the trial data.

REFERENCES

1. Wang X, Li Y, Deloria-Knoll M, et al; Respiratory Virus Global Epidemiology Network. Global burden of acute lower respiratory infection associated with human metapneumovirus in children under 5 years in 2018: a systematic review and modelling study. *Lancet Glob Health*. 2021;9(1):e33-e43. doi:10.1016/S2214-109X(20)30393-4

2. Wang X, Li Y, O'Brien KL, et al; Respiratory Virus Global Epidemiology Network. Global burden of respiratory infections associated with seasonal influenza in children under 5 years in 2018: a systematic review and modelling study. *Lancet Glob Health*. 2020;8(4):e497-e510. doi:10.1016/S2214-109X(19)30545-5

3. World Health Organization. *Recommendations for Management of Common Childhood Conditions: Evidence for Technical Update of Pocket Book Recommendations: Newborn Conditions, Dysentery, Pneumonia, Oxygen Use And Delivery, Common Causes of Fever, Severe Acute Malnutrition and Supportive Care*. World Health Organization; 2012.

4. Rambaud-Althaus C, Althaus F, Genton B, D'Acremont V. Clinical features for diagnosis of pneumonia in children younger than 5 years: a systematic review and meta-analysis. *Lancet Infect Dis*. 2015;15(4):439-450. doi:10.1016/S1473-3099(15)70017-4

5. ANZPIC Registry. Intensive care admissions for children. Accessed May 9, 2022. https://www.anzics.com.au/

6. Maitland K, Kiguli S, Opoka RO, et al. Children's Oxygen Administration Strategies Trial (COAST): a randomised controlled trial of high flow versus oxygen versus control in African children with severe pneumonia. *Wellcome Open Res*. 2018;2:100. doi:10.12688/wellcomeopenres.12747.2

7. Maitland K, Kiguli S, Opoka RO, et al; FEAST Trial Group. Mortality after fluid bolus in African children with severe infection. *N Engl J Med*. 2011;364(26):2483-2495. doi:10.1056/NEJMoa1101549

8. Hough JL, Pham TM, Schibler A. Physiologic effect of high-flow nasal cannula in infants with bronchiolitis. *Pediatr Crit Care Med*. 2014;15(5):e214-e219. doi:10.1097/PCC.0000000000000112

9. 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(9998):1057-1065. doi:10.1016/S0140-6736(15)60249-5

10. Franklin D, Fraser JF, Schibler A. Respiratory support for infants with bronchiolitis, a narrative review of the literature. *Paediatr Respir Rev*. 2019;30:16-24. doi:10.1016/j.prrv.2018.10.001

11. Frat JP, Thille AW, Mercat A, et al; FLORALI Study Group; REVA Network. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. *N Engl J Med*. 2015;372(23):2185-2196. doi:10.1056/NEJMoa1503326

12. Franklin D, Babl F, Schlapbach LJ, et al. A randomized trial of high-flow oxygen therapy in infants with bronchiolitis. *N Engl J Med*. 2018;378(12):1121-1131.

13. Franklin D, Shellshear D, Babl FE, et al; PARIS and PREDICT. High flow in children with respiratory failure: a randomised controlled pilot trial—a paediatric acute respiratory intervention study. *J Paediatr Child Health*. 2021;57(2):273-281. doi:10.1111/jpc.15259

14. Franklin D, Shellshear D, Babl FE, et al; PARIS and PREDICT. Multicentre, randomised trial to investigate early nasal high-flow therapy in paediatric acute hypoxaemic respiratory failure: a protocol for a randomised controlled trial—a Paediatric Acute respiratory Intervention Study (PARIS 2). *BMJ Open*. 2019;9(12):e030516. doi:10.1136/bmjopen-2019-030516

15. Hess DR. Aerosol therapy during noninvasive ventilation or high-flow nasal cannula. *Respir Care*. 2015;60(6):880-891. doi:10.4187/respcare.04042

16. Martin S, Martin J, Seigler T. Evidence-based protocols to guide pulse oximetry and oxygen weaning in inpatient children with asthma and bronchiolitis: a pilot project. *J Pediatr Nurs*. 2015;30(6):888-895. doi:10.1016/j.pedn.2015.02.003

© 2023 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ by a University of Toronto Libraries User on 02/16/2023