1. Participant flow

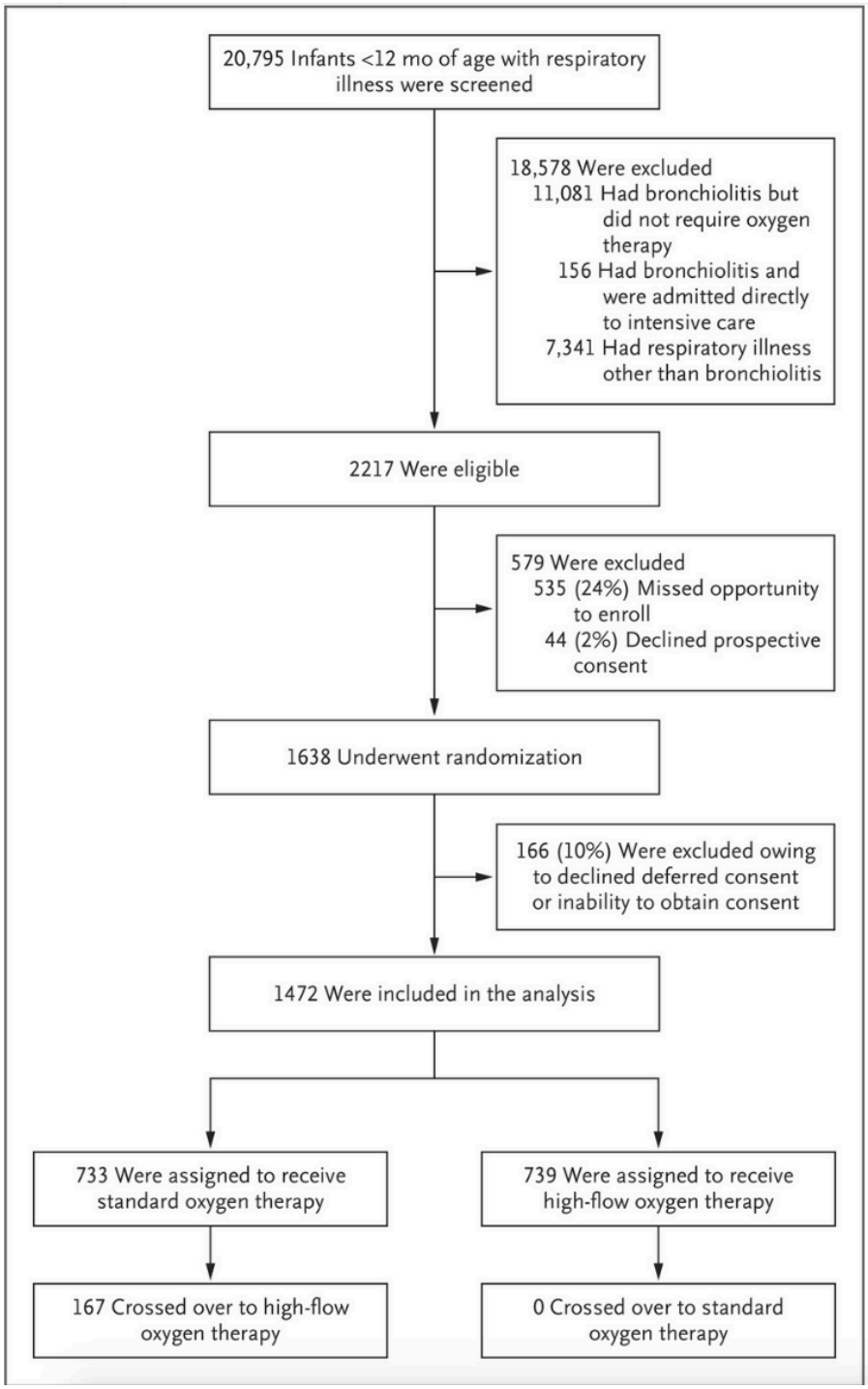

Figure 1. ***Numbers of Infants Who Were Screened, Assigned a Trial Group, and Included in the Primary Analysis***.
Infants younger than 12 months of age who had respiratory illness were screened for eligibility in the participating hospitals. Informed consent was obtained from parents or guardians with 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.

2. Baseline characteristics

Table.1 Baseline Characteristics of Infants with Bronchiolitis

Characteristic	Standard-oxygen group N=733	High-flow group N=739
Age (months)	6.10±3.44	5.76±3.54
≤ 3 months no. (%)	186 (25.4)	211 (28.6)
> 3 to 6 months no. (%)	170 (23.2)	187 (25.3)
> 6 months no. (%)	377 (51.4)	341 (46.1)
Weight (kg)	7.60±2.21	7.27±2.25
Sex female no. (%)	262 (35.7)	285 (38.6)
Ethnicity		
Caucasian no. (%)	379 (51.7)	390 (52.8)
Aboriginal/Torres Strait Islander no. (%)	31 (4.2)	28 (3.8)
Maori/Pacific Islander no. (%)	217 (29.6)	199 (26.9)
Other/unknown no. (%)	106 (14.5)	122 (16.5)
Prematurity <37 weeks ¶ no (%)	128 (17.5)	137 (18.6)
Need for neonatal respiratory support no. (%)	101 (13.9)	116 (15.7)
Oxygen only no. (%)	37 (5.0)	30 (4.1)
Non-invasive ventilation no. (%)	70 (9.5)	76 (10.3)
Invasive ventilation no. (%)	20 (2.7)	28 (3.8)
Previous hospital admissions for respiratory disease postnatal ¶ no (%)	225 (30.7)	187 (25.3)
Intensive care admission for respiratory support no. (%)	45 (6.2)	27 (3.7)
Invasive ventilation no. (%)	7 (1.0)	4 (0.5)
Non-invasive ventilation no. (%)	6 (0.8)	2 (0.3)
High-flow therapy no. (%)	34 (4.6)	20 (2.7)
Chronic Lung Disease no. (%)	13 (1.8)	16 (2.2)
Congenital Heart Disease no. (%)	16 (2.2)	8 (1.1)
Patient history of wheeze no. (%)	176 (24.1)	160 (21.8)
Family history of asthma no. (%)	361 (50.0)	328 (45.4)
Family history of allergy no. (%)	162 (22.5)	133 (18.4)
Currently attending child care no. (%)	92 (13.0)	96 (13.5)
Viral etiology*	N=584	N=610
Respiratory syncytial virus	322 (55.1)	334 (54.8)
Other viruses	201 (34.4)	177 (29.0)
Multiple viruses	110 (15.0)	102 (13.8)
No virus detected on nasopharyngeal aspirate	112 (19.2)	146 (23.9)

3. Outcome measures

Table 2. Primary Outcome and Outcomes in Subgroups as per Escalation

Outcome	Standard-oxygen N=733	High Flow N=739	Relative risk (95%-CI)	Risk Difference (95%-CI)	P Value
Escalation					
Treatment failure no (%)	167 (22.8)	87 (11.8)	0.52 (0.40-0.66)	-11% (-15% to -7%)	<0.001
Interval between enrollment and escalation days	0.67±0.83	0.72±0.82	0.05 (-0.17-0.26)		0.67
Age					0.60¶
≤ 3 months no (%)	55/186 (29.6)	34/211 (16.1)	0.55 (0.36-0.81)	-13% (-22% to -5.2%)	
> 3 to 6 months no (%)	34/170 (20.0)	22/187 (11.8)	0.59 (0.35-0.99)	-8.2% (-16% to -0.7%)	
> 6 months no (%)	78/377 (20.7)	31/341 (9.1)	0.44 (0.29-0.66)	-12% (-17% to -6.5%)	
Hospital levels					<0.001¶
No on-site ICU no (%)	69/247 (27.9)	20/270 (7.4)	0.27 (0.16-0.43)	-21% (-27% to -14%)	
On-site ICU no (%)	98/486 (20.2)	67/469 (14.3)	0.71 (0.53-0.95)	-5.9% (-11% to -1.1%)	
Prematurity <37 weeks					
Yes no (%)	38/128 (29.7)	27/137 (19.7)	0.66 (0.42-1.05)	-10% (-20% to 0.4%)	0.19¶
No no (%)	129/605 (21.3)	60/601 (10.0)	0.47 (0.35-0.63)	-11% (-15% to -7.3%)	
Virus detected					0.57¶
RSV no (%)	81/322 (25.2)	50/334 (15.0)	0.60 (0.43-0.83)	-10% (-16% to -4.1%)	
Other virus no (%)	35/150 (23.3)	15/130 (11.5)	0.50 (0.27-0.89)	-12% (-21% to -3.1%)	
Not tested (%)	N=261	N=275			

Table 2. continued					
Infants received escalation meeting ≥ 3 out of 4 criteria					
Treatment failure no (%)	115 (15.7)	53 (7.2)	0.46 (0.33, 0.63)	-8.5% (-12% to -5.3%)	<0.001
Interval between enrollment and escalation days	0.64±0.64	0.73±0.80	0.09 (-0.14-0.32)		0.43
Age					0.85¶
≤ 3 months no (%)	35/186 (18.8)	19/211 (9.0)	0.48 (0.27, 0.83)	-10% (-17%, -3.0%)	
> 3 to 6 months no (%)	29/170 (17.1)	15/187 (8.0)	0.47 (0.25, 0.88)	-9.0% (-16%, -2.2%)	
> 6 months no (%)	51/377 (13.5)	19/341 (5.6)	0.41 (0.24, 0.70)	-8.0% (-12%, -3.7%)	
Hospital levels					<0.001¶
No on-site ICU no (%)	51/247 (20.7)	12/270 (4.4)	0.22 (0.11, 0.40)	-16% (-22%, -11%)	
On-site ICU no (%)	64/486 (13.2)	41/469 (8.7)	0.66 (0.45, 0.98)	-4.4% (-8.4%, -0.5%)	
Prematurity <37 weeks					
Yes no (%)	27/128 (21.1)	19/137 (13.9)	0.66 (0.37, 1.16)	-7.2% (-16%, 1.9%)	0.85¶
No no (%)	88/605 (14.6)	34/601 (5.7)	0.39 (0.26, 0.58)	-8.9% (-12%, -5.5%)	

Plus-minus values are means±SD. RSV denotes respiratory syncytial virus. ICU denotes intensive care unit.
¶P-value for all subgroup analyses represents test of homogeneity across the odds ratios compared between subgroups

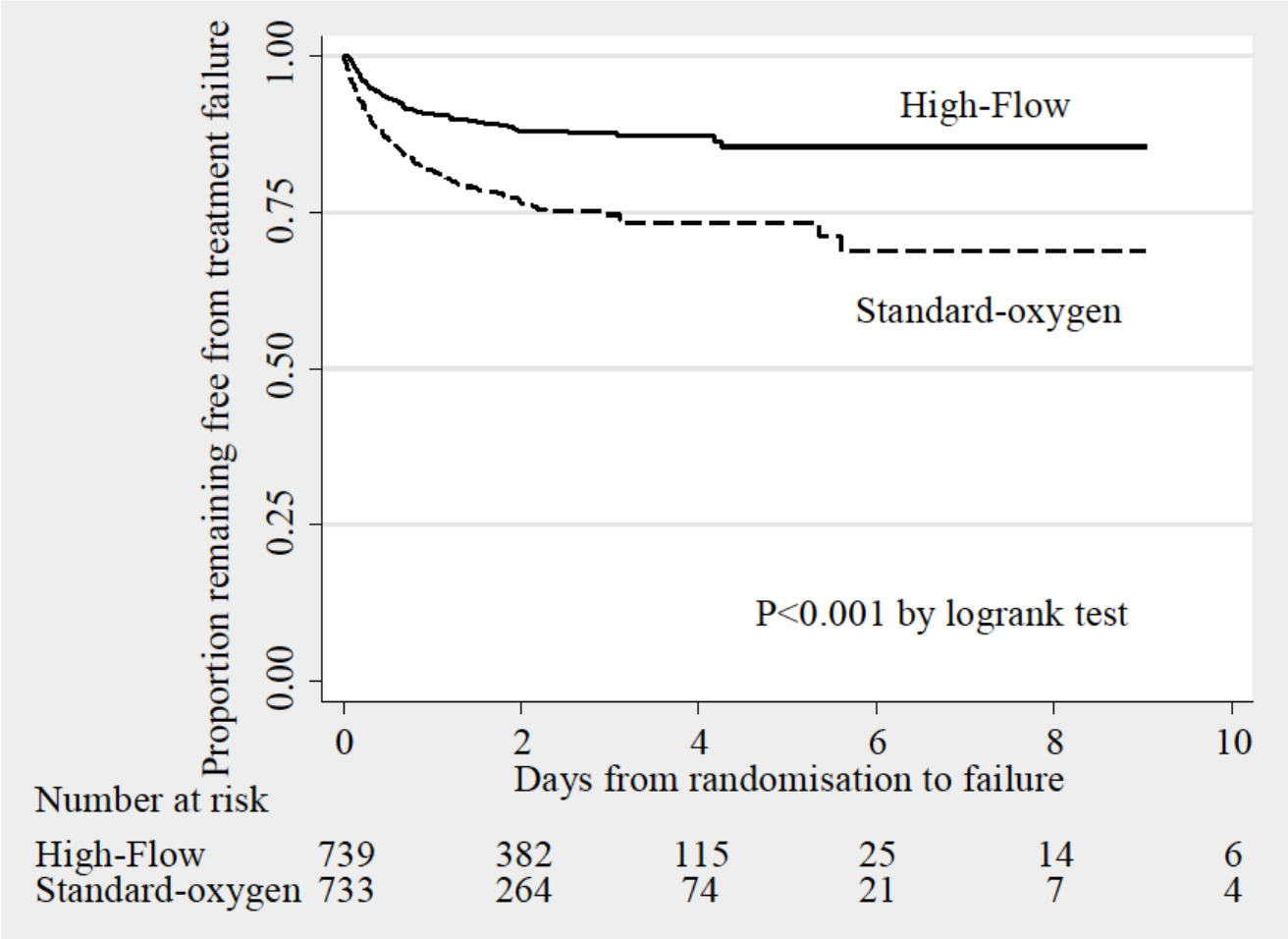

Figure 2. Kaplan-Meier Plot of the Proportion of Infants with Bronchiolitis Remaining Free from Treatment Failure.

Primary Outcome results

Treatment failure with escalation of care occurred in 167 of 733 infants (23%) in the standard-oxygen group and in 87 of 739 infants (12%) in the high-flow group with a risk difference of -11% (95% confidence interval -15% to -7%; P<0.001). The Kaplan Meier plot (Fig. 2) showed a higher success rate in infants treated with high-flow with a log-rank test confirming a decreased hazard of failure (P<0.001). The interval to failure did not differ significantly between the groups for those infants who failed (Table 2). The number needed to treat was 9 (95% confidence interval 7 to14).

The effect of the intervention on escalation of care was independent of age. The treatment effect of the intervention was significantly different between hospitals with and without on-site intensive care (P = 0.003). The need for escalation in hospitals without an on-site intensive care unit was 69 of 247 (27.9%) in the standard-oxygen group vs. 20 of 270 (7.4%) in the high-flow group (risk difference of -21%, confidence interval -27% to -14%), whereas in hospitals with on-site intensive care units 98 of 486 (20.2%) failed standard-oxygen therapy and 67 of 469 (14.3%) high-flow (risk difference of -5.9%, confidence interval -11% to – 1.1%). History of prematurity or previous hospital admission showed no impact on the primary outcome. There were no differences in outcome between RSV-positive and -negative infants.

The results were similar for all infants receiving escalation of care who were independently confirmed to meet three or more out of four clinical criteria (Table 2 and Fig. S1 in the Supplementary Appendix 4.6). A total of 115 infants (15.7%) in the standard-oxygen and 53 in the high-flow group (7.2%) met the ≥3 out of 4 clinical criteria and received escalation in care with a risk difference of -8.5% (95% confidence interval -12.0% to -5.3%; P<0.001) (Table 2). The severity of disease measured immediately prior to the time of escalation was similar in both study groups in relation to the absolute heart rate and oxygen requirement; however, the respiratory rate was significantly higher in the high-flow group (Table 3). The most common reason triggering escalation was based on the hospital early warning tool. The proportion of infants meeting the clinical criteria triggering escalation was similar in hospitals with and without onsite ICU (Table S2 in the Supplementary Appendix 4.8). There were no primary outcome differences in subgroups (Table S3 in the Supplementary Appendix 4.9).

Secondary Outcomes

There were no significant between-group differences in length of hospital stay, length of intensive care stay or duration of oxygen-therapy (Table 3 and Figs S2a and S2b in the Supplementary Appendix 4.8). For all 167 infants (100%) who failed standard-oxygen and received escalation of therapy, clinicians opted to offer high-flow as a “rescue” treatment. In 65 (39%) of these infants “rescue” high-flow was ineffective, and the infants were transferred to an intensive care unit. Over all 35 infants (2.4%) required transfer from a hospital without on-site intensive care to another hospital. Twelve (0.8%) infants required intubation-- four in the standard-oxygen group and eight in the high-flow group (P=0.39). Data on medication is provided in Table S4 in the Supplementary Appendix 4.13. The rate of adverse events was low in both groups, with one pneumothorax in each of the treatment arms (no drainage needed). No life-threatening serious adverse-events were observed, specifically no emergency intubation or cardiac arrest.

4. Adverse events/harms

The rate of adverse events was low in both groups, with one pneumothorax in each of the treatment arms (no drainage needed). No life-threatening serious adverse-events were observed, specifically no emergency intubation or cardiac arrest.

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