ORIGINAL ARTICLE

A Randomized Trial of High-Flow Oxygen Therapy in Infants with Bronchiolitis

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ABSTRACT

BACKGROUND

High-flow oxygen therapy through a nasal cannula has been increasingly used in infants with bronchiolitis, despite limited high-quality evidence of its efficacy. The efficacy of high-flow oxygen therapy through a nasal cannula in settings other than intensive care units (ICUs) is unclear.

METHODS

In this multicenter, randomized, controlled trial, we assigned infants younger than 12 months of age who had bronchiolitis and a need for supplemental oxygen therapy to receive either high-flow oxygen therapy (high-flow group) or standard oxygen therapy (standard-therapy group). Infants in the standard-therapy group could receive rescue high-flow oxygen therapy if their condition met criteria for treatment failure. The primary outcome was escalation of care due to treatment failure (defined as meeting ≥3 of 4 clinical criteria: persistent tachycardia, tachypnea, hypoxemia, and medical review triggered by a hospital early-warning tool). Secondary outcomes included duration of hospital stay, duration of oxygen therapy, and rates of transfer to a tertiary hospital, ICU admission, intubation, and adverse events.

RESULTS

The analyses included 1472 patients. The percentage of infants receiving escalation of care was 12% (87 of 739 infants) in the high-flow group, as compared with 23% (167 of 733) in the standard-therapy group (risk difference, –11 percentage points; 95% confidence interval, –15 to –7; P<0.001). No significant differences were observed in the duration of hospital stay or the duration of oxygen therapy. In each group, one case of pneumothorax (<1% of infants) occurred. Among the 167 infants in the standard-therapy group who had treatment failure, 102 (61%) had a response to high-flow rescue therapy.

CONCLUSIONS

Among infants with bronchiolitis who were treated outside an ICU, those who received high-flow oxygen therapy had significantly lower rates of escalation of care due to treatment failure than those in the group that received standard oxygen therapy. (Funded by the National Health and Medical Research Council and others; Australian and New Zealand Clinical Trials Registry number, ACTRN12613000388718.)

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Bronchiolitis, an acute lower airway lung disease that is generally caused by respiratory viruses, is the most common reason worldwide for nonelective hospital admission in infants. In the United States, bronchiolitis is responsible for $1.7 billion in hospitalization costs annually.[1,2] In Australia and New Zealand, there has been a population-based increase in admissions to the intensive care unit (ICU) for bronchiolitis, with associated increases in hospital costs.[3]

Numerous studies have investigated the role of medical therapies[4] in infants with bronchiolitis; none of these interventions have shown efficacy.[5] The American Academy of Pediatrics guidelines recommend only supportive therapy that includes oxygen therapy for hypoxemia, respiratory support, and the maintenance of hydration.[5,6]

Respiratory support as provided in emergency and ward settings has been limited to oxygen delivered through a standard nasal cannula, at a rate of up to 2 liters of 100% oxygen per minute, to treat hypoxemia.[7] The hallmark of severe bronchiolitis is small airway inflammation resulting in hypoxemia, hypercarbia, and increased work of breathing,[1] all of which respond to the provision of positive pressure. However, respiratory support involving continuous positive airway pressure, intubation, and mechanical ventilation[8-10] has traditionally been restricted to the intensive care setting.

High-flow oxygen therapy through a nasal cannula has emerged as a new method to provide respiratory support for respiratory diseases in neonates, infants, children, and adults.[11-13] Humidified and heated air that is blended with oxygen and delivered through a nasal cannula provides a degree of positive airway pressure.[14,15] Observational and physiological studies suggest that decreased work of breathing,[16] improved oxygenation, and reduced rates of intubation are associated with high-flow oxygen therapy.[17,18] We conducted a multicenter, randomized trial to test whether early treatment with high-flow therapy in infants with bronchiolitis and hypoxemia in emergency departments and general pediatric wards would result in fewer infants having treatment failure that leads to the escalation of care.

METHODS

TRIAL DESIGN AND OVERSIGHT

Emergency departments and general pediatric inpatient units in 17 tertiary and regional hospitals in Australia and New Zealand participated in the trial. The human research ethics committee at each participating site approved the trial. The protocol, available with the full text of this article at NEJM.org, has been published previously.[19] The trial was overseen by a steering committee with a principal investigator at each site. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. The first drafts of the manuscript were written by the first and last authors with input from all the authors. Although the intervention could not be masked, all the investigators remained unaware of the trial outcome until all the data were locked at the end of trial in December 2016, after the analysis of data from all recruited patients. The high-flow equipment and consumables for all the trial sites were donated by Fisher and Paykel Healthcare, which had no involvement in the design and conduct of the trial, the analysis of the data, or in the preparation of the manuscript or the decision to submit it for publication.

PATIENTS

Infants younger than 12 months of age were eligible for inclusion on presentation to an emergency department or inpatient unit if they had clinical signs of bronchiolitis and a need for supplemental oxygen therapy to keep the oxygen-saturation level in the range of 92 to 98% (or 94 to 98% at the 11 hospitals with higher saturation thresholds for intervention in hypoxemia, in alignment with their institutional practice). Bronchiolitis in an infant was defined according to the American Academy of Pediatrics[20] criteria as symptoms of respiratory distress associated with symptoms of a viral respiratory tract infection.[5] We excluded critically ill infants who had an immediate need for respiratory support and ICU admission; infants with cyanotic heart disease, basal skull fracture, upper airway obstruction, or craniofacial malformation; and infants who were receiving oxygen therapy at home.

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Written informed consent was obtained from all the parents or guardians with the use of either an immediate (prospective) or a deferred (retrospective) consent process (see Section 4.3 in the Supplementary Appendix, available at NEJM .org). At the time of the trial, high-flow therapy was considered to be the normal standard practice in the trial centers; therefore, the ethics committee allowed the deferred-consent process.

RANDOMIZATION

A computer-generated randomization sequence with a block size of 10 was used, and infants were stratified according to participating center. Sequentially numbered, sealed, opaque envelopes containing the treatment assignment (in a 1:1 ratio) were opened when eligibility criteria were met. Masking of the assigned treatment was not possible, given the visually obvious differences between the two interventions.

TRIAL INTERVENTIONS

Infants in the high-flow group received heated and humidified high-flow oxygen at a rate of 2 liters per kilogram of body weight per minute, delivered by the Optiflow system with the use of an age-appropriate Optiflow Junior cannula and the Airvo 2 high-flow system (Fisher and Paykel Healthcare). The fraction of inspired oxygen (F_{IO_2}) for high-flow use was adjusted to obtain oxygen-saturation levels in the range of 92 to 98% (or 94 to 98% at the 11 hospitals with higher saturation thresholds). Weaning of the F_{IO_2} to the level of ambient air (0.21) was permitted at any time to provide the lowest possible oxygen percentage to maintain an oxygen-saturation level of at least 92% (or ≥94% in the 11 specified hospitals). High-flow oxygen therapy was stopped after 4 hours of receiving an F_{IO_2} of 0.21 while oxygen levels were maintained in the expected range.

Infants in the standard-therapy group received supplemental oxygen through a nasal cannula, up to a maximum of 2 liters per minute, to maintain an oxygen-saturation level in the range of 92 to 98% (or 94 to 98%, depending on institutional practice). Weaning from supplemental oxygen was permitted at any time to provide the lowest possible oxygen level delivered to maintain an oxygen-saturation level of at least 92% (or ≥94%).

Enteral feeding was recommended, depending on the clinician's preference. Oral intake of food (liquid or solid) was allowed, particularly during weaning from the treatment.

TRIAL OUTCOMES

The primary outcome was treatment failure that resulted in escalation of care during that hospital admission. At the point of care, the treating clinicians determined the presence of treatment failure if at least three of four clinical criteria were met and clinicians decided that escalation of care was required. The criteria were as follows: the heart rate remained unchanged or increased by any amount since admission (by contrast, a decrease of >5 beats per minute or into the normal range indicated treatment success); the respiratory rate remained unchanged or increased by any amount since admission (by contrast, a decrease of >5 breaths per minute or into the normal range indicated treatment success); the oxygen requirement in the high-flow group exceeded an F_{IO_2} of at least 0.4 to maintain an oxygen-saturation level of at least 92% (or ≥94%, depending on the institution) or the requirement for supplemental oxygen in the standard-therapy group exceeded 2 liters per minute to maintain an oxygen-saturation level of at least 92% (or ≥94%); and the hospital internal early-warning tool triggered a medical review and escalation of care (see below). Clinicians were allowed to escalate therapy if they were concerned for other clinical reasons that were not captured in the four clinical criteria.

All the participating hospitals used an early-warning tool to trigger escalation of care, with 11 of the 17 centers using an identical scoring system and 6 using comparable systems (see Section 4.14 in the Supplementary Appendix). The early-warning tools were all based on multiple physiological and clinical variables that mandated medical review and escalation of care when limits were breached. Escalation of treatment or the level of care was defined as an increase in respiratory support or transfer to an ICU. For infants in the standard-therapy group who received escalation of care, it was suggested to change to

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high-flow therapy in the inpatient environment at the discretion of the clinician.

Prespecified secondary outcomes included the proportion of infants who were transferred to an ICU, which included admission to an on-site ICU or transfer to an ICU at a tertiary hospital; the duration of hospital stay; the duration of ICU stay; the duration of oxygen therapy; intubation rates; and adverse events. Data regarding treatment that was not specified as part of the trial were recorded, as were data regarding medications. The nine centers that had no on-site ICU had to transport infants who required intensive care to a hospital that provided these pediatric services. A serious adverse event was defined as any event that was fatal, life-threatening, permanently disabling, or incapacitating or that resulted in a prolonged hospital stay.

STATISTICAL ANALYSIS

Assuming a baseline rate of treatment failure of 10% in the standard-therapy group and a 50% lower rate (5%) in the high-flow group, we calculated that 582 infants per group would provide the trial with 90% power at a type I error of 0.05 to show a rate of treatment failure that was significantly lower with high-flow therapy than with standard therapy (see Section 4.4 in the Supplementary Appendix). Assuming a rate of withdrawal or loss to follow-up of approximately 10 to 20%, we calculated an overall sample size of 1400. The primary and secondary outcomes were analyzed on the basis of the assigned treatment group.

Data were analyzed first for all infants who received escalation of care. Data were then analyzed again for all infants who received escalation of care and for whom secondary chart review independently confirmed that at least three of the four clinical criteria for treatment failure had been met. Descriptive statistics were used to report the baseline characteristics of the total trial cohort, according to treatment group. The primary outcome measure for the investigation of the escalation of care due to treatment failure was analyzed with the use of a chi-square test and was reported as the relative risk and the risk difference with 95% confidence intervals and P values. The continuous outcome measure of the duration of hospital stay was approximately normally distributed; hence, Student's t-test of independent samples was used. Analyses of secondary outcomes were based on the chi-square test for proportions and on Student's t-tests of independent samples for continuous measures.

Prespecified subgroups included infants who had been born prematurely (at <37 weeks of gestation), infants with a previous hospital admission for respiratory disease, infants with a congenital heart defect, infants younger than 3 months of age and those younger than 6 months of age (with correction for prematurity), and infants presenting to hospitals with an on-site ICU and those without an on-site ICU. A test for interaction between treatment group and subgroup on the basis of a log binomial regression model was used to test for homogeneity of relative risks between subgroups. If there was no evidence of heterogeneity in a subgroup analysis, the overall relative risk was assumed for that subgroup. Exploratory analyses involved patients who received escalation of care.

RESULTS

CHARACTERISTICS OF THE PATIENTS

Infants were recruited between October 2013 and August 2016. A total of 2217 infants were eligible for inclusion, of whom 1638 (74%) underwent randomization (Fig. 1). A total of 210 parents or guardians (12%) declined consent (166 with deferred consent and 44 with immediate consent); thus, 1472 infants were included in the analyses. The baseline demographic and physiological characteristics of the infants were similar in the two groups (Table 1, and Table S1A and S1B in the Supplementary Appendix). Respiratory syncytial virus (RSV) was the most common virus detected, and premature birth was the most common coexisting condition.

PRIMARY OUTCOME

Treatment failure with escalation of care occurred in 87 of 739 infants (12%) in the high-flow group, as compared with 167 of 733 (23%) in the standard-therapy group (risk difference, –11 percentage points; 95% confidence interval [CI], –15 to –7; P<0.001). The Kaplan–Meier plot showed a higher rate of treatment success among infants treated with high-flow oxygen therapy than among those who received standard oxygen therapy, and a log-rank test confirmed a lower

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hazard of treatment failure in the high-flow group (P<0.001) (Fig. 2). Among infants who had treatment failure, the interval between enrollment and escalation of care did not differ significantly between the two groups (Table 2). The number needed to treat to prevent one instance of escalation of care was 9 (95% CI, 7 to 14).

The effect of the intervention on escalation of care was independent of age. The treatment effect of the intervention differed significantly between hospitals with an on-site ICU and those without an on-site ICU (P<0.001). In hospitals without an on-site ICU, escalation of care occurred in 20 of 270 infants (7%) in the high-flow group, as compared with 69 of 247 (28%) in the standard-therapy group (risk difference, –21 percentage points; 95% CI, –27 to –14). However, in hospitals with an on-site ICU, escalation of care occurred in 67 of 469 (14%) in the high-flow group and in 98 of 486 (20%) in the standard-therapy group (risk difference, –6 percentage points; 95% CI, –11 to –1). Analyses that considered a history of prematurity or previous hospital admission showed no effect on the primary outcome. There were no significant differences in outcome between RSV-positive infants and RSV-negative infants.

The results were similar in all the infants receiving escalation of care who were independently confirmed to meet at least three of the four clinical criteria for treatment failure (Table 2, and Fig. S1 in the Supplementary Appendix). According to independent chart review, clinicians escalated therapy in 86 of 254 infants (34%; 34 infants in the high-flow group and 52 in the standard-therapy group) who did not meet three of the four prespecified clinical criteria. A total of 53 infants in the high-flow group (7%) met this threshold and received escalation of care, as compared with 115 (16%) in the standard-therapy group (risk difference, –9 percentage points; 95% CI, –12 to –5; P<0.001) (Table 2). The severity of disease as measured immediately before the time of escalation of care was similar in the two trial groups with regard to the absolute heart rate and the transcutaneous oxygen saturation level; however, the respiratory rate was significantly higher in the high-flow group than in the standard-therapy group (Table 3). The most common reason that triggered escalation of care was the hospital early-warning tool. The proportion of infants meeting the clinical criteria triggering escalation of care was similar in hospitals with an on-site ICU and in those without an on-site ICU

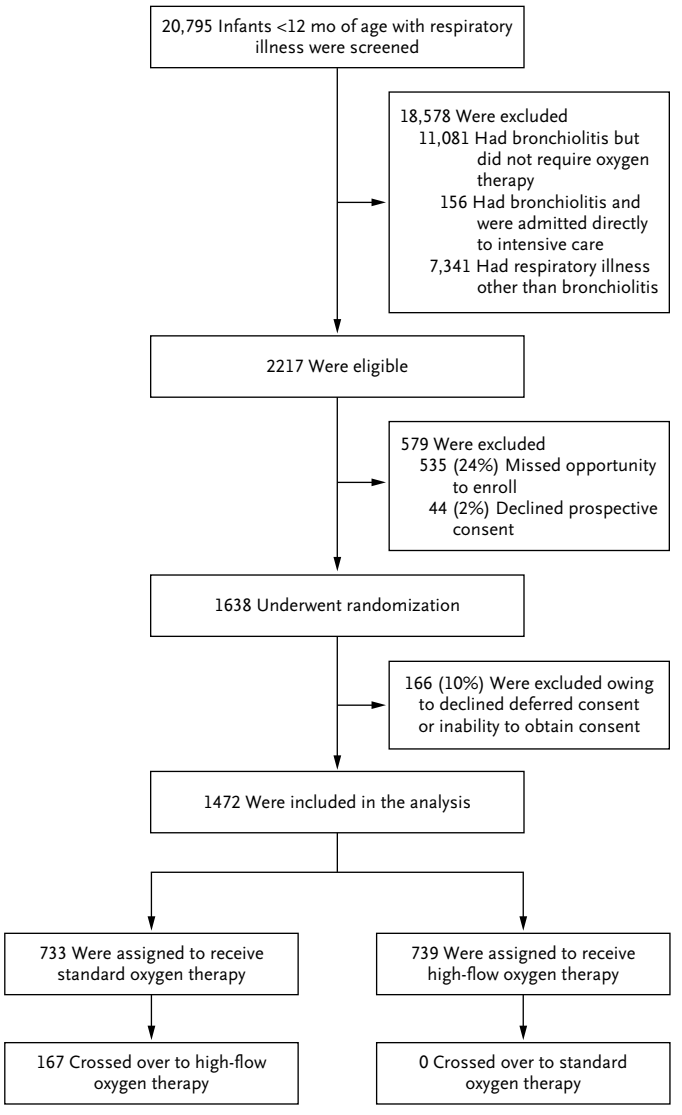


Figure 1. Numbers of Infants Who Were Screened, Assigned a Trial Group, and Included in the Primary Analysis.

Infants younger than 12 months of age who had respiratory illness were screened for eligibility in the participating hospitals. Informed consent was obtained from parents or guardians with the use of either an immediate (prospective) or a deferred (retrospective) consent process. At the time of the trial, high-flow therapy was considered to be the normal standard practice in the trial centers, so the ethics committee allowed the deferred-consent process.

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Table 1. Baseline Characteristics of the Infants with Bronchiolitis.*

Characteristic	Standard-Therapy Group (N=733)	High-Flow Group (N=739)
Age		
Mean — mo	6.10±3.44	5.76±3.54
Distribution — no. (%)		
≤3 mo	186 (25)	211 (29)
>3 to 6 mo	170 (23)	187 (25)
>6 mo	377 (51)	341 (46)
Weight — kg	7.60±2.21	7.27±2.25
Female sex — no. (%)	262 (36)	285 (39)
Race or ethnic group — no. (%)†		
White	379 (52)	390 (53)
Aboriginal or Torres Strait Islander	31 (4)	28 (4)
Maori or Pacific Islander	217 (30)	199 (27)
Other or unknown	106 (14)	122 (17)
Premature birth — no. (%)‡	128 (17)	137 (19)
Neonatal respiratory support — no. (%)§	101 (14)	116 (16)
Oxygen only	37 (5)	30 (4)
Noninvasive ventilation	70 (10)	76 (10)
Invasive ventilation	20 (3)	28 (4)
Previous hospital admission for respiratory disease — no. (%)	225 (31)	187 (25)
ICU admission for respiratory support — no. (%)§	45 (6)	27 (4)
Invasive ventilation	7 (1)	4 (1)
Noninvasive ventilation	6 (1)	2 (<1)
High-flow therapy	34 (5)	20 (3)
Chronic lung disease — no. (%)	13 (2)	16 (2)
Congenital heart disease — no. (%)	16 (2)	8 (1)
Patient history of wheeze — no. (%)	176 (24)	160 (22)
Family history of asthma — no. (%)	361 (49)	328 (44)
Family history of allergy — no. (%)	162 (22)	133 (18)
Currently attending child care — no. (%)	92 (13)	96 (13)
Viral cause — no./total no. (%)¶		
Respiratory syncytial virus	322/584 (55)	334/610 (55)
Other virus	201/584 (34)	177/610 (29)
Multiple viruses	110/584 (19)	102/610 (17)
No virus detected on nasopharyngeal aspirate	112/584 (19)	146/610 (24)

* Plus–minus values are means ±SD. There were no significant between-group differences regarding the demographic and physiological characteristics of the infants at baseline.
† Race or ethnic group was reported by the parent or guardian.
‡ Prematurity was defined as birth before 37 weeks of gestation.
§ Multiple options were possible.
¶ Viral testing was not mandated, so a lower number of tests overall were obtained.

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(Table S2 in the Supplementary Appendix). There were no primary-outcome differences in the subgroups (Table S3 in the Supplementary Appendix).

SECONDARY OUTCOMES

There were no significant between-group differences in the duration of hospital stay, the duration of stay in the ICU, or the duration of oxygen therapy (Table 3, and Fig. S2A and S2B in the Supplementary Appendix). In all 167 infants in the standard-therapy group who had treatment failure and received escalation of care, clinicians opted to offer high-flow therapy as a rescue treatment. Among these 167 infants, 102 (61%) had a response to high-flow rescue therapy; in 65 infants (39%), rescue high-flow therapy was ineffective, and the infants were transferred to an ICU. Overall, 35 infants (2%) were transferred from a hospital without an on-site ICU to another hospital. A total of 12 infants (1%) underwent intubation, including 8 infants in the high-flow group and 4 in the standard-therapy group (P=0.39). Data regarding medications are provided in Table S4 in the Supplementary Appendix. The rate of adverse events was low in each group, with one pneumothorax occurring in each group (no drainage needed). No life-threatening serious adverse events were observed, including no instances of emergency intubation or cardiac arrest.

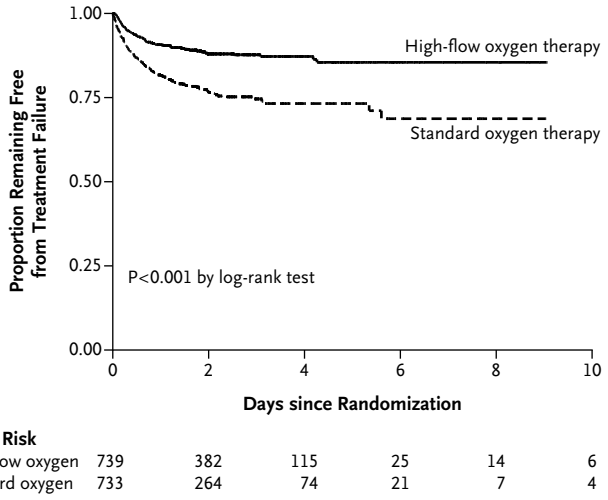


Figure 2. Kaplan–Meier Plot of the Proportion of Infants with Bronchiolitis Remaining Free from Treatment Failure.

DISCUSSION

In this multicenter, randomized, controlled trial involving infants with bronchiolitis and hypoxemia, we found that significantly fewer infants in the high-flow group than in the standard-therapy group received escalation of care. There was no significant between-group difference in the incidence of adverse events. There was no evidence of a shorter duration of oxygen therapy, lower rate of ICU admission, or shorter duration of hospital stay in infants receiving high-flow oxygen therapy than in those receiving standard subnasal oxygen therapy.

Our findings are supported by the results of a recent smaller trial,[21] which showed a similar effect size, with a lower treatment-failure rate in the high-flow group than in the standard-therapy group (14% vs. 33%). No significant differences in the duration of oxygen therapy and the duration of hospital stay were found in that trial. As in our trial, clinicians were allowed to use rescue high-flow oxygen therapy for infants in the standard-therapy group if they had treatment failure. Oxygen-saturation levels of less than 90% were an exclusion criterion. In contrast, our trial specifically targeted infants with hypoxemia and bronchiolitis, and we excluded infants with acutely life-threatening bronchiolitis leading to immediate respiratory support and intubation.

The primary outcome in our pragmatic trial included escalation of care and the meeting of at least three of four clinical criteria. Escalation of care was allowed if clinically warranted in the judgment of the treating clinician; this was necessary as a safeguard, given that our trial tested an intervention that had been previously performed only in ICUs. Clinicians escalated care in 34% of the infants who did not meet at least three of the four prespecified clinical criteria, according to the independent chart review we conducted. This relatively high percentage indicates that the selected clinical criteria may not comprehensively cover the clinical decision pro-

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Table 2. Primary Outcome in the Trial Cohort and Outcomes in Subgroups of Infants Who Received Escalation of Care.*

Outcome	Standard-Therapy Group (N=733)	High-Flow Group (N=739)	Relative Risk or Mean Difference (95% CI)†	Risk Difference (95% CI)	P Value
				percentage points	
Escalation of care in overall trial cohort					
Treatment failure — no. (%)	167 (23)	87 (12)	0.52 (0.40 to 0.66)	−11 (−15 to −7)	<0.001
Interval between enrollment and escalation — days	0.67±0.83	0.72±0.82	0.05 (−0.17 to 0.26)	—	0.67
Treatment failure according to age — no./total no. (%)					0.60‡
≤3 mo	55/186 (30)	34/211 (16)	0.55 (0.36 to 0.81)	−13 (−22 to −5)	
>3 to 6 mo	34/170 (20)	22/187 (12)	0.59 (0.35 to 0.99)	−8 (−16 to −1)	
>6 mo	78/377 (21)	31/341 (9)	0.44 (0.29 to 0.66)	−12 (−17 to −7)	
Treatment failure according to on-site ICU status — no./total no. (%)					<0.001‡
No	69/247 (28)	20/270 (7)	0.27 (0.16 to 0.43)	−21 (−27 to −14)	
Yes	98/486 (20)	67/469 (14)	0.71 (0.53 to 0.95)	−6 (−11 to −1)	
Treatment failure according to premature birth status — no./total no. (%)					
Yes	38/128 (30)	27/137 (20)	0.66 (0.42 to 1.05)	−10 (−20 to 0)	0.19‡
No	129/605 (21)	60/601 (10)	0.47 (0.35 to 0.63)	−11 (−15 to −7)	
Treatment failure according to virus detected — no./total no. (%)					0.57‡
Respiratory syncytial virus	81/322 (25)	50/334 (15)	0.60 (0.43 to 0.83)	−10 (−16 to −4)	
Other	35/150 (23)	15/130 (12)	0.50 (0.27 to 0.89)	−12 (−21 to −3)	
Not tested	261	275	—	—	
Escalation of care in infants who met ≥3 of 4 criteria					
Treatment failure — no. (%)	115 (16)	53 (7)	0.46 (0.33 to 0.63)	−9 (−12 to −5)	<0.001
Interval between enrollment and escalation — days	0.64±0.64	0.73±0.80	0.09 (−0.14 to 0.32)	—	0.43
Treatment failure according to age — no./total no. (%)					0.85‡
≤3 mo	35/186 (19)	19/211 (9)	0.48 (0.27 to 0.83)	−10 (−17 to −3)	
>3 to 6 mo	29/170 (17)	15/187 (8)	0.47 (0.25 to 0.88)	−9 (−16 to −2)	
>6 mo	51/377 (14)	19/341 (6)	0.41 (0.24 to 0.70)	−8 (−12 to −4)	
Treatment failure according to on-site ICU status — no./total no. (%)					<0.001‡
No	51/247 (21)	12/270 (4)	0.22 (0.11 to 0.40)	−16 (−22 to −11)	
Yes	64/486 (13)	41/469 (9)	0.66 (0.45 to 0.98)	−4 (−8 to −1)	
Treatment failure according to premature birth status — no./total no. (%)					0.85‡
Yes	27/128 (21)	19/137 (14)	0.66 (0.37 to 1.16)	−7 (−16 to 2)	
No	88/605 (15)	34/601 (6)	0.39 (0.26 to 0.58)	−9 (−12 to −6)	

* Plus–minus values are means ±SD. Escalation of care occurred if infants met three of four prespecified clinical criteria. ICU denotes intensive care unit.
† The difference between rates is expressed as a relative risk, and the difference between outcomes that were assessed in days are shown in days.
‡ The P values for all the subgroup analyses represent the test of homogeneity across the odds ratios that were compared among subgroups.

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Table 3. Secondary Outcomes, Reasons for Escalation of Care, and Adverse Events.*

Variable	Standard-Therapy Group (N=733)	High-Flow Group (N=739)	Odds Ratio or Mean Difference (95% CI)†	P Value
Secondary outcomes				
Duration of stay in hospital — days	2.94±2.73	3.12±2.43	0.18 (−0.09 to 0.44)	0.19
Duration of stay in ICU — days‡	2.72±2.31	2.63±1.70	−0.09 (−0.74 to 0.55)	0.78
Duration of oxygen therapy — days§	1.87±2.09	1.81±2.18	−0.06 (−0.28 to 0.16)	0.61
Escalation of care				
Failure of standard therapy and rescue high-flow therapy — no./total no. (%)	65/167 (39)	NA	—	—
Transfer to ICU — no. (%)	65 (9)	87 (12)	1.37 (0.96 to 1.95)	0.08
Transfer to ICU in another hospital — no./total no. (%)	15/247 (6)	20/270 (7)	1.24 (0.59 to 2.61)	0.60
Transfer to on-site ICU — no./total no. (%)	50/486 (10)	67/469 (14)	1.45 (0.97 to 2.19)	0.07
Intubation — no./total no. (%)	4/733 (1)	8/739 (1)	1.99 (0.60 to 6.65)	0.39
Adverse event — no. (%)¶				
Serious adverse event	0	0	—	—
Pneumothorax	1 (<1)	1 (<1)	—	—
Emergency intubation	0	0	—	
Cardiac arrest	0	0	—	—
Respiratory arrest	0	0	—	—
Apneas	3 (<1)	3 (<1)	—	—
Clinical criteria met at escalation of care — no./total no. (%)				
Met ≥3 of 4 criteria	115/167 (69)	53/87 (61)	0.71 (0.40 to 1.26)	0.26
Persistent tachycardia	115/167 (69)	49/87 (56)	0.58 (0.33 to 1.03)	0.06
Persistent tachypnea	128/167 (77)	63/87 (72)	0.80 (0.43 to 1.51)	0.55
Increasing use of oxygen	50/167 (30)	37/87 (43)	1.73 (0.98 to 3.08)	0.06
Early-warning tool–triggered review	129/167 (77)	68/87 (78)	1.05 (0.54 to 2.07)	0.99
Severity of disease at time of escalation of care				
No. of patients with data	165	87		
Heart rate — beats/min	164.1±19.9	162.5±20.9	−1.62 (−6.90 to 3.66)	0.55
Respiratory rate — breaths/min‖	54.6±12.4	62.6±15.2	8.02 (4.51 to 11.5)	<0.001
Transcutaneous oxygen saturation — %	96.4±3.96	96.3±2.99	−0.11 (−1.07 to 0.84)	0.82

* Plus–minus values are means ±SD. NA denotes not applicable.
† Odds ratios are presented for differences between rates, and mean differences are presented for other outcomes.
‡ Duration of stay in the ICU was assessed in the 65 patients in the standard-therapy group and in the 87 in the high-flow group who were admitted to the ICU.
§ Data on the duration of oxygen therapy were missing for two patients in the standard-therapy group and for one in the high-flow group.
¶ Because the analysis was based on small numbers, no statistical values are given.
‖ Data on the respiratory rate were missing for one patient in the standard-therapy group.

cess and suggests that other elements in clinical judgment were not captured in this trial when escalation of care occurred. However, the relative effect size was similar in analyses involving all infants receiving escalation of care and in those involving infants receiving escalation of care in the presence of at least three of the four prespecified clinical criteria. Considering that the trial was not blinded and that a similar proportion of infants in each group met the clinical criteria, we conclude that there was unlikely to be a major bias due to variation in judgment among the attending clinicians.

All 167 infants in the standard-therapy group

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who had escalation of care to high-flow therapy in a general pediatric inpatient ward, including 65 (39%) who had treatment failure with rescue high-flow therapy, were admitted to a pediatric ICU. The trial protocol did not offer any "rescue" option in the general inpatient unit for infants who had treatment failure with high-flow therapy; these infants were all admitted directly to a pediatric ICU. The overall rate of ICU admissions was lower than rates in a previous report[2]; only 1% of the patients in our trial underwent intubation (Table 3).

Our study had certain limitations. It was not possible to mask the oxygen-delivery method. To minimize bias, we used prespecified clinical criteria for the escalation of care. This pragmatic design reflects current practice across many institutions. The rescue use of high-flow oxygen therapy reflected a real-world scenario, because high-flow therapy was used as standard practice in Australia and New Zealand at the time of our trial. Denying clinicians the option to use rescue high-flow oxygen therapy in infants in the standard-oxygen group would have prevented us from performing the trial.

In conclusion, our randomized, controlled trial involving infants with bronchiolitis showed a significantly lower rate of escalation of care due to treatment failure when high-flow oxygen therapy was used early during the hospital admission than when standard oxygen therapy was used.

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APPENDIX

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REFERENCES

1. Meissner HC. Viral bronchiolitis in children. N Engl J Med 2016;374:62-72.
2. Hasegawa K, Tsugawa Y, Brown DF, Mansbach JM, Camargo CA Jr. Trends in bronchiolitis hospitalizations in the United States, 2000-2009. Pediatrics 2013;132:28-36.
3. Schlapbach LJ, Straney L, Gelbart B, et al. Burden of disease and change in practice in critically ill infants with bronchiolitis. Eur Respir J 2017;49(6):1601648.
4. Fernandes RM, Hartling L. Glucocorticoids for acute viral bronchiolitis in infants and young children. JAMA 2014;311:87-8.
5. Zorc JJ, Hall CB. Bronchiolitis: recent evidence on diagnosis and management. Pediatrics 2010;125:342-9.
6. Oakley E, Borland M, Neutze J, et al. Nasogastric hydration versus intravenous hydration for infants with bronchiolitis: a randomised trial. Lancet Respir Med 2013;1:113-20.
7. Long E, Babl FE, Duke T. Is there a role for humidified heated high-flow nasal cannula therapy in paediatric emergency departments? Emerg Med J 2016;33:386-9.
8. Essouri S, Chevret L, Durand P, Haas V, Fauroux B, Devictor D. Noninvasive positive pressure ventilation: five years of experience in a pediatric intensive care unit. Pediatr Crit Care Med 2006;7:329-34.
9. Javouhey E, Barats A, Richard N, Stamm D, Floret D. Non-invasive ventilation as primary ventilatory support for infants with severe bronchiolitis. Intensive Care Med 2008;34:1608-14.
10. Lazner MR, Basu AP, Klonin H. Noninvasive ventilation for severe bronchiolitis: analysis and evidence. Pediatr Pulmonol 2012;47:909-16.
11. Manley BJ, Owen LS, Doyle LW, et al. High-flow nasal cannulae in very preterm

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infants after extubation. N Engl J Med 2013;369:1425-33.
12. Lee JH, Rehder KJ, Williford L, Cheifetz IM, Turner DA. Use of high flow nasal cannula in critically ill infants, children, and adults: a critical review of the literature. Intensive Care Med 2013;39:247-57.
13. 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.
14. Mayfield S, Bogossian F, O'Malley L, Schibler A. High-flow nasal cannula oxygen therapy for infants with bronchiolitis: pilot study. J Paediatr Child Health 2014; 50:373-8.
15. Bressan S, Balzani M, Krauss B, Pettenazzo A, Zanconato S, Baraldi E. High-flow nasal cannula oxygen for bronchiolitis in a pediatric ward: a pilot study. Eur J Pediatr 2013;172:1649-56.
16. Pham TM, O'Malley L, Mayfield S, Martin S, Schibler A. The effect of high flow nasal cannula therapy on the work of breathing in infants with bronchiolitis. Pediatr Pulmonol 2015;50:713-20.
17. Schibler A, Pham TM, Dunster KR, et al. Reduced intubation rates for infants after introduction of high-flow nasal prong oxygen delivery. Intensive Care Med 2011;37:847-52.
18. Green CA, Yeates D, Goldacre A, et al. Admission to hospital for bronchiolitis in England: trends over five decades, geographical variation and association with perinatal characteristics and subsequent asthma. Arch Dis Child 2016;101: 140-6.
19. Franklin D, Dalziel S, Schlapbach LJ, et al. Early high flow nasal cannula therapy in bronchiolitis, a prospective randomised control trial (protocol): a Paediatric Acute Respiratory Intervention Study (PARIS). BMC Pediatr 2015;15:183.
20. Ralston SL, Lieberthal AS, Meissner HC, et al. Clinical practice guideline: the diagnosis, management, and prevention of bronchiolitis. Pediatrics 2014;134(5): e1474-e1502.
21. Kepreotes E, Whitehead B, Attia J, et al. High-flow warm humidified oxygen versus standard low-flow nasal cannula oxygen for moderate bronchiolitis (HFWHO RCT): an open, phase 4, randomised controlled trial. Lancet 2017;389:930-9.
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